Glycemic Control in the Intensive Care Unit: A control systems perspective

J. Geoffrey Chase¹, Balazs Benyo² and Thomas Desaive³

1. Mechanical Engineering, Centre of Bio-Engineering, University of Canterbury, Christchurch, NZ; Geoff.chase@canterbury.ac.nz
2. Department of Control Engineering and Information Technology, Budapest University of Technology and Economics, Budapest, Hungary; bbényo@iit.bme.hu
3. GIGA In Silico Medicine, Liege University, Liege, Belgium; tdesaive@uliege.be

Abstract:

Computers and automation have revolutionised quality and productivity in many industries, but not in medicine. Healthcare costs are thus growing beyond the ability of society to pay for them, multiplied by the impact of increasingly aging populations, and specifically in the demand placed on intensive care unit (ICU) services. Glycemic control is a core ICU therapy with the potential to reduce both mortality and cost, which makes it an area where greater personalisation and automation could play a leading role in improving productivity and care. This review presents the background to the problem and the main issues arising in this area of care from a control systems technology perspective. It then presents a vision of a more automated future with specific goals in the areas of dynamic systems modeling, system identification and control. These areas are then given a state of the art review, mixing both medicine and control systems perspectives. It is concluded by specific recommendations for the field, where control systems expertise can be leveraged to best advantage.

Keywords: Glycemic Control, Control Systems, Dynamic Systems Modeling, System Identification, Identifiability, Intensive Care, ICU, Critical Care.
1.0 Introduction:

Intensive care unit (ICU) patients are very difficult to manage safely and effectively as a result of their complex, nonlinear, and highly variable physiology and equally complex response to therapy. The cost of intensive care has risen dramatically in the last decade, primarily due to aging demographics and increasing average lifespans (e.g. [1, 2]), reducing the ability of health care systems to maintain equity of access to care, which is an increasingly important social and policy issue [3-8]. Thus, improving productivity and cost are the major current challenges for ICU care, where the personalisation and/or automation of care to better capture the intra- and inter- patient variability in core ICU therapies offers an opportunity to make a significant impact. In particular, changing from current “one size fits all” protocolised care, which can be problematic in the ICU [9-11], to a “one method fits all” personalised care, based on physiological models enabling optimised and automated therapy, could provide a means to address rising demand and costs.

High blood glucose (BG) or hyperglycemia is prevalent in critical care, and is one example area where such changes in care could have great impact. It is caused by a complex interaction of multiple feedback loops associated with inflammation resulting from immune responses, counter-regulatory responses, and high BG itself [12-15], and is thus a classic control systems problem in multiple variables. It is exacerbated by unsuppressed glucose production by the body [12-15], medications [16], high levels of naso-gastric nutrition [17], suppression of the body’s insulin secretion [12-15], and loss of sensitivity to insulin [18, 19]. All these factors effectively damage the body’s normal feedback control mechanisms, resulting in reduced insulin-mediated glucose uptake, and thus hyperglycemia – in short the feedback loop is broken and control is extremely sub-optimal. Thus, there is a need for some form of supplemental, closed-loop, highly personalized glycemic control (GC) in critical care.

Hence, there are strong associations between BG level and/or variability with patient death [20-27]. However, poor control leading to low BG or hypoglycemia is also linked with increased mortality [25, 28-30], indicating the difficulty of the control problem in regulating BG to a band. These issues clearly state any control, automated or manual, must be achieved safely, despite the high inter- and intra-patient variability in response to care [18, 19, 24, 27, 31-33], which can define these patients.
Equally, and in contrast, safe, effective control has shown equivalent association of high times in intermediate BG bands with reduced mortality [34-39]. Thus, control quality must be consistent over time and most (or all) patients. However, relatively few studies achieved this level of consistent control [40-43], further demonstrating the problem difficulty and potential need for automation.

Thus, patient outcomes are driven by the quality and consistency of GC, as further demonstrated in recent analyses showing those patients who live and those who die are equally easy, or difficult, to control [44] – a control systems analysis of a clinical problem. However, GC in the ICU is still a controversial subject [45-51]. Some studies improved mortality with GC to a tight or intermediate range [40-43, 52], but several studies could not repeat these results [53-63]. The salient differences between these studies is based around the inability to directly manage inter- and intra- patient variability, yielding variable control quality for a given patient, inconsistency of control across patients, and thus a failure to deliver safe, effective control to all patients.

