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Evaluation and Enhancement of an Intraoperative Insulin Infusion Protocol via In-Silico Simulation

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Abstract

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Keywords

Intraoperative glycemic control, in-silico evaluation, proportional-derivative controller, insulin infusion protocol, computer model

Disciplines

Computer Engineering | Computer Sciences

Comments

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Evaluation and Enhancement of an Intraoperative Insulin Infusion Protocol via In-Silico Simulation

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Abstract—Intraoperative glycemic control, particularly in cardiac surgical patients, remains challenging. Patients with impaired insulin sensitivity and/or secretion (i.e., type 1 diabetes mellitus) often manifest extremely labile blood glucose measurements during periods of stress and inflammation. Most current insulin infusion protocols are developed based on clinical experiences and consensus among a local group of physicians. Recent advances in human glucose metabolism modeling have established a computer model that invokes algorithms representing many of the pathways involved in glucose dysregulation for patients with diabetes. In this study, we used an FDA approved glucose metabolism model to evaluate an existing institutional intraoperative insulin infusion protocol via closed-loop simulation on the virtual diabetic population that comes with the computer model. A comparison of simulated responses to actual retrospective clinical data from 57 type 1 diabetic patients undergoing cardiac surgery managed by the institutional protocol was performed. We then designed a proportional-derivative controller that overcomes the weaknesses exhibited by our old protocol while preserving its strengths. In-silico evaluation results show that our proportional-derivative controller more effectively manages intraoperative hyperglycemia while simultaneously reducing hypoglycemia and glycemic variability. By performing in-silico simulation on intraoperative glucose and insulin responses, robust and seemingly efficacious algorithms can be generated that warrant prospective evaluation in human subjects.

Index Terms—Intraoperative glycemic control, in-silico evaluation, proportional-derivative controller, insulin infusion protocol, computer model

I. INTRODUCTION

Background. Hyperglycemia, unless iatrogenic, typically represents a secondary manifestation (i.e., epiphenomenon) of myriad physiologic, pharmacologic and/or metabolic derangements. While glucose is essential to life, in excess it is associated with increased cardiovascular morbidity and mortality in both diabetics and non-diabetics [1], [2]. Currently, one in every twelve people in the United States has diabetes mellitus and the risk of death among this group is roughly twice that of age-matched controls [3], [4], [5], [6]. It is therefore not surprising that the prevalence of diabetes mellitus and its associated complications among hospitalized patients

are increasing [7], [8], [9]. While outpatient management of hyperglycemia has historically been the primary focus in this population, and has unquestionably reduced diabetic morbidity and mortality, mounting evidence suggests that inpatient glycemic control may impart a similar benefit [10], [11], [12], [13], [14], [15], [16], [17], [18].

More recent investigations have begun focusing efforts towards reducing hyperglycemia specifically among critically ill and perioperative patients. The primary genesis of this approach stems from a 2001 randomized, controlled study that reported significant decreases in ICU and hospital mortality when blood glucose levels (BGLs) were maintained between 80 – 100 mg/dL compared to a less aggressive level of 180 – 200 mg/dL [19]. Subsequent enthusiasm for aggressive glucose management, however, has tempered as multiple groups attempting to replicate those results were unable to show comparable reductions in morbidity and mortality and have consistently observed high rates of hypoglycemia [20], [21], [22], [23], [24], [25]. Whether the lack of mortality benefit in these studies can be directly attributed to the high rates of hypoglycemia is uncertain. Many groups that have effectively maintained euglycemia whilst avoiding hypoglycemia have demonstrated improved outcomes in those treated more aggressively with insulin [26], [27], [28], [29]. Furthermore, wide and frequent oscillations in plasma glucose (so called, glycemic variability) appear to be as, if not more, important as absolute glucose values in critically ill patients and may compound any deleterious effects of hyperglycemia [30], [31], [32], [33].

While the appropriate target of plasma glucose in critically ill or perioperative patients remains elusive, there is general consensus with regards to three points: 1) Profound and sustained hyperglycemia in critically ill patients is likely harmful; 2) Isolated or sustained hypoglycemia in critically ill patients is likely harmful; 3) Wide and frequent variations in serum glucose values are likely harmful. As these three goals, nebulous as they may be, appear to be recurrent and unifying themes, attention must be directed towards methods, protocols and/or devices that can aid in achieving all three. Until accurate and reliable continuous glucose monitors are

available for critically ill patients, we remain limited in our ability to measure, respond, and predict future glucose values. Protocols that take into account prior glucose readings and rates of change have been more successful but are far from foolproof [34], [35], [36], [37], [38], [39], [40].

Motivation. Designing a protocol to reliably achieve glucose control, particularly when faced with frequent changes in physiologic parameters such as insulin sensitivity (as is seen perioperatively) is, at best, challenging and, at worst, harmful [41], [42], [43]. Current protocols are mostly derived from experience and intuition and are developed by local consensus, often taking into account available resources. Unlike many engineering systems (e.g., electronic circuits and automobiles), where first-principle plant models can be derived from classical physics, it is extremely difficult to identify a mathematical model that would accurately predict the glucose-insulin dynamics of an individual with only limited measurable clinical data [44]. Furthermore, it is neither feasible nor ethical to test all potential insulin protocols in human patients.

While attempts to model glucose metabolism using computer simulation were first proposed in the 1960s, newer simulations that incorporate data-driven plant modeling of glucose metabolism now exist and are able to more accurately mimic gluco-regulation in diabetic patients [45], [46], [47]. System identification, a variant of classical plant modeling, incorporates observed “real person” data (input and output of the plant) into a dynamic system allowing one to develop new mathematical models representative of the data entered [48]. Repeated evaluations of numerous insulin infusion protocols, all slightly different, on live patients is neither realistic nor feasible. In-silico evaluation and simulation is a well accepted and validated means to examine a large number of iterative changes and is only recently being used to evaluate insulin infusion protocols [49].

Contributions. The contribution of this paper is twofold. First, we use the Type 1 Diabetes Metabolic (T1DM) Simulator to evaluate an institutional intraoperative insulin protocol (IIP) for our diabetic cardiac surgery patient population and reveal its weaknesses by closed-loop in-silico simulation on the virtual population that comes with the simulator. We compare the simulated glucose responses to the actual retrospective clinical data collected from 57 type 1 diabetic patients undergoing cardiac surgery managed by the IIP, and show that the in-silico simulation is able to closely reproduce the glucose variability observed in the real clinical data. Second, we develop a novel proportional-derivative (PD) algorithm for the target population, propose a parameter tuning method to identify the optimal controller setting, evaluate its performance by in-silico simulations and show that the PD algorithm overcomes the weaknesses of IIP by reducing hypoglycemia and glucose variability, while preserving the strengths of the IIP by keeping most glucose readings within the target range. Our work demonstrates that in-silico simulation is a cost and time effective means of evaluating existing insulin infusion algorithms and generating more efficacious ones that warrant prospective evaluation in clinical trials.

