

REVIEW

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# Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice?

J Geoffrey Chase<sup>1\*</sup>, Aaron J Le Compte<sup>1</sup>, J-C Preiser<sup>2</sup>, Geoffrey M Shaw<sup>3</sup>, Sophie Penning<sup>4</sup> and Thomas Desaive<sup>4\*</sup>

## Abstract

Critically ill patients are highly variable in their response to care and treatment. This variability and the search for improved outcomes have led to a significant increase in the use of protocolized care to reduce variability in care. However, protocolized care does not address the variability of outcome due to inter- and intra-patient variability, both in physiological state, and the response to disease and treatment. This lack of patient-specificity defines the opportunity for patient-specific approaches to diagnosis, care, and patient management, which are complementary to, and fit within, protocolized approaches.

Computational models of human physiology offer the potential, with clinical data, to create patient-specific models that capture a patient's physiological status. Such models can provide new insights into patient condition by turning a series of sometimes confusing clinical data into a clear physiological picture. More directly, they can track patient-specific conditions and thus provide new means of diagnosis and opportunities for optimising therapy. This article presents the concept of model-based therapeutics, the use of computational models in clinical medicine and critical care in specific, as well as its potential clinical advantages, in a format designed for the clinical perspective. The review is presented in terms of a series of questions and answers. These aspects directly address questions concerning what makes a model, how it is made patient-specific, what it can be used for, its limitations and, importantly, what constitutes sufficient validation.

To provide a concrete foundation, the concepts are presented broadly, but the details are given in terms of a specific case example. Specifically, tight glycemic control (TGC) is an area where inter- and intra-patient variability can dominate the quality of care control and care received from any given protocol. The overall review clearly shows the concept and significant clinical potential of using computational models in critical care medicine.

## The critically ill patient

Critically ill patients can be defined by the high variability in response to care and treatment. In particular, variability in outcome arises from variability in care and variability in the patient-specific response to care. The greater the variability, the more difficult the patient's management and the more likely a lesser outcome becomes. Hence, the recent increase in importance of protocolized care to minimize the iatrogenic component due to variability in care. Recent articles [1,2] have

noted that protocols are potentially most applicable to groups with well-known clinical pathways and limited comorbidities, where a "one size fits all" approach can be effective. Those outside this group may receive lesser care and outcomes compared with the greater number receiving benefit.

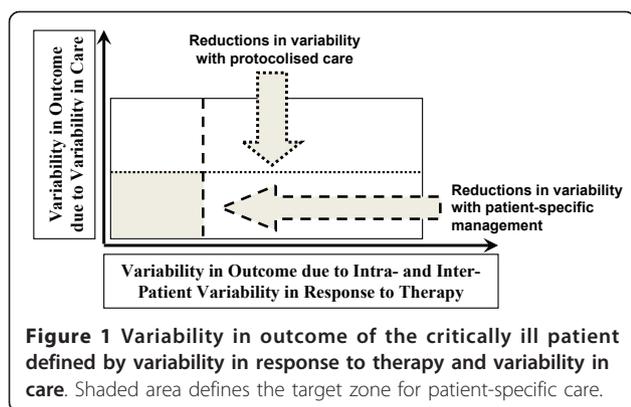
Figure 1 defines this problem in terms of variability in care that protocolized care can reduce, and a different, potentially less reducible, component due to inter- and intra-patient variability in response to treatment. The larger the area, the more difficult the patient can be to manage. Thus, protocolized care reduces only the non-patient portion of this diagram. Equally, those whose clinical pathway is "straightforward" and can benefit most from protocolized care are likely to have limited inter- and intra-patient variability in response to

\* Correspondence: geoff.chase@canterbury.ac.nz; tdesaive@ulg.ac.be

<sup>1</sup>Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, Christchurch, Private Bag 4800, New Zealand

<sup>4</sup>Cardiovascular Research Centre, Universite de Liege, B4000 Liege, Liege, Belgium

Full list of author information is available at the end of the article



treatment. Hence, the smallest, least variable case is one in which intra-patient response is reduced or managed in a patient-specific fashion, thus separating the final area into several smaller ones. A focus of this paper is that the model-based methods discussed here can provide patient-specific care that is robust to these intra- and inter-patient variabilities.

This issue is evident in many areas of care. For example, why are the complications of diabetes and therapeutic anticoagulation a leading cause of death or iatrogenic harm when they are amongst the most highly researched and understood fields in medicine? A PubMed search using the key words “diabetes mellitus” and “anticoagulation” returned 19,008 and 288,774 references, respectively, and a Google search multiplied these numbers to 1.14 M and 9.48 M pages. The collective experience of the drugs used in these conditions also is enormous; insulin, heparin, and warfarin were first used in humans more than 89, 76, and 57 years ago, respectively, and yet despite huge knowledge and experience, management of these conditions is fraught with problems.