Overall, this analysis indicates the need for consistent, safe, effective control, which human driven or human in the loop driven protocols are unable to deliver. This need is reinforced by data from the single study that reduced mortality and hypoglycemia with GC [40]. This study also reduced organ failure, the leading cause of cost and mortality in ICU patients, and demonstrated that GC affects outcome for only an unidentifiable 15-20% of patients, which in turn reinforces the need to obtain safe, effective control for all patients [64], thus demanding a more rigorous control systems approach over clinical protocols.

This review discusses how physiological modelling of the complex, nonlinear metabolic system of the ICU patient can provide a means of identifying patient state, using that state to personalise care and manage intra- and inter- patient variability, and thus providing safe, effective and generalizable GC to all patients. A particular focus is put on how these elements can lead towards automated or semi-automated GC solutions, which would offer the opportunity to reduce nursing and doctor workload, while improving care, thus providing a context for merging physiology, health care, and control systems.
2.0 Vision of the Future:

The problem can be summarised as the need to provide safe, generalizable, and effective GC to a diverse group of highly variable patients, in the presence of limited data. More specifically, it is possible to know the metabolic inputs of exogenous insulin and nutrition given to support the patient, but only the BG level is measured. In particular, this BG measurement can be intermittent in 1-4 hourly intervals, but with low error [65-69], or effectively continuous at intervals of 1-5 minutes using continuous glucose monitors (CGMs), but with increased error and drift [70-76]. Hence, automation must account for either intermittent control with high quality measurements of patient response, or more continuous feedback control with lower quality measurements, both of which will impact the shape and structure of control.

In all cases, the use of computational modelling offers the ability to turn these glucose measurements and known inputs into a better metric by which to guide care. In metabolic systems and GC, model-based assessment of insulin sensitivity (SI) relates input changes of insulin and nutrition, to expected glycemic response. This value could be monitored and thus potentially used as a broader metric of patient condition. Finally, in an ideal case, model-based control using a metric of insulin sensitivity could be used not only to guide care, but to assess risk in terms of patient variability, thus offering the potential to manage patient variability directly in a risk-based approach to care.

Overall, models thus offer the ability to computationally derive a metric to guide control based on patient condition. They thus offer the potential to personalise that care, and to manage it based not only on condition, but on risk of variability, which would be unique in medicine today. This approach would be applicable to both direct closed-loop control, as well as semi-closed human in the loop control. This vision is illustrated schematically in **Figure 1**.
Figure 1: Model-based decision support to mimic the human pancreas with a nurse in the loop, but eventually automated. Measurements and other data are given to a decision support system that identifies patient-specific information, such as insulin sensitivity, to personalise the model. A control protocol uses that data to generate personalised recommendations for patient care.
3.0 State of the Art:

Computers and automation have revolutionised quality and productivity in many industries, but not in medicine [7, 77, 78]. Equally, and as noted, countries and health care systems are increasingly unable to pay for increasing demand and costs of medical care [79]. Computational physiological models and model-based control thus offer an important opportunity to personalise care, and improve costs and productivity, by combining clinical data with system identification methods to generate “virtual patient” [80-87] models to represent patients directly, the first step towards automating care.

In particular, there is, in general, an increasing range of physiological models, methods and databases, from simple to high complexity multi-scale models (e.g. [88-120]). Other reviews have delineated how each type of model might be used to guide care [83]. Validated models paired with appropriate control methods thus offer an avenue to translate computation into health care. The following sections outline the state of this art, specifically in relation to metabolic systems and glycemic control in the ICU.

3.1 Dynamic System Models of the Metabolic System:

There are several metabolic models of human metabolism particularly related to studies in diabetes and general physiology [82, 91, 96, 121-126]. They are primarily deterministic compartment models with specific terms for all relevant physiology and dynamics [91]. There are also black-box or data driven models with no direct physiological analogy or relevance (e.g. [127-134]). However, these black-box models do not offer the ability to generate patient-specific metabolic markers or accurate predictions of resulting glucose levels for an intervention of insulin or nutrition, which are necessary for model-based control and personalized GC to run in real-time with safety and efficacy.

Hence, this review focuses on less-complex models, where the minimum fundamental model inputs to simulate and/or personalize these models are the insulin and nutrition given, and blood glucose measurements. They thus offer the ability to be personalized to patient condition at a given BG measurement, and in turn used to predict the outcome to a next intervention. However, no discussion of possible models is complete due to the large number of models studied, so this review focuses on
nonlinear metabolic system models used in critical care to create virtual patients, and use them to guide care, a much more limited set. Specifically:

- ICU Minimal Model [135, 136]
- Glucosafe [110]
- Cambridge [85]
- ICING [137-139]
- UVA/Padova [84, 140]

The ICU Minimal Model is based on the Bergman Minimal Model [113, 121], and is integral to the LOGiC controller [141]. It is the least physiologically relevant, with a minimal number of terms aggregating all glucose appearance and disappearance routes. An insulin sensitivity parameter derived from two model parameters makes it patient-specific and is used to guide care. It has been tested and improved control over nurse led GC [142], but was over aggressive in some cases. It is not currently a standard of care nor adopted for regular use.

