A Comparison of Clinical Control Strategies for the Hyperglycemia of Injury and Illness

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Abstract—The performances of several closed-loop algorithms for the automated regulation of blood glucose in an intensive care unit are compared in simulation studies. A nonlinear compartmental model with 15 distinct sets of patient parameter values is used to mimic the difficulties faced by an ICU treating many patients with different insulin sensitivities. A major advantage to the classical PID strategy is that the tuning parameters are a clear function of sample time, whereas other published strategies are specific to a given sample time. It is difficult to regulate extreme patients (extremely low or high insulin sensitivities) with any of the controllers with fixed-parameter control laws.

1.0 Background

A clinical study by Van den Berghe et al. [9] showed that administering insulin infusion therapy to maintain blood glucose (BG) below 110mg/dl reduces overall in-hospital mortality by 34%, bloodstream infection by 46% and acute renal failure by 41%. The patients in these studies were not necessarily diabetic, but experienced acute "stress" hyperglycemia associated with their injury or illness. The discovery of the benefits that Tight Glycemic Control (TGC) offers to patient outcome resulted in a rapid adoption throughout ICU's worldwide. Recent follow-up studies, however, now caution the practice of TGC primarily due to the increased risk of hypoglycemia associated with insulin infusion. Still the general belief throughout the medical community is that TGC does more benefit than harm and so caregivers continue its use.

The practice of TGC in the ICU can strain hospital resources because more frequent and accurate blood glucose measurements are required than hospitals are able to currently provide manually. TGC also requires insulin dosing protocols that rapidly but safely lower glucose levels. BG measurements in the ICU today are largely accomplished by either finger sticks using the same meters used by diabetics or by point of care (bedside) meters designed for hospital use. Results are used to determine insulin dosing from protocols which determine if and how much insulin should be administered. The process often involves table look-up methods but the final decision from the nurse properly qualifies the process as a human-in-the-loop feedback control system. Although such a system maintains the safety of human oversight, it can also introduce delayed, erratic or missing measurements and/or dosing, which is recognized as a drawback. The dosing protocols (control algorithms) are mostly synthesized ad-hoc, do not necessarily take into account physiological differences, and do not always lead to a steady desired state of normal BG (normoglycemia). Clearly, it is important that hospitals implement automatic monitoring and control methods that are safe and effective.

2.0 Introduction

Previous work (Bequette, [2]) analyzes some of the insulin dosing methods currently used for TGC. Its purpose was to compare performance of these methods from a control theoretic perspective, suggest potential improvements for practical use, and introduce an emerging area of study to the control community. Since that paper, industry has been busy developing new devices to provide the much needed capabilities of automatic and frequent sampling of BG, and the release of these devices is expected soon. This paper revisits two of the control methods from the first article and introduces another. It further considers a new issue. ICUs may apply existing algorithms with the new measurement devices but how will these changes affect performance? Will the algorithms require adjustments? To address these questions we revisit simulations, provide faster sampling rates and compare the performance of each algorithm, with a PID control algorithm as an additional point of reference.

Comparisons are all based on a three-state model that simulates the metabolic regulation of BG and its response to insulin infusion. The model uses 15 sets of parameters (equivalently 15 distinct *in-silico* subjects). The simulation operates under time-invariant physiological parameters which are not necessarily realistic, but suitable for comparison. Open-loop steady-state and dynamic behavior of the system are studied to assist in the design of an Internal Model Control (IMC)-based discrete Proportional-Integral-Derivative (PID) feedback controller. The response of this controller is compared to the following clinical insulin dosing protocols: (1) Columnar Insulin Dosing (CID) by Osburne et al. [8], (2) Glucose Regulation for Intensive Care Patients (GRIP) by Vogelzang et al. [10], and (3) The Biostator II algorithm by Albisser [1]. In addition to the comparison of the 4 control methods for the 15 subjects at a fixed measurement rate, other results include the effects of parameter tuning and sample rate on control performance.

