Mathl Comput. Modelling, Vol. 11, pp. 546–551, 1988
Printed in Great Britain

0895-7177/88 $3.00 + 0.00
Pergamon Press plc

INTRODUCTION TO S-SYSTEMS AND THE UNDERLYING POWER-LAW FORMALISM

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Abstract. A novel approach to the development of an appropriate formalism for representing organizationally complex systems began in the mid 1960's with a search for a general systematic formalism that would retain the essential nonlinear features and that would still be amenable to mathematical analysis. The set of nonlinear differential equations that most closely approached this goal was called an "S-system", because it accurately captures the saturable and synergistic properties intrinsic to biological and other organizationally complex systems. In the early 1980's it was found that essentially any nonlinear differential equation composed of elementary functions could be recast *exactly* as an S-system. Thus, S-systems may be considered a canonical form with the ability to represent an enormous variety of nonlinear differential equations. This has given rise to new strategies for the mathematical modeling of nonlinear systems.

Keywords. Canonical nonlinear forms; differential equations; organizationally complex systems; strategies for nonlinear modeling; synergistic systems.

INTRODUCTION

A set of ordinary nonlinear differential equations of the following form has been defined as an S-system because of its ability to capture the essential saturable and synergistic characteristics of biological and other organizationally complex systems (Savageau, 1969b; 1979; 1985).

$$dX_i/dt = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \qquad i=1,\ldots,n \quad (1)$$

The variables of the system X_i are positive real, the multiplicative ("rate constant") parameters α_i and β_i are non-negative real, and the exponential ("kinetic order") parameters g_{ij} and h_{ij} are real. The system is autonomous if $m=0$, but when there are independent variables ("forcing functions") present $m>0$. These equations have remarkable properties that recommend them for the modeling of complex nonlinear systems.

S-systems consist of a simple collection of mathematical elements that nonetheless is sufficient to represent an enormous range of nonlinear phenomena in nature, as we shall see shortly. These elements are: (1) derivatives, (2) power-law functions, (3) products, and (4) differences. Where did this particular form originate and what is the basis for its justification?

THE POWER-LAW FORMALISM

Background

In searching for an appropriate general formalism to characterize biological and other organizationally complex systems one cannot help being influenced by the paradigm of linear systems. The linear formalism is attractive because it is a general symbolic formalism, because there are powerful mathematical methods for analysis, and because there are cases of successful application in a variety of fields. However, it has distinct disadvantages in that it cannot adequately represent most biological systems, which are nonlinear. Nevertheless, even in cases for which it is inappropriate as a representation, linear mathematics provides us with useful tools for analysis and a guide in our search for analogous nonlinear techniques.

The only widely used nonlinear approach to biological systems is that provided by the Michaelis-Menten Formalism. This approach too has its attractions. It has been shown to provide a good approximation for many specific processes, and there are well-recognized procedures for estimating the parameter values in simple cases. One of the principal disadvantages lies in the fact that it is not a general formalism -- general in the sense that there is an explicit mathematical structure within which all the special cases are contained. Each system must be developed on an *ad hoc* basis. Such systems are difficult to analyze symbolically and to compare with alternatives; furthermore, computer implementation is unsystematic and conventional general-purpose algorithms often are expensive to run. For further discussion see Savageau (1972; 1976) and Voit & Savageau (1987).

