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Automated Solutions of Breathing Pattern Optimizations

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Abstract—A numerical procedure which allows the convenient exploration of various optimization hypotheses of breathing pattern regulation is described. The method is based on the calculus of variations and uses a novel technique for the automatic evaluation of all required derivatives. Advantages of this approach include: exact calculation of all derivatives, parsimonious computer code, and speed of execution. By eliminating the need for hand calculation of derivatives, a major reduction was made in the tedium involved in exploring various optimization strategies. Examples are presented of determining the optimal breathing pattern characteristics for minimum work or force (pressure) required for breathing, based on linear and nonlinear models of respiratory mechanics. The developed procedure can be used to predict the optimal volume-time trajectory and breathing frequency which minimizes a criterion function subject to constraints.

INTRODUCTION

Beginning with the pioneering work of Rohrer [1], respiratory physiologists have been interested in explaining the characteristics of breathing pattern regulation by optimization. Rohrer assumed a criterion of minimum external work of breathing to explain how respiratory frequency changed with the level of minute ventilation. Otis, Fenn, and Rahn [2] extended this hypothesis to include a flow dependent resistance to breathing. A different criterion based on forcing pressure amplitude was studied by Mead [3] and judged to better explain human and animal breathing rates from rest to exercise.

In a more recent work, Yamashiro and Grodins [4] found it possible to use the minimum work criterion to explain the volume-time trajectory of breathing as well as the breathing rate. Predictions of the volume-time trajectory based on an optimization criterion have also been made by Ruttiman and Yamamoto [5] and Hamalainen and Viljanen [6].

A major obstacle to the more widespread exploration of these optimization hypotheses lies in the difficulties in obtaining solutions to optimization models. The earlier models involved only a single variable (respiratory frequency) and constrained the form of the trajectory (sinusoidal or square wave). This required only differentiation for getting a solution. Consideration of the optimal volume-time trajectory requires the solution of the Euler-Lagrange equation and consid-

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erably more mathematical sophistication for either a closed form or a numerical solution. What is needed is a simplified but reliable approach which would minimize the mathematical tedium of exploring optimization models. This would make it possible for a respiratory physiologist to focus on the consequences of different optimization hypotheses rather than on the solution details. The purpose of the present paper is to fulfill this objective. The focus here is on the formulation requirements for the use of a FORTRAN computer program (available from the authors) which incorporates automated solutions.

METHODS

Predictions of the optimal breathing pattern which minimizes the work or force requirements of a breath can be cast as a problem in the calculus of variations. The volume-time trajectory $V(t)$ which minimizes an objective function

$$J = \int_0^{T_I} F(t, V, \dot{V})\, dt \tag{1}$$

is desired where the initial condition is $V(0) = 0$ (initial volume) and $\dot{V}$ is the airflow. The final values $V(T_I) = V_T$ (tidal volume), and T_I (inspiratory duration) will be treated as constants. Since both final values are fixed, this is considered a Type 1 problem. The first requirement is the specification of the function F. While the requirement of the integral in equation (1) may appear restrictive at first glance, it comes up naturally for some criteria as will be shown later, and it can be considered to describe constraints of neural processing. Neurons operate by summation of synaptic inputs which are integrated by a membrane potential.

Minimization of (1) requires the solution of the Euler-Lagrange condition

$$F_V - \frac{dF_{\dot{V}}}{dt} = 0, \tag{2}$$

where $F_V = \dfrac{\partial F}{\partial V}$ and $F_{\dot{V}} = \dfrac{\partial F}{\partial \dot{V}}$ (∂ indicates partial differentiation). Equation (2) constitutes a second order differential equation which has the initial $V(0)$ and final $V(T_I)$ conditions specified. The need for multiple derivative evaluations becomes obvious from the second term of equation (2), which according to the chain rule of differentiation is

$$\frac{dF_{\dot{V}}}{dt} = F_{\dot{V}t} + F_{\dot{V}V}\, \dot{V} + F_{\dot{V}\dot{V}}\, \ddot{V}, \tag{3}$$

