SOME MATHEMATICAL MODELS IN BIOLOGY

Revised Edition

Compiled and Edited by:

Robert M. Thrall

James A. Mortimer

Kenneth R. Rebman

Richard F. Baum

This report, prepared at the University of Michigan, was sponsored jointly by the National Institutes of Health and the Committee on the Undergraduate Program in Mathematics.

December 1967

40241-R-7

5-T01-GM01457-02

TABLE OF CONTENTS

CA17: Dynamics of Cell Growth

Linear Algebra and Computer Applications
CL1: Selective Radiation Effects in Cell Populations
CL2: Some Measures of Synchrony in Cell Populations

Probability and Stochastic Processes
CS1: Stochastic Considerations in a Diffusion Problem
CS2: Age Distributions of Cells in Growing Cell Populations

BIOLOGY OF ORGANS AND ORGANISMS

Precalculus Mathematics and Elementary Functions
OE1: A Simple Example in Respiration
OE2: Respiration as a Function of Time
OE3: The Flow of Blood in the Body
OE4: Facilitation and Occlusion in Motoneuron Pools
OE5: Graphical Analysis of Some Electroencephalographic Data
OE6: Using Matrices to Aid in Diagnosing the Condition of a Patient

Mathematical Analysis
OA1: The Rate of Cooling of a Body
OA2: The Maximum Velocity of the Flow of Air through the Respiratory System while Coughing
OA3: The Form of the Heartbeat in the Aorta
OA4: Blood Flow in an Arteriole
OA5: Some Problems in Visco-elasticity
OA6: Vibrations of a Taut Wire
OA7: Muscle Tension as a Function of the Time of Contraction
OA8: Feedback Regulation of the Concentration of Thyroid Hormone in the Blood
OA9: The Response of the Body to a Drug
OA10: Concentration of Glucose in the Body after Glucose Infusion
OA11: Visual Threshold Summation
OA12: The Subjective Brightness of Light

Linear Algebra and Computer Applications
OL1: A Dietary Problem
OL2: Insulin Requirements as a Linear Process in Time
OL3: A Psychophysical Matching Experiment
OL4: A Stochastic Model for Learning
OL5: A Classification Problem

Probability and Stochastic Processes
OS1: A Simplified Balance System with Stochastic Considerations
OS2: Purifying Noisy Biological Data by Averaging
OS3: Simple Model for Adaptation in a Neural Network
OS4: Visual Adaptation

POPULATION BIOLOGY

Precalculus Mathematics and Elementary Functions
PE1: Population Growth Described by a Function

P R E F A C E

This collection of 95 models is presented as an intermediate output which comes at the close of one phase of what I hope will be a continuing activity. In a preliminary version, issued earlier this year, many of the models had had no careful critical review either for biological or for mathematical content. For the present report each model has had such review; in the process quite a few of the original models have been either discarded or laid aside for future revision, and many new models have been added.

As project director, I have had the responsibility for determining the general framework of the activity; however, the principal work of the revision has been done by James Mortimer. He has written the Introduction and several of the new models, has assigned models to classes, and has done the final writing, incorporating corrections and other changes suggested by many readers (especially in the working sessions described in the Introduction). Kenneth Rebman has prepared the Guide to Mathematical Notation, has written several of the new models, and has made important contributions in the review process. Richard Baum was the most prolific assembler of new models for the present edition; he also made important contributions to the general review process. The Rationale for Mathematical Models in Biology was written by Professors John L. Howland of Bowdoin College and H. R. Van der Vaart of the North Carolina State University at Raleigh. Jeanne Sappington assisted in the editorial revisions and assembled the bibliography. Typing and general secretarial assistance have been provided by Judy Leslie, Laura Hammond, Diana Wright and Betty G. Ash. I wish to give my personal thanks to all of the persons named above plus the many authors and the following persons who participated in the review sessions: D. Cardus, J. L. Howland, A. E. Humphrey, R. H. McDowell T. G. Overmire, B. C. Patten, M. W. Pownall, G. B. Price, F. A. Roberge, W. W. Sleater, H. R. Van der Vaart, and G. Weiss.

Robert M. Thrall
Ann Arbor, Michigan

I N T R O D U C T I O N

In recent years there has been an increased awareness among biologists that mathematics can be an important tool in biological research. As a consequence, there has been much interest in the mathematical education of prospective life scientists, particularly at the undergraduate level. This interest has motivated a search for mathematical models in biology suitable for classroom use. It is apparent that at least two classes of models are needed: mathematics courses require models from biology that illustrate mathematical concepts and provide interesting applications of mathematical theory; biology courses need mathematical developments of parts of their theories. In response to these needs, a collection of examples illustrating mathematical applications to biological subjects, Some Mathematical Models in Biology (January, 1967) was prepared. This collection has been extensively revised and expanded to the present form.

It is anticipated that the present report will serve a threefold function: to delineate areas of mathematics that are applicable to modern biology, to provide a source of biomathematical examples for authors of mathematical and biological textbooks, and to be used as a supplement in lectures and coursework in cases where standard texts are deficient.

The impetus for preparing the collection came originally from several sources. The Committee on the Undergraduate Program in Mathematics (CUPM) of the Mathematical Association of America, supported by the National Science Foundation, has long been interested in determining the mathematical needs of biologists and has investigated various ways in which these needs can be met. A subpanel of the CUPM Panel on Mathematics in the Biological, Management and Social Sciences and its successor, the newly-formed Panel on Mathematics in the Life Sciences have established an active working relationship with the Panel on Interdisciplinary Cooperation of the Commission on the Under-

graduate Education in the Biological Sciences (CUEBS). At several joint meetings of the two groups common needs and interests have been discussed. Both panels have encouraged the preparation of teaching materials and have taken steps to sponsor the construction and collection of mathematical models in biology.

In addition to the NSF supported CUPM and CUEBS groups, the National Institute of General Medical Sciences of the National Institutes of Health (NIH) has been a major sponsor of projects that relate mathematics to biology, notably an NIH sponsored Summer Mathematics Institute for Life Scientists held in Ann Arbor, Michigan, in the summer of 1966. The earlier report is in part an outgrowth of that Summer Institute, and a number of models in the present report were prepared or reworked by its junior and senior staff.

The present report was prepared under the joint sponsorship of NIH and CUPM, with the cooperation of CUEBS. The models included in it utilize a wide spectrum of mathematics, from foundations and elementary calculus to more advanced topics in linear algebra, probability, and differential equations. Most have been extensively reviewed in joint working sessions of CUPM and CUEBS.

The models were collected from a variety of sources. A number of models were prepared by Professors R. Katane, M. Abeles, and R. Rahwinoff of the Hebrew University, Jerusalem. These were translated into English at the Hebrew University, put into smoother form during the NIH Summer Institute for Life Scientists, and included in the first edition. These models have been substantially revised once again for inclusion in this report. It should be noted that the editors of the present collection assume full responsibility for the current form of the models taken from the Hebrew University Report and for any errors that may have entered as part of the final revisions.

Drs. Bernard C. Patten and Jerry Olson of the Oak Ridge National Laboratory, and Professor G. M. Van Dyne of Colorado State University have kindly permitted the reprinting of a number of their papers pub-

lished elsewhere. Original models were also obtained from Dr. Julia Apter of Presbyterian-St. Luke's Hospital, Chicago; Professor James O. Brooks of Villanova University; Professor Harold Slater of Alma College; James Mortimer, Kenneth Rebman, Richard Baum and Roger Wright of the University of Michigan; and John Almasi of the University of Minnesota.

In addition to the models included in the report, a number of other models which were collected were not included for various reasons. Several were too long; others appeared elsewhere in print in an accessible form; and some required extensive revisions which were not possible to make within the time alloted for compiling and editing. The editors of this report will make these available to later workers who undertake similar projects.

The revised edition has been prepared with a new format to increase its usefulness as a source of teaching materials. A loose-leaf binding permits the addition of new models to the collection as they become available. Each model begins with a title page on which the contributor of the model, a description of the mathematics used, and a brief abstract are given. In addition, the models have been classified according to the principal area of biology and level of mathematics. Each model has been assigned an identification number of the basis of this two-way classification which was proposed by Dean Fred M. Snell of the State University of New York at Buffalo.

The three-part identification number can be interpreted as follows: The first letter denotes the main area of biology from which the model was taken.

M denotes molecular biology;

C, the biology of cells and tissues;

O, the biology of organs and organisms; and

P, population biology.

The second letter represents the level of mathematics which is primarily illustrated in the model.

E denotes precalculus mathematics and elementary functions;

A, mathematical analysis (calculus and differential equations);

L, linear algebra, combinatorial techniques, and computer applications; and

S, probability and stochastic processes.

The third part of the identification number is the serial number of the model within one of the sixteen categories indexed by the first two letters.

Although in many cases a model could appropriately have been assigned to more than one category, a unique allocation was made. If a model illustrated an application of two or more of the four primary divisions of mathematics, it was classified mathematically into the area which would logically be taught latest in a mathematics curriculum. The sequence, E, A, L, S was used in accordance with CUPM recommendations. No similar hierarchy was evident for the biological areas, so that biological classification was more arbitrary. It is hoped that the section on mathematics used and the abstract on the title page of each model will compensate for any deficiencies in the classification scheme.

For each model the title page contains a list of specific topics within the broad mathematical areas indexed by the identification number and each such topic is accompanied by a reference to the CUPM recommended mathematics course in which that topic is considered. The references used in this report correspond to the CUPM recommended courses: Math. 0, elementary functions and coordinate geometry; Math. 1, introductory calculus; Math 2P, probability; Math. 2 and 4, mathematical analysis; and Math. 3, linear algebra, as described in the CUPM report A General Curriculum in Mathematics for Colleges, 1965.

The models in this report are grouped into four major sections corresponding to the four principal areas of biology indexed by the identification number. Within each biological area, the models are further subdivided into four mathematical sections corresponding to the levels described above.

The Guide to Mathematical Notation, which appears following the models, is designed primarily for the reader having a limited mathe-

matical background, and who may be unfamiliar with modern mathematical notation. This guide defines and explains the great variety of notation used in elementary mathematics today. Most of the notation used in this book can be found in the guide, along with many additional ideas not explicitly used in these models. Also, in several cases poor, but common, notations are included in the guide. The reader is assumed to have some familiarity with a few basic mathematical concepts; however, definitions are provided for the more modern and/or less common topics.

The bibliography includes biological books containing mathematical models, mathematical textbooks with interesting applications of mathematics to biology, and journals which frequently carry biomathematical papers. As in any effort of this type, significant books are occasionally overlooked or omitted. Any additions to the bibliography would be greatly appreciated by the editors.

Although this report can make no claim to completeness, it represents a continuing effort to present mathematical models in biology in a form accessible to both biologists and mathematicians. Any additional models, bibliographic references, or other correspondence concerning this report should be addressed to CUPM Central Office, P.O. Box 1024, Berkeley, California 94701.

James A. Mortimer

THE RATIONALE FOR MATHEMATICAL MODELS IN BIOLOGY

The construction of models is central to virtually all investigations in biology or any of the natural sciences. A model may be explicit, as in the case of a formal mathematical construct representing properties of a measurable system, or implicit in cases where a verbal or diagrammatic representation of a body of information is produced. In this report we are concerned with only the explicit model which, for our purposes, may be defined as a mathematical analog of the system under study. For example, a mathematical model might serve as an analog in the sense of exhibiting reponses to changes in a parameter similar to corresponding changes actually observed.

The great value of mathematical models resides largely in the natural economy and precision of mathematical notation. Construction of a model requires a focusing of attention upon central features of a system and a rejection of anything non-essential or vague. Thus, at least as much benefit often comes from the production of the model as from the finished model itself. If the choice of central features has been made wisely, then the formal model, once it is obtained, may exhibit considerable utility in suggesting additional experiments or measurements and predicting their outcomes. The validity of a model is, of course, conditional on its ability to predict correctly, but even an "unsuccessful" model, i.e., one that leads to erroneous predictions, may be exceedingly fruitful in the sense of leading to interesting experimental approaches or suggesting relationships previously unsuspected.

Inasmuch as an incorrect model may have great utility, it is important to point out that there are two senses in which a model may be "correct." First, a model may be correct in the sense of not containing mathematical errors, although it may still lead to erroneous predictions. Second, the model may lead to correct predictions, presumably because the central features have been well-selected and well-

represented. Clearly, a model should always be correct in the first sense. If a model is found to be incorrect in the second sense, then usually the investigator will try to improve on it, making it "more realistic." These attempts will often set in motion an interesting dialogue between models and experiments.

John L. Howland

H. R. Van der Vaart

MOLECULAR BIOLOGY

****

CONVERSION BETWEEN TEMPERATURE SCALES

Contributor: Hebrew University Report

****

Mathematics: elementary algebra

Abstract: The conversion among Fahrenheit, Centigrade and Kelvin scales is considered.

1. Write the temperature in degrees Fahrenheit as a function of the temperature in degrees Centigrade, assuming that the relationship is linear, and given that

$0^{\circ}C$ is the same as $32^{\circ}F$
$100^{\circ}C$ is the same as $212^{\circ}F$

SOLUTION:

Let y represent degrees F and x represent degrees C, then

$$y = ax + b$$

$$a = \frac{y_1 - y_2}{x_1 - x_2} = \frac{-180}{-100} = \frac{9}{5}$$

$$b = y - ax = 32 - \frac{9}{5}(0) = 32$$

$$t^{\circ}F = \frac{9}{5}\, t^{\circ}C + 32$$

Calculate the following temperature conversions using the above formula: express $37^{\circ}C$, $38^{\circ}C$, $300^{\circ}C$, $20^{\circ}C$ in degrees Fahrenheit; $-100^{\circ}F$, $99^{\circ}F$, $97^{\circ}F$, in degrees Centigrade.

2. Temperature is also measured in degrees Kelvin, $t^{\circ}K$; the Kelvin scale has the same unit of measurement as the Centigrade scale and $0^{\circ}C$ is the same as $273^{\circ}K$. Give the function for degrees Kelvin in terms of degrees Fahrenheit, and define in which region the formula is meaningful. The meaningful region is $t^{\circ}F \geq -459.4$.

****

A COMBINATORIAL PROBLEM ABOUT PROTEINS

Contributor: Harold Slater

****

Mathematics: permutations (Math. 0)

Abstract: The number of different proteins which can be synthesized from various combinations of amino acid residues is considered.

A protein is a collection of amino acid residues arranged in a particular order with a suitable spatial configuration. If a certain protein consists of n amino acid residues of m types such that there are r_i of type i, find the number of ways these can be arranged in a straight chain.

SOLUTION:

The number of ways in which a population of n elements can be divided into m ordered parts of which the first has r_1 elements, the second r_2 elements, etc., is $n!/(r_1!\ r_2!\ \ldots\ r_m!)$.*

For a polypeptide with five residues find the number of different polypeptides if

a) all the residues are different.

b) only two different amino acid residues are present--three glycines and two phenylalamines.

SOLUTION:

If all the residues are different, there are 5! different polypeptides.

If the protein is composed of three glycine and two phenylalanine residues, there are $5!/(3!\ 2!) = 10$ different polypeptides.

---

*See W. Feller, An Introduction to Probability Theory and its Applications, Vol. 1. (New York: Wiley and Sons, 1957), p. 35.

****

SPECIFIC HEAT

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The rate of change of the specific heat of ethyl alcohol is obtained at various temperatures.

The specific heat of a substance is the amount of heat needed to raise the temperature of a unit mass of that substance one degree in temperature. The value of specific heat depends upon the substance temperature. Further, it depends upon whether the specific heat value was determined at constant pressure or constant volume conditions. The former specific heat is usually designated by C_p; the latter is designated by C_v. The usual practice in describing variation of specific heat with temperature is to use a polynominal expression in temperature; i.e.

$$C_p = a + bT + cT^2 + \text{----}$$

where T is the temperature and a, b, c, ---- are constants. In estimating thermodynamic functions such as heats of reaction, it is often necessary to evaluate at a particular temperature the rate of change(with respect to temperature) of the specific heat, i.e. $C_p'(T)$.

Experimentally it has been found that the specific heat of ethyl alcohol can be approximated over the temperature range of 0^oC to 60^oC by the following equation:

$$C_p(T) = 5.068 \times 10^{-1} + 2.86 \times 10^{-3} \quad T + 5.4 \times 10^{-6} T^2$$

where T is given in ^oC.

Question:

What is the rate of change of specific heat (C_p) at (a) 0^oC and (b) 10^o C?

Answer:

(a) $C_p'(0^oC) = 0.00286$ heat units/unit mass

(b) $C_p'(10^oC) = 0.00286 + 10.8 \times 10^{-6} \times 10^2$

$= 0.00394$ heat units/unit mass

****

THE SPECIFIC WEIGHT OF WATER

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The temperature at which the specific weight of water is maximal is obtained from differentiation of an equation for the specific weight as a function of time.

The specific weight of water (s) at a temperature $\underline{t^{\circ}c}$ is given by the equation:

$$s = 1 + at + bt^2 + ct^3 . \quad (\text{For } 0^{\circ} < t < 100^{\circ} C)$$

where

t = temperature in degrees centigrade

$$a = 5.3 \times 10^{-5}$$

$$b = -6.53 \times 10^{-6}$$

$$c = 1.4 \times 10^{-8}$$

At which temperature will the water have the maximum specific weight?

Solution: $\frac{ds}{dt} = a + 2bt + 3ct^2$. When $\frac{ds}{dt} = 0$, $t = 4.09^{\circ}C$

Since the second derivative, $\frac{d^2s}{dt^2} = 2b + 6ct$, is negative in the above-mentioned range $(0 < t < 100$ - all temperatures at which water is liquid - under pressure conditions) s is a maximum when $t = 4.09$.

****

THE FIRST LAW OF THERMODYNAMICS

Contributor: Hebrew University Report

****

Mathematics: exact differentials (Math. 1)

Abstract: The equation for entropy is obtained from one form of the first law of thermodynamics.

The equation,

$$(1) \qquad dq = PdV + C_v dT$$

gives one of the forms of the first law of thermodynamics for one mole of ideal gas, which satisfies PV = RT.

Explanation of Symbols:

R = the gas constant

P = the pressure

V = the volume

T = the absolute temperature

C_v = the specific heat of the gas, when it is heated without a volume change. (In an ideal gas C_v does not depend on the volume.)

dq = the amount of heat entering or leaving the gas, with a small change in temperature or volume.

Check whether (1) is an exact differential, and if it is not, change it into one.

SOLUTION:

By Euler's criterion, for the differential to be exact, the equation $\frac{\partial P}{\partial T} = \frac{\partial C_v}{\partial V}$ must hold.

It does not hold because the right-hand side equals zero (C_v is independent of V) and the left-hand side equals R/V because P = RT/V.

Therefore, we divide the equation by T:

$$(2) \qquad \frac{dq}{T} = \frac{P}{T} dV + \frac{C_v}{T} dT \ .$$

The right hand side is exact, since

$$\frac{\partial P/T}{\partial T} = \frac{\partial (C_v/T)}{\partial V} = 0.$$

We call (2) the equation of entropy, since by the definition of entropy, the left-hand side, dq/T, is the change in entropy, ds.

****

AN ELEMENTARY PROBLEM IN THERMODYNAMICS

Contributor: Hebrew University Report

****

Mathematics: integration (Math. 1)

Abstract: The work done by an ideal gas in expanding in volume at constant pressure is obtained.

Find the work that an (ideal) gas does when it expands from V_o to V_t at (constant) pressure P.

$dW = PdV$

$PV = nRT$

W = work

P = pressure (in atmospheres)

V = Volume (in liters)

n = number of moles

R = Gas Constant

T = Temperature in degrees Kelvin

Solution

$$dW = PdV = \frac{nRT}{V}\, dV$$

$$W = \int_{V_o}^{V_t} \frac{nRT}{V}\, dV = nRT\, \ell n\, V_t - nRT\, \ell n\, V_o = nRT\, \ell n\, \frac{V_t}{V_o}$$

****

VAN DER WAAL'S EQUATION

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: Van der Waal's equation is differentiated to obtain the critical values of pressure, temperature, and volume at which the graph of pressure has an inflection point.

If we are dealing with a real gas where

P = the pressure of the gas
V = the volume of the gas
a,b = constants
R = the universal gas constant
n = the number of moles of gas
T = the temperature in degrees Kelvin

Van der Waals' equation reads:

$$(1) \qquad (P + \frac{an^2}{V^2})(V - nb) = nRT \qquad V \neq nb$$

At the critical temperature T_C, the graph of P as a function of V has a horizontal inflection point at the critical point.

Find the critical values P_C and V_C (corresponding to T_C) in terms of a, b, n and R.

SOLUTION:

From equation (1)

$$(2) \qquad P(V) = \frac{nRT_C}{V-nb} - \frac{an^2}{V^2}$$

$$(3) \qquad P'(V) = -\frac{nRT_C}{(V - nb)^2} + 2\frac{an^2}{V^3}$$

$$(4) \qquad P''(V) = \frac{2nRT_C}{(V - nb)^3} - \frac{6an^2}{V^4}$$

Due to the horizontal inflection point at the critical point, $P'(V_C) = 0$ and $P''(V_C) = 0$, and thus we get

$$(5) \qquad 2V_C^4RT_C = 6an(V_C - nb)^3 \qquad \text{(from equation (4))}$$

$$(6) \qquad V_C^3RT_C = 2an(V_C - nb)^2 \qquad \text{(from equation (3))}$$

By dividing equation (5) by equation (6), we get

$$V_C = 3nb \ .$$

From equation (6)

$$T_C = \frac{2an[3nb - nb]^2}{R[3nb]^3} = \frac{8a}{27Rb} \quad .$$

Substituting the values V_C and T_C into equation (2) we get

$$P_C = \frac{a}{27\ b^2} .$$

****

THE VAN'T HOFF ISOBAR

Contributor: Hebrew University Report

****

Mathematics: integration (Math.1)

Abstract: The rate constant of a reaction which depends upon temperature is obtained by integration.

Using the theory of thermodynamics, Van't Hoff found that k (the constant of the rate of a reaction, in which one mole of substance takes part) depended on the temperature T (in degrees Kelvin) according to the following formula: $\frac{d \ln k}{dT} = \frac{Q}{RT^2}$

Q = heat freed (or absorbed in the reaction)

R = gas constant

We shall assume that R and Q do <u>not</u> change with a change in temperature (the actual change is quite small and we shall ignore it). Find k.

<u>Solution</u>

$$d \ln k = \frac{Q}{RT^2} dT$$

$$\int d \ln k = \frac{Q}{R} \int \frac{dT}{T^2}$$

$$\ln k = -\frac{Q}{R} \cdot \frac{1}{T} + C$$

$$k = e^{-\frac{Q}{RT} + C} = C_1 e^{-\frac{Q}{RT}}, \text{ where } C_1 = e^C$$

****

CONCENTRATION OF HYDROGEN AND HYDROXYL IONS

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The ratio of the concentrations of hydrogen and hydroxyl ions at which the sum of the concentrations is minimal is obtained.

In water and in solution the product of the concentrations of the hydrogen ions, $[H^+]$ and the hydroxyl ions $[OH^-]$ is very close to 10^{-14} mole.

Find the ratio $\frac{[H^+]}{[OH^-]}$ that minimizes the sum of the concentrations.

A Suggested Solution:

$$\text{Let } S = [H^+] + [OH^-]$$

$$\text{Since } [H^+] \cdot [OH^-] = 10^{-14}$$

$$S = [H^+] + \frac{10^{-14}}{[H^+]}$$

Thus S is a function of $[H^+]$ alone, $S = S([H^+])$

$$S'([H^+]) = 1 - \frac{10^{-14}}{[H^+]^2}$$

$$S''([H^+]) = 2\,\frac{10^{-14}}{[H^+]^3}$$

The first derivative vanishes when $[H^+] = 10^{-7}$ and for this value the second derivative is positive. Thus S is a minimum when $[H^+] = 10^{-7}$ and $[OH^-] = 10^{-7}$ and $\frac{[H^+]}{[OH^-]} = 1$

****

THE RATE OF AN AUTOCATALYTIC REACTION

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The time at which the rate of an autocatalytic reaction is maximal is obtained by differentiation.

The rate of a certain auto-catalytic reaction, is given by the following expression:

$$v = k \cdot x(a - x)$$

where

x = the amount of the product

a = the amount of substance at the beginning

k = a positive constant

The rate of the reaction depends on the concentration of the substance $(a - x)$ and the concentration of the product.

When will the rate be maximal (at what concentration x)?

Solution:

$$\frac{dv}{dx} = ka - 2kx$$

when

$$\frac{dv}{dx} = 0 , \quad x = \frac{a}{2} .$$

At this value of x, v is a maximum because $\frac{d^2v}{dx^2} = -2k$.

****

A SECOND ORDER CHEMICAL REACTION

Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2), partial fraction expansion

Abstract: The rate at which two types of molecules collide to form a product is described by a differential equation.

Most chemical reactions can be viewed as an interaction between two molecules that undergo a change and result in a new product. The rate of a reaction therefore depends on the number of interactions or collisions, which in turn depends on the concentrations of both types of molecules.

Consider the simple reaction

$$A + B \longrightarrow X$$

in which molecules of substance A collide with molecules of substance B to create X.

We shall designate the concentrations at time 0 of A and B by a and b. We assume that the concentration of X at the beginning is 0, and that at time t it is x.

The concentrations of A and B at time t are, correspondingly, a - x and b - x. Therefore, the rate of formation of X is given by the following differential equation:

$$\frac{dx}{dt} = k(a - x)(b - x)$$

where k is a constant.

We want to find a function f relating t and x such that $t = f(x)$.

SOLUTION:

$$(1) \qquad \int_0^x \frac{du}{(a - u)(b - u)} = k \int_0^t ds \ .$$

To simplify the integrand, $1/(a - x)(b - x)$, we set

$$\frac{1}{(a - x)(b - x)} = \frac{R}{a - x} + \frac{P}{b - x} \ .$$

To find P and R in this identity we must find a common denominator. The numerators must satisfy:

$$1 = R(b - x) + P(a - x) = -x(R + P) + Rb + Pa \ .$$

For an identity to exist the following equations must hold:

$$R + P = 0$$
$$Rb + Pa = 1$$

From these two equations we get

$$R = \frac{1}{b - a}, \quad P = \frac{1}{a - b}.$$

Therefore,

$$\frac{1}{(a - x)(b - x)} = \frac{1}{(b - a)(a - x)} + \frac{1}{(a - b)(b - x)}$$

Substituting the above expansion into (1), we obtain:

$$\int_0^x \frac{du}{(a - u)(b - u)} = \frac{1}{b - a} \int_0^x \frac{du}{a - u} + \frac{1}{a - b} \int_0^x \frac{du}{b - u}$$

$$= -\frac{1}{b - a} \ln \frac{a - x}{a} - \frac{1}{a - b} \ln \frac{b - x}{b} = \frac{1}{a - b}\left(\ln \frac{a - x}{a} - \ln \frac{b - x}{b}\right)$$

$$= \frac{1}{a - b} \ln \frac{b(a - x)}{a(b - x)}.$$

Integrating the right-hand side of the equation,

$$\int_0^t k\,ds = kt.$$

Therefore,

$$t = \frac{1}{k(a - b)} \ln \left(\frac{b}{a} \cdot \frac{a - x}{b - x}\right).$$

****

HEMOGLOBIN SATURATION DEPENDENCE ON THE PARTIAL PRESSURE OF OXYGEN

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The dependence of hemoglobin saturation on the partial pressure of oxygen is used to determine the number of molecules of oxygen that may combine with one molecule of hemoglobin.

Oxygen is transferred from the lungs to the rest of the body by a substance in the blood called hemoglobin. The rate of combination of hemoglobin and oxygen depends upon the partial pressure of oxygen, which, in turn, is proportional to the concentration of oxygen in the air.

We will call the hemoglobin molecules Hb, and hemoglobin molecules combined with oxygen, HbO_2.

The saturation of hemoglobin (designated by S) is defined as the quotient of the following concentrations:

$$S = \frac{[HbO_2]}{[Hb] + [HbO_2]} \quad , \tag{1}$$

(S is the ratio of the amount of oxygen absorbed to the maximum quantity of absorbable oxygen.)

The graph showing the relationship between the saturation of hemoglobin and oxygen pressure is sigmoidal (i.e., it has the shape of an S.) The inflection point on this graph has an important physiological interpretation. It was found that under certain conditions the changes in concentration at this point, were maximal with respect to certain changes in the oxygen pressure.

Something important about the hemoglobin molecule may be learned by investigating this curve mathematically. It can be shown that the hemoglobin molecule is complex and may combine with more than one oxygen molecule.

Let us assume that only one oxygen molecule can combine with a hemoglobin molecule.

$$Hb + O_2 \rightleftharpoons HbO_2 \tag{2}$$

According to the law of mass action we have, at equilibrium

$$\frac{[HbO_2]}{[Hb] \cdot pO_2} = K$$

where K is a constant. On the left hand side of the equation the symbols

represent concentrations (pO_2 - the oxygen pressure - is proportional to its concentration.)

Dividing the numerator and denominator of (1) by [Hb], we get:

$$S = \frac{[HbO_2]/[Hb]}{1 + [HbO_2]/[Hb]} :$$

From (2)

$$K \cdot pO_2 = \frac{[HbO_2]}{[Hb]} .$$

Thus, by substitution, we get

$$S = \frac{K \cdot pO_2}{1 + K \cdot pO_2} .$$

This equation shows the dependence of the saturation on the oxygen pressure, assuming the hemoglobin combines with only one molecule of oxygen.

If we assume that the hemoglobin can combine with two molecules of oxygen, we get the following equations:

(3) $$Hb + O_2 \rightleftharpoons HbO_2$$

(4) $$HbO_2 + O_2 \rightleftharpoons HbO_4$$

the equilibrium constant of the first reaction, $k_1 = \frac{[HbO_2]}{[HbO_2] \cdot pO_2}$

the equilibrium constant of the second reaction, $k_2 = \frac{[HbO_4]}{[HbO_2] \cdot pO_2} .$

Using these, we obtain a new equation for S:

$$S = \frac{1/2[HbO_2] + [HbO_4]}{[Hb] + [HbO_2] + [HbO_4]}$$

or

$$S = \frac{1/2([HbO_2]/[Hb]) + ([HbO_4]/[Hb])}{1 + \left(\frac{[HbO_2]}{[Hb]}\right) + \left(\frac{[HbO_4]}{[Hb]}\right)} .$$

But since $k_1 = [HbO_2]/[Hb] \cdot pO_2$, we have $[HbO_2]/[Hb] = k_1 pO_2$.

Also $k_2 = [HbO_4]/[HbO_2]\cdot pO_2$ and so

$$k_2 pO_2 = \frac{[HbO_4]}{[HbO_2]} = \frac{[HbO_4]}{k_1 pO_2 [Hb]} .$$

Thus

$$\frac{[HbO_4]}{[Hb]} = k_1 k_2 (pO_2)^2$$

and hence

$$S = \frac{k_1 pO_2 + 2k_1 k_2 (pO_2)^2}{2\left(1 + k_1 pO_2 + k_1 k_2 (pO_2)^2\right)} .$$

QUESTION:

Using the fact that S is a sigmoidal function of pO_2 (with an inflection point), show that the second assumption about the hemoglobin is better than the first assumption.

PROOF:

$$S = \frac{k\cdot pO_2}{1 + k\cdot pO_2} , \text{ according to the first assumption.}$$

$$\frac{dS}{d(pO_2)} = \frac{k}{(1 + kpO_2)^2}$$

$$\frac{d^2S}{d(pO_2)^2} = \frac{-2k^2}{(1 + kpO_2)^3}$$

According to the second assumption:

$$S = \frac{k_1 pO_2 + 2k_1 k_2 (pO_2)^2}{2\left(1 + k_1 pO_2 + k_1 k_2 (pO_2)^2\right)}$$

$$\frac{dS}{d(pO_2)} = \frac{k_1 + 4k_1 k_2 pO_2 + k_1^2 k_2 (pO_2)^2}{2\left(1 + k_1 pO_2 + k_1 k_2 (pO_2)^2\right)^2}$$

$$\frac{d^2S}{d(pO_2)^2} = k_1\Big(1 + k_1pO_2 + k_1k_2(pO_2)^2\Big)\Big((k_2 + 2k_1k_2pO_2) - 2[1 + k_2pO_2 + k_1k_2(pO_2)^2][k_1 + 2k_1k_2(pO_2)]\Big)/2\Big(1 + k_1pO_2 + k_1k_2(pO_2)^2\Big)^4$$

It is obvious that only the equation obtained using the second assumption approximates the experimental results: an increase in saturation with an increase in oxygen pressure (the first derivative is always positive) with an inflection point (the second derivative vanishes).

(It can be shown that k_2 must be larger than k_1 for the second derivative to vanish.)

Note: To be precise, it must be noted that after exacting investigations of the obtained curve (and other experimental data), an experimenter managed to prove that the hemoglobin molecule absorbed four oxygen molecules. The appropriate saturation formula is, therefore,

$$S = \frac{k_1pO_2 + 2k_1k_2(pO_2)^2 + 3k_1k_2k_3(pO_2)^3 + 4k_1k_2k_3k_4(pO_2)^4}{4\Big(1 + k_1pO_2 + k_1k_2(pO_2)^2 + k_1k_2k_3(pO_2)^3 + k_1k_2k_3k_4(pO_2)^4\Big)}.$$

****

GEOMETRY OF A VIRUS

Contributor: Harold Slater

****

Mathematics: analytic geometry (Math.0), elementary calculus (Math.1)

Abstract: The geometry of a trout virus is considered, and bounds are obtained for its length from geometrical considerations.

Consider the geometric structure of a trout virus consisting of a helix wound around a "hot dog." To describe the geometry of this virus we first find the equation of a surface that resembles a "hot dog":

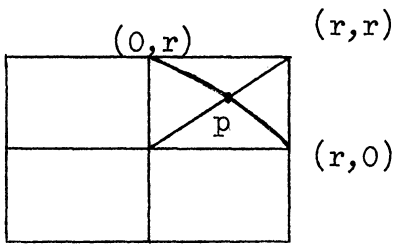
$$x^{2n} + y^{2n} = r^{2n} \quad . \tag{1}$$

For n = 1, this is the familiar equation of a circle with center at the origin and radius r. For n, an arbitrary integer, the curve will pass through the points (0,r), (0,-r), (r,0) and (-r,0). As n increases the point P where the curve intersects the line y = x in the first quadrant will approach the point (r,r), and the resulting curve will look like a "flattened circle." To see this we set y = x in (1). Then

$$2x^{2n} = r^{2n} \tag{2}$$

or

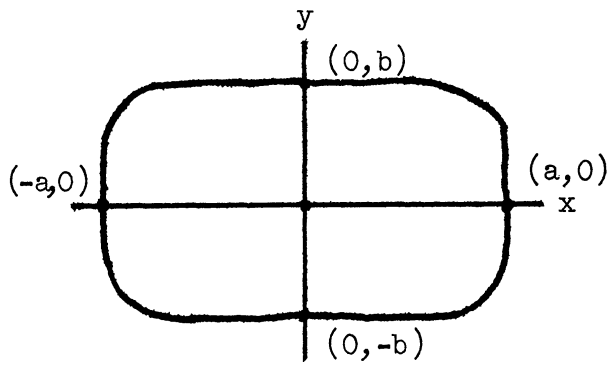
$$x = \frac{r}{2^{1/2n}} \quad . \tag{3}$$

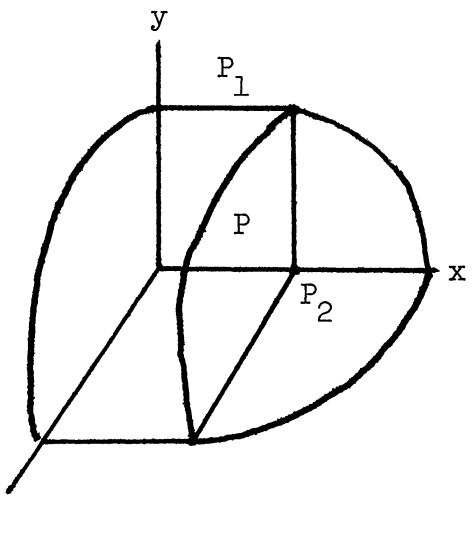


Since $\lim_{n\to\infty} 2^{1/2n} = 1$, $P \to (r,r)$ as n increases. Similarly

$$\frac{x^{2n}}{a^{2n}} + \frac{y^{2n}}{b^{2n}} = 1 \ , \tag{4}$$

which for a > b is an ellipse if n = 1 and a flattened ellipse if n > 1.





To obtain the "hot dog" we rotate the flattened ellipse about the x-axis.

Let $P_1(x_1,y_1,0)$ be any point on the original curve. As the curve is rotated about the x-axis, the point P_1 describes a circle with center at $P_2(x_1,0,0)$ and radius y_1, lying in a plane perpendicular to the x-axis. Let $P(x,y,z)$ be any point on this circle. Since P lies in a plane through P_1 parallel to the y,z plane, $x = x_1$. P also lies on a circle with center at P_2 and radius y_1. Thus,

$$\sqrt{y^2 + z^2} = y_1 \,. \tag{5}$$

Since $P_1(x_1,y_1,0)$ lies on the original curve,

$$\frac{x_1^{2n}}{a^{2n}} + \frac{y_1^{2n}}{b^{2n}} = 1 \,, \tag{6}$$

and, on substituting the values for x_1 and y_1 into this equation, we obtain

$$\frac{x^{2n}}{a^{2n}} + \frac{\left(\sqrt{y^2 + z^2}\right)^{2n}}{b^{2n}} = 1 \tag{7}$$

or

$$\frac{x^{2n}}{a^{2n}} + \frac{(y^2 + z^2)^n}{b^{2n}} = 1 \,. \tag{8}$$

To find the equations of a helix wrapped around the "hot dog" we first consider the equation of a cylinder circumscribed about the "hot dog":

$$y^2 + z^2 = b^2 \,, \qquad -a \leq x \leq a \,. \tag{9}$$

A helix wrapped around this cylinder is given the set of equations:

$$\begin{aligned} z &= b \cos t \\ y &= b \sin t \\ x &= \mu t \end{aligned} \tag{10}$$

where μ is the pitch of the helix and b is the radius of the cylinder.

We have seen before that the radius of a cross-section of the "hot dog" varies and is given by $\sqrt{y^2 + z^2}$. (Eq.5) From equation 7

$$\sqrt{y^2 + z^2} = b\left(1 - \frac{x^{2n}}{a^{2n}}\right)^{1/2n} = \frac{b}{a}\left(a^{2n} - x^{2n}\right)^{1/2n} . \tag{11}$$

If we let $x = \mu t$, the radius of the "hot dog" will be a function of t. Let $r(t) = \sqrt{y^2 + z^2}$. Then

$$r(t) = \frac{b}{a}\left(a^{2n} - (\mu t)^{2n}\right)^{1/2n} . \tag{12}$$

The equations for the helix wrapped around the "hot dog" are

$$\begin{aligned} z &= r(t) \cos t \\ y &= r(t) \sin t \\ x &= \mu t \end{aligned} \tag{13}$$

We can investigate the length of the helix. If a space curve is given in parametric form, the formula for the length of arc is

$$L = \int_I \sqrt{\left(\frac{dx}{dt}\right)^2 + \left(\frac{dy}{dt}\right)^2 + \left(\frac{dz}{dt}\right)^2}\, dt$$

over some interval I. For the helix given above,

$$\frac{dz}{dt} = -r(t) \sin t + r'(t) \cos t$$

$$\frac{dy}{dt} = r(t) \cos t + r'(t) \sin t$$

$$\frac{dx}{dt} = \mu .$$

If we square dz/dt and dy/dt and add them, we find after simplifying that

$$\left(\frac{dy}{dt}\right)^2 + \left(\frac{dz}{dt}\right)^2 = r^2(t) + [r'(t)]^2$$

so that

$$L = 2\int_0^{a/\mu} \sqrt{r^2(t) + [r'(t)]^2 + \mu^2}\, dt .$$

Because

$$r^2(t) = \frac{b^2}{a^2}\left(a^{2n} - (\mu t)^{2n}\right)^{1/n}$$

and

$$[r'(t)]^2 = \frac{b^2\mu^{4n}}{a^2}\, t^{4n-2}\left(a^{2n} - (\mu t)^{2n}\right)^{\frac{1-2n}{n}},$$

$$L = 2\int_0^{a/\mu} \sqrt{\frac{b^2}{a^2}\left(a^{2n} - (\mu t)^{2n}\right)^{1/n}\left[1 + \frac{t^{4n-2}}{\left[a^{2n} - (\mu t)^{2n}\right]^2}\right] + \mu^2}\, dt\ .$$

Direct integration of the above expression is difficult, and no useful estimates are apparent. If numerical values a, b, μ, and n are available, numerical integration can be performed.

****

FATTY ACID IDENTIFICATION

Contributor: Roger Wright

****

Mathematics: elementary matrix operations (Math. 3)

Abstract: An example of the use of elementary matrix operations in order to solve a system of simultaneous linear equations occurring in lipid research.

A single species of triglycerides may be isolated by chromatographic methods. It contains the three fatty acids A, B and C so that there are six possible isomers, denoted ABC, ACB, BAC, BCA, CAB, CBA. Here, for instance, BAC is the isomer with B in the first position, A in the second, and C in the third position. It is desired to measure the proportion of each isomer, denoted x_1, x_2, x_3, x_4, x_5, and x_6 respectively. Pancreatic lipolysis and stereospecific analysis will give the total fatty acid composition in each position. This leads to a table similar to one given below. The numbers have been invented for this discussion.

		Fatty Acid		
		A	B	C
Position	1	.60	.30	.10
	2	.10	.60	.30
	3	.30	.10	.60

The first row, for example, specifies that in the first position, .60 of the species has A, .30 has B, and .10 has C. The content of the table must be expressed in terms of the unknown quantities, but this is not difficult. For instance, the only isomers that have A in the first position are ABC and ACB, so that the total proportion of these two must be .60, i.e.,

$$x_1 + x_2 = .60 .$$

Similarly, each entry of the table may be expressed as an equation in the unknown proportions. This leads to the following system of equations:

$$x_1 + x_2 = .60$$
$$x_3 + x_4 = .30$$
$$x_5 + x_6 = .10$$
$$x_3 + x_5 = .10$$
$$x_1 + x_6 = .60$$
$$x_2 + x_4 = .30$$
$$x_4 + x_6 = .30$$
$$x_2 + x_5 = .10$$
$$x_1 + x_3 = .60$$

The solution is an elementary exercise in linear algebra. The system may be represented by the augmented matrix:

$$\begin{bmatrix} 1 & 1 & 0 & 0 & 0 & 0 & .60 \\ 0 & 0 & 1 & 1 & 0 & 0 & .30 \\ 0 & 0 & 0 & 0 & 1 & 1 & .10 \\ 0 & 0 & 1 & 0 & 1 & 0 & .10 \\ 1 & 0 & 0 & 0 & 0 & 1 & .60 \\ 0 & 1 & 0 & 1 & 0 & 0 & .30 \\ 0 & 0 & 0 & 1 & 0 & 1 & .30 \\ 0 & 1 & 0 & 0 & 1 & 0 & .10 \\ 1 & 0 & 1 & 0 & 0 & 0 & .60 \end{bmatrix}$$

which may be transformed by rearranging the rows of the matrix to the form:

$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 1 & .60 \\ 0 & 1 & 0 & 0 & 1 & 0 & .10 \\ 0 & 0 & 1 & 0 & 1 & 0 & .10 \\ 0 & 0 & 0 & 1 & 0 & 1 & .30 \\ 0 & 0 & 0 & 0 & 1 & 1 & .10 \\ 1 & 1 & 0 & 0 & 0 & 0 & .60 \\ 1 & 0 & 1 & 0 & 0 & 0 & .60 \\ 0 & 1 & 0 & 1 & 0 & 0 & .30 \\ 0 & 0 & 1 & 1 & 0 & 0 & .30 \end{bmatrix}.$$

This may easily be transformed by row operations to the echelon form:

$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 1 & .60 \\ 0 & 1 & 0 & 0 & 0 & -1 & .00 \\ 0 & 0 & 1 & 0 & 0 & -1 & .00 \\ 0 & 0 & 0 & 1 & 0 & 1 & .30 \\ 0 & 0 & 0 & 0 & 1 & 1 & .10 \\ 0 & 0 & 0 & 0 & 0 & 0 & .00 \\ 0 & 0 & 0 & 0 & 0 & 0 & .00 \\ 0 & 0 & 0 & 0 & 0 & 0 & .00 \\ 0 & 0 & 0 & 0 & 0 & 0 & .00 \end{bmatrix}$$

so that

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{bmatrix} = \begin{bmatrix} .60 \\ .00 \\ .00 \\ .30 \\ .10 \\ .00 \end{bmatrix} + \begin{bmatrix} -1 \\ 1 \\ 1 \\ -1 \\ -1 \\ 0 \end{bmatrix} C$$

is a solution for any C.

Certain values of C give solutions which make no sense. For instance if C = -.5, x_3 is -.5 which is an impossible proportion. In fact, the appropriate range for C is from 0 to .10.

Thus, our analysis ties down the unknown proportions to 10%. But the analysis implies more than this. If one proportion is measured, then the others may be determined. More generally, if any additional measurement can be made leading to an equation independent of the others, then the proportions may be determined.

BIOLOGY OF CELLS AND TISSUES

****

RELATIONS BETWEEN NERVE CELLS

Contributor: Richard F. Baum

****

Mathematics: properties of binary relations (Math. 0)

Abstract: The properties of the relation "sends impulses to" or "excites" in a network of nerve cells are considered.

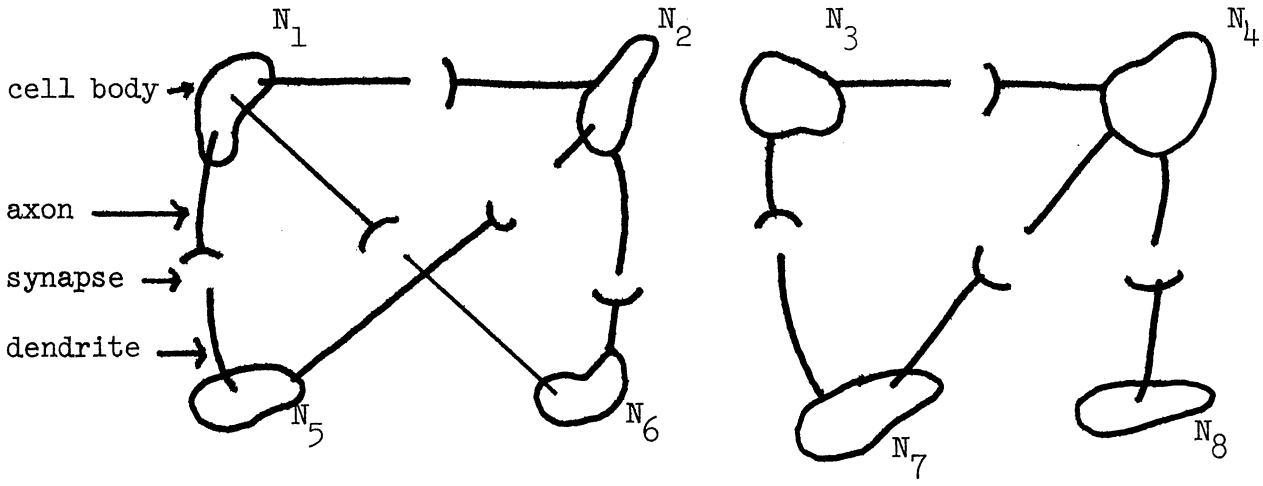
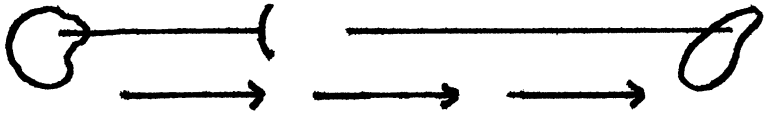


Figure 1

Figure 1 represents a ganglion or nerve net in which eight nerve cells, or neurons, N_1, N_2, ..., N_8, are interconnected as shown. We will assume that impulses travel in the normal direction, i.e., from the axons to the dendrites, or, pictorially:



Let $N = \{N_i | i = 1, 2, \ldots, 8\}$. Let R be a relation in $N \times N$ defined by:

$$R = \{(a,b) | a \text{ sends impulses to or excites } b,\ a, b \in N\} .$$

Note that a can excite b indirectly via a path which includes neuron c. (For example, see Figure 2.)

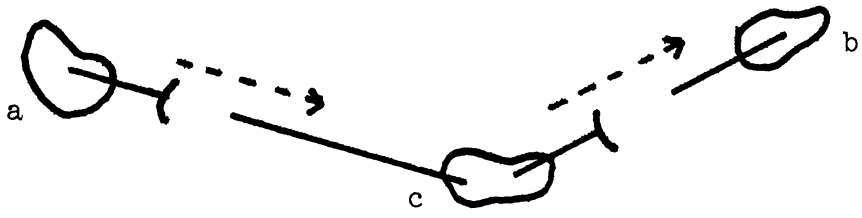


Figure 2

If a neuron re-excites itself, i.e., indirectly excites itself due to its pulse travelling in a closed loop, starting and ending at the neuron in question, then from the definition of R, aRa.

Let us now determine the properties of R in N.

(1) Transitive: By construction of R, if aRc and cRb, then aRb. (See Figure 2.) Therefore, R is transitive.

(2) Reflexive: Since N_8RN_8 is not true, R is not reflexive.

(3) Irreflexive: From Figure 1, since N_5RN_2 and N_2RN_1, we have by transivity N_5RN_1. Also, from Figure 1, N_1RN_5. Thus we have N_1RN_1, and therefore R is not irreflexive.

(4) Symmetric: Since we have N_8RN_4, but we do not have N_4RN_8, R is not symmetric.

(5) Antisymmetric: Since we have N_1RN_5 and N_5RN_1 with $N_1 \neq N_5$, R is not antisymmetric.

(6) Asymmetric: From (5), R is clearly not asymmetric.

(7) Acyclic: Again, N_1RN_5, N_5RN_1, $N_1 = N_1$ implies R is not acyclic.

(8) Complete:
(9) Trichotomous: Since we have neither N_1RN_7 nor N_7RN_1, R is neither complete nor trichotomous.

Let us now restrict R to M, where M is defined by:

$$M = \{N_i \mid i = 1, 2, 3, 4, 5, 6, 7,\} \subset N .$$

We can determine the properties of R on M.

(1) Transitive: Clearly R is still transitive by construction.

(2) Reflexive: Referring to Figure 1 and using transitivity, we see that R is reflexive in M. For example, since N_2RN_1 and N_1RN_5, we have N_2RN_5. Because N_5RN_2, we get N_2RN_2.

(3) Irreflexive: Clearly from (2), R is not irreflexive.

(4) Symmetric: Again from Figure 1 R is symmetric. For example, N_6RN_2 and N_2RN_1 and N_1RN_6 implies N_2RN_6.

(5) Antisymmetric: } Clearly, from (4), R is not anti-

(6) Asymmetric: } symmetric or asymmetric.

(7) Acyclic: Again, N_1RN_5 and N_5RN_1 imply R is not acyclic.

(8) Complete: } As before, we have neither N_1RN_7 nor N_7RN_1, while

(9) Trichotomous: } $N_1 \neq N_7$. Thus R is neither complete nor trichotomous.

The relation R, restricted to M, is thus seen to be reflexive, symmetric, and transitive on M, so that M can be partitioned into equivalence classes for this relation. One equivalence class is $R(N_1)$. Since N_1RN_5, N_1RN_6, N_1RN_2 (from N_6RN_2), and N_1RN_1, the equivalence class to which N_1 belongs is the set:

$$M_1 = \{N_1, N_2, N_5, N_6\} = R(N_1) ,$$

where $N_i \in M_1$ if and only if N_1RN_i. The second equivalence class is M_2, where

$$M_2 = R(N_3) = \{N_3, N_4, N_7\}; \quad N_i \in M_2 \text{ if and only if } N_3RN_i .$$

Clearly, $M_1 \cup M_2 = M$, $M_1 \cap M_2 = \phi$. Thus R partitions the set M into equivalence classes M_1, M_2.

EXERCISES:

1. Show that R, restricted to D,

$$D = \{N_1, N_2, N_5, N_6\}$$

is complete but not trichotomous.

2. Draw a ganglion or nerve net for which R, in addition to being transitive, is

   (a) Reflexive
   (b) Symmetric
   (c) Not Acyclic
   (d) Trichotomous

3. Now repeat 2, where R, in addition to being transitive is

(a) Symmetric

(b) Not Reflexive

4. Now repeat 2, but with R

(a) Asymmetric

(b) Trichotomous

****

THE RATE OF DISSOLUTION

Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: A simple differential equation for the rate of dissolution of a substance in water is solved.

A substance dissolves in water at a rate which may under some circumstances be proportional to the product of the amount of substance undissolved times the difference between the concentration of a saturated solution and the concentration of the present solution.

Suppose that a saturated solution of a certain substance was obtained by dissolving 50 grams of a substance in 100 grams of water.

If 30 grams of the same substance are put into 100 grams of water, and ten grams dissolve after two hours, how much will be dissolved after another three hours?

SOLUTION:

Let x represent the amount of substance undissolved after t hours. At this time the concentration of the solution will be $(30 - x)/100$.

As stated, the concentration of a saturated solution is $50/100$. If dx/dt is the speed at which the substance x dissolves, then

$$\frac{dx}{dt} = kx\left(\frac{50}{100} - \frac{30 - x}{100}\right) = kx\left(\frac{x + 20}{100}\right)$$

where k is a constant. By separation of variables we obtain

$$kdt = \frac{100dx}{x(x + 20)} = 5\left(\frac{dx}{x} - \frac{dx}{x + 20}\right)$$

or

$$\frac{dx}{x} - \frac{dx}{x + 20} = \frac{k}{5}\,dt\ .$$

Therefore,

$$\int_0^t \frac{k}{5}\,dt = \int_{30}^{x}\left(\frac{dy}{y} - \frac{dy}{y + 20}\right)$$

and hence

$$\ln x_t - \ln(x_t + 20) - \ln 30 + \ln 50 = \frac{k}{5}\,t$$

or

$$\ln\left[\frac{5}{3}\cdot\frac{x_t}{x_t + 20}\right] = \frac{k}{5}\,t\ .$$

Since 10 grams dissolve after 2 hours, $x_2 = 20$ and

$$\ln\left[\frac{5}{3} \cdot \frac{20}{40}\right] = \frac{k}{5} \cdot 2 .$$

Thus

$$k = \frac{5}{2} \ln \frac{5}{6} .$$

We can now find x_5. Substituting for k, we obtain

$$\ln\left[\frac{5}{3} \cdot \frac{x_5}{x_5 + 20}\right] = \frac{5}{2} \ln \frac{5}{6} .$$

Using a table we find that $x_5 \approx 12$. From this value it is apparent that after five hours approximately 18 grams of the 30 present at the beginning was dissolved.

****

SIMPLE CHEMICAL REACTIONS

Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: First and second order chemical reactions are considered with illustrative examples.

I. Let us suppose that a substance A is converted into another substance B. We first assume that this takes place in a first order reaction; that is, the (instantaneous) rate of change of A at time t is proportional to the amount of A at t. If we let x(t) denote this amount ($0 \leq t$), this can be expressed mathematically by the equation

$$x'(t) = -kx(t),$$

where k is a positive constant (the minus sign occurs because x is a decreasing function and, consequently, x'(t) must be negative.) This reaction is often schematically described by the diagram

$$A \xrightarrow{k} B,$$

and k is called the rate constant of the reaction (given for moles when the concentration is given in moles.)

We assume that at time t = 0 there is no substance B. We want to (1) find an expression for x as a function of t and (2) using this expression, determine the time t when x(t) = a/2, where a = x(0) is the amount of substance A at t = 0.

Since $\frac{x'(t)}{x(t)} = -k$, we must have

$$\ln \frac{x(t)}{a} = \ln x(t) - \ln x(0) = \int_0^t \frac{x'(s)}{x(s)}\, ds = -\int_0^t k\, ds = -kt .$$

Thus,

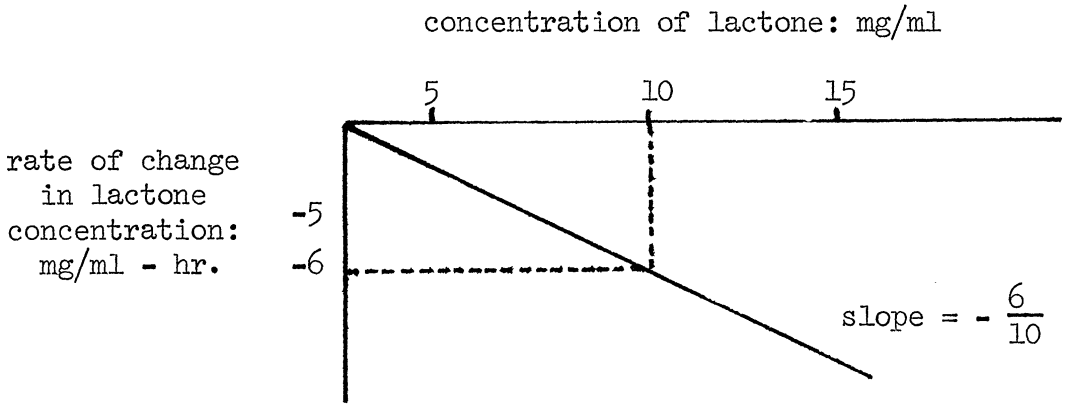
$$x(t) = ae^{-kt}.$$

Many other processes are described by the above equation. One such phenomenon is radioactive decay. In this case, the time obtained in the answer to (2) is called the half-life of the original substance. We have $a/2 = x(t) = ae^{-kt}$ when $\ln \frac{1}{2} = -kt$. Thus, x(t) = a/2 when $t = -\frac{\ln (1/2)}{k} = \frac{\ln 2}{k}$.

An example of such a reaction occurs when A is δ-glucono lactone and B is gluconic acid:

$$\delta\text{-gluconolactone} \xrightarrow[\text{pH = 6.8}]{\text{non-enzymatic hydrolysis}} \text{gluconic acid}$$

The following data have been obtained:



We see that $k = -\frac{x'(t)}{x(t)} = \frac{6}{10}$. Supposing that one has a solution containing 100 mg/ml of δ-glucono lactone at t = 0 (x(0) = 100). then after ln 2/0.6 = 1.155 (approximately) hours, we should be left with 50 mg/ml of this substance.

II. Now, suppose A is converted into substance B in a second order reaction; that is, the rate of change of A at time t is proportional to the square of the amount of A at t. This happens for instance when it is necessary for two molecules of A to collide in order to create B. We express this mathematically by the equation

$$x'(t) = -k[x(t)]^2 .$$

Thus $x'(t)/[x(t)]^2 = -k$, and

$$\frac{1}{a} - \frac{1}{x(t)} = -\frac{1}{x(t)} - \frac{-1}{x(0)} = \int_0^t \frac{x'(s)}{[x(s)]^2}\,ds = -\int_0^t k\,ds = -kt ,$$

from which we obtain $x(t) = \frac{a}{1 + akt}$.

III. Most first order reactions are reversible; that is, A converted into B with rate constant k and, at the same time, B is converted into A with rate constant k'

$$A \underset{k'}{\overset{k}{\rightleftarrows}} B$$

Using the notation introduced in part I and assuming that at time $t = 0$ there is no substance B, the amount of B at time t is given by

$$y(t) = a - x(t) = x(0) - x(t).$$

Since $y(t) + x(t) = a$ we must have

$$y'(t) + x'(t) = 0$$

or, equivalently,

$$y'(t) = -x'(t).$$

The rate of change from A into B is given by the equation

$$x'(t) = -y'(t) = -kx(t) + k'y(t).$$

(The first term takes into account the change from A into B due to the first order reaction $A \xrightarrow{k} B$, while the second term corresponds to the reaction $B \xrightarrow{k'} A$.) Thus,

$$y'(t) = k[a - y(t)] - k'y(t). \tag{1}$$

If we put $\alpha = ka$ and $\beta = k + k'$ we have

$$\frac{y'(t)}{\alpha - \beta y(t)} = 1.$$

Consequently

$$\int_0^t \frac{y'(s)}{\alpha - \beta y(s)}\, ds = \int_0^t ds = t.$$

But the left hand side equals

$$\frac{1}{\beta} \ln \frac{1}{\alpha - \beta y(t)} - \frac{1}{\beta} \ln \frac{1}{\alpha - \beta y(0)} = \frac{1}{\beta} \ln \frac{\alpha}{\alpha - \beta y(t)}.$$

From this we obtain

$$\frac{\alpha - \beta y(t)}{\alpha} = e^{-\beta t}$$

or, equivalently,

$$y(t) = \frac{(1 - e^{-\beta t})}{\beta} = \frac{(ka(1 - e^{-(k+k')t})}{k + k'} \tag{2}$$

This gives an expression for y as a function of t (since $x(t) = a - y(t)$ we can then easily express x as a function of t).

We observe that this reaction can never reach a stationary state (a state in which there are no changes in the amounts of A or B.) For, during this state we must have $0 = y'(t)$; equation (1) shows that then $y(t) = ka/(k + k')$. Equation (2) then implies $e^{-(k + k')} = 0$, which is impossible. We do approach such a state asympotically, however, as $t \longrightarrow \infty$. Since

$$y'(t) = a\, k\, e^{-(k+k')} \geq 0$$

and

$$y''(t) = -(k + k')\, k\, a\, e^{-(k+k')t} \leq 0,$$

we see that the asymptotic value $\frac{ka}{k + k'}$ (approached by $y(t)$ as $t \longrightarrow \infty$) is the least upper bound for the amount of substance B that will be produced in this reaction. If k and k' are large (which is most often the case) this upper bound is approached swiftly. From (2) we see that half this "maximal" amount is reached at time $t = \ln 2/(k + k')$; ninety per cent of this amount is reached when $t = \ln 10/(k + k')$.

****

MEASURING THE RATE OF A REACTION

Contributor: Hebrew University Report

****

Mathematics: derivatives (Math. 1)

Abstract: The velocity of a chemical reaction is considered as the limit of the average rate.

Consider a chemical process which produces some product over time; we may partially describe the process by a function

$$Q: \quad t \longrightarrow Q(t)$$

where $Q(t)$ is the cumulative total amount produced by time t.

The <u>average rate</u> (or <u>average velocity</u>) of the reaction in a time interval from t_1 to t_2 is defined to be the amount $Q_2(t) - Q_1(t)$ produced in the interval divided by the duration $t_2 - t_1$ of the interval. This average rate depends not only upon the function Q but also upon the duration of the interval.

If we are interested in the average rate of a reaction in the neighborhood of a particular time, t^*, we must decide where to locate t_1 and t_2, that is, we can either determine values of $Q(t)$ for times t taken close to t^* and on both sides of t^*, or if we can evaluate $Q(t)$ only for certain values of t, we may be able to plot $Q(t)$ against t and draw a smooth curve through the plotted points and again evaluate $Q(t)$ for times t taken close to t^* and on both sides of t^* by measuring the ordinates at these points. Again note that these average rates are not necessarily equal.

If, however, a sequence of values of t is taken so that the distance of these values from t^* becomes smaller, the average rate $\dfrac{Q(t_2) - Q(t_1)}{t_2 - t_1}$, $t_1 < t^* < t_2$ may approach a unique limit which can be called the <u>velocity</u> (or <u>Q rate</u>) of the reaction at t^*. We denote this limit by $Q'(t^*)$. This quantity is called the derivative of the function Q evaluated at time t^*. The correspondence Q': $t^* \longrightarrow Q'(t^*)$ is again a function and is called the derivative of Q.

<u>EXERCISES</u>: (Data as given below)

1. Find the average rate of the reaction around the 25th minute using different values for t_1 and t_2 where $t_1 < 25 < t_2$.
2. Graph the function and draw a smooth curve through the given points.
3. Estimate the velocity of the reaction at $t^* = 25$.

DATA:

t - in minutes	10	15	20	25	30	35	40
c - the amount of the product in moles	26.5	36.5	44.8	52.1	57.1	61.3	64.4

****

AN AUTO-CATALYTIC REACTION

Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: The solution of a differential equation by separation of variables gives the amount of product as a function of time in an auto-catalytic reaction.

In an auto-catalytic reaction one substance is converted into a new substance called the product in such a way that the product catalyzes its own formation. We consider a simple example in which the rate of formation of the product dx/dt is given by the equation:

$$\frac{dx}{dt} = kx(a - x)$$

where

x = the amount of the product at time t
k = constant, $k \geq 0$
a = total initial amount of product.

Note that the rate of formation is proportional to the amount, a - x, of unreacted substance and the amount, x, of the product.

Solution:

$$\frac{dx}{x(a - x)} = k\ dt.$$

In order to integrate the left-hand side of this equation, we break it into partial fractions:

$$\frac{1}{x(a - x)} \equiv \frac{P}{x} + \frac{R}{a - x}$$

where P and R are constants to be determined so that this identity is valid. Thus, we have

$$1 \equiv P(a - x) + Rx$$

$$1 \equiv Pa - (P - R)x.$$

The solution of the identity is P = R = 1/a, and the differential equation is given by:

$$\frac{dx}{ax} + \frac{dx}{a(a - x)} = k\ dt.$$

Its solution is

$$\ln x - \ln(a - x) = akt + c.$$

If the initial amount of product is x_o ($x_o > 0$), then

$$\ln \frac{x_o}{a - x_o} = c$$

and thus

$$\ln \frac{x(a - x_o)}{x_o(a - x)} = akt.$$

****

SUCCESSIVE REACTIONS

Contributor: Hebrew University Report

****

Mathematics: differentiation and integration (Math. 1)

Abstract: The differential equations describing the change in the amounts of reactants in successive reactions are considered in the simple two reaction non-enzymatic case.

In living systems one rarely encounters a single chemical reaction, but rather observes a series of interdependent chemical reactions.

We shall deal with the simplest type of successive reaction in which substance A reacts to form B which, in turn, reacts to form C.

We shall assume that the successive reactions are first order reactions, and for simplicity can assume that at time 0 the concentration of A is a and the concentration of B and C is 0. At time t let the concentrations of A, B and C be denoted by $C_A(t)$, $C_B(t)$, and $C_C(t)$. Assuming a closed system,

$$a = C_A(t) + C_B(t) + C_C(t)$$

for all t.

Because these reactions are of the first order,

(1) $$C'_A(t) = -k_1 C_A(t) .$$

Integrating, we obtain:

(2) $$C_A(t) = ae^{-k_1 t} .$$

The rate of formation of C is given by

$$C'_C(t) = k_2 C_B(t) .$$

Since B is increased by dissolution of A and is decreased as C is formed, we have

(3) $$C'_B(t) = C'_A(t) - C'_C(t)$$

(Note that this result can also be obtained by differentiating the relation $a = C_A(t) + C_B(t) + C_C(t)$).

If now we use the previous equations to substitute new expressions for $C'_A(t)$ and $C'_C(t)$, we obtain the equation:

$$C'_B(t) + k_2 C_B(t) = k_1 C_A(t) = k_1 ae^{-k_1 t}$$

Multiplying by an integrating factor, we get:

$$(4) \qquad C'_B(t)e^{k_2 t} + k_2 e^{k_2 t} C_B(t) = (C_B(t)\cdot e^{k_2 t})' = k_1 a e^{(k_2-k_1)t}$$

and after integration:

$$(5) \qquad C_B(t)e^{k_2 t} = a\,\frac{k_1}{k_2 - k_1}\, e^{(k_2-k_1)t} + b,$$

where b is a constant. When $t = 0$, $C_B(t) = 0$; therefore

$$b = -a\,\frac{k_1}{k_2 - k_1}$$

and the equation for the concentration of the intermediary substance $C_B(t)$ is:

$$(6) \qquad C_B(t) = a\,\frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right).$$

If we are interested in finding the maximum concentration of B, we must find a time t^* such that $C_B(t^*) = 0$. By differentiation of C_B we get

$$(7) \qquad C'_B(t) = a\,\frac{k_1}{k_2 - k_1}\left(-k_1 e^{-k_1 t} + k_2 e^{-k_2 t}\right).$$

This is zero when $k_2 e^{-k_2 t} = k_1 e^{-k_1 t}$, or for

$$t^* = \frac{\ln k_1 - \ln k_2}{k_1 - k_2}\ .$$

The concentration of B at this time is found by substituting t^* into (6):

$$C_B(t^*) = a\,\frac{k_1}{k_2 - k_1}\left(e^{-k_1\left((\ln k_1 - \ln k_2)/(k_1-k_2)\right)} - e^{-k_2\left((\ln k_1 - \ln k_2)/(k_1-k_2)\right)}\right)$$

$$= a\,\frac{k_1}{k_2 - k_1}\left(\left(\frac{k_2}{k_1}\right)^{k_1/(k_1-k_2)} - \left(\frac{k_2}{k_1}\right)^{k_2/(k_1-k_2)}\right)$$

$$= a \frac{k_1}{k_2 - k_1} \left(\frac{k_2}{k_1} \left(\frac{k_2}{k_1} \right)^{k_2/(k_1-k_2)} - \left(\frac{k_2}{k_1} \right)^{k_2/(k_1-k_2)} \right)$$

$$= a \left(\frac{k_2}{k_1} \right)^{k_2/(k_1-k_2)}$$

The above model neglects the effects of enzymes in the control of successive reactions. In a more advanced model we might investigate their influence. In the body there are interreactions between the products of reactions and enzymes at various stages. For instance, the following series of reactions is quite common:

A forms B with the aid of an enzyme catalyst E. B reacts to form C. C can combine with E to form an inactive complex which is no longer capable of catalyzing the reaction A $\longrightarrow$ B. Thus C can inhibit the formation of B, and therefore its own formation, by inactivating the enzyme catalyzing the first in a series of reactions by which it is produced. This negative feedback system is an important biological mechanism which prevents over-accumulation of the final product in a series of reactions.

****

UNIFORM, INSTANTANEOUS MIXING IN A TWO COMPARTMENT SYSTEM

Contributor: Richard F. Baum*

****

Mathematics: linear differential equations (Math. 2)

Abstract: The techniques of differential equations are used to investigate mixing in a simple two compartment model.

*Based upon: Jacquez, John A. "Mathematical and Statistical Techniques." Principles of Nuclear Medicine. Edited by Henry Wagner. Philadelphia: W. B. Saunders, 1968.

Let Figure 1 represent a chamber of constant volume V with constant volume inflow and outflow rates of r. Mixing in such a chamber is often rapid in comparison to other processes under study so that it is often adequate to assume that there is instantaneous and complete mixing of inflowing material in the chamber. This assumption is frequently made for simplified models in physiology, especially for "compartmental" systems*, in which a group of cells or an organ is treated as one "compartment".**

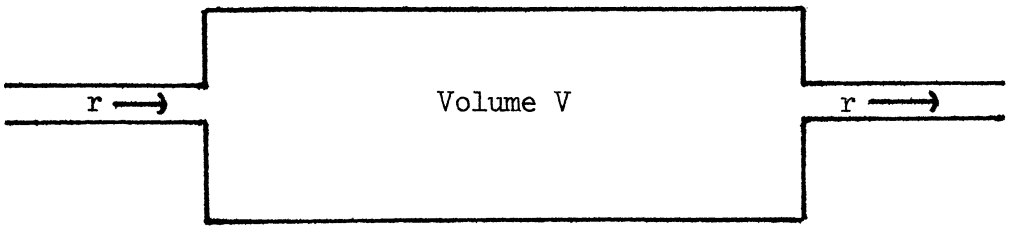


Figure 1

Let $x(t)$ be the concentration of compound M in the chamber. Let $x(0)$ be the concentration of M at $t = 0$ and let $m(t)$ be the concentration of M in the liquid flowing into the chamber.

