IN SILICO SIMULATION ENVIRONMENT AND GLUCOSE CONTROL IN CRITICALLY ILL SUBJECTS: STRATEGIC CONSIDERATIONS

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Abstract: Tight glucose control reduces mortality and complications in critically ill subjects. However, tight glucose control is not easily achievable with standard treatment practices and novel glucose protocols, controllers, and treatment systems are being developed. This work outlines specific aspects of glucose control in critically ill subjects. The main focus is to demonstrate the central importance of *in silico* simulation environment in the development of glucose controllers. Four roles of the simulation environment are considered, (i) to support debugging, (ii) to facilitate improvements of or comparison among glucose controllers, (iii) to facilitate technical evaluation, and (iv) to predict outcome of clinical trials. Issues related to validation of the simulation environment are also considered. It is concluded that *in silico* simulation environment should be considered an integral part of projects concerned with glucose controllers and systems for the intensive care units to provide rational means for efficient and effective development and evaluation.

Key words
Simulation, control, glucose, critically ill subjects

Introduction

In 2001, a large randomized controlled trial demonstrated that tight control of glucose levels within a narrow range 4.4 to 6.1mmol/l by intensive insulin infusion improved clinical outcomes in patients admitted to a surgical intensive care unit (ICU) [1]. The study reduced ICU mortality by 42% and also reduced the incidence of bloodstream infections, the incidence of acute renal failure, the need for prolonged ventilatory support, and the duration of ICU stay. Tight glucose control is also beneficial in other intensive care settings such as in diabetic subjects following acute myocardial infarction [2].

In 2004, the EC funded project "Closed Loop Insulin Infusion for Critically Ill Patients" (Clinicip) started with the aim to develop prototype systems for closed loop control for the use at ICUs (www.clinicip.org). As part of the Clinicip project, glucose controllers are being developed and evaluated such as that based on the model predictive control.

Following experience from another EC funded project Adicol [3], the development and use an *in silico* simulation environment is considered crucial to facilitate rational, timely, and efficient development and evaluation of glucose controllers.

The rationale is simple and appealing. Clinical testing is costly, time consuming, resource intensive, and is confounded by ethical dilemmas. By offloading a significant part of the clinical evaluation to *in silico* simulation environment, considerable savings are achieved and the development is accelerated.

The present article briefly reviews specific conditions of the critically ill patients in relation to glucose control. This includes the consideration of patient categories, glucose monitoring and insulin delivery, and treatment protocols. Two types of controllers are considered, those based on spot and those based on continuous glucose measurements.

In silico simulation environment is then considered in detail, specifically the roles of the simulation environment in the development of glucose controllers and validation issues, see Fig. 1 for the use of the environment.

Clinical Environment

Patient Categories. Two main categories of critically ill patients can be identified, medical and surgical patients.

Medical patients are admitted, for example, for primary respiratory failure, gastrointestinal haemorrhage, sepsis, hypotension, acute renal failure, and primary cardiovascular events. These subjects stay longer (median 48hours or more) at the ICU compared to surgical patients but their glucose control may be simpler due to lower inherent variability of insulin resistance in these subjects.

Surgical patients stay shorter at the ICU (median 24 hours or less) and are admitted following major surgical intervention such as cardiac or thoracic surgery.

Glucose Monitoring and Insulin Delivery. Current clinical practice requires hourly to four-hourly glucose measurements using either standard glucose meters or near patient testing devices such as blood gas analysers.

ISSN: 1727-1983

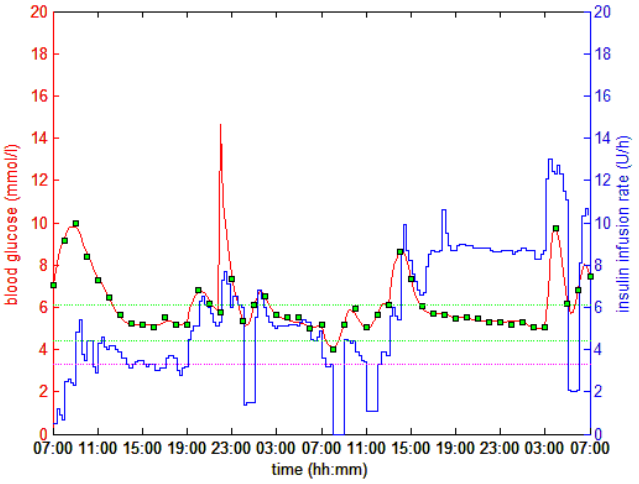

Figure 1: Sample 48h study in an *in silico* simulation environment mimicking a clinical trial with a model predictive controller (MPC)[4]. Hourly intravenous glucose measurements (squares, green) are provided to the MPC controller, which generates advice on insulin infusion (piecewise constant line, blue). Simulated blood glucose is also shown (solid smooth line, red). Various parenteral glucose infusion rates (0 – 12g/h) were used (not shown).

The measurement error of these devices is 2% (blood gas analyser) to 10% (standard glucose meter).