Derivation

Fruitful development of a general nonlinear formalism -- general in the sense given above -- that would retain many of the advantages of these existing alternatives began with the hint that rational functions, which provide a good representation for many processes, often can be approximated over a wide range by a straight line in a log-log plot (Bode, 1945). This property suggested the Power-Law Formalism (Savageau, 1969a; b), analogous to the Linear Formalism, based on Taylor's Theorem but in a logarithmic space (Savageau, 1972). Thus, the rate of a process is approximated by the first two terms of its Taylor series in logarithmic space.

$$\log v_i(X_1,\ldots,X_n) = \log v_i(X_{1O},\ldots,X_{nO}) + \sum_{j=1}^{n} \frac{\partial [\log v_i(X_{1O},\ldots,X_{nO})]}{\partial [\log X_j]} (\log X_j - \log X_{jO}) + \ldots \quad (2)$$

where $v_i(X_1,\ldots,X_n)$ is the rate of the process in question, and the X_j's are variables that affect the process. The additional "O" subscript signifies evaluation about a given operating point, and, in the case of derivatives, evaluation at the operating point after performing the appropriate partial differentiation. By regrouping terms, Eqn. (2) can be rewritten as

$$\log v_i(X_1,\ldots,X_n) = \log \alpha_i + g_{i1} \log X_1 + \ldots + g_{in} \log X_n \quad (3)$$

and then, when it is transformed back into Cartesian coordinates, expressed as a product of power-law functions

(Savageau, 1969b).

$$v_i(X_1,...,X_n) = \alpha_i \prod_{j=1}^{n} X_j^{g_{ij}} \quad (4)$$

where

$$g_{ij} = (\log v_{iO})/(\log X_j) = (v_{iO}/X_j)(X_{jO}/v_{iO}) \quad (5)$$

and

$$\alpha_i = v_{iO} \prod_{j=1}^{n} X_{jO}^{-g_{ij}} \quad (6)$$

It should be emphasized that this formalism is valid for any function and for all types of variables, provided the logarithmic derivatives exist and the excursions of the variables about their nominal values are small. (Later, in the "Recasting" section, we shall see that this representation also can describe systems whose variables exhibit large excursions.)

Alternative Representations for Systems

There are a variety of hierarchical levels at which systems can be described by this formalism (Savageau, 1969a; b; 1979; 1985). At each of these levels, comparisons with experimental data show that this Power-Law Formalism is accurate over a surprisingly wide range of variation in concentrations *in vivo* [e.g., see (Savageau, 1976; Voit & Savageau, 1982a)].

For example, suppose we have a system given by the following equations:

$$dX_i/dt = \sum_r v_{+ir} - \sum_s v_{-is} \qquad i=1,..,n \quad (7)$$

where there are a number of rate processes (the positive terms v_{+ir}) that lead to an increase in X_i and a number rate processes (the negative terms v_{-is}) that lead to a decrease in X_i. At one level, each process can be represented as a product of power-law functions, and the resulting equations become

$$dX_i/dt = \sum_r \alpha_{ir} \prod_{j=1}^{n+m} X_j^{g_{ijr}} - \sum_s \beta_{is} \prod_{j=1}^{n+m} X_j^{h_{ijs}} \qquad i=1,...,n \quad (8)$$

There is one equation for each of the n dependent variables, which may be thought of as variables "internal" to the system, there are m independent variables, which may be thought of as "external" variables that are determined by factors outside the system of interest (e.g., by the experimentalist, the environment, or other systems within the same organism), and the summation in each case is over the relevant processes.

At another level, one first could aggregate the individual processes into two net processes, one for the positive terms in Eqn. (7) and one for the negative terms, and then represent each of these by a product of power-law functions. The resulting equations become

$$dX_i/dt = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \qquad i=1,...,n \quad (9)$$

This is the S-system representation described in the first section.

It must be emphasized that these two representations -- Eqn. (8) and Eqn. (9) -- are equally valid for infinitesimal variations about a steady state for the system (Voit & Savageau, 1987). Nevertheless, as we shall see, there are distinct advantages to aggregation in the form of Eqn. (9).