The rate at which M leaves the chamber at time t is equal to the product of the outflow rate r and the concentration of M in the outflow $x(t)$, i.e., it is $r \cdot x(t)$. Similarly, the rate at which M enters at time t is $r \cdot m(t)$. Thus, $r[m(t) - x(t)]$ must be the rate at which the total amount of M in the chamber changes at time t. This, in turn, is equal to $D[Vx](t)$, since $V \cdot x(t)$ is the total amount of M in the chamber at time t. Since V is assumed constant, we have:

$$V \cdot Dx(t) = r[m(t) - x(t)] \quad . \tag{1}$$

---

* An amount of a material which acts like a homogeneous, kinetically distinct component is called a "compartment".

** See, for example: "Balance Studies of Compartmental Systems with Stochastic Inputs," by Jacquez, John A., and Mather, Frances, J., in Journal of Theoretical Biology, Volume 11, 1966, p. 446-458.

Table 1 lists the solutions for (1) under various assumptions for $x(0)$ and $m(t)$, with the general case appearing in the last line. The results in this table are obtained by simple integration. Note that for $m(t) = 0$, equation (1) takes the form of an equation for radioactive decay. For $m(t)$ equal to a constant and $x(0) = 0$, the concentration approaches asymptotically the level $x(t) = C$.

Table 1

$x(0)$	$m(t)$	Solution ($t \geq 0$)
x_o	0	$x(t) = x_o e^{-(r/V)t}$
0	C	$x(t) = C\left[1 - e^{-(r/V)t}\right]$
x_o	C	$x(t) = x_o e^{-(r/V)t} + C\left[1 - e^{-(r/V)t}\right]$
x_o	$m(t)$	$x(t) = x_o e^{-(r/V)t} + \int_0^t m(s) e^{-(r/V)(t-s)} ds$

For another example yielding an equation of the form (1) consider the reversible chemical reaction taking place in a closed system.

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$$

Let $X_1(t)$ denote the concentration of A at time t, and $X_2(t)$ denote the concentration of B at time t, $t \geq 0$. From the law of mass action, we obtain:

$$DX_1(t) = -K_1 x_1(t) + K_2 x_2(t), \quad t \geq 0 \tag{2}$$

where $K_1 x_1(t)$ is the rate at which A is being converted to B at time t and $K_2 x_2(t)$ is the rate at which B is being converted to A at time t. Since the total amount of A and B in the system is fixed at some constant value S,

$$x_1(t) + x_2(t) = S, \quad t \geq 0 . \tag{3}$$

Using equation (3), equation (2) may be written

$$(4) \qquad Dx_1(t) = K_2S - (K_1 + K_2)x_1(t) \ .$$

This is the same as equation (1) if we set

$$(4a) \qquad \frac{r}{V} = K_1 + K_2$$

and

$$(4b) \qquad m(t) = \frac{K_2}{K_1 + K_2} \ S \ .$$

Since the right-hand side of (4b) is a constant, the solution to (4) is obtained from the third line in Table 1, i.e.,

$$(5) \quad x_1(t) = x_1(0)e^{-(K_1+K_2)t} + \left[\frac{K_2S}{K_1 + K_2}\right]\left[1 - e^{-(K_1+K_2)t}\right], \ t \geq 0 \ .$$

Exercise:

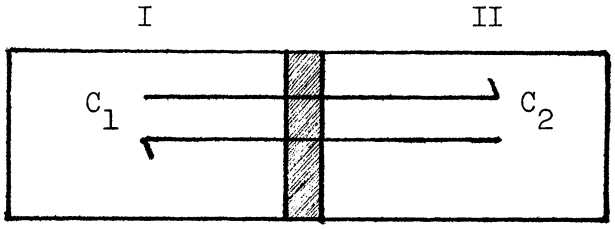


Figure 2

Consider a two-compartment model (see Figure 2.) Assume that a material M crosses the boundary or membrane in common with compartments I and II very slowly compared to the rates of diffusion and of mixing within the compartments. This is equivalent to assuming that the concentration of material M inside each of the compartments is uniform at all times.

Let $C_1(t)$ denote the concentration of M in compartment I at time t and $C_2(t)$ denote the concentration of M in compartment II at time t.

Let $V_1(t)$ denote the volume of compartment I at time t and A(t) denote the area of the surface of the membrane between compartments I and II at time t.

If $A(t)$ and $V_1(t)$ are constant for all $t \geq 0$, i.e.,

$$A(t) = A$$
$$V_1(t) = V_1$$

(which is possible to do experimentally), then it can be shown from Fick's law of diffusion that

$$DC_1(t) = \frac{kA}{V_1}[C_1(t) - C_2(t)] , \tag{6}$$

where k is the permeability constant and is usually given in the units of cm/sec or cm/min.

Show that with minor changes, equation (6) is the same as equation (1). If the concentration $C_2(t)$ is held constant, show that the solution of (6) is given by the second line in Table 1, so that

$$C_1(t) = C_2\left[1 - e^{-(kA/V_1)t}\right] . \tag{7}$$

****

LINEAR COMPARTMENTAL SYSTEMS

Contributor: Richard F. Baum*

****

Mathematics: linear algebra (Math. 3), simultaneous differential equations (Math. 4), Laplace transformations

Abstract: An N-compartment system is described using differential equations.

*Based upon: Jacquez, John A. "Mathematical and Statistical Techniques." Principles of Nuclear Medicine. Edited by Henry Wagner. Philadelphia: W. B. Saunders, 1968.

A. Two Compartment System with Excretion

Figure 1 represents a two compartment system. Such systems are used to study physiological processes, where an amount of material which acts like a homogeneous component is called a compartment.

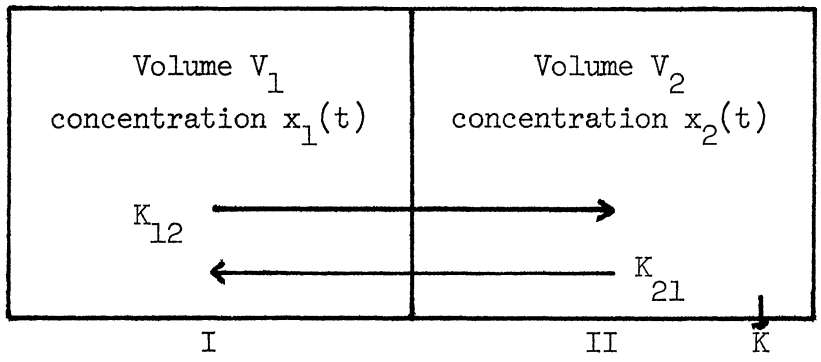


Figure 1

The following assumptions are made:

(a) Compartments I and II have fixed volumes V_1 and V_2, respectively, consisting of a mixture of a solvent and a solute M.

(b) The compartments are well-mixed with uniform concentrations of M at time t. Concentrations x_1 and x_2 are measured relative to volumes, i.e., the concentration is measured as the ratio of the volume of M to the total volume in that compartment.

(c) Diffusional exchange takes place between compartments I and II across a membrane of area A.

(d) Excretion of M occurs from compartment II, the rate at time t being proportional to $x_2(t)$.

Let $q_1(t)$, $q_2(t)$ be the total mass of compound M in compartments I and II, respectively, at time t. Then:

$$(1) \qquad \begin{cases} q_1(t) = V_1 x_1(t) \\ q_2(t) = V_2 x_2(t) \ . \end{cases}$$

Let K_{12}, K_{21} be the rate constants for flow of compound M from compartment I to II, and II to I, respectively. Then from the law of mass action, we obtain:

$$(2)\qquad \begin{aligned} q_1'(t) &= -K_{12}Ax_1(t) + K_{21}Ax_2(t) \\ q_2'(t) &= K_{12}Ax_1(t) - K_{21}Ax_2(t) - Kx_2(t) \,. \end{aligned}$$

Let

$$(3)\qquad \frac{K_{12}A}{V_1} = \lambda_{12}\,, \qquad \frac{K_{21}A}{V_2} = \lambda_{21}\,, \qquad \frac{K}{V_2} = \lambda_{20}\,.$$

Note that

$$\lambda_{12}\,,\ \lambda_{21}\,,\ \lambda_{20} > 0\,.$$

Equation (2) becomes with equation (1):

$$(4)\qquad \begin{aligned} q_1'(t) &= -\lambda_{12}q_1(t) + \lambda_{21}q_2(t) \\ q_2'(t) &= \lambda_{12}q_1(t) - \lambda_{21}q_2(t) - \lambda_{20}q_2(t) \end{aligned} \qquad t \geq 0\,.$$

It can be shown that (see Appendix), upon combining terms, the solution to (4) is given by:

$$(5)\qquad \begin{aligned} q_1(t) &= B_1e^{-(\alpha+\beta)t} + B_2e^{-(\alpha-\beta)t} \\ q_2(t) &= \left[\frac{m_1 + \lambda_{12}}{\lambda_{21}}\right]B_1e^{-(\alpha+\beta)t} + \left[\frac{m_2 + \lambda_{12}}{\lambda_{21}}\right]B_2e^{-(\alpha-\beta)t} \end{aligned}$$

where B_1 and B_2 are two arbitrary constants which can be determined by the initial conditions $q_1(0)$, $q_2(0)$, and where

$$\alpha = \frac{\lambda_{12} + \lambda_{21} + \lambda_{20}}{2}\,, \qquad m_1 = -(\alpha + \beta)\,,$$

$$\beta = \frac{\sqrt{(\lambda_{12} + \lambda_{21} + \lambda_{20})^2 - 4\lambda_{12}\lambda_{20}}}{2}\,, \qquad m_2 = -(\alpha - \beta)\,.$$

B. General Linear Compartment System

In the general case of an N compartment system, we assume that each compartment may interchange with any other and that there may be an intake into and an excretion from each compartment. See Figure 2.

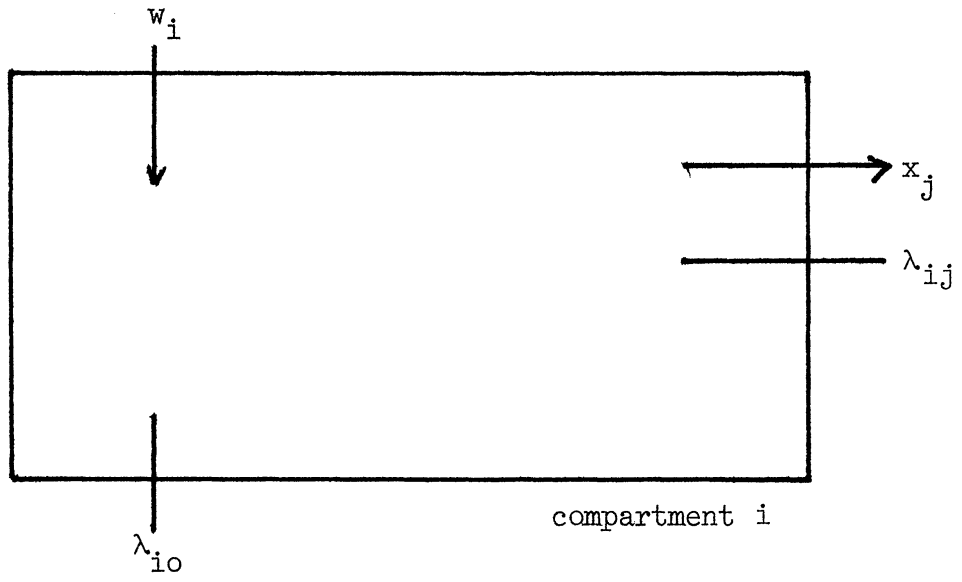


Figure 2

Let

w_i be the rate of input from the environment at time t.

$q_i(t)$ be the total volume of compound M in compartment i .

λ_{io} be a constant such that $[\lambda_{io} q_i(t)]$ is the rate of excretion at time t (as for equation (3)).

λ_{ij} be a constant such that $[\lambda_{ij} q_i(t)]$ is the rate of transfer of compound M from compartment i to compartment j.

Then, as before, by the law of mass action:

$$(6) \qquad q_i'(t) = w_i + \sum_{\substack{j=1 \\ j\neq i}}^{N} \lambda_{ji}\, q_j(t) - \left[\sum_{\substack{j=0 \\ j\neq i}}^{N} \lambda_{ij}\right] q_i(t) , \quad t \geq 0 .$$

Let λ_{ii} be defined by:

$$\lambda_{ii} = -\sum_{j \neq i} \lambda_{ij} \ .$$

Then (6) becomes:

$$(7) \qquad q_i'(t) = \sum_{j=1}^{N} \lambda_{ij}\, q_j(t) + w_i \ , \ t \geq 0, \quad i = 1,2,\ldots,N \ .$$

The above system is again a set of first order linear differential equations, and this system may be solved in the same way as before, except now our differential equation is:

$$\bar{q}'(t) = A\bar{q}(t) + \bar{w}(t)$$

where

$$\bar{q}(t) = \begin{bmatrix} q_1(t) \\ \vdots \\ q_N(t) \end{bmatrix} \ , \quad A = \begin{bmatrix} \lambda_{11} & \cdots & \lambda_{1N} \\ \vdots & & \vdots \\ \lambda_{N1} & \cdots & \lambda_{NN} \end{bmatrix} \ , \quad \bar{w}(t) = \begin{bmatrix} w_1(t) \\ \vdots \\ w_N(t) \end{bmatrix} \ .$$

To solve (7), we use the same technique as before. Taking the Laplace transform of both sides of (7), we get:

$$s\bar{r}(s) - \bar{q}(0) = A\bar{r}(s) + \bar{M}(s) \ ;$$

$$\bar{M}(s) = \mathcal{L}[\bar{w}(t)] \ ;$$

$$\bar{r}(s) = \mathcal{L}[\bar{q}(t)] \ .$$

Therefore,

$$(sI - A)\bar{r}(s) = \bar{q}(0) + \bar{M}(s) \ .$$

If we let

$$P(s) = (sI - A) \ ,$$

we get

$$(8) \qquad \bar{r}(s) = P^{-1}(s)\bar{q}(0) + Q^{-1}(s)\bar{M}(s) \ .$$

Note that $P^{-1}(s)$ exists if s is not equal to one of the eigenvalues of A. From (8), we obtain:

$$(9) \qquad \bar{q}(t) = \mathcal{L}^{-1}[P^{-1}(1)]\bar{q}(0) + \mathcal{L}^{-1}[P^{-1}(s)M(s)] \ .$$

Thus, our problem can still be solved in the same way as before as long

as the λ_{ij}'s are constants. If they are not constants, our problem is considerably more difficult.

EXERCISES:

1. Solve system (4) if $m_1 = m_2$, i.e., if the eigenvalues of A are equal.

2. Show that we obtain the same solution as (5) (for $m_1 \neq m_2$) if we assume that the solutions of (4) are of the form:

$$q_1(t) = Ae^{m_1 t} + Be^{m_2 t}$$
$$q_2(t) = Ce^{m_1 t} + De^{m_2 t} .$$

3. Show that the solution of (7) can be represented as:

$$\bar{q}(t) = e^{At}\bar{q}(0) + e^{At}\int_0^t e^{-As}\bar{M}(s)\,ds \ , \ t \geq 0 .$$

[Hint: Use equation (9).]

APPENDIX:

Let

$$\bar{q}(t) = \begin{bmatrix} q_1(t) \\ \\ q_2(t) \end{bmatrix} , \quad A = \begin{bmatrix} -\lambda_{12} & \lambda_{21} \\ \\ \lambda_{12} & -(\lambda_{21} + \lambda_{20}) \end{bmatrix} .$$

Then

$$\bar{q}'(t) = \begin{bmatrix} q_1'(t) \\ \\ q_2'(t) \end{bmatrix} ,$$

and equation (4) can be written in matrix notation as:

(10) $$\bar{q}'(t) = A\bar{q}(t) , \quad t \geq 0$$

with boundary conditions

$$\bar{q}(0) = \begin{bmatrix} q_1(0) \\ \\ q_2(0) \end{bmatrix} .$$

The solution to (10) can be written:

(11) $$\bar{q}(t) = e^{At}\bar{q}(0) ,$$

where e^{At} is defined by:

(12) $$e^{At} \equiv I + At + A^2 \frac{t^2}{2!} + \ldots + A^N \frac{t^N}{N!} + \ldots = \sum_{k=0}^{\infty} A^k \frac{t^k}{k!} .$$

Unless A has a particularly simple form, such as a diagonal matrix, equation (12) is not a good way to find e^{At}. Instead, we use the method of Laplace transformation. Let $\mathcal{L}[\ ]$ denote the Laplace transform. Then from (10):

$$\mathcal{L}[\bar{q}'(t)] = \mathcal{L}[A\bar{q}(t)] ,$$

or, setting

$$\mathcal{L}[\bar{q}(t)] = \bar{r}(s) ,$$

$$s\bar{r}(s) - A\bar{r}(s) = \bar{q}(0) .$$

Therefore:

(13) $$(sI - A)\bar{r}(s) = \bar{q}(0) .$$

Let

$$P(s) = sI - A .$$

Then

$$\det P(s) = 0$$

if and only if s is an eigenvalue of A, since det (sI - A) is the characteristic equation of A. Let m_1 and m_2 be two eigenvalues of A. P(s) is non-singular for all $s \neq m_1, m_2$. Thus, $P^{-1}(s)$ exists for all $s \neq m_1, m_2$. Therefore, (13) gives:

(14) $$\bar{r}(s) = P^{-1}(s)\bar{q}(0) = (sI - A)^{-1}\bar{q}(0) , \quad s \neq m_1, m_2 .$$

Taking the inverse Laplace transform, $\mathcal{L}^{-1}[\ ]$ of both sides of (14) gives:

(15) $$\bar{q}(t) = \mathcal{L}^{-1}[(sI - A)^{-1}] \cdot \bar{q}(0) , \quad s \neq m_1, m_2 .$$

Since the solution of our system is unique, we can conclude from (11) and (13) that:

(16) $$e^{At} = \mathcal{L}^{-1}[(sI - A)^{-1}] .$$

From the definition of the matrix A given above, we have:

$$sI - A = \begin{bmatrix} s + \lambda_{12} & -\lambda_{21} \\ -\lambda_{12} & s + \lambda_{21} + \lambda_{20} \end{bmatrix} .$$

Thus,

(17) $$\det (sI - A) = s^2 + s(\lambda_{21} + \lambda_{20} + \lambda_{12}) + \lambda_{12}\lambda_{20} .$$

Note that det (sI - A) is also called the characteristic equation of system (4).

Let

$$\alpha = \frac{\lambda_{12} + \lambda_{21} + \lambda_{20}}{2} , \quad \beta = \frac{\sqrt{(\lambda_{12} + \lambda_{21} + \lambda_{20})^2 - 4\lambda_{12}\lambda_{20}}}{2} .$$

Then it is left as an exercise to the reader to show that the solution of

$$\det (sI - A) = 0$$

is

(18) $$s = m_1 = -(\alpha + \beta)$$

$$s = m_2 = -(\alpha - \beta) .$$

Thus

$$\det (sI - A) = (s - m_1)(s - m_2) .$$

Thus

$$(19)\quad (sI - A)^{-1} = \begin{bmatrix} \dfrac{s + \lambda_{12}}{(s - m_1)(s - m_2)} & \dfrac{-\lambda_{21}}{(s - m_1)(s - m_2)} \\ \dfrac{-\lambda_{12}}{(s - m_1)(0 - m_2)} & \dfrac{s + \lambda_{21} + \lambda_{20}}{(s - m_1)(s - m_2)} \end{bmatrix}.$$

Assume $m_1 \neq m_2$. By suitable tables, we find from (19):

$$(20)\quad \mathcal{L}^{-1}[(sI - A)^{-1}] =$$

$$\begin{bmatrix} \dfrac{(\lambda_{12}+m_1)e^{m_1 t} - (\lambda_{12}+m_2)e^{m_2 t}}{m_1 - m_2} & \dfrac{-\lambda_{21}(e^{m_1 t} - e^{m_2 t})}{m_1 - m_2} \\ \dfrac{-\lambda_{12}(e^{m_1 t} - e^{m_2 t})}{m_1 - m_2} & \dfrac{(\lambda_{21}+\lambda_{20}+m_1)e^{m_1 t} - (\lambda_{21}+\lambda_{20}+m_2)e^{m_2 t}}{m_1 - m_2} \end{bmatrix}.$$

By substituting (20) into (15) or, recalling that (20) is also e^{At}, substituting into (11), we obtain $\bar{q}(t)$.

****

AN ELEMENTARY DIFFUSION EXAMPLE

Contributor: Hebrew University Report

****

Mathematics: linear differential equations (Math. 2)

Abstract: A system of two linear differential equations is derived from simple assumptions about diffusion.

Every cell is surrounded by a membrane, a type of envelope. Blood vessels only reach the outer surfaces of this membrane. In order for a substance to pass from the blood to the cell it must twice undergo diffusion: first when it passes from the blood into the membrane, and second when it passes from the membrane into the cell. Inside the blood, in the fluids of the membrane, or in the fluids of the cell, the substances spread out very quickly; the concentration of the substance can thus be assumed to be equal at any point in the blood, and the same is true for the other fluids. Concentration differences exist, therefore, only at the two boundaries.

Let C_o be the concentration of the substance in the blood. It is assumed that it does not change because there exist mechanisms in the body to keep a constant concentration. Let C_1 be the concentration in the membrane and C_2 be the concentration inside the cell.

By the law of diffusion, the amount of substance entering the membrane from the blood equals a constant a times the difference in concentrations:

$$a(C_o - C_1)$$

The same is true for the amount of substance passing from the membrane into the cell,

$$b(C_1 - C_2).$$

The change in the concentration of the substance in the membrane dC_1/dt is therefore given by

$$\frac{dC_1}{dt} = e(C_o - C_1) - f(C_1 - C_2)$$

where $e = V_1 a$ and $f = V_1 b$, and V_1 is the volume of the fluids in the membrane. The change in concentration in one cell is given by

$$\frac{dC_2}{dt} = g(C_1 - C_2)$$

where $g = V_2 b$, and V_2 is the volume of the intracellular fluid.

The only variables are C_1 and C_2, so that these two concentrations may be calculated as functions of the time.

****

A DIFFUSION EXAMPLE

Contributor: Harold Slater*

****

Mathematics: partial differential equations (Math.4)

Abstract: The concentration of material in a tube is shown to satisfy a partial differential equation in distance and time.

*Based upon: Setlow, R.B., and Pollard, E.C. Molecular Biophysics. Reading, Massachusetts: Addison-Wesley, 1962, 48.

Consider a tube parallel to the x-axis containing fluid. Suppose that along with the fluid the tube also contains other material. If the concentration of the material increases to the right, there will be a net flow of molecules to the left.

The concentration c of the material will be a function of both distance and time, and from Fick's law can be shown to satisfy

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \tag{1}$$

where D is a proportionality constant known as the diffusion constant.

Show that $c = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$

satisfies (1).

SOLUTION:

$$\frac{\partial c}{\partial t} = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}\left(\frac{x^2}{4Dt^2}\right) + e^{-x^2/4Dt}\left[\frac{1}{\sqrt{4\pi D}}\left(-\frac{1}{2}t^{-3/2}\right)\right]$$

$$= \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}\left[\frac{x^2}{4Dt^2} - \frac{1}{2t}\right]$$

$$\frac{\partial c}{\partial x} = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}\left(-\frac{2x}{4Dt}\right)$$

$$\frac{\partial^2 c}{\partial x^2} = \frac{1}{\sqrt{4\pi Dt}}\left[e^{-x^2/4Dt}\left(\frac{4x^2}{16D^2t^2}\right) + e^{-x^2/4Dt}\left(-\frac{2}{4Dt}\right)\right]$$

$$= \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}\left[\frac{x^2}{4D^2t^2} - \frac{1}{2Dt}\right]$$

$$= \frac{1}{D}\left[\frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}\left(\frac{x^2}{4Dt^2} - \frac{1}{2t}\right)\right].$$

Therefore,

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} .$$

****

DIFFUSION OF SOLUTES THROUGH A CELL MEMBRANE

Contributor: James O. Brooks

****

Mathematics: first order differential equations with separable variables (Math.2)

Abstract: Simple differential equations are used to model the process of diffusion across a cellular membrane.

The movement of solutes through a cell membrane is analyzed, and we are led to a separable differential equation.*

We assume Fick's law: the time rate of movement of a solute across a thin membrane is proportional to the area of the membrane and to the difference in concentration of the solute on the two sides of the membrane. The direction of movement, of course, will be such that the concentration on the two sides tends to be equalized. Let

c be the concentration of solute outside the cell (which we assume to be constant throughout the process, i.e., unaffected by the small influx or loss of solute across the membrane),

s the amount of solute inside the cell, which is a function of the time t,

V the volume of the cell, which is assumed to remain constant,

A the area of the cell membrane, and

y the concentration of solute inside the cell.

Then by definition, $y = s/V$. Differentiating both sides of this equation with respect to t, we obtain

$$\frac{dy}{dt} = \frac{1}{V}\frac{ds}{dt} .$$

By our assumption, there is a constant k, called the <u>permeability coefficient</u>, such that

$$\frac{ds}{dt} = kA(c - y) .$$

Combining the last two equations, we have

$$\frac{dy}{dt} = \frac{kA}{V}(c - y) . \tag{1}$$

Equation (1) tells us that the rate of change of <u>concentration</u> at

---

* The development is based on that of Giese, A. C. <u>Cell Physiology</u>, 2nd Edition. Philadelphia: W. B. Saunders, 1962, 241-242.

any time t is proportional to the difference between the outside concentration and the inside concentration at time t.

We now solve equation (1), assuming that at time t = 0, the value of y is some number $y_o \neq c$.

We rewrite equation (1) as

$$(2) \qquad -\frac{1}{c - y}\frac{dy}{dt} = -\frac{kA}{V} .$$

Here we have assumed that $c - y \neq 0$; if $c - y = 0$, there will evidently be no flow at all.

Integrating both sides of (2), we get

$$-\int_{y_o}^{y} \frac{1}{c - \eta}\, d\eta = \int_{o}^{t} -\frac{kA}{V}\, d\lambda ,$$

i.e.,

$$\log|c - y| - \log|c - y_o| = -\left(\frac{kA}{V}\right)t$$

or

$$(3) \qquad \log\frac{|c - y|}{|c - y_o|} = -\frac{kAt}{V} .$$

Since y is a continuous function of t, and y is never equal to c, $c - y$ and $c - y_o$ always have the same sign. So (3) may be written

$$(4) \qquad \log\frac{(c - y)}{(c - y_o)} = -\left(\frac{kA}{V}\right)t .$$

Solving for y, we obtain

$$(5) \qquad y = c - (c - y_o)e^{-kAt/V} .$$

In the case where $c > y_o$, the graph of (5) looks like that represented in Figure 1.

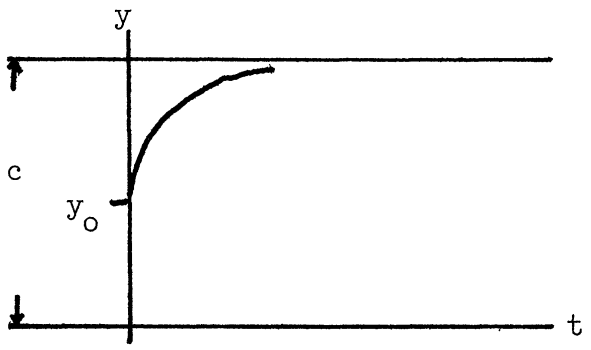


Figure 1

If $c < y_o$, we have the graph represented in Figure 2.

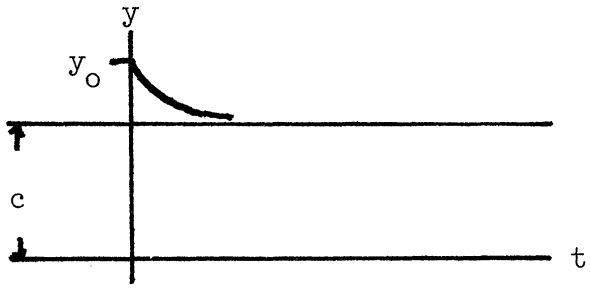


Figure 2

If we know the concentration y_1 at some other time t_1, then we can use equation (4) to determine the permeability coefficient k:

$$k = \frac{V}{At_1} \log\left(\frac{c - y_o}{c - y_1}\right) . \tag{6}$$

This result appears as equation 12.9 in Giese (loc. cit.).

****

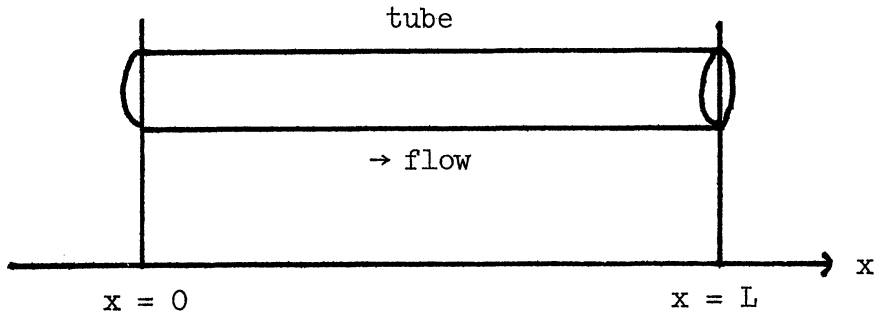
SOME PROBLEMS CONCERNING MEAN VALUES FOR LOCAL DIFFUSION AND CONCENTRATION ALONG A TUBE

Contributor: James O. Brooks

****

Mathematics: elementary calculus (Math. 1), separable differential equations (Math. 2)

Abstract: Four problems concerning the passive diffusion of a solute through a tube wall are considered.



x = position along tube, $0 \leq x \leq L$ (cm)

v = flow of solvent (ml/min)

z = z(x) flow of solute (mgms/min)

y = z/v concentration (mgms/ml)

y_o, z_o initial values at x = 0

y_1, z_1 terminal values at x = L

w = concentration of solute around the tube. We assume $w < y_o$, so the net diffusion is outward

r = tube radius

PROBLEM 1:

Find z as a function of x, z_o, z_1, and w. According to Fick's diffusion equation,

$$(\text{time rate of diffusion}) = (\text{membrane area})\left(\begin{matrix}\text{concentration}\\ \text{difference}\end{matrix}\right)\left(\begin{matrix}\text{permeability}\\ \text{coefficient}\end{matrix}\right).$$

Thus $z(x) - z(x + \Delta x)$ = net flow of solute through tube wall between points x and $x + \Delta x = (2\pi r \Delta x)(y(\bar{x}) - w)k$, for some $x \leq \bar{x} \leq x + \Delta x$, where k is the permeability coefficient.

Dividing both sides by Δx, we obtain

$$\frac{z(x + \Delta x) - z(x)}{\Delta x} = -(2\pi rk)(y(\bar{x}) - w) .$$

Letting $b = (2\pi rk)$, and taking the limit* as $\Delta x \to 0$:

$$\frac{dz}{dx} = - b(y - w) .$$

To solve the differential equation we substitute z/v for y, so that

$$\frac{dz}{dx} = -b\left(\frac{z - vw}{v}\right) = - \left(\frac{b}{v}\right)(z - vw) = - B(z - vw)$$

or

$$\frac{1}{z - vw}\frac{dz}{dx} = - B .$$

Since $y_o > w$, $z = vy > vw$, $z - vw > 0$; thus $\log(z - vw) = - Bx + c$, for some constant c.

(1) $$z - vw = e^{-Bx+c} = Ae^{-Bx} .$$

When $x = 0$, $z = z_o$ and $z_o - vw = A$. When $x = L$, $z = z_1$ and $z_1 - vw = Ae^{-BL}$. Therefore,

(2) $$e^{-BL} = \frac{z_1 - vw}{z_o - vw} .$$

Substituting (2) into (1), we get:

(3) $$\boxed{z = vw + (z_o - vw)\left(\frac{z_1 - vw}{z_o - vw}\right)^{x/L} .}$$

PROBLEM 2:

Find the permeability coefficient k in terms of z_o, z_1, v, w, L, r.

---

* Compare with equation (1) in Walser, M. "Mathematical Aspects of Renal Function: The Dependence of Solute Reabsorption on Water Reabsorption, and the Mechanism of Osmotic Natriuresis," Journal of Theoretical Biology, X (1966), 307-326.

From (2),

$$-BL = \log e^{-BL} = \log\left(\frac{z_1 - vw}{z_o - vw}\right)$$

$$B = -\frac{1}{L}\log\left(\frac{z_1 - vw}{z_o - vw}\right) = \frac{1}{L}\log\left(\frac{z_o - vw}{z_1 - vw}\right)$$

(4) $$\boxed{k = \frac{b}{2\pi r} = \frac{vB}{2\pi r} = \frac{v}{2\pi rL}\log\left(\frac{z_o - vw}{z_1 - vw}\right).}$$

PROBLEM 3:

Find: (a) the global rate of diffusion of solute through the tube wall, (b) the local rate of diffusion at a point x, and (c) the mean value over the total tube of the local rate.

3a: Solute enters the tube at one end at the rate of z_o mgms/min and leaves at the other end at the rate of z_1 mgms/min. The difference $z_o - z_1$ is the rate of diffusion through the tube wall.

3b: By the same reasoning as in the global case, the rate at which solute diffuses out through the tube wall between points x and $x + \Delta x$ is $z(x) - z(x + \Delta x)$. The average rate per unit length of tube, computed between x and $x + \Delta x$, is

$$\frac{z(x) - z(x + \Delta x)}{\Delta x} \quad \text{(mgms/cm-min)} .$$

The "instantaneous" or local rate at a point x is

$$\lim_{\Delta x \to 0} \text{(average rate)} = -\frac{dz}{dx} \quad \text{(mgms/cm-min)} .$$

But from (3),

$$-\frac{dz}{dx} = -(z_o - vw)\left(\frac{z_1 - vw}{z_o - vw}\right)^{x/L} \cdot \frac{1}{L} \cdot \log\left(\frac{z_1 - vw}{z_o - vw}\right)$$

$$= \left(\frac{z_o - vw}{L}\right)\log\left(\frac{z_o - vw}{z_1 - vw}\right)\left(\frac{z_1 - vw}{z_o - vw}\right)^{x/L} .$$

Observe that this is a decreasing, positive valued function of x: positive valued since the coefficient of $\left(\frac{z_1 - vw}{z_o - vw}\right)^{x/L}$ is positive, and decreasing since $0 < \left(\frac{z_1 - vw}{z_o - vw}\right) < 1$. This conforms with the physical situation in which solute diffuses out faster near x = 0 and more slowly near x = 1.

3c: The mean value μ of a function f over an interval [a,b] is

$$\mu = \frac{1}{b - a} \int_a^b f(x)\, dx \ .$$

In the present case, the mean value of the local diffusion rate -dz/dx over [0,L] is

$$\mu = \frac{1}{L} \int_o^L - \frac{dz}{dx} \cdot dx = - \frac{1}{L} \int_o^L dz = - \frac{1}{L} \Big(z(L) - z(0)\Big)$$

$$(5) \qquad = - \frac{1}{L} (z_1 - z_o) = \boxed{\frac{z_o - z_1}{L} \text{ mgms/cm-min .}}$$

Here the solution to Problem 3c depends in a simple fashion on only the initial and terminal flow values. Any other diffusion mechanism (with a different concentration function y = y(x)), which had the same initial and terminal flows z_o and z_1, respectively, would give the same mean value. That fact is appreciated with the help of the following discrete model.

Suppose that a P.T.C. subway-surface car enters a subway tube with z_o passengers and leaves at the end of the tube with z_1 passengers. Suppose there are N intermediate stops, and that at the ith stop, the net number of passengers leaving the car is s_i (i = 1,...,N). The function $i \to s_i$ is, in general, nonconstant: more persons get off at 15th Street than at 33rd Street. The net number of passengers leaving the car at all the intermediate stops is

$$s_1 + s_2 + \ldots + s_N = z_o - z_1 \ ,$$

and the mean "diffusion" per stop is

$$\mu = \frac{s_1 + s_2 + \dots + s_N}{N} = \frac{z_o - z_1}{N} ,$$

which depends on the initial and terminal values z_o and z_1, and on the number of stops N, but which is independent of the particular diffusion mechanism and function $i \to s_i$.

PROBLEM 4:

Find the mean concentration along the tube.

Remark: In contrast to 3c, this will depend on the particular diffusion mechanism of our problem, as well as on z_o, z_1, L, etc.

As in 3c, and using (1),

$$\text{mean concentration} = \mu = \frac{1}{b-a}\int_a^b f(x)\,dx = \frac{1}{L}\int_o^L y\,dx$$

$$= \frac{1}{vL}\int_o^L z\,dx = \frac{1}{vL}\int_o^L [vw + Ae^{-Bx}]\,dx$$

$$= \left[\frac{w}{L}x + \frac{A}{vL}\frac{e^{-Bx}}{(-B)}\right]_o^L = w - \frac{A}{vLB}(e^{-BL} - 1)$$

$$= w - \frac{z_o - vw}{v \log\left(\frac{z_o - vw}{z_1 - vw}\right)}\left(\frac{z_1 - vw}{z_o - vw} - 1\right)$$

$$= w - \left(\frac{z_1 - z_o}{v}\right)\frac{1}{\log\left(\frac{z_o - vw}{z_1 - vw}\right)}$$

(6)
$$= \boxed{w + \frac{y_o - y_1}{\log\left(\frac{y_o - w}{y_1 - w}\right)} \text{ mgms/ml} .}$$

Analysis of the plausibility of this result:*

$$\text{For } h > 0\ , \quad \frac{h}{1+h} < \log\,(1+h) < h\ .$$

Thus $\dfrac{1}{1+h} < \dfrac{\log\,(1+h)}{h} < 1,$

$$(7) \qquad 1 + h > \frac{h}{\log\,(1+h)} > 1\ .$$

Let $h = \left(\dfrac{y_o - y_1}{y_1 - w}\right) > 0$. Then $1 + h = \dfrac{y_o - w}{y_1 - w}$,

and $$\frac{y_o - w}{y_1 - w} > \frac{1}{y_1 - w} \cdot \frac{y_o - y_1}{\log\left(\dfrac{y_o - w}{y_1 - w}\right)} > 1$$

from (7). Thus,

$$y_o - w > \frac{y_o - y_1}{\log\left(\dfrac{y_o - w}{y_1 - w}\right)} > y_1 - w$$

$$y_o > \mu = w + \frac{y_o - y_1}{\log\left(\dfrac{y_o - w}{y_1 - w}\right)} > y_1\ .$$

Thus μ does, indeed, lie between the maximum y_o and minimum y_1, as it should.

---

* See: Lang, C. A First Course in Calculus. Reading, Massachusetts: Addison-Wesley Publishing Co., 1964, p. 122.

****

A DIFFUSION PROBLEM

Contributor: James O. Brooks

****

Mathematics: separable differential equations (Math.2)

Abstract: The diffusion of a substance across the wall of a tube from a fluid flowing through the tube is considered in this problem.

PROBLEM:

A solution moves along a thin tubular membrane of length L and a solute diffuses across the tube wall according to Fick's law. The concentration of the solute outside the tube, C, is assumed to be constant. At the beginning of the tube the inside concentration is y_o and is greater than C. At the end the concentration inside the tube is y_1. Find the equation which expresses the concentration y(x) of the solute at a point x, $0 \leq x \leq L$ along the length of the tube.

SOLUTION:

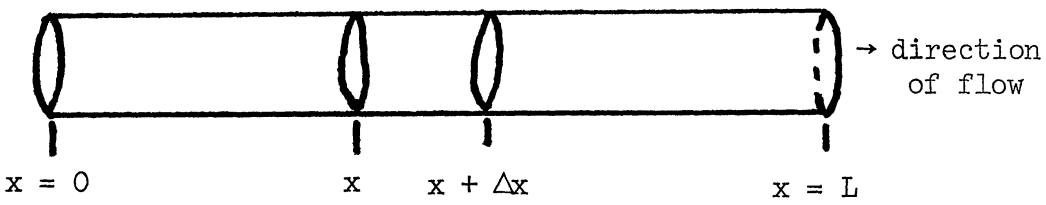
Let us assume:

(a) The tube is a right circular cylinder of radius r and length L.

(b) The particles in solution move with constant velocity v along the tube and do not change lateral position.

(c) Fick's law is valid for a short length interval $[x, x + \Delta x]$ along the tube and short time interval $[t, t + \Delta t]$. Thus the amount of solute which diffuses out across the tube wall is given by the product (wall surface)(average concentration difference over the given short interval $x, x + \Delta x$) (permeability)Δt.

Let r = radius of the tube,
y(x) = concentration of solute at point x along the tube,
v = velocity of the solution along the tube,
k = permeability coefficient.



Since y is a continuous function, the average concentration difference can be written in the form y(c) - c, where c is some point in the interval $x, x + \Delta x$. Consider a small time interval from time t to $t + \Delta t$. Because of assumption (b), $\Delta x = v\Delta t$. Consider a small cylindrical

chamber of tube between position x and position $x + \Delta x$ along the tube. The volume of that chamber is $\pi r^2 \Delta x$, and the lateral surface area is $2\pi r \Delta x$. During the time interval $[t, t + \Delta t]$ the chamber fills with solution entering the left end with concentration $y(x)$. Thus the total amount of entering solute is (concentration of solute in solution) (volume of solution) $= y(x)(\pi r^2 \Delta x)$. The chamber completely exhausts its previous content of solution so that an amount of solute equal to $y(x + \Delta x)\pi r^2 \Delta x$ leaves the chamber at the right end. The difference

$$[y(x) - y(x + \Delta x)]\pi r^2 \Delta x$$

is the amount of solute which leaves the chamber by diffusion across the chamber wall. This amount is equal to

$$(2\pi r \Delta x)(y(c) - c)k\Delta t$$

by assumption (c).

Thus,

$$(y(x) - y(x + \Delta x))\pi r^2 \Delta x = (2\pi r \Delta x)(y(c) - c)k\Delta t \ .$$

But $\Delta x = v\Delta t$, so that

$$\frac{y(x) - y(x + \Delta x)}{\Delta x} = \frac{2(y(c) - c)k}{vr} \ .$$

Taking the limit as $\Delta t \to 0$,

$$-\frac{dy}{dx} = \frac{2(y(x) - c)}{vr} k \ .$$

Hence,

$$\frac{1}{y(x) - c} \frac{dy}{dx} = \frac{-2k}{vr} \ .$$

Integrating from 0 to x and from y_o to $y(x)$,

$$\int_0^x \frac{y'(s)\, ds}{y(s) - c} = \int_0^x \frac{-2k\, ds}{vr}$$

we obtain

$$\ln \frac{y(x) - c}{y_o - c} = \frac{-2kx}{vr} \ .$$

When $x = L$,

$$\ln \frac{y_1 - c}{y_o - x} = - \frac{2k}{vr} L ,$$

so that

$$- \frac{2k}{vr} = \frac{n}{L} \left(- \frac{2kL}{vr} \right) = \frac{x}{L} \ln \left(\frac{y_1 - c}{y_o - c} \right) .$$

Therefore,

$$\ln \left(\frac{y(x) - c}{y_o - c} \right) = \frac{x}{L} \ln \left(\frac{y_1 - c}{y_o - c} \right) .$$

and

$$y(x) = c + (y_o - c) \left(\frac{y_1 - c}{y_o - c} \right)^{x/L} .$$

****

MODELS OF BIOLOGICAL GROWTH

Contributors: James Mortimer, Hebrew University Report

****

Mathematics: integration, differentiation (Math. 1)

Abstract: Four models of biological growth are presented: exponential growth, exponential growth to constant value, logistic growth, and Gompertz's growth curve.

Many mathematical models have been used to describe biological growth. Frequently the same mathematical description serves as a model for population growth and the growth of tissues or organs. The first three models given below are based upon simple assumptions about the nature of the growth process and have been used to fit both population and tissue growth data. The fourth model, although not based upon such intuitive assumptions, has been frequently used to fit growth data.

1. Exponential growth:

From the assumption that the rate of growth is proportional to the instantaneous value of the relevant variable being investigated (e.g., the weight of a cellular mass or the number of individuals in a population) we obtain the following mathematical relation:

$$W'(t) = RW(t) \tag{1}$$

where $W(t)$ is the value of the relevant variable at time t (e.g., the weight at time t), and R is a constant of proportionality.

By simple integration, the growth function can be derived:

$$W(t) = W_o e^{Rt} , \tag{2}$$

where W_o is the value of W at time t.

2. Exponential growth to constant value:

If it is assumed that the rate of growth is proportional to the difference between the instantaneous value of W and some asymptotic value K, then we obtain the following relation:

$$W'(t) = R[K - W(t)] \tag{3}$$

where R is a proportionality constant as before. Separating variables and integrating (3) with respect to t, the following growth function is obtained:

$$W(t) = K - (K - W_o)e^{-Rt} , \tag{4}$$

where W_o is the value of W at time 0.

It is seen that when t approaches infinity, W approaches the asymptotic value K as required.

From equation (3) it is apparent that the rate of growth is maximal at time **0**, and decreases asymptotically to 0 as t approaches infinity and W(t) approaches K.

3. Logistic growth:

One of the most frequently used models combines the assumptions of models 1. and 2., that is, the rate of growth is assumed to be proportional to both the instantaneous value of W and to the difference between the instantaneous value and some asymptotic value K. We can represent these two assumptions by the equation:

$$W'(t) = RW(t)[K - W(t)] \tag{5}$$

If the variables are separated and the integration performed, we get the equation for logistic growth:

$$W(t) = \frac{KW_o}{W_o + (K - W_o)e^{-KRt}} \tag{6}$$

which can easily be shown to satisfy the conditions, $W(0) = W_o$ and $W(t) \longrightarrow K$ as $t \longrightarrow \infty$.

If equation (5) is investigated, it is seen that the maximum rate of growth need not occur at time 0 as in model 2., but can occur at some positive time t when the second derivative is equal to 0. As t approaches infinity, W(t) approaches K, so that the rate of growth approaches 0 as in model 2.

If equation (5) is differentiated and the second derivative thus obtained is set to 0, we can solve for the time t when W'(t) reaches its maximum value.

Differentiating (5)

$$W''(t) = RKW'(t) - 2RW(t)\,W'(t)$$
$$= R^2W(t)[K - 2W(t)][K - W(t)]$$

which is equal to zero if

(i) $W(t) = 0$,

(ii) $K = W(t)$, or

(iii) $K = 2W(t)$.

Cases (i) and (ii) correspond to the trivial solutions obtained from the degenerate cases of models 1. and 2.. Investigating case (iii) we find that

$$W(t) = \frac{K}{2} = \frac{KW_o}{W_o + (K - W_o)e^{-KRt}}$$

or

$$(K - W_o)e^{-KRt} = W_o$$

so that

$$t = -\frac{1}{KR} \log \frac{W_o}{K - W_o} .$$

Therefore, we conclude that if $K - W_o > W_o$, then there exists some time $t_1 > 0$, at which $W'(t)$ reaches its maximum; but if $K - W_o < W_o$, the maximum rate of growth occurs at time 0 and thereafter the growth rate decreases monotonically.

4. Gompertz's growth curve:

The following curve is sometimes used to fit growth data:

$$W(t) = ae^{(-be^{-Rt})}$$

where R, a and b are constants. Differentiating the function we obtain

$$W'(t) = abRe^{(-Rt-be^{-Rt})}$$

$$W''(t) = abR(bRe^{-Rt} - R)e^{(-Rt-be^{-Rt})}$$

and the following conclusions can be made:

1. When $t = 0$, $W = ae^{-b}$.
2. When $t = \ln b/R$, $W = ae^{-1}$.
3. At this latter time the rate of growth reaches a maximum and equals Ra/e.
4. As t approaches infinity, W approaches a, and W' approaches 0.

****

THE SPECIFIC RATE OF GROWTH

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The specific growth rate of a limb is obtained by differentiation.

The weight W of a limb of a plant or animal body is, among other things, a function of age (time); i.e.

$$W = f(t)$$

This value can be approximated by the expression

$$W = kt^n$$

where k and n are constants that depend upon the particular species and the environment in which the species is growing. (Note that generally $n \leq 1$.)

Not only is one interested in the rate of growth $f'(t)$ of the limb but also for comparison purposes one is interested in the rate of growth of a unit weight of cells in the limb. This latter rate is referred to as the specific rate of growth and is given by the following expression:

$$\frac{f'(t)}{W} = \frac{f'(t)}{f(t)} = \frac{d(\ln W)}{dt}$$

QUESTION:

How does the specific growth rate of a limb vary with its age?

ANSWER:

$$\frac{f'(t)}{W} = \frac{nkt^{n-1}}{kt^n} = \frac{n}{t}$$

****

IDEAL GROWTH OF CELLS

Contributor: Harold Slater*

****

Mathematics: differentiation (Math.1)

Abstract: A simple case of exponential growth is considered.

*Based upon: Setlow, R.B., and Pollard, E.C. Molecular Biophysics. Reading, Massachusetts: Addison-Wesley, 1962, 29.

The growth of a population of cells which reproduce by simple division can be assumed to satisfy the following equation in an idealized environment:

$$N(r) = N(0)2^r \quad (1)$$

where $N(0)$ is the initial number of cells in the population, and $N(r)$ is the number of cells in the rth generation.

If the generation time is assumed to be constant, equation (1) can be rewritten in terms of time:

$$N(t) = N(0)2^{t/T} ,$$

where T is the generation time, and $N(t)$ is the number of cells in the population at time t.

EXERCISES:

1. Find the rate of increase of the population.

SOLUTION:

$$\log N(t) = \log N(0) + \frac{t \log 2}{T} . \quad (2)$$

Taking the derivative of both sides and rearranging, we have:

$$\frac{dN}{dt} = \frac{N \log 2}{T} = \frac{N(0) \log 2 \cdot 2^{t/T}}{T} .$$

2. Find the generation time, T.

SOLUTION:

From (2),

$$\frac{t}{T} = \frac{\log N(t) - \log N(0)}{\log 2} .$$

so that

$$T = \frac{t \log 2}{\log\left(\frac{N(t)}{N(0)}\right)} .$$

****

GROWTH OF A BACTERIAL POPULATION

Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: The number of bacteria in a culture at a given time is obtained from the solution of a simple differential equation.

Bacteria reproduce by simple division. It follows that the instantaneous rate of reproduction of bacteria - the change in their number with time - is proportional to the existing number of bacteria.

Write the differential equation for the rate of the reproduction as a function of the number of bacteria. From the equation, find an answer to the following question: If at the end of three hours there are ten thousand (10^4) bacteria, and at the end of five hours there are forty thousand, how many were present initially?

SOLUTION:

The differential equation describing the growth process is

(1) $$\frac{dx}{dt} = kx .$$

Separating variables, we obtain:

(2) $$\frac{dx}{x} = k \cdot dt .$$

where

x = the number of bacteria at time t,

x_o = the number of bacteria at time 0,

t = the time in hours,

k = a constant, $k \geq 0$,

$\frac{dx}{dt}$ = instantaneous time rate of change of the number of bacteria.

Integrating (2) we obtain

(3) $$\ln x = kt + d$$

where $d = \ln x_o$ is a constant obtained by evaluating (3) at time 0.

Substituting the given data into (3), we obtain two equations:

(4) $$3k = \ln \frac{x_3}{x_o}$$

and

(5) $$5k = \ln \frac{x_5}{x_o} .$$

Subtracting (4) from (5)

$$2k = \ln \frac{x_5}{x_o} - \ln \frac{x_3}{x_o} = \ln \frac{x_5}{x_3} = \ln \left(\frac{4 \times 10^4}{10^4} \right) = \ln 4$$

so that

$$k = \ln 2 \, .$$

Now we can solve for x_o. Substituting $k = \ln 2$,

$$\ln \frac{x_3}{x_o} = \ln \frac{10^4}{x_o} = (\ln 2)3 = \ln 8$$

so that

$$x_o = \frac{10^4}{8} \, .$$

****

DYNAMICS OF CELL GROWTH

Contributor: James Mortimer*

****

Mathematics: linear differential equations (Math.4)

Abstract: The solution of systems of simultaneous differential equations in a simple two compartment growth model yields relations for the growth dynamics of batch and chemostat cultures.

*Based upon: Williams, F.M. "A Model of Cell Growth Dynamics," Journal of Theoretical Biology, XV (1967), 190-207.

Many characteristic dynamics of cell growth can be accounted for in a simple two-compartment cell growth model. In this model it is assumed that:

(a) Each cell is composed of a synthetic compartment, s and a structural-genetic compartment, n.

(b) The s-portion is fed entirely by uptake of nutrient from the external environment of the cell.

(c) The n-portion is formed solely from the s-portion.

(d) A necessary and sufficient condition for cell division is the doubling of the size of the n-portion, irrespective of the size of s.

For a single cell it can be assumed that the rates of the reactions by which nutrient is converted into s and s into n are proportional to the amounts of the reactants present.

Let $\underline{c}$ denote the amount of nutrient available to s, and $\underline{s}$ and $\underline{n}$ represent the volume of the s and n compartments. Assuming that the amount of each reactant is directly proportional to the volume of its compartment, the following set of equations is obtained:

(1) $$\frac{d\underline{s}}{dt} = k_1 \underline{c}\,\underline{m} - k_2 \underline{s}\,\underline{n}$$

(2) $$\frac{d\underline{n}}{dt} = k_2 \underline{s}\,\underline{n}$$

(3) $$\frac{d\underline{m}}{dt} = k_1 \underline{c}\,\underline{m}$$

where $\underline{m} = \underline{s} + \underline{n}$ = total volume of the cell, and k_1, k_2 are constants.

Since cell division occurs whenever $\underline{n}(t) = 2\underline{n}(0)$, where $\underline{n}(t)$ is the volume of n at age t, the overall size of the cell at division depends upon both $\underline{s}(0)$, the size of the synthetic portion at $t = 0$, and $\underline{c}(t)$, the amount of nutrient available to the cell.

The relationship between cell growth and nutrient dynamics is best studied by observing populations of cells. To extend the single

cell model described by equations (1) through (3) to populations, the following additional assumptions can be made:

(e) Cell division in the culture is asynchronous. (See CL2.)

(f) The nutrient is constantly replenished, and spent medium and cells removed, both at a rate, r(t), called the turnover rate of the nutrient.

With these assumptions a new set of equations is obtained from equations (1) through (3):

$$\frac{dC}{dt} = r(t)\,(C_o - C) - k_1 CM \tag{4}$$

$$\frac{dS}{dt} = k_1 CM - k_2 SN - r(t)S \tag{5}$$

$$\frac{dN}{dt} = k_2 SN - r(t)N \tag{6}$$

$$\frac{dM}{dt} = k_1 CM - r(t)M \tag{7}$$

where S, N, and M are the total population amounts of s, n, and m; C is the amount of nutrient available to the population; and C_o represents the amount of nutrient in the entering fluid.

Equations (4) through (7) have a solution, given initial values for C, S, N, and M, and a function r(t). We shall consider two special cases corresponding to the most common cell cultures, i.e., batch and chemostat cultures.

BATCH CULTURE: A culture which is inoculated with fresh nutrient and allowed to grow until either 1) the nutrient is exhausted, or 2) metabolic accumulation stops growth, is called a batch culture. Because of the limited scope of the model only the first condition, exhaustion of the nutrient, can be considered.

In a batch culture the nutrient turnover rate, r(t) is 0 for all t. In this case equations (4) through (7) can be rewritten:

(8) $$\frac{dC}{dt} = - k_1 CM$$

(9) $$\frac{dS}{dt} = k_1 CM - k_2 SN$$

(10) $$\frac{dN}{dt} = k_2 SN$$

(11) $$\frac{dM}{dt} = k_1 CM \ .$$

Representing the initial value of biomass by M_o, from considerations of the total biomass of the system, it follows that $C = M_o + C_o - M$. Substituting this expression for C into (11), we obtain

(12) $$\frac{dM}{dt} = k_1 (C_o + M_o) M - k_1 M^2 \ .$$

Finally, solving equation (12),

(13) $$M = \frac{C_o + M_o}{1 + \frac{C_o}{M_o} \exp\left(\frac{-k_1 t}{C_o + M_o}\right)} \ .$$

The solutions for C, N, and S may be obtained from (13) if the initial values of N and S are given. One common set of initial conditions corresponding to a culture composed of so-called "stationary" cells, is $N(0) = N_o = M_o$, $S_o = 0$. (See exercise 1.)

CHEMOSTAT CULTURE: In a chemostat culture, nutrient is introduced at a constant rate and spent medium and cells removed at the same rate. Under these conditions the culture is described by equations (4) through (7) where $r(t) = r_o > 0$ for all t.

To examine such a culture, we can consider the steady state and transient behavior of the system. Setting the right-hand sides of equations (4) through (7) equal to zero with $r(t) = r_o$ and solving for C, S, N, and M, gives the steady state solution:

(14) $$C = \frac{r_o}{k_1}$$

(15) $$S = \frac{r_o}{k_2}$$

(16) $$M = C_o - \frac{r_o}{k_1}$$

(17) $$N = C_o - \frac{r_o(k_1 + k_2)}{k_1 k_2} .$$

Observe that by setting $r_o = 0$, the above steady state solution reduces to that for a batch culture.

In an asynchronous population the number of cells will be proportional to N. Therefore, if N is measured in average cell equivalents, the number of cells in the population will be equal to N. With this interpretation of N, the quantity M/N represents the average cell size in the population. From (16) and (17)

$$\frac{M}{N} = 1 + \frac{r_o k_1}{k_1 k_2 C_o - r_o(k_1 + k_2)} .$$

It is apparent from this equation that the average steady state cell size, M/N, increases with r_o. Furthermore, it can be shown from (15) and (16) that the relative steady state size of the synthetic portion, S, increases with respect to the steady state size of the N-portion, with increasing turnover rate.

The transient solution for a chemostat culture may be obtained by solving the set of equations given $r(t) = r_o$ and the initial values of M, N, C, and S. (See exercise 2.)

EXERCISES:

1. A batch culture is prepared from an inoculum of stationary cells, i.e., cells in which $dS/dt = dN/dt = dM/dt = 0$ at $t = 0$. According to the model, what kind of growth dynamics can be expected of this culture?

SOLUTION:

a) Setting equations (8) through (11) equal to zero with the constraint that M and N are greater than zero for all t, we get M = N

and S = 0; i.e., a stationary cell contains no effective synthetic portion.

When stationary cells are added to fresh nutrient the S-portion begins to grow immediately, because $dS/dt = k_1CM > 0$. After the initial growth of S, k_2SN becomes greater than zero and N begins to build up. We can analyse this lag in growth of the N-portion with respect to the S-portion mathematically.

For t = 0,

$$\frac{dM}{dt} = k_1C_oM_o > 0 ,$$

whereas

$$\frac{dN}{dt} = k_2S_oN_o = 0 ,$$

because $S_o = 0$. $dM/dt > dN/dt$ for small t, and since M = N at t = 0, M > N for small t.

During this initial phase of growth, the so-called "lag" phase, cells grow in size, but very little cell division occurs.

b) From (14) through (17) with $r_o = 0$, the steady state values S = 0, $M = N = C_o$, for a batch culture are obtained. Thus, for large t, M = N and S = 0. When the nutrient is exhausted, cells return to their initial minimum size with S = 0, and no further growth or division takes place.

c) Between the "lag" phase and the steady state, both M and N increase exponentially. (Solution left to the reader.)

2. A chemostat culture is prepared from an inoculum of stationary cells. What differences are there, if any, between the growth dynamics of this chemostat culture and the dynamics of the culture in exercise 1?

SOLUTION:

For t = 0,

$$\frac{dN}{dt} = k_2S_oN_o - r_oN_o = - r_oN_o < 0 ,$$

so that the total number of cells shows a slight initial decrease. But

$$\frac{dM}{dt} = k_1 C_o M_o - r_o M_o > 0$$

because $k_1 C_o \gg r_o$, so that while the total number of cells decreases initially, the total biomass increases.

On the other hand, in a batch culture dM/dt, $dN/dt \geq 0$ for all t; thus there is an initial increase in both the number of cells and biomass.

****

SELECTIVE RADIATION EFFECTS IN CELL POPULATIONS

Contributor: James Mortimer*

****

Mathematics: matrix multiplication (Math.3)

Abstract: The selective destruction of malignant cells in a tissue culture is examined by means of matrix algebra.

*Based upon: Han, G.M. "State Vector Description of Mammalian Cells in Tissue Culture." Paper presented at the Gordon Research Conference on Biomathematics, July 10, 1967.

The success of radiation therapy for the treatment of cancer depends on the ability to kill malignant cells while leaving non-malignant cells unharmed. To a certain extent, this is accomplished by confining radiation to the area of malignancy, but even with the best techniques many non-malignant cells are destroyed. It is desirable to maximize the ratio of malignant cells killed to non-malignant cells destroyed. The following model illustrates the use of the technique of synchronization of cell populations in the selective destruction of cells in a tissue culture.

Consider a population of malignant cells. We can represent the life history of one such cell by a circle where P corresponds to the period of DNA synthesis, M corresponds to mitosis, and G_1 and G_2 are the pre- and postsynthetic phases (see Figure 1).

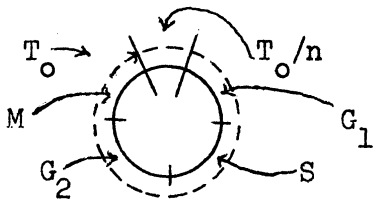


Figure 1

If the generation time T_o of the population is constant and the circle is divided into n equal subunits of length T_o/n, we can define a state vector of the culture of cells by

$$S(t) = \begin{pmatrix} S_1(t) \\ S_2(t) \\ \vdots \\ S_n(t) \end{pmatrix}$$

where $S_i(t)$ represents the relative frequency of cells in the i^{th} subunit at time t.

Suppose that upon division each cell yields two daughter cells. Assuming that the time unit is chosen such that one time unit is T_o/n, we can define a recursive relation for S:

$$S(t + 1) = \Delta^{nxn} S(t)$$

where

$$\Delta^{nxn} = \begin{pmatrix} 0 & 0 & \cdots & 0 & 2 \\ 1 & 0 & \cdots & & 0 \\ 0 & 1 & 0 & \cdots & 0 \\ \vdots & & & & \vdots \\ 0 & 0 & \cdots & 1 & 0 \end{pmatrix} \quad ;$$

that is, if $S(t) = (a,\ldots, k_{n-1}, k_n)$, then $S(t+1) = (2k_n, a, \ldots, k_{n-1})$.

In general, the generation time, T, will not be constant, but will have some distribution with mean, T_o. To account for the effects of this distribution in the decay of synchronization, we introduce a dispersion operator,

$$\delta^{nxn} = \begin{pmatrix} (1-\alpha-\beta) & \beta & 0 & \cdots & 0 & \alpha \\ \alpha & (1-\alpha-\beta) & \beta & 0 & & 0 \\ 0 & \alpha & (1-\alpha-\beta) & \cdots & 0 & 0 \\ \vdots & & & & & \vdots \\ \beta & 0 & \cdots & \alpha & & (1-\alpha-\beta) \end{pmatrix}$$

where

$$\alpha + \beta < 1$$

In the general case, therefore, $S(t+1) = (\Delta^{nxn}\delta^{nxn})\, S(t)$.

One radiation treatment does not, in general, kill all cells. Assume that the surviving fraction of cells is $F = 1 - (1 - e^{D/D_o})^n$, where D is the dose of radiation and D_o and n are parameters whose values depend upon the portion of the cycle through which the cell is passing. There exist values of D_o and n for every subunit i of the cycle. Let these be donoted by D_{o_i} and n_i. Then the surviving fraction of cells in the i^{th} subunit is given by $F_i = 1 - (1-e^{D/D_{o_i}})^{n_i}$. If

$$\bar{F} = \begin{pmatrix} F_1 & 0 & \cdots & 0 \\ 0 & F_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & F_n \end{pmatrix}$$

and S is the state of the culture before radiation, $S' = \bar{F}\, S$ is state of the culture after radiation.

At certain phases of the cell cycle sensitivity to radiation is maximum, e.g., just prior to DNA synthesis. The F_i's corresponding to these phases are small. To take advantage of this fact, a population of malignant cells can be synchronized by various chemicals which block DNA synthesis, so that most of the malignant cells are in the pre-DNA synthesis interval.

Consider a mixed population of malignant and non-malignant cells. Suppose a chemical is chosen selectively so that it does not significantly synchronize the non-malignant cell population. Then if the malignant population is synchronized so that most of its cells are in the pre-DNA synthesis interval, radiation of the total population will affect a significantly larger proportion of malignant cells than non-malignant cells. Even if synchronization cannot be induced selectively, selective radiation can be accomplished if the populations of malignant and non-malignant cells have different generation times. Thus, during the period of decay of synchronization (see CL2), the populations will tend to separate in phase. By giving radiation at appropriate times, $t = nT_o$ where T_o is the mean generation time of the malignant cell population and $n = 1, 2, 3, \ldots$, the proportion of malignant cells in joint population can be reduced.

EXERCISE

1. Suppose $F = \begin{pmatrix} .9 & 0 & 0 & 0 & 0 & 0 \\ 0 & .9 & 0 & 0 & 0 & 0 \\ 0 & 0 & .8 & 0 & 0 & 0 \\ 0 & 0 & 0 & .5 & 0 & 0 \\ 0 & 0 & 0 & 0 & .9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$ and the population of malignant cells is synchronized such that $S_{mal} = \begin{pmatrix} 0 \\ .1 \\ .2 \\ .6 \\ .1 \\ 0 \end{pmatrix}$, while the non-malignant cells continue to grow in an exponential, completely asynchronous manner. What is the ratio of the surviving fraction of non-malignant cells to the surviving fraction of malignant cells after

only one radiation treatment?

SOLUTION:

$$S'_{mal} = FS_{mal} \quad \text{so that} \quad S'_{mal} = \begin{pmatrix} .9 & 0 & 0 & 0 & 0 & 0 \\ 0 & .9 & 0 & 0 & 0 & 0 \\ 0 & 0 & .8 & 0 & 0 & 0 \\ 0 & 0 & 0 & .5 & 0 & 0 \\ 0 & 0 & 0 & 0 & .9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 0 \\ .1 \\ .2 \\ .6 \\ .1 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 \\ .09 \\ .16 \\ .30 \\ .09 \\ 0 \end{pmatrix}$$

The total surviving fraction of malignant cells = $\sum_i S'_{mal_i} = .64$

In CS2 the age distribution of an exponentially growing population was obtained. Using that result, $S_{nonmal_i} = (2 \ln 2 \cdot 2^{-i/5})/6$, so that

$$S'_{nonmal} = \begin{pmatrix} .9 & 0 & 0 & 0 & 0 & 0 \\ 0 & .9 & 0 & 0 & 0 & 0 \\ 0 & 0 & .8 & 0 & 0 & 0 \\ 0 & 0 & 0 & .5 & 0 & 0 \\ 0 & 0 & 0 & 0 & .9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 1 \\ 2^{-1/5} \\ 2^{-2/5} \\ 2^{-3/5} \\ 2^{-4/5} \\ 1/2 \end{pmatrix} \times \frac{2 \ln 2}{6} = \begin{pmatrix} .9 \\ .783 \\ .607 \\ .330 \\ .498 \\ .500 \end{pmatrix} \times \frac{2 \ln 2}{6} .$$

As before the total surviving fraction is the sum of the $S'_{nonmal_i} = .813$. The ratio of the surviving fraction of non-malignant cells to the surviving fraction of malignant cells then is given by .813/.640 = 1.27, or the ratio of malignant cells destroyed to non-malignant cells killed is (1 - .640)/(1 - .813) = .360/.187 = 1.925.

****

SOME MEASURES OF SYNCHRONY IN CELL POPULATIONS

Contributor: James Mortimer*

****

Mathematics: elementary calculus (Math. 1), vector geometry (Math. 3)

Abstract: Two measures of synchrony applicable to cell division are presented.

*Based upon: Engleberg, J. "A Method of Measuring the Degree of Synchronization in Cell Populations," Experimental Cell Research, XXIII (1961), 218-227; and Engleberg, J., and Hirsch, H.R. "On the Theory of Synchronous Cultures." Cell Synchrony. Edited by I.L. Cameron and G.M. Padilla. New York: Academic Press, 1966, 14-37.

If in most of the cells of a population simultaneous or nearly simultaneous changes occur, that population is described as "synchronous" with respect to those changes. For example, in a cell population synchronized with respect to cell division nearly all cells divide within some small time interval. Because of the usefulness of synchronized populations in experimental investigations, it is desirable to have a mathematical measure of the degree of synchrony. Such a measure might also be of value in assessing various techniques used to induce synchrony in populations of cells.

The following measures have been developed for evaluating synchrony of cell division in growing populations:

1. AVERAGE RATE MEASURE OF SYNCHRONY:

Let E be an event which occurs with fixed periodicity, T, in each cell of a population. Denote by $\mathcal{E}(t)$, the number of times the event E has occurred in time t, and by N(t) the number of cells in the population at time t. Then $f(t) = (d\mathcal{E}/dt)/N(t)$ represents the instantaneous rate of occurrence of the event per individual in the population. If the population is sufficiently large, f can be assumed to be continuous over the interval of measurement (t_1,t_2).

Let R be the average rate of occurrence of the event per cell over (t_1,t_2) . Then

$$R = \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} f(t)dt$$

Figure 1 shows the relationship of f(t) to R on (t_1,t_2) for a hypothetical population. From the definition of R it follows that if the population is at all synchronized, then part of the curve for f(t) lies above R.

If the population were perfectly synchronized and $t_2 - t_1 = T$, f(t) would be an impulse of strength RT occurring at some time t, $t_1 \leq t \leq t_2$.

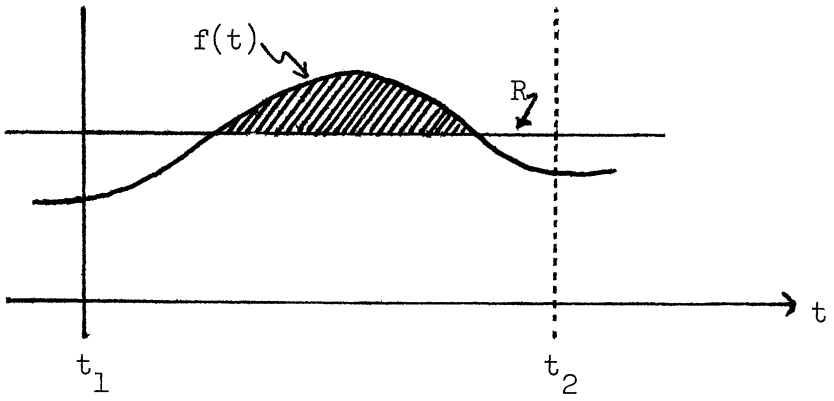


Figure 1

On the other hand, for perfect asynchrony, f(t) = R for all t.

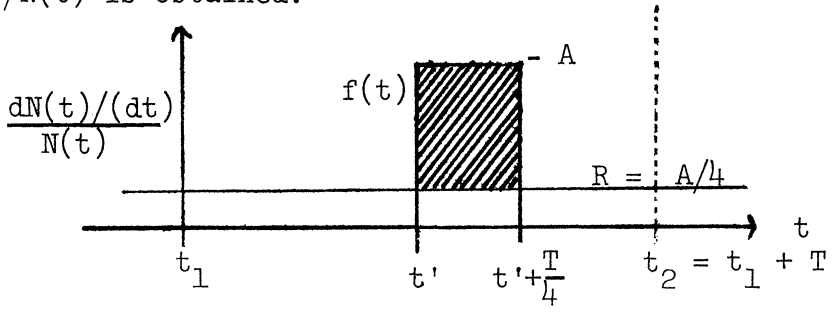
A measure of synchrony should, at least, give appropriate values for these two extremes. Therefore, we will require the measure to give a value of 100% for perfect synchrony and 0% for perfect asynchrony. The following measure satisfies this condition:

$$\text{Degree of synchrony} = M(f) = \frac{\text{area under f above R}}{R(t_2 - t_1)} \times 100\% \ .$$

It can be shown that this measure also gives appropriate values for intermediate levels of synchrony and therefore might be useful for the evaluation of synchrony in cell populations. (See Exercises.)

