

Full Length Article

Is normoglycemia a reachable state in safe, effective glycemic control in critical care? A review and steady-state analysis showing the need for dual insulin and nutrition control

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ABSTRACT

Critically ill patients frequently experience stress-induced hyperglycemia, leading to increased morbidity and mortality. Safe, effective glycemic control (GC) with insulin therapy alone has proven difficult to achieve consistently. One successful, personalized and model-based GC system overcomes this issue by modulating nutrition, as well as insulin, to control glucose levels. However, no other published protocol takes this approach. Thus, the question arises on whether both control inputs are required to be able to reach normoglycemia safely and effectively.

This work uses a well-validated metabolic system model to show how nonlinear insulin saturation dynamics, and the interaction of insulin sensitivity with nutrition and insulin inputs, combine to require modulation of nutrition as well as insulin to achieve a desired outcome glycemic level – effectively analysing the ability of glycemic control to reach normoglycemia. In doing so, it also shows without nutrition control, insulin resistant patients will be uncontrollable to a given glycemic level in a theoretical sense and derives the mathematical conditions when this situation occurs. Next, it derives how insulin sensitivity variability, common in intensive care unit (ICU) patients as condition evolves, leads to changes in glucose levels, increasing hyper- and hypoglycemic risk if nutrition is not controlled to allow lower insulin doses and thus a reduced range of glycemic variability. The analysis is augmented by a shared visual analysis, illustrating the metabolic dynamics to provide better insight and understanding.

The primary result is a mathematical, clinical, and control centred review and analysis of the clinical glycemic control problem in the context of assessing the conditions for normoglycemia to be reached safely and consistently. It mathematically demonstrates the necessity of using nutrition modulation, along with controlling insulin, to achieve safe, effective GC for all patients when nonlinear clinical and physiological limits are considered. This main outcome is contrary to a lot of current clinical practice and thinking, and contrary to a strictly mathematical analysis without consideration of known, but often ignored, nonlinear physiological and clinical limitations.

1. Introduction

Poor glycemic control (GC) and hyperglycemia are prevalent in critical care (McCowen, Malhotra & Bistran, 2001; Dungan, Braithwaite & Preiser, 2009; Chase, Benyo & Desaive, 2019). Inability to avoid hypoglycemia and glycemic variability, both associated with increased risk of death (Egi et al., 2006; Egi & Bellomo, 2009; Egi et al., 2010; Finfer

et al., 2012; Penning et al., 2015; Signal et al., 2012; Krinsley & Preiser, 2015), with almost all protocols is a major hazard for patients and care (Griesdale et al., 2009; Yamada et al., 2017). The result is major debate over GC (Gunst & Van den Berghe, 2016; Marik, 2016; Preiser & Straaten, 2016), rising targets or permissive hyperglycemia (Moghissi et al., 2009), and an inability to see the benefit of emerging glycemic control (GC) methods (Chase & Dickson, 2017), despite several reviews

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on the topic (Chase, Benyo & Desai, 2019; Chase et al., 2018; Chase et al., 2018; Preiser et al., 2016; Krinsley et al., 2017; Vanhorebeek, Langouche & Van den Berghe, 2006).

A recent analysis of patient-specific metabolic variability over time clearly showed survivors and non-survivors with glycemic control were equally difficult to control, with no impact or association with severity of illness or diagnosis (Uyttendaele et al., 2017). More specifically, the inter- and intra- patient variability and its evolution over time, which are what makes control difficult (Chase et al., 2011; Chase et al., 2011; Chase, Desai & Preiser, 2016), were equivalent between survivors and non-survivors. Thus, it should be possible to achieve equivalent safe, effective control for all patients regardless of eventual patient outcome mortality, or other factors. More succinctly, patients who (eventually) die are not more difficult to control, and thus the associations of mortality with high variability and increased hypoglycemia (Egi et al., 2006; Egi & Bellomo, 2009; Egi et al., 2010; Finfer et al., 2012; Penning et al., 2015; Signal et al., 2012; Krinsley & Preiser, 2015; Furushima et al., 2020) are due to poor control of glycemia, rather than patient severity. This conclusion supports studies showing success in GC (Chase et al., 2008; Krinsley, 2004; Van den Berghe et al., 2001; Van den Berghe et al., 2006), and a high level of evidence linking increased time in intermediate glycemic bands with improved mortality and morbidity outcomes (Penning et al., 2015; Signal et al., 2012; Krinsley & Preiser, 2015; Chase et al., 2010; Penning et al., 2014; Lanspa et al., 2019), and thus a large amount of physiological evidence showing the negative impact of higher glucose levels on cells, tissues, and immune response (Ingels, Vanhorebeek & Van den Berghe, 2018; Lush & Kvietys, 2000; Fernandez-Real et al., 2003; Chase et al., 2006; Monnier et al., 2006; Weekers et al., 2003) and benefits of insulin (Vanhorebeek, Langouche and Van den Berghe (2006), Vanhorebeek, Langouche and Van den Berghe (2005)).

This summarised evidence points strongly towards the need for personalised GC to manage the significant inter- and intra- patient variability (Pretty et al., 2012) driving poor control and increased hypoglycemia (Chase et al., 2011; Wernerman et al., 2019). Personalised model-based GC is an emerging tool (Chase, Benyo & Desai, 2019; Chase et al., 2018; Chase et al., 2023), built on control systems modeling and methods, and there are a handful of validated GC protocols with proven clinical results (Evans et al., 2011; Evans et al., 2012; Fisk et al., 2012; Stewart et al., 2016; Dubois et al., 2017; Amrein et al., 2010; Blaha et al., 2016; Tanenberg et al., 2017; Seret et al., 2026). These protocols employ digital twin models, personalised using clinical data to identify patient-specific parameters, which are then used to guide care (Chase, Benyo & Desai, 2019; Chase et al., 2018; Chase et al., 2023).

All these protocols include physiological models of insulin-glucose metabolism and identify a patient-specific insulin sensitivity (SI) parameter to guide care, in whole or in part. However, they differ in two key respects. First, only the stochastic targeted (STAR) protocol has fully validated its virtual patient model with independent data and cross validation (Chase et al., 2010; Dickson et al., 2018), as well as accurate prediction of clinical trial results before implementation (Fisk et al., 2012; Uyttendaele et al., 2018). Second, and critically only STAR modulates nutrition, in addition to insulin dosing, to achieve tight, safe control across multiple centres (Suhaimi et al., 2010; Stewart et al., 2018).

Nutrition delivery is a second potential metabolic control input but is also a highly debated topic in intensive care unit (ICU) medicine (Wernerman et al., 2019; Cahill et al., 2010; Heyland, Cahill & Day, 2011; Heyland, 2013; Weissman, 1999; Wischmeyer, 2013). Several studies have shown <100% goal feed may yield a best delivery rate for improved outcomes and/or increased nutrition delivery early in ICU stay has no benefit (Cahill et al., 2010; Casaer et al., 2013; Martin et al., 2004; Singer et al., 2011). Typically, nutrition is left to clinical discretion and local standards and is often not accounted for in glycemic control protocols, thus ignoring a potential control input and possibly limiting the level of control possible. STAR has successfully delivered

high levels of nutrition, while also controlling its delivery, to achieve safe, effective control (Stewart et al., 2018; Stewart et al., 2018), which implies it controls nutrition to a patient's ability to utilize it, simultaneously controlling glycemia and optimising nutrition delivery.

However, controlling nutrition as part of this clinical control scheme is a more "radical" approach, and STAR is the only glycemic control protocol to do so. A clear proof of the need to control nutrition delivery, particularly in the early first 1–2 days of stay when patients are most acute, insulin resistant, and variable (Uyttendaele et al., 2017; Pretty et al., 2012), would help unify thinking about how to achieve safe, effective GC. The STAR protocol directly manages inter- and intra- patient variability in SI using stochastic models to optimise the dose and modulation of both insulin and glucose (Uyttendaele et al., 2018; Lin et al., 2006; Lin et al., 2008; Davidson et al., 2019). Since SI and its variability drive metabolic response and thus glycemic levels, it is necessary to clearly demonstrate the input-output interaction of SI , insulin and nutrition administration, and resulting glycemic control outputs to show safe, effective glycemic control requires modulating both insulin and nutrition.

