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Integral Based Identification For Physiological Models

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MATH 305

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Abstract

Recently a model-based protocol has been developed for controlling glucose in the Christchurch ICU which has already had a significant clinical impact. A major part of the development involved an integral-based parameter identification method. This paper addresses the importance of an integral formulation for stability in glucose control. The method is compared to a standard derivative based method which is shown to be unstable. The integral method is shown to be highly robust to both modelling and measurement error.

Introduction

The scientific basis of insulin in diabetes is already well known and proven. Simply, the reduction of hyperglycaemia can be achieved through the infusion of exogenous insulin to the bloodstream, via infusion or bolus doses or by reducing exogenous glucose inputs. In addition, the intensive treatment of diabetes has shown significant long-term benefits in ambulatory diabetic individuals and has been shown to improve mortality in critically ill patients. A model-based protocol [1,2] has recently achieved significant mortality savings with very high apache scores and tighter controls as compared to other studies. The integral method [3] was a major part of developing the protocol [1,2]. The integral method has also been applied in many other areas [10,11,12,13,14,15].

It is very crucial to determine the reason of why the mentioned techniques were very reliable as this may enable us to improve any other methods that have been applied currently.

The integral formulation turns a non-convex problem into a convex problem. This is because the data is plugged directly into an integral formulation of the model which results in a set of linear equations in the unknown parameters. However, a potentially equivalent approach would be to plug the data directly into the usual differential form of the model. Therefore at first sight it would appear the derivative formulation should give similar answers to an integral formulation since they are essentially the same DE (just in different forms). However it is shown in this paper that the integral formulation is in fact fundamentally important to the overall method, and the derivative approach goes unstable. In particular, the derivative approach even goes unstable with smooth curves and no noise. It is also sensitive to measurement noise. The integral method on the other hand is shown to be robust to both modelling error and measurement.

Thus, in summary, in this paper, a comparison has been made between the Integral Method and Derivative Method. This comparison has been made since in general, the assumption is that both Derivative and Integral formulation should give a similar answer. By pointing out the importance of the Integral Method, this may explain the reason for the successful implementation of Integral Method in this and other applications [10-15].

2.Methodology

2.1 Integral Formulation

2.1.1 Kidney Clearance

Recent research has shown that kidney function can be studied by observing the concentration of serum Creatinine.

The research has suggested an equation as

$$\dot{C} = -KC + \frac{u}{V} \qquad (1)$$

where C is the concentration of creatinine in mmol/L, u is the constant creatinine production (mmol/min), K is kidney clearance (/min) and V is the volume of distribution (L). The normal serum creatinine concentration is about 0.06 to 0.12 mmol/L, and a healthy kidney clearance is about K=2.5e-3/min. The volume of distribution V is total body water (60% of body weight), thus for a 70 kg person, V=42L.

Integrating equation (1) will give us result as below;

$$C(t) - C(0) = -K \int_{t_0}^{t_1} C \, dt + \int_{t_0}^{t_1} \frac{u}{V} dt$$

$$= -K \int_{0}^{t_1} C \, dt + \frac{u}{V}(t_1 - t_0) \qquad (2)$$

Now the only unknown parameter is K. However, the value of K can easily computed

using the least square system. Then, the equation need to be fitted as;

$$\vec{A}\{K\} = \vec{b}$$

Thus the equation will look like,

$$\int_{0}^{t_1} C \, dt \, \{K\} = \frac{u}{V}(t_1 - t_0) - C(t) + C(0) \qquad (3)$$

2.1.2 Application on Creatinine data

The approach above can also be extended to a time varying K, either constant piecewise or linear piecewise. One application of this method has been applied to Creatinine data from ICU patients. A previously well held belief by doctors is that the production rate uc of creatinine is always constant with the formula:

$$uc=(120-1.0*age)*weight/814.464 \quad (mmol/min) \qquad (a1)$$

For a female, uc=0.85*uc. However creatinine can be measured by experiment which is a way of testing the constant uc assumption. Three patients are considered and a piecewise linear K value is found using an integral method similar to section 2.1.1. The results are shown in Figures a1-a3 which show that the constant uc assumption results in significant errors of the K values compared to the measured which is denoted by circles. In otherwords to obtain K values which best correspond to the measured, uc must be time varying. Figure a4 shows with an example, that using the integral-based parameter identification method results in a very accurate fitting of creatinine values and thus accurate resulting K values based on the constant uc assumption.