EXERCISES

1. Suppose that the generation time in a population of cells is constant for all cells. If such a population were synchronized perfectly such that all cells divided at time t, the future growth of the population would be entirely determined, since all cells would divide at times t + nT, where T denotes the generation time and n = 1,2,3,.... Assume that the population is sampled over an interval of length T and that from the data the following plot of (dN(t)/dt)/N(t) is obtained:



Using the measure of synchrony given above, determine the degree of synchrony of such a population with respect to the event of cell division.

SOLUTION:

From the plot of $(dN/dt)/N(t)$ above,

$$f(t) = A, \quad t' \leq t \leq t' + T/4$$

$$= 0, \text{ otherwise.}$$

$$M(f) = \frac{\text{area under f above R}}{R(t_2 - t_1)} \times 100\% = \frac{3A/4 \cdot T/4}{AT/4} = 75\% .$$

2. Suppose that a population of cells is exponentially growing such that $N(t) = N_o 2^{t/T}$. What is the degree of synchrony with respect to cell division over any interval (t_n, t_m)?

SOLUTION:

$$f(t) = (dN(t)/dt)/N(t) = \ln 2/T = \text{constant},$$

so that

$$M(f) = \frac{\text{area under f above R}}{R(t_m - t_n)} \times 100\% = \frac{0 \times 100\%}{R(t_m - t_n)} = 0\%$$

over any interval (t_n, t_m) .

2. VECTORIAL MEASURE OF SYNCHRONY OF CELL-DIVISION

Let n_t be the size of the population at time t. Then we can define $\Delta n_t = n_{t+1} - n_t$ to be the number of cells in which cell division occurs in the interval (t, t+1), where the time unit is selected so that not more than one division per cell can occur in this interval. In general, the time between cell divisions in a given cell will be distributed according to some probability density function, g.

Assuming the time scale to be discrete, this probability density function becomes a set of probabilitites $g(1),\ldots,g(i),\ldots$ corresponding to generation or doubling times of $1,\ldots,i,\ldots$. This set of probabilities may change with environmental conditions. However, we shall consider only the case of large populations in which such changes do not occur.

Let $S_k(t)$ denote the proportion of cells in the culture at time t which will divide again for the first time after t in the interval (t+k, t+k+1). It can be shown that

$$S_k(t) = \left(\Delta n_{t+k} + 2 \sum_{j=1}^{k} g(j)\Delta n_{t+k-j}\right)/n_t \ *$$

Although it is possible for the generation time to be infinite, e.g., with non-dividing cells, it will be assumed here that there is some maximum time m, such that

$$g(m) \neq 0 \text{ and } g(m+i) = 0 \text{ for all } i > 0 .$$

With $S_k(t)$ as defined above, the growth dynamics of the culture are completely specified by a state vector, $S(t) = \langle S_o(t), S_1(t), \ldots S_n(t)\rangle$, signifying the state of the culture at time t, and the distribution function, g, of generation times. In particular, the initial state of a culture is obtained by evaluating S(t) at t = 0 .

The state vector can be represented by a point in n + 1 dimensional space. From the definition of $S_k(t)$, it follows that $\sum_{k=0}^{n} S_k(t) = 1$ for all t, that is, all points representing states of the culture lie in a bounded subset of an n-dimensional hyperplane in the n+1-dimensional space sometimes called the probability simplex. In the case of perfect synchrony the state vector of the culture will consist of n coordinates 0 and one coordinate 1, while in all other conditions the state vector will lie somewhere inside the hyperplane bounded by the points of perfect synchrony.

As an example, consider the three-dimensional case. All possible cultures will be represented by points in the two-dimensional plane bounded by the points, (1,0,0), (0,1,0), (0,0,1). Suppose that a culture is synchronized such that it can be described by one of the points, (1,0,0), (0,1,0) or (0,0,1). Because of the distribution of generation times, there will be a decay of synchrony with time.

---

* By convention, we shall take $\sum_{j=1}^{k=0}$ ( ) to be the empty sum; so that $S_o(t) = \Delta n_t/n_t$.

As this occurs, the vector representing the culture will trace out a trajectory which asymptotically approaches an equilibrium point in the bounded hyperplane. It can be shown that there exists only one equilibrium point corresponding to a completely asynchronously dividing culture, and that its location can be computed from the function, g.

The distance between this equilibrium point and the point representing the present state of the culture represents the divergence from complete asynchrony or the degree of synchrony of the culture with respect to cell division. A logical choice for a measure of synchrony would, therefore, be the distance between these points divided by the maximum distance in the bounded hyperplane.

Let $M'(S(t),g)$ be the degree of synchrony in a culture described by $S(t)$ and distribution function, g. Then

$$M'(S(t),g) = \frac{\sqrt{\sum_{i=0}^{n} (S_i(t) - S_{ie})^2}}{\text{Max.} \sqrt{\sum_{i=0}^{n} (S_i - S_{ie})^2}}$$

where

S_{ie} = value of i^{th} coordinate at equilibrium

$S_i(t)$ = value of i^{th} coordinate at t .

The use of this measure requires a knowledge of $S(t)$. Various procedures are available by which $S(t)$ can be calculated. However, due to the extensive calculations involved, the main function of this measure is to provide a theoretical tool for examining decay of synchrony.

REMARK:

Calculations of trajectories show that as the culture desynchronizes the state point tends to spiral around the equilibrium point without ever reaching it. The distance between the current state point and the equilibrium point, however, does not decrease monotonically with time, but increases and decreases during each revolution. What similar

measure can be used so that the degree of synchrony is monotonically decreasing with time?

It can be shown that a trajectory never crosses itself in the phase space. Therefore, the mean distance of the state points from the equilibrium point must decrease on the average each revolution. If this mean distance over one revolution is used rather than the instantaneous distance, a new measure is obtained with the property that degree of synchrony is monotonically decreasing in time.

---

1. Engleberg, J. "A Method of Measuring the Degree of Synchronization of Cell Populations." Experimental Cell Research, 23 (1961), 218-227.

2. Engleberg, J., and Hirsch, H.R. "On the Theory of Synchronous Cultures." Cell Synchrony. Edited by I.L. Cameron and G.M. Padilla. New York: Academic Press, 1966, 14-37.

****

STOCHASTIC CONSIDERATIONS IN A DIFFUSION PROBLEM

Contributor: Richard F. Baum*

****

Mathematics: elementary probability (Math. 2P), differential equations (Math. 4)

Abstract: Stochastic elements of a typical diffusion problem are stated, and the effect of these elements upon the usual deterministic solution is indicated.

*Based upon: Jacquez, John A. "Some Mathematical Problems in Physiology: Statistical Ensembles." Mathematical Problems in the Biological Sciences, Proceedings of the Fourteenth Symposium in Applied Mathematics. Edited by R. E. Bellman. Providence, Rhode Island: American Mathematical Society, 1962.

An experiment commonly carried out by the cell physiologist is one in which he tries to measure the permeability of a cell to some compound. The permeability of a cell with respect to a given compound S is often determined in the following way.

Suppose the cell is immersed at time t = 0 in a mixture of the compound S. Due to diffusion, the cell will absorb an amount of S. Let x(t) be the intracellular concentration of S at time t, and assume that the extracellular concentration of the compound is maintained constant, equal to s. Finally, let A(t) be the surface area of the cell at time t and let V(t) be the volume at time t. Let us assume that the intracellular concentration is always uniform and that the compound is not destroyed inside the cell. Furthermore, the rate of change of x(t) at time t will be assumed to be directly proportional to A(t), inversely proportional to V(t), and directly proportional to [s - x(t)] --- the difference in concentration of S between the outside and inside of the cell. Thus,

$$Dx(t) = k \frac{A(t)}{V(t)} [s - x(t)] .$$

The proportionality constant k is called the permeability constant of the cell with respect to the compound S.

In the simplest experiment to determine permeability, the cell physiologist will mix a suspension of cells (all of which are of the same type) with a solution of the compound being investigated. After incubating this mixture for various times, the cells are separated from the supernatant solution by centrifugation, and the supernatant solution and cells are then analyzed.

Suppose we idealize this experiment somewhat. We have a system consisting of a large number of functional units or cells, U_i, i = 1,2, ...,N, each spherical (but not necessarily all of the same volume) and each unit of the same type, so that the permeability of each U_i is the same, i.e.,

$$k_i = k , \quad i = 1,2,\ldots,N .$$

Assume that we can keep the suspension well-mixed by agitation and

that the rate at which the compound crosses the cell membrane is so slow in comparison to the diffusion in the cell that we can consider the intracellular concentration of each uniform at any given time. These are not unreasonable assumptions in many cases. Furthermore, let us assume that the extracellular concentration is constant from the start of the process at t = 0. This makes each unit independent of the others. From the above, the intracellular concentration in unit U_i is given by the solution of

$$Dx_i(t) = k \frac{A_i(t)}{V_i(t)} [s - x_i(t)] , \quad i = 1,2,\ldots,N , \tag{2}$$

where

$x_i(t)$ = the intracellular concentration of the compound in unit U_i at time t

k = the permeability constant

$A_i(t)$ = the surface area of unit U_i at time t

$V_i(t)$ = the volume of the compound in unit U_i at time t

s = the fixed extracellular concentration

The physiologist commonly neglects the statistical nature of this problem (which we will see below) and writes equation (3) for the total system:

$$Dx(t) = k \frac{A(t)}{V(t)} [s - x(t)] \tag{3}$$

where

$A(t)$ = total surface area at time t

$V(t)$ = total volume at time t

$x(t)$ = the intracellular concentration

Equation (3) represents an approximation of the behavior of the system, and has the distinct advantage that instead of having to deal with the N equations of form (2), we have only one equation. Even if this is a good approximation, we must ask how $x(t)$ is measured or more fundamentally, what quantity does the experimenter actually measure. As indicated in the above description, the experimenter measures the total amount of the compound in the N cells of his

sample and the total volume of these cells, i.e., he measures

$$\sum_{i=1}^{N} V_i(t)x(t) \text{ and } \sum_{i=1}^{N} V_i(t)$$

at some time t. From this measurement, he obtains $x(t)$ in the form of a weighted mean concentration of the sample of N cells, $\bar{x}_N(t)$,

$$\bar{x}_N(t) = \frac{\sum_{i=1}^{N} V_i(t)x_i(t)}{\sum_{i=1}^{N} V_i(t)} \quad . \tag{4}$$

Let us assume that $V_i(t) = V_i$, a constant, for all t and $A_i(t) = A_i$, a constant, for all t. That is, the change in the size of the cells is small with respect to the other parameters in (2), and can thus be assumed to be constant. Then (2) can be replaced by:

$$Dx_i(t) = k \frac{A_i}{V_i} [s - x_i(t)] \; ; \tag{5}$$

equation (3) becomes

$$Dx(t) = k \frac{A}{V} [\, s - x] \; ; \tag{6}$$

and we can write (4)

$$\bar{x}_N(t) = \frac{\sum_{i=1}^{N} V_i x_i(t)}{\sum_{i=1}^{N} V_i} \; . \tag{7}$$

Using (7),

$$D\bar{x}_N(t) = \frac{\sum_{i=1}^{N} V_i Dx_i(t)}{\sum_{i=1}^{N} V_i}$$

Therefore from (5)

$$(8) \qquad D\bar{x}_N(t) = k \left[\frac{s \sum_{i=1}^{N} A_i}{\sum_{i=1}^{N} V_i} - \frac{\sum_{i=1}^{N} A_i x_i}{\sum_{i=1}^{N} V_i} \right] .$$

Thus, even after the simplifying assumption resulting in (5) and (6), we see that the differential equation pertaining to the quantity that the experimenter measures is certainly different from equation (6). From this one may conclude that the size distribution of cells may alter results obtained experimentally for a permeability constant measurement of this type. Correct results using equation (6) would be obtained for a population of cells of uniform size, but not for a population with widely varying cell sizes.

****

AGE DISTRIBUTIONS OF CELLS IN GROWING CELL POPULATIONS

Contributor: James Mortimer

****

Mathematics: elementary calculus (Math. 1), probability (Math. 2P)

Abstract: The age distribution of a growing cell population is derived for a culture in which the generation time is constant.

It is often valuable to be able to relate such variables as volume, mass, and DNA content to the characteristics of the age distribution of a population. In many cell cultures these variables have rather predictable values which depend upon the ages of the cells that make up the culture. In a cell population which is growing exponentially in time, a knowledge of the age distribution of the cells allows one to obtain some information about the properties of a single cell in relation to its age.

The age distribution of a growing population of cells will be derived under the following three assumptions:

(a) Each parent cell gives rise upon division to two daughter cells.

(b) The time between cell divisions (the generation time) is invariant in the population.

(c) Cell divisions of different cells in the population are independent of one another.

Consider an exponentially growing population of cells. Let N_o represent the total number of cells in the initial population at time 0, and N_t represent the total number of cells in the population at time t.

From assumptions (a) to (c)

$$N_t = N_o 2^{t/T} \tag{1}$$

where T is the generation time and hence the maximum age of a cell in the population.

If $n_o(t)$, $n_1(t)$, ..., $n_T(t)$ represent the number of cells of age 0, 1, ..., T respectively, at time t, then the frequency of age class i at time, t, is given by

$$f_i(t) = \frac{n_i(t)}{N_t} = \frac{n_i(t)}{N_o 2^{t/T}} \quad . \tag{2}$$

Consider the filial cell class (the class of age 0). At t = 0, its frequency is given by

$$f_o(0) = \frac{n_o(0)}{N_o} ;$$

i time units later these cells will belong to class i and

$$(3) \qquad f_i(i) = \frac{n_o(0)}{N_o\, 2^{i/T}} .$$

Similarly, i + 1 time units later

$$(4) \qquad f_{i+1}(i+1) = \frac{n_o(0)}{N_o\, 2^{i+1/T}} ,$$

where it is assumed $0 \leq i < i+1 \leq T$. From equations (3) and (4), it can be shown that

$$(5) \qquad f_i(i) = 2^{1/T} f_{i+1}(i+1) .$$

To obtain the age distribution function we must first prove the following Lemma:

LEMMA: $f_i(t) = f_i(t+1)$ for all t and all i, $0 \leq i \leq T$

PROOF: From assumptions* (a) and (b)

$$(6) \qquad 2n_T(t) = n_o(t) .$$

Letting i = 0 in equation (2), we obtain

$$f_o(t) = \frac{n_o(t)}{N_o\, 2^{t/T}}$$

and

$$f_o(t+T) = \frac{n_o(t+T)}{N_o\, 2^{t+T/T}} .$$

Using (6) and recalling that $n_i(t) = n_{i+1}(t+1)$, $0 \leq i \leq T$, we get

---

* The assumption is made here that the frequency of cells of age 0 is twice that of cells of age T. This is clearly an approximation in the discrete case. The approximation is reasonable if the number of classes is large.

$$n_o(t + T) = 2n_T(t + T) = 2n_{T-1}(t + T - 1) = \ldots = 2n_o(t) ,$$

so that

$$f_o(t + T) = \frac{2n_o(t)}{N_o\, 2^{t/T} \cdot 2} = \frac{n_o(t)}{N_o\, 2^{t/T}} = f_o(t) .$$

With the aid of (5) it can be shown that

$$f_i(t + T) = f_i(t) \tag{7}$$

for all t and all i, $0 \leq i \leq T$. Recalling that $f_i(t) = n_i(t)/N_t$ and observing from equation (1) that both numerator and denominator are exponentially increasing, $f_i(t)$ must be either a monotone or constant function.

But from (7) it is apparent that $f_i(t)$ is periodic and not monotone. Therefore, $f_i(t)$ must be a constant, f_i, for all t, so that

$$f_i(t) = f_i(t + 1) \quad \text{for all t and all i, } 0 \leq i \leq T$$

Q. E. D.

A process satisfying this lemma is said to be stationary. In this case, we have shown that the age distribution does not change as a function of time even though the population is constantly growing at an exponential rate.

With the above result equation (5) becomes

$$f_i = 2^{1/T} f_{i+1} , \tag{8}$$

where f_i and f_{i+1} are constants.

Solving this equation recursively for f_i in terms of f_o we get

$$f_i = f_o\, 2^{-i/T} .$$

If the number of age classes in the population is sufficiently large, the distribution function can be approximated by a continuous function. Let g(h) be the probability that a cell selected at random

from the population will be of age h, where h takes on all values between 0 and T. Then

$$g(h) = g(0)\, 2^{-h/T} , \tag{9}$$

g(h) is called the probability density function. To obtain g(0) we use the fact that $\int_{-\infty}^{\infty} g(h)\, dh = 1$ if g(h) is a probability density function. In this case

$$\int_{0}^{T} g(0)\, 2^{-h/T}\, dh = 1 . \tag{10}$$

Integrating (10) and solving for f(0) we obtain

$$g(0) = \frac{2 \ln 2}{T} ,$$

so that the desired age density function is given by

$$g(h) = \frac{2 \ln 2}{T} \cdot 2^{-h/t} , \quad 0 \leq h \leq T$$

$$= 0 , \quad \text{otherwise.}$$

EXERCISES:

1. The derivation above was for the case in which a single cell upon division yielded two daughter cells. What changes would have to be made if division yielded instead four daughter cells?

SOLUTION:

In this case equation (9) would be replaced by

$$g(h) = g(0)\, 4^{-h/T} .$$

Solving for g(0) as before,

$$g(0) = \frac{4 \ln 4}{3T} ,$$

so that

$$g(h) = \frac{4 \ln 4}{3T} \cdot 4^{-h/T} , \quad 0 \leq h \leq T$$

$$= 0 , \quad \text{otherwise.}$$

The result can be extended in a similar manner to divisions of higher order.

2. Suppose that it is known that 10% of a population is actively engaged in the process of cell division at some time t. What length of time is required on the average for this process if the generation time is T and each parent cell yields two daughter cells upon division?

SOLUTION:

Assume that cell division takes some interval of time from t_m to T to be completed. From the data given above, the area under the density function in this interval must equal .10, i.e.,

$$\int_{t_m}^{T} g(h)\,dh = .10 = \int_{t_m}^{T} \frac{2 \ln 2}{T} \cdot 2^{-h/T}\,dh = 2^{1-t_m/T} - 1 .$$

Solving for t_m,

$$t_m = T\left(1 - \frac{\ln 1.10}{\ln 2}\right) .$$

3. A random sample of cells from the population is selected and the average amount of DNA content is calculated for this sample. Assuming that DNA content is a linear function of the age of the cell, what is the age of a cell which contains the average amount of DNA?

SOLUTION:

If x(t) = DNA content at time t, by assumption

$$x(t) = a + bt , \tag{11}$$

where a and b are constants. The average DNA content $\bar{D}$ is obtained from the density function:

$$E(D) = \bar{D} = \int_0^T g(h)(a + bh)\,dh$$

$$= \int_0^T \frac{2 \ln 2}{T} \cdot 2^{-h/T} \cdot a\,dh + \int_0^T \frac{2 \ln 2}{T} \cdot 2^{-h/T} \cdot bh\,dh$$

$$= a + bT\left(\frac{1}{\ln 2} - 1\right) .$$

To obtain the age of a cell with the average DNA content, we substitute $\overline{D}$ for $x(t)$ in equation (11) and solve for t:

$$t = T\left(\frac{1}{\ln 2} - 1\right) = .443T \ ,$$

the age of a cell containing the average amount of DNA.

---

1. Cook, J. R., and James, T. W., "Age Distribution of Cells in Logarithmically Growing Cell Populations." Synchrony in Cell Division and Growth. Edited by Erik Zeuthen. New York: Wiley and Sons, 1964, 485-495.

BIOLOGY OF ORGANS AND ORGANISMS

****

A SIMPLE EXAMPLE IN RESPIRATION

Contributor: Hebrew University Report

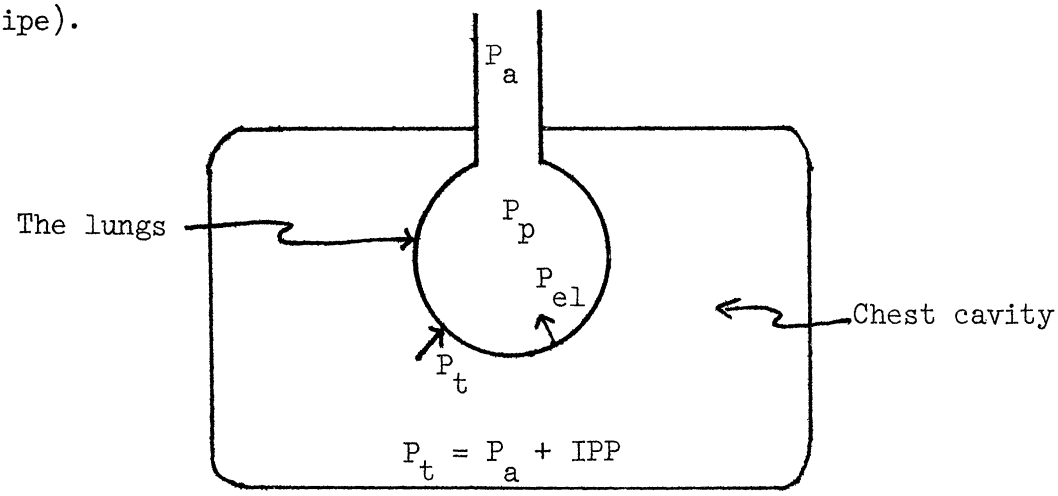
****

Mathematics: positive and negative numbers

Abstract: The relationship between pressure differences and respiration is investigated in this simple mathematical example

In the process of respiration air flows into the lungs (inhalation) and out (exhalation). This flow of air is caused by the difference of pressure between the air in the lungs and the external air. We shall call this pressure difference ΔP.

Let us think of the lungs as an elastic sack inside a closed box (the chest cavity) connected to the outside by a tube (the windpipe).



The total pressure in the chest cavity is denoted by P_t. The pressure of the air in the lungs due to the elasticity of the lungs we call P_{el}.

The pressure (P_p) of the alveolar air in the lungs is the sum of the elastic pressure of the lung walls and the total chest cavity pressure, i.e.,

$$P_p = P_t + P_{el}$$

Therefore the pressure difference (ΔP) between the air in the lungs and the external air (P_a) is given by

$$P = P_p - P_a = P_t + P_{el} - P_a = (P_t - P_a) + P_{el}$$

The difference between the total pressure in the chest cavity and in the external air is called the Intra-Pleural-Pressure (IPP).

Thus IPP = $P_t - P_a$ so

$$\Delta P = IPP + P_{el}$$

When ΔP is positive it means that the alveolar pressure is greater than that outside. In other words, when the airways are open, if ΔP is positive we are exhaling, and if ΔP is negative we are inhaling. P_{el} is always positive and the major variable is IPP; it is subject to voluntary change.

In the 4 cases listed below decide whether the person is inhaling or exhaling (all pressures are given in centimeters of water.)

	IPP	P_{el}
A	+2	+5
B	-21.5	+15
C	-10	+10
D	-5	+15

Answers:

A: exhaling B: inhaling C: no air flow D: exhaling

Question: Make a table showing when inhalation and exhalation take place according to the relative pressures of IPP and P_{el}. Take P_{el} as always being positive.

Answer:

$IPP > 0$		exhalation
$IPP < 0$	$\lvert IPP \rvert > P_{el}$	inhalation
$IPP < 0$	$\lvert IPP \rvert < P_{el}$	exhalation
$IPP < 0$	$\lvert IPP \rvert = P_{el}$	no air flow

****

RESPIRATION AS A FUNCTION OF TIME

Contributor: Hebrew University Report

****

Mathematics: elementary algebra

Abstract: Intra-pleural pressure and blood pressure are expressed as periodic functions of time, and the relationship between them is derived.

Respiration or, to be more precise, the flow of air (through the windpipe, for instance), is a periodic function of the time.

Let us assume that

$$V = A \sin wt$$

where

$\dot{V}$ = flow of air (the respiration)

and

A = maximum flow during exhalation and inhalation (although in exhalation this may differ slightly from flow in inhalation, we shall assume them to be equal.)

In reality A changes with time (when breathing deeply or less deeply), but in this problem assume A to be constant.

$w = \frac{2\pi}{T}$, where T is the time of one period.

As may easily be seen the periodic time is a variable (when running the frequency of breathing is much greater than when resting), but since this variation is not a function of the time we will ignore it. The cause of this respiration is the pressure difference between the air in the lungs and the external air. The major factor in this pressure difference is the IPP (Intra-Pleural-Pressure) - the difference between the total pressure in the chest cavity and in the outside air (see OE1 .) It is clear that the IPP changes periodically; with a small phase change (designated 'p'), in a healthy person, and a much larger one in a person suffering from asthma or fibrosis of the lungs.

$$IPP = C - a\dot{V}_{(t-p)}$$

C = IPP at rest, assuming it does not change from breath to breath

a = a constant of proportion (this also depends on the health of the lungs)

a and C are <u>not</u> functions of the time

Problem 1: Express the IPP as a function of the time.

SOLUTION:

$$IPP = C - aA \sin(wt + p)$$

It is important to remember that p is independent of w (or t), because it represents a phase difference and not a time difference.

Blood pressure depends on the IPP in the following manner: Blood pressure is created by the heart (we will deal with the blood pressure in the systemic system - in other words, the blood which flows through most of the body). It is usually measured in the limbs, and depends on the amount of contraction of the left chamber of the heart. The force of contraction of the heart muscles depends on the amount of blood entering the chamber, which in turn depends on the pressure on the pulmonary veins which return to the heart. If the pressure on the pulmonary veins (it equals the IPP) is great, little blood will return to the heart.

Thus blood pressure (designated by BP) is a function of IPP; although with a time difference.

It takes time for the IPP to take effect, the time required for the blood to pass through the pulmonary (lung) circuit. We shall call this time u. (Most of the blood returns from the body to the right chamber, and only after being sent to the lungs will the blood reach the left chamber where it is sent under pressure to most of the body.)

$$BP = k - b \cdot IPP \quad (t - u)$$

b = coefficient of proportion

k = a constant

IPP may be either positive or negative.

PROBLEMS:

1. Express blood pressure as a function of time.
2. Express blood pressure as a function of the respiration.
3. Express IPP as a function of respiration.

SOLUTIONS:

1. $BP(t) = k - b \cdot IPP(t - u)$

$BP(t) = k - b\{C - aA \sin(wt + p)\}\ (t - u)$

$BP(t) = k - b\{C - aA\ [\sin w(t - u) + p]\}$

It is important that u is multiplied by w ($= 2\pi/T$) because we are not dealing with a phase difference but a difference in time.

2. $IPP(t) = C - a\dot{V}(wt + p)$

We want $IPP(\dot{V})$

$$\dot{V} = A \sin wt$$

$$\frac{\dot{V}}{A} = \sin wt$$

$$\cos wt = \sqrt{1 - \sin^2 wt} = \sqrt{1 - (\frac{\dot{V}}{A})^2}$$

$$IPP = C - a\dot{V}[\sin wt \cdot \cos p + \cos wt \cdot \sin p]$$

$$IPP(V) = C - a\dot{V}\ [\frac{\dot{V}}{A} \cos p + \sqrt{1 - (\frac{\dot{V}}{A})^2}\ \sin p]$$

$$IPP(V) = C - \frac{a\dot{V}}{A}\ [\dot{V} \cos p + \sqrt{A^2 - \dot{V}^2}\ \sin p].$$

****

THE FLOW OF BLOOD IN THE BODY

Contributor: Hebrew University Report

****

Mathematics: elementary algebra

Abstract: Poiseuille's formula for non-turbulent flow through a tube is applied to the flow of blood in the body.

Poiseuille's formula for the non-turbulent flow of liquid through a tube is:

$$\dot{V} = \frac{\pi r^4 p}{8 \ell \eta}$$

η = viscosity, measured in poises (dyne-sec./cm^2)

r = radius of tube (in cm.)

ℓ = length of tube (in cm.)

p = pressure difference between the ends of the tube (in dyne/cm^2)

$\dot{V}$ = flow (in cm^3/sec.) [For the student who knows calculus we note that $\dot{V} = dV/dt$.]

1. Assume that the total peripheral resistance to the flow of blood is constant, that the mean arterial pressure is 100 mm. of mercury, and that the blood pressure in the great veins entering the heart is zero. If the heart is pumping 5 liters of blood per minute, what is the resistance ?

$$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$$

$$1 \text{ atmosphere} = 760 \text{ mm. mercury} = 1.013 \times 10^6 \text{ dyne/cm}^2$$

Answer:

$$R = \frac{p}{\dot{V}} = 1599 \text{ dyne-sec/cm}^5$$

2. If the average length of path for blood flowing from the heart through the peripheral tissues and back to the heart is 1 meter, and

the viscosity of blood is 0.04 poise (4 centipoise), find the radius of a tube which would give the same flow of blood under the conditions assumed for the previous question.

Answer:

$$r^4 = \frac{8\ell\eta\dot{V}}{\pi p} = \frac{8\ell\eta}{\pi} \cdot \frac{1}{\text{resistance}}$$

$$r = 0.283 \text{ cm.}$$

3. In the human body, blood flow is largely regulated by changes in the radius of certain small blood vessels (arterioles) which have muscle fibers in their walls. When the muscle contracts, the blood vessel narrows and the resistance increases.

In the preceding problem, by what per cent would the radius of the tube have to increase in order to double the blood flow ? (Assume that pressure, length, and viscosity are unchanged).

Answer:

$$r^4 = \frac{8\ell\eta\dot{V}}{\pi p} = \frac{8(100)(0.04)\,\frac{10{,}000}{60}}{(3.1416)(1.333)10^5} =$$

$$= \frac{\frac{32}{6} \cdot 10^3}{4.1888 \cdot 10^5} = 1.273 \cdot 10^{-2} = 127.3 \cdot 10^{-4} \text{cm}^4$$

$$r \doteq \sqrt[4]{128 \cdot 10^{-1}} = 3.36 \cdot 10^{-1} = -.336 \text{ cm.}$$

Increased radius 0.336 cm.

Original radius 0.283 cm.

Increase 0.053

% increase = 100(0.053/0.283) = 18.7%

Thus an increase in the radius of less than 20% causes an increase of 100% in the flow!

****

FACILITATION AND OCCLUSION IN MOTONEURON POOLS

Contributor: James Mortimer

****

Mathematics: cardinality and elementary set operations (Math.0)

Abstract: An example of the application of cardinality and elementary set operations to the description of facilitation and occlusion in motoneuron pools.

The stretch reflex of skeletal muscle in man provides for the maintenance of erect posture by causing the contraction of muscle fibers in response to extension of the muscle. Extension causes nerve impulses to be generated in the stretch receptors and to be sent back along dorsal root fibers into the spinal cord, where these dorsal root fibers synapse onto motoneurons serving the same and other muscles. If a large enough number of excitatory fibers synapsing onto the motoneuron are excited simultaneously, its threshold is exceeded and the motoneuron emits impulses. These impulses, in turn, serve to stimulate muscle contraction, thereby decreasing the electrical activity of the stretch receptors in the muscle. This negative feedback system helps the organism maintain erect posture.

Each dorsal root fiber branches and synapses onto many motoneurons (divergence), and every motoneuron is excited by a large number of different dorsal root fibers (convergence). Because of the relatively small influence of each synapse, it is only through joint excitation of many dorsal root fibers that the threshold is exceeded and the motoneuron fires. The set of motoneurons serving a single muscle is said to be the "motoneuron pool" of that muscle.

Consider the following experiment which is performed to investigate the stretch reflex.

The dorsal root is cut and separated into two sections which can be individually, electrically stimulated. (See Figure 1.) The compound action potential resulting from the simple algebraic summation of all impulses generated in the motoneuron pool is recorded by means of a macroelectrode.

Let A be the set of all motoneurons affected by a given stimulus delivered to bundle a of dorsal root fibers.

Let A' be the set of motoneurons which fire after bundle a is stimulated.

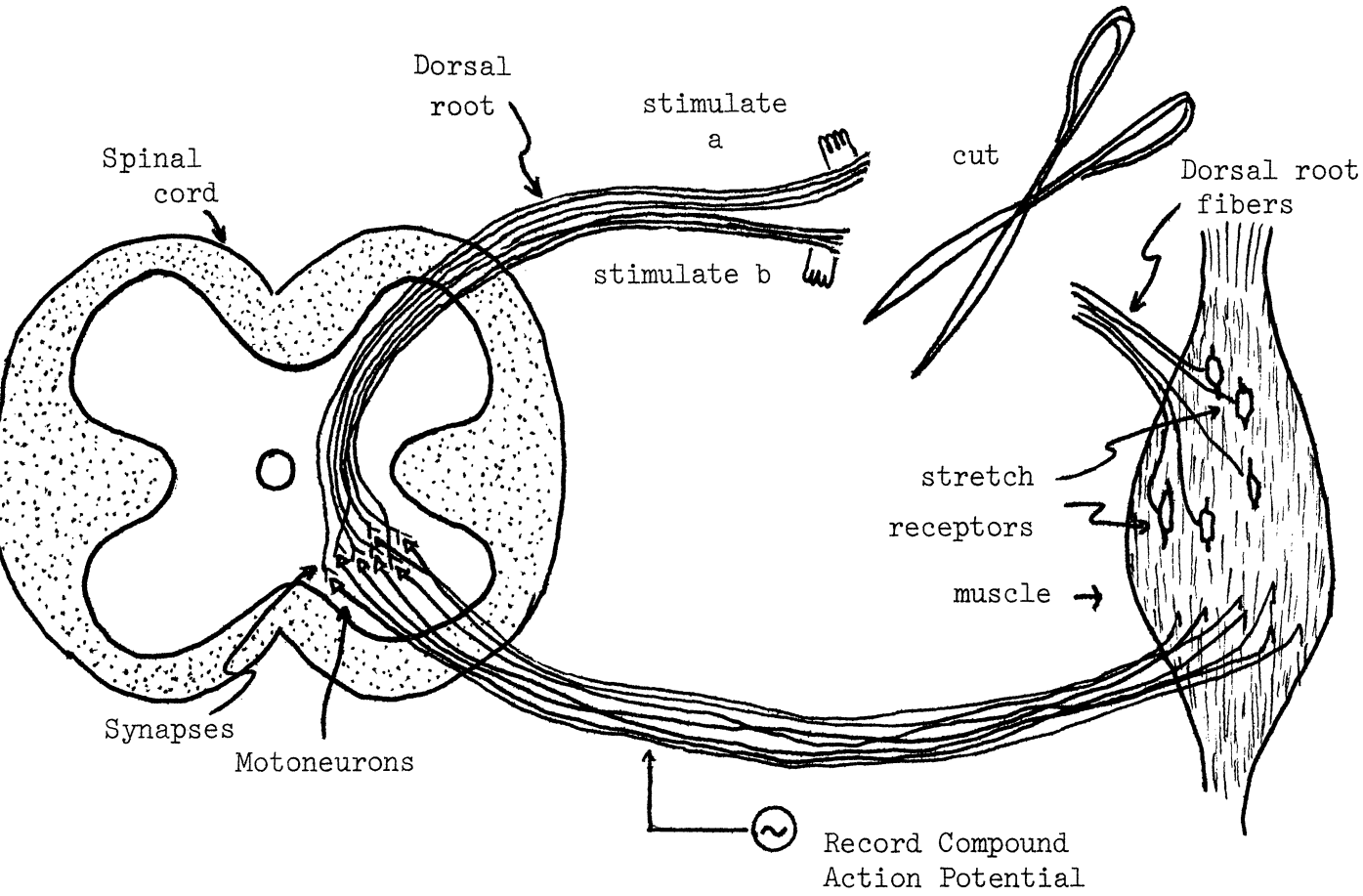


Figure 1

Because of divergence, not all motoneurons which have some synapses with fibers of bundle a will receive a sufficient number of impulses to fire. Therefore, $A' \subset A$.

Let B be the set of all motoneurons affected by a stimulus delivered to bundle b, and let B' be defined in the same way as A'. Thus, $B' \subset B$.

Suppose that a stimulus is delivered to a and the amplitude of the compound action potential generated is recorded, and that the same is done for a stimulus delivered to b. It is known that the amplitude of the compound action potential is directly proportional to the number of motoneurons fired. Thus, for example, if x_a is the amplitude of the compound action potential resulting from stimulation of a, then $x_a = k_1 K(A')$, where k_1 is a positive constant reflecting the thresholds of the motoneurons involved and the

amount of convergence and divergence, and K(A') is the cardinality or number of elements in A'.

[More formally the cardinality of a set can be defined recursively by:

1. $K(\emptyset) = 0$, where $\emptyset$ is the null set.
2. If j is a single element and $j \notin Y$, then $K(Y \cup \{j\}) = K(Y) + 1$.]

In like manner, the amplitude of the compound action potential resulting from stimulation of bundle b, x_b, is given by

$$x_b = k_1 K(B') \ .$$

Because fibers from a and b synapse onto some of the same motoneurons, the compound action potential resulting from stimulation of both a and b is not equal to the simple algebraic summation of the action potentials resulting from stimulation of a and b separately. It is also apparent that stimulation of a and b together will fire some neurons in the intersection of A and B, which were not fired by either a or b stimulation alone. From Figure 2, it can be seen that the set of neurons not fired by a or b alone but fired by a and b together is some subset of the shaded set,

$$((A \cap B) - [(A' \cup B') \cap (A \cap B)]),$$

where

$$X - Y = \{ x \mid x \in X \wedge x \notin Y\}$$

denotes the complement of Y with respect to X.

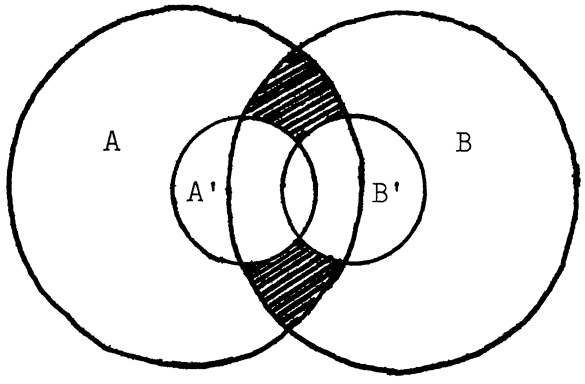


Figure 2

The cardinality of this subset can be written in the form

$$k_2K((A \cap B) - [(A' \cup B') \cap (A \cap B)]),$$

where k_2 depends upon a and b and $0 \leq k_2 \leq 1$.

If $x_{a \cap b}$ denotes the amplitude of the compound action potential resulting from stimulation of both a and b, then

$$x_{a \cap b} = k_1[K(A' \cup B') + k_2K[(A \cap B) - ((A' \cup B') \cap (A \cap B))])] .$$

But from the definition of cardinality and from elementary set operations

$$K(A' \cup B') = K(A') + K(B') - K(A' \cap B')$$

so that

$$x_{a \cap b} = k_1(K(A') + K(B')) - k_1K(A' \cap B') + k_1k_2K((A \cap B) - [(A' \cup B') \cap (A \cap B)]) .$$

In the above expression the first term represents the expected amplitude if both a and b are stimulated and the intersection of A and B is the null set. The resultant amplitude is simply the algebraic summation of the compound action potential amplitudes, x_a and x_b: $x_{a \cap b} = x_a + x_b$.

The second term is the decrement resulting from the fact that some neurons fired by a are also in the set fired by b. This reduction in amplitude of the compound action potential is referred to as occlusion.

The increment in amplitude resulting from convergence of a and b fibers is attributed to mutual facilitation in cases where neither a nor b alone had the capacity to fire these motoneurons but a and b together could fire them. This is represented in the third term.

Under natural conditions, both occlusion and facilitation occur in the motoneuron pools of muscles which act together in coordinated movements.

****

GRAPHICAL ANALYSIS OF SOME ELECTROENCEPHALOGRAPHIC DATA

Contributor: Hebrew University Report, James Mortimer

****

Mathematics: analytical geometry (Math. 0)

Abstract: A graphical analysis is used to interpret the results of an EEG experiment.

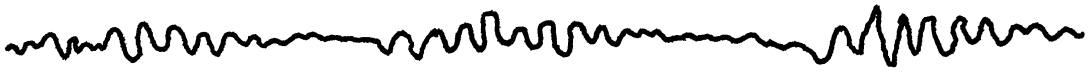
It is known that a deficiency of oxygen and an excess of carbon dioxide influences the EEG (electroencephalogram), which is the electrical potential obtained from electrodes attached to the surface of the head. This potential (EEG) is an indicator of the overall activity of the cortex.

The following three EEG traces are typical of recordings one might obtain (1) during sleep, (2) during alert wakefulness, and (3) during drowsiness.

(1) During sleep (synchronized):

(2) During alert wakefulness (desynchronized):

(3) During drowsiness (intermediate):



During sleep the electrical potential is large in amplitude and low in frequency. It has been hypothesized that this type of record is caused by the synchronization of sinusoidal electrical potential changes in individual cortical neurons. During alert wakefulness the pattern is broken due to the desynchronization of the electrical potentials of individual neurons. Because of the cancellation of unsynchronized potentials a rather flat record is obtained. During drowsiness an alternation of the synchronized and desynchronized waveforms is apparent.

It was found that the composition of inspired air affected the EEG of a sleeping cat; it could change from (1) synchronized to (2) desynchronized or (3) intermediate. Research was carried out to determine which was the influencing factor: the low concentration of oxygen or the high concentration of carbon dioxide.

These were the results:

AIR MIXTURE (partial pressure of the gas in mm. of mercury)		
O_2	CO_2	E.E.G.
84	15	synchronized
120	20	intermediate
140	18	intermediate
155	14	synchronized
100	25	desynchronized
140	19	intermediate
90	27	desynchronized
145	22	desynchronized
140	16	synchronized
94	15	synchronized
85	18	intermediate
105	22	desynchronized
120	11	synchronized
105	20	intermediate
120	29	desynchronized
110	18	intermediate
89	12	synchronized

Draw a graph in which the x-axis represents the concentration of carbon dioxide and the y-axis the oxygen concentration. Label a point "d" if the EEG was desynchronized, "i" if it was intermediate, and "s" if it was synchronized.

If the EEG was synchronized, it was interpreted that the cat continued sleeping undisturbed. If it became desynchronized or intermediate, it was interpreted that the cat had become disturbed and awakened by a change in its breathing. Using the table, decide for yourself which affects the EEG, the oxygen or the carbon dioxide (in the range of concentration with which we are dealing.)

SOLUTION:

It is dependent on the concentration of carbon dioxide:

from 11 to 16 --- synchronized

from 18 to 20 --- intermediate

from 22 to 29 --- desynchronized

****

USING MATRICES TO AID IN DIAGNOSING THE CONDITION OF A PATIENT

Contributor: Richard F. Baum*

****

Mathematics: elementary properties of matrices

Abstract: The possible reactions of a patient to various tests are represented in matrix notation.

*Based upon: Bellman, R. Adaptive Control Processes: A Guided Tour. The RAND Corporation, 1961, 119-120.

Consider the following situation. Suppose a patient is known to have one and only one of N disorders, and we wish to find out which disorder he has. We have M tests we can perform on him by administering various drugs or changing his environmental conditions. We can observe his reaction to these tests by noting changes in a number of his physiological variables, such as body temperature, blood pressure, etc. Of course, we know the initial value of these variables before testing. Assume that we also know the result we would get for each test if the patient had a given disorder. We would like to set up a table or an array of numbers to aid diagnoses.

As a particular example of the above, suppose we are given a patient with normal temperature, low blood pressure, and acidic blood. We also know that this patient has one and only one of three disorders: diabetes, pulmonary insufficiency, or the heart malfunction Myocardial Infarct. Suppose for some reason we have only two tests we can perform: giving the patient 100% oxygen, or giving the patient glucose, and subsequently observing whether the patient's temperature, blood pressure, and blood acidity increases, remains the same, or decreases. We can associate a vector (m_1,m_2,m_3) with our patient, where m_1, m_2 and m_3 represent the patient's body temperature, blood pressure and blood acidity, respectively.

Due to the nature of our tests, we can simplify our discussion by letting:

m_1, m_2, or m_3	equal -1 if a decrease in temperature, blood pressure, or blood acidity, respectively, is observed.
m_1, m_2, or m_3	equal 0 if no change in temperature, blood pressure, or blood acidity, respectively, is observed.
m_1, m_2, or m_3	equal 1 if an increase in temperature, blood pressure, or blood acidity, respectively, is observed.

The possible initial states for our patient are X_1, X_2, and X_3, where:

X_1	denotes the patient has diabetes, normal temperature, low blood pressure, and acidic blood.

X_2 denotes the patient has pulmonary insufficiency, normal temperature, low blood pressure, and acidic blood.

X_3 denotes the patient has the heart malfunction, normal temperature, low blood pressure, and acidic blood.

The possible "inputs" are I_1 and I_2 for two tests, where:

I_1 denotes the input of 100% oxygen.

I_2 denotes the input of glucose.

Finally, the possible responses, or 'outputs' of our patient are (m_1,m_2,m_3), where m_1, m_2, and m_3 take values -1, 0, or 1. For example, if we give our patient 100% oxygen to breathe, and if he has diabetes or the heart malfunction, his temperature will remain the same, his blood pressure will increase, and his blood acidity will decrease, giving an output of (0,1,-1). If instead he has pulmonary insufficiency, his temperature and blood pressure will decrease, and his blood acidity will increase, giving an output of (-1,-1,1). Similarly, if we inject glucose into our patient, and if the patient has pulmonary insufficiency or the heart malfunction, the response is (0,0,0); if he has diabetes, the output is (-1,-1,-1). To summarize the above observations, we can set up a table denoting the output of the patient for a given state of the patient, as follows:

	Present State		
Present Input	X_1	X_2	X_3
I_1	(0,1,-1)	(-1,-1,1)	(0,1,-1)
I_2	(-1,-1,-1)	(0,0,0)	(0,0,0)

This table provides us with a quick indication of the patient's state or condition. Suppose we use input I_1, 100% oxygen. If the result is (-1,-1,1), we know the patient is in state X_2. If the result is (0,1,-1), then the patient is in state X_1 or X_3; his reaction to I_2, glucose, will tell us in which state he is (assuming we apply this test after the effects of test 1 have worn off, so that the above table is applicable.) Similarly, if we use I_2 first, by use of this table we can arrive at the state of our patient using one other test.

We can abbreviate the above table by writing the following matrix:

$$\begin{pmatrix} (0,1,-1) & (-1,-1,1) & (0,1,-1) \\ (-1,-1,-1) & (0,0,0) & (0,0,0) \end{pmatrix}$$

where the (i,j) entry represents the output of a patient in state X_j for an input of I_i. Here, the elements of our matrix are three-dimensional vectors.

We can obviously generalize this example to M inputs, I_1, I_2, $\ldots I_M$; N states X_1, X_2,$\ldots X_N$; and v possible outputs, O_1, O_2,$\ldots O_v$; where I_i, X_j, O_k are, in general, vectors. Assume, as above, we can construct the following "multiplication table":

	Present State		
Present Input	X_1	X_2	X_N
I_1	O_{11}	O_{12}	O_{1N}
I_2	O_{21}	O_{22}	O_{2N}
.	.	.	.
.	.	.	.
I_M	O_{M1}	O_{M2}	O_{MN}

or matrix Q,

$$Q = \begin{pmatrix} O_{11} & O_{12} & O_{1N} \\ O_{21} & O_{22} & O_{2N} \\ . & . & . \\ . & . & . \\ O_{M1} & O_{M2} & O_{MN} \end{pmatrix}$$

where O_{ij} is the output for input I_i if the patient is in state X_j.

If the X_i are sufficiently different states, such as diabetes, flat-footedness, and halitosis, then we can expect our tests or inputs I_i to indicate only if we are, or are not, in state X_i. The other outputs O_{ij}, $i \neq j$, will be neutral, i.e., they will show no

change in the patient's condition. Let 0, i.e., the zero vector, denote such a neutral response, and assume we have as many tests as there are disorders or states, i.e., M = N, thus making Q a square matrix. Then the above situation is equivalent to saying that the output matrix Q is a diagonal matrix.

****

THE RATE OF COOLING OF A BODY

Contributor: Hebrew University Report

****

Mathematics: integration (Math. 1)

Abstract: The temperature of a cooling body as a function of time is obtained by integration.

At this moment the temperature of a certain body is 60° above room temperature and 20 minutes ago it was 70° above room temperature.

The rate of cooling is proportional to the difference between the temperature of the body and the room temperature.

What will the temperature be in another 15 minutes ? Another two hours ? When will the temperature be 10° above room temperature ?

Solution:

$$\frac{dT}{dt} = -k(T - T_r)$$

T = temperature of the body

T_r = room temperature

k = constant

t = time in minutes

T_o = initial temperature ($T = T_o$ when $t = 0$)

$$\frac{dT}{dt} = -k(T - T_r)$$

$$\frac{dT}{T - T_r} = -k \cdot dt$$

$$\int_{T_o}^{T} \frac{dT}{T - T_r} = -\int_{0}^{t} k \cdot dt$$

$$\ell n \frac{T - T_r}{T_o - T_r} = -k\,t; \quad T = (T_o - T_r)e^{-k\,t} + T_r$$

$$\text{or} \quad T = 60\, e^{-k\,t} + T_r$$

By replacing the given data in the last equation, we can find that $k = 0.00775$. Likewise the rest of the results may be calculated. (For instance: after 15 minutes the temperature difference will be 53.7 degrees centigrade.)

****

THE MAXIMUM VELOCITY OF THE FLOW OF AIR THROUGH THE RESPIRATORY SYSTEM WHILE COUGHING

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The radius of the trachea at which the velocity of the flow of air is maximum is obtained by differentiation.

X-ray examination shows that when one coughs, the diameters of the trachea (windpipe) and/or bronchi shrink. It has been assumed that the pressure which serves to empty the lungs during strong exhalations, such as a cough, has an undesirable (on precursory consideration) side-effect: the pressure also compresses the trachea and bronchi impeding exhalation of mucus, foreign bodies and respired air. By making the simplest approximation for the character of air flow in the trachea and bronchi, one can show that this compression may indeed be beneficial.

One of the simplest assumptions to make concerning the effect of pressure on respiratory constriction is that the change in circumference (which is proportional to the change in radius of trachea and/or bronchi tubes)is a linear function of the differential pressure on the tube. This is to say

$$r = r(P)$$

where

P = the differential pressure on the respiratory system (the excess above atmospheric pressure)

r = the specific trachea or bronchial tube radius at any P

r_o = the radius when there is no differential pressure on the tube ($P = 0$)

a = the constant of linear proportionality

then

$$(r_o - r) = aP$$

Experimentation has shown that this relationship is a close approximation only when P lies between 0 and $r_o/2a$. When P is greater than this and the radius of the tube is less than half its value at rest, the resistance of the tube to compression becomes greater. This is the reason we do not suffocate when we cough.

The velocity of air, $V(r)$, through a tube of radius r is given by the air flow rate divided by the cross-sectional area of the tube, i.e.

$$V(r) = \frac{\text{flow rate}}{\pi r^2}$$

Poiseuille has shown for ideal fluids (which air approximates) flowing in smooth circular tubes, the resistance to flow through such a tube is approximately proportional to the reciprocal of the fourth power of the radius, i.e.

$$R = k/r^4$$

where

R = resistance
r = radius of tube
k = constant of proportionality

In this instance resistance to flow has the same conceptual function as resistance in Ohm's law in current flow, i.e.,

$$\text{rate of current flow} = \frac{\text{electrical potential}}{R} ,$$

and in this case

$$\text{rate of air flow} = \frac{\text{pressure driving force}}{R} .$$

Now since

$$\text{rate of air flow} = V(r) \times \pi r^2$$

and

$$\text{rate of air flow} = \frac{P}{R} = \frac{Pr^4}{k} = \frac{(r_o - r)r^4}{ak} ,$$

then the velocity in the tube is given by

$$V(r) = \frac{r^4(r_o - r)}{akr^2\pi} = \frac{r^2(r_o - r)}{\pi ak} .$$

QUESTION:

What tube radius will give maximum air velocity, i.e., the most effective condition for cleaning the lungs?

ANSWER:

$$V'(r) = \frac{2r_o r - 3r^2}{\pi ak} = \frac{3r}{\pi ak}[(2/3)(r_o - r)]$$

$$V''(r) = \frac{2r_o - 6r}{\pi ak}$$

When $V'(r) = 0$, $r = (2/3)r_o$ and $V''(r)$ is negative. Therefore $V(r)$ is a maximum when the tube radius is two-thirds of the value at rest ($P = 0$).

Note: In order for $r = (2/3)r_o$, the pressure differential must increase to $r_o/3a$. Since this is less than $r_o/2a$, the original simplifying assumption of the linear relationship between tube radius and differential pressure is justified.

****

THE FORM OF THE HEARTBEAT IN THE AORTA

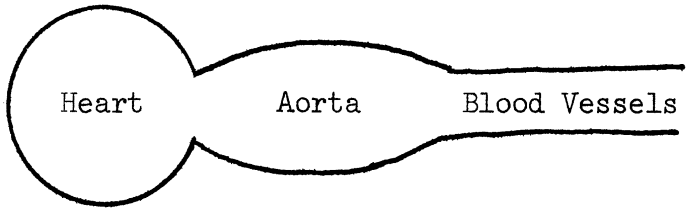
Contributor: Hebrew University Report

****

Mathematics: differential equations with separable variables (Math. 2), integrating factors

Abstract: The flow of blood in the aorta during diastole and systole is obtained by the solution of differential equations.

We consider the flow of blood in the aorta during the systole and the diastole phases of the heartbeat (systole is the period of contraction of the heart, diastole is the period of relaxation).



During diastole the volume V of the aorta decreases as blood flows away from it into the blood vessels. This flow is described by Poiseuille's law which states that the rate of change of the volume is proportional to the pressure P:

$$V'(t) = -\frac{1}{W} P(t). \tag{1}$$

This relation is analogous to Ohm's law and W corresponds to the resistance. While W is independent of time, it does depend on the viscosity η of the liquid, the length ℓ, and the radius r of the tube. In fact, it is given by the formula

$$W = \frac{8\ell\eta}{\pi r^4}.$$

We assume that P is proportional to V, i.e., there exists a constant C such that

$$P = CV. \tag{2}$$

Let us find the blood pressure in the aorta during diastole. Combining (1) and (2) we have

$$P'(t) = CV'(t) = -\frac{C}{W} P(t). \tag{3}$$

Consequently, letting $P_o = P(0)$--assuming that the diastole phase begins at t = 0--we obtain

$$\ln P(t) - \ln P(0) = \int_0^t \frac{P'(s)}{P(s)}\, ds$$

$$= -\frac{C}{W} \int_0^t ds = -\frac{C}{W} t.$$

Thus,

$$P(t) = P_o e^{-(C/W)t}. \tag{4}$$

Now let us consider the flow of blood in the aorta during systole. The blood is pumped into the aorta by the heart at the same time that it flows out into the blood vessels. This inward flow (rate of change of volume) can be represented by a sinusoidal function; assuming systole occurs during the time interval [0, T], the flow at time t, $0 \leqq t \leqq T$, is

$$A \sin \frac{\pi}{T} t = A \sin Bt.$$

We are letting $B = \pi/T$ and A represent the maximal flow which occurs during the middle of systole. Taking into account the outflow (see equation (1)) we obtain (see also (2)):

$$\frac{P'(t)}{C} = V'(t) = A \sin Bt - \frac{P(t)}{W}. \tag{5}$$

Equivalently,

$$P'(t) + \frac{C}{W} P(t) = CA \sin Bt. \tag{6}$$

Multiplying both sides by the integrating factor, $e^{(C/W)t}$, we obtain

$$e^{(C/W)t} P'(t) + \frac{C}{W} e^{(C/W)t} P(t) = CA\, e^{(C/W)t} \sin Bt.$$

Since the left-hand side is the derivative of $P(t)\, e^{(C/W)t}$, we have

$$P(t)\, e^{(C/W)t} - P_o = \int_0^t CA\, e^{(C/W)s} \sin Bs\, ds. \tag{7}$$

Integrating by parts, we get

$$\int_0^t \sin Bs \cdot e^{(C/W)s}\, ds$$

$$= \frac{W}{C}\, e^{(C/W)t} \cdot \sin Bt - \frac{WB}{C} \int_0^t e^{(C/W)s} \cos Bs \cdot ds.$$

If we integrate the second integral by parts, we get:

$$\int_0^t e^{(C/W)s} \cdot \cos Bs \cdot ds = \frac{W}{C} \; e^{(C/W)t} \cos Bt \Big|_0^t + \frac{W}{C} B \int_0^t e^{(C/W)s} \sin Bs \cdot ds.$$

Thus,

$$\int \sin Bs \cdot e^{(C/W)s} dt = \frac{W}{C} \; e^{(C/W)t} \sin Bt - \frac{WB}{C} \left[\frac{W}{C} \; e^{(C/W)t} \cos Bt - \frac{W}{C} + \frac{WB}{C} \int \sin Bs \cdot e^{(C/W)s} dt \right].$$

Solving for the integral, we get

$$\int \sin Bs \cdot e^{(C/W)s} ds = \frac{W}{C^2 + W^2B^2} \left[Ce^{(C/W)t} \sin Bt - WB \; e^{(C/W)t} \cos Bt + WB \right].$$

Substituting the above expression into (7) and solving for P(t), we obtain:

$$P(t) = P_o \; e^{-(C/W)t} + \frac{CAW}{C^2 + W^2B^2} \left[C \sin Bt - WB \cos Bt + WB \; e^{-(C/W)t} \right].$$

where P(t) is the pressure as a function of the time during the systole.

****

BLOOD FLOW IN AN ARTERIOLE

Contributor: Hebrew University Report

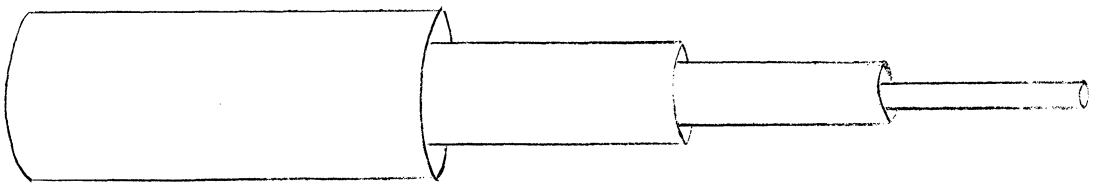
****

Mathematics: integration (Math. 1)

Abstract: The total flow of blood in an arteriole is computed from summation and integration.

If the area of the cross-section of an arteriole is A and the velocity of the blood in the arteriole is v, then the flow of blood is given by

$$F = v \cdot A \tag{1}$$



The flow in the arteriole is laminar. Due to the viscosity of the blood, the layer closest to the arteriole wall will cling to the wall and its velocity will be zero. The velocity will increase with the distance from the wall and attain a maximum in the central lamina. We may think of the flow as being layer on layer of concentric tubes sliding relative to each other with the central tube having the greatest velocity and the outer tube at rest. We consider the velocity in each layer to be constant, and from Pouiseville's Law we can derive the velocity of the blood in a given layer.

$$v(r) = \frac{P}{4\eta\ell} (R^2 - r^2) \tag{2}$$

where

r = distance between the layer and the center of the tube in cm.

R = radius of the tube in cm.

P = pressure difference between the two ends of the tube in $\frac{\text{dyne}}{\text{cm}^2}$

ℓ = length of the tube in cm.

η = viscosity in Poise

The area of the cross-section of the layer r units from the center is the area of the annulus:

$$A(r) = \pi(r + \Delta r)^2 - \pi r^2 = 2\pi r\Delta r + \pi(\Delta r)^2 \qquad (3)$$

Thus the flow in this lamina is

$$F(r) = \frac{P\pi}{2\eta\ell} r(R^2 - r^2)\Delta r + \frac{P\pi}{4\eta\ell} (R^2 - r^2)(\Delta r)^2 \qquad (4)$$

assuming no turbulence.

To find the total flow in the tube we may assume that the width of each layer can be chosen arbitrarily small (in which case we can drop the second term on the right hand side of equation 4) and integrate $F(r)$ from $r = 0$ to $r = R$. But the width of the layers cannot be made smaller than, say, the width of the red blood cells (about 2 microns or 2×10^{-4} cm.) Thus rather than integrating we must add the flows in each lumina. For simplicity we will assume that the width of the lumini are all equal.

Find the speed of flow in an arteriole whose length is one cm and the pressure difference between its ends is $10{,}000 \frac{\text{dyn}}{\text{cm}^2}$ (7.5 mm mercury), assuming its diameter to be:

i) 100 microns

ii) 40 microns

iii) 20 microns

η, the viscosity of the blood, is 2.5 poise.

Find the flow (the speed of flow - in other words, the volume per unit time) by both methods, by integration and by addition of flow through cylinders 5 microns thick.

Solution by integration:

$$F = \int_0^R \frac{P\pi}{2\eta\ell} r(R^2 - r^2)\, dr = \frac{P\pi R^4}{8\eta\ell}$$

Solution by Summation:

$$F(r) = \frac{P\pi}{2\eta\ell}[r(R^2 - r^2)\Delta r + \tfrac{1}{2}(R^2 - r^2)(\Delta r)^2]$$

Since each lamina width is Δr, the values of r will be integral multiples of Δr and the flow in the kth lamina from the center (where $r = k\Delta r$) will be

$$F(k) = \frac{P\pi}{2\eta\ell}[(k\Delta r)(R^2 - k^2(\Delta r)^2)\Delta r + \tfrac{1}{2}(R^2 - k^2(\Delta r)^2)(\Delta r)^2].$$

R is some fixed multiple of the width of the laminas, say,

$$R = n\Delta r$$

Thus replacing R by $n\Delta r$

$$F(k) = \frac{P\pi}{2\eta\ell}(\Delta r)^4[n^2k - k^3 + \tfrac{1}{2}n^2 - \tfrac{1}{2}k^2]$$

The total flow

$$F = \frac{P\pi}{2\eta\ell}(\Delta r)^4 \sum_{k=1}^{n}[n^2k - k^3 + \tfrac{1}{2}n^2 - \tfrac{1}{2}k^2]$$

Given that

$$\sum_{k=1}^{n} 1 = n$$

$$\sum_{k=1}^{n} k = \frac{n(n+1)}{2}$$

$$\sum_{k=1}^{n} k^2 = \frac{n}{6}(n+1)(2n+1)$$

$$\sum_{k=1}^{n} k^3 = \frac{n^2(n+1)^2}{4}$$

Show that

$$F = \frac{P\pi}{8\eta\ell}(\Delta r)^4\left[n^4 + \frac{4}{3}n^3 - 2n^2 - \frac{1}{3}n\right]$$

Since $n = \frac{R}{\Delta r}$ show that

$$F = \frac{P\pi}{8\eta\ell}\left[R^4 + \frac{4}{3}R^3\Delta r - 2R^2(\Delta r)^2 - \frac{1}{3}R(\Delta r)^3\right]$$

Note that the first term on the right hand side is the same as the result by integration.

****

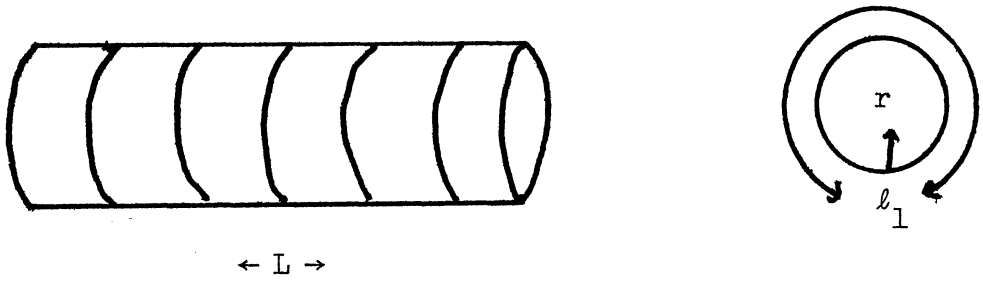
SOME PROBLEMS IN VISCO-ELASTICITY

Contributor: Julia Apter

****

Mathematics: ordinary differential equations (Math. 4)

Abstract: Several illustrative examples of visco-elasticity are presented with references.



In many <u>in vivo</u> situations the aorta may be considered as a tube made up of a layer of many circumferentially arranged springs, each of rest length, ℓ_{1_o}, which is the circumference of the unstretched artery. Here we neglect the thickness of the wall in comparison with the diameter of the lumen. Derive an expression for the pressure in an aorta of length L, stretched circumferentially, in terms of the force constant a of the springs and their length ℓ_1. Neglect the change in length L of the artery. (This is reasonable since <u>in situ</u> the aorta stretches circumferentially 16 times more than longitudinally.)

SOLUTION:

The work dW done in increasing the volume of such a tube by an amount dV is

(1) $$dW = PdV \ .$$

Since $\ell_1 = 2\pi r$, the volume V is given by:

(2) $$V = \pi r^2 L = \ell_1^2 \, L/4\pi \ .$$

Differentiating (2), we get:

(3) $$dV = L/2\pi \ (\ell_1 d\ell_1) \ .$$

Another expression for dW can be obtained by considering the work done in increasing the circumference of the tube from $\ell_1 > \ell_{1_o}$ to $\ell_1 + d\ell_1$. This work depends on the number n of springs per unit length of tube and on the amount the springs are stretched past ℓ_{1_o}. The increment in work dW in stretching the springs $d\ell_1$ is given by $Fd\ell_1$. For

a tube L cm. long

$$F = naL(\ell_1 - \ell_{1_o}) \,, \tag{4}$$

where a is the force constant of all springs. Then the work done in going from ℓ_1 to $\ell_1 + d\ell_1$ is

$$dW = Fd\ell_1 \,, \tag{5}$$

or, with (4)

$$dW = naL(\ell_1 - \ell_{1_o})d\ell_1 \,. \tag{6}$$

Equating the right-hand side of (6) to the right-hand side of (1), we get

$$\frac{PL}{2\pi} = naL(\ell_1 - \ell_{1_o})d\ell_1 \,. \tag{7}$$

Solving (7) for P,

$$P = \frac{2\pi na(\ell_1 - \ell_{1_o})}{\ell_1} \,. \tag{8}$$

Other derivations give the pressure in an elastic tube as

$$P = \frac{f}{r} \tag{9}$$

where f is the tangential force per unit length; hence with L = 1

$$f = na(\ell_1 - \ell_{1_o}) \,. \tag{10}$$

By geometry

$$r = \frac{\ell_1}{2\pi} \,; \tag{11}$$

so that if (10) and (11) are substituted into (9), we obtain

$$P = \frac{2\pi na(\ell_1 - \ell_{1_o})}{\ell_1} \,, \tag{12}$$

which is identical to (8) (Apter, 1964).

What is the pressure-volume relation of such a tube? (It has been assumed that a non-linear P-V relation implies non-Hookean behavior. However, the following derivation shows that, even for a tube with walls which obey Hooke's law, the P-V relation is not linear.) From (2),

$$V = \frac{\ell_1^2 L}{4\pi} .$$

When the tube is unstretched, we have

$$V_o = \frac{\ell_{1_o}^2 L}{4\pi} . \tag{13}$$

Solving for ℓ_{1_o} and ℓ_1,

$$\ell_{1_o} = \sqrt{\frac{4\pi V_o}{L}} ; \qquad \ell_1 = \sqrt{\frac{4\pi V}{L}} . \tag{14}$$

Substituting (14) into (12), we obtain

$$P = \frac{2\pi na \left[\sqrt{V} - \sqrt{V_o}\right]}{\sqrt{V}} , \tag{15}$$

which is certainly not a straight-line relation between P and V, even if the force constant a is a constant (Apter, 1966a).

Similarly, find P-r and P-V relations for an elastic spherical shell (like an eye). An elastic spherical shell can be approximated by a number N of springs of rest length $\ell_o = 2\pi r_o$, where r is the radius of the sphere. Curve all springs to form rings and combine them randomly around a common center to form a spherical shell. The density of springs is n per unit length along a circumference of the sphere.

The work dW done in stretching such a shell from circumference $\ell > \ell_o$ to $\ell + d\ell$ will be

$$dW = PdV . \tag{16}$$

The volume V is

$$V = \frac{4\pi r^3}{3} = \frac{\ell_1^3}{6\pi^2} , \tag{17}$$

which can be differentiated to give

$$dV = \frac{1}{2\pi^2} \ell_1^2 d\ell_1 , \tag{18}$$

where $\ell_1 = 2\pi r$.

Substituting (18) into (16), we get

$$dW = \frac{P\ell_1^2}{2\pi^2} d\ell_1 . \tag{19}$$

The work done in stretching one spring is

$$a(\ell_1 - \ell_{1_o}) \, d\ell_1 . \tag{20}$$

To include all springs in the spherical shell, we multiply n by one-half the circumference. Then the work done in stretching all springs is

$$dW = 1/2 \cdot n\ell_1 a(\ell_1 - \ell_{1_o}) \, d\ell_1 . \tag{21}$$

If the right-hand side of (21) is equated to the right-hand side of (19), we can solve for P to get (Apter, 1966b):

$$P = \frac{\pi^2 na(\ell_1 - \ell_{1_o})}{\ell_1} . \tag{22}$$

The pressure-volume relation can be found by solving (17) for ℓ_1:

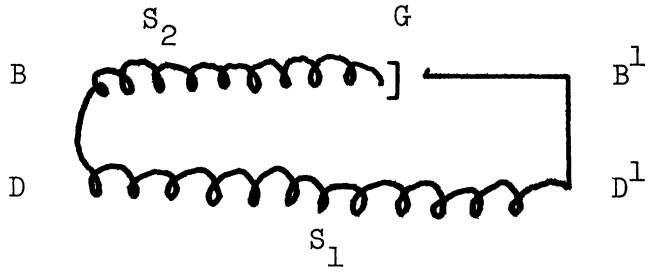
$$\ell_1 = \sqrt[3]{6\pi^2 V} ; \qquad \ell_{1_o} = \sqrt[3]{6\pi^2 V_o} . \tag{23}$$

Substituting (23) into (22), we have:

$$P = \pi^2 na \frac{\sqrt[3]{V} - \sqrt[3]{V_o}}{\sqrt[3]{V}} . \tag{24}$$

Therefore, even if the walls are Hookean, as exemplified by a constant value for the force constant a, the P-V relation is certainly not a straight line.

Both arteries and eyes show stress-relaxation following a step-function increase in circumference. A model which can be used to study this phenomenon is the following combination of springs, S_1 and S_2, and a dashpot, G:



How can the stress-relaxation curve be used to supply the force constants of the two springs and the viscosity of the fluid in dashpot G (Apter, 1964)?

Derive the differential equation of motion of a tube formed by curving B to meet B^1 and D to D^1 and then combining many such rings to make a tube L cm. long (Apter, 1965).

SOLUTION:

$$(25) \qquad L\ell_1 \dot{\ell}_1 = 2\pi \left\{ W(t) - \frac{2\pi[a'(\ell_1 - \ell_{1_o}) + a''(\ell_2 - \ell_{2_o})]}{R\ell_1} \right\}$$

where R is the resistance to outflow, W(t) is the inflow rate, a_1 and a_2 are the force constants of the springs, $a'' = a_2 n$, $a' = a_1 n$, and ℓ_1 and ℓ_2 are the spring lengths.

The strain rate of the dashpot piston $\dot{\ell}_3$ is directly proportional to the deforming force and indirectly proportional to the viscosity g of the fluid in the dashpot. Thus, we have

$$\dot{\ell}_3 = \frac{a''(\ell_2 - \ell_{2_o})}{gn} \tag{26}$$

where $\dot{\ell}_3 > 0$, and

$$\dot{\ell}_3 = \frac{-a'(\ell_1 - \ell_{1_o})}{gn} \tag{27}$$

when $\dot{\ell}_3 < 0$, if $a'' = \infty$ for $\ell_2 < \ell_{2_o}$.