Glucosafe is a dynamic model in its insulin kinetics, which are derived from an earlier form of the ICING model. However, its pharmacodynamics are based on a glucose-insulin dynamic model for diabetes control [143]. Insulin sensitivity is identified from data and has been used to create virtual patients to develop glycemic controllers [110]. It is more physiologically relevant than the ICU Minimal Model with specific pharmacodynamics terms for each form of glucose removal. However, it demonstrated limited performance in pilot GC trials in regular and neuro ICU patients [31, 144].

The Cambridge Model is highly physiologically relevant [85]. It was developed from frequently sampled bedside data collected at the ICU and underlying models developed for physiology and diabetes experiments and control [99, 145-147]. It has been used to simulate and design GC in critical care, specifically in creating multi-day clones [85, 119, 148] of critical care patients. It uses identified time-varying insulin sensitivity (SI) to guide care and mitigate errors in combination with a black-box auto-regressive model [146].
The ICING model also has high physiological relevance with specific pathways modeled for the main forms of glucose appearance and uptake [137, 139]. It also has a neonatal ICU (NICU) version based on the same dynamics scaled for the specific case [87, 138, 149]. It is driven by an insulin sensitivity parameter identifiable from bedside data [150, 151], which can be used to monitor patient condition and its evolution over time [18, 152, 153]. It has been used in virtual patients [139, 154, 155], GC design [155-157] and real-time GC [155-159]. In particular, it has been used to create multi-day virtual patient clones, where predicted cohort level glycemic results were matched by subsequent clinical results (e.g. [80, 156]) with good correlation of median per-patient glucose levels. It has also demonstrated cross-validation of its virtual patients on independent data on multiple data sets [139, 154], and is thus the most completely validated model based on a recent framework [83]. All these results indicate that its monitoring of patient condition accurately captures the necessary dynamics.

The UVA/Padova simulator was developed for type 1 diabetes [84, 140], and is a collection of highly physiologically relevant sub-models, rather than a single mode. Its high physiological relevance and detail are an advantage in physiological studies. It has been used for single day virtual patient clones [160]. However, a given insulin sensitivity or other key parameters cannot necessarily be identified from bedside data with this model, and it has multiple insulin sensitivities. It is thus limited it to simulations of generic patients, and while it is not yet validated for direct clinical use in model-based control, it has been approved by the US FDA for replacing the need for some clinical trials [84].

While this brief overview is not exhaustive, it clearly highlights the need for “valid models” meeting three main criteria. First, an identifiable insulin sensitivity parameter capturing patient-specific glucose responses to insulin-nutrition inputs to enable personalisation. Second, a large enough degree of physiological relevance to ensure identified parameter(s) accurately capture patient-specific behavior so they can be used to design and/or guide care. Third, rigorous validation via use in design and/or implementation of safe, effective GC. These issues are inter-related, and thus reviewed in subsequent sections in terms of the use of these models as Virtual Patients to design and guide care, and their subsequent use in guiding GC.
Overall, 4 of the 5 models have been used to both design GC, as well as implement it. However, only the Cambridge and ICING models have had outcome success clinically, where the ICING model modified for the NICU (called the NICING model) has been generalized to other critical care cases clinically [138, 158]. This difference may be due to the fact that, to date, only these 2 models have been validated using independent cohorts and protocols [139, 148, 154].

Equally, both models use a model-identified insulin sensitivity parameter (SI) which has been proven in independent insulin sensitivity studies [152, 161-164]. This metric is critical as it is used to guide care, and inaccuracy will translate through to any control derived using its value with potential patient harm. Perhaps more importantly, such model-based SI [19, 33, 85, 109, 110, 114, 117, 137, 154, 161, 165-173] can be monitored and its level and/or variation assessed relative to condition [16, 18, 19, 153, 171, 174-182]. Thus, if accurate, this value offers not only the potential of good, personalised control, but also further insight into patient condition.

Overall, the current state of the art in terms of metabolic models for this application is limited. In particular, model-based control in other industries may have several models to choose from. However, these models have performed well. Still, further research may be required and there is no “best” control relevant dynamic system model of human metabolism, for the critically ill or in diabetes, at this time.