This article hypothesises there is a need to control nutrition to achieve full control. It further hypothesises it will not be possible to reach normoglycemic glucose states, and thus to provide effective glycemic control, in some situations with insulin alone (i.e. without also controlling nutrition inputs). The analysis presented is thus one of demonstrating the ability or inability to reach normoglycemia in model-based glycemic control.

The study reviews the necessary metabolic modeling and presents a mathematical analysis demonstrating the limits of control, and from them the necessity of controlling nutrition, along with insulin, to achieve safe, effective glycemic control. Particularly, in the presence of well-documented nonlinear saturation dynamics. It defines the context within which controlling, in particular reducing, nutrition is required to maintain a goal glycemic level as well as to minimise risk from intra-patient variability, thus showing the necessity of managing nutrition, as well as insulin. The entire analysis is presented in the context of a well-validated and clinically used metabolic digital twin model and a graphical schematic of the same dynamics analysed mathematically to hopefully enhance comprehension for all readers.

2. Methods

2.1. Model and insulin sensitivity (SI)

The metabolic system dynamics of the ICING (Intensive Control Insulin Nutrition Glucose) physiological model used in STAR are defined (Lin et al., 2011):

$$\dot{G} = -p_G G(t) - SI * G(t) \frac{Q(t)}{1 + a_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \quad (1)$$

$$\dot{I} = -n_k I(t) - n_L \frac{I(t)}{1 + a_I I(t)} - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_{en}(G)}{V_I} \quad (2)$$

$$\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + a_G Q(t)} \quad (3)$$

Where $G(t)$ is blood glucose (mmol/L), $I(t)$ is plasma insulin (mU/L), $Q(t)$ is interstitial insulin (mU/L), $P(t)$ is plasma glucose from nutrition intake (mmol/min), $u_{ex}(t)$ and $u_{en}(G)$ are exogenous insulin delivery and endogenous insulin secretion rates (mU/min), where the latter is a function of glucose level, $G(t)$, and can be modeled using feedback control paradigms (e.g. (Othman et al., 2017; Toffolo et al., 2006; Othman, Docherty & Chase, 2014; Steil et al., 2003)). Finally, EGP and CNS are population values for endogenous glucose production and the brain's non-insulin mediated glucose uptake, and the critical value identified from data (typically) is insulin sensitivity, SI , (L/mU/min). All parameter values and the full detailed model can be found (Stewart

Table 1

Coefficients used to determine an ICU patients daily caloric goal using STAR.

Frame Size (<i>F</i>)	Small	Average	Big
	0.9	1.0	1.1
Age (<i>A</i>)	≤39 1.1	40–59 1.0	60–79 0.9 ≥80 0.8
Gender (<i>G</i>)	Male 1.0	Female 0.8	
Formula For Goal Feed			
$A * F * G * 80 * 25 = \text{kCal Goal/Day}$			

et al., 2018) and in the Supplemental Appendix, but are not needed in this analysis, which is kept at the level of these variables and parameters.

Importantly, in the clinical use of this model with STAR, nutrition is modulated on a patient-specific goal feed basis. In particular, the American College of Chest Physicians (ACCP) caloric goal of 25kcal/kg/day (Stewart et al., 2018; Cerra et al., 1997) is used for setting the goal total nutrition delivery. Patients are also not always weighed so this ACCP caloric goal can be approximated by first assuming an 80 kg individual and then modifying this value based on frame size (subjective), age, and sex, using Table 1 with a resulting 20–30% range possible in goal feed rate. Note the weight approximation and other values can be updated to meet any current standards or to set goal feed by day and/or include other clinical factors (Wernerman et al., 2019; Preiser et al., 2015; Dupuis et al., 2026; Reignier et al., 2025). Equally, if weight is measured it can be updated regularly or the estimated frame size, which is a surrogate, may be adjusted.

In clinical use, model-based insulin sensitivity (*SI*) and its hour-to-hour relative change captures inter- and intra- patient metabolic ability for insulin mediated glucose uptake (Uyttendaele et al., 2018; Lin et al., 2006; Lin et al., 2008; Davidson et al., 2019). Integral based identification can be used to identify *SI* with clinical data (Docherty et al., 2011; Docherty, Chase & David, 2012). The model has been validated in clinical use in STAR (Evans et al., 2011; Evans et al., 2012; Fisk et al., 2012; Stewart et al., 2016; Seret et al., 2026) and a NICU version (Stewart et al., 2016; Uyttendaele et al., 2018; Knopp et al., 2019; Le Compte et al., 2012), insulin sensitivity testing (McAuley et al., 2011; Docherty et al., 2009; Docherty et al., 2011; Docherty et al., 2011), and as virtual patients for design and analysis of GC protocols (Dickson et al., 2018; Uyttendaele et al., 2019; Lonergan et al., 2006; Seret et al., 2025). It is thus a proven foundation for this

analysis. Fig. 1 shows how this model is applied clinically in a control loop around the patient and this personalised model for both ICU and neonatal ICU (NICU), where the nurse remains in the loop although it could be automated with access to devices and using continuous glucose monitors (CGMs) (Chase et al., 2023).

Notably, STAR uses a stochastic model of future insulin sensitivity, *SI*, based on its current identified value (Uyttendaele et al., 2018; Lin et al., 2006; Lin et al., 2008; Davidson et al., 2019) to assess the risk of hypo- or hyper- glycemia for a given insulin-nutrition intervention using these models. It creates a novel risk-based dosing approach (Chase et al., 2021). Fig. 2 shows the stochastic models used in both adult ICU and NICU cases for just 1-hour ahead, which can be relatively very large away from the median hour-to-hour change of zero. Fig. 3 shows STAR patient examples with blood glucose, identified *SI*, and associated interventions and model fit to illustrate both stable and rapidly changing *SI* over time, and resulting changes in interventions and with relatively constant impact on BG. Changes in *SI* can be relatively very rapid, with some major changes occurring as fast as 15–30 min (Wong et al., 2006).

2.2. Proof and steady state analysis approach

The approach to this proof is based on steady state analysis of Eqs. (1)–(3). While “static” it demonstrates the reachable steady states, where steady state values for $G(t)$, $I(t)$, $Q(t)$, and $P(t)$ are defined by setting:

$$\dot{G} = \dot{Q} = \dot{I} = 0 \quad (4)$$

Solving for the resulting steady state values of $G(t)$, $I(t)$, $Q(t)$, and $P(t)$, will yield steady state approximations used for the analysis presented in the next section.

For this analysis, Eq. (1) is simplified by grouping terms, yielding:

$$G\dot{(t)} = -p_G G(t) - SI * G(t)\bar{Q}(t) + \bar{P}(t) \quad (5)$$

Where the values $\bar{Q}$ and $\bar{P}$ are defined:

$$\bar{Q} = \frac{Q(t)}{1 + a_G Q(t)} \quad (6)$$

$$\bar{P} = \frac{P(t) + EGP - CNS}{V_G} \quad (7)$$

Where both are $\bar{Q}$ and $\bar{P}$ functions of time.