What has led to this paradox? If, for example, managing diabetes was as straightforward as popping a few tablets or a daily insulin injection, doctors and patients would not still be struggling to get this right. Unfortunately, patients with diabetes have a widely variable clinical response, both within and between individuals, which often leaves clinicians unsuccessfully grappling with these nonlinear behaviors and responses. The randomized controlled trial (RCT) is regarded as the most reliable instrument on which to base treatment selection. However, recommendations from RCTs are based on overall cohort responses, not individual responses, and therefore cannot provide the necessary patient-specific therapeutic guidance, particularly when variability can have a major impact in titrating treatment.

We examine and review a new, emerging therapeutic approach that provides for individualized care that accounts for intra- and inter-patient variability within an overall protocolized and evidence-based framework. This

review is done with reference to the management of glucose intolerance and diabetes in critically ill patients, but the overall approach is readily generalizable to other areas of intensive care medicine.

### Physiological and clinical problem

Critically ill patients often experience stress-induced hyperglycemia and high insulin resistance [3-5] associated with increased morbidity and mortality [6-8]. Strong counter-regulatory (stress) hormone and pro-inflammatory immune responses lead to extreme insulin resistance and hyperglycemia, often exacerbated by high carbohydrate nutritional regimes and (relative) insulin deficiency. Inter- and intra-patient variability over different patients and as patient condition evolves make providing consistently tight glycemic control (TGC) across every individual patient a significant challenge, despite the growing use of protocolized care approaches.

This article uses TGC to present how computer models can be used at the bedside, within protocolized care, to provide patient-specific care and thus reduce the impact of intra- and inter-patient variability and provide care (within the shaded lower corner of Figure 1). TGC is a particularly apt example for model-based methods, as intra- and inter-patient variability in response to insulin can be extreme, leading to significant difficulty in providing safe and effective control [9].

In particular, recent randomized trials of TGC have failed to repeat promising early results [10-12]. Equally, reduced outcomes due to hyperglycemia, hypoglycemia (if control is poor), and glycemic variability [13,14], and the overall physiological basis in inflammatory and oxidative stress responses are increasingly understood [15-17]. Thus, it seems increasingly clear that protocolization of care alone has not been able to reduce the variability in patient outcomes and that patient-specific solutions that manage inter- and intra-patient variation may be required to determine if TGC offers significant benefit. Hence, this review examines (physiological) model-based methods for TGC as a case example of the patient-specific solutions that are possible and the potential of these methods to improve care.

### A series of questions

This review takes the reader through mathematical models in the context of TGC based on a series of clinically focused questions.

#### What is a mathematical model? Physiological relevance and representation

A mathematical model is a mathematical description of reality. In physiology, such a model underlies a certain number of assumptions about the physical, chemical, and biological processes involved. These mathematical

models may vary significantly in their complexity and their objectives. They can range from relatively simple lumped-compartment models [18-20] to very complex network representations and finite element models of several million degrees of freedom [21,22].