Control limitations are discussed regarding extreme metabolic parameters (e.g., low insulin sensitivity S_I or high glucose clearance rate p_G). Certain extremes can result in poor control regardless of the algorithm used. In some cases for PID, the control difficulties are mitigated by tuning the discrete PID parameters based on the specific subject's physiological parameters. Though this may not be practical in the case of a commercial device it perhaps further supports the need for adaptive methods.

3.0 Simulation Model

There have been three metabolic models used in the analysis and simulation of critical care patients and glycemic control: that of Chee et al. [7], and Chase et al. [6]. The model used in the present simulation study is the one developed by Chase.

The Chase model is loosely based on Bergman's minimal model [4] with additional nonlinear terms and a grouped term for insulin sensitivity. Unlike its precedent and the model developed by Chee, Chase et al takes into account saturation effects of plasma insulin disappearance and insulin-dependent glucose clearance by using Michaelis-Menten functions. It is a simple model, consisting of only 3 differential equations. This model has been used in several glycemic control trials using different control approaches. Summarily, for the purpose of comparing closed-loop control accuracy and stability, the Chase model captures most if not all the essential characteristics of glucose-insulin dynamics.

3.1 Model Equations

The Chase model consists of the following set of nonlinear differential equations.

$$\frac{dG}{dt} = -p_G G - S_I (G + G_E)\frac{Q}{1+\alpha_G Q} + \frac{G_f}{V_G} \quad (1)$$

$$\frac{dQ}{dt} = -kQ + kI \quad (2)$$

$$\frac{dI}{dt} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}}{V_I} \quad (3)$$

where the parameters and variables are defined as:

G   is the glucose concentration, relative to G_E (mg/dl)
G_E equilibrium glucose concentration, with no external glucose feeding or insulin infusion (mg/dl)
Q   interstitial insulin concentration (mU/L)
I   plasma insulin concentration (mU/L)
p_G glucose clearance rate (min^{-1})
S_I insulin sensitivity (liters/(min*mU))
α_G a parameter that accounts for saturation of the insulin effect on glucose (liters/mU)
G_f plasma glucose feed rate (mg/min)
V_G glucose distribution volume (L)
k   rate constant for insulin transfer into the effective compartment (min^{-1})
n   a parameter (min^{-1})
α_I a saturation parameter(liters/mU)
V_I insulin distribution volume (L)
u_{ex} exogenous insulin infusion rate (mU/sec)

Table 1. Nominal parameter values

Parameters	α_G	V_G	k	n	α_I	V_I
Values	1/65	15	0.0099	0.16	0.0017	12

15 sets of simulation model parameters were selected to span the expected envelope of physiological response. The parameters which have the greatest impact, and which are varied in the simulation, are equilibrium glucose concentration, G_E; insulin sensitivity, s_I; and glucose clearance rate, p_G. The other parameters were held constant. Figure 1 illustrates the range of these patient cases in terms of steady-state glucose response vs. steady rates of insulin infusion.
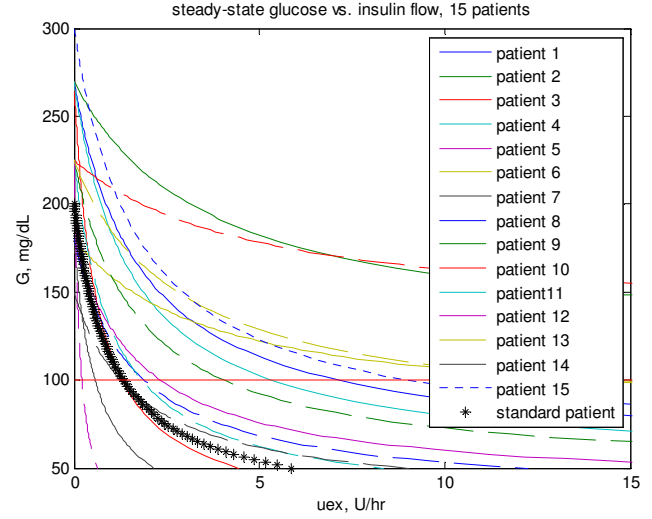

Figure 1. Steady-state input-output (insulin delivery rate-glucose concentration) curves for 15 subjects used in the simulation study.

