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Optimal Inputs for Blood Glucose Regulation Parameter Estimation, Part 3[1]

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Abstract. The estimation of the parameters for blood glucose regulation can be improved by utilizing optimal inputs to enhance the sensitivity of observed data to the unknown parameters. The optimal inputs for a linear two-compartment model were derived previously for the Bolie blood glucose regulation parameters. The design of the optimal inputs involves the maximization of a quadratic performance index subject to an input energy constraint. A Lagrange multiplier is introduced whose value is an unknown constant. An improved method for the numerical determination of the optimal inputs was recently presented in which the Lagrange multiplier is introduced as a state variable and evaluated simultaneously with the optimal input. In this paper, the equations for the optimal inputs are rederived using the improved method, and numerical results are given for both Bolie and Bergman parameters.

Key Words. Optimal inputs, blood glucose regulation, parameter estimation, Newton–Raphson method, Lagrange multipliers, linear two-compartment models.

1. Introduction

The estimation of the parameters of blood glucose regulation was first investigated by Bolie (Ref. 1) utilizing a linear, two-compartment model. Bolie extrapolated experimental data to estimate the magnitude of the parameters for humans and utilized an analog computer to study the blood glucose response to glucose infusion. Ackerman *et al.* (Refs. 2 and 3) used experimental data to estimate the damped natural frequency and the damping constant of blood glucose response to orally administered glucose.

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Similar studies for infused glucose were made by Ceresa *et al.* (Ref. 4) and, more recently, by Segre *et al.* (Ref. 5), who used labeled glucose to obtain better estimates of certain parameters.

This paper is the third by the authors on optimal inputs for blood glucose regulation parameter estimation. In Ref. 6, it is assumed that only one or at most relatively few measurements of blood glucose concentration were to be made. In Ref. 7, it is assumed that several measurements are to be made. Optimal inputs can be utilized to increase the accuracy of the estimated parameters (Refs. 8–18). Increasing the accuracy of the estimated blood glucose regulation parameters yields an improved estimate of the blood glucose response and may have possible clinical application. It may be possible to determine whether or not a patient has diabetes by estimating the magnitude of one or more of the patient's blood glucose regulation parameters.

Traditionally, diabetes is diagnosed by performing a glucose tolerance test wherein glucose is taken orally by the patient and the concentration of glucose in the blood is determined 2 h later. Although standards vary, in general, a patient given 100 g of glucose per kilogram orally who shows a blood glucose concentration 2 h later of 140 mg/100 ml or more is considered diabetic. If the glucose concentration is lower, some other diagnosis will apply. Although the standard glucose tolerance test procedure has been successful in elucidating the severity of diabetes, it has been suggested that alternative patterns of glucose infusion may be more successful in differentiating among the various diabetic states.

Using a linear two-compartment model, the estimation of the parameters for blood glucose regulation can be enhanced by using a glucose infusion input which is optimal in some mathematical sense. The values of the parameters will be different for the diabetic patient from those of an average normal adult. The perturbation equations for blood glucose regulation are given by the simplified linear differential equations (Refs. 1–5)

$$\dot{x}_1 = -ax_1 + bx_2, \tag{1}$$

$$\dot{x}_2 = -cx_1 - dx_2 + y, \tag{2}$$

where x_1 is the deviation of the extracellular insulin concentration from the mean (units/liter), x_2 is the deviation of the extracellular glucose concentration from the mean (g/liter), and y is the rate of glucose intravenous injection [g/(liter $\times$ h)]. It is assumed that the rate of insulin production per gram b is the parameter that is to be estimated. The derivations which follow are given only for the single parameter b, with the values of the other parameters assumed to be known. The equations can easily be modified, however, for the case where any one of the other parameters is unknown, or extended to the case where several parameters are unknown (Ref. 8).

Since b is unknown, an initial estimate of b must be utilized in order to obtain the optimal input. Then, if necessary, utilizing the optimal input with the parameter estimation techniques described in Ref. 15, a new estimate of b is found and the process repeated until a satisfactory estimate of b is obtained.

The numerical determination of the optimal inputs is far from trivial. The performance index for the optimal input is selected such that the sensitivity of the measured state variables to the unknown parameters is maximized, subject to an input energy constraint. The performance index is maximized using Pontryagin's maximum principle. The solution requires the evaluation of a two-point boundary-value problem.

Using a quadratic performance criterion and a scalar example for simplicity, the optimal input is determined such that the integral

$$M=\int_0^T x_b^2(t)\,dt \tag{3}$$

is maximized, subject to the input energy constraint

$$E=\int_0^T y^2(t)\,dt, \tag{4}$$

where

$$x_b(t)=\partial x(t)/\partial b; \tag{5}$$

here, $x(t)$ is a scalar state variable, $y(t)$ is the input, and b is an unknown system parameter. The performance index is maximized via the classical method by the maximization of the integral

$$J=\max\,(1/2)\int_0^T [x_b^2(t)-q(y^2(t)-E/T)]\,dt, \tag{6}$$

where q is the Lagrange multiplier and is equal to a constant. The magnitude of the Lagrange multiplier must be selected such that the input energy constraint is satisfied.