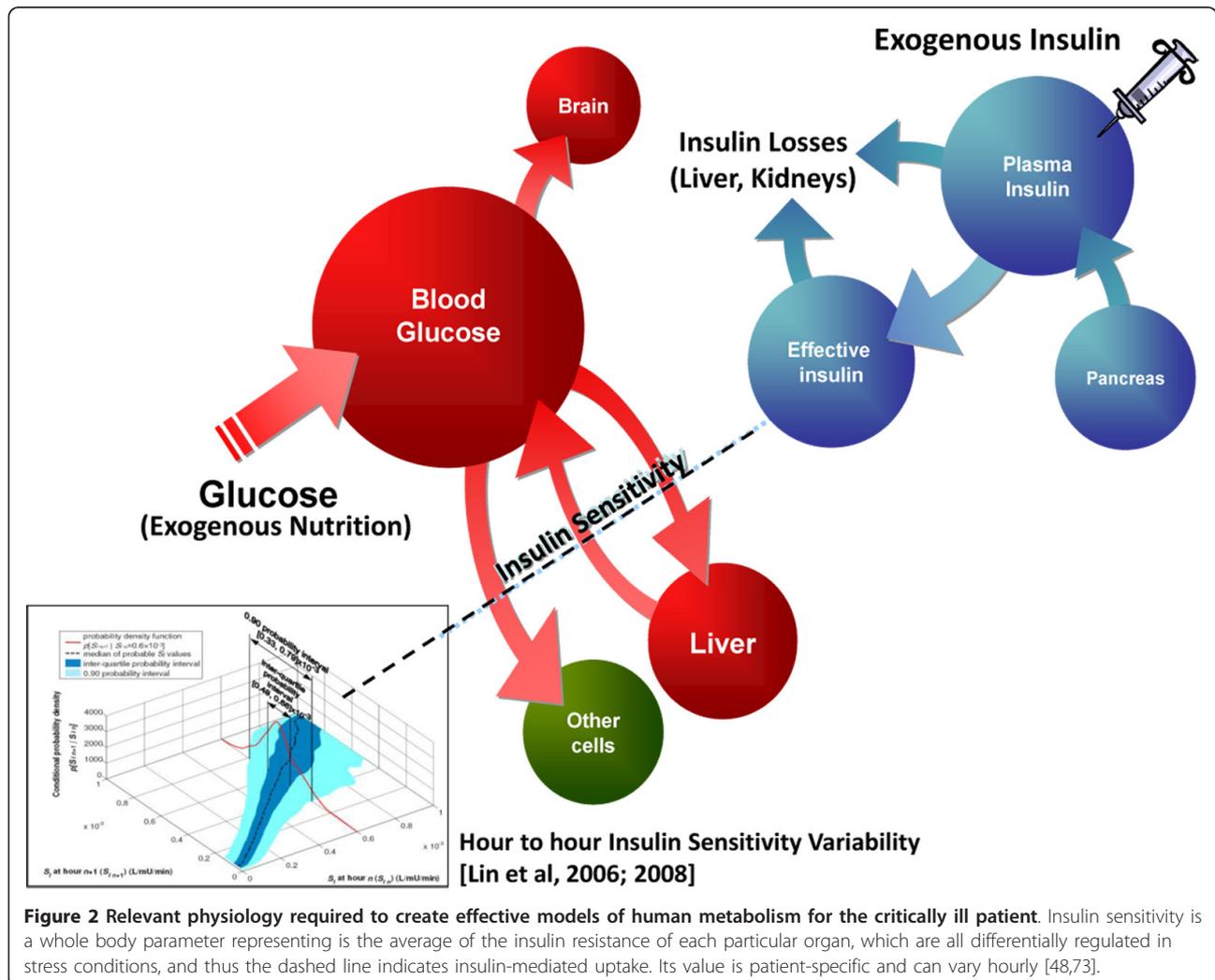
For model-based TGC, the models should capture the fundamental underlying physiology as illustrated schematically in Figure 2. In particular, they should capture the transport of exogenous insulin, the production of endogenous insulin, the appearance of endogenous and exogenous carbohydrate as blood glucose, and, critically, both insulin-mediated and insulin-independent uptake of glucose. In addition, insulin-mediated uptake must have the ability to capture inter- and intra-patient variability in the time-varying insulin resistance observed in these patients. The model structure and physiological relevance of Figure 2 is detailed in several references [23,24] and in the appendix in Additional File 1 {AU Query: please cite the appendix as Additional file 1}

with TGC specific modeling details for the interested reader.

In the critical care arena, the use of in silico physiological models is only emerging. However, there are already model-based or model-derived applications for managing sedation [25,26], cardiovascular diagnosis and therapy [27,28], mechanical ventilation [29,30], and the diagnosis of sepsis [31,32]. Particular to TGC, there are already some attempts at modeling for both understanding and implementing TGC [23,33-42], with a review of many in [43].

**What can a model do? Capabilities and limitations**

All models have different uses or goals. A model may be used to describe, interpret, predict, or explain [18,19] a physiological process. Real capabilities depend on the chosen degree of approximation, based on a combination of the knowledge of the physiological processes involved and implementation goal.



However, a model definition is not enough. Model parameter values must be assumed from clinical data or reports, or identified (mathematically) from clinical data. These values determine whether the model is generic to a population or (more) patient-specific with parameters identified from a particular patient's data. In reality, most models are a mixture of both approaches, where patient-specific parameters are identified for those parameters critical to the application.

However, once identified, patient-specific models in particular offer a range of potential opportunities, including, for TGC, the:

- Simulation of so-called virtual patients [41,44-48] to design [33,41], analyze [49,50], or optimize glyce-mic control methods.
- Implementation at the bedside for patient-speci-fic care in which patient-specific model para-meters are identified in real-time to guide care [34-36,40,47,51-53].

Equally, metabolic models can be used with patient data to investigate a range of physiological behaviors [54-56].

In intensive care, patient-specific metabolic model parameters also have been used as sepsis biomarkers because they can accurately reflect the inflammatory status of the patient and severity of illness [31,32]. These studies showed that model-based insulin sensitivity alone could provide 70-80% sensitivity and specificity in assessing sepsis compared with a control cohort, yielding a negative predictive value (NPV) greater than 99%, thus clearly identifying periods where antibiotic therapy was not necessary. Such an outcome thus uses model-based physiological insight not otherwise available to provide a novel, non-invasive diagnostic.

Similarly, model-based insulin sensitivity has been used to assess the impact of glucocorticoid therapy on glyce-mic control [57]. In particular, it has been thought that glucocorticoid therapy would significantly increase insulin requirements in TGC based on the results of studies showing significantly increased insulin resistance when given to healthy individuals. However, this model-ing showed the effect to be 5-10 times smaller in ICU patients, to be highly patient-specific depending on patient status, and to (overall) have very little impact on TGC dosing requirements, as a result. The ability to discern patient-specific impacts at the bedside using the model can provide significant insight.