Algebraic Constraints

Algebraic constraints among the variables of a system are treated in the Power-Law Formalism no differently than the descriptions of the component processes themselves (Savageau, 1969b; 1979). In general,

$$X_t = X_t(X_1,...,X_j,...) \quad (10)$$

and the constraint expression is represented in the Power-Law Formalism as

$$X_t = \gamma_t \prod_j X_j^{f_{tj}} \quad (11)$$

where

$$f_{tj} = (\partial X_{tO}/\partial X_j)(X_{jO}/X_{tO}) \quad (12)$$

and

$$\gamma_t = X_{tO} \prod_j X_{jO}^{-f_{tj}} \quad (13)$$

A common example is

$$X_t = \sum_j X_j \quad (14)$$

where the sum over the relevant dependent variables is an aggregate variable; in general the function need not be a simple sum. It may be considered an independent variable of the system or it might be a dependent variable; in either case, each such constraint reduces by one the number of differential equations for the system (Eqn. 9) [See Savageau (1979) for details.]. For the specific case in Eqn. (14), note that the exponent f_{tj} is simply the fraction of the aggregate represented by X_{jO} in the steady state, i.e., $f_{tj} = X_{jO}/X_{tO}$.

We shall not deal explicitly with such algebraic constraints in this paper because, as indicated above, systems with these types of constraints can be reformulated and then treated in exactly the same fashion as systems without such constraints.

ADVANTAGES OF S-SYSTEM REPRESENTATION

There is no way of obtaining an explicit steady-state solution for the general balance or conservation equations [e.g., Eqn. (1) in Savageau (1969b)] that characterize a system when these involve arbitrary nonlinear rate laws. Even specific numerical solutions are not always feasible for such equations. These severe difficulties for any general theory are overcome with the Power-Law Formalism, provided one chooses an appropriate form of aggregation.

In steady state, the time derivatives are equal to zero, and the S-system [Eqn. (9)] can be written in conventional matrix notation as

$$[A]y] = b] \quad (15)$$

where

$y_i = \log X_i$

$b_i = \log(\beta_i/\alpha_i)$

$a_{ij} = g_{ij} - h_{ij}$

In the other representations there is no simple algebraic equivalent to Eqn. (15); e.g., the logarithmic transformation of Eqn. (8) does not produce a linear system because of the form of aggregation used.

Existence theorem

A system described by Eqns. (9) and (15) has a positive steady-state solution provided

$$\text{rank } [A] = n \tag{16}$$

If the system is autonomous (i.e., it has no independent variables), then Eqn. (16) can be expressed as

$$|A| \neq 0 \tag{17}$$

where $|A|$ is the determinant of the matrix [A]. Thus, an nxn determinant of the differences between the corresponding exponential parameters (kinetic orders) for net increase and net decrease -- and only these parameters -- determines whether or not a positive steady-state solution for the system will exist (Savageau, 1969b).

In the other representations, e.g. Eqn. (8), there is no corresponding existence theorem that can be obtained explicitly in a general symbolic form for the steady-state solutions.

Explicit solutions

When the existence theorem is satisfied, Eqn. (15) can be solved to yield the "internal" (or dependent) variables as an explicit function of the parameter values and the "external" (or independent) variables of the system (Savageau, 1971):

$$y]_{in} = [L]y]_{ex} + [M]b] \tag{18}$$

where $y]_{in}$ and $y]_{ex}$ are vectors whose elements are the logarithms of the internal and external variables, [L] and [M] are matrices determined by inversion of the underdetermined system in Eqn. (15) and composed of elements that are functions only of the exponential parameters, and $b]$ is a vector whose elements are functions only of the multiplicative parameters (rate constants) (c.f. Eqn. 15).

From Eqn. (9) and the solution in Eqn. (18) the net rates follow trivially. From the general symbolic solution in Eqn. (18) one can calculate directly systemic properties and exhibit their relation to the parameters of the underlying molecular mechanisms, as was first shown by Savageau (1971). These same systemic or global properties also can be obtained graphically from appropriate experimental data plotted in log-log coordinates (Savageau, 1971; 1976).

In the other representations, steady-state solutions cannot be obtained explicitly in a general symbolic form analogous to Eqn. (18), but only numerically in specific cases, and this may not always be feasible.