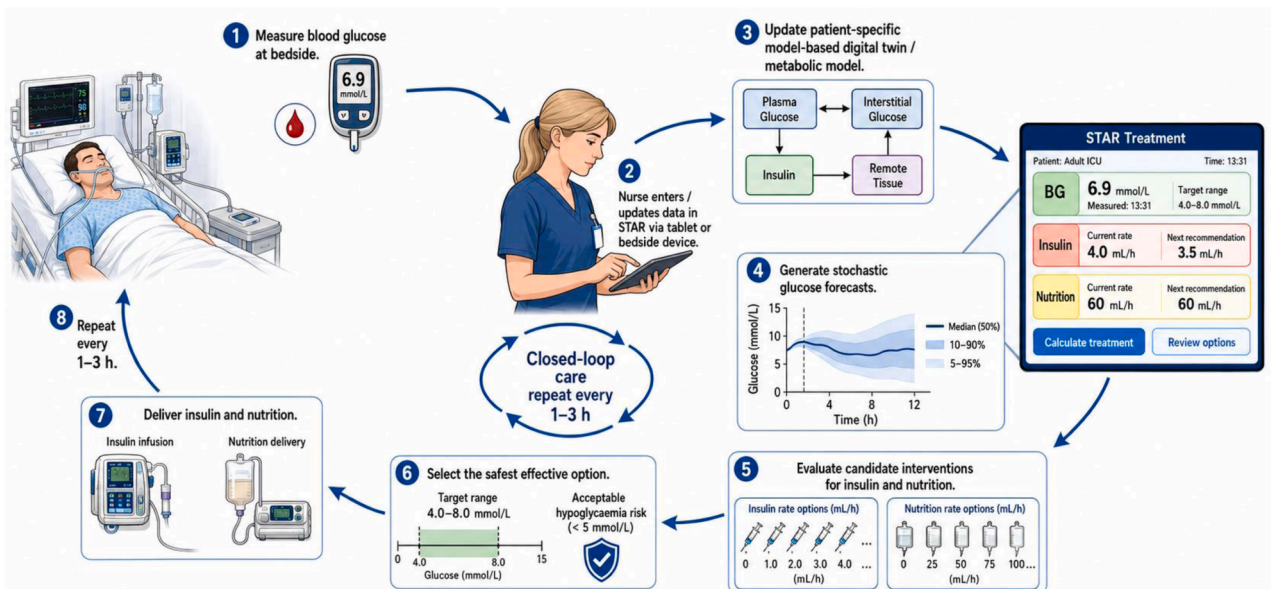


Fig. 1. Control loop for adult ICU use of STAR. The NICU version uses a 2–4 h control loop, but the same overall digital twin model-based approach.

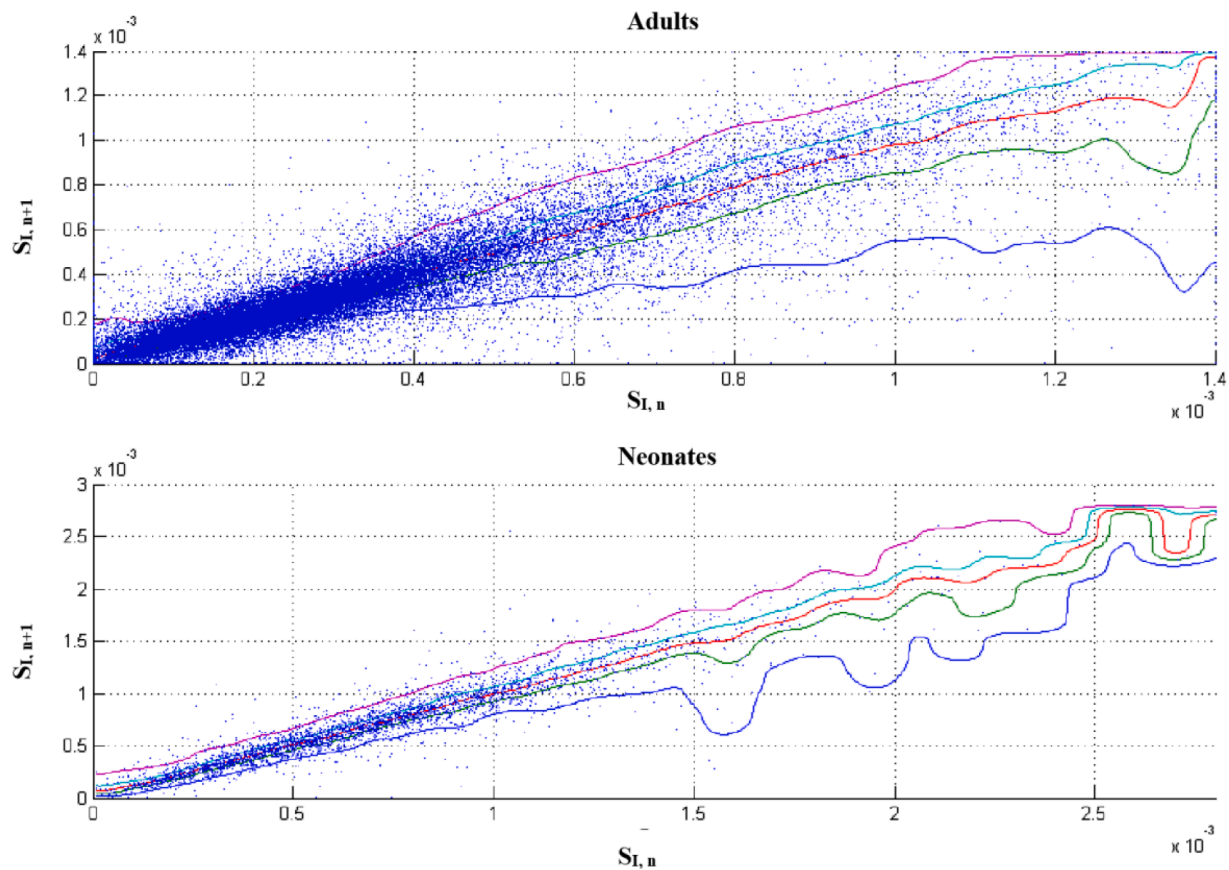


Fig. 2. Hour-to-hour variation of SI (current time on x-axis and hour $n + 1$ on y-axis) with percentiles for stochastic models created for adult ICU (top) and pre-term NICU neonates data from LeCompte et al. (2009) (bottom). Axes are scaled differently by $\sim 2x$, and ranges for the 5th, 25th, 50th, 75th and 95th percentiles are more variable in regions of scarce data.

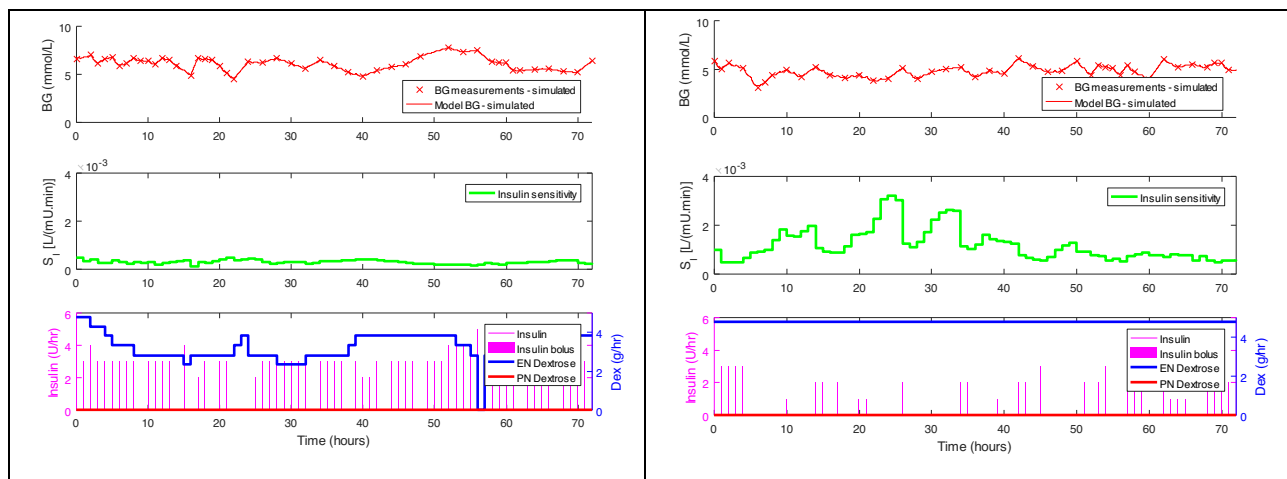


Fig. 3. Example patients from clinical data, showing measured blood glucose (BG), clinically delivered insulin and nutrition, and model fitted insulin sensitivity (SI). A more 'stable' SI profile (left) and more variable SI profile (right).

In particular, Eq. (6) captures insulin effect and its saturation (Docherty et al., 2010; Natali et al., 2000; Prigeon et al., 1996), which limits the maximum value of $\bar{Q}$ to a value, $\bar{Q}_{Max}$. Eq. (7) is net non-insulin mediated glucose balance. Finally, non-insulin-mediated uptake, $-p_G G(t)$, is relatively small and can be ignored in this analysis for simplicity (Lin et al., 2011).

In the complementary mechanistic graphical approach presented here, Eqs. (1)–(7) defining the model are shown in Fig. 4. The illustrated

model includes insulin and nutrition administration and appearance, and their levels. It also shows insulin clearance routes and uptake of glucose into the cells, and the role of insulin sensitivity, SI , where lower SI requires more insulin to remove the same amount of glucose. The proportions and numbers are illustrative only.