Finally, TGC models can be used to assess the quality of control achieved clinically relative to other protocols using virtual patients [24,33,46,50]. In Suhaimi et al [50] the multi-center Glucontrol trial [12] protocol was evaluated versus the control achieved with the Specialized

Relative Insulin and Nutrition Titration (SPRINT) [58] protocol. The model and analysis yielded clear direc-tions on protocol compliance and the importance of understanding nutrition delivery in the provision of TGC. It also was able to show a surprising similarity in the inter- and intra-patient metabolic variability of criti-cally ill patients between the centers and studies compared.

Finally, physiologically relevant computer models have a longer, similar history in the broader diabetes field, primarily for research to gain patho-physiological insight rather than direct use in controlling glycemia [18,54,55,59-64].

All models have limitations. Limited bedside data and the quality of the mathematical process used to find model parameters from data (identification method) can have a significant impact on identified parameter accuracy and model performance [24,64-66], as well as entailing specific assumptions [23,24,46,67]. In particular, models that are not physiologically rele-vant [37] or do not have all the necessary physiology relevant to the patient group to which it is applied [68-70] can yield inaccurate results. These studies failed to capture the enhanced glyce-mic production and reduced renal and hepatic clearances, the balance of which can dominate the overall metabolic behavior of the critically ill. Similarly, one can over-model a situation with too much complexity and create models that are not useful for implementation. As a result, their predictive ability and use in control was less effective. Such limitations must be rigorously quanti-fied [23,57] to understand the quality of answer that any given model can provide.

#### **How do we know that a model is good? Prediction and validation**

Making suitable assumptions and choosing a desired degree of approximation do not naturally generate a "good" model. Similarly, being able to find model para-meters that ensure it fits a set of clinical data does not make a model valid, except to show that it can capture the dynamics observed clinically. It is critical to validate the model to determine if its performance is acceptable for its intended application.

For designing and/or implementing model-based TGC, where the model is directly used to provide patient-specific advice, it is necessary to ensure the models ability to:

- For design: predict the overall glyce-mic outcomes (median *and* variation) of patients and/or cohorts for a (simulated) protocol [44,46]
- For implementation: predict the glyce-mic outcome of a clinical intervention during a relevant 1- to

4-hour timeframe typical of TGC intervention frequencies [24,38,46,47,49,50,71,72].

These metrics define validity in its ability to capture patient-specific behaviors to a clinically acceptable level (approximately equivalent to measurement error). Errors thus reflect model limitations.

To date, only two ICU focused metabolic model structures have been validated with respect to individual patient-specific predictions (for implementation and design) [23,24,39,44,46]. Only one has been validated for cohorts [46].

The specific models in these studies define the critically ill patients by their time varying counter-regulatory and inflammatory status, as seen metabolically via their overall insulin sensitivity or metabolic balance that can vary hourly in acute cases, as illustrated in Figure 2. All other parameters were set at population constants following detailed parametric sensitivity studies based on assessing parameters impact on predictive performance [23,24,48]. Hence, the models provide median blood glucose prediction errors for specific interventions that are less than 3-4%. When an independent clinical protocol was simulated on virtual patients created the median cohort and patient glycemia and its variation were captured to within 3% and 5% respectively compared with the original clinical data (see [46] and appendix). Hence, validate the models and modeling approach, as well as show how they capture, through one main parameter, the metabolic dynamism of the critically ill patient.

#### **Why use models? Patient-specific insight and care from available data**

The time-scale for decision making in the ICU ranges from 1-2 minutes in acute cases to hours for some therapies, such as mechanical ventilation or TGC. It often requires the synthesis of a wide range of patient-specific data across a number of monitors, assays, and physiological systems. Typically, clinicians apply their experience and intuition to make diagnoses and develop treatment plans, based on how they aggregate that data and how it fits their mental model of what they are observing. More specifically, they are using this data and a mental model to estimate occult physiological variables (i.e., make a diagnosis or determine patient state) and from that developing decisions for treatment. Given the range of experience, intuition, and mental models across clinicians, diagnosis is open to error and care can be quite variable.

A validated and relevant physiological model can create a more consistent, high-resolution physiological picture of the overall physiological system that also is potentially more accurate than the clinician's mental model. In particular, computer models and methods

offer the ability to aggregate more data and to discern subtle trends in data that may otherwise be easily missed.

For model-based TGC, the patient-specific model variable that determines patient-specific state and response to therapy is the overall, whole body insulin sensitivity [42,48,73]. This value is itself the average of the insulin resistance of each particular organ, each of which is differentially regulated in stress conditions and sets the balance between insulin and nutrition inputs and outcome glycemia. However, given the variations in patient kinetics and levels of these inputs, it is very difficult, if not impossible, for a clinician to review these and arrive at an accurate assessment of its current value. But, without such a value, optimal dosing of insulin, including the effects of insulin saturation, for example, is not possible with any resolution.

Hence, the ability of a validated, physiologically relevant model to provide a patient-specific value and its potential variation in future offers unique insight and potential to optimize interventions that is not otherwise available [48,72,73]. Thus, validated, patient-specific models can test these insights and proposed treatments in silico, before application, improving safety. Because they use existing data and can predict accurately they offer the clinician a window on past and present behaviors, as well as a view of how to customize treatment for optimal future behaviors.