II. OUR APPROACH

This section presents our in-silico simulation based approach for evaluating and improving the IIP. We first introduce the software platform for in-silico simulation. Then we describe the IIP and explain how it is evaluated on a virtual population as well as how the simulated results are validated against real clinical data. After evaluating the IIP and identifying its weaknesses, we design a PD algorithm and tune its parameters according to several performance metrics that are clinically important.

A. In Silico Testing Platform

The T1DM Simulator is a software package that was developed in MATLAB/Simulink® [50]. The patient glucose model that it utilizes is based on a previously published high-dimensional, non-linear differential equation model [51], [52]. The T1DM Simulator (academic version) was provided with 10 pre-identified type 1 diabetic “virtual” adult subjects. Each virtual subject is a configuration of the patient-specific parameters that are used by the simulation model (e.g., body weight and insulin/glucose transportation rates among different body compartments). Many of these parameters cannot be directly identified from the clinical data that hospitals currently have (e.g., total insulin/glucose distribution volumes). The virtual population in the software was identified based on real data collected from a group of individuals who participated in a triple-tracer meal study [52]: the meals were marked with isotope tracers so that the glucose/insulin fluxes in the body can be directly measured. In 2008, the T1DM Simulator (together with its group of 300 virtual subjects) received FDA approval for computer simulations that could be substituted for animal trials in pre-clinical testing and has become an accepted method of evaluation for studies in patients with type 1 diabetes mellitus [53].

The simulator is a Simulink® model file within MATLAB® that includes the patient model, glucose sensor and insulin pump models, and an interface for user-defined controllers [54]. We implemented the control algorithms in Simulink using the Stateflow® toolbox.

B. Evaluation of Insulin Infusion Protocol (IIP) and Validation of the Virtual Population

After obtaining acknowledgment from the University of Pennsylvania Institutional Review Board (IRB), blood glucose measurements were retrospectively evaluated on 57 type 1 diabetic patients controlled with the IIP during the period of cardiopulmonary bypass. The IIP used in the real patient population was a paper-based protocol that consisted of two parts: 1) a table that categorized the BGL into a finite number of intervals and, based upon the current interval, set a fixed intravenous bolus and infusion rate; 2) a set of infusion rate adjustment rules that took into account the relative change in BGL with respect to the previous value (Figure 1). The target BGL defined by the IIP was 70 – 130 mg/dL. The protocol rules were entered and evaluated in-silico on 10 virtual patients and the experiments were repeated with different initial BGL

Target Glucose: 70 - 130 mg/dL

**** Glucose must be checked every 30 minutes ****

*** INSULIN Bolus / Infusion Protocol ***

Initiation of Protocol

Initiate protocol if *any one* of the following criteria exist:

- Previous diagnosis of diabetes mellitus
- Any blood glucose (BG) > 120 mg/dL
- Any patient arriving to operating room on I.V. Insulin
- Anticipated administration of steroids
- Planned circulatory arrest

| Blood Glucose (mg/dL) | Insulin Bolus (U)* (No bolus pre-CPB) | Insulin Infusion (U/h) |
|-----------------------|---------------------------------------|------------------------|
| < 100 | 0 | 0 |
| 100 – 110 | 0 | 2 |
| 111 - 130 | 0 | 4 |
| 131 – 150 | 2 | 4 |
| 151 – 170 | 4 | 6 |
| 171 – 190 | 4 | 8 |
| 191 – 210 | 6 | 8 |
| 211 – 230 | 8 | 10 |
| 231 – 250 | 10 | 10 |
| 251 – 300 | 12 | 14 |
| > 300 | 15 | 15 |

INSULIN TITRATION PROTOCOL (start after INITIATING insulin infusion)

*** If BG unchanged- repeat action on Infusion Protocol ***

| Blood Glucose (mg/dL) | Action |
|-----------------------|---|
| < 60 | 25 mL of D₅₀ I.V. AND STOP ALL INSULIN |
| 60 – 99 | <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, stop infusion • If BG ↓ by greater than 30 mg/dL from last BG, 25 mL of D₅₀ I.V. • If BG ↑ from last BG, NO infusion and NO bolus |
| 100 – 150 | <p><u>BG Less than Prior</u></p> <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, ↓ infusion by 2 U/h and NO bolus • If BG ↓ by greater than 30 mg/dL from last BG, ↓ infusion by 4 U/h and NO bolus <p><u>BG Greater than Prior</u></p> <ul style="list-style-type: none"> • If BG ↑ by 10 mg/dL or less from last BG, continue infusion with ½ bolus • If BG ↑ by greater than 10 mg/dL from last BG, continue per infusion protocol |
| 151 – 170 | <p><u>BG Less than Prior</u></p> <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, continue per infusion protocol, NO bolus • If BG ↓ by greater than 30 mg/dL, start ½ recommended infusion, NO bolus <p><u>BG Greater than Prior</u></p> <ul style="list-style-type: none"> • If BG ↑ by 10 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↑ by greater than 10 mg/dL from last BG, continue per infusion protocol |
| 171 – 200 | <p><u>BG Less than Prior</u></p> <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↓ by greater than 30 mg/dL, continue per infusion protocol, NO bolus <p><u>BG Greater than Prior</u></p> <ul style="list-style-type: none"> • If BG ↑ by 10 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↑ by greater than 10 mg/dL from last BG, continue per infusion protocol |
| 201 – 250 | <p><u>BG Less than Prior</u></p> <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↓ by greater than 30 mg/dL, continue per infusion protocol, NO bolus <p><u>BG Greater than Prior</u></p> <ul style="list-style-type: none"> • If BG ↑ by 10 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↑ by greater than 10 mg/dL from last BG, continue per infusion protocol |
| 251 – 300 | <p><u>BG Less than Prior</u></p> <ul style="list-style-type: none"> • If BG ↓ by 30 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↓ by greater than 30 mg/dL, continue per infusion protocol, NO bolus <p><u>BG Greater than Prior</u></p> <ul style="list-style-type: none"> • If BG ↑ by 10 mg/dL or less from last BG, continue per infusion protocol with ½ bolus • If BG ↑ by greater than 10 mg/dL from last BG, continue per infusion protocol |
| > 300 | Continue per infusion protocol |

Fig. 1. Insulin infusion protocol used for real patient population (n=57). Abbreviations: BG, Blood glucose; CPB, Cardiopulmonary bypass; D50, 50 percent Dextrose (50 gram/100 mL).

values to more thoroughly investigate protocol performance. Blood glucose measurements were taken every 30 minutes (as defined in the IIP). For each real patient’s measured BGL trajectory, we ran closed-loop simulation on the 10 virtual subjects starting from the same initial BGL and picked the virtual subject whose simulated BGL trajectory best matched (i.e., had the lowest maximum deviation from) the measured BGLs. Simulated BGL data was then compared with the actual BGL data measured.