Almost all subjects are able to achieve normal glucose levels within what can be reasoned as safe insulin dosing rates however several subjects (subject 2 and 10 are highly insulin resistant and subject 12 is highly insulin sensitive) were purposely included to represent extreme and difficult to control cases as a challenge to each control strategy.

4.0 Control Strategies

4.1 PID

An Internal Model Control (IMC) based Proportional Integral Derivative (PID) control law has the form

$$u(k) = u_0 + k_c\left[e(k) + \frac{\Delta t}{\tau_I}\sum_{i=0}^{k}e(i) + \frac{\tau_D}{\Delta t}(e(k) - e(k-1))\right]$$
$$e(k) = r(k) - y(k) \quad (4)$$

where the parameters and variables are defined as:

$u(k)$ insulin delivery rate (units/hr)
u_o basal insulin infusion rate (units/hr)
k_c loop gain (units/hr/mg/dL)
Δt sampling interval (min)
τ_I integral component rate (min)
τ_D derivative component rate (min)
$e(k)$ error (mg/dL)
$r(k)$ BG reference trajectory (mg/dL)
$y(k)$ BG measurement (mg/dL)

The values k_c, $k_c\Delta t/\tau_I$, and $k_c\tau_D/\Delta t$ respectively are the effective proportional, integral and derivative gains. These gains were determined using a second-order linear approximation of the Chase model and the strategy described by Bequette [3] which reduces gain determination to the selection of one parameter, λ. Gains were determined by two methods using simulations to sequentially increase the value of λ and finally selecting a value that best minimized the objective function

$$\Phi = \sum_{i=1}^{n}e(i)^2 \quad (5)$$

with a constraint that the lowest glucose measurement be no less than 60 mg/dl. The second method used a quadratic optimization method with the same objective function as shown above. This process was repeated for each of the 15 subjects to determine fixed gains for the controller that could best manage all patients. A $\lambda = 90.1$ min was used. r(k) is an exponential trajectory with a time constant of 120 minutes. Note that the PID control strategy is not used in clinical practice but rather provided here as an additional point of reference for comparisons.

4.2 CID (Columnar Insulin Dosing)

Among the three algorithms compared to PID, CID represents the more commonly applied clinical method for insulin dosing; a simple table based control strategy that's easily followed by nurses and physicians. Dosing charts typically provide clinicians with an appropriate multiplying factor to determine the next dosing rate based on current and previous BG measurements. The multiplying factor ranges from 0.1 in the 1st column to 1 in 10th column. For CID usage rules, if BG is within the normal range (80-110mg/dl), there is no column change, however if BG remains high on the hourly measurement; a column change to the right is required which generally increases dosing rate. Osburne et al. [8] interpreted the CID table procedure in terms of an iterative algorithm, summarized below:

$$\bar{y}(k) = \frac{1}{2}(y(k) + y(k-1)) \tag{6}$$

where $y(k)$ is the glucose measurement in mg/dL. The multiplying factor, $f(k)$, is calculated in the following

If $\bar{y}(k) \leq 80$ then

$$f(k) = f(k-1) - 0.01 \tag{7}$$

Else if $80 < \bar{y}(k) < 110$ then

$$f(k) = f(k-1) \tag{8}$$

Else if $\bar{y}(k) > \bar{y}(k-1)$ then
$$f(k) = f(k-1) + 0.01 \tag{9}$$

Else
$$f(k) = f(k-1) \tag{10}$$

and the insulin dosing, u(k), in units/hr is calculated as:

$$u(k) = (\bar{y}(k) - 60) f(k) \tag{11}$$

CID was originally designed for hourly BG measurements. Since the rate of change of gain, $f(k)$, is a constant ± 0.01 (units/hr)/(mg/dL) when BG is outside the range of 80 to 110 mg/dL, halving the rate of change to ± 0.005 (units/hr)/(mg/dL) for 30 minute sampling seemed a reasonable adjustment for the purposes of this investigation.