Telescopic properties

It has been realized for decades that complex systems exhibit not only organizational (or structural) hierarchies but also temporal hierarchies, because of the wide spectrum of relaxation times that characterize such systems. Consciously or unconsciously, one studies systems at one hierarchical level and often attempts to relate behavior at this level to that at adjacent levels. For this one requires a formalism that is capable of representing different hierarchical levels and that retains its mathematical character as one focuses upon more refined component behavior or upon larger aggregates of systems behavior. I have called this the "telescopic" property (Savageau, 1985).

When the first k variables of the S-system are temporally dominant and the remaining n-k variables have relaxed to a quasi-steady state, then the last n-k variables can be obtained algebraically in terms of the first k variables. These quasi-steady state relationships can be substituted back into the first k dynamical equations to obtain k equations having exactly the same S-system form as the original n equations [e.g, see (Savageau, 1976 Ch 15; 1979; 1985)]. Conversely, one can take any subsystem in quasi-steady state and expand it into a full dynamic model and the resulting equations for the entire system again will have exactly the same S-system form.

Linear systems also possess this telescopic property. Michaelis-Menten systems (characterized by rational function nonlinearities), on the other hand, do not. If one attempts to solve for the relaxed variables in this case, one can obtain transcendental functions. When these are substituted back into the temporally dominant equations, these will no longer have the same form as the original system of equations.

Accuracy

In spite of the mathematical advantages possessed by the S-system representation, one might continue to use other representations if they had some overriding practical advantage such as accuracy of representation. This after all is the motivation for going beyond the Linear Formalism in search of a general nonlinear formalism.

We have therefore examined in some detail the relative accuracy of the Linear Formalism, the S-system representation, and alternative representations within the Power-Law Formalism (Savageau, 1969b; Voit & Savageau, 1987). The results can be summarized as follows. Processes for which the change in rate is a monotonically decreasing (or increasing) function of the variables (e.g., Michaelis-Menten rate laws) are always represented more accurately by power law than linear functions. Processes for which the change in rate increases, goes through an inflection and then decreases as a function of the variables (e.g., Hill rate laws) are in some cases best modeled by power-law functions, in other cases by linear functions. Aggregation of processes and representation in the S-system form almost always improves the accuracy over the alternative power-law representation with such aggregation. This improvement in accuracy is one of several factors that contribute to the wide range of validity of S-system representations. Other contributing factors have been discussed elsewhere (Savageau, 1976).

Efficiency of dynamic solutions

Although the steady-state solutions in the S-system representation are readily obtained, the dynamic solutions pose a more substantial difficulty. Explicit solutions have been obtained for a subclass of the n=2 case (Voit & Savageau, 1984) that is important because almost all of the growth laws and probability distribution functions fall within this class (Savageau, 1979; 1982). A general explicit solution for S-systems appears to be impossible because they include as special cases well-known functions, such as the elliptical equations, which have no solution in terms of elementary mathematical functions (Courant, 1955). For these reasons we have focused attention on the development of efficient algorithms for solving S-systems numerically.

It was shown that the logarithmic transformation not only facilitates the steady-state solution, but also improves the efficiency of dynamic solutions (Savageau, 1970). A package of interactive programs for numerical solution and graphical display were developed for IBM-type mainframe computers during the 1970's, for the most part utilizing available numerical methods. These programs have greatly facilitated the analysis of S-system models [e.g, see (Voit & Savageau, 1982a;b)].

More recently, we have gone back to first principles and designed a numerical integration algorithm specifically for S-systems (Irvine & Savageau, submitted). Tests to date show that this algorithm is typically one to two orders of magnitude faster than other state-of-the-art general purpose algorithms. The S-system algorithm is particularly efficient for large systems requiring high accuracy. This and other algorithms designed specifically for S-systems have been incorporated into a user-friendly interactive package called ESSYNS that runs efficiently on the IBM-PC microcomputer (Irvine & Savageau, submitted). These S-system algorithms, when coupled with the results discussed in the next section, provide an new approach to efficient general purpose solution of nonlinear differential equations.