In Ref. 8, Mehra shows that, for a linear system with homogeneous boundary conditions, the solution exists only for certain values of q which are the eigenvalues of the two-point boundary-value problem. The eigenvalues q are functions of the interval length T. For a fixed q, the critical length T' can be determined by the integration of the Riccati-matrix equation. When the elements of the Riccati-matrix equation become very large, the critical length has been reached. By integrating for several values of q, a curve relating q to T can be obtained.

Kalaba and Spingarn show in Ref. 17 that, for a linear system with nonhomogeneous boundary conditions, the performance index increases as the critical length is approached for a given value of q. The desired input energy is obtained by plotting a curve of input energy versus interval length T and finding the value of T corresponding to the desired input energy. The optimal input for a system with homogeneous boundary conditions is nearly identical to that of the system with nonhomogeneous boundary conditions when the input energy is the same and the latter has a small initial condition with terminal time near the critical length.

For both homogeneous and nonhomogeneous boundary conditions, the Lagrange multiplier q must be found by trial and error, such that the input energy constraint is satisfied. In Refs. 19 and 20, a new approach for the numerical determination of optimal inputs is presented. The Lagrange multiplier q is introduced as a state variable. The solution simultaneously yields the optimal input and the value of q for which the input energy constraint is satisfied. The method is applicable to both linear and nonlinear systems.

The optimal inputs for the linear, two-compartment model were given in Ref. 7 for the Bolie blood glucose regulation parameters with terminal time $T=2.32$ h. The equations for the numerical determination of the optimal inputs were derived using the methods described in Refs. 8 and 17. In this paper, the equations are rederived using the improved method (Ref. 20). Numerical results are given for the Bolie parameters for humans with $T=1$ h and for the parameters for dogs derived by Bergman, Kalaba, and Spingarn in Ref. 21.

2. Two-Point Boundary-Value Problem

Equations (1) and (2) can be expressed in vector form by the time-invariant linear system

$$\dot{x}(t)=Fx(t)+Gy(t), \tag{7}$$

where x is a 2×1 state vector, y is a scalar input, and

$$F=\begin{bmatrix}-a & b\\ -c & -d\end{bmatrix}, \tag{8}$$

$$G=\begin{bmatrix}0\\ 1\end{bmatrix}. \tag{9}$$

Assume that the measurements are contaminated with white noise

$$z(t)=Hx(t)+v(t), \tag{10}$$

where $z(t)$ is a scalar measurement and $v(t)$ is a zero-mean Gaussian white noise process,

$$E\{v(t)\}=0,$$
$$E\{v(t)v^T(\tau)\}=R\delta(t-\tau)=\sigma^2\delta(t-\tau), \tag{11}$$

with measurement matrix

$$H=\{0, 1\}. \tag{12}$$

Assume that b is an unknown parameter. Then, the optimal input is to be determined such that the Fisher information matrix (Ref. 8)

$$M=\int_0^{T_f} x_b^T H^T R^{-1} H x_b\, dt \tag{13}$$

is maximized, subject to the input energy constraint

$$\int_0^{T_f} y^2\, dt = E, \tag{14}$$

where x_b is the sensitivity vector defined by

$$x_b=\partial x/\partial b. \tag{15}$$

Equations (13) and (14) are made up of quadratic forms of the sensitivity and the control, the latter being utilized to limit the input dosage. The inverse M^{-1} of the Fisher information matrix is the Cramer–Rao lower bound.

Two performance indices are used (Ref. 20), the performance index J_1,

$$J_1=\max_y (1/2)\int_0^T (x_b^T H^T R^{-1} H x_b - qy^2)\, dt + q(T)E/2, \tag{16}$$

and the performance index J_2,

$$J_2=\max_y (1/2)\int_0^T (x_b^T H^T R^{-1} H x_b - qy^2)\, dt + q(T)E/2 - q^2(0)/2. \tag{17}$$

The performance index J_1 is derived by integrating out the term $qE/2T$ in Eq. (6) and placing the result outside of the integral. The performance index J_2 contains the additional term $-q^2(0)/2$ and is found to have better convergence properties. The equations for the performance index J_1 are derived first, with changes for the performance index J_2 indicated at the end of the next section.