When evaluating the control algorithms (the IIP and PD controller) on the in-silico population, the simulation time length for each in silico experiment was 24 hours. While the typical cardiac surgical procedure usually takes only 3 – 4 hours, running the simulation for longer periods revealed the “stable” control pattern. A pattern typical of all controllers is an initial variability around the set target prior to stability. It is essential to evaluate for an extended period of time to ensure prolonged stability, enabling a steady state error to

eventually be applied. Each BGL trajectory was then divided into two epochs: 0 – 5 hours (“initial” phase) and 12 – 24 hours (“oscillating” phase).

In addition to comparing the mean and standard deviation of the per-subject BGL values, we calculated the normalized glucose liability index (NGLI, $[\text{mg/dL}]^2/\text{hour}^2$), akin to the weekly glucose liability index (GLI) previously published [55]. The GLI $\sum_{i=1}^{N(\text{of 1 week})} \frac{(Glu_{i+1}-Glu_i)^2}{T_{i+1}-T_i}$ is a measure of the weekly sum of the rate of change of BGL, where Glu_i is the i -th glucose reading (mg/dL) taken at time T_i . Because the length of surgery is different for each patient, the GLI must be normalized to the total length of the measurement time, $T_N - T_1$, where N is the total number of glucose values obtained for the patient (dependent on the length of surgery), T_N is the final time of the measurement period and T_1 is the initial time. We define this normalized metric as the NGLI. The NGLI was thus calculated as follows:

$$NGLI = \frac{\sum_{i=1}^N \frac{(Glu_{i+1}-Glu_i)^2}{T_{i+1}-T_i}}{T_N - T_1}$$

A higher NGLI implies that the BGL trajectory exhibits more variability.

C. Proportional Derivative (PD) Controller Design

After evaluating the weaknesses and strengths of the IIP in silico, we designed a PD controller, which belongs to the broad category of well-known proportional-integral-derivative (PID) controllers (Figure 2). The controller was designed so that the sampling period would be the same as the IIP (30 minutes) and only the calculation method of insulin and dextrose dose would change. Similar to the IIP, the PD controller only makes use of the current and previous BGL readings so that caregivers do not have to collect any additional information in order to evaluate the PD controller in real clinical environment. In our future work we will investigate whether the performance can be further enhanced by adding the integral control, which requires keeping log of all past BGLs. For safety purposes, we retained the same fixed actions of the IIP if and when the BGL reached an extreme (e.g., $BGL < 60$ mg/dL or $BGL > 300$ mg/dL). The critical part of our controller design is that when the BGL is in the control zone (60 – 300 mg/dL), the intravenous insulin infusion rate is calculated and changed in response to a proportional-derivative law, where K_P , K_D , Target, and R_B are the proportional gain (U/hr per mg/dL), derivative gain (U/hr per mg/dL), target value (mg/dL), and basal insulin rate (U/hr), respectively. Since one cannot administer “negative” insulin, when the rate (calculated by the PD) is less than zero, we set the rate to zero. Additionally, if BGL drops too fast (defined as: $BGL(n) - BGL(n-1) < -30$) and the current BGL(n) is already below 100 mg/dL, we stop the insulin infusion and give intravenous dextrose to counteract impending hypoglycemia. The amount of dextrose (D_{50}) administered is proportional to the magnitude of BGL decrease using the derivative law.

D. Proportional Derivative (PD) Controller Tuning

All controllers require manipulation of the independent variables such that performance, however it is defined, can be optimized (tuning). For this study we picked three performance metrics to monitor and optimize: 1) percentage of BGL values in-target (70 – 130 mg/dL), 2) percentage of BGL values lower than target (< 70 mg/dL), and 3) NGLI. These represent the quality of target tracking, hypoglycemia risk control, and variability minimization, respectively. Additionally, from a clinical standpoint, when tuning the controller we considered hypoglycemia to be the primary safety concern. Thus, if a trade-off had to be made between very low BGL and higher than target BGL, we favored the latter.

There are classic control theory methods that allow one to analytically calculate the optimal PID controller setting based on the mathematical model of the control plant (i.e., the patient model). However, it is very challenging to apply the analytical methods to the patient simulator we were using, because the underlying plant model is highly nonlinear (most classic control approaches assume linear plant models) and many model variables cannot be directly measured in real time on general patients (the tracer experiment used to identify the virtual subjects is clearly too resource demanding to be applied to all ICU patients). Therefore, we tune the controller parameters based on numerical simulations. To identify the optimal setting of the PD controller parameters, we systematically changed K_P , K_D , and R_B on a wide range of values and examined how the performance metrics were affected by different controller settings. The optimal setting of K_P , K_D , and R_B is the one such that the three performance metrics (in-target percentage, lower-than-target percentage, and NGLI) are optimized.

III. EXPERIMENTAL RESULTS

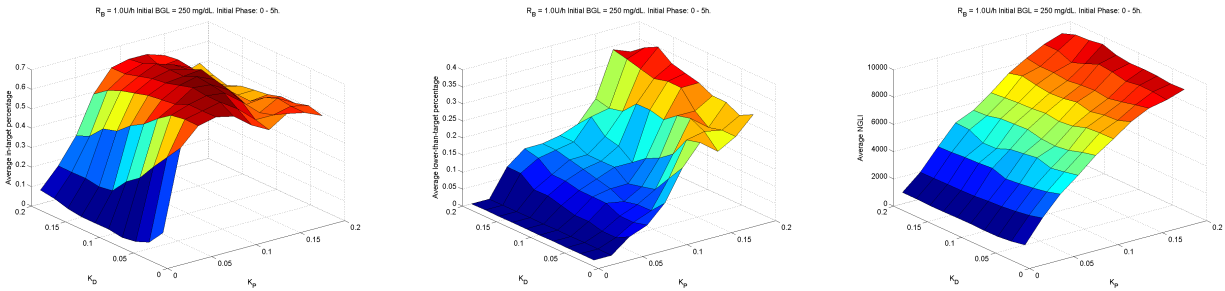
This section enumerates the experimental results of the IIP evaluation, virtual population validation, PD control parameter tuning, and performance comparison between the PD algorithm and the IIP. In the next section, we will further analyze the experimental data and discuss the results in the clinical context.