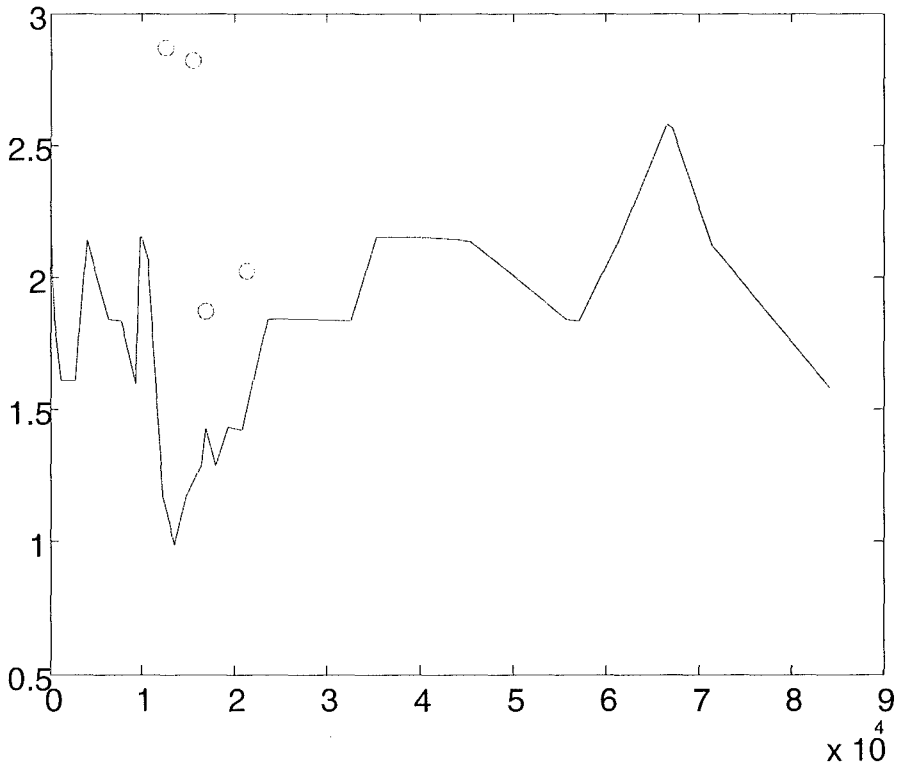

Figure a1: Patient 1's clearance rate versus time (minutes) using integral-based method (solid line) versus measured (circles)