Taking the partial derivative of Eq. (7) with respect to b, we have

$$\dot{x}_b = F x_b + F_b x, \tag{18}$$

where

$$F_b=\partial F/\partial b. \tag{19}$$

The value of the Lagrange multiplier q, for which the input energy constraint (14) is satisfied, can be obtained along with the optimal input by adjoining the differential constraint

$$\dot{q}(t) = 0, \tag{20}$$

with unknown initial condition $q(0)$.

Let χ_A be equal to the 5×1 augmented state vector

$$\chi_A = \begin{bmatrix} x \\ x_b \\ q \end{bmatrix}. \tag{21}$$

Then,

$$\dot{\chi}_A = F_A \chi_A + G_A y, \tag{22}$$

where

$$F_A = \begin{bmatrix} F & 0 & 0 \\ F_b & F & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} -a & b & 0 & 0 & 0 \\ -c & -d & 0 & 0 & 0 \\ 0 & 1 & -a & b & 0 \\ 0 & 0 & -c & -d & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{23}$$

$$G_A = [0, 1, 0, 0, 0]^T. \tag{24}$$

The performance index J_1 is then expressed in the form

$$J_1 = \max_y (1/2) \int_0^T (\chi_A^T H_A^T R^{-1} H_A \chi_A - q y^2)\, dt + q(T)E/2, \tag{25}$$

where

$$H_A = [0, 0, 0, 1, 0]. \tag{26}$$

Utilizing Pontryagin's maximum principle, the Hamiltonian function is

$$\mathscr{H} = (1/2)(-\chi_A^T H_A^T R^{-1} H_A \chi_A + K \chi_A y^2) + p^T (F_A \chi_A + G_A y), \tag{27}$$

where

$$K = [0, 0, 0, 0, 1]. \tag{28}$$

The 5×1 costate vector $p(t)$ is the solution of the vector differential equation

$$\dot{p} = -[\partial \mathscr{H} / \partial \chi_A]^T = H_A^T R^{-1} H_A \chi_A - F_A^T p - K^T y^2/2. \tag{29}$$

The input $y(t)$ that maximizes H is

$$\partial\mathcal{H}/\partial y = K\chi_A y + G_A^T p, \tag{30}$$

$$y = -(1/q)G_A^T p = -(1/q)p_2. \tag{31}$$

When the value of y is substituted into Eqs. (22) and (29), the two-point boundary-value problem becomes

$$\begin{bmatrix} \dot{\chi}_A \\ \dot{p} \end{bmatrix} = \begin{bmatrix} F_A & -(1/q)G_A G_A^T \\ H_A^T R^{-1} H_A & -F_A^T \end{bmatrix} \begin{bmatrix} \chi_A \\ p \end{bmatrix} + \begin{bmatrix} 0 \\ -(1/2q^2)p_2^2 K^T \end{bmatrix}, \tag{32}$$

with boundary conditions

$$\chi_A(0) = \begin{bmatrix} 0 \\ x_2(0) \\ 0 \\ 0 \\ q(0) \end{bmatrix}, \qquad p(T) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -E/2 \end{bmatrix}; \tag{33}$$

where

$x_2(0)$ = an initial condition; for convenience, $x_2(0)$ is set equal to 0.1 for most of the numerical calculations; (34)

$q(0)$ = initial estimate of the unknown Lagrange multiplier q; (35)

$$p_5(T) = (\partial/\partial q)[-qE/2]_{t=T} = -E/2; \tag{36}$$

$$p_5(0) = 0. \tag{37}$$

The unknown initial conditions are $p_1(0)$, $p_2(0)$, $p_3(0)$, $p_4(0)$, $q(0)$.

Equation (32) can be expressed in the form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_{1b} \\ \dot{x}_{2b} \\ \dot{q} \\ \dot{p}_1 \\ \dot{p}_2 \\ \dot{p}_3 \\ \dot{p}_4 \\ \dot{p}_5 \end{bmatrix} = \left[\begin{array}{ccccc|ccccc} -a & b & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -c & -d & 0 & 0 & 0 & 0 & -1/q & 0 & 0 & 0 \\ 0 & 1 & -a & b & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -c & -d & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0 & 0 & 0 & 0 & a & c & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -b & d & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a & c & 0 \\ 0 & 0 & 0 & 1/\sigma^2 & 0 & 0 & 0 & -b & d & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{array}\right] \begin{bmatrix} x_1 \\ x_2 \\ x_{1b} \\ x_{2b} \\ q \\ p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \end{bmatrix} + \begin{bmatrix} 0 \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ -(1/2q^2)p_2^2 \end{bmatrix}, \tag{38}$$

or

$$\dot{\chi} = A\chi + \phi. \tag{39}$$

3. Solution via Newton–Raphson Method

Using the Newton–Raphson method (Ref. 22), the unknown initial conditions are assumed to be given by

$$p_1(0) = C_1, \quad p_2(0) = C_2, \quad p_3(0) = C_3, \quad p_4(0) = C_4, \quad q(0) = C_5. \tag{40}$$

