Modeling β-Cell Insulin Secretion—Implications for Closed-Loop Glucose Homeostasis

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ABSTRACT

Glucose sensing and insulin delivery technology can potentially be linked to form a closed-loop insulin delivery system. Ideally, such a system would establish normal physiologic glucose profiles. To this end, a model of β-cell secretion can potentially provide insight into the preferred structure of the insulin delivery algorithm. Two secretion models were evaluated for their ability to describe plasma insulin dynamics during hyperglycemic clamps (humans; n = 7), and for their ability to establish and maintain fasting euglycemia under conditions simulated by the minimal model. The first β-cell model (SD) characterized insulin secretion as a static component that had a delayed response to glucose, and a dynamic component that responded to the rate of increase of glucose. The second model (PID) described the response in terms of a proportional component without delay, an integral component that adjusted basal delivery in proportion to hyper/hypoglycemia, and a derivative component that responded to the rate of glucose change. Both models fit the β-cell response during the clamp, and established fasting euglycemia under simulated closed-loop conditions; however, the SD model did not maintain euglycemia following simulated changes in insulin sensitivity or glucose appearance, whereas the PID model did. The PID model was more stable under the simulated closed-loop conditions. Both the SD and PID models described β-cell secretion in response to a rapid increase in glucose. However, the PID model could maintain fasting euglycemia and was more stable under closed-loop conditions, and thus is more suited for such conditions.

INTRODUCTION

Advances in glucose sensing and insulin delivery technology can potentially be used to develop an automated closed-loop insulin delivery system. Ideally, such a system would calculate an insulin delivery rate that would recreate normal physiologic profiles for both glucose and insulin—that is, profiles that are typically observed in normal glucose-tolerant individuals with healthy β-cells. To this end, understanding how healthy β-cells maintain glucose tolerance may provide valuable insight into how an artificial β-cell system should respond to glucose challenges. Ultimately, a model that characterizes β-cell insulin secretion as a function of glucose might form the basis for an algorithm linking a glucose sensor to an insulin pump. However, if such a model is to be adapted for this purpose, its characteristic behavior under “closed-loop” needs to be understood.
When operating under closed-loop, the structure of secretion model determines how the system would be expected to respond to acute challenges such as meals and exercise, and how the composite system would respond to changes in the subject. Changes in the subject that affect closed-loop behavior include changes in insulin sensitivity\textsuperscript{6–8} and changes in the rate of endogenous glucose appearance.\textsuperscript{9–11} Many closed-loop properties can be inferred from the structure of the β-cell model per se, while others are determined both by the structure of the secretion model and by the assumed structure for the system being controlled—that is, the underlying assumptions regarding the dynamics of insulin action.

To date, few models have been proposed to quantify the β-cell insulin response as a function of plasma glucose.\textsuperscript{12–19} Of these, the one developed by Cobelli and colleagues\textsuperscript{13–16} is perhaps the best characterized. This model—here called SD—separates the secretion response into static and dynamic components. The dynamic component reacts to the rate of increase in plasma glucose and is 0 when the glucose level is stable or falling. The static component provides a delayed response to an increase in plasma glucose. The SD model has been shown to capture the β-cell secretory response during relatively slow physiologic changes in glycemia (e.g., the oral glucose tolerance test or a graded glucose infusion\textsuperscript{15,16}).

In the present study, the ability of the SD model\textsuperscript{13–16} to fit the insulin secretory dynamic during the more rapid glucose dynamics observed with hyperglycemic clamps was investigated, together with its properties under the assumption that insulin action is characterized by the minimal model of glucose kinetics.\textsuperscript{20,21} The SD model was compared with a physiologic insulin delivery (PID) model we previously proposed for an artificial β-cell algorithm.\textsuperscript{22} Both models were evaluated for their ability to fit the β-cell secretion during the clamps, and for their ability to establish and maintain euglycemic fasting conditions during simulated changes in insulin sensitivity (S\textsubscript{I}) and rate of endogenous glucose appearance (R\textsubscript{a}).