3.2 Model Validation:
Model validation is a difficult topic, although clinical application, as discussed in Section 3.1, provides a final proof if the resulting control is good. Many models in physiology focus on the ability to fit the data, meeting the simplest standard. However, such limited validation does not ensure the dynamics modelled are those produced by the actual system. In particular, a model may fit measured data using the as-identified parameters, but while the fit is good, the identified model cannot accurately predict forward when conditions or inputs change. As a result, the identified cannot be said to accurately represent the same dynamics as those observed in the patient when conditions change. Thus, prediction of outcome has emerged as the necessary minimum in physiological modelling for control or decision support, where the identified model needs to be able to predict the outcome of an intervention and thus demonstrate its potential for safe, effective control, which is the end goal in this case.
A recent review [83] thus developed a framework for validation, beginning at prediction. It also proposed validation in predicting the outcome of groups of experiments or clinical interventions over cohorts, expanding from single virtual patient predictions using an identified model, to prediction accuracy across groups of patients, an added level of robustness. Finally, it proposed cohort level cross-validation using independent clinical data to identify similar cohorts and test their prediction on the protocols or interventions applied to the other cohort, the highest level of validation. To date, as noted previously, only the ICING and Cambridge models offer the first two levels of validation, and only the ICING model the third level.

3.3 Closed Loop and Decision Support to Guide Care:

Figure 1 schematically shows the use of these models as part of either partial or full closed loop automation. As noted, both the Cambridge and ICING models have been used in clinical GC, and have been used as standard of care in multiple ICUs. Notably, and as illustrated, the field has devolved in model predictive forms of control, using glucose measurements for closed loop control of BG levels. More specifically, predictive control requires a model using current measurements and other inputs to identify patient-specific model parameters to personalize GC. The patient-specific model is then used to predict the outcome of insulin-nutrition interventions to optimize glycemic performance. Thus, the model is used directly in the control loop.

Although several model-based predictive controllers have been tested in short or limited trials, only a few have been used regularly in major trials [141, 142] or as standard of care [159, 171]. There are two essential control approaches taken to date:

- Target to value (TTV), where GC is optimized to achieve a specified BG target value;
- Target to range or risk (TTR), where GC is optimized using models of metabolic variability to provide a specified risk of hypo- and/or hyper- glycemia.

The LOGIC-Insulin system is a TTV approach and nutrition is clinically set and not controlled, and thus it does not use one potential control input in achieving desired BG levels. The single-center LOGIC-I
trial [141] compared standard care at a unit with a very strong reputation for nursing-led GC to model-based care with very good results. This performance was confirmed in a smaller multicenter trial [142]. However, it is not yet a standard of care yet in the original study unit or elsewhere.

The TTV eMPC (B. Braun, Germany) [146] is based on the Cambridge model, and has been used several trials [171, 183-186]. It also controls only insulin infusions, leaving nutrition as clinically set, and thus also does not use one potential control input in achieving desired BG levels. Compared to standard care, eMPC does well [183, 186]. Comparisons across centers and cohorts show similar, but not identical, performance [171, 185]. Workload is 14-18 measurements/day, and thus higher than standard care in most ICUs. Thus, eMPC provides improved care and safety, but increases potential workload. It is used regularly in some ICUs. More recently, the Cambridge model and similar controller has been used in guiding infusions in type 2 diabetes patients in the ICU and less acute wards [187].

STAR is the only TTR system and controls both insulin and nutrition inputs [188, 189], thus using both possible control inputs. It uses a unique risk-based stochastic forecasting [71] based on unique and increasingly complex stochastic models of future insulin sensitivity variability over 1-4 hours ahead [166, 167, 176, 177, 190, 191]. The approach is used in both the ICU [156, 159] and NICU [87, 138, 158, 170], where notably insulin is the only control variable in the NICU for clinical reasons. STAR is thus the only GC system to directly account for future variability and to directly manage it in the control scheme. Within the control systems engineering field, there are potentially other methods of approaching this capability, such as a range of auto-regressive models, which again could be built from increasing clinical data in use.

STAR also has good performance and safety, including high times in intermediate glycemic bands, approaching 80% with 10-13 measurements/day [156, 159], and similar results in NICU [158, 192]. More importantly, it has very low rates of hypoglycemia, which is especially important in the NICU case where GC leads to excessive hypoglycemia in other clinical studies [193, 194]. STAR in the adult ICU has generalized well, with almost identical glycemic outcomes across very different cohorts and ICUs [159]. Notably, eMPC and LOGIC-Insulin have shown some generalizability, but not to the near identical level across very different cohorts.
An important difference for STAR over the other two controllers is its use of nutrition in control. Increased insulin and reduced nutrition are two control inputs available to reduce BG levels. In a control systems context, particularly given the risk of hypoglycemia with excessive insulin, it is sensible to control both inputs, and there is no major clinical difficulty in doing so, particularly with automation. However, it is not typical clinical practice, and there is fear of underfeeding patients [195-198]. However, in separate analyses STAR was shown to provide nutrition near to best in the world compared to a large survey of international ICUs [199], and further analysis has shown the potential to control nutrition at a range of time resolutions or servo-rates to overcome clinical hesitancy though they have not yet been tested [200].