Expanding the boundary conditions

$$p(T, C) = \begin{bmatrix} p_1(T, C) \\ p_2(T, C) \\ p_3(T, C) \\ p_4(T, C) \\ p_5(T, C) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -E/2 \end{bmatrix} \tag{41}$$

in a Taylor's series around the kth approximation, retaining only the linear terms, and rearranging, we have

$$\begin{bmatrix} C_1^{k+1} \\ C_2^{k+1} \\ C_3^{k+1} \\ C_4^{k+1} \\ C_5^{k+1} \end{bmatrix} = \begin{bmatrix} C_1^{k} \\ C_2^{k} \\ C_3^{k} \\ C_4^{k} \\ C_5^{k} \end{bmatrix} - \begin{bmatrix} p_{1c1} & p_{1c2} & \cdots & p_{1c5} \\ p_{2c1} & p_{2c2} & \cdots & p_{2c5} \\ \vdots & \vdots & \cdots & \vdots \\ p_{5c1} & p_{5c2} & \cdots & p_{5c5} \end{bmatrix}^{-1} \begin{bmatrix} p_1(T, C^k) \\ p_2(T, C^k) \\ p_3(T, C^k) \\ p_4(T, C^k) \\ p_5(T, C^k) + E/2 \end{bmatrix}, \tag{42}$$

where

$$p_{icj} = \partial p_i / \partial C_j, \tag{43}$$

$$C = \{C_1, C_2, C_3, C_4, C_5\}^T. \tag{44}$$

The equations for the p_{icj}'s are obtained by differentiating Eq. (39) with respect to the C_i's. One has

$$\dot{\chi}_{ci} = A\chi_{ci} + \phi_{ci}, \qquad i = 1, 2, \ldots, 5, \tag{45}$$

where

$$\chi_{ci} = \partial\chi / \partial C_i, \tag{46}$$

$$\phi_{ci} = (\partial A / \partial C_i)\chi + \partial\phi / \partial C_i = \{0, \phi_{2ci}, 0, 0, 0, 0, 0, 0, 0, \phi_{10ci}\}^T, \tag{47}$$

$$\phi_{2ci} = (1/q^2) q_{ci} p_2, \tag{48}$$

$$\phi_{10ci} = -(1/q^2) p_{2ci} p_2 + (1/q^3) q_{ci} p_2^2. \tag{49}$$

The initial conditions are obtained by differentiating Eqs. (22) and (29). One has

$$\chi_{Aci}(0)=\begin{bmatrix}0\\0\\0\\0\\\delta_{5i}\end{bmatrix},\qquad p_{ci}(0)=\begin{bmatrix}\delta_{1ci}\\\delta_{2ci}\\\delta_{3ci}\\\delta_{4ci}\\0\end{bmatrix}, \tag{50}$$

where

$$\begin{aligned}\delta_{jci}&=0, & j&\neq i,\\ \delta_{jci}&=1, & j&=i.\end{aligned} \tag{51}$$

Equations (32) and (45) can be expressed in the matrix form

$$\dot{Z}=AZ+\Phi, \tag{52}$$

where

$$Z=\begin{bmatrix} x_1 & x_{1c1} & x_{1c2} & x_{1c3} & x_{1c4} & x_{1c5}\\ x_2 & x_{2c1} & x_{2c2} & x_{2c3} & x_{2c4} & x_{2c5}\\ x_{1b} & x_{1bc1} & x_{1bc2} & x_{1bc3} & x_{1bc4} & x_{1bc5}\\ x_{2b} & x_{2bc1} & x_{2bc2} & x_{2bc3} & x_{2bc4} & x_{2bc5}\\ q & q_{c1} & q_{c2} & q_{c3} & q_{c4} & q_{c5}\\ p_1 & p_{1c1} & p_{1c2} & p_{1c3} & p_{1c4} & p_{1c5}\\ p_2 & p_{2c1} & p_{2c2} & p_{2c3} & p_{2c4} & p_{2c5}\\ p_3 & p_{3c1} & p_{3c2} & p_{3c3} & p_{3c4} & p_{3c5}\\ p_4 & p_{4c1} & p_{4c2} & p_{4c3} & p_{4c4} & p_{4c5}\\ p_5 & p_{5c1} & 5_{5c2} & p_{5c3} & p_{5c4} & p_{5c5} \end{bmatrix}, \tag{53}$$

$$\Phi=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0\\ 0 & \phi_{2c1} & \phi_{2c2} & \phi_{2c3} & \phi_{2c4} & \phi_{2c5}\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ \phi_{10} & \phi_{10c1} & \phi_{10c2} & \phi_{10c3} & \phi_{10c4} & \phi_{10c5} \end{bmatrix}. \tag{54}$$