Importantly, the variables of Eqs. (1)–(7) are nonlinearly associated so their changes over time in the schematic of Fig. 4 cannot be shown directly. In particular, SI changes over time as shown in Figs. 2–3. Thus,

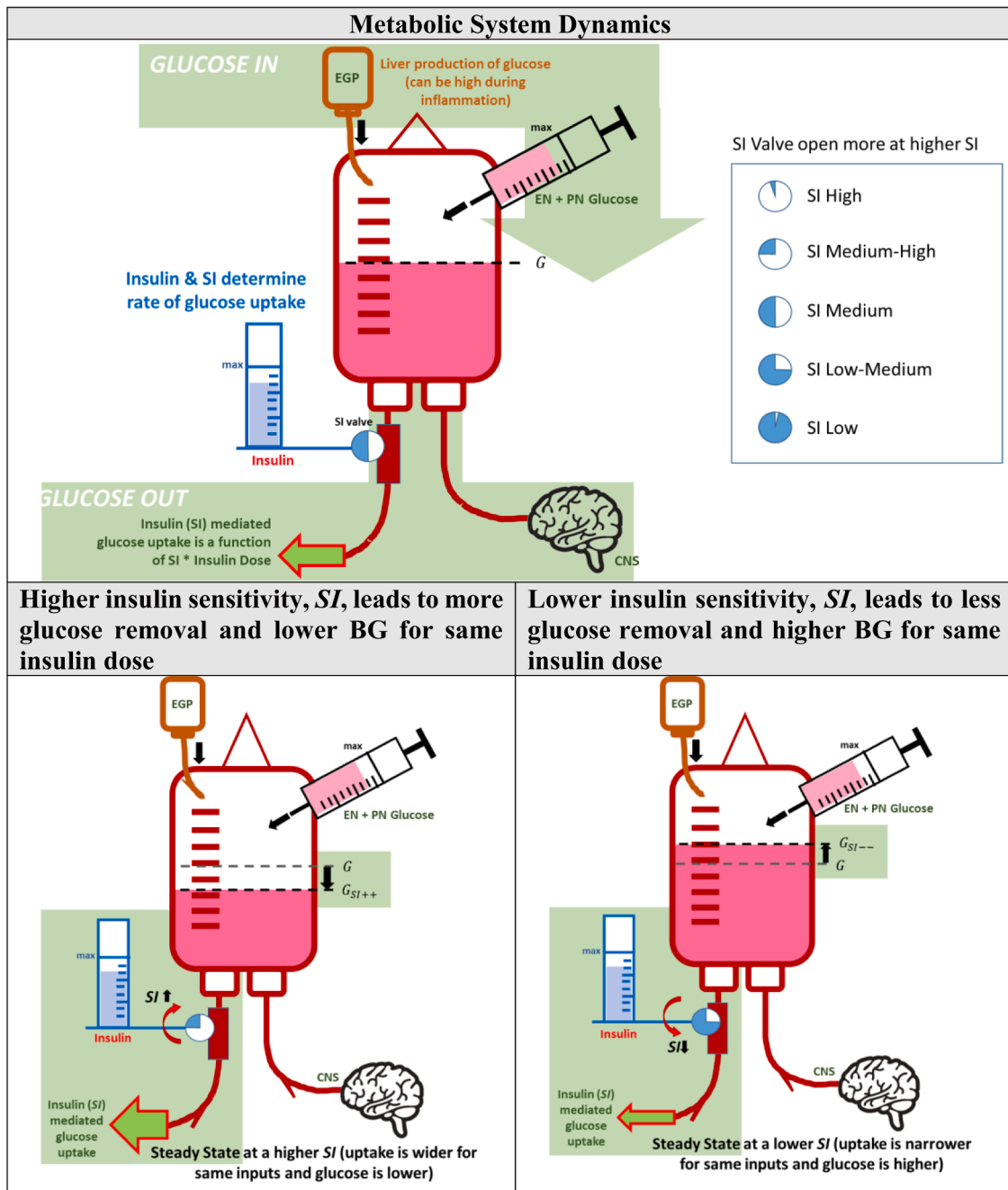


Fig. 4. A graphical representation of Eqs. (1)-(7) showing insulin administration, net glucose appearance from nutrition and other sources, and their interaction to remove glucose to the cells, including the role of insulin sensitivity, where lower SI requires more insulin to remove the same amount of glucose. The blue bar on the left shows insulin level, the syringe shows insulin dose, including endogenous secretion, up to or beyond a maximum value, and the width of the green arrow shows the amount of removal in total as moderated by the valve which is the insulin sensitivity regulating glucose removal per unit of insulin delivered. The bag shows the BG level relative to a steady state due to some change.

the interventions are modified as shown in Fig. 3, with a resulting change in blood glucose. With both physiological and input variables changing it is not possible to relate an output glucose change to any one change using clinical data because not enough variables are fixed. Hence, individual changes over time of these variables and inputs with all else equal can only be shown, even in steady state analysis, for limited cases which don't occur in the reality of clinical use.

2.3. Main glycemic control questions and reachable glucose states

The main question asked is under what patient and control input

conditions is normoglycemia reachable, safely and effectively. Thus, using steady state analysis to demonstrate the effective reachable glycemic states, two main questions are asked:

- **Equilibrium Question:** Defining the relationship of a range of steady state input values, SI , and outcome steady state glycemia, can any patient achieve normoglycemia controlling only insulin inputs?
- **Variability Question:** What is the impact of SI variability, $\pm \Delta SI$, on outcome steady state glycemia and its relationship to nutrition inputs?

The Equilibrium Question addresses control efficacy in terms of the ability to reach any specific glycemic state using insulin alone. The Variability Question assesses safety, where metabolic variability is a major cause of hypoglycemia and poor control (Egi et al., 2006; Egi & Bellomo, 2009; Chase et al., 2011; Pretty et al., 2012; Ali et al., 2008; Bagshaw et al., 2009). All results are defined in terms of the parameters of the model in Eqs. (1)-(3).

More specifically, analytical results are derived to show whether or not it is possible to achieve any desired steady state glucose level without also controlling nutrition delivery, in addition to insulin. The result is extended to assess the need to modulate nutrition delivery to manage intra-patient variability over time and ensure safe control. In this sense, the analysis presented is demonstrating whether constant, clinically specified normoglycemic or lower glucose levels can be “reached” and under what conditions it would require controlling nutrition as well as insulin. Thus, overall, the analysis presented addresses if normoglycemia is reachable in this glycemic control problem.

3. Results: steady state analyses

3.1. Equilibrium question

The steady state form of Eq. (5) is defined:

$$\dot{G} = 0 = -p_G G_{ss} - SI * G_{ss} * \bar{Q}_{ss} + \bar{P}_{ss} \quad (8)$$

Solving for the steady state, G_{ss} , and letting $p_G \rightarrow 0$ for simplicity, as this term is small, yields:

$$G_{ss} = \frac{\bar{P}_{ss}}{p_G + SI * \bar{Q}_{ss}} \approx \frac{\bar{P}_{ss}}{SI * \bar{Q}_{ss}} \quad (9)$$

Where the approximation is due to the very low value of p_G and the overall non-insulin-mediated glucose uptake term in general when compared to insulin-mediated uptake in these patients (Lin et al., 2011), and is thus a simplification making the derived results clearer without losing generality.

Further, the steady state effective insulin, $\bar{Q}_{ss} = Q_{ss} / (1 + a_G Q_{ss})$, is defined using Eqs. (2), (4) and (6) and steady state plasma insulin, I_{ss} , is defined using Eqs. (3)-(4), yielding:

steady state results in Eqs. (10a,b) are complex due to the coupling of Eqs. (2)-(3) and the saturation of insulin uptake in Eq. (2) via the term a_G and insulin clearance in Eq. (3) via the term with a_I . Finally, it is important to note Eqs. (10a,b) show the insulin dynamics at steady state, assuming inputs $u_{ex}(t)$ and $u_{en}(G)$ are steady, but they are also not necessary for the glucose control questions posed beyond demonstrating saturation dynamics of glucose removal.

