Rethinking glycaemic control in critical illness — from concept to clinical practice change

Geoffrey M Shaw, J Geoffrey Chase, Jason Wong, Jessica Lin, Thomas Lotz, Aaron J Le Compte, Timothy R Lonergan, Michael B Willacy and Christopher E Hann

Hyperglycaemia is prevalent in critical care, even when the patient has no prior diabetes. Increased secretion of counter-regulatory hormones stimulates endogenous glucose production and increases effective insulin resistance. Studies also indicate that high glucose nutritional regimens often result in excess glucose, exacerbating hyperglycaemia.

Hyperglycaemia worsens outcomes, increasing the risk of severe infection, myocardial infarction, and critical illnesses such as polyneuropathy and multiple-organ failure. Evidence also exists of significant reductions in other therapies with aggressive glycaemic control. More importantly, van den Berghe et al and Krinsley showed that tight glucose control to a limit of 6.10–7.75 mmol/L reduced mortality in intensive-care patients by up to 30%–45%, overall or for various subgroups.

Regulating blood glucose levels in critical care using simple model-based protocols and insulin alone has been moderately successful, while using of sliding scales and other ad hoc methods have not always been effective. Additionally, some studies find intensive insulin therapy “taxing”, noting that the study by van den Berghe et al required additional specialised staff. Hence, despite the potential, many ICUs do not use fixed protocols or necessarily agree on what constitutes acceptable or desirable glycaemic management and performance.

Non-linear, model-based control protocols for insulin-mediated glycaemic control have been developed. These protocols are challenged by the significantly elevated insulin resistance often encountered in broad critical care cohorts. In particular, insulin effect saturates at high concentrations, limiting the reductions in glycaemia that can be achieved in the presence of significant insulin resistance through use of insulin alone. However, effective glycaemic control is still possible by also controlling the exogenous nutritional inputs exacerbating the original problem. In fact, interventions that specifically lowered glucose nutrition significantly reduced average blood glucose levels without added insulin for example, Krishnan et al showed that feeding 33%–66% of rates recommended by the ACCP (American College of Chest Physicians) guidelines minimised mortality and hyperglycaemia.

Overall, any glycaemic control protocol must reduce elevated glucose levels in a controlled, predictable manner, while accounting for inter-patient variability, conflicting difficulties and patient variation, while also providing safe, tight control.

Objective: To examine the practical difficulties in managing hyperglycaemia in critical illness and to present recently developed model-based glycaemic management protocols to provide tight control.

Background: Hyperglycaemia is prevalent in critical care. Current published protocols require significant added clinical effort and have highly variable results. No currently published methods successfully address the practical clinical difficulties and patient variation, while also providing safe, tight control.

Methods: We developed a unique model-based approach that manages both nutritional inputs and exogenous insulin infusions. Computerised glycaemic control methods and proof-of-concept clinical trial results are presented. The protocol has been simplified to a set of tables and adopted as a clinical practice change. Eight pilot test cases are presented to demonstrate the overall approach.

Results: Computerised control methods lowered blood glucose (BG) levels to the range 4.0–6.1 mmol/L within 10 hours. Over 90% of pre-set hourly blood glucose targets were achieved within measurement error. Eight pilot tests of the simplified, table-based SPRINT protocol, covering 1651 patient-hours produced an average BG level of 5.7 mmol/L (SD, 0.9 mmol/L). BG levels were in the 4.0–6.1 mmol/L band for 60% of the controlled time. Just under 90% of measurements were in the range 4.0–7.0 mmol/L, with 96% in the range 4.0–7.75 mmol/L. There were no hypoglycaemic episodes, with a minimum glucose level of 3.2 mmol/L, and no additional clinical intervention was required.

Summary: The overall approach of modulating nutrition as well as insulin challenges the current practice of relying on insulin alone to reduce glycaemic levels, which often results in large variability and poor control. The protocol was developed from model-based analysis and proof-of-concept clinical trials, and then generalised to a simple, clinical practice improvement. The results show extremely tight control within safe glycaemic bands.
therapies and varying physiological conditions. Hence, it must be adaptive or able to identify changes in patient metabolic status, particularly with respect to insulin sensitivity. It must also be simple enough to be easily implemented, and effective enough to be essentially automated, to minimise the consumption of clinical time and expertise.