Insulin infusion is administered intravenously and is altered hourly to four-hourly following glucose sampling.

Treatment Protocols. Compared to subjects with type 1 diabetes, critically ill patients are generally more resistant to insulin requiring 2U/h or more to achieve normoglycaemia. It is not unusual to require 10U/h or more.

The other distinguishing aspect of these subjects is that they demonstrate higher temporal variability in insulin resistance, which is attributable both to the underlying pathophysiological conditions, e.g. sepsis and inflammation, and the effect of the treatment such as corticosteroids or vasopressors.

Generally, both categories of patients, surgical and medical, receive parenteral and enteral nutrition although there exist considerable differences among ICUs in terms of nutrition policies and practices. This may significantly impact the functionality of the glucose controller as nutrition influences insulin delivery.

Glucose Controllers. Two types of glucose controllers are envisaged for the critically ill patients, controllers based on spot (infrequent) glucose measurements and controllers based on continuous glucose measurements.

Spot Measurement. The current clinical practice adopts hourly to four-hourly measurements to adjust insulin infusion. It is expected that the first family of commercially available glucose controllers for critically ill patients will adopt this existing sampling scheme and will avoid additional workload to nurses by avoiding more frequent measurements.

An example of such a "controller" is the insulin infusion protocol by Goldberg *et al* [5].

Continuous Measurement. Controllers based on continuous monitoring of glucose either in the blood or in the interstitial fluid will have the possibility to achieve tighter glucose control in an autonomous fashion. However, this approach poses additional demands with respect of safety and will be more demanding from the regulatory approval point of view.

The Biostator is an example of such a system.

In Silico Simulation Environments

Roles of In Silico Simulation Environment. An i*n silico* simulation environment plays four roles in the development of glucose controllers. It (i) supports debugging, (ii) facilitates improvements of or comparison among glucose controllers, (iii) facilitates technical evaluation, and (iv) simulates clinical trials.

The simulation environment would normally be used in the order given above (see section on Debugging below for additional comments). However, as new information become available from clinical trials, the simulation environment is normally improved and the cycle can be repeated.

Debugging. This is the "simplest" form of the use of the simulation environment. It parallels verification of the glucose controller.

Prior to its use in the clinical, glucose controller as any other piece of software needs to be verified. All paths of the software should be tested and evaluated against an expected behaviour.

Invariably, as the number of paths is extensive, it is not possible or feasible to test all possible combinations by hand. The simulations environment then complements system verification.

Debugging is often executed as part of the other roles of the simulation environment. This assumes that the simulation environment faithfully represents the operating conditions in which the controller is expected to operate. This may include variable sampling interval, missed samples, errors and revisions of inputs, misaligned events (meals, insulin doses, insulin infusions), unexpected inputs (hypoglycaemia intervention), and other "protocol" deviations.

Debugging increases confidence in the implementation of the controller and can prevent major failures during clinical evaluation.

Improvements of or comparison among glucose controllers. Following the initial design of a glucose controller, the simulation environment is an ideal tool to improve the performance of the glucose controller and to compare its function to "state-of-art" or widely-used controllers.

ISSN: 1727-1983

This usually involves testing the controller during a single experimental protocol. In case of a glucose controller working at the ICU environment, this might be a protocol which starts with elevated glucose, is carried out for 12 or 24 hours, and might include periods with intravenous glucose infusion.

Occasionally this might include testing the controller on a single "individual" rather on a population of individuals.

The improvements of the controller come in the form of optimising certain quantities in the controller design such as the prediction and control windows for model predictive controllers.

This form of controller comparison is traditionally accompanying the description of glucose controllers in the literature. It is inevitably limited in the scope and reliability. It serves as an initial pointer to indicate the potential merit of the controller.

This initial testing is invariably "optimistic" in the sense that it does not represent the rich behaviour observed in clinical trials. For example, it does not investigate the effect of inter-subject variability, intra-subject variability, technical failures, and treatment protocols, or patho-physiological conditions.

Thus, skipping the following two roles of the simulation environment is associated with a high risk of failure or unexpected observations during clinical trialling.

Technical evaluation. This evaluation should constitute the bulk use of the simulation environment during the development of a glucose controller. It expands on the previous role being more thorough and inclusive.

The objective is to provide feedback on controller performance, in terms of safety and efficacy, from two viewpoints, the physiological/treatment conditions, and the operating conditions [6].

The physiological/treatment conditions reflect the expected range of physiological and treatment conditions. In case of critically ill subjects, for example, different clinical centres adopt different approaches to parenteral and enteral nutrition. These differences need to be taken into consideration when testing a controller for general use.

Differences are also pronounced between medical and surgical patients in terms of treatment protocols and variations of insulin sensitivity due to underlying pathophysiological conditions and treatment interventions.

The second dimension, operating conditions, distinguishes among expected operating conditions, adverse operating conditions, and system failures.

