An Adaptive Plasma Glucose Controller Based on a Nonlinear Insulin/Glucose Model

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Abstract— **The design of plasma glucose controllers traditionally relies on linear approaches. The implementation of an appropriate nonlinear model of the insulin/glucose regulatory system into an adaptive controller should predict the insulin-dependent glucose removal more reliably and hence provide better control over a wide spectrum of insulin signals. A discretized form of the model leads to a two-step procedure. First, the measured plasma glucose levels associated with the exogenous glucose infusion rates are used in the estimation of the past removal rates which, in turn, can be expressed as a weighted sum of past insulin inputs and previous values of the removal rate. Parameters of the sum are adjusted on-line by a recursive method of estimation which features a prefiltering of data to account for a corrupting coloured process noise. The same equation is in turn used to predict the time course of the insulin-dependent fractional rate of glucose removal. The performance of the controller, tested in vivo in three pigs, is presented for various intravenous or subcutaneous rapid injections and staircase infusions of insulin. Plasma glucose is maintained at an average level of 99.9 ± 8.7% of the target value (% set point ± coefficient of variation). The controller reacts promptly to large and rapid variations in insulin action. Although control improves with the number of glucose measurements, the prediction of glucose removal allows for some flexibility in the monitoring of the plasma glucose. Sampling frequency varied from a 2 min interval during transient periods to 7 min as steady states were reached.**

I. Introduction

ONE of the principal actions of insulin is to accelerate the uptake of glucose from the circulation by certain peripheral tissues. Impaired response to the insulin signal reflects dysfunction of the system due to pathologies such as diabetes. Therefore, in vivo evaluation of the properties of the insulin/glucose system is an important tool in diagnosis, in providing insights into regulatory mechanisms, and in assessing the effectiveness of new treatments [1]. Nevertheless, any in vivo procedure that involves a significant manipulation of the plasma insulin and perturbations of the insulin/glucose system dramatically affects the glycemia that therefore requires an external control of plasma glucose.

Various approaches have been developed in the context of glucose clamps for the purpose of assessment of insulin action and secretion [1]. This is a technique that uses feedback control either to keep a constant basal glycemia during continuous insulin infusion or to reach steady hyperglycaemic levels with or without concomitant insulin infusions. The feedback regulation aimed at maintaining the predefined set point is based either on empirical transfer functions (combining proportional and derivative or integral terms) [1]–[5] or on a model linked to an adaptive method of estimation of the glucose removal rate [6]–[10]. These models acknowledge either explicitly [6] or implicitly [7–10] the dependence of glucose removal on insulin. In the latter cases, this dependence is embedded in the coefficient of the glucose concentration in the glucose removal term of a one-compartment model for glucose kinetics. For the purposes of the control model, this coefficient becomes time-varying and its prediction beyond the last observation point is made by extrapolation. The dependence of this parameter (the coefficient of glucose in the term describing its removal or the fractional disappearance rate of glucose) on insulin has been described using a two-compartment system with the fractional disappearance rate of glucose (k) directly proportional to insulin in the compartment remote from the sampling compartment [11]–[14].

The purpose of the work described here is to implement this specific model structure in the prediction of the behaviour of k beyond the last interval of observation. This is easier in the context of a hyperinsulinemic glucose clamp since information on the rate and site of insulin administration is available. The utilization of this information could allow better prediction of glucose levels than that which might occur based on less flexible constructs, especially during rapid and large variations of the insulin signal. The improved prediction could, in turn, obviate the need for as rigorous a monitoring of glucose levels as is otherwise required.

Using this nonlinear model, for glucose and insulin kinetics one might expect better control over a wider range of insulin signals such as iv and sc injections, staircase infusions or after the shut off of a constant infusion. The model predicts the time course of the insulin action for any insulin signal and thus allows a certain flexibility in the regularity and frequency of the plasma glucose monitoring at a minimal cost in performance. Good performance of such a controller would, in turn, validate the ability of the model to mimic the physiological regulation and provides experience of value in the development of an "artificial pancreas."

II. Methods

The controller is based on a straightforward approach (Fig. 1). A physiological model of the glucose-insulin system allows for the estimation of the time course of the insulin-dependent removal rate of plasma glucose. Thus, the exogenous glucose infusion required to achieve a predefined

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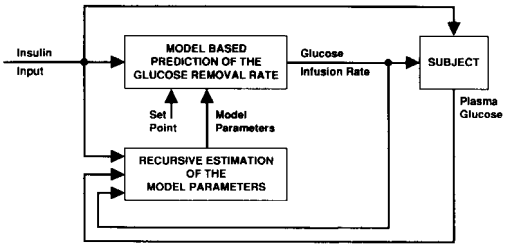

Fig. 1. Block diagram of the adaptive controller.

plasma glucose profile is calculated according to the predicted insulin action. Concurrently, plasma glucose monitoring provides information which, in conjunction with the past glucose infusion and the known insulin signal, allows for the adjustment of the parameters to the specific values for the subject. This adaptive mechanism finetunes the control during the ongoing experiment. A preliminary version of a controller based on the model below was used successfully in generating preset plasma glucose profiles using exogenous glucose infusion [15].

A. The Model

Several sets of mathematical relationships have been proposed to describe the action of insulin on glucose but a nonlinear model that has long been identified [11]–[12] is demonstrably more appropriate [13]–[16] under many circumstances particularly in the control context where the model structure should remain as simple as possible or "minimal". The following set of equations describing glucose/insulin kinetics was used in the design of a controller for the maintenance of basal glycemia during euglycemic hyperinsulinemic clamps.

$$\frac{dG(t)}{dt} = -[k_o + k(t)]G(t) + \mathrm{RG}(t) \quad (1)$$

$$\frac{dk(t)}{dt} = -a_1 \cdot k(t) + a_2 \cdot i(t) \quad (2)$$

$$\frac{di(t)}{dt} = -a_3 \cdot i(t) + a_4 \cdot k(t) + a_6 \cdot i_3(t) + \mathrm{RI}(t) \quad (3)$$

$$\frac{di_3(t)}{dt} = -a_6 \cdot i_3(t) + a_5 \cdot i(t) \quad (4)$$

where

$G(t)$ = plasma glucose concentration (mg/ml)
k_o = insulin-independent fractional removal rate of glucose (min^{-1})
$k(t)$ = insulin-dependent fractional removal rate of glucose (min^{-1})
$i(t)$ = insulin mass in the central compartment (μU)
$i_3(t)$ = insulin mass in a peripheral compartment non-active in glucose removal (μU)
$\mathrm{RG}(t)$ = glucose systemic appearance rate (mg/ml·min)
$\mathrm{RI}(t)$ = insulin systemic appearance rate (μU/min)
a_1–a_6 = fractional transfer rates of the 3-compartment model of insulin kinetics (min^{-1}, except $[a_2] = \mathrm{min}^{-2}\mu\mathrm{U}$ and $[a_4] = \mu\mathrm{U/min}^{-2}$)