However, simulating and plotting for typical parameter values yields saturated curves for Eq. (10a) the effective insulin for glucose removal, and thus demonstrates how insulin-mediate glucose removal is saturated and has an upper limit. Thus, Fig. 5 illustrates this dynamic in Eq. (9). It shows how this balance can be used proportionally, but only if insulin saturation effects have no impact and insulin levels remain below the maximum level in these figures.

Saturation occurs at relatively high insulin administration levels of 6–8 U/hour (Docherty et al., 2010; Natali et al., 2000; Prigeon et al., 1996; Chase et al., 2005; Thorsteinsson, 1990), typically only given in the most insulin resistant (low SI) patient hours in selected patients (Ormsbee, Knopp & Chase, 2021). Thus, at higher insulin sensitivity, where glucose is removed with proportionately less insulin, this proportion can be used to increase or maximise nutrition administration and provide effective control to desired glycemic level, G_{ss} . However, at low insulin sensitivity, glucose removal saturates, and glucose levels will rise for any added nutrition input, thus showing how nutrition needs to be modulated to maintain normoglycemia (in these cases).

Thus, mathematically, insulin saturation effects yield a maximum effective insulin:

$$\bar{Q}_{ss} \rightarrow \bar{Q}_{ss,Max} \quad (11)$$

Where the insulin available for uptake saturates at a maximum value (Docherty et al., 2010; Natali et al., 2000; Prigeon et al., 1996). Fig. 6 illustrates this insulin saturation case in the same graphical manner as Fig. 5, showing how no further glucose can be removed at this level, leading to additional, ineffective insulin in the blood (right panel). The bottom panel of Fig. 6 shows simulation for reasonable exogenous insulin values (u_{ex}) of Eqs. (2)-(3) to show how the value of $\bar{Q}_{ss}$ in Equation (10) saturates over time with decreasing peak value as exogenous input rises, showing clearly the limitation in increasing insulin inputs

$$\frac{Q_{ss}}{1 + a_G Q_{ss}} = \frac{n_I}{n_C} \left(I_{ss} - \frac{-(n_I a_G I_{ss} - n_I - n_C) + \sqrt{(n_I a_G I_{ss} - n_I - n_C)^2 + 4n_I^2 a_G I_{ss}}}{2n_I a_G} \right) \quad (10a)$$

and how the value of $\bar{Q}_{ss,Max}$ is reached.

Nutrition administration is limited so the following range must hold:

$$I_{ss} = \frac{-\left(n_k + n_I + n_L - a_I \left(\frac{u_{ex} + (1-x_L)u_{en}}{V_I} + n_I Q_{ss} \right)\right) + \sqrt{\left(n_k + n_I + n_L - a_I \left(\frac{u_{ex} + (1-x_L)u_{en}}{V_I} + n_I Q_{ss} \right)\right)^2}}{2(n_k + n_I)a_I} + \frac{4(n_k + n_I)a_I \left(\frac{u_{ex} + (1-x_L)u_{en}}{V_I} + n_I Q_{ss} \right)}{2(n_k + n_I)a_I} \quad (10b)$$

Where both equations have kept the positive root of the resulting quadratic equations in solving for the steady state values. Note, the

$$0 \leq \bar{P}_{ss} < \infty \quad (12)$$

Where the infinity is an obviously limited value but observed clinical nutrition delivery rates can be very large compared to the maximum

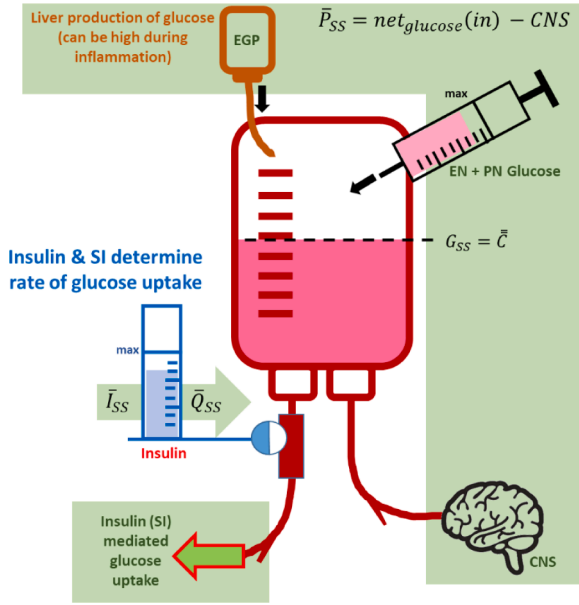


Fig. 5. Steady state dynamics of Eq. (9): showing how, without insulin saturation, insulin and nutrition levels may be raised in balance to achieve the same steady state glucose, G_{ss} , outcome. IMGU is insulin-mediated glucose uptake.

insulin available for insulin mediated uptake in Equation (10), leading to unconstrained rises in glucose level.

Hence, any specified goal blood glucose value of $G_{ss} = \bar{C}$ may be obtained up until insulin saturates at $\bar{Q}_{ss,Max}$, which is usually at doses of 6–8 U/hour in adults (Natali et al., 2000; Prigeon et al., 1996). After this value is reached, any further nutrition input will raise glucose levels. Equally, for any given SI in Eq. (9) the value of $\bar{Q}_{ss,Max}$ will continue to rise, increasing the insulin-mediated glucose removal possible. This dynamic behavior is shown in Fig. 6.

Thus, for any given SI value, and considering insulin saturation limits, there is a maximum value of $\bar{P}_{ss}$ beyond which hyperglycemia occurs, as shown in Fig. 6 (top), and defined:

$$\bar{P}_{ss,Upper}^C = (SI * \bar{Q}_{ss,Max}) = f(SI) \quad (13)$$

Where both Eq. (13) and the results of (Stewart et al., 2018) show this upper level of nutrition delivery to maintain goal glycemic level, $\bar{C}$, are patient-specific and time-varying as a function of SI .

Therefore, it is necessary to modify nutrition delivery as a function of SI to achieve glycemic goal levels. The most insulin resistant patients (low SI) will otherwise become hyperglycemic. As SI rises with changing patient condition (Pretty et al., 2012), the need to control nutrition to achieve a desired glycemic level will go away, leaving the condition in Fig. 5.

In short, summarising Figs. 4–6 and Eqs. (9)–(13), insulin saturation limits the insulin-mediate glucose removal rate at (relatively) clinically high insulin infusion rates. Up to this point more insulin yields a proportional removal of glucose. Thus, the lower the insulin sensitivity (SI) the lower the rate of removal and the more likely it is to be limited by saturation. Hence, insulin saturation limiting glucose removal also leads to a limited maximum nutrition rate at which normoglycemia can be maintained. Beyond this nutrition administration leads to increasing glucose levels which cannot be reduced with insulin – leaving only the reduction of nutrition to achieve this goal (if desired, clinically).

3.2. Variability question

For a given G_{ss} steady state level, defining $SI \rightarrow SI \pm \Delta SI$ in Eq. (9)

yields a new $G_{ss}^* \neq G_{ss}$ value, which varies from the G_{ss} value based on the change in SI , and is defined:

$$G_{ss}^* = \frac{\bar{P}_{ss}}{(SI \pm \Delta SI) * \bar{Q}_{ss}} \quad (14)$$

Where the change in steady state glycemia due to a variation in insulin sensitivity (ΔSI) using Eqs. (9) to (14) is: $\Delta G_{ss} = G_{ss}^* - G_{ss}$.

In short, Eq. (14) defines (all else equal) the new steady state glucose value as it moves from G_{ss} to G_{ss}^* due to a change in insulin sensitivity. Algebraic manipulation and using Eqs. (9) and (14) in $\Delta G_{ss} = G_{ss}^* - G_{ss}$ yields the variation, ΔG_{ss} :

$$\Delta G_{ss} = \left(\frac{\bar{P}_{ss}}{SI \bar{Q}_{ss}} \right) \left(\frac{\Delta SI}{SI \pm \Delta SI} \right) = \mp G_{ss} \left(\frac{\Delta SI}{SI \pm \Delta SI} \right) \quad (15)$$

Where the differences in $\pm$ and $\mp$ signs should be noted, and where the second definition manipulates the results so ΔG_{ss} is a function of G_{ss} and the percentage change in SI . In short, Eq. (15) defines the change in glucose is a function of the change in SI where rising SI yields falling glucose, and vice versa, as expected physiologically.