### METHODS

#### Hyperglycemic clamps

Seven nondiabetic subjects [five men, two women, 48 ± 2 years old (mean ± SEM); body mass index (BMI), 25.7 ± 0.8 kg/m\textsuperscript{2}] were admitted to the UCLA General Clinical Research Center. After a 10-h overnight fast an intravenous catheter was placed in an antecubital vein for glucose administration. Another catheter was placed retrograde in a dorsal vein of the contralateral hand for blood withdrawal. The hand was placed in a heating pad to arterialize the blood. A glucose bolus (0.15 g/kg; 50% solution) was given over 1 min at time 0 followed by a variable glucose infusion (20% solution) to maintain plasma glucose at ~180 mg/dL. Blood samples were collected at −20, −10, −1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, and 180 min. The UCLA Institutional Review Board approved the experimental protocol, and all subjects gave written informed consent.

#### Biochemical analysis

Plasma glucose concentration was measured by the glucose oxidase method with a Beckman Instruments (Fullerton, CA) glucose analyzer. Plasma insulin was determined by radioimmunoassay with reagents from Linco Research, Inc. (St. Louis, MO).

#### Secretion model analysis

Details of the SD model have been previously reported.\textsuperscript{13–16} Briefly, the model is composed of a static secretion response (SR\textsubscript{S}) and a dynamic secretion response (SR\textsubscript{D}):

\[
SR(t) = SR_S(t) + SR_D(t), \quad SR(t) \geq 0 \text{ all } t
\]

where

\[
\frac{dSR_S(t)}{dt} = -\alpha[SR_S(t) + \gamma(G(t) - h)]; \\
SR_S(0) = \gamma(G_B - h)
\]

\[
SR_D(t) = \begin{cases} 
K_D \frac{dG}{dt} & \text{if } \frac{dG}{dt} > 0 \\
0 & \text{if } \frac{dG}{dt} \leq 0
\end{cases}
\]
As formulated, $1/\alpha$ determines the delay time in the static response (in min; time to 63% maximal response), $\gamma$ ($\mu$U/min per mg/dL) determines the magnitude of the static response, and $K_D$ ($\mu$U/min per mg/dL per min) determines the magnitude of the dynamic response. The value at which secretion would theoretically be 0 is given by $h$ (mg/dL). Plasma glucose was assumed to be below the saturation threshold for glucose-induced insulin secretion.\(^{12}\)

The SD model was compared with the PID model. The PID model divides the secretory response into three components—a proportional component ($P$) that reacts to the difference between plasma glucose and basal glucose (the putative $\beta$-cell set point for fasting glucose), an integral component ($I$) that reacts to the rate of change in plasma glucose, and a derivative component ($D$) that reacts to the rate of change in plasma glucose. The model is partially based on the well-known proportional-integral-derivative controller that is ubiquitous in industrial control systems.\(^{23}\) Expressed as the sum of its individual components the model is:

$$\text{PID}(t) = P(t) + I(t) + D(t); \text{PID}(t) \geq 0 \text{ all } t$$

where

$$P(t) = K_P(G - G_B)$$

$$\frac{dI(t)}{dt} = K_P(G - G_B)/T_I; \quad I(0) = ID_B$$

$$D(t) = K_P T_D \frac{dG}{dt}$$

(2)

Here, $K_P$ determines the rate of insulin secretion in response to glucose above basal ($\mu$U/min per mg/dL), $T_I$ (min) determines the ratio of proportional to integral release, and $T_D$ (min) determines the ratio of derivative to proportional release.