RECASTING NONLINEAR EQUATIONS IN CANONICAL S-SYSTEM FORM

The applications of S-systems and the Power-Law Formalism prior to 1976 were largely restricted to biochemical and genetic systems with relatively few variables. While on sabbatical in Goettingen during 1976-77 I began to consider large complex systems and the analogy to statistical mechanics. Suppose the S-system representation is a reasonable description of the elements in a large complex system, in much the same way that Newtonian mechanics applied to point masses undergoing elastic collisions is a reasonable description of the molecules in a gas. What would be the implications for the macroscopic behavior of the system? Would the inaccuracies in the local descriptions "average out" and accurately predict phenomenological laws, analogous to the the gas laws, on the macroscopic level? The discovery that a great many nonlinear functions could be recast *exactly* as S-systems was a by-product of this line of investigation.

The most common macroscopic behavior of biological and other organizationally complex systems is growth. Abundant experimental data is available and numerous phenomenological growth laws have been developed to account for these data. Could these well-known growth laws be deduced from the essential characteristics of the elemental processes as represented by their S-system description? By assuming only S-system descriptions and a limited number of temporally dominant processes, one could show that the macroscopic behavior of the intact system also would be described by an S-system with a limited number of variables. It then became necessary to show that all the well-established growth laws were special cases of a general growth law consisting of a low dimensional S-system. This was done in the fall of 1977. The principal tool was the chain rule of differentiation, which takes composite functions and decomposes them into products of simpler functions. These results were summarized in two papers (Savageau, 1979; 1980). A third paper (Savageau, 1982) extended these results to probability distribution functions, which are closely related to growth laws.

By the early 1980's many additional specific cases of recasting were discovered, and, although a few of these were reported [e.g., (Savageau & Voit, 1982)], most have never been published. The recasting of equations that contain sums of terms had been accomplished in various *ad hoc* ways, but it was not until 1985 that a systematic procedure for reducing sums was developed in our laboratory by Eberhard Voit. It then became clear that linear systems are special cases of S-systems, and that there are a number of equivalent nonlinear canonical forms including S-systems, Generalized Mass Action systems (arbitrary sums of products of power-law functions), Half systems (S-systems with α_i or $\beta_i = 0$ for all i), Binary systems (Half systems with all exponents either 1 or 0), and Volterra systems (Voit & Savageau, 1986). Peschel & Mende (1986) independently have come to the same conclusions.

Our algorithm for recasting can be stated in terms of three rules that are applied iteratively:

1. Translocate all variables into the positive orthant
2. Decompose composite functions into products of power-law functions by the chain rule of differentiation
3. Reduce sums of products of power-law functions by the product rule of differentiation.

With these methods one can recast any nonlinear function composed of elementary functions, or nested elementary functions of elementary functions. For further information see Savageau & Voit (1987).

This concludes my brief overview of recasting; this topic will be treated more fully in the following paper by Dr. Voit.

STRATEGIES FOR NONLINEAR MODELING WITH S-SYSTEMS

We have seen that S-systems arise in two different contexts: in the exact recasting of known nonlinear functions, and in the approximate nonlinear representation of unknown (or known) processes. In each domain, questions of modeling strategy present themselves because one always has a variety of S-systems from which to chose.