Equation 1 describes the variations in plasma glucose $G(t)$ according to the principle of mass conservation. The first term on the right side accounts for glucose removal while the second term $\mathrm{RG}(t)$ represents both the endogenous and the exogenous glucose input. A single compartment description is appropriate since in the euglycemic control situation, dG/dt will be minimized (16). The fractional removal rate of glucose consists of a constant component k_o added to an insulin-dependent term $k(t)$.

The insulin-dependent component of the fractional removal rate of glucose, $k(t)$, has been shown to be directly proportional to the presence of insulin in a compartment remote from plasma [11–15]. The latter is thus assumed directly proportional to the insulin mass in a peripheral compartment of a multicompartment model of insulin kinetics. The two-compartment description is generally considered to be minimal [14]. In this application, however, a higher order ARMA model (see below) was found to yield better control. A three compartment model for insulin kinetics [13] which was previously developed and which yielded the desired ARMA model order was therefore chosen to describe the insulin kinetics (eqn's 2–4 but with $a_4 = a_1$).

$k(t)$ appears explicitly in the system of equations 2–4 rather than the insulin mass in the compartment acting on glucose removal. The coefficient of proportionality between these two variables is simply lumped together with the fractional rates of transfer between plasma insulin and this pool. $\mathrm{RI}(t)$ represents the entry of both the endogenous and the exogenous insulin into the systemic circulation. The controller presented in this paper has been tested to maintain euglycemia while the endogenous secretion of insulin was inhibited by the infusion of somatostatin; $\mathrm{RI}(t)$ thus strictly corresponds to the rate of the exogenous iv administration $\mathrm{RI}_{\mathrm{iv}}(t)$. Similarly, $\mathrm{RG}(t)$ accounts for the rate of appearance of glucose in the systemic circulation from both the endogenous and the exogenous sources. At steady state, prior to the onset of the insulin signal, the basal glucose removal simply equals the endogenous production but higher levels of circulating insulin would reduce the hepatic glucose production [19]. In this application however it was set equal to the basal endogenous production throughout each clamp study [9]. This assumption removes the necessity of separately estimating k_o since:

$$[k_o + k(o)]G(o) = \mathrm{RG}(o)$$

and $-[k_o + k(t)]G(t)$ can be rewritten as:

$$-[k_o + k(t)]G(t) + [k_o + k(o)]G(t) - [k_o + k(o)]G(t) + [k_o + k(o)]G(o) - \mathrm{RG}(o)$$

or $$-[k(t) - k(o)]G(t) - [k_o + k(o)][G(t) - G(o)] - \mathrm{RG}(o)$$

The second term above is near zero since $G(t)$ is clamped at $G(o)$ and $k_o + k(o)$ are in general much less than $k(t) - k(o)$ when hyperinsulinemia prevails.

Therefore, in the context of the clamp, $k(t), \mathrm{RG}(t). i(t)$ and $i_3(t)$ can be treated as deviations from the basal conditions which are in effect at the very low insulinemia which corresponds to the somatostatin infusion. Equation (1) can be replaced by: $\frac{dG}{dt} = -(k(t) - k(o))G(t) + \mathrm{RG}(t) - \mathrm{RG}(o)$ with analogous substitutions for equations (2)–(4).

In some experiments, the insulin is subcutaneously (sc) injected which requires an additional first order model to describe the transfer of the insulin mass from the sc depot toward the systemic circulation (eqn's. 5–6).

$$\frac{dM(t)}{dt} = -k_{\mathrm{sc}} \cdot M(t) + \mathrm{RI}_{\mathrm{sc}}(t) \tag{5}$$

$$\mathrm{RI}(t) = k_{\mathrm{sc}} \cdot M(t) \tag{6}$$

where
$M(t)$ = insulin mass in the sc depot (μU)
$\mathrm{RI}_{\mathrm{sc}}(t)$ = insulin rate of appearance in the sc depot (μU/min)
$k_{\mathrm{sc}}(t)$ = fractional transfer rate from sc depot toward the systemic circulation (min^{-1})

B. The Control Strategy

The strategy of the control is based on an open-loop approach that counters the glucose removal induced by the exogenously imposed insulin signal with an exogenous infusion of glucose. The insulin action on glucose removal is a linear process consisting in a single output, $k(t)$ that is a function of a single input $\mathrm{RI}(t)$. The process parameters are recursively adjusted after each new observation of the glucose concentration in order to utilize all available information from the controller operation and thus to improve the prediction of $k(t)$ and to account for possible drifts and fluctuations of the parameter values. Control is then achieved by using the equation of the glucose kinetics (eqn. 1) in an inverse fashion to calculate the glucose infusion required to maintain a preset profile for $G(t)$: here $G(t) = G(o)$. The glucose infusion, and only the glucose infusion, $\mathrm{RG}(t)$ is thus the control input.

C. The Parameter Estimation

Intravenous injection For the purpose of the on-line evaluation of the process dynamics, eqn's. 2–4 are discretized for incremental times Δt (eqn's. 7–9),

$$k_{i+1} = [1 - \Delta t \cdot a_1]k_i + \Delta t \cdot a_2 \cdot i_i \tag{7}$$

$$i_{i+1} = [1 - \Delta t \cdot a_3]i_i + \Delta t \cdot a_4 \cdot k_i + \Delta t \cdot a_6 \cdot i_{3i} + \Delta t \cdot \mathrm{RI}_{\mathrm{iv}i} \tag{8}$$

$$i_{3i+1} = [1 - \Delta t \cdot a_5]i_{3i} + \Delta t \cdot a_6 \cdot i_i \tag{9}$$

where the index i refers to values when time equals $i \cdot \Delta t$. Successive substitutions and algebraic manipulations can convert eqn's. 7–9 into a single (ARMA) relationship expressing k_i as a weighted sum of the past process inputs and outputs:

$$k_i = A_1 \cdot k_{i-1} + A_2 \cdot k_{i-2} + A_3 \cdot k_{i-3} + A_4 \cdot \mathrm{RI}_{\mathrm{iv}i-2} + A_5 \cdot \mathrm{RI}_{\mathrm{iv}i-3} \tag{10}$$

with the following relationships between the $\{A_i\}$ and the compartmental parameters $\{a_i\}$:

$$C_1 = 1 - \Delta t \cdot a_1 \qquad A_1 = C_1 + D_1$$
$$C_2 = \Delta t \cdot a_2 \qquad A_2 = D_2 - C_1 \cdot D_1 + C_2 \cdot C_4$$
$$C_3 = 1 - \Delta t \cdot (a_2 + a_3 + a_5) \qquad A_3 = -(C1 \cdot D2 + C_2 \cdot C_4 \cdot C_6)$$
$$C_4 = \Delta t \cdot a_1 \qquad A_4 = C_2$$
$$C_6 = 1 - \Delta t \cdot a_6 \qquad A_5 = -C_2 \cdot C_6$$
$$D1 = C_3 + C_6$$
$$D2 = \Delta t^2 \cdot a_5 \cdot a_6 - C_3 \cdot C_6$$

Considering a sequence of observations $\{k, \mathrm{RI}\}_i$ from $i = 0$ to n, corrupted by a coloured noise e, equation 10 leads to the following system:

$$k_0 = A_1 \cdot k_{-1} + A_2 \cdot k_{-2} + A_3 \cdot k_{-3} + A_4 \cdot \mathrm{RI}_{\mathrm{iv}-2} + A_5 \cdot \mathrm{RI}_{\mathrm{iv}-3} + e_0$$

$$k_1 = A_1 \cdot k_0 + A_2 \cdot k_{-1} + A_3 \cdot k_{-2} + A_4 \cdot \mathrm{RI}_{\mathrm{iv}-1} + A_5 \cdot \mathrm{RI}_{\mathrm{iv}-2} + e_1$$

$$k_2 = A_1 \cdot k_1 + A_2 \cdot k_0 + A_3 \cdot k_{-1} + A_4 \cdot \mathrm{RI}_{\mathrm{iv}0} + A_5 \cdot \mathrm{RI}_{\mathrm{iv}-1} + e_2$$

$$\vdots$$

$$k_n = a_1 \cdot k_{n-1} + a_2 \cdot k_{n-2} + A_3 \cdot k_{n-3} + A_4 \cdot \mathrm{RI}_{\mathrm{iv}n-2} + A_5 \cdot \mathrm{RI}_{\mathrm{iv}n-3} + e_3$$

for which the matrix form reads:

$$\mathbf{k} = \mathbf{X}_{\mathrm{iv}} \cdot \mathbf{\Theta}_{\mathrm{iv}} + \mathbf{e} \tag{11}$$

where

$$\mathbf{k}^T = [k_0, k_1, k_2, k_3 \ldots, k_n]$$
$$\mathbf{X}_{\mathrm{iv}} = [z^{-1}\mathbf{k}, z^{-2}\mathbf{k}, z^{-3}\mathbf{k}, z^{-2}\mathrm{RI}_{\mathrm{iv}}, z^{-3}\mathrm{RI}_{\mathrm{iv}}]$$
$$\mathbf{RI}_{\mathrm{iv}} = [\mathrm{RI}_{\mathrm{iv}0}, \mathrm{RI}_{\mathrm{iv}1}, \mathrm{RI}_{\mathrm{iv}2} \ldots, \mathrm{RI}_{\mathrm{iv}n}]$$
$$\mathbf{\Theta}_{\mathrm{iv}}^T = [A_1, A_2, A_3, A_4, A_5]$$
$$e^T = [e_0, e_1, e_2, e_3 \ldots, e_n]$$

and z^{-1} represents the unit delay operator.

Subcutaneous injection In their discretized form, equations 5 and 6 read:

$$M_{i+1} = (1 - \Delta t \cdot k_{\mathrm{sc}})M_i + \mathrm{RI}_{\mathrm{sc}i} \tag{12}$$

$$\mathrm{RI}_{\mathrm{iv}i} = k_{\mathrm{sc}} \cdot M_i \tag{13}$$

Using equations 12 and 13 to express $\mathrm{RI}_{\mathrm{iv}}$ in terms of $\mathrm{RI}_{\mathrm{sc}i}$ and then substituting in eqn. 10 leads to another relationship, although in a similar form, for k_i (eqn. 14).

$$k_i = B_1 \cdot k_{i-1} + B_2 \cdot k_{i-2} + B_3 \cdot k_{i-3} + B_4 \cdot k_{i-4} + B_5 \cdot \mathrm{RI}_{\mathrm{sc}i-3} + B_6 \cdot \mathrm{RI}_{\mathrm{sc}i-4} \tag{14}$$

with $\{B_1\}$ defined as follows:

$$B_1 = A_1 + (1 - k_{\mathrm{sc}}) \qquad B_4 = -A_3 \cdot (1 - k_{\mathrm{sc}})$$
$$B_2 = A_2 - A_1 \cdot (1 - k_{\mathrm{sc}}) \qquad B_5 = A_4 \cdot k_{\mathrm{sc}}$$
$$B_3 = A_3 - A_2 \cdot (1 - k_{\mathrm{sc}}) \qquad B_6 = A_5 \cdot k_{\mathrm{sc}}$$

where the $\{A_i\}$ have been defined for equation (10) above. A sequence of observations from $i = 0$ to n is thus written:

$$\mathbf{k} = \mathbf{X}_{\mathrm{sc}} \cdot \mathbf{\Theta}_{\mathrm{sc}} + \mathbf{e} \tag{15}$$

where

$$\mathbf{X}_{\mathrm{sc}} = [z^{-1}\mathbf{k}, z^{-2}\mathbf{k}, z^{-3}\mathbf{k}, z^{-4}\mathbf{k}, z^{-3}\mathrm{RI}_{\mathrm{sc}}, z^{-4}\mathrm{RI}_{\mathrm{sc}}]$$
$$\mathrm{RI}_{\mathrm{sc}} = [\mathrm{RI}_{\mathrm{sc0}}, \mathrm{RI}_{\mathrm{sc1}}, \mathrm{RI}_{\mathrm{sc2}} \ldots, \mathrm{RI}_{\mathrm{sc}n}]$$
$$\mathbf{\Theta}_{\mathrm{sc}}^T = [B_1, B_2, B_3, B_4, B_5, B_6]$$

Insulin injections correspond to a delta function which in discrete form reads: $\mathrm{RI}_0 = M(0)/\Delta t$ and $\mathrm{RI}_i = 0$ for $i \neq 0$.