Model identification

Both the SD and the PID models were identified from the plasma insulin response using a one-compartment model of insulin clearance:

$$\frac{dI(t)}{dt} = -p_4 I + p_5 ID(t)$$

(3)

For the insulin clearance model, $1/p_4$ defines the insulin clearance time constant (min), and $p_5$ is the reciprocal of the insulin distribution volume ($V$; in mL). The insulin delivery ($ID$) term was set to $SR(t)$ (Eq. 1) and to $PID(t)$ (Eq. 2) for the respective model identifications. For this approach, the insulin distribution volume ($p_5 = 1/V$) is a priori unidentifiable\(^{24}\) and was set to $p_4$. This normalizes $\gamma$, $K_D$ (SD model), and $K_P$ (PID model) to the insulin clearance rate (in mL/min). Absolute values for these parameters may be obtained by adjusting to insulin clearance estimates available in the literature.\(^{25–28}\)

Minimal model simulations

To investigate the closed-loop characteristics of each model, simulations were performed using the minimal model of glucose kinetics\(^{21}\):

$$\dot{G} = -(GEZI + Y)G + GEZI \cdot GZI; \quad G(0) = GZI$$

$$\dot{Y} = -p_2 Y + p_3 I_p(t); \quad Y(0) = 0$$

with

$$GZI = KZI \times nRA(t)$$

(4)

The effect of insulin to enhance fractional glucose clearance [$Y(t)$; in min\(^{-1}\)] is expressed relative to the plasma insulin concentration [$I_p(t)$] and is commonly assumed to be proportional to insulin in the remote interstitial fluid compartment.\(^{29}\) The rate at which insulin enters the remote compartment ($p_3$; in min\(^{-2}\) per $\mu$U/mL) and the rate at which it is cleared from the compartment ($p_2$; in min\(^{-1}\)) determine insulin sensitivity ($S_1 = p_3/p_2$; in min\(^{-1}\) per $\mu$U/mL). The effect of glucose to increase its uptake and suppress endogenous glucose appearance was expressed as the “glucose effect at zero insulin” ($GEZI$).\(^{30}\) Glucose at zero insulin ($GZI$) was assumed to increase with the net rate of glucose appearance [$nRA(t)$] defined as the predicted net hepatic glucose balance at zero glucose minus the predicted glucose uptake at zero glucose ($B_0 - R_{d0}$ in the notation of Bergman et al.\(^{21}\)).

Closed-loop simulations

The insulin secretion models were combined with the insulin clearance model (Eq. 3) and minimal model (Eq. 4) to form a closed-loop
system (Fig. 1). Simulations were performed assuming an initial plasma glucose level ($G_{zi}$) of 150 mg/dL, a GEZI of 1/60 min, a rate constant for insulin action ($p_2$) of 1/30 min, and a rate constant of insulin clearance ($p_4$) of 1/5 min. Under closed-loop, insulin clearance, insulin secretion gain, and insulin sensitivity only appear in combination (i.e., doubling insulin secretion and decreasing insulin sensitivity by a factor of 2 has no effect on the closed-loop glucose response provided the rate constants $p_2$ and $p_4$ do not change). Simulations in which insulin sensitivity was assumed to change were attributed to changes in $p_3$.

For the SD model, steady-state glucose is a function of both the secretion gain ($\gamma$) and the glucose intercept parameter ($h$). Thus, for simulations establishing euglycemia ($G_B = 100$ mg/dL), $h$ was calculated from the steady-state relations of Eqs. 1, 3, and 4:

$$h = G_B - GEZI \left[ \frac{G_{zi}}{G_B} - 1 \right] \frac{p_2}{p_3} \frac{p_4}{p_5} \gamma$$

(5)

For simulations in which $\gamma$ was changed, the ratio of $\gamma/K_D$ (min) was held constant. Once euglycemia was established, the predicted closed-loop responses to decreases in insulin sensitivity (50% decrease in $p_3$ with $p_2$ constant) and increases in rate of endogenous glucose appearance (50% increase in $G_{zi}$) were evaluated.

In addition to the model simulations, a system stability analysis was performed using a root-locus approach. This method, briefly described in the Appendix and more fully by Ogata,23 evaluates the effect of increasing the system gain ($\gamma \times p_3/p_2 \times p_5/p_4$), or altering the rate constants defined in each of the components of Figure 1. Briefly, each of the components in Figure 1 is characterized by its “open-loop” kinetic rate parameters (parameters whose units are min$^{-1}$); however, the closed-loop system is characterized by a different set of rate parameters, and a requirement for stability is that the “closed-loop” rate parameters be stable (this is determined by the root-locus; see Appendix).