A. Virtual Population Validation and IIP Evaluation

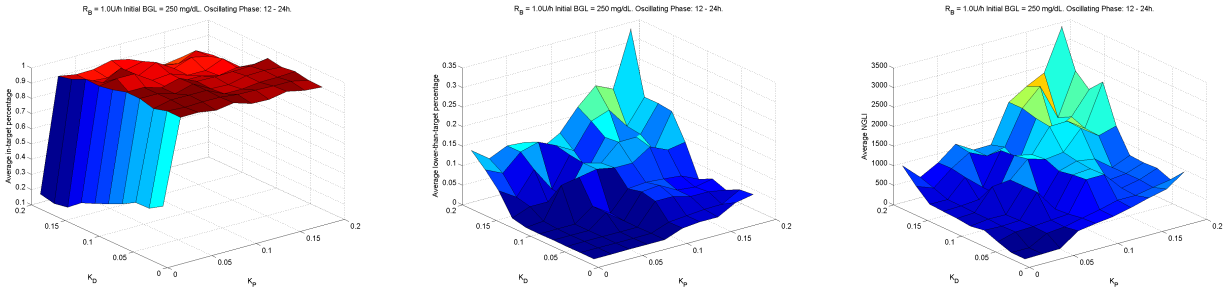
The summative data for validation of the virtual subjects can be seen in Table I. This represents the effect of the IIP on the virtual patients compared with the retrospectively observed data in the actual 57 patients. By adjusting the initial BGL in all 10 virtual patients, we evaluated the efficacy of the IIP in-silico. Key metrics of the simulated BGL trajectories on the 10 virtual subjects in response to the IIP are shown in Table II. For each initial BGL, a simulation run generates 10 BGL trajectories (from 10 virtual subjects) and metrics are reported for the initial (0 – 5 hours) phase and the oscillating (12 – 24 hours) phase.

| BGL (n) (mg/dL) | Action |
|-----------------|--|
| ≤ 60 | Give 25 mL D ₅₀ |
| 60 - 300 | Rate (U/hr) = $\max(0, K_P[BGL(n) - \text{Target}] + K_D[BGL(n) - BGL(n-1)] + R_B)$ IF $[BGL(n) - BGL(n-1)] < -30$ AND $BGL(n) < 100$ THEN Rate = 0 and give $[(BGL(n-1) - BGL(n)) \times 0.2]$ mL D ₅₀ |
| > 300 | Rate (U/hr) = 15 and give 15 U Insulin bolus |

Fig. 2. Proportional-Derivative algorithm for controlling blood glucose intraoperatively. Abbreviations: BGL Blood glucose level; U Units; D50 50 percent Dextrose (50 g/100 mL); BGL(n) current blood glucose reading; BGL(n-1) previous blood glucose reading; K_P Proportional gain (U/hr per mg/dL; after tuning=0.05); K_D Derivative gain (U/hr per mg/dL; after tuning=0.06); Target Blood glucose target (set to 100 mg/dL); R_B Basal insulin rate (U/hr; after tuning= 1.0).



(a) Initial (0 – 5 hr) phase. $R_B = 1.0$ U/hr and (b) Initial (0 – 5 hr) phase. $R_B = 1.0$ U/hr and (c) Initial (0 – 5 hr) phase. $R_B = 1.0$ U/hr and initial BGL = 250 mg/dL. Metric= in-target (70 – 130 mg/dL) percentage. Metric= lower-than-target (< 70 mg/dL) percentage. Metric= NGLI.



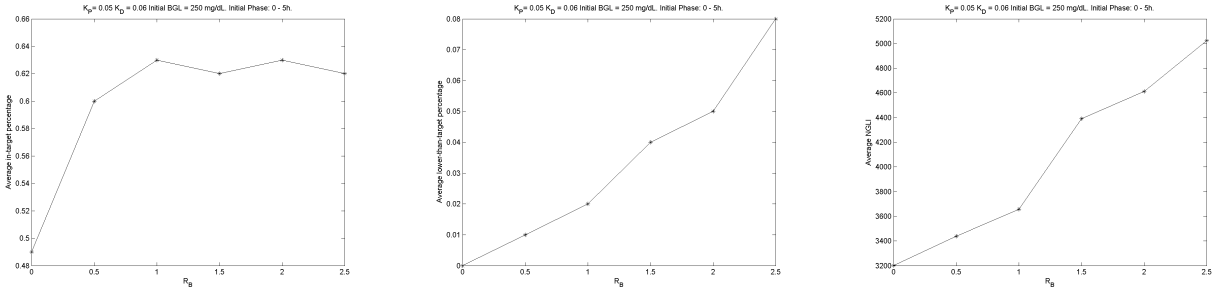
(d) Oscillating (12 – 24 hr) phase. $R_B = 1.0$ U/hr (e) Oscillating (12 – 24 hr) phase. $R_B = 1.0$ U/hr and initial BGL = 250 mg/dL. Metric= in-target and initial BGL = 250 mg/dL. Metric= lower-than-target (< 70 mg/dL) percentage. Metric= NGLI.

Fig. 3. Impact of K_P and K_D . Abbreviations: K_P Proportional gain (U/hr per mg/dL); K_D Derivative gain (U/hr per mg/dL); R_B Basal insulin rate (U/hr).

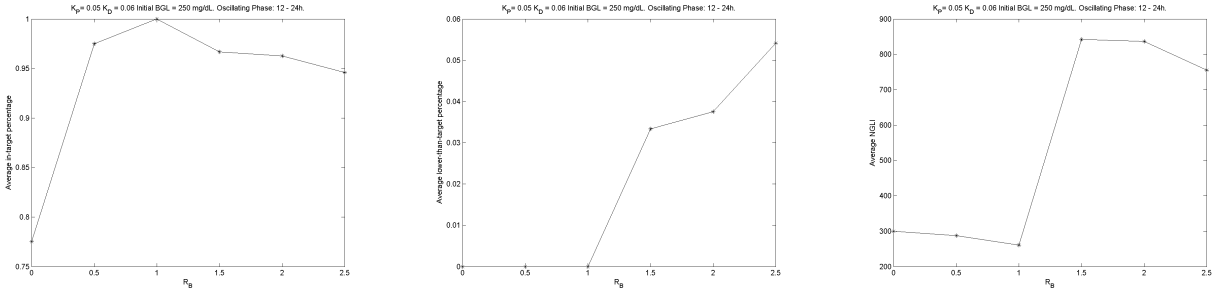
B. Proportional Derivative (PD) Controller Tuning

We chose the target for the controller to be fixed at 100 mg/dL, which represents a value in the middle of the IIP target range (70 – 130 mg/dL) and is also the insulin action start point in the IIP. The impact of incremental changes of K_P and K_D on our three primary metrics, both for the initial phase (0 – 5 hours) and oscillating phase (12 – 24 hours) are shown in Figure 3. Simulation results show that R_B , in its variance range, does not significantly change the shapes of the K_P - K_D performance surfaces shown in Figure 3, in which $R_B = 1.0$ U/hr. Therefore, we first identified the optimal