where $F_{\dot{V}t} = \dfrac{\partial^2 F}{\partial \dot{V} \partial t}$, $F_{\dot{V}V} = \dfrac{\partial^2}{\partial \dot{V} \partial V}$, $F_{\dot{V}\dot{V}} = \dfrac{\partial^2 F}{\partial \dot{V}^2}$, and $\ddot{V} = \dfrac{d^2 V}{dt^2}$ (volume acceleration). The mathematical tedium represented by equation (3) was eliminated by the incorporation of a new procedure for automatic calculation of derivatives [7]. This technique allows for an exact derivative evaluation in a numerically efficient manner.

A specific example will be used to illustrate the approach. Consider the function:

$$z = x + \ln xy. \tag{4}$$

The evaluation of z, z_x, z_y, and z_{xx} for given values of x and y can be accomplished sequentially as shown in Table 1.

Table 1. Example of derivative evaluation.

Variable	$\frac{\partial}{\partial x}$	$\frac{\partial}{\partial y}$	$\frac{\partial^2}{\partial x^2}$
$A = x$	$A_x = 1$	$A_y = 0$	$A_{xx} = 0$
$B = y$	$B_x = 0$	$B_y = 1$	$B_{xx} = 0$
$C = A\,B$	$C_x = A_x\,B + A\,B_x$	$C_y = A_y\,B + A\,B_y$	$C_{xx} = A_{xx}\,B + 2A_x\,B_x + A\,B_{xx}$
$D = \ln C$	$D_x = \frac{C_x}{C}$	$D_y = \frac{C_y}{C}$	$D_{xx} = \frac{-C_x^2}{C^2} + \frac{C_{xx}}{C}$
$Z = A + D$	$Z_x = A_x + D_x$	$Z_y = A_y + D_y$	$Z_{xx} = A_{xx} + D_{xx}$

Each row in Table 1 can be coded as a separate **FORTRAN** subroutine with the calling sequence proceeding from the top of the table to the bottom. In this way, any arbitrary function can be similarly handled in terms of combinations of subroutine calls provided the function can be broken down to standard operations such as shown in the first column of Table 1. Higher order partial derivatives can be simply added by adding additional columns to the table. Partial derivatives up to the third order were required for solution of the present optimization problem.

Solution of the differential equation of equation (2) subject to initial and final conditions must be done by iteration. A Newton-Raphson iterative procedure was used for this purpose [7].

By using the automated procedure, one can avoid the mathematical complications of dealing with the solution details defined by equations (2) and (3). It is only necessary to input the objective function and parameter values, as will now be illustrated by several simple examples.

Case 1. Work of Breathing

We begin with the simplest formulation of the breathing pattern optimization, as first studied by Rohrer. An inspiration of volume V_T is to be made during time duration T_I. The force or pressure P_m supplied by the inspiratory muscles is opposed by resistive R_{rs} and elastic C_{rs} mechanical elements as described by the equation

$$P_m = R_{rs}\,\dot{V} + \frac{V}{C_{rs}}, \tag{5}$$

where V is the instantaneous volume and $\dot{V}$ the airflow. The work required for an inspiration is

$$W_{in} = \int_0^{V_T} P_m\,dV = \int_0^{T_I} P_m\,\dot{V}\,dt = \int_0^{T_I} \left(R_{rs}\,\dot{V} + \frac{V}{C_{rs}}\right)\dot{V}\,dt. \tag{6}$$

equation (6) constitutes the main requirement for use of the automated solution method. Given the inputs

$$\begin{aligned} V(0) &= 0, \\ V(T_I) &= V_T, \qquad \text{and} \\ F &= \left(R_{rs}\,\dot{V} + \frac{V}{C_{rs}}\right)\dot{V}, \end{aligned} \tag{7}$$

the computer program solves for V as a function of time t. Note that numerical values for all parameters (V_T, T_I, R_{rs}, C_{rs}) must also be supplied. The **FORTRAN** program user inputs required for defining this problem is shown in Table 2.

