Simulation of Glycemic Variability in Critically Ill Burn Patients

---

A Thesis
Presented to
the Faculty of the School of Engineering and Applied Science
University of Virginia

In partial Fulfillment

of the requirements for the Degree

Master of Science (Systems and Information Engineering)

by

Edward A. Ortiz

August 2012

APPROVAL SHEET

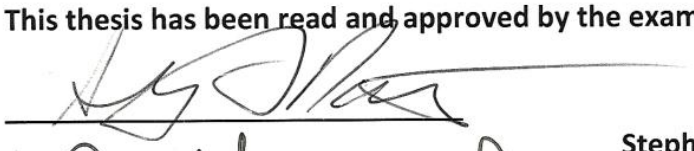
The thesis is submitted in partial fulfillment of the

requirements for the degree of

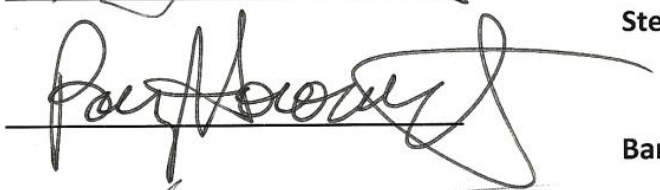
Master of Science (Systems and Information Engineering)

Edward A. Ortiz

This thesis has been read and approved by the examining Committee:



Stephen Patek, Advisor



Barry Horowitz, Committee Chair

Marc Breton

Accepted for the School of Engineering and Applied Science:

Dean, School of Engineering and
Applied Science

August 2012

Acknowledgement

Without the patient, thoughtful guidance of my advisor, Dr. Stephen Patek, I could not have come this far or look forward to so much more. Thank you, Steve.

The faculty of the Center for Diabetes Technology, Drs. Boris Kovatchev, Marc Breton, Leon Farhi, and Stephen Patek, have created and nurtured a first-class learning environment, which I was extremely fortunate to have experienced. They employ and share their knowledge with a zest that I am sure comes from their love of the work they do.

I am grateful to my thesis committee, Drs. Barry Horowitz, Stephen Patek, and Marc Breton, for their time and willingness to marshal me through the work necessary to earn my degree.

To all my fellow students and to all the post-docs in the lab, I extend my thanks. Your example too helped me.

It has been a delight to be with all of you.

Abstract

Tight glycemic control with insulin therapy protocols in the intensive care unit (ICU) can reduce mortality and morbidity from stress-induced hyperglycemia, but this control comes with the risk of hypoglycemia. Computer simulation can be an essential tool in evaluating protocols for insulin delivery in this setting, and to this end, it is necessary to have mathematical models that explain BG variability within this patient population. Current models of stress-induced hyperglycemia do not adequately incorporate the known physiology of stress hyperglycemia and are limited in their ability to account for the resistance to the actions of insulin found in these patients. In this thesis, we develop, validate, and illustrate applications for a new model of glucose variability. The new model is built from an existing model of glucose-insulin interactions for normal, pre-diabetic, and type II diabetic patients, with new features that account for the effects of trauma and physiological stress commonly experienced in the ICU. Hourly blood glucose, insulin, and feeding data from 154 burn-unit patients were input to our model. The *in silico* patient whose simulated BG most closely matched the BG of a burn-unit patient was determined with the method of least squares. For this *in silico* patient, a time-varying coefficient ("SA", stress action) was fitted to modify hepatic glucose production (HGP) and peripheral glucose uptake (PGU) to produce a simulated BG that matched a BG of a burn-unit patient. HGP was limited to a literature-derived maximum of 4.25 mg/kg/min. From the data of the 154 unique burn-unit patients, 212 SA vectors of at least 24 hours each and 86 unique *in silico* patients were identified. The simulator incorporating this model is validated by comparing cumulative distributions of simulated

BGs with the cumulative distribution of real burn-unit BGs under the same intensive insulin therapy protocol used in the original data collection. This simulator, coded into a MATLAB Simulink simulation model, allows for testing insulin protocols *in silico*, before use in patients. As an illustrative application, the simulation model is used to optimize process control thresholds for an insulin protocol used in the burn unit.

Table of Contents

Table of Contents

List of Figures

List of Tables

1. Introduction

1.1 Stress Hyperglycemia

It has long been recognized that seriously ill or injured animals and humans are prone to abnormally elevated blood glucose (BG) levels [1–3] often referred to as "stress-induced hyperglycemia", or "stress hyperglycemia" [4]. Depending on the patient population studied, the incidence of stress-induced hyperglycemia in the intensive care unit (ICU) is reported as 5-30% [5], sometimes as high as 50% [3]. Normal glucose homeostasis (a fasting BG concentration of 70-100 mg/dl) [6], is achieved with a dynamic balance of the regulatory hormone insulin, which decreases BG concentration, and of counterregulatory hormones, which increase BG concentration. Serious illnesses, such as myocardial infarction, stroke, sepsis, burns, and multiple trauma, promote an excessive and highly variable release of these counterregulatory hormones, causing hyperglycemia that can vary greatly over brief periods of time [3], [7].

Until relatively recently clinicians followed a permissive approach to the treatment of stress hyperglycemia, using insulin (intravenously--the only rapidly effective pharmacologic treatment), only when BG levels exceeded a threshold of about 200 mg/dl [3]. It was thought that stress hyperglycemia was an adaptive response to serious illness [7] , one in which the body ensured adequate energy nutrition to vital organs. However, multiple studies have lately linked stress-induced hyperglycemia to poor outcomes, such as an increase in infectious complications, poor wound healing, and

mortality [7]. In 2001, with this link in mind, Van den Berghe et al. [8] performed a landmark randomized clinical trial involving adults in a surgical ICU. Using a continuous intravenous insulin infusion algorithm in order to control BG to a near-normal target range of 80-110 mg/dl, they obtained an overall in-hospital mortality reduction of 34%, as compared to those patients whose BG was controlled to a target range of 180-200 mg/dl. In addition, there were reductions in morbidity: bloodstream infections, need for dialysis, need for transfusion, prolonged mechanical ventilation. Following that remarkable study, other researchers, including Van den Berghe's group itself, performed studies using the same or similar insulin infusion algorithms, attempting to achieve the results of the 2001 study. Some of these studies demonstrated limited success [9], [10], but others demonstrated a disturbing net harm with a high rate of hypoglycemia (BG less than 70 mg/dl) [11–13].

The beneficial results of some studies and the call to use an insulin infusion protocol "with demonstrated safety and efficacy" [14] continue to drive interest in developing better protocols. The conflicting results of the various ICU insulin infusion studies have raised the possibility that important variables other than, or in addition to, the insulin treatment algorithm may impact outcomes, such as the ICU population studied (medical vs. surgical), target level of BG control ("tight" vs. "loose"), frequency of BG measurement, measurement error, and human error in the implementation of treatment algorithms. Further studies of insulin treatment algorithms on critically ill patients will help determine the effects of such variables, but performing them can be

costly in terms of danger to the patient (hypoglycemia), time, and resources. There is a need for a tool, a computerized simulator, that can assist in identifying those variables and protocols worthy of clinical study.

A computerized simulator of stress hyperglycemia in critically ill patients should have certain characteristics: it should be based on a model of the physiology of stress hyperglycemia; it should account for a critically ill patient's rapidly varying responsiveness to insulin; it should enable the creation and use of various populations of virtual, *in silico* ICU patients; it should be validated on data from actual ICU patient treatment protocols.

To our knowledge, there have been two models of ICU stress hyperglycemia incorporated into simulators using *in silico* patients in the evaluation of insulin infusion protocols[15],[16]. Both models require one real patient to create one corresponding *in silico* ICU patient ("experimental *in silico* cloning" [17]), limiting the number of virtual patients that can be tested. Both models apply the concept of "insulin sensitivity", through time-varying modification of the model's site of insulin action in order to account for stress hyperglycemia. We propose a method that differs in two respects: it more closely models the physiology of stress hyperglycemia by incorporating the effect of the *actors* in stress hyperglycemia at *their* sites of action; and it permits the creation of many new *in silico* ICU patients from the data of one real ICU patient.

1.2 Hypothesis

It is our hypothesis that a simulator of stress hyperglycemia can be created and validated that incorporates virtual ICU patients composed of real patient parameters and patient-independent time-varying hyperglycemic stress parameters, which will then enable the construction of many *new* virtual ICU patients to extend the study of insulin infusion therapy of stress hyperglycemia.

1.3 Summary of Contributions

Insulin is the only effective pharmacologic treatment for stress hyperglycemia, and the mathematical modeling focus so far has been on the sites of insulin's action on glucose homeostasis (insulin sensitivity [17], [18]). We make the case that, since stress hyperglycemia is mediated by various agents, including counterregulatory hormones, cytokines, and administered drugs, a model should incorporate the hyperglycemic actions of these stress agents at the sites of their respective actions in the model. This applies the known physiology in critically ill patients and opens the model to growth as more is learned about these actors. Using literature on counterregulatory hormones, epinephrine in particular, and an adaptation of a previously validated model of the glucose-insulin system, we show that the time-varying action of stress from critical illness on BG levels ("Stress Action") can be quantified and *abstracted* from the treatment data of actual ICU patients to develop numerous, *novel*, and realistic *in silico* ICU patients for use in simulation. We then validate a simulator which uses these new

in silico ICU patients and demonstrate its application to the study of an insulin infusion protocol.

2. Background

2.1 Physiology of Stress Hyperglycemia

Glucose, a carbohydrate distributed throughout the body in circulating blood plasma, is the chief energy currency of the body. Its concentration in the blood is the result of a dynamic balance between the rate of glucose entering the blood and the rate of glucose leaving the blood [19]. If the arrival of glucose in the blood exceeds its disposal, hyperglycemia occurs. Glucose's arrival in the blood is the sum of its rate of appearance from food in the gastrointestinal tract, the rate hepatic glucose production (HGP), the rate of renal glucose production, and the rate of any glucose administered intravenously. Net renal glucose production is thought to be negligible and is generally ignored [20]. Glucose "disposal" from the blood is the rate of glucose uptake (or utilization) by the body's tissues, some of which depend on insulin for this uptake (eg. skeletal muscle, adipose tissue), and some that do not (eg. brain, liver, kidney, red blood cells). In addition, muscle activity (exercise) permits glucose to enter skeletal muscle cells without the requirement for insulin [21]. For this discussion, because of the bedridden nature of critically ill patients, exercise will not be addressed.

Normally, after a meal, BG concentration rises and stimulates the secretion of insulin into the bloodstream from the beta cells in the pancreas. Insulin is the most powerful of the hormones known to lower (regulate) blood glucose concentrations and acts by suppressing hepatic glucose production (HGP) and stimulating peripheral glucose uptake (PGU). Additionally, as long as there is a basal level of insulin in the blood, the liver is also sensitive to hyperglycemia *per se*, responding more quickly to BG concentration and with greater effect than to insulin [22],[23]. In the fasting state, the situation is reversed, as the BG concentration decreases and insulin secretion is minimal, releasing hepatic glucose production (HGP) to be the main source of glucose in the blood. The liver produces glucose initially, and quickly, by glycogenolysis, whereby glycogen, stored previously in the liver after a meal, is metabolized to glucose and then released into the bloodstream. Later, if the fasting state persists and the glycogen is depleted, the liver can create, more slowly, new glucose (gluconeogenesis) from lactate that was released from muscles or from amino acids [24].

In the abnormal situation of a critically ill patient, altered carbohydrate metabolism resulting in stress hyperglycemia is only one of the manifestations of major injury or illness (stress). Other physiological responses to stress include an increased metabolic rate, altered protein metabolism, increased release of free fatty acids into the bloodstream, and sodium and water retention [25]. In general, the more severe the injury or illness is, the greater is the stress response [3],[26].

With respect to stress hyperglycemia, the chief mediators between stress and altered carbohydrate metabolism are the counterregulatory hormones and cytokines [3],[25]. Additionally, certain medications, such as pressors for maintenance of blood pressure, can act as counterregulatory agents (eg epinephrine). As a result, these agents are often referred to as "stress hormones" [27], or as is used here, "stress agents". These include glucagon from the alpha cells in the pancreas, cortisol from the adrenal cortex or from exogenous administration, catecholamines (chiefly epinephrine from the adrenal medulla), growth hormone from the pituitary gland, and cytokines from tissue injury. The stress hormones are released in response to afferent neural signals or hormonal signals to the hypothalamus [25]. Pain, anxiety, or tissue injury provoke the hypothalamus to release factors that then stimulate the pituitary to ultimately release adrenocorticotropic hormone (ACTH) and growth hormone (GH), among others. ACTH in turn stimulates the release of cortisol. The hypothalamus also channels signals through the sympathetic nervous system to the adrenal medulla to release epinephrine. Epinephrine itself can then stimulate glucagon secretion [25].

Stress agents cause an inappropriate hyperglycemia by counteracting, to varying degrees, the regulatory effect of insulin by increasing hepatic glucose production (HGP) through glycogenolysis and gluconeogenesis and by decreasing the utilization of glucose by inhibiting peripheral glucose uptake (PGU) of insulin-dependent tissues. The stress hormones have different onsets and durations of action, with glucagon and epinephrine having the most rapid, potent, and brief hyperglycemic effects, peaking within 15

minutes and possessing half-lives of 2-3 minutes [28]. In contrast, the effect of large amounts of cortisol (such as that given in the ICU) on peripheral glucose uptake (PGU) is much slower, developing 4-6 hours after administration, but lasting as long as 16 hours [29]. In addition to their individual effects, these stress agents are synergistic in their hyperglycemic action [30].

It is the above actions of stress agents that must be considered in designing a model and simulator of stress hyperglycemia.