Expected operating conditions correspond to the expected technical and also physiological aspects, such as the expected level of the measurement error, expected deviation in the sampling interval, expected number of missed measurements, and expected number of disconnected equipment. This also includes expected variation in insulin sensitivity (treatment-related and underlying intra-subject variability) and expected variation among subjects (inter-subject variability).

Adverse operating conditions correspond to the situation when such conditions deteriorate. Usually, each deterioration is tested separately, such as the elevated measurement error is evaluated independently from other effects.

System failures correspond to the situations when some crucial aspect(s) of the system fail(s), such as when continuous glucose monitor fails, the intravenous glucose infusion is stopped or discontinued without notice (the fluid run out).

The system, and often it is not just glucose controller but also an additional layer to assist in risk minimisation, is evaluated at this stage from the viewpoint of safety and efficacy. However, these measures could be relatively crude and technically oriented. One could for example indicate the number of hypoglycaemia events and their severity to pass the safety criterion. Similarly the efficacy criteria include sharp cut-off points to indicate yes/no result and are not generally suitable for the assessment of true clinical utility.

This may be further underlined by the fact that the population of virtual subjects might be limited (ten to several tens of subjects) and that some of these subjects might represent extreme cases, for which the achievement of safe and efficacious control might not be possible. The inclusion of these extreme subjects is important at this stage to modify the controller to achieve safe control.

In terms of satisfactory performance, a glucose controller should be safe and efficacious for expected operating conditions in the target population/treatment regimes. It needs to be safe with some decrease in efficacy in adverse operating conditions, and it should be safe but not necessary efficacious in system failures.

The process of testing the glucose controller in these conditions is usually repeated following the improvements and modifications of the controller and its "safety" lawyer. The cycle represents an "adaptation" of the controller to the virtual subjects and the tested conditions. It is therefore crucial to have as realistic as possible the virtual population and treatment scenarios.

Predict clinical trial outcome. This role of the simulation environment is specialised and could be seen as a follow up of the previous stage, the technical evaluation.

Once controller appears to be working well, a decision will be taken to conduct clinical trial(s) to evaluate the performance of the controller under particular clinical conditions or in a particular subpopulation of critically ill patients.

Clinicians will be instrumental in designing the trial, its objectives, experimental design etc. This differs from previous stages where the developer was the primary person responsible for the evaluation perhaps in consultation with clinician(s).

The clinical trial will have specific assessment criteria, which are likely to differ from those adopted during the

ISSN: 1727-1983

technical evaluation. These will be more clinically oriented, perhaps more refined, and more understandable to the clinical audience than those adopted during the technical evaluation.

Prior to conducting the clinical trial, where possible, it is of great benefit to predict its outcome. This might require specialisation of the simulation environment to represent the conditions of the clinical trial, i.e. the subject population, the experimental design including interventions, and the likely protocol deviations.

The outcome of the simulated trial could also be used to support ethic submission and pinpoint critical aspects of the trial.

Validation of In Silico Simulation Environment. Validation of the simulation environment is a necessary and integrated task, which is addressed at various stages of the development of the environment and its use.

The primary aim of the validation is to demonstrate that it satisfies it objectives, i.e. that the interaction between the simulation environment and the glucose controller is a realistic representation of the interaction between the controller and the real environment.

This ultimately means that the simulation environment should correctly predict the outcome of the clinical trial in terms of its primary and secondary measures.

The simulation environment will not be able to predict the outcome of a particular subject in a clinical trial, but it should be able to predict the "population" outcome. Any discrepancy between expected and observed "population" outcome should be considered in the light that there might be true difference between the "simulated" and "real" subjects as there would be a difference in the outcome of a trial executed in two distinct subsets of the population.

Thus the clinical trial serves two fundamental purposes. First, it serves to demonstrate the utility of the controller. Second, it demonstrates the validity of the simulation environment.

This ultimate validation of the simulation environment should be preceded by the validation of the components. For example, the model of endogenous insulin secretion or insulin action in subjects with critically ill subjects should be validated separately. This also includes the validation of the technical components of the simulator, i.e. the insulin pump or the glucose sensor.

A balance has to be struck when validating components of the simulation environment. As we are dealing with a biological system, a model will always be an approximation of the true system and will therefore have limited functional and structural validity. The challenge is to represent these functions and structures so that the overall behaviour of the simulation environment is correct. This is not a well defined task and must be considered with respect to the intended use of the simulation environment.

Conclusions

An *in silico* simulation environment should be considered an integral part of the any project concerned with glucose controllers and systems for ICUs to provide rational means for efficient and effective development and evaluation.

A fully-featured *in silico* simulation environment has four fundamental roles. It is recognized that some roles overlap or are achieved in parallel with others. The benefits are only achievable if the simulation environment represents realistically clinical environment. Thus, validation is essential and should be included in the development process.

Acknowledgements

Supported by an EPSRC Grant (GR/S14344/01) and the 6th EC Framework Programme project Clinicip (IST FP6-506965).

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ISSN: 1727-1983