Derive the differential equation of motion of a spherical shell with the same properties. The outflow resistance is R and the inflow rate is W(t) (Apter, 1966c).

$$P = \frac{\pi^2[a'(\ell_1 - \ell_{1_o}) + a''(\ell_2 - \ell_{2_o})]}{\ell_1} . \tag{28}$$

From material balance,

$$\dot{V} = W(t) - Q . \tag{29}$$

From geometry,

$$V = \frac{4\pi r^3}{3} = \frac{\ell_1^3}{6\pi^2} . \tag{30}$$

Differentiating (30) with respect to time we get

$$\dot{V} = \frac{\ell_1^2 \dot{\ell}_1}{2\pi^2} . \tag{31}$$

If outflow Q is laminar against R, then

$$Q = \frac{\pi^2[a'(\ell_1 - \ell_{1_o}) + a''(\ell_2 - \ell_{2_o})]}{R\ell_1} . \tag{32}$$

Substituting (32) and (31) into (29) we get

$$(33) \qquad \ell_1^2 \dot{\ell}_1 = 2\pi^2 \left\{ W(t) - \frac{\pi^2[a'(\ell_1 - \ell_{1_o}) + a''(\ell_2 - \ell_{2_o})]}{R\ell_1} \right\} .$$

In the model it is also apparent that

$$(34) \qquad \ell_1 = \ell_2 + \ell_3 \qquad \text{or} \qquad \dot{\ell}_1 = \dot{\ell}_2 + \dot{\ell}_3 .$$

Equations (33) and (34) are the differential equations of motion of the spherical shell (Apter, 1966c).

---

1. Apter, J. T. "Mathematical Development of a Physical Model of Some Visco-elastic Properties of the Aorta," Bulletin of Mathematical Biophysics, XXVI (1964), 367-388.

2. Apter, J. T. "An Analysis of Aortic Pressure Curves Taking into Account Visco-elastic Properties of the Aorta and Variations in Peripheral Resistance," Bulletin of Mathematical Biophysics, XXVII (1965), 27-52.

3. Apter, J. T., Rabinowitz, M., and Cummings, D. "Correlation of Visco-elastic Properties of Large Arteries with Microscopic Structure," Circulation Research, XIX (1966a), 104-121.

4. Apter, J. T. "A Visco-elastic Shell Model for the Eye," Biophysics Journal, VI (1966b), 31. (Abstract)

5. Apter, J. T. "Computer Solution of Non-linear Differential Equations of Motion of Ocular Walls," Proceedings of the 19th Annual Conference of Engineering Medicine and Biology (San Fransicso, 1966c).

****

VIBRATIONS OF A TAUT WIRE

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The effects of changes in wire diameter, length, density, and tension on the frequency of vibrations are discovered by finding partial derivatives.

The concepts of natural frequency are pertinent to such subjects as sound production and perception by animals, resonant frequencies of plant and animal tissue perturbed by mechanical vibrations, etc. Parameters of the one dimensional case which may be applicable in voice box control and stridulations by insects, can be illustrated by vibrations of a taut wire. The frequency of such vibrations, ω, depends, upon:

b = wire diameter
L = wire length
ρ = wire density
τ = tension (force) holding the wire taut.

Thus ω is a function of four variables, $\omega = f(b, L, \rho, \tau)$. This explicit relationship is given by

$$\omega = \frac{1}{bL}\sqrt{\tau/\pi\rho}$$

If we keep all variables except one constant, then ω can be alternately thought of as four different functions of one variable, i.e., $\omega = \alpha(b)$ or $\omega = \beta(L)$, or $\omega = \gamma(\rho)$ or $\omega = \delta(\tau)$.

QUESTION:

What would be the effect of a change in each variable on the frequency of vibrations when the other variables are held constant?

ANSWER:

$$\alpha'(b) = -\frac{1}{b^2}\left(\frac{1}{L}\sqrt{\tau/\pi\rho}\right) = \text{constant} \times (b)^{-2}$$

$$\beta'(L) = -\frac{1}{L^2}\left(\frac{1}{b}\sqrt{\tau/\pi\rho}\right) = \text{constant} \times (L)^{-2}$$

$$\gamma'(\rho) = -\frac{1}{2}(\rho)^{-3/2}\left(\frac{1}{bL}\sqrt{\tau/\pi}\right) = \text{constant} \times (\rho)^{-3/2}$$

$$\delta'(\tau) = +\frac{1}{2}(\tau)^{-1/2}\left(\frac{1}{bL}\sqrt{1/\pi\rho}\right) = \text{constant} \times (\tau)^{-1/2}$$

****

MUSCLE TENSION AS A FUNCTION OF THE THE TIME OF CONTRACTION

Contributor: Hebrew University Report

****

Mathematics: differential equation solution with integrating factors (Math. 4)

Abstract: The muscle tension as a function of the time of contraction is obtained by the solution of a simple differential equation.

A simplified model of a muscle divides the muscle into two parts. One part of the muscle contracts with force (a biochemical process of molecular binding takes place, forcing the muscle to shrink) and the other part stretches according to the laws of elasticity.

In reality these parts of the muscle are mixed both in position and in operation. Sometimes all of the muscle contracts and the limb moves at constant tension (isotonic contraction), and sometimes the tension in the muscle increases without motion of the limb (isometric contraction).

In an isometric contraction we will assume that the contractible part shrinks but the elastic part is extended so that there is no change in the position of the limb.

The force that the muscle must exert is thus the sum of the two forces which produce the extension and the contraction. The first, as we noted above, follows the laws of elasticity, that is, if ℓ is the length of the extension and a is a proportionality constant,

$$F_1 = a \cdot \ell .$$

The second force is the force of friction. This friction is of the viscous type since the parts of the muscle are either liquid or covered with cell fluid. Viscous friction is proportional to the rate of contraction, the coefficient of viscosity and the area of the surface of contact. Since here the last two factors are constant, we may write

$$F_2 = b \frac{d\ell}{dt}$$

where

F_2 = the force resisting the friction,
b = a constant, and
$\frac{d\ell}{dt}$ = the change in distance per time.

The total force which the muscle must expend against elasticity and viscosity is

$$F = F_1 + F_2 = a\ell + b \frac{d\ell}{dt} .$$

EXERCISE:

1. Find the dependence of the muscular tension on the time of contraction.

SOLUTION:

(1) $$F = a\ell + b\frac{d\ell}{dt}$$

$$\frac{d\ell}{dt} + \frac{a}{b}\ell = \frac{F}{b} .$$

An obvious integrating factor is $e^{\frac{a}{b}t}$, since

$$\frac{d(\ell e^{\frac{a}{b}t})}{dt} = \frac{F}{b} e^{\frac{a}{b}t} .$$

Therefore, one solution to (1) is

(2) $$\ell e^{\frac{a}{b}t} = \frac{F}{a} e^{\frac{a}{b}t} + C$$

where C is the constant of integration. If at $t = 0$, $\ell = 0$; then

$$0 = \frac{F}{a} + C .$$

Therefore,

$$\ell = \frac{F}{a}\left(1 - e^{-\frac{a}{b}t}\right)$$

or

(3) $$a\ell = F\left(1 - e^{-\frac{a}{b}t}\right)$$

We see that the muscle tension is a function of the time of contraction.

When we excite a muscle, the amount of time in which it contracts - exerts a force of contraction - is limited, around 0.1 - 0.01 seconds. As soon as the force of contraction stops, the elastic forces take over,

relaxing and re-extending the contractible muscles. (Also when re-extending the muscles the viscous friction is a factor. The decrease in friction is similar in nature to the increase.)

By repeated excitations the time of contraction may be prolonged (tetanic contraction). And as we can see from the equation, in this case where we prolong the time of contraction by repeated, tetanic, excitations, there will be an increase in the muscular tension.

A contraction due to a single excitation is known as a twitch. Usually the body does not use contractions of this type to move muscles (except, possibly, the eyelid muscles when blinking); instead it uses repeated excitations, so that tetanic contractions are formed and the muscle tension is much greater (for the same amount of force applied - as stated, the muscle always imparts the same force F).

Find, for instance, how many times greater is the tension when we increase the time of contraction by 4.

SOLUTION:

$$a\ell(t) = F\left(1 - e^{-\frac{a}{b}t}\right)$$

$$a\ell(4t) = F\left(1 - e^{-\frac{a}{b}4t}\right)$$

$$\frac{a\ell(4t)}{a\ell(t)} = \frac{1 - e^{-\frac{a}{b}4t}}{1 - e^{-\frac{a}{b}t}}$$

$$= \frac{\left(1 - e^{-\frac{a}{b}t}\right)\left(1 + e^{-\frac{a}{b}t} + e^{-\frac{a}{b}2t} + e^{-\frac{a}{b}3t}\right)}{\left(1 - e^{-\frac{a}{b}t}\right)}$$

$$= 1 + e^{-\frac{a}{b}t} + e^{-\frac{a}{b}2t} + e^{-\frac{a}{b}3t}$$

If the ratio a/b is close to zero, it can be seen that muscles with a normal action time of 0.0075 seconds, when they are prolonged to 0.03 seconds, will provide almost four times as much tension.

****

FEEDBACK REGULATION OF THE CONCENTRATION OF THYROID HORMONE IN THE BLOOD

Contributor: James Mortimer*

****

Mathematics: linear differential equations (Math. 4)

Abstract: A system of linear differential equations is presented and solved to yield the concentrations of TSH and thyroid hormone in the blood as functions of time.

*Based upon: Roston, S. "Mathematical Representation of Some Endocrinological Systems," Bulletin of Mathematical Biophysics, XXI (1959), 271-282.

Regulation of the concentration of thyroid hormone in the blood is essential to the normal functioning of the human organism. The homeostatic mechanism providing this regulation consists of a negative feedback system in which the release of thyroid hormone is stimulated by the release of TSH (thyroid stimulating hormone) from the anterior pituitary gland and the release of thyroid hormone in turn inhibits the release of TSH.

As in most physiological systems the differential equations describing this process are non-linear. In order to study the system in terms of linear differential equations, various assumptions must be made:

1. The rate of secretion of TSH from the anterior pituitary gland is directly proportional to the difference in concentration of thyroid hormone in the blood and some reference concentration; whereas the rate of destruction of TSH is proportional to its concentration outside of the pituitary gland.
2. The rate of secretion of thyroid hormone from the thyroid gland is directly proportional to the rate at which TSH passes through the thyroid gland, and the rate of destruction of this hormone is proportional to its concentration outside of the thyroid gland.

Let

x = concentration of thyroid hormone in the blood

x' = reference concentration of thyroid hormone

y = concentration of TSH in the blood

F = rate of blood flow through the thyroid gland

From assumptions 1. and 2. a system of linear differential equations is obtained:

$$Dx = k_3 \cdot F \cdot y - k_4 x \tag{1}$$

$$Dy = -k_1(x - x') - k_2 y \tag{2}$$

where k_1, k_2, k_3, k_4, F, x' are positive constants.

Equations (1) and (2) are of the form

(3) $$Dx = -ax + by$$

(4) $$Dy = -a'x - b'y + c$$

where a, b, a', b', and c are positive constants.

A. To simplify the solution of equations (3) - (4), we assume that c = 0, i.e., that the reference concentration, x', of thyroid hormone is zero. This assumption yields the related homogeneous system of equations:

(5) $$Dx = -ax + by$$

(6) $$Dy = -a'x + b'y$$

Let us assume that solutions to equations (5) - (6) are of the form $x = \alpha e^{\lambda t}$, $y = \beta e^{\lambda t}$. Substituting these trial solutions into equations (5) - (6), a system of two linear equations is obtained:

(7) $$-(a + \lambda)\alpha + b\beta = 0$$

(8) $$-a'\alpha - (b' + \lambda)\beta = 0$$

which has a non-trivial solution for α and β whenever the determinant of the coefficients is equal to zero, i.e., whenever

$$\begin{vmatrix} -(a + \lambda) & b \\ -a' & -(b' + \lambda) \end{vmatrix} = 0 .$$

This is called the characteristic equation, and solving it for λ, two solutions are obtained:

$$\lambda_1 = \frac{-(a + b') + \sqrt{(a - b')^2 - 4a'b'}}{2}$$

$$\lambda_2 = \frac{-(a + b') - \sqrt{(a - b')^2 - 4a'b'}}{2}$$

Since a and b' are positive constants, $-(a + b') < 0$, so that the roots of the characteristic equation are either real or complex, not purely imaginary. Furthermore,

$$\sqrt{(a - b')^2 - 4a'b'} = \sqrt{(a + b')^2 - 4(ab' + a'b')} < (a + b'),$$

so that the real parts are negative.

If $(a - b')^2 \geq 4a'b'$, then the roots will be negative and real, otherwise complex with negative real parts. In the former case steady state solutions of the system will be approached without oscillations, while in the latter case the steady states will be approached with damped oscillations.

To get the values of α and β corresponding to these two characteristic values, we substitute each λ_i into equations (7) - (8) and solve for α_i and β_i.

For $\lambda = \lambda_i$

$$-(a + \lambda_1)\alpha_1 + b\beta_1 = 0$$

$$-a'\alpha_1 - (b' + \lambda_1)\beta_1 = 0 .$$

Therefore

$$\alpha_1 = \frac{b}{a + \lambda_1} \beta_1 .$$

By similar reasoning

$$\alpha_2 = \frac{b}{a + \lambda_2} \beta_2 .$$

Using the values of λ_1, λ_2, α_1, α_2, β_1, β_2 derived above, the general solution of the related homogeneous system of equations (5)-(6) is given by:

(9) $$x = c_1\alpha_1 e^{\lambda_1 t} + c_2 d_2 e^{\lambda_2 t}$$

(10) $$y = c\,\beta_1 e^{\lambda_1 t} + c\,\beta_2 e^{\lambda_2 t}$$

B. Suppose that the reference concentration, x', of the thyroid hormone is greater than zero. In this case, what is the general solution of the system of differential equations?

SOLUTION:

If the constants c_1 and c_2 in the general solution given above in (9) - (10) are replaced by variables v_1 and v_2, we obtain:

$$x = v_1\alpha_1 e^{\lambda_1 t} + v_2\,{}_2 e^{\lambda_2 t} \tag{11}$$

$$y = v_1\beta_1 e^{\lambda_1 t} + v_2\beta_2 e^{\lambda_2 t} \; . \tag{12}$$

Substituting (11) - (12) into the original system of differential equations and rearranging terms, we get two new equations:

$$\alpha_1 e^{\lambda_1 t} Dv_1 + \alpha_2 e^{\lambda_2 t} Dv_2 = 0$$

$$\beta_1 e^{\lambda_1 t} Dv_1 + \beta_2 e^{\lambda_2 t} Dv_2 = c \; .$$

Solving for Dv_1, Dv_2:

$$Dv_1 = \frac{c_3\alpha_2 e^{-\lambda_1 t}}{\alpha_2\beta_1 - \alpha_1\beta_2}$$

$$Dv_2 = \frac{-c_3\alpha_1 e^{-\lambda_2 t}}{\alpha_2\beta_1 - \alpha_1\beta_2} \; .$$

By simple integration:

$$v_1 = \frac{c_3\alpha_2 e^{-\lambda_1 t}}{\lambda_1(\alpha_1\beta_2 - \alpha_2\beta_1)} \; ,$$

$$v_2 = \frac{-c_3\alpha_1 e^{-\lambda_2 t}}{\lambda_2(\alpha_1\beta_2 - \alpha_2\beta_1)} \; .$$

If the values of v_1 and v_2 are substituted into (11) - (12), the particular solution (x_o, y_o) is obtained for a reference concentration $x' > 0$.

$$x_o = (\lambda_2 - \lambda_1)\frac{c_3\alpha_1\alpha_2}{\lambda_1\lambda_2(\alpha_1\beta_2 - \alpha_2\beta_1)}$$

$$y_o = (\lambda_2 - \lambda_1)\frac{c_3\alpha_1\beta_1}{\lambda_1\lambda_2(\alpha_1\beta_2 - \alpha_2\beta_1)}$$

The general solution in the non-homogeneous case is then given by:

$$x = c_1\alpha_1 e^{\lambda_1 t} + c_2\alpha_2 e^{\lambda_2 t} + x_o$$

$$y = c_1\beta_1 e^{\lambda_1 t} + c_2\beta_2 e^{\lambda_2 t} + y_o$$

EXERCISES:

1. Suppose that due to a malfunction of the thyroid gland that it fails to respond to TSH. What are the new steady state values of x and y?

Equations (1) and (2) become:

(13) $$Dx = -k_4 x$$

(14) $$Dy = -k_1(x - x') - k_2 y$$

Equation (13) is now an equation in one variable, and as such the solution does not depend upon y.

The solution of this equation is $x = ge^{-k_4 t}$, where g is a positive constant, so that x_{ss} is the steady state value of $x = 0$.

Substituting $x = 0$ into (14), we obtain:

$$Dy = +k_1 x' - k_2 y$$

It can be shown that the solution to this equation is

$$y = he^{-k_2 t} + \frac{k_1}{k_2} x'$$

where h is a positive constant. Therefore

$$y_{ss} = \frac{k_1}{k_2} x'$$

2. Consider the case in which the pituitary gland fails to respond to the concentration of thyroid hormone in the blood. What are the steady state values of x and y?

Equations (1) and (2) become:

(15) $$Dx = k_3 Fy - k_4 x$$

(16) $$Dy = -k_2 y$$

Equation (16) is now an equation in one variable. Thus, the solution is

$$y = me^{-k_2 t},$$

where m is a positive constant, so that

$$y_{ss} = 0 .$$

Substituting y = 0 in equation (15), we obtain:

$$\frac{dx}{dt} = -k_4 x .$$

The solution to this equation is straightforward:

$$x = ne^{-k_4 t},$$

where n is a positive constant. Therefore

$$x_{ss} = 0 .$$

It should be remarked that experiments have shown that $k_2 \gg k_1$ Therefore, in both cases above the final concentrations of thyroid hormone and TSH will be approximately zero.

(Note: the use of variation of parameters to solve the non-homogeneous case was motivated by the desire to illustrate this important concept. Obviously, more elementary methods could have been used.)

****

THE RESPONSE OF THE BODY TO A DRUG

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The dose of a drug at which the change in the strength of reaction with respect to a change in the dose is greatest is obtained by repeated differentiation.

The reaction of the body to a dose of a drug can be represented by the following function:

$$R(D) = D^2\left(\frac{C}{2} - \frac{D}{3}\right)$$

where

C = a positive constant

R = the strength of the reaction (for example - if R is the change in blood pressure, it is measured in mm mercury, if R is the change in temperature, it is measured in degrees, and so on.)

D = the amount of the drug.

We will assume that whenever the drug is administered, the concentration of the drug already in the body is insignificant; for if there is already a certain concentration of the drug in the body, the reaction will depend upon this initial concentration (Weber-Fechner Law).

D is defined in the range of 0 to C. (In other words, C is the maximum amount that may be given.)

Find the range of dose for which the medicine has maximum sensitivity, in other words, where there is the greatest change in R for a small change in D, or equivalently where R'(D) is at a maximum.

SOLUTION:

$$R'(D) = DC - D^2$$

$$R''(D) = C - 2D$$

$$R'''(D) = -2 .$$

R'(D) has a maximum when D = C/2. At this value of D the second derivative vanishes and the third derivative is negative. It is easy to see that R at this point ($R = C^3/12$) is one-half of the R obtained when maximum dose is given ($R = C^3/6$).

This phenomenon - that when the strength of the reaction is 50% of the maximum strength, the change in the strength of the

reaction with respect to a change in dose is greatest - is used in order to ascertain the exact dose of a drug to be given, since at this dose, small changes in dose will give the greatest changes in the reaction.

****

CONCENTRATION OF GLUCOSE IN THE BODY AFTER GLUCOSE INFUSION

Contributor: Hebrew University Report

****

Mathematics: solution of differential equations with integrating factors (Math. 4)

Abstract: The concentration of glucose in the body after glucose infusion is obtained by solving a differential equation.

Infusion is the process of admitting a substance into the veins at a steady rate.

Let A be the amount of glucose admitted (in m.g./minute) and let V be the volume of the liquids of the body. Thus, the concentration of the glucose in the body increases by A/V m.g. per minute.

A drop in the concentration of the free glucose depends on the concentration of the glucose, i.e., the concentration of free glucose will decrease by kc where k is a constant of proportionality and c is the concentration of glucose in the blood.

Find the change in the concentration of the glucose with time (dc/dt).

SOLUTION:

$$\frac{dc}{dt} = \frac{A}{V} - kc \ .$$

Rearranging terms and multiplying by an integrating factor, we obtain

$$\frac{dc}{dt} e^{kt} + kce^{kt} = \frac{A}{V} e^{kt}$$

or

$$\frac{d(ce^{kt})}{dt} = \frac{A}{V} e^{kt}$$

so that

$$ce^{kt} = \frac{1}{k} \frac{A}{V} e^{kt} + \text{constant} \ .$$

Since at the beginning of the infusion the concentration of glucose was not 0, let c_o represent the concentration at t = 0.

Taking t = 0,

$$ce^{k0} = \frac{1}{k} \frac{A}{V} + \text{constant} \ .$$

Therefore,

$$c_o - \frac{1}{k} \frac{A}{V} = \text{a constant}$$

and the concentration is given by

$$c = \frac{A}{kV} (1 - e^{-kt}) + c_o e^{-kt} \ .$$

****

VISUAL THRESHOLD SUMMATION

Contributor: Harold Slater*

****

Mathematics: integration (Math. 1)

Abstract: A summation model is derived to account for increased excitation at the center of an illuminated area of the retina.

*Based upon: Bartlett, N.R. "Thresholds as Dependent on Some Energy Relations." Vision and Visual Perception. Edited by C. Graham. New York: Wiley and Sons, 1965, 177-178.

In an experiment in which a circular area of the retina was illuminated uniformly it was discovered that the maximum excitation of the receptors occurred in the center of the circular region. In a simple model constructed to explain this phenonemon, it is hypothesized that the excitation of receptors in the periphery of the illuminated area contributes to the excitation at the center. Let us assume that there is a distance bias involved in the contribution of excitation, i.e., the contribution of some small area is inversely proportional to r^k, where r is the distance of the area from the center and k is a constant less than 2. To obtain the total excitation at the center, we form the integral:

$$(1) \qquad mE \int_0^{2\pi} \int_0^{\rho} \frac{r\,dr\,d\theta}{r^k}$$

where ρ is the radius of the circular area, E is a constant related to the incident light intensity, and m is a constant of proportionality. Integrating (1) we obtain:

$$\text{Total excitation at the center} = mE \int_0^{2\pi} \left(\int_0^{\rho} r^{1-k}\, dy \right) d\theta$$

$$= \frac{2\pi m E \rho^{2-k}}{2 - k} .$$

****

THE SUBJECTIVE BRIGHTNESS OF LIGHT

Contributor: Hebrew University Report

****

Mathematics: differentiation (Math. 1)

Abstract: The differences in sensitivity between light and dark adapted subjects are considered.

The subjective brightness of a source (that which the viewer senses) - designated by F - can be described by the following power function:

$$F = kL^b$$

where L is the brightness of the source and is measured in cd./m^2, and the constants k and b depend upon the previous history according to the following table:

	People who were in light previous to the experiment	People who were in darkness previous to the experiment
k	0.25×10^{-3}	10×10^{-3}
b	0.49	0.33

QUESTIONS:

1. For what range of light intensities will the people who were in darkness think that the light is stronger (than the people who were previously in light) and for what range will the opposite be true, i.e., the people who were previously in light think the light was brighter?

2. For what range will the sensitivity to changes in the strength of the light be greater for those who were previously in darkness, and for what range will this be true for people who were in light?

ANSWERS:

1. When $F_1 = F_2$ (1 and 2 represent the people who were previously in light and darkness, respectively),

$$k_1 L^{b_1} = k_2 L^{b_2}$$

At this point L is given by

$$L = \left[\frac{k_2}{k_1}\right]^{\frac{1}{b_1 - b_2}} = \left[\frac{10 \times 10^{-3}}{0.25 \times 10^{-3}}\right]^{\frac{1}{0.16}} = 1.03 \times 10^{10} \text{cd./m}^2$$

When L is smaller than this value, the light will be stronger for people who were in darkness, and when L is greater, the light

will be stronger for people who remained in light. (It is obvious that people who were in darkness blind faster.)

2. Since F is a function of L, the sensitivity to changes in light is given by

$$F'(L) = bkL^{b-1} .$$

When both types of people have equal sensitivity

$$F_1'(L) = F_2'(L)$$

$$b_1 k_1 L^{b_1-1} = b_2 k_2 L^{b_2-1}$$

and L is given by

$$L = \left[\frac{b_2 k_2}{b_1 k_1}\right]^{\frac{1}{b_1-b_2}} = \left[\frac{0.33 \times 10 \times 10^{-3}}{0.49 \times 0.25 \times 10^{-3}}\right]^{\frac{1}{0.16}} = 8.88 \times 10^8 \text{ cd./m}^2$$

If L is smaller than this value, people who were in the dark have greater sensitivity; if L is greater, the opposite is true.

****

A DIETARY PROBLEM

Contributor: Richard F. Baum

****

Mathematics: matrix algebra (Math. 3)

Abstract: The product of relations is used to determine a menu for a group of persons, given that each person is allergic to certain foods.

The manager of a summer lodge expects for a given two week period that along with his usual guests there will be four special guests who have allergies to certain foods. In particular,

G_1 (guest 1) is allergic to oregano, which will be called ingredient I_1, and to garlic, which will be called ingredient I_2.

G_2 (guest 2) is allergic to mozzarella cheese, which will be called ingredient I_3.

G_3 (guest 3) is allergic to olive oil, which will be called ingredient I_4, and to mushrooms, which will be called ingredient I_5.

G_4 (guest 4) is allergic to oregano, I_1; to mozzarella cheese, I_3; and to olive oil, I_4.

Thus, this defines a relation R in G x I, where:

$$G = \{G_i | i = 1, 2, 3, 4\} \; ; \quad I = \{I_j | j = 1, 2, 3, 4, 5\}$$

namely,

$$R = \{(x,y) | x \text{ is allergic to ingredient } y,\ x \in G,\ y \in I\} \; ,$$

i.e., R is the relation "is allergic to". For a matrix representation of R, we can form the matrix A, $A = [a_{ij}]_{4x5}$, where

$a_{ij} = 1$ if G_i (guest i) is allergic to ingredient j

$a_{ij} = 0$ if G_i is not allergic to ingredient j

$i = 1, 2, 3, 4 \; ; \quad j = 1, 2, 3, 4, 5 \; .$

Thus,

$$A = \begin{bmatrix} 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 & 0 \end{bmatrix} \; .$$

The manager, who has the above information, wants to plan his dinner menus so that on any given night, each of these four special guests can find at least one main course which does not contain ingredients to which he is allergic, while still keeping the menu interesting

for the rest of his guests. Suppose the manager can place any four of seven possible main courses on each dinner menu. The seven possible main courses are:

M_1: spaghetti and meat sauce

M_2: beef stew

M_3: veal parmigiana

M_4: fondue

M_5: lasagne

M_6: shish kebab

M_7: chicken a la king .

These meals are always prepared so that

M_1 contains ingredients I_1, I_2, and I_5 .

M_2 contains ingredient I_2 .

M_3 contains ingredients I_1 and I_3 .

M_4 contains ingredient I_3 .

M_5 contains ingredients I_2, I_3, and I_4 .

M_6 contains ingredients I_1, I_4, and I_5 .

M_7 contains ingredient I_5 .

Therefore, we have relation S, in M x I, where

$$M = \{M_k | k = 1, 2, 3, 4, 5, 6, 7\} ,$$

i.e.,

$$S = \{(u,v) | M \text{ contains ingredient } v,\ u \in M,\ v \in I\} ,$$

i.e., S is the relation "contains". Again, S can be represented by a matrix B, $B = (b_{kj})_{7x5}$, where:

$$b_{kj} = 1 \text{ if } M_k \text{ contains } I_j ;$$

$$b_{jk} = 0 \text{ if } M_k \text{ does not contain } I_j ,$$

$$i = 1, 2, 3, 4, 5, 6, 7 ; \quad j = 1, 2, 3, 4, 5 .$$

Therefore,

$$B = \begin{bmatrix} 1 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 1 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

In order to find out which main course each of the four special guests can eat, we would like to know, for each ingredient I_j, which main course M_k contains I_j, since from R we know the ingredients to which each of the four special guests are allergic. Thus, we should use S^T, since:

$$vS^Tu \leftrightarrow uSv ,$$

i.e., $(v,u) \in S^T$ if and only if u contains ingredient v or, if and only if ingredient v is contained in main course u. Thus, S^T is the relation "contained in". The matrix representation for S^T is $C = B^T$, $C = [C_{jk}]_{5x7}$, where:

$$C_{jk} = 1 \text{ if ingredient } I_j \text{ is contained in } M_k .$$

$$C_{jk} = 0 \text{ if ingredient } I_j \text{ is not contained in } M_k .$$

$$j = 1, 2, 3, 4, 5 ; \quad k = 1, 2, 3, 4, 5, 6, 7 .$$

Thus,

$$C = B^T = \begin{bmatrix} 1 & 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix} .$$

Finaly, to find which main courses contain ingredients to which G_i is allergic, we need only determine the relation RS^T in G x M, since xRS^Tu if and only if there exists a $v \in I$ such that xRv and vS^Tu, i.e., if and only if x is allergic to some ingredient v which is contained in main course u. To obtain RS^T in matrix form, we can refer to matrix D, $D = [d_{ik}]_{4x7}$, where $D = A \cdot C$

$$D = A \cdot C = \begin{bmatrix} 2 & 1 & 1 & 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 & 1 & 0 & 1 \end{bmatrix} .$$

Since xRS^Tu if and only if main course u contains one or more ingredients, it is easy to verify that

d_{ik} = number of ingredients contained in main course M_k to which G_i is allergic.

Thus, RS^T is represented by the matrix H, $H = [h_{ik}]_{4x7}$, where

$h_{ik} = 1$ if main course M_k contains an ingredient to which G_i is allergic;

$h_{ik} = 0$ if main course M_k does not contain an ingredient to which G_i is allergic;

and

$$H = \begin{bmatrix} 1 & 1 & 1 & 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 & 1 & 0 & 1 \end{bmatrix}$$

since xRS^Tu if and only if main course u contains one or more ingredients to which x is allergic. Thus, H is the same as D except that any element in D which is greater than zero becomes 1 in H, i.e.:

$$h_{ik} = 0 \text{ if } d_{ik} = 0 ,$$

$$h_{ik} = 1 \text{ if } d_{ik} \neq 0 ,$$

$$i = 1, 2, 3, 4 ; \quad j = 1, 2, 3, 4, 5, 6, 7 .$$

Thus we see that if the menu of the lodge contains four main courses each evening, the manager should have no trouble preparing menus so that any guest can find at least one main course which he can safely eat. Occasionally in fact, he may provide some of his special guests a choice of two or more main dishes. This will occur, for example, of the menu contains main courses M_2, M_4, and M_7.

****

INSULIN REQUIREMENTS AS A LINEAR PROCESS IN TIME

Contributor: Richard F. Baum

****

Mathematics: matrix algebra (Math. 3)

Abstract: A linear system and matrix-by-vector multiplication are used to describe the insulin requirements of a group of diabetics.

The manager of a summer vacation lodge expects four guests, each of whom has diabetes. These guests plan to stay at the lodge for 7, 14, 21, and 28 days respectively. Due to the great distance of the lodge from the nearest drug supplier, the manager plans to obtain from a drug supplier just before the lodge opens the total amount of three different types of insulin (lente, semi-lente, and ultra-lente), which will be needed by these guests. He then plans to store these three different types of insulin, so that the lodge can administer the daily dose of the different types of insulin to each of the guests.

The daily requirements of the four guests are:

Guest 1 needs (per day): 20 insulin units of semi-lente, 30 units lente, 10 units ultra-lente.

Guest 2 needs (per day): 40 insulin units of semi-lente, 0 units lente, 0 units ultra-lente.

Guest 3 needs (per day): 30 insulin units of semi-lente, 10 units lente, 30 units ultra-lente.

Guest 4 needs (per day): 10 insulin units of semi-lente, 10 units lente, 50 units ultra-lente.

Thus, we can write a "requirement" matrix A,

$$A = [a_{ij}]_{3 \times 4}\ , \quad \text{where A is given by}$$

	Daily Requirements			
	Guest 1	Guest 2	Guest 3	Guest 4
semi-lente insulin	20	40	30	10
lente insulin	30	0	10	10
ultra-insulin	10	0	30	50

.

We know that Guest 1 will stay for 7 days, Guest 2 for 14 days, Guest 3 for 21 days, and Guest 4 for 28 days. If we let the vector T stand for the number of days each patient is staying at the lodge, i.e.,

$$T = \begin{bmatrix} 7 \\ 14 \\ 21 \\ 28 \end{bmatrix}$$

then it is easy to verify that:

$$AT = \begin{bmatrix} 20 & 40 & 30 & 10 \\ 30 & 0 & 10 & 10 \\ 10 & 0 & 30 & 50 \end{bmatrix} \begin{bmatrix} 7 \\ 14 \\ 21 \\ 28 \end{bmatrix} = 70 \begin{bmatrix} 2 & 4 & 3 & 1 \\ 3 & 0 & 1 & 1 \\ 1 & 0 & 3 & 5 \end{bmatrix} \cdot \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \end{bmatrix}$$

$$= \begin{bmatrix} 1610 \\ 700 \\ 2100 \end{bmatrix} = B .$$

The vector B gives the total amounts of the different types of insulin needed by the four guests, i.e., 1610 insulin units of semi-lente, 700 insulin units of lente, and 2100 insulin units of ultra-lente.

Suppose each guest decided to double the amount of time he originally intended to stay. The vector giving the total amount of semi-lente, lente, and ultra-lente insulin needed would clearly be:

$$A(2T) = 2(AT) = 2B = \begin{bmatrix} 3220 \\ 1400 \\ 4200 \end{bmatrix}$$

and, in general, if each guest planned to spend a factor α ($\alpha \geq 0$) of his original time at the lodge, i.e., Guest 1 planned to stay for $\alpha \cdot 7$ days, Guest 2 for $\alpha \cdot 14$ days, Guest 3 for $\alpha \cdot 21$ days, and Guest 4 for $\alpha \cdot 28$ days, then the insulin requirements would be:

$$A \cdot (\alpha T) = \alpha(AT) = \alpha B = \begin{bmatrix} \alpha \cdot 1610 \\ \alpha \cdot 700 \\ \alpha \cdot 2100 \end{bmatrix} ,$$

i.e., we would have constant returns to scale. Clearly, this is true for any T.

Similarly, if the guests decided to add 1, 3, 4, and 6 days, respectively, to the times they originally intended to stay, the new amounts of insulin required would be

$$A(T + T^1) = AT + AT^1 \qquad \text{where } T^1 = \begin{bmatrix} 1 \\ 3 \\ 4 \\ 6 \end{bmatrix} ,$$

i.e., the system is additive. Therefore, the system is linear and can be represented by:

$$AX = B \quad \text{or} \quad \begin{bmatrix} 20 & 40 & 30 & 10 \\ 30 & 0 & 10 & 10 \\ 10 & 0 & 30 & 50 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix}$$

or

$$\begin{aligned} 20x_1 + 40x_2 + 30x_3 + 10x_4 &= b_1 \\ 30x_1 \qquad\quad + 10x_3 + 10x_4 &= b_2 \\ 10x_1 \qquad\quad + 30x_3 + 50x_4 &= b_3 \ , \end{aligned}$$

where x_i is the number of days guest i stays at the lodge, and b_1, b_2, b_3 give respectively the total number of insulin units of semi-lente, lente, and ultra-lente insulin needed by the four guests for their entire stay at the lodge.

Finally, suppose once again that vector T represented the number of days each guest planned to stay at the lodge. In addition, suppose vector C gave the cost (in cents) per insulin unit of the three types of insulin, where

$$C = \begin{bmatrix} 3 \\ 2 \\ 4 \end{bmatrix} = \text{cost vector},$$

i.e., one unit of semi-lente costs 3ϕ, one unit of lente costs 2ϕ, and one unit of ultra-lente costs 4ϕ. Then the total purchase price paid by the lodge, for all the insulin required by the four guests would be:

$$C^T(AT) = C^T B = \begin{bmatrix} 3 & 2 & 4 \end{bmatrix} \begin{bmatrix} 1610 \\ 700 \\ 2100 \end{bmatrix} = (14{,}630) \ ,$$

i.e., $14{,}630\phi$ or \$146.30.

****

A PSYCHOPHYSICAL MATCHING EXPERIMENT

Contributor: Richard F. Baum*

****

Mathematics: linear independence, vector spaces (Math. 3)

Abstract: A psychophysical matching experiment is investigated using algebraic techniques.

*Based upon: Judd, D. B. "Basic Correlates of the Visual Stimulus." Handbook of Experimental Psychology. Edited by S. S. Stevens. New York: Wiley and Sons, 1951.

Consider an experiment in which we are given two screens. On screen I is flashed a light of a certain color. On screen II we are attempting to duplicate the light shown on screen I both in color and "intensity" by projecting combinations of various lights of given colors onto screen II. Experimentation in color perception has shown that any color can be duplicated by using a proper additive mixture of three primary colors: red (denoted S_1), green (S_2), and blue (S_3). Assume that we can project combinations of these colors onto screen II.

Let $\mathcal{L}$ be the set of all 3-tuples $\begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix}$, where s_i denotes the amount of light of color S_i measured in foot candles, which is projected onto screen II, $i = 1,2,3$. Note that $s_i \geq 0$, $i = 1,2,3$. Thus

$$\mathcal{L} = \left\{ \begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix} \middle| s_i \geq 0,\ i = 1,2,3 \right\}.$$

The addition of 3-tuples in $\mathcal{L}$, such as

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} \text{ and } \begin{bmatrix} w_1 \\ w_2 \\ w_3 \end{bmatrix}, \quad v_i \geq 0, \quad w_1 \geq 0, \quad i = 1, 2, 3$$

is defined as component-wise addition, i.e.,

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} + \begin{bmatrix} w_1 \\ w_2 \\ w_3 \end{bmatrix} \equiv \begin{bmatrix} v_1 + w_1 \\ v_2 + w_2 \\ v_3 + w_3 \end{bmatrix} \in \mathcal{L}$$

and represents the light produced by projecting $v_1 + w_1$ foot candles of color S_1, $v_2 + w_2$ foot candles of color S_2, and $v_3 + w_3$ foot candles of color S_3 onto screen II.

Scalar multiplication of 3-tuples in $\mathcal{L}$ is also defined component-wise, i.e.,

$$b \cdot \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} \equiv \begin{bmatrix} bv_1 \\ bv_2 \\ bv_3 \end{bmatrix}, \quad b \geq 0 ,$$

and represents the light produced by projecting $b \cdot v_1$ foot candles of color S_1, $b \cdot v_2$ foot candles of color S_2, and $b \cdot v_3$ foot candles of color S_3 onto screen II.

Observe that $\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$ represents the color white, and that b must be non-negative in order for the above to make sense in terms of mixing colors.

Let

$$e_1 = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \; e_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}, \text{ and } e_3 = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}$$

denote respectively, the projection of 1 foot candle of S_1, S_2, and S_3 onto screen II. As we stated above, a light of any color and intensity projected onto screen I can be duplicated by the proper additive mixture of S_1, S_2, and S_3; i.e., there exist non-negative real numbers m_1, m_2, m_3 such that this light can be represented by:

$$m_1 e_1 + m_2 e_2 + m_3 e_3 \quad \text{or} \quad \begin{bmatrix} m_1 \\ m_2 \\ m_3 \end{bmatrix},$$

where m_1, m_2, m_3 are chosen so that:

1. The resulting color of the mixture on screen II is the same as the color projected onto screen I

2. The brightness of the mixture on screen II is the same as that on screen I.

If we only wish to match the color, but not the brightness, we would be satisfied with a positive scalar multiple of $\begin{bmatrix} m_1 \\ m_2 \\ m_3 \end{bmatrix}$. Conversely,

if the color projected onto screen I can be represented by $\begin{bmatrix} t_1 \\ t_2 \\ t_3 \end{bmatrix}$, then there exists a scalar $b > 0$ such that:

$$\begin{bmatrix} t_1 \\ t_2 \\ t_3 \end{bmatrix} = b \begin{bmatrix} m_1 \\ m_2 \\ m_3 \end{bmatrix} .$$

$\mathcal{L}$ does not form a vector space. It can, however, be imbedded into the first octant of the three-dimensional vector space, $\mathcal{R}^3$, and we can perform vector addition and scalar multiplication in $\mathcal{L}$ as long as we are careful to remain in the first octant of $\mathcal{R}^3$, i.e., to keep the components of our 3-tuples non-negative. From the above discussion we also know that any color can be represented by:

$$b \begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix} ,$$

where $b > 0$ and $\begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix}$ results in a light of this color. Conversely, any 3-tuple in $\mathcal{L}$ represents a light of some color. Thus, the classification of color partitions the set $\mathcal{L}$ into classes of the form:

$$\begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix} \equiv \left\{ x \begin{bmatrix} s_1 \\ s_2 \\ s_3 \end{bmatrix} \mid x > 0 \right\} .$$

For example,

$$\begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} = \left\{ x \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \mid x > 0 \right\}$$

represents the color "purple".

The color purple, or more precisely, any vector of the form $x \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix}$,

$x > 0$, is a member of the convex cone $ae_1 + be_2$, where $a, b \geq 0$. We are dealing with a three-dimensional vector space; thus, any three linearly-independent vectors would form a basis. How do we interpret, in our case, one spanning property of such a basis $\{\alpha,\beta,\gamma\}$? If α, β, γ are lights of color C_α, C_β, C_γ, respectively, then α, β, γ are linearly independent if and only if no one of the above colors can be duplicated using an additive mixture of the other colors.

Assume that we can only use additive mixtures of C_α, C_β, C_γ for projection onto screen I. The lights obtained by these mixtures are represented by the convex cone:

$$\mathcal{S} = \{a\alpha + b\beta + c\gamma \mid a, b, c \geq 0\} .$$

Note that since a, b, c must be non-negative, the above convex cone in general will not include all of $\mathcal{L}$. In fact, $\mathcal{S} = \mathcal{L}$ if and only if $\{C_\alpha, C_\beta, C_\gamma\} = \{S_1, S_2, S_3\}$.

If $\mathcal{S} = \mathcal{L}$, α, β, γ can be written in terms of e_1, e_2, e_3, i.e.,

$$\alpha = a_1e_1 + a_2e_2 + a_3e_3 .$$

Similarly,

(1)
$$\beta = b_1e_1 + b_2e_2 + b_3e_3$$
$$\gamma = c_1e_1 + c_2e_2 + c_3e_3$$

where all the scalar coefficients are non-negative.

Let

(2)
$$A = \begin{bmatrix} a_1 & a_2 & a_3 \\ b_1 & b_2 & b_3 \\ c_1 & c_2 & c_3 \end{bmatrix} .$$

Then α, β, γ will be linearly independent if and only if

$$(\det\ A) \neq 0 .$$

Note that from the system of equations (1), any color which can be represented by a point, $x\alpha + y\beta + z\gamma$, on the convex cone $\mathcal{S}$ can be represented by a suitable linear combination of e_1, e_2, e_3;

$$x(a_1e_1 + a_2e_2 + a_3e_3) + y(b_1e_1 + b_2e_2 + b_3b_3)$$
$$+ z(c_1e_1 + c_2e_2 + c_3e_3)$$
$$= \sum_{i=1}^{3} (xa_i + yb_i + zc_i)e_i \ , \quad xa_i + yb_i + zc_i \geq 0$$

by construction. As noted before, however, if we assume that $\{C_\alpha, C_\beta, C_\gamma\} \neq \{S_1, S_2, S_3\}$, then there are lights of certain colors which can be represented by e_1, e_2, e_3 that cannot be represented by α, β, γ. Let us solve equation (1) for e_1, e_2, e_3 in terms of α, β, γ. We can certainly do this since α, β, γ are linearly independent.

$$e_1 = \frac{\begin{vmatrix} a_1 & a_2 & a_3 \\ b_1 & b_2 & b_3 \\ c_1 & c_2 & c_3 \end{vmatrix}}{\det A} = \frac{(b_2c_3 - b_3c_2)\alpha - (a_2c_3 - a_3c_2)\beta + (a_2b_3 - a_3b_2)\gamma}{\det A} \ .$$

In a similar manner we can obtain expressions for c_2 and c_3. Thus, we can write:

(3)
$$e_1 = p_1\alpha + p_2\beta + p_3\gamma$$
$$e_2 = q_1\alpha + q_2\beta + q_3\gamma$$
$$e_3 = r_1\alpha + r_2\beta + r_3\gamma \ .$$

Some of the coefficients in (3) may be negative. Therefore, (3) does not represent a real combination of colors, C_α, C_β, C_γ. In fact, if

$$\{C_\alpha, C_\beta, C_\gamma\} \neq \{S_1, S_2, S_3\}$$

then, as stated before, it must be the case that a light of some color can be produced by some suitable mixture of S_1, S_2, S_3, that cannot be produced by a mixture of C_α, C_β, C_γ. Therefore, at least one of the coefficients of (3) must be negative. However, we can still make some conclusions from (3). For example, assume $a_1 < 0$ and $c_2 < 0$ and all other coefficients of (3) are non-negative. Then in terms of color combinations, we can conclude from (3) that:

(4)
$$e_1 + (-p_1)\alpha = p_2\beta + p_3\gamma$$
$$e_2 = q_1\alpha + q_2\beta + q_3\gamma$$
$$e_3 + (-r_2)\beta = r_1\alpha + r_3\gamma$$

where $(-p_1)$ and $(-r_2)$ are positive numbers. From line 1 of equation (4) we can conclude that if one foot candle of color S_1 is mixed with $(-p_1)$ foot candles of color $C_\alpha[-p_1 > 0]$, this gives the same result as adding p_2 foot candles of C_β to p_3 foot candles of C_γ. We can make similar observations for lines 2 and 3 of equation (4). Thus, only if we transpose terms of (3) in such a manner that all coefficients are non-negative do we have an equation which makes sense in the context of combining colors.

EXERCISES:

1. Show how matrix A given by equation (2) (or perhaps A^T) can be used to "change co-ordinates" from the α, β, γ (or C_α, C_β, C_γ) system to the e_1, e_2, e_3 (or S_1, S_2, S_3) system.

2. Show how matrix A^{-1} (or perhaps $(A^T)^{-1}$) can be used to "change co-ordinates from the e_1, e_2, e_3 (or S_1, S_2, S_3) system to the α, β, γ (or C_α, C_β, C_γ) system.

****

A STOCHASTIC MODEL FOR LEARNING

Contributor: Richard F. Baum*

****

Mathematics: linear combinations, elementary matrix operations, inverses (Math. 3)

Abstract: Stochastic matrices, linear combinations, and inverses are used in a model for conditioning.

*Based upon: Bush, R. R., and Mosteller, F. Stochastic Models for Learning . New York: Wiley and Sons, 1955.

Suppose we are conditioning an animal to respond in a certain way to a given stimulus. For example, we might be conditioning an animal to push (or not push) a lever. At each stage of our conditioning, we present the same stimulus to the animal, note its response, and then give a reward based on the response of the animal. We then repeat this process for the desired number of times. Suppose that at a given stage, say the nth stage, it is determined experimentally that, with our schedule of rewards, the response pattern is as follows:

If the lever is pushed, the probability that the lever will be pushed at the next stage is M_{11} and the probability that it will not be pushed at the next stage is M_{21}. On the other hand, if the lever is not pushed, the probability that the lever will be pushed at the next stage is M_{12} and the probability that it will not be pushed at the next stage is M_{22}. It will be assumed that these probabilities do not change with time.

Let p_1 denote the probability that the lever is pushed at the nth stage. Then $p_2 = 1 - p_1$ is the probability that the lever is not pushed at the nth stage. Similarly, we can define q_1 and q_2 as the probabilities that the lever is or is not pushed at the $(n + 1)$th stage. We can represent the probabilities of possible outcomes by probability vectors p, q, given by:

$$p = \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} \qquad q = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix} .$$

The reader should verify that

$$q = T \cdot p , \qquad \text{where } T = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix} .$$

From the definition of the M_{ij}'s, $0 \leq M_{ij} \leq 1$, $i,j, = 1,2$, and $M_{11} + M_{21} = M_{12} + M_{22} = 1$, i.e., the columns of T must sum to one, and the elements of T must be numbers between 0 and 1. Also note that

$$p_1 + p_2 = 1 \qquad 0 \le p_2 \le 1$$

$$q_1 + q_2 = 1 \qquad 0 \le q_2 \le 1 .$$

In general, suppose we are conditioning an animal to respond in a certain way to a given stimulus, and assume that there are N mutually exclusive possible responses $A_1, A_2, \ldots, A_N$. On each trial, we present an identical stimulus to the animal, note its response, and then reward the animal according to a table of rewards based on the animal's past response. We then repeat this procedure for the desired number of times.

As above, let M be a fixed number and let M_{ij} be the probability of response A_i at the $(n + 1)$ stage if the response at the nth stage is A_j (and is followed by the appropriate reward), $i,j = 1,2,\ldots,N$. Then, if

$$p = \begin{bmatrix} p_1 \\ \vdots \\ p_i \\ \vdots \\ p_N \end{bmatrix} , \qquad Q = \begin{bmatrix} q_1 \\ \vdots \\ q_i \\ \vdots \\ q_N \end{bmatrix}$$

where

p_i = probability of response A_i at stage J

q_i = " " " " " " $(J = 1)$

then

(1) $$q = Tp \qquad \text{where } T = (M_{ij}) .$$

Notice that as before,

$0 \le M_{ij} \le 1$, $i,j = 1,2,\ldots,N$; $0 \le p_i \le 1$, $0 \le q_i \le 1$, $i = 1,2,\ldots,N$,

$\sum_{K=1}^{N} M_{Kj} = 1$ $\quad j = 1,\ldots,N$, i.e., the columns of T sum to one,

and

$$\sum_{K=1}^{N} p_K = 1, \qquad \sum_{K=1}^{N} q_K = 1 .$$

As an example, Bush and Mosteller in Stochastic Models for Learning (§3.9) discuss a conditioning experiment where T is:

$$T = \begin{bmatrix} 1 & B \\ 0 & 1-B \end{bmatrix} \qquad 0 \leq B \leq 1$$

and

A_1 is the event that a rat turns right in a T-maze

A_2 " " " " " " " left " " " .

Define $p = \begin{bmatrix} p_1 \\ p_2 \end{bmatrix}$ $q = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix}$ by:

p_1 = probability that the rat turns right on trial n

q_1 = " " " " " " " " (n + 1)

p_2 = " " " " " left " " n

q_2 = " " " " " " " " n + 1 .

Again,

$$q = Tp .$$

Note that this implies that the rat is rewarded on trial N for a right turn so that he makes a right turn on the next trial, as shown by

$$\begin{bmatrix} 1 & B \\ 0 & 1-B \end{bmatrix} \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \end{bmatrix},$$

and that the rat is "rewarded" for a left turn in such a way that his inclination to choose the left path decreases, as shown by

$$\begin{bmatrix} 1 & B \\ 0 & 1-B \end{bmatrix} \begin{bmatrix} 0 \\ 1 \end{bmatrix} = \begin{bmatrix} B \\ 1-B \end{bmatrix}.$$

Let us now study the general "2x2" conditioning experiment, i.e., the case where

$$p = \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} \qquad q = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix}, \qquad T = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}, \text{ and}$$

$$q = Tp .$$

Since the columns of T must sum to one, this allows us to write T as:

$$T = \begin{bmatrix} 1-b & a \\ b & 1-a \end{bmatrix} \text{ where } a = M_{11},\ b = M_{21}, \text{ and } 0 \leq a,b \leq 1 .$$

T can be rewritten as:

$$T = \begin{bmatrix} 1-b & a \\ b & 1-a \end{bmatrix} = \begin{bmatrix} 1-a+b+a & a \\ b & 1-a-b+b \end{bmatrix}$$

$$= \begin{bmatrix} 1-a-b & 0 \\ 0 & 1-a-b \end{bmatrix} + \begin{bmatrix} a & a \\ b & b \end{bmatrix}$$

$$= (1-a-b) \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} + \begin{bmatrix} a & a \\ b & b \end{bmatrix} .$$

Letting

$$\alpha = 1 - a - b$$

$$\beta = a/1-\alpha$$

we have for $\alpha \neq 1$:

$$T = \alpha \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} + (1-\alpha) \begin{bmatrix} \beta & \beta \\ 1-\beta & 1-\beta \end{bmatrix} .$$

Thus,

$$q = Tp = \alpha \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} + (1-\alpha) \begin{bmatrix} \beta & \beta \\ 1-\beta & 1-\beta \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \end{bmatrix}$$

$$= \alpha \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} + (1-\alpha) \begin{bmatrix} \beta \\ 1-\beta \end{bmatrix}.$$

q is a linear combination of the vectors $p = \begin{bmatrix} p_1 \\ p_2 \end{bmatrix}$ and $\begin{bmatrix} \beta \\ 1-\beta \end{bmatrix}$.

Geometrically, the point q lies on the line joining the points $\begin{bmatrix} p_1 \\ p_2 \end{bmatrix}$ and $\begin{bmatrix} \beta \\ 1-\beta \end{bmatrix}$, and lies between these points for $0 < \alpha < 1$. Note that β depends upon α except when $\alpha = 1$. If $\alpha = 1$, β is not defined; but since $\alpha = 1-a-b$, $\alpha = 1$ implies $a + b = 0$. But by assumption $a,b \geq 0$. Therefore $\alpha = 1$ implies $a = b = 0$, so that $T = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$ and $Tp = p$, i.e., our schedule of rewards has no effect on the animal's response from trial n to trial $(n + 1)$.

Suppose we applied our schedule of rewards to transform p to q as described above. One question which we can ask is: can we change our method of rewards so that on the next trial q is transformed back to the original p, i.e., the probability vector is the same as it was on trial n. Let us assume the probabilities p_1, q_1 are the same for stage n and stage $(n + 1)$. Then the answer to this question depends on the form of T, since we are really asking if there exists a matrix, or transformation whose matrix representation is S, such that:

$$p = Sq = S[Tp] = [ST]p ,$$

i.e., does the inverse of T exist? If it does, does it possess the properties of T, i.e., are the elements of $S = T^{-1}$ numbers between 0 and 1, and do the columns of $S = T^{-1}$ sum to one? Consider the example of the rat in the T-maze. We know that

$$T = \begin{bmatrix} 1 & b \\ 0 & 1-b \end{bmatrix}.$$

Since the columns of $S = T^{-1}$ must sum to one, we know that

$$S = \begin{bmatrix} s & t \\ 1-s & 1-t \end{bmatrix}$$

and we want:

$$\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \begin{bmatrix} s & t \\ 1-s & 1-t \end{bmatrix} \begin{bmatrix} 1 & s \\ 0 & 1-b \end{bmatrix} = \begin{bmatrix} s & bs-bt-t \\ 1-s & b(1-s)+(1-t)(1-b) \end{bmatrix}.$$

It is easy to show that this implies

$$s = 1$$

$$t = b/b-1$$

Observe that t is less than zero when $0 < b < 1$. Thus, there does not exist a way to vary our rewards on the $(n + 1)$ trial to "undo" the effect of our reward on the previous trial.

****

A CLASSIFICATION PROBLEM

Contributor: Richard F. Baum*

****

Mathematics: elementary probability (Math. 2P), matrix algebra (Math. 3)

Abstract: Matrix multiplication and real-valued functions of matrices are used to obtain "optimum" classification schemes.

*Based upon: Bush, R. R.; Abelson, R.P.; Hyman, R. "Mathematics for Psychologists, Examples and Problems." Washington, D.C.: Social Sciences Research Council, 1956, example M22.

Suppose that a psychiatric screening test is administered to a group of naval recruits. There are two categories of interest: "normal" and "deviate". Suppose that a cutting score is established to divide the examinees into two groups--those below and those above the cutting point.

The problem is to place people into two categories, deviate or normal, on the basis of their performance (above or below the cutting score) to optimize the correct assignment made, i.e., to optimize the number of people who are put into their true category.

Table 1

	above	below
Normal	3/10	7/10
Deviate	9/10	1/10

Suppose a naive personnel clerk, knowing the probabilities presented in Table 1, feels he should assign people to categories with probabilities based on Table 1. Specifically, he decides that if a person scores above the cutting point, he will designate him as normal (deviate) with probability 2/10 (8/10), (obtained by "scaling down" 3/10 and 9/10 so that their sum is one); and if a person scores below the cutting point, he will designate him as normal (deviate) with probability 9/10 (1/10) (the 1/10 being obtained from Table 1). If this "weighting strategy" is used, then the probability that an individual who is normal is correctly classified is: [(Probability of normal individual scoring above cuttoff point) × (probability of classifying an individual scoring above the cutoff point as normal)] + [(Probability of normal individual scoring below cuttoff point) × (probability of classifying an individual scoring below the cutoff point as normal)] = $(.3)(.2) + (.7)(.9) = .06 + .63 = .69$. Similarly, the probability of a deviate being correctly classified is: $(.9)(.8) + (.1)(.1) = .73$.

By using matrices we can display our numbers and calculations in a more convenient fashion which will save notation, and by using matrix multiplication we can discuss ways of evaluating assignments such as the above.

For the sake of generality suppose we have a group of people, each of whom we are going to classify into one and only one of n categories $C_1, C_2, \ldots, C_n$. (In our above example C_1 must denote normal and C_2 deviate.) To decide into which category to place an individual, we administer a test and based on his performance we place him with a certain probability in category C_i, $i = 1, 2, \ldots, n$. Suppose we can list the responses of interest to us as:

$$R_1, R_2, \ldots, R_m .$$

In our above example R_1 would denote scoring above a fixed cutting score and R_2 would denote scoring below the fixed cutting score. Assume, as in our above example, that we know p_{ij}, the probability of an individual whose true category is C_i exhibiting the response R_j on the test. Let P denote the matrix: $[p_{ij}]_{n \times m}$. In our above example,

$$P = \begin{bmatrix} 0.3 & 0.7 \\ 0.9 & 0.1 \end{bmatrix} .$$

It is also assumed that we know w_{ij}, the probability of assigning an individual with test response R_i to category C_j. Therefore, matrix $W = [w_{ij}]_{m \times n}$ is also known. In our above example,

$$W = \begin{bmatrix} 0.2 & 0.8 \\ 0.9 & 0.1 \end{bmatrix} .$$

Now the probability of assigning an individual actually in category C_i to category C_j is seen to be

$$v_{ij} = \sum_{k=1}^{m} p_{ik} w_{kj} .$$

When $i = j$, v_{ij} represents the probability of correctly assigning a person to category C_i. Also, by the definition of matrix multiplication, we have:

$$V = P \cdot W$$

where matrix $V = [v_{ij}]_{n \times n}$. In our above example,

$$V = P \cdot W = \begin{bmatrix} 0.3 & 0.7 \\ 0.9 & 0.1 \end{bmatrix} \cdot \begin{bmatrix} 0.2 & 0.8 \\ 0.9 & 0.1 \end{bmatrix} = \begin{bmatrix} .69 & .31 \\ .27 & .73 \end{bmatrix}.$$

Thus, if we use the naive personnel clerk's method to classify people, the probability is .69(.73) that a normal (deviate) person will be correctly designated as being normal (deviate), and the probability is .27(.73) that a normal (deviate) person will be classified as deviate (normal).

Next, we shall attempt to improve the accuracy of the results of classifications. However, in order to define what is meant by "improvement," we need a criterion function which will give us a numerical measure of how good a given classification scheme is. In the case of our example, we need a measure of the effectiveness of the values of matrix W in properly assigning people. One obvious criterion function of W is the sum of the diagonal elements of V, i.e.,

$$f(W) = \sum_{i=j}^{n} v_{ij} \equiv \text{trace of } V \ ,$$

since v_{ij} represents the correct assignment of an individual to category C_i. For our example,

$$f(W) = \text{trace of } V = .69 + .73 = 1.42 \ .$$

Can we improve this figure by varying the w_{ij} and increasing the trace of $V = P \cdot W$? From the construction of W it is clear that:

$$\sum_{j=1}^{m} w_{ij} = 1 \ , \quad i = 1, 2, \ldots, n \ ,$$

i.e., the sum of the elements in any row is one because for any response, an individual must be assigned to one and only one category. The same is true, of course, for P. Thus, for our example, W must be in the form:

$$W = \begin{bmatrix} 1-x & x \\ y & 1-y \end{bmatrix} \qquad \begin{matrix} 0 \le x \le 1 \\ 0 \le y \le 1 \end{matrix} \ .$$

Thus,

$$V = \begin{bmatrix} .3 & .7 \\ .9 & .1 \end{bmatrix} \begin{bmatrix} 1-x & x \\ y & 1-y \end{bmatrix} .$$

Therefore, the trace of

$$\begin{aligned} V &= f(W) = g(x,y) \\ &= [.3(1 - x) + .7y] + [.9x + .1(1 - y)] \\ &= .6x + .6y + .4 . \end{aligned}$$

If we set

$$z = .6x + .6y + .4 , \qquad 0 \leq x,y \leq 1 ,$$

the graph of this equation in x,y, z-space is a plane, as shown in Figure 1.

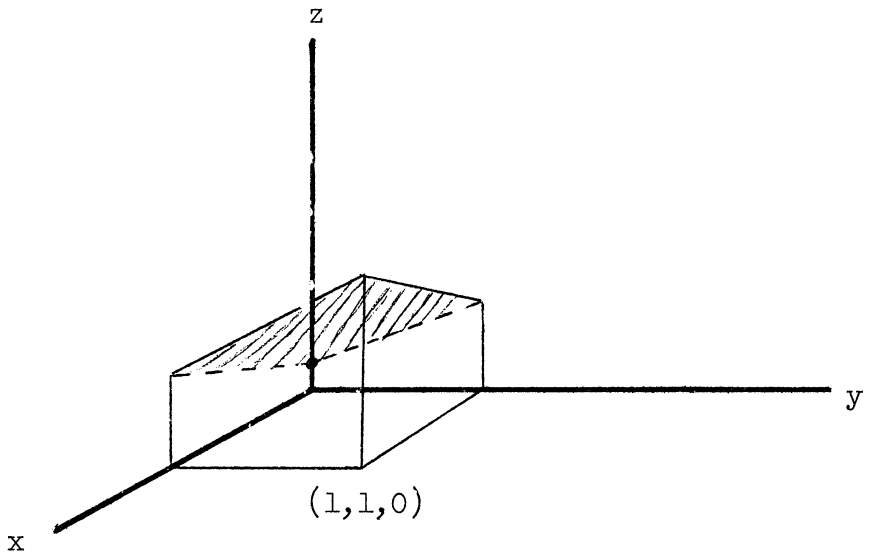


Figure 1

Clearly, z is at a maximum when x + y is at a maximum, since

$$z = .6(x + y) + .4 .$$

Thus, the maximum of z occurs for x = 1, y = 1, for an assignment:

$$W = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix},$$

i.e., we should classify all those who score above the cutoff score as deviate and all those who score below as normal. Then

$$V = \begin{bmatrix} .3 & .7 \\ .9 & .1 \end{bmatrix} \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} = \begin{bmatrix} .7 & .3 \\ .1 & .9 \end{bmatrix}$$

and

$$f(W) = \text{trace of } V = .9 + .7 = 1.6 > 1.42 ,$$

where 1.42 is the value obtained by using the classification scheme of the personnel clerk.

Other criterion functions are possible. For example, we can establish a criterion which weights each of the entries in V by a different amount, depending upon how much is saved by each type of correct classification and how much is lost by each type of incorrect classification. In the above problem, for example, we might adjust our weights so that it is much less costly to screen out a normal person than allow a deviate to pass.

EXERCISES:

1. In our example, $P = \begin{bmatrix} .3 & .7 \\ .7 & .3 \end{bmatrix}$. What interpretation can be given to the criterion function, $f(W) = 5v_{11} + 5v_{12} + v_{21} + 5v_{22}$? For what W is f(W) at a maximum?

2. Construct a criterion function f(W) which will maintain a low probability of classifying a deviate incorrectly, but need not keep low the probability of classifying a normal person as a deviate. Solve for the W giving f(W) the maximum value.

3. Again, for $P = \begin{bmatrix} .3 & .7 \\ .7 & .3 \end{bmatrix}$, interpret:

$$f(W) = v_{11} + v_{22} = \text{trace of } V , \quad \text{and } v_{21} = .1 .$$

Maximize f(W).

4. We know that the sum of the elements in any row of the matrices P and W is one. Show for the 2 × 2 case that the same is true for V, $V = P \cdot W$. Can this be generalized to the n × n case?

****

A SIMPLIFIED BALANCE SYSTEM WITH STOCHASTIC CONSIDERATIONS

Contributor: Richard F. Baum*

****

Mathematics: differential equations (Math. 4), stochastic processes

Abstract: A simplified balance system is examined in which the inputs are samples from a random process.

*Based upon: Jacquez, John A. "Balance Studies on Compartmental Systems with Stochastic Inputs," Journal of Theoretical Biology, XI (1966), 446-458.

The clinical investigator is frequently interested in measuring the intake, utilization, and excretion, of various dietary constituents and the balance between intake and excretion. Under ideal conditions, such a "balance study" is carried out by putting the patient on a constant dietary intake and measuring both intake and excretion. However, it is often not possible to maintain a constant intake over a long period of study. In this model a simple situation is studied in which intake is a stationary stochastic process.

Consider a uniformly and instantaneously mixed one-compartment system for which the intake of a given element occurs as a single instantaneous input at the same time each day.

Let $x_i(w)$ [$w \in S$, S a sample space] denote the amount of the element ingested on day i, $i = 1,2,\ldots,N$. It is assumed that this is a random sample from a (wide-sense) stationary stochastic process.* In addition, assume that the intake is instantaneous and occurs at the start of day i. Also let $q_i(w)$ denote the total amount of the element in the compartment at the start of day i, just before the intake $x_i(w)$.

Assume that the rate of excretion of the element at any time is equal to K times the amount of the element in the compartment. K is called the excretion constant. The basic unit of time is assumed to be one day.

From the above, the amount present in the compartment just after the start of day i is $(q_i(w) + x_i(w))$. Let $A_i(w,t)$ denote the amount of the element present in the compartment at day i at time t, $0 \leq t < 1$ where t is measured in days. From the assumption on excretion, we get, for constant w,

$$DA_i(w,t) = -KA_i(w,t) \; . \tag{1a}$$

Solving (1a), we obtain:

---

* A stochastic process for which the mean is a constant, and the autocorrelation is a function only of the difference of times, i.e., $E[x(w,t)] = \text{constant}$, $E[x(w,t_1)\cdot x(w,t_2)] = \text{function of } (t_1 - t_2)$.

$$(1) \qquad A_i(w,t) = [q_i(w) + x_i(w)]\, e^{-Kt}\ *, \quad i = 1,2,\ldots,N\ .$$

The meaning of (1) is as follows: At the start of day i, an "event" $w_o \in S$ is determined, which in turn determines $x_i(w)$, $w = w_o$. The quantity $q_i(w)$ was determined by an event $w_i \in S$ the day before (as we will see). Finally q_{i+1} is determined, since $q_{i+1} = A_i(w,1)$.

Thus, if $q_{i+1}(w)$ denotes the amount of element remaining in the system at the end of day i just before another "feeding",

$$(2) \qquad q_{i+1}(w) = [q_i(w) + x_i(w)]\, e^{-K}$$

by equation (1). It follows that the amount excreted on the i^{th} day is

$$[q_i(w) + x_i(w)][1 - e^{-K}]\ .$$

Suppose that this process has been going on for N days, and that the amount in the compartment at the start of the process was $q_i(w)$. Substituting the corresponding equations for $q_i(w)$, $q_{i-1}(w)\ldots$ into equation (2) gives:

$$(3) \qquad q_{i+1}(w) = x_i(w)\, e^{-K} + x_{i-1}(w)\, e^{-2K} + x_{i-1}(w)\, e^{-3K} + \ldots$$
$$+ x_{i-N-1}(w)\, e^{-NK} + q_i(w)\, e^{-NK}\ .$$

From the assumption that x_j is a random sample from a stationary process, we have

$$E[x_i(w)] = E[x_{i-1}(w)] = \ldots = E[x_{i-N-1}(w)] = M_x$$

where E( ) is the expected value operator. Taking the expected value of both sides of equation (3), and denoting $E[q_{i+1}(w)]$ as $M_{q_{i+1}}$, we get:

$$(4) \qquad M_{q_{i+1}} = M_x\, e^{-K} \sum_{j=0}^{N-1} e^{-jK} + E[q_i(w)]\, e^{-NK}\ .$$

---

* Under circumstances of uniform periods, the exponential factor becomes a simple multiplicative constant. However, in the case of variable feeding intervals, it is an important variable.

The first term on the right-hand side of (4) is a truncated power series which may be summed to give the equation:

$$(5) \qquad M_{q_{i+1}} = M_x\, e^{-K}\left[\frac{1 - e^{-NK}}{1 - e^{-K}}\right] + E[q_i(w)]\, e^{-NK} .$$

If N is large, $E(q_i(w))$ is of the same order of magnitude as M_x, and e^{-NK} is small, the last term of (5) may be neglected. Note that the requirement that e^{-NK} be very small is not stringent, for if $e^{-K} = 0.5$, $e^{-10K} < 0.001$, so that the above assumption is reasonable for $N > 10$. This means equation (5) can be approximated by

$$(6) \qquad M_{q_{i+1}} = M_x \frac{e^{-K}}{1 - e^{-K}} ,$$

i.e., we can write $\sum_0^{N-1} e^{-jK}$ in (4) as $\sum_0^{\infty} e^{-jK}$, i.e., we can assume that the process has been going on for an infinitely long time. Since equation (6) holds for all i, i = 1,2,...,N, we see that

$$E(q_i(w)) = E(q_{i-1}(w)) = \ldots = M .$$

Equation (6) may be written as

$$(7) \qquad M_q = M_x \frac{e^{-K}}{1 - e^{-K}} .$$

Define diet balance for day i, $b_i(w)$, as the intake minus the excretion. Thus,

$$b_i(w) = x_i(w) - (q_i(w) + x_i(w))[1 - e^{-K}]$$

or

$$(8) \qquad b_i(w) = x_i(w)\, e^{-K} - q_i(w)[1 - e^{-K}] .$$

Let

$$M_{b_i} = E[b_i/x_i]$$

be the conditional expected value of $b_i(w)$ given the intake x_i. By taking the expected values of both sides of equation (8), but treating x_i as fixed (i.e., conditioning on x_i) we get:

$$M_{b_i} = x_i e^{-K} - M_q[1 - e^{-K}] .$$

By (7) this gives:

(9) $$M_{b_i} = (x_i - M_x) e^{-K} .$$

Thus, the expected daily balance is a linear function of the intake. In other words, equation (9) predicts a linear regression of daily balances on the intakes with a slope of e^{-K} and an intercept of $-M_x e^{-K}$.

Note that the parameters of the regression line depend only on the mean value of the process representing the intakes, and are independent of the distribution of intakes. The essential property of these intakes, used above, is the assumption of (wide-sense) stationarity. If σ_x^2 is the variance of process x_i, it can be shown that the variance about the regression line,

$$\sigma_b^2 = E\left[(b_i - M_{b_i})^2\right] ,$$

is given by:

$$\sigma_b^2 = E\left[(b_i - M_{b_i})^2\right] = \frac{e^{-2K}\left[1 - e^{-K}\right]^2}{1 - e^{-2K}} \sigma_x .$$

****

PURIFYING NOISY BIOLOGICAL DATA BY AVERAGING

Contributor: John Almasi

****

Mathematics: mean and variance of random variables (Math. 2P)

Abstract: The purification of biological signals in the presence of noise is considered as an averaging problem.