Now, consider the two cases: $\Delta SI > 0$ and $\Delta SI < 0$ for rising and falling SI values, respectively. Each case yields different ΔG_{ss} , due to type of SI variability, which are defined:

$$\Delta SI > 0 \rightarrow \Delta G_{ss} = -G_{ss} \left(\frac{\Delta SI}{SI + \Delta SI} \right) < 0 \quad (16)$$

$$\Delta SI < 0 \rightarrow \Delta G_{ss} = G_{ss} \left(\frac{\Delta SI}{SI - \Delta SI} \right) > 0 \quad (17)$$

Where when $\Delta SI > 0$, glucose falls, and when $\Delta SI < 0$, glucose rises, as expected physiologically for rising or falling insulin sensitivity, and as equally reflected in the mathematics. These dynamics are shown graphically in the same format in Fig. 7.

Therefore, to account for risk in changing patient condition represented by changes in SI given by $\pm \Delta SI$, nutrition should be controlled or modulated to (also help) manage any future variation of SI . In particular, nutrition should be controlled to a lower rate so the resulting required insulin dose required will simultaneously:

- Not saturate while maintaining a goal $G_{ss} = \bar{C}$ glycemic level based on the Equilibrium Question
- Maintain G_{ss} within an accepted normoglycemic range for any rise in glucose level due to a reduction in insulin sensitivity, per the $SI-\Delta SI$ case in Eq. (17)
- Avoid hypoglycemia in the case of a rise in SI for the $SI+\Delta SI$ case in Eq. (16)

Thus, restricting nutrition, which in turn lowers insulin requirements, may also be a means to avoid hypoglycemia and hyperglycemia due to variability. Thus, the Variability Question addresses safety from hyper- as well as hypo- glycemia.

These contrasting points in the prior two paragraphs further highlight the difficulty of this balance and control problem. Importantly, reducing nutrition as a function of the overall glycemic control approach reduces the required insulin dose to maintain a fixed goal glycemia (Figs. 5–6). As a result, the impact of SI variability due to variability ($\pm \Delta SI$) is reduced per Eq. (15). This dynamic of reducing insulin (and nutrition) to narrow the range of glycemic variability for safety from hypo- and hyper- glycemia is illustrated in Fig. 8.

Overall, reducing nutrition reduces the required insulin all else equal, and thus mitigates the impact of SI variability by avoiding higher insulin doses while controlling glucose to a desired level. STAR makes these choices automatically by knowing the 5–95th range of likely $\pm \Delta SI$ changes over a forthcoming insulin dosing interval, and using this knowledge in a way similar to Eq. (15) to choose insulin and nutrition

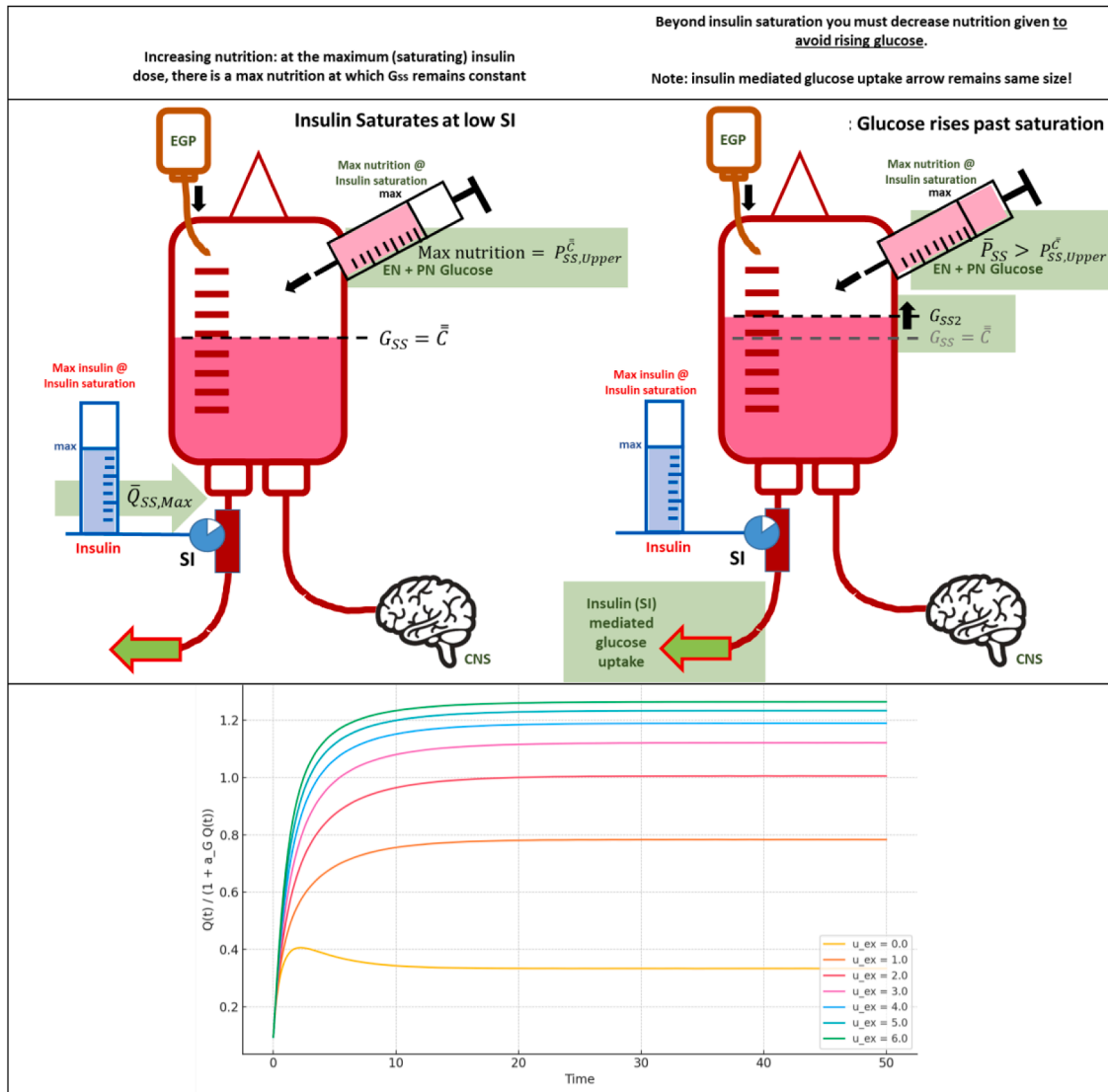


Fig. 6. Top: Insulin saturation limits the maximum insulin utilisation, and thus limits insulin-mediated glucose uptake to cells. Beyond saturation any added glucose input (shown) or reduction in SI causing glucose to rise (not shown) leads to higher blood glucose as insulin has no more effect to remove glucose. Bottom: The bottom panel shows simulations using typical parameter values and a range of exogenous insulin input values to show how effective insulin saturates despite towards a fixed value as exogenous insulin inputs increase.

dose recommendations and thus account for both insulin saturation in achieving target glycemia, as well as potential future variability.

3.3. Summary and reachable glucose states

The overall results demonstrate the reachable glucose states using this clinically well-validated model. In particular, the following conditions hold and are demonstrated mathematically using the steady state analysis presented:

- Nutrition can be increased to any level, if and only if the insulin required to remove excess blood glucose with increased nutrition does not saturate.
- Insulin saturation implies a maximum level of insulin-mediated glucose removal.
- The lower the insulin sensitivity, reflective of patient condition and counter-regulatory responses, the lower this total insulin-mediated glucose removal and the lower the total nutrition which may be delivered while maintaining normoglycemia.

- Lower insulin doses also mitigate risk of large(r) glycemic excursions due to variability in insulin sensitivity, but require concomitantly lower nutrition doses, all else equal.

Thus, insulin saturation and insulin sensitivity can limit the reachable normoglycemic states in ICU glycemic control unless nutrition modulation is considered as a control input beyond the typical use of insulin alone in all protocols other than STAR and its predecessor SPRINT (Chase et al., 2008).