Adaptive-recursive estimation Both equations 11 and 15 are solved for $\mathbf{\Theta}_{\mathrm{iv}}$ and $\mathbf{\Theta}_{\mathrm{sc}}$, respectively, using the recursive generalized-least-square method (17, 18). For any new observation $\{k, \mathrm{RI}\}_{n+1}$, eqn's. 11 and 15 can be expanded to the general form:

$$\begin{bmatrix} \mathbf{k} \\ k_{n+1} \end{bmatrix} = \begin{bmatrix} \mathbf{X} \\ x_{n+1} \end{bmatrix} \cdot \mathbf{\Theta} + \begin{bmatrix} \mathbf{e} \\ e_{n+1} \end{bmatrix} \tag{16}$$

where

$$\left.\begin{array}{l} \mathbf{X} = \mathbf{X}_{\mathrm{iv}}, \mathbf{\Theta} = \mathbf{\Theta}_{\mathrm{iv}} \\ \mathbf{x}_{n+1} = [k_n, k_{n-1}, k_{n-2}, \mathrm{RI}_{\mathrm{iv}n-1}, \mathrm{RI}_{\mathrm{iv}n-2}] \end{array}\right\} \text{iv insulin input}$$

or

$$\left.\begin{array}{l} \mathbf{X} = \mathbf{X}_{\mathrm{sc}}, \mathbf{\Theta} = \mathbf{\Theta}_{\mathrm{sc}} \\ \mathbf{x}_{n+1} = [k_n, k_{n-1}, k_{n-2}, k_{n-3}, \mathrm{RI}_{\mathrm{sc}n-2}, \mathrm{RI}_{\mathrm{sc}n-3}] \end{array}\right\} \text{sc insulin input}$$

It is also assumed that the colored noise e_i can be estimated ($\hat{e}_i$) by an autoregressive series (eqn. 17).

$$\hat{e}_i = [1 + E(z^{-1})]\xi_i \tag{17}$$

where

$$E(z^{-1}) = E_1 \cdot z^{-1} + E_2 \cdot z^{-2} + \cdots + E_5 \cdot z^{-5}$$
$$\xi_i = \text{ estimated } k_i - \text{ measured } k_i$$

Determination of the number of terms in $E(z^{-1})$ is empirical. The error term is estimated for each new set of observed and estimated k_{n+1} and then used to recursively update the parameters $\hat{\mathbf{E}}$ of the error model.

Unbiased estimation of $\mathbf{\Theta}$ requires the prefiltering of the process input RI and of the process output k using the noise model equation (eqn. 11). Thus the algorithm is actually based on the filtered data:

$$k^F = [1 + \hat{E}(z^{-1})]k \tag{18}$$
$$\mathrm{RI}^F = [1 + \hat{E}(z^{-1})]\mathrm{RI} \tag{19}$$

and $\mathbf{x}_{n+1}^F = [k_n^F, k_{n-1}^F, k_{n-2}^F, \mathrm{RI}_{\mathrm{iv}n-1}^F, \mathrm{RI}_{\mathrm{iv}n-2}^F]$ for an iv input or $= [k_n^F, k_{n-1}^F, k_{n-2}^F, k_{n-3}^F, \mathrm{RI}_{\mathrm{sc}n-2}^F, \mathrm{RI}_{\mathrm{sc}n-3}^F]$ for a sc input

The estimate of $\mathbf{\Theta}$ is then adjusted according to the following formula:

$$\mathbf{\Theta}_{n+1} = \mathbf{\Theta}_n + \frac{\mathbf{S_n} \cdot X_{n+1}^{FT} \cdot (k_{n+1}^F - x_{n+1}^{FT} \cdot \mathbf{\Theta}_n)}{\rho + X_{n+1}^{FT} \cdot \mathbf{S_n} \cdot X_{n+1}^F} \tag{20}$$

where

$$\underline{\mathbf{S}}_n = [\mathbf{X}^{FT} \cdot \mathbf{X}^F]_n^{-1}$$
$$\rho = \text{ adaptive gain factor}$$

$\underline{\mathbf{S}}$ is subsequently updated to be used in the next adjustmei of $\hat{\mathbf{\Theta}}_{n+2}$:

$$\mathbf{S_{n+1}} = \frac{1}{p}\left(\mathbf{S_n} - \frac{\mathbf{S_n} \cdot X_{n+1}^F \cdot X_{n+1}^{FT} \cdot \mathbf{S_n}}{\rho + X_{n+1}^{FT} \cdot \mathbf{S_n} \cdot X_{n+1}^F}\right) \tag{21}$$

The adaptive gain factor exponentially weighs out the pa estimates in order to emphasize more recent observations i the correction. A factor of 1 attributes equal weight to a observations. Estimation of the error model parameters, $\hat{E}$ relies on recursive procedure analagous to the above.

D. Algorithm

The algorithm that is summarized in Fig. 2 is based on th following sequence:

(i) k_n is estimated from the discretized form of eqn. 1 fc every G_{n+1}:

$$G_{n+1} = [1 - \Delta t(k_o + k_n)]G_n + \Delta t \cdot \mathrm{RG}_n \tag{22}$$

(ii) this new observation is filtered and used to adjust $\hat{\mathbf{\Theta}}$, $\underline{\mathbf{S}}$ and $\hat{\mathbf{E}}$. The time course of k_i is subsequently re-calculate from equation 10 or 14 for any $i > n + 1$,

(iii) these discrete values of the insulin-dependent fractiona rate of glucose removal are introduced back in eqn. 2. to calculate the glucose infusion required to achieve th preset G_i's ($i > n + 2$).

The recursive parameter estimation is initiated with a prior reasonable values that are deduced from the metabolic parame ters of the insulin/glucose system identified from the literatur [13] The $\{a_i\}$ of equations (2)–(4) are (0.394, 0.142, 0.251 0.394, 3.15×10^{-8}, 2.8×10^3) where a_5 and a_6 from [13] ar modified by the proportionality factor between k and i_2 (7.: $\times 10^{-6}$) and k_{sc} is assumed to be 0.03 min^{-1}. From these the initial values of the $\{A_i\}$ and $\{B_i\}$ are derived using th formulae given after equations (10) and (14): ($\hat{\mathbf{\Theta}}_{\mathrm{iv\_initial}}^T$ = $[2.50, -2.05, 0.55, 1.58 \times 10^{-7}, -1.26 \times 10^{-7}]$ and $\hat{\mathbf{\Theta}}_{\mathrm{sc\ initia}}^T$ = [3.47, −4.48, 2.54, −0.53, 4.73×10^{-9},-3.79×10^{-9}]) The initial value of the matrix $\underline{\mathbf{S}}$ equals $p \cdot I$ where I is th identity matrix and the scalar $p = 5.10^5$. The adaptive-gai factor is set at 0.975. A clock signal interrupts the progran every Δt (30 s in the present version) and the pre-calculatec infusion rate from a storage array, appropriate for that interva is used to set up the flow rate of the pump through a seria interface. Then, the program resumes where interrupted.

The recursive adjustment of the parameters assumes th availability of regular plasma glucose values regardless o the experimental procedures and the dynamic properties o the physiological system. The adjustment of the parameters t individuals or to transient periods where $k(t)$ varies rapidl can require frequent sampling, though the maintenance o a well established steady state should allow the assessmen of the plasma glucose at more widely-spaced intervals. Th following procedure is used to circumvent irregular samplin of the plasma glucose. The intermediate values G_i betwee two measurements G_n and $G_{n+h} (h > 1)$ are interpolated b adjusting the expected glucose value G_i^* predicted prior to th

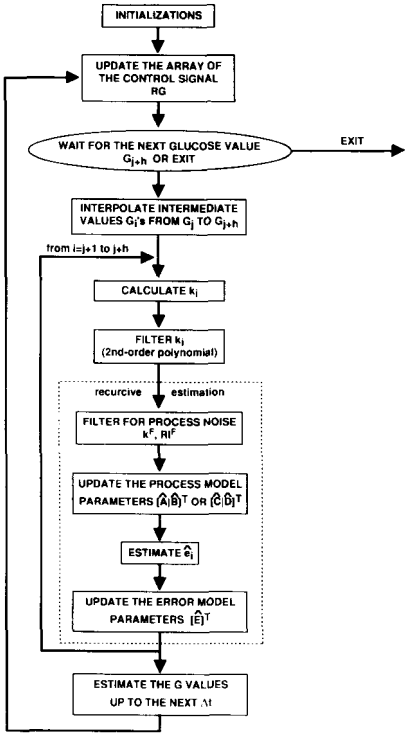

Fig. 2. Flow-chart diagram of the control program.

availability of G_{n+h}:

$$G_i = G_i^* + (i-j)\frac{[G_{n+h} - G_n]}{h} \tag{23}$$

The factor of correction added to G_i^* is a time-dependent offset varying linearly from O to $(G_{n+h} - G_{n+h})$ between n and $n+h$, respectively. Moreover, each new value of k_i obtained from eqn. 22 is smoothed by a second-order polynomial equation that best fits the last 20 values.

III. Experimental Tests

The controller was tested to maintain the glycemia at the fasting level (euglycemia) in 3 pigs receiving various inputs of insulin as follows: (a) an iv rapid injection of 0.125 U/kg bw followed 2 hr later by a 2 hr long infusion of 0.25 U/kg bw.hr, (b) an iv infusion of 0.15 U/kg bw.hr for the first hour then 0.30 U/kg bw.hr for the next hour followed by 0.45 U/kg bw.hr for the last hour, and (c) a sc injection of 0.5 U/kg bw. Every experiment was performed once on each animal with a minimum delay of 5 days between each of these (9 experiments total). Plasma glucose monitoring and control was performed from the onset of the insulin input for a duration of 5 hr in experiments (a) and (b), and 4 hr in experiment (c). Endogenous insulin secretion was inhibited with an infusion of 0.5 μg somatostatin/kg bw.min primed with an injection of 7.5 μg/kg bw 15 min before the onset of the insulin signal. Blood samples were drawn at time intervals ranging from 2 to 7 min. Glucose determination was performed in duplicate on plasma with a Beckman Glucose Analyzer. This operation introduced a delay ranging from 2 to 3 min before the glucose value of the most recent sample could be entered for the adjustment of parameters. The infusion required to maintain euglycemia according to the updated estimates was provided by a pump (IVAC 560M IVAC Corp., San Diego, CA) infusing a 20% dextrose solution. A volume of distribution of 150 ml/kg bw was assumed throughout the calculations.

IV. Results and Discussion

Fig. 3 illustrates the time courses of the plasma glucose obtained with the present controller for the 3 experiments performed on the same animal. It also shows the profile of the infusion rate of the dextrose solution as it was updated during the experiment in order to maintain plasma glucose at the basal value measured before each experiment. In experiment (a), a disruption in communication between the computer and the pump stopped the experiment a few minutes before the insulin was shut off. However, experiment (c) allows the assessment of the performance of the controller under similar circumstances when the insulin infusion was stopped 180 min after a prolonged staircase infusion.

The performance of the controller is evaluated in Table I for experiments (a), (b), and (c) in each of the three animals. Overall, for all the studies, an average glucose level 99.9 $\pm$ 8.7% of the target (% desired level $\pm$ CV) was achieved. The coefficient of variation corresponds to fluctuations that represent less than twice the physiological variations under basal conditions (CV = 4.5%) as measured in fasted animals under similar conditions. The final estimates of the parameters $\{A_i\}$ are summarized by: $\hat{\Theta}_{\text{iv final}} = (2.46 \pm 0.092, -2.15 \pm 0.16, 0.695 \pm 0.066, 6.74 \times 10^{-7} \pm 6.42 \times 10^{-7}, 1.42 \times 10^{-6} \pm 1.34 \times 10^{-6})$.

These means are based on the 8 studies where insulin was administered intravenously. For $A_1 \cdots A_3$, convergence to within 5% of the final estimate was achieved within 30min of the initiation of infusion. Three subcutaneous injections of insulin were tested. $B1 \cdots B4$ converged to a mean of $(2.68 \pm 0.17, -2.85 \pm 0.43, 1.45 \pm 0.38, -0.29 \pm 0.12)$ for the 4 studies with similar convergence characteristics. $A4$, $A5$, $B4$ and $B5$ exhibited increased fluctuations particularly in the situations where only an initial perturbation was applied (iv. or sc. injection). Clearly, under these conditions their contribution to the prediction of $k(t)$, which effectively decays after the initial perturbation, is minimal. Even the infusion protocols do not provide a persistent excitation for optimal parameter estimation. These are, however, typical experimental circumstances under which the controller is required to operate.

Observation of Fig. 3 clearly shows that most of the fluctuations and spikes in the controlling signal occur during the first period of the experiments extending over 45 to 60 min after the onset of the insulin signal. This corresponds to the adjustment of the parameter values to the characteristics of the specific animal used during the experiment. With time, spikes smooth out even during transient periods as shown

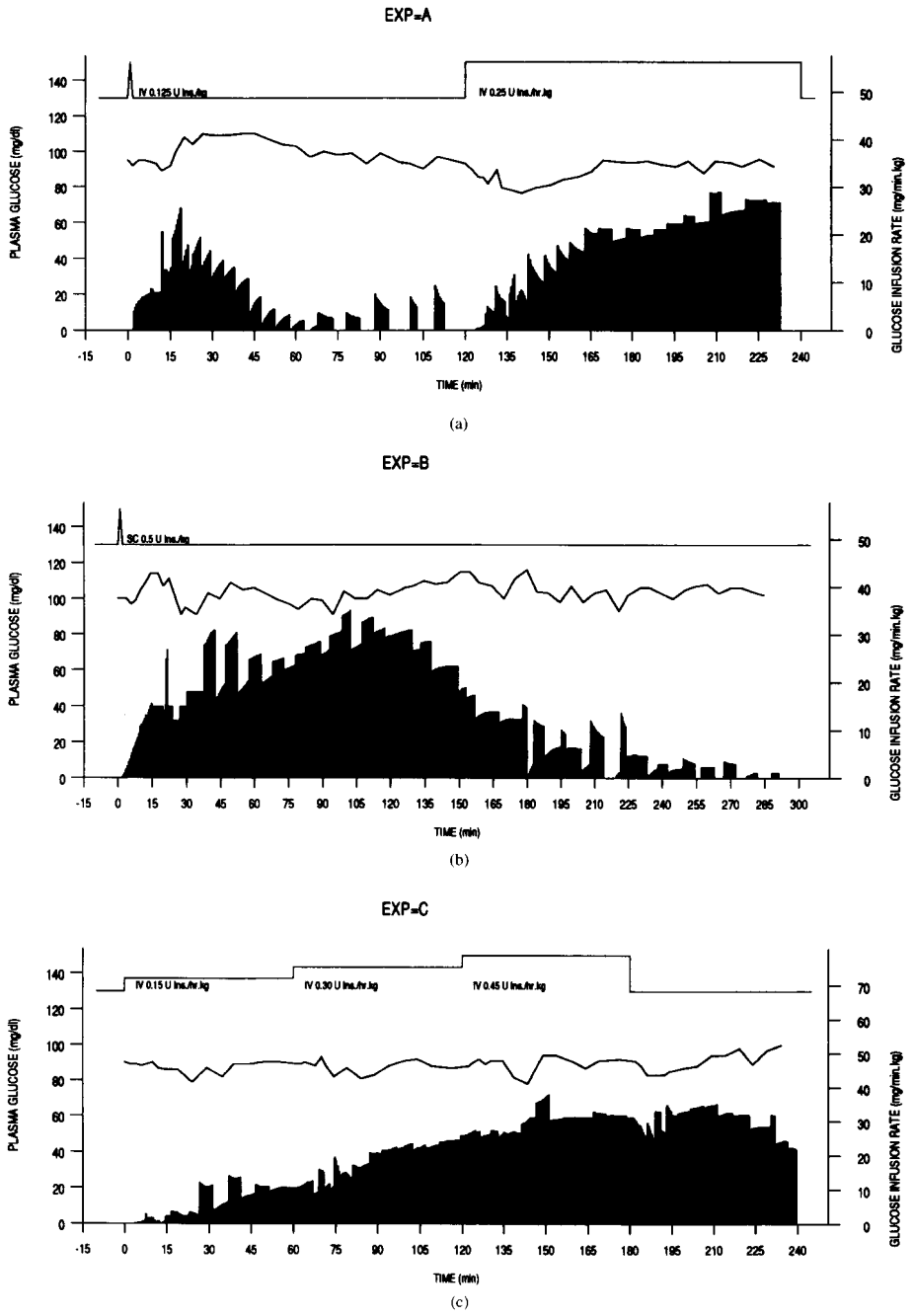

Fig. 3. Plasma glucose (–) and glucose infusion rate(■) for a single animal during 3 distinct experiments where various inputs of insulin were administered as follows: a) a rapid iv injectionfollowed 2 hr latter by a 1 hr long constant infusion (b) a sc injection, and (c) a staircase iv infusion.

in experiment (c) at 60, 120, and 180 min. For practical reasons, the 2 phases of experiments (a) were conducted independently from one another. The controller was stopped 120 min after the rapid insulin injection and restarted with the arbitrary set of initial parameters immediately before the insulin infusion.

TABLE I
BASAL PLASMA GLUCOSE AND AVERAGE PLASMA GLUCOSE FOLLOWING THE ONSET OF THE INSULIN SIGNAL EXPRESSED IN MG/DL AND IN PERCENT OF THE SET-POINT, I.E. THE BASAL VALUE. PLASMA GLUCOSE IS MONITORED FOR 5 HR IN EXPERIMENTS (A) AND (B), AND FOR 4 HR IN EXPERIMENT (C).

		animal #1	animal #2	animal #3
Exp. (a)	Basal glucose (mg/dl)	95.0	90.0	95.0
	Mean glucose ± SE (mg/dl)	95.0 ± 1.0	85.3 ± 1.4	94.0 ± 1.1
	% basal ± CV*	100. ± 9.3	94.8 ± 14.	99.0 ± 8.9
Exp. (b)	Basal glucose (mg/dl)	100.	97.0	100.
	Mean glucose ± SE (mg/dl)	102.9 ± 1.0	98.8 ± 1.2	103.6 ± 0.7
	% basal ± CV*	103. ± 7.9	102. ± 9.8	104. ± 5.6
Exp. (c)	Basal glucose (mg/dl)	73.0	94.	90.
	Mean glucose ± SE (mg/dl)	72.6 ± 0.9	92.8 ± 1.0	88.5 ± 0.6
	% basal ± CV*	99.5 ± 9.5	98.8 ± 8.1	98.4 ± 4.9

*: CV is defined as standard deviation ·100 / mean

A. Model Structure

Glucose is removed from the system proportionally to its concentration. The coefficient expressing this proportionality is variable and is in turn proportional to insulin concentrations in a compartment, remote from plasma. This structural principle has been directly incorporated into the control situation in the context of insulin infusions where glycemia is maintained constant by using a compartmental description of insulin kinetics and the proportionality of the coefficient of glucose removal (the fractional disappearance rate of glucose, k) to predict values of k beyond the point of the last observation.