Consider the problem of determining the response of an organism to an applied stimulus when there is much noise present; i.e., when there is extraneous information present along with the desired information. An example of this would be the study of evoked electroencephalographic response in the presence of random electrical noise such as background brain waves. We can effectively "filter" the noise out of the desired response (signal) by taking the average of many responses.

Suppose our measuring system is recording responses which can be represented by the following time function:

$$f(t,\omega) = s(t) + \epsilon(\omega) \ .$$

Here $s(t)$ is a deterministic, single-valued function of time and $\epsilon(\omega)$ is a normally distributed random variable which has mean or expected value 0 and variance σ^2, or

$$E[\epsilon(\omega)] = 0 \ , \qquad \text{var}[\epsilon(\omega)] = \sigma^2 \ ,$$

where $\omega \in \Omega$, the sample space of observations.

To analyze the problem, we introduce a performance, or purity, index which indicates the relative purity of the data obtained. We shall define this index as the signal-to-noise ratio which is a function of time:

$$\left(\frac{S}{N}\right)_{f(t_1,\omega)} \equiv \frac{E[f(t_1,\omega)]}{\sqrt{\text{var}[f(t_1,\omega)]}}$$

$$= \frac{\text{Expected value of } f(t,\omega) \text{ at } t = t_1}{\sqrt{\text{variance of } f(t,\omega) \text{ at } t = t_1}}$$

where t_1 is an arbitrary time selected from the interval of observation. Since the expected value of a sum equals the sum of the expected values of its terms, we can write

$$E[(f(t_1,\omega)] = E[s(t_1) + \epsilon(\omega)] = E[s(t_1)] + E[\epsilon(\omega)] \ .$$

But the expected value of a constant is that constant, so that

$$E[s(t_1)] + E[\epsilon(\omega)] = s(t_1) + E[\epsilon(\omega)] \ .$$

Finally, since $E[\epsilon(\omega)]$ is 0 by assumption,

$$E[(f(t_1,\omega)] = s(t_1) \ .$$

If we consider the variance, we see that

$$\begin{aligned} \text{var}[f(t_1,\omega)] &= \text{var}[s(t_1) + \epsilon(\omega)] \\ &= \text{var}[s(t_1)] + \text{var}[\epsilon(\omega)] \\ &= \text{var}[\epsilon(\omega)] \\ &= \sigma^2 \ , \end{aligned}$$

since the variance of a constant plus a random variable is the variance of the random variable. Therefore, we can write

$$\left(\frac{S}{N}\right)_{f(t_1,\omega)} = \frac{s(t_1)}{\sqrt{\sigma^2}} = \frac{s(t_1)}{\sigma} \ ,$$

the purity index without averaging.

We can obtain (by successive measurement) n values of $f(t_1,\omega)$ and find their average. Let the n values be denoted $f(t_1,\omega_1)$, $f(t_2,\omega_2)$, ..., $f(t_n,\omega_n)$. Then

$$\begin{aligned} f(t_1,\omega_1) &= s(t_1)_1 + \epsilon(\omega_1) \\ f(t_1,\omega_2) &= s(t_1)_2 + \epsilon(\omega_2) \\ &\vdots \\ f(t_1,\omega_n) &= s(t_1)_n + \epsilon(\omega_n) \ . \end{aligned}$$

The sum,

$$\begin{aligned} \frac{1}{n} F(t_1,\omega) &= \frac{1}{n} \sum_{j=1}^{n} f(t_1,\omega_j) \\ &= \frac{1}{n} \sum_{j=1}^{n} s(t_1)_j + \frac{1}{n} \sum_{j=1}^{n} \epsilon(\omega_j) \\ &= s(t_1) + \frac{1}{n} \sum_{j=1}^{n} \epsilon(\omega_j) \end{aligned}$$

(because $s(t_1)$ is a deterministic function, $s(t_1)_1 = s(t_1)_2 = \ldots = s(t_1)_n$.)

We can now compute

$$\left(\frac{S}{N}\right)_{F(t_1,\omega)_{av}}$$

to determine whether we have improved the purity index by averaging. Let

$$F(t_1,\omega)_{av} = \frac{1}{n} F(t_1,\omega) = s(t_1) + \frac{1}{n} \sum_{j=1}^{n} \epsilon(\omega_j) .$$

As before, the expected value of a sum is the sum of the expected values, so that

$$\begin{aligned} E[\ F(t_1,\omega)_{av}] &= E[s(t_1)] + \frac{1}{n} E[\epsilon(\omega_1) + \epsilon(\omega_2) + \ldots + \epsilon(\omega_n)] \\ &= s(t_1) + \frac{1}{n} (E[\epsilon(\omega_1)] + E[\epsilon(\omega_2)] + \ldots + E\ \epsilon(\omega_n)]) \\ &= s(t_1) + \frac{1}{n} (0 + 0 + \ldots + 0) \\ &= s(t_1) \end{aligned}$$

$$\begin{aligned} \mathrm{var}[F(t_1,\omega)_{av}] &= \mathrm{var}[s(t_1)] + \mathrm{var}[\tfrac{1}{n}(\epsilon(\omega_1) + \ldots + \epsilon(\omega_n))] \\ &= 0 + \frac{1}{n^2}\Big(\mathrm{var}[\epsilon(\omega_1)] + \mathrm{var}[\epsilon(\omega_2)] + \ldots + \mathrm{var}[\epsilon(\omega_n)]\Big) \ , \end{aligned}$$

since $\epsilon(\omega_1)$, $\epsilon(\omega_2)$, ..., $\epsilon(\omega_n)$ are independent. But

$$\mathrm{var}[\epsilon(\omega_1)] = \mathrm{var}[\epsilon(\omega_2)] = \ldots = \mathrm{var}[\epsilon(\omega_n)] = \sigma^2$$

so that

$$\mathrm{var}[F(t_1\omega)_{av}] = \frac{1}{n^2} (\sigma^2 + \sigma^2 + \ldots + \sigma^2) = \frac{1}{n^2} (n\sigma) = \frac{\sigma^2}{n} .$$

Therefore,

$$\left(\frac{S}{N}\right)_{F(t_1,\omega)av} = \frac{s(t_1)}{\sqrt{\sigma^2/n}} = \sqrt{n}\,\frac{S(t_1)}{\sigma} \ .$$

Thus, the performance of purity index has been improved by $\sqrt{n}$ by adding up n responses and taking the average.

****

SIMPLE MODEL FOR ADAPTATION IN A NEURAL NETWORK

Contributor: Richard F. Baum

****

Mathematics: eigenvalues, eigenvectors, linear transformations (Math. 3), limits of vectors, stochastic matrices

Abstract: The adaptation of a neural network is investigated using a simplified mathematical model.

Consider a chain of neurons controlled by a feedback mechanism to the extent that once fired, they can be refired with a certain probability. Such a situation might occur in the reflex arcs governing a nervous twitch or "rocking," i.e., periodic actions which are not under conscious control during each cycle. Due to such physiological characteristics as "refractory time," which is the time needed for a neuron to recover from a previous firing so that it is able to fire again, we may assume that the neurons comprising the chain fire at discrete times. Let τ (in seconds) be the minimum period between successive firings. Although it is true that if a neuron does not refire after a delay of τ seconds, it may refire at any time after this, let us assume that firing occurs at discrete times separated by a delay period of τ seconds. This assumption has been made for a number of models studying the interaction of neurons, and allows us to speak of "stages," or discrete times, in the sense that we can ask: If a neuron in the chain fires at stage i, will it also fire at stage (i + 1) when the time between stages is τ? Let us define $P_i(F|F)$ as the probability that the chain will fire at stage i if it fired at stage (i - 1), and $P_i(H|F)$ as the probability that the chain will not fire at stage i if it fired at stage (i - 1). $P_i(F|H)$ and $P_i(H|H)$ are defined in a similar manner. We shall also assume that the firing of the chain has continued for a sufficiently long time so that these probabilities are at their steady-state values, i.e., they are constant, independent of i. Thus,

$$P_i(F|F) = P(F|F), \quad i = 0,1,\ldots$$

$$P_i(H|F) = P(H|F), \quad i = 0,1,\ldots$$

and similarly for the other two. Finally, let $\pi(i)$ be the vector

$$\pi(i) = \begin{bmatrix} P_i(F) \\ P_i(H) \end{bmatrix}, \qquad \begin{aligned} 0 \le P_i(F), P_i(H) \le 1 \\ P_i(F) + P_i(H) = 1 \end{aligned}$$

where $P_i(F)$ is the probability that the chain will fire at stage i,

$P_i(H)$ is the probability that the chain will not fire at stage i. For i = 0, $\pi(0)$ denotes the "initial" conditions for the chain. For example, $\pi(0)$ may be determined by stimuli external to the network. Once $\pi(0)$ is known, $\pi(N)$ can be calculated for any N using the above data. Let T be the matrix:

$$T = \begin{bmatrix} P(F|F) & P(F|H) \\ P(H|F) & P(H|H) \end{bmatrix}$$

Then, $\pi(1)$ is given by:

$$\pi(1) = T \cdot \pi(0) \tag{1}$$

Similarly, $\pi(2)$ is equal to:

$$\begin{aligned} \pi(2) &= T \cdot \pi(1) \\ &= T^2 \cdot \pi(0) \ . \end{aligned}$$

and in general,

$$\pi(N) = T^N \cdot \pi(0) \ . \tag{2}$$

Note that the elements of each column of T sum to 1, and that each element of T is a number between zero and one. Such a matrix is called a stochastic matrix.

As an example of the above, assume T and $\pi(0)$ are given by

$$T = \begin{bmatrix} 3/4 & 1/8 \\ 1/4 & 7/8 \end{bmatrix}$$

and

$$\pi(0) = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

i.e., it is certain that the network will not fire at stage 1. Then

$$\pi(1) = T \cdot \pi(0) = \begin{bmatrix} 3/4 & 1/8 \\ 1/4 & 7/8 \end{bmatrix} \begin{bmatrix} 0 \\ 1 \end{bmatrix} = \begin{bmatrix} 1/8 \\ 7/8 \end{bmatrix}$$

i.e., at stage 2 the probability that the network will fire and the

probability that it will not fire is 7/8. Similarly,

$$\pi(2) = T\cdot\pi(1) = T^2\,\pi(0) = \begin{bmatrix} 13/64 \\ 51/64 \end{bmatrix}$$

$$\pi(3) = T^3\pi(0) = \begin{bmatrix} 129/512 \\ 383/512 \end{bmatrix}$$

$$\pi(4) = T^4\,\pi(0) = \begin{bmatrix} 1157/4096 \\ 2939/4096 \end{bmatrix}$$

It can be shown that $\pi(N)$ approaches

$$q = \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix}$$

i.e.,

$$q = \lim_{N\to\infty} T^N\,\pi(0)$$

in the sense that for

$$\pi(N) = \begin{bmatrix} P_N\,(F) \\ P_N\,(H) \end{bmatrix} \quad \text{and} \quad q = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix} = \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix}$$

if

$$\lim_{N\to\infty} P_N(F) = q_1 = 1/3$$

and

$$\lim_{N\to\infty} P_N(H) = q_2 = 2/3,$$

we can show that if

$$W = \lim_{N\to\infty} T^N\,\pi(0)$$

then W must satisfy TW = W. This follows directly from the con-

tinuity of the linear transformation, i.e.,

$$TW = T[\lim_{N\to\infty} T^N \pi(0)]$$

$$= \lim_{N\to\infty} [T[T^N \pi(0)]]$$

$$= \lim_{N\to\infty} T^{N+1} \pi(0)$$

$$= W.$$

For the above example we have, by matrix multiplication,

$$T_q = \begin{bmatrix} 3/4 & 1/8 \\ 1/4 & 7/8 \end{bmatrix} \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix} = \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix} = q$$

as is required.

Thus, if we don't fire the network at the first stage, then in the long run, we will have a probability of: 1/3 that the chain will fire at a stage $N > N_o$, where N_o is a large number; and 2/3 that the chain will not fire at a stage $N > N_o$, where N_o is a large number. If we set

$$\pi(0) = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

we find that

$$\pi(1) = \begin{bmatrix} 3/4 \\ 1/4 \end{bmatrix}, \qquad \pi(2) = \begin{bmatrix} 19/32 \\ 13/32 \end{bmatrix},$$

$$\pi(3) = \begin{bmatrix} 127/256 \\ 129/256 \end{bmatrix}, \qquad \pi(4) = \begin{bmatrix} 891/2048 \\ 1157/2048 \end{bmatrix}.$$

By the same reasoning as before, we obtain the limiting value

$$\lim_{N\to\infty} T^N \pi(0) = \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix}$$

i.e., even if we fire the network at the fire stage, the long run

situation does not change. In fact, in this case $\lim_{N\to\infty} T^N \pi(0)$ is unique; after a large number of stages, the network "forgets" what first happened. This can be seen by the following. Let

$$T = \begin{bmatrix} 1 - a & b \\ a & 1 - b \end{bmatrix}, \quad 0 \leq a, \; b \leq 1, \; 0 < a + b .$$

The characteristic polynomial of T is $(x - 1)(x - [a + b - 1])$. Therefore, T has characteristic values 1 and $(a + b - 1)$. The second has an absolute value less than one by assumption. Because

$$\lim_{N\to\infty} T^N \pi(0) = q$$

is a characteristic vector associated with the characteristic value 1 and has non-negative components that sum to 1, it must be unique.

EXERCISES

1. Using mathematical induction, show that $\lim_{N\to\infty} T^N \pi(0) = \begin{bmatrix} 1/3 \\ 2/3 \end{bmatrix}$ (For a more general result, see Parzen (1962), p. 196.)

2. To "break a habit," we exert a conscious effort to prevent networks from firing. What effects will this have on T?

3. Let
$$T = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} .$$
What is $\lim_{N\to\infty} T^N \pi(1)$ for different $\pi(1)$. Be sure to interpret what the above T implies about the chain.

4. Repeat 3. for
$$T = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} .$$

****

VISUAL ADAPTATION

Contributor: James Mortimer*

****

Mathematics: differentiation (Math.1), Poisson series (Math.2P)

Abstract: The absorption of light quanta and subsequent bleaching of rhodopsin in the rods is examined, and a model for light adaptation is derived.

*Based upon: Wald, G.; Brown, P.K.; and Smith, P.M. "Iodopsin," Journal of General Physiology, XXXVIII (1955), 623-691.

It is known that the eye loses sensitivity in the light and regains it in darkness. These changes, referred to as light and dark adaptation, are generally attributed to the bleaching and resynthesis of visual pigments - rhodopsin in the rods and other pigments in the cones.

Experiments have shown that a dark-adapted rod can respond to a single quantum of light, i.e., to the bleaching of a single molecule of rhodopsin. Furthermore, measurements of the amount of rhodopsin as a function of visual threshold, have shown that the amount of visual pigment in the rods is approximately proportional to 1/ log threshold, where the threshold is defined as the lowest value of luminance (in millilamberts) at which the stimulus is perceived. In order to explain the relationship between the amount of rhodopsin and threshold and to take into account the fact that the threshold depends on the entire content of rhodopsin in the rod, a compartmentalized structure of the rod has been postulated with the following properties:

1. Each compartment responds in an all-or-none way when the first molecule of rhodopsin in that compartment is bleached, i.e., when the first quantum of light is absorbed.
2. Further absorption of light by that compartment has no effect on the electrical signal generated by the rod.

Let N_o be the number of compartments in a rod. Suppose N_x compartments have absorbed at least one quantum of light. If T_o is the dark-adapted threshold (with no compartments "discharged"), then let T_x, the new threshold with N_x compartments discharged, be given by:

$$T_x = T_o \frac{N_o}{N_o - N_x} \tag{1}$$

It can be seen that relatively few molecules of rhodopsin need to be bleached in order for the threshold to change significantly, since only one molecule in each compartment needs to be bleached in order for the whole compartment to "discharge".

Consider a single rod. Let X be the number of molecules of visual pigment bleached by the light in discharging N_x compartments. Clearly min [X] = minimum value of $X = N_x$.

The mean number of molecules bleached per compartment is X/N_o.

If all compartments are equally likely to absorb incident light quanta and if the mean number $\mu = X/N_o$ per compartment is small, then the number of compartments absorbing 0, 1,...N,... quanta is given by a Poisson series. (Actually, because of the layered structure of a rod, not all compartments have an equal chance of absorbing incident light quanta. For small μ, however, the series gives a good approximation.) Thus, if y is the number of quanta absorbed by a compartment, then the probability that a compartment will absorb exactly y quanta is given by

$$p(y) = \frac{e^{-\mu}\mu^y}{y!} = \frac{e^{-X/N_o}(X/N_o)^y}{y!} \tag{2}$$

The fraction of compartments absorbing no quanta, i.e., those not discharged, is given by

$$\frac{N_o - N_x}{N_o} = \frac{e^{-X/N_o}(X/N_o)^0}{0!} = e^{-X/N_o} \tag{3}$$

But $T_x/T_o = N_o/(N_o - N_x)$, so that

$$e^{X/N_o} = \frac{T_x}{T_o} \tag{4}$$

Solving for X, we get

$$X = N_o \ln \frac{T_x}{T_o} = N_o \ln T_x - N_o \ln T_o \tag{5}$$

Since X and T_x are the only variables in equation (5) this equation describes a linear relationship between the logarithm of the visual threshold and the number of molecules of pigment bleached in a receptor, X.

Suppose that there were initially X_o molecules of rhodopsin in a dark-adapted receptor and that X were bleached. The remaining amount, C, of rhodopsin would then be given by

$$C = X_o - X = X_o - N_o \ln \frac{T_x}{T_o}$$

$$(6) \qquad = (X_o + N_o \ln T_o) - N_o \ln T_x$$

which is of the form

$$C = a - b \ln T_x, \text{ where a and b are constants.}$$

so that if C-a is viewed as the change in concentration from the dark-adapted state, this change is directly proportional to $-\log_e$ threshold or to $\log_e$ sensitivity, where S_x = sensitivity = $1/T_x$.

EXERCISES

1. Suppose that light quanta strike a rod at a rate of m quanta per second and that all quanta are absorbed by molecules of rhodopsin. What is the rate of light adaptation (of change of sensitivity)?

SOLUTION:

Assume that the rod is initially dark-adapted with X_o molecules of rhodopsin distributed equally among N_o compartments. We are interested in the rate of change of S_x with time. From (1):

$$(7) \qquad S_x = \frac{1}{T_x} = \frac{1}{T_o}\left(1 - \frac{N_x}{N_o}\right)$$

so that

$$(8) \qquad \frac{dS_x}{dt} = -\frac{1}{N_o T_o}\frac{dN_x}{dt}$$

but N_x = the number of compartments discharged = N_o - number of undischarged compartments, or

$$(9) \qquad N_x = N_o\left(1 - e^{-X/N_o}\right)$$

$$(10) \qquad dN_x/dt = d/dt\left(N_o - N_o e^{-X/N_o}\right) = e^{-X/N_o}\, dX/dt = e^{-X/N_o} \cdot m$$

so that

$$(11) \qquad \frac{dS_x}{dt} = -\frac{1}{N_o T_o} e^{-X/N_o} \cdot m = \text{rate of light adaptation}$$

2. Consider the limiting case in which there is exactly 1 molecule of pigment in each compartment. In the cones of the fovea this is approximately the situation. How does the number of molecules per

compartment affect the rate of light adaptation?

SOLUTION:

From (10)

$$\frac{dS_x}{dt} = \frac{1}{N_o T_o} e^{-X/N_o} \cdot m$$

With one molecule per compartment, $X = N_x$ and

$$\left.\frac{dS_x}{dt}\right|_{X=N_x} = -\frac{1}{N_o T_o} e^{-N_x/N_o} \cdot m$$

But, in general, $X \geq N_x$, so $e^{-N_x/N_o} \geq e^{-X/N_o}$, with equality iff $N_x = X$. Therefore,

$$\left.\frac{dS}{dt}\right|_{X=N_x} > \left.\frac{dS}{dt}\right|_{X \neq N_x}$$

so that the rate of adaptation is increased by decreasing the number of molecules per compartment (when the total number of molecules is held constant.) This result is supported by experimental evidence.

3. Suppose $N_o = 100$ and that initially the rod in question is dark-adapted, so that $N_x\ (t = 0) = 0$. How long will it take for the sensitivity to decrease to one-half of its initial value?

SOLUTION:

$S_x = 1/T_x = 1/T_o(1 - N_x/N_o) = S_o(1 - N_x/N_o)$, where $S_o = 1/T_o =$ initial sensitivity .

We want the time when $N_x = N_o/2$, so that $S_x = S_o/2$.

From (9)

$$N_x = N_o(1 - e^{-X/N_o}) .$$

Substituting, we get

(12) $$50 = 100(1 - e^{-X/100}) .$$

Solving (12) for X:

$$X = 100 \ln 2$$

and since $X = mt$

$$t = 100 \ln 2/m,$$

the time at which the sensitivity is decreased by a factor of two.

---

1. Bartlett, N.R. "Threshold as Dependent on Some Energy Relations and Characteristics of the Subject." Vision and Visual Perception. Edited by C.H. Graham. New York: Wiley and Sons, 1965, 154-184.

2. Wald, G. "On the Mechanism of the Visual Threshold and Visual Adaptation." Science, 119 (1954), 887-892.

3. Wald, G. "The Photoreceptor Process in Vision." Handbook of Physiology: Neurophysiology. Edited by J. Field, H.W. Magoon, and V.E. Hall. Washington, D.C.: American Physiological Society, 1959, 671-692.

POPULATION BIOLOGY

****

POPULATION GROWTH DESCRIBED BY A FUNCTION

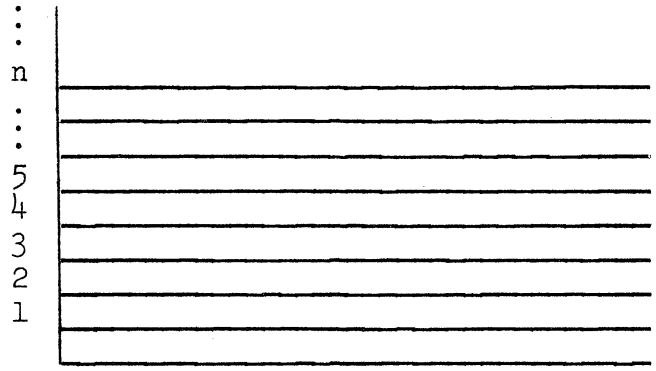
Contributor: Kenneth R. Rebman

****

Mathematics: elementary functions (Math. 0)

Abstract: The basic notions of a function (domain, range) are illustrated for a function describing population growth, a very common function in biology.

Let T be $\{t \mid t \text{ is a real number} \geq 0\}$ and Z be the set of positive integers. We can interpret $t \in T$ as representing some time after a fixed starting time $t = 0$. Then, $T \times Z$ is $\{(t,n) \mid t,n \text{ are real numbers} \geq 0, n \text{ an integer}\}$. $T \times Z$ can be represented graphically by:



If we have a certain population, say P, in mind, e.g., P may be a population of people or bacteria, we can define a relation R in $T \times Z$ by tRn if and only if population P has exactly n members at time t. It is clear that R is a function, since at a given instant the total population is a single number.

Since R is a function, it is more convenient to write $n = f(t)$ if tRn .

The domain of f is the set T; the range is some subset of Z.

It may well be that physical considerations make it impossible for the population to become arbitrarily large. Then, our range would be a subset of Z whose elements are less than or equal to N, where N is the maximum size of the population.

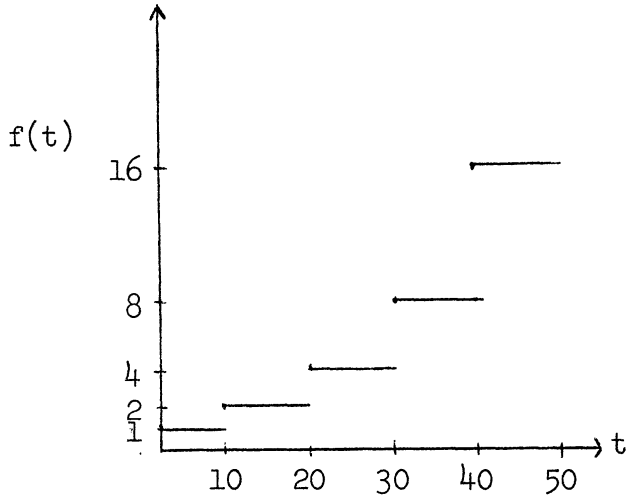
An interesting problem is to describe the function f. As a specific example, suppose that in a population of microscopic organisms, each organism divides to form two organisms every 10 seconds, and that at time $t = 0$, one organism is present. (If no organisms were present at $t = 0$, then $f(t) = 0$ for all $t \in T$.) Thus, until the 10 seconds have elapsed, there is one organism. After 10 seconds this organism divides, and there are two until 20 seconds, four from 20 to 30 seconds, eight from 30 to 40 seconds, etc. The function f can be written:

$$f(t) = 2^{g(t)}$$

where g(t) represents the greatest integer in t/10. This is usually denoted by g(t) = [t/10] .

Notice that g is also a function, and in fact has exactly the same domain as the function f. That is, the domain of g is all positive real numbers and the range of g is all positive integers.

In the above example, f has domain T and range all powers of 2. Its graph is given below.



****

A GRAPHIC DESCRIPTION OF A GROWTH PROCESS

Contributor: Hebrew University Report

****

Mathematics: analytical geometry

Abstract: The growth of a culture of bacteria is analyzed graphically.

When bacteria are put into a nutrient broth, we will usually notice the following behavior: in the beginning a period of adaptation (without a change in the number of bacteria); afterwards the number of bacteria increases and finally decreases. In the period of adaptation the bacteria form the enzymes necessary for them to use the food in the broth. After the period of adaptation they begin reproducing and after they finish all the food they begin to die.

In a certain (idealized) experiment the following results were obtained:

Time in Hours	Number of Bacteria
0	1,000
$\frac{1}{2}$	1,000
1	1,000
$1\frac{1}{2}$	3,200
2	10,000
$2\frac{1}{2}$	32,000
3	100,000
$3\frac{1}{2}$	320,000
4	10^6
$4\frac{1}{2}$	3.2×10^6
5	10^7
$5\frac{1}{2}$	3.2×10^7
6	10^8
$6\frac{1}{2}$	3.2×10^8
7	10^9
$7\frac{1}{2}$	10^9

Table continued

Time in Hours	Number of Bacteria
8	10^9
$8\frac{1}{2}$	10^9
9	7.5×10^8
$9\frac{1}{2}$	5.6×10^8
10	2.1×10^8
$10\frac{1}{2}$	1.6×10^8

EXERCISES:

Draw two curves

1) The number of bacteria as a function of the time.

2) The logarithm of the number of bacteria as a function of the time.

i) In which of the two curves can you clearly distinguish the period in which there is no reproduction (the period of adaptation)?

ii) In which of the two curves can you measure the amount of time in which the bacteria reproduced exponentially ?

****

EXTERMINATION OF BACTERIA

Contributor: Hebrew University Report

****

Mathematics: logarithms, analytical geometry (Math. 0)

Abstract: The decline in the number of bacteria in response to a bacteriocidal agent is obtained as a function of time.

The following experiment was conducted:

A bacteriocidal agent - i.e. an agent that kills bacteria - was added at time zero to a nutrient broth containing 10^6 viable bacteria per milliliter. The following table shows the number of viable bacteria remaining in the broth at various times after adding the anti-bacterial agent:

Time in minutes	0	10	20	30	40	50	60
Approximate number of bacteria	10^6	10^5	10^4	10^3	10^2	10	1

Draw two curves:

i) The number of viable bacteria as a function of the time.

ii) The logarithm of the number of viable bacteria as a function of the time.

With the help of these curves derive the number of viable bacteria, N(t), as a function of time.

SOLUTION:

Since the second curve is a straight line, whose equation is $y = ax + b$, and a few points on it are given, it is easy to see that

$$\log_{10} N(t) = -\frac{t}{10} + 6$$

and

$$N(t) = 10^{\frac{60 - t}{10}}$$

****

BLOOD TYPES AS SETS

Contributor: Kenneth R. Rebman

****

Mathematics: set theory (Math. 0)

Abstract: Elementary set operations are illustrated, using blood types as the sets.

In typing blood, the factors considered are the presence or absence of three antigens, usually denoted by A, B, and Rh.

Let the universal set U be the population that has been tested for blood type. Furthermore, let

$$X = \{x \mid x \in U \text{ and } x \text{ has antigen A}\}$$
$$Y = \{y \mid y \in U \text{ and } y \text{ has antigen B}\}$$
$$Z = \{z \mid z \in U \text{ and } z \text{ has antigen Rh}\} .$$

If $V \subseteq U$, the complement of V in U, i.e. U - V, will be denoted by V' .

Then:

I. $X \cap Y \cap Z = \{u \mid u \in U \text{ and } u \text{ has type } (AB, Rh^+)\}$

II. $X \cap Y \cap Z' = \{u \mid u \in U \text{ and } u \text{ has type } (AB, Rh^-)\}$

III. $X \cap Y' \cap Z = \{u \mid u \in U \text{ and } u \text{ has type } (A, Rh^+)\}$

IV. $X \cap Y' \cap Z' = \{u \mid u \in U \text{ and } u \text{ has type } (A, Rh^-)\}$

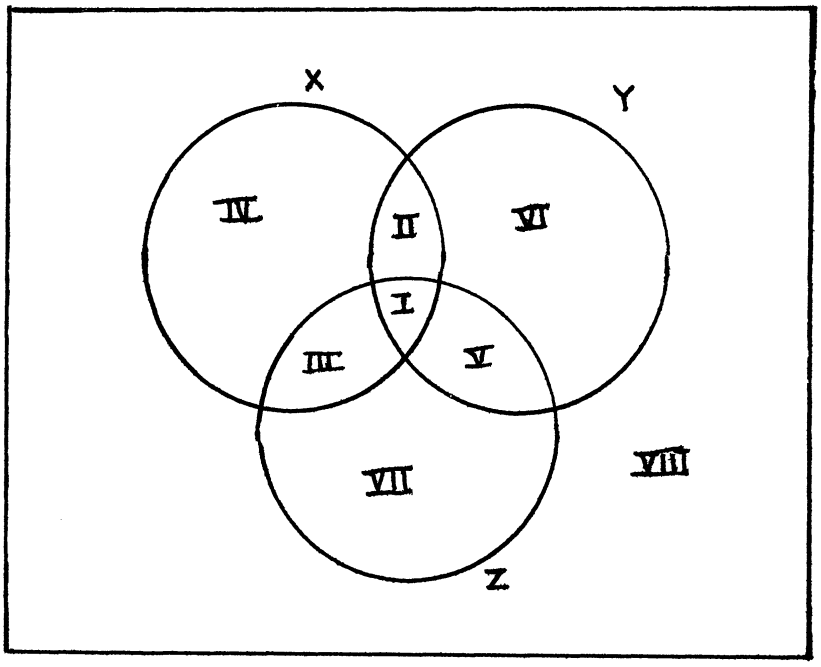
V. $X' \cap Y \cap Z = \{u \mid u \in U \text{ and } u \text{ has type } (B, Rh^+)\}$

VI. $X' \cap Y \cap Z' = \{u \mid u \in U \text{ and } u \text{ has type } (B, Rh^-)\}$

VII. $X' \cap Y' \cap Z = \{u \mid u \in U \text{ and } u \text{ has type } (O, Rh^+)\}$

VIII. $X' \cap Y' \cap Z' = \{u \mid u \in U \text{ and } u \text{ has type } (O, Rh^-)\}$

We can represent these sets by a Venn diagram:



****

RELATIONAL PROPERTIES AMONG BLOOD DONORS

Contributor: Kenneth R. Rebman

****

Mathematics: relations (Math. 0)

Abstract: A biological example, namely the problem of blood donations, is used to illustrate the definitions and properties of relations.

Let S be some set of human beings. $S \times S$ consists of all ordered pairs (x,y) where x and y are human beings.

Consider the relation on $S \times S$ defined by $\sim$ where $x \sim y$ if and only if x and y are in the same blood group, i.e., A, B, AB, O. So $\sim$ consists of all ordered pairs (x,y), where x and y are in the same blood group.

Clearly $\sim$ is an equivalence relation.

For $x \sim x$

$x \sim y \Rightarrow y \sim x$

$x \sim y$ and $y \sim z \Rightarrow x \sim z$

Thus $\sim$ induces a partition of the set of hymans into disjoint equivalence classes. These are just the classes found by the usual grouping of people by blood type. There are four such classes, and they will be denoted by A, B, AB, and O. Let $\bar{S} = \{A, B, AB, O\}$.

We will define a relation R on $\bar{S}$ by the following:

If $\bar{x}, \bar{y} \in \bar{S}$, then $\bar{x}R\bar{y}$ if and only if a person in class $\bar{x}$ (i.e., with blood type $\bar{x}$) may <u>receive</u> blood from a person in class $\bar{y}$. Thus R consists of the following subset of $\bar{S} \times \bar{S}$.

$$R = \{(A,A)(A,O)(B,B)(B,O)(AB,AB)(AB,A)(AB,B)(AB,O)(O,O)\} .$$

A matrix representation of this relation would be

	A	B	AB	O
A	1	0	0	1
B	0	1	0	1
AB	1	1	1	1
O	0	0	0	1

The transpose of this relation is

$$R^T = \{(A,A)(O,A)(B,B)(O,B)(AB,AB)(A,AB)(B,AB)(O,AB)(O,O)\}$$

and can be represented by the transpose of the above matrix.

The interpretation in this case of R^T is: For $\bar{x}, \bar{y} \in \bar{S}$, $\bar{x}R^T\bar{y}$ if and only if a person in class $\bar{x}$ (i.e., with blood type $\bar{x}$) may <u>donate</u> blood to a person in class $\bar{y}$.

It is clear that neither R nor R^T is a function.

What properties does the relation R have?

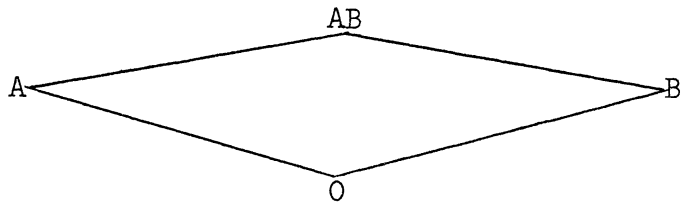
Reflexive?	yes, since $\bar{x}R\bar{x}$.
Symmetric?	no, since, e.g., BRO but not ORB .
Transitive?	yes, i.e., if x,y, and z are such that x can receive blood from y and y from z, then x can safely receive blood from z also.

Thus the symmetry property fails, so R is not an equivalence relation. This particular relation is in fact anti-symmetric, since $\bar{x}R\bar{y}$ and $\bar{y}R\bar{x} \Rightarrow \bar{x} = \bar{y}$.

Acyclic?	no, since if a relation is reflexive, it cannot be acyclic. (i.e., $\bar{x}R\bar{x}$).
Complete?	no, since, e.g., neither ARB nor BRA.

Since R is reflexive, anti-symmetric, and transitive, it is a partial order on $\bar{S}$.

We can illustrate this diagrammatically as:



If we had defined our relation originally in $S \times S$ instead of $\bar{S} \times \bar{S}$ by xRy if and only if x can receive blood from y, then we would have a relation that is reflexive and transitive, i.e., a pre-order. A pre-order can be decomposed into an equivalence relation and a partial order, as this model has demonstrated.

****

A COMBINATORIAL EXAMPLE IN GENETICS

Contributor: Harold Slater

****

Mathematics: combinations (Math. 0)

Abstract: The number of distinct diploid genotypes with n-alleles is obtained with the aid of combinations.

A certain gene has n alleles. What is the total number of distinct diploid genotypes?

SOLUTION:

Let $g^1, g^2, \ldots, g^n$ be the n alleles. A diploid genotype will have the form $g^i g^j$ (i and j are not necessarily distinct), and $g^i g^j = g^j g^i$.

The number G of distinct genotypes is the number of ways we can choose two different alleles from n plus the number of the form $g^i g^i$. Thus,

$$G = \binom{n}{2} + n = \frac{n(n+1)}{2} .$$

****

PARENTS AND THEIR POSSIBLE OFFSPRING

Contributor: Kenneth R. Rebman

****

Mathematics: relations (Math. 0)

Abstract: A very simple genetic model is used to illustrate the mathematical idea of relations.

Suppose that a single inherited characteristic is under consideration, and that this characteristic is determined by gene types A and a, A being dominant. Thus, any individual may be of type AA, Aa, or aa.

Let S = {AA,Aa,aa} represent the set of types. Then

$$S \times S = \{(AA,AA)(AA,Aa)(AA,aa)(Aa,AA)(Aa,Aa)(Aa,aa)(aa,AA)(aa,Aa)(aa,aa)\} .$$

S × S can be considered the collection of all possible sets of parents---the first member male, the second female.

However, from a genetic viewpoint, it may not be necessary to distinguish sex, but only the make-up of the individual parents.

Let us define the relation $\sim$ in S × S by

$$(x,y) \sim (x',y')$$

if either (1) x = x' and y = y' or (2) x = y' and y = x' . It is easy to verify that $\sim$ is an equivalence relation in S × S . This equivalence relation partitions S × S into disjoint equivalence classes. It is convenient to represent each equivalence class by one of its elements (much as the set of all "equal" fractions, 1/2, 2/4, 3/6, ..., is represented by the single symbol 1/2). Thus we can write

$$T = \{(AA,AA)(AA,Aa)(AA,aa)(Aa,Aa)(Aa,aa)(aa,aa)\} .$$

The selected representatives are sometimes called "canonical" representatives . Here T may be regarded as being like S × S but with the order within pairs disregarded.

Let R, a relation in T × S, be defined by:

$$(x,y)Rx$$

if and only if z could be the gene type of an offspring of parents with types x and y.

Then

(AA,AA)R(AA)

(AA,Aa)R(AA) (AA,Aa)R(Aa)

(AA,aa)R(Aa)

(Aa,Aa)R(AA) (Aa,Aa)R(Aa) (Aa,Aa)R(aa)

(Aa,aa)R(Aa) (Aa,aa)R(aa)

(aa,aa)R(aa)

The matrix representation of the above relation would be:

	Offspring		
Parents	AA	Aa	aa
AA, AA	1	0	0
AA, Aa	1	1	0
AA, aa	0	1	0
Aa, Aa	1	1	1
Aa, aa	0	1	1
aa, aa	0	0	1

****

FREQUENCY OF RECESSIVE TRAITS IN A POPULATION IN WHICH RECESSIVE HOMOZYGOTES ARE NOT ALLOWED TO REPRODUCE

Contributor: Richard F. Baum*

****

Mathematics: elementary probability, proof by mathematical induction (Math. 0)

Abstract: A theorem is proved about the decrease in frequency of recessive genes under selection against the recessive homozygote.

*Based upon: Dahlberg, Gunner. Mathematical Methods for Population Genetics. New York: Interscience Publishers, 1948.

Suppose that we are studying a characteristic of a species, which is determined by a single pair of genes at a given locus. If we assume complete dominance and neglect the effect of the environment, we may expect two phenotypes, corresponding to the recessive homozygote and the heterozygote or dominant homozygote. Let a denote the recessive gene and A, the dominant gene. Furthermore, let C_a represent the phenotype corresponding to the recessive homozygote and C_A, the phenotype associated with the dominant homozygote or heterozygote.

Suppose that an individual with phenotype C_a is prevented from entering into reproduction, as would be the case if the individual died before sexual maturity. Assume that:

(a) At a given moment genotypes aa, aA, and AA have respective proportions s_1, t_1, u_1;

(b) these proportions are the same for males and females;

(c) mating is random among persons of genotypes aA and AA, but persons of genotype aa do not mate.

Then the probability that one partner in a mating will donate gene a to an offspring is

$$r_1 = \left(\frac{1}{2}\right)\left(\frac{t_1}{t_1 + u_1}\right) ,$$

where $t_1(t_1 + u_1)$ is the probability that the partner is aA and 1/2 is the probability that such a parent will donate gene a. Then for the proportions in the succeeding generation, we have

$$(1) \qquad s_2 = r_1^2 , \qquad t_2 = 2r_1(1 - r_1) , \qquad u_2 = (1 - r_1)^2 ,$$

where the factor 2 in the expression for t_2 accounts for the fact that either parent can contribute gene a. Observe that in generation 2 the probability that a parent will transmit gene a is

$$r_2 = \frac{t_2}{2(t_2 + u_2)} = \frac{2r_1(1 - r_1)}{2[2r_1(1 - r_1) + (1 - r_1)^2]}$$

which can be simplified to yield

$$r_2 = \frac{r_1}{r_1 + 1} . \tag{2}$$

Claim:

The probability r_N that a parent in the Nth generation will transmit gene a is

$$r_N = \frac{r_1}{1 + (N - 1)r_1} , \tag{3}$$

where r is the corresponding probability in the first generation.

Proof:

Proof will be by mathematical induction.

For N = 1, equation (3) reduces to

$$r_1 = \frac{r_1}{1 + or_1} ;$$

and for N = 2, equation (3) reduces to equation (2). For the induction step, assume that equation (3) is valid for N = k so that

$$r_k = \frac{r_1}{1 + (k - 1)r_1} . \tag{4}$$

Next, we observe that equation (2) holds for any two consecutive generations, so that, in particular,

$$r_{k+1} = \frac{r_k}{1 + r_k} . \tag{5}$$

Now, combining (4) and (5), we get

$$r_{k+1} = \frac{\frac{r_1}{1 + (k - 1)r_1}}{\frac{1 + r_1}{1 + (k - 1)r_1}}$$

$$= \frac{r_1}{1 + (k - 1)r_1 + r_1}$$

$$= \frac{r_1}{1 + kr_1} .$$

This is equation (3) for $N = k + 1$. Therefore, the induction step is verified and the proof is complete.

As a consequence of equation (3) and the fact that equation (1) is valid for any two consecutive generations, we see that

$$s_N = (r_{N-1})^2 = \frac{r_1^2}{(1 + (N - 2)r_1)^2} , \tag{6}$$

$$t_N = 2r_{N-1}(1 - r_{N-1}) = \frac{2r_1(1 + (N - 3)r_1}{(1 + (N - 2)r_1)^2} , \tag{7}$$

and

$$u_N = (1 - r_{N-1})^2 = \frac{(1 + (N - 3)r_1)^2}{(1 + (N - 2)r_1)^2} . \tag{8}$$

Consider as an example a case where $s_1 = .25$, $t_1 = .5$, and $u_1 = .25$. Then

$$r_1 = \frac{t_1}{2(t_1 + u_1)} = \frac{.5}{2(.5 + .25)} = \frac{1}{3} .$$

Now using equations (6), (7), and (8) we derive Table 1 below. Note that:

Table 1

Taken from: Dahlberg, Gunner: Mathematical Methods for Population Genetics. New York: Interscience, 1948.

Generation	aa	aA	AA
1	0.2500	0.5000	0.2500
2	0.1111	0.4444	0.4444
3	0.0625	0.3750	0.5625
4	0.0400	0.3200	0.6400
5	0.0278	0.2778	0.6944
6	0.0204	0.2449	0.7347
7	0.0156	0.2188	0.7656
8	0.0123	0.1975	0.7901
9	0.0100	0.1800	0.8100
10	0.0083	0.1653	0.8264
20	0.0023	0.0907	0.9070
30	0.0010	0.0624	0.9365
40	0.0006	0.0476	0.9518
50	0.0004	0.0384	0.9612
100	0.0001	0.0196	0.9803

(A) The individuals of type aa are eliminated very rapidly. By the fourth generation their frequency has dropped to 4%. However, if we begin with $r_1 = 0.1\%$ (30th generation), in ten generations, their frequency will have dropped only about half, to 0.06%.

(B) The effect on heterozygotes, i.e., individuals of type aA, is considerably weaker. Between the fourth and ninth generation, the

individuals of type aa are decreased from 4% to 1%, while the aA individuals are decreased only from 32% to 18%. After 100 generations, there are only 0.01 individuals of type aA, i.e., 1.96%.

It is clear from equations (6) and (7) that s_N and t_N both tend to zero as N becomes large and hence that eventually gene a will disappear from the population. The fact that s_N tends to zero much more rapidly than t_N means that overt appearance of gene a (i.e., persons of type aa) will probably cease long before the gene itself is entirely gone.

****

A CONJECTURE ABOUT THE CURVE REPRESENTING THE "AVERAGE" OF A NUMBER OF CURVES

Contributor: Richard F. Baum*

****

Mathematics: Taylor series expansion

Abstract: Taylor's formula is used to test a conjecture about the form of a curve given the average values for a fixed number of known exponential curves.

*Based upon: Bush, R.R.; Abelson, R.P.; Hyman, R. "Mathematics for Psychologists, Examples and Problems." Washington, D.C.: Social Science Research Council, 1956, examples C87 and C88.

Suppose that we conduct an experiment in learning in which a person is given x practice trials to perform in a pre-instructed manner (e.g., pushing one of three buttons) and is then tested to find out how well he performs. Let $y = f(x)$ be the proportion per unit time of the successful actions to the total number of actions performed by the person during the testing period. Assume that for k individuals $I_1, I_2, \ldots, I_k$, we find that the function f_i relating y and x for individual I_i is

$$y = f_i(x) = 1 - e^{-b_i x} ,$$

where b_i is a positive constant. While the $f_i(x)$ are defined only for integer values of x, it is useful to consider x as varying continuously in order to approximate the behavior of, and change in, $f_i(x)$ at given values of x. Indeed, the form of $f_i(x)$ naturally leads to such an extension. Thus, assume x varies between 0 and T, i.e., $0 \leq x \leq T$. Then

$$f_i'(x) = b_i e^{-b_i x} = b_i[1 - f_i(x)] .$$

We can say that b_i is the "rate parameter" for the ith individual I_i. The instantaneous rate of improvement in performance for I_i at a particular level of performance $f_i(x)$ is b_i multiplied by $[1 - f_i(x)]$, the proportion of unsuccessful acts performed by I_i for this value of x. That is, for a given number of practice trials x, the rate of improvement $f_i'(x)$ is directly proportional to the proportion of unsuccessful acts, where the constant of proportionality is b_i. Note that $0 \leq f_i(x) < 1$, with $f_i(x)$ approaching 1 asymptotically.

If we were now interested in averaging our findings, we might study the behavior of the function:

$$y = g(x) = \frac{1}{k} \sum_{i=1}^{k} (1 - e^{-b_i x}) .$$

A reasonable conjecture might be that g(x) has the same form as the $f_i(x)$, i.e.,

$$y = g(x) = 1 - e^{-Ax}$$

for some positive constant A. For example, if all the b_i are equal to b, then

$$y = g(x) = \frac{1}{k} \sum_{i=1}^{k} (1 - e^{-bx}) = 1 - e^{-bx} .$$

We can test this conjecture by representing the $f_i(x)$ by a Taylor series. To find A we must sum the $e^{-b_i x}$ over i. It is ordinarily difficult to obtain this sum in a convenient form by direct summation. Thus, let us expand $f_i(x) = 1 - e^{-b_i x}$ in a Taylor series about the point x = 0, and then sum over i. Since for $0 \leq x \leq T$, we have:

$$f_i(x) = f_i(0) + f_i'(0) + f_i''(0)\frac{x^2}{2!} + \ldots + f_i^{(n-1)}(0)\frac{x^{n-1}}{(n-1)!}$$

$$+ R_{in} ,$$

where

$$R_{in} = f^{(n)}(z)\frac{x^n}{N} , \qquad 0 \leq z \leq x ,$$

or

$$1 - e^{-b_i x} = b_i x - \frac{(b_i x)^2}{2!} + \frac{(b_i x)^3}{3!} + \ldots +$$

$$+ (-1)^n \frac{(b_i x)^{n-1}}{(n-1)!} + R_{in} .$$

As an example, let n = 3. Then,

$$(1) \qquad y = g(x) = \frac{1}{k} \sum_{i=1}^{k} [b_i x - \frac{(b_i x)^2}{2} + R_{i3}]$$

$$(2) \qquad y = \frac{1}{k} \sum_{i=1}^{k} b_i x - \frac{1}{k} \sum_{i=1}^{k} \frac{(b_i x)^2}{2}$$

$$+ \frac{1}{k} \sum_{i=1}^{k} R_{i3} = \bar{b} \cdot x - \frac{1}{2} \overline{b^2} \cdot x^2 + \bar{R}_3$$

where

$$\bar{b} = \frac{1}{k} \sum_{i=1}^{k} b_i ,$$

the average value of b_i,

$$\overline{b^2} = \frac{1}{k} \sum_{i=1}^{k} b_i^2 ,$$

the average value of the b_i^2, and

$$\bar{R}_3 = \frac{1}{k} \sum_{i=1}^{k} R_{i3} ,$$

the average value of the R_{i3}. Note that $\overline{b^2}$ is not the same quantity as $(\bar{b})^2$. Note also that since R_{i3} depends upon powers of b_i and x higher than the second power, so does $\bar{R}_3$.

Now, if $y = g(x) = 1 - e^{-Ax}$, then by the McLaurin expansion for n = 3 we have

$$y = g(x) = Ax - A^2 \frac{x^2}{2!} + r_3 \tag{3}$$

where A has yet to be determined, and r_3 is the remainder term depending only upon the third and higher powers of A and x. To evaluate A, we equate (3) and (2). Thus, we get

$$\bar{b}x - \overline{b^2} \frac{x^2}{2!} + \bar{R}_3 \equiv Ax - A^2 \frac{x^2}{2!} + r_3 .$$

For this to hold over the entire interval $0 \leq x \leq T$, we must have, by the principle of undetermined coefficients,

$$\bar{b} = A \qquad \text{(coefficient of } x\text{)}$$

$$\overline{b^2} = A^2 \qquad \text{(coefficient of } x^2\text{)}$$

$$\bar{R}_3 = r_3 \qquad \text{(terms in } x^N \text{ , } N \geq 3\text{)} .$$

Therefore, $(\bar{b})^2 = A^2 = \overline{b^2}$, or

(4) $$\overline{b^2} - (\bar{b})^2 = 0 \ .$$

But the b_i are quantities with a frequency distribution over different individuals. Thus, the mean of the b_i's squared minus the square of the mean of the b_i is precisely the variance σ_b^2 of the b_i. Thus, (4) tells us:

$$\sigma_b^2 \equiv \frac{1}{k} \sum_{i=1}^{k} (\bar{b} - b_i)^2 = 0 \ ,$$

i.e., the variance must be zero. The only way this can occur is for all the b_i to be identical (see Exercise 3).

Thus, we see that g(x) will be of the form

$$y = g(x) = 1 - e^{-Ax}$$

if and only if $b_1 = b_2 = \ldots = b_k = b$, our original conjecture about the form of g(x).

EXERCISES:

1. If $y = f(x) = 1 - e^{-.01x}$, write the McLaurin expansion for f for n = 3. Assuming $0 \leq x \leq 10$, show that the maximum value of the remainder term R_3 does not exceed .005 and that this maximum occurs at x = 10.

2. Show that if b is such that $bT < 0.1$ for $0 \leq x \leq T$, the function $y = bx$ approximates the function $y = 1 - e^{-bx}$ to within 5 percent or better for all $0 \leq x \leq T$. What can be concluded about our conjecture on y = g(x) for this case?

3. Show directly that

$$\overline{b^2} - (\bar{b})^2 = 0$$

implies

$$\frac{1}{k} \sum_{i=1}^{k} (\bar{b} - b_i)^2 = 0$$

which in turn implies

$$b_1 = b_2 = \ldots = b_k \ .$$

****

A SIMPLIFIED MATHEMATICAL MODEL OF THE SPREAD OF A DISEASE

Contributor: Richard F. Baum*

****

Mathematics: calculus (Math. 1), differential equations (Math. 2)

Abstract: The spread of a disease is described by an elementary differential equation which is solved by separation of variables and integration by substitution.

*Based upon: Bush, R.R.; Abelson, R.P.; Hyman, R. "Mathematics for Psychologists, Examples and Problems." Washington, D.C.: Social Sciences Research Council, 1956, example D 29.

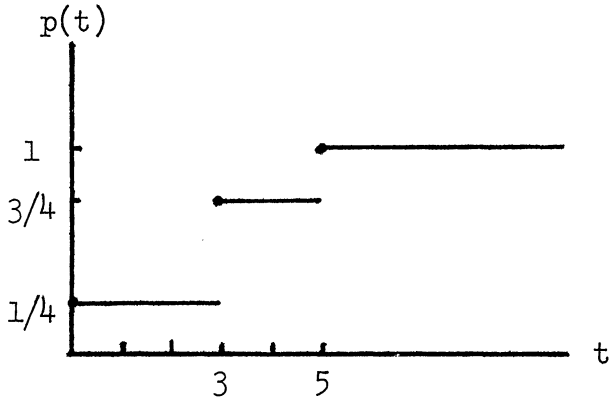
Let p(t) denote the proportion of the people in a country who have been infected with a communicable disease prior to time t. If there are no forces present to check the spread of the epidemic, then p(t) will increase monotonically with t so that either p(t) = 1 at some time t, or p(t) asymptotically approaches the value 1. If the epidemic starts at t = 0, then the domain of p(t) is the set of T = $\{t | t \geq 0\}$ with $0 \leq p(t) \leq 1$.

For a finite population of N people, p(t) will not be continuous but must increase in jumps of integral multiples of 1/N at N or less discrete times. Thus p(t) is a step function. For example, if N = 4, p(t) might be

$p(t) = 1/4$ for $0 \leq t < 3$

$p(t) = 3/4$ for $3 \leq t < 5$

$p(t) = 1$ for $5 \leq t$



For large populations, i.e., for large values of N, the jumps 1/N will be small enough to assume that p(t) is continuous without serious distortion. Thus for the remainder of the model we will assume that p(t) is a continuous, monotonically increasing function, bounded by 0 and 1.

Differentiability

If h denotes a positive time interval, then

(1) $$p(t_o + h) - p(t_o)$$

represents the proportion of the population that has been infected in the time interval $[t_o, t_o + h]$, and

(2) $$\frac{p(t_o + h) - p(t_o)}{h}$$

represents the proportion of the population that has been infected per unit time in the same time interval.

Since infection occurs instantaneously, it is logical to study quantities such as (2) for any $h > 0$. In particular, we can ask if

$$(3) \qquad p'_+(t_o) = \lim_{h \to o^+} \frac{p(t_o + h) - p(t_o)}{h}$$

exists, i.e., can we assign a limiting value to the proportion of the population that has been infected per unit time in the interval $[t_o, t_o + h]$, $h > 0$? Mathematically we are asking: Does $p(t)$ have a right-hand derivative?

Similarly we can ask if

$$(4) \qquad p'_-(t_o) = \lim_{h \to o^-} \frac{p(t_o + h) - p(t_o)}{h}$$

exists, i.e., does $p(t)$ have a left-hand derivative? Even though $p(t)$ is continuous, bounded and monotonically increasing we cannot conclude that either $p'_+(t_o)$ or $p'_-(t_o)$ exist. However, because $p(t)$ is a "well-behaved" and smooth function, little generality is lost if we assume that not only do $p'_+(t_o)$ and $p'_-(t_o)$ exist, but that they are equal, i.e., that $p(t)$ is differentiable. Finally we will assume that $p(t)$ is twice differentiable for all $t > 0$.

The Model

This epidemic model assumes that infection spreads by contact between members of a community, in which there is no removal from circulation by death, recovery or isolation. Ultimately, therefore, all "susceptibles" become infected. These assumptions are approximately applicable to a situation in which:

(a) The disease is highly infectious, but not sufficiently serious for cases to be withdrawn by death or isolation.

(b) No infective becomes clear of infection during the main part of the epidemic.

The common cold is an example of such an infection.

The model also assumes that the rate at which the disease is spread at time t is directly proportional to both the proportion of people who have been infected and the proportion of people who have not yet been infected.

Thus,

$$(5) \qquad p'(t) = cp(t)[1 - p(t)], \quad c > 0, \quad 0 \leq p(t) \leq 1, \quad t > 0 .$$

Such an hypothesis may be reasonable if the disease is spread primarily by direct contact with previously infected people, and no quarantine is in effect. Let $q(t) = 1 - p(t)$. Then $q(t)$ is the proportion of healthy people at time t. Thus, if two people meet at time t, the probability that one is infected and one is healthy is given by $p(t) \cdot q(t)$. We assume that the infected people still move about the community in a normal fashion. If there is a probability of c that such a meeting will cause infection, then the increase in the proportion of the population which is infected is $cp(t)q(t)$, as given by equation (5).

Note that this hypothesis is in accord with our previous assumptions about p(t). These are:

(a) p(t) is continuous

(b) $0 \leq p(t) \leq 1$

(c) p(t) is monotonic increasing and

(d) p(t) is twice differentiable for $t > 0$.

(c) follows from the fact that $p'(t) \geq 0$ whenever $0 \leq p(t) \leq 1$, i.e., for $t > 0$. To show (d) below we differentiate p'(t).

$$(6) \qquad \begin{aligned} &\text{i)} \quad p''(t) = cp'(t) - 2cp(t)p'(t) \\ &\text{ii)} \quad p''(t) = cp'(t)[1 - 2p(t)] \\ &\text{iii)} \quad p''(t) = c^2 p(t)[1 - p(t)][1 - 2p(t)] \end{aligned}$$

We can now deduce various properties of p(t) without actually solving for it.

First we note that $p(t)$ is strictly monotonic increasing for all t such that $0 \leq p(t) < 1$ since, by (5), $p'(t_1) > 0$ where t_1 is any t such that $p(t_1) < 1$. Thus $p(t)$ is a one-one function in this interval. If we assume that the initial number of people infected is less than one half of the population, i.e., $p(0) < 1/2$, then there is exactly one time t^* such that $p(t^*) = 1/2$. From (6) we see that $p''(t^*) = 0$. Let us show that at t^* $p(t)$ has an inflection point. Let I be an open interval containing t^* and let $t \in I$, $t < t^*$. Then since $p(t)$ is monotonic increasing, $p(t) < p(t^*) = 1/2$ and $p''(t) > 0$ from (6). Thus $p(t)$ is concave upward in an interval to the left of t^*. Similarly if $t \in I$, $t > t^*$ then $p(t) > p(t^*) = 1/2$ and $p''(t) < 0$. Therefore, $p(t)$ is concave downward for $t > t^*$, so that at t^*, $p(t)$ has an inflection point. It should be noted that the discussion above not only shows that $p(t)$ has an inflection point at t^* but that $p'(t)$ has a maximum value at t^*. That is, if $p'(t)$ is considered to be the dependent variable and $p(t)$ the independent variable, then the graph of this function (Figure 1) is clearly a parabola with its vertical axis at $p(t) = 1/2$ and "turning point" at $(1/2, 1/4)$. The maximum of $p'(t)$ occurs at $p(t) = 1/2$ which in turn occurs uniquely at t^*. Therefore, the rate at which the epidemic is spread reaches a maximum when one half of the population is infected.

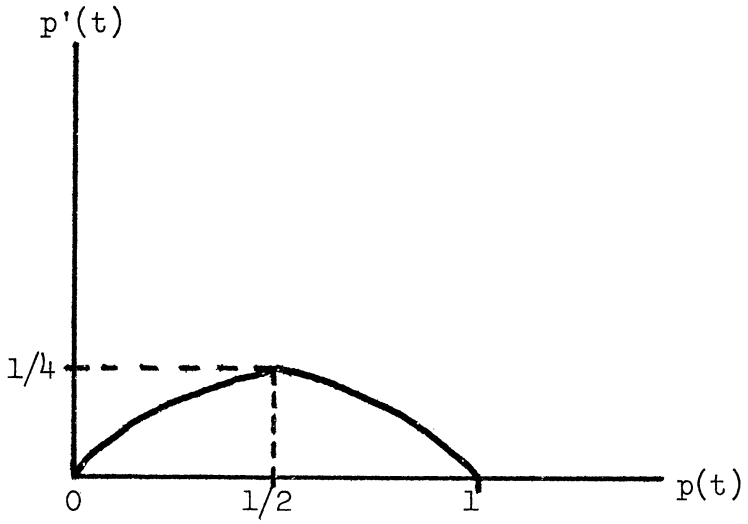


Figure 1

From the above information we can determine the form of p(t). It is given in Figure 2.

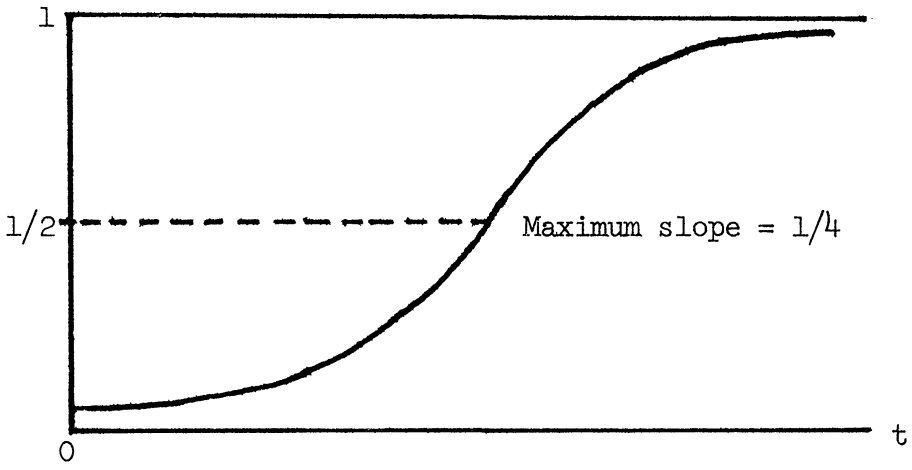


Figure 2

We will now solve the differential equation (5) and determine p(t) explicitly. We know from the theory of differential equations, that any two functions that satisfy (5) can differ at most by a constant k, and that if we specify the value of p(t) at some point, say p(0), there can be only one function p(t) that satisfies (5). Thus, if we were to determine a solution for p(t) in some interval (0,t), then this solution is unique in [0,t) up to a constant.

Now let t_1 be any point such that $p(t_1) < 1$. Assume $p(0) > 0$. $p'(t) > 0$ for $0 < t \leq t_1$ and we know by the implicit function theorem that the inverse function of $y = p(t)$ exists. Call it $t = g(y)$. We also know that $g(y)$ is differentiable for $0 < y < 1$ and that

$$g'(y) = \frac{1}{p'(t)}$$

or

$$g'(y) = \frac{1}{cy(1 - y)}$$

and thus,

$$(7) \qquad t = g(y) = \frac{1}{c} \int \frac{1}{y(1 - y)}\, dy \ .$$

The integral in (7) can be evaluated by the method of substitution of variables. Substituting $w = 1/y$ into (7) and integrating,

$$(8) \qquad ct = \ln \frac{y}{1 - y} + k \ ,$$

where k is a constant. Equation (8) can be solved for $y = p(t)$ to yield

$$(9) \qquad p(t) = \frac{Be^{ct}}{Be^{ct} + 1} \ ; \quad B = e^{-k} > 0 \quad \text{for} \quad 0 \leq t < t_1 \ .$$

By the uniqueness of p(t), once we specify a value for p(t) for some t we can determine B. If, for instance, we specify p(0), we can solve for B, since $p(0) = B/(B + 1)$ where p(0) is the proportion of the population initially infected with the disease.

We have shown that (9) is the solution for equation (5) in the interval $0 < t < t_1$, i.e., where $0 < p(t) < 1$. Since p(t) is an increasing function, and by assumption $p(0) > 0$, we can ask whether $p(t) = 1$ for any t. Suppose there is a first time T' such that $p(T') = 1$. By the uniqueness property p(t) is of the form given by (9) for any interval (0,T), $T < T'$. Since p(t) is continuous for all $t > 0$, we have:

$$p(T') = \lim_{\substack{t \to T' \\ t < T'}} p(t) = \lim_{\substack{t \to T' \\ t < T'}} \frac{Be^{ct}}{Be^{ct} + 1} < 1 \ ,$$

where B is a constant. Therefore, it is impossible for p(T') to be equal to 1. Because $p(t) = 1$ for no finite t, we can make t as large as we wish, i.e., equation (9) is valid for $0 \leq t < \infty$, or $0 \leq t$. (The reader should investigate the case when $p(0) = 0$).

Finally, note that as $t \to \infty$, p(t) approaches $B/B = 1$ asymptotically.

EXERCISES:

1. Evaluate $y = p(t)$ if $p(0) = 0$. Interpret your result. Find where in the above argument it was implicitly assumed that $p(0) > 0$. Does this assumption seem reasonable?

2. If $p'(t) = 5p(t)[1 - p(t)]$, how long will it take for one half the population to be infected if the initial fraction of the population infected is $1/22$?

3. If $p'(t) = p(t) - 1$, give an interpretation about the spread of the disease. Solve for $y = p(t)$. Note that $p(0) = 0$. Does $p(t)$ approach $y = 1$ asymptotically? Why?

4. Find an expression for $p'(t)$ in terms of $p(t)$, so that $p(t)$ approaches $3/4$ asymptotically. Interpret all expressions.

5. Show by using critical points that a maximum of $p(t)$ occurs when $p(t) = 1/2$.

Alternative treatment using totals rather than proportions:

Let us again assume that the size of the community is N, $N < \infty$. Assume a single infective is introduced into the community. Let $x(t)$ and $y(t)$ denote the number of susceptibles and infectives at time t, respectively, so that

$$x(t) + y(t) = N + 1 , \quad t \geq 0 . \tag{10}$$

We suppose that the whole population is subject to some process of homogeneous mixing, so that the number of new infections occurring in time dt is $\beta x(t)\, y(t)\, dt$, where β is the infection rate. Using the same type of reasoning as that used in deriving equation (5), we see that

$$\frac{dx(t)}{dt} = - \beta x(t)\, y(t) . \tag{11}$$

Let $\tau = \beta t$. Then (11) becomes dimensionless so far as the infection rate is concerned, i.e., (11) becomes:

(12) $$\frac{dx(\tau)}{d\tau} = - x(\tau)\, y(\tau) = - x(\tau)[N - x(\tau) + 1] \ , \ \tau \geq 0$$

where the last expression in (12) follows from equation (10). The boundary conditions for (12) are

(13) $$x(0) = N \ .$$

It is left as an exercise to show that the solution of (12) and (13) is

(14) $$x(\tau) = \frac{N(N + 1)}{N + e^{(N+1)\tau}} \ , \quad \tau \geq 0 \ .$$

(Hint: Use the method used to derive equation (8), i.e., separation of variables.)

In practice one is often more interested in the epidemic curve, which gives the rate at which new cases accrue, i.e., $\frac{dx(\tau)}{d\tau}$. From (14), we see that the function defined by

$$z(\tau) = \frac{-dx(\tau)}{d\tau} = x(\tau)\, y(\tau)$$

has the formula

(15) $$z(\tau) = \frac{N(N + 1)^2 \, e^{(N + 1)\tau}}{\left[N + e^{(N+1)^2}\right]^2} \ , \quad \tau \geq 0 \ .$$

EXERCISE:

6. Show that $z(\tau)$ attains its maximum when

$$\tau = \frac{\log N}{N + 1} \ ; \quad x(\tau) = \frac{N + 1}{2} \ ; \quad z(\tau) = \frac{(N + 1)^2}{4} \ .$$

Sketch $z(\tau)$, $\tau \geq 0$ for $N = 10$ and $N = 20$. Show that $z(\tau)$ is symmetrical about the line

$$\tau = \frac{\log N}{N + 1} \ .$$

Compare the above results to those obtained by the first method.

---

1. Bailey, Norman T. J., The Mathematical Theory of Epidemics. Hafner Publishing Co., New York, 1957.

****

THE GROWTH OF A POPULATION IN A RESTRICTED ENVIRONMENT

Contributor: Richard F. Baum*

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: The growth of a population in an isolated, limited environment is examined.

*Based upon: D'Ancona, Umberto. The Struggle for Existence. Leiden: E. J. Brill, 1954.

Consider an animal or plant population which is living in isolation in a constant environment, in which there is no intervention by another species. Assume that the total number of births and deaths in a unit time is approximately proportional to the total number of individuals in the population with constants of proportionality ν, ω, respectively. Let $N(t)$ denote the number of individuals at time t, $t \geq t_o$. Then, by our assumptions,

$$(1) \qquad DN(t) = \nu N(t) - \omega N(t) = (\nu - \omega)N(t), \quad t \geq t_o .$$

Let $\epsilon = \nu - \omega$. Substituting this expression into equation (1), we find that

$$(2) \qquad DN(t) = \epsilon N(t), \quad t \geq t_o .$$

If we let

$$N_o = N(t_o),$$

then (2) can be integrated to give:

$$(3) \qquad N(t) = N_o e^{\epsilon(t-t_o)}, \quad t \geq t_o .$$

From equation (3), we note that:

a) As time increases in an arithmetic progression, the total number of individuals increases or decreases in a geometric progression, in agreement with Malthus' Law.

b) If $\epsilon > 0$, $N(t)$ is increasing, i.e., if the number of births exceeds the number of deaths, the population will increase.

c) If $\epsilon < 0$, $N(t)$ is decreasing.

d) If $\epsilon = 0$, $N(t)$ is constant.

Suppose $\epsilon > 0$, and let T be the the time interval in which the population doubles in size. Then equation (3) can be used to calculate ϵ, since

$$e^{\epsilon T} = 2 .$$

Thus

$$\epsilon = \frac{\ln 2}{T} \approx \frac{0.693}{T} .$$

ϵ can also be calculated for $\epsilon < 0$, i.e., for a decrease in the size of the population. In this case we need to know the time interval from $t = t_o$ in which the population is halved. From similar reasoning, we get

$$\epsilon = \frac{-0.693}{T} .$$

Under the assumption of ϵ constant and positive,

$$\lim_{N \to \infty} N(t) = \infty .$$

In reality, of course, this does not occur; the coefficient ϵ decreases as $N(t)$ increases in such a way that $N(t)$ does not become infinite as $t \longrightarrow \infty$. One reason ϵ decreases is limited food supply. Thus, for a given species in a limited environment, the "growth coefficient" will be modified as the number of individuals increases. In practice it has been shown that as long as the number of individuals remains below a certain number, which depends on the environment, the growth coefficient can be assumed constant; but once the population is greatly increased, the growth coefficient must be reduced. As a first approximation of this situation, we can replace ϵ by $(\epsilon - \lambda N)$ in equation (2). Assume $\epsilon > 0$. Then by the above, $\lambda > 0$, in order for an increase in population to lead to a decrease in the food available to each individual (clearly, if $\epsilon < 0$, then $\lambda < 0$). Equation (2) now becomes:

$$DN(t) = [\epsilon - \lambda N(t)]N(t) . \tag{4}$$

Integrating, we obtain:

$$Ce^{\epsilon t} = \frac{N(t)}{\epsilon - \lambda N(t)} , \quad t \geq t_o . \tag{5}$$

where C is a constant. Thus,

$$N(t) = \frac{C\epsilon e^{\epsilon t}}{1 + C\lambda e^{\epsilon t}} , \quad t \geq t_o , \tag{6}$$

so that

$$\lim_{N\to\infty} N(t) = \frac{\epsilon}{\lambda} ,$$

i.e., the number of individuals will tend in the limit to ϵ/λ.

Let $t_o = 0$, and $N_o = N(0)$. Then from (5),

$$C = \frac{N_o}{\epsilon - \lambda N_o}$$

Substituting into (6), we get:

$$N(t) = \frac{\epsilon N_o e^{\epsilon t}}{\epsilon + N_o \lambda (e^{\epsilon t} - 1)} \quad . \tag{7}$$

From this it follows that the number of individuals is always maintained between N_o and ϵ/λ.

