CLINICAL SIMULATION OF OGTT GLUCOSE RESPONSE MODEL FOR DIAGNOSIS OF DIABETIC PATIENT

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Diagnosis of diabetes is usually achieved by obtaining a single reading of blood-glucose concentration value from the Oral Glucose Tolerance Test (OGTT). However, the result itself is inadequate in providing insight into the glucose-regulatory etiology of diabetes disease disorder, which is important for treatment purposes. The objective of this project was to conduct clinical simulation and parametric identification of OGTT model for diagnosis of diabetic patient, so as to classify diabetic or at-risk patients into different categories, depending on the nature of their blood-glucose tolerance response to oral injection of a bolus of glucose. In other words, the patient classification depends on how the blood-glucose concentration varies with time; i.e. how much does it peak, how long does it takes to reach its peak value, how fast does it return to the fasting value, etc. during the oral glucose tolerance test.

To represent this blood-glucose concentration \[y(t)\] regulatory dynamics, the model selected is a second-order differential equation, \[y'' + 2Ay' + \omega^2 y = G\delta(t)\] of blood-glucose concentration response to a bolus of ingested glucose \(G\delta(t)\). This model was then applied to the test subjects by making the model solution-expression for \(y(t)\) match the monitored clinical data of blood-glucose concentration at different time intervals, through clinical simulation and parametric identification. The solutions obtained from the model to fit the clinical data were different for normal and diabetic test subjects. The clinical data of “normal” subjects could be simulated by means of an under-damped solution of the model, as: \[y(t) = \frac{G}{\omega} e^{-At} \sin \omega t\]. The data of “diabetic” patients needed to be simulated by means of an over-damped solution of the model, as: \[y(t) = \frac{G}{\omega} e^{-At} \sin h\omega t\], where \(G\) represents the magnitude of the impulse input \(G\delta(t)\) to the model (in gms of glucose per litre of blood pool volume), \(\omega\) is the damped oscillatory frequency of the model, \(w_n\) is the natural frequency of the system and \(T_d = 2A/\omega^2\).

In order to facilitate differential diagnosis, we developed a non-dimensional diabetic index (DI) expressed as: \[\frac{Ay_{\text{max}}T_d}{GT_{\text{max}}}\]. This index can be used to facilitate the diagnosis of diabetes as well as for assessing the risk to becoming diabetic.

\textbf{Keywords:} Diabetes; glucose; model; tolerance; oral; index.

1. Introduction

1.1. Background

Currently, diabetes affects about 151 million people worldwide and the number will double by 2010, according to Prof Paul Zimmet, a diabetes expert from World
Health Organization, who heads the WHO’s collaborating center for the epidemiology of diabetes and is the director of the International Diabetes Institute.\textsuperscript{1}

In the Singapore context, according to the 1998 National Health Survey, about 300,000 people in Singapore have diabetes and another 450,000 have impaired glucose tolerance, which is the stage before becoming full-blown seriously diabetic. This makes the republic an unpalatable fourth on the world diabetes ranking, just after Hong Kong, Pakistan and the Czech Republic.\textsuperscript{2}

Diabetes is a leading cause of blindness, renal-failure and limb-amputation all over the world. The need to detect diabetic risk factors and treat organ disorders and complications associated with diabetes has provided the motivation for this project.

1.2. Objective and scope

The objective of this project was to conduct clinical simulation and parametric identification of the Oral Glucose Tolerance Test (OGTT) model, entailing a 2nd order differential-equation of blood glucose concentration response to an impulse input of ingested glucose bolus.\textsuperscript{3} This project is concerned mainly with Type-2 diabetes. Obtaining a reading of blood glucose concentration values from oral glucose tolerance test is a common method for detecting diabetes. However, it does not provide adequate insight into the glucose-regulatory etiology of diabetes disease/disorder or a measure of effectiveness of an anti-diabetic drug therapy.

Therefore, this project has involved conducting clinical studies to monitor the blood-glucose concentration time-response to administered input of glucose during the oral glucose tolerance test. The clinical simulation of the OGTT model with the time-dependent blood-glucose concentration clinical-data has yielded the values of the model parameters, employed for patient diagnosis.

2. Literature Review

2.1. Glucose-insulin regulatory system (GIRS)

In the Oral Glucose Tolerance Test (OGTT), the role of the gut is to facilitate transport of glucose across the intestinal wall. However, the commonly-employed single-reading of blood-glucose concentration does not reliably diagnose risk-to-diabetes, resistance-to-insulin and severity index. On the other hand, our model simulates the glucose