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Fast Algorithms for Model Based Therapeutics

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Abstract

In critical care tight control of glucose has been shown to lead to better clinical outcomes and reductions in length of stay. The need arises to develop new protocols for maintaining tight control of patients' glucose. The current hindrance to developing new protocols is the large amount of computational time and resources that are needed. This paper is based on finding fast analytical based methods for the insulin-glucose model. Exploiting the structure and partial solutions in a subset of the model was the key in finding accurate solutions to the full model. This successfully reduced the computing time compared to the numerical methods used currently by a factor of 6000 whilst introducing minimal error. This will allow new protocols to be rapidly developed leading to better clinical outcomes for patients in critical care.

Fast algorithms for model based therapeutics

1 Introduction

Tight control of glucose has gained significant importance in critical care after Van den Berghe et al. [1] showed that up to 45% reductions in mortality are possible. In [2,3], a glucose-insulin model was used to guide feed and insulin inputs for critical care patients and maintained tight blood sugar levels for trials of up to 12 hours long. However, to simplify the clinical application of the algorithm, a nutrition-insulin table protocol [4,5] was developed to mimic the model based algorithm of [2,3]. The trials in [4,5] represent the first model-based protocol to report a significant clinical outcome with a 30% mortality reduction, significantly higher APACHE scores and the tightest glucose control reported so far as compared to other studies [e.g. 6].

A critical part of the development of [4,5] was the creation of a virtual patient database and the implementation of virtual patient clinical trials to optimize the protocol before application on real patients. The virtual patient database represents a summary of the metabolic changes of patients in a cohort over the entire length of stay in the intensive care unit (ICU). The primary parameter used to represent a patients' metabolic status was insulin sensitivity (S_I) which was made time varying, with changes over a one hour period, and was found from retrospective trials using an integral-based parameter identification method [7]. Shorter trials in [2,3] were also added to the database. In these trials ([2,3]) the S_I profile was generated in real time using the algorithm of [7] and were used to predict patient response in the following hour, thus calculating the amount of insulin and reduction/addition of feed required to maintain blood glucose concentration in the 4-6 mmol/L band.

The insulin sensitivity profiles obtained in the retrospective [7] and model-based glucose control trials [2,3] provide the means to carry out "virtual" clinical trials to test glucose control protocols. The process of creating a virtual patient cohort and then testing new protocols using the physiological model is referred to as "model-based therapeutics".

This model-based therapeutics (MBT) approach led to the development of the SPRINT (Specialized Relative Insulin + Nutrition Tables) protocol that has been implemented in the Christchurch hospital ICU [4,5]. One key feature of the MBT approach is the close

similarity between the probability density of the real and virtual clinical trials as shown in Figures 1 and 2.

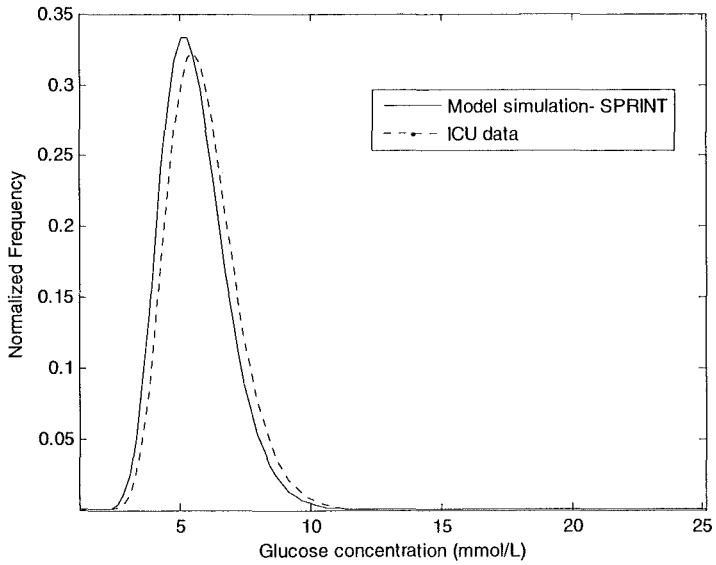

Figure 1: Frequency distribution of real and virtual trials

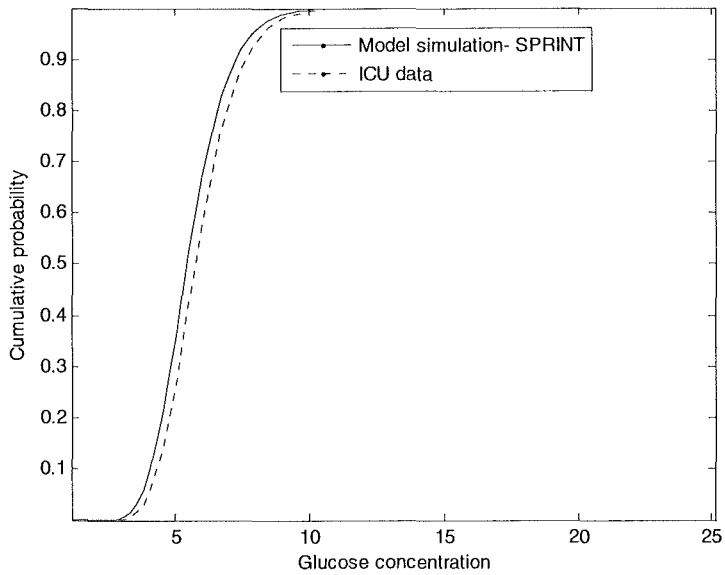

Figure 2: Cumulative probability function of real and virtual trials.

Figures 1 and 2 provide a strong motivation to further develop MBT technologies and initial successful results have been obtained in several other areas, including model based cardiac diagnosis [8-10], insulin sensitivity [11-12] agitation-sedation and lung ventilation.

A fundamental element in the MBT approach is highly accurate, easily programmable, fast forward solutions to non-linear physiological models. Fast forward simulations are required to trial many therapeutic options to find the best treatment. Some initial work in

a cardiac model has shown that with certain mathematical reformulation, significant speed increases are possible [13]. However, a major is that practical analytical solutions to most non-linear physiological models are very difficult to obtain and thus computationally intense numerical solvers are required. For example in the testing and development of the SPRINT protocol [4,5], each patient must be simulated at least 20 times with random noise on the "measured data" to ensure the algorithm is robust to noise, which is a standard Monte-Carlo approach. Each patient involves on average, around 5 days or 120 hours of data, which after Monte-Carlo simulation amounts to a minimum of 2400 hours per patient. In practice, to obtain an accurate sample, up to 100 Monte-Carlo simulations are done for each patient. The virtual database has now grown to 165 patients. This would correspond to 3,960,000 patient hours required to simulate a new protocol.

The SPRINT protocol [4,5] has tended to slightly underfeed patients. Thus one new protocol would be to increase the overall feed of patients, while maintaining the same tight glucose control. Other potential protocols include minimizing the number of measurements required for general wards, developing a protocol for pediatrics and improving the current SPRINT protocol.

To get an idea of the computation time required, a standard ODE solver in MATLAB takes 0.5656s to simulate one patient hour on a laptop with a 1.73GHz processor. This would amount to 24days of simulation or alternately 2.4 days with 10 computers. However as many more patients are added, greater numbers of protocols are tested; and potentially more dynamics are added to the glucose-insulin model, (e.g. more detailed feed model); significant computing time and resources would be required. This would limit the number of patients and protocols that could be tested, potentially hindering research outcomes.

The glucose control protocols only require a simulated measurement at most on the hour, yet numerical ODE solvers compute the glucose at every time step throughout the hour [e.g. Maki, 2006]. In other words a large percentage of computation is spent calculating glucose values that are not used.
The non-linear glucose-insulin model equation [3] however has no direct analytical solution. The approach in this research, is to form partial analytical solutions to a subset of the model in terms of simpler approximating functions that are valid within known physiological bounds. These simpler functions then enable an analytical solution to the whole model. In other words, the approach is to reformulate and tailor solutions to the specific application required. With careful construction and the use of both elementary and advanced mathematical solutions to differential equations, it is shown that an approximate, but highly accurate analytical solution can be found to the full non-linear glucose insulin model. This solution dramatically increases the forward simulation speed of the model, thus allowing the rapid development of new protocols aimed to improve patient outcome.
The solution is compared rigorously to the numerical solution over many virtual simulations and is found to be highly accurate.

An example of the application of the method is given by testing a protocol aimed to increase the overall feed to patients.

2 Methodology

2.1 Model of glucose and insulin kinetics

The model of glucose and insulin kinetics [3] used to run virtual trials is loosely based on Bergman's minimal model with additional non-linear terms and a time varying insulin sensitivity $S_I = S_I(t)$, defined as follows:

$$\dot{G} = -p_g \cdot G - S_I(G + G_{eq})\frac{Q}{1+\alpha_G Q} + P(t) \tag{1}$$

$$\dot{Q} = -kQ + k\mathrm{I} \tag{2}$$

$$\dot{I} = -\frac{n\mathrm{I}}{1+\alpha_\mathrm{I}\mathrm{I}} + \frac{u_{ex}}{V} \tag{3}$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (P(t_i) - \overline{P}_{i+1})e^{-k_p(t-t_i)} \tag{4}$$

where:

$$k_p = \begin{cases} k_{pd} \\ k_{pr} \end{cases} \begin{matrix} if\ \overline{P}_{i+1} < P(t_i) \\ if\ \overline{P}_{i+1} > P(t_i) \end{matrix},$$

G_{eq} is the equilibrium plasma glucose concentration and G is the plasma glucose concentration above G_{eq}. The exogenous feed input rate is denoted $P(t)$; $I(t)$ is the plasma insulin resulting from exogenous insulin input $u_{ex}(t)$; $Q(t)$ is the concentration of insulin bounded to interstitial sites; k accounts for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_g and S_I respectively; V is the insulin distribution volume and n is the constant first order decay rate for insulin from plasma. Michaelis-Menten functions are used to model saturation, with α_I used for the saturation of insulin disappearance, and α_G for the saturation of insulin-dependent glucose clearance; k_{pr} and k_{pd} are the effective half lives for increasing and decreasing feed rates where $\overline{P}_i$ and $\overline{P}_{i+1}$ are the steps in enteral glucose feed rates.

The parameters k, n, α_I, V, k_{pd} and k_{pr} are held at population values and G_{eq} is estimated from the mean glucose concentration over the patients stay [3,7]. The parameters S_I and p_g are patient specific. Note that for simplicity the model of equation (1) is reformulated by replacing G by $G_{total} - G_{eq}$ in Equation (1):

$$\dot{G}_{total} = -p_g(G_{total} - G_{eq}) - S_I G_{total}\frac{Q}{1+\alpha_G Q} + P(t) \tag{5}$$

2.2 Virtual patient cohort

For this research, 17 uncontrolled patients were used from the study in[7], and 51 controlled patients on the SPRINT system [4,5] to form the virtual patient cohort. The patients physiology were summarized by their insulin sensitivity $S_I(t)$ as well as glucose effectiveness $p_g(t)$, and were obtained using the integral based parameter identification method[7]. Given nutritional and insulin inputs, and a patients $S_I(t)$ and $p_g(t)$ profile, equations (2)-(5) can then be solved, which is referred to as a "virtual trial". Different protocols can be applied on a specific patient by changing the nutritional and insulin inputs while keeping the $S_I(t)$ and $p_g(t)$ profile the same. In other words potential improvements to the current protocol can be tested without requiring a full intervention clinical trial. This approach ensures that before any new clinical trial, a protocol would have been shown to be "safe" and is optimized for the best possible patient outcome.

2.3 Plasma Insulin response

In the SPRINT protocol [4,5], a bolus of insulin is given on the hour with a lower background infusion given throughout the hour. The magnitude of the bolus depends on the patients' physiology and what is required in the protocol. For example, the current protocol (SPRINT) maintains a glucose concentration between 4 and 7 mmol/L. The insulin bolus is modeled as a constant infusion over one minute. Figure 3 shows a typical patient response over one hour to both a bolus and constant infusion of insulin.

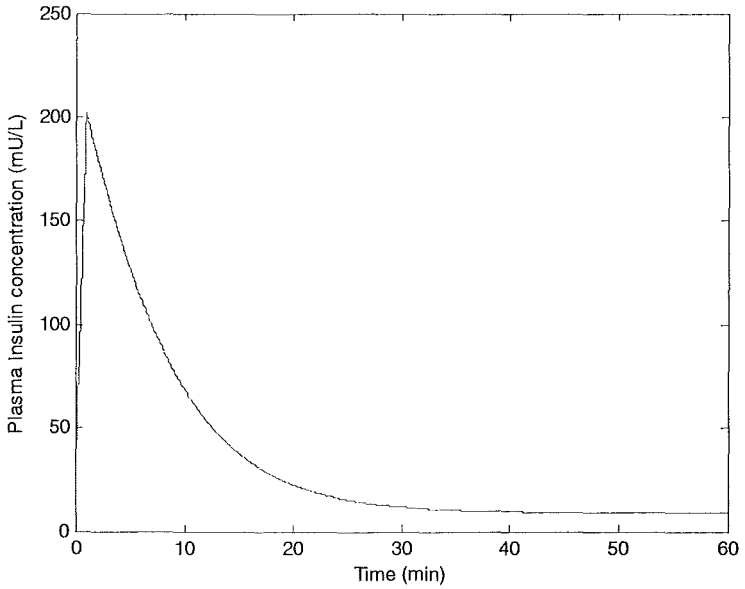

Figure 3: Typical patient Insulin response to a bolus and background infusion.

Figure 3 is obtained by solving equation (3) numerically given the parameters:

$$n = 0.16,\ \alpha_I = 0.0017,\ V = 12,\ u_{ex} = \begin{cases} 2400\dfrac{mU}{\min} \\ 17\dfrac{mU}{\min} \end{cases},$$

and the initial condition $I(0) = 17\dfrac{mU}{L}$.

The goal in this section is to find an accurate closed form analytical expression for $I(t)$ that is very fast to evaluate. Another important requirement on the expression for $I(t)$ is that it is easily integrable and thus can be put into equation (2) to obtain a simple analytical solution for $Q(t)$.

However, the major problem with finding a relatively simple solution to equation (3) is the saturation term; $-n \cdot I(t)/(1+\alpha_1 \cdot I(t))$. Therefore it was initially investigated to see what effect the assumption $\alpha_1 = 0$ has on results. Figure 4 overlays the solution of Equation (3) with $\alpha_1 = 0.0017$ and $\alpha_1 = 0$.

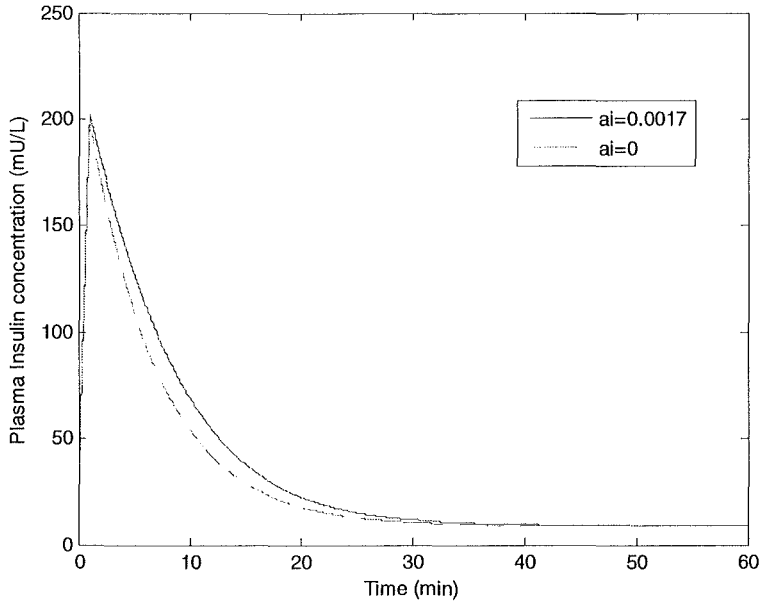

Figure 4: Plasma Insulin response with and without saturation

The error between the two curves in figure 4 is significant, especially from 1 to 30 minutes where the mean relative error is 14.8%. However it is the effect on the glucose concentration which is the most important. To test this one patient was simulated with and without the saturation term. Figures 5 and 6 show two examples of the effect that the saturation term has on the glucose concentration. In Figure 5 only an insulin bolus is

given, and the effect of the saturation term is very prominent producing a relative mean error of 14.92%. The error also propagates through the trial. In Figure 6 the glucose response is to a background infusion of insulin only, and the effect of the saturation is far less than Figure 5, producing a mean relative error of 1.91%. Since, the SPRINT protocol uses bolus insulin inputs the saturation term cannot be ignored.

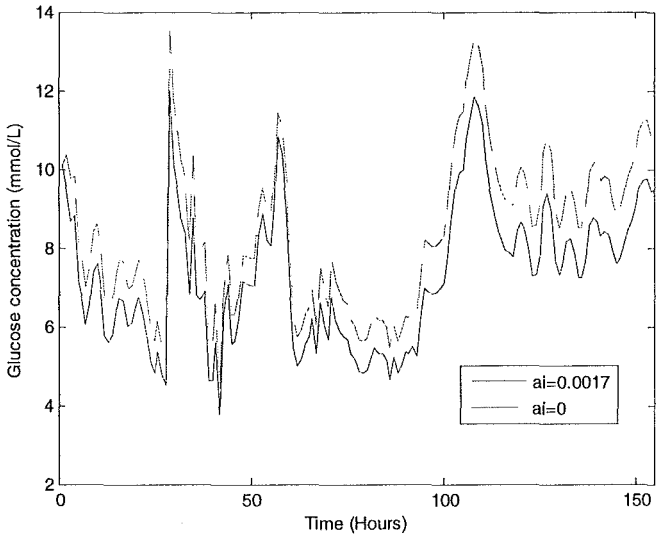

Figure 5: Glucose response of patient 87 (#REF) to insulin bolus only.

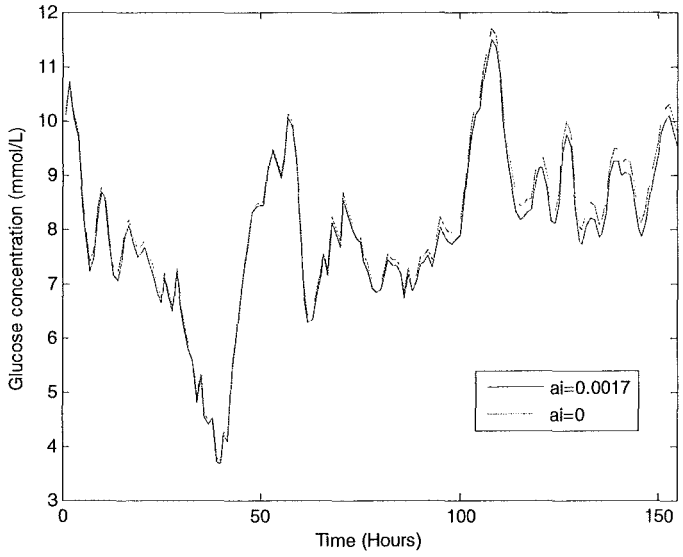

Figure 6: Glucose response of patient 87 (#REF) to background infusion only.

With $\alpha_1 \neq 0$ in Equation (3) an analytical solution was found in MAPLE in the period from 1 to 60 where there is no bolus and only a background constant infusion. The solution could not be extended to include the first minute and thus could not handle the sudden jump in u_{ex} of Equation (3) due to the bolus. One option here would be to

numerically solve equation (3) over 1 minute, but this typically requires a step size of less than 0.01 for sufficient accuracy, potentially slowing the algorithm down.
However, as can be seen in figure 3 the plasma insulin concentration in the first minute is close to linear. Thus one approach to speed up the solution to $I(t)$ in the first minute would be to assume a general linear function for $I(t)$ defined as follows:

$$I(t) = I(0) + a_0 \cdot t \quad , 0 \le t \le 1 \tag{6}$$

Where the parameter a_0 is found so that equation (6) satisfies equation (3) at $t = 1$.
To find a_0, both sides of Equation (3) are multiplied by $(1 + \alpha_I I(t))$ and is thus written in the following form:

$$(1 + \alpha_I I(t))\dot{I}(t) + nI(t) - \frac{u_b}{V}(1 + \alpha_I I(t)) = 0 \tag{7}$$

where $u_{ex} = u_b$ is the magnitude of the bolus.
Substituting equation (6) into Equation (7) and putting $t = 1$ yields:

$$\alpha_1 \cdot a_0^{\,2} + \left(1 + \frac{u_b \cdot \alpha_1}{V} + \alpha_I \cdot I(0) + n\right) \cdot a_0 + n \cdot I(0) - \frac{u_b}{V} - \frac{u_b \cdot \alpha_I \cdot I(0)}{V} = 0 \tag{8}$$

Equation (8) is a quadratic equation in a_0 and has two roots:

$$a_0 = \frac{-b \pm \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}; \tag{9}$$

where:

$$a = \alpha_I \,,\; b = \left(1 + \frac{u_b \cdot \alpha_1}{V} + \alpha_I \cdot I(0) + n\right),\; c = \left(n \cdot I(0) - \frac{u_b}{V} - \frac{u_b \cdot \alpha_I \cdot I(0)}{V}\right) \tag{10}$$

Through extensive numerical simulation with physiological bounds on u_b and $I(0)$, the root that gave the correct insulin value on forward simulation was found to consistently be:

$$a_0 = \max\left(\frac{-b \pm \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}\right) \tag{11}$$

where a, b, c are given In equation (10).
The approach of Equations (6)-(11) is referred to as a differential method as it involves differentiating the model curve approximation. An example of the differential method is given in Table 1 below, which shows that the approximated $I(t)$ significantly undershoots the true $I(t)$.

Table 1: Comparison of different methods of approximating insulin response

Approximation Method	Differential	Integral
Linear	172.5983236	179.8588913
Parabolic	180.7999280	180.0200918
Actual	180.00533936	N/A

An alternative approach is to integrate equation (7) first from 0 to t then substitute equation (6). Integrating and expanding Equation (7) yields:

$$\int_0 \dot{I}(t)dt + \alpha_I \int_0 I(t)\cdot \dot{I}(t)dt + n\int_0 I(t)dt - \frac{u_b \cdot \alpha_I}{V}\int_0 I(t)dt - \frac{u_b}{V}\int_0 dt = 0 \tag{12}$$

Replacing $I(t)\cdot \dot{I}(t)$ with $\left(\frac{1}{2}I(t)^2\right)'$ and collecting terms:

$$\int_0 \dot{I}(t)dt + \alpha_I \int_0 \left(\frac{1}{2}I(t)^2\right)' dt + \left(n - \frac{u_b \cdot \alpha_I}{V}\right)\int_0 I(t)dt - \frac{u_b}{V}\int_0 dt = 0 \tag{13}$$

which after further simplification yields:

$$I(t) - I(0) + \frac{\alpha_I}{2}\left(I(t)^2 - I(0)^2\right) + \left(n - \frac{u_b \cdot \alpha_I}{V}\right)\cdot \int_0 I(t)dt - \frac{u_b}{V}\cdot t = 0 \tag{14}$$

In a similar way to equation (8), equation (6) is then substituted into the integral formulation of equation (14) with $t=1$, giving a quadratic equation in a_0 defined as follows:

$$\frac{1}{2}\alpha_I a_0^{\,2} + \left(\alpha_I I(0) + \frac{n}{2} - \frac{u_b \alpha_I}{2V} + 1\right)a_0 + nI(0) - \frac{u_b \alpha_I I(0)}{V} - \frac{u_b}{V} = 0 \tag{15}$$

After simulation, the correct root a_0 of Equation (15) is found to be:

$$a_0 = \max\left(\frac{-b \pm \sqrt{b^2 - 4\cdot a\cdot c}}{2\cdot a}\right) \tag{16}$$

where:

$$a = \frac{1}{2}\alpha_I, b = \left(\alpha_I I(0) + \frac{n}{2} - \frac{u_b \alpha_I}{2V} + 1\right) \text{and } c = nI(0) - \frac{u_b \alpha_I I(0)}{V} - \frac{u_b}{V} \tag{17}$$

Equations (12)-(17) is referred to as an integral method and the results of an example are given in Table 1, which shows a significantly more accurate approximation to $I(t)$ than the differential method of equations (6)-(11) This was also found to be the case with many simulations of different bolus sizes and initial conditions, showing that the integral method is significantly more accurate than the differential method. These results could be explained by the well known fact that differentiation in general magnifies noise/error where integrals are more robust [14].

Even though the linear function in Equation (6) gave a good approximation to the solution for the integral method, in practice, equations (2)-(5) must be solved with a potentially different S_I, p_g, u_{ex} and $P(t)$ every hour. Thus an error in one hour will carry over to an error in the next hour and so on. To reduce this propagation of error, the slight non-linearity in the first minute of $I(t)$ is modeled by adding a parabolic term to equation (6) and setting $a_0 = \dot{I}(0)$, yielding:

$$I(t) = I(0) + \dot{I}(0)\cdot t + a_1 \cdot t^2 \tag{18}$$

For the integral method, substituting equation (18) into equation (14) also yields a quadratic equation, which has the following correct root:

$$a_1 = \max\left(\frac{-b \pm \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}\right) \tag{19}$$

where:

$$a = \frac{\alpha_I}{2}, b = 1 + \frac{n}{3} - \frac{u_b}{3 \cdot V} + \alpha_I \left(I(0) + i(0)\right),$$

$$c = i(0) + \frac{\alpha_I}{2}\left(I(0) + \left(I(0) + i(0)\right)^2\right) - \frac{u_b}{V} + \left(n - \frac{u_b \alpha_I}{V}\right)\left(I(0) + \frac{i(0)}{2}\right) \tag{20}$$

The derivative method is similar to equations (6)-(11) so the details are omitted.
Table 1 shows that for a parabolic approximation both methods improve the result but the integral method is significantly more accurate. Note that given the a_1 from the integral method of Equations (18)-(20), a cubic term could be added, or a quartic term and so on to improve accuracy, but the parabolic approximation was found to be sufficiently accurate.

2.4 Insulin approximation after first minute

Using the MAPLE software package the solution of Equation (3) is written in the form:

$$I(t) = b_0 e^{\left(b_1 - n_1 t - LambertW(\bar{t})\right)} + b_2 \tag{21}$$

where:

$$u_I = \frac{u_{ex}}{V}, b_0 = -\frac{\left(u_I - I(1)n + I(1)\alpha_I u_I\right)}{-n + u_I \alpha_I}, n_1 = -\frac{\left(-n + u_I \alpha_I\right)^2}{n}$$

$$, b_1 = \frac{{u_I}^2 {\alpha_I}^2 - 2nu_I \alpha_I - I(1){\alpha_I}^2 u_I + n^2 - u_I \alpha_I + I(1)\alpha_I n}{n}, \quad b_2 = \frac{u_I}{-n + u_I \alpha_I} \quad \text{and}$$

$$\bar{t} = \frac{\alpha_I \left(-n + u_I \alpha_I\right)}{n} b_0 e^{(n_1 t + b1)} \tag{22}$$

The LambertW function is defined as the solution $y = LambertW(t)$ to the equation:

$$y \cdot e^y = t \tag{23}$$

Equation (21) can be further simplified as follows:

$$I(t) = b_0 e^{-lambertW(\bar{t})} e^{b_1 - n_1 t} + b_2 \tag{24}$$

From Equation (23);

$$e^{-lambertW(\bar{t})} = e^{-y} = \frac{y}{\bar{t}} = \frac{lambertW(\bar{t})}{\bar{t}} \tag{25}$$

Equation (25) can then be simplified:

$$I(t) = b_0 \left(\frac{lambertW(\bar{t})}{\bar{t}}\right) e^{b_1 - n_1 t} + b_2 \tag{26}$$

$$= B_0 \left(\frac{lambertW(\bar{t})}{\bar{t}}\right) e^{-n_1 t} + b_2 \tag{27}$$

where:

$$B_0 = b_0 e^{b_1} \tag{28}$$

Figure 7 shows the function $B_o\left(\frac{lambertW(\bar{t})}{\bar{t}}\right)$ over the range of t from 1 to 60 with the input of: $I(0)=140$, $u_1 = 3$. To satisfy the criteria that $I(t)$ function is integrable and that the resulting Equation (2) can be solved easily.

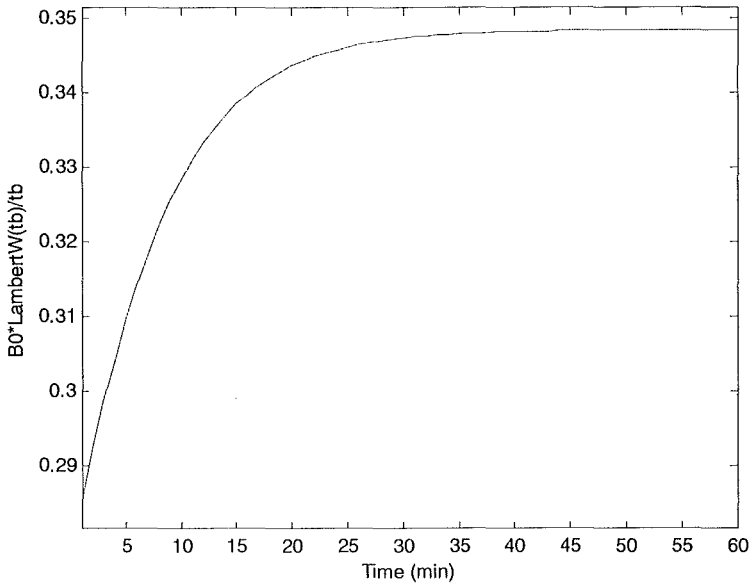

Figure 7: The $B_0 \frac{lambertW(\bar{t})}{\bar{t}}$ function over t from 1 to 60 min

The curve in Figure 7 is represented by a linear function:

$$B_0 \frac{lambertW(\bar{t})}{\bar{t}} \approx B_1 + B_2 t \tag{29}$$

where B_1 and B_2 are arbitrary constants. Substituting into Equation (27) yields:

$$I(t) = (B_1 + B_2 t)e^{-n_1 t} + b_2 \tag{30}$$

$$= b_2 + B_1 e^{-n_1 t} + B_2 t e^{-n_1 t} \tag{31}$$

For further accuracy the linear term $b_3 t$ is added to take up some of the modeling error introduced in the approximation of Equation (29):

$$I(t) = b_2 + b_3 t + B_1 e^{-n_1 t} + B_2 t e^{-n_1 t} \tag{32}$$

In Equation (32) the parameters; B_1, B_2, b_2, b_3 are initially unknown constants that are determined by fitting Equation (32) to predefined points of the analytical solution $I(t)$ defined in Equations (21)-(22). Importantly, Equation (32) is easily integrated, so is suitable for developing an analytical solution for $Q(t)$ in equation (2). Note that polynomial only approximations to Equation (21) were not suitable as they required too

many terms (up to order 10) for sufficient accuracy, significantly slowing down the algorithm.

To uniquely determine the 4 constants in equation (32) at least 4 values of $I(t)$ in equation (21) would be required. However, evaluating Equation (21) was found to be very slow, predominantly due to the LambertW function which requires a numerical iterative solution y to equation (23) for every evaluation. The LambertW function was thus reformulated to speed up evaluation as follows:

Approximating ye^{y} by $e^{c_1 \cdot y} + c_2$ in equation (23) yields:

$$e^{c_1 \cdot y} + c_2 = t \tag{33}$$

Equation (33) is easily solved for y:

$$y = lambertW(t) = d_1 \ln(t + d_2) \tag{34}$$

where : $$d_1 = \frac{1}{c_1} \text{ and } d_2 = -c_2 \tag{34a}$$

The approximation of equation (34) introduces modeling error, so a third degree polynomial is added. This gives the final approximated LambertW function as:

$$LambertW(t) = a_1 \cdot \ln(t + a_2) + a_3 + a_4 \cdot t + a_5 \cdot t^2 + a_6 \cdot t^3 \tag{35}$$

Note that without the $d_1 \ln(t + d_2)$ term, very high order polynomials (>10) are required for a similar accuracy, significantly increasing the number of multiplications/divisions. The parameters a_1, a_2, a_3, a_4, a_5, a_6 best approximating the LambertW function, are found for the range $0 \le t \le 50$. The range is more than enough for representing the required evaluation of the LambertW function in equation (21) which is typically $0 \le t \le 16$.

Using equations (21)-(22) and (35) the plasma insulin concentration can be calculated throughout the hour. This information is used to find the solution to equation (32) so that a sufficiently integrable function is available to solve equation (3) for the interstitial insulin compartment. The plasma insulin concentration is found using equations (21)-(22) at 3 points through the hour: $I(10)$, $I(40)$, $I(60)$. Also using the concentration $I(1)$ obtained from equations (17)-(19). These four points are used to set up a set of linear equations:

$$\begin{bmatrix} 1 & 1 & e^{-n} & e^{-n} \\ 1 & 10 & e^{-10n} & 10e^{-10n} \\ 1 & 40 & e^{-40n} & 40e^{-40n} \\ 1 & 60 & e^{-60n} & 60e^{-60n} \end{bmatrix} \cdot \begin{bmatrix} b_2 \\ b_3 \\ B_1 \\ B_2 \end{bmatrix} = \begin{bmatrix} I(1) \\ I(10) \\ I(40) \\ I(60) \end{bmatrix} \tag{36}$$

The solution of Equation (35) gives the coefficients of equation (32).

2.5 Interstitial Insulin compartment

The interstitial insulin compartment represents insulin that has been bounded to the interstitial sites [15] which can be utilized over time. Figure 6 shows a typical interstitial insulin response to an exogenous insulin bolus and background infusion.

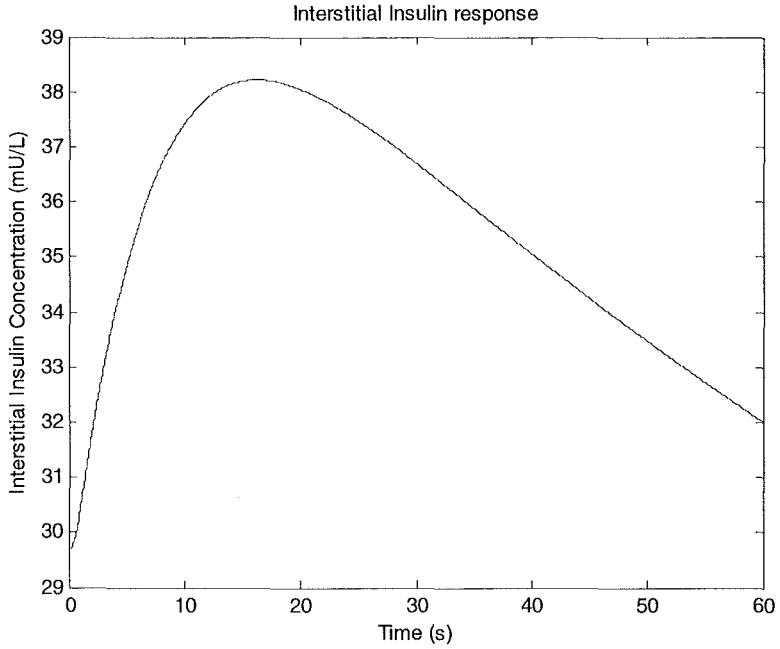

Figure 6: Interstitial Insulin response

The curve in figure 6 is obtained by numerically solving equations (2) and (3) with $k = 0.0099$ and plotting $Q(t)$. An analytical solution for $Q(t)$ is constructed in two parts. In the first part, the parabolic approximation of the plasma insulin response in the first minute given by equations (18)-(20) are substituted into equation (2) which yields:

$$\dot{Q}(t) = -k \cdot Q(t) + k \cdot \left(I(0) + \dot{I}(0) \cdot t + a_1 \cdot t^2\right), \quad 0 \le t \le 1 \tag{37}$$

Equation (36) is then solved in MAPLE producing an analytical solution over the first minute defined as follows:

$$Q(t) = I(0) + \dot{I}(0) \cdot t - \frac{\dot{I}(0)}{k} + a_1 \cdot t^2 - \frac{2 \cdot a_1 \cdot t}{k} + \frac{2 \cdot a_1}{k^2} - \frac{\left(I(0) \cdot k^2 - \dot{I}(0) \cdot k + 2 \cdot a_1 - Q(0) \cdot k^2\right) \cdot e^{-k \cdot t}}{k^2} \tag{38}$$

The solution for the rest of the hour is obtained by substituting equation (32) into equation (2) and solving in MAPLE with the initial condition $Q(1) = Q_1$:

$$\begin{aligned} Q(t) = &\left(\frac{b_0 k - b_1 k t - b1}{k}\right)\left(1 - e^{k(1-t)}\right) + k\left(\frac{b_2}{k-n} + \frac{b_3\left(t(k-n)-1\right)}{(k-n)^2}\right)e^{-nt} \\ &- \left(\frac{k\left(b_2(k-n) + b_3(k-n-1)\right)}{k^3 - 2kn + n^2}\right)e^{k(1-t)-n} + Q_1 e^{k(1-t)} \end{aligned} \tag{39}$$

The value of Q_1 in Equation (39) is found by setting $t = 1$ in equation (38).

Equation (39) can then be evaluated to find the interstitial insulin concentration throughout the hour.

2.6 Glucose response

Given a closed form, integral expression for $\overline{Q}(t)$ the glucose Equation (1) can be solved by an integrating factor so that it can be solved as shown below:

Equation (5) is rewritten in the form:

$$\dot{G}_{total} + \overline{Q}(t)G_{total} = d_0 + d_1 e^{-k_p t} \tag{40}$$

where:

$$\overline{Q}(t) = p_G + S_I \frac{Q(t)}{1+\alpha_I Q(t)} \text{ and } d_0 + d_1 e^{-k_p t} = p_g G_{eq} + P(t) \tag{41}$$

The integrating factor is introduced as:

$$\mu(t) = e^{\int_0^t \overline{Q}(t)dt} \tag{42}$$

$$\mu'(t) = \overline{Q}(t) e^{\int_0^t \overline{Q}(t)dt} \tag{43}$$

However currently even though the $\overline{Q}(t)$ is integrable a cubic polynomial is used as an approximation:

$$\overline{Q}(t) = f_0 + f_1 t + f_2 t^2 + f_3 t^3 \tag{44}$$

The coefficients of equation (44) were found by evaluating $\overline{Q}(0)$, $\overline{Q}(20)$, $\overline{Q}(40)$ and $\overline{Q}(60)$, then setting up the set of equations:

$$\begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 20 & 20^2 & 20^3 \\ 1 & 40 & 40^2 & 40^3 \\ 1 & 60 & 60^2 & 60^3 \end{bmatrix} \cdot \begin{bmatrix} f_0 \\ f_1 \\ f_2 \\ f_3 \end{bmatrix} = \begin{bmatrix} \overline{Q}(0) \\ \overline{Q}(20) \\ \overline{Q}(40) \\ \overline{Q}(60) \end{bmatrix} \tag{45}$$

Solving equation (45) gives the coefficients of equation (44).

Substituting equation (44) into (42) gives:

$$\mu(t) = e^{\int_0^t f_0 + f_1 t + f_2 t^2 + f_3 t^3 dt} \tag{46}$$

$$= e^{f_0 t + f_1 \frac{t^2}{2} + f_2 \frac{t^3}{3} + f_3 \frac{t^4}{4}} \tag{47}$$

This integrating factor is used by multiplying Equation (40) by Equation (42) giving:

$$\mu(t)\dot{G}_{total} + \overline{Q}(t)\mu(t)G_{total} = \mu(t)\left(d_0 + d_1 e^{-k_p t}\right) \tag{48}$$

By making the substituting of Equation (43) yields:

$$\mu(t)\dot{G}_{total} + \mu'(t)G_{total} = \mu(t)\left(d_0 + d_1 e^{-k_p t}\right) \tag{49}$$

The term on the RHS of equation is recognized as the derivative of a product:

$$\left(\mu(t)\cdot G_{total}(t)\right)' = \mu(t)\cdot\left(d_0 + d_1 e^{-k_p t}\right) \tag{50}$$

Integrating both sides of equation (46) from 0 and t yields:

$$\int_0^t \left(\mu(t)\cdot G_{total}(t)\right)' dt = \int_0^t \mu(t)\cdot\left(d_0 + d_1 e^{-k_p t}\right)dt \tag{51}$$

Giving:

$$\mu(t)G_{total}(t) - \mu(0)G(0) = \int_0^t \mu(\tau)\cdot\left(d_0 + d_1 e^{-k_p \tau}\right)d\tau \tag{52}$$

Which can be rearranged for $G_{total}(t)$ as follows:

$$G_{total}(t) = \int_0^t \left(\left(d_0 + d_1\cdot e^{-k_p\cdot\tau}\right)\cdot\frac{\mu(\tau)}{\mu(t)}\right)d\tau + \frac{G_{total}(0)}{\mu(t)} \tag{53}$$

The function inside the integral in equation (53) is not readily integrable due to the $\frac{\mu(\tau)}{\mu(t)}$ term. Similarly to equations (44)-(45) $\overline{\mu}(t) = \frac{\mu(\tau)}{\mu(t)}$ is approximated with the cubic:

$$\overline{\mu}(t) = g_0 + g_1 t + g_2 t^2 + g_3 t^3 \tag{54}$$

This makes equation (53) integrable giving:

$$G_{total}(t) = \int_0^t \left(\left(d_0 + d_1 e^{-k_p\tau}\right)\left(g_0 + g_1\tau + g_2\tau^2 + g_3\tau^3\right)\right)\cdot d\tau \tag{55}$$

Evaluating the equation (55) yields:

$$G_{total}(t) = \left(-\frac{d_1\cdot\left(\left(g_3\cdot t^3 + g_2\cdot t^2 + g_1\cdot t + g_0\right)\cdot k_p{}^3 + \left(3\cdot g_3\cdot t^2 + 2\cdot g_2\cdot t + g_1\right)\cdot k_p{}^2 + \left(6\cdot g_3\cdot t + 2\cdot g_2\right)\cdot k_p + 6\cdot g_3\right)}{k_p{}^4}\right)\cdot e^{-k_p\cdot t}$$
$$+\left(\frac{1}{4}\cdot g_3\cdot t^4 + \frac{1}{3}\cdot g_2\cdot t^3 + \frac{1}{2}\cdot g_1\cdot t^2 g_0\cdot t\right)d_0 + \frac{\left(6\cdot g_3 + 2\cdot g_2\cdot k_p + g_1\cdot k_p{}^2 + g_0\cdot k_p{}^2\right)\cdot d_1}{k_p{}^4} \tag{56}$$

3 Results

3.1 Uncontrolled virtual patients

In the retrospective trial of 17 ICU patients in [7] the patients were effectively uncontrolled due to insulin being administered "ad-hoc" by clinical staff using their own discretion and experience. The insulin sensitivity profiles obtained in [7] provided the means to carry out "virtual" clinical trials using the method explained in section 4 and also numerical simulation methods. Comparing the method in section 2 with the numerical simulation provides the metric to determine how robust and accurate the new method is. Figure 8 below shows both simulation methods of patient 87 from the ICU cohort. The absolute relative percentage error between the curves is 0.089% with the 90% confidence interval from 0.069% to 0.078%.

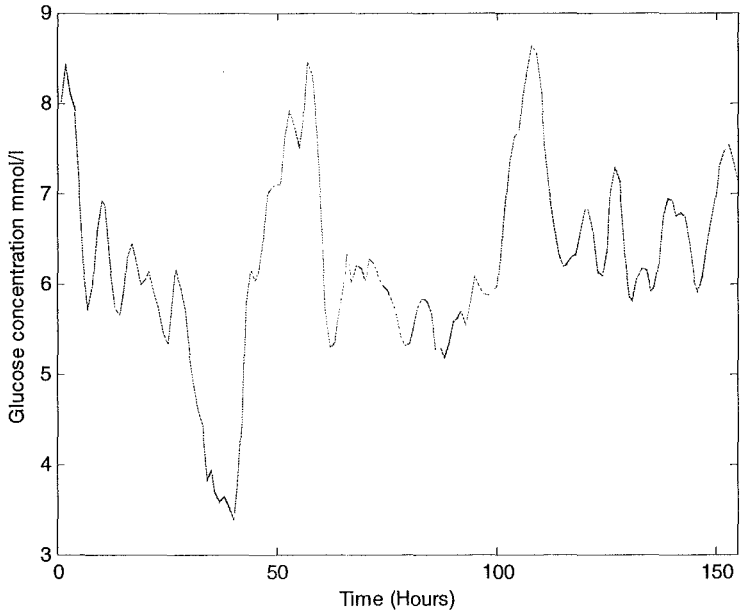

Figure 8: Numerical and analytical simulations of patient 87

Table 1 below shows the statistics of the relative percentage error between the numerical simulation and the method described in this paper, for the whole 17 patient cohort. The patients were simulated twice, one with only a background infusion of insulin input and the other with only bolus insulin input. Over the whole cohort the mean relative error was found to be very small especially for simulation receiving insulin through background error. Whereas the mean relative error for the simulation with only bolus insulin input, was found to be larger due to the saturation term in equation (3) effecting the insulin bolus input far more than the background infusion.

Table 2: Statistics of uncontrolled patient virtual trials

Patient Number	Mean		Median	Median	Lower quartile	Upper quartile	Lower quartile	Upper quartile	Lower 90% CI	Upper 90% CI	Lower 90% CI	Upper 90% CI
	Infusion	Bolus	Infusion	Bolus	Infusion	Infusion	Bolus	Bolus	Infusion	Infusion	Bolus	Bolus
1	0.111	0.126	0.084	0.115	0.041	0.135	0.052	0.077	0.040	0.178	0.094	0.338
	0.089	0.229	0.078	0.169	0.486	0.106	0.211	0.053	0.069	0.078	0.132	0.110
	0.166	0.173	0.061	0.094	0.087	0.018	0.435	0.304	0.064	1.125	0.166	0.506
4	0.112	0.359	0.072	0.277	0.079	0.306	0.181	0.244	0.096	0.059	0.024	1.017
	0.115	0.399	0.060	0.348	0.050	0.056	0.209	0.573	0.002	0.129	0.503	0.253
	0.102	0.240	0.050	0.144	0.050	0.024	0.116	0.072	0.227	0.069	0.511	0.328
7	0.168	0.095	0.158	0.070	0.095	0.247	0.014	0.103	0.062	0.235	0.019	0.063
	0.140	0.192	0.043	0.123	0.002	0.028	0.465	0.382	0.036	0.238	0.578	0.366
	0.094	0.381	0.057	0.294	0.142	0.247	0.084	0.591	0.036	0.011	0.379	0.106
10	0.128	0.255	0.084	0.199	0.024	0.019	0.065	0.223	0.187	0.074	0.175	0.032
	0.045	0.169	0.018	0.147	0.014	0.052	0.032	0.075	0.073	0.007	0.212	0.155
	0.190	0.465	0.138	0.388	0.152	0.212	0.168	0.400	0.030	0.121	0.562	0.160
13	0.065	0.190	0.043	0.121	0.055	0.089	0.001	0.278	0.026	0.043	0.647	0.212
	0.156	0.258	0.127	0.199	0.276	0.086	0.014	0.133	0.116	0.013	0.030	0.096
	0.062	0.245	0.042	0.136	0.024	0.083	0.150	0.021	0.079	0.042	0.375	0.194
16	0.492	0.395	0.381	0.289	0.717	0.145	1.532	0.520	0.635	0.119	0.113	0.024
	0.064	0.360	0.035	0.227	0.045	0.002	0.158	0.140	0.038	0.088	0.251	0.030

3.2 SPRINT trials

Similarly the patients that were on the SPRINT protocol were simulated using both simulation methods. Table 3 below shows the statistics of the relative error between the two methods of a random selection of the 51 patients. Similarly to the patients in the 17 patient ICU cohort the errors are very minimal. Table 4 below shows similar statistics but for the whole cohort.

Table 3: Statistics of SPRINT patients

Patient	Mean	Median	Lower quartile	Upper Quartile	Lower 90% CI	Upper 90% CI
2	0.188118	0.184593	0.132298	0.235058	0.268436	0.168518
20	0.15563	0.150717	0.126189	0.186866	0.126653	0.183414
35	0.155091	0.140964	0.17444	0.241625	0.106719	0.094491
43	0.32469	0.279172	0.375171	0.267716	0.717453	0.281026
46	0.234352	0.209837	0.204789	0.253927	0.133744	0.307065

Table 4: Statistics of whole SPRINT cohort

Patient	Mean	Median	Lower quartile	Upper Quartile	Lower 90% CI	Upper 90% CI
Total cohort	0.232189	0.196952	0.259557	0.438311	0.386066	0.276299

4 Discussion and Conclusions

The concept of "Model-based Therapeutics" and the importance of fast forward simulation for enabling the rigorous testing of protocols was introduced in this paper. For a non-linear glucose-insulin model an analytical solution was created by exploiting structure and partial solutions in a subset of model and writing in terms of integrable functions in physiological ranges. The key idea was to taylor the solutions to the specific application which was the rapid calculation of glucose values only on the hour given bolus, infusion and feed inputs. The current method uses a numerical solution which computes the glucose at every small time step within the hour dramatically slowing down simulation speed and hindering the number of protocols etc that could be tested.

The analytical approach gave speed increases 6000 times faster than the current numerically based approach and very accurate solutions were found with means typically around 0.1% and a standard deviation similar. This has already had a significant impact on the ability to develop improved SPRINT protocols as turn around time has been massively improved.

Future work will look at extending and applying the concept in this paper to other areas of bio-medical engineering, in particular, cardiac modelling and insulin sensitivity testing. Note that the most fundamental aspect of the approach is the highly efficient storing and manipulation of data based on knowledge of the structure as compared to a black box interpolation based look up table which would require huge numbers of data points to store and be very computationally expensive.

Another way of looking at the approach in this paper is that the partial solutions found are invariant expressions with respect to the varying inputs, in this case infusion, bolus and feeds. By separating parts of the model which have generalizable solutions with respect to these inputs, dramatic computational savings can be obtained. The solutions themselves represent invariants in the respect that their structure (e.g. always a LambertW function structure) remains the same no matter what the input.

5 References

[1] G. Van den Berghe, A. Wilmer, G. Hermans, W. Meersseman, P. J. Wouters, I. Milants, E. Van Wijngaerden, H. Bobbaers, and R. Bouillon, "Intensive Insulin Therapy in the Medical ICU," *N Engl J Med*, vol. 354, pp. 449-61, 2006.

[2]. Chase, JG, Shaw, GM, Lin, J, Doran, CV, Hann, CE, Robertson, MB, Browne, PM, Lotz, T, Wake, GC and Broughton, R (2005). "Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care," Medical Engineering and Physics, Vol 27(1), pp. 1-11, ISSN: 1350-4533.

[3] Wong, XW, Chase, JG, Shaw, GM, Hann, CE, Lotz, T, Lin, J, Singh-Levett, I, Hollingsworth, L, Wong, OS and Andreassen, S (2006). "Model Predictive Glycaemic Regulation in Critical Illness using Insulin and Nutrition Input: a Pilot Study," Medical Engineering and Physics, Vol. 28(7) pp. 665-681, ISSN: 1350-453

[4]. Lonergan, T, LeCompte, A, Willacy, M, Chase, JG, Shaw, GM, Wong, XW, Lotz, T, Lin, J, and Hann, CE (2006). "A Simple Insulin-Nutrition Protocol for Tight Glycemic Control in Critical Illness: Development and Protocol Comparison," Diabetes Technology & Therapeutics (DT&T), Vol 8, pp. 191-206, ISSN: 1520-9156.

[5] Lonergan, T, LeCompte, A, Willacy, M, Chase, JG, Shaw, GM, Hann, CE, Lotz, T, Lin, J, and Wong, XW (2006). "A Pilot Study of the SPRINT Protocol for Tight Glycaemic Control in Critically Ill Patients," Diabetes Tech & Therapeutics (DT&T), Vol. 8(4), pp. 449-462, ISSN: 1520-9156

[6] J.S. Krinsley, Effect of an intesnsvie glucose management protocol on the mortalit of critically ill adult patients, Mayo Clin. Proc. 79 (8) (2004) 992-1000.

[7] Hann, CE, Chase, JG, Lin, J, Lotz, T, Doran, CV, and Shaw, GM (2005). "Integral-Based Parameter Identification For Long-Term Dynamic Verification Of A Glucose-Insulin System Model," Computer Methods and Programs in Biomedicine, Vol 77(3), pp. 259-270, ISSN: 0169-2607

[8]. Hann, CE, Chase, JG and Shaw, GM (2006). "Integral-Based Identification of Patient Specific Parameters for a Minimal Cardiac Model," Computer Methods and Programs in Biomedicine, 81(2), pp. 181-192, ISSN: 0169-2607

[9]. Hann, CE, Chase J G, Andreassen S, Smith B W, Shaw G M (2005). "Diagnosis Using a Minimal Cardiac Model Including Reflex Actions," Intensive Care Medicine, Vol 31(S1), pp. S18, September 2005, ISSN: 0342.

[10]. Starfinger C, Hann, CE, Chase, JG, Desaive T, Ghuysen A and Shaw, GM (2006). "Model-based Cardiac Diagnosis of Pulmonary Embolism," Computer Methods and Programs in Biomedicine, accepted December 2006 – to appear, ISSN: 0169-2607

[11]. Lotz, T, Chase, JG, Shaw, GM, McAuley, KA, Wong, XW, Lin, J, LeCompte, A, Hann, CE and Mann, JI (2007). "Monte Carlo analysis of a new model-based method for insulin sensitivity testing," Computer Methods and Programs in Biomedicine, accepted 12/06 – to appear, ISSN: 0169-2607.

[12]. Lotz, T, Chase, JG, McAuley, KA, Lee, DS, Lin, J, Hann, CE and Mann, JI (2006). "Transient and steady state euglycemic clamp validation of a model for glycemic control & insulin sensitivity testing," Diabetes Technology & Therapeutics (DT&T), Vol 8(3), pp. 338-346, ISSN: 1520-9156.

[13] **Hann, CE,** Chase, JG and Shaw, GM (2005). "Efficient implementation of nonlinear valve law and ventricular interaction dynamics in the minimal cardiac model," Computer Methods and Programs in Biomedicine, Vol 80(1), pp. 65-74, ISSN: 0169-2607

[14] **Hann, CE** and Hickman, MS (2002) "Projective Curvature and Integral Invariants", Acta Applicandae Mathematicae, 74: 177-193.

[15] A.C. Guyton, J.E. Hall, Textbook of Medical Physiology.