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SYMPOSIUM

Analysis of Algorithms for Intensive Care Unit Blood Glucose Control

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Abstract

Intensive care unit (ICU) blood glucose control algorithms were reviewed and analyzed in the context of linear systems theory and classical feedback control algorithms. Closed-loop performance was illustrated by applying the algorithms in simulation studies using an *in silico* model of an ICU patient. Steady-state and dynamic input–output analysis was used to provide insight about controller design and potential closed-loop performance. The proportional-integral-derivative, columnar insulin dosing (CID, Glucommander-like), and glucose regulation for intensive care patients (GRIP) algorithms were shown to have similar features and performance. The CID strategy is a time-varying proportional-only controller (no integral action), whereas the GRIP algorithm is a nonlinear controller with integral action. A minor modification to the GRIP algorithm was suggested to improve the closed-loop performance. Recommendations were made to guide control theorists on important ICU control topics worthy of further study.

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Motivation and Background

Individuals who are critically ill may suffer from hyperglycemia and insulin resistance, even if they do not have diabetes. A healthy individual has a basal glucose concentration of approximately 80 mg/dl, but patients suffering from stress hyperglycemia can have blood glucose values greater than 200 mg/dl. A landmark study by Van den Berghe *et al.*[1] showed that maintaining blood glucose below 110 mg/dl reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, and acute renal failure by 41%. In addition, patients receiving intensive insulin therapy were less likely to require prolonged mechanical ventilation.

It is thus becoming standard to monitor blood glucose in the intensive care unit (ICU) by taking blood samples every hour or two, depending on the variability of the blood glucose values. Many hospitals and clinics use table lookup or paper-based protocols to enable nurses to change intravenous insulin infusion rates based on current and previous glucose measurements. Computer-based methods have been developed to enable more complex protocols for insulin adjustment to be used. Indeed, the implementation of simple protocols within an automated computer-based environment can reduce the error rate of paper-based protocols.

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Abbreviations: (CID) columnar insulin dosing, (GRIP) glucose regulation for intensive care patients, (ICU) intensive care unit, (IV) intravenous, (MPC) model predictive control, (PID) proportional-integral-derivative

Keywords: closed-loop glucose control, hyperglycemia, *in silico* model

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The primary goal of this article was to review recently published ICU glucose–insulin protocols in the context of feedback control systems design and analysis. The objective was not to provide a detailed literature review of ICU blood glucose control algorithms, as these are readily available in Chase *et al*.[2] Also, we did not study advanced model-based algorithms, such as those proposed by Hovorka and co-workers,[3] Chase and co-workers,[4] and Van den Berghe and co-workers.[5] Instead, we chose to assess characteristics of several selected low-order algorithms based on principles of control theory. A tutorial approach was taken so that clinicians can appreciate how control theory could better be used to understand and improve current control algorithms. Another goal was to point out limitations of widely used control analysis techniques and encourage control engineers to further study these relevant problems. For a broader historical perspective of control theory and applications, with a focus on algorithms for a closed-loop artificial pancreas, readers are referred elsewhere.[6]

While there is a clear motivation to use continuous glucose sensors, with frequent glucose measurements and insulin infusion adjustments,[7,8] the focus of this article was on the current state of ICU glucose control, where glucose measurements are available at roughly 1-hour intervals. The characteristics of control strategies were analyzed with respect to nonlinearity, integral action, tuning, and stability characteristics. This article first presents characteristic steady-state and dynamic physiological input–output (insulin-glucose) behavior, followed by a review of the classical proportional-integral-derivative (PID) control algorithm. The characteristics of recent ICU computer-based protocols are then discussed in the context of linear analysis and PID control. These protocols and algorithms are then compared in a study involving a simulation (*in silico*) model of an ICU subject.

Steady-State and Dynamic Behavior of an *in Silico* Patient

To be able to design control strategies it is important for control engineers to understand the steady-state and dynamic behavior of the system/process/subject to be controlled. In this article, we used the *in silico* patient model presented by Chase and co-workers[4]; for convenience, the modeling equations and parameter values are shown in the **Appendix**. This model is a modified version of the Bergman minimal model,[9,10] which is often used to identify insulin sensitivity using intravenous (IV) glucose tolerance tests. The model by Chase and co-workers[4] includes saturation terms for plasma insulin disappearance and insulin-dependent glucose clearance.

Figure 1 shows the steady-state behavior for three hypothetical subjects with different equilibrium glucose values (before insulin infusion is initiated), but with all other parameters constant as given in the **Appendix**. The slope (derivative of the output with respect to the input) of the input–output curve is known as the process gain. In this case, the process is nonlinear, as the slope is not constant. There is a high gain at low insulin infusion rates (high glucose values) and a low gain at high insulin infusion rates (low glucose values). This indicates that it is relatively easy to reduce glucose values when they are high, but it takes proportionally more insulin when the glucose is lower; this is a consequence of insulin saturation effects. For equivalent closed-loop performance, because the controller gain is generally inversely related to the process gain, it would be expected that the controller gain should be low at high glucose concentrations (low insulin infusion rates) and high at low glucose concentrations (high insulin infusion rates).