The initial conditions are

$$Z(0)=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ x_2(0) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ C_5 & 0 & 0 & 0 & 0 & 1 \\ C_1 & 1 & 0 & 0 & 0 & 0 \\ C_2 & 0 & 1 & 0 & 0 & 0 \\ C_3 & 0 & 0 & 1 & 0 & 0 \\ C_4 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}. \tag{55}$$

To obtain the numerical solution, an initial guess is made for the set of initial conditions C_i, $i=1, 2, \ldots, 5$, in Eq. (40). The initial-value equations (52) are then integrated from time $t=0$ to $t=T$. A new set of values for the C_i's is calculated from Eq. (42), and the above sequence is repeated to obtain a second approximation, etc.

For the performance index J_2, the boundary conditions in Eqs. (36), (37), and the last component of Eq. (50) are

$$p_5(T)=-E/2+q(0), \tag{56}$$

$$p_5(0)=q(0), \tag{57}$$

$$\partial p_5(0)/\partial C_5=1. \tag{58}$$

4. Optimal Input Solution for Bolie Parameters

Numerical results were obtained using the Newton–Raphson method. A fourth-order Runge–Kutta method was utilized with grid intervals of 1/50 h (when the terminal time T is expressed in hours) and grid intervals of 1 min (when the terminal time is expressed in minutes). The Bolie parameter values are given in Table 1, along with other assumed parameters and the final numerical results for q and M. The units of the parameters are given in Table 2. The terminal time and the input energy constraint were assumed to be as follows:

$$T=1\text{ h}, \qquad E=0.0489402. \tag{59}$$

The final converged value of q for these conditions is $q=0.015$. The algorithm is initialized as follows:

$$p_1(0)=0, \qquad p_2(0)=0, \qquad p_3(0)=0, \qquad p_4(0)=0, \qquad q(0)=0.02. \tag{60}$$

Table 1. Parameter values.

	Parameters	Bolie parameter values	Bolie parameter values (Bergman units)	Bergman parameter values
Differential equation parameters	a	0.78	0.013	0.185
	b	0.208	0.034667	0.342
	c	4.34	0.007233	0.0349
	d	2.92	0.048667	0.0263
Other assumed parameters	$x_2(0)$	0.1	10	10
	T	1	60	60
	σ^2	1	10^4	10^4
	E	0.04894	8.153	8.153
Numerical results for above parameters	q	0.015	0.1944	0.05607
	M	0.00136	2.9367	0.766

Table 2. Parameter units and conversions.

Parameters, state variables, and input	Bolie units	Bergman units	Multiplication factors for conversion of Bolie units to Bergman units
a	1/h	1/min	1/60
b	units/gram × h	100 μunits/mg × min	1/6
c	grams/unit × h	mg/100 μunits × min	1/600
d	1/h	1/min	1/60
σ^2	$(\text{gram})^2/(\text{liter})^2$	$(\text{mg})^2/(100\ \text{ml})^2$	10^4
E	$(\text{gram})^2/(\text{liter})^2/\text{h}$	$(\text{mg})^2/(100\ \text{ml})^2 \times \text{min}$	166.67
q	$\text{h}^4 \times \text{liter}^2/\text{units}^2$	$(\text{min})^4 \times (\text{ml})^2/(\mu\text{units})^2$	12.96
$x_1(t)$	units/liter	μunits/ml	10^3
$x_2(t)$	gram/liter	mg/100 ml	10^2
$x_{1b}(t)$	gram × h/liter	mg × min/100 ml	6000
$x_{2b}(t)$	$(\text{gram})^2 \times \text{h}/\text{liter} \times \text{units}$	$(\text{mg})^2 \times \text{min}/100\ \text{ml} \times 100\ \mu\text{units}$	600
$y(t)$	gram/liter × h	mg/100 ml × min	1.667

The input energy constraint E is introduced via the boundary condition

$$p_5(T) = -E/2. \tag{61}$$

At the end of the first iteration, q is reset to 0.02, so that initial estimates of $p_1(0)$, $p_2(0)$, $p_3(0)$, $p_4(0)$ can be obtained for a given q. Table 3 shows the

Table 3. Convergence of q and $E(q)$ for Bolie parameters and performance index J_1.

Iteration number	q	$E(q)$
0	0.02	0.096991
1	0.02	0.0145198
2	0.00670042	0.661891
3	0.0136762	1.17911
4	0.0118949	0.296771
5	0.0124931	0.10936
6	0.0139345	0.0619369
7	0.0148426	0.0503973
8	0.0149968	0.0489675
9	0.015	0.0489402
$q(0)=0.02$,	$E=0.0489402$	

convergence of q and $E(q)$ for the performance index J_1. The solution converges within nine iterations.