4.3 GRIP

Vogelzang et al. [10] developed a dosing algorithm for surgical intensive care patients (Glucose Regulation for Intensive Care Patients, GRIP). The GRIP algorithm is

$$u(k) - u(k-1) = \Delta u(k) =$$
$$(1 + 0.25\bar{u}_{-4h})(\frac{-0.2}{18}(r - y(k)) + \frac{0.3}{18}\Delta y_{-4h}) \tag{12}$$
where

$$\bar{u}_{-4h} = 0.25[u(k-1) + u(k-2) + u(k-3) + u(k-4)] \tag{13}$$

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

This original algorithm demonstrated instability in some patients (Bequette [2]), resulting in a revised definition of Δy_{-4h} as

$$\Delta y_{-4h} = y(k) - y(k-1) \tag{15}$$

The intended measurement sampling (and dosing) rate for GRIP was published at between 30 minutes to 6 hours. Without any factors proportional to sampling time one can only expect different dynamic behavior depending on sampling time. Figure 2 confirms this expectation where one subject was simulated over 30 min to 6 hour sampling times. Even with the revised algorithm, a 2 hour sampling rate results in unstable behavior.
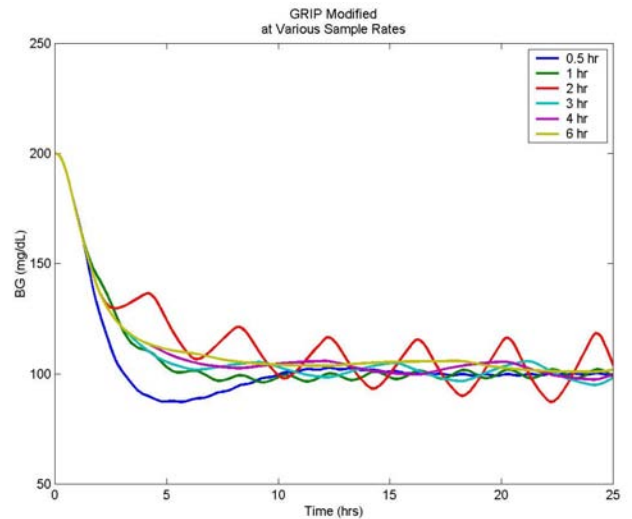

Figure 2. Transient glucose control response for standard patient using GRIP at various BG measurement and control rates.

4.4 Biostator II
The Biostator II algorithm by Albisser [1] is
$$IR_{CALC} = IR_1 \quad if \quad GY - B < 0 \tag{16}$$
$$IR_{CALC} = IR_1 + IR_2 \quad if \quad GY - B \geq 0 \tag{17}$$
$$IR_{CALC} = IR_{max} \quad if \quad IR_{calc} > IR_{max}$$

where

$$IR_1 = \begin{cases} R[(GY-B)/Q+1]^2 & if \quad [(GY-B)/Q+1] \geq 0 \\ 0 & [(GY-B)/Q+1] < 0 \end{cases} \tag{18}$$

$$IR_2 = \begin{cases} \dfrac{R \cdot KR \cdot m}{1000}(GY-B) & m \geq 0 \\ \dfrac{R \cdot KF \cdot m}{1000}(GY-B) & m < 0 \end{cases} \tag{19}$$

$$m = (2G_0 + G_1 - G_3 - 2G_4)/10 \tag{20}$$

$$GY = 2m + (G_0 + G_1 + G_2 + G_3 + G_4)/5 \qquad (21)$$

IR_1 is a nonlinear proportional action and IR_2 is derivative action. Note the choice of proportional or derivative control actions is based on the error trend (GY - B). The Biostator II algorithm consists of multiple parameters that are set by the clinician:

IR_{CALC}	Insulin dosing rate (units/hr)
IR_{max}	maximum insulin infusion rate (units/hr)
B	glucose setpoint or target (mg/dL)
G_x	glucose measurement at step x (mg/dL)
Q	gain of the controller function
R	basal infusion rate (units/hr)
KR	constant for rising glycemia
KF	constant for falling glycemia

The Biostator II was originally designed for a 1 minute sample rate. To accommodate a 30 minute sampling rate it is reasonable to reduce the control components, IR_1 and IR_2 each by a factor of 30 to obtain equivalent control action. Typical values of KF, KR and Q were adjusted accordingly for the simulations. Values of parameters are listed as below for both 1min (Albisser [1]) and 30mins sample times.