4. Discussion

The analysis of Eqs. (9) and (15)–(17), as illustrated in Figs. 5–8, clearly shows nutrition has to be controlled, and typically reduced, to maintain a desired or set glycemic level in the case of low SI and/or high insulin doses. In particular, nutrition control is required to account for insulin dose saturation. This saturation behavior is a patient specific, time varying effect leading to hyperglycemia in the face of uncontrolled and pre-set nutrition rates, and may also lead to hypoglycemia due to SI variability, as well. Hence, the overall results characterise an operating

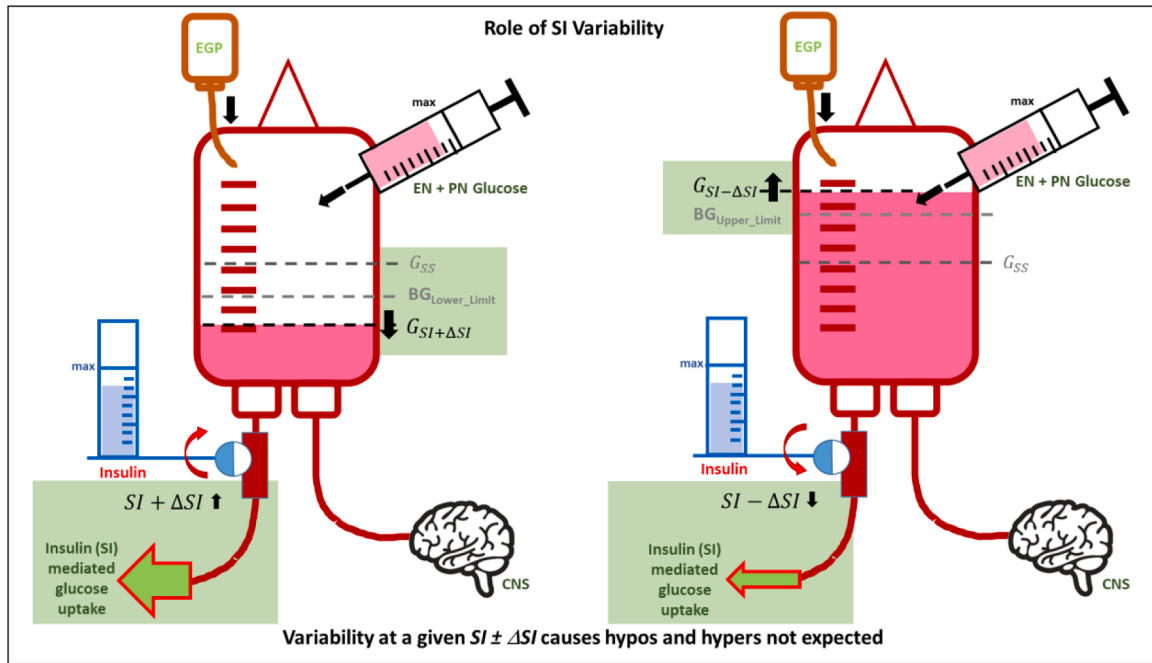


Fig. 7. Role of SI variability in raising or lowering glucose levels for a given insulin and nutrition dose.

regime for safe, effective glycemic control, which, as patients improve over time, should lead towards full nutrition delivery at low to no insulin required and stopping the protocol with no need for further external control.

It is important to point out insulin saturation is an extremely well-documented physiological phenomena (Docherty et al., 2010; Natali et al., 2000; Prigeon et al., 1996; Thorsteinsson, 1990; Mari et al., 2008; Eaton et al., 1984; Eaton, Allen & Schade, 1983; Duckworth, Bennett & Hamel, 1998; Ferrannini et al., 1983; Ferrannini & Cobelli, 1987; Ferrannini & Cobelli, 1987; Rizza, Mandarino & Gerich, 1981; Thorsteinsson et al., 1987; Thorsteinsson, Fugleberg & Binder, 1986;

Venkatesan et al., 2016; Koschorreck & Gilles, 2008; Black et al., 1982; Sowell et al., 2003; Kolterman et al., 1980; Olefsky, Ciaraldi & Kolterman, 1985; Laakso et al., 1990). The analysis and proof-by-analysis presented shows it is a critical factor to consider in the glycemic control of highly insulin resistant (lower SI) critically ill patients. Perhaps most importantly, it matches similar analyses around controlling nutrition (or not) in the presence of increasing nutrition loads (Knopp, Chase & Shaw, 2021).

The limiting case is defined in Eq. (13) and is patient-specific due to inter- and intra- patient variability in SI, as well as the patient-specific level of insulin saturation, which cannot be measured directly without

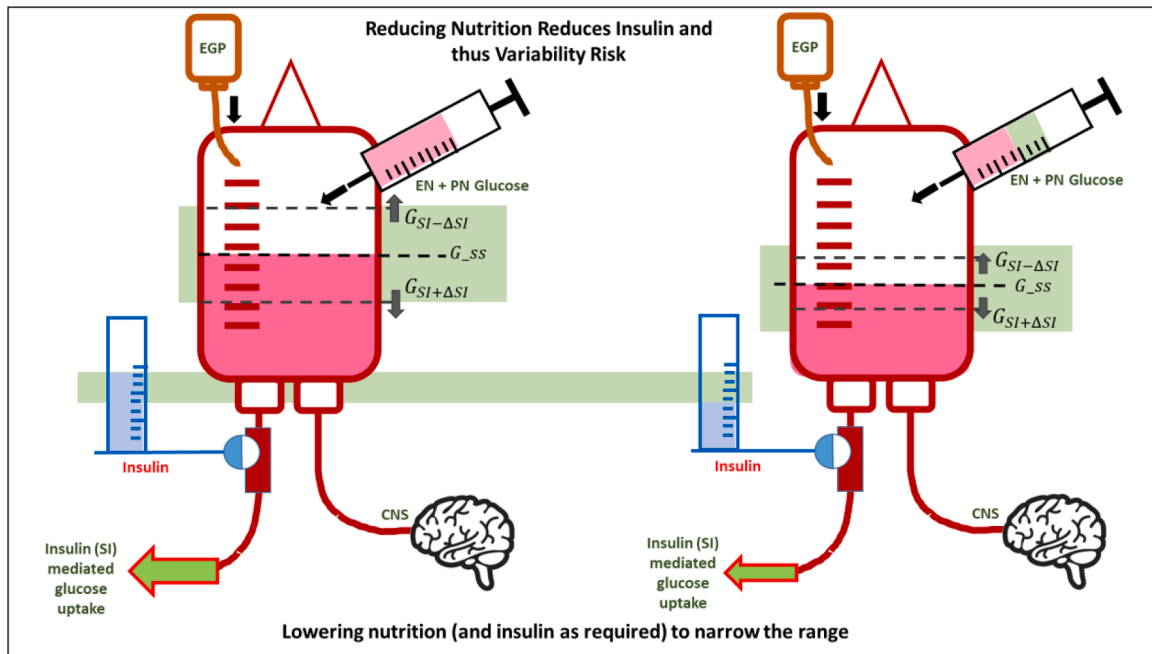


Fig. 8. Risk-based dosing where insulin inputs are reduced, with corresponding reductions to nutrition at the same SI level to reduce the excursions due to variability in SI. Green bars show also the reduced insulin and nutrition inputs and narrowing glycemic variability from the left to the right reduced case(s).

specific, invasive clinical tests. This conclusion is strongly supported by the clinical results examining nutrition delivery of several hundred well-controlled patients using STAR, as summarised in (Stewart et al., 2018). Further clinical reports showing modestly hypocaloric nutrition below 100% target levels may be beneficial provide further clinical evidence and show a clinical trend towards nutrition lower than 100% guideline goal nutrition rates (Wernerman et al., 2019; Cahill et al., 2010; Heyland, Cahill & Day, 2011; Wischmeyer, 2013; Krishnan et al., 2003; Kalfon & Preiser, 2008; Preiser & Wernerman, 2017; Preiser, Fraipont & Lheureux, 2019; Gunst, Egi & Van den Berghe, 2025). These results further support the mathematically focused analysis presented here, which in turn gives a fundamental, mathematical basis for these trends.

Clinically, higher insulin resistance (lower SI) and greater variability in insulin sensitivity (larger $\pm\Delta SI$) occur in the first days of ICU stay, immediately after the initial insult or disease (Uyttendaele et al., 2017; Pretty et al., 2012; Langouche et al., 2007), and then ameliorate over time. Further, a majority of hypoglycemic events and high glycemic variability occur in the first days of stay (Bagshaw et al., 2009). More critically, this greater variability and hypoglycemia are associated with increased mortality (Egi et al., 2006; Egi & Bellomo, 2009; Egi et al., 2010; Finfer et al., 2012; Penning et al., 2015; Signal et al., 2012; Krinsley & Preiser, 2015; Furushima et al., 2020), where good control to normoglycemic bands with low to no variability and hypoglycemia are associated with reduced organ failure and mortality (Penning et al., 2015; Signal et al., 2012; Krinsley & Preiser, 2015; Chase et al., 2010). Hence, the mathematical analysis presented and its conclusions, as shown schematically in Figs. 6–8, are supported by a range of published clinical evidence, including very recent analyses (Gunst, Egi & Van den Berghe, 2025).

The nutrition input $\bar{P}(t)$ in Eq. (7) is also a function of EGP and CNS. While CNS is a constant, EGP can vary a great deal (Dickson, Gunn & Chase, 2014). It is possible for it to change by up to 2–3x over a patient's stay (Black et al., 1982; Tappy, Tounian & Paquot, 1997; Chambrier et al., 2000), a high level of variability observed in other cohorts (Dickson et al., 2013). This variability is due to the strength of the stress response, which leads to unsuppressed EGP at high glucose levels acting like an added exogenous nutrition input in Eq. (7) and exceeding any limit on glucose appearance, which in turn, mathematically, reduces the nutrition delivery possible. This uncertainty gives further strength to the need presented here to also control nutrition inputs to safely and effectively control glucose levels.

The overall derivation and analysis presented is done in a steady state, quasi-static manner. However, the analysis is extensible to dynamic equations, where it is critical to note this dynamic system is entirely passive (overdamped), and there is no risk of bifurcation or local stability. In addition, while patient-specific dynamics do not change rapidly, with time constants from 15 min to 1–2 h enabling the simplified approach presented, they do change rapidly relative to the typically 3+ hour measurement intervals for control, thus justifying the need and impact of the variability analysis presented.

Further, a full dynamic analysis of all reachable states would be exhaustive and still show the same fundamental results, which are, in short, insulin saturation in the presence of insulin resistance (low SI) limits the total nutritional load which can be given if a desired glycemic level is to be reached. Equally, some studies choose to tolerate hyperglycemia, sometimes called permissive hyperglycemia, in these periods, despite the risk of deleterious effects, primarily to avoid the risk of hypoglycemia due to variability (Chase et al., 2023). There are thus many trade-offs in such an analysis leading to the same place as this steady state analysis.

Overall, the analysis presented mathematically relates fundamental metabolic system dynamics and the control inputs of insulin and nutrition to glycemic outcomes. The model used is well-validated and used clinically to control glycemia in critical care, and the analysis clearly shows how these dynamics interact for both the equilibrium and

variability questions posed. The results clearly show a need to control both insulin and nutrition administration, particularly when insulin resistance is high, and formulate the limits around which this need arises.

This overall study was based on the digital twin model of Eqs. (1)–(3) which is well-validated clinically. However, other model-based and data-driven approaches exist, which are well-reviewed (e.g. (Chase, Benyo & Desaive, 2019; Chase et al., 2023)). The most common and successful approach, which has also showed good results, is model-predictive control using linear or near-linear physiological models and auto-regressive models to account for the nonlinearity of Eqs. (1)–(3) (Amrein et al., 2010; Blaha et al., 2016; Blaha et al., 2005; Blaha et al., 2009; Plank et al., 2006). Black box approaches are also emerging but (to date) lack the clinical results of MPC approaches to date (e.g. (Cai et al., 2025; Symeonidis et al., 2025; Chowdhury et al., 2026; Faulds et al., 2026)). There are thus several approaches, where model-based systems have the greatest clinical application and validation to date. What is unique to this analysis is the approach of modulating insulin and also nutrition, where the other approaches noted here control only insulin, limiting, as shown, the potential control capability.

Finally, this study has broader implications for automation and, particularly, full automation of the control loop in Fig. 1. Digital twins enable full automation if the blood glucose measurements can be automated and the insulin-nutrition infusion pumps can be automated. This situation has already arrived with the type 1 diabetes artificial pancreas (Doyle & Kovatchev, 2025; Kovatchev et al., 2025) automating a continuous glucose monitor (CGM) measurement with a subcutaneous insulin pump, including an open source artificial pancreas system (Lee et al., 2017; Lewis, Leibrand & Open, 2016) with more emerging.

For the ICU and NICU case, CGMs are well-studied for both cases (Krinsley et al., 2017; McKinlay et al., 2017; Beardsall et al., 2013; Galderisi et al., 2017; Iglesias Platas et al., 2009; Signal et al., 2012; Thomas et al., 2014; Finfer et al., 2013; Signal et al., 2010; Holzinger et al., 2010; Hovorka, 2006; Jacobs et al., 2010) including their use in automation (Chase et al., 2018; Preiser et al., 2016; Beardsall et al., 2019; Wernerman et al., 2014; Kopecky et al., 2013). Unlike the outpatient case, CGM accuracy has been variable in these studies and may not be ready for automated use in the ICU or NICU, particularly for patients with severe sepsis and high levels of edema (Signal et al., 2013). However, CGMs improve regularly and have increasingly standardised reference measurements for assessing and comparing accuracy, trend accuracy, and clinical results (Klonoff, Ahn & Drincic, 2017; Klonoff et al., 2022; Klonoff et al., 2024).

Equally, automation of the infusion pump hardware systems is technologically straightforward but remains more difficult to create in actuality. The main limitations arise due to closed systems, regulatory requirements, and proprietary / safety concerns for both inpatients and outpatients alike (Payne et al., 2022; Payne et al., 2024). Hence, full automation remains technologically possible, but faces barriers to adoption, as well as clinical barriers to use, where innovation uptake and social science can play an increasing role (Chase et al., 2023; Wong et al., 2023).

5. Conclusions

Glycemic control is an important ICU therapy but has proven extremely difficult to provide safely and effectively, particularly using typical clinical protocols and approaches. Virtually all glycemic control protocols do not control exogenous nutrition administration, nor even directly account for its input in some cases. This choice risks hyperglycemia when insulin dose saturates, as well as hypoglycemia when insulin sensitivity rises in the presence of the large insulin doses used to combat persistent hyperglycemia. The model-based analysis presented is the first to examine this control problem from a mathematical perspective to delineate the impact of clinical and physiological limits in achieving desired control outcomes. It specifically shows

normoglycemia cannot be effectively or safely reached and maintained using insulin alone for specific patient conditions. In short, using insulin alone, normoglycemia is not always a reachable state or/and cannot be safely maintained in the presence of patient variability.

The clinical and physiological limits and rationale for the overall control problem are reviewed. Using a well-validated metabolic system model, specific mathematical model analysis results show how a desired equilibrium glucose may not be achievable for some patients due to nonlinear insulin saturation combined with higher insulin resistance (lower insulin sensitivity). It also defines the concomitant patient-specific maximum exogenous nutrition rate able to be delivered and taken up by the patient. Further analysis of insulin sensitivity variability mathematically demonstrates the need to control nutrition delivery to allow safe, effective control of glucose in the presence of potentially significant changes in insulin sensitivity in highly variable patients. Together these mathematical analysis results show the necessity of controlling both insulin and nutrition administration, for at least some patients some of the time, to ensure normoglycemia is a reachable state for model-based glycemic control.

This overall conclusion is counter to current clinical approaches but validated by a very large and broad range of clinical observations when they are put into the mathematical context presented. The inability to reach normoglycemia in some cases, such as when insulin sensitivity is low and nutrition and insulin doses are high or/and saturated, also clearly shows how and why many other protocols have failed to deliver consistent, safe, effective control for all patients, leading many to consider glycemic control unnecessary or/and unsafe. Thus, the analysis presented clearly highlights the definition of the ability to reach normoglycemia, the need to control both inputs rather than one, as well as indirectly highlighting in the results of other studies the cost of not doing so.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.arcontrol.2026.101072](https://doi.org/10.1016/j.arcontrol.2026.101072).

Data availability

No data was used for the research described in the article.

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