Table 4 compares the regions of convergence for the performance indices J_1 and J_2. For the performance index J_1, convergence is obtained for an initial estimate of q at least 33 percent greater than the final value of q. For the performance index J_2, however, convergence is obtained for an initial estimate of q at least 10 times greater than the final value. If the input energy constraint is increased to $E=0.713753$, with the other parameters

Table 4. Regions of convergence.

	Convergence	
$q(0)$	Performance index J_1	Performance index J_2
0.15	no	yes
0.025	no	yes
0.02	yes	yes
$q(\text{final})=0.015$,	$E=0.0489402$	
0.012	no	no
0.011	yes	yes
$q(\text{final})=0.01$,	$E=0.713753$	

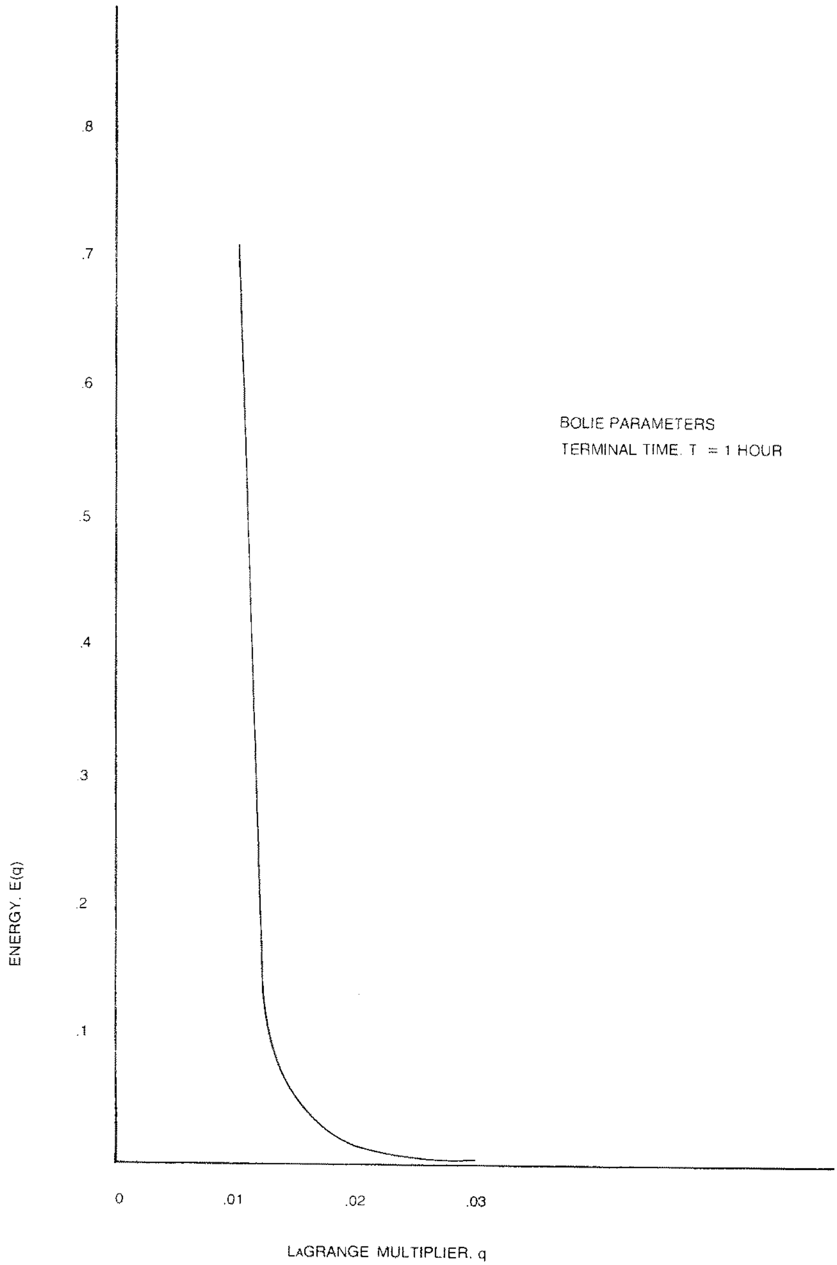

Fig. 1. Input energy versus q.

kept the same, then the final value of q is 0.01. Table 4 shows that, for this case, convergence for both performance indices J_1 and J_2 is obtained for an initial estimate of q of only about 10 percent greater than the final value of q.