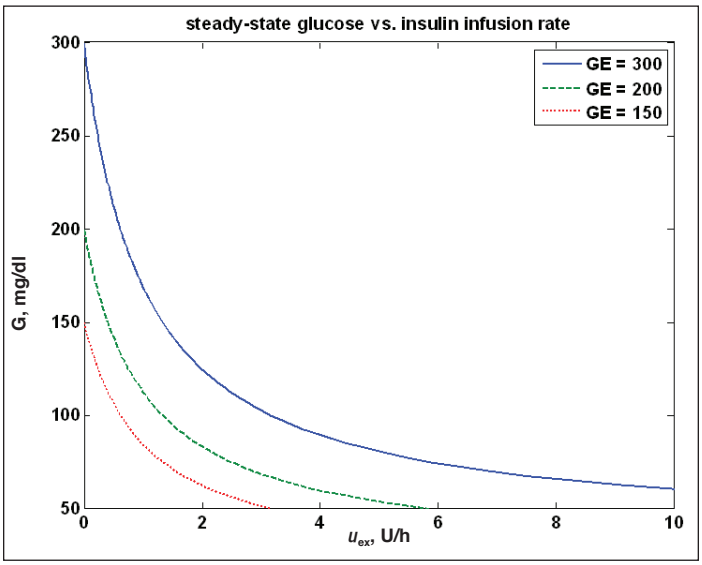

Figure 1. Steady-state input–output (insulin delivery rate – glucose concentration) curves for three hypothetical subjects with identical parameters except for equilibrium glucose concentration (concentration when no exogenous insulin is delivered).

Example dynamic behavior is shown in **Figure 2** for the intermediate subject from **Figure 1** ($G_E = 200$ mg/dl). Here, two different step changes in insulin infusion rate are made (0.4024 and 1.3346 U/h), resulting in relatively slow decreases in the glucose concentration; note that, for 1.3346 U/h, it takes over 3 hours to bring the glucose concentration below 110 mg/dl. While the long-term

glucose response is consistent with the steady-state curve shown in **Figure 1**, it is clear that, to achieve the desired final glucose concentration in a shorter period of time, either a bolus of insulin must be given or the insulin infusion must be substantially increased above the long-term value for a brief period of time. Also, note that the overall process gain (change in output/change in input) is larger for the small step input change [–124 (mg/dl)/(U/h)] than for the large step input change [–75 (mg/dl)/(U/h)].

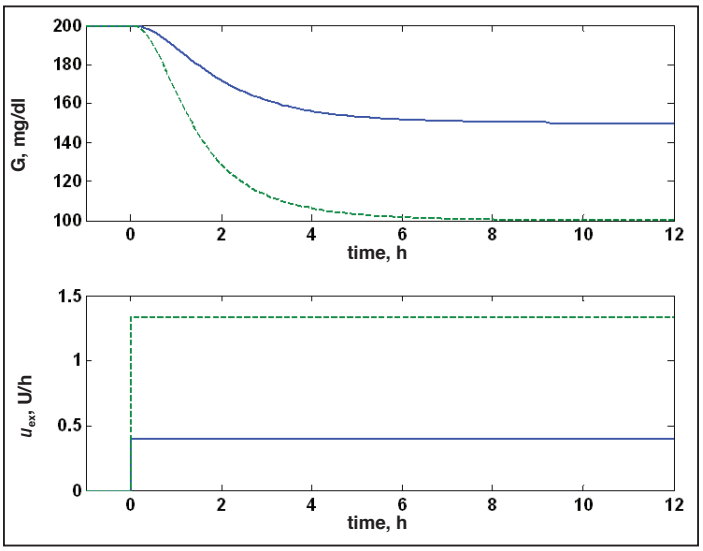

Figure 2. Dynamic behavior of a simulated subject ($G_E = 200$ mg/dl) for two different magnitude changes in insulin infusion rate at $t = 0$ hour. A change of 0.4024 U/h results in a decrease of 50 mg/dl, whereas a change of 1.3346 U/h results in a decrease of 100 mg/dl. Initial and final glucose concentrations are consistent with the steady-state input–output curve (**Figure 1**).

Proportional-Integral-Derivative Algorithm

The PID controller is the "workhorse" algorithm of the process industries. PID controllers are intuitive and presented in almost all undergraduate control textbooks.[11,12] The continuous-time representation of the PID algorithm finds the manipulated input (insulin delivery rate) as a function of the deviation of a measured output (glucose) from its desired setpoint, in the following fashion

$$u(t) = u_0 + k_c\left[e(t) + \frac{1}{\tau_I}\int_0^t e(t)dt + \tau_D\frac{de(t)}{dt}\right] \quad (1)$$

where, for the ICU application, $u(t)$ is the manipulated insulin infusion rate (U/h), u_0 is the initial or basal insulin infusion rate, and e is the error, which is the difference between the setpoint (r, desired glucose) and measured output (y, measured glucose)

$$e(t) = r(t) - y(t). \quad (2)$$

The manipulated input is proportional to the error, the integral of the error, and the derivative of the error, and there are three adjustable tuning parameters: proportional gain (k_c), integral time (τ_I), and derivative time (τ_D). Typical control textbooks present a number of techniques to select or adjust the values of these tuning parameters. The main limitation to the use of integral action is that so-called integral windup can occur when the manipulated inputs hit a constraint. In artificial pancreas applications, the integral term sometimes leads to hypoglycemia, thus many artificial pancreas algorithms do not have integral action. For example, Shimoda *et al.*[13] used a proportional-derivative controller in a wearable artificial pancreas-based subcutaneous glucose measurement and several insulin infusion methods (IV regular insulin, subcutaneous regular insulin, and subcutaneous insulin lispro). Also, the algorithm used in the Biostator[14] does not have integral action.