K_P - K_D setting by integrating the three performance metrics discussed in Section II-D. Key findings in this analysis were that hypoglycemia (< 70 mg/dL) and NGLI are minimized when K_P and K_D are relatively small. The in-target (70 – 130 mg/dL) percentage is maximized when K_P and K_D are in the lower middle range (see Figure 3 and Table III). Integrating the data analysis with the performance metrics, we identified the optimal K_P - K_D setting, $K_P = 0.05$ U/hr per mg/dL and $K_D = 0.06$ U/hr per mg/dL, in the region where the peak areas of in-target percentages (Figures 3 (a) and (d)) overlap the low areas of lower-than-target range and NGLI (Figures 3 (b), (c), (e), and (f)). The metrics were then further optimized



(a) Initial (0 – 5 hr) phase. Initial BGL = 250 mg/dL. Metric= In-target (70 – 130 mg/dL) percentage. (b) Initial (0 – 5 hr) phase. Initial BGL = 250 mg/dL. Metric= Lower-than-target (< 70 mg/dL) percentage. (c) Initial (0 – 5 hr) phase. Initial BGL = 250 mg/dL. Metric= NGLI.



(d) Oscillating (12 – 24 hr) phase. Initial BGL = 250 mg/dL. Metric= In-target (70 – 130 mg/dL) percentage. (e) Oscillating (12 – 24 hr) phase. Initial BGL = 250 mg/dL. Metric= Lower-than-target (< 70 mg/dL) percentage. (f) Oscillating (12 – 24 hr) phase. Initial BGL = 250 mg/dL. Metric= NGLI.

Fig. 4. Impact of R_B on performance metrics after optimal tuning of PD parameters ($K_P = 0.05$, $K_D = 0.06$). Abbreviations: K_P Proportional gain (U/hr per mg/dL); K_D Derivative gain (U/hr per mg/dL); R_B Basal insulin rate (U/hr).

TABLE I

COMPARISON OF THE EFFECT OF IIP ON BGL IN 10 VIRTUAL PATIENTS IN-SILICO WITH THOSE OF IIP ON BGL IN REAL PATIENTS. ABBREVIATIONS: IIP, INSULIN INFUSION PROTOCOL; STD, STANDARD DEVIATION; BGL, BLOOD GLUCOSE LEVEL; NGLI, NORMALIZED GLUCOSE LABILITY INDEX; NS, NOT SIGNIFICANT. MEAN VALUES WERE COMPARED VIA TWO-TAILED UNPAIRED T-TEST.

| | Real patients (n=57) | Virtual patients (n=10) | p |
|---|----------------------|-------------------------|--------|
| Average per-subject Mean STD of BGL (mg/dL) | 130 ± 16.0 | 114 ± 15.3 | 0.0047 |
| Average per-subject NGLI ([mg/dL] ² /hr ²) | 1775 | 1782 | NS |

by evaluating incremental increases in basal insulin rate (R_B) (Figure 4) according to the same performance metrics and the optimal PD control parameter setting is $K_P = 0.05$ U/hr per mg/dL, $K_D = 0.06$ U/hr per mg/dL, $R_B = 1.0$ U/hr.

C. Proportional Derivative (PD) Controller Evaluation

Table IV shows the performance metrics of the PD controller on the virtual population. When comparing the PD controller to the IIP (Table II) there are some notable differences. With regard to target tracking, in the oscillating phase the PD controller is able to maintain close to 100% of the BGL readings within the target range. In the initial phase, when the BGL starts within the target range (70 – 130 mg/dL), the PD controller is able to maintain almost 100% of BGL values in target. When the BGL starts > 130 mg/dL, the average in-target percentages are similar between the two algorithms. When comparing the risk of hypoglycemia between the IIP and the PD controller, the PD controller is noted to almost completely eliminate occurrences of BGL < 70 mg/dL in

both phases, though this comes with a concomitantly greater frequency of BGL values > 130 mg/dL in the initial phase compared with the IIP. Furthermore, the average minimum BGL achieved by the PD controller is also significantly higher (but within the target-range), especially for the “extreme” subjects (the min minimum BGL, or lowest minimal BGL) thus further reducing the chance of hypoglycemia. Finally, with regards to BGL variability, the PD controller achieves significantly lower NGLI than the IIP (less than half the variability in both phases for most initial BGLs).

IV. EXPERIMENTAL DATA ANALYSIS AND DISCUSSION

A. Validation of the Virtual Population

By implementing in-silico testing of glycemic control with a validated simulator of diabetes mellitus, we have developed a testable algorithm to be studied in live patients undergoing cardiac surgery. Of note, the T1DM Simulator does not (and cannot) account for all parameters, both in-vivo (i.e., time varying insulin sensitivity) and ex-vivo (i.e., effect of

TABLE II
KEY METRICS OF SIMULATED BGL CONTROLLED BY THE IIP IN VIRTUAL PATIENTS (N=10)

| Init BGL (mg/dL) | Simulated BGL (0 - 5h) | | | | | | Simulated BGL (12 - 24h) | | | | | | | |
|------------------|-------------------------------|---------------------------------|---|-----------------------|--------------------|-------------------|------------------------------|-------------------------------|---------------------------------|---|-----------------------|--------------------|-------------------|------------------------------|
| | Mean BGL (mg/dL) ¹ | STD of BGL (mg/dL) ¹ | NGLI ((mg/dL) ² /h ²) ¹ | 70 - 130 ² | > 130 ² | < 70 ² | Min BGL (mg/dL) ¹ | Mean BGL (mg/dL) ¹ | STD of BGL (mg/dL) ¹ | NGLI ((mg/dL) ² /h ²) ¹ | 70 - 130 ² | > 130 ² | < 70 ² | Min BGL (mg/dL) ¹ |
| 70 | 86[80.92] | 15[9.18] | 411[55.1533] | 99% | 0% | 1% | 70[66.70] | 104[91.108] | 10[4.29] | 882[19.5088] | 94% | 2% | 4% | 88[60.101] |
| 80 | 93[89.98] | 12[9.16] | 286[48.1253] | 99% | 0% | 1% | 78[63.80] | 104[91.108] | 10[2.27] | 878[9.5083] | 92% | 2% | 6% | 89[64.104] |
| 90 | 99[97.102] | 8[5.19] | 216[16.915] | 99% | 1% | 0% | 88[78.90] | 104[92.108] | 10[1.30] | 877[4.5045] | 94% | 2% | 4% | 87[60.105] |
| 100 | 98[88.101] | 7[2.15] | 318[9.1400] | 99% | 0% | 1% | 89[68.98] | 104[91.109] | 10[1.31] | 927[4.5782] | 92% | 2% | 6% | 89[59.106] |
| 110 | 104[97.107] | 6[2.16] | 388[10.1781] | 99% | 0% | 1% | 95[69.105] | 104[91.111] | 10[3.31] | 951[12.5707] | 93% | 2% | 5% | 87[59.100] |
| 120 | 102[91.111] | 12[5.22] | 789[24.3044] | 95% | 0% | 5% | 85[60.106] | 104[89.109] | 10[1.29] | 889[8.5030] | 93% | 2% | 5% | 88[59.105] |
| 130 | 107[96.119] | 14[6.25] | 928[37.3278] | 97% | 0% | 3% | 90[58.112] | 104[89.109] | 10[2.30] | 879[3.4997] | 93% | 2% | 5% | 89[59.106] |
| 140 | 104[91.117] | 17[11.28] | 1314[112.4226] | 84% | 11% | 5% | 85[53.106] | 104[94.109] | 10[2.29] | 903[10.5411] | 94% | 2% | 4% | 89[59.101] |
| 150 | 107[93.125] | 20[12.31] | 1719[129.5728] | 81% | 14% | 5% | 87[55.113] | 104[91.111] | 10[2.31] | 962[4.5690] | 92% | 2% | 6% | 89[59.103] |
| 160 | 101[85.113] | 26[20.36] | 2734[415.7501] | 80% | 12% | 8% | 74[41.98] | 104[91.110] | 10[1.29] | 921[4.5441] | 93% | 2% | 5% | 89[59.106] |
| 170 | 103[87.115] | 29[22.38] | 2992[605.8214] | 79% | 14% | 7% | 75[42.99] | 104[91.109] | 10[2.29] | 901[9.5410] | 93% | 2% | 5% | 89[59.105] |
| 180 | 103[88.112] | 34[27.41] | 3633[778.8644] | 73% | 17% | 10% | 70[38.90] | 106[97.109] | 10[2.29] | 984[8.5315] | 95% | 2% | 3% | 89[59.104] |
| 190 | 106[89.119] | 36[30.43] | 3984[860.9464] | 74% | 17% | 9% | 72[39.95] | 105[96.110] | 10[2.32] | 1049[15.5867] | 94% | 2% | 4% | 89[59.105] |
| 200 | 105[89.130] | 39[31.48] | 5310[966.1978] | 71% | 17% | 12% | 69[32.108] | 104[90.108] | 10[2.32] | 972[12.5804] | 93% | 2% | 5% | 88[58.103] |
| 210 | 106[91.118] | 43[36.50] | 5829[1435.13084] | 71% | 17% | 12% | 67[33.94] | 104[90.108] | 10[2.32] | 954[8.5767] | 93% | 2% | 5% | 89[58.105] |
| 220 | 101[89.115] | 49[40.56] | 7301[2065.15537] | 65% | 17% | 18% | 57[26.85] | 105[95.109] | 9[2.28] | 868[10.4954] | 95% | 1% | 3% | 89[58.106] |
| 230 | 105[92.117] | 51[43.59] | 8207[2243.16927] | 69% | 17% | 14% | 60[27.88] | 105[95.108] | 10[1.28] | 874[2.4967] | 95% | 1% | 3% | 89[58.107] |
| 240 | 102[89.117] | 55[46.62] | 9286[2788.18936] | 63% | 17% | 20% | 56[24.84] | 105[91.109] | 9[2.27] | 869[13.5005] | 94% | 2% | 4% | 91[58.105] |
| 250 | 105[91.121] | 58[49.65] | 10204[3010.21115] | 63% | 17% | 20% | 57[24.87] | 105[92.109] | 9[1.27] | 849[6.5005] | 95% | 2% | 4% | 90[58.105] |

All data are presented on a per-trajectory basis. Each row represents a starting BGL value and data from 10 trajectories (each virtual patient). ¹Data represent Mean[Minimum, Maximum]. Target range for IIP was 70 - 130 mg/dL. ²Values represent Mean % [minimum %, maximum %] BGL within stated range for each trajectory. Abbreviations: BGL, blood glucose level; STD, standard deviation; NGLI, normalized glucose liability index; Min, minimum BGL. Example: when initial BGL is 70 mg/dL and simulation is run using IIP on the 10 virtual patients, the mean value for the mean BGL of each trajectory (virtual patient) was 86 mg/dL. The virtual patient with the lowest mean had a mean BGL of 80 mg/dL and the trajectory with the highest mean had a mean of 92 mg/dL. Similar interpretations can be made for the STD BGL, NGLI and Min. Within this same trajectory, the mean % of BGLs that were within target was 99%. At the lowest end, 90% of the BGLs were within target and at the highest end 100% of the BGLs were within target. Similar interpretations can be made for the > 130 and < 70 mg/dL ranges.

TABLE III
OBSERVATIONS NOTED WHEN TUNING THE PD CONTROLLER.

| PD Parameter | Metric | | |
|--------------|--|--|--|
| | In-target (70 - 130 mg/dL) BGLs | Less-than-target (< 70 mg/dL) BGLs | NGLI |
| K_P | Initial phase: As K_P increases, metric first increases then decreases Oscillating phase: As K_P increases, metric decreases (except when K_D is large) | Initial phase: As K_P increases, metric increases Oscillating phase: As K_P increases, metric increases when K_D is low | Initial phase: As K_P increases, metric increases Oscillating phase: As K_P increases, metric increases |
| K_D | Initial phase: As K_D increases, the peak K_P increases Oscillating phase: As K_D increases, metric decreases | Initial phase: K_D is not the dominating factor Oscillating phase: As K_D increases, metric increases | Initial phase: K_D is not the dominating factor Oscillating phase: K_D is not the dominating factor |
| R_B | Initial phase: metric is maximized when $R_B \geq 1$ Oscillating phase: metric is maximized when $R_B \geq 1$ | Initial phase: As R_B increases, metric increases Oscillating phase: As R_B increases, metric increases | Initial phase: As R_B increases, metric increases Oscillating phase: As R_B increases, metric is minimized (when $R_B \leq 1$) |

Abbreviations: PD, proportional derivative (controller); K_P , proportional gain (U/hr per mg/dL); K_D , derivative gain (U/hr per mg/dL); R_B , basal insulin rate (U/hr); BGL, blood glucose level; NGLI, normalized glucose liability index [(mg/dL)²/hr²].

cardiopulmonary bypass). As such, one of the limitations of this study is that by evaluating the data from 57 type I diabetic patients we may not have identified all variables involved in gluoregulation and insulin dynamics. However, as seen in Table I, the standard deviation of BGL values and normalized glucose liability index (NGLI) of the two groups (virtual and real) were similar. Thus, the virtual population was able to closely reproduce the BGL variability observed in the real data. While the standard deviation and NGLI were quite similar, the per-subject means in the two populations were significantly different. We believe this is due to several reasons. First, the initial “physiological” state of the two populations was mismatched. Each virtual patient needs an initial configuration that includes all physiological states at simulation “time zero” which defines the initial condition for the differential equations that describe the patient model. Most of these physiological states are not directly measurable (i.e., total mass of glucose and insulin in different compartments). In our experiments, these physiological variables were set to be started at a perfectly “stable” state. In other words, given a starting glucose value, the model functions on the premise that the physiological state will not change over time. Mathematically this means that differential equations are solved on the assumption that all derivatives are zero. However, such exquisite homeostasis is unlikely to be present

in a real patient at the start of surgery. An additional reason for the observed mean inter-subject variability is that we had a limited quantity of real population data from which we could draw conclusions. Intraoperatively, the BGL was measured at a relatively low frequency (every 30 minutes) and therefore, for each individual patient there were usually fewer than 10 BGL readings over the entire surgery. If the initial states of the two populations are mismatched, the virtual population may not be able to converge to the state of the real patients within such limited time and with such few measurements. Furthermore, while our protocol dictates measuring the BGL every 30 minutes, the reality is that sampling unlikely occurred exactly every 30 minutes in our actual patient population. Finally, we used a relatively small group size for our virtual patient population. The “best match” for each patient could only be chosen from 10 virtual subjects and may not include a good match for each real patient. This would explain why the population standard deviation and NGLI match better than individual data.

B. Performance Comparison between the IIP and the PD algorithm

Evaluation of the IIP on the 10 virtual subjects is shown in Table II. This data illustrates that during the oscillating phase, the IIP is able to keep most BGLs within the target

TABLE IV
KEY METRICS OF SIMULATED BGL CONTROLLED BY THE PD CONTROLLER.

| Init BGL (mg/dL) | Simulated BGL (0 – 5h) | | | | | Simulated BGL (12 – 24h) | | | | | | | | |
|------------------|-------------------------------|---------------------------------|---|-----------------------|--------------------|--------------------------|------------------------------|-------------------------------|---------------------------------|---|-----------------------|--------------------|-------------------|------------------------------|
| | Mean BGL (mg/dL) ¹ | STD of BGL (mg/dL) ¹ | NGLI ((mg/dL) ² /h ²) ¹ | 70 – 130 ² | > 130 ² | < 70 ² | Min BGL (mg/dL) ¹ | Mean BGL (mg/dL) ¹ | STD of BGL (mg/dL) ¹ | NGLI ((mg/dL) ² /h ²) ¹ | 70 – 130 ² | > 130 ² | < 70 ² | Min BGL (mg/dL) ¹ |
| 70 | 85[79.91] | 12[8.16] | 76[36.163] | 100% | 100% | 0% | 70[70.70] | 110[98.116] | 3[0.14] | 255[0.1603] | 100% | 100% | 0% | 106[81.116] |
| 80 | 91[87.96] | 9[6.12] | 34[17.56] | 100% | 100% | 0% | 80[80.80] | 110[99.116] | 3[0.15] | 230[0.1571] | 100% | 96% | 0% | 106[81.116] |
| 90 | 95[92.99] | 6[3.9] | 33[8.14] | 100% | 100% | 0% | 89[85.90] | 110[98.116] | 3[0.15] | 271[0.1744] | 100% | 100% | 0% | 106[81.116] |
| 100 | 99[96.102] | 5[1.9] | 59[21.252] | 100% | 100% | 0% | 93[84.99] | 110[98.116] | 3[0.15] | 258[0.1731] | 100% | 100% | 0% | 106[80.116] |
| 110 | 103[97.106] | 6[3.12] | 121[5.546] | 100% | 100% | 0% | 95[82.103] | 110[98.116] | 3[0.15] | 258[0.1632] | 100% | 100% | 0% | 106[82.116] |
| 120 | 106[98.111] | 8[6.14] | 187[16.744] | 100% | 100% | 0% | 96[79.105] | 110[98.116] | 3[0.15] | 271[0.1779] | 100% | 100% | 0% | 106[82.116] |
| 130 | 109[99.116] | 11[8.16] | 272[39.905] | 100% | 100% | 0% | 97[77.106] | 110[98.116] | 3[0.14] | 246[0.1526] | 100% | 100% | 0% | 106[82.116] |
| 140 | 112[100.121] | 14[12.17] | 343[68.963] | 83% | 17% | 0% | 98[81.108] | 110[98.116] | 3[0.15] | 267[0.1745] | 100% | 100% | 0% | 106[82.116] |
| 150 | 115[102.126] | 18[15.20] | 496[114.1371] | 77% | 23% | 0% | 99[80.110] | 110[99.116] | 3[0.14] | 212[0.1484] | 100% | 100% | 0% | 107[86.116] |
| 160 | 118[103.131] | 21[18.24] | 662[166.1760] | 76% | 24% | 0% | 99[78.111] | 110[98.116] | 3[0.15] | 261[0.1689] | 100% | 100% | 0% | 106[83.116] |
| 170 | 121[104.135] | 25[22.27] | 861[237.2211] | 72% | 28% | 0% | 99[77.113] | 110[99.116] | 3[0.15] | 245[0.1562] | 100% | 100% | 0% | 105[78.116] |
| 180 | 123[105.139] | 28[25.31] | 1095[312.2796] | 70% | 30% | 0% | 99[76.114] | 110[98.116] | 3[0.14] | 238[0.1450] | 100% | 100% | 0% | 106[81.116] |
| 190 | 126[105.144] | 32[28.34] | 1356[399.3383] | 69% | 31% | 0% | 99[74.116] | 110[98.116] | 3[0.15] | 253[0.1600] | 100% | 100% | 0% | 106[81.116] |
| 200 | 128[106.148] | 35[32.38] | 1661[504.4129] | 68% | 32% | 0% | 98[72.116] | 110[98.116] | 3[0.15] | 253[0.1613] | 100% | 96% | 0% | 106[81.116] |
| 210 | 131[106.152] | 39[35.41] | 1997[629.4874] | 67% | 33% | 0% | 98[70.117] | 110[98.116] | 3[0.15] | 267[0.1745] | 100% | 100% | 0% | 106[82.116] |
| 220 | 133[108.156] | 43[38.45] | 2353[758.5576] | 65% | 34% | 1% | 98[69.118] | 110[98.116] | 3[0.15] | 257[0.1641] | 100% | 100% | 0% | 105[78.116] |
| 230 | 135[108.160] | 46[42.48] | 2770[904.6468] | 64% | 34% | 2% | 97[67.118] | 110[98.116] | 3[0.15] | 249[0.1560] | 100% | 100% | 0% | 105[78.116] |
| 240 | 138[109.164] | 50[45.52] | 3195[1062.7374] | 63% | 35% | 2% | 97[65.119] | 110[98.116] | 3[0.14] | 239[0.1467] | 100% | 100% | 0% | 106[82.116] |
| 250 | 140[110.167] | 53[49.56] | 3656[1236.8272] | 63% | 35% | 2% | 97[64.119] | 110[98.116] | 3[0.15] | 261[0.1675] | 100% | 100% | 0% | 105[80.116] |

All data are presented on a per-trajectory basis. Each row represents a starting BGL value and data from 10 trajectories (each virtual patient). ¹Data represent Mean [Minimum, Maximum]. Target for PD controller was 100 mg/dL. ²Values represent Mean % [minimum%, maximum%] BGL within stated range for each trajectory. Abbreviations: BGL, blood glucose level; STD, standard deviation; NGLI, normalized glucose liability index; Min, minimum BGL. Example: when initial BGL is 70 mg/dL and simulation is run using the PD controller on the 10 virtual patients, the mean value for the mean BGL of each trajectory (virtual patient) was 85 mg/dL. The virtual patient with the lowest mean had a mean BGL of 79 mg/dL and the trajectory with the highest mean had a mean of 91 mg/dL. Similar interpretations can be made for the STD BGL, NGLI and Min. Within this same trajectory, the mean % of BGLs that were within range of 70 – 130 mg/dL was 100%. There were no trajectories that fell out of this range. Similar interpretations can be made for the > 130 and < 70 mg/dL ranges.

range (70 – 130 mg/dL) for most subjects. Interestingly, given that the minimum of in-target percentage during this phase is less than 60% in most runs, it is also apparent that there exist subjects whose BGLs do not track the target well. On the contrary, in the initial phase, the quality of target tracking with IIP is very dependent on the initial BGL. However, when the initial BGL is high, the number of in-target BGLs decrease and the number of below-target (< 70 mg/dL) BGLs increase significantly. This is typical of many currently used insulin infusion protocols and results from the “overshooting” phenomenon. That is, most protocols start with a high dose of insulin bolus and infusion when the initial BGL is high resulting in the subsequent BGL going below the target range. The resultant hypoglycemia is caused by two primary factors: 1) the overshooting during the initial phase, and 2) extreme oscillation in the oscillating phase. In the initial phase, when the initial BGL is > 130 mg/dL, overshooting causes a significant percent (as high as 50%) of low BGL readings. In the oscillating phase, when considering out-of-target BGL readings, there are more low BGL readings (as high as 42%) than high BGL readings. Thus, even when the control pattern stabilizes, the risk of hypoglycemia remains significant with the IIP for some subjects. This is in stark contrast to the performance of the PD controller (Table IV). Similar to the IIP, when initial BGL values were within the target range, the PD controller maintained the majority of BGLs within the target range during the initial phase. However, while both algorithms led to a decrease of in-target BGLs when the initial BGL was > 130 mg/dL, the IIP did so at a cost of significantly increasing the frequency of hypoglycemia (as high as 50%). No such increase was seen in the PD controller.

The NGLI with the IIP is noted to significantly increase in the initial phase as the initial BGL increases. This is a result of the magnitude and slope of the overshooting. No such relationship is seen in the oscillating phase since the

trajectories have stabilized. The average NGLI for the IIP in the initial period was 3466 (mg/dL)²/hr². This translates into an average BGL change of 58.8 mg/dL per hour. The maximum NGLI was greater than 21,000 (mg/dL)²/hr² which equates to a BGL change of more than 145 mg/dL per hour. The PD controller, however, very effectively reduced the variability seen with the IIP. In the initial phase, the average NGLI was 1117 (mg/dL)²/hr², which corresponds to a BGL change of 33.4 mg/dL per hour (a 43% reduction in variability). The maximum NGLI with the PD controller was 8272 (mg/dL)²/hr². This is 63% less than the IIP and equates to a BGL change of 91 mg/dL per hour.

Thus, it appears that the risk of hypoglycemia with our (or any) IIP is significantly increased by two primary mechanisms. The first involves the “overshooting” phenomenon during the initial phase. Indeed, data in Table II show that when the initial BGL is high, overshooting causes a significant percent (as high as 20% with a maximum of 50%) of low BGL readings. The second mechanism of hypoglycemia is by wide variation during the oscillating phase. In the oscillating phase, when considering out of target readings, there is a higher rate of hypoglycemia than hyperglycemia (with the maximum of low BGL percentage being above 40%). Thus, for some subjects, the risk of hypoglycemia persists even when the control pattern stabilizes.

Thus, strengths of the IIP during in-silico evaluation included most BGLs being kept within the target range during the “oscillating” phase as well as during the “initial” phase when the starting BGL was within target range. Weaknesses of the protocol include episodes of severe overshooting and oscillations (sometimes large) in BGL trajectory. These oscillations appear to be the result of the discrete nature of the infusion rules in the IIP. That is, because infusion rates are determined by a limited number of adjustment rules, the insulin bolus amount and infusion rate take jumps as the BGL changes. As

a result, the IIP controller may fail to stabilize an individual at the “equilibrium” state and, instead, oscillate between different infusion values. Finally, the IIP (as a result of overshooting and oscillation) was not very effective at reducing hypoglycemia and BGL variability.

The performance of any PD controller is highly dependent on the accuracy of tuning. Tuning controller parameters on the BGL simulator represents a challenging optimization problem. As explained in Section II-D, it is difficult to apply classic linear system PID tuning theories to the highly complex glucose simulation model. Our strategy in solving this complex non-linear optimization problem was to systematically characterize the impact of control parameters on performance metrics by running numerical simulations and finding the optimal trade-off configuration (Figures 3 and 4). One particular challenge with this is the inter-subject variability. While an insulin insensitive subject may favor a more aggressive controller, that same controller may cause significant hypoglycemia in subjects who are highly insulin sensitive. We intentionally designed our algorithm to minimize hypoglycemia over a broad range of glucose trajectories as the optimal controller configuration must achieve good control performance on the larger population.

V. CONCLUSION

By utilizing a validated, FDA approved simulator for type 1 diabetes, we evaluated an existing insulin infusion algorithm and developed a novel proportional-derivative algorithm for insulin and dextrose therapy for use during cardiac surgery. The new algorithm emphasizes the strengths of our pre-existing insulin infusion protocol, and minimizes its weaknesses. Most importantly, the PD controller algorithm maximizes the BGL values that are in target range (70 – 130 mg/dL), minimizes hypoglycemia (< 70 mg/dL) and minimizes glucose variability. These results warrant further prospective evaluation. We believe our novel PD controller achieves this goal and warrants prospective investigation in-vivo. Furthermore, we have demonstrated that in-silico simulation can be used to assess protocol performance and devise novel algorithms for the intraoperative period.

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