Figure 1 shows the input energy $E(q)$ versus q, obtained by the method of complementary functions (Ref. 7). Using this one-sweep method, E is obtained for a given input value of q (final). The curve shows that a possible cause of the small region of convergence for the larger input energy constraint is the steep slope of the energy-versus-q curve in the vicinity of $q = 0.01$. A much larger region of convergence is obtained for $q = 0.015$, as shown in Table 4, where the slope of the curve is considerably less steep. These results seem to indicate that, when using the Newton–Raphson method, the input energy constraint should be small in order to obtain a large region of convergence. Once a good estimate of q is obtained for a given value of E, the latter can be increased to determine another estimate of q. This situation appears to be similar to the case given in Ref. 7 where the terminal time is $T = 2.32$ h. When the Newton–Raphson method is used, convergence is extremely difficult to obtain for the large value of E used in that reference.

The optimal input for a linear system need not be determined for a large value of E, however. If the optimal input is obtained for a small value of E, it needs only to be scaled upward to obtain the optimal input for any desired value of E. For example, Fig. 2 shows the optimal input curves $y(t)$, for

$$E = 0.0489402, \qquad q = 0.015, \tag{62}$$

and

$$E = 0.713753, \qquad q = 0.01. \tag{63}$$

In the first case, $y(0) = 0.417284$; in the second case, $y(0) = 1.5603$. Multiplying the curve for $q = 0.015$ by $1.5603/0.417284 = 3.739$, we obtain the dashed curve in Fig. 2. The dashed curve is extremely close to the optimal input curve for $q = 0.01$.

5. Conversion of Units

The blood glucose regulation parameters for dogs were estimated by Bergman, Kalaba, and Spingarn in Ref. 21. The units of the parameters in that paper, referred to for simplicity as the Bergman units, were different from those used by Bolie for estimating the human parameters. Table 2 gives the conversion factors for converting the Bolie units to Bergman units. The Bolie parameter values in Bergman units are given in Table 1. Note the large increase in the parameter values for the initial condition $x_2(0)$, the variance

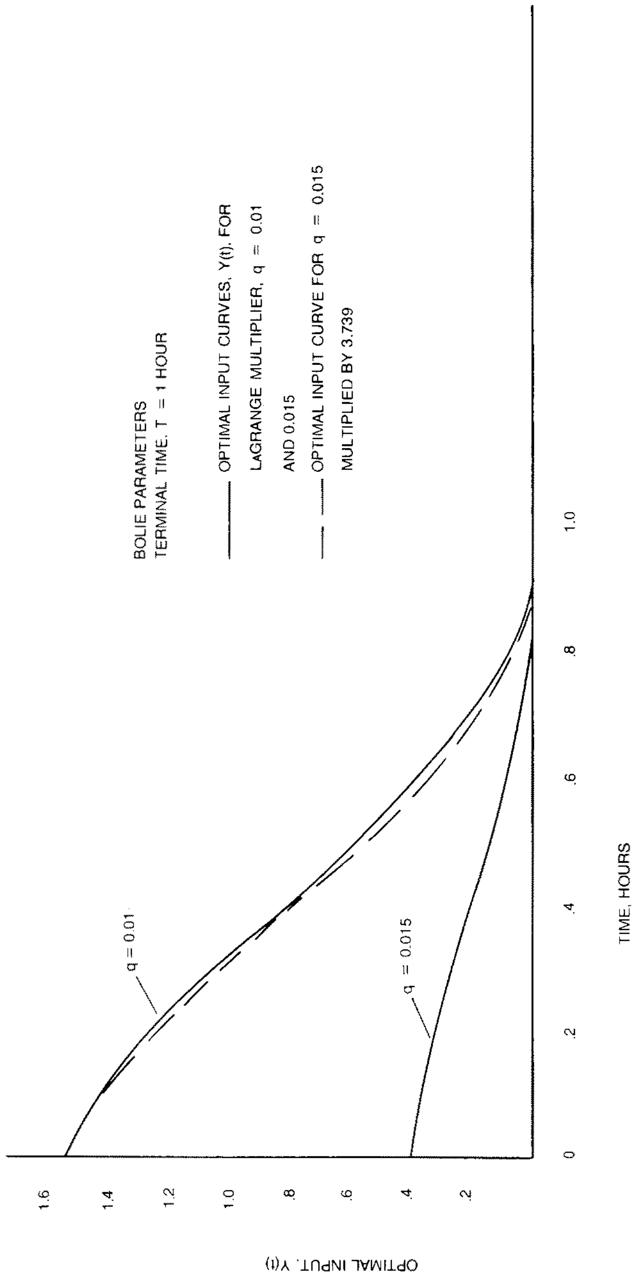

Fig. 2. Optimal input versus time.