We describe the application of models and control theory to this problem. The goal is to use these tools to better manage this complex problem for improved outcome. A second, equally important, goal is to use these tools in a way that can be readily transferred to non-engineering-trained clinical staff without adding excessive training or task burden. In itself, satisfying these two goals creates a significant and challenging opportunity to integrate engineering and clinical practice to provide improved patient care.

Methods

Model of glucose–insulin regulation and computerised control

Tight blood glucose control requires a patient-specific glucose–insulin regulatory system model that captures the fundamental dynamics. Chase et al.16,17 and Hann et al.27 used a system model that captured rate of insulin utilisation, insulin losses and saturation dynamics, and is also used in this study. The model equations and basic justification are shown in the Appendix, along with references detailing its use for interested readers or potential users.

With regard to safe clinical application, the model has been validated over long periods in a retrospective audit of data from 17 patients.27,31,32 These patients had an average length of stay of 3.1 days and an average APACHE II score of 21.8, representing a broad cross section of the typical ICU cohort. Fitted data and forward glucose predictions had errors of 2%–10%, which is at or within the measurement error. The model was also validated over short, highly dynamic periods using data from 146 hyperinsulinaemic, euglycaemic clamp trials obtained from the intervention study of McAuley et al.33 All glucose and insulin fitting errors were within reported measurement errors. More importantly, the model-based insulin sensitivity parameter, SI, correlated strongly with the clamp-derived insulin sensitivity index (ISI) (correlation coefficient, $r=0.985$).34,35 Hence, the model is more than capable of capturing the metabolic status of the highly dynamic ICU patient, and is thus suitable for implementing tight control in critical care.

We conducted proof-of-concept studies of the computerised blood glucose control method in seven patients over 10 hours each, beginning at 09:00. In this method, blood glucose concentration at 09:00 is taken as the equilibrium level, $G_E$, after which the feed rate is decreased by 20%–40% as an initial challenge, depending on current glucose level and feed rate. Blood glucose concentration is measured at 15 minute intervals until 10:00 using a Glucometer (Arkray Inc., Kyoto, Japan) and data are analysed. At 10:00, insulin sensitivity, SI, is evaluated, and a blood glucose target set for a 10%–15% reduction to a minimum of 5 mmol/L. Blood glucose concentration is monitored half-hourly after 10:00, and each hour a new target is set after re-evaluating SI from the previous hour’s data. Each hour, the controller determines the required combination of control inputs (insulin bolus size, insulin infusion rate and feed rate) to achieve the target, depending on fitted SI and estimated levels of insulin effect saturation. The overall clinical trial procedure is outlined in Figure 1.

Total insulin prescribed is limited to 6 U/h to minimise saturation and administration of ineffective insulin.17,29,30 Insulin is given predominantly in bolus form for safety. The minimum feed rate is 280 kcal/day (1172 kJ/day) of glucose or 40% of the average maximum goal feed rate. Using the RESOURCE Diabetic feed formulation (Novartis, Minneapo-
Figure 2. The SPRINT feed wheel with dial (top) and with dial removed (bottom)*

Feed Wheel

START:
1. Use the feed conversion sticker to find the current percentage feed level.
2. Rotate wheel to patient’s current percentage feed level marked in grey.
3. Is the latest blood glucose 7mmol/L or under and has it dropped from the previous measurement by more than 1.5%?
   YES: Use side “B” of wheel
   NO: Use side “A” of wheel
4. Using the selected side of the wheel from 3, match the current glucose level to the new feed level.
5. Use the feed conversion sticker to find the absolute feed in [ml/hr].
6. Use Insulin Wheel if you have not done so already.

* Animated and downloadable copies of the SPRINT feed wheel are available at http://www.geocities.com/active_insulin_control.
Figure 3. The SPRINT insulin wheel with dial (top) and with dial removed (bottom)*

**Insulin Wheel**

**START:**

1. Is the latest blood glucose 7mmol/L or under and has it dropped from the previous measurement by more than 1.5%?

   **YES:** Do not give any insulin this hour

   **NO:** Follow the steps below

2. Rotate wheel to patient’s current glucose level marked in grey.

3. Determine whether the glucose level has increased or decreased and select the correct side of the wheel.

4. Using the selected side of the wheel from 3, match the previous insulin bolus to the new insulin bolus.

5. Administer new insulin bolus and have colleague double check.

6. Use Feed Wheel if you have not done so already.

* Animated and downloadable copies of the wheel are available at http://www.geocities.com/active_insulin_control.
lis, USA) at 280 kcal/day of glucose, the total energy (caloric) intake is still 778 kcal/day for a typical patient, exceeding the minimum level below which there is an increased risk of bloodstream infections.