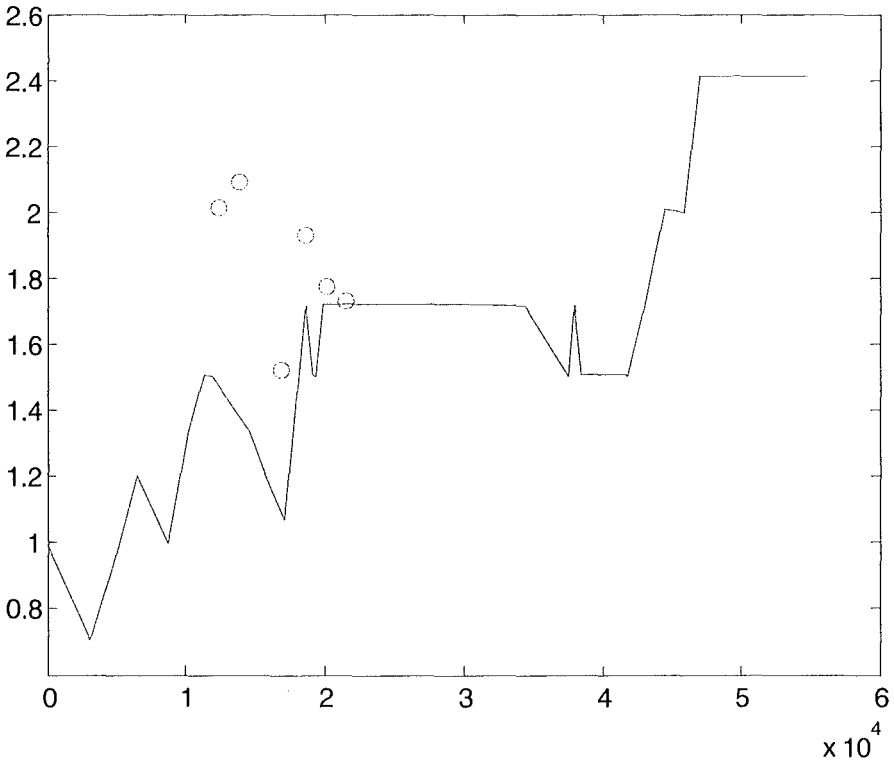

Figure a2: Patient 2's clearance rate versus measured

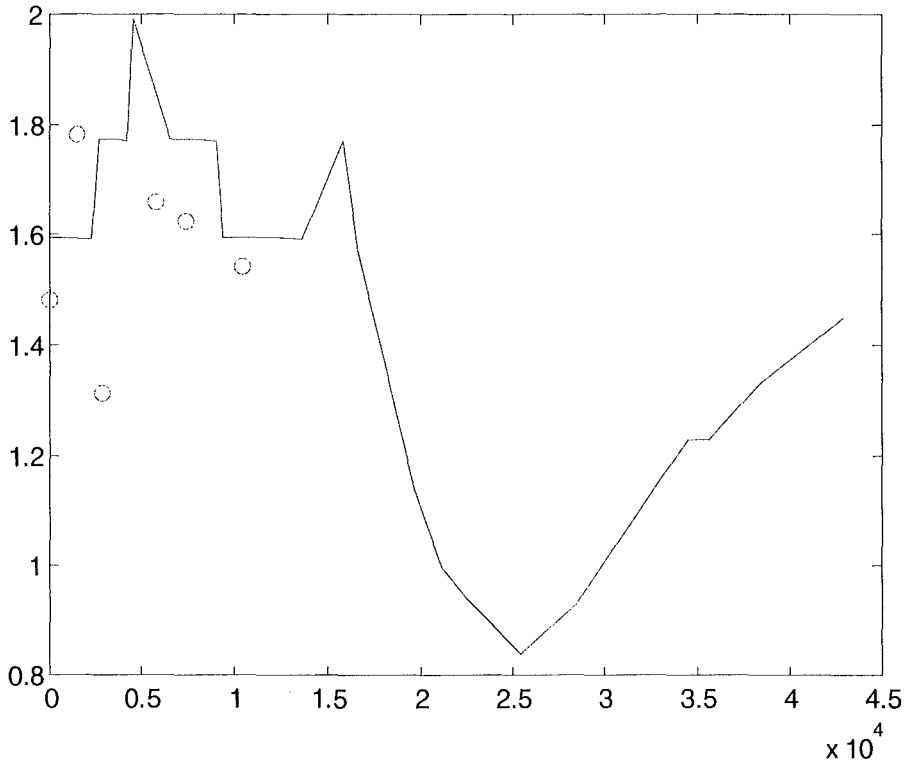

Figure a3: Patient 3's clearance rate versus measured

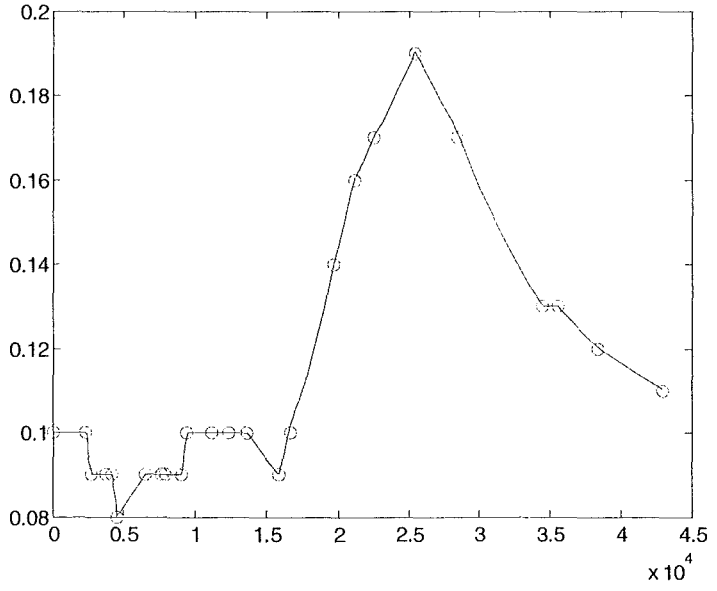

Figure a4: Fitted Creatinine values compared to measured

2.2 Application to metabolic system

The insulin sensitivity profile of a patient is used to summarize changes to the metabolic system and is the basis for testing various insulin and feed protocol.

2.2.1 Glucose-Insulin Model

Insulin sensitivity is modelled with a glucose insulin system as follows:

$$\dot{G} = -p_G G - S_I (G + G_E) \frac{Q}{1 + \alpha_G Q} + P(t) \qquad (4)$$

$$\dot{Q} = -kQ + kI \qquad (5)$$

$$\dot{I} = \frac{nI}{1 + \alpha_I I} + \frac{u(t)}{V} \qquad (6)$$

where G(t) concentration of plasma glucose above the equilibrium level.

G_E the equilibrium level of plasma glucose conc, I(t) the concentration of the plasma insulin above basal level(mU/L), I_B the basal level of plasma insulin concentration (mU/L), P(t) the exogenous glucose infusion rate (mmol/(Lmin)),u(t) the inslin infusion rate (mU/min), V_I the assumed insulin distribution volume (L), n the delay in interstitial transfer of insulin (min-1), S_I the time-varying insulin sensitivity, k the parameter controlling the effective half life of insulin (min-1), α_I the Michaelis-Menten parameter for insulin transport saturation and α_G the Michaelis-Menten parameter for glucose clearance saturation.

2.2.2 Integral-based identification of S_I

In equation (1)-(3), the parameters $n, \alpha, V_I, k, p_G, and\ \alpha_G$ are held at population values and G_E is approximated based on the mean of the patients glucose[Hann et al].