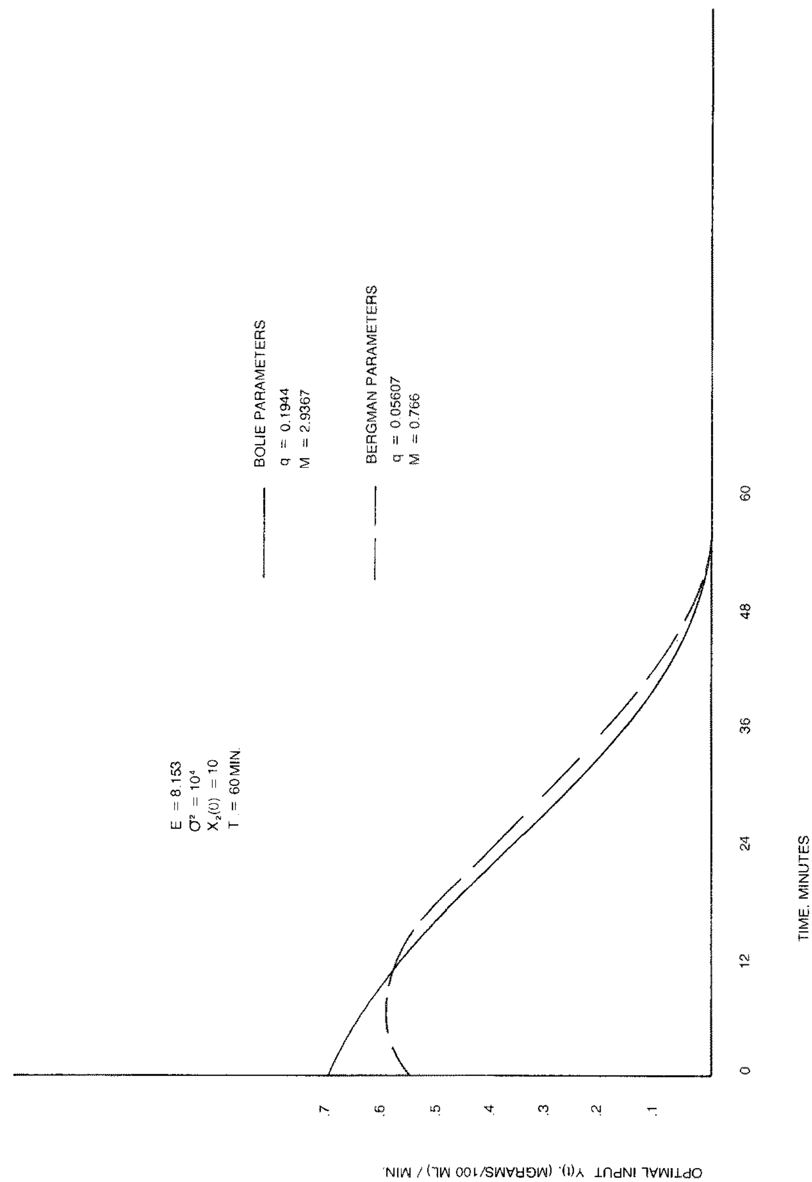

Fig. 3. Optimal inputs for Bolie and Bergman parameters with the same input energy *E*.

σ^2, and the input energy constraint E in the Bergman units. For the conditions given,

$$T = 60 \text{ min}, \qquad E = 8.15302, \qquad x_2(0) = 10, \tag{64}$$

the final converged value of q is 0.1944. For an initial estimate of $q(0)$ equal to 5 times the final value of q, the Newton–Raphson method diverged when the performance index J_2 is used. The problem in this case appeared again to be that the input energy constraint E was too large. Decreasing $x_2(0)$ from 10 to 2 decreases $y(t)$ by a factor of 5 and decreases E by a factor of 25. The final value of q remains the same. Thus, for the conditions

$$E = 0.326121, \qquad x_2(0) = 2, \tag{65}$$

convergence was obtained in 12 iterations for an initial estimate of $q(0)$ equal to 5 times the final value of q, using the performance index J_2. Convergence was also obtained for $x_2(0) = 1$; however, in this case, convergence was much slower. The initial rate of decrease of q was approximately equal to $E/2$.

6. Optimal Input Solution for Bergman Parameters

The Bergman parameter estimates for the blood glucose regulation parameters are given in Table 1. The optimal input for the Bergman parameter values was obtained for the same input energy constraint E as for the Bolie parameter values in Bergman units. Figure 3 shows the optimal inputs for the Bolie and Bergman parameters. The optimal inputs are not considerably different.

The variance $\sigma^2 = 10^4$ is unrealistically large in the Bergman units, because of the assumption that $\sigma^2 = 1$ in the Bolie units. Decreasing σ^2 by 100 has the following effects: (i) $y(t)$, $x_1(t)$, $x_2(t)$, $x_{1b}(t)$, $x_{2b}(t)$, E all remain the same; and (ii) q and M are increased by 100. The effect is obviously to decrease the Cramer–Rao lower bound M^{-1}

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