Table 2. FORTRAN code user inputs for Case 1.

User Input	Purpose
TIMEINIT=0	Define initial time
TIMEEND = T_I	Define final time
XINITAL=0	Define initial condition
XEND=V_T	Define final condition
CON1= R_{rs}	Define constant value
CON2=$\frac{1}{C_{rs}}$	Define constant value
CALL CONST(CON1,D1)	Stores CON1 and partial derivatives into vector D1
CALL CONST(CON2,D2)	Stores CON2 and partial derivatives into vector D2
CALL MULT(D1,C,D3)	Forms product $R_{rs}\,\dot{V}$ and partial derivatives and stores values in D3 (vector C corresponds to $\dot{V}$)
CALL MULT(D2,B,D4)	Forms product $\frac{V}{C_{rs}}$ and partial derivatives and stores values in D4 (vectorB corresponds to V)
CALL ADD(D3,D4,D5)	Forms the sum $R_{rs}\,\dot{V} + \frac{V}{C_{rs}}$ and partial derivatives and stores values in D5
CALL MULT(D5,C,F1)	Forms the product $\left(R_{rs}\,\dot{V} + \frac{V}{C_{rs}}\right)$ and partial derivatives and stores values in F1

Case 2. Mean Squared Pressure

The criterion used by Mead [3] was based on average peak pressure requirements of the respiratory muscles. This criterion was felt to correspond to muscle energetic costs such as oxygen consumption and was motivated by the failure of the work criterion to place a cost on isometric muscle activity. Mean squared pressure is a convenient way to place a cost on peak pressure, and based on equation (5), it is

$$J = \int_0^{T_I} P_m^2 \, dt = \int_0^{T_I} \left(R_{rs} \dot{V} + \frac{V}{C_{rs}} \right)^2 dt. \tag{8}$$

The required F for this case is

$$F = \left(R_{rs} \dot{V} + \frac{V}{C_{rs}} \right)^2. \tag{9}$$

The `FORTRAN` user input required for describing equation (9) is identical to Case 1 except for the last instuction listed in Table 2. The last instruction must be replaced by:

```
CALLMULT(D5,D5,F1).
```

Cases 3 and 4. Volume Dependent Resistance

These cases were chosen to illustrate the ease of handling more realistic but analytically difficult problems. Resistance of the lungs is known to vary inversely with the lung volume. This requires a non-linear term for R_{rs} such as

$$R_{rs} = \frac{K}{A + V}, \tag{10}$$

where K and A are empirical constants. For Case 3, equation (10) was used with the work criterion, resulting in a F value of

$$F = \left(\frac{K \dot{V}}{A + V} + \frac{V}{C_{rs}} \right) \dot{V}. \tag{11}$$

The `FORTRAN` user input required for this case is similar to Cases 1 and 2 except that a division subroutine `DIV(U,V,W)` must be used where `U`=numerator, `V`=denominator of the quotient, and `W` contains the stored outputs.

For Case 4, equation (10) was used with the mean squared pressure criterion, which required a F of

$$F = \left(\frac{K \dot{V}}{A + V} + \frac{V}{C_{rs}} \right)^2. \tag{12}$$

Cases 3 and 4 present no additional difficulties using the automated solution approach, but lead to difficult, if not impossible problems to solve in closed form. Other known sources of nonlinearities, such as flow dependent resistance change or volume dependent elasticity can be handled with equal ease.

RESULTS

The predicted optimal volume-time trajectories for all cases are shown in Figures 1–4. Case 1 results in a linear volume-time trajectory, which corresponds to constant airflow or a rectangular airflow pattern shape as shown in Figure 1.

This solution is easily derived from the Euler-Lagrange relation or other approaches [1,5] in closed form. Here, the obvious agreement of the automated and analytically derived solution serves as a validation of the method. Predictions for Case 2 are shown in Figure 2.

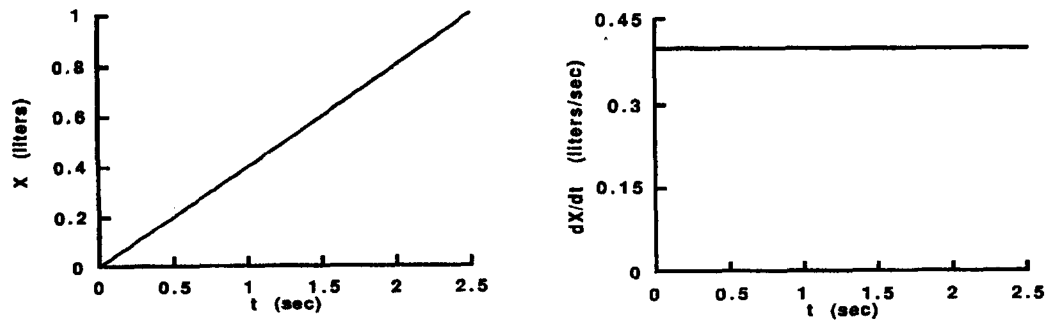

Figure 1. Volume and flow predictions for Case 1.

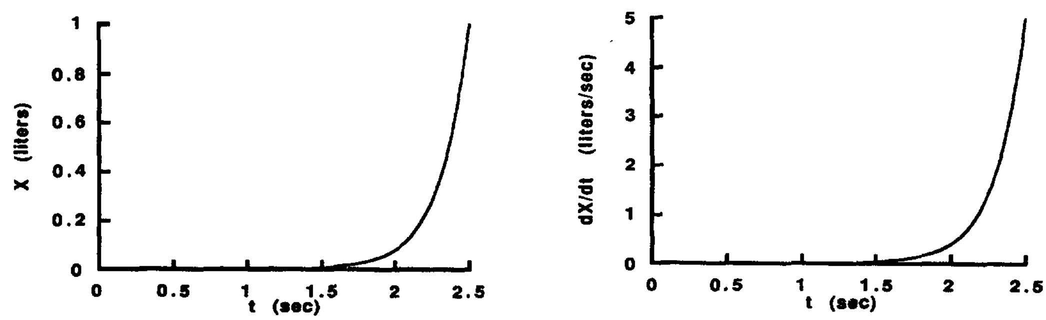

Figure 2. Volume and flow predictions for Case 2.

Case 2 can also be solved in closed form from the Euler-Lagrange relationship resulting in

$$V = \alpha \sinh\left(\frac{t}{R_{rs}\, C_{rs}}\right), \tag{13}$$

where $\alpha = \dfrac{V_T}{\sinh(T_I/R_{rs}\, C_{rs})}$. Comparison of equation (13) with the automated solutions show complete agreement. For this reason, an explicit comparison is not made in the figure. Predictions for Cases 3 and 4 are shown in Figures 3 and 4, respectively.

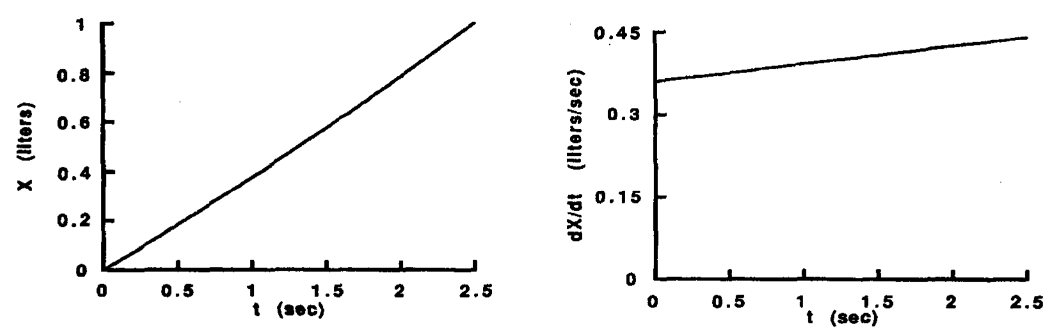

Figure 3. Volume and flow pedictions for Case 3.

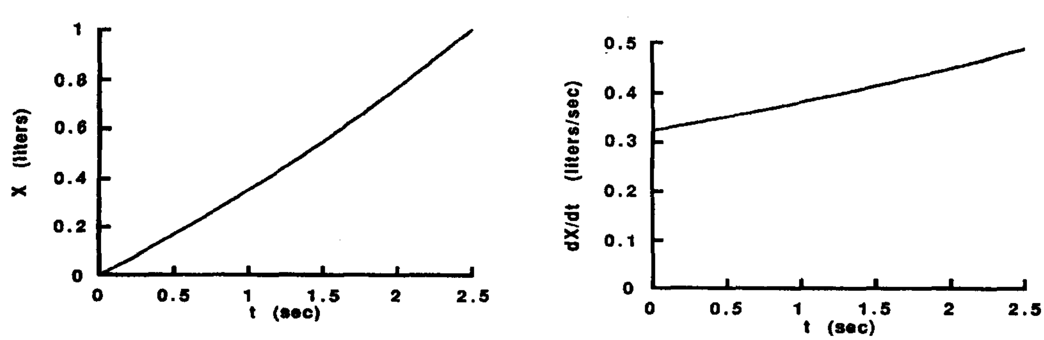

Figure 4. Volume and flow predictions for Case 4.

Cases 3 and 4 have no known closed form solutions so can only be compared to the other two cases. The solutions will be given as a function of the assumed parameter values, but some generalizations can be made. A decrease in resistance with increasing volume leads to an optimal strategy of delaying flow and volume changes. A work criterion with nonlinear resistance (Case 3) gives predictions qualitatively similar to the minimum mean squared pressure case (Case 2).

DISCUSSION

The pioneering efforts of Rohrer [1], Otis, Fenn and Rahn [2], and Mead [3] led to fruitful experimental investigations of the regulation of respiratory frequency according to an optimization hypothesis. Conceptually, other characteristics of breathing pattern, such as the volume-time trajectory can be treated in the same way and some work has been done along these lines [4–6]. However, these investigations have been hampered by the mathematical difficulties of dealing with realistic models and associated nonlinearities. The automated solution methodology outlined here eliminates most of the mathematical tedium involved without sacrificing accuracy. The cases considered were purposely kept simple to stress the basic simplicity of the approach. However, handling more realistic models with additional nonlinearities is easily done by expanding the form of the criterion function F.

Inspiratory duration was treated as a constant here with no consideration of expiration. This again was done in the interest of focusing on the essence of solving this type of problem. There are a variety of ways of handling variable durations and expiration. For example, the durations of inspiration and expiration could be assumed equal and expiration assumed to occur passively, to extend the work criterion to cover a complete breathing cycle. The optimal volume-time trajectory can be solved for a variety of tidal volume-inspiratory duration, V_T-T_I pairs to achieve a given level of alveolar ventilation;

$$V_A = f\,(V_T - V_D),$$

where $f=$ breathing rate, $f = \frac{1}{2T_I}$, $V_D=$ dead space volume, and $V_A=$ alveolar ventilation. The optimal breathing rate can then be determined from the pair that requires the least work.

The specific predictions of the different cases were indended to be more for purposes of illustrating the use of the automated method rather than physiological relevance. Cases 1 and 2 have some connection to previously studied optimality criteria and have closed form solutions which serve as convenient validation runs. Case 1's solution has been previously reported and discussed in terms of successfully predicting airflow pattern shapes during exercise [4]. Case 2's solution results in a different volume-time trajectory which must then be judged to not be consistent with most exercise observations. However, even during exercise, spontaneous deep breaths are observed which resemble such trajectories [8]. These augmented breaths are felt to serve an important gas exchange function and involve different neural circuitry than normal breathing. Thus, both cases may have physiological relevance. Both work and peak pressure have led to breathing rate predictions [2,3] which are in reasonable agreement with exercise data, so consideration of the volume-time predictions offer a means of further testing either hypothesis.

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