Variations in Recasting

As a simple example, consider the conventional Monod equations for microbial growth in a chemostat:

$$\begin{aligned} dX_1/dt &= \alpha_1 X_1X_2/(X_2+1) - X_1 & X_1(0) &= X_{10} \\ dX_2/dt &= (X_r - X_2) - \beta_2 X_1X_2/(X_2+1) & X_2(0) &= X_{20} \end{aligned} \qquad (19)$$

where X_1 is concentration of cells in the chemostat, X_2 is concentration of growth-determining substrate normalized with respect to the Monod constant K_2, X_r is the constant concentration of X_2 in the reservoir normalized with respect to K_2, time is normalized with respect to the dilution rate D of the chemostat, α_1 is the exponential growth rate constant for the cells when substrate concentration is in excess, and β_2 is α_1 divided by the yield coefficient Y [see Pirt (1975) for details].

As discussed previously (Savageau & Voit, 1982), these equations can be recast exactly into an S-system by letting $X_2 + 1 = X_3$ and $X_r - X_2 = X_4$.

$$\begin{aligned} dX_1/dt &= \alpha_1 X_1X_2X_3^{-1} - X_1 & X_1(0) &= X_{10} \\ dX_2/dt &= X_4 - \beta_2 X_1X_2X_3^{-1} & X_2(0) &= X_{20} \\ dX_3/dt &= X_4 - \beta_2 X_1X_2X_3^{-1} & X_3(0) &= X_{20}+1 \\ dX_4/dt &= \beta_2 X_1X_2X_3^{-1} - X_4 & X_4(0) &= X_r - X_{20} \end{aligned} \qquad (20)$$

Alternatively, one could let $X_2 = X_4X_5$ and $(X_2+1)^{-1} = X_6X_7$ and the following S-system would be obtained:

$$\begin{aligned} dX_1/dt &= \alpha_1 X_1X_4X_5X_6X_7 - X_1 & X_1(0) &= X_{10} \\ dX_4/dt &= X_rX_5^{-1} - X_4 & X_4(0) &= X_{20} \\ dX_5/dt &= -\beta_2 X_1X_5X_6X_7 & X_5(0) &= 1 \\ dX_6/dt &= \beta_2 X_1X_4X_5X_6^3X_7^2 - X_rX_6^2X_7 & X_6(0) &= (X_{20}+1)^{-1} \\ dX_7/dt &= X_4X_5X_6X_7^2 & X_7(0) &= 1 \end{aligned} \qquad (21)$$

For detailed considerations of recasting equations by this method see Savageau & Voit (1987). There are other alternatives to Eqn. (20), but Eqn. (21) is sufficient for the purposes of this introduction.

In each case, recasting has increased the number of variables. This may be considered analogous to the conversion of a single nth order differential equation into n first-order differential equations by introducing new variables for the higher derivatives. This increase in number of variables may be seen as the price one pays for reducing the rational function nonlinearities to the simpler canonical form involving a product of power-law functions. It also implies a cost in terms of efficiency of numerical solution. However, this cost is more than recouped by efficiencies in ESSYNS, an algorithm designed for solution of equations in the S-system canonical form. Dr. Irvine will have more to say on this topic in a subsequent paper.

The first method has several attractive features. (1) The original variables X_1 and X_2 are retained in the recast equations. (2) The behavior of the original system on the two-dimensional plane corresponds to the behavior of the recast

system on a two-dimensional manifold within the four-dimensional space. (3) The nonzero stable steady state of the original system is preserved as a rest point of the recast system. A notable disadvantage of this method is that one must have the insight to define new variables in such a way that the extra sums in the original equation are avoided and that all the variables are nonnegative. Such choices are generally not obvious.

The second method of recasting can be done according to a straightforward prescription [see (Savageau & Voit, 1987)]; this is its principal virtue. On the other hand, it has a number of disadvantages. (1) There is one extra variable in the recast system and one of the original variables (X_2) is no longer present explicitly. (2) Although the behavior of the recast system still is exhibited on a two-dimensional manifold within the five-dimensional space (Savageau & Voit, 1987), this is not as obvious as it is in the first method. (3) The nonzero stable steady state of the original system now corresponds to a "stable steady-state trajectory" in the recast system. By this I mean the following. Different initial conditions X_{10},X_{20} lead to different trajectories for the recast system, but as time increases these trajectories all approach a "stable steady-state trajectory" asymptotically. This trajectory corresponds to increasing values of X_5 and decreasing values of X_4 such that X_4X_5 = constant $[=(\alpha_1-1)^{-1}]$, increasing values of X_7 and decreasing values of X_6 such that X_6X_7 = constant $[=(\alpha_1-1)/\alpha_1]$, and a fixed value of X_1 $[=\alpha_1\beta_2^{-1}(\alpha_1-1)^{-1}(\alpha_1X_r-X_r-1)]$.