Equation (1) is first written in the form:

$$\dot{G}_T = -p_G G_T - S_I G\overline{Q} + P(t) + p_G G_E \qquad (7)$$

where

$$\overline{Q} = \frac{Q}{1+\alpha_G Q} \qquad \text{and} \quad G_T = G + G_E \text{ is the total glucose.}$$

The parameter Qbar can be precomputed for a given exogeneuos insulin input Uex(t).

In this study Uex(t) is defined as;

Uex(t)=U_i + U_b , 0<t<1

=U_i , 1<t<60

where U_i is a constant infusion over one hour and U_b is a bolus which is modelled as a constant infusion over 1 minute. The feed is assumed constant with P(t)=Po

Then, integrating equation (7) from 0 to t leads to:

$$G_T(t) - G_T(0) = -p_G \int_0^t G_T - S_I \int_0^t G_T \overline{Q} + p_G G_E (t - t_0) + P_0 t \qquad (8)$$

Insulin sensitivity Si is an unknown parameter and can be estimated from the measured glucose as follow;

Value of time t is chosen every minute in equation (8)

$$S_I \int_0^t G_T \overline{Q} = -(G_T(1) - G_T(0)) - p_G \int_0^t G_T - S_I \int_0^t G_T \overline{Q} + p_G G_E (1-0\ ) + P_0(1) \ldots\ldots\ldots$$

:

:

$$S_I \int_0^{60} G_T \overline{Q} = -(G_T(60) - G_T(0)) - p_G \int_0^{60} G_T - S_I \int_0^{60} G_T \overline{Q} + p_G G_E(60 - 0\ ) + P_0(60)$$

(10)

Equation (10) represents 60 equations in 1 unknown Si which can be rewritten as a

matrix system:

$$\vec{A}\{S_I\} = \vec{b} \qquad (11)$$

where:

$$A = [\ \int_0^{1} G_T \overline{Q}\ , \ldots, \int_0^{60} G_T \overline{Q}\ ]$$

$$B = [\ -(G_T(1) - G_T(0)) - p_G \int_0^{1} G_T + p_G G_E(1 - 0\ ) + P_0(1), \ldots\ldots\ldots\ldots$$
$$, -(G_T(60) - G_T(0)) - p_G \int_0^{60} G_T - S_I \int_0^{60} G_T \overline{Q} + p_G G_E(60 - 0\ ) + P_0(60)\ ]$$

Si is determined by solving equation (11) by least squares.

2.2.3 Derivative approach

An equivalent way and potentially simpler for construction and implementation is to substitute the data directly into the differentiation equation (4) without integrating it first.

At first sight this would appear to be the more natural way to proceed since equation (4) is the original form of the model. Furthermore, since both equation (4) and (8) have exactly the same solution for G(t), it may be reasonable to suggest that on average the parameter identification of Si based on equation (4) would give very similar results to equation (8).

In a similar way to equation (10) to (11) , a value of t in equation (4) is chosen every minute:

$$S_I G(1)\ \overline{Q}(1) = -\dot{G}_T(1) - p_G G_T(1) + p_G G_E + P_0$$

•

•

•

$$S_I G(60)\ \overline{Q}(60) = -\dot{G}_T(60) - p_G G_T(60) + p_G G_E + P_0 \qquad (12)$$

where Gt(t) can be determined by numerical differentiation.

Equation (12) is now written in matrix form:

$$\vec{A}_d \{S_I\} = \vec{b}_d \qquad (13)$$

where

Ad=[G(1) $\overline{Q}$ (1),...,.....G(1) $\overline{Q}$ (1)]

$$\text{b=[} -\dot{G}_T(1) - p_G G_T(1) + p_G G_E + P_0 \ldots\ldots -\dot{G}_T(60) - p_G G_T(60) + p_G G_E + P_0 \text{]} \qquad (14)$$

•

Equation (13) can be solved by least square to determine Si.

2.2.4 Alternative Integral Formulation

With measurement error, the value of Gt(0) may happen to be bad thus potentially corrupting equation (8) since Gt(0) is present in every equation. Thus an alternative formulation is presented as follow.

Equation (11) is written in the form:

$$\vec{A}\{S_I \quad , G_0\} = \vec{b} \qquad (15)$$

where

$$\text{A=} \quad \int_0 G_T \overline{Q}$$

$$\int_0^{60} G_T \overline{Q}$$

$$B=[\begin{matrix} -G_T(1) - p_G \int_0^1 G_T + p_G G_E(1-0\ ) + P_0(1),..... \\ ,-G_T(60) - p_G \int_0^{60} G_T - S_I \int_0^{60} G_T \overline{Q} + p_G G_E(60-0\ ) + P_0(60) \end{matrix}] \quad (16)$$

And Go=Gt(0) is treated as an extra unknown parameter

2 Results

The main goal is to test how important an integral formulation is for parameter identification and to assess the impact on glucose control applications. This is done by comparing with a potentially more natural and simpler derivative-based approach which at first sight should give similar results.

2.1 Determining the best integral method

Two different integral methods are presented in equation (10)-(11) and equation (14)-(15). To test which method is the most reliable, tests have been conducted using MATLAB. For these tests, both methods used the following parameter values

```
n=0.16;          delay in interstitial transfer of insulin
v=12;            assumed insulin distribution volume
k=0.0099;        %parameter controlling effective half life of insulin
alp_g=1/65;      %Michaelis-menten parameter for glucose clearance saturation
alp_i=0.0017;    %Michaelis-menten parameter for insulin transport saturation
S_i=0.0005;      %time varying insulin sensitivity
%S_i=0.00038;
%S_i=6.118e-4;
Pt=0.05;;        %exogenous glucose infusion rate
p_g=0.01;        %time varying fractional clearance of glucose at basal insulin
G_e=7;           %total glucose concentration or g_initial i.e G0? ask Chris or Piers
u_b=1000;
u_i=0/3;     %
```

A forward simulation of equation (4) was used to generate "measured data" every minute.

Random normally distributed measurement noise of 7% was then put on the generated

data based on the GlucoCard.

1000 sets of measurement noise were used and Si was calculated using the original

method of equations (12)-(13) and the alternative method of equations (15)-(16).

The results are shown in Table 1

Table 1 : Comparison of Integral Method 1 and Integral Method 2 with different number of points

Test 1 Noise = 7%
Ub = 4000
Ui = 0/3
The interval = minute

	Integral Method 1		**Integral Method 2 (Optimising Si and G0)**	
No of pts	Si	stdev	Si	stdev
60	4.943e-4	1.59 e-4	4.995e-4	3.69E-05
12	4.995e-4	1.57 e-4	4.980e-4	7.66E-05
6	5.045e-4	1.43 e-4	5.025e-4	9.91E-05
3	5.135e-4	1.43 e-4	5.022e-4	1.244e-4
2	5.226e-4	1.68 e-4	5.067e-4	1.347e-4

From table 1, it can be deduced that both integral method have similar results for the mean of the insulin sensitivity. However, the standard deviation on method 2 is significantly smaller than method 1, particularly for a greater number of points. Thus integral method 2 is more robust to noise and is used for future tests.

2.2 Derivative versus Integral Method

2.2.1 Varying infusion

The first test for comparing Derivative and integral methods was to let the infusion vary accordingly with no noise. The value for Si was computed for each infusion value for the integral method of equation (15)-(16) and the derivative method of equation (12)-(13). In this case only 2 measurements at t=0 and t=60 are assumed which is the case in ICU trials. Table 2 gives the results.

Table 2 : Comparison of Derivative Method and Integral Method with increasing infusion rate.

Test 2 Noise = 0%

	Derivative Method	**Integral Method 2**
u_i	Si	Si
0/3	7.542e-4	4.813e-4
100/3	5.840e-4	4.981e-4
200/3	5.396e-4	5.061e-4
300/3	5.257e-4	5.121e-4
400/3	5.233e-4	5.152e-4

From table 2, it is clear that derivative method is highly dependent on infusion rate with a very bad estimation of Si at 0 infusion even with 0% noise. The interval method remains robust to the changes. The derivative method appear to be converging to the correct value of 0.0005 as the infusion increases.

When u_i=400/3, the glucose response is close to a straight line which explain why the derivative method works well as the slope is relatively constant and there is minimum modelling error.
On the other hand as more dynamics occur, which happens for u_i=0/3, there is significantly more modelling error which the derivative approach would tend to amplify where an integral approach would reduce.

The results for the same test with 7% noise are given in Table 3.

Table 3: Comparison of Derivative Method and Integral Method with increasing infusion rate while noise is set to be 7%

Test 3 Noise = 7%

	Derivative Method		**Intergral Method 2**	
u_i	Si(mean)	stdev	Si(mean)	stdev
0/3	7.846e-4	4.313e-4	4.877e-4	2.477e-4
100/3	5.994e-4	2.457e-4	5.066e-4	1.779e-4
200/3	5.583e-4	1.850e-4	5.080e-4	1.420e-4
300/3	5.415e-4	1.503e-4	5.115e-4	1.163e-4
400/3	5.312e-4	1.389e-4	5.175e-4	1.036e-4

The means are similar to that of Table 2 as would be expected and the standard deviation

of the derivative method is significantly higher than the integral method, but this depends

on the infusion rate. With lower infusion rates (more dynamics) the standard deviation in both methods increase but the derivative method's standard deviation increases at significantly greater rate.

3.2.2 Varying number of measurement points

A new test is conducted using all the same parameters in section 2.3. The infusion rate is set to zero. The Si values are then computed for each of the different number of points with 7% error and run 1000 times simultaneously.

Table 4 : Comparison of Derivative Method and Integral Method with different number of points.

Test 4 Noise = 7%
Ub = 4000
Ui = 0/3

	Derivative Method		**Integral Method 2**	
No. of pt	Si	stdev	Si	stdev
60	1.100e-3	2.058e-4	4.998e-4	6.817e-5
12	6.198e-4	2.047e-4	4.980e-4	1.448e-4
6	5.321e-4	2.393e-4	5.003e-4	1.879e-4
3	3.708e-4	3.335e-4	5.074e-4	2.470e-4
2	7.901e-4	4.270e-4	4.960e-4	2.234e-4

For the test above, Si values from Integration Method can be seen to be stable with respect to a varying number of points. For the derivative method, the Si values follow two trends. As the number of points increase from 6 to 60, the mean Si becomes steadily worse. This is because the larger the number of points the greater the chance of one bad measurement occurring. Since a numerical derivative is required this will magnify the error corrupting result. As the number of points decrease from 6 to 2, the mean Si are

significantly unstable. This is due to the fact that for a smaller number of points the modelling error is increasing thus adding to the already present measurement error, thus further corrupting the solution. This added modelling error effect also shows up in the standard deviations of the derivative method. The integral method remains robust and gives consistent results for all number of points.

3.2.3 Impact on Glucose Control

The next step was to implement the differential and integral method into a real life scenario. The case considered is the problem of working out how much insulin bolus is needed to inject after feed is added in order to bring glucose level down to a pre-decided amount.

Figure 1 shows the glucose response response in one hour after the feed is added. The parameters are Po=0.05, Ub=2000, Ui=0, Ge=7, Go=6, Si=0.0005, where Pt is the feed, Ub is the Bolus infusion, Ui is the constant infusion, and Go is the initial glucose level.

The goal in this case is to work out the patient Si and then decide how much bolus to inject after feed is cut off in the next hour such that the glucose comes down to 7mmol/L. Figure 2 shows the result after a bolus of 0.95 units is given which is the correct amount. The integral method and derivative method are then applied to find Si by taking the median over 1000 (7%) noise simulations, and then working the at the bolus required to bring the patient to 7mmol/L.

Table 6 shows the derivative method significantly overestimated the required bolus resulting in 17.53% error in the target glucose level. The integral method was accurate with error of 1%. These results are also shown pictorially in Figure 3.

Case 1

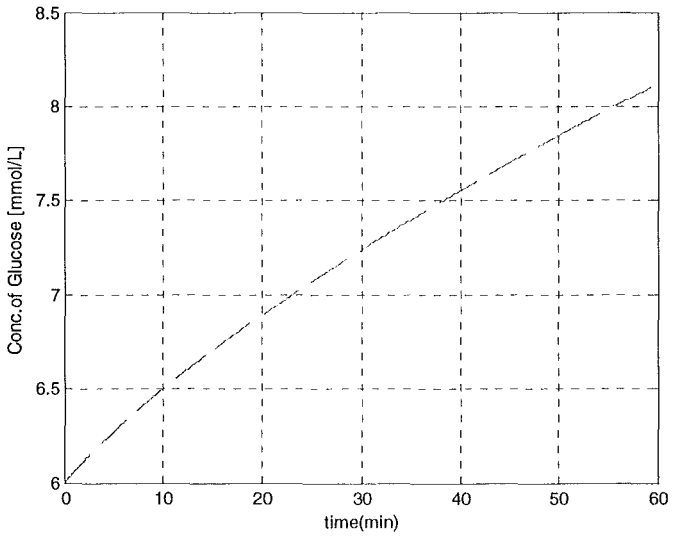

Figure 1 : Plot of patient glucose level over time before bolus was injected.

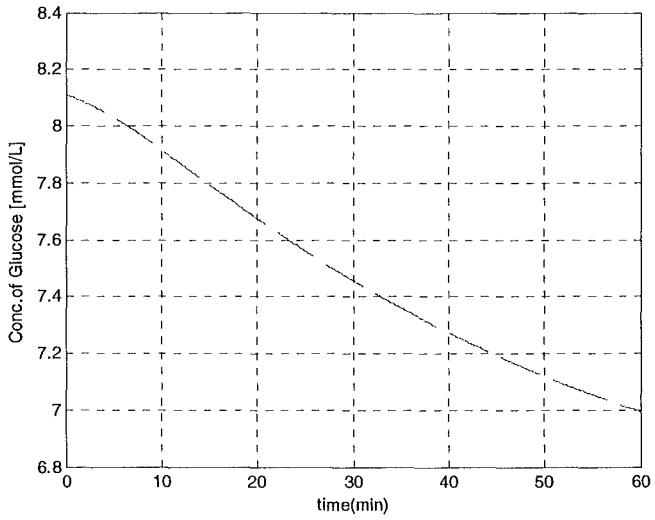

Figure 2 : Model plot of patient glucose level over time after bolus was injected.

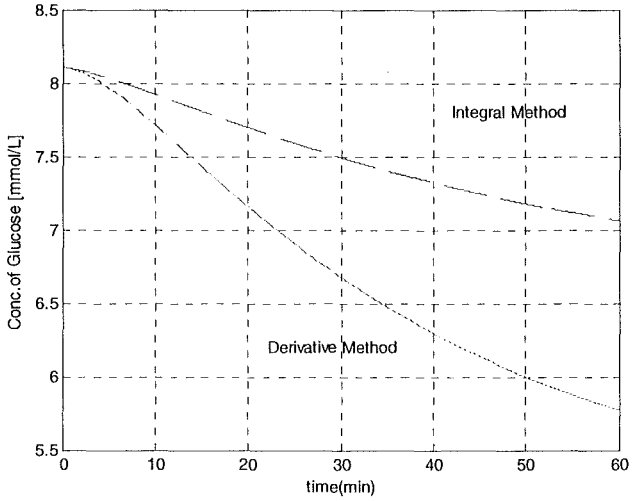

Figure 3 : Real plot of patient glucose level over time after bolus was injected.

Table 6 : Comparison of Derivative Method and Integral Method for a simulated real case scenario.

	Derivative Method	Integral Method
Bolus calculated to reach 7mmol/L	2.8 units	0.89 units
Calculated Si	1.853e-4	5.973e-4
Target glucose level	7	7
Obtained final glucose level	5.7731	7.0614
Percentage error	17.53%	0.88%

Case 2

Figure 4 shows another similar example with Po=0.03, Ub=2000, Ui=0, Ge=7, Go=5, Si=0.0005.
The goal here is to bring the patient's glucose level back down to 5 mmol/L after setting the feed to zero. The required bolus was 3.5 units and the result of applying this is shown in Figure 5.

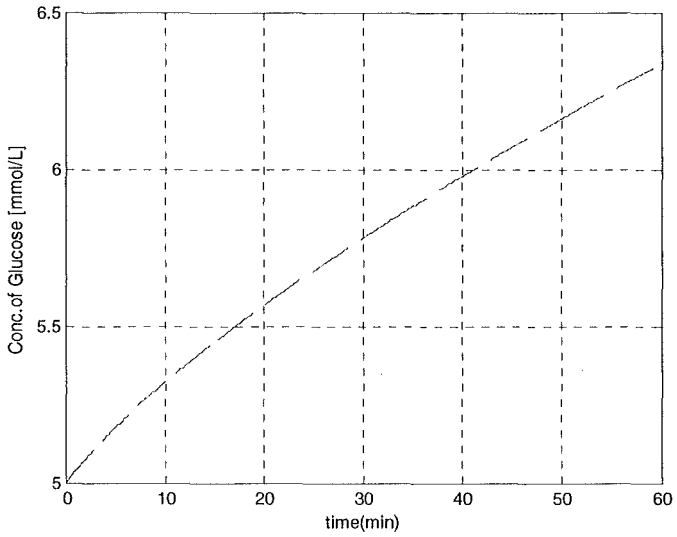

Figure 4 : Plot of patient glucose level over time before bolus was injected.

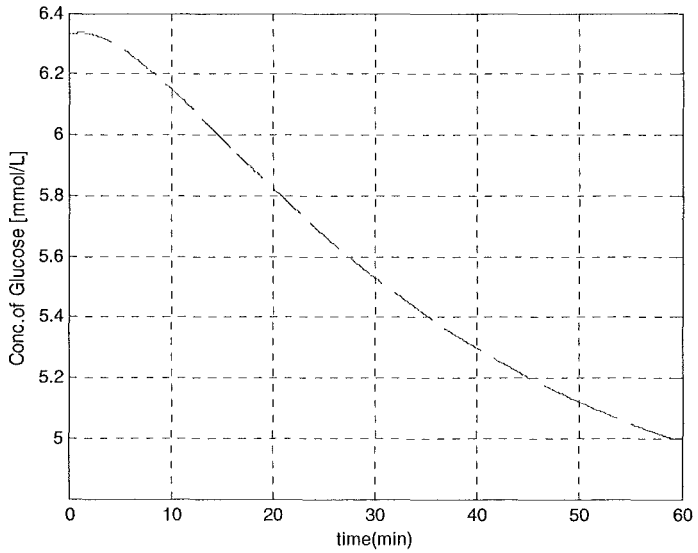

Figure 5 : Model plot of patient glucose level over time after bolus was injected.

The integral and derivative method were then applied and the results are given in Figure 6 and Table 6. In this case the derivative method greatly overestimated the bolus resulting in a glucose value of less than 4 which is the state of hypoglycaemia and dangerous for the patient.

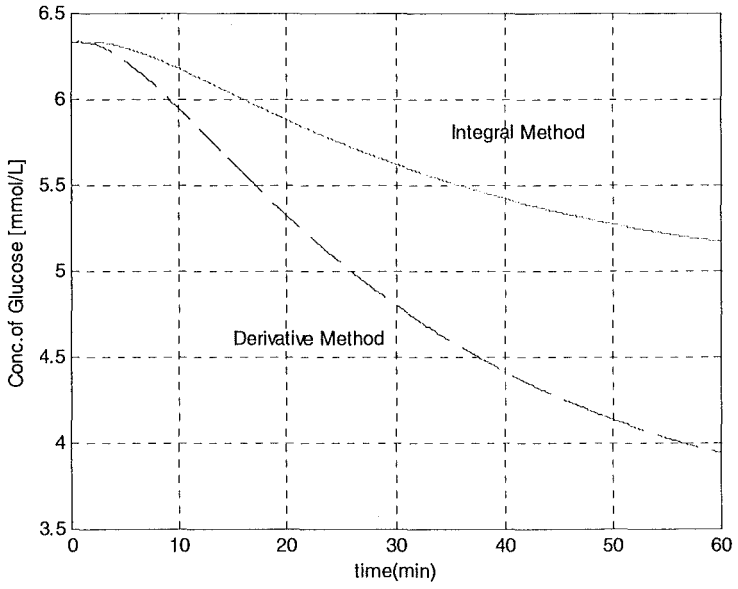

Figure 6 : Real plot of patient glucose level over time after bolus was injected.

Table 6 : Comparison of Derivative Method and Integral Method for a simulated real case scenario.

	Derivative Method	Integral Method
Bolus needed to get Si, u(t)	7.8 units	3.3 units
Calculated Si	2.651e-4	5.660e-4
Target glucose level	5	5
Obtained final glucose level	3.900	5.166
Percentage error	22%	3.2%

Case 3

A futher similar case is demonstrated with the following values;
Feed, Pt=0.05;
Bolus infusion, ub=1000;
Infusion rate, ui=0;
Initial glucose level, g0=4.5;

The Derivative and integral methods are applied to compute the Si values and the results are given in Table 7.

Table 7 : Comparison of Derivative Method and Integral Method using a specific values for all the parameters.

	Si Median values	Si Mean values
Derivative Method	-3.336e-4	-2.596e-4
Integral Method	5.783e-4	5.423e-4

By looking at the values at table 5, it can be seen that using Derivative method, we have negative values for both median and mean Si values. This is non-physiological and shows that in this case the derivative method goes unstable and thus fails. The integral method remains quite robust.

Discussion

Table 1 results has shown to us that the Integral Method 2 is the most preferable method due to its consistency compared to the Integral Method 1. This proves that optimising the initial glucose concentration will lead to better integration result. Hence as Integral Method 2 is better, all subsequent problems have used that method for computation.

It has been noted that the Derivative Method is highly dependent on dynamics of glucose as when infusion is increased, the Si values is getting better. This can be proven by looking at table 2. It is believed that the closer the result to straight line, the better the Si value using derivative. As for Integration Method, the calculated values were always stable and possessing very little modelling error. This has proven that Integration Method is independent of dynamics.

The Derivative Method is also proven to be extremely sensitive to the number of points. This can be seen by increasing the number of points or the step size of the model graph. By observing generated data from table 4, the Derivative Method has calculated an extremely large value for Si at the interval of 1. Thus at 60 points, probably an outlier has occurred and affecting the final value for Si as the derivative has gone very large.

Derivative method is also highly dependent on the number of points. This can be shown from table 4, where at interval 1, 60 points were used for derivative methods, the result is really surprising as Si values turned to be as high as 0.0011.

As for the example cases, it has been shown in the first case that derivative method can lead to dangerous situation where it has severely underestimate Si value and causing the glucose level to drop more that what aimed value. By comparing the error, the Derivative Method has 17.53% of error while for Integral Method, the error was only 0.88%. Hence, the unreliability for Differential Method is clearly justified as the ratio for its error compared to Integral Method is 20 times.

In another cases, Derivative Method has caused the patient to experience hyperglycaemia. This is because glucose level has decreased to the hyperglycaemia level which is about 3 mmol/L and it will be more serious if the level reaches 2.2 mmol that may cause death.

The last case shows when Derivative Method can be wrong. The calculated median and mean Si values were negative and this has opposed the physiological properties of glucose-insulin based system and thus proving that Derivative Method is unreliable.

Conclusion

Based on the results and discussion, only the Integral Method shows a consistent and reliable ability to rapidly identify the time-varying parameter Si. The Derivative Method can significantly underestimate the parameter Si. The standard deviation for Integral Method is also significantly smaller than the Derivative Method.

From the discussion, it can be concluded that Integral Method has been robust to measurement and modelling error. As for Derivative Method, the results simply goes unstable.

The error analysis for Integral Method has been very good compared to the Derivative Method. For most cases, the error for Integral Method has been significantly small and thus providing a reliable result.

Hence, based on all the arguments, it can be concluded that Integral Method is very important for parameter identification and thus, making it as the most ideal method for any application that requires parameter identification.

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