Previous model-based control strategies did not use this specific structure for prediction. A discussion of the approach to more physiological prediction and its possible implications is included in [15]. This can be summarized by indicating that, where insulin concentrations were used in predicting glycemic response [6], both the mass effect of glucose and the fact that it is peripheral insulin that directly affects glucose removal were not taken into account. In controllers where the insulin effect specifically on the fractional disappearance rate is acknowledged, [7–10] no specific structure for this relationship is incorporated into the prediction of $k(t)$ beyond the last point of observation. An implementation of the model currently considered most physiologic in describing this relationship [11–15] in the prediction of $k(t)$ is the intrinsic difference between the control strategy proposed here and previous work.

A two-compartment model is generally used to describe the relationship between k and plasma insulin (11–15) and is considered minimal (14). In the development of this controller, however, it was found empirically that a higher order ARMA model (eqn's 10 and 14) improved control by the criteria used (Table 1). This could be generated from the assumption of a three-compartment system for insulin kinetics (eqn's. 2–4). These equations are analogous to those proposed in [13] but are by no means unique in generating the ARMA model actually implemented [20].

B. Parameter Identification

The constant parameters $\{a_i\}$ in equations (1) to (5) cannot be completely separated from the estimates of $\{A_i\}$ and $\{B_i\}$. Initial estimates of the latter are however derived from the $\{a_i\}$ using the formulae given after equations (10) and (14). It can be seen that the final estimates of these parameters are of similar order to the initial values. Insulin values were not available in these studies, done on-line, to retrospectively evaluate the model parameters and compare them to individual experimental estimates. The small deviations of the mean final estimates of $\{A_i\}$ and $\{B_i\}$ from the initial values which were derived from a previously published model [13] add further support of the appropriateness of the basic model structure. The differences can be attributed to interindividual variations as well as species differences.

Simulations performed using equation (10) with imposed variations on the parameters $\{A_i\}$, demonstrate a much higher sensitivity to the parameters $A_1 \cdots A_3$ than to A_4 and A_5. Similar results were obtained by evaluating the sensitivity function $(S_{Ai}(j\omega)S_{Ai}(-j\omega))^{1/2}$ over a range of ω, where:

$$S_{Ai}(z) = \frac{\partial}{\partial A_i} H(z)$$

and

$$H(z) = (A_4 z^{-2} + A_5 z^{-3})/(1 - A_1 z^{-1} - A_2 z^{-2} - A_3 z^{-3})$$

is the transfer function based on equation (10). Moreover, the overall contrubtion of A_4 and A_5 to the estimates was near 20%.

It should finally be emphasized that the sensitivity problem is mitigated since the one step-ahead controller used here is based on parameters that are adaptively estimated and adjusted so that the model output coincides with the system output (glucose levels).

An assumption made in the development of the controller was that endogenous glucose production, $\mathrm{RG_{endog}}$, was not altered during the course of a hyperinsulinemic glucose clamp. As indicated this is likely not true [19]. This assumption does however obviate the determination of k_o since under these circumstances only increments in k above basal are considered and $\mathrm{RG}(t) - \mathrm{RG}(O)$ is the rate of exogenous glucose infusion. The reasoning has been detailed above (Methods, the Model). If $\mathrm{RG}(o)$ were to be reduced, since the basal glucose production is near 2 mg/kg-min, *maximal* errors (reduction of $\mathrm{RG}(o)$ to zero) would be approximately 20%, 10% and 7% during the staircase infusion where (steady-state) glucose infusion rates average 10, 24 and 30 mg/hg-min at each step. Since suppression is likely not complete, errors would, in practice be lower. Moreover, the bias introduced in the calculation by a constant $\mathrm{RG_{endog}}$ is, at least partially,

accounted for by the estimate of the coloured noise embedded in the adaptive-recursive procedure of estimation of the process parameters. Given the robust nature of the controller therefore, the assumptions about RG_{endog}, although they will affect the reliability of the estimates of the insulin-dependent fractional removal of glucose, have less impact on the overall performance of the glucose clamp.

C. Stability

The effectiveness of an adaptive control formulation may be determined in relation to the hypothetical nonadaptive system where complete knowledge of the system is available (the reference model). Stability must be preserved in the context of both structured uncertainties in the parameters as well as unstructured errors in modelling. The glucose system, which is to be controlled is assumed to be characterized by equation 1. This system is stable provided that $(k_o + k(t)) < O \ \forall \ t$. Clearly, the precision of the control (the glucose clamp) will depend on the knowledge of $k(t)$ as it varies with time. If $k(t)$ is completely known and the system structure is correct, a simple one-step-ahead control law will apply. When $k(t)$ is not known, it can be estimated in a number of ways. The simplest is by extrapolation from the previous interval of observation (7–9).

As discussed above, the algorithm presented here is an attempt to use additional structural knowledge of the dependence of the parameter $k(t)$ on insulin and available information on rates and sites of insulin administration in the context of hyperinsulinemic glucose clamps, to improve glycemic control under these conditions. It is the hypothesis of this approach that reducing the unstructured modelling error in this way, should increase stability and improve control. The stability of the insulin model (equations 10, 14) is critical to the extrapolations which are made in $k(t)$ particularly as the sampling intervals increase. Both the initial and final estimates of the $\{A_1\}$, for example, lead to transfer functions with poles within the unit circle or simple poles on the unit circle. It was necessary to set $\Delta t \leq 0.5$ in equations (7)–(9) to achieve this stability. Simulations using equations (10) or (14) further confirm this stability. It should be noted that, because of the adaptive nature of the algorithm, only short-time stability is required. This could be verified by specifying a maximum value for k_i for an initial value k_o and using the inequality $k_i^2 \leq \lambda_{\max} k_0^2$ where $\lambda_{\max}$ is the maximum eigenvalue of the matrix, $A^T A$, where $A = (A_1, A_2, A_3)$. For reasonable changes in k_i/k_o, finite times for adequate extrapolation can be estimated, even with parameter variations which could lead to long-term instabilities. Errors in the observed glucose values, G_n, and hence estimates of k_n obtained from equation (22) are also minimized by constraining k_n using the smoothing filter described.