At this point there is no definitive strategy for recasting that is optimal. This is a topic for further study.

Various Approximations

All mathematical models of the real world are approximations to some degree. One generally cannot claim to know exactly the "actual" process under study. Thus, there are various approximate representations of a system in the Power-Law Formalism that yield different mathematical solutions. These different representations are the result of different strategies for aggregating the elemental processes before making the power-law approximation.

One of the most common issues in modeling networks such as biochemical pathways is the treatment of branch points. In the simplest case of diverging pathways X_1 is converted to two different products X_2 and X_3

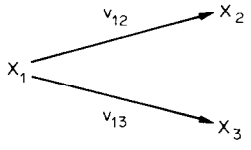

Fig. 1. Model of a diverging branch point.

The net rate of utilization of X_1 can be formulated as

$$V_{net} = v_{12} + v_{13} \tag{22}$$

where v_{ij} is the rate of the process converting X_i to X_j.

In the Power-Law Formalism without aggregation, each process is represented by an individual power-law function.

$$V_{net} = \alpha_2 X_1^{g_{21}} + \alpha_3 X_1^{g_{31}} \tag{23}$$

Alternatively, one can aggregate the two rate processes v_{12} and v_{13} into a single mathematical function and then represent the net process in the Power-Law Formalism.

$$V_{net} = \beta_1 X_1^{h_{11}} \tag{24}$$

This difference in representation gives rise to Generalized Mass Action systems in the case of Eqn. (23) and to S-systems in the case of Eqn. (24) (see also the "Alternative Representations" subsection).

In the "Advantages" section, reasons were given for preferring the S-system to the Generalized Mass Action representation. In the present context we are interested in which is more accurate. Recent results (Voit & Savageau, 1987) have shown that the aggregate representation [Eqn. (24)] is more accurate than the representation without aggregation [Eqn. (23)]. Similar results have shown that aggregation of converging processes also leads to greater accuracy (Voit & Savageau, 1987).

Another common issue in modeling biochemical pathways is the explicit treatment of reversible processes.

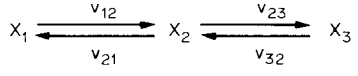

Fig. 2. Model of a reversible process.

Without aggregation, each irreversible process is represented by one power-law function:

$$dX_2/dt = \alpha_1 X_1^{g_1} - \beta_1 X_2^{h_1} - \beta_3 X_2^{h_3} + \alpha_3 X_3^{g_3} \tag{25}$$

With aggregation there are several alternatives. One could aggregate v_{12} with v_{32} and v_{21} with v_{23}, and then form the power-law representation:

$$dX_2/dt = \alpha_2 X_1^{g_{21}} X_3^{g_{23}} - \beta_2 X_2^{h_{22}} \tag{26}$$

Each of these two aggregations involving irreversible processes is of the type considered in Voit & Savageau (1987), and thus one can expect that this aggregate representation [Eqn. (26)] would be more accurate than the case without any aggregation [Eqn. (25)].

One also could aggregate v_{12} with v_{21} and v_{23} with v_{32}, and thus consider the change in X_2 to result from the difference between net influx from X_1 and net outflux to X_3.

$$dX_2/dt = \alpha_2 X_1^{g_{21}} X_2^{g_{22}} - \beta_2 X_2^{h_{22}} X_3^{h_{23}} \tag{27}$$

This situation is quite different from those treated previously because differences rather than sums of positive-valued functions are being aggregated.