#### **What are the differences between computer-based, model-based, and model-derived TGC? The model, the implementation, and the level of patient-specificity**

There are an increasing number of computer-based TGC protocols that are not model-based [74-79] and thus do not offer the same physiological insight or "picture." They are, more accurately, an extension of protocolized care in that they take a protocol and put it on the computer. Equally, such protocolized care provides a cohort-based approach that is consistent ("one size fits all") but not necessarily patient-specific. Thus, the main element that differentiates a model-based system is the use of a physiologically relevant, validated model to create a patient-specific picture of patient state and provide patient-specific ("one method fits all") advice.

A hybrid path uses what we denote "model-derived" protocols. The only current example of this approach is the SPRINT protocol [58]. This paper-based system was created and optimized in silico by using clinically validated models and virtual patients [33,80]. However, it provides patient-specific care, based on its design using the model, within the paper-based abstraction used to provide easy uptake in the ICU.

Hence, the critical difference is that model-based methods implicitly enforce a protocol, but, in their

patient-specificity, translate the “one size fits all” approach of a fixed protocol to a “one method fits all” patient-specific form of care. For TGC these methods are already (increasingly) proven in both model-derived [44,58] and model-based [36,47,48,52,53] formats. Their success is due to their unique ability, when properly modeled and validated, to provide much better, real-time management of both intra- and inter-patient variability that typical non-model-based clinical protocols cannot and, as a result, provide a level of care that is beyond existing clinical protocols.

## Summary

Models and model-based methods have a lot to offer in a wide range of clinical areas in medicine, and in critical care specifically. Using TGC as an example, they can offer significant physiological insight into patient status and behavior that are not readily available at the bedside or part of the typical, clinical mental model. Hence, they enable the means to develop and implement “one method fits all” patient-specific approaches to diagnosis and care. Their ability to reduce the impact of intra- and inter-patient variability, within a protocolized framework that reduces variability in care, can improve care and outcomes for all patients. Hence, models and model-based methods represent an important area of potentially increasing significance to the practice of critical care medicine, and TGC in particular, in the coming years.

## Additional material

**Additional file 1: Appendix: Metabolic System Model and Insulin Sensitivity (SI).** This file contains a full description of the metabolic system model equations, their validation and physiological validity, the methods to identify the model-based insulin sensitivity (SI) parameter, its correlation to gold-standard tests, and, finally, the definition and application of stochastic models of model-based insulin sensitivity (SI).

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## Author details

<sup>1</sup>Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, Christchurch, Private Bag 4800, New Zealand

<sup>2</sup>Department of Intensive Care, Erasme University Hospital, B1070 Brussels, Belgium <sup>3</sup>Department of Intensive Care, Christchurch Hospital, Christchurch, 8054, New Zealand <sup>4</sup>Cardiovascular Research Centre, Universite de Liege, B4000 Liege, Liege, Belgium

## Authors' contributions

JGC, GS, TD, JCP, SP, and ALC conceived and developed the review and written manuscript. All authors approved the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

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## References

1. Wendon J: Critical care “normality”: individualized versus protocolized care. *Crit Care Med* 2010, **38**(10 Suppl):S590-599.
2. Kavanagh BP, Meyer LJ: Normalizing physiological variables in acute illness: five reasons for caution. *Intensive Care Med* 2005, **31**(9):1161-1167.
3. McCowen KC, Malhotra A, Bistrian BR: Stress-induced hyperglycemia. *Crit Care Clin* 2001, **17**(1):107-124.
4. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000, **355**(9206):773-778.
5. Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW: Mechanisms of insulin resistance following injury. *Ann Surg* 1982, **196**(4):420-435.
6. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003, **78**(12):1471-1478.
7. Van den Berghe G, Wouters P, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001, **345**(19):1359-1367.
8. Waeschle RM, Moerer O, Hilgers R, Herrmann P, Neumann P, Quintel M: The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. *Crit Care (London)* 2008, **12**(5):R129.
9. Chase JG, Le Compte AJ, Suhaimi F, Shaw GM, Lynn A, Lin J, Pretty CG, Razak N, Parente JD, Hann CE, et al: Tight glycaemic control in critical care. The leading role of insulin sensitivity and patient variability: a review and model-based analysis. *Comput Methods Programs Biomed* 2010, Online Early Release.
10. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, et al: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009, **360**(13):1283-1297.
11. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008, **358**(2):125-139.
12. Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, LEVERVE X, Nitenberg G, Singer P, et al: A prospective randomized multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009, **35**(10):1738-1748.
13. Egi M, Bellomo R, Stachowski E, French CJ, Hart G: Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006, **105**(2):244-252.
14. Bagshaw SM, Bellomo R, Jacka MJ, Egi M, Hart GK, George C: The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care* 2009, **13**(3):R91.
15. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001, **414**(6865):813-820.
16. Dandona P, Chaudhuri A, Ghanim H, Mohanty P: Anti-inflammatory effects of insulin and pro-inflammatory effects of glucose: relevance to the management of acute myocardial infarction and other acute coronary syndromes. *Rev Cardiovasc Med* 2006, **7**(Suppl 2):S25-34.
17. Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters PJ, Skogstrand K, Hansen TK, Van den Berghe G: Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005, **115**(8):2277-2286.
18. Carson ER, Cobelli C: Modelling methodology for physiology and medicine. *Acad Press Series Biomed Eng* 2001, **xiv**:421.
19. Keener JP, Sneyd J: *Mathematical Physiology* New York: Springer; 1998.
20. Smith BW, Chase JG, Nokes RI, Shaw GM, Wake G: Minimal haemodynamic system model including ventricular interaction and valve dynamics. *Med Eng Phys* 2004, **26**(2):131-139.
21. Kerckhoffs RC, Neal ML, Gu Q, Bassingthwaite JB, Omens JH, McCulloch AD: Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonary circulation. *Ann Biomed Eng* 2007, **35**(1):1-18.