Equation (1) is based on continuous-time, or analog, systems where measurements are available and manipulated inputs are adjusted continuously. In practice, measurements are taken, and control actions are made, at discrete intervals of time. A simple (finite differences) discretization of the continuous PID algorithm yields

$$u(k) = u_0 + k_c\left[e(k) + \frac{\Delta t}{\tau_I}\sum_{i=0}^{k} e(i) + \frac{\tau_D}{\Delta t}\left(e(k) - e(k-1)\right)\right] \quad (3)$$

for the control action (insulin infusion) at the current time step (k), where Δt is the sample time, assumed to be constant. More generally, the PID algorithm is implemented in "velocity form," which is obtained by subtracting **Equation (3)** evaluated at time step $k-1$ from **Equation (3)** evaluated at time step k to find

$$u(k) = u(k-1) + k_c\left[\left(1 + \frac{\Delta t}{\tau_I} + \frac{\tau_D}{\Delta t}\right)e(k) + \left(-1 - \frac{2\tau_D}{\Delta t}\right)e(k-1) + \frac{\tau_D}{\Delta t}e(k-2)\right] \quad (4)$$

and the current control action, $u(k)$, is based on the previous control action, $u(k-1)$, and the current and previous two error values. The formulation also helps alleviate problems associated with reset windup because of manipulated input saturation.

The PID algorithm is considered a "nonmodel-based" algorithm, but it should be noted that many model-based control algorithms can be put into PID form, with the tuning parameters directly related to model parameters and a desired closed-loop response time.[11,15]

Wintergerst and colleagues[16] applied a version of discrete PID feedback control to six subjects in a pediatric ICU. Their implementation clearly showed contributions of each term (P,I,D) and, in particular, placed constraints on the integral contribution. For all individuals, the integral time was 150 minutes and the derivative time was 30 minutes. The proportional gain was adjusted by a factor of roughly two for each individual, depending on their initial response to feedback control (during the first 2 hours). Initial hourly infusion rates were typically 0.05–0.1 U/kg/h, with proportional gains roughly 0.5, with a range of 0.3–1.6 mU/kg/h per mg/dl. Wintegerst *et al.*[16] also developed an algorithm, based on glucose values and their rates of change, to choose sample intervals of 20, 40, or 60 minutes.

Now that the PID algorithm has been reviewed, we are able to discuss columnar insulin dosing (CID) (Glucommander-like) and glucose regulation for intensive care patients (GRIP) algorithms in the context of PID control. The focus of this article was on analysis of a constant sample time system, where blood glucose is sampled and insulin infusion adjustments are made at 1-hour intervals. While there are several algorithms for changing sample time values, we feel that it is important that underlying control algorithms implemented at a fixed sample interval exhibit desirable characteristics.

The Glucommander and Related Algorithms

Davidson and co-workers[17] provided a detailed analysis of 5080 studies using the Glucommander computer-based algorithm for advising on the delivery of intravenous insulin by nurses working in many different areas of a general hospital. The basic idea behind the Glucommander algorithm is shown in **Figure 3**. In this example, the subject has an initial blood glucose value of 295 mg/dl. Starting on the bold curve with a 0.02 slope, the first infusion rate is 4.7 U/h. Because the next glucose value has only decreased to 259 mg/dl (<15%), the multiplier (slope) is increased to 0.025, resulting in an insulin infusion rate of 4.9 U/h. The next few infusions are based on the 0.025 slope.

One of the goals of this article was to study an algorithm similar to the Glucommander, known as the CID algorithm,[18] primarily because the procedure for selecting changes in the multiplier factor (slope) is defined more clearly. The Glucommander and CID algorithms are based on the following formula presented by White *et al.*[19]

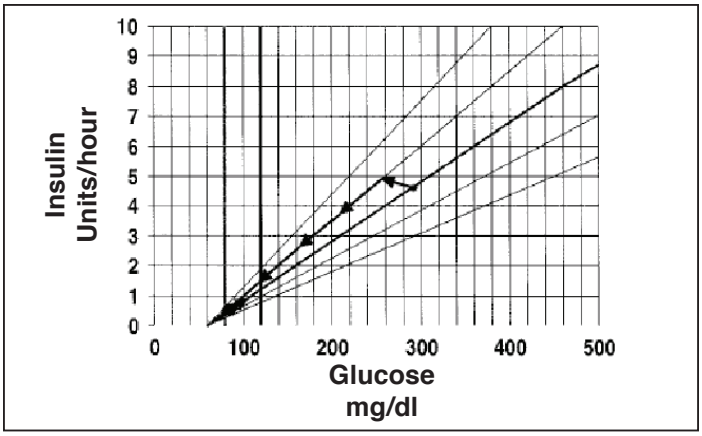

Figure 3. Basic operation of the Glucommander algorithm (from Davidson *et al.*[17]). In this example, the individual has an initial blood glucose value of 295 mg/dl. Starting on the curve with a 0.02 slope, the first infusion rate is 4.7 U/h. Because the next glucose value has only decreased to 259 mg/dl (<15%), the multiplier (slope) is increased by 25% (to 0.025), resulting in an insulin infusion rate of 4.9 U/h. The next few infusions are based on the 0.025 slope.