V. Conclusion

An adaptive controller of plasma glucose based on a nonlinear model of the insulin/glucose regulatory system is presented and has proven effective over a wide spectrum of insulin signals. Low coefficients of variation of the plasma glucose demonstrate the adequacy of this approach to react promptly under circumstances where insulin action varies widely and rapidly. Under these circumstances, taking into account the nonlinear dynamics of the insulin/glucose system is expected to enhance the predictive and hence the control capabilities of the algorithms. This is also demonstrated in the sampling flexibility.

In the experiments that have been presented, sampling frequency may vary from 2 to 7 min with no noticeable loss in performance. No test signal is required to prime the adaptive-recursive method of determination of the process parameters if reasonable initial values allow sufficient control while the parameters are adjusted to individual values from the early measurements.

The performance of the controller adds to the validation of the selected model structure. The extension of the approach which models the nonlinearity in the glucose/insulin system to the regulation of glycemia using variable insulin infusions (artificial pancreas) can therefore be considered [15]. Pagurek [6] suggested that the achievement of good adaptive control using linear models is inversely dependent on the severity of the non-linearity which actually exists in the glucose system. This limitation can be overcome by the evaluation of the nonlinear element of the glucose kinetics, as implemented in the present controller and may therefore allow the controller to handle more general situations.

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References

[1] R. A. DeFronzo, J. D. Tobin and R. Andres, "Glucose clamp technique: A method for quantifying insulin secretion and resistance," *Amer. J. Physiol.*, vol. 237, no. 3, pp. E214–E223, 1979.

[2] C. A. Verdonk, R. A. Rizza, R. E. Westland, R. L. Nelson, J. E. Gerich and F. J. Service, "Glucose clamping using the biostator GCIIS," *Horm. Metab. Res.*, vol. 12, no. 4, pp. 133–135, 1980.

[3] S. M. Furler, G. S. Zelenka and E. W. Kraegen, "Development and testing of a simple algorithm for a glucose clamp," *Med. Biol. Eng. Comp.*, vol. 24, no. 6, pp. 365–370, 1986.

[4] D. R. Matthews and J. P. Hosker, "Unbiased and flexible iterative computer program to achieve glucose clamping." *Diabetes Care*, vol. 12, no. 2, pp. 156–159, 1989.

[5] P. Palazzo and V. Viti, "A new glucose-clamp algorithm—Theoretical considerations and computer simulations," *IEEE Trans. Biomed. Eng.*, vol. 37, no. 5, pp. 535–543, 1990.

[6] B. Pagurek, J. S. Riordon and S. Mahmoud, "Adaptive control of the human glucose-regulatory system." *Med. Biol. Eng.*, vol. 10, no. 6, pp. 752–761, 1972.

[7] K. H. Norwich, G. Fluker, J. Anthony, I. Popescu, B. Pagurek and G. Hetenyi, Jr., "The development of a glucose clamp," *Metabolism*, vol. 24, no. 11, pp. 1221–1230, 1975.

[8] G. Hetenyi, Jr., B. Pagurek, G. Fluker, J. Anthony, I. Popescu and K. H. Norwich, "Computer controlled glucoregulation in the diabetic dog," *Annals of Biomedical Engineering*, vol. 5, no. 1, pp. 61–69, 1977.

[9] G. Pacini and R. N. Bergman, "PACBERG: An adaptive program for controlling the blood sugar," *Comp. Proc. Biomed.*, vol. 16, no. 1–2, pp. 13–20, 1983.

[10] L. L. Ng and S. W. Coppack, "The derivation of a minimal model insulin sensitivity index from euglycaemic clamps in man," *Diabetes Research*, vol. 11, no. 3, pp. 103–107, 1989.
[11] M. Vranic, J. Radziuk and A. Cherrington, "The role of glucagon and insulin in the glucoregulatory system, as assessed by tracer methods," in *Regulation and Control in Physiological Systems*, pp. 487–490, 1973.
[12] J. Radziuk, K. H. Norwich and M. Vranic, "Measurement and validation of nonsteady turnover rates with application to the insulin and glucose systems." *Fed. Proc.*, Vol. no. 7, 1855–64, 1974.
[13] P. A. Insel, J. E. Liljenquist, J. D. Tobin, R. S. Sherwin, P. Watkins, R. Andres and M. Berman, "Insulin control of glucose metabolism in man. A new kinetic analysis," *J. Clin. Invest.*, vol. 55, no. 5, pp. 1057–1066, 1975.
[14] R. N. Bergman, Y. Z. Ider, C. R. Bowden and C. Cobelli, "Quantitative estimation of insulin sensitivity," *Amer. J. Physiol.*, vol. 236, no. 6, pp. E667–E677, 1979.
[15] J. Radziuk and G. Hetenyi Jr., "Modelling and the use of tracers in the analysis and exogenous control of glucose homeostasis," In: *Quantitative Approaches to Metabolism: The Role of Tracers and Models in Clinical Medicine.*, D. Cramp (ed.) John Wiley and Sons, London, pp. 73–142, 1982.
[16] J. Radziuk, K. H. Norwich and M. Vranic, "Experimental validation of measurements of glucose turnover in nonsteady state," *Amer. J. Physiol.*, vol. 234, no. 1, pp. E84–E93, 1978.
[17] R. Hastings-James and M. W. Sage, "Recursive generalised-least-squares procedure for on-line identification of process parameters," *Proc. IEE*, vol. 116, no. 12, pp. 2057–2062, 1969.
[18] A. P. Sage and J. L. Melsa, "*Estimation theory with applications to communications and control*," McGraw Hill, New York, 1971.
[19] R. A. Rizza, L. J. Mandarino and J. E. Gench, "Dose-response characteristics for effects of insulin on production and utilization of glucose in man," *Am. J. Physiol.*, vol. 240, E630–E639, 1981.
[20] E. A. McGuire, J. D. Tobin, M. Berman and R. Andres, "Kinetics of native insulin in diabetics, obese and aged men," *Diabetes*, 29:110–120. 1979.

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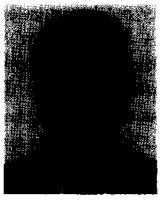

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