22. Hunter PJ, Nielsen PM, Smaill BH, LeGrice IJ, Hunter IW: **An anatomical heart model with applications to myocardial activation and ventricular mechanics.** *Crit Rev Biomed Eng* 1992, **20**(5-6):403-426.
23. Lin J, Razak NN, Pretty CG, Le Compte A, Docherty P, Parente JD, Shaw GM, Hann CE, Geoffrey Chase J: **A physiological Intensive control insulin-nutrition-glucose (ICING) model validated in critically ill patients.** *Comput Methods Programs Biomed* 2011.
24. Hann CE, Chase JG, Lin J, Lotz T, Doran CV, Shaw GM: **Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model.** *Comput Methods Programs Biomed* 2005, **77**(3):259-270.
25. Rudge AD, Chase JG, Shaw GM, Lee D: **Physiological modelling of agitation-sedation dynamics.** *Med Eng Phys* 2006, **28**(1):49-59.
26. Chase JG, Rudge AD, Shaw GM, Wake GC, Lee D, Hudson IL, Johnston L: **Modeling and control of the agitation-sedation cycle for critical care patients.** *Med Eng Phys* 2004, **26**(6):459-471.
27. Starfinger C, Chase JG, Hann CE, Shaw GM, Lambert P, Smith BW, Sloth E, Larsson A, Andreassen S, Rees S: **Prediction of hemodynamic changes towards PEEP titrations at different volemic levels using a minimal cardiovascular model.** *Comput Methods Programs Biomed* 2008, **91**(2):128-134.
28. Starfinger C, Hann CE, Chase JG, Desai T, Ghuyen A, Shaw GM: **Model-based cardiac diagnosis of pulmonary embolism.** *Comput Methods Programs Biomed* 2007, **87**(1):46-60.
29. Sundaresan A, Yuta T, Hann CE, Geoffrey Chase J, Shaw GM: **A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients.** *Comput Methods Programs Biomed* 2009, **95**(2):166-80.
30. Sundaresan A, Chase JG, Hann CE, Shaw GM: **Cardiac output estimation using pulmonary mechanics in mechanically ventilated patients.** *Biomed Eng Online* 2010, **9**(1):80.
31. Blakemore A, Wang S, LeCompte A, Wong X, Shaw G, Lin J, Lotz T, Hann C, Chase J: **Model-based insulin sensitivity as a sepsis diagnostic in critical care.** *J Diabetes Sci Technol (JoDST)* 2008, **2**(3):468-477.
32. Lin J, Parente JD, Chase JG, Shaw GM, Blakemore AJ, Lecompte AJ, Pretty C, Razak NN, Lee DS, Hann CE, et al: **Development of a model-based clinical sepsis biomarker for critically ill patients.** *Comput Methods Programs Biomed* 2010.
33. Lonergan T, LeCompte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE: **A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison.** *Diabetes Technol Ther* 2006, **8**(2):191-206.
34. Chase JG, Shaw GM, Lin J, Doran CV, Hann C, Lotz T, Wake GC, Broughton B: **Targeted glycemic reduction in critical care using closed-loop control.** *Diabetes Technol Ther* 2005, **7**(2):274-282.
35. Blaha J, Kopecky P, Matias M, Hovorka R, Kunstyr J, Kotulak T, Lips M, Rubes D, Stritesky M, Lindner J, et al: **Comparison of three protocols for tight glycemic control in cardiac surgery patients.** *Diabetes Care* 2009, **32**(5):757-761.
36. Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, Squire S, Haluzik M, Kremen J, Svacina S, et al: **Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients.** *Diabetes Care* 2006, **29**(2):271-276.
37. Van Herpe T, Espinoza M, Pluyms B, Goethals I, Wouters P, Van den Berghe G, De Moor B: **An adaptive input-output modeling approach for predicting the glycemia of critically ill patients.** *Physiol Meas* 2006, **27**(11):1057-1069.
38. Pielmeier U, Andreassen S, Nielsen BS, Chase JG, Haure P: **A simulation model of insulin saturation and glucose balance for glycemic control in ICU patients.** *Comput Methods Programs Biomed* 2010, **97**(3):211-222.
39. Pielmeier U, Andreassen S, Juliusen B, Chase JG, Nielsen BS, Haure P: **The Glucosafe system for tight glycemic control in critical care: a pilot evaluation study.** *J Crit Care* 2010, **25**(1):97-104.
40. Hovorka R, Kremen J, Blaha J, Matias M, Anderlova K, Bosanska L, Roubicek T, Wilinska ME, Chassin LJ, Svacina S, et al: **Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial.** *J Clin Endocrinol Metab* 2007, **92**(8):2960-2964.
41. Wilinska ME, Chassin L, Hovorka R: **In silico testing-impact on the progress of the closed loop insulin infusion for critically ill patients project.** *J Diabetes Sci Technol* 2008, **2**(3):417-423.