$$\text{Insulin dose (U/h)} = 0.02\ (\text{glucose} - 60), \tag{5}$$

where the glucose measurement has units of mg/dl. Here we show that this is a proportional-only control algorithm by removing the integral and derivative terms from **Equation (3)** to find

$$u(k) = u_0 + k_c\left(r - y(k)\right). \tag{6}$$

The White *et al.*[19] algorithm can be rewritten as

$$u(k) = -0.02\left(-40 + 100 - y(k)\right) \tag{7}$$

or

$$u(k) = 0.8 - 0.02\left(100 - y(k)\right) \tag{8}$$

where, for convenience, a setpoint glucose value of 100 mg/dl is assumed. Note then that the White *et al.*[19] algorithm is a proportional-only controller, with a basal infusion rate of 0.8 U/h and a proportional gain of –0.02 (U/h)/(mg/dl).

The CID algorithm[18] can be written

$$u(k) = 40 f(k) - f(k)\left(100 - \bar{y}(k)\right), \tag{9}$$

which is clearly a proportional-only control law

$$u(k) = u_0(k) + k_c(k)\left(100 - \bar{y}(k)\right), \tag{10}$$

where the basal (or nominal) infusion rate and controller proportional gain are no longer constant, but can vary from time step to time step. Also, the glucose value used

is an average over the past two samples (also known as a two-point moving average filter):

$$\bar{y}(k) = 0.5\big(y(k) + y(k-1)\big). \quad (11)$$

The algorithm for adjusting the multiplying factor (proportional gain) is shown in the **Appendix**. The initial controller gain in this strategy is $k_c = -0.02$ (U/h)/(mg/dl).

The display of a control algorithm in the form of **Figure 3** motivated us to reconstruct the steady-state input–output curves shown in **Figure 1** by simply switching the dependent and independent axes. In **Figure 4** we superimposed a proportional-only controller curve [with a bias of 1 U/h and gain of –0.04 (U/h)/(mg/dl)] on the physiological output–input (glucose–insulin) diagram. The resulting steady-state operating point can be found as the intersection of the controller curve and the physiological system curve. Note that, in general, the final steady state does not occur at the desired setpoint of 100 mg/dl. The steady-state glucose concentrations are approximately 90, 110, and 130 mg/dl for the $G_E = 150$, 200, and 300 curves, respectively; in each case there is an "offset" in the glucose concentration from its desired setpoint value of 100 mg/dl.

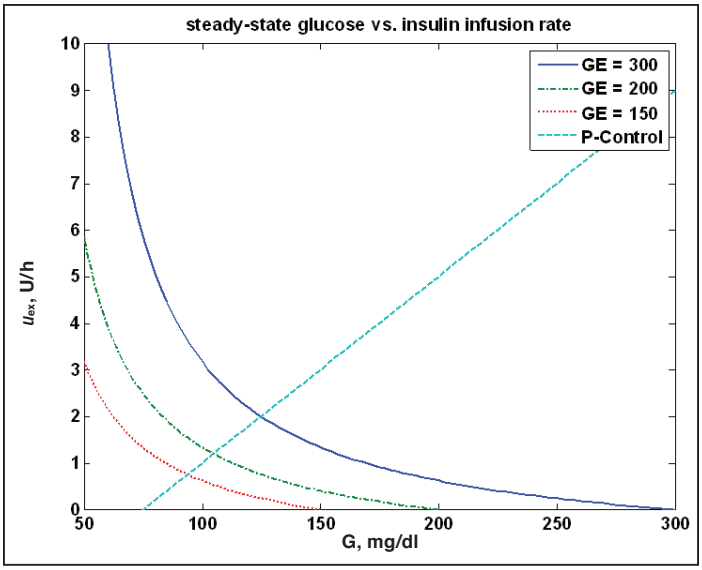

Figure 4. A proportional control operating curve is superimposed on the steady-state output–input curve for three hypothetical subjects (independent and dependent axes are switched from **Figure 1** to be consistent with **Figure 3**). The steady-state solution is the intersection of the controller and physiological system operating curves. For this example, the proportional controller parameters are $k_c = -0.04$ (U/h)/(mg/dl) and $u_0 = 1$ U/h, with a set point of 100 mg/dl.