Parameters	KF	KR	Q	R
1 min	165	45	30	11.26
30 min	5.5	1.5	164.32	11.26

5.0 Simulations

The simulation of each patient begins at the value of G_E specified for that patient and the first measurement and control is applied at time zero. CID and GRIP are both designed for 1 hour sample time and Biostator II is designed for 1 minute sampling. Since figure 2 shows that GRIP works well with 30 minute sample time. We assume 30 minute sampling and control for our simulations.

Actual clinical application requires a maximum limit on the insulin dosing rate and calls for special interventions when BG levels begin to approach dangerous levels of hypoglycemia, this investigation excludes any limiting to level the comparisons and see where the course of control takes each patient over a 12 hour period. Limits can sometimes mask inherent control instabilities.

Although the goal of TGC is to reach a metabolic state of normoglycemia in the 80 to 110 mg/dL range, it is not clear how rapidly a patient should be controlled to this range. Indications are that 12 hours might be acceptable but that a period of 6 hours or less might be more desirable. But for many cases approaching normoglycemia in less than 3 hours could require significant infusion rates of insulin, elevating the risk of hypoglycemia. To represent a reasonable target for glucose rate of change and time to control, this analysis used an exponential trajectory for the PID control strategy with time constant of 120 minutes. This choice was also applied to the three other control strategies to further level comparisons. The trajectory is initialized at the first BG reading and exponentially targets 100 mg/dL in each case.

6.0 Results

Results compare the 4 control methods for the 15 subjects at a fixed BG measurement and control rate of 30 minutes by the illustrated plots in figures 3 through 6.
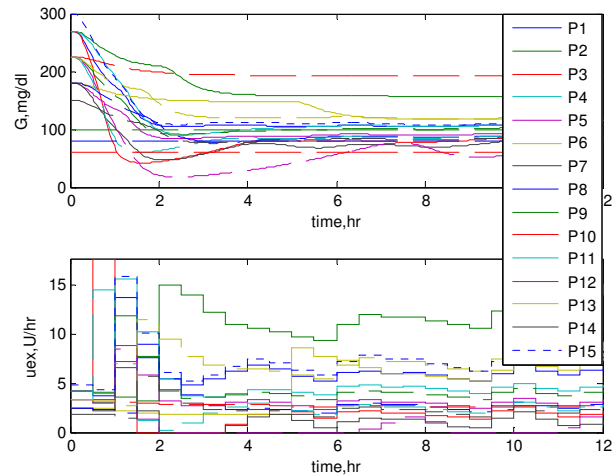

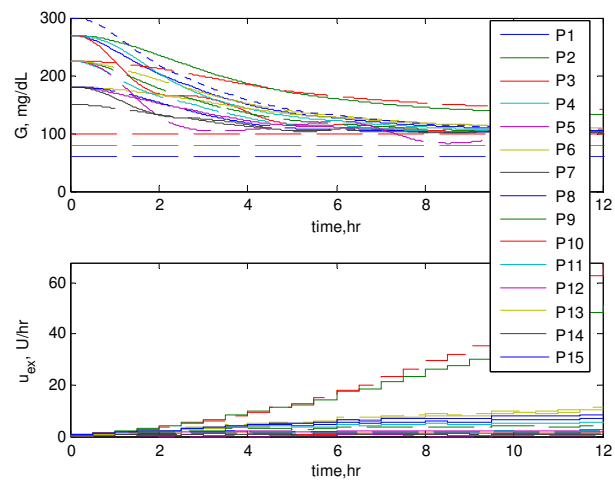Figure 3. Modified CID for 15 patients at 30 minute sampling.

