Virtual Trials with \textit{b-spline} Basis Functions and Stochastic Differential Equations

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Abstract: Virtual trials have proved useful in developing safe and efficacious glycaemic control protocols. However, these trials rely on lumping all changes in patient condition into the insulin sensitivity parameter. As electronic data collection provides higher temporal resolution than paper-based charts, irregular timings of both therapies and measurements clash with a regular, hourly insulin sensitivity profile. Additionally, unobservable endogenous changes are a factor for hour-to-hour variability. This research extends the virtual trial protocol to natively handle irregular data by regularising the insulin sensitivity profile, and utilising a simple stochastic differential equation. The insulin sensitivity profile was re-interpreted as a \textit{b-spline} basis, allowing a higher order description with greater local support. The fitting error resulting from this regularisation was absorbed by a stochastic element in the glucose compartment, representing the hour-to-hour changes that cannot be attributed to changes in insulin sensitivity. The resulting virtual patients were demonstrated to be equivalent to the originals when a $0$th order basis was used. Inclusion of the stochastic element in this case simply ensured the model still fitted during periods of unmodelled high endogenous glucose production, while a $2$nd order basis uses this element to natively control the balance between changes in patient state and hour-to-hour unmodelled changes due to noise and endogenous processes. The resulting virtual trials are thus better able to preserve information in irregular data sets, and regulate the balance between controllable and uncontrollable glycaemic changes.

Keywords: Identification and validation; chronic care and/or diabetes; decision support and control.

1. INTRODUCTION

Virtual trials [Chase et al., 2010] are a valuable tool for \textit{in-silico} development of control algorithms. However, validity of this methodology relies heavily on how model parameters are identified. Chase et al. describe a rigid parameter identification procedure that is not readily generalisable to more irregular data. This research describes a robust parameter identification and simulation procedure that features continuous parameter variation and native inclusion of internal noise.

Virtual trials were a key technique used to develop the STAR (Stochastic Targeted [Fisk et al., 2012]) and SPRINT (Specialised Relative Insulin and Nutrition Tables [Chase et al., 2008]) protocols \textit{in-silico}. Avoiding physical trials during initial development enabled pre-informed protocols to be implemented in pilot studies, with the virtual trial results giving a high degree of confidence in safety and efficacy. Virtual trials also provide context analysing clinical trial results, as shown in [Chase et al., 2010]. An indicative measure of compliance and performance can be provided by the comparison between virtual trial results and true observations. Virtual trials are thus an valuable tool for model-based control design.

The key steps in a virtual trial are: A) fitting the underlying “true” parameter profile, B) using a protocol to choose the new treatment, and C) using the “true” parameter profile to solve for the resulting virtual blood glucose (BG) measurement. Correctly fitting the data is the critical step for a representative virtual trial, as failure to fit translates directly to loss of information and lesser virtual trial confidence. Due to low data density in a real-world glycaemic control setting only one parameter, insulin sensitivity, can be reliably identified.

Prior research developed the virtual trial methodology using the ICING (Intensive Control Insulin-Nutrition-Glucose [Lin et al., 2011]) model and integral-based fitting [Hann et al., 2005]. The available data was from SPRINT [Chase et al., 2008] in a summary spreadsheet with hourly slots for measurements leading to hourly-binned data. Consequently, fitting was carried out with an hourly piecewise-constant insulin sensitivity ($SI$) profile, and linear interpolation to create intermediate BG estimates for 2-hourly intervals.

Implementation of the STAR protocol on a computerised tablet led to more precise timestamps recorded for measurements and therapy. With BG measurement times often
offset from the hour, and nutrition changes happening between measurements, the use of piecewise-constant SI and interpolated measurements introduced new difficulties in creating virtual trials. A more physiological description of \( S_T \) was deemed possible and desirable.

It is possible to address the concerns created by the nature of the irregularly dataset by modifying the virtual trial approach. In this work, the \( S_T \) profile was made into a continuous function, and the error introduced regularising \( S_T \) was captured in an additional term appended to the ICING model. The glucose model was thus converted to a novel, simplistic stochastic differential equation (SDE [Van Kampen, 1976]).

2. METHODS

2.1 ICING model

The ICING model defines glucose and insulin kinetics and dynamics in critically ill patients:

\[
i = \frac{U_x + (1 - xL)U_n - nI(I - Q) - nKI - nLI}{V_I} + \frac{I}{1 + \alpha G I} \quad (1)
\]

\[
\dot{Q} = nI(I - Q) - nCQ - \frac{Q}{\alpha G Q} \quad (2)
\]

\[
\dot{G}(t) = -pG G - S_I(t) \frac{G(t)Q(t)}{1 + \alpha G Q(t)} + P_{EGP} - P_{CNS} + \sum_{i=1}^{m}(P_{max, i}d_2P_2(t)) \quad (3)
\]

where \( G(t) \) [mmol.L\(^{-1}\)] is the total plasma glucose, \( I(t) \) [mU.L\(^{-1}\)] is the plasma insulin, and interstitial insulin is represented by \( Q(t) \) [mmol.L\(^{-1}\)]. Exogenous insulin input is represented by \( U_x(t) \) [mU.min\(^{-1}\)], and glucose-dependent endogenous insulin production is estimated with \( U_{en} \) [mU.min\(^{-1}\)] [Pretty, 2012]. \( S_I(t) \) [L.mU^{-1}.min^{-1}] is the identified insulin sensitivity profile, \( P_1(t) \) [mmol] represents the glucose in the stomach and \( P_2(t) \) [mmol] represents glucose in the gut. Enteral glucose input is denoted \( P(t) \) [mmol.min^{-1}], while parental glucose input is denoted \( P_N(t) \) [mmol.min^{-1}]. All model constants are shown in Table 1.

2.2 Parameter Identification

A simple version of the integral-based fitting method will be introduced via a differential equation with an unknown linear parameter, \( \theta \):

\[
\dot{x} = f_0(t, x) + \theta f_1(t, x) \quad (6)
\]

where \( x \) is the conserved quantity, \( \theta \) the unknown constant parameter, \( f_1(t, x) \) is the function corresponding to this parameter, and \( f_0(t, x) \) contains the remaining known parameters and functions. The model estimate of \( x \) at time \( t \) is:

\[
x_{mod}(t) = x_0 + \int_{t_0}^{t} f_0 dt + \theta \int_{t_0}^{t} f_1 dt \quad (7)
\]

Assuming multiple data points, a residual error \( \epsilon \) will occur. The error at the \( i \)th measurement, \( \epsilon_i = x_{mod}(t_i) - x(t_i) \), is:

\[
\epsilon_i = -x(t_i) + x_0 + \int_{t_0}^{t_i} f_0 dt + \theta \int_{t_0}^{t_i} f_1 dt \quad (8)
\]

which, provided the integrals can be numerically estimated, can be minimised using least squares for \( n \) measurements:

\[
\begin{bmatrix}
\int_{t_0}^{t_1} f_1 dt \\
\vdots \\
\int_{t_0}^{t_n} f_1 dt
\end{bmatrix}
\theta =
\begin{bmatrix}
\int_{t_0}^{t_1} f_0 dt \\
\vdots \\
\int_{t_0}^{t_n} f_0 dt
\end{bmatrix}
\quad (9)
\]

If measured data is dense enough, or appropriate assumptions used, these integrals can be fully formed without further computation, and the linear system solved directly [Hann et al., 2005]. If sparse data or noise causes these integrals to be poorly approximated by the available data, this approach can be applied iteratively, where new parameters produce a modified solution, which is then used to update the integrals [Docherty et al., 2012].

As SPRINT data consisted of intermittent 1 and 2 hour measurement intervals, a distinct parameter value was fitted for each hour interval. Thus, \( \theta \) was described as \( m \) piecewise-constant functions, where:

\[
\theta(t) = \sum_{j=1}^{m} \gamma_j g_j(t) \quad (10)
\]

where \( \gamma_j \) is the \( j \)th \( \theta \) value and \( g_j(t) \) is a rectangle function, non-zero on a single hour interval. This description of \( \theta \) is equivalent to a \( 0 \)th order uniform \( b \)-spline basis [De Boor, 1972] with \( m+1 \) knots, each an hour apart. Equation (7) thus expands to:

\[
x_{mod}(t) - x_0 = \int_{t_0}^{t} f_0 dt + \gamma_1 \int_{t_0}^{t} g_1 f_1 dt + \ldots + \gamma_m \int_{t_0}^{t} g_m f_1 dt \quad (11)
\]

Accordingly, Equation (9) becomes:

\[
\hat{\theta}_{1,n,m} \equiv \hat{b}_{1,n,1} \quad (12)
\]

where \( \hat{\theta}_{1,m} = [\gamma_1, \ldots, \gamma_m]^T \), and:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_G )</td>
<td>Non-insulin mediated uptake</td>
<td>0.006 min^{-1}</td>
</tr>
<tr>
<td>( n_I )</td>
<td>Insulin transport rate</td>
<td>0.006 min^{-1}</td>
</tr>
<tr>
<td>( n_K )</td>
<td>Renal clearance</td>
<td>0.0542 min^{-1}</td>
</tr>
<tr>
<td>( n_L )</td>
<td>Hepatic clearance</td>
<td>0.1578 min^{-1}</td>
</tr>
<tr>
<td>( n_G )</td>
<td>Interstitial clearance</td>
<td>0.006 min^{-1}</td>
</tr>
<tr>
<td>( d_1 )</td>
<td>Stomach clearance</td>
<td>0.0151 min^{-1}</td>
</tr>
<tr>
<td>( d_1 )</td>
<td>Gut clearance</td>
<td>0.00301 min^{-1}</td>
</tr>
<tr>
<td>( P_{max} )</td>
<td>Maximal gut cl.</td>
<td>6.11 mmol.min^{-1}</td>
</tr>
<tr>
<td>( P_{EGP} )</td>
<td>Endogenous glucose production</td>
<td>1.16 mmol.min^{-1}</td>
</tr>
<tr>
<td>( P_{CNS} )</td>
<td>Nervous system glucose disposal</td>
<td>0.3 mmol.min^{-1}</td>
</tr>
<tr>
<td>( x_L )</td>
<td>First-pass hepatic extraction</td>
<td>0.67</td>
</tr>
<tr>
<td>( V_I )</td>
<td>Insulin volume of distribution</td>
<td>4.0 L</td>
</tr>
<tr>
<td>( V_G )</td>
<td>Glucose volume of distribution</td>
<td>13.3 L</td>
</tr>
<tr>
<td>( \alpha_I )</td>
<td>Saturation of hepatic insulin</td>
<td>0.0017 L.mU^{-1}</td>
</tr>
<tr>
<td>( \alpha_G )</td>
<td>Saturation of insulin-mediated glucose uptake</td>
<td>0.01538 L.mU^{-1}</td>
</tr>
</tbody>
</table>
\[
\hat{A}_{1,(n,m)} = \begin{bmatrix}
\int_{t_0}^{t_1} g_1 f_1 \, dt & \cdots & \int_{t_0}^{t_1} g_m f_1 \, dt \\
\vdots & \ddots & \vdots \\
\int_{t_0}^{t_n} g_1 f_1 \, dt & \cdots & \int_{t_0}^{t_n} g_m f_1 \, dt
\end{bmatrix}
\] (13)

\[
b_{1,(n,1)} = \begin{bmatrix}
x(t_1) - x_0 - \int_{t_0}^{t_1} f_0 \, dt \\
\vdots \\
x(t_n) - x_0 - \int_{t_0}^{t_n} f_0 \, dt
\end{bmatrix}
\] (14)

If \( m + 1 > n \), the linear system is clearly indeterminate. Such a case almost always occurs with SPRINT data, as 2 hour BG measurements were common [Chase et al., 2008]. To circumvent this issue, SPRINT data was resampled hourly, an assumption that introduces fitting error if measurements are offset and can force unusual parameter spikes if additional glucose is added parenterally close to a resampled measurement. A continuous profile would therefore be beneficial, and controlling the order of the basis and knot locations provides a natural method for regularising the shape of the \( S_I \) profile. However, using a knot at each measurement forces the shape of the \( S_I \) profile to reach a maxima/minima in the middle of the measurement period, as well as forcing all changes to be the direct result of changes in \( S_I \).

### 2.3 \( SI \) profile

A distinction should be made in the use of this model for control and for virtual trials. In control, the model is refitted over a 6 hour period to ensure the initial conditions for the past hour are insensitive to modified data, and thus can be relied on for prediction. Previously, all dynamic changes were lumped into the data, and thus can be relied on for prediction. Previously, conditions for the past hour are insensitive to modified fitting error with real data. As the \( SI \) profile becomes smoother, greater error is introduced. Thus, additional fitting is required to prevent information being lost in the generation of virtual patients. Such information loss would result in virtual trials showing an artificial improvement. Returning to Equation (6), a zero-mean internal noise (process noise, \( \phi(t) \)) can be added:

\[
\dot{x} = \phi(t) + f_0(t, x) + \theta f_1(t, x)
\] (15)

Typically, \( \phi(t) \) would take the form of a wiener process. However, the added computational intensity associated with the increased resolution, and non-deterministic forward simulation, is not necessary in this application. In this simple SDE, \( \phi(t) \) becomes the integral of a wiener process between two measurements, and captures unmodelled dynamics and measurement noise that cannot be incorporated by the now-regularised \( SI \) profile. Thus, \( \phi(t) \) is a piecewise-constant function, individual values of which can be fitted using:

\[
[\hat{A}_{1,(n,m)}, \hat{A}_{2,(n,n)}] \begin{bmatrix}
\Gamma_{(m,1)} \\
\Phi_{(n,1)}
\end{bmatrix} = b_{1,(n,1)}
\] (16)

where \( \hat{\Phi}_{(n,1)} = [\phi_1, \ldots, \phi_n]^{\top} \) (\( \phi_i \) is the \( i^{th} \) value of the piecewise constant \( \phi(t) \)), and:
\[
\hat{A}_{2,(n,n)} = \begin{bmatrix}
-(t_1 - t_0) & 0 & \ldots & 0 \\
-(t_1 - t_0) & -(t_2 - t_1) & \ldots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
-(t_1 - t_0) & -(t_2 - t_1) & \ldots & -(t_n - t_{n-1})
\end{bmatrix}
\]

As \( n + m > n \) when \( m > 0 \) this system is always rank-deficient. However, the definition of \( \phi(t) \) as zero-mean noise can be utilised to fill the rank of the system. As zero-mean noise, \( \int_{t_0}^{t_1} \phi(t)dt = 0 \), and by the definition of the basis functions, \( \sum_{m=1}^{m} g_i(t) = 1 \ \forall \ t \). Thus, \( \phi(t) \equiv \sum_{i=1}^{m} \phi(t)g_i(t) \). If zero-mean is enforced for each component \( \phi(t)g_i(t) \):

\[
\int_{t_0}^{t_1} \phi(t)g_i(t)dt = 0 \ \forall \ i = 1, \ldots, m
\]

As \( \phi(t) \) is constant between two measurements:

\[
\phi_1 \int_{t_0}^{t_1} g_i(t)dt + \ldots + \phi_n \int_{t_{n-1}}^{t_n} g_i(t)dt = 0
\]

Thus, the system in Equation (16) can be made full rank, and can be solved for all variables:

\[
\begin{bmatrix}
\hat{A}_{1,(n,m)} & \hat{A}_{2,(n,m)} & \hat{B}_{1,(n,1)} & \hat{B}_{2,(n,1)} \\
\hat{0}_{(m,m)} & \hat{A}_{3,(m,n)} & \hat{0}_{(m,1)} & \hat{0}_{(m,1)}
\end{bmatrix}
\]

where:

\[
\hat{A}_{3,(m,n)} = \begin{bmatrix}
\int_{t_0}^{t_1} g_1(t)dt & \ldots & \int_{t_0}^{t_n} g_1(t)dt \\
\vdots & \ddots & \vdots \\
\int_{t_0}^{t_1} g_m(t)dt & \ldots & \int_{t_0}^{t_n} g_m(t)dt
\end{bmatrix}
\]

The new form of the ICING model is therefore:

\[
\begin{align*}
\hat{G}(t) &= G_x(t) - p_G \Gamma - S_I(t) \\
&= \frac{G(t)Q(t)}{1 - \alpha_G Q(t)} + \frac{P_{EFP}}{V_G} - P_{CGS} + P_N(t) + \max \left( \frac{G}{d_2P_2(t)} \right)
\end{align*}
\]

where \( S_I(t) = \theta(t) \) consists of b-spline basis functions, and \( G_x(t) = \phi(t) \) is the new stochastic element. During a virtual trial, \( G_x(t) \) is treated as the observed realisation of the stochastic process, and used in conjunction with \( S_I(t) \) to calculate deterministic outcomes to modified therapeutic inputs.

### 2.5 STAR Cohort

BG, insulin, and nutrition data was collected as part of routine use of the STAR protocol in Christchurch Hospital medical and surgical ICU between July 2011 and February 2013. For use in this study, datasets were split when a gap greater that 5 hours occurred between consecutive BG measurements. Observational ethics was granted by the National Ethics Advisory Committee (New Zealand). Available cohort details are shown in Table 2.

### 2.6 Analyses

The intent of this research is to develop and implement a new fitting method to be used for virtual trials. Accordingly, two main categories of analyses were carried out. The first analysis was intended to demonstrate the problem solved by the research, and thus justify the added complexity. The second analysis was intended to give an understanding of the behaviour of the new methodology. For the iterative fits, convergence was assumed if maximum RMS error was within 0.1 mmol.L\(^{-1}\) (minimum resolution of a glucometer). To speed iterations, the \( G_x \) profile was updated between iterations by using the current \( S_I \) profile.

Initially, STAR data was fitted using the standard methodology yielding an hourly piecewise-constant \( S_I \) profile fitted non-iteratively to linearly-interpolated hourly BG measurements. The fit was analysed with RMS error between BG measurements and modelled plasma glucose, to quantify how well a virtual trial would reproduce the original dataset. Fitting error in any patient indicates a virtual trial run using this patient could not recreate the original observed data, and thus error is an important metric.

The closest analogue of this method was then fitted using the basis function SDE approach. An hourly piecewise-constant profile was not possible to fit without introducing further constraints, and so constant \( S_I \) and \( G_x \) values were fitted for each measurement interval using the presented methodology. RMS error in BG was presented for comparison with the original, and the \( G_x \) distribution was presented as a cumulative density function (CDF). Finally, the regularised \( S_I \) profile was fitted and error in BG was calculated.

The nature of the \( G_x \) profile was then investigated graphically. The \( G_x \) value for a measurement interval was plotted against the initial BG, time between measurements, mean exogenous glucose delivery (enteral and parenteral), and mean exogenous insulin. The contribution of \( G_x \) to glucose disposal was also calculated.

### 3. RESULTS

Figure 2 shows the dramatic reduction in fitting error when the SDE approach is used. No discernable difference is visible between the 0th and 2nd order basis functions. The difference between the two basis function shapes is shown in Figure 3, where the 0th order SDE forces \( G_x \to 0 \) except at extreme cases. The regularised basis of the 2nd order SDE forces \( G_x \) to absorb the remaining BG changes, hence producing a more variable \( G_x \) profile. The method thus permits control over the contribution of noise to hour-to-hour BG changes.
Fig. 2. Fitting error comparison between the methods. No discernible differences is visible between the two SDE approaches.

Fig. 3. Noise signal comparison. The 0th order SDE was fitted with a constant $S_I$ between BG measures, while the 2nd order SDE was fitted with a 2nd order b-spline basis with knot widths of 240 min.

Fig. 4. Scatter diagram of all fitted $G_x$ values with a 2nd order basis, plotted against measurement interval, exogenous insulin, exogenous glucose, and initial BG. Hourly insulin is only indicative, as timing errors will affect the value when insulin is delivered in a bolus.

Fig. 5. 0th order basis functions compared to the original methods. $S_I$ is similar, and $G_x$ is only non-zero when $S_I$ is constrained to the lower limit.

Fig. 6. 2nd order basis functions compared to the original method. $S_I$ is much smoother, and $G_x$ is non-zero both when $S_I$ is constrained and when differences exist between the new and old profiles.

4. DISCUSSION

An updated fitting methodology is needed when using higher resolution data. An hourly $S_I$ value is useful for control, but timing errors cause information to be lost when creating virtual patients. During a virtual trial, this discrepancy means the original data cannot be created when the original inputs are used. Generalising $S_I$ to a series of b-spline basis functions permits timing errors to be natively captured, but introduces fitting error if the basis function local support extends beyond an individual measurement interval. To permit greater local support, and thus regularise the $S_I$ profile, a new time-varying parameter, $G_x$, was introduced to eliminate fitting error. The methodology presented here is a robust way identify a virtual patient. During a virtual trial, this discrepancy means the original data cannot be created when the original inputs are used. Generalising $S_I$ to a series of b-spline basis functions permits timing errors to be natively captured, but introduces fitting error if the basis function local support extends beyond an individual measurement interval. To permit greater local support, and thus regularise the $S_I$ profile, a new time-varying parameter, $G_x$, was introduced to eliminate fitting error. The methodology presented here is a robust way identify a virtual trial that fully recreates the data if the original intervals are used. As $S_I$ is regularised with a higher order basis, and wider knot widths, shorter-term changes in BG are mediated by $S_I$, while short term changes predominantly affect the $G_x$ profile.

Finally, Figures 5 and 6 show the new methods implemented on the same patient and compared to the original. This patient was chosen as the episode includes an initial period of high BG that cannot be fitted by the original method, and has some minor interpolation artefacts near the end of the episode. Figure 5 shows the 0th order basis has almost equivalent $S_I$, barring some minor timing differences, and $G_x$ is zero everywhere except for the initial high BG period that is impossible to fit using the non-stochastic model. In comparison, the regularised basis used in Figure 6 has a much smoother $S_I$ profile, and where there are disparities between the original and new $S_I$ profiles $G_x$ is forced to be non-zero.
changes cannot be captured by \( S_I \), instead being forced into the \( G_x \) profile. This effect is seen in both Figure 3 and the example patient in Figures 5 and 6. In this way, direct control can be exerted over the balance between changes in \( S_I \) and observed noise.

This balance between noise and changes in \( S_I \) may also be useful in control. Figure 4 shows a lack of dependence of noise on both exogenous inputs and current BG, showing only the expected dependence on measurement interval. This knowledge may be leveraged to improve model prediction. In particular, a continuous \( S_I \) profile and a cohort \( G_x \) profile could be used in a non-parametric prediction algorithm, replacing the computationally intensive stochastic model of STAR [Fisk et al., 2012]. Such a non-parametric approach could feasibly be updated in real-time, improving the quality of glycaemic control for longer-stay ICU patients. Safety would be improved for more variable (higher noise) patients, and performance would be improved for more stable patients, neither of whom benefit from a whole-cohort approach. The novel simplicity of this SDE permits stable parameter identification with a relatively computationally light algorithm, which permits use in real-time glycaemic control.

One final possibility created by using this SDE approach is analysis of noise around changes in exogenous inputs. Patterns in the noise profile may possibly be used to identify areas where the model could be improved. For example, changes in nutrition rate may affect BG faster than the glucose absorption submodel permits, which will appear as positive \( G_x \) values immediately after nutrition changes. Consistent patterns could be used to update parameter values either for an individual or for the whole-cohort ICING model.

5. CONCLUSIONS

A robust parameter identification method was introduced, permitting identification of a smooth \( S_I \) profile, and capturing remaining variation in a simple stochastic element, \( G_x \). This method suits the high resolution data available to STAR. Thus, future work will centre around implementation of a non-parametric prediction algorithm using these two parameters, allowing for direct inclusion into STAR.

REFERENCES