Glucose Regulation for Intensive Care Patients Algorithm

Vogelzang and colleagues[20] presented a computerized control system for a surgical intensive care unit. In the GRIP algorithm, the change in insulin infusion rate from step $k-1$ to step k is computed from

$$u(k) - u(k-1) = \Delta u(k) = \big(1 + 0.25\bar{u}_{-4h}\big)\left(\frac{-0.2}{18}\big(r - y(k)\big) + \frac{0.3}{18}\Delta y_{-4h}\right), \quad (12)$$

where the -4h subscript is used to indicate either averages over the past 4 hours or a change in the past 4 hours [for convenience, we assume a sample time of 1 hour and use glucose units of mg/dl rather than mmol, hence the factor of 18 appearing in **Equation (12)**]. For insulin infusion, a four-point moving average filter results in the following term

$$\bar{u}_{-4h} = 0.25\big[u(k-1) + u(k-1) + u(k-3) + u(k-4)\big] \quad (13)$$

the change in glucose over a 4-hour period is used

$$\Delta y_{-4h} = y(k) - y(k-4). \quad (14)$$

It is likely that the 4-hour interval is used to reduce the effect of measurement noise. The GRIP algorithm is essentially a "gain scheduled" PID controller, where the proportional gain is a function of the average insulin infusion rate over the previous 4 hours. Gain scheduling is often used in flight control systems, for example, where controller tuning parameters are varied depending on the flight condition. For blood glucose control, increasing the controller gain as a function of average insulin infusion rate makes physiological sense. Because of saturation effects, each increase in insulin infusion tends to have less of an effect; this is shown clearly in the curves in **Figure 1**; an increasing controller gain is needed to compensate for this effect. It should be noted that equal-percentage valves are often used in chemical process manufacturing to compensate for a similar problem with pressure drop as a function of flow rate.

The GRIP algorithm also imposes a maximum constraint of 10 U/h and limits the increase to 1.5 U/h at any time step. We found that the closed-loop algorithm, as published, is actually unstable, as shown in the analysis in the **Appendix**. The primary difficulty arises from the term (a derivative component in the algorithm) for the change in glucose over a 4-hour period. Following the spirit of the GRIP algorithm, we suggest the following minor substitution to assure a stable closed-loop algorithm. Rather than considering the change in glucose over a 4-hour period, we suggest that the change in glucose over the 1-hour sample time be used

$$\Delta y(k) = y(k) - y(k-1). \quad (15)$$

If the rate of change of glucose is roughly constant over the 4-hour period, then the following approximation

$$\Delta y_{-4h} = y(k) - y(k-4) \approx 4\Delta y(k) = 4\left[y(k) - y(k-1)\right] \quad (16)$$

results in the algorithm

$$u(k) = u(k-1) + \left(1 + 0.25\bar{u}_{-4h}\right)\left(\frac{-0.2}{18}\left(r - y(k)\right) + \frac{1.2}{18}\left(y(k) - y(k-1)\right)\right). \quad (17)$$

Further, because the controller gain associated with the derivative ($y(k) - y(k-1)$) term is too high, we recommend using the value of 0.3. Thus, our recommended revision to the GRIP algorithm is

$$u(k) = u(k-1) + \left(1 + 0.25\bar{u}_{-4h}\right)\left(\frac{-0.2}{18}\left(r - y(k)\right) + \frac{0.3}{18}\left(y(k) - y(k-1)\right)\right) \quad (18)$$

As shown in the simulation studies that follow, **Equation (18)** results in a stable feedback system, whereas **Equation (12)** results in an unstable closed-loop system. It should be noted that the GRIP system is much more than an algorithm, as it includes an integrated database management system that interfaces with the nursing staff and the hospital information system. Another important component is an algorithm that chooses the time for the next blood sample (over a range of 30 minutes to 6 hours) depending on recent glucose measurements and their rate of change. Also, the insulin infusion rate calculated is a recommendation that can be modified easily by a nurse or physician. The variable sample time strategy, and nurse overrides, may help stabilize the feedback system, and we have not included these effects in the simulation study. Philosophically, however, we feel than an underlying control algorithm should satisfy stability characteristics in the limit of a fixed sample time.

Comparison of Control Algorithms on Simulated Subjects

Here, each of the control strategies was compared on a simulated subject, using the Chase *et al.*[4] model and parameters shown in the **Appendix**. Each simulation started at the equilibrium glucose concentration with no insulin infusion, followed by a single setpoint change to 100 mg/dl, with a sample time of 1 hour. The first simulation study, shown in **Figure 5**, compared the performance of the published GRIP algorithm with my suggested revision. Clearly, the published version is unstable (as proved in the **Appendix**), while my suggested revision has satisfactory performance.

The PID simulations used the Wintergerst *et al.*[16] recommendations of 150 and 30 minutes for the integral and derivative times, respectively; we have found similar values for integral and derivative times using the internal model control-based PID design procedure.[11] A value of –0.035 (U/h)/(mg/dl) was selected for the proportional gain to give response times and insulin infusion rates similar to the GRIP and CID algorithms. A comparison of PID, GRIP (revised), and CID is shown in **Figure 6** for a G_E value of 200 mg/dl. All of the algorithms exhibited similar performance, with the GRIP being the most conservative; the offset exhibited by the CID algorithm was quite small in this case. The G_E value was increased