Equation (5) is of the form

$$y = \frac{be^{ax}}{1 + Ce^{ax}} , \quad x \geq 0 . \tag{8}$$

It is left as an exercise to show that the graph of (8) is S-shaped.

The above results were verified experimentally in 1920 by Pearl and Reed, using Drosophila. In general, it has been shown that all biological populations which are limited by a situation which they themselves create, have similar S-shaped or sigmoid growth curves.

****

THE INTENSITY OF REPRODUCTION AS A FACTOR IN THE GROWTH OF A SPECIES

Contributor: Richard F. Baum*

****

Mathematics: differential equations with separable variables (Math. 2)

Abstract: The intensity of reproduction is considered in the growth of a population in a restricted environment.

*Based upon: D'Ancona, Umberto. The Struggle for Existence. Leiden: E. J. Brill, 1954.

The growth of a species may depend not only upon the availability of food, but also upon the rate of reproduction. We illustrate this in a growth model for a given species which lives in a constant environment and is isolated from intervention by any other species.

Let $N(t)$ denote the total number of individuals of the species at time t, $t \geq 0$. Assume that the number of deaths in a unit time is proportional to $N(t)$ with proportionality constant ϵ, $\epsilon > 0$, i.e., the death rate is

$$\epsilon N(t), \quad t \geq 0 . \tag{1}$$

Let us assume that

(a) The proportion of males and females remains the same, i.e., $\alpha N(t)$ denotes the number of males at time t, $t \geq 0$; $\beta N(t)$ denotes the number of females at time t, $t \geq 0$, where α and β are constants such that $0 \leq \alpha, \beta \leq 1$, and $\alpha + \beta = 1$.

(b) The number of encounters of individuals of different sexes is proportional to the product of the number of individuals in each sex

$$(\alpha N(t))\,(\beta N(t)) = \alpha\beta N^2(t) . \tag{2}$$

This type of assumption is frequently made in epidemic models.

(c) Every w encounters among individuals of different sexes results in ν births.

From assumptions (b) and (c), the number of births in a unit time, i.e., the birth rate, is given by

$$\alpha\beta \frac{\nu}{w} N^2(t) = \lambda N^2(t) , \tag{3}$$

where $\lambda = \alpha\beta \frac{\nu}{w} > 0$ is a positive constant. Combining equations (1) and (3), we obtain:

$$\begin{aligned} DN(t) &= \text{birth rate - death rate} \\ &= \lambda N^2(t) - \epsilon N(t) \end{aligned}$$

or

$$DN(t) = [-\epsilon + \lambda N(t)]N(t) , \quad t \geq 0 . \tag{4}$$

The reader should verify that the solution to equation (4) can be written as

$$(5) \qquad N(t) = \frac{-\epsilon N_o e^{-\epsilon t}}{-\epsilon - N_o\lambda(e^{-\epsilon t} - 1)}$$

$$= \frac{N_o}{(1 - h)e^{\epsilon t} + h}, \quad t \geq 0$$

where $N_o = N(0)$ and $h = N_o \frac{\lambda}{\epsilon}$. From equation (5) we see that three cases may occur:

Case 1: $h = 1$, i.e., $\epsilon - \lambda N_o = 0$

Case 2: $h < 1$, i.e., $\epsilon - \lambda N_o > 0$

Case 3: $h > 1$, i.e., $\epsilon - \lambda N_o < 0$

For Case 1, the population $N(t)$ remains constant, equal to

$$N_o = \frac{\epsilon}{\lambda} .$$

For Case 2,

$$\lim_{t\to\infty} (1 - h)e^{\epsilon t} = h = \infty .$$

Thus,

$$\lim_{t\to\infty} N(t) = 0$$

or the population becomes exhausted.

For Case 3 we investigate the denominator of (5). It will be zero if $e^{\epsilon t} = h/(h-1) = N_o\lambda/(N_o\lambda - \epsilon)$, and hence if $t = t_1$ where

$$t_1 = \frac{1}{\epsilon} \ln N_o\lambda/(N_o\lambda - \epsilon) .$$

Clearly t_1 is positive, since $\epsilon > 0$. Therefore,

$$\lim_{t\to t_1^-} N(t) = \infty .$$

(Here the minus exponent on t_1 means that t approaches t_1 from the left side.) Thus, for Case 3 there will be an infinite population attained in a finite time interval.

From the above, we see that there is a critical population at time t = 0, namely

$$N_o = \frac{\epsilon}{\lambda} .$$

If N_o is greater than ϵ/λ, there is an explosive growth of the population; if N_o is less than this, the population tends to become exhausted, and if $N_o = \epsilon/\lambda$, the population will be maintained at that value indefinitely. See Figure 1 for a graph of Cases 1, 2, and 3.

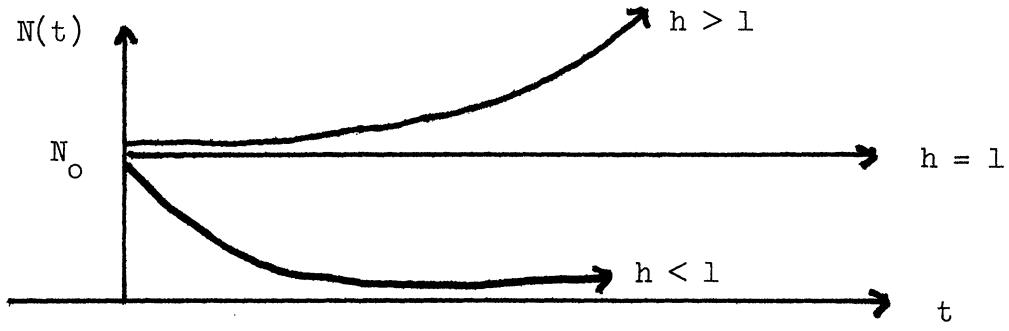


Figure 1

A serious flaw in equation (4) is that the "growth coefficient" $[-\epsilon + \lambda N(t)]$ does not decrease as N(t) increases. Thus, as we have seen, for h >1, or $\epsilon - \lambda N_o < 0$, N(t) actually becomes infinite. However, due to factors such as a limited food supply, we would expect the growth coefficient to decrease as N(t) increases. We attempt to incorporate this observation by introducing a term m, m > 0, into equation (4). The growth coefficient now becomes

$$-\epsilon + (\lambda - m)N(t) .$$

Thus equation (4) becomes

$$DN(t) = [-\epsilon + (\lambda - m)N(t)]N(t) , \quad t \geq 0 . \tag{6}$$

We assume that m is a constant. Then, if $\lambda - m > 0$, we have a repetition of Case 3; and if $\lambda - m < 0$, N(t) decays to zero. Thus, if we wish to obtain a model for which the growth coefficient decreases as

N(t) increases, while

$$\lim_{t\to\infty} N(t) = a < \infty \ , \ a > 0 \ ,$$

we must abandon the assumption that the growth coefficient is a linear function of the population.*

---

* For a study of this model with a growth coefficient of the form:

$$- \epsilon + (\lambda - m)N(t) - \gamma N^2(t) \ ,$$

see: D'Ancona, Umberto. The Struggle For Existence. Amsterdam: E. J. Brill, 1954, Chap. 9.

****

COMPETITION AMONG SPECIES

Contributor: Harold Slater*

****

Mathematics: linear differential equations (Math. 4)

Abstract: The growth equations for populations of two competing species are obtained from the solution of simultaneous differential equations under various assumptions.

*Based upon: Slobodkin, L. B. Growth and Regulation of Animal Populations. New York: Holt, Rinehart and Winston, 1961.

The saturation value of a species relative to some territory is the maximum number K of individuals that the territory will support. The species will also have a rate of growth r. If two competing species occupy the same territory, the self-inhibition of each can be expressed by $1/K_i$, $i = 1, 2$. The competitive inhibition of species 2 by one individual of species 1 is, say, β/K_2, and the corresponding inhibition of species 1 by an individual of 2 is α/K_1. If r_i are the (constant) rates of increase of the two species, and H_i are their population sizes as functions of time, then according to Gause

$$\frac{dN_1}{dt} = r_1 N_1 \frac{K_1 - N_1 - \alpha N_2}{K_1}$$

$$\frac{dN_2}{dt} = r_2 N_2 \frac{K_2 - N_2 - \beta N_1}{K_2}.$$

EXERCISE:

a) Find the family of isoclines for each of these equations.

b) Find and plot the zero isoclines for the system at equilibrium.

If $\alpha = \beta = 0$, i.e., the species are no longer competing, then both equations have the form

$$\frac{dx}{dt} = ax - bx^2$$

so that

$$\frac{dx}{ax - bx^2} = dt.$$

By partial fraction expansion, we obtain:

$$\frac{1}{ax - bx^2} = \frac{1}{x(a - bx)} = \frac{1}{a}\left(\frac{1}{x} + \frac{b}{a - bx}\right).$$

Thus, with the initial conditions, $x = x_o$ when $t = 0$,

$$\frac{1}{a}\int_{x_o}^{x}\left(\frac{1}{x}+\frac{b}{a-bx}\right)\,dx=\int_{0}^{t}dt$$

$$\frac{1}{a}\left[\ln x-\ln x_o-\ln(a-bx)+\ln(a-bx_o)\right]=t$$

$$\frac{1}{a}\ln\frac{x(a-bx_o)}{x_o(a-bx)}=t$$

$$x=x_o a\frac{e^{at}}{a+bx_o(e^{at}-1)}$$

Another model of species competition postulates the following equations:

$$\frac{dN_1}{dt}=N_1[r_1-\epsilon_1 F(N_1,N_2)]$$

$$\frac{dN_2}{dt}=N_2[r_2-\epsilon_2 F(N_1,N_2)]$$

where $F(N_1, N_2)$ represents the amount of food consumed by N_1 and N_2 individuals of species 1 and 2, respectively, and ϵ_1 and ϵ_2 (constants) can be called coefficients of voracity.

To solve the system, we first solve both equations for $F(N_1,N_2)$:

$$F(N_1,N_2)=\frac{r_1}{\epsilon_1}-\frac{1}{\epsilon_1 N_1}\frac{dN_1}{dt}=\frac{r_2}{\epsilon_2}-\frac{1}{\epsilon_2 N_2}\frac{dN_2}{dt}$$

so that

$$\frac{1}{\epsilon_1}\frac{dN_1}{N_1}-\frac{1}{\epsilon_2}\frac{dN_2}{N_2}=\left(\frac{r_1}{\epsilon_1}-\frac{r_2}{\epsilon_2}\right)dt$$

$$\epsilon_2\int_{N_1^o}^{N_1}\frac{dN_1}{N_1}-\epsilon_1\int_{N_2^o}^{N_2}\frac{dN_2}{N_2}=(r_1\epsilon_2-r_2\epsilon_1)\int_{t_0}^{t}dt.$$

Integrating both sides, we get

$$\epsilon_2 \ln \frac{N_1}{N_1^o} - \epsilon_1 \ln \frac{N_2}{N_2^o} = (r_1\epsilon_2 - r_2\epsilon_1)(t - t_0)$$

or

$$\frac{(N_1)^{\epsilon_2}}{(N_2)^{\epsilon_1}} = \frac{(N_1^o)^{\epsilon_2}}{(N_2^o)^{\epsilon_1}} \, e^{(r_1\epsilon_2 - r_2\epsilon_1)(t - t_o)}$$

where N_i^o are the population sizes at the initial time t_o.

****

THE RELATIONSHIP BETWEEN HOST AND PARASITE

Contributor: Richard F. Baum*

****

Mathematics: Taylor series, linear differential equations (Math. 4)

Abstract: The interaction between a species of parasites and a host species is described by differential equations.

*Based upon: D'Ancona, Umberto. The Struggle for Existence. Leiden: E. J. Brill, 1954.

Suppose that one species of insects S_1, the host, is being "exploited" by a second species of insects S_2, the parasites. Let

$N_1(t)$ denote the number of individuals in the host species at time $t \geq 0$.

$b_1(t)$ denote the birth rate of S_1 at time $t \geq 0$, i.e., the number of eggs deposited per individual of S_2 per unit time (one day) at time t.

$d_1(t)$ denote the death rate of S_1 which is not attributable to parasitic infection.

$N_2(t)$ denote the number of parasites at time $t \geq 0$.

$d_2(t)$ denote the death rate of S_2 at time $t \geq 0$.

$d_p(t)$ denote the death rate of S_1 attributable to parasites.

Assume that for $t \geq 0$:

(a) $b_1(t) = b_1$

(b) $d_1(t) = d_1$ and $d_2(t) = d_2$,

where b_1, d_1, and d_2 are constants.

(c) $d_p(t) = KN_2(t)$, i.e., $d_p(t)$ is proportional to the number of parasites.

Assumption (c) follows from the assumption that the number of deaths of S_1 per unit time is directly proportional to both $N_1(t)$ and $N_2(t)$. This is essentially the same assumption made in epidemic models, where it is assumed that the rate of spread of a disease is directly proportional to both the proportion of people who have been infected and the proportion of people who have not yet been infected.

Let us further assume that the birth of a parasite is contingent upon the laying of an egg in a host, and that even if a parasite does not develop from the egg inplanted in the host, the host ultimately dies. This is frequently the case with insect parasitism. For the sake of simplicity, assume that at most only one parasite develops for

each host attacked. Thus, if each host which is attacked develops one parasite, the total natality of the parasite species will equal KN_1N_2. However, we will assume that only a fraction θ of the hosts attacked develops a parasite, and thus the total natality of the parasite species will be given by

$$\theta KN_1(t)N_2(t) .$$

From the above assumptions, we obtain two differential equations:

$$\frac{dN_1(t)}{dt} = n_1N_1(t) - KN_1(t)N_2(t)$$

$$\frac{dN_2(t)}{dt} = \theta KN_1(t)N_2(t) - d_2N_2(t)$$

where $t \geq 0$ and $n_1 = b_1 - d_1$. The above equations can be written

(1)
$$\frac{dN_1(t)}{dt} = N_1(t)\left(n_1 - KN_2(t)\right)$$

$$\frac{dN_2(t)}{dt} = N_2(t)\left(\theta KN_1(t) - d_2\right) .$$

Using the chain rule, we can deduce from the set of equations (1) that

(2)
$$\frac{dN_1}{dN_2} = \frac{N_1(n_1 - KN_2)}{N_2(\theta KN_1 - d_2)} .$$

One way to solve (2) is to let:

$$x(t) = N_1 - \frac{d_2}{\theta K} = N_1 - p$$

$$y(t) = N_2 - \frac{n_1}{K} = N_2 - q .$$

Then equation (2) becomes:

$$\frac{dx}{dy} = \frac{dN_1}{dN_2} = \frac{N_1K(n_1/K - N_2)}{N_2\theta K(N_1 - d_2/\theta K)}$$

(3)
$$= \frac{(x(t) + p)\ (-y(t))}{\theta(y(t) + q)\ (x(t))} .$$

Equation (3) can be solved, e.g., by separation of variables, to give

$$(4) \qquad d_2 \log(x + p) + n_1 \log(y + q) - \theta Kx - Ky = M$$

in which M is an arbitrary constant of integration. By expanding $\log(x + p)$ and $\log(y + q)$ in a Taylor series about $x = 0$ and $y = 0$, respectively, equation (4) can be written:

$$(5) \quad d_2\left[\log p - \frac{x^2}{2p^2} + \frac{x^3}{3p^3} - \ldots\right] + n_1\left[\log q - \frac{y^2}{2q^2} + \frac{y^3}{3q^3} - \ldots\right] = M .$$

It can be shown that equation (5) gives a family of closed curves on the usual xy cartesian system, each curve being derived from a different value for the arbitrary constant M.

Near the point of origin, where terms higher than those of second degree are negligible, the equation can be reduced to

$$(6) \qquad \frac{d_2 x^2}{p^2} + \frac{n_1 y^2}{q^2} = \text{constant}$$

whose integral curves are ellipses.

The time-course of phenomena represented by equations of this form is cyclic and periodic. By representing (6) parametrically, it can be shown that the period of oscillation near the origin is given by

$$T = \frac{2\pi}{\sqrt{n_1 d_2}} .$$

Many different types of relations between species can be represented by an equation of the form of (1) or (3). Consider the situation in which species S_2 feeds upon species S_1 which derives its nourishment from a source abundant enough to be considered constant for the duration of the study. Let $x_1(t)$ and $x_2(t)$ denote the total mass of individuals of species S_1 and S_2 respectively at time t.

The growth of S_1 in a unit time interval $[dx_1(t)]/dt$, is given by the mass of new S_1 individuals formed in unit time minus the mass of

the S_1 individuals killed by S_2 individuals in the same time, and the amount of dead or excreted material eliminated by S_1 during that unit time interval.

Assume that the mass of the S_1 individuals which has been produced in a unit time interval is given by

$$b_1 x_1(t) , \quad b_1 = \text{constant} .$$

Similarly, assume that the amount of dead and excreted materials eliminated by S_1 during unit time is:

$$d_1 x_1(t) .$$

Once again, the mass of S_1 individuals destroyed in a unit time interval by the S_2 individuals usually depends on both $x_1(t)$ and $x_2(t)$, and in many cases, can be approximated by

$$K x_1(t) x_2(t) .$$

With this approximation,

$$\frac{dx_1(t)}{dt} = n_1 x_1(t) - K x_1(t) x_2(t) \tag{7}$$

where $n_1 = b_1 - d_1$.

The increase in S_2 in a unit time interval $[dx_2(t)]/dt$ is given by the mass of the S_2 individuals newly born during the unit time interval and derived from S_1 in the form of assimilated food material, minus the mass of the S_2 individuals which die and the amount of materials eliminated during the period. Making the same assumptions for $x_2(t)$ as for $x_1(t)$, we can write

$$\frac{dx_2(t)}{dt} = w x_1(t) x_2(t) - d_2 x_2(t) . \tag{8}$$

Again, equations (7) and (8) give, by the chain rule:

$$\frac{dx_1}{dx_2} = \frac{x_1[n_1 - K x_2]}{x_2[w x_1 - d_2]} \tag{9}$$

which is the same form as equation (3).

EXERCISE:

1. Examine the following situation: Suppose there are three species living together. Species S_2 depends on the other two, S_1 and S_3, for food.

Using the assumptions made above, derive the appropriate equations for $dx_1(t)/dt$, $dx_2(t)/dt$ and $dx_3(t)/dt$.

****

INTERACTIONS BETWEEN TWO SPECIES

Contributor: Richard F. Baum*

****

Mathematics: ordinary differential equations (Math. 4)

Abstract: Two relationships between species are studied, and equations describing their population growth are derived. Two cases are investigated: (1) the species compete for the same food; (2) one species finds food in the environment, and the second species feeds on the first.

*Based upon: D'Ancona, Umberto. The Struggle for Existence. Leiden: E. J. Brill, 1954.

Assume two species, S_1 and S_2, exist together in the same environment. Two ways in which these species can interact are:

1. Two species have the same nutritional requirements and thus compete for the same food. The more similar the species ecology is, the more the species will compete.

2. One species finds food in the environment, not consisting of the second species, while the food for the second species consists of the first species.

Let us examine the first situation. Let $N_1(t)$, $N_2(t)$ denote the number of individuals in species S_1, S_2, respectively at time $t \geq 0$. If the food supply were unlimited, it would be reasonable to assume that the number of births and deaths for each species would be proportional to the number of existing individuals of that particular species, i.e.,

$$DN_1(t) = M_1N_1(t) - \nu_1N_1(t) = \epsilon_1N_1(t) , \quad t \geq 0$$

$$DN_2(t) = M_2N_2(t) - \nu_2N_2(t) = \epsilon_2N_2(t) , \quad t \geq 0 .$$

If $N_1(t)$ and $N_2(t)$ are increasing functions, we have $\epsilon_1 > 0$, $\epsilon_2 > 0$.

However, the food supply is usually limited; thus the "growth coefficients" ϵ_1 and ϵ_2 must be modified so as to decrease as $N_1(t)$ and $N_2(t)$ increase. This can be accomplished by assuming that the amount of food available to the total number of individuals of both species decreases in proportion to $h_1N_1(t)$ due to species S_1 and decreases in proportion to $h_2N_2(t)$ due to species S_2, $h_1 > 0$, $h_2 > 0$. Thus, the decrease of the growth coefficients for species S_1 and S_2 will be proportional to

$$h_1N_1(t) + h_2N_2(t) .$$

We get:

$$(1) \qquad DN_1(t) = [\epsilon_1 - \gamma_1 [h_1N_1(t) + h_2N_2(t)]]N_1(t) , \quad t \geq 0$$

$$(2) \qquad DN_2(t) = [\epsilon_2 - \gamma_2 [h_1N_1(t) + h_2N_2(t)]]N_2(t) , \quad t \geq 0$$

where γ_1, γ_2, h_1, h_2 are positive and, as above, ϵ_1 and ϵ_2 are assumed positive.

We have two cases for these differential equations.

Case 1: $$\frac{\epsilon_1}{\gamma_1} = \frac{\epsilon_2}{\gamma_2} = K .$$

If $h_1N_1(0) + h_2N_2(0) = K$, then $N_1(t)$ and $N_2(t)$ are constants, $t \geq 0$.

Case 2: $$\frac{\epsilon_1}{\gamma_1} \neq \frac{\epsilon_2}{\gamma_2} .$$

In this case, we can assume without loss of generality that

(3) $$\frac{\epsilon_1}{\gamma_1} > \frac{\epsilon_2}{\gamma_2} .$$

The reader should verify that Case 2 implies that S_2 will be affected by the shortage of food which will have been mainly eaten by the first species. One might guess from this that the population size of S_2 will gradually diminish and tend to become exhausted, while that of S_1 will increase until it reaches a positive limit. It will be shown below that this conjecture is correct.

Let us solve equations (1) and (2) for $N_1(t)$ and $N_2(t)$. From these equations, we know:

$$DN_1(t) = \epsilon_1N_1(t) - \gamma_1h_1N_1^2(t) + \gamma_1h_2N_1(t)N_2(t) , \quad t \geq 0$$

$$DN_2(t) = \epsilon_2N_2(t) + \gamma_2h_2N_2^2(t) - \gamma_2h_1N_1(t)N_2(t) .$$

Assume that $N_1(t)$, $N_2(t) > 0$ for $0 \leq t \leq T$. Then we can write, for $0 \leq t \leq T$:

$$\frac{1}{N_1(t)} \cdot DN_1(t) = \epsilon_1 - \gamma_1h_1N_1(t) + \gamma_2h_2N_2(t)$$

$$\frac{1}{N_2(t)} \cdot DN_2(t) = \epsilon_2 - \gamma_2h_1N_1(t) + \gamma_2h_2N_2(t) .$$

From the above, we can easily obtain

$$\gamma_2 \frac{1}{N_1(t)} DN_1(t) - \gamma_2\epsilon_1 = \gamma_1 \frac{1}{N_2(t)} DN_2(t) - \gamma_1\epsilon_2 .$$

Thus, upon integration:

$$\gamma_2 \log N_1(t) - \gamma_2\epsilon_1 t = \gamma_1 \log N_2(t) - \gamma_1\epsilon_2 t + C'$$

where C' is a constant, so that

$$\log [N_1(t)]^{\gamma_2} - \log [N_2(t)]^{\gamma_1} = \gamma_2\epsilon_1 t - \gamma_1\epsilon_2 t + C' .$$

It follows that

$$\log \left[\frac{N_1(t)^{\gamma_2}}{N_2(t)^{\gamma_2}} \right] = \gamma_2\epsilon_1 t - \gamma_1\epsilon_2 t + C'$$

and

$$\frac{[N_1(t)]^{\gamma_2}}{[N_2(t)]^{\gamma_1}} = Ce^{\gamma_2\epsilon_1 - \gamma_1\epsilon_2 \epsilon}, \quad 0 \leq t \leq T , \tag{4}$$

where C is a constant. From equation (3),

$$\gamma_2\epsilon_1 - \gamma_1\epsilon_2 > 0$$

so that if equation (4) holds for $0 \leq t \leq \infty$, we have

$$\lim_{t\to\infty} \frac{[N_1(t)]^{\gamma_2}}{[N_2(t)]^{\gamma_2}} = \infty . \tag{5}$$

Given that $N_1(0)$, $N_2(0)$ are positive, the reader should verify that $N_1(t) > 0$, $N_2(t) > 0$ for $0 \leq t \leq \infty$, i.e., equation (4) does indeed hold for $0 \leq t \leq \infty$. (What is the situation for $N_1(0) = 0$, or $N_2(0) = 0$?)

Now, from equation (1), we see that $N_1(t)$ can not increase

indefinitely. Consider the equation:

$$DN_1(t) = [\epsilon_1 - \gamma_1 h_1 N_1(t)]N_1(t) , \quad t \geq 0 . \tag{6}$$

The solution of equation (6) is:

$$N_1(t) = \frac{C\gamma_1 e^{\epsilon_1 t}}{1 + C\gamma_1 h_1 e^{\epsilon_1 t}}$$

and thus

$$\lim_{t\to\infty} N_1(t) = \frac{\epsilon_1}{\gamma_1 h_1} < \infty . \tag{7}$$

The right-hand side of equation (6) does not exceed the right-hand side of equation (1) since

$$\gamma_1 h_2 N_2(t) \geq 0 .$$

Thus, if the initial conditions at $t = 0$ are the same for both differential equations, the graph of the solution of equation (1) is never above the graph of the solution of equation (6). Thus, from equation (7),

$$\lim_{t\to\infty} N_1(t) < \infty$$

so that

$$\lim_{t\to\infty} [N_1(t)]^{\gamma_2} < \infty .$$

From equation (5),

$$\lim_{t\to\infty} [N_2(t)]^{\gamma_1} = 0$$

or

$$\lim_{t\to\infty} N_2(t) = 0 \tag{8}$$

as asserted above. Using equation (8), it can be shown that

$$\lim_{t\to\infty} N_1(t) = \frac{\epsilon_1}{\gamma_1 h_1} .$$

Let us now consider the second situation, where species S_2 feeds on species S_1, which, in turn, gets its food from the environment.

If these two species were isolated and S_1 were given an abundant food supply, we would have as above,

$$DN_1(t) = \epsilon_1 N_1(t) , \quad \epsilon_1 > 0, \quad t \geq 0 .$$

Since species S_2 would have no food, its population would decrease; and we could assume, as before, that

$$DN_2(t) = - \epsilon_2 N_2(t) , \quad t \geq 0$$

where $\epsilon_2 > 0$, so that $N_2(t)$ decreases to zero.

However, when these species are together, species S_2 will increase with $N_1(t)$. As a first approximation, we can suppose that the growth coefficient for S_2 increases in proportion to $N_1(t)$, i.e.,

$$DN_2(t) = [- \epsilon_2 + \gamma_2 N_1(t)]N_2(t) \tag{9}$$

where $\gamma_2 > 0$. The growth coefficient for S_1 will clearly decrease as $N_1(t)$ increases, and as a first approximation, we can suppose that the growth coefficient for S_1 decreases in proportion to $N_1(t)$:

$$DN_1(t) = [\epsilon_1 - \gamma_1 N_2(t)]N_1(t) \tag{10}$$

where $\gamma_1 > 0$.

The reader should verify that γ_1 and γ_2 depend both on the ability of the members of S_2 to eat the members of S_1, and on the ability of the members of S_1 to defend themselves from members of S_2. If the members of S_2 become more predatory, γ_1 and γ_2 will increase; if the members of S_1 improve their defense mechanisms, γ_1 and γ_2 will decrease.

By applying the techniques used to derive equation (4) from

equations (1) and (2), we can use equations (9) and (10) to obtain

$$[N_1(t)]^{-\epsilon_2} e^{\gamma_2 N_1(t)} = C[N_2(t)]^{\epsilon_1} e^{-\gamma_1 N_2(t)}$$

where C is a constant.

****

PERIPHYTON GROWTH ON ARTIFICIAL SUBSTRATES

Contributor: Bernard C. Patten*

****

Mathematics: differential equations (Math. 2)

Abstract: Growth and vertical distribution of mass in a periphyton community are considered in this ecological example.

*Reprinted from: Patten, B.C.; Neal, Ernest, C.; Depoe, Charles "Periphyton Growth on Artificial Substrates in a Radioactive Contaminated Lake," Ecology, XXXXVIII (1967), 918-924, with permission of authors and publisher.

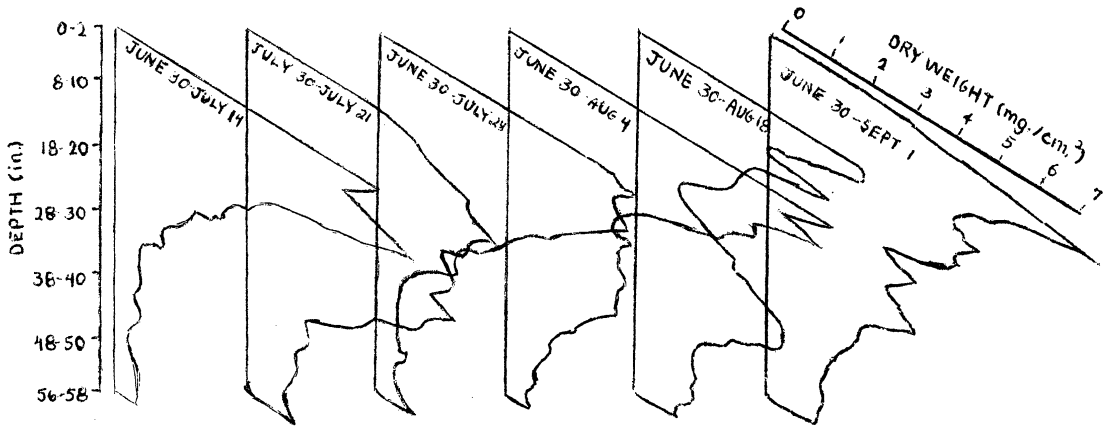
Periphyton are communities of microorganisms (bacteria, algae, fungi) which grow on surfaces submerged in water. Figure 1 indicates that the autotrophic community of the upper water column grows most rapidly. At any depth, growth is a balance between income and loss processes. Gains are effected through microbial and producer colonization, primary productivity, and subsequent invasion by detritus-feeders and animals of higher trophic levels. Losses occur through respiration, secretion and excretion, sloughing, and grazing by non-periphytic animals. These processes can be related by a mathematical expression,

$$
\begin{aligned}
\frac{\partial B}{\partial t} &= \text{income} - \text{loss} \\
&= [f_1(\text{colonization}) + f_2(\text{photosynthesis}) + \\
&\quad f_3(\text{animal invasion})] - [f_4(\text{respiration}) + \\
&\quad f_5(\text{secretion, excretion}) + f_6(\text{sloughing}) \\
&\quad + f_7(\text{grazing})],
\end{aligned} \tag{1}
$$

where $B(z,t)$ is the biomass at depth z and time t, and f_i, $i = 1,2,\ldots,7$, denotes each process in functional notation.

Gain Processes . Initial colonization, f_1, is probably similar at all depths, although selective processes may begin to act quickly to produce early vertical differences in species composition. Photosynthesis, f_2, depends on nutrients, floral composition and light. In general, light is probably more limiting than nutrients. The effect of strong light in reducing periphyton immediately beneath the surface is apparent. In the optimum illumination zone (perhaps 20.3-30.5 cm. (8-12 in.)) biomass develops fastest and to the greatest extent, and photosynthesis is maximal (Figure 1). Below the photosynthetic zone reduced light slows the rate of biomass development (Figure 1). Invasion by grazers and decomposers, f_3, makes a small addition to the standing crop, but may be proportional to the total periphytic mass. Thus, biomass addition by this process may also be regulated indirectly by illumination.

Loss Processes. High respiratory rates, f_4, may prevail immediately beneath the surface in summer. This would tend to retard the



Biomass

Figure 1

rate of biomass development (Figure 1). This factor may be just as significant as photoinhibition and wave action in reducing periphyton in the upper few centimeters. In the optimum illumination zone warm water temperatures may tend to decrease net production. However, in deeper, cooler layers reduced respiration would favor higher development rates. This tendency would be absent with complete mixing. Material losses by secretion and excretion, f_5, may be considerable, and probably occur in proportion to metabolic rates. Sloughing, f_6, is a function of growth, currents and animal activities. This factor is difficult to assess, but it is probably most important where biomass and turbulence are highest. It may be the prime factor which places an upper limit on the amount of biomass which can develop on a submerged surface. Differential effects of grazing, f_7, at different levels also cannot be evaluated in absence of data. Grazing may tend to be proportional to producer standing crops, but it is also related to accessibility of the substrate to herbivores.

The question arises whether the vertical biomass patterns in Figure 1 represent an equilibrium tendency or, given enough time and all other factors equal (e.g., as in a homogenous water column with light the only vertical variable), would a uniform surface-to-bottom development of periphytic mass be expected? This can be answered in general terms by an extension of equation (1), and specific exceptions would have to be due to unusual quantitative relations between the incomes and losses.

At every depth each loss process $f_4, \ldots f_7$, is dependent on the amount of material present, B. Hence, each loss function can be written $f_i = \varphi_i \times B$, where φ_i is the loss transfer function for the i^{th} process. Biomass equilibrium at any depth occurs when $\partial B/\partial t = 0$, that is when gains balance losses:

$$\sum_{i=1}^{3} f_i = \sum_{i=4}^{7} f_i ,$$

or

$$\sum_{i=1}^{3} f_i = B \sum_{i=4}^{7} \varphi_i .$$

The amount of biomass at equilibrium is then

$$B_{(eq)} = \frac{\sum_{i=1}^{3} f_i}{\sum_{i=4}^{7} \varphi_i} . \qquad (2)$$

This states, in effect, that the equilibrium periphyton mass at each depth is the ratio of the sum of input fluxes (dimensions $ML^{-2}T^{-1}$) to the sum of loss rates (dimensions T^{-1}), as expressed by the numerator and denominator, respectively. Thus, as in the growth discussion above, concern about steady states still centers on an income-and-loss relation.

Equation (2) shows that for a uniform vertical distribution of periphyton mass to occur (i.e., $\partial B_{(eq)}/\partial z = 0$) the ratio of input flux to loss rate must be the same at every depth. The improbability of this is obvious. Compare, for example, the 20.3-25.4 cm. (8-10 in.) interval with the 121.9-127.0 cm. (48-50 in.) interval in Figure 1. Decreased photosynthesis, f_2, at the deeper level would have to be compensated by decreased <u>rates</u> (not fluxes) of one or more of the loss processes; changes of sufficient magnitude seem highly unlikely. Therefore, it can be concluded as a general rule that uniform vertical distributions of periphyton mass do not tend to develop, but that patterns like those in Figure 1 (exclusive of the June 30 - August 18 tape) would be typical of steady state communities ("steady state" implying a dynamic equilibrium due to seasonal changes in income and loss factors.)

****

^{134}Cs DISTRIBUTION AND TRANSPORT IN THE CARP

Contributors: N. R. Kevern and N. A. Griffith*

****

Mathematics: analog computer simulation

Abstract: An analog computer simulation of a compartment model for distribution of ^{134}Cs in the carp is described.

*Reprinted from: Health Physics Division Annual Progress Report, July 31, 1965, 85-86, reprinted with permission of Oak Ridge National Laboratory operated by Union Carbide Corporation, Nuclear Division for the U.S. Atomic Energy Commission.

The distribution of ^{134}Cs in carp (Cyprinus carpio) was determined by feeding a single tagged meal to the fish, sacrificing and dissecting the fish, and counting the various parts. The redistribution of ^{134}Cs was studied by sacrificing a series of fish from 16 hours to 79 days. The tissues and organs counted were blood, gut, liver, heart, gills, kidney, spleen, skin, scales, flesh, and bone. The carp used were similar but not uniform in size, and the amount of ^{134}Cs ingested was not constant for each fish, necessitating that the data be normalized. Data were plotted as the ratio of activity per gram of tissue to initial activity per gram of whole body. Analog computer traces which fit the data are shown in Figure 1.

The ^{134}Cs was absorbed and transferred rapidly by the gut. Although blood is the common vehicle for transferring cesium throughout the fish, analog computer analysis suggested that lymph may be important in conveying cesium from the gut to the blood. Activity in the gut peaked before the first sample was taken and thus showed a sharp decline (Figure 1a). The uptake and subsequent loss of ^{134}CS by the tissues indicated three types of cesium metabolism. Skin, scales, and spleen paralleled the blood, having peak activities between 3 and 5 days and then declining rapidly (Figure 1a). Liver, heart, gills, and kidney, active organs which process blood in some manner in addition to having a blood supply, demonstrated the highest and earliest (about 1 day) initial activity and then declined exponentially (Figure 1b). Bone and flesh accumulated cesium slowly, probably through an active transport system, peaked at 6 and 15 days, respectively, and then declined very slowly (Figure 1c).

Estimates of the biological half-life for cesium in the various tissues were calculated from the computer curves. The biological half-life in days for each tissue was as follows: heart, 16; kidney, 17.4; liver, 17.8; gills, 21.2; scales, 22.3; spleen, 24.1; skin, 26.6; blood, 39.5; bone, 97.0; and flesh, 280.0. The half-life for cesium in the gut was 1.8 days for the initial rapid loss and 25 days for the slower component. The long half-life of cesium in the flesh may be of significance when considering contaminated fish

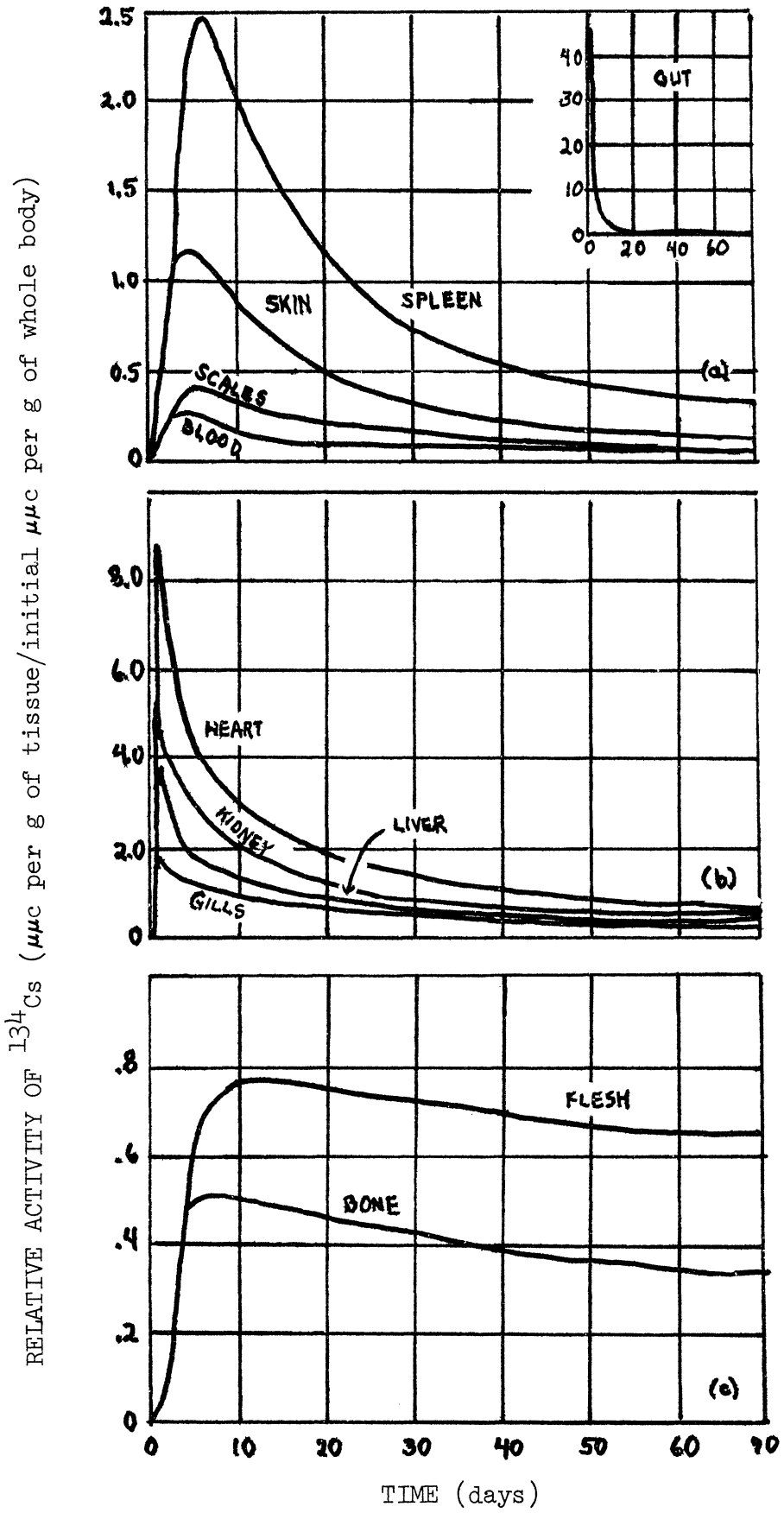


Figure 1

Uptake and Loss of ^{134}Cs by Organs and Tissues of Carp. (a) Spleen, skin, scales, blood, and gut; (b) heart, liver, kidney, and gills; and (c) flesh and bone.

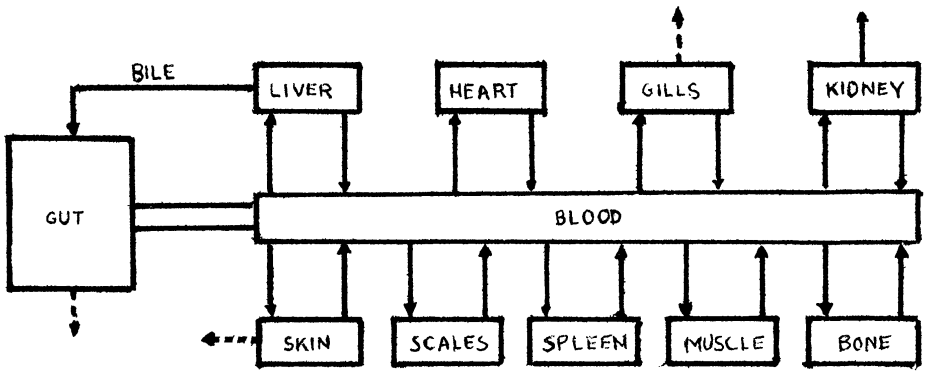


Figure 2

Block Diagram of Original Compartment Model for Distribution of ^{134}Cs in Carp.

for human consumption. The whole-body half-life for ^{134}Cs in carp at similar water temperatures would be about 80 days. Fish that were contaminated with radioactive cesium and kept in uncontaminated water to allow biological turnover to reduce the body burden would have a higher flesh burden than would be indicated by whole-body data.

A compartment model was formulated (Figure 2) and programmed for an analog computer study of exchange kinetics between the different organs. To obtain computer-generated curves which fit the empirical data for each organ, a synthetic blood curve was generated to which each organ could be coupled separately to determine transfer coefficients.

With this procedure it was possible to fit the data for skin, scales, and spleen (Figure 1a) with constant transfer coefficients. The data for flesh and bone (Figure 1c) could not be duplicated in this way, and several alternative hypotheses were explored on the computer. The one accepted was that ^{134}Cs transfer from blood to flesh and blood to bone required active transport.

The liver, heart, gills, and kidney, which in addition to having a blood supply also serve some blood-processing function, could not be simulated with any of the hypotheses previously explored. To obtain suitable fits to the data (Figure 1b) it was necessary to postulate some kind of connections (direct or indirect) between these organs and the gut. This required a revision of the model shown in Figure 2. The new model is shown in Figure 3 as a block diagram, with a schematic representing the postulated movement of ^{134}Cs between the four organs. Reference to anatomical and physiological literature led to the tentative conclusion that the pathways required to simulate the experimental data have real counterparts in the fish, namely, the lymphatic and hepatic portal systems.

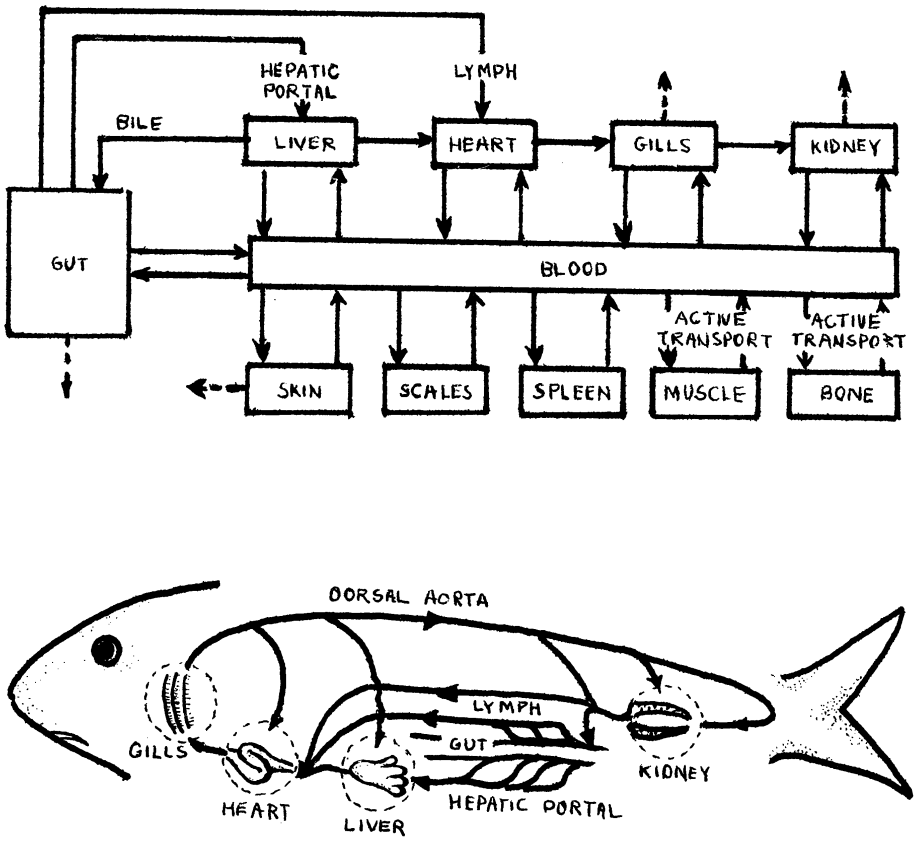


Figure 3

Block Diagram of Revised Model for ^{134}Cs Distribution in Carp, and Schematic Showing Transfer Pathways Between Kidney, Liver, Heart, and Gills.

****

KÖNIG'S THEOREM

Contributor: Kenneth R. Rebman

****

Mathematics: combinatorial analysis

Abstract: A famous combinatorial theorem is stated, along with a possible biological application.

In a certain population of p males, $M_1, M_2, \ldots, M_p$, and n females, $F_1, F_2, \ldots, F_n$, there is a trait C, which, if a specific mutation occurs in either parent, can be eliminated from all offspring of that parent. Let us assume that a specific mutagen exists so that the elimination of C can be carried out at will with 100% efficiency. For practical reasons, an experimenter may wish to perform a minimum number of mutagen treatments on individuals of the population in order to achieve complete elimination of C in the progeny from all possible matings within the population.

The problem can be described in matrix notation as follows: Let the p males represent the p rows and the n females represent n columns. Entry (i,j) is 1 if the offspring of M_i and F_j could exhibit the specified characteristic and is 0 otherwise. The entire situation can be represented by a p × n matrix with 0 - 1 entries.

For example, if the experimenter has 5 males and 7 females, the following matrix could represent the problem:

	F_1	F_2	F_3	F_4	F_5	F_6	F_7
M_1	0	0	1	0	0	1	0
M_2	1	0	1	0	1	0	1
M_3	0	0	0	0	0	1	0
M_4	1	1	1	1	0	0	1
M_5	0	0	1	0	0	1	0

With this matrix formulation, the problem of performing the minimum number of mutations can be restated: Choose the minimum number of rows and columns so that <u>all</u> 1's appear in the chosen rows and columns. The mutations can then be performed on the individuals corresponding to the chosen rows and columns. If the mutation is 100% successful, then the characteristic cannot appear in the offspring of any possible mating.

The mathematical theory of combinatorics deals with problems such as this. In fact, there is a theorem, called König's theorem, that

treats this problem directly.

Assume we have a matrix of arbitrary size, with all entries either 0 or 1.

Definition: A set of independent 1's is a collection of 1 entries from the matrix, such that no two are in the same row or column. Let M be the maximum number of independent 1's.

Definition: A covering set is a set of rows and columns that contain all of the 1 entries in the matrix. Let m be the minimum number of lines (rows and columns) in a covering set.

König's Theorem: $m = M$.

The significance of König's theorem for the experimenter's problem is:

The minimum number of mutations necessary is equal to the maximum number of matings that could produce offspring with the characteristic, using distinct pairs for parents.

Of course, the theorem also answers the reverse question: If the experimenter wishes to make one series of matings using distinct parents, what is the maximum possible number of occurrences of the characteristic?

It is, of course, equal to the minimum number of covering lines. In the example, note that row 2, row 4, column 3, and column 6 completely cover all 1's. Also, positions (1,3) (2,1) (3,6) (4,4) are independent. Hence, this is a minimal covering set and a maximal set of independent 1's.

****

HALL'S THEOREM

Contributor: Kenneth R. Rebman

****

Mathematics: combinatorial analysis

Abstract: A combinatorial theorem of Philip Hall is presented, along with a possible biological application.

Suppose that an experimenter is testing a population of p individuals. He has decided that there are m relevant characteristics to be studied. But these characteristics are not mutually exclusive: a single member of the population may exhibit several of the characteristics. The experimenter's problem is to find a set of m distinct individuals, each representing a different characteristic.

To rephrase the problem in mathematical terms, define the m sets $T_1, \ldots, T_m$ where T_i is the set of individuals exhibiting characteristic i. These sets are not necessarily disjoint. The experimenter's problem is thus:

$$\text{Find a set } \{a_1, \ldots, a_m\} \text{ such that } a_i \neq a_j \text{ for } i \neq j ,$$
$$\text{and } a_i \in T_i , \; i = 1, \ldots, m .$$

This is called a set of distinct representatives (SDR) for the collection $\{T_1, \ldots, T_m\}$.

It is possible, of course, that an SDR does not exist. (For example, if three of the characteristics were present in but two of the individuals.) It is clearly a necessary condition that any k of the characteristics must be found in at least k individuals.

A combinatorial theorem, proved first by Philip Hall, posits that this is a sufficient condition as well. That is, the experimenter is guaranteed the existence of a SDR if any k of the characteristics appear in at least k individuals for k = 1, ..., m. (It is interesting to note that this theorem is mathematically equivalent to König's Theorem -- see Model PL1).

At this point, the experimenter must realize what is meant by an "existence" theorem. This theorem gives him conditions which assure that there is an SDR, but gives no indication of how to find it.

Fortunately, one of the many proofs of this theorem is actually a constructive algorithm for finding an SDR, if one exists. If no SDR exists, this algorithm terminates by exhibiting k characteristics that are found in fewer than k individuals.

This algorithm is due to Marshall Hall, and can be found in his article, "A Survey of Combinatorial Analysis," appearing in Vol. 4 of Surveys in Applied Mathematics. The algorithm itself is quite straightforward and could be easily programmed for automatic computation.

****

FINDING A FEASIBLE AND OPTIMAL BLOOD TRANSFUSION SCHEME

Contributor: Kenneth R. Rebman

****

Mathematics: linear programming (transportation problem)

Abstract: The problem of giving several transfusions to various patients, when it is also desired to minimize the cost of blood replacement, is formulated as a capacited transportation problem.

Consider the following problem:

Seven patients (R, S, T, U, V, W, X) require blood transfusions. For the purposes of this example, assume only four blood types (A, B, AB, O) where AB is a universal recipient and O a universal donor.

The blood is available as follows:

Type	Supply	Cost/pt. of Replacement
A	7 pts.	\$1
B	4 pts.	\$4
AB	6 pts.	\$2
O	5 pts.	\$5

The patients' data are:

Patient	Type	Requirement
R	A	2
S	AB	3
T	B	1
U	O	2
V	A	3
W	B	2
X	AB	1

The problem is to see that each patient receives the required amount of the proper blood and to use the existing supply so that the cost of replacement is minimized.

The mathematical model to be used is the capacitated transportation problem. It can be described as follows:

A commodity is to be shipped from p origins to n destinations. Each origin i has a supply a_i which cannot be exceeded and each destination j has a demand b_j which must be met. Without loss of generality, assume that the total supply is equal to the total demand. The cost of shipping from origin i to destination j is given by c_{ij}. The problem is to find a shipping scheme that meets demands, does not exceed supplies, and does so with minimum cost. This is usually called the transportation problem. In addition, some (or all) of the routes may have capacities which cannot be exceeded, giving the so-called capacitated problem.

If we let x_{ij} be the amount shipped from origin i to destination j, the problem can be formulated more precisely as follows:

Subject to:

$$\sum_{j=1}^{n} x_{ij} = a_i \qquad i = 1,\ldots,p$$

(an amount equal to a_i leaves origin i)

$$\sum_{i=1}^{p} x_{ij} = b_j \qquad j = 1,\ldots,n$$

(an amount equal to b_j arrives at destination j)

$$0 \leq x_{ij} \leq e_{ij} \qquad \begin{matrix} i = 1,\ldots,p \\ j = 1,\ldots,n \end{matrix}$$

(only positive shipments allowed and the capacity e_{ij} of route i,j must not be exceeded)

Minimize

$$\sum_{i=1}^{p} \sum_{j=1}^{n} c_{ij}x_{ij} \ .$$

(minimize total cost)

Once a problem has been formulated as a transportation problem, there are many methods available for its solution. Such a problem is in fact a linear programming problem, and linear programming techniques could be used. However, more efficient algorithms that treat the transportation problem specifically have been developed.

The blood transfusion problem can be stated as a transportation problem as follows:

The four types of blood represent four origins for the commodity "blood", and the seven patients represent destinations. Since total demand is only 14, while total supply is 22, we introduce a "dummy patient" with a demand of 8. All unused blood will then be "shipped" to this destination, with cost of zero. All other shipping costs are given by the cost of replacing one pint of blood.

The fact that some patients cannot receive certain types of blood can be incorporated into the model by placing a capacity of 0 on those "routes".

The following matrix describes the problem completely. The capacities of 0 appear to the upper left of the costs.

	R(A)	S(AB)	T(B)	U(O)	V(A)	W(B)	X(AB)	Dummy	Supplies
A	1	1	$^{o}1$	$^{o}1$	1	$^{o}1$	1	0	7
B	$^{o}4$	4	4	$^{o}4$	$^{o}4$	4	4	0	4
AB	$^{o}2$	2	$^{o}2$	$^{o}2$	$^{o}2$	$^{o}2$	2	0	6
O	5	5	5	5	5	5	5	0	5
Demands:	2	3	1	2	3	2	1	8	

The X matrix which gives the optimal shipping (transfusion) scheme is:

	R	S	T	U	V	W	X	D
A	2	1			3		1	
B			1			2		1
AB		2						4
O				2				3

Blanks indicate a zero entry. Thus patient S receives one pint of type A and two pints of type AB; there are four pints of type AB left but none of type A; etc.

The total cost of replacing the blood will be $33 and this is minimal.

This answer, incidentally, was found by using the Thrall-Graves algorithm for capacitated transportation problems, as programmed for a digital computer. A remote console linked to a time-sharing system was used, so the result was "instantaneous". It is, however, feasible to work such small problems by hand in a relatively short period of time.

****

A LINEAR PROGRAMMING MODEL OF SELECTIVE TREATMENT

Contributor: Kenneth R. Rebman*

****

Mathematics: linear systems, linear programming

Abstract: If the effect of various treatments on a biological system is linear, then a linear programming model is proposed to solve the problem of destroying unwanted parts of the system while leaving the desirable parts unharmed.

*Based upon: MacQueen, J. "A Theoretical Model for Achieving Selective Biological Effects." Berkeley: Western Management Science Institute, The University of California, unpublished paper.

Suppose we have a system $\mathcal{S}$ that is composed of subsystems S_o, S_1, ...,S_n. In order that the system $\mathcal{S}$ survive, it is required that the subsystem S_o be destroyed.

Examples:

1. $\mathcal{S}$ consists of several body organs (e.g., heart, liver, lungs, kidneys, stomach) The undesirable system might be a diseased kidney.

2. $\mathcal{S}$ consists of several types of desirable grass (e.g., Kentucky blue, clover), and unwanted crabgrass is called S_o.

3. In an aquarium, $\mathcal{S}$ might consist of several species of protozoa, each species denoted by an S_i. All of the species except one are helpful (or necessary) for a balanced aquarium. The harmful species is denoted by S_o.

4. $\mathcal{S}$ may be collections of body tissue, and a cancerous tissue would be denoted by S_o.

In such situations, there are often many alternative procedures or treatments that can be used in attempting to destroy S_o. However, in general these treatments are also harmful to the "good" systems $S_1,\ldots,S_n$. For example, a weed killer is apt to kill healthy grass; a chemical used to kill protozoa may not be able to distinguish among them; radiation treatment destroys healthy as well as cancerous cells.

It may well happen that although all available treatments are harmful to all sub-systems $S_o,S_1,\ldots S_n$, they are harmful in differing degrees. If some treatment were used exclusively to destroy S_o, it might also destroy S_1, say, and slightly harm S_2. An alternative treatment used in sufficient quantity to destroy S_o might harm S_1 only slightly, but destroy S_2. If S_1 and S_2 are essential for the survival of $\mathcal{S}$, then clearly neither treatment used alone is feasible. However, there may be a combination of the two treatments that will destroy S_o and yet permit both S_1 and S_2 to survive. This note describes a procedure for finding such a combination, if it exists, and further, for finding one that will minimize some specific objective function.

We hypothesize that the problem is a linear problem. More specifically, our assumptions are as follows:

Suppose that the basic treatments available are $t_1,\ldots,t_m$. However, these basic treatments may be given in any quantity and used in any combination with one another. Practically, there may be an upper limit to the quantity involved in a basic treatment or combination of basic treatments.

Example:

The two basic treatments are:

t_1: inject one unit of drug 1
t_2: inject one unit of drug 2 .

The drugs may be combined as desired, but the maximum total injection is governed by the capacity of the hypodermic.

Let $T = \{t\}$ be the set of all possible allowable treatments. T contains all allowable quantitites of the m basic treatments, $t_1,t_2,\ldots t_m$, in possible combinations.

If t_1 and t_2 are as in the above example, and if no more than two total units of the drug can be injected, then

$$T = \{t = (x,y) \mid x,y \geq 0 \text{ and } x + y \leq 2\}$$

where x and y are the number of units of drugs 1 and 2, respectively. There are 6 allowable treatments, $\{(0,0),(0,1),(1,0),(1,1),(2,0),(0,2)\}$ with integer components, and infinitely many with fractional components, e.g., (1/2,1/2) or (1/2,3/2).

After a treatment t has been administered, it has a certain effect on $\mathcal{S}$. That is, the treatment affects each S_i, $i = 0,1,\ldots,n$. For the purposes of this model, we assume that S_i can be partially destroyed, completely destroyed, or over-destroyed; by the latter we mean that a "lesser" treatment would also have fully destroyed S_i. These effects can be expressed by $\bar{g}_i(t)$, where $0 \leq \bar{g}_i(t) < 1$ denotes partial destruction; $\bar{g}_i(t) = 1$, total destruction; and $\bar{g}_i(t) > 1$, over-destruction. By "lesser" treatment is meant one in which all components of the treatment vector are smaller. Thus, we have defined

$n + 1$ functions $\bar{g}_0, \bar{g}_1, \ldots, \bar{g}_n$. The domain of each function is the set T. The range of each function is some subset of $[0,\infty]$.

We now make the key assumptions that enable us to carry out our analysis.

Assumption A (Constant Returns to Scale):

> We assume that if any treatment is increased or decreased by some ratio, then the result of that treatment on each S_i, that is, the fraction of each S_i destroyed, is increased or decreased by the same ratio.
>
> Thus, if 1 unit of a drug will destroy 1/3 of S_o, then we assume that 1/2 unit of the drug will destroy 1/6 of S_o, that two units will destroy 2/3 of S_o, etc.

Assumption B (Additivity):

> If two treatments are used, then the result will be the sum of the individual results for the two treatments. So if 1 unit of drug 1 destroys 1/3 of S_o and 1 unit of drug 2 destroys 1/4 of S_o, then the treatment consisting of 1 unit of drug 1 and 1 unit of drug 2 will destroy 7/12 of S_o.

For $t \in T$ where t is any allowable treatment, we will let $a \cdot t$ denote the treatment t multiplied by the factor a.

If t_1 and t_2 are two treatments in T, then we will let $t_1 \oplus t_2$ be the combination of the two treatments.

From assumption A,

$$\bar{g}_i(at) = a\, \bar{g}_i(t) ,$$

and from assumption B,

$$\bar{g}_i(t_1 \oplus t_2) = \bar{g}_i(t_1) + \bar{g}_i(t_2) .$$

These results hold for all i, $i = 0,1,\ldots,n$.

It is clear that if $t \in T$, then t can be written as

$$t = a_1 t_1 \oplus \ldots \oplus a_m t_m = \sum_{j=1}^{m} \oplus a_j t_j$$

where the t_i are the basic treatments.

So for each i, i = 0,1,...n, we have

$$\bar{g}_i(t) = a_1\bar{g}_i(t_1) + \ldots + a_m\bar{g}_i(t_m) = \sum_{j=1}^{m} a_j\bar{g}_i(t_j) \ .$$

Thus it is clear that in order to determine the effect of treatment $t \in T$ on S_i, it is only necessary to know the effect of each basic treatment t_j on S_i, j = 1,2,...,m.

Suppose then that these numbers have been determined. That is, let

$$\bar{g}_i(t_j) = d_{ij}, \begin{cases} i = 0,1,\ldots,n \\ j = 1,2,\ldots,m \end{cases}, \ d_{ij} \geq 0 \ .$$

Thus, applying basic treatment t_j will destroy d_{ij} of S_i.

Until now, the domain of each function $\bar{g}_i$ has been T, a set of treatments. But since any treatment in T can be written in our new notation as $a_1t_1 \oplus \ldots \oplus a_mt_m$, we can see that associated uniquely with each treatment is an ordered m-tuple of real numbers. Conversely, an ordered m-tuple of real numbers either corresponds exactly to one treatment or to none at all.

Thus, we have a one-to-one correspondence between T and a subset of E^m, Euclidean m-space, which is just the set of all ordered m-tuples.

In T	In E^m
$t = a_1t_1 \oplus \ldots \oplus a_mt_m$	$(a_1,\ldots,a_m)$
$t' = b_1t_1 \oplus \ldots \oplus b_mt_m$	$(b_1,\ldots,b_m)$
$t \oplus t' = (a_1 + b_1)t_1 \oplus \ldots \oplus (a_m + b_m)t_m$	$(a_1 + b_1,\ldots,a_m + b_m)$
basic treatment t_j	$(0,\ldots,0,\underset{j\text{th}}{1},0,\ldots,0)$

Let K be that subset of E^m corresponding to T. If there are no constraints of quantity, then $K = E^m_+$, the positive orthant. If there is an upperbound on the total quantity of treatment, say k, then

$$K = \{\bar{x} \in E^m \mid x_j \geq 0, \sum_{j=1}^{m} x_j \leq k\} .$$

Now, we define n + 1 functions, $g_o, g_1, \ldots, g_n$, each function having domain K. For

$$\bar{x} = (x_1, x_2, \ldots, x_m) \in K \subset E^m ,$$

we define

$$g_i(\bar{x}) = \bar{g}_i(t)$$

where

$$t = x_1 t \oplus \ldots \oplus x_m t_m .$$

The new functions are just like the old, except that the domain of these functions is now a subset of E^m. The values of the new functions at a point in E^m are the same as the values of the old functions at the corresponding point of T.

Observe that

$$g_i(a\bar{x}) = \bar{g}_i(at) = a\bar{g}_i(t) = ag_i(\bar{x})$$

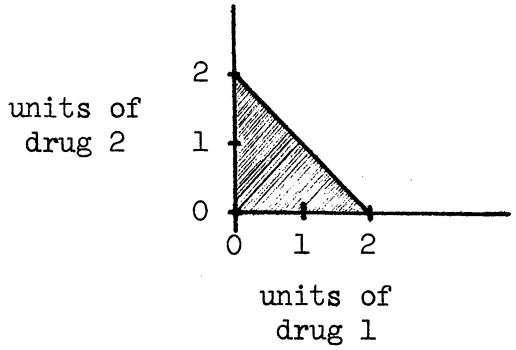
and

$$g_i(\bar{x} + \bar{x}') = \bar{g}_i(t \oplus t') = \bar{g}_i(t) + \bar{g}_i(t') = g_i(\bar{x}) + g_i(\bar{x}') ,$$

so properties A and B hold for these new functions also.

Example:

As before, t_1 corresponds to injection of 1 unit of drug 1; t_2 corresponds to injection of 1 unit of drug 2. No more than two total units may be used.



The shaded region is $K \subset E^2$.

Also, if $\bar{x} = (x_1,\ldots,x_m) \in K$, then

$$\begin{aligned} g_i(\bar{x}) &= g_i\Big((x_1,0,\ldots,0) + \ldots + (0,..,0,x_j,0,..,0) + \ldots + (0,\ldots,0,x_m)\Big) \\ &= x_i g_i\ (1,0,\ldots,0) + \ldots + x_j g_i\ (0,..0,1,0,..,0) + \ldots + x_m g_i\ (0,..,0,1) \\ &= x_1\bar{g}_i(t_1) + \ldots + x_j\bar{g}_i(t_j) + \ldots + x_m\bar{g}_i(t_m) \\ &= x_1 d_{i1} + \ldots + x_j d_{ij} + \ldots + x_m d_{im} \\ &= \sum_{j=1}^{m} x_j d_{ij} \ . \end{aligned}$$

Recall that our problem is to destroy S_o but permit $\mathcal{S}$ to survive. $\mathcal{S}$ consists of subsystems $S_o, S_1,\ldots,S_m$; for $\mathcal{S}$ to survive it may not be necessary that <u>all</u> of $S_1,..,S_n$ survive, but only that <u>some</u> survive. Thus we introduce the notion of <u>essential sets</u>.

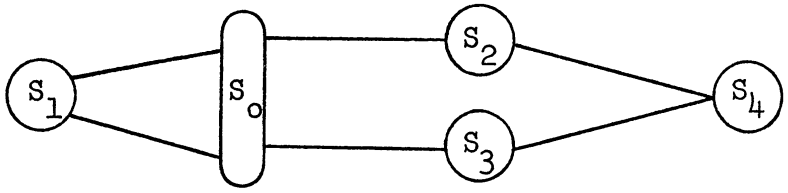
L is an essential set for $\mathcal{S}$ if:

a) $L \subset \{1,2,\ldots,n\}$

b) if S_i survives for each $i \in L$, then the entire system $\mathcal{S}$ survives.

<u>Example</u>:

$\mathcal{S}$ can be represented by:



For $\mathcal{S}$ to survive, an uninterrupted flow from S_1 to S_4 is required. S_o blocks this flow. Hence the essential sets are

$$L_1 = \{1,2,4\} \ ,$$
$$L_2 = \{1,3,4\} \ .$$

As long as S_o is destroyed, flow from S_1 to S_4 will be possible, even if S_2 or S_3 is destroyed, but not if both are destroyed.

Finally, assume there is a certain critical level for each S_i. That is, S_i will survive if the fraction of S_i destroyed is less than or equal to C_i, but will be destroyed otherwise. (Assume that S_o will survive only if the fraction destroyed is strictly less than C_o).

With these assumptions and definitions, we can now formulate the problem.

We wish to find an allowable treatment t that destroys S_o and permits $\mathcal{S}$ to survive.

Since there is a unique correspondence between allowable treatments and the points of $K \subset E^m$, we can rephrase the problem as follows:

Find a point $\bar{x} = (x_1,\ldots,x_m) \in K$ such that

$$\left[x_j \geq 0,\ j = 1,\ldots,m;\ \text{and}\ \sum_{j=1}^{m} x_j \leq k\right]$$

so that the treatment corresponding to $\bar{x}$ will destroy S_o

$$\left[g_o(\bar{x}) = \sum_{j=1}^{m} d_{oj}x_j \geq C_o\right]$$

but will permit $\mathcal{S}$ to survive,

$$\left[g_i(\bar{x}) = \sum_{j=1}^{m} d_{ij}x_j \leq C_i \quad \text{for each i in some essential set L}\right].$$

The problem is thus one of solving a system of <u>linear</u> inequalities. Find an $\bar{x} = (x_1,\ldots,x_m)$ satisfying:

$$x_j \geq 0, \qquad j = 1,\ldots,m$$

$$\sum_{j=1}^{m} x_j \leq k$$

$$\sum_{j=1}^{m} d_{oj}x_j \geq C_o$$

$$\sum_{j=1}^{m} d_{ij}x_j \leq C_i \qquad \text{for all } i \in L, \text{ where L is any essential set.}$$

There will be, in general, an infinite number of solutions to this system. If we also introduce a function $f(\bar{x})$, then we may find the solution to the linear inequalities that minimizes f. If f is

a linear function, that is, $f(\bar{x}) = \sum_{j=1}^{m} a_j x_j$,, then we have a <u>linear programming</u> problem.

For example, $f(\bar{x})$ might represent the cost of the treatment corresponding to $\bar{x}$. If cost has the properties of constant return to scale and additivity (so that the cost of a double treatment is twice the cost of one, and the cost of a combination treatment is the sum of the individual costs), then $f(\bar{x}) = \sum_{j=1}^{m} a_j x_j$ where a_j is the cost of basic treatment t_j.

Or, we may wish to minimize the total amount that is destroyed. That is, we assumed that S_i survives if the amount destroyed is less than or equal to C_i. But an error in calculating C_i could be disastrous if exactly C_i of S_i is destroyed. Thus, certain of the S_i may be critical and we will want to minimize the total damage to these systems. Let $\Omega \subseteq \{1,\ldots,n\}$ be this collection of critical subsystems.

We can formulate our problem as a linear programming problem: The constraints are the linear inequalities given above. The objective function is

$$\min \sum_{j=1}^{m} a_j x_j \text{ (minimize cost);}$$

or it could be

$$\min \sum_{i \in \Omega \cap L} \left(\sum_{j=1}^{m} d_{ij} x_j \right)$$

which would minimize the total damage to the critical systems that are in the essential set that permits $\mathcal{L}$ to survive; or some combination of these may be minimized.

---

1. MacQueen, J. "A Theoretical Model for Achieving Selective Biological Effects." Berkeley: Western Management Science Institute, The University of California, unpublished paper.

****

TWO BIOLOGICAL EXAMPLES OF THE USE OF MATRIX MULTIPLICATION

Contributor: Kenneth R. Rebman

****

Mathematics: definition of matrix product (Math. 3)

Abstract: The row-by-column rule for matrix multiplication is motivated by two examples in a biological context.

The row-by-column rule for matrix multiplication may seem unnatural to some students. We provide here two examples in a biological context which show that row-by-column multiplication answers some quite natural questions.

EXAMPLE 1: Food Consumption.

Suppose that in a particular ecological system, the species can be divided into three categories:

1. Vegetation which provides food for certain animals. We shall denote these plants by $p_1, p_2, \ldots, p_r$.

2. Plant-eating animals which feed on the plants that are described in 1. These animals are denoted by $a_i, \ldots, a_s$.

3. Carnivorous animals which live on the plant-eating animals. The carnivores are denoted by $c_1, c_2, \ldots, c_t$.

Let us define a season as some fixed period of time. We assume that it is known how much of each type of food is used by each animal in one season. More precisely, let x_{ik} denote the amount of plant p_i that is eaten by animal a_k, and let y_{kj} be the number of animals a_k devoured by a carnivore c_j.

A natural question to be answered is:

What is the amount of plant p_i that is used indirectly by carnivore c_j?