A simpler protocol — SPRINT

However, the computational resources needed for computerised control methods are not typically available in critical care. In addition, the complexity of these methods limits the easy large-scale implementation required to test overall safety and efficacy. In addition, the measurement frequency of every 30 minutes is currently unsustainable in regular clinical practice, where 1–2 hourly measurements can be managed at best. Hence, a simpler paper-based method has been developed to mimic this protocol, as described by Lonergan et al.

The SPRINT (Specialised Relative Insulin + Nutrition Tables) protocol comprises two “wheels” dedicated to enteral nutrition optimisation (specifically RESOURCE Diabetic or Glucerna [Abbott Laboratories, Illinois, USA] in this case) and insulin bolus administration (Actrapid [Novo Nordisk, Baegsverd, Denmark]). These wheels are shown in Figures 2 and 3. They carry printed instructions, and a more detailed guide is located at each patient workstation. The current starting criterion for the SPRINT protocol is two successive blood glucose measurements over 8.0 mmol/L. Blood glucose concentration is then measured hourly and used to determine the next hour's intervention. Criteria for 2-hourly measurement and for stopping the protocol are shown in Figures 4 and 5, respectively.

The SPRINT feed wheel (Figure 2) is used to determine the feed rate as a percentage of the patient’s clinically determined goal feed. The result is based on the previous hour’s feed rate, current blood glucose level, and whether blood glucose level is rising or falling. The percentage goal feed is converted into an absolute feed rate (in mL/h) using a patient-specific conversion sticker attached to the table. The SPRINT insulin wheel (Figure 3) is then used to determine the insulin bolus size based on the previous insulin bolus size, current blood glucose level, and whether blood glucose level has decreased more than 1.5 mmol/L. The feed and insulin interventions are also recorded on the patient’s chart. Hence, the method is effectively fully automated.

Hourly blood glucose measurements are used to ensure tight control. Two-hourly measurements are used when the

---

**Figure 4. SPRINT guidelines for 2-hourly blood glucose measurements**

When can I measure blood glucose level (BG) every 2 hours instead of every 1 hour?

(Reducing the frequency of measurement saves time, yet will lose optimum control of the patient’s condition; it is in the patient’s best interests to measure and act every hour.)

- **Does the patient have an arterial line?**
  - No
  - Yes

- **Has the patient’s BG been within the band 4-6 mmol/L for the previous three measurements?**
  - Yes
  - No

- **Measure BG every 2 hours**
  - Determine feed
  - Hold feed constant for 2 hours
  - Determine bolus
  - Deliver this bolus twice: once now and the next in 1 hour’s time

- **Measure BG every 1 hour**
  - Determine feed
  - Set feed for 1 hour
  - Determine bolus
  - Deliver bolus now

**Important:** if the BG comes out of the 4–6 mmol/L band on the next measurement, return to 1 hour measurement intervals immediately.

---

**Figure 5. Guidelines for stopping the SPRINT protocol**

When can I stop the SPRINT protocol?

- **Has the patient’s blood glucose (BG) level been within the band 4-6 mmol/L for at least 6 hours**
  - No
    - **Is the feed at 80% or greater?**
      - Yes
        - **Is the insulin at 2 U/h or less?**
          - Yes
            - **Stop SPRINT**
          - No
            - **Continue SPRINT and measure BG 2-hourly**
        - No
          - **Continue SPRINT and measure BG 2-hourly**
    - No

Critical Care and Resuscitation • Volume 8 Number 2 • June 2006

Patient’s condition is stable, defined as three consecutive measurements in the 4.0–6.0 mmol/L band (Figure 4). For 2-hourly measurements, the feed rate is maintained constant, and the same insulin bolus is administered again on the hour between measurements. Two-hourly measurements are continued until the patient’s blood glucose level leaves the 4.0–6.0 mmol/L band or until the SPRINT protocol is stopped.

SPRINT is stopped when the patient is stable, normoglycaemic, and adequately self-regulating. Figure 5 defines this state as 6 or more hours in the 4.0–6.0 mmol/L band, with over 80% of goal feed rate, and a maximum of 2 U/h of insulin. Finally, insulin is always administered as a bolus for patient safety, thus avoiding infusions being left on at levels inappropriate for a patient’s evolving condition.

Results

Trial of computerised tight glucose control

The patient cohort for seven proof-of-concept tests is described in Table 1. The resulting target errors and interventions over the course of each trial are shown in Table 2. The overall mean target error for all trials was 8.9% (0.5 mmol/L), with an absolute range, 0–2.9 mmol/L; 46% of targets were achieved within ±5%, and 20% were outside the 3%–10% measurement error. For errors > 5%, mean target error was 14.3% (0.79 mmol/L). Out of 63 targets, four had errors > 20%, so that 94% of all target measurements were within ±20% of targets. Overall, 90% of target errors could be explained by reported measurement errors. Larger errors were attributable to sudden changes in the patient’s condition, such as the onset of atrial fibrillation, as described in detail in previous studies.38,39

Clinical application of the SPRINT protocol

SPRINT has been implemented as a clinical practice change in the Department of Intensive Care at Christchurch Hospital, New Zealand, and ethics committee approval was obtained for the audit, analysis and publication of these data. For proof of concept, the first eight patients tested as an initial pilot are presented. There were no specific exclusion criteria for the patients selected. There were four men and four women, with average APACHE II score of 24 (range, 11–37), and mean age of 58 years (range, 43–80 years). The mean trial period was 206 hours (range, 32–355 hours).

Figure 6 shows a typical trial period covering 163 hours for a patient with an APACHE II score of 21. The average blood glucose level was 5.4 mmol/L, which was achieved with an average hourly bolus of 2.3 U insulin and an average feed rate of 85% (595 kcal/day of glucose; 1700 kcal/day total). Note that 85% of all measurements were in the 4.0–6.1 mmol/L band, and 97% were in the 4.0–7.75 mmol/L band.

Over the eight patients, there were 1651 hours of blood glucose control with 1206 measurements, indicating that 54% of the duration (445 measurements) was controlled with 2-hourly measurements, minimising clinical effort. The average blood glucose level was 5.7 mmol/L (standard deviation, 0.9 mmol/L). More importantly, 69% of measurements were in the 4.0–6.1 mmol/L band, 89% in the 4.0–7.0 mmol/L band, and 96% in the 4.0–7.75 mmol/L band. The lowest blood glucose measurement was 3.2 mmol/L, which is not extreme, and only 22 (1.8%) of all measurements were less than 4.0 mmol/L. The average insulin used was 2.6 U/h, and the average enteral nutrition rate was 68% of goal feed (1308 kcal/day total). Note that the feed rate was 15% higher than retrospective Christchurch Hospital data for a similar cohort.27,32 ICU mortality for this pilot was one of eight patients.

These results show that extremely tight blood glucose control was achieved using an extremely simple insulin and nutrition protocol. Almost 90% of all blood glucose measurements were less than 7.0 mmol/L, which is much tighter control than reported in other studies.2,15,19,26,40 More impor-
### Table 2. Results of the 10-hour clinical trial of computerised blood glucose control in seven patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Insulin bolus (U)</th>
<th>Hour</th>
<th>Target glucose (mmol/L)</th>
<th>Target error (mmol/L)</th>
<th>Target error (%)</th>
<th>Feed rate (%)*</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0</td>
<td>1</td>
<td>12.2</td>
<td>1.2</td>
<td>9.8</td>
<td>56</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>10.2</td>
<td>0.3</td>
<td>2.5</td>
<td>42</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>8.0</td>
<td>0.2</td>
<td>2.4</td>
<td>28</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>6.8</td>
<td>0.0</td>
<td>–</td>
<td>28</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6</td>
<td>6.6</td>
<td>1.0</td>
<td>–</td>
<td>28</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>7.1</td>
<td>0.9</td>
<td>–</td>
<td>28</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8</td>
<td>5.3</td>
<td>0.8</td>
<td>–</td>
<td>12.7</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9</td>
<td>5.0</td>
<td>0.9</td>
<td>–</td>
<td>16.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>10</td>
<td>5.0</td>
<td>0.8</td>
<td>–</td>
<td>20.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* Feed rate was determined as a percentage of 1000 kcal/day (4184 kJ/day).
tantly, SPRINT required no specialised clinical intervention at any time.

Finally, the specific layout of the tables/wheels resulted from extensive consultation with ICU staff and brief one-to-one training. Clinical staff became proficient in minutes and reported that the system is very easy to use. The covered wheel concept avoids table complexity and reduces user error. More specifically, nursing staff were surveyed for their opinions of the SPRINT system with a three-item questionnaire. Results are summarised in Table 3. Twenty-seven nursing staff responded to the three items, with a total of five items not completed. Of the 76 responses to individual items, 72 (95%) rated SPRINT as satisfactory or better, with 74% rating it good or very good. Thus, SPRINT is simple enough to readily integrate with any typical ICU practice.

Discussion

This approach of modulating nutrition as well as exogenous insulin is a significant departure from other approaches, which use insulin alone to reduce glycaemic levels.\(^2,13-19,21\) Despite concerns, recent studies show that low-calorie nutritional inputs reduce hyperglycaemia\(^5,8,41,42\) and, above approximately 30% of standard goal feed rate, do not increase infectious complications.\(^5,42\) More specifically, Krishnan et al\(^10\) showed that feeding over 66% of the ACCP recommended rates increased ICU mortality, and suggested that the ACCP caloric targets may thus be set too high.

In addition, hyperglycaemia has been shown to exacerbate muscle protein catabolism in burn patients,\(^43\) indicating that excessive nutrition and hyperglycaemia should also be avoided in these patients. However, lower amounts of glucose up to 12.5 kcal/kg (1000 kcal per day for an 80 kg man) did not significantly increase hyperglycaemia or infectious complications.\(^42\) Finally, reduced caloric nutritional support has been effective in paediatric cases and for obese patients.\(^44-46\) Thus, there is reasonable evidence that temporary, moderate reductions in nutrition will not reduce other clinical outcomes. However, extreme, long-term underfeeding should be avoided.\(^47\)

![Figure 6. Typical patient response to the SPRINT protocol](image)

Finally, it is also important to note the effect of patient cohort and particularly illness severity, as measured by APACHE II score, on the results. Overall, the clinical results showed tight control to less than 6.1 mmol/L for a cohort with a median APACHE II score of 23 (range, 17–31). In comparison, van den Berghe et al\(^2\) achieved similarly tight control for a cohort with a median APACHE II score of 9 (interquartile range, 7–13), which represents a much lower level of critical illness. Kinsley showed tight control to a higher level (7.75 mmol/L) for an ICU cohort more comparable to ours (median APACHE II score, 16; interquartile range, 10–23).\(^14,15\) Both studies used insulin alone. Hence, the added glycaemic control achievable through modulating nutrition as well as insulin is illustrated by the tight control that we obtained, to a level similar to that reported by van den Berghe et al,\(^2\) for an ICU cohort whose illness was significantly more critical.

Conclusions

These clinical case studies demonstrate the potential of the control algorithms to achieve tight, set-point regulation of hyperglycaemia across a range of critically ill patients. The model and algorithms developed are capable of capturing a patient’s metabolic status, despite variability between patients and variation in physiological condition over time, by accounting for all critical, physiologically justified nonlinear dynamics. More importantly, the results indicate that extremely tight control can be achieved for significantly ill ICU patients through careful application of insulin and nutritional feed rate reductions. The simplified SPRINT protocols outperformed other published strategies in initial

Table 3. Nurse evaluation survey of the SPRINT protocol

<table>
<thead>
<tr>
<th></th>
<th>Very good</th>
<th>Good</th>
<th>Satisfactory</th>
<th>Poor</th>
<th>No answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of use</td>
<td>2</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Quality</td>
<td>6</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Suitability</td>
<td>7</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>41</td>
<td>16</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
pilot studies, and can be implemented in any typical ICU. Overall, the research presented is a significant step towards more fully automated adaptive control of hyperglycaemia in critically ill patients, leading to reduced complications and mortality.

To aid dissemination of these results, the SPRINT wheels and related data for implementation are available directly from the corresponding author.

Author details
Geoffrey M Shaw, Clinical Senior Lecturer1,2
J Geoffrey Chase, Reader/Associate Professor,3 and Honorary Senior Lecturer4
Jason Wong, Research Assistant3
Jessica Lin, Research Assistant1
Thomas Lotz, Research Assistant3
Aaron J Le Compte, Research Assistant3
Timothy R Lonergan, Research Assistant3
Michael B Willacy, Research Assistant3
Christopher E Hann, Postdoctoral Research Associate3

1 Christchurch School of Medicine and Health Sciences, University of Otago, Christchurch, New Zealand.
2 Department of Intensive Care, Christchurch Hospital, Christchurch, New Zealand.
3 University of Canterbury, Centre for Bio-Engineering, Department of Mechanical Engineering, Christchurch, New Zealand.

Correspondence: geoff.shaw@cdhb.govt.nz

References
11 Bistrian BR. Hyperglycemia and infection: which is the chicken and which is the egg? JPEN J Parenter Enteral Nutr 2001; 25: 180-1.
Appendix. Model of the insulin–glucose metabolic system

The metabolic system model equations are defined:16,17,27,39

\[
\dot{G} = -p_G G - S_I (G + G_E) \frac{Q}{1 + \alpha_G Q} + P(t) \quad (1)
\]

\[
\dot{Q} = -kQ + kI \quad (2)
\]

\[
\dot{I} = -\frac{nl}{1 + \alpha_I I} + \frac{u_{st}(t)}{V} \quad (3)
\]

\[
P(t_i < t < t_{i+1}) = p_{i+1} + (P(t_i) - p_{i+1}) e^{-k_{ip}(t-t_i)} \quad \text{where } p_{i+1} < P(t_i) \quad (4)
\]

\[
P(t_i < t < t_{i+1}) = p_{i+1} + (P(t_i) - p_{i+1}) e^{-k_{ip}(t-t_i)} \quad \text{where } p_{i+1} > P(t_i) \quad (5)
\]

Glossary

- \( G(t) \): plasma glucose concentration above equilibrium [mmol/L]
- \( I(t) \): plasma insulin concentration [mU/L]
- \( G_E \): equilibrium plasma glucose concentration [mmol/L]
- \( Q(t) \): interstitial insulin concentration [mU/L]
- \( k \): rise rate of interstitial insulin concentration from plasma and decay rate of insulin concentration from interstitium [min\(^{-1}\)]
- \( p_G \): fractional glucose clearance rate [min\(^{-1}\)]
- \( S_I \): insulin sensitivity [L/(mU.min)]
- \( I \): decay rate of insulin from plasma [min\(^{-1}\)]
- \( P(t) \): total plasma glucose input [mmol/(L.min)]
- \( u_{st}(t) \): total insulin input into plasma (exogenous) [mU/min]
- \( \alpha_I \): Michaelis–Menten saturation parameter for plasma insulin disappearance [L/mU]
- \( \alpha_G \): Michaelis–Menten saturation parameter for insulin-dependent glucose clearance [L/mU]
- \( k_{ip} \): rise rate of plasma glucose input from enterally administered feed rate [min\(^{-1}\)]
- \( k_{gl} \): decay rate of rate of glucose input into plasma from enterally administered feed rate [min\(^{-1}\)]
- \( t \): time elapsed since beginning of trial [min]
- \( P_i, P_{i+1} \): stepwise consecutive enteral glucose feed rates [mmol/L.min]
- \( t_i, t_{i+1} \): time at which stepwise consecutive enteral glucose feed rate is altered [min]

Generally, \( k, n, \alpha_I, \alpha_G \) and \( V \) can be identified from generic population values.16,28 The model does not include endogenous insulin or specific terms for endogenous glucose production. Any immeasurable, endogenous insulin supply is thus accounted for in the identification of the time-varying endogenous clearance parameter (\( p_G \)). Similarly the level of the patient’s stress-induced insulin resistance is captured in the identified insulin sensitivity (\( S_I \)) value and can thus serve as an additional metric for severity of illness.16,17,27,31,38 Computational methods used to evaluate this model are described in Chase et al.16 and include integral-based parameter identification techniques described in Hann et al.27