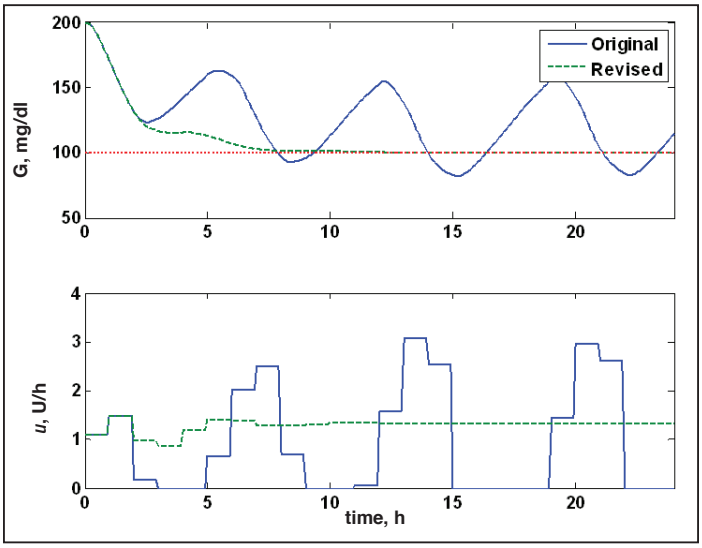

Figure 5. Comparison of closed-loop responses of the published GRIP [**Equation (12)**] with our suggested revision [**Equation (18)**]. (**Top**) Glucose response. (**Bottom**) Insulin infusion rate.

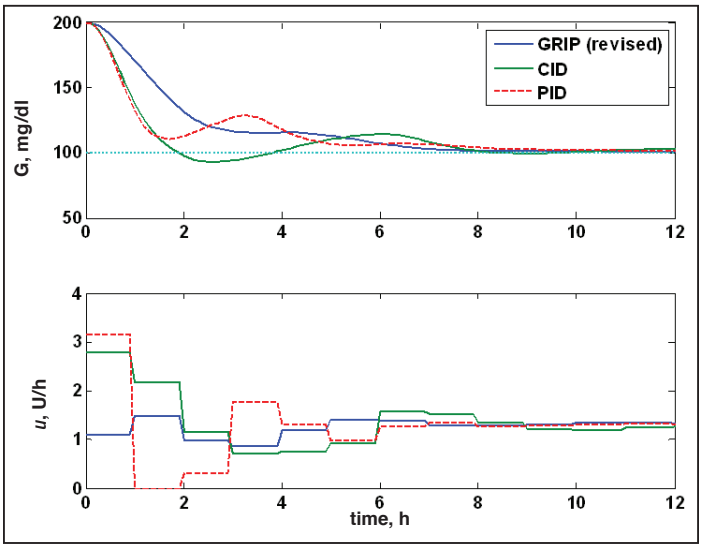

Figure 6. Comparison of closed-loop responses for CID, GRIP (revised), and PID for a simulated subject. (**Top**) Blood glucose values. (**Bottom**) Insulin infusion rates.

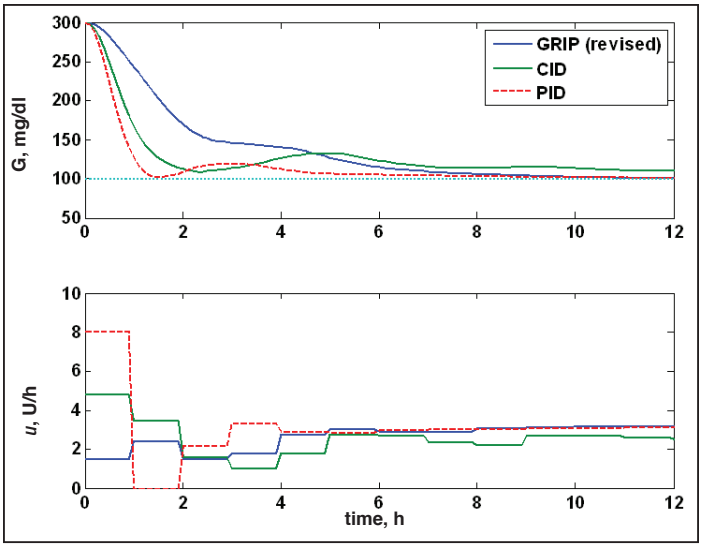

Figure 7. Comparison of closed-loop responses for CID, GRIP (revised), and PID for a simulated subject (G_E = 300 mg/dl). (**Top**) Blood glucose values. (**Bottom**) Insulin infusion rates.

to 300 mg/dl in the studies presented in **Figure 7**, where the offset exhibited by the CID algorithm was more transparent. It should be noted that this offset may not be important when sensor noise or uncertainty is considered.

The goal of this study was not to explore all of the possible sets of parameters or dynamic behaviors that could be observed in subjects, but to delineate the relevant features of the various control algorithms. Clearly, it is also important to incorporate realistic measurement noise and, for more frequently sampled systems, the effect of sample collection and analysis delays. Because these mathematical models take fractions of a second to simulate, it is easy to conduct Monte Carlo-type simulations where parameters are varied over physiologically relevant ranges to test the robustness of proposed algorithms. The approach developed by Lin and co-workers[21] created a virtual cohort of 200 patients tested in simulated clinical trials. This procedure was validated by statistical comparison of simulation results with actual clinical trials, providing confidence in new control strategies that are tested using simulated trials.

Remarks on Important Topics for Further Analysis

There is a need for critical analysis of blood glucose sample time selection and updating based on current and recent glucose values. It is likely that industrial statistical process control techniques, which are often used in discrete manufacturing systems, can play an important role in glucose measurement time modification. In discrete parts production there is a desire to not make frequent adjustments to manufacturing equipment, as this often involves manual shutdown and mechanical adjustments. Note that this is a problem related to "input" changes. In the ICU there is a desire to minimize the frequency of glucose measurements performed, as this involves substantial effort from the nursing staff to collect a blood sample and analyze the glucose concentration. This is a problem related to "output" collection. Even when there is automated collection and measurement of a blood sample, there may be a desire to limit the frequency of collection because of blood loss and/or analyzer "wear and tear."