All three model-based systems noted have very low rates of hypoglycaemia (<5% by patient) and are very generalizable. Note, the Glucosafe system was not included as it has only been used for trials of 10-20 patients and thus not demonstrated the same robustness in care as the other three, and that only two of those three models are used in standard of care over time. Overall, this analysis shows predictive, model-based methods can overcome many of the hurdles that have hindered clinical trials in the field.

In summary, at this time, in addition to very simple, model-free PID (Proportional-Integra-Derivative) feedback control systems used in some hospitals in the US [201-203], three model-based predictive GC methods have proved reliable over multiple patient types and centers. Two are used as standards of care in multiple hospitals, and one has a NICU version [138] as standard of care, which is currently being used in a wider randomized trial [204]. Two methods consider nutrition (STAR, eMPC), although only one (STAR) controls it, which may account for some differences in performance and generalizability across diverse cohorts with different levels of insulin sensitivity [205].

3.4 Summary and Future Possibilities:

This section presented an overview of the metabolic models available for GC in the ICU, and how they can be, or have been, used in clinical care. To date, there are limited models and most are limited in the scale, number, and level of validation. There is thus significant research opportunity for new developments, including in the inclusion or clinical use of device dynamics, where, for example, insulin
adsorption to infusion lines [206, 207] and infusion pump dynamics [208, 209] are not accounted for as yet, but may play a major role. Equally, the use of continuous glucose monitors (CGMs) for far higher bandwidth control has been only little studied in this context (e.g. [73, 210]), and there is a dearth of CGM dynamics models to help design and guide control, where their drift and error could significantly impact control quality.
4.0 Recommendations:

From the analysis and review there are significant areas in which the control of blood glucose in hospital, and with outpatients (not covered here) cross over into the realms typically covered by control systems engineers. As devices and systems provide the ability for greater real-time measurement and control, these inputs will become increasingly relevant. Thus, the following recommendations might be made relevant to the control systems field as a whole:

- There is a growing need for far better methods of dynamic systems modelling in this area, with a particular focus on accurate, nonlinear models, which capture more relevant dynamics based either on existing data or data taken during care. In particular, better modelling of insulin kinetics, glucose appearance from the gut, and endogenous glucose production, all of which are highly variable in critical illness and difficult to measure directly would significantly improve model-based control accuracy. However, these models must also be simultaneously identifiable from the data available, which could be used to efficiently implement personalised, model predictive forms of control. Thus, model creation, analysis, and identifiability, all of which are core areas of control systems engineering, are an increasing need in this field to advance the models and methods, as the potential of real-time control emerges in the area.

- There is a growing need to better process those measurements available, such as those from continuous glucose monitors, where, in particular, the identification of sensor drift or unusual measurements indicating sensor fault would dramatically enhance control capability. Again, these points cross into traditional and current areas of control systems engineering.

- Finally, there is a major need for better, and computationally faster optimisation methods for parameter identification, both deterministic, direct approaches, as well as approaches including or solely using machine learning and bigger data sets. Better, faster identification of more parameters to maximise the data available will enable better, more accurate control, and is a direct application of control systems engineering to this biomedical problem.
All three points above are noted to first show the crossover of these areas with traditional control systems theory and methods, as well as to drive home the key areas where current methods are lacking, and new approaches could have significant impact on the field, as well as on patients.
5.0 Conclusions:

The systematic review presented has addressed model-based, personalised glycemic control. It has presented the problem and the current state of the art. There has been an ongoing focus to relate the ideas and current state back to traditional control systems methods and engineering approaches. The review shows that while the field itself is vibrant, the results to date are narrow and there is significant room for innovation and new approaches, particularly as more and more data becomes available to engineers, and clinicians become increasingly willing to take on more novel approaches driven by rapid changes in technology and the ability to measure and control patients. These changes will only occur more rapidly as both technology and economics drives a need for both better patient care and outcomes, as well as a need for greater productivity so the care remains affordable for patients and payers. There is thus significant impetus to see control systems and automation in this area, as well as other areas of medicine, and a range of technologies increasingly capable of enabling next-generation, personalised, predictive, and productive forms of care.
6.0 References:


