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An Evaluation of "I, Pancreas" Algorithm Performance *In Silico*

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Abstract

Background:

The objective of this study was to investigate the performance of a newly proposed insulin titrating algorithm to achieve tight glycemic control in the critically ill.

Methods:

A simulation environment with 10 critically ill virtual subjects was employed to evaluate the "I, Pancreas" algorithm proposed by Braithwaite *et al*. and described in an article in this issue of *Journal of Diabetes Science and Technology*. The algorithm was coded in MATLAB® and was "plugged in" to a simulation environment to provide glucose control in a 48-hour-long simulated study.

Results:

Mean blood glucose was 6.5 ± 0.4 mmol/liter (118 ± 7.8 mg/dl), percentage of time spent in the target glucose range was 38% (32–44%), and the hyperglycemic index was 0.6 (0.4 –1.0) mmol/liter [11.1 (7.7–18.1) mg/dl]. A single episode of mild hypoglycemia at 3.8 mmol/liter (69 mg/dl) was observed during 480 hours of glucose control.

Conclusion:

In this initial *in silico* evaluation, the "I, Pancreas" algorithm provided a safe control of glucose in the simulated study and achieved tight glycemic control 38% of the time.

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Abbreviations: (BG) blood glucose, (CLINICIP) Closed Loop Insulin Infusion for Critically Ill Patients, (CV) coefficient of variation, (eMPC) enhanced model predictive control, (HGI) hyperglycemic index, (ICU) intensive care unit, (IR) infusion rate, (IV) intravenous, (MR) maintenance rate, (SD) standard deviation, (TGC) tight glycemic control

Keywords: algorithm, critical illness, glucose control, simulation environment

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Introduction

Several computer- and paper-based insulin titration algorithms have been proposed with the aim to improve the delivery of tight glycemic control (TGC) in an intensive care unit (ICU).[1–7] The algorithms are usually evaluated in resource-demanding and time-consuming clinical studies. This evaluation process could be accelerated and made more efficient if a computer simulation environment was used prior to full-scale clinical studies in humans. A simulation environment with a virtual population of critically ill subjects can provide invaluable information about the safety, limitations, and efficacy of a newly developed algorithm.

In this study the simulation environment developed at the University of Cambridge was used to evaluate the "I, Pancreas" algorithm proposed by Braithwaite *et al.*[8] For the purpose of simulations, this paper-based but programmable algorithm was coded in MATLAB® (The MathWorks Inc., Natick, MA). A 48-hour-long simulation study was conducted employing 10 virtual adult subjects from a surgical ICU and using the coded version of the "I, Pancreas" algorithm to provide TGC of blood glucose (BG).

Materials and Methods

Simulation Environment

The simulation environment was developed at the University of Cambridge and was used extensively during the European Commission-funded Closed Loop Insulin Infusion for Critically Ill Patients (CLINICIP) project.[9] The main components of the environment reflect the setup of a clinical trial designed to test glucose control algorithms. The components shown in **Figure 1** include the virtual patient, the clinical protocol, the error models of the glucose measuring device and the insulin pump, the glucose control algorithm, and, finally, the outcome measures used to assess the quality of control.

Virtual subjects are represented by individual parameter sets, which characterize the physiological model of glucose regulation in critical illness described in detail by Hovorka and associates.[10] The model depicted in **Figure 2** combines five submodels: endogenous insulin secretion, insulin kinetics, enteral glucose absorption, insulin action, and glucose kinetics. An important feature of this model is a time-variant representation of insulin resistance.

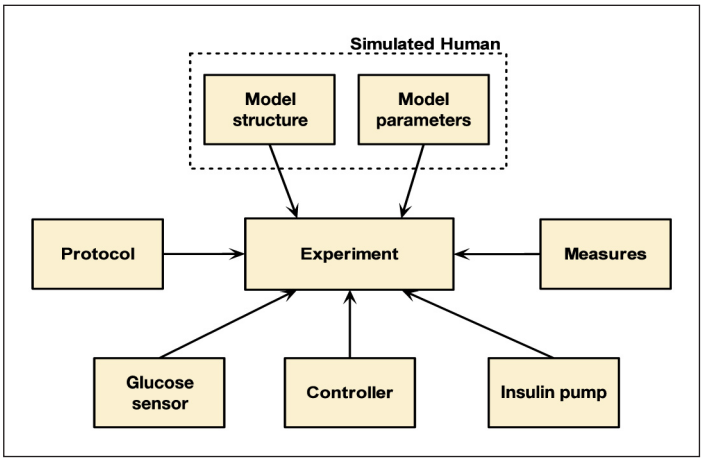

Figure 1. Simulation environment—main components.

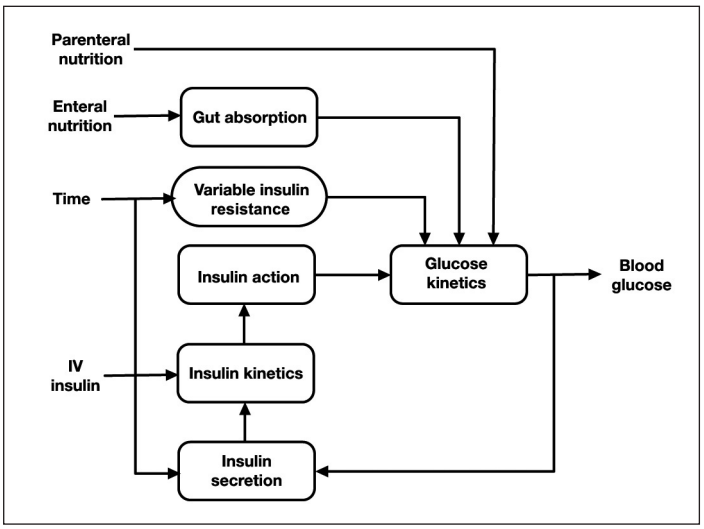

Figure 2. Model of glucose regulation in the critically ill adopted with minor changes from Hovorka and colleagues.[10]

Virtual Population of Critically Ill Subjects

The complete virtual population comprised 56 critically ill subjects; 29 of those subjects came from a medical ICU and 27 from a surgical ICU. Each virtual subject was generated by utilizing clinical data recorded in a specific critically ill patient in a particular experimental scenario—a process referred to by Hovorka as "experimental *in silico* cloning."[10] For the purpose of this study, a subset of 10 virtual subjects from a surgical ICU was selected.

In Silico Study Design

An *in silico* simulation environment was used to simulate a 48-hour- long clinical trial with the objective to achieve TGC. The simulated study protocol reflected the events that took place in the original clinical trial in which clinical data for "*in silico* cloning" were obtained. The clinical studies described by Plank and colleagues[6] were conducted in Prague, Graz, and London, with the CLINICIP project collaborating clinical centers.

The starting glucose and the parenteral and enteral carbohydrate infusions in the simulated study were set to match those in the original clinical study. Glucose measurements were simulated assuming a measurement error of a professional blood gas analyzer [coefficient of variation (CV) 1.5%], and intravenous insulin infusion was simulated assuming a CV of insulin delivery error of 5% for continuous infusion and 3% for an insulin bolus. The "I, Pancreas" algorithm proposed by Braithwaite and colleagues[8] was used to control glucose in the simulated study.

The treatment of hypoglycemia was adopted from the Braithwaite protocol[8] and consisted of administration of a bolus infusion of 12.5 grams of glucose followed by BG testing every 10 minutes while the BG <3.9 mmol/liter (70 mg/dl). Retreatment and further retesting were used only to monitor the hypoglycemic episode and were not included in the coded "I, Pancreas" algorithm test times.

"I, Pancreas" Algorithm

The '"I, Pancreas" algorithm described in detail by Braithwaite and colleagues[8] is a two-step maintenance rate (MR) seeking or "MR" algorithm. At each iteration, the algorithm estimates a MR of insulin infusion, which, in turn, is used to calculate an insulin infusion rate (IR). The algorithm also advises on a 1- or 2-hour BG monitoring regime.

The algorithm was coded in the MATLAB environment as an iterative three-function process. A schematic representation of the inputs and outputs of the functions of the algorithm is shown in **Figure 3**. At each iteration, the three MATLAB functions (*function_mr*, *function_ir*, and *function_time* in **Figure 3**) are called to calculate the MR, the insulin IR for the next step (IR_{next}), and the next test time (test $time_{next}$). The latter two parameters are then passed on to the simulation environment. Population parameters such as glycemic targets, $MR_{initial}$, $IR_{@BG70}$, and others are assigned values as defined for an adult surgical ICU in Appendix 3 of the article by Braithwaite and colleagues.[8]

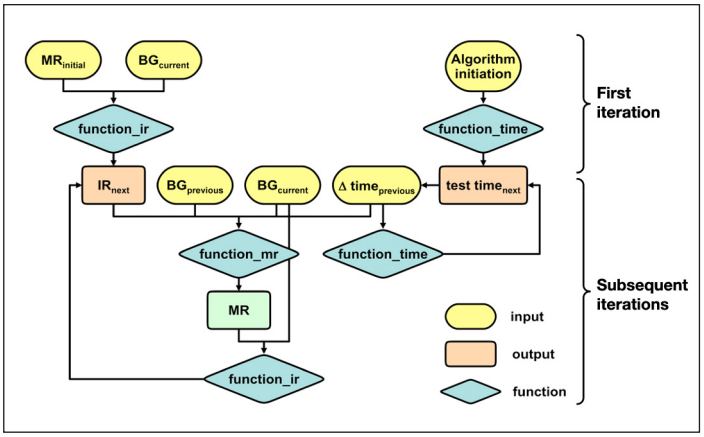

Figure 3. Schematic representation of inputs and outputs of the functions of the coded "I, Pancreas" algorithm.

Results

Table 1 summarizes the demographic and diagnosis details of the 10 selected virtual subjects from the surgical ICU.

Table 2 contains the summary results. Blood glucose at the start of the 48-hour-long simulated experiment was 7.6 ± 0.6 mmol/liter (136 ± 11 mg/dl). Mean insulin infusion rates and their standard deviations (SD) were 2.1 (1.8–3.2) and 1.0 (0.7–1.2) U/h, respectively. The mean blood glucose over the 48-hour study period was 6.5 ± 0.4 mmol/liter (118 ± 7.8 mg/dl), and the "I, Pancreas" algorithm maintained BG in the target glucose range 4.4–6.1 mmol/liter (80–110 mg/dl) for 38% of the time. The magnitude and duration of hyperglycemia expressed in terms of the hyperglycemic index (HGI)[11] was 0.62 (0.43–1.00) mmol/liter [11.1 (7.7–18.1) mg/dl] (HGI is defined as the area under the curve above the glucose level of 6.0 mmol/liter divided by the length of ICU stay).

Table 1.
Baseline Characteristics of Surgical ICU Virtual Population; Values Reported as Mean ± SD or Number of Cases

N	10
Male (No. of subjects)	8
Age (years)	70.2 ± 7.8
Weight (kg)	82.2 ± 14.0
Surgical procedure category (No. of subjects) Coronary artery bypass graft Aortic valve replacement Aortocoronary bypass	 7 2 1
History of type 2 diabetes (No. of subjects)	3

There was a single episode of mild hypoglycemia at 3.8 mmol/liter (69 mg/dl) (subject 2010202 in **Figure 4**), which was treated with 12.5 grams of glucose delivered as an intravenous (IV) bolus.

Graphical outputs from the 10 simulated studies are shown in **Figure 4**.

Discussion

The present simulation study demonstrated that the "I, Pancreas" algorithm proposed by Braithwaite *et al.*[8] can safely control blood glucose in 10 virtual subjects from a surgical ICU. The single episode of mild hypoglycemia below 3.9 mmol/liter (70 mg/dl) in subject 2010202 shown in **Figure 4** was treated with 12.5 grams of glucose delivered as an IV bolus. No episodes of severe hypoglycemia below 2.8 mmol/liter (50 mg/dl) were recorded in the study.