Standard discrete control theory techniques are based on a constant sample time. Also, parameters and variables are assumed to vary continuously rather than having discrete values. Algorithms such as CID have calculated gains that take on discrete values and thus need to be analyzed in a hybrid analysis framework using integer and continuous variables.

We are a proponent of model-based techniques, such as model predictive control (MPC), that calculate control actions (insulin infusion rates) based on a mathematical model relating insulin and glucose dynamics. For high-performance systems it is important to have a model that adapts to match current input–output behavior. For ICU blood glucose control with samples available at 1-hour intervals, data may not be "rich" enough to update model parameters enough to have a significant impact on control system performance. When more frequent glucose samples are taken (perhaps using a continuous subcutaneous sensor), and more frequent insulin infusion adjustments are made, model adaptation is more likely to be successful.

Plank and co-workers[3] presented results of a trial of 60 patients undergoing cardiac surgery at three different ICU using MPC to manipulate insulin infusion rates to regulate blood glucose. The MPC strategy resulted in a significantly higher percentage of time spent in the targeted glycemic range compared to the use of routine protocols. Van Herpe *et al.*[5] also developed a MPC strategy for ICU blood glucose control. While not tested in a clinical study, MPC-recommended infusions were compared with those actually administered by nurses to confirm the viability of the algorithm.

In this article we have not discussed enteral or IV glucose feeding strategies, although it is clearly

important to consider this in control system design and implementation. Hovorka and Cordingley[22] studied the effect of parenteral glucose feeding on glucose control in critically ill patients using the insulin infusion protocol proposed by Kanji *et al*.[23] Hovorka and Cordingley[22] showed that the dynamic response of glucose concentration to insulin infusion is much faster when parenteral glucose feeding is used compared to the case of no glucose feeding. Wong *et al*.[4] and Lonergan *et al*.[24] discussed simultaneous manipulation of nutrition (using enteral glucose feeding) and insulin infusion rate to regulate blood glucose based on the three-state physiological model presented in the **Appendix**.

An advantage to model-based algorithms is that they can change glucose feeding on a short interval to improve glucose concentration control, while assuring that a desired daily nutrition requirement is maintained. A major advantage to model predictive control is that it is easy to implement two manipulated inputs (insulin infusion and glucose feed) with one desired output (glucose concentration) and to incorporate constraints such as meeting daily average glucose feed requirements.

Conclusions

The PID, CID, and GRIP algorithms for ICU blood glucose control were analyzed based on systems theory and classical feedback control principles. The basis for the CID algorithm was shown to be a proportional-only controller, without an integral term, resulting in offset (steady-state glucose differing from the desired setpoint), although the varying gain factor did act to reduce offset somewhat. The GRIP algorithm has a controller gain that varies as a function of the average insulin infusion rate and includes integral and derivative terms. A minor modification to the GRIP algorithm was proposed to substantially improve its closed-loop performance. In an *in silico* simulation study, the three algorithms were shown to have similar closed-loop performance. It was suggested that statistical process control techniques may be useful for recommending changes in the glucose sample time and that hybrid analysis (combined integer and continuous variables) techniques are appropriate for further study of these algorithms.

Acknowledgement:

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Appendix. Simulation Model and Algorithm Details

A1. Simulation Model

The physiological model used in our simulation studies is presented elsewhere.[4]

The equations are

$$\frac{dG}{dt} = -p_G G - S_I\left(G + G_E\right)\frac{Q}{1+\alpha_G Q} + \frac{G_f}{V_G}$$
$$\frac{dQ}{dt} = -kQ + kI$$
$$\frac{dI}{dt} = \frac{-nI}{1+\alpha_I I} + \frac{u_{ex}}{V_I}$$

where the parameters and variables are defined as (example values are shown in parentheses)

G is the glucose concentration, as a perturbation from G_E
G_E is the equilibrium glucose concentration, with no external glucose feeding or insulin infusion
Q is the insulin concentration that affects glucose directly
I is the insulin concentration in the insulin compartment
p_G is the glucose clearance rate (0.02 min^{-1})
S_I is the insulin sensitivity [0.002 liters/(min·mU)]
α_G is a parameter that accounts for saturation of the insulin effect on glucose (1/65 liters/mU)
G_f is the glucose feed rate directly into the glucose compartment
V_G is the glucose distribution volume (15 liters)
k is the rate constant for insulin transfer into the effective compartment (0.0099 min^{-1})
n is a parameter (0.16 min^{-1})
α_I is a saturation parameter (0.0017 liters/mU)
V_I is the insulin distribution volume (12 liters)
u_{ex} is the exogenous insulin infusion rate

Hann and colleagues[25] presented a novel integral-based technique to estimate the time-varying values of p_G and S_I. For the simple examples in this article, we assumed that these parameters were constant for each simulation. In practice, it is important to account for the time-varying nature of insulin sensitivity, in particular.