The point I wish to make here is that reversible pathways can be aggregated in a large variety of ways. The question is whether it is advantageous to aggregate at all and, if so, which types of aggregation yield the best results. Dr. Sorribas has been exploring these questions and we shall hear about his interesting results in another paper.

NEW TOOLS FOR THE ANALYSIS OF S-SYSTEMS

There is no fully developed nonlinear systems theory currently available. However, the identification of a canonical form for nonlinearities seems to be an important step in initiating the development of such a theory, which would provide the basis for a general classification of differential equations and for the development of general techniques for treating nonlinear differential equations with analytical or numerical methods. As yet, such general techniques are known only for linear systems, one reason being that no unifying structural form was known that included arbitrary nonlinear equations as special cases. However, I wish to mention two recent examples of

methodological development along these lines that already have significant practical implications for nonlinear modeling with S-systems.

I made reference in an earlier subsection to an efficient numerical algorithm for the solution of S-systems (ESSYNS) that has been developed in our laboratory by Dr. Irvine. It is not surprising that this algorithm is generally superior to existing methods for the numerical solution of this class of problems, often one to two orders of magnitude faster. Usually, what one gains by such specificity, one loses in terms of general applicability. However, because a wide range of nonlinear equations can be recast exactly as S-systems, ESSYNS is in fact a general purpose method. It compares favorably with other state-of-the-art general purpose methods. It seems to be particularly advantages for the solution of large systems requiring stringent tolerances. In such cases it can be as much as 100-times faster than other methods (Savageau & Voit, 1987).

Parameter estimation is another important area with practical implications for nonlinear modeling with S-systems. It has long been known that when the elements of a systems governed by power-law functions can be studied in isolation, one can estimate the relevant parameters by simple linear regression in a log-log plot (Savageau, 1971; 1972). Similarly, when one can determine the necessary parameter sensitivities and transfer functions by making measurements on the intact system in a series of steady states, it is possible to estimate the underlying parameters of the S-system model [e.g., (Savageau *et al.*, 1987b)]. However, there is more information to be had from the dynamic responses of a system, and in the more general situation, where a system does not exhibit simple steady-state behavior, it becomes essential to estimate parameters from the system's dynamic behavior. Although we made some early attempts in this direction (Voit & Savageau, 1982a; b), and although the results proved satisfactory for the particular system of interest, the approach has certain limitations that restrict its general utility. Dr. Johnson has been addressing the estimation problem in S-systems and we shall hear about the results of his efforts in a paper elsewhere in this volume.
We are convinced that there are still rich opportunities here if one were to focus specifically upon the canonical S-system form and develop methods that work reliably and efficiently for this class of functions. In analogy with progress that has previously been made using this philosophy, one might expect to make significant improvements for this specific functional form and, by recasting, to make these improvements available to a wider class of problems.

CONCLUDING REMARKS

In this introduction I have tried to deal briefly with some of the larger overall issues related to mathematical modeling with the canonical S-system form for nonlinear functions. I began with the definition of an S-system as a set of ordinary nonlinear differential equations. I reviewed the origins of these systems: (1) the Power-Law Formalism, which represents a local linear approximation in a logarithmic space, and (2) the Recasting process, by which nonlinear functions composed of arbitrary combinations of elementary functions are transformed into an S-system with equivalent mathematical solution. I then turned to evaluation of the various modeling strategies that are available using S-systems and the Power-Law Formalism. Finally, I alluded to goals for the future. I indicated that the S-system canonical form provides a focus that could lead to the development of a nonlinear systems theory. One example was given of how this focus already has led to the development of a new class of efficient general purpose algorithms for the numerical solution of nonlinear differential equations. Another example, parameter estimation, was used to indicate the need for new analytical and numerical tools for analyzing S-system models.

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