42. Hovorka R, Chassin LJ, Ellmerer M, Plank J, Wilinska ME: **A simulation model of glucose regulation in the critically ill.** *Physiol Meas* 2008, **29**(8):959-978.
43. Chase J, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE: **Model-based glycaemic control in critical care - a review of the state of the possible.** *Biomed Signal Process Control* 2006, **1**(1):3-21.
44. Chase JG, Shaw GM, Lotz T, LeCompte A, Wong J, Lin J, Lonergan T, Willacy M, Hann CE: **Model-based insulin and nutrition administration for tight glycaemic control in critical care.** *Curr Drug Deliv* 2007, **4**(4):283-296.
45. Chase J, LeCompte A, Shaw G, Blakemore A, Wong J, Lin J, Hann C: **A benchmark data set for model-based glycaemic control in critical care.** *J Diabetes Sci Technol (JoDST)* 2008, **2**(4):584-594.
46. Chase JG, Suhaimi F, Penning S, Preiser JC, Le Compte AJ, Lin J, Pretty CG, Shaw GM, Moorhead KT, Desai T: **Validation of a model-based virtual trials method for tight glycaemic control in intensive care.** *Biomed Eng Online* 2010, **9**:84.
47. LeCompte A, Chase J, Lynn A, Hann C, Shaw G, Wong X, Lin J: **Blood glucose controller for neonatal intensive care: virtual trials development and 1st clinical trials.** *J Diabetes Sci Technol (JoDST)* 2009, **3**(5):1066-1081.
48. Lin J, Lee D, Chase JG, Shaw GM, Le Compte A, Lotz T, Wong J, Lonergan T, Hann CE: **Stochastic modelling of insulin sensitivity and adaptive glycaemic control for critical care.** *Comput Methods Programs Biomed* 2008, **89**(2):141-152.
49. Pielmeier U, Chase J, Andreassen S, Haure P, Nielsen B, Shaw G: **Prediction validation of two glycaemic control models in critical care.** *17th IFAC World Congress (IFAC WC2008): July 6-11 2008; Seoul, Korea* 2008, 8074-8079.
50. Suhaimi F, Le Compte A, Preiser JC, Shaw GM, Massion P, Radermecker R, Pretty C, Lin J, Desai T, Chase JG: **What makes tight glycaemic control (TGC) tight? The impact of variability and nutrition in 2 clinical studies.** *J Diabetes Sci Technol* 2010, **4**(2):284-298.
51. Chase JG, Shaw GM, Lin J, Doran CV, Hann C, Robertson MB, Browne PM, Lotz T, Wake GC, Broughton B: **Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care.** *Med Eng Phys* 2005, **27**(1):1-11.
52. Wong XW, Singh-Levett I, Hollingsworth LJ, Shaw GM, Hann CE, Lotz T, Lin J, Wong OS, Chase JG: **A novel, model-based insulin and nutrition delivery controller for glycaemic regulation in critically ill patients.** *Diabetes Technol Ther* 2006, **8**(2):174-190.
53. Wong XW, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Singh-Levett I, Hollingsworth LJ, Wong OS, Andreassen S: **Model predictive glycaemic regulation in critical illness using insulin and nutrition input: a pilot study.** *Med Eng Phys* 2006, **28**(7):665-681.
54. Dalla Man C, Caumo A, Basu R, Rizza R, Toffolo G, Cobelli C: **Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method.** *Am J Physiol Endocrinol Metab* 2004, **287**(4):E637-E643.
55. Dalla Man C, Campioni M, Polonsky KS, Basu R, Rizza RA, Toffolo G, Cobelli C: **Two-hour seven-sample oral glucose tolerance test and meal protocol: minimal model assessment of beta-cell responsivity and insulin sensitivity in nondiabetic individuals.** *Diabetes* 2005, **54**(11):3265-3273.
56. Thorsteinsson B: **Kinetic models for insulin disappearance from plasma in man.** *Dan Med Bull* 1990, **37**(2):143-153.
57. Pretty C, Chase JG, Lin J, Shaw GM, Le Compte A, Razak N, Parente JD: **Impact of glucocorticoids on insulin resistance in the critically ill.** *Comput Methods Programs Biomed* 2011.
58. Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C: **Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change.** *Crit Care* 2008, **12**(2):R49.
59. Bergman RN, Prager R, Volund A, Olefsky JM: **Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycaemic glucose clamp.** *J Clin Invest* 1987, **79**(3):790-800.
60. Kovatchev BP, Breton M, Man CD, Cobelli C: **In Silico Preclinical Trials: a proof of concept in closed-loop control of type 1 diabetes.** *J Diabetes Sci Technol (Online)* 2009, **3**(1):44-55.
61. Lehmann ED, Deutsch T: **A physiological model of glucose-insulin interaction in type 1 diabetes mellitus.** *J Biomed Eng* 1992, **14**(3):235-242.
62. Lehmann ED: **AIDA: a computer-based interactive educational diabetes simulator.** *Diabetes Educator* 1998, **24**(3):341.