A2. Discrete PID Algorithms

Wintergerst *et al.*[16] used the following form

$$u(k) = P(k) + I(k) + D(k),$$

where the P, I, D terms are

$$P(k) = k_c\left(r - y(k)\right)$$
$$I(k) = I(k-1) + \frac{k_c}{\tau_I}\left(r - y(k)\right)\left(t(k) - t(k-1)\right)$$
$$D(k) = -\frac{k_c \tau_D}{t(k) - t(k-1)}\left(y(k) - y(k-1)\right)$$

and the integral term is "clipped" depending on the glucose level. The sample time can vary from 20 to 120 minutes, as selected by the following algorithm

$$
\begin{aligned}
&\textit{if} \quad y(k) \le 80 \; \textit{or} \left|\frac{dy}{dt}\right| > 1.2 mg/dL/\min \; \textit{or} \left(|\Delta u(k)| > 0.05 \frac{U}{kg \cdot hr} \; \textit{and} \; |\Delta u(k)| > 0.4 \, |\Delta u(k-1)| \right) \; \textit{then} \\
&\quad t(k+1) = t(k) + 20 \\
&\textit{elseif} \quad \left|\frac{dy}{dt}\right| > 0.75 mg/dL/\min \quad \textit{then} \\
&\quad t(k+1) = t(k) + 40 \\
&\textit{elseif} \quad \left|\frac{dy}{dt} > 0.25 mg/dL/\min\right| \quad \textit{then} \\
&\quad t(k+1) = t(k) + 60 \\
&\textit{else} \\
&\quad t(k+1) = t(k) + 120 \\
&\textit{endif}
\end{aligned}
$$

Their studies used $\tau_I = 150$ minutes and $\tau_D = 30$ minutes, with k_c varied from –0.3 to –1.6 (mU/kg/h)/(mg/dl).

In our simulation studies, **Equation (4)** is used with $k_c = -0.035$ (U/h)/(mg/dl), $\tau_I = 150$ minutes, and $\tau_D = 30$ minutes.

A3. Columnar Insulin Dosing

The CID algorithm includes a method to modify the "multiplying factor," which is really the proportional gain in a proportional-only control strategy. First, an average of the current and previous glucose measurements is made

$$\bar{y}(k) = \frac{1}{2}\left(y(k) + y(k-1)\right)$$

The multiplying factor is calculated in the following fashion

$$
\begin{aligned}
&\textit{if} \quad \bar{y}(k) \le 80 \quad \textit{then} \\
&\quad f(k) = f(k-1) - 0.01 \\
&\textit{elseif} \quad 80 < \bar{y}(k) < 110 \quad \textit{then} \\
&\quad f(k) = f(k-1) \\
&\textit{elseif} \quad \bar{y}(k) > \bar{y}(k-1) \quad \textit{then} \\
&\quad f(k) = f(k-1) + 0.01 \\
&\textit{else} \\
&\quad f(k) = f(k-1) \\
&\textit{endif}
\end{aligned}
$$

The multiplying factor is initiated with $f(1) = 0.02$, and a constraint of $f(k) \ge 0.01$ is imposed.

Also, the insulin infusion rate at time step k is found from the average glucose value (previous and current time steps) and the multiplying factor at the current time step

$$I(k) = \left(\bar{y}(k) - 60\right) \cdot f(k)$$

A4. Stability Analysis of the GRIP Algorithm

Using standard techniques,[11] we linearized the subject model for $G_E = 200$ mg/dl (**Appendix A1**) at a steady-state glucose value of 100 mg/dl to find

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix} = \begin{bmatrix}-0.04 & -0.007955 & 0\\ 0 & -0.0099 & 0.0099\\ 0 & 0 & -0.1538\end{bmatrix}\begin{bmatrix}x_1\\ x_2\\ x_3\end{bmatrix} + \begin{bmatrix}0\\ 0\\ 1.389\end{bmatrix}u$$

$$y = \begin{bmatrix}18 & 0 & 0\end{bmatrix}\begin{bmatrix}x_1\\ x_2\\ x_3\end{bmatrix}$$

and discretized the linear model with a sample time of 60 minutes. Taking the Z transform of the model, we obtained

$$g_p(z) = \frac{-8.282z^2 - 4.847z - 0.03866}{z^3 - 0.6429z^2 + 0.05015z - 4.933\times 10^{-6}}.$$

Similarly, we linearized the discrete GRIP algorithm, as published, at the steady-state glucose value of 100 mg/dl and used Z transforms to obtain

$$g_c(z) = \frac{0.007409z^4 - 0.0223}{z^4 - z^3}.$$

The stability test is then performed by finding the poles of $1 + g_c(z)g_p(z)$, which are

1.0920 + 0.2767i
1.0920 – 0.2767i
0.1382 + 0.6599i
0.1382 – 0.6599i
–0.3740 + 0.2104i
–0.3740 – 0.2104i
–0.0081

Poles with a magnitude greater than 1 indicate that the closed-loop system is unstable. However, our modification to the control law yields

$$g_c(z) = \frac{0.007409z - 0.02223}{z - 1}.$$

Analysis of $1 + g_c(z)g_p(z)$ yields poles with values of

0.8832 + 0.4122i
0.8832 – 0.4122i
–0.0382
–0.0238

which all have a magnitude less than 1, indicating that the closed-loop system is stable.