Now, x_{ik} is the amount of plant p_i that animal a_k eats, and carnivore c_j eats y_{kj} of animal a_k. So the amount of plant p_i that carnivore c_j uses indirectly because he feeds on animal a_k is $x_{ik}y_{kj}$. Thus, the <u>total</u> amount that carnivore c_j uses of plant p_i is given by the sum:

$$x_{i1}y_{1j} + \cdots + x_{is}y_{sj} = \sum_{k=1}^{s} x_{ik}y_{kj}.$$

Let us arrange the original information in matrix form:

	a_1	a_2	$\cdots$	a_k	$\cdots$	a_s
p_1	x_{11}	x_{12}	$\cdots$	x_{1k}	$\cdots$	x_{1s}
p_2	x_{21}	x_{22}		x_{2k}	$\cdots$	x_{2s}
$\vdots$	$\vdots$	$\vdots$		$\vdots$		$\vdots$
p_i	x_{i1}	x_{i2}	$\cdots$	x_{ik}	$\cdots$	x_{is}
$\vdots$	$\vdots$	$\vdots$		$\vdots$		$\vdots$
p_r	x_{r1}	$\cdots$ x_{r2}	$\cdots$	x_{rk}	$\cdots$	x_{rs}

Call this matrix X.

	c_1	$\cdots$	c_2	$\cdots$	c_j	$\cdots$	c_t
a_1	y_{11}		y_{12}	$\cdots$	y_{1j}	$\cdots$	y_{1t}
a_2	y_{21}		y_{22}	$\cdots$	y_{2j}	$\cdots$	y_{2t}
$\vdots$	$\vdots$		$\vdots$		$\vdots$		$\vdots$
a_k	y_{k1}		y_{k2}	$\cdots$	y_{kj}	$\cdots$	y_{kt}
$\vdots$	$\vdots$		$\vdots$				
a_s	y_{s1}	$\cdots$	y_{s2}	$\cdots$	y_{sj}	$\cdots$	y_{st}

Call this matrix Y.

Then the matrix product XY = Z is defined, and from the row-by-column rule for multiplication of matrices, we obtain the ij entry, Z_{ij}, of the product Z:

$$Z_{ij} = \sum_{k=1}^{s} x_{ik}y_{kj}.$$

The matrix product Z provides an answer for the question posed before; for each i and j, Z_{ij} is the amount of plant a_i used by carnivore c_j.

EXAMPLE 2: Spread of a Contagious Disease.

Suppose that five persons were infected by a very contagious disease. A group of seven persons was then questioned to determine who had had contact with any of the first five. Next, a group of ten persons was questioned to see if they contacted any of the group of seven. The data is arranged in matrix form as follows:

	1	2	3	4	5	6	7
1	1	0	0	1	0	1	1
2	1	1	0	0	0	1	0
3	0	0	1	0	0	1	1
4	0	0	0	1	0	0	0
5	0	0	0	0	1	1	1

Matrix A = (a_{ij}),

	1	2	3	4	5	6	7	8	9	10
1	0	0	0	0	1	0	0	0	1	0
2	0	0	1	0	1	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	1
4	1	0	1	0	1	0	0	0	0	0
5	0	0	0	1	1	0	0	0	1	0
6	0	0	0	0	0	0	0	0	0	0
7	0	1	0	0	0	1	1	1	0	0

Matrix B = (b_{ij}),

where a 1 in position (i,j) indicates that person i had contact with person j, a 0 indicates that he did not. Notice that in matrix A, the sum of the entries in column j indicates how many times person j was exposed to the disease.

A natural question to ask is: How many times was each person in the group of ten indirectly exposed to the disease? First, we can ask a simpler question: If j is in the group of ten, how many exposures did he have that can be traced to person i in the original group of five? For indirect exposure, i must have contacted some k in the group of seven, and k in turn would have contacted j. This is the case if and only if $a_{ik} = 1$ and $b_{kj} = 1$. Thus, i contacts j through k if and only if $a_{ik}b_{kj} = 1$.

The total number of exposures of j traceable to i will then be $\sum_{k=1}^{7} a_{ik}b_{kj}$, which is just the product of the ith row of A by the jth column of B. This is the (i,j) entry in AB. Here the matrix product is:

	1	2	3	4	5	6	7	8	9	10
1	1	1	1	0	2	1	1	1	1	0
2	0	0	1	0	2	0	0	0	1	0
3	0	1	0	0	0	1	1	1	0	1
4	1	0	1	0	1	0	0	0	0	0
5	0	1	0	1	1	1	1	1	1	0

Matrix AB.

Now the total number of indirect exposures of that person j can be found by adding the elements in column j of this product matrix. (Note that this sum requires some interpretation. For example, in the group of seven, person 4 had contact with 1 and 4 of the original group of five. Hence, in the final group, person 1 had indirect contact with 1 and 4 of the original group, but both were because of his single contact with person 4 in the group of seven.)

****

MAINTAINING A PROFITABLE ECOLOGICAL BALANCE

Contributors: G. M. van Dyne and Kenneth R. Rebman

****

Mathematics: linear programming

Abstract: The model building methods of linear programming are used to solve a problem of maximizing the profit realized from keeping a composite group of livestock.

The following model is not only an interesting application of linear programming to a bio-economic situation; it also gives a graphic illustration of how it is necessary to sift and interpret the given information in order to formulate a useful mathematical model.

The situation has the following description:

In the Edwards Plateau country of west Texas the vegetation is easily modified by grazing animals from a mixed vegetation to a dominance of grasses, or forbs, or browse or various combinations of these. It is common to see in pastures in this area herds of cattle, bands of sheep, and flocks of mohair goats. Whitetail deer and wild turkey are common if there is sufficient browse and mixed vegetation. Catfish will thrive in ponds if there is suitable vegetation cover to prevent siltation. Ranchers sell beef, wool, mutton, mohair and lease deer and turkey hunting and catfishing rights. The relative monetary income values per animal are: cattle, 10.; goats, 1.; sheep, 1. (wool and mutton combined); deer, 0.5; turkey, 0.05; and fish, 0.001. A rancher owns 10 sections of such land which has a maximum carrying capacity of 10 animal units per section per year. The animal unit equivalents for the various species per animal are: cattle, 1.; sheep, 0.2; goats, 0.25; deer, 0.3; and essentially zero for turkeys and fish. To properly organize his operation for livestock production he has to have at least 20 cattle and at least 20 goats on his ranch. The rancher wants at least some sheep and some deer on his ranch. He can maintain the desired vegetation cover for turkey and fish if he has (a) cattle, sheep, goats, and deer, (b) cattle, sheep, and goats, or (c) cattle, goats and deer, but no more than 75% of the grazing load (measured in animal units) may be due to cattle and goats combined. Of course, he wants his total stocking rate of all organisms combined to be equal to or less than the carrying capacity of the range. Furthermore, he can put in no more than one pond per section each of which will support no more than 500 fish each, and can harvest no more than 25% of the catfish per pond per year. The requirements and habits of the wild turkey are such that he cannot maintain more than 2 flocks of 10 birds per

flock per section and he cannot harvest more than 20% of the population per year. He keeps only castrated male goats for mohair and shears them once each year. His cattle, sheep, and deer harvests which will maintain a given population are respectively about 25, 35, and 15% of the population per year. For simplification, the 35% for sheep includes both wool and mutton.

The first step is to isolate the salient points from this description. They are:

1) The relative monetary income values per animal are:

cattle	10
goats	1
sheep	1
deer	.5
turkey	.05
fish	.001

2) There are 10 sections of land, each with a maximum carrying capacity of 10 animal units per year.

3) Animal unit equivalents for the species are:

cattle	1
goats	.25
sheep	.2
deer	.3
turkey	0
fish	0

4) The ranch must have at least 20 cattle and 20 goats.

5) There must be some sheep and some deer.

6) If there are to be any turkey and fish, there must be

a) cattle, sheep and goats

or

b) cattle, goats, and deer.

7) Cattle and goats can comprise no more than 75% of the animal units.

8) Total animal units cannot exceed the carrying capacity.

9) A maximum of 500 fish per section, with a 25% annual harvest.

10) A maximum of 20 birds per section, with a 20% annual harvest.

11) Harvest percentages:

cattle	25%
goats	100%
sheep	35%
deer	15%

12) How many individuals of each species should the rancher have in order to maximize annual profit?

The next step is to quantify these conditions.

In the first place the rancher is hoping for an answer that is something like: have 30 cattle, 22 sheep, etc. He will be understandably upset if he is told that to realize a maximum profit, he requires 33.25 cattle and 21.7 sheep. The rancher is certainly anticipating the answer to be in integers. However, any programming problem that imposes integer constraints on the variables is apt to be extremely difficult to solve. Thus, the first simplification is to treat the problem as a continuous programming problem. It may even turn out that all or some of the optimal values of the variables of this problem <u>are</u> actually integers. If not, the solution can be rounded to the nearest integer solution. It is important to realize that this rounded solution may <u>not</u> be the best integer solution. However, if

p_o is the maximum profit for the continuous problem,
p_1 is the profit obtained by rounding the optimal solution
p_2 is the maximum profit to the integer problem

then clearly $p_1 \leq p_2 \leq p_o$. If $p_o - p_1$ is very small, the rancher will not care anyway.

The next step is to determine the variables. Since he has 10 parcels of land, each being able to support 6 different species, the first inclination is to use 60 variables x_{ij}, $i = 1 \ldots 6, j = 1 \ldots 10$. Then x_{ij} will represent the number of species i to be placed on parcel j. However, since the conditions for survival are the same in any parcel, it is much simpler to consider the entire ten parcels as a single unit. Then only 6 variables x_i, $i = 1 \ldots 6$ are needed, where x_i represents the total number of species i. In the final solution, 1/10 of x_i can be placed in each parcel. (Or other

adjustments can be made, at the rancher's preference.) (Note that we cannot just maximize profit over a single parcel. The constraints would require some deer on every parcel, which is not required in the given problem.)

Thus we have the following 6 variables:

x_1: number of cattle
x_2: number of goats
x_3: number of sheep
x_4: number of deer
x_5: number of turkey
x_6: number of fish

The conditions then give the following constraints:

Condition 2) says the maximum carrying capacity available is 100 units. Condition 3) gives the animal units for each species. Then, condition 7) gives the constraint:

$$1x_1 + .25x_2 \leq 75$$

Condition 8) becomes:

$$1x_1 + .25x_2 + .2x_3 + .3x_4 \leq 100$$

Condition 4) is:

$$x_1 \geq 20$$
$$x_2 \geq 20$$

Condition 5) is:

$$x_3 \geq \text{"some"}$$
$$x_4 \geq \text{"some"}$$

where "some" is the minimum number of sheep and deer the rancher wants. Since the rancher is vague about this, let us assume that "some" = 1. So lower bound constraints are:

$$x_1 \geq 20$$
$$x_2 \geq 20$$
$$x_3 \geq 1$$
$$x_4 \geq 1$$

Now we see that condition 6) is irrelevant. The lower bound constraints guarantee that 7) a) and b) will always be satisfied. Hence, it will always be possible to have turkey($x_5 > 0$) and fish ($x_6 > 0$). Condition 9) gives

$$x_6 \leq 5000$$
$$x_5 \leq 200$$

Finally, it is only needed to calculate the profit. Condition 1) gives profit per animal. Not all animals can be harvested, however. Harvest percentages are given in 9), 10), and 11). The annual profit from each species is:

cattle	$(10)(.25x_1)$
goat	$(1)(x_2)$
sheep	$(1)(.35x_3)$
deer	$(.5)(.15x_4)$
turkey	$(.05)(.20x_5)$
fish	$(.001)(.25x_6)$

Thus the rancher's problem is:
Subject to the constraints

$$x_1 + .25\,x_2 \leq 75$$
$$x_1 + .25x_2 + .2x_3 + .3x_4 \leq 100$$
$$x_1 \geq 20$$
$$x_2 \geq 20$$
$$x_3 \geq 1$$
$$x_4 \geq 1$$
$$0 \leq x_5 \leq 200$$
$$0 \leq x_6 \leq 5000$$

maximize the objective function

$$z = 2.5x_1 + x_2 + .35x_3 + .075x_4 + .01x_5 + .00025x_6.$$

It now becomes clear that the only constraints affecting x_5 and x_6 (number of turkey and fish) are their upper bound constraints. So to maximize profit, the rancher should have as many turkey and

as many fish as possible, regardless of the other species. Thus, each parcel of land should have a pond with 500 fish and should support 2 flocks of 10 birds each.

The annual profit from birds and fish is thus

$$(.01)(200) + (.00025)(5000) = 2 + 1.25 = 3.25.$$

Next, in order to have only non-negativity constraints, introduce four new variables:

$$\begin{aligned} z_1 &= x_1 - 20 \\ z_2 &= x_2 - 20 \\ z_3 &= x_3 - 1 \\ z_4 &= x_4 - 1 \end{aligned} \qquad z_i \geq 0,\ i = 1 \ldots 4$$

So z_i is the amount by which species i exceeds its lower bound.
Note that

$$\begin{aligned} x_1 &= z_1 + 20 \\ x_2 &= z_2 + 20 \\ x_3 &= z_3 + 1 \\ x_4 &= z_4 + 1 \,. \end{aligned}$$

So the original problem is equivalent to:
Subject to

$$(z_1 + 20) + .25(z_2 + 20) \leq 75$$
$$(z_1 + 20) + .25(z_2 + 20) + .2(z_3 + 1) + .3(z_4 + 1) \leq 100$$
$$z_1 \geq 0 \quad z_2 \geq 0 \quad z_3 \geq 0 \quad z_4 \geq 0$$

maximize

$$2.5(z_1 + 20) + (z_2 + 20) + .35(z_3 + 1) + .075(z_4 + 1) + 3.25$$

Simplification gives:
subject to

$$z_1 + .25z_2 \leq 50$$
$$z_1 + .25z_2 + .2z_3 + .3z_4 \leq 74.5$$
$$z_i \geq 0 \quad i = 1 \ldots 4$$

maximize

$$z_o = 2.5z_1 + z_2 + .35z_3 + .075z_4 + 73.675$$

This problem is easily solvable by hand calculations. After introducing non-negative slacks z_5 and z_6, and changing the sign of the objective function (in order to minimize), we have the following simplex tableau:

	z_1	z_2	z_3	z_4	z_5	z_6
50	(1)	.25	0	0	1	0
74.5	1	.25	.2	.3	0	1
73.675	-2.5	-1	-.35	-.075	0	0

Pivot on the circled 1, giving the following tableau:

	z_1	z_2	z_3	z_4	z_5	z_6
50	1	.25	0	0	1	0
24.5	0	0	(.2)	.3	-1	1
198.675	0	5.25	-.35	-.075	+2.5	0

The next pivot, on the circled .2, gives

	z_1	z_2	z_3	z_4	z_5	z_6
50	1	.25	0	0	1	0
122.5	0	0	1	1.5	-5	5
241.55	0	5.25	0	.45	.75	1.75

This tableau is optimal. The optimal solution is:

$$z_1 = 50$$
$$z_2 = 0$$
$$z_3 = 122.5$$
$$z_4 = 0$$
$$(z_5 = z_6 = 0)$$

Thus for maximum annual profit, the rancher's selection should be:

70	cattle for a profit of	175.
20	goats for a profit of	20.
123.5	sheep for a profit of	43.225
1	deer for a profit of	.075
200	turkeys for a profit of	2.
5000	fish for a profit of	1.25

giving a profit of 241.55 units.

Of course, the rancher will have to have only 123 sheep, reducing his profit by .175. He will not be able to realize any profit on his single deer, which he insisted on having. So his profit is further reduced by .075.

Thus, his total profit, with an integral number of species, is 241.30.

Since the best integral solution can give no more than 241.55 profit, it is probably not worth finding it. (In fact this is very likely it.)

If the rancher now decides that one deer does not constitute "some", then the problem can be re-done, giving a larger lower bound for x_4.

It only remains to distribute the species over the 10 parcels if each parcel must have an integral number of species to itself. Each parcel then will have

7 cattle
2 goats
2 flocks of 10 birds each
1 pond with 500 fish

Putting an integral number of sheep on each parcel means that only 12 sheep can be on any parcel. This further reduces the profit by 1.05, since only 120 sheep are present. (Now, the total profit is only 240.25, but the best integral solution can give a profit no greater than 241.55.)

Note that the 7 cattle, 2 goats, and 12 sheep on each parcel use a total of 9.9 land units. Thus, no single parcel can support the deer. However, the deer can presumably roam over all 10 parcels, in which case there are enough land units to support three deer, which are still not enough for a deer "harvest".

****

THE OPTIMUM SITE PROBLEM

Contributor: G. M. Van Dyne*

****

Mathematics: linear programming

Abstract: A linear programming model is presented for maximizing protein production at a site.

*Reprinted from: Health Physics Division An
port, July 31, 1966, 117-119, with permission of Oak Ridge National Laboratory operated by Union Carbide Corporation, Nuclear Division for the U.S. Atomic Energy Commission.

Assessing the combined effects of site variables on measures of vegetation production has undergone long development, originating with qualitative site classifications and more recently turning to regression models for prediction purposes. In this study multiple linear regression functions were used as objective functions in linear programming models, along with appropriate constraints to find optimum sites for nutrient production measures. Protein yield, grass and sedge composition, perennial grass yield, phosphorus yield, and lignin composition in the herbage (Y_i) from foothill grassland were expressed as linear functions of topographic factors of elevation, exposure, and slope, and soil factors of concentration or content of sand, rock, clay, phosphorus, organic matter, conductivity, and pH of the A horizon (X_i).

The regression equation (1),

$$Y_{1\times 1} = X_{1\times m} B_{m\times 1} , \tag{1}$$

became the objective function (2),

$$f_{max} = X_{1\times m} B_{j\times 1} , \tag{2}$$

of a linear programming model which was to be maximized according to the constraints (3),

$$A_{j\times m} X_{m\times 1} = C_{j\times 1} , \tag{3}$$

where A and C respectively are a matrix and a column vector of constants.

The problem was to maximize protein production for use by cattle and sheep during the nonwinter period. Sites having higher-than-average grass and sedge composition in their herbage were being sought, in contrast to those having a large percentage of woody vegetation. The site must have better-than-average grass and sedge yield, better-than-average phosphorus yield, as well as having herbage with less-than-average lignin concentration. The four multiple linear regression equations relating site factors to grass and sedge composition and phosphorus yield, and lignin concentration were used to derive these inequality constraints (constraints 12 to 16 in Table 1).

Table 1

The Objective Function and Constraints[a] of the Linear Programming Model for Determination of Site Characteristics (X_i) for Optimum Crude Protein Yield (Y)

Objective function:

$$Y = 14 + 0.02X_1 - 11X_2 - 0.78X_3 - 1.6X_4 + 0.47X_5 + 0.02X_6 + 3.4X_7 - 4.6X_8 - 22X_9 - 0.09X_{10} + 6.0X_{11}$$

Constraints:

(1) $4780 \leq X_1 \leq 5980$

(2) $0 \leq X_2 \leq 2.0$

(3) $46 \leq X_3 \leq 93$

(4) $2 \leq X_4 \leq 19$

(5) $1.2 \leq X_5 \leq 62$

(6) $33 \leq X_6 \leq 222$

(7) $0.3 \leq X_7 \leq 56$

(8) $5.8 \leq X_8 \leq 8.0$

(9) $0 \leq X_9 \leq 18$

(10) $1 \leq X_{10} \leq 55$

(11) $2 \leq X_{11} \leq 24$

(12) $X_3 + X_4 \leq 100$

(13) $0.01X_1 - 6.1X_2 - 1.7X_3 - 0.88X_4 - 0.36X_5 + 0.03X_6 - 3.4X_7 - 4.4X_8 + 3.2X_9 - 0.32X_{10} - 0.24X_{11} \leq -150$

(14) $0.13X_1 - 79X_2 - 16X_3 - 12X_4 - 6.9X_5 + 0.26X_6 - 39X_7 + 140X_8 - 519X_9 - 4.3X_{10} + 24X_{11} \leq 73$

(15) $0.01X_1 + 0.01X_2 - 0.02X_3 - 0.03X_4 + 0.01X_5 - 0.01X_6 - 0.07X_7 - 0.17X_8 + 4.7X_9 - 0.01X_{10} + 0.08X_{11} \leq -2.1$

(16) $0.01X_1 - 1.0X_2 + 0.05X_3 - 0.03X_4 + 0.01X_5 + 0.01X_6 + 0.59X_7 - 0.28X_8 - 20X_9 + 0.04X_{10} + 0.12X_{11} \leq 3.4$

[a]The first 11 constraints were imposed to keep the solution within the range of variables found in the field; the next constraint is due to definition of mechanical composition of the soil; the last four constraints are biological or economical considerations.

The final model, with objective function and constraints, is given in Table 1. The optimum site determined by linear programming analysis showed that the maximum protein yield, under these constraints, was about 139 lb/acre as compared to a measured range of protein yield

of from 24 to 211 lb/acre with a mean of 77 lb/acre. To maximize protein yield under this particular set of constraints requires sites at relatively low elevation on north or east exposures. These sites need low sand and clay content, therefore implying a relatively high silt value. The soil would be relatively high in rock, phosphorus, and organic matter content, but relatively low in pH and conductivity. The optimum site needs nearly level topography and slightly deeper than average A horizons.

This example shows how combining linear programming and regression models provides a new means of evaluating macroenvironmental problems. This approach also can be used in forestry in determining site characteristics for simultaneous maximization of site index of several tree species. Another important use would be in renewable resource management in the situation where more than one species of livestock and game animals utilize a given rangeland, and it is desired to select optimum combinations of grazing animals.

****

OPTIMUM DIVERSITY OF ECOLOGICAL COMMUNITIES

Contributor: Bernard C. Patten

****

Mathematics: linear programming

Abstract: The allocation of resources in a community to produce an optimum species composition is considered as a linear programming problem.

*Reprinted from Science, CXXXX (1963), 894-898, with the permission of the author, copyright 1963 by the American Association for the Advancement of Science.

How energy balance is achieved in a natural community can be viewed from the standpoint of linear programming. Communities can be construed as having a pool of resources, such as nutrients, growth substances, stocks of organisms with various requirements and properties, and an energy supply. The problem is how to allocate the resources in such a way as to produce an optimum species composition, one which would bring to maximum the community's energy profit under existing conditions in the biotope.

To set this up for linear programming, we might define m as the number of species i in the pool ($i = 1,2,\ldots,m$); n as the number of resources $j(j = 1,2,\ldots,n)$; a_{ij} as the number of units of resource j required to produce a unit of species i; b_j as the maximum number of units of resource j available; p_i as the energy profit per unit of species i produced; and x_i as the number of units of species i produced. Then, the total amount of the j^{th} resource used is

$$a_{1j}x_1 + a_{2j}x_2 + \ldots + a_{mj}x_m$$

subject to the constraint

$$\sum_{i=1}^{m} a_{ij}x_i \leq b_j \ .$$

Since $x_i < 0$ has no meaning, we stipulate $x_i \geq 0$. The profit derived from producing x_i units of organism i is then $p_i x_i$, giving for a profit function

$$p_1x_1 + p_2x_2 + \ldots + p_mx_m \ ,$$

which is to be maximized. The solution, readily obtained by established procedures, represents the optimum composition (diversity) of the community corresponding to the prescribed conditions of the problem and the profit-maximizing motive.

****

^{134}Cs LEACHING FROM TERRESTRIAL MICROCOSMS

Contributors: B. C. Patten, M. Witkamp*

****

Mathematics: linear differential equations (Math. 2)

Abstract: An analog computer simulation of a compartmental model of the litter-soil-microflora-millipede-leachate microecosytem is described.

*Reprinted from: Health Physics Divis
, July 31, 1965, 94-95, with permission
Laboratory operated by Union Carbide Corporation, Nuclear Division
for the U.S. Atomic Energy Commission.

In experiments with ^{134}Cs-tagged white oak leaves with and without microflora, soil, and leaf-eating millipedes, it was found that the microflora decreased ^{134}Cs leaching from the litter by 30 to 50%, while millipedes increased leaching by 15 to 20%. The presence of soil increased loss of ^{134}Cs from the overlying leaves by 17 to 20%, and all but 1 or 2% of this loss was adsorbed by the soil.

To determine the kinetics of ^{134}Cs exchange in this system and the effects of various combinations of compartments, a model was constructed for simulation by analog computer (Figure 1). Six computer experiments were conducted to obtain values of the λ_{ij}'s (Figure 1) for various partial systems and for the complete system. In all cases, constant λ_{ij}'s were adequate to fit computer-generated curves to the empirical data. Results are shown in Table 1.

Table 1

Values of the λ_{ij}'s for Two-, Three-, Four-, and Five-Compartment Microcosms

Parameters	Expt. 1, (X_1,X_5)	Expt. 2, (X_1,X_2,X_5)	Expt. 3, (X_1,X_3,X_5)	Expt. 4, (X_1,X_2, X_3,X_5)	Expt. 5, (X_1,X_3, X_4,X_5)	Expt. 6, (X_1,X_2,X_3 X_4, X_5)
λ_{12}		0.071		0.083		0.097
λ_{13}			0.033	0.033	0.015	0.012
λ_{14}					0.012	0.006
λ_{15}	0.073	0.002	0.038	0.025	0.045	0.001
$\sum$	0.073	0.073	0.071	0.141	0.072	0.116
λ_{21}		0		0		0
λ_{23}				0		0
λ_{24}						0
λ_{25}		0		0		0
$\sum$		0		0		0
λ_{31}			0	0	0	0
λ_{32}				0		0
λ_{34}					0	0
λ_{35}			0	0	0	0
$\sum$			0	0	0	0
λ_{41}					0	0
λ_{42}						0
λ_{43}					0	0
λ_{45}					0	0
$\sum$					0	0

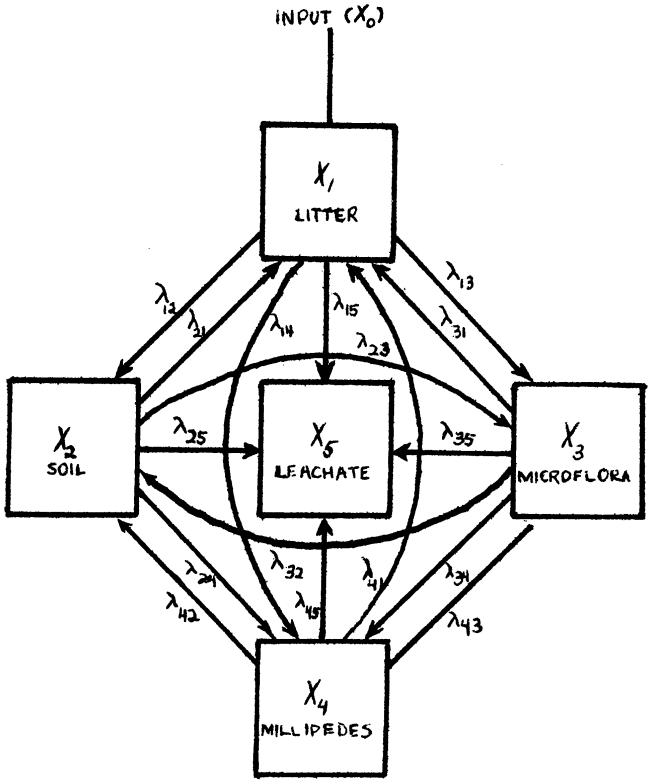


Figure 1

Compartment Model of Litter-Soil-Microflora-Milliped-Leachate Micro-ecosystem. Partial systems are produced by letting appropriate $\lambda_{ij} = 0$ in the system equations:

$$\dot{X}_1 = X_0 + \lambda_{21}X_2 + \lambda_{31}X_3 + \lambda_{41}X_4 - (\lambda_{12} + \lambda_{13} + \lambda_{14} + \lambda_{15})X_1 ,$$

$$\dot{X}_2 = \lambda_{12}X_1 + \lambda_{32}X_3 + \lambda_{42}X_4 - (\lambda_{21} + \lambda_{23} + \lambda_{24} + \lambda_{25})X_2 ,$$

$$\dot{X}_3 = \lambda_{13}X_1 + \lambda_{23}X_2 + \lambda_{43}X_4 - (\lambda_{31} + \lambda_{32} + \lambda_{34} + \lambda_{35})X_3 ;$$

$$\dot{X}_4 = \lambda_{14}X_1 + \lambda_{24}X_2 + \lambda_{34}X_3 - (\lambda_{41} + \lambda_{42} + \lambda_{43} + \lambda_{45})X_4 ,$$

$$\dot{X}_5 = \lambda_{15}X_1 + \lambda_{25}X_2 + \lambda_{35}X_3 + \lambda_{45}X_4,$$

where $\dot{X}_i$ are first derivatives with respect to time of ^{134}Cs activity, X_i, in compartments i, and $\lambda_{ij}(t)$ are functions expressing rates of ^{134}Cs exchange (day^{-1}) from compartments i to j (i,j = 1,2,...5).

In experiment 1, consisting of a litter-leachate system, 7.3%/day was transferred from litter to leachate. When soil was added (experiment 2), the loss rate from litter was unchanged, but 7.1%/day was transferred to soil and only 0.2%/day to the leachate.

There was no exchange from soil back to litter (indicated by $\lambda_{21} = 0$), verifying that ^{134}Cs is adsorbed by the soil. When microflora were added without soil (experiment 3), loss rate from the litter was again essentially unchanged, but the partition was 3.3%/day transferred to microflora and only 3.8%/day to leachate. Microflora activity was not indicated to be exchangeable ($\lambda_{31} = \lambda_{35} = 0$). In experiment 4, with both soil and microflora present, interaction doubled the rate of activity loss from litter to 14.1%/day. Of this, 8.3%/day was transferred to soil (representing an increase over experiment 2), 3.3%/day to microflora (no change compared to experiment 3), and 2.5%/day to the leachate (different from all preceding experiments). Activities of soil and microflora were again both non-exchangeable ($\lambda_{21} = \lambda_{23} = \lambda_{25} = \lambda_{32} = \lambda_{35} = 0$).

Since millipedes could not be sterilized, it was impossible to obtain experimental data on a litter-millipede-leachate or a litter-soil-millipede-leachate system. A litter-microflora-millipede-leachate system was studied in experiment 5. Total activity loss rate from litter was unchanged over experiments 1, 2, and 3. The parition was 1.5%/day to microflora (a decrease compared to experiments 3 and 4), 1.2%/day to millipedes and 4.5%/day to leachate (slightly higher than in experiment 3, where only microflora were present). Microflora and millipede activity were again non-exchangeable ($\lambda_{31} = \lambda_{34} = \lambda_{35} = \lambda_{41} = \lambda_{43} = \lambda_{45} = 0$). In experiment 6, with the complete system, activity loss from the litter (11.6%/day) was increased over experiment 5 (soil absent) but was not as great as in experiment 4 (millipedes absent). Hence, while millipedes cause increased leaching from the litter (experiment 4), this effect is reduced in the presence of soil (experiment 6). In experiment 6 transfer to soil was the highest recorded (9.7%)/day) and that to leachate the lowest (0.1%/day); 1.2%/day went to microflora and 0.6%/day to millipedes. Soil, microflora, and millipede activities were again indicated to be nonexchangeable ($\lambda_{ij} = 0$, where $i = 2,3,4$, $j = 1,2,\ldots,5$, and $i \neq j$).

****

FIRST SUMMER REDISTRIBUTION OF ^{137}Cs IN LIRIODENDRON FOREST

Contributor: J. S. Olson*

****

Mathematics: digital computer simulation

Abstract: A compartment model is used in simulating the redistribution of ^{137}Cs in a tagged Liriodendron forest.

A Fortran program for ecosystem simulation was completed and tested using a generalized compartment model. The state of the system is here defined by a row vector V, which must be specified as an initial state $V^{(0)}$ in the input. The continuous changes specified by the system of differential equations $\dot{V} = VF$ are approximated by a sequence of matrix multiplications specifying the redistribution of the variable from part J to part K of the system. Here $F = (f_{JK})$ specifies the fractions of the total variable associated with part J which are transferred to part K per unit time and can be allowed to vary as a function of time, environmental variables, or the current state of the system. Control cards allow many options on output, including numerical and graphical expression of the integrated change of as many ecosystem compartments as required.

This program was written with flexibility for digital simulation of compartment models, but was especially motivated by problems of simulating ecological succession. One aspect of succession concerns the redistribution of biomass (or energy or other constituents) among species, or between living and nonliving compartments, within some bounded unit area. The postulate which explains succession is that environmental changes diminish the flow of energy into species groups (including many pines) which can develop readily under initial conditions, and increase the flow into certain other species which are favored by environmental conditions which the pioneer species created. Mathematically, this corresponds with the changes in one or more terms in the matrix F, which now require further attention for empirical evaluation.

A second aspect of succession in a heterogeneous landscape follows from existence of changes in any given module of that landscape. This is reflected in a redistribution of ground (or water) <u>area</u> occupied by different community types. This requires expressing fractional rates of change of a given community type J to another community type K as a matrix F, which operates on the vector of community areas just as a matrix of fractional energy flow rates operates on a vector of compartment distributions within a given community.

The compartment model program described above was used in simulating the redistribution of ^{137}Cs in a seven-compartment model of the tagged 20- by 25-m Liriodendron forest. The initial dose of 467 mc was initially distributed in a "source" compartment (No. 1) consisting of the immediate vicinity of the trough through which the nuclide was introduced, 1 m above the ground, and the tree wood through which the cesium is quickly moved, as by transpiration. To account for the initial rise and later decline of radioactivity in foliage (compartment No. 2) shown in Figure 1, certain losses from foliage (to undercover, No. 5, and the forest floor litter, No. 6) had been estimated directly, but these were found quite inadequate to account for observed changes. The fractional turnover rates specified in Table 1 were adjusted by successive simulation runs to account for the summer decrease in foliage by translocation to bark and coarse roots (compartment No. 3) and to medium-fine roots (compartment No. 4) which were sampled along with soil (compartment No. 7). Initially, almost all the soil activity consisted of material in roots rather than soil per se, but through late summer and autumn there was a continuing increase in amounts that were inseparable from mineral soil by mechanical means of flotation.

Table 1

Constant Coefficient Model for ^{137}Cs Transfer During First Year in Liriodendron Forest

J, Compartment of Origin	K, Receiving Compartment						
	1, "Source"	2, Leaves	3, Bark	4, Roots	5, Undercover	6, Litter Mat	7, Soil
1 "Source"	-0.036	0.028	0.008				
2 Leaves		-0.0444	0.044		0.00005	0.00035	
3 Bark	0.005	0.005	-0.03	0.015			
4 Roots			0.007	-0.01			0.003
5 Undercover					-0.02	0.02	
6 Litter mat						-0.02	0.02
7 Soil				0.0001	0.00001		-0.00011

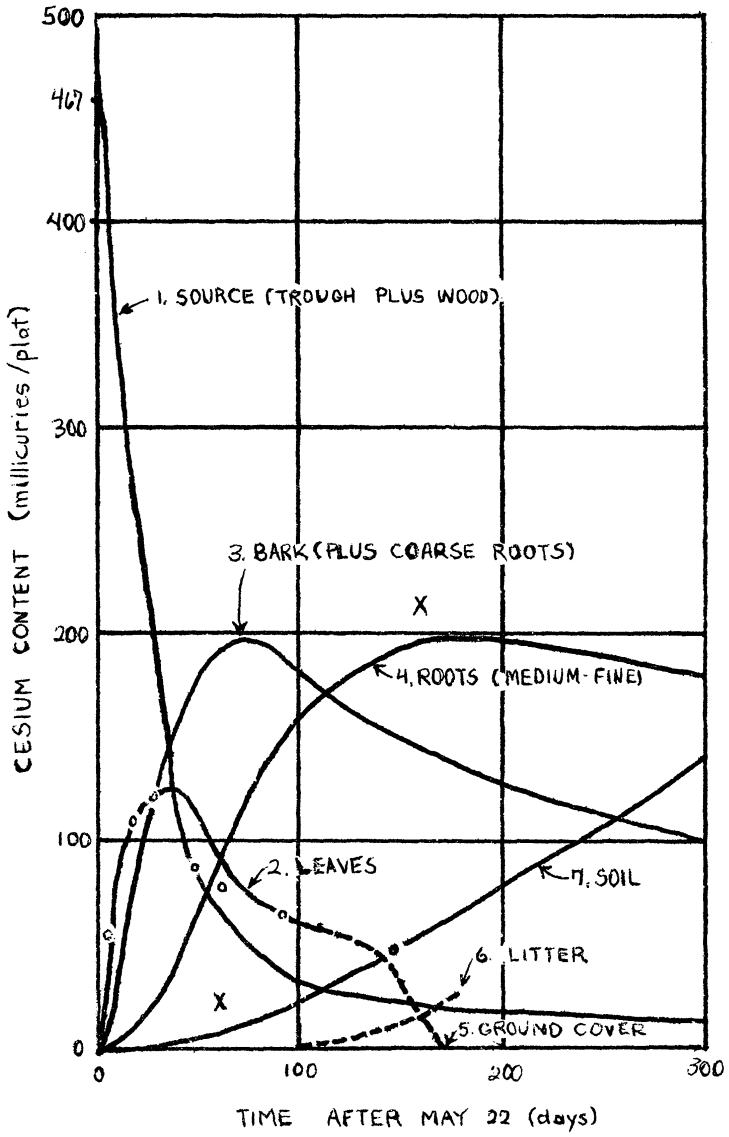


Figure 1

Comparison of Observed Foliage Radioactivity (Circles) with Simulated Changes in Compartment Model for Radioactivity in Foliage (Compartment 2) and Other Parts of an Idealized Liriodendron Forest, Tagged in Tree Trunks May 22, 1962. Estimated soil and medium to fine root activity (X's) was based on 0 to 10 cm of soil in July and 0 to 30 cm in October and is expected to be slightly less than the total for these two compartments (7 and 4 respectively).

The simulations in Figure 1 were based on the matrix of Table 1, that is, on constant fractional coefficients f_{JK} of transfer from compartment J to compartment K. Hence, it was not expected to treat seasonal fluctuations, like those involving the autumn dropping of leaves, the corresponding seasonal peak in litter radioactivity, and the seasonal changes in translocation inside the trees.

****

LETHAL MUTATIONS DUE TO RADIATION

Contributor: Harold Slater*

****

Mathematics: probability (Math. 2P), geometric series

Abstract: The effect of a single dose of radiation on future generations is examined by means of the Hardy-Weinberg Law.

*Based upon: Wallace, B., and Dobzhansky, T.G. Radiation, Genes, and Man. New York: Holt, Rinehart and Winston, 1959, 139.

Consider a population in which the frequency of a recessive lethal mutant a is q at a particular gene locus. If the population is exposed to radiation for a limited time, let us assume that the number of recessive genes increases so that its total frequency is q + i, where i is small compared with q. The occurrence of the homozygote aa is lethal. We wish to determine how many deaths are caused by the initial dose of radiation in each generation.

The frequency of the lethal homozygote according to the Hardy-Weinberg Law is $q^2 + 2qi + i^2$. Since i is small, the number of individuals carrying a pair of irradiated genes will be negligible. Therefore, the frequency of lethal homozygotes due to the radiation will be approximately 2qi. The frequency of irradiated genes in the next generation will be $i - 2qi = i(1 - 2q)$ and, by a second application of the Hardy-Weinberg Law, the frequency of a lethal homozygote due to irradiation will be $2qi(i - 2q)$. In the nth generation the latter frequency will be $2qi(i - 2q)^{n-1}$. If the population size in the nth generation is N_n, then $2qi(1 - 2q)^{n-1} \times N_n$ individuals will die due to the initial dose of radiation.

If the population size in each generation remains constant (= N), the total number of deaths due to irradiation in n generations is

$$L = 2Nqi \sum_{j=o}^{n-1} (1 - 2q)^i .$$

$\sum_{j=o}^{n-1} (1 - 2q)^i$ is a finite geometric series. If the series is evaluated, we obtain

$$L = 2Nqi\frac{[1 - (1 - 2q)^n]}{2q} = Ni[1 - (1 - 2q)^n] .$$

Since q is generally small (in the order of 10^{-3}), we can use the approximation

$$(1 - 2q)^n \approx (1 - 2nq) , \quad \text{provided } nq \leq 1/2 ,$$

so that

$$L \approx 2Nnqi \ .$$

****

BALANCED POLYMORPHISM

Contributor: James Mortimer*

****

Mathematics: probability (Math.2P)

Abstract: The equilibrium in gene frequences is investigated for the case in which both the dominant homozygote and the recessive homozygote are less fit than the heterozygote.

*Based upon: Spuhler, James N. "The Scope for Natural Selection in Man." Genetic Selection in Man, Third Macy Conference on Genetics. Edited by W. J. Schull. Ann Arbor: The University of Michigan Press, 1963, 1-111.

Through the process of natural selection, the frequencies of those recessive genes which cause incapacitating illness or death or in some way limit the organism's capacity to reproduce, are gradually decreased. A number of factors, however, tend to hinder this decrease. Among these is the selective advantage of a heterozygote over a dominant homozygote. In cases in which the heterozygote, which carries one of the incapacitating genes, has a better chance of reproducing than the homozygote in which no recessive genes are present, the frequency of the recessive gene can be preserved in the population despite its deleterious or even lethal effect in the recessive homozygote. The situation in which both the dominant homozygote and recessive homozygote are selected against is referred to as a balanced polymorphism.

Let p = the freqency of the dominant gene, A, in the population. $q = 1 - p$ = the frequency of the recessive gene, a.

Then, according to the Hardy-Weinberg Law, the ratio of AA individuals to Aa to aa in a large, randomly mating population without selection is

$$p^2 : 2pq : q^2$$

where, since $p + q = 1$, $p^2 + 2pq + q^2 = 1$.

If the fitness of an organism is defined in terms of its contribution to the progeny, its so-called reproductive value, then a fitness can be assigned to each genotype. In general, the fitness will be designated by $1 - c_i$, where c_i represents the decrement in reproductive value due to selection.

The table below gives the genotypes with their frequencies before and after selection on the basis of fitness.

Table I

Genotype	Frequency before selection	Fitness	Frequency after selection
AA	p^2	$1 - c_1$	$p'^2 = \dfrac{p^2(1 - c_1)}{1 - c_1p^2 - c_2q^2}$
Aa	$2pq$	1	$2p'q' = \dfrac{2pq}{1 - c_1p^2 - c_2q^2}$
aa	q^2	$1 - c_2$	$q'^2 = \dfrac{q^2(1 - c_2)}{1 - c_1p^2 - c_2q^2}$

where p' and q' are the gene frequencies after selection.

$$q'^2 + p'q' = q'(q' + p') = q'$$

since q' + p' must equal one.

From the values of q'^2 and 2p'q' given in the table, it follows that the change in q resulting from selection = $\Delta q = (q' - q) =$

$$(1) \qquad \frac{pq(c_1p - c_2q)}{1 - c_1p^2 - c_2q^2} .$$

In order for the selection against the dominant homozygote, AA, to be balanced by the selection against the recessive homozygote, aa, Δq must be zero. Therefore,

$$(2) \qquad c_1p = c_2q$$

or since p = 1 - q,

$$(3) \qquad q = \frac{c_1}{c_1 + c_2} .$$

Example of balanced polymorphism:

The most cited example of balanced polymorphism in humans is the preservation of the sickle cell anemic gene by the selective advantage of the sickle heterozygote over the normal homozygote in resistance to malarial infection. Despite the lethality of the sickle homozygote, the frequency of the heterozygote has been maintained as high as .40 in certain African populations in which malaria is prevalent.

EXERCISES:

1. On a certain island off the coast of Africa, 32% of the people tested were found to be carriers of the sickle gene. Because of the lethality of the homozygote it can be assumed that none of those tested were heterozygotes. Assume that the population of this island mate randomly and that sufficient time has elapsed for a condition of equilibrium to be reached. Calculate the frequencies of the A and S genes, p and q, where A is the normal gene and S is the sickle gene.

SOLUTION:

$$2pq = .32$$

$$pq = .16,$$

but $p = 1 - q$. Therefore,

$$q^2 - q + .16 = 0 .$$

Solving for q,

$$q = \frac{1 \pm \sqrt{1 - .64}}{2} = .8, \ .2 .$$

With $q = .8$, $p = 1 - q = .2$; for $q = .2$, $p = .8$. Therefore, the values of p and q are symmetric. To determine which of the two solutions, $(p,q) = (.8, .2)$ or $(p,q) = (.2, .8)$ is correct we must reexamine the biology.

Because of the lethality of the sickle homozygote, c_2 in equation (1) is equal to one. It is known that c_1 is less than one. (Not all heterozygotes die of malaria before reproducing.) From (2), therefore,

$$\frac{c_1}{c_2} = \frac{q}{p} .$$

But $c_2 = 1 > c_1$. Therefore $p > q$, so that

(4)
$$p = \text{frequency of A gene} = .8$$
$$q = \text{frequency of S gene} = .2 .$$

2. Assuming that the sickle homozygote is incapable of reproducing and using the resulting gene frequencies in 1, find the selection constant c_1, which represents the relative disadvantage of the dominant homozygote in resistance to malaria.

SOLUTION:

The equilibrium frequencies of A and S from (4) are .8 and .2 . Therefore $q_{eq} = .2 = c_1/(c_1 + c_2) = c_1/(c_1 + 1)$.

Solving for c_1, $c_1 = .25$.

3. Studies have shown that in West African populations the reproductive value or fitness of the heterozygote is about 1.25 that of the normal homozygote. At what frequencies of q is the change in q, Δq, a maximum?

SOLUTION:

From (1)

$$\Delta q = \frac{pq(c_1 p - c_2 q)}{1 - c_1 p^2 - c_2 q^2} = \frac{q(1 - q)(c_1 - (c_1 + c_2)q)}{(1 - c_1) + 2c_1 q - (c_1 + c_2)q^2} .$$

$c_2 = 1$, since it is assumed that sickle homozygotes do not reproduce.

$c_1 = 1.00 - (1.00/1.25) = .20$.

With these values of c_1 and c_2 we can plot Δq versus q.

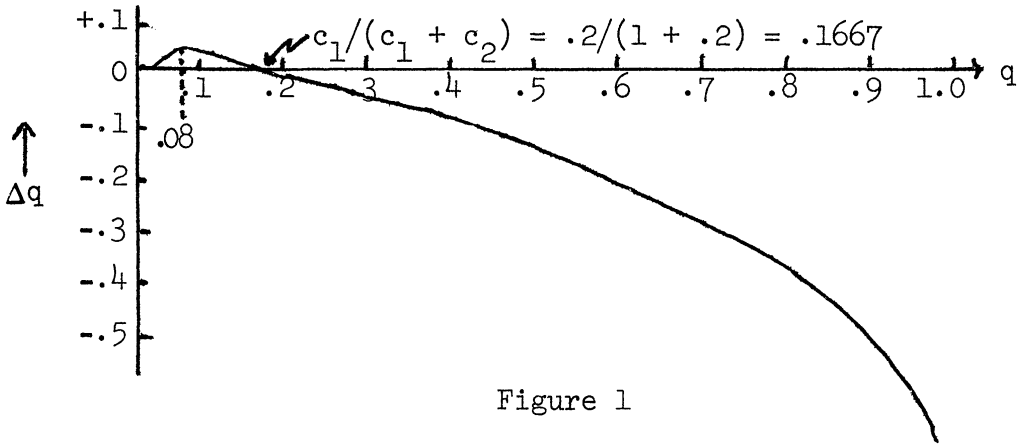


Figure 1

From the graph it can be seen that for frequencies of q below its equilibrium frequency, $c_1/(c_1 + c_2)$, that the change in q, Δq, is positive and has a maximum at $q = .08$. For frequencies above the equilibrium frequency, Δq is an accelerated function of q; the further from equilibrium q is, the larger the decrement, Δq. Selection tends to reduce the difference between q and q' such that the stable equilibrium is achieved.

---

1. Proceedings of the Conference on Genetic Polymorphisms and and Geographic Variations in Disease, B. S. Blumberg, ed., Grune and Stratton, New York, 1961.

2. Spuhler, James N., "The Scope for Natural Selection in Man."

Genetic Selection in Man, Third Macy Conference on Genetics. Edited by W. J. Schull. Ann Arbor: The University of Michigan Press, 1963, 1-111.

3. Stern, C. Principles of Human Genetics, 2nd ed. San Francisco: W.H. Freeman, 1960.

****

ECOSYSTEM MAINTENANCE AND TRANSFORMATION MODELS AS MARKOV PROCESSES WITH ABSORBING BARRIERS

butors: J. S. Olson, V. R. R. Uppuluri*

****

Mathematics: matrix algebra (Math. 3), Markov processes

Abstract: Ecological compartment models are considered in the context of Markov processes with absorbing barriers.

*Reprinted from: Health Physics Division Annual Progress Report, July 31, 1966, 104-105, with permission of Oak Ridge National Laboratory operated by Union Carbide Corporation, Nuclear Division for the U.S. Atomic Energy Commission.

Ecological compartment models have been expressed in terms of a system of n differential equations for the continuous rates of change of the variables v_k (k = 1,2,..,n), that is, for the vector V = (v_k) = $(v_1 v_2 \cdots v_n)$ describing the state of n compartments. In ecological applications one or more of the last compartments can be thought of as an absorbing compartment, in the sense that matter or energy arriving there has zero rate (or very low probability) of return to circulation within the remaining compartments, for example, $(v_1 v_2 \cdots v_{n-2})$.

For example, where the variable V is energy, v_n may be that energy which has been dissipated by respiratory processes (generating low-grade heat), and which cannot again furnish free energy for the operation of biological processes of the ecosystem according to the second law of thermodynamics; replenishment of biologically usable free energy requires photosynthetic input from solar radiation. Where V is carbon and the model is for the carbon cycle, v_n may be the C in CO_2 which has been respired and mixed with the air outside the local ecosystem; because of rapid turbulent mixing throughout the troposphere, the probability of re-entry for any particular atom is exceedingly low, though not quite zero. Where V stands for a radio-nuclide, v_n can be defined as that which has finally undergone radioactive decay to another element, and which accordingly has entered a different chemical cycle and been permanently removed from the cycle of the original element in question.

Another class of absorbing barriers (here labeled as v_{n-1}) encompasses various exports from the local ecosystem to surrounding systems, possibly including harvest by man for food or raw materials in the energy or material technology of the human ecosystem. As before, return of units to the local system may be impossible in some cases, or may have sufficiently low probability that it is expressed as having probability 0 for purposes of modeling.

An extension of previous deterministic ecological compartment models in the context of Markov processes encompasses all possible transfers of a specified energy or mass unit by a matrix P = (p_{jk}).

Probabilities of transfer within the local ecosytem (i.e., excluding two absorbing compartments) are represented by the submatrix

$$(1) \qquad Q = \begin{bmatrix} p_{11} & \cdots & p_{1k} & \cdots & p_{1(n-2)} \\ \vdots & & \vdots & & \vdots \\ p_{j1} & \cdots & p_{jk} & \cdots & p_{j(n-2)} \\ \vdots & & \vdots & & \vdots \\ p_{(n-2)1} & \cdots & p_{(n-2)k} & \cdots & p_{(n-2)(n-2)} \end{bmatrix} .$$

Probabilities of transfer to the absorbing states are given by another submatrix

$$(2) \qquad R = \begin{bmatrix} p_{1(n-1)} & p_{1n} \\ \vdots & \vdots \\ p_{j(n-1)} & p_{jn} \\ \vdots & \vdots \\ p_{(n-2)(n-1)} & p_{(n-2)n} \end{bmatrix} .$$

By definition, the absorbing states have probability 1 for retention of units which have arrived there, as represented by the identity matrix (here 2 × 2):

$$(3) \qquad 1 = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \begin{bmatrix} p_{(n-1)(n-1)} & p_{(n-1)n} \\ p_{n(n-1)} & p_{nn} \end{bmatrix} .$$

Another way of expressing this exclusion of a unit's return to the local ecosystem is the null matrix for the probabilities of contribution from variables v_{n-1} and v_n to the state vector of this system $(v_1 v_2 \cdots v_{n-2})$:

$$(4) \qquad 0 = \begin{bmatrix} 0 & \cdots & 0 & \cdots & 0 \\ 0 & \cdots & 0 & \cdots & 0 \end{bmatrix}$$

$$= \begin{bmatrix} p_{(n-1)1} & \cdots & p_{(n-1)k} & \cdots & p_{(n-1)(n-2)} \\ p_{n1} & \cdots & p_{nk} & \cdots & p_{n(n-2)} \end{bmatrix} .$$

Matrices (1) to (4) are thus submatrices of the overall matrix

$$(5) \qquad P = (p_{jk}) = \begin{bmatrix} Q & R \\ 0 & 1 \end{bmatrix} ,$$

which expresses the transformations of matter or energy within and from any ecosystem.

The postulate that ecosystems are never isolated [R = (0) for energy] and with rare, artificial exceptions are not closed [R = (0) for materials] implies that an ecosystem would "run down" if its energy and nutrient losses were not replenished. In nature energy losses are counteracted by the input vector $W = (w_1 \cdots w_k \cdots w_{n-1})$ including primary production by photosynthesis, and in some cases by immigration of plant propagules, or animals or other materials. Nutrient depletion (e.g., by erosion, leaching, harvesting) is counteracted by rainfall, dust, and, in agriculture, by fertilizer treatments. A quantitative theory of this deterioration, and of the means by which nature or man may counteract it, is being developed from the following implications of the preceding postulate and definitions.

If the initial state of the system is $V^{(0)}$ at time 0, the expected values, $v^{(t)}$, for time t = 1, 2, ... steps of operation of the system are given by the sequence:

$$(6) \qquad \begin{aligned} V^{(1)} &= V^{(0)}Q^{(0)} + W^{(0)} , \\ V^{(2)} &= V^{(1)}Q^{(1)} + W^{(1)} \\ &= [V^{(0)}Q^{(0)} + W^{(0)}]Q^{(1)} + W^{(1)} , \\ V^{(3)} &= V^{(2)}Q^{(2)} + W^{(2)} \\ &= [V^{(1)}Q^{(1)} + W^{(1)}]Q^{(2)} + W^{(2)} \\ &= V^{(0)}Q^{(0)}Q^{(1)}Q^{(2)} + W^{(0)}Q^{(1)}Q^{(2)} + W^{(1)}Q^{(2)} + W^{(2)} . \end{aligned}$$

For the simple case of constant input (e.g., gross primary production) and constant transfer probability operator Q, these equations simplify into a sum of two terms, one representing the product of the initial

condition multiplied by a power of Q, and the second representing the input vector multiplied by a sum of decreasing powers of Q:

$$V^{(t)} = V^{(0)}Q^t + W(Q^{t-1} + Q^{t-2} + \ldots + 1) \quad (7)$$

If $R \neq 0$, individual terms in Q contain terms which are progressively closer to zero (Q^n tends to a zero matrix). It follows that the influence of the initial state $V^{(0)}$ on the current state $V^{(t)}$ diminishes with time, in a way that can be predicted from the t^{th} power of the matrix P or Q. The input vector influences the current state of the system in a way that can be predicted from the properties of the geometric series in the parentheses of Equation (7). In the limit, the expected steady state for the local ecosystem can be shown to be

$$V^{(\infty)} = W[1 - Q]^{-1} \quad (8)$$

where 1 here is an $(n - 2)(n - 2)$ identity matrix. Digital and analog computer model simulations suggest that steady states predicted by this formula are commonly reached early enough to be of significance for interpreting the behavior of natural and managed ecosystems.

****

MINIMIZING THE EXPECTED NUMBER OF BLOOD TESTS

Contributor: Kenneth R. Rebman*

****

Mathematics: probability (random variables, expectation) (Math. 2P), differentiation (Math. 1)

Abstract: Blood tests can be analyzed singly or in groups; the expected value of the random variable which denotes the number of required tests is minimized as a function of the group size.

*Based upon: Feller, W. An Introduction to Probability Theory and its Applications, Vol. 1, 2nd edition. New York: Wiley and Sons, 1957, solution of exercise 26, Chapter 9, p. 225.

Suppose it is required to test a large number of people for some characteristic using a completely reliable test, the results of which are either positive or negative. Moreover, suppose that it is possible to take specimens from several people and test the combined specimens as a unit. Assume that the combined test will give a positive result if and only if one contributing specimen is positive. In the case of a positive result all of the specimens must be retested individually to determine which are positive.. For example, certain types of blood tests would fit this description.

If the test is expensive, either in terms of time or money, then it is reasonable to attempt to minimize the number of tests necessary for reliable results. If N people are to be tested individually, then N separate tests are required. But if they are tested in groups of k people each, then for each such group, if the combined test is negative, only 1 test is needed; if the combined test is positive, then k + 1 tests are needed for that group. If the probability that the test be positive is known, then we may consider the expected number of tests required in the combination-test method. This will of course depend upon k, the size of the groups combined. If we minimize the expected number of tests as a function of k, then compare with the expected number of tests if individual testing is used (namely, N tests), we can choose a policy that will minimize the cost of testing.

We make the following assumptions:

(a) The probability that the results of the test will be positive is p, the same for all persons. Moreover, individuals within a group are stochastically independent, i.e., the result of an individual test does not depend upon the results of the tests on other members of the group.

(b) The group of N persons is divided into n groups of k persons each.

Thus, $N = nk$. (Assume that N is large compared to k, so that later

we may ignore any remainder if k does not divide N.) Let $q = 1 - p$; q is the probability that the test will be negative.

Let the random variable X denote the number of tests required to test all N persons. Our aim is to find $E(X)$ and to minimize it with respect to k.

Since there are n groups, let X_i denote the number of tests required for the i^{th} group. Then

$$X = X_1 + X_2 + \ldots + X_n .$$

By the linearity of E,

$$E(X) = E(X_1) + \ldots + E(X_n) .$$

But by assumption (a), $E(X_i)$ is the same for each i. Hence

$$E(X) = nE(X_1) .$$

Thus, we need only compute the expected number of tests for a single group of k persons.

The random variable X_1 can assume only two values --- 1, k + 1 .

Recall that

$$E(X_1) = 1 \cdot [Pr(X_1 = 1)] + (k + 1)[Pr(X_1 = k + 1)] .$$

$$Pr(X_1 = 1) = Pr \text{ (all k people in the group are negative)}$$
$$= q^k \text{ (by assumption (a))}$$

$$Pr(X_1 = k + 1) = Pr \text{ (at least one person is positive)}$$
$$= 1 - q^k .$$

Hence,

$$E(X_1) = q^k + (k + 1)(1 - q^k) = q^k + k - kq^k + 1 - q^k$$
$$= k - kq^k + 1 = k[1 - q^k + 1/k] .$$

So

$$E(X) = nE(X_1) = nk[1 - q^k + 1/k]$$
$$= N[1 - q^k + 1/k]$$

is the expected number of tests required if groups of k are used.

Notice that for k = 1, this formula gives

$$E(X) = N[1 - q + 1]$$
$$= N[1 - (1 - p) + 1]$$
$$= N + pN .$$

However, this result is clearly invalid, because with N people to be tested no more than N tests are necessary to obtain the required information. Thus, the formula is valid only if k is greater than one.

Although our model is valid only for integral values of k, we may consider $E(X) = N[1 - q^k + 1/k]$ as a continuous function of the real variable k, with domain $\{k \mid 1 \leq k \leq N\}$. The behavior of this function will give some insight into the behavior of E(X) for integer k's.

First note that the first derivative of E(X) with respect to k is given by

$$D_k[N(1 - q^k + 1/k)] = ND_k(1 - e^{k \ln q} + 1/k)$$
$$= N(- \ln q \, e^{k \ln q} - 1/k^2)$$
$$= (-N)(q^k \ln q + 1/k^2) .$$

Setting the first derivative equal to 0, we see that the critical points are the solutions of

$$k^2 q^k = \frac{1}{- \ln q} .$$

We can compare the values of E(X) at these critical points with N (the number of tests for k = 1) and with E(X) evaluated at k = N (the expected number of tests for k = N). This will give us the k giving rise to the minimum expected number of tests. If k is not an integer, the nearest integer to k may not give the best integer value of k.

An alternative approach, probably better, would be to simply minimize $1 - q^k + 1/k$ over integer values of k. Such a procedure could be easily programmed.

A few additional observations clarify the problem. In order that $E(X)$ be less than N, it is clearly necessary that $1 - q^k + 1/k$ be less than 1. That is, if we find a k that gives a better result than $k = 1$, we must have $1/k < q^k$.

But, if $q < 1/2$, then $q^k < (1/2)k$ and $(1/2)k < 1/k$ since $k < 2^k$, for all k.

If $q < (1/2)$, then we cannot find a k such that $1/k < q^k$. Hence, there does not exist a k such that $E(X) < N$ if $q < (1/2)$. We can conclude that if the probability of a positive test is greater than $1/2$, then it is never an optimal policy to group the samples before testing. Individual tests should be made.

****

PROBABILISTIC MEDICAL DIAGNOSIS

Contributor: Roger Wright

****

Mathematics: Bayes' theorem (Math. 2P)

Abstract: The use of Bayes' theorem in medical diagnosis is considered.

When a patient is examined, information, typically incomplete, is obtained about his state of health. Probability theory provides a mathematical model appropriate for this situation as well as a procedure for quantitatively interpreting this partial information.

To do this we list the states of health that we hope to distinguish in such a way that the patient can be in one and only one state at the time of examination. Let $\mathcal{H}$ be the set of states. For each state of health H we associate a number P(H) between 0 and 1 such that the sum of all these numbers is 1. This number represents the probability, before examination, that a patient is in the state of health H and may be chosen subjectively from personal experience using any information not related to the examination itself. The probability may be most conveniently established from the clinical files, i.e., a mean probability is established for all patients, although the number might vary from patient to patient. For example, P(H) could be established for a patient from the output of a similar analysis for a preliminary examination. Of course, the more information that is brought to bear at this stage, the better the diagnosis.

Having selected P(H), the information of the examination is processed. First the results of the examination must be classified. The examination itself consists of observing the state of a number, say m, of characteristics of the patient and classifying each characteristic. This may be done by associating an appropriate number to the state of each characteristic. In this way the outcome of the examination may be represented by an array $C = (C_1, C_2, \ldots, C_m)$ of m numbers. We call the set of all possible such arrays $\mathcal{C}$.

It remains to assess for each state of health H the conditional probability $P(C|H)$ of each examination outcome C using only the knowledge that a patient is in that state of health. This may be based on total medical knowledge and the clinical experience of the doctor. It will reduce the complexity of the problem to assume, whenever possible, the conditional independence of some of the characteristics for a fixed state of health. The conditional probabilities $P(C|H)$ will not vary from patient to patient so that they may be built into a

diagnostic system, although they should be reviewed periodically.

Now for a given patient the appropriate probability associated with each state of health H after examination is $P(H|C)$ where C is the outcome of the examination. By Bayes Theorem this may be calculated from the above information using the equation

$$P(H|C) = \frac{P(C|H)\,P(H)}{\sum_{H_o \in \mathcal{H}} P(C|H_o)P(H_o)} \quad .$$

However, in the examination the state of a characteristic may not be determined. In this case the appropriate conditional probability of the incomplete examination outcome given a state of health H is the sum of the conditional probabilities $P(C|H)$ of each complete examination outcome H which is compatible with the incomplete outcome. The concept of marginal probability is used here.

---

1. Overall, J. E. and Williams, C. M. "Conditional Probability Program for Diagnosis of Thyroid Function," Journal of the American Medical Association, CLXXXIII (1963), 307-313.

2. Overall, J. E. and Gorham, D. R. "A Pattern Probability Model for the Classification of Psychiatric Patients," Behavioral Science, VIII (1963), 108-116.

3. Warner, H. R.; Toronto, A. F.; Veasey, L. G.; Stephenson, R. "A Mathematical Approach to Medical Diagnosis," Journal of the American Medical Association, CLXXVII (1961), 177-183.

GUIDE TO MATHEMATICAL NOTATION

GUIDE TO MATHEMATICAL NOTATION

by Kenneth R. Rebman

Mathematical notation is by no means uniform or even always logically consistent. In fact, mathematicians seem to worry most about the aptness of their notation when writing advanced mathematics for other mathematicians. But often in elementary mathematical texts containing material which may be conceptually difficult for the student anyway, poor notation leads to further confusion. An attempt has been made to eliminate the most obvious notational inconsistencies from the models in this book. However, since the models were submitted by many authors, there is bound to be non-uniformity of notation, and even a few instances of notation that is not completely free from objection on logical grounds. Thus, it seems desirable to include this brief discussion of mathematical notation.

VARIABLE NAMES:

Letters (lower case and capital) of various alphabets are used as the names of mathematical objects. In the models which follow, the alphabets used are usually English and Greek. Any reader of mathematics will soon learn the Greek alphabet:

	lower case	capital
alpha	α	A
beta	β	B
gamma	γ	Γ
delta	δ	Δ

	lower case	capital
epsilon	ϵ	E
zeta	ζ	Z
eta	η	H
theta	θ	Θ
iota	ι	I
kappa	κ	K
lambda	λ	Λ
mu	μ	M
nu	ν	N
xi	ξ	Ξ
omicron	o	O
pi	π	Π
rho	ρ	P
sigma	σ	Σ
tau	τ	T
upsilon	υ	Υ
phi	ϕ φ	Φ
chi	χ	X
psi	ψ	Ψ
omega	ω	Ω

Often, script letters are used in addition to lower case and capitals. A script $\mathcal{S}$ is not the same as a capital S. A general rule is that larger and more elaborate mathematical objects are designated by larger and fancier symbols. For example, if a mathematician studied taxonomy, he might devise the following notational system:

a: species,
A: genus,
$\mathcal{A}$: order,
$\mathfrak{A}$: phylum.

Variable names often appear with one or more subscripts (and occasionally superscripts). For example,

$$x_{ij} \qquad A^{i} \qquad d_{3}^{k} .$$

It is by no means a hard and fast rule, but integer variables are usually represented by i, j, k, l, m, n. Conversely, these letters usually (though not always) represent integer variables.

A reader of computer literature (both by and about computers) will often see an essentially new kind of notation. The restrictive nature of the printer associated with most computers necessitates a language that uses only numbers, English capitals, and a few symbols, and which must be written on a single line (no super- or subscripts).

ARITHMETICAL NOTATION:

+ and - have the ordinary meaning. Multiplication is denoted by · or more often by juxtaposition. The sign × is seldom used in arithmetic (although it is used in set theory). E.g.,

$a \times b$	rarely used
$a \cdot b$	sometimes used
ab	most common

The division sign ÷ is practically never used. Division is virtually always signified by fractions. E.g.,

$a \div b$ would be written as

a/b or $\frac{a}{b}$.

Because of the frequency that one encounters sums and products of many terms, a special notation is used.

Summation is denoted by a capital sigma: Σ

$$\sum_{i=1}^{5} x_i \quad \text{is by definition} \quad x_1 + x_2 + x_3 + x_4 + x_5$$

$$\sum_{\substack{k=3 \\ k\neq 6}}^{\infty} a_k \quad \text{is} \quad a_3 + a_4 + a_5 + a_7 + a_8 + \ldots$$

$$\sum_{i=1}^{n} \frac{b^i}{i!} \quad \text{is} \quad b/1 + b^2/2 + b^3/6 + \ldots + b^n/n!$$

Multiplication is denoted by a capital pi: Π

$$\prod_{i=1}^{n} (1 + z_i)^{i-1} \text{ is } (1)(1 + z_2)(1 + z_3)^2 \ldots (1 + z_n)^{n-1} .$$

Other common symbols:

$=$	equals
$\leq$ or $\leqq$	less than or equal
$<$	strictly less than
$\geq$ or $\geqq$	greater than or equal
$>$	strictly greater than
$\neq$	does not equal
$\not<$	is not less than
	etc.
∞	infinity
$\lvert x \rvert$	absolute value of x
$[x]$	the greatest integer less than or equal to x
$\sqrt{}$	square root
Δ	"del", short for "delta", used to mean "the change in" as in Δp
$\doteq$ or $\cong$	approximately equals

LOGICAL NOTATION:

$\Longrightarrow$	"implies", as in A $\Longrightarrow$ B
$\Longleftrightarrow$	"implies and is implied by". So A $\Longleftrightarrow$ B means A $\Longrightarrow$ B and B $\Longrightarrow$ A. This could also be read "A only if B and A if B" or more simply "A if and only if B". In current exposition, this is frequently written as "A iff B". Thus, "$\Longleftrightarrow$" and "iff" have identical meanings.

Other standard logical connectives are:

$\wedge$	and
$\vee$	or (inclusive)
$\neg$ or $\sim$	not

These last three notations from formal logic are not often used in expository writing. However, some formal symbols are now commonly used to replace phrases that are frequently encountered:

$\forall$	for all
$\exists$	there exists
$\exists!$	there exists uniquely
$\ni$	such that

For example, consider the following two statements, and their mathematical "translations".

Every positive number has a square root.

$$\forall\, x > 0 \;\; \exists\, y \ni y^2 = x \; .$$

Every positive number has a unique positive square root.

$$\forall\, x > 0 \;\; \exists!\;\; y > 0 \;\; \ni \;\; y^2 = x \; .$$

SET THEORY:

$\in$	"is an element of"	$a \in A$ means a is an element of the set A
$\subseteq$	"is a subset of"	$A \subseteq B$ means the set A is a subset of the set B. Note that this does not rule out the case A = B
$\subset$	"is a proper subset of"	$A \subset B$ means $A \subseteq B$ and $A \neq B$
$\supseteq$	"contains"	$A \supseteq B$ means $B \subseteq A$
$\supset$	"properly contains"	$A \supset B$ means $B \subset A$
$\not\subseteq$	"is not a subset of"	
etc.		

(This subset notation is essentially the algebraists' notation. An analyst is more apt to use $\subset$ as the general inclusion symbol. $A \subset B$ will mean A is a subset, not necessarily proper, of B. If he ever needs the sharper result that A is a proper subset, he devises a new notation, such as $<$. So $A < B$ means $A \subset B$ and $A \neq B$.)

$\cup$	union or cup	$A \cup B$ is the set of all elements in either A or B
$\cap$	intersection or cap	$A \cap B$ is the set of all elements in both A and B
-	set difference	A - B is the set of all elements in A but not in B

(An older notation, frequently found in probability books, is:

$A + B$ means $A \cup B$

AB means $A \cap B$.)

ϕ	the empty set
U, $\mathfrak{U}$, etc.	the universal set
$c_B(A)$	the complement of A in B. $c_B(A) = B - A$. When B is the universal set U, $c_U(A)$ is usually replaced by just $c(A)$. The complement of A in U is just called the complement of A. Other common notations for the complement of A are: $\overline{A}$, A', $\sim A$, A^c.

A set is frequently specified by listing the collection of attributes that define its members. If A is the set of all elements that satisfy $p_1(z)$, $p_2(z)$, ..., $p_n(z)$, then the notation is:

$$A = \{x | p_1(x), p_2(x), \ldots, p_n(x)\} .$$

This is called the set builder notation and is read:

A is the set of all x such that $p_1(x)$ and ... and $p_n(x)$ are all true.

The colon ":" sometimes replaces the vertical line. Either is read "such that".

For two sets, A and B, their cartesian product, $A \times B$, is defined to be the set of all ordered pairs, the first element from A, the second from B; in symbolic form:

$$A \times B = \{(a,b) \mid a \in A, b \in B\} .$$

This can be extended to the cartesian product of n sets.

$$A_1 \times A_2 \times \ldots \times A_n = \{(a_1, a_2, \ldots, a_n) \mid a_1 \in A_1, a_2 \in A_2, \ldots, a_n \in A_n\} .$$

Thus, $A \times B$ consists of ordered pairs, whereas $A_1 \times \ldots \times A_n$ consists of ordered n-tuples.

$A \times A \times \ldots \times A$ (n factors A) is often written A^n .