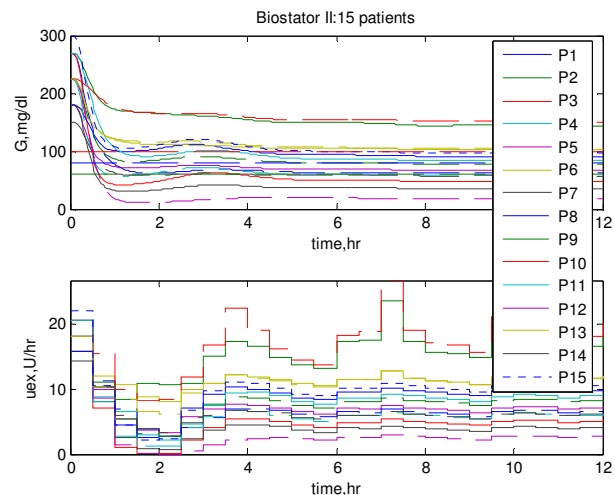Figure 4. GRIP for 15 patients at 30 minute sampling.

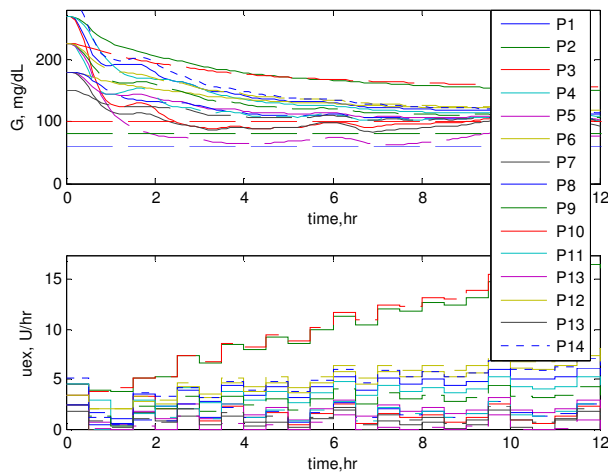Figure 5. Biostator II for 15 patients at 30 minute sampling

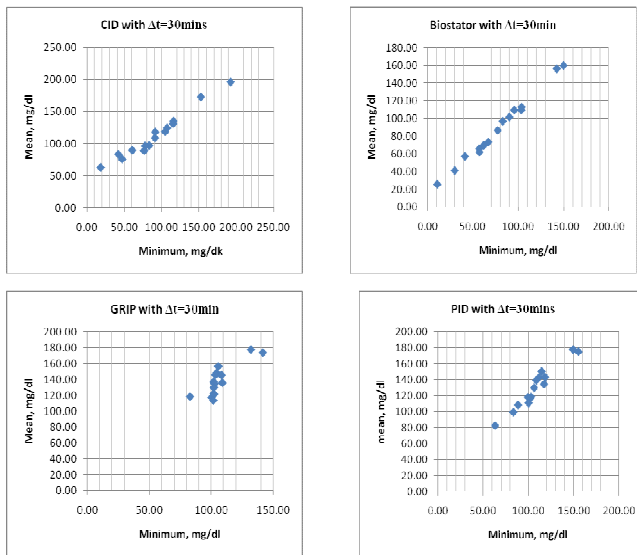Figure 6. PID for 15 patients at 30 minute sampling.

Figure 7. Mean vs Minimum of glucose concentration of all four algorithms at 30 min sampling. Each dot represents one patient.

For PID, a single λ value is found to minimize the objective function over all 15 patients

$$\Phi = \sum_{j=1}^{15} \sum_{i=1}^{n} (r_i - y_i)^2 \qquad (22)$$

Figure 7 shows that the PID has most of the patients in the normal range while GRIP has a higher glucose range, and CID and Biostator II yield highly variable control.

7.0 Conclusions

The main results show that of the four control strategies, GRIP and PID appear to provide the best control, avoiding any dangerous levels of hypoglycemia and reaching a suitable BG level within 12 hours for all patients except the high insulin resistant cases (patient 2 and 10). None of the control methods were able to lower BG for these patients.

Also, no algorithms except GRIP can elevate the glucose to normal range for the case of patient 12. It should be noted that patient 12 is characterized by combination of extreme physiological parameters which does not exist realistically. The PID however appears to be more aggressive than the GRIP, and although it achieves a closer approach to acceptable BG levels at 12 hours, PID does result in extended low BG for the insulin sensitive patient. For this patient, the GRIP algorithm appears to provide the best performance. Still GRIP does not accommodate some longer sample rates as evidenced in figure 2.

Although CID provided control for a good number of subjects it also led to lethal levels of extended hypoglycemia in several subjects. In practice the CID protocol recognizes this shortcoming and specifically instructs the clinician to dose D50W (dextrose and water) should BG measurements fall below 80 mg/dL.

The Biostator II showed the poorest response, with 5 or 6 patients reaching extended levels of hypoglycemia; some at lethal levels. Modifications may not have been necessarily adjusted at optimum scale, but even simulation work at the normal 1 minute sampling shows the Biostator II to be aggressive compared to the other algorithms, reaching target BG in less than 2 hours.

The results of this investigation demonstrate that changes in BG measurement frequency can impact the effectiveness of BG control depending on the choice of control strategy and whether or how these strategies are modified to accommodate sampling frequency. Of the three strategies selected for this investigation none include parameters that automatically adjust for different measurement and control frequencies as does the PID control strategy.

Automatic BG measurement devices that are soon expected on the market will likely provide clinicians with a range of selectable measurement frequencies. Selectable frequencies will probably range from those currently practiced (typically hourly measurements) to much higher frequencies with multiple measurements within an hour.

Effective dosing protocols for these new devices will therefore require the ability to accommodate this range of measurement frequencies to achieve a stable and suitable rate of control. Each of the control strategies evaluated in this simulation study requires further refinement to be deemed effective.

Further simulation work with the PID control strategy demonstrates that improved response is effectively managed by tuning PID gains for each patient case. Offering the ability for a user or clinician to 'tune' dosing controls for each patient would be impractical unless the process could be automated. A general conclusion is that strictly linear controls are not entirely effective and that nonlinear controls are likely the better choice. Each of the three clinical methods selected for investigation in this paper represent different nonlinear control strategies presumably derived using empirical methods. Although the comparative simulations show these methods are somewhat effective, none are more effective than the PID. Imagine the improvements a nonlinear control strategy might have to offer if approached by the same rigor as used in the PID strategy presented here.

Control engineers should be aware of the rapidly evolving need for sound control algorithms to implement TGC. New automated sensors will soon be available on the market, and researchers should be working now to develop more effective algorithms that take proper advantage of the improved

accuracy and increased measurement frequency capability they will offer. Future work should focus on nonlinear and adaptive control algorithms that accommodate variable sampling and models that include realistic time-varying parameters.

Acknowledgements

References

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Appendix

Table A1. 15 patient physiological parameters

Patient	S_I(liters/(min*mU))	p_G(min^{-1})	G_E (mg/dl)
1	0.004088	0.080537	269.5898
2	0.001412	0.080537	269.5898
3	0.004088	0.023463	269.5898
4	0.001412	0.023463	269.5898
5	0.004088	0.080537	180.4102
6	0.001412	0.080537	180.4102
7	0.004088	0.023463	180.4102
8	0.001412	0.023463	180.4102
9	0.00275	0.052	225
10	0.0005	0.052	225
11	0.005	0.052	225
12	0.00275	0.004	225
13	0.00275	0.1	225
14	0.00275	0.052	150
15	0.00275	0.052	300

IMC-Based PID Controller Design

For a second-order process model

$$g_P(s) = \frac{k_P}{(\tau_p s + 1)^2}$$

The IMC-based PID parameter values are [3]

$$k_c = \frac{2\tau}{k_p \lambda}, \quad \tau_I = 2\tau, \quad \tau_D = \frac{\tau}{2}$$