2.2 Insulin Infusion Therapy Debate -- A Role for Systems Engineering

After Van den Berghe's landmark study demonstrating the effectiveness of intensive insulin therapy (IIT) by targeting BG concentrations of 80-110 mg/dl, other studies showed encouragingly similar results [31],[32]. Intensive insulin therapy was subsequently widely adopted outside of the clinical trial setting, but questions arose as newer studies failed to reproduce the initially positive reports [33]. Two studies, VISEP [12], and GLUCONTROL [34], had to be discontinued due to excessive rates of hypoglycemia. Then Van den Berghe et al. were unable to demonstrate a reduction of in-hospital mortality in a trial of IIT on medical rather than surgical ICU patients that used the same treatment protocol as their earlier study [9]. Following that, the largest multicenter trial of IIT, the NICE-SUGAR trial [11], found excessive rates of hypoglycemia, leading to their recommendation of a higher BG target of 180 mg/dl. As a result of the danger of hypoglycemia and the uncertain benefits of controlling BG to near-normal levels, a consensus statement [14] of endocrinologists and the American

Diabetes Association was released containing these recommendations: that insulin infusion therapy be started at a threshold BG of no higher than 180 mg/dl; to aim at a target BG range of 140-180 mg/dl; and to use "insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of occurrence of hypoglycemia."

In reviewing the studies concerning IIT, many differences become apparent, leading one to question whether or not these differences could account for the disparate outcomes. For instance, Van den Berghe's studies were done at a single center, with a high ratio of nurses to patients, using an insulin infusion protocol that entailed considerable clinical judgment from providers [35], and with the majority of BG measurements made from arterial blood on a point-of-care (POC) blood gas/glucose analyzer [33]. The NICE-SUGAR trial was an international, multicenter effort, which used a detailed insulin infusion protocol posted on the internet, contained a wide variety of patients, and permitted each hospital to use whatever BG measurement method that was in its normal practice—point-of-care handheld glucose monitors, blood gas/glucose analyzers, or laboratory (Simon Finfer, personal communication, February 17, 2010). Consider some of the variables brought up by these two conflicting studies:

Blood glucose measurement -- With insulin doses being determined by BG measurements, anything that affects the accuracy of BG measurement could affect clinical outcome. "Fingerstick" (capillary) point-of-care (POC) handheld glucometer BGs are less accurate than arterial POC handheld glucometer BGs; arterial POC handheld

glucometer BGs are less accurate than arterial POC blood gas/glucose analyzer BGs; and arterial POC blood gas/glucose analyzer BGs are less accurate than laboratory reference values [36]. In applying an insulin infusion protocol, Kanji et al. found that BG differences in different measurement methods "led to frequent clinical disagreements regarding insulin dose titration**"** [36]. The use of less accurate techniques has so far been justified by their practicality and the thought that benefits (e.g. rapid turnaround, less blood loss, infection risk) outweighed risks of methods to obtain more accurate BG measurements [33]. Besides the source of blood (capillary, venous, or arterial), the state of the patient's circulatory perfusion (peripheral vasoconstriction, shock) and interfering substances (e.g. acetaminophen) can affect POC BG measurements [37].

Patient population -- Rather than treat all hyperglycemic ICU patients with IIT, some subsets of patients may benefit and some may not. Surgical patients, as in Van den Berghe's first study [8] and in a meta-analysis by Griesdale et al. [38], may benefit from IIT. Patients with stroke or those with severe head injury are subpopulations whose outcomes are worse when hyperglycemic [39],[40], suggesting that IIT may be beneficial.

Protocol attributes -- To our knowledge all but one of the insulin infusion protocols [41] studied have deferred nutritional intake to the judgment of the treating clinicians, perhaps because of specialized needs for certain conditions (e.g. the hypermetabolic state of burn victims). Since the appearance of glucose from the gastrointestinal tract is

one of the three sources of glucose in blood (i.e. GI, HGP, intravenous glucose), variation in feeding may impact control of hyperglycemia and hence clinical outcomes [42]. Another protocol attribute that varies is insulin dosing [33], with many differences seen: choice of starting insulin dose; continuous insulin infusion with or without insulin boluses; insulin boluses alone; sliding scale or "static" dosing; "dynamic" dosing in which rate of BG change is considered; ranges of insulin, with choice of dose left to the discretion of the clinician; and the potential frequency of insulin changes.

Protocol implementation -- Nursing takes the brunt of the workload in implementing an insulin infusion protocol, as it is they who perform the frequent BG measurements (often with variable intervals of 1-4 hours, sometimes as often as every 15 minutes when there is hypoglycemia) and calculate and administer the prescribed insulin dose. The workload involved with protocol implementation, plus any concomitant other burden (e.g. changing clinical condition, caring for another patient) may limit compliance with the protocol, such as deviation from the prescribed timing of BG measurement and insulin dose changes. Potentially adding resistance to implementation, nurses also express some professional concern over the effectiveness and safety of the protocol itself [43].

From the overall level of workplace and personnel interaction, through protocol choice and implementation, through selection and employment of BG measurement techniques, to the measure and control of hyperglycemia, the Systems Engineering tools

of statistical and systems analysis, modeling and simulation, risk and decision analysis, optimization and control, and systems integration can be used. This thesis focuses on developing a model and simulator at the level of an individual patient's glucose-insulin system for the purpose of assisting study and improvement of insulin infusion therapy protocols.

2.3 Existing Mathematical Models / Simulation Tools

So far, the concept of insulin sensitivity, defined as "the dependence of fractional glucose disappearance on plasma insulin" [44], has been central to modeling ICU hyperglycemia. Chase et al. built their ICU hyperglycemia model upon the minimal model of Bergman and Cobelli [44], using population parameters and fitting insulin sensitivity with an integral technique as an hourly piecewise-linear time-varying parameter to account for the BGs observed in a real ICU patient [45]. When running the simulation, the fitted insulin sensitivity values are held piecewise constant at each hour. Like the minimal model, Chase's model "lumps" HGP and PGU together. Each of the resultant *in silico* ICU patients is comprised of the combination of population parameters and the corresponding fitted vector of time-varying insulin sensitivity.

The model of Hovorka et al. [17] is more complex, being composed of 5 submodels, and uses parameters drawn from a "univariate informed probability distribution", fitted time-invariant parameters, and an hourly-varying piecewise-linear parameter ("insulin sensitivity modifier") fitted to the data of real ICU patients. The time-varying parameter

modifies separately the terms for HGP and PGU, using equal weights. Additionally, a regularization approach is employed to achieve smoothness of fitting, assessed visually. The assembled parameters from fitting one real ICU patient constitute a corresponding *in silico* ICU patient.

The models upon which these two simulators are built use the concept of time-varying insulin sensitivity at the sites of insulin action rather than posing the problem more physiologically in terms of hyperglycemic actions of stress agents at *their* sites of action. Also, both simulators depend on the creation of a virtual patient from one corresponding real patient, rather than enabling the abstraction of stress action from one real patient that can be applied to the creation of multiple virtual patients.

3. Modeling Stress Hyperglycemia via Stress Hormone Actions

3.1 Epinephrine as Representative Stress Hormone

The hyperglycemic actions of stress hormones are synergistic, with the best studied hormones being epinephrine, glucagon, and cortisol [46]. Already noted is the delayed hyperglycemic action of cortisol alone [29], but it was also shown in [30] that, for the short term of 5 hours or less, although cortisol did not provoke hyperglycemia by itself, it potentiated the effects of epinephrine and glucagon. Epinephrine in turn stimulates glucagon release [47], and glucagon stimulates epinephrine release and cortisol release (via ACTH) [48]. Epinephrine and glucagon have onsets of action and clearances that are

each on the order of 2-3 minutes, although glucagon's role in early glucose mobilization due to injury has been described as "equivocal" [26]. Epinephrine, glucagon, and cortisol increase hepatic glucose production (HGP) [26]. Epinephrine [49] and cortisol [25] suppress peripheral glucose uptake (PGU); glucagon does not.

Since it is likely that all three of the above stress hormones are present in significant levels in critically ill patients [50], since some of them stimulate the release of the others, since their individual actions overlap, and since each individual hormone's level is unknown in clinical cases, it would be useful to have a "composite" stress hormone that embodies their combined synergistic hyperglycemic effects.

Epinephrine's relatively well quantified stress-related actions would serve well as stand-ins for those of such a composite stress hormone. Its metabolic actions appear to plateau at plasma levels of approximately 1000 pg/ml [51]. In injured patients the plasma levels of epinephrine are positively correlated to the severity of injury. The greater the severity of injury, the higher the levels of epinephrine [26]. Stepped increments of infusions of epinephrine, yielding blood levels seen in the critically ill, were given to normal volunteers by Clutter et al. [49] who demonstrated increasing hyperglycemia with increasing plasma levels of epinephrine. Also demonstrated in that study, increasing epinephrine levels were simultaneously correlated with increases in endogenous glucose production and decreases in glucose clearance. With respect to the relative effects of epinephrine on production versus disposal, Gustavson et al. [28]

showed an increase of HGP in non-ICU patients from complete suppression without epinephrine to an output of 3.3 mg/kg/min with epinephrine. This compares well with the measured HGP of 4.25 mg/kg/min in critically ill burn patients in a study by Wolfe [2] and 3.5 mg/kg/min in a study of septic patients by Chambrier [52]. Guy et al. [53] showed an approximately 65% suppression from baseline of peripheral glucose uptake by epinephrine. In studies of epinephrine's effects, HGU suppression was found to be only transiently released despite the use of sustained epinephrine infusions[28][54][55], but countering this observation, some of these studies also show the liver's ability to increase HGP with additional infusions of epinephrine [56], which is more consistent with the expected variable physiology of stress hyperglycemia.

Assembled together, these actions of epinephrine make it a useful representative, or stand-in, for all of the stress agents to incorporate into a model of stress hyperglycemia. Ultimately, as more is learned about the individual mediators of hyperglycemic stress, the contribution of each agent can be synergistically combined to model reality more closely.

3.2 Stress Modified Meal Model

The model used for this research is an adaptation of the Glucose-Insulin-Meal (GIM) model of Dalla Man et al. [57], which was designed around glucose and insulin flux data obtained from 204 normal and 14 Type 2 diabetic subjects with the use of triple-tracer techniques [58]. From that database, along with additional data from 62 normals, 35

prediabetics, and 23 type 2 diabetics, 300 *in silico* meal-model patients were derived. One hundred of these *in silico* patients were "normals", who after removal of endogenous insulin parameters, had spanned the "observed variability of key metabolic parameters in the general population of people with T1DM in a previous application" [59]. One hundred were "prediabetic" *in silico* patients and another 100 were "type 2 diabetic" *in silico* patients whose range of simulated BGs approximated the variability of observed BGs from the real population. As adapted, the model has 28 free parameters for each *in silico* patient, of which those dealing with hepatic glucose production and peripheral glucose uptake are the most important for our purposes. Any one of these 300 *in silico* patient parameter sets can potentially serve to approximate a non-critically ill, "unstressed" patient, which can then be modified in a time-varying manner by the actions of stressors in order to match the BG course of a real, treated ICU patient.

Stress Modified GIM Model – The Glucose Subsystem

The glucose subsystem is represented by two compartments: plasma, which is rapidly equilibrating, and peripheral tissues, such as muscle and fat, which are slowly equilibrating.

Plasma:

$$\dot{G_p} = EGP(t) - U_{ii} - E(t) + k_2 \cdot G_t(t) - k_1 \cdot G_p(t) + R_a(t) + IVG$$

$$G = \frac{G_p}{V_g}$$

Tissues:

$$\dot{G}_t = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t)$$

Where:

G_p (mg/kg) is the glucose mass in the plasma

G_t (mg/kg) is the glucose mass in the slowly equilibrating tissues

G (mg/dl) is the plasma glucose concentration

R_a(mg/kg/min) is the rate of glucose appearance in the plasma

EGP (mg/kg/min) is the rate of endogenous glucose production

IVG (mg/kg/min) is intravenous glucose feeding

U_{id} (mg/kg/min) is insulin-dependent glucose utilization in tissues

U_{ii} (mg/kg/min) is insulin-independent glucose utilization

E (mg/kg/min) is renal excretion of glucose

k_1 & k_2 (min^{-1}) are rate parameters

Glucose Subsystem--Appearance of Glucose (R_a) from feeding

In the Burn ICU of our study, critically ill patients were fed by continuous enteral infusion of a partially elemental formula that provided calories as 20% protein, 65% carbohydrate, and 15% fat. Because the enteral feeding was through a tube placed into the upper part of the intestine (jejunum), bypassing the stomach, the equations of the original GIM model for the transit of glucose through the stomach and gut were

removed for the adapted model. The rate of appearance (R_a) of glucose into the glucose subsystem from feeding is described by:

$$R_a(t) = \frac{(f \cdot meal)}{BW}$$

Where *f* is the fraction (0.9) of the glucose load in the intestine that appears as glucose in the plasma, irrespective of the composition of the meal [60], [61]. The *meal* is the continuous enteral feeding in carbohydrate mg/min. *BW* is the patient's body weight in kilograms.

<u>Glucose Subsystem--Endogenous Glucose Production (EGP)</u>

In the original GIM model, because renal glucose production is ignored, endogenous glucose production (*EGP*) is equated with hepatic glucose production (HGP):

$$EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) - k_{p4} \cdot I_{po}(t)$$

Where:

G_p (mg/kg) is the glucose mass in the plasma

I_d (pmol/L) is a delayed insulin signal

I_{po} (pmol/kg) is the amount of insulin in the portal vein

k_{p1} (mg/kg/min) is EGP extrapolated at zero insulin and glucose

k_{p2} (min^{-1}) is the liver glucose effectiveness

k_{p3}(mg/kg/min per pmol/L) governs amplitude of insulin action on the liver

k_{p4}(mg/kg/min per pmol/kg) governs amplitude of portal insulin action on liver

In our adapted model, in order to match the BG data of an actual ICU patient, hyperglycemic "Stress Action" (***SA(t)***) on *EGP* is incorporated by fitting it hourly with a

minimum value of zero (“no stress”) to a maximum value of one (“maximum stress”). Using epinephrine’s actions as our guide, ***SA(t)*** is applied to the terms of the EGP equation such that it counteracts suppression of *EGP* anywhere from completely to none at all:

$$EGP(t) = k_{p1} - (1 - \boldsymbol{SA}(\boldsymbol{t})) \cdot (k_{p2} \cdot G_p(t) + k_{p3} \cdot I_d(t) + k_{p4} \cdot I_{po}(t))$$

During the fitting, EGP is constrained to be nonnegative and less than or equal to a literature-derived maximum value of 4.25 mg/kg/min [2].