The efficacy of the algorithm was assessed by mean blood glucose, the percentage of time spent in the target glucose range from 4.4 to 6.1 mmol/liter (80 to 110 mg/dl) and the HGI. The "I, Pancreas" algorithm compared reasonably well with other published clinical studies that used the same target glucose range. The average blood glucose concentration in our simulated study was 6.5 ± 0.4 mmol/liter compared to 6.1 ± 0.7 mmol/liter reported by Kulnik and colleagues[12] and 6.2 ± 1.1 mmol/liter reported by Hovorka and associates.[13] The percentage of time within the TGC range was smaller at 38% compared to 47% obtained with an integrated enhanced model predictive control (eMPC) algorithm,[12] but higher than values reported in control arms of randomized controlled studies. In the study reported by Hovorka and colleagues,[13] conventional care resulted in 27.5% time spent in the target glucose range, whereas Plank *et al.*[6] reported 19%. HGI was 0.6 mmol/liter (11.1 mg/dl) compared to 10 mg/dl reported by Kulnik *et al.*[12]

In a recently published randomized study, Blaha and colleagues[14] compared three insulin titrating protocols for TGC in a surgical ICU: an absolute glucose (Matias) protocol, a relative glucose change (Bath) protocol, and the eMPC algorithm. The three protocols performed better than "I, Pancreas" in terms of mean blood glucose and percentage of time spent in the target glucose range, although severe episodes of hypoglycemia below 2.3 mmol/liter (41 mg/dl) were reported in the Matias and Bath protocols. Hence, based on the results of this initial evaluation with a small cohort of 10 virtual subjects from a surgical ICU, the "I, Pancreas" algorithm appears less efficacious but safer than the Matias and Bath protocols.[14] In order to obtain more reliable and comparable results, a more thorough evaluation of "I, Pancreas" with a larger cohort of virtual or real subjects, including subjects from a medical ICU, would be required.

Table 2.
Glucose Control Measures Based on Simulated Blood Glucose; *N* = 10, Values Are Median (Interquartile Range), Mean ± SD, or Number of Events

Blood glucose (mmol/liter)	6.5 ± 0.4
Blood glucose SD (mmol/liter)	1.0 ± 0.6
Starting blood glucose (mmol/liter)	7.6 ± 0.6
Time in target[a] (%)	38 (32–44)
Time to target[a] (minutes)	111 (49–314)
HGI[b] (mmol/liter)	0.62 (0.43–1.00)
Hypo episodes[c] (unitless)	1
Insulin infusion rate (U/h)	2.1 (1.8–3.2)
Insulin infusion rate SD (U/h)	1.0 (0.7–1.2)

[a] Target glucose range from 4.4 to 6.1 mmol/liter (80 to 110 mg/dl).
[b] The hyperglycemic index is defined as the area under the curve above glucose level 6.0 mmol/liter divided by the total length of stay.[11]
[c] Blood glucose <3.9 mmol/liter (<70 mg/dl).

Although the median insulin infusion rate in the simulated study appeared to be low at 2.1 U/h, two of the virtual subjects (subjects 1010121 and 1010122 in **Figure 4**) required considerably higher insulin infusion rates, suggesting that these subjects were characterized by a relatively higher insulin resistance. As mentioned previously, an important feature of the model of glucose regulation in the critically ill built into this simulation environment is time-variant insulin resistance. Hence, the insulin resistance of the individual virtual subject changes over the course of the simulated study. The steep and dramatic increases in insulin resistance can be observed in the glucose profiles presented in **Figure 4**. In particular, the two significant peaks observed in subjects 2010220 and 2010202 in the second 24 hours of the simulated study (see **Figure 4**) correspond closely to the peaks in time-variant insulin resistance observed in these virtual subjects (modeling data not shown).

Conclusion

The simulation environment with 10 virtual subjects originating from a surgical ICU was used to evaluate

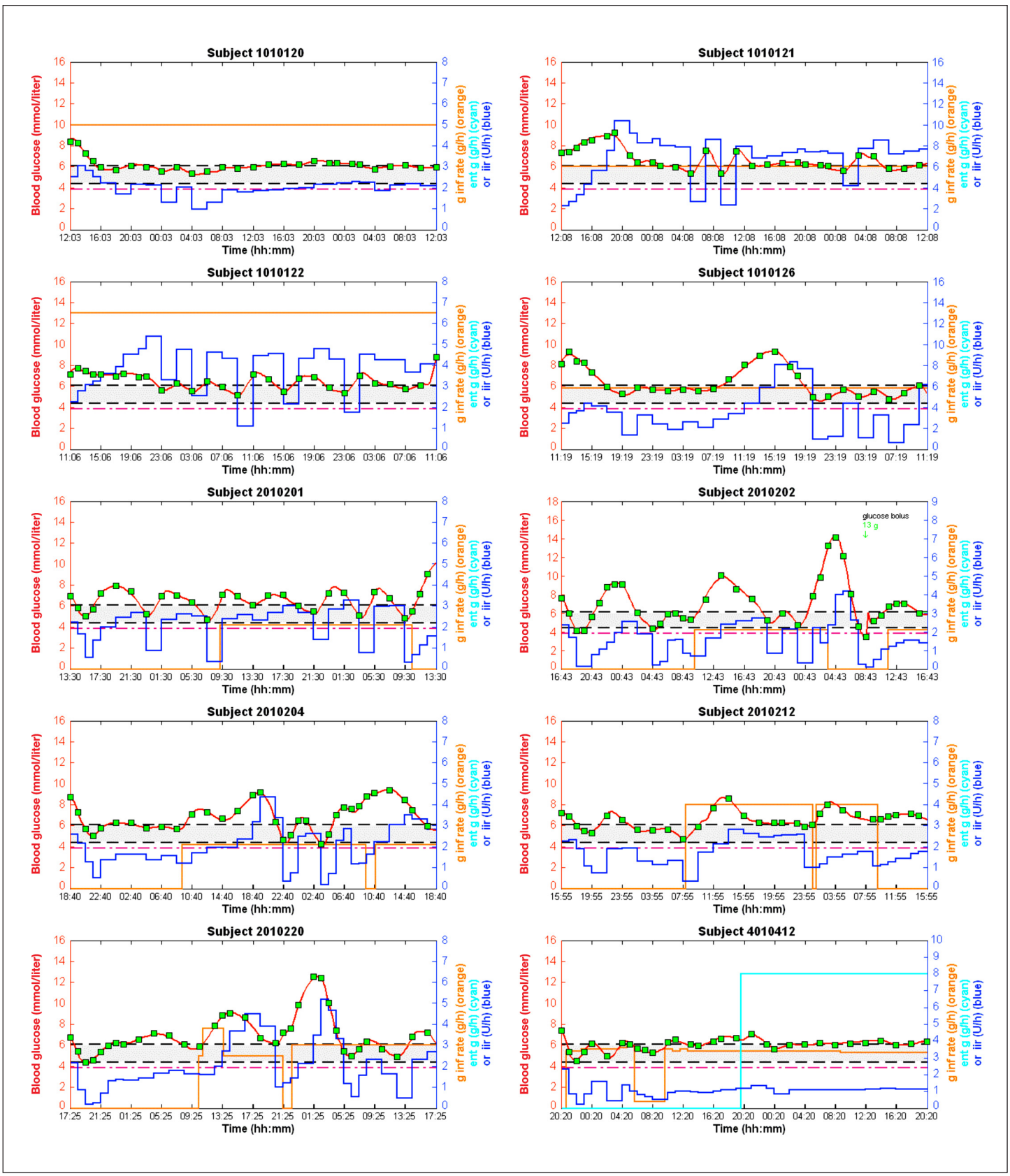

Figure 4. Graphical output from 10 simulated studies; in all figures: green squares represent simulated measurement, red continuous line represents simulated BG, blue piecewise constant represents advised insulin infusion rate (iir), green horizontal lines indicate target glucose range of 4.4 to 6.1 mmol/liter (80 to 110 mg/dl); the magenta horizontal line indicates hypoglycemia range of 3.9 mmol/liter (70 mg/dl); orange and cyan lines represent parenteral (g inf rate) and enteral (ent g) carbohydrate infusions, respectively; green down arrow indicates glucose bolus.

the "I, Pancreas" algorithm proposed by Braithwaite and colleagues.[8] The algorithm was shown to be safe and achieved tight glycemic control 38% of the time.

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