63. Arleth T, Andreassen S, Federici MO, Benedetti MM: **A model of the endogenous glucose balance incorporating the characteristics of glucose transporters.** *Comput Methods Programs Biomed* 2000, **62**(3):219-234.
64. Cobelli C, Caumo A, Omenetto M: **Minimal model SG overestimation and SI underestimation: improved accuracy by a Bayesian two-compartment model.** *Am J Physiol* 1999, **277**(3 Pt 1):E481-488.
65. Hann C, Chase J, Ypma M, Elfring J, Nor N, Lawrence P, Shaw G: **The impact of parameter identification methods on drug therapy control in an intensive care unit.** *Open Med Inform J* 2008, **2**:92-104.
66. Pillonetto G, Sparacino G, Cobelli C: **Numerical non-identifiability regions of the minimal model of glucose kinetics: superiority of Bayesian estimation.** *Math Biosci* 2003, **184**(1):53-67.
67. Cobelli C, Bettini F, Caumo A, Quon MJ: **Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling.** *Am J Physiol* 1998, **275**(6 Pt 1):E1031-1036.
68. Van Herpe T, Pluymers B, Espinoza M, Van den Berghe G, De Moor B: **A minimal model for glycemia control in critically ill patients.** *Conf Proc IEEE Eng Med Biol Soc* 2006, **1**:5432-5435.
69. Chee F, Fernando TL, Savkin AV, van Heeden V: **Expert PID control system for blood glucose control in critically ill patients.** *IEEE Trans Inf Technol Biomed* 2003, **7**(4):419-425.
70. Doran CV, Hudson NH, Moorhead KT, Chase JG, Shaw GM, Hann CE: **Derivative weighted active insulin control modelling and clinical trials for ICU patients.** *Medical Engineering & Physics* 2004, **26**(10):855-866.
71. Le Compte A, Chase JG, Russell G, Lynn A, Hann C, Shaw G, Wong XW, Blakemore A, Lin J: **Modeling the glucose regulatory system in extreme preterm infants.** *Comput Methods Programs Biomed* 2010.
72. Le Compte AJ, Lee DS, Chase JG, Lin J, Lynn A, Shaw GM: **Blood glucose prediction using stochastic modeling in neonatal intensive care.** *IEEE Trans Biomed Eng* 2010, **57**(3):509-518.
73. Lin J, Lee DS, Chase JG, Hann CE, Lotz T, Wong XW: **Stochastic modelling of insulin sensitivity variability in critical care.** *Biomed Signal Process Control* 2006, **1**:229-242.
74. Davidson PC, Steed RD, Bode BW: **Glucommander: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation.** *Diabetes Care* 2005, **28**(10):2418-2423.
75. Vogelzang M, Zijlstra F, Nijsten MW: **Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit.** *BMC Med Inform Decis Mak* 2005, **5**(38):10.
76. Cochran S, Miller E, Dunn K: **EndoTool software for tight glucose control for critically ill patients.** *Crit Care Med* 2006, **34**(Suppl 2):A68.
77. Thomas AN, Marchant AE, Ogden MC, Collin S: **Implementation of a tight glycaemic control protocol using a web-based insulin dose calculator.** *Anaesthesia* 2005, **60**(11):1093-1100.
78. Eslami S, Abu-Hanna A, de Jonge E, de Keizer NF: **Tight glycaemic control and computerized decision-support systems: a systematic review.** *Intensive Care Med* 2009, **35**(9):1505-1517.
79. Morris AH, Orme J Jr, Truwit JD, Steingrub J, Grissom C, Lee KH, Li GL, Thompson BT, Brower R, Tidswell M, et al: **A replicable method for blood glucose control in critically ill patients.** *Crit Care Med* 2008, **36**(6):1787-1795.
80. Lonergan T, Compte AL, Willacy M, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Wong XW: **A pilot study of the SPRINT protocol for tight glycaemic control in critically ill patients.** *Diabetes Technol Ther* 2006, **8**(4):449-462.

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