Unlike previous models, our model modifies not only the insulin-dependent terms of EGP, but also the insulin-*in*dependent term of liver glucose effectiveness. This is based on evidence that indicates a physiological role for epinephrine in modulating HGP separately from insulin [54], [62]. Also, indirect evidence for this is found in the observation by Lin et al. [63] that fitted values of liver glucose effectiveness for their ICU model were at the lower range of those for non-ICU patients in other studies.

Glucose Subsystem – Insulin-dependent Glucose Utilization (U_{id})

Insulin-dependent glucose utilization is the uptake of glucose from the slowly equilibrating glucose compartment into the peripheral tissues, mostly muscle and adipose tissue, that requires insulin. Insulin-dependent transport of glucose into these tissues is saturable and is modeled by:

$$U_{id}(t) = \frac{(V_{m0} + V_{mx} \cdot X(t)) \cdot G_t(t)}{K_{m0} + G_t(t)}$$

Where:

G_t (mg/kg) is the glucose mass in the slowly equilibrating tissues

X (pmol/L) is insulin in the interstitial fluid

V_{m0}(mg/kg/min), V_{mx} (mg/kg/min per pmol/L), and K_{m0} (mg/kg)

are parameters of the Michaelis-Mentin equation

Adapting this equation to incorporate Stress Action on insulin-dependent peripheral glucose uptake, the equation becomes:

$$U_{id}(t) = \frac{(V_{m0} + (1 - 0.65 \cdot \boldsymbol{SA}(\boldsymbol{t})) \cdot V_{mx} \cdot X(t)) \cdot G_t(t)}{K_{m0} + G_t(t)}$$

The weight of 0.65 was obtained from normal subjects in Guy, et al [26], who measured the suppression of glucose disposal during an epinephrine infusion. This functions to allow at least a minimal level of insulin responsiveness, even when a patient is maximally stressed.

Glucose Subsystem – Insulin-Independent Glucose Utilization (U_{ii})

Not all glucose disposal in the body requires insulin. Brain, splanchnic tissue (liver, spleen, intestine), red blood cells, kidney, and cornea do not require insulin for glucose to be transported into their cells. This insulin-independent glucose uptake rate *(U_{ii})* is essentially constant under most conditions, so our model retains the original model's constant value, estimated at 1 mg/kg/min.

Stress Modified GIM Model –The Insulin Subsystem

Insulin is also modeled with two compartments. It appears in the plasma compartment by direct intravenous injection or from the liver compartment after its secretion from the pancreas and passage through the portal vein. Plasma insulin can then re-enter the liver. This subsystem is adopted unchanged from the original model.

Plasma compartment:

$$\dot{I_p} = m_1 \cdot I_L(t) - (m_2 + m_4) \cdot I_p(t) + J$$

$$I = \frac{I_p}{V_I}$$

Liver compartment:

$$\dot{I_L} = -(m_1 + m_3) \cdot I_L(t) + m_2 \cdot I_p(t) + S(t)$$

Where:

I (pmol/L) insulin concentration in the plasma

I_p (pmol/kg) is the mass of insulin in the plasma

I_L (pmol/kg) is the mass of insulin in the liver

J (pmol/kg/min) is the rate of exogenous insulin injection given intravenously

S (pmol/kg/min) rate of endogenous insulin secretion

V_I (L/kg) distribution volume of insulin

m_1, m_2 (min^{-1}) rate parameters between liver and plasma

m_3, m_4 (min^{-1}) degradation rate parameters

Insulin Subsystem – Insulin Secretion

The patients in our study were identified as "normal" or as "any type" of diabetic (Type 1 or Type 2). Unlike normals and Type 2 diabetics, Type 1 patients, who tend to be younger, do not create their own insulin. Since our study population was mostly military and the average age of the 11 identified diabetics was 51, we made the assumption in our model that all of the 11 diabetics were Type 2. Our model thus retains endogenous insulin secretion for all patients. This portion of the subsystem is adopted unchanged from the original model.

$$S(t) = gamma \cdot Ipo(t)$$

$$\dot{I_{po}} = -gamma \cdot I_{po}(t) + S_{po}(t)$$

$$S_{po}(t) = \begin{cases} Y(t) + K \cdot \dot{G}(t) + S_b & for\ \dot{G} > 0 \\ Y(t) + S_b & for\ \dot{G} \leq 0 \end{cases}$$

$$\dot{Y} = \begin{cases} -alpha \cdot [Y(t) - beta \cdot (G(t) - h)] & if\ beta \cdot \big(h - G(t)\big) \leq S_b \\ -alpha \cdot Y(t) - alpha \cdot S_b & if\ beta \cdot (h - G(t)) > S_b \end{cases}$$

Where:

S (pmol/kg/min) is rate of endogenous insulin secretion into plasma

S_{po} (pmol/kg/min) is rate of endogenous insulin secretion into portal vein

Y (pmol/kg/min) rate, above basal, of endogenous insulin release from pancreas

$alpha$ (min^{-1}) delay between glucose signal and insulin secretion

$beta$ (pmol/kg/min per mg/dl) pancreatic responsivity to glucose

$gamma$ (min^{-1}) transfer rate constant between portal vein and liver

h (mg/dl) level of glucose above which the β-cells produce more insulin

K (pmol/kg per mg/dl) pancreatic responsivity to glucose rate of change

Insulin Subsystem – Insulin Signaling

This portion of the subsystem is adopted unchanged from the original model. The insulin signal that stimulates peripheral tissue glucose utilization is modeled as:

$$\dot{X} = p2u \cdot (I(t) - I_b) - p2u \cdot X(t)$$

Where:

X(pmol/L) is insulin concentration in interstitium affecting tissue glucose use

I (pmol/L) is the insulin concentration in the plasma

I_b (pmol/L) is basal insulin concentration

$p2u$ (min^{-1}) rate constant for movement of plasma insulin into interstitium

In addition to the insulin signal that increases peripheral glucose utilization, there is a delayed insulin signal that suppresses endogenous glucose production by the liver. It is modeled with a chain of two compartments as shown below:

$$\dot{I}_1 = -k_i \cdot (I_1(t) - I(t))$$

$$\dot{I_d} = -k_i \cdot \left(I_d(t) - I_1(t)\right)$$

Where:

I_1 (pmol/L) insulin signal in first of two compartments

I_d (pmol/L) delayed insulin signal to the liver

k_i (min^{-1}) rate parameter for the delay between insulin signal and its action

3.3 Study Data

Our data was from patients who were treated with insulin for hyperglycemia after admission between January, 2002 through December, 2008 to the burn ICU at the U.S. Army Institute of Surgical Research in Fort Sam Houston, Texas. The clinical data was obtained from treatment during the first 8 days of ICU hospitalization that was recorded in an inpatient electronic charting database (not from a clinical trial) and the demographic information was obtained from the burn registry. The data included age, sex, height, weight, preexisting diabetes mellitus, military status, presence of inhalation injury, ICU and hospital length of stays, total body surface area of burn (TBSA), injury severity score (ISS), and mortality. Approximately 77 % of the blood glucose readings were point-of-care (SureStep Flexx, Lifescan, Milpitas, CA), with the remainder done by the hospital lab. Most were corrected for anemia if a hematocrit was less than 34%. Some of these BG values in the database were corrected retroactively, which means that the actual treatment may have been based on a BG not corrected for anemia.

A total of 1513 patients were in the database. In order to create a simulator to evaluate insulin infusion protocols, it was decided to select those patients who had at least 24 hours of continuous insulin infusion data, preferably longer. However, even though the insulin infusion protocol applied in the burn unit during that time called for hourly measurements of BG, missing data limited the number of patients and treatment durations. To remedy this, treatment data with an average of no more than one missing data point (making for a 2 hour interval) in any 12 hour period was allowed. Linear

interpolation was done through the missing data point. If a BG value was recorded at an earlier or later time than scheduled per the protocol, that value was also linearly interpolated to the scheduled time. This yielded 212 BG and insulin data segments from 154 unique burn patients, with minimum lengths of 24 hours and a maximum length of 140 hours (median of 52 hours). The total duration of insulin treatment was 10,939 hours, with 5.2% of those hourly BG data points having been interpolated due to missing data.

Demographic characteristics of the 154 unique burn patients are shown in tables 3.1 & 3.2 .

	Number (%)
Male	132 (85.7)
Female	22 (14.3)
Lived	103 (66.9)
Died	51 (33.1)
Any DM	11 (7.1)

Table 3.1 - Demographic characteristics of the study population. Any DM = any type of Diabetes Mellitus

	Mean (sd)	Median [IQR]
Age	34.4 (16)	
Height (cm)	175.5 (8.6)	
Weight (kg)	87.4 (15.7)	
Hospital Days		56 [31 89]
ICU Days		31 [14 58]
TBSA (%)		44.4 [31 60]
ISS (0-75)		26 [25 34]
CHO/day (gm)	622 (154)	

Table 3.2 - Additional demographics. TBSA=Total Body Surface Area (burn); ISS=Injury Severity Score (max=75); CHO=Carbohydrates, per estimation formula

Actual feedings were not provided with the burn patient data. Instead they were calculated using the same formula employed by the clinicians in the burn ICU. Adopting the practice of the burn ICU, we made the assumptions that all patient feedings

followed the formula and that all feedings were continuously given by enteral tube (bypassing the stomach).

The feedings were calculated using the "Carlson Equation" [64]:

$$EER = (BMR \cdot (0.89142 + (0.01335 \cdot TBSA\ burn)) \cdot BSA \cdot 24 \cdot AF)$$

Where:

$EER =$ Estimated Energy Requirement (kilocalories/day, or Calories/day)

$BMR =$ Basal Metabolic Rate (kilocalorie/m^2/day, or Calorie/m^2/day)

$TBSA =$ Total Body Surface Area of burn (%)

$BSA =$ Body Surface Area (m^2) $= \frac{Height \cdot Weight}{3600}$

$AF =$ Activity Factor (1.4), estimates the increment by which metabolic expenditure in the clinical environment exceeds resting energy expenditure

BMR is calculated by the Fleisch equation for males or females:

$$BMR_{males} = 54.337821 - (1.19961 \cdot Age) + (0.02548 \cdot Age^2) - (0.0018 \cdot Age^3)$$

$$BMR_{females} = 54.74942 - (1.54884 \cdot Age) + (0.03580 \cdot Age^2) - (0.0026 \cdot Age^3)$$

From the total Calories/day determined with the EER formula, since the enteral feeding consisted of 65% carbohydrates, the portion of the feeding Calories due to carbohydrates was calculated as $0.65 \cdot EER$. The remainder of the Calories were in the form of fat and proteins, which do not enter into our model.

3.4 Determining Hyperglycemic Stress Action

The original, unadapted Glucose-Insulin-Meal Model of Dalla Man et al. [58] permits one to choose from any of 300 *in silico* patient parameter sets (referred to hereafter as "*MM in silico patients*") to simulate BG output with any desired sequence of testing inputs of carbohydrate feeding and insulin. Our adaptation of the model uses the rationale that a parameter set of one of the 300 *MM in silico patients* can be found that approximates that of a real ICU patient. Further, any modifications of those parameters that are required to better fit the BG tracing of a real ICU patient represents the stress of being critically ill in an ICU. Those time-varying modifications define a Stress Action vector ("SA vector"). The pairing of the *MM in silico patient* with its corresponding fitted SA vector that most closely matches the real ICU patient defines an "*ICU in silico patient*". At this point, that pairing is a "virtual clone" of the real ICU patient.

All calculations were done in the MATLAB software environment. First, the calculated feeding and the recorded intravenous insulin rates for each of the 212 real burn ICU patients were input to the simulator with each of the 300 *MM in silico patients* without any parameter fitting. These simulated BG tracing outputs were stored for a later step. Stress Action, "SA", was then fitted hourly in our model using nonlinear least squares with the same feeding and insulin inputs as above, simulating 300 candidate "stressed" ICU patients for each burn ICU patient. Initial conditions in both cases were constructed by first simulating BG with the real feeding and insulin rates from the first hour of each burn patient together with the parameters of each *MM in silico patient* until steady

state was achieved (12 hours was used). After that, for fitting hourly SA, the final conditions of the previous hour's fitting were used as initial conditions for the next hour.

After all of the simulations were performed, the SA vector for each of the 212 real burn ICU patients was identified by selecting the ***MM in silico patient*** **+ SA vector** pairing with the smallest Mean Absolute Percentage Error (MAPE) between the simulated "stressed" BG tracing and the real ICU BG tracing. If more than one pairing had the same MAPE or if it was within 3% of the best MAPE, then the previously simulated BG tracing of a *MM in silico patient* with the largest Coefficient of Determination was used to choose the best pairing of those. An example of a best fitting is shown in Figure 3.1.

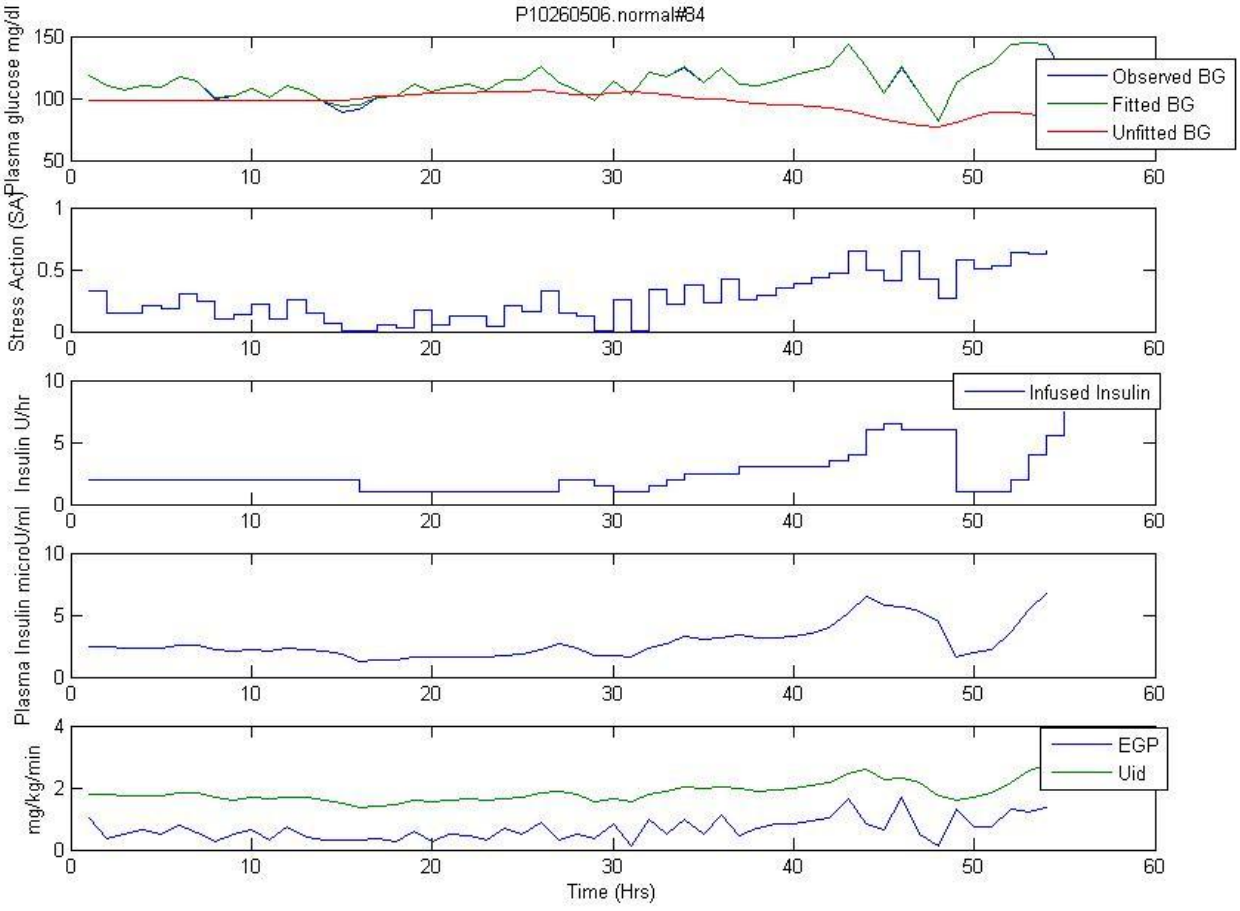


Figure 3.1 - Example fitting. EGP=Endogenous Glucose Production; Uid=insulin dependent

This procedure identified 212 SA vectors, each paired with one of 86 (of the original 300) unique *MM in silico patients*. Over the 10,939 hourly fittings with these pairings, 96.7% had less than 10% fitting error, and 91% had less than 1% fitting error (Figure 3.2).

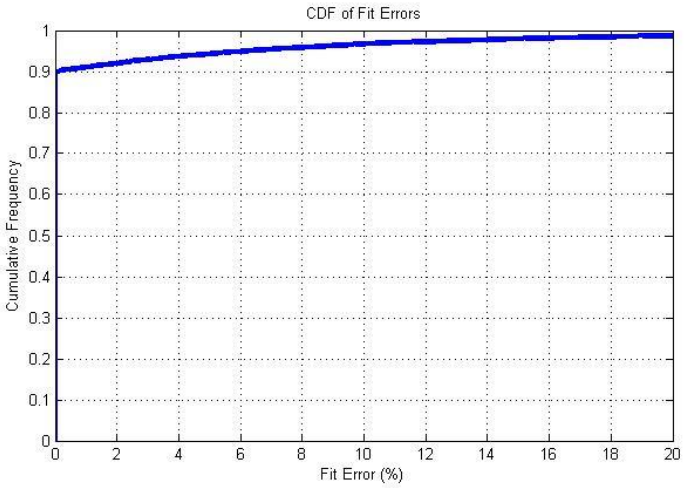


Figure 3.2- CDF of fit error for 10,939

These 212 SA vectors plus matching *MM in silico patients* then defined *ICU in silico patients*, or "virtual clones" of the original burn ICU patients. If we stopped at this point, our model and *ICU in silico patient*s would offer little more than offered by previous ICU hyperglycemia models: we would have one virtual ICU patient having been derived from one real ICU patient.

If one makes the assumption that the parameters of the matched *MM in silico patient* approximate those of a real ICU patient, then the SA vector represents the stress of being critically ill in an ICU. Our model uses the concept of a stand-in agent with the hyperglycemic actions of epinephrine to mediate this stress. Since the SA vector then

embodies the hyperglycemic stress imposed upon the *MM in silico patient*, it can stand alone, allowing it to be combined with a completely different *MM in silico patient* to yield a completely new *ICU in silico patient*. This extends our model considerably. The potential variability from such recombination would be advantageous in testing treatment protocols. In addition to their use in the creation of new *ICU in silico patients*, the SA vectors from a study population could serve as a basis for creating a model of Stress Action for that population. For the purpose of validation of our simulator, we chose to use the already identified set of 86 *MM in silico patients*.

4. Validation of the Simulator

In this section we first describe verification of the simulator by using it together with the "virtual clones" of real burn ICU patients to reproduce, in aggregate, the outcome measures of the real burn ICU patient population. Secondly, we describe the validation of the simulator by using it with new, "non-cloned" *ICU in silico patients* to recreate, again in aggregate, the outcome measures of the real burn ICU patient population.

4.1 Verification: Reproduction of burn ICU BG tracings

The earlier-calculated initial conditions used for fitting our "virtual clone" *ICU in silico patients* were not used for simulation, since those conditions will not be known for the remaining "non-cloned" *ICU in silico patients* and we wanted to be consistent across the populations. Instead, we initialized the system at its steady state with the known

feeding of the real ICU patient and the already-known basal BG of the *MM in silico patient* that was paired with the SA vector of the burn ICU patient.

In order to verify our model, we simulated the 212 fitted "virtual clone" pairings using the Army Insulin Infusion Protocol (coded in Simulink) employed by the clinicians in the burn ICU of the study population (Appendix) to reproduce, in aggregate, the outcome measures of the real burn ICU patient population. This was done twice: once, starting the simulation with the real ICU patient's initial insulin rate and then continuing with dosing per the protocol; the second time, the entire course of insulin dosing was per protocol. This was done to compare the effects of initial conditions on outcome measures.

The outcome measures chosen were calculated on a per-patient basis which were then reported in average for the simulated population: mean blood glucose (mg/dl), time to target BG range of 80-110 mg/dl (hours), time in target range (% of treatment time), percent of time in hypoglycemia (BG less than 60 mg/dl), mean insulin use (Units/hr), and Average Daily Risk Range (ADRR).

A measure not previously employed in the context of simulation of ICU hyperglycemia was taken from Hermanides et al. [65]. In order to find other factors potentially affecting ICU outcomes besides hyperglycemia *per se*, the Mean Absolute Glucose change per hour ("MAG") was used in that study to evaluate glucose variability in the

ICU, because it would pick up variability that standard deviation may underestimate. They found that high BG variability, as determined by a high MAG score, was associated with ICU and in-hospital death. The combination of high mean BG levels and high MAG scores was synergistically associated with ICU death. We calculated the per-patient MAG for our simulations as another means to compare the results of simulations of different populations of *ICU in silico patients*.

Examples of a simulated "virtual clone" *ICU in silico patient* are in Figures 4.1 and 4.2. Both figures show the originally observed BG and insulin tracings in blue, with the simulated tracings in green. The simulation in Figure 4.1 used the original, real first-hour insulin dose, whereas the simulation in Figure 4.2 used the protocol-determined initial insulin dose. The lower initial insulin dose dictated by the protocol permitted the simulated BG to rise above the observed BG level, which ultimately affected the outcome measures.

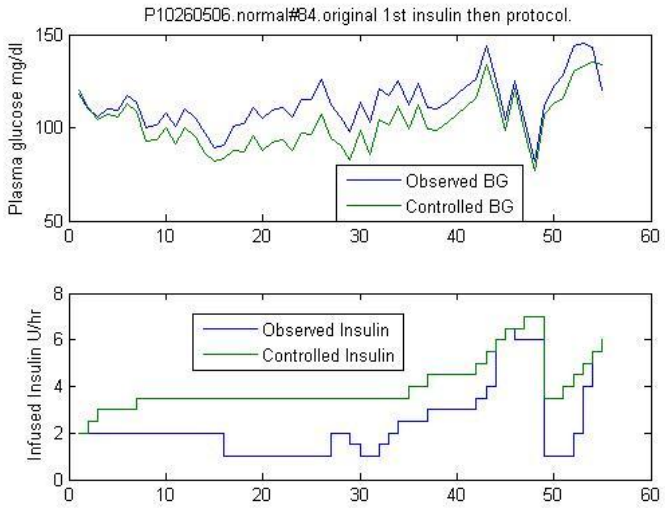


Figure 4.1 - Simulation using "virtual clone" ICU *in silico* patient with first hour of insulin the same as real ICU patient

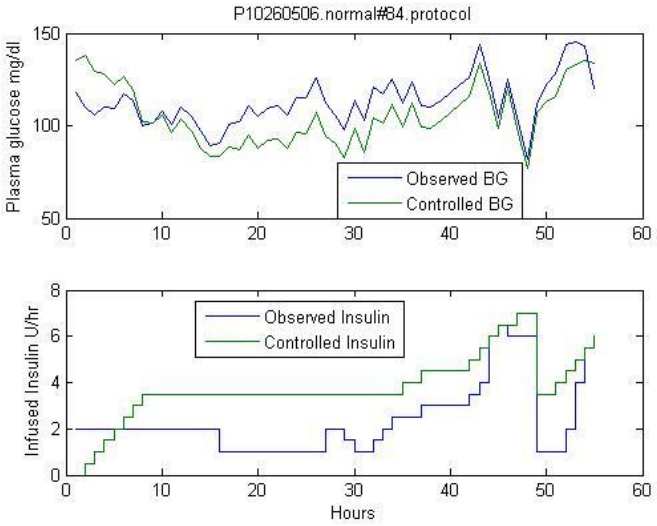


Figure 4.2 - Simulation using "virtual clone" ICU *in silico* patient with all insulin given per protocol

The differences between observed and simulated tracings could be explained by several factors: real initial conditions were unknown, and those we used may not have approximated them well; because real feedings were not provided, we input feedings according to a formula, which may not have been used for any particular real patient; feedings were assumed to be continuous, but in reality may be started and stopped for various reasons; intravenous boluses of glucose to treat hypoglycemia were assumed to have been given per protocol, but they are not recorded in our data and may not have been given; protocol compliance may have varied, especially the recording of timing of BG measurements and timing of insulin changes; administered medicines and surgical procedures were not recorded in our data and are not incorporated in our model.

Table 4.1 shows the per-patient outcome measures of the original burn ICU patients, and the two simulated versions.

Per Patient Stats
mean(sd)

	Group 1 (black) 212 Real ICU patients	Group 2 (blue) Sim 212 w 1st insulin, then protocol	Group 3 (red) Sim 212 w all insulin per protocol
Achieve target (%)	98.11	99.53	99.53
Time to target (hr)	6.68 (6.36)	6.72 (5.81)	8.14 (5.25)
Time in range (%)	39.13 (18.94)	42.86 (15.98)	39.7 (15.31)
Time in Hypoglycemia (%)	0.78	0.33	0.35
BG mean (mg/dl)	116.73 (15.03)	115.99 (10.52)	119.71 (12.64)
BG median (mg/dl)	113.63	112.73	115.14
MAG (mg/dl)	14.02 (4.54)	13.78 (4.27)	14.5 (4.32)
ADRR	13.86 (6.4)	12.12 (4.6)	13.95 (5.73)
Insulin (U/hr)	7.01 (4.41)	7.32 (3.92)	6.89 (3.72)

Table 4.1 - Per patient outcome measures of original burn ICU patients and of two simulated versions using different starting doses of insulin

Figure 4.3 shows the empirical CDF of all the BGs of each population.

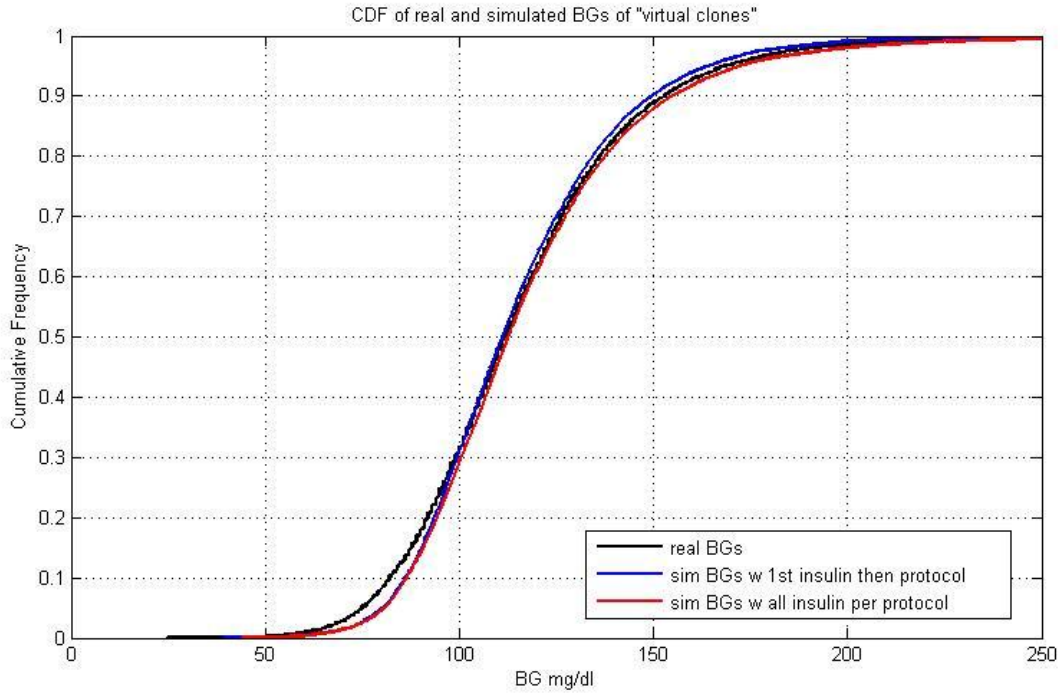


Figure 4.3 CDF of whole-cohort BGs of real ICU patients and simulated "virtual clone" ICU *in silico* patients

As expected, in Figure 4.3 the simulation (group 3, red) with the lower initial insulin has a greater proportion of high BGs and a longer time-to-target compared to the others. The simulation (group 2, blue) with the higher initial insulin rate has a smaller proportion of high BG levels and a greater time-in-range. Interestingly, both simulations decrease the number of low BGs as compared to the real BG tracing. The two sample Kolmogorov–Smirnov test rejects the null hypothesis of any of the population BG CDFs being from the same distribution.

Table 4.1 shows that the per-patient BG means of all three cases are within 3 mg/dl of each other, and ANOVA of per-patient BG means of the three groups (Figure 4.4) implies that at least the first two groups (the ones with the same starting doses of insulin) are from the same population. Group 3, although statistically rejecting the null hypothesis of being from the same population as the others, is well within measurement error clinically.

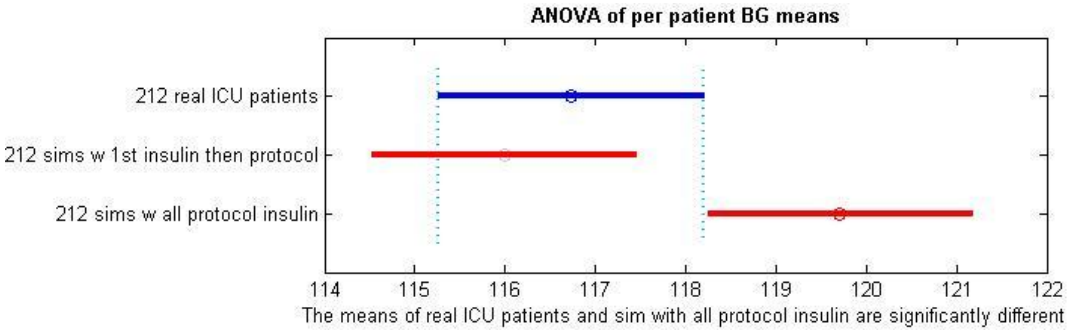


Figure 4.4

ANOVA of the per-patient BG medians (Figure 4.5) argues for no significant difference among all three groups.

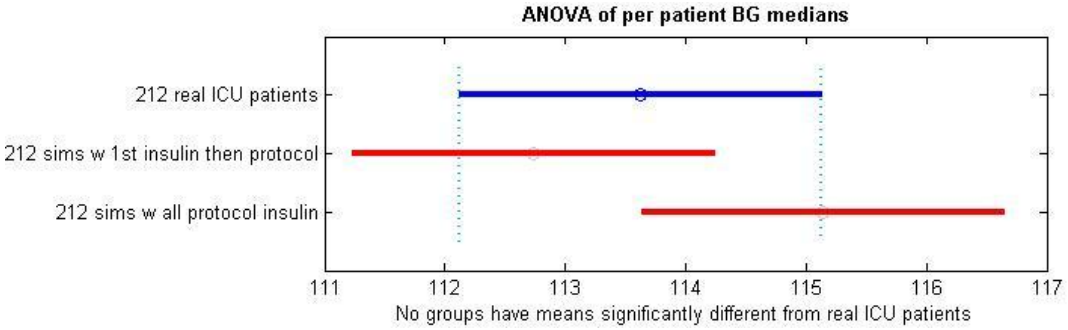


Figure 4.5

ANOVA of MAG, a measure of BG variability, also implies no significant difference among all three groups (Figure 4.6).

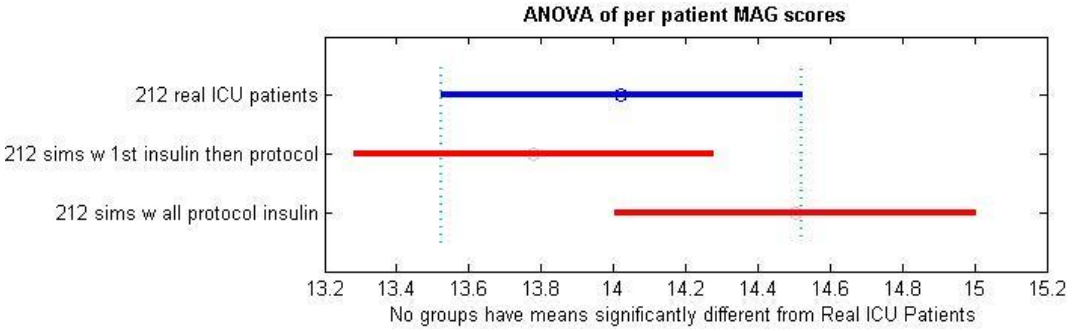


Figure 4.6

Lastly, ANOVA of per-patient insulin means shows no significant difference among the three groups (Figure 4.7).

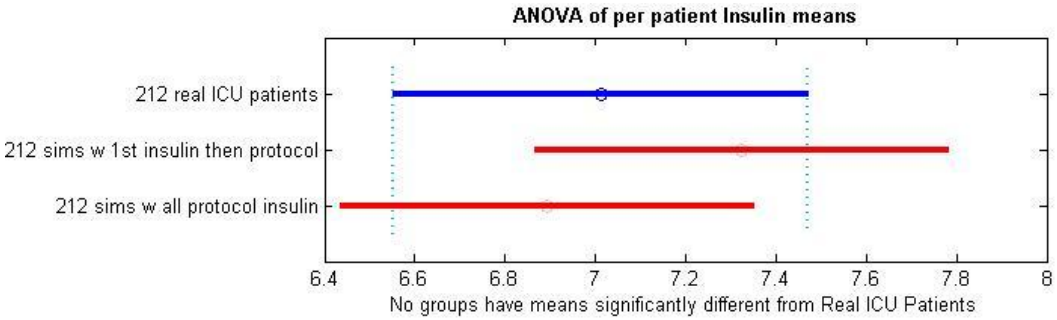


Figure 4.7

The reasons given earlier for differences between real and simulated outcomes once again come into play, with initial conditions, feeding variability, and protocol compliance probably being the most important. Keeping those qualifiers in mind, these results of these simulations are verification that our simulator produces, in aggregate, acceptably similar BG means and medians, hypoglycemia time, time-in-target, MAG score, ADRR score, and insulin dosing to those of the original burn population.

4.2 Validation: Simulation with new ICU in silico patients

We intend to use our simulator for testing the sensitivity of outcome measures (frequency of hypoglycemia, time in BG target range, BG mean, insulin mean) to changes in protocol variables (e.g. measurement error, sampling intervals, choice of treatment thresholds) for burn ICU patients. For validation for this purpose we looked for the ability of our simulator, while using newly created *ICU in silico patients* from a burn ICU, to produce aggregate outcome measures that were not significantly different from real burn patients at the p=0.05 level. Further validation will be sought later for application of the simulator in different patient populations.

Departing from the use of our 212 "virtual clone" *ICU in silico patients*, we performed simulations with new *ICU in silico patients* by combining an SA vector with a completely different *MM in silico patient* from that which it was originally matched. These simulations were done by combining each of the 212 SA vectors with randomly selected

MM in silico patients from the remainder of the pool of originally-matched 86 unique *MM in silico patients*.

The simulations were varied as follows:

Sim #1- 212 SA vectors x 3 random *MM in silico patients* + 4.1 gm/kg/day CHO feeding

Sim #2- 212 SA vectors x 3 random *MM in silico patients* + 5.5 gm/kg/day CHO feeding

Sim #3- 212 SA vectors x 3 random *MM in silico patients* + 7 gm/kg/day CHO feeding

The different feedings were used because these new *ICU in silico patients* did not necessarily have the same nutritional requirements as the real ICU patients (e.g. TBSA and ISS determinants of Estimated Energy Requirement were unknown). The value of 7 carbohydrate (CHO) gm/kg/day was obtained from the average of all the originally calculated feedings. It was noted during retrospective review of the original-feeding simulations that 5.5 CHO gm/kg/day was a feeding level above which insulin requirements rose quickly, leading to the selection of that value for simulation. The lowest feeding of 4.1 CHO gm/kg/day was derived from the recommendations of [66] for nutrition of ICU patients. It is apparent that our study population, as is usual for hypermetabolic burn patients, was fed at significantly high rates. As we shall see later, feeding is an important variable with respect to evaluating outcome measures.

Examples of simulations of one SA vector with 3 different *MM in silico patients*, using the original feeding (Figure 4.8):

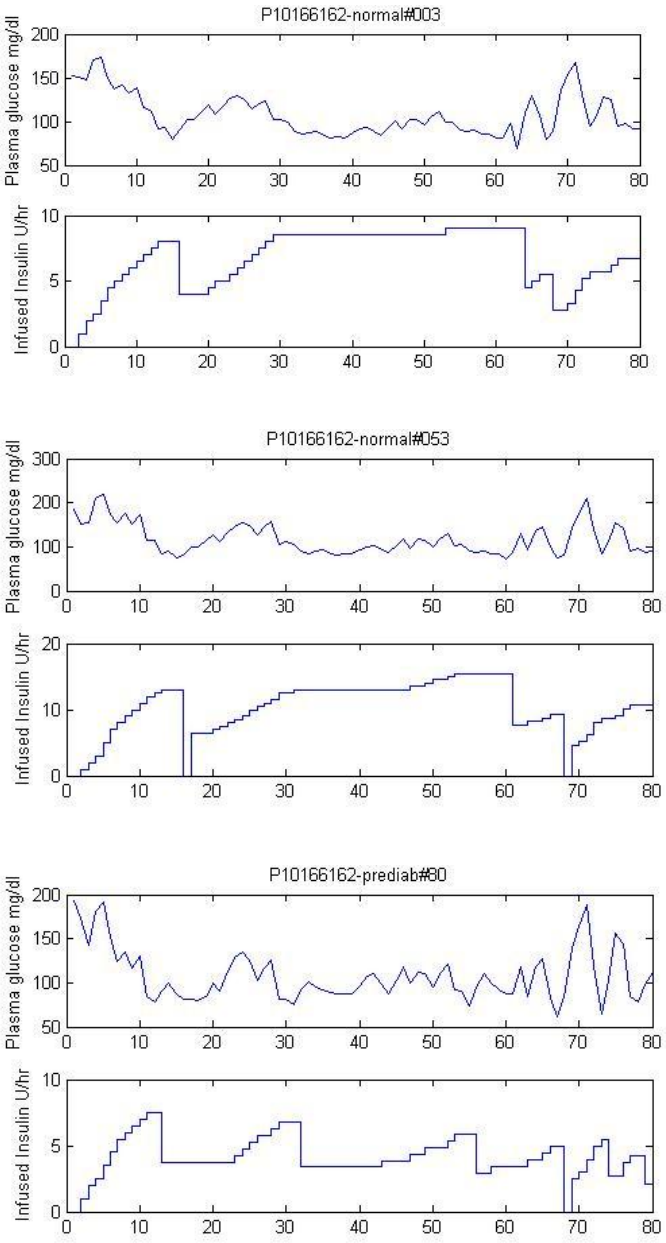


Figure 4.8 – Examples of simulations of 3 ICU *in silico* patients derived from one real ICU patient

Each of these tracings represents the output of a new *ICU in silico patient* interacting with the Army Insulin Infusion Protocol. Differences in BG control and insulin dosing reflect the different parameter sets for each patient.

Per-patient statistics for each simulation group are summarized in Table 4.2. CDFs of group population BGs are in Figure 4.9.

Per Patient Stats mean(sd)	Real ICU patients Orig. feed	Sim #1 4.1 gm/kg/d	Sim #2 5.5 gm/kg/d	Sim#3 7 gm/kg/d
Achieve target (%)	98.11	99.36	98.56	94.27
Time to target (hr)	6.68 (6.36)	6.71 (5.59)	7.61 (6.08)	9.94 (8.43)
Time in range (%)	39.13 (18.94)	44.27 (22.49)	42.53 (20.58)	38.15 (21.8)
Time in Hypoglycemia (%)	0.78	1.05	0.59	0.32
BG mean (mg/dl)	116.73 (15.03)	115.03 (14.66)	118.23(15.81)	123.69 (18.73)
BG median (mg/dl)	113.63	113.07	115.16	119.14
MAG (mg/dl)	14.02 (4.54)	13.69 (5.13)	14.53 (5.37)	14.56 (5.11)
ADRR	13.86 (6.4)	15.25 (7.49)	14.1 (6.02)	13.65 (5.96)
Insulin (U/hr)	7.01 (4.41)	5.11 (3.85)	6.48 (4.86)	8.96 (7.23)

Table 4.2 Per-patient statistics for each simulation group of new ICU *in silico* patients

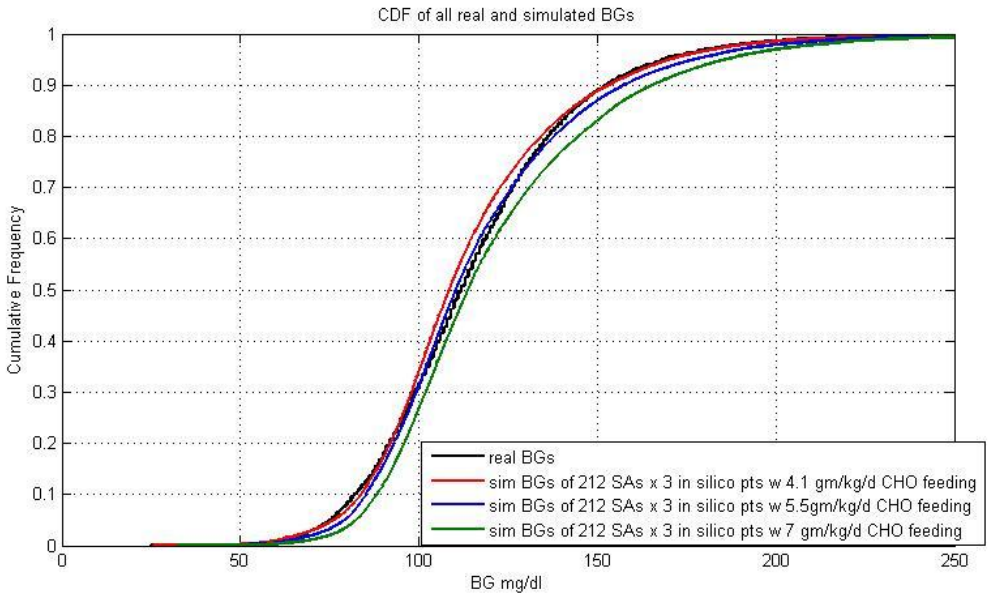


Figure 4.9 – CDFs of whole-cohort BGs for real and for each simulation group of new ICU *in silico* patients

The simulation in which the average of the original feedings was used with new *ICU in silico patients* (Sim #3 in Table 4.2) is notable for higher BG mean and median, for longer time-to-target, for less time-in-range, and for higher insulin needs than the lower feeding values. This may have arisen because our fitting procedure for SA did not account for differences in body weight between real and *in silico* patients. Also, this may reflect a mismatch, on average, between the feeding rate and the new *ICU in silico patients'* nutritional needs, which are unknown. The lower feeding rates (low with respect to burn patients, not other patient populations) probably lessen the effect of any such nutritional mismatch, and they are associated with outcome measures more similar to the original ICU patients. Efforts to find correlations between patient demographic characteristics (e.g. TBSA, ISS) and high Stress Action values or high insulin needs were unsuccessful. There may be other factors in play that were not in our data, such as medications. It may be that some of the high calculated levels of feeding were not in reality given, because of interruptions, bowel immotility, or intolerance of the rate, and this would skew the SA values to be higher than they would have been otherwise. Another possible explanation for nutritional mismatches may be that, despite the variability of the parameters in the 300 *MM in silico patients*, the *MM in silico patient* which was matched most closely with the real ICU patient may still not be "close enough". This would contaminate the SA vector with patient-specific characteristics.

The times-in-hypoglycemia for the simulations were inversely proportional to feedings and mostly were lower than for the real patient results. This probably reflects the absence of real-life feeding errors and treatment variation with our "perfect" implementation of the protocol.

The two sample Kolmogorov–Smirnov test rejects the null hypothesis of any of the population BG CDFs being from the same distribution.

Comparing per-patient outcome measures for statistical significance, ANOVA of per-patient BG means and medians (Figures 4.10 & 4.11) reflects the feeding differences already mentioned. The per-patient BG mean and median for the higher feedings are significantly different from the real ICU and lower feeding groups.

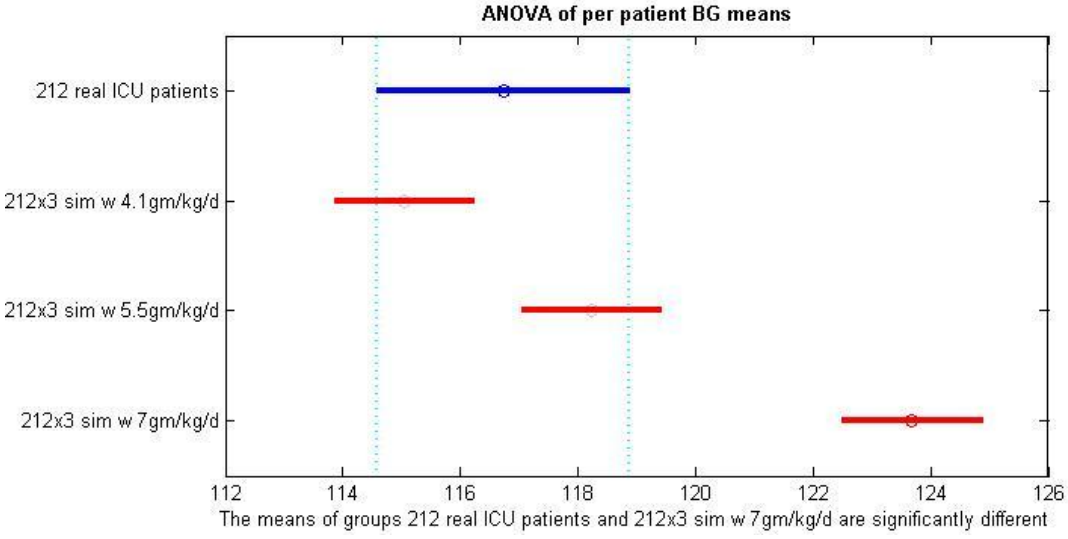


Figure 4.10

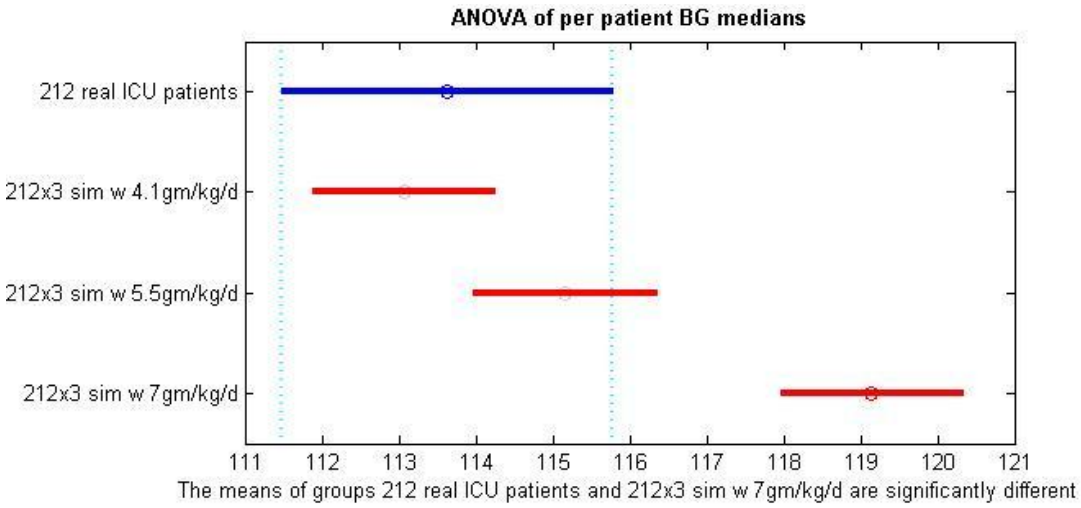


Figure 4.11

When comparing the characteristic of BG variability using the MAG score, none of the groups are significantly different with respect to MAG from the real ICU group (Figure 4.12).

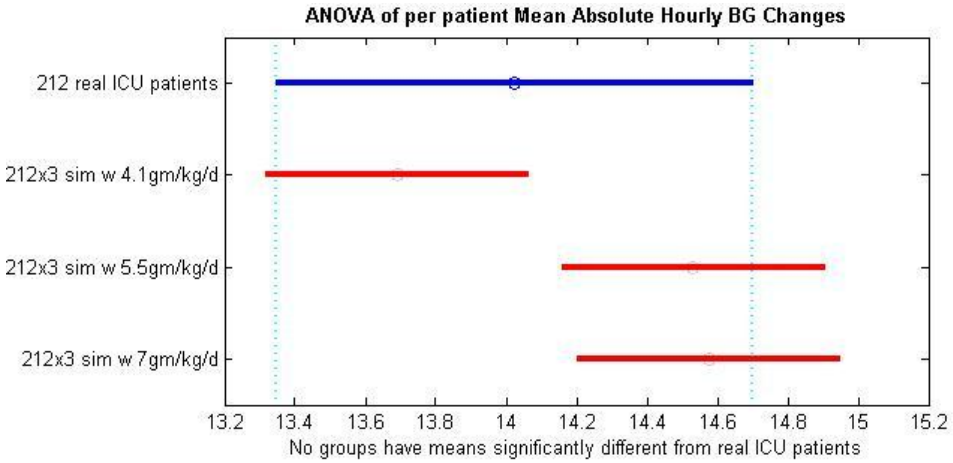


Figure 4.12

Lastly, per-patient insulin use is significantly different in the groups with feedings at either extreme (Figure 4.13).

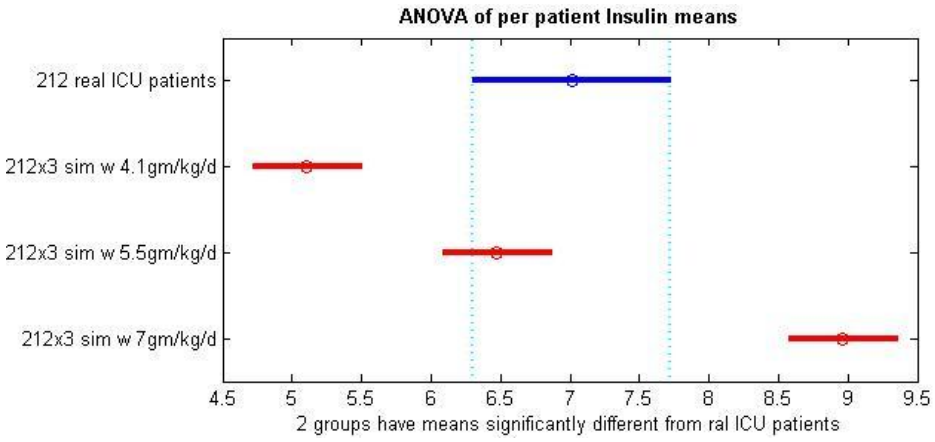


Figure 4.13

When it comes to reproducing the outcome measures of our original ICU patients with new *ICU in silico patients*, our simulator is sensitive to the lower and higher ends of the feeding rate range, for possible reasons as given above. However, new *ICU in silico patients* don't necessarily have to behave as the real ones, since they are indeed *new* and they theoretically comprise a totally different patient population.

We conclude that our simulator incorporating new *ICU in silico patients* is validated, when using 5.5 gm/kg/day of carbohydrate intake, to begin studying the sensitivity of outcome measures to changes in protocol variables.

5. Analysis of Protocols via Simulation

5.1 Addressing Treatment Variables

Our goal in creating this simulator was to enable us to evaluate insulin infusion protocols for ICU hyperglycemia. As mentioned earlier, several variables have been discussed in the literature that may confound the results of studies of insulin infusion therapy, such as measurement error, measurement frequency, protocol compliance, protocol attributes, and patient populations. Already seen in the process of validating our simulator is the importance of a variable as simple as feeding. Using our simulator, we can isolate, control, or change some of these variables, beginning to apply Systems Engineering to the study of insulin infusion therapy for ICU hyperglycemia. An example follows.

5.2 "Tuning" of the Army Insulin Infusion Protocol

In the process of validating our simulator, we observed an increase in the per patient outcome measure of time-in-hypoglycemia as feeding rates were decreased (Table 4.2). In an application of our simulator, we hypothesized that we could reduce time-in-hypoglycemia, without adversely altering other outcome measures, by changing the BG treatment target range of the protocol. Taking a cue from [67], we altered the Army Insulin Infusion Protocol, already presented above, to have a more narrow treatment BG target range of 90-110 mg/dl and incorporated it into our simulator. However, we still used the *outcome measure of 80-110 mg/dl*, reasoning that "shooting" for a smaller

target may improve our chances of hitting the surrounding, larger target. Using the changed protocol, we ran a simulation with each of the 212 SA vectors combined with 3 random *MM in silico patients* and with the feeding rate of 5.5 CHO gm/kg/day. The results are in Table 5.1.

Per Patient Stats mean(sd)	Sim #1 212x3 Target 80-110 Outcome Target 80-110	Sim #2 212x3 Treatment Target 90-110 Outcome Target 80-110
Achieve target (%)	98.56	98.89
Time to target (hr)	7.61 (6.08)	7.64 (6)
Time in range (%)	42.53 (20.58)	38.15 (20.15)
Time in Hypoglycemia (%)	0.59	0.44
BG mean (mg/dl)	118.23 (15.81)	121.8 (16.33)
BG median (mg/dl)	115.16	119.11
MAG (mg/dl)	14.53 (5.37)	15.01 (5.23)
ADRR	14.1 (6.02)	12.66 (5.93)
Insulin (U/hr)	6.48 (4.86)	5.88 (4.66)

Table 5.1 – Per patient outcome statistics comparing simulations using two different treatment target ranges in the Army insulin protocol

Time-in-hypoglycemia decreased slightly from 0.59% to 0.44%. And somewhat to be expected, since the protocol needed to order less insulin, the BG mean and median increased from 118.23 to 121.8 mg/dl and 115.16 to 119.11 mg/dl, respectively. ADRR appropriately improved with the lessened risk of hypoglycemia. But the outcome measure of percent time in the BG target range of 80-110 mg/dl *worsened* from 42.53% to 38.15%, probably because of the increased hyperglycemia.

Then hypothesizing that we needed to narrow the BG target range further by both raising the lower limit and lowering the upper limit, we changed the treatment BG target range to a very narrow 90-100mg/dl and performed the simulations again. We

retained the *outcome measure* of BG target range of 80-110mg/dl as before. The results are summarized in Table 5.2.

Per Patient Stats mean(sd)	Sim #1 212x3 with 5.5gm/kg/day Treatment Target 80-110mg/dl Outcome Target 80-110mg/dl	Sim #2 212x3 with 5.5gm/kg/day Treatment Target 90-110mg/dl Outcome Target 80-110mg/dl	Sim #2 212x3 with 5.5gm/kg/day Treatment Target 90-100mg/dl Outcome Target 80-110mg/dl
Achieve target (%)	98.56	98.89	98.57
Time to target (hr)	7.61 (6.08)	7.64 (6)	7.75 (7.32)
Time in range (%)	42.53 (20.58)	38.15 (20.15)	42.64 (21.88)
Time in Hypoglycemia (%)	0.59	0.44	0.44
BG mean (mg/dl)	118.23 (15.81)	121.8 (16.33)	119.33 (17.68)
BG median (mg/dl)	115.16	119.11	116.50
MAG (mg/dl)	14.53 (5.37)	15.01 (5.23)	15.28 (5.03)
ADRR	14.1 (6.02)	12.66 (5.93)	13.06 (5.61)
Insulin (U/hr)	6.48 (4.86)	5.88 (4.66)	6.05 (5.11)

Table 5.2 – Per patient outcome statistics comparing simulations using three different treatment target ranges in the Army insulin protocol

Compared to the previous protocol change, time-in-hypoglycemia stayed at the lower value, while hyperglycemia improved, and time-in-target returned to the original level. We achieved a mild improvement in time-in-hypoglycemia.

While such a narrow treatment BG target range may ultimately prove unworkable once other variables are factored in, such as measurement error and protocol compliance, this exercise with the simulator illustrates its ability to handily perform “what if” scenarios that may hasten the development of improved treatment protocols.

5.3 Protocol Comparisons and Optimization

Insulin infusion protocols have so far been based on discrete BG measurements at intervals from 15 minutes to 4 hours. But protocols based on continuous glucose monitoring (CGM), already in use in the outpatient setting for Type 1 diabetics, could yield improved outcome measures. Limitations such as sensor error, sensor drop out, and BG measurement lag time, could be modeled in a proposed CGM-controlled insulin protocol in our simulator, and those outcomes could be compared with current, discrete BG measurement protocols.

Our simulator should also be a useful tool in determining which combinations of desired outcomes are achievable, and to what degree. As seen above, optimizing an insulin infusion protocol to avoid the most obviously dangerous outcome of hypoglycemia carries the risk of adversely affecting other outcome measures, such as BG time-in-range. These other outcome measures, including BG variability *per se*, have also been shown to detrimentally affect mortality [63], and need to be assigned some weight in optimization.

6. Conclusions and Future Work

The tantalizing success of Van den Berghe et al. [8] in using insulin infusion therapy, particularly for “tight glucose control”, to reduce mortality and morbidity from stress hyperglycemia in critically ill patients has been overshadowed by subsequent mixed and sometimes conflicting reports. Many differences in the studies that potentially contribute to the confusion have been identified, such as patient populations, protocol attributes, measurement error, and protocol compliance. More research addressing these variables is called for, but studying them directly in clinical settings on real patients carries costs of money, time, and danger. A tool, a computerized simulator of stress hyperglycemia, could greatly assist and hasten this research.

This thesis has presented such a simulator. It started with a detailed model by Dalla Man et al. [57] which was built on a database of glucose and insulin fluxes and levels measured from real, non-critically ill patients. We presented an approach to adapt the model for stress hyperglycemia that uses the known physiology of stress mediators, such as epinephrine. Using treatment data from critically ill patients in an Army burn ICU, we matched the original model *in silico patient* parameter sets to real ICU patients and used them to fit Stress Action (SA) vectors that account for the time-varying stresses experienced by them. This yielded a collection of 212 “virtual clone” *ICU in silico patients*, from which the SA vectors and patient parameter sets can be extracted and variously recombined to create totally new *ICU in silico patients*. We validated our simulator using both the “virtual clones” and the new *ICU in silico patients*.

Our model and simulator differ from other ICU simulators [18], [46] in two respects. First, instead of the concept of insulin sensitivity, we employ the idea of "hyperglycemic stress" mediated by agents, such as epinephrine, that work at their own sites of action in the model. This opens the model to the addition of new knowledge concerning stress mediators, and insulin sensitivity returns to being an observed characteristic of the patient. Second, from one population of real ICU patients, we are able to generate numerous, new *ICU in silico patients*, amplifying our efforts and providing our simulator with a larger number of patients for study.

For the future:

- Fittings of the SA vectors were done without regard to matching the body weights of real burn patients with *MM in silico patient* weights. This may partially explain feeding mismatches when doing simulations with new *ICU in silico patients*. A fitting procedure that accounts for body weight should be developed.
- The use of epinephrine as a stand-in for all of the stress hormones is adequate for our intended use, but future applications of the simulator may require the incorporation of the specific actions of the stress hormones.
- The sensitivity of simulation outcome measures to the weights assigned to the differential effects of epinephrine on HGP and PGU should be evaluated.
- Improvements to, and increased confidence in, our simulator can come from applying and validating it on new patient populations and different insulin infusion

protocols. A library of Stress Action vectors could be compiled from these different patient populations, enabling study of different protocols on various populations.

- This time we relied on a formula-based estimation of feeding and the assumption of continuous enteral feeding during our fitting process, which may have overestimated patient intake. Patient data with more detailed feeding information could improve the accuracy of our fitting process, lessening potential nutritional mismatches between "cloned" and newly created *ICU in silico patients*.
- The distance spanned between each metabolic parameter of the 300 *MM in silico patients* may be too great. Creating a finer gradation of metabolic variability, or "filling gaps", by adjusting current parameter sets and creating new *in silico* patients to fill those spaces, would expand the database of *in silico* patients for potential matches with real patients. This would lessen the risk of contaminating a fitted Stress Action vector with patient-specific characteristics.
- A stochastic SA "generator" based on a model of the SA vectors from our burn patient population, or from any future population studied, would extend our simulator, particularly simulating longer treatment durations.

As our simulator is applied to various populations and protocols, it will be undoubtedly be modified and refined, but in its current state the simulator is ready to begin studying the sensitivity of outcome measures to changes in protocol variables.

7. Appendix

CLINICAL PRACTICE GUIDELINES:
INSULIN PROTOCOL

1. Discontinue all previous orders for insulin and oral hypoglycemic agents.

2. If IV nutrition, IV dextrose or enteral nutrition is decreased or stopped for more than 5 minutes, decrease insulin infusion rate by 50%, and recheck blood glucose levels q 1 hr until blood glucose is stable.

3. Pharmacy will deliver 100 units of Human Regular insulin in 100 mL Normal Saline (1 mL = 1 unit). Before connection to patient, prime IV tubing and allow it to set for 30 minutes to saturate the tubing. Flush it with an additional 20cc of insulin solution then connect it to the patient. A subsequent bag of insulin does not need to be primed until the tubing is changed. The tubing is good for 72 hours. Infuse the insulin drip into the maintenance IV.

4. Blood glucose levels may be measured using blood from capillary (fingerstick), arterial line, or central venous catheter sources. (In the latter case, do not use the line if glucose is infusing.) Initiate IV insulin infusion rate according to the blood glucose (BG) level:

BG = 120-150	1 unit/hour
BG = 151-200	2 units/hour
BG ≥ 201	4 units/hour

5. Measure blood glucose levels q 1 hr with the Lifescan SureStep Flex Glucometer. Chart all levels and hourly insulin rate.

6. Titrate insulin to obtain a target between 80-110 mg/dl using the following scheme:

Goal is to achieve glucose control within 6-8 hrs. If still high thereafter, contact MD or PA.	
Blood Glucose	**Action**
≤ 59	Give 25 mL 50% dextrose IV, stop insulin, recheck glucose in 15 min. If glucose > 80, restart insulin at 50% of earlier dose. If not, call MD or PA.
60-79	Stop insulin, recheck glucose in 15 min. If glucose > 80, restart insulin at 50% of earlier dose. If not, call MD or PA.
80-110	RN adjusts rate up or down by 0-0.5 unit/hr, depending on trend in glucose. (E.g., if glucose is 80 one hour, and 100 the next, an increase may be appropriate. If glucose is 100 one hour and 80 the next, a decrease may be appropriate. If stable in the 80-110 range, no change is needed.)
111-150	Increase insulin dose by 0.5 unit/hr.
151-200	Increase insulin dose by 1 unit/hr.
201-250	Increase insulin dose by 2 units/hr.
≥251	Notify MD or PA.

Maximum dose of insulin is 50 units/hr. Once reached, notify MD or PA.

Figure 7.1 – Copy of Army burn ICU insulin therapy protocol during the time of patient data acquisition

8. References

[1] C. Bernard, Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux (Lessons on the phenomena of life common to animals and plants), vol. 1. Paris, France: J.B. Baillière et Fils, 1878.

[2] R. R. Wolfe, M. J. Durkot, J. R. Allsop, and J. F. Burke, “Glucose metabolism in severely burned patients,” Metabolism, vol. 28, no. 10, pp. 1031–1039, 1979.

[3] K. C. McCowen, A. Malhotra, and B. R. Bistrian, “Stress-Induced Hyperglycemia,” Critical Care Clinics, vol. 17, no. 1, 2001.

[4] K. M. Dungan, S. S. Braithwaite, and J. C. Preiser, “Stress hyperglycaemia,” The Lancet, vol. 373, no. 9677, pp. 1798–1807, 2009.

[5] A. B. J. Groeneveld, A. Beishuizen, and F. Visser, “Insulin: a wonder drug in the critically ill?,” Critical Care, vol. 6, no. 2, pp. 102–105, 2002.

[6] American Diabetes Association, “Diagnosis and Classification of Diabetes Mellitus,” Diabetes Care, vol. 33, no. Supplement_1, pp. S62–S69, Dec. 2009.

[7] G. G. Gauglitz, D. N. Herndon, and M. G. Jeschke, “Insulin Resistance Postburn: Underlying Mechanisms and Current Therapeutic Strategies,” Journal of Burn Care & Research, vol. 29, no. 5, pp. 683–694, Sep. 2008.

[8] G. Van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers, and R. Bouillon, “Intensive Insulin Therapy in Critically Ill Patients,” N Engl J Med, vol. 345, no. 19, pp. 1359–1367, Nov. 2001.

[9] G. Van den Berghe, A. Wilmer, G. Hermans, W. Meersseman, P. J. Wouters, I. Milants, E. Van Wijngaerden, H. Bobbaers, and R. Bouillon, “Intensive Insulin Therapy in the Medical ICU,” N Engl J Med, vol. 354, no. 5, pp. 449–461, Feb. 2006.

[10] I. Vanhorebeek, L. Langouche, and G. Van den Berghe, “Tight Blood Glucose Control With Insulin in the ICU: Facts and Controversies,” Chest, vol. 132, no. 1, pp. 268–278, Jul. 2007.

[11] NICE-SUGAR Study Investigators, S. Finfer, D. R. Chittock, S. Y. Su, D. Blair, D. Foster, V. Dhingra, R. Bellomo, D. Cook, P. Dodek, W. R. Henderson, P. C. Hebert, S. Heritier, D. K. Heyland, C. McArthur, E. McDonald, I. Mitchell, J. A. Myburgh, R. Norton, J. Potter, B. G. Robinson, and J. J. Ronco, “Intensive versus conventional glucose control in critically ill patients,” N.Engl.J.Med., vol. 360, no. 13, pp. 1283–1297, Mar. 2009.

[12] F. M. Brunkhorst, C. Engel, F. Bloos, A. Meier-Hellmann, M. Ragaller, N. Weiler, O. Moerer, M. Gruendling, M. Oppert, and S. Grond, “Intensive insulin therapy and pentastarch resuscitation in severe sepsis,” New England Journal of Medicine, vol. 358, no. 2, pp. 125–139, 2008.

[13] P. Devos, J. Preiser, and C. Melot, “Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the Glucontrol study [abstract],” Intensive Care Med, vol. 33, no. Supplement, p. S189, 2007.

[14] E. S. Moghissi, M. T. Korytkowski, M. DiNardo, D. Einhorn, R. Hellman, I. B. Hirsch, S. E. Inzucchi, F. Ismail-Beigi, M. S. Kirkman, and G. E. Umpierrez, “American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control,” Diabetes Care, vol. 32, no. 6, pp. 1119–1131, Jun. 2009.

[15] J. G. Chase, F. Suhaimi, S. Penning, J. C. Preiser, A. J. Le Compte, J. Lin, C. G. Pretty, G. M. Shaw, K. T. Moorhead, and T. Desaive, “Validation of a model-based virtual trials method for tight glycemic control in intensive care,” BioMedical Engineering OnLine, vol. 9, no. 1, p. 84, 2010.

[16] M. E. Wilinska, J. Blaha, L. J. Chassin, J. J. Cordingley, N. C. Dormand, M. Ellmerer, M. Haluzik, J. Plank, D. Vlasselaers, and P. J. Wouters, “Evaluating Glycemic Control Algorithms by Computer Simulations,” Diabetes Technology & Therapeutics, vol. 13, no. 7, pp. 713–722, 2011.

[17] R. Hovorka, L. J. Chassin, M. Ellmerer, J. Plank, and M. E. Wilinska, “A simulation model of glucose regulation in the critically ill,” Physiological Measurement, vol. 29, no. 8, pp. 959–978, 2008.

[18] J. G. Chase, G. M. Shaw, X. W. Wong, T. Lotz, J. Lin, and C. E. Hann, “Model-based glycaemic control in critical care--A review of the state of the possible,” Biomedical Signal Processing and Control, vol. 1, no. 1, pp. 3–21, Jan. 2006.

[19] A. Vella and R. A. Rizza, “Application of Isotopic Techniques Using Constant Specific Activity or Enrichment to the Study of Carbohydrate Metabolism,” Diabetes, vol. 58, no. 10, pp. 2168–2174, Oct. 2009.

[20] K. Ekberg, B. R. Landau, A. Wajngot, V. Chandramouli, S. Efendic, H. Brunengraber, and J. Wahren, “Contributions by kidney and liver to glucose production in the postabsorptive state and after 60 h of fasting.,” Diabetes, vol. 48, no. 2, pp. 292–298, 1999.

[21] P. Goodyear and M. D. Kahn, “Exercise, glucose transport, and insulin sensitivity,” Annual review of medicine, vol. 49, no. 1, pp. 235–261, 1998.

[22] R. N. Bergman and R. J. Bucolo, “Interaction of insulin and glucose in the control of hepatic glucose balance,” American Journal of Physiology--Legacy Content, vol. 227, no. 6, p. 1314, 1974.

[23] A. Vella, A. S. Reed, N. Charkoudian, P. Shah, R. Basu, A. Basu, M. J. Joyner, and R. A. Rizza, “Glucose-induced suppression of endogenous glucose production: dynamic response to differing glucose profiles,” American Journal of Physiology - Endocrinology And Metabolism, vol. 285, no. 1, pp. E25 –E30, Jul. 2003.

[24] J. Radziuk and S. Pye, “Hepatic glucose uptake, gluconeogenesis and the regulation of glycogen synthesis,” Diabetes/Metabolism Research and Reviews, vol. 17, no. 4, pp. 250–272, 2001.

[25] C. Weissman, “The metabolic response to stress: an overview and update,” Anesthesiology, vol. 73, no. 2, p. 308, 1990.

[26] K. N. Frayn, “Hormonal control of metabolism in trauma and sepsis,” Clinical endocrinology, vol. 24, no. 5, pp. 577–599, 1986.

[27] T. Heise, L. Heinemann, and A. A. R. Starke, “Simulated postaggression metabolism in healthy subjects: Metabolic changes and insulin resistance,” Metabolism, vol. 47, no. 10, pp. 1263–1268, Oct. 1998.

[28] S. M. Gustavson, C. A. Chu, M. Nishizawa, B. Farmer, D. Neal, Y. Yang, E. P. Donahue, P. Flakoll, and A. D. Cherrington, “Interaction of glucagon and epinephrine in the control of hepatic glucose production in the conscious dog,” American Journal of Physiology-Endocrinology And Metabolism, vol. 284, no. 4, p. E695, 2003.

[29] L. Plat, M. M. Byrne, J. Sturis, K. S. Polonsky, J. Mockel, F. Fery, and E. Van Cauter, “Effects of Morning Cortisol Elevation on Insulin Secretion and Glucose Regulation in Humans,” Am J Physiol Endocrinol Metab, vol. 270, no. 1, pp. E36–E42, Jan. 1996.

[30] N. Eigler, L. Sacca, and R. S. Sherwin, “Synergistic interactions of physiologic increments of glucagon, epinephrine, and cortisol in the dog: a model for stress-induced hyperglycemia,” Journal of Clinical Investigation, vol. 63, no. 1, p. 114, 1979.

[31] J. S. Krinsley, “Effect of an intensive glucose management protocol on the mortality of critically ill adult patients,” in Mayo Clinic Proceedings, 2004, vol. 79, pp. 992–1000.

[32] B. E. Taylor, M. E. Schallom, C. S. Sona, T. G. Buchman, W. A. Boyle, J. E. Mazuski, D. E. Schuerer, J. M. Thomas, C. Kaiser, W. Y. Huey, M. R. Ward, J. E. Zack, and C. M. Coopersmith, "Efficacy and Safety of an Insulin Infusion Protocol in a Surgical ICU," Journal of the American College of Surgeons, vol. 202, no. 1, pp. 1–9, Jan. 2006.

[33] S. Honiden and S. E. Inzucchi, "Glucose Controversies in the ICU," Journal of Intensive Care Medicine, Nov. 2010.

[34] J.-C. Preiser, P. Devos, S. Ruiz-Santana, C. Mélot, D. Annane, J. Groeneveld, G. Iapichino, X. Leverve, G. Nitenberg, P. Singer, J. Wernerman, M. Joannidis, A. Stecher, and R. Chioléro, "A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study," Intensive Care Medicine, vol. 35, pp. 1738–1748, Jul. 2009.

[35] J. Blaha, J. Kremen, K. Anderlova, and M. Haluzik, "Treatment of Hyperglycemia in critically ill patients: comparison of different glucose management protocols.," http://www.clinicip.org/fileadmin/clinicip/glucosemanagement_mug_rbh_kul_cup__2_.pdf.

[36] S. Kanji, J. Buffie, B. Hutton, P. S. Bunting, A. Singh, K. McDonald, D. Fergusson, L. A. McIntyre, and P. C. Hebert, "Reliability of point-of-care testing for glucose measurement in critically ill adults," Critical care medicine, vol. 33, no. 12, p. 2778, 2005.

[37] B. G. Fahy and D. B. Coursin, "Critical glucose control: The devil is in the details," in Mayo Clinic Proceedings, 2008, vol. 83, pp. 394–397.

[38] D. E. G. Griesdale, R. J. De Souza, R. M. Van Dam, D. K. Heyland, D. J. Cook, A. Malhotra, R. Dhaliwal, W. R. Henderson, D. R. Chittock, and S. Finfer, "Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data," Canadian Medical Association Journal, vol. 180, no. 8, pp. 821–827, 2009.

[39] K. Kimura, Y. Iguchi, T. Inoue, K. Shibazaki, N. Matsumoto, K. Kobayashi, and S. Yamashita, "Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage," Journal of the Neurological Sciences, vol. 255, no. 1–2, pp. 90–94, Apr. 2007.

[40] A. Salim, P. Hadjizacharia, J. Dubose, C. Brown, K. Inaba, L. S. Chan, and D. Margulies, "Persistent Hyperglycemia in Severe Traumatic Brain Injury: An Independent Predictor of Outcome," The American Surgeon, vol. 75, no. 1, pp. 25–29, 2009.

[41] J. G. Chase, G. Shaw, A. Le Compte, T. Lonergan, M. Willacy, X.-W. Wong, J. Lin, T. Lotz, D. Lee, and C. Hann, “Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change,” Critical Care, vol. 12, no. 2, p. R49, 2008.

[42] L. Tappy, M. Berger, J.-M. Schwarz, M. McCamish, J.-P. Revelly, P. Schneiter, E. Jéquier, and R. Chioléro, “Hepatic and Peripheral Glucose Metabolism in Intensive Care Patients Receiving Continuous High- or Low-Carbohydrate Enteral Nutrition,” JPEN J Parenter Enteral Nutr, vol. 23, no. 5, pp. 260–268, Sep. 1999.

[43] P. Sauer and E. R. Van Horn, “Impact of Intravenous Insulin Protocols on Hypoglycemia, Patient Safety, and Nursing Workload,” Dimensions of Critical Care Nursing, vol. 28, no. 3, p. 95, 2009.

[44] R. N. Bergman, Y. Z. Ider, C. R. Bowden, and C. Cobelli, “Quantitative estimation of insulin sensitivity,” Am J Physiol Endocrinol Metab, vol. 236, no. 6, pp. E667–677, 1979.

[45] J. G. Chase, G. M. Shaw, J. Lin, C. V. Doran, C. Hann, M. B. Robertson, P. M. Browne, T. Lotz, G. C. Wake, and B. Broughton, “Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care,” Medical Engineering & Physics, vol. 27, no. 1, pp. 1–11, Jan. 2005.

[46] H. Shamoon, R. Hendler, and R. S. Sherwin, “Synergistic Interactions Among Antiinsulin Hormones in the Pathogenesis of Stress Hyperglycemia in Humans,” JCEM, vol. 52, no. 6, pp. 1235–1241, Jun. 1981.

[47] J. E. Gerich, J. H. Karam, and P. H. Forsham, “Stimulation of Glucagon Secretion by Epinephrine in Man,” JCEM, vol. 37, no. 3, pp. 479–481, Sep. 1973.

[48] B. J. Jones, T. Tan, and S. R. Bloom, “Minireview: Glucagon in Stress and Energy Homeostasis,” Endocrinology, vol. 153, no. 3, pp. 1049–1054, Mar. 2012.

[49] W. E. Clutter, D. M. Bier, S. D. Shah, and P. E. Cryer, “Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man.,” Journal of Clinical Investigation, vol. 66, no. 1, p. 94, 1980.

[50] R. R. Wolfe, D. N. Herndon, F. Jahoor, H. Miyoshi, and M. Wolfe, “Effect of severe burn injury on substrate cycling by glucose and fatty acids,” New England Journal of Medicine, vol. 317, no. 7, pp. 403–408, 1987.

[51] J. Wortsman, “Role of epinephrine in acute stress,” Endocrinology & Metabolism Clinics of North America, vol. 31, pp. 79–106, Mar. 2002.

[52] C. Chambrier, M. Laville, K. R. Berrada, M. Odeon, P. Bouletreau, and M. Beylot, "Insulin sensitivity of glucose and fat metabolism in severe sepsis," Clinical Science, vol. 99, no. 4, pp. 321–328, 2000.

[53] D. A. Guy, D. Sandoval, M. A. Richardson, D. Tate, P. J. Flakoll, and S. N. Davis, "Differing physiological effects of epinephrine in type 1 diabetes and nondiabetic humans," American Journal of Physiology - Endocrinology And Metabolism, vol. 288, no. 1, pp. E178 –E186, Jan. 2005.

[54] R. Rizza, M. Haymond, P. Cryer, and J. Gerich, "Differential effects of epinephrine on glucose production and disposal in man," American Journal of Physiology-Endocrinology And Metabolism, vol. 237, no. 4, p. E356, 1979.

[55] R. A. Rizza, P. E. Cryer, M. W. Haymond, and J. E. Gerich, "Adrenergic mechanisms for the effects of epinephrine on glucose production and clearance in man," Journal of Clinical Investigation, vol. 65, no. 3, p. 682, 1980.

[56] R. S. Sherwin and L. Sacca, "Effect of epinephrine on glucose metabolism in humans: contribution of the liver," American Journal of Physiology-Endocrinology And Metabolism, vol. 247, no. 2, p. E157, 1984.

[57] C. D. Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," IEEE Transactions on Biomedical Engineering, vol. 54, no. 10, pp. 1740–1749, 2007.

[58] R. Basu, B. Di Camillo, G. Toffolo, A. Basu, P. Shah, A. Vella, R. Rizza, and C. Cobelli, "Use of a novel triple-tracer approach to assess postprandial glucose metabolism," Am J Physiol Endocrinol Metab, vol. 284, no. 1, pp. E55–69, 2003.

[59] B. P. Kovatchev, M. Breton, C. D. Man, and C. Cobelli, "In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes," J.Diabetes Sci.Technol., vol. 3, no. 1, pp. 44–55, 2009.

[60] C. Dalla Man, A. Caumo, R. Basu, R. Rizza, G. Toffolo, and C. Cobelli, "Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method," *American Journal of Physiology-Endocrinology And Metabolism*, vol. 287, no. 4, pp. E637–E643, 2004.

[61] J. Radziuk, T. J. McDonald, D. Rubenstein, and J. Dupre, "Initial splanchnic extraction of ingested glucose in normal man," *Metabolism*, vol. 27, no. 6, pp. 657–669, Jun. 1978.

[62] R. W. Stevenson, K. E. Steiner, C. C. Connolly, H. Fuchs, K. G. Alberti, P. E. Williams, and A. D. Cherrington, “Dose-related effects of epinephrine on glucose production in conscious dogs,” American Journal of Physiology-Endocrinology And Metabolism, vol. 260, no. 3, p. E363, 1991.

[63] J. Lin, N. N. Razak, C. G. Pretty, A. Le Compte, P. Docherty, J. D. Parente, G. M. Shaw, C. E. Hann, and J. Geoffrey Chase, “A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients,” Computer Methods and Programs in Biomedicine, vol. 102, no. 2, pp. 192–205, May 2011.

[64] D. E. Carlson, W. G. Cioffi Jr, A. D. Mason Jr, W. F. McManus, and B. A. Pruitt Jr, “Resting energy expenditure in patients with thermal injuries.,” Surgery, Gynecology & Obstetrics, vol. 174, no. 4, p. 270, 1992.

[65] J. Hermanides, T. M. Vriesendorp, R. J. Bosman, D. F. Zandstra, J. B. Hoekstra, and J. H. DeVries, “Glucose variability is associated with intensive care unit mortality,” Critical care medicine, vol. 38, no. 3, p. 838, 2010.

[66] F. B. Cerra, M. R. Benitez, G. L. Blackburn, R. S. Irwin, K. Jeejeebhoy, D. P. Katz, S. K. Pingleton, J. Pomposelli, J. L. Rombeau, and E. Shronts, “accp consensus statement: Applied Nutrition in ICU Patients,” Chest, vol. 111, pp. 769–78, 1997.

[67] C. S. Hughes, S. D. Patek, M. D. Breton, and B. P. Kovatchev, “Hypoglycemia Prevention via Pump Attenuation and Red-Yellow-Green ‘Traffic’ Lights Using Continuous Glucose Monitoring and Insulin Pump Data,” J Diabetes Sci Technol, vol. 4, no. 5, pp. 1146–1155, Sep. 2010.