Some sets of numbers are used so often that they are given special names:

$\mathcal{J}$ or $\mathcal{Z}$ or $\mathcal{N}$	the set of natural numbers (1, 2, 3, ...)
	the set of integers (0, ±1, ±2, ...)
$\mathcal{Q}$	the set of rational numbers (from "quotient")
$\mathcal{R}$	the set of real numbers
$\mathcal{C}$	the set of complex numbers

The set of ordered n-tuples of real numbers can thus be denoted by $\mathcal{R}^n$ Since this just n-dimensional Euclidean space, it is also often called $\mathcal{E}^n$.

Certain subsets, namely intervals, of the set of real numbers $\mathcal{R}$ are quite important, and have a special notation.

Closed interval

$$[a,b] = \{x \in \mathcal{R} \mid a \leq x \leq b\} .$$

Open interval

$$(a,b) = \{x \in \mathcal{R} \mid a < x < b\} .$$

Combinations are possible. For example

$$(-2,1] = \{x \in \mathcal{R} \mid -2 < x \leq 1\} .$$

RELATIONS AND FUNCTIONS:

Some of the most flagrant abuse of notation has occurred in this area, so it might be a good idea to examine briefly the mathematical theory that fosters a rather natural notation.

A relation R in $A \times B$ is an arbitrary subset of the cartesian product $A \times B$. That is, $R \subseteq A \times B$. (Actually, this is a binary

relation. More generally, an n-ary relation is a subset of $A_1 \times A_2 \times \ldots \times A_n$. Since binary relations are most common, the single word "relation" usually refers to a binary relation.)

The set of all elements of A that appear as the <u>first</u> member of some element of R is called the <u>domain</u> of R. The set of all second members of elements of R is called the <u>range</u> of R, i.e.,

$$\text{domain } R = \{a \in A \mid (a,b) \in R \text{ for some } b \in B\} \subseteq A$$

$$\text{range } R = \{b \in B \mid (a,b) \in R \text{ for some } a \in A\} \subseteq B \ .$$

If $(a,b) \in R$, then a is said to be related to b. In practice, the notation $(a,b) \in R$ is often replaced by aRb. This is in keeping with traditional verbal usage. Remember that R just stands for the name of some relation. For example, "less than" is a relation. For it we almost always write $a < b$, and rarely $(a,b) \in <$, although the latter is correct.

If the sets A and B are identical, then $R \subseteq A \times A$, and R is said to be a relation <u>on</u> A. Various kinds of order relations fall into this category. A relation R on A is said to be an <u>equivalence relation</u> if R is

i) reflexive $\quad xRx \quad \forall x \in A$

ii) symmetric $\quad xRy \implies yRx$

iii) transitive $\quad xRy \text{ and } yRz \implies xRz \ .$

An arbitrary equivalence relation is designated by the symbol "$\sim$" (called "tilde").

Consider again the more general situation $R \subseteq A \times B$. If every element of the domain is related to <u>exactly</u> one element of the range, then this relation is called a <u>function</u>. That is, R is a function if and only if

$$aRb \text{ and } aRc \implies b = c \ .$$

Functions are often named by the letters f, g, h. Although both $(a,b) \in f$ and afb are correct notations, if the relation f is actually a function, related pairs are designated by writing $fa = b$ or $f(a) = b$ (or $f(x) = y$).

Sometimes it is convenient to think of a function as a rule that associates with every member of the domain a unique member of the range. If x is in the domain, then the member of the range associated with it is $y = f(x)$. This should be read: y is the value of the function f at x. This description of a function leads to a notation that is much more common than $f \subseteq A \times B$. Instead, one writes $f:A \longrightarrow B$ which is read: f is a function from A to B. Also as frequently is the case, if the domain of f is all of A, we say that "f is a function on A to B."

For an arbitrary function $f:A \longrightarrow B$, the sets A and B can be any sets. If A is the set of real numbers, f is said to be a function of a real variable. If B is the set of reals, f is called a real-valued function. Elementary calculus deals almost exclusively with real-valued functions of real variables. That is, $f: \mathcal{R} \longrightarrow \mathcal{R}$.

Elementary calculus books are notorious for incorrect statements such as:

"the function f(x)"

"the function y = f(x)" .

Correct terminology would be:

"the function f with value y = f(x) at x" .

That is, f(x) is the <u>value</u> of the function f at x, but f(x) is not the <u>name</u> of the function.

Consider again an arbitrary relation $R \subseteq A \times B$. The <u>transpose relation</u>, denoted by R^T, is a relation in $B \times A$ defined by

$$(b,a) \in R^T \quad \text{iff} \quad (a,b) \in R .$$

Thus,

$$\text{domain } R^T = \text{range } R$$

$$\text{range } R^T = \text{domain } R .$$

It is easy to see that $(R^T)^T = R$.

Even if a relation f is actually a function, the transpose relation f^T is not necessarily a function. By the definition of function, f^T will be a function if and only if

$$(b,a) \in f^T \text{ and } (b,c) \in f^T \Longrightarrow a = c \ .$$

This holds if and only if

$$(a,b) \in f \text{ and } (c,b) \in f \Longrightarrow a = c$$

that is, if and only if f assigns distinct elements of the range to distinct elements from the domain. A function f with this property is called one-to-one, often written 1-1.

Thus, for a function f, f^T is also a function if and only if f is 1-1. If f^T is actually a function, it is called the <u>inverse</u> of f, written f^{-1}.

If f^T is not a function, it is frequently convenient to restrict the domain of f (which is the range of f^T) so that a new function $\overline{f}$ (which is just f restricted to the smaller domain) is 1-1. Then $\overline{f}^{-1}$ is a function.

<u>SOME SPECIAL FUNCTIONS AND THEIR INVERSES</u>:

Certain real-valued functions of a real variable arise so often that they have been given special names. Prominent among these are the trigonometric functions: sin, cos, tan, cot, sec, csc. The transposes of these functions are <u>not</u> functions. They are denoted by arcsin, arccos, arctan, arccot, arcsec, arccsc, respectively. Occasionally, arcsin, etc., is written $\sin^{-1}$, etc., but this is particularly bad since these transpose relations are not functions. It is possible, however, to suitably restrict the ranges of the transpose relations (i.e., the domains of the trigonometric functions) so that the transpose relations become functions. When the natural restrictions are made, the <u>inverse</u> functions are denoted by:

Arcsin, Arccos, Arctan, Arccot, Arcsec, Arccsc .

(Or occasionally by Sin^{-1}, Cos^{-1}, etc.)

The log and exponential are two other important functions.

$$\text{If } f(x) = a^x \text{ then } f^{-1}(x) = \log_a x \ .$$

The most common value of the base a for the high school student is 10. But the mathematician uses most often the number denoted by e as the base. In this case, the function f is given the name exp ($\exp(x) = e^x$) and f^{-1} is named ln ($\ln x = \log_e x$).

The power function is very common but has no special name. If $f(x) = x^k$, then $f^{-1}(x) = x^{1/k}$ and has domain $\mathbb{R}$ if k is odd and domain $\{x \in \mathbb{R} \mid x \geq 0\}$ if k is even.

One very useful function is the identity function, but historically, it has been without a name. Recently, this function has been denoted by E (or $E_{\mathbb{R}}$) in some literature. Thus,

$$E(x) = x \ .$$

DIFFERENTIATION:

Here the notation is least uniform. The most common notations are the worst logically. But there is no real agreement on what should be a good notation.

One logical way to view differentiation is as follows:

Given a function f, a new function, called the derivative of f, is formed.

This derivative should have a name, and the previous discussion cautions us not to confuse the name of this function with the value of the function. The great differences of opinion arise in deciding what name to use. Any of the following three notations are logically consistent, and the context of the discussion could dictate which to choose:

If f is a function, the name of its derivative is

$$f'$$
$$\dot{f}$$
$$Df \ .$$

(The notation Df is useful when one wishes to think of D as being an operator on some class of functions.)

The two notations:

$$D_x f$$

$$\frac{df}{dx}$$

are common but seem less suitable because the variable name is also part of the function name. For example, a function f could have value f(x) or f(t). The name of the derivative of f should not depend on what we call the variable, but common usage claims that $D_x f(x)$ and $D_x f(t)$ are not the same.

The very worst notation is also the most common. For a function f, we write the value y of f at x as y = f(x). But in this notation, the value of the derivative function at x is given by dy/dx and the derivative function itself remains nameless!

The second derivative (i.e., the derivative of the derivative) is denoted by: f", $\ddot{f}$, $D^2 f$, $D_x^2 f$, $d^2 f/dx^2$, $d^2 y/dx^2$ in the respective notations.

The nth derivative is denoted by:

$$f^n, \ (\dot{f} \text{ notation not suitable here}), \ D^n f, \ D_x^n f, \ \frac{d^n f}{dx^n}, \ \frac{d^n y}{dy^n}$$

respectively.

INTEGRATION:

In contrast to differentiation, the notation for integration is quite consistent from author to author and is on better logical ground as well.

Indefinite integration can be thought of as a process of finding a new function F whose derivative is given function f. The name of this new function is given by $\int f(x)\,dx$, where x here is a purely "dummy variable". The standard confusion of name with value arises here again,

however, since this same notation must also denote the value of the function. One often sees:

$$F(x) = \int f(x)\, dx \ .$$

Indefinite integration is sometimes called anti-differentiation since F is a function such that $F' = f$.

Definite integration associates a number with an interval and a function defined on that interval. This number gives the signed area of the region under the function on this interval. If the function is f and the interval is [a,b], the associated number, called the definite integral of f over [a,b], is denoted by

$$\int_a^b f(x)\, dx \ .$$

The dissimilar definitions of indefinite and definite integration might lead one to believe that the similar names and notations are confusing. However, the Fundamental Theorem of Calculus relates the two ideas, and makes the notation a natural one.

VECTORS:

It is easiest to think of vectors as simply being elements of $\mathcal{R}^n$ (i.e., ordered n-tuples of real numbers). This is basically an analytic viewpoint. The algebraist has abstracted this notion to encompass much more general mathematical objects, but this generality is not needed in most of this book.

A vector is usually named by:

$\mathbf{X}$ (bold face), $\vec{X}$, $\overrightarrow{X}$, $\bar{x}$ or most simply, X.

That is, $X = (x_1, x_2, \ldots, x_n) \in \mathcal{R}^n$, x_i is called the ith component of X, and X is said to be n-dimensional. A 1-dimensional vector, i.e., a real number, is called a scalar.

The ordering of vectors has some interesting terminology

and notation. Of course, only vectors of the same dimension can be compared. One common ordering is the lexicographic (or dictionary) order, in which vectors are compared on the basis of their first unequal component.

If vectors are compared component by component, then some vectors are not comparable. There are basically two distinct notations for this type of ordering.

Let $X, Y \in \mathbb{R}^n$.

	System I	System II
$x_i \geq y_i \quad \forall i$	$X \geq Y$	$X \geqq Y$
$x_i \geq y_i \ \forall i$ and $\exists\, i_o$, $x_{i_o} > y_{i_o}$	$X > Y$	$X \geqq Y$
$x_i > y_i \quad \forall i$	$X \gg Y$	$X > Y$

Certain operations can be performed on vectors of the same dimension. So assume X and $Y \in \mathbb{R}^n$.

Addition X + Y is a vector, found by adding X and Y component by component:

$$X + Y = (x_1 + y_1,\ x_2 + y_2,\ \ldots,\ x_n + y_n) .$$

Scalar Multiplication αX, where $\alpha \in \mathbb{R}$, is a vector, found by multiplying each component of X by α.

$$\alpha X = (\alpha x_1, \alpha x_2,\ \ldots,\ \alpha x_n) .$$

Dot Product (or Inner Product) $X \cdot Y$ is a scalar defined by

$$X \cdot Y = x_1 y_1 + x_2 y_2 + \ldots + x_n y_n = \sum_{i=1}^{n} x_i y_i .$$

[The cross (or outer) product is a very special operation usually defined only in $\mathbb{R}^3$. Its significance lies mostly in physical applications of mathematics.]

The magnitude (or length) of a vector X is denoted by $|X|$ or $||X||$. By definition,

$$|X| = \sqrt{x_1^2 + x_2^2 + \ldots + x_n^2} = \sqrt{X \cdot X} .$$

FUNCTIONS FROM $\mathcal{R}^m$ TO $\mathcal{R}^n$:

In this section we consider the notation and terminology associated with functions of the form $F: \mathcal{R}^m \longrightarrow \mathcal{R}^n$. The previously considered real-valued functions of a real variable are a special case for $m = n = 1$.

Case i) $F: \mathcal{R}^m \longrightarrow \mathcal{R}$.

Here F is often called a real (or scalar) valued function of several (i.e., m) variables. The value of F at $X \in \mathcal{R}^m$ could be denoted by $y = F(X)$, but is more often written $y = F(x_1, x_2, \ldots, x_m)$. This is because one frequently wishes to consider changes in the individual variables independently of one another. The "graph" of this function is a "surface" in m + 1 dimensional space that "lies over" the "$(x_1, x_2, \ldots, x_m)$ plane."

The ith partial derivative of F is the derivative of F when all variables but the ith are assumed constant. That is, F is considered as a function of the ith variable alone, and its derivative is found. This is a new function from $\mathcal{R}^m$ to $\mathcal{R}$ and should have a name. Unfortunately, the same bad notational problems of the single derivative occur again. There is an abundance of notation, some of it logically undesirable.

If F is a function from $\mathcal{R}^m$ to $\mathcal{R}$, two good notations for the name of the ith partial derivative are

$$D_i F \quad \text{and} \quad F_i .$$

More common but less good are

$$D_{x_i} F \quad \text{and} \quad F_{x_i} .$$

These have the drawback of using the variable name in the name of the function.

An even more common notation, $\partial F/\partial x_i$, has the same fault, and is quite clumsy. Also, many authors write $y = F(x_1, x_2, \ldots, x_m)$ and use $\partial y/\partial x_i$ to mean the value of the ith partial derivative, and leave this function nameless. This notation is (unfortunately) the most common.

Since the ith partial derivative of F is itself a function from $\mathbb{R}^m \longrightarrow \mathbb{R}$, it makes sense to talk about the jth partial derivative of the ith partial derivative. Notations for this function are (the first two are preferred):

$$D_{ij}F\ ,\quad F_{ij}\ ,\quad D_{x_i x_j}F\ ,\quad F_{x_i x_j}\ ,\quad \frac{\partial^2 F}{\partial x_j \partial x_i}\ ,\quad \frac{\partial^2 y}{\partial x_j \partial x_i}\ .$$

Note the order of variables in the last two notations. This can be justified (and remembered) by considering

$$\frac{\partial^2 y}{\partial x_j x_i} = \frac{\partial}{\partial x_j}\left(\frac{\partial y}{\partial x_i}\right)\ .$$

If j = i, these latter notations often read

$$\frac{\partial^2 y}{\partial x_i^{\,2}}\ .$$

Higher order partial derivatives are defined similarly.

The <u>definite integral</u> of F "over" a subset $S \subseteq \mathbb{R}^m$ is written as

$$\int_S F\,(x_1, x_2, \ldots, x_m)\ dV\ ,$$

where dV is called the "volume element". Such an integral is often called a multiple integral, and it is not uncommon, particularly for m = 2 or 3, to have m integral signs $\int$ instead of one.

In practice, a multiple integral is evaluated by finding an equivalent iterated integral, which is of the form

$$\int_a^b dx_1 \int_{\phi_2(x_1)}^{\psi_2(x_1)} dx_2 \cdots \int_{\phi_m(x_1,x_2,\ldots,x_{m-1})}^{\psi_m(x_1,x_2,\ldots,x_{m-1})} f(x_1,x_2,\ldots,x_m)\, dx_m \,.$$

Case ii) $F: \mathcal{R} \longrightarrow \mathcal{R}^n$.

This is the case of a vector-valued function of a real variable. The fact that the value of the function is a vector is sometimes indicated by giving the function a name such as $\vec{f}$, $\bar{x}$, etc.

For example, suppose $\bar{f}: \mathcal{R} \longrightarrow \mathcal{R}^n$. Then for $t \in \mathcal{R}$, $\bar{f}(t) \in \mathcal{R}^n$.

In fact, we can write $\bar{f}(t) = (f_1(t), f_2(t), \ldots, f_n(t))$. That is, $\bar{f}$ can be represented by n functions f_i, where $f_i: \mathcal{R} \longrightarrow \mathcal{R}$, and this approach is usually taken. We write

$$\bar{f} = (f_1, f_2, \ldots, f_n) \,.$$

The derivative and integral of such a function are again functions from $\mathcal{R}$ to $\mathcal{R}^n$ and they are defined in terms of the component functions of $\bar{f}$.

For example, $D\bar{f}$ is a function from $\mathcal{R}$ to $\mathcal{R}^n$ and the vector value of $D\bar{f}$ at t is given by

$$D\bar{f}(t) = (Df_1(t), Df_2(t), \ldots, Df_n(t)) \,.$$

Likewise, $\int_a^b \bar{f}(t)\, dt$ is defined to be the vector

$$\left(\int_a^b f_1(t)\, dt, \int_a^b f_2(t)\, dt, \ldots, \int_a^b f_n(t)\, dt \right) .$$

Case iii) $F: \mathcal{R}^m \longrightarrow \mathcal{R}^n$.

In this most general case, the function F is a vector valued function of a vector variable. Proceeding as in Case ii), F can be replaced by n real valued functions of a vector variable. The notation pertaining to these n functions each from $\mathcal{R}^m$ to $\mathcal{R}$, would then be the same as in Case i).

If $X \in \mathcal{R}^m$, then $F(X) \in \mathcal{R}^n$ and we could write

$$F(X) = \Big(F_1(X),\ F_2(X),\ \ldots,\ F_n(X) \Big) \ .$$

Care must be taken not to confuse the names of the component functions F_i with the partial derivative notation. In this instance, an alternate partial derivative notation, such as D_i, should be used.

THE OPERATOR "del" AND THE JACOBIAN:

An important notational device that one is apt to encounter quite often is the operator ∇, read "del". (Do not confuse this with the notation Δ, introduced earlier.)

∇ is defined to be a "vector" $(D_1, D_2, \ldots, D_m)$ or more commonly

$$\left(\frac{\partial}{\partial x_1},\ \frac{\partial}{\partial x_2},\ \ldots,\ \frac{\partial}{\partial x_m} \right) .$$

This operator is used in the following ways:

a) If $F: \mathcal{R}^m \longrightarrow \mathcal{R}$ then F has scalar values. Thus, it is possible to think of ∇F as a vector times a scalar, giving another vector. Formal multiplication gives

$$\nabla F = (D_1 F,\ D_2 F,\ \ldots,\ D_m F) \quad \text{or} \quad \left(\frac{\partial F}{\partial x_1},\ \frac{\partial F}{\partial x_2},\ \ldots,\ \frac{\partial F}{\partial x_m} \right) .$$

This is taken to be the definition of ∇F. ∇F is a function from $\mathcal{R}^m$ to $\mathcal{R}^m$ and the value of ∇F at $X \in \mathcal{R}^m$ is given by

$$\nabla F(X) = \Big(D_1 F(X),\ D_2 F(X),\ \ldots,\ D_m F(X) \Big) \ .$$

∇F is generally called the gradient of F.

Since ∇ and ∇F are, in a formal sense at least, vectors, both of dimension m, their dot product $\nabla \cdot \nabla F$ can be defined formally by

$$\nabla \cdot \nabla F = D_{11} F + D_{22} F + \ldots + D_{mm} F \quad \text{or} \quad \frac{\partial^2 F}{\partial x_1^2} + \frac{\partial^2 F}{\partial x_2^2} + \ldots + \frac{\partial^2 F}{\partial x_m^2} \ .$$

$\nabla \cdot \nabla F$ is usually written $\nabla^2 F$ and by definition is a function from $\mathcal{R}^m$

to $\mathbb{R}$ such that the value of $\nabla^2 F$ at $X \in \mathbb{R}^m$ is given by

$$\nabla^2 F(X) = D_{11}F(X) + D_{22}F(X) + \ldots + D_{mm}F(X) .$$

$\nabla^2 F$ is called the Laplacian of F. The equation

$$\nabla^2 F = 0$$

is called Laplace's differential equation.

b) In the very special case where $F: \mathbb{R}^m \longrightarrow \mathbb{R}^m$, the symbol ∇ is again sometimes used. Since F is a function whose value is an m-dimensional vector, it makes sense here to talk about the formal dot product $\nabla \cdot F$.

If $F = (F_1, F_2, \ldots, F_m)$, then $\nabla \cdot F = D_1F_1 + D_2F_2 + \ldots + D_mF_m$. $\nabla \cdot F$ is called the divergence of F.

Also, if $m = 3$, the cross product $\nabla \times F$ is called the curl of F.

These notations are not too common, but should be recognized if encountered.

There is one more very important notion that arises when considering functions from $\mathbb{R}^m$ to $\mathbb{R}^n$, and that is the concept of the Jacobian.

If $F: \mathbb{R}^m \longrightarrow \mathbb{R}^n$, we can write F in terms of its component functions, $F = (F_1, F_2, \ldots, F_n)$.

The Jacobian matrix of F is the $m \times n$ matrix

$$J(F) = \begin{bmatrix} D_1F_1 & D_1F_2 & \cdots & D_1F_n \\ D_2F_1 & D_2F_2 & \cdots & D_2F_n \\ \vdots & \vdots & & \vdots \\ D_mF_1 & D_mF_2 & \cdots & D_mF_n \end{bmatrix} \quad \text{or} \quad \begin{bmatrix} \frac{\partial F_1}{\partial x_1} & \frac{\partial F_2}{\partial x_1} & \cdots & \frac{\partial F_n}{\partial x_1} \\ \frac{\partial F_1}{\partial x_2} & \frac{\partial F_2}{\partial x_2} & \cdots & \frac{\partial F_n}{\partial x_2} \\ \vdots & \vdots & & \vdots \\ \frac{\partial F_1}{\partial x_m} & \frac{\partial F_2}{\partial x_m} & \cdots & \frac{\partial F_n}{\partial x_m} \end{bmatrix} .$$

The notation for this Jacobian is often

$$\frac{\partial(F_1, F_2, \ldots, F_n)}{\partial(x_1, x_2, \ldots, x_m)} .$$

This notation then generalizes. An example can best describe it. Suppose F, G, H are functions from $\mathcal{R}^6$ to $\mathcal{R}$. Then

$$\frac{\partial(G,F,H)}{\partial(x_2,x_1,x_5)} = \begin{bmatrix} G_2 & F_2 & H_2 \\ G_1 & F_1 & H_1 \\ G_5 & F_5 & H_5 \end{bmatrix} = \begin{bmatrix} D_2G & D_2F & D_2H \\ D_1G & D_1F & D_1H \\ D_5G & D_5F & D_5H \end{bmatrix} .$$

If n = m then the determinant of the Jacobian matrix (written det J(F)) is called the Jacobian.

MATRICES:

Matrices are used in several different contexts in mathematics. Their most notable application is in linear algebra, and it is their use there that has motivated most of the matrix operations, terminology, and notation. For the purposes of description, however, it seems advisable to ignore the many mathematical uses of matrices and adopt a more simplistic point of view.

A matrix is a two-dimensional array of numbers. If this array has p rows and n columns, it is called a p by n (p × n) matrix. Matrices are frequently denoted by capital letters, and their entries by small letters. Each entry can be uniquely identified by the row and column in which it appears. If A is a matrix, then the (i,j) position of A is the position in the ith row and the jth column. The (i,j) entry is the number that appears in the (i,j) position, and is often denoted by a symbol such as a_{ij}. Sometimes, the notation $A = (a_{ij})_{ij}$ is used. This is read: A is the matrix with a_{ij} in the (i,j) position.

The transpose of a matrix A is formed by inter-changing the rows and columns, and is denoted by A^T or A'. If $A = (a_{ij})_{ij}$, then $A^T = (a_{ji})_{ij}$. That is, a_{ji} appears in the (i,j) position of A^T. If A is p × n, then A^T is n × p. $(A^T)^T = A$.

What has been defined as an n-dimensional vector in the section on "vectors" can really be thought of as a $1 \times n$ matrix. We now call this a row vector and then a column vector is an $n \times 1$ matrix. Most authors use the word "vector" to mean exactly one of "column vector" or "row vector". In this section, the word vector will mean specifically column vector. Then, if X is a vector, X^T is a row vector.

MATRIX OPERATIONS

a) Scalar multiplication

If α is a number, $A = (a_{ij})_{ij}$, then $\alpha A = (\alpha a_{ij})_{ij}$. That is, every entry of A is multiplied by α.

b) Scalar addition

If $A = (a_{ij})_{ij}$, $B = (b_{ij})_{ij}$, and A and B are both $p \times n$, then $A + B$ is a $p \times n$ matrix defined by $A + B = (a_{ij} + b_{ij})_{ij}$. That is, matrices of the same size can be added by adding the entries in corresponding positions.

c) Multiplication

Matrix multiplication of A times B is defined only if A is $p \times r$ and B is $r \times n$. That is, A must have the same number of columns as B has rows. If this criterion is met, then

$$AB = C = (c_{ij})_{ij}$$

is a $p \times n$ matrix where

$$c_{ij} = \sum_{k=1}^{r} a_{ik} b_{kj} .$$

That is, the (i,j) entry of C is found by taking the inner product of the ith row of A with the jth column of B, where both are considered as r-dimensional vectors. Matrix multiplication is associative (A(BC) = (AB)C) but not in general commutative. (AB does not necessarily equal BA. In fact, BA may not be defined, even though AB is.)

Note that if X and Y are $n \times 1$ matrices (column vectors) then X^T is a $1 \times n$ matrix (row vector), and the matrix product X^TY is defined. The resulting matrix is 1×1 (a scalar) and is just the ordinary inner product of X and Y. Thus, the algebraist frequently denotes inner product by X^TY, since for him, $X \cdot Y$ would be undefined as matrix multiplication. Other notations sometimes used for inner product are (X,Y) and $\langle X,Y \rangle$.

The power of matrix notation can be seen in considering the following set of p linear equations in n unknowns.

$$\begin{aligned} a_{11}x_1 + a_{12}x_2 + \ldots + a_{1n}x_n &= b_1 \\ a_{21}x_1 + a_{22}x_2 + \ldots + a_{2n}x_n &= b_2 \\ \vdots \quad\quad \vdots \quad\quad\quad\quad \vdots \quad\quad \vdots & \\ a_{p1}x_1 + a_{p2}x_2 + \ldots + a_{pn}x_n &= b_p \, . \end{aligned}$$

If A is the $p \times n$ matrix $(a_{ij})_{ij}$, $X = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix}$ and $B = \begin{bmatrix} b_1 \\ b_2 \\ \vdots \\ b_n \end{bmatrix}$,

then this system is more succinctly represented by

$$AX = B \, .$$

The <u>square matrices</u> form an important subclass of matrices, and there is some special terminology associated with them.

If A is square ($n \times n$), the <u>diagonal</u> of A is the set of positions (i,i), $i = 1 \ldots n$.

The matrix A is said to be <u>upper triangular</u> if $a_{ij} = 0$ for all entries where $i > j$. That is, the only non-zero entries of A are on or above the diagonal.

A <u>lower triangular</u> matrix is defined similarly.

A matrix which is both upper and lower triangular is said to be a diagonal matrix. It has non-zero entries only on the diagonal.

An $n \times n$ diagonal matrix with all 1's on the diagonal is called the $n \times n$ identity matrix, often denoted by I_n, or simply I, if n is understood. The name "identity matrix" is motivated by the following important property:

$$\text{If } A \text{ is } p \times n, \text{ then } AI_n = A \text{ and } I_p A = A .$$

For A a $p \times n$ matrix, there may exist an $n \times p$ matrix B such that $AB = I_p$. B is then called a right inverse for A. Likewise, if C is $n \times p$ such that $CA = I_n$, then C is a left inverse for A. If A is rectangular ($p \neq n$) then it cannot have both a right and a left inverse. If A is square and has either a left or a right inverse, then it must have the other, and the two inverses are equal. This matrix is called the inverse of A and is written A^{-1}. Not all square matrices have inverses; those that do are called non-singular.

The determinant of a matrix is the concept from linear algebra that is most common to many people. However, its role in the theory and applications of linear algebra is quite limited. The determinant of a matrix A is sometimes denoted by det A or $|A|$. It should be noted that the non-singular matrices are exactly those that have a non-zero determinant.

PROBABILITY:

Probability usually begins with a discussion of the sample space or event space, often denoted by $\mathcal{E}$. This is just a set, whose elements are the individual outcomes of some experiment. These elements are often called basic events. The subsets of $\mathcal{E}$ are called events. If $A \subset \mathcal{E}$, then the probability of the event A is denoted by P(A) or Pr(A). Thus, P is a function from the set of all subsets of $\mathcal{E}$ to the real numbers. If A is any set, the collection of all subsets of A is called the power set of A, and is denoted by 2^A. Thus, if $B \subset A$, then $B \in 2^A$. The probability function can then be written as $P: 2^{\mathcal{E}} \longrightarrow \mathbb{R}$.

In fact, a probability function on $\mathcal{C}$ is any function P from the subsets of $\mathcal{C}$ to the real numbers that satisfies the following three axioms:

i) $P(A) \geq 0 \quad \forall A \subseteq \mathcal{C}$

ii) $P(\mathcal{C}) = 1$

iii) If $A, B \subset \mathcal{C}$ and $A \cap B = \emptyset$ then $P(A \cup B) = P(A) + P(B)$.

Conditional probability uses the notation $P(A|B)$, which is read "the probability of A, given that B is true," and is defined by

$$P(A|B) = \frac{P(A \cap B)}{P(B)} \qquad \text{for } P(B) \neq 0 .$$

If A does not depend on B, that is $P(A|B) = P(A)$, then A is said to be independent of B. But if A is independent of B, then

$$P(A) = P(A|B) = \frac{P(A \cap B)}{P(B)} .$$

(Assume $P(A) \neq 0$ and $P(B) \neq 0$.) Thus

$$P(A)P(B) = P(A \cap B)$$

or

$$P(B) = \frac{P(A \cap B)}{P(A)} = P(B|A) .$$

That is, if A is independent of B, then B must also be independent of A, and A and B are called independent events.

One particularly confusing aspect of probability theory for the beginner is that some of the most important functions in probability are not called functions, but are called random variables. A random variable (r.v. for short) is a function that associates a real number with every basic event; random variables are usually denoted by X, Y, or Z. Thus, if X is an R.V., then $X: \mathcal{C} \longrightarrow \mathcal{R}$.

The probability associated with the original sample space $\mathcal{C}$ can now be associated with the random variable X in the following way:

> If s is a statement about the values of an r.v. X, then the probability that the value of X will make s true is denoted by P(s(X)) and is defined by

$$P(s(x)) = P\{e \in \mathcal{E} \mid s(X(e)) \text{ is true}\} .$$

Examples:

$$P(X^2 \geq 10) = P\{e \in \mathcal{E} \mid [X(e)]^2 \geq 10\}$$

$$P(0 < X \leq 1) = P\{e \in \mathcal{E} \mid 0 < X(e) \leq 1\}$$

$$P(X = 5) = P\{e \in \mathcal{E} \mid X(e) = 5\} .$$

(Note that while calculus texts often let the value of the function stand for the name of the function, in the probability notation we sometimes compare the name of the function with its values, e.g., $X = 5$.)

Associated with any r.v. X is its distribution function F_X (or simply F). The distribution function is a real valued function of a real variable and its value at a point x is defined by:

$$F_X(x) = P(X \leq x) = P\{e \in \mathcal{E} \mid X(e) \leq x\} .$$

The study of probability can really be reduced to the study of these distribution functions.

There are basically three kinds of random variables (and hence distribution functions) which can best be illustrated by examples.

a) The r.v. X takes on only a finite number of values, say a_1, a_2, ..., a_n arranged so that $a_1 < a_2 < \ldots < a_n$.

Let $p_i = P(X = a_i)$. So we must have

$$\sum_{i=1}^{n} p_i = 1 .$$

Then

$$F_X(x) = P(X \leq x) = \sum_{i=1}^{k} p_i$$

where k is the greatest index such that $a_k \leq x$.

Define the funtion f_X as follows:

$$f_X(x) = 0 \qquad \text{if } x \neq a_i \qquad i = 1, 2, \ldots, n$$

$$f_X(a_i) = p_i \ .$$

f_X is called the density function of X.

Note that we can write

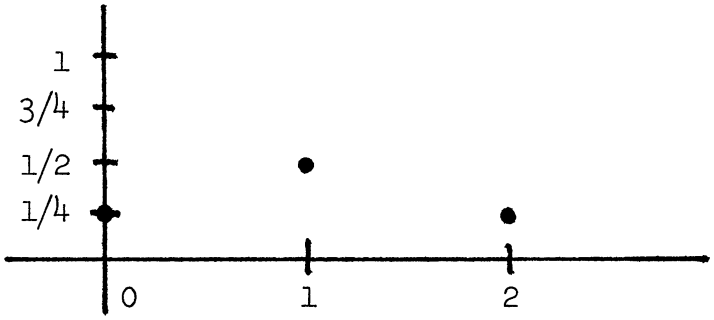
$$F_X(x) = \sum_{i=1}^{k} f_X(a_i)$$

where k is greatest index such that $a_k \leq x$, or

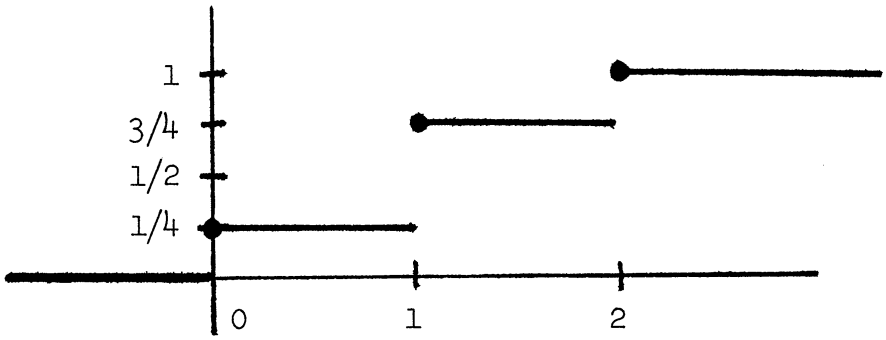
$$F_X(x) = \sum_{y \leq x} f_X(y) \ .$$

Example

X can take on only the values 0, 1, 2, with respective probabilities 1/4, 1/2, 1/4.



f_X



F_X

(This is the Bernoulli--or binomial--distribution with 2 trials, probability of success equal to 1/2.)

Other important distributions where the range of the random variable is a finite set are the symmetric distribution (each of n basic events has probability 1/n) and the hypergeometric distribution.

b) The r.v. X takes on an infinite, but <u>discrete</u>, set of values, say $a_1, a_2, \ldots$, arranged so that $a_1 < a_2 < \ldots$. Let $p_i = P(X = a_i)$. So we must have

$$\sum_{i=1}^{\infty} p_i = 1 .$$

Then

$$F_X(x) = P(X \leq x) = \sum_{i=1}^{k} p_i$$

where $a_k \leq x < a_{k+1}$. Define the function f_X as follows:

$$f_X(x) = 0 \qquad \text{if } x \neq a_i$$

$$f_X(a_i) = p_i .$$

f_X is called the <u>density</u> function of X. Also,

$$F_X(x) = \sum_{i=1}^{k} f_X(a_i) \qquad \text{where } a_k \leq x < a_k$$

$$= \sum_{y \leq x} f_X(y) .$$

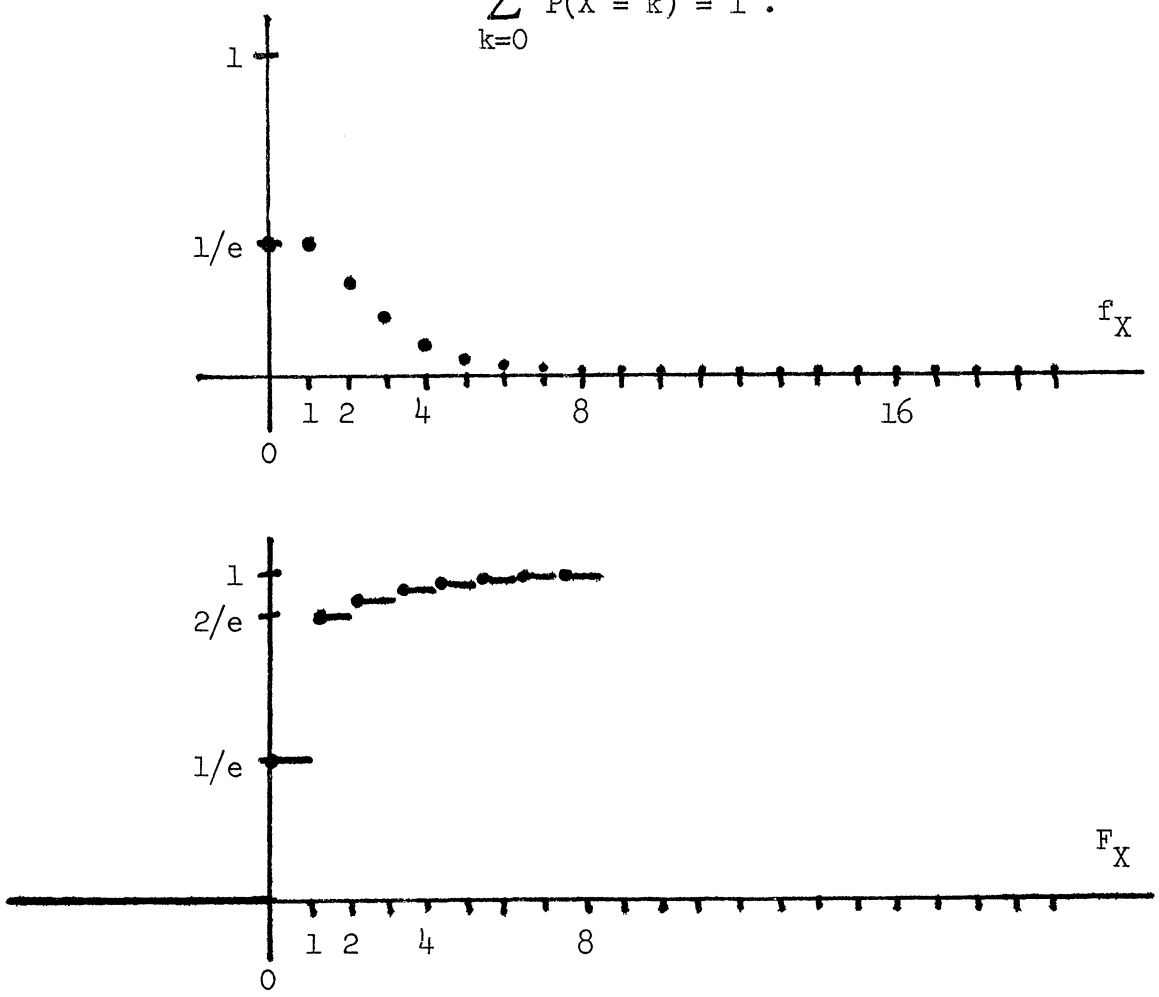
<u>Example</u>

X can take on any non-negative integer value. The probability that $X = k$ ($k = 0, 1, 2, \ldots$) is given by $\frac{1}{e}\frac{1}{k!}$. Since

$$e = \sum_{k=0}^{\infty} \frac{1}{k!} ,$$

we have that

$$\sum_{k=0}^{\infty} P(X = k) = 1 .$$



This is a special case of the Poisson distribution when the parameter is 1.

Other important distributions of this type are the geometric and negative binomial distributions.

c) X takes on a continuous range of values. In this case, if it is possible to write

$$F_X(x) = \int_{-\infty}^{x} f_X(y)\, dy$$

for some function f_X, then f_X is called the <u>density</u> function of X.

Notice the parallel with the discrete case; the $\int$ replaces the Σ. In most elementary examples, the density function f_X does exist, and is, in fact, the derivative of F_X ($F_X' = f_X$). One interpretation that can be given to f_X is

$$f_X = F_X'(x) = \lim_{\Delta x \to 0} \frac{F_X(x + \Delta x) - F_X(x)}{\Delta x}$$

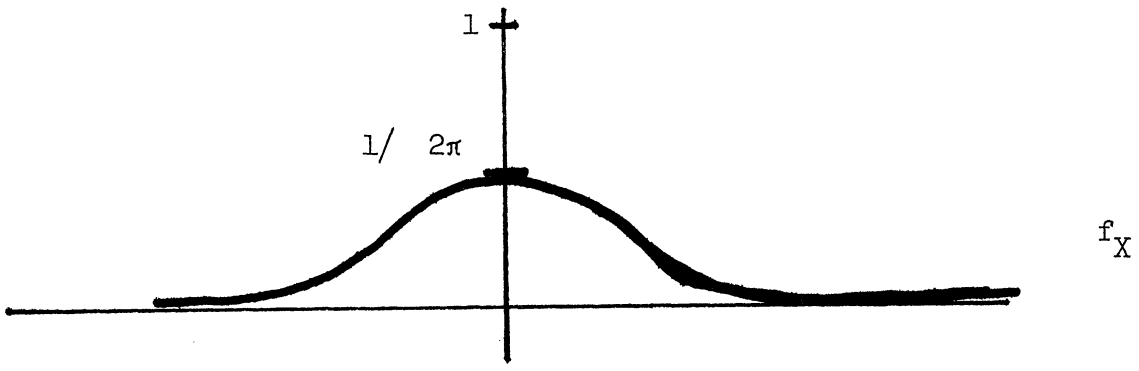
$$= \lim_{\Delta x \to 0} \frac{P(X \leq x + \Delta x) - P(X \leq x)}{\Delta x}$$

$$= \lim_{\Delta x \to 0} \frac{P(x < X \leq x + \Delta x)}{\Delta x} .$$

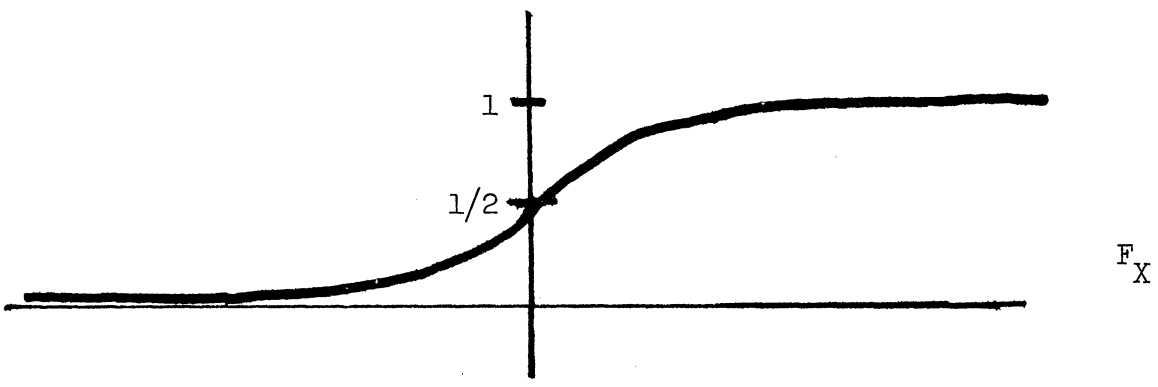
Example

$$f(x) = \frac{1}{\sqrt{2\pi}} e^{-x^2/2}$$

$$F(X) = \int_{-\infty}^{x} f(y)\, dy = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} e^{-y^2/2}\, dy .$$



f_X



F_X

This is one case of the normal distribution. Other important distributions of type c) are the uniform, exponential, gamma, and chi-squared.

EXPECTATION OR MEAN:

For a discrete r.v. X, the expectation of X is denoted by E(X) and is defined by

$$E(X) = \sum_{x} x\, f_X(x) \ .$$

Expectation is defined similarly for continuous r.v.'s, namely

$$E(X) = \int_{-\infty}^{\infty} y\, f_X(y)\, dy \ .$$

Note that E(X) is a number, and not a function.

E(X) is often called the mean, and the Greek letter mu (μ) often denotes the mean.

VARIANCE:

Variance is defined to be $E[(X - E(X))^2]$.

Variance is also a number, sometimes called σ^2. The standard deviation σ is the square root of the variance.

There are, of course, many additional definitions and notations peculiar to probability. This brief section has only considered the most common terms and concepts likely to be encountered at an early level of study. Indeed, we have discussed only single-variate probability. Multivariate probability means that the sample space can be considered as a subset of $\mathbb{R}^m$. Definitions and notations are analogous to the single-variate case. Also keep in mind that the theory of statistics, which utilizes probability theory, has additional terminology of its own.

BIBLIOGRAPHY

Abramson, H.A. Dimensional Analysis for Students of Medicine. New York: Josiah Macy, Jr. Foundation, 1950.

Ackerman, E. Biophysical Science. Englewood Cliffs, New Jersey: Prentice-Hall, 1962.

Adolph, E.F. Physiological Regulations. Lancaster, Pennsylvania: Jaques Cattell, 1943.

Ainsworth, G.C., and Sneath, P.H.A., Eds. Microbial Classification. London: Cambridge University Press, 1962.

Allen, I.G. Extracorporal Circulation. Springfield, Illinois: Charles C. Thomas, 1957.

Ancona, U. d'. The Struggle for Existence. Leiden: E. J. Brill, 1954.

Anfinsen, C.B. The Molecular Basis of Evolution. New York: Wiley & Sons, 1959.

Ashby, W.R. Design for a Brain. New York: Wiley & Sons, 1960.

Ashby, W.R. Introduction to Cybernetics. New York: Wiley & Sons, 1963.

Aschoff, J., Ed. Circadian Clocks. Amsterdam: North Holland Publishing, 1965.

Attinger, E.O., Ed. Pulsatile Blood Flow. New York: McGraw-Hill, 1964.

Bailey, N.T. The Elements of Stochastic Processes with Applications to the Natural Sciences. New York: Wiley & Sons, 1964.

Bailey, N.T. Mathematical Approach to Biology and Medicine. New York: Wiley & Sons, 1967.

Bailey, N.T. The Mathematical Theory of Epidemics. New York: Hafner Publishing Co., 1957.

Bailey, N.T. The Mathematical Theory of Genetic Linkage. Oxford: Clarendon Press, 1961.

Baker, H.G., and Stebbins, G.L., Eds. Symposium on the Genetics of Colonizing Species. New York: Academic Press, 1964.

Balakrishnan, A.V., Ed. Advances in Communication Systems. London: Academic Press, Vol. 1, 1965; Vol. 2, 1966.

Baldwin, E. Dynamic Aspects of Biochemistry. London: Cambridge University Press, 1957.

Barker, D., Ed. Symposium on Muscle Receptors. Hong Kong: Hong Kong University Press, 1962.

Bartlett, M.S. Introduction to Stochastic Processes. London: Cambridge University Press, 1955.

Bartlett, M.S. Stochastic Population Models in Ecology and Epidemiology. London: Metheun, 1960.

Bell, D.A. Intelligent Machines: An Introduction to Cybernetics. New York: Wiley & Sons, 1958.

Bell, E. Molecular and Cellular Aspects of Development. New York: Harper and Row, 1967.

Bellman, R. Adaptive Control Processes: A Guided Tour. Santa Monica: The RAND Corporation, 1961.

Bellman, R.; Kagiwada, H.H.; Kalaba, R.E.; Prestrud, M.C. Invariant Imbedding and Time-Dependent Transport Processes. New York: American Elsevier, 1964.

Bender, M.B., Ed. The Oculomotor System. New York: Harper and Row, 1964.

Berge, C. The Theory of Graphs and its Applications. London: Metheun, 1966.

Bertalanffy, L. von. Modern Theories of Development: An Introduction to Theoretical Biology. London: Oxford, 1933. Reissued New York: Harper and Row, 1962.

Bharucha-Reid, A.T. Elements of the Theory of Markov Processes and Their Applications. New York: McGraw-Hill, 1960.

Van Birgeijk, W.A.; Pierce, J.R.; David, E.E. Waves and the Ear. Garden City, New Jersey: Doubleday, 1960.

Blumberg, B.S., Ed. Proceedings of the Conference on Genetic Polymorphisms and Geographic Variations in Disease. New York: Grune & Stratton, 1961.

Bourne, G.H., Ed. The Structure and Function of Muscle. New York: Academic Press, 1960.

Boyer, P.D.; Lardy, H.; Myrbäck, K., Eds. The Enzymes. New York: Academic Press, 1959.

Brachet, J., and Mirsky, A.E., Eds. The Cell. New York: Academic Press, 1960.

Brennan, M.S., and Simpson, W.L., Eds. Biological Interactions in Normal and Neoplastic Tissue. Boston: Little, Brown and Co., 1962.

Brillouin, L. Science and Information Theory. New York: Academic Press, 1956.

Britton, J.E., and Kushner, H.J. Reference Bibliography: Adaptive or Self-Optimizing Control Systems. Cambridge: M.I.T. Press, 1961.

Burns, B.D. The Mammalian Cerebral Cortex. London: Edward Arnold, Ltd., 1958.

Burton, A.C. Physiology and Biophysics of the Circulation: An Introductory Text. Chicago: Year Book Publishers, 1965.

Bush, R.R.; Abelson, R.P.; Hyman, R. Mathematics for Psychologists, Examples and Problems. Washington, D.C.: Social Sciences Research Council, 1956.

Bush, R.R., and Estes, W.K., Eds. Studies in Mathematical Learning Theory. Stanford, California: Stanford University Press, 1959.

Bush, R.R., and Mosteller, F. Stochastic Models for Learning. New York: Wiley & Sons, 1955.

Cairns, J.; Stent, G.; Watson, J.D., Eds. Phage and the Origins of Molecular Biology. New York: Cold Springs Harbor Laboratory of Quantitative Biology, 1966.

Campbell, D.P. Process Dynamics. New York: Wiley & Sons, 1958.

Casey, E.J. Biophysics: Concepts and Mechanisms. New York: Reinhold Publishing Co., 1962.

Chang, S.S.L. Synthesis of Optimal Control Systems. New York: McGraw-Hill, 1961.

Christensen, H.N. Biological Transport. New York: Benjamin Publishers, 1962.

Ciba Foundation Symposia. Proceedings.

Clark, L.G., and Medawar, P.B., Eds. Essays on Growth and Form. Oxford: Clarendon Press, 1945.

Clarke, H.T., and Nachmansohn, D., Eds. Ion Transport Across Membranes.

New York: Academic Press, 1954.

Cold Spring Harbor Symposia on Quantitative Biology. Proceedings.

Comar, C.L., and Bronner, F. Mineral Metabolism. New York: Academic Press, 1960.

Comroe, J.H. The Lung. Chicago: The Year Book Publishers, 1962.

Comroe, J.H. Physiology of Respiration. Chicago: The Year Book Publishers, 1965.

Conferences on Control Technology. Proceedings.

Copley, A.L., and Stainsby, G., Eds. Flow Properties of Blood and Other Biological Systems. New York: Pergamon Press, 1960.

Cox, D.R., and Miller, H.D. The Theory of Stochastic Processes. New York: Wiley & Sons, 1965.

Crank, J. The Mathematics of Diffusion. London: Oxford University Press, 1956.

Creese, R. Recent Advances in Physiology. Boston: Little, Brown, and Co., 1963.

Culbertson, J.T. Consciousness and Behavior: A Neural Analysis of Behavior and Consciousness. Dubuque, Iowa: W.C. Brown, 1950.

Cunningham, D.J.C., and Lloyd, B.B., Eds. The Regulation of Human Respiration. Philadelphia: F.A. David, 1963.

Dahlberg, G. Mathematical Methods for Population Genetics. New York: Interscience Publishers, 1948.

Davidson, J.N., and Cohn, W.E., Eds. Progress in Nucleic Acid Research and Molecular Biology. New York: Academic Press, 1964.

Defares, J.G., and Sneddon, I.N. An Introduction to the Mathematics of Medicine and Biology. Chicago: Year Book Publishers, 1960.

Doebelin, E.O. Dynamic Analysis and Feedback Control. New York: McGraw-Hill, 1962.

DuNouy, D.L. Biological Time. New York: Macmillan, 1937.

Annual Conferences on Engineering Medicine and Biology. Proceedings.

Falconer, D.S. Introduction to Quantitative Genetics. New York: Ronald Press, 1960.

Farley, F.J.M. Elements of Pulse Circuits. London: Methuen, 1962.

Feldman, W.M., and Smith, C.A.B. Biomathematics: The Principles of Mathematics for Students of Biological Science. London: Griffin, 1954.

Feller, W. An Introduction to Probability Theory and its Applications. New York: Wiley & Sons, Vol. 1, 1957; Vol. 2, 1966.

Field, J., Ed. Handbook of Physiology. Washington, D.C.: American Physiological Society, 1959.

Fields, W.S., and Abbott, W., Eds. Information Storage and Neural Control: Proceedings of the 10th Annual Meeting, Houston Neurological Society. Springfield, Illinois: Charles C. Thomas, 1963.

Finney, D.J. Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve. Cambridge: English Universities Press, 1952.

Fisher, R.A. The Genetical Theory of Natural Selection. New York: Dover, 1958.

Fisher, R.A. The Theory of Inbreeding. Edinburgh: Oliver and Boyd, 1949.

Fishman, A.P., Ed. Symposium on the Plasma Membrane. New York: New York Heart Association, Inc., 1962.

Fisz, M. Probability Theory and Mathematical Statistics. New York: Wiley & Sons, 1967.

Florey, E., Ed. Nervous Inhibition. New York: Pergamon, 1962.

Fogg, G.E., Ed. The State and Movement of Water in Living Organisms. New York: Academic Press, 1965.

Fox, W.S., Ed. The Origins of Pre-Biological Systems and of Their Molecular Matrices. New York: Academic Press, 1965.

Frey-Wyssling, A. Deformation and Flow in Biological Systems. Amsterdam: North Holland Publishing, 1952.

Friedberg, C.K., Ed. Progress in Cardiovascular Diseases. New York: Grune & Stratton, 1964.

Gause, G.F. The Struggle for Existence. Baltimore: Williams & Wilkins, 1934.

Geldard, F.A., Ed. Communication Processes. New York: Pergamon, 1965.

George, F.H. Cybernetics and Biology. San Francisco: W.H. Freeman, 1965.

George, F.H. The Brain as a Computer. Oxford: Pergamon, 1961.

Gerard, R.W., Ed. Information Processing in the Nervous System. Amsterdam: Excerpta Medica Foundation, 1964.

Gergely, J., Ed. Biochemistry of Muscle Contraction. Boston: Little, Brown and Co., 1964.

Giese, A.C. Cell Physiology. Philadelphia: W.B. Saunders, 1962.

Glasser, O., Ed. Medical Physics. Chicago: The Year Book Publishers, Vol. 1, 1944; Vol. 2, 1950; Vol. 3, 1960.

Graham, C.H., Ed. Vision and Visual Perception. New York: Wiley & Sons, 1965.

Granit, R. Receptors and Sensory Perception. New Haven: Yale University Press, 1955.

Gray, J.S. Pulmonary Ventilation and Physiological Regulation. Springfield, Illinois: Charles C. Thomas, 1950.

Grodins, F.S. Control Theory and Biological Systems. New York: Columbia University Press, 1963.

Gurland, J., Ed. Stochastic Models in Medicine and Biology. Madison: University of Wisconsin Press, 1964.

Hagen, W.E., Ed. Readings in Population and Community Ecology. Philadelphia: W.B. Saunders, 1964.

Haldane, J.B.S. A Mathematical Theory of Natural and Artificial Selection. London: Cambridge University Press, 1924.

Harris, J.D. Transport and Accumulation in Biological Systems. New York: Academic Press, 1956.

Himsworth, H.P., and Godber, Eds. Mathematics and Computer Science in Biology and Medicine. London: H.M. Stationery Office, 1965.

Hinshelwood, C.N. The Chemical Kinetics of the Bacterial Cell. Oxford: Clarendon, 1946.

Hodgkin, A.L. The Conduction of the Nervous Impulse. Springfield, Illinois: Charles C. Thomas, 1964.

Hogben, L.T. An Introduction to Mathematical Genetics. New York: W.W. Norton, 1946.

Householder, A., and Landahl, H.D. Mathematical Biophysics of the Central Nervous System. Bloomington, Indiana: Principia Press, 1945.

Hughes, G.M., Ed. Homeostasis and Feedback Mechanisms. London: Cambridge University Press, 1964.

Iberall, A.S. Study of the General Dynamics of the Physical-Chemical System in Mammals. Washington, D.C.: NASA Contract Report CR-129, October, 1964.

Jepsen, G.L.; Simpson, G.G.; Mayr, E., Eds. Genetics, Paleontology, and Evolution. Princeton, New Jersey: Princeton University Press, 1949.

Johnson, F.H.; Eyring, H.; Polissary, M.J. The Kinetic Basis of Molecular Biology. New York: Wiley & Sons, 1954.

Jones, R.W. Some Properties of Physiological Regulators: Automation and Remote Control. London: Butterworth, 1961.

Kalmus, H. Regulation and Control in Living Systems. New York: Wiley & Sons, 1966.

Katchalsky, A., and Curran, P.F. Nonequilibrium Thermodynamics. Cambridge: Harvard University Press, 1965.

Kemeny, J.G.; Snell, L.J.; Thompson, G.L. Introduction to Finite Mathematics. Englewood Cliffs, New Jersey: Prentice-Hall, 1956.

Kemeny, J.G., and Snell, J.L. Mathematical Models in the Social Sciences. New York: Blaisdell, 1962.

Kleinzeller, A., and Kotyk, A., Eds. Membrane Transport and Metabolism. New York: Academic Press, 1961.

Lack, D. The Natural Regulation of Animal Numbers. Oxford: Clarendon Press, 1954.

Lang, R.D.; Kavaler, F.; Roberts, J. Factors Influencing Myocardial Contractility. New York: Academic Press, 1967.

Langhaar, H.L. Dimensional Analysis and the Theory of Models. New York: Wiley & Sons, 1951.

Lawrence, J.H., and Tobias, C.A., Eds. Biological and Medical Physics. New York: Academic Press, 1956.

Lawrence, J.H.; Gofman, J.W.; Hayes, T.L. Advances in Biological and Medical Physics. New York: Academic Press, 1963.

Lekhnitski, S.G. Theory of Elasticity of an Anisotropic Elastic Body. San Francisco: Holden-Day, 1963.

Leondes, C.T., Ed. Advances in Control Systems. New York: Academic Press, 1964.

Levens, A.S. Nomography. New York: Wiley & Sons, 1959.

Li, C.C. Population Genetics. Chicago: University of Chicago Press, 1955.

Ling, G.N. A Physical Theory of the Living State. New York: Blaisdell, 1962.

Lotka, A.J. Elements of Mathematical Biology. New York: Dover, 1956 (reissue of 1925 edition)

Lucas, H.L. The Cullawhee Conference on Training in Bio-Mathematics. Raleigh, North Carolina: Institute of Statistics, North Carolina State College, 1962.

Luneberg, R.K. Mathematical Analysis of Binocular Vision. Princeton, New Jersey: Princeton University Press, 1947.

MacArthur, R., and Connell, J. The Biology of Populations. New York: Wiley & Sons, 1966.

McCulloch, W.S. Finality and Form. Springfield, Illinois: Charles C. Thomas, 1952.

McDonald, D.A. Blood Flow Through Arteries. Baltimore: Williams & Wilkins, 1960.

McElroy, W.H., and Glass, B., Eds. The Mechanism of Enzyme Action. Baltimore: Johns Hopkins University Press, 1954.

McLennan, H. Synaptic Transmission. Philadelphia: W.B. Saunders, 1963.

Macmillan, R.H. Nonlinear Control Systems Analysis. New York: Macmillan, 1962.

Martin, R.B. Introduction to Biophysical Chemistry. New York: McGraw-Hill, 1964.

Massarik, F., and Ratoosh, P. Mathematical Explorations in Behavioral Science. Homewood, Illinois: Dorsey Press, 1965.

Mather, K. Elements of Biometry. London: Metheun, 1967.

Mechanization of Thought Process. London: H.M. Stationery Office, 1958.

Medicine and Electronics, International Conferences on. Proceedings. London: I.E.E.

Milhorn, H.T. The Application of Control Theory to Physiological Systems. Philadelphia: W.B. Saunders, 1966.

Mill, C.C., Ed. Rheology of Disperse Systems. New York: Pergamon, 1959.

Milsun, J.H. Biological Control Systems Analysis. New York: McGraw-Hill, 1966.

Mishkin, E., and Braun, L., Eds. Adaptive Control Systems. New York: McGraw-Hill, 1961.

National Research Council of Canada. Modern Control Theory Seminar: Proceedings. Ottawa, Canada: The Queen's Printer, 1963.

Murphy, Q.R., Ed. Metabolic Aspects of Transport Across Cell Membranes. Madison: University of Wisconsin Press, 1957.

Nahikian, H.M. A Modern Algebra for Biologists. Chicago: University of Chicago Press, 1964.

von Neumann, J. Cerebral Mechanics in Behavior. New York: Wiley & Sons, 1951

Newton, G.C.; Gould, L.A.; Kaiser, J.F. Analytical Design of Linear Feedback Controls. New York: Wiley & Sons, 1957.

Ochs, S. Elements of Neurophysiology. New York: Wiley & Sons, 1965.

Oncley, J.L., et al. Biophysical Science--A Study Program. New York: Wiley & Sons, 1959.

Oster, G., and Pollister, A.W. Physical Techniques in Biological Research. New York: Academic Press, 1962.

Parzen, E. Probability Theory and its Applications. San Francisco: Holden-Day, 1962.

Parzen, E. Stochastic Processes. San Francisco: Holden-Day, 1962.

Paul, W.M.; Daniel, E.E.; Kay, C.M.; Monckton, G.G., Eds. Muscle. New York: Pergamon, 1965.

Paynter, H.M. Analysis and Design of Engineering Systems. Cambridge: M.I.T. Press, 1960.

Peacocke, A.R., and Drysdale, R.D. The Molecular Basis of Heredity. London: Butterworth, 1965.

Perkel, D.H. Neurophysiological Models: Methods and Applications. Santa Monica: The RAND Corporation, RM-4247-NIH, 1965.

Peterson, E.L. Statistical Analysis and Optimization of Systems. New York: Wiley & Sons, 1961.

Pincus, G., Ed. Recent Progress in Hormone Research. New York: Academic Press, 1962.

Pitts, R.F. Physiology of the Kidney and Body Fluids. Chicago: The Year Book Publishers, 1963.

Pollock, S.V., and Sterling, T. Computers and the Life Sciences. New York: Columbia University Press, 1965.

Pullman, B., and Pullman, A. Quantum Biochemistry. New York: Interscience Publishers, 1963.

Quastler, H. The Emergence of Biological Organization. New Haven: Yale University Press, 1964.

Quastler, H., and Augenstine, L., et al., Eds. Essays on the Use of Information Theory in Biology. Urbana: University of Illinois Press, 1953.

Quastler, H., and Morowitz, J., Eds. National Biophysics Conference Proceedings. New Haven: Yale University Press, 1959.

Ramsey, J.A., and Wigglesworth, V.B., Eds. The Cell and the Organism. London: Cambridge University Press, 1961.

Randall, J.E. Elements of Biophysics. Baltimore: Williams and Wilkins, 1963.

Rashevsky, N. Advances and Applications of Mathematical Biology. Chicago: University of Chicago Press, 1940.

Rashevsky, N. Mathematical Biophysics: Physico-Mathematical Foundations of Biology. New York: Dover, 1960.

Rashevsky, N. Physical-Mathematical Aspects of Biology. New York: Academic Press, 1962.

Rashevsky, N. Some Medical Aspects of Mathematical Biology. Springfield; Illinois: Charles C. Thomas, 1964.

Rasmussen, W.F., and Windle, T., Eds. Neural Mechanisms of the Auditory and Vistibular Systems. Springfield, Illinois: Charles C. Thomas, 1960.

Reiner, J.M. Behavior of Enzyme Systems. Minneapolis: Burgess Publishing, 1959.

Reiner, J.M. The Organism as an Adaptive Control System. Englewood Cliffs, New Jersey: Prentice-Hall, 1967.

Remington, J., Ed. Tissue Elasticity. Washington, D.C.: American Physiological Society, 1957.

Rescigno, A., and Segre, G. Drug and Tracer Kinetics. New York: Blaisdell, 1965.

Richards, O.W. Analysis of Constant Differential Growth Ratio. Washington, D.C.: Carnegie Institute, Lortugus Laboratory Papers, 1936.

Riegel, J.A. Energy, Life and Animal Organization. London: English Universities Press, 1966.

Riggs, D.S. The Mathematical Approach to Physiological Problems: A Critical Primer. Baltimore: Williams and Wilkins, 1963.

Rodahl, K., and Horvath, S., Eds. Muscle as a Tissue. New York: McGraw-Hill, 1962.

Rosen, R. Optimality Principles in Biology. London: Butterworth, 1966.

Rosenblith, W.A., Ed. Processing Neuroelectric Data. Cambridge: M.I.T. Press, 1961.

Rosenblith, W.A., Ed. Sensory Communication. Cambridge: M.I.T. Press, 1961.

Ruch, T.C., and Patton, H.D. Physiology and Biophysics. Philadelphia: W.B. Saunders, 1965.

Rushmer, R.F. Cardiovascular Dynamics. Philadelphia: W.B. Saunders, 1961.

Schull, W.J., Ed. Genetic Selection in Man: Third Macy Conference on Genetics. Ann Arbor: University of Michigan Press, 1963.

Setlow, R.B., and Pollard, E.C. Molecular Biophysics. Reading, Massachusetts: Addison-Wesley, 1962.

Shanes, A.M., Ed. Biophysics of Physiological and Pharmacological Actions. Washington, D.C.: American Association for the Advancement of Science, 1961.

Shannon, C.E., and Weaver, W. The Mathematical Theory of Communication. Urbana: The University of Illinois Press, 1949.

Shedlovsky, D., Ed. Electrochemistry in Biology and Medicine. New York: Wiley & Sons, 1955.

Sheppard, C.W. Basic Principles of the Tracer Method: Introduction to Mathematical Tracer Kinetics. New York: Wiley & Sons, 1962.

Simpson, G.; Gaylord, A.R.; Lewantin, R.C. Quantitative Zoology. New York: Harcourt, Brace, 1960.

Sleigh, M.A. The Biology of Cilia and Flagella. London: Pergamon, 1962.

Slobodkin, L.B. Growth and Regulation of Animal Populations. New York: Holt, Rinehart, and Winston, 1961.

Smith, A.G., Ed. Communication and Culture. New York: Holt, Rinehart and Winston, 1966.

Smith, C.A.B. Biomathematics: Algebra, Geometry, Calculus, Vol. 1. New York: Hafner, 1966.

Smith, O.J.M. Feedback Control Systems. New York: McGraw-Hill, 1958.

Snell, F.M. Biophysical Principles of Structure and Function. Reading, Massachusetts: Addison-Wesley.

Society for Experimental Biology. Symposia. (particularly, Models and Analogues in Biology, 4, 1960. London: Cambridge University Press.)

Society for the Study of General Systems. General Systems Yearbooks.

Sommerhoff, G. Analytical Biology. London: Oxford University Press, 1950.

Srb, A.M., and Oven, R.D. General Genetics. San Francisco: W.H. Freeman, 1953.

Stacy, R.W., and Waxman, B., Eds. Computers in Biomedical Research. New York: Academic Press, 1965.

Stacy, R.W.; Williams, D.T.; Worden, R.E.; McMorris, R.O. Essentials of Biological and Medical Physics. New York: McGraw-Hill, 1955.

Stern, C. Principles of Human Genetics. San Francisco: W.H. Freeman, 1960.

Stibitz, G.R. Mathematics in Medicine and the Life Sciences. Chicago: Yearbook Publishers, 1966.

Stohlman, F., Ed. The Kinetics of Cellular Proliferation. New York: Grune & Stratton, 1959.

Stubberud, Allen R. Analysis and Synthesis of Linear Time-Variable Systems. Berkeley: University of California Press, 1964.

Symposium in Applied Mathematics. Mathematical Problems in the Biological Sciences, XIV (1962). Providence, Rhode Island: American Mathematical Society.

Symposium on Active Networks and Feedback Systems. Proceedings. New York: Polytechnic Press, 1960.

Tasaki, I. Nervous Transmission. Springfield, Illinois: Charles C. Thomas, 1956.

Thrall, R.M.; Coombs, C.H.; Davis, R.L., Eds. Decision Processes. New York: Wiley & Sons, 1954.

Thompson, D'Arcy. On Growth and Form. London: Cambridge University Press, 1952. (Abridged edition, Bonnor, Ed., 1961.)

Trimmer, J.D. Response of Physical Systems. New York: Wiley & Sons, 1950.

Troshin, A.S. Problems of Cell Permeability. London: Pergamon, 1966 (translated from Russian (1956) edition).

Truxal, J.G. Automatic Feedback Control System Synthesis. New York: McGraw-Hill, 1955.

Waddington, C.H. The Strategy of the Genes. London: Macmillan, 1957.

Wallace, B., and Dobzhansky, T.G. Radiation, Genes and Man. New York: Holt, Rinehart, and Winston, 1959.

Waterman, T.H., and Morowitz, H.J., Eds. Theoretical and Mathematical Biology. New York: Blaisdell, 1965.

Watt, K.E., Ed. Systems Analysis in Ecology. New York: Academic Press, 1966.

Weibel, E.R. Morphometry of the Human Lung. New York: Academic Press, 1963.

Wiener, N. Cybernetics: or Control and Communication in the Animal and the Machine. Cambridge: M.I.T. Press, 1961.

Wiener, N., and Schade, J.P., Eds. Nerve, Brain, and Memory Models. Amsterdam: Elsevier, 1963.

Wiener, N., and Schade, J.P., Eds. Progress in Biocybernetics. Amsterdam: Elsevier, 1964.

Woodger, J.H. The Axiomatic Method in Biology. Cambridge: English Universities Press, 1937.

Wooldridge, D.E. The Machinery of the Brain. New York: McGraw-Hill, 1963.

Yamamoto, W.S., and Brobeck, J.R., Eds. Physiological Controls and Regulations. Philadelphia: W.B. Saunders, 1965.

Yockey, H.P.; Platzman, R.L.; Quastler, H., Eds. Symposium on Information Theory in Biology. Gatlinburg, Tennessee, 1956. New York: Pergamon, 1958.

Yovits, M.C.; Jacobs, G.T.; Goldstein, G.D. Self Organizing Systems. Washington, D.C.: Spartan Books, 1962.

Acta Physiological Scandinavica

Advances in Biological and Medical Physics

American Journal of Physiology

Annals of the New York Academy of Science

Australian Journal of Experimental Biology and Medical Science

Behavioral Science

Bell System Technical Journal

Biochemica et Biophysica Acta

Biochemical and Biophysical Research Communications

Biological Reviews

Biophysical Journal

Biorheology

Bioscience (formerly A.I.B.S. Bulletin)

Brookhaven Sumposia on Biology

Bulletin of Mathematical Biophysics

Communications in Behavioral Biology (Vol. 1, 1968)

Computers and Biomedical Research

Currents in Modern Biology

Genetics

Heredity

Human Factors

Human Organization

Information and Control

I.B.M. Journal of Research and Development

I.B.M. Systems Journal

I.E.E.E. Proceedings

I.E.E.E. Spectrum

I.E.E.E. Transactions on Information Theory

International Symposia on Quantitative Biology

Journal of the Acoustical Society of America

Journal of Applied Behavioral Science

Journal of General Physiology

Journal of Genetics

Journal of Mathematical Psychology

Journal of Molecular Biology

Journal of Physiology

Journal of Theoretical Biology

Kybernetik

Kybernetika

Life Sciences

Management Science

Mathematical Reviews

Mathematical Biosciences

New Biology

Perspectives in Biology and Medicine.

Physiological Review

Proceedings, National Academy of Science

Proceedings, Royal Society, Series B (London)

Progress in Biophysics and Biophysical Chemistry

Psychometric Monographs

Psychometrika

Science

Transactions of the Faraday Society