Model parameters and fractional standard deviations (FSD) were identified from nonlinear least squares (Matlab; Civilized Software, Inc.). Root-locus analysis was performed using routines available in Matlab (MathWorks Inc.). Statistical tests (paired t-tests where SD and PID model parameters are analogous) were performed using GraphPad Prism (GraphPad Software Inc., San Diego, CA) with $p < 0.05$ considered significant.

RESULTS

Hyperglycemic glucose clamps

Both the SD and PID models (Eqs. 1 and 2) fit the $\beta$-cell clamp secretory profile well (Fig. 2B) with only minor residual runs being observed (Fig. 2C and D). Parameters of the PID model were, however, consistently identified with lower FSDs (Table 1). In addition to the secretion model parameters, the insulin clearance time constant (1/$p_4$ in Eq. 4) was also identified. This time constant was not different when identified using the SD and PID models (4.85 ± 0.96 vs. 5.47 ± 1.27 min; $p = 0.23$). Of the other model parameters, the only directly comparable pair is $K_D$ in the SD model and the product of $K_P T_D$ in the PID model—these too were not different (6.6 ± 2.8 vs. 6.5 ± 3.4 $\mu$U/mL per mg/dL per min; $p = 0.90$). Steady-

![FIG. 1.](image-url) Structure of closed-loop simulations. Two sets of simulations were performed: one in which the SD insulin secretion model was used (Eq. 1 with setpoint equal $h$), and one in which the PID secretion model was used (Eq. 2 with setpoint = $G_B$).
state basal insulin concentration estimated from the SD model tended to be higher than the measured level (Fig. 2), but the mean values were not significantly different (7.91 ± 1.02 vs. 6.98 ± 1.08 μU/mL; p = 0.2). For the PID model, basal insulin release was determined by the integrator initial condition \[ I(0) \] in Eq. 2.

### Minimal model simulations

To evaluate the behavior of the models under simulated closed-loop conditions, the block diagram of Figure 1 was used with average secretion parameters defined in Table 1 (cf. Methods for minimal model parameters). Multiple

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**Table 1. Identified Model Parameters Using the SD Model (Eq. 1) and PID Model (Eq. 2)**

<table>
<thead>
<tr>
<th>Model, parameter</th>
<th>SD</th>
<th>PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma ) (μU/min per mg/dL)</td>
<td>0.76 ± 0.15 (29.0%)</td>
<td>0.17 ± 0.05 (24.3%)</td>
</tr>
<tr>
<td>( 1/\alpha ) (min)</td>
<td>89.9 ± 24 (28.1%)</td>
<td>98.8 ± 34.5 (14.4%)</td>
</tr>
<tr>
<td>( K_D ) (μU/min per mg/dL per min)</td>
<td>6.6 ± 2.8 (15.2%)</td>
<td>37.6 ± 9.4 (14.7%)</td>
</tr>
<tr>
<td>( h ) (mg/dL)</td>
<td>92.5 ± 8.1 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>( K_P ) (μU/min per mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( T_I ) (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( T_D ) (min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The parameters \( \gamma \), \( K_D \) (SD model), and \( K_P \) (PID model) are normalized to insulin clearance rate of 1 mL/min (cf. Methods). Average FSD for each parameter is given in parentheses.
simulations were performed with each model under increasing secretion gains. For the system under SD control, $h$ was calculated on each simulation so as to achieve the desired basal rate (Eq. 5; Fig. 3A); under PID control basal euglycemia was achieved irrespective of system gain (Fig. 3B). The maximal gain without undershoot (thick solid lines in Fig. 3A and B) was determined in each case, and simulations were repeated at one-half, twice, and five times this gain. For the SD model this resulted in $h$ equal $-89$ (maximal gain without undershoot), $-277$ (half gain), $6$ (twice gain), and $62$ mg/dL (five times gain). For the systems operating at maximal gain without undershoot, PID closed-loop resulted in faster normalization (Fig. 3C). A more detailed examination of the relationship between stability and system gain is provided in the Appendix.

Although both models were able to normalize the glucose level to the desired basal level (Fig. 3), the SD model required parameter $h$ to be adjusted for each change in static secretion gain ($\gamma$). Under closed-loop, the secretion gain is multiplied by the clearance coefficient ($p_5$) and the minimal model insulin effect ($p_3$). Thus, changes in either of these parameters will affect the SD model closed-loop steady state as will changes in endogenous glucose production. To investigate these phenomena, the sim-

![Diagram A](image)

**FIG. 3.** Stability of the minimal model system under SD control (A) and PID control (B) together with a comparison of the two at the critical gains (SD crit, PID crit) where undershoot first appears (C).
ulation results of Figure 3 were extended to include conditions in which the subject’s insulin sensitivity decreases 50% ($p_3$ decrease with $p_2$ unchanged; Fig. 4A) and where the endogenous glucose production rate increases 50% ($G_{zi}$ increases by 50%; Fig. 4B). Each simulation was performed using the maximal gain without undershoot established in Figure 3. In all cases the PID secretion model renormalized fasting glucose over a period of 12 h (similar to an overnight fast). Conversely, the same changes resulted in systematic hyperglycemia when controlled using the SD model.

**DISCUSSION**

The present study evaluated the ability of two models of insulin secretion to describe β-cell dynamics during hyperglycemic clamps, and the ability of the models to establish and maintain fasting euglycemia under closed-loop conditions simulated by the minimal model. Both secretion models fit the clamp insulin secretory profile well (Fig. 2), and both established stable euglycemic fasting levels under simulated conditions (Fig. 3). However, of the two models, only the PID model was able to adjust to the varying insulin need following changes in insulin sensitivity (Fig. 4A) and endogenous glucose appearance (Fig. 4B).

The ability of the PID insulin secretion model to fit the plasma insulin profile during a hyperglycemic glucose clamp supports the contention that the biphasic insulin response acts in an analogous manner to a proportional-integral-derivative controller. Under this hypothesis, the slow rise in second-phase response [$I(t)$ in Eq. 2] would maintain fasting euglycemia irrespective of changes in insulin sensitivity or endogenous glucose appearance. Thus, the fasting hyperglycemia often seen in individuals with type 2 diabetes would necessarily require a defect in second-phase insulin release. This same mechanism—integration—could potentially be used to establish basal insulin delivery rates in individuals with type 1 diabetes undergoing closed-loop insulin delivery. There are two caveats to these conclusions: (1) the use of the hyperglycemic clamp as an experimental paradigm for the identification of the insulin secretion model; and (2) the use of the minimal model to predict changes in basal glucose given changes in plasma insulin.

The hyperglycemic clamp has long been used to characterize first- and second-phase insulin release; however, the clamp profile is clearly an unphysiologic stimulus. In the pres-

![FIG. 4. Adaptation of the PID and SD control systems to a 50% increase in the rate of endogenous glucose appearance (A) and a 50% decrease in insulin sensitivity (B).](image-url)
ent study, both the PID and the SD models fit the clamp profile equally well (Fig. 2). In this regard, the SD model has been validated for the more physiologic oral glucose tolerance test (OGTT). Neither model has been shown to fit the fall in glucose dynamics that occurs following a hyperglycemic clamp. The performance of the PID model under meal and OGTT conditions, and under the conditions where glucose falls very rapidly (post-clamp), will need to be evaluated if the PID insulin secretion hypothesis is to be validated.

The second caveat relates to the use of the minimal model for predicting changes in fasting glucose levels in response to changes in fasting insulin. Although the model has had extensive validation for the assessment of insulin sensitivity and glucose effectiveness, studies validating it for predicting changes in fasting glucose as a function of fasting insulin have not been performed. In particular, the dose response (Fig. 5A) has not been validated, nor has the predicted time course of glucose following an increase in plasma insulin (Fig. 5B).

With these caveats aside, there are several important conclusions that can be derived from the present study. The fact that both the PID and SD models characterize β-cell secretion during a clamp emphasizes that they are similar—both have a rapid first phase followed by a slow second phase. However, the differences in model structure that do exist have important implications for the closed-loop regulation of glucose. First, the PID model has a rate term \(K_D\) that is applied to both increases and decreases in glucose. Second, the PID model characterizes the β-cell second phase response with a component that reacts immediately to hyperglycemia/hypoglycemia. And third, the slow component of the PID is due to an integration component (the static term of the SD can be made to equal the integral term in the PID model by setting \(\alpha = 0\)). These differences result in a more stable closed-loop system under PID control, and an innate ability to adapt to changes in insulin sensitivity or glucose appearance.

The increased stability inherent in the PID model is due to the derivative effect on falling glucose, and to the immediate response (proportional) to changes in glycemia. In the SD model, the lack of derivative action during falling glucose compromises system stability in that the fall is anticipatory of pending hypoglycemia. The stability is further compromised by the delay in the static response. The ability of the PID model to compensate for changes in basal insulin requirement is due solely to the integration component \((I\) in Eq. 2\) as the proportional \([K_P(G - G_B)]\) and derivative \((K_DdG/dt)\) components are 0 at steady-state euglycemia \((G_B)\). While the SD model could be
made to compensate for these changes by setting $\alpha$ to 0, this would further compromise stability (move the pole at $s = -\alpha$ close to the unstable right hand $s$-plane; cf. Appendix). The compromised stability, inherent in the SD model together with its inability to adapt to changes in basal insulin requirement, makes it an unlikely candidate for closed-loop insulin delivery.

The hypothesis that the $\beta$-cell can adapt its basal rate in response to insulin resistance is supported by early work from Porte and colleagues showing that, between individuals, fasting insulin is independent of fasting glucose. Support for the adaptation to increased rates of glucose appearance is provided by studies showing that low-level glucose infusions (100 mg/min) are completely normalized in some individuals after 20 h with higher rates (300 mg/min and $\sim$400 mg/min) being required to generate a significant increase in glycemia. The salient observation in these studies is that $\beta$-cell secretion can increase despite a lowering of plasma glucose. This is consistent with the PID model in that both the proportional and the derivative components can fall during periods where the integrator continues to increase (the integrator increases for the duration that plasma glucose is above basal)—the balance of the three components could thus account for the increase in plasma insulin observed in the low-dose glucose infusion study. For the studies using a higher glucose infusion rate, 20 h may not have been sufficient time for the $\beta$-cell to increase secretion. Although a longer glucose infusion study (48 h with 4 mg/min/kg glucose infusion) did indicate an elevation in glucose, the elevated glucose was based on the average glucose measured every 4 h during the infusion during which time the subjects had five carbohydrate-enriched meals. In rodents, 3-day glucose (rate of glucose appearance) or intralipid (decreased insulin sensitivity) infusion is normalized with a concomitant increase in fasting insulin level. Irrespective of whether the $\beta$-cell can integrate glucose above basal as its means to adapt to changing insulin requirement, it is clear that an artificial system that achieves a stable steady state would necessarily be at the desired basal glucose setpoint.

In conclusion, the present study demonstrated the feasibility of the PID model to describe $\beta$-cell secretion during a hyperglycemic clamp. If the PID hypothesis is correct, it implies that fasting hyperglycemia, observed in individuals with type 2 diabetes, can only occur with a defect in second-phase insulin release. Further work will be needed to validate the PID model during more physiologic glucose challenges such as meals and the OGTT. If the PID model is validated, it can potentially be adapted for use in an artificial insulin delivery algorithm.

**APPENDIX**

The relationship between system gain and stability can be assessed using the method of root-locus. The analysis requires that a linearized form of the minimal model be derived, and that the remaining system equations (Eqs. 1–4) be transformed into an algebraic form (Laplace transform). A linear approximation to the minimal model can be obtained by fitting the minimal model response to a step increase in plasma insulin (Fig. 5B, solid line) to a second-order dynamic model (equation A1). This approximation results in a linear model (Fig. 5, open circles; $r^2 > 0.95$) with time constants $1/a_1$ and $1/a_2$ both equal $\sim$33 min and linearized gain and $K$ ($\Delta G/\Delta I_p$; Fig. 5A) equal $\sim$3.3 mg/dL per $\mu$U/mL:

$$\frac{\Delta G}{\Delta I_p} = \frac{a_1 a_2 K}{(s + a_1)(s + a_2)}$$  \hspace{1cm} (A1)

The linearized model is only valid in the glucose range 150–100 mg/dL with greater increases being approximated by lower gain (Fig. 5A) and faster time constants (data not shown). Laplace transforms for the remaining model equations are:

$$\frac{SD}{G - h} = \frac{K_D(s^2 + \alpha s + \gamma/K_D)}{s + \alpha}$$  \hspace{1cm} (rise) (A2)

$$\frac{PID}{G - G_B} = \frac{K_P(T_1 T_D s^2 + T_1 s + 1)}{s}$$  \hspace{1cm} (A3)

$$\frac{I_p}{ID} = \frac{p_5}{s + p_4}$$  \hspace{1cm} (A4)

Equations A1–A4 form a complete closed-loop system with open-loop “poles” wherever a de-
nominator equals 0 (e.g., $s = -p_4$ in Eq. A4) and open-loop “zeros” wherever a numerator equals 0 (e.g., $s = (-T_1 \pm \sqrt{T_1^2 - 4T_1T_D})/(2T_1T_D)$ in Eq. A3). Generally, “$s$” is a complex number, and the pole-zero locations are plotted in the so-called “$s$-plane.” Under closed-loop, each open-loop system “pole” moves in a characteristic pattern determined by the system gain—specifically, poles move from their open loop locations toward a corresponding 0 (each pole has a corresponding closed-loop 0; 0 values may occur at all values of infinity). Systems in which all poles lie on the real axis are overdamped (nonoscillatory). For increasing system gain, poles tend to move along the real axis and then break off to become complex. Systems with complex poles are underdamped (oscillatory but with oscillations that diminish with time). Further increases in gain may continue to move the closed-loop poles to the right-hand $s$-plane, where the system is unstable (oscillations that increase with time). A plot of all the closed-loop system poles for different values of system gain is known as the root-locus.

For the SD system, under conditions in which the glucose is falling, the closed-loop system poles (Fig. 6A) can be seen to move from their open-loop locations ($s = -\alpha, -p_4, -a_1, -a_2$) along the real axis, break from the real axis, and ultimately move to the right-hand $s$-plane. Thus, for SD control during falling glucose increasing gain yields an unstable system. This can be contrasted to the condition when glucose is rising (Fig. 6B), in which the presence of the derivative ($K_D$) generates two “open-loop” 0 values, which effectively prevent the loci from entering the right-hand $s$-plane. Thus under conditions where glucose is rising, the SD model results in a stable closed-loop system for all system gains.

**FIG. 6.** Root-locus plots for the closed-loop system of Figure 1 under SD control during falling glucose (A), under SD control with rising glucose (B), under SD control during falling glucose in the absence of an SR delay ($\alpha = 0$; C), and under PID control (D). For the closed-loop system to be stable each root must reside in the left-hand plane. Comparison of loci A with B indicates a dramatic increase in stability. Comparison of loci A with C indicates an improvement in stability. Loci D (PID) is most stable.
The effect of the delay term in the static secretion response can be isolated by comparing the fall in SR values without the delay (Fig. 6C) with the loci with the delay (Fig. 6A), which shows a clear left shift of the poles away from the unstable right-hand s-plane. PID control is stable for all system gains (Fig. 6D); constraining $T_D < T_I/4$ can eliminate the complex poles nearest the imaginary axis [i.e., prevent $s = (-T_I \pm \sqrt{T_I^2 - 4T_I T_D})/(2T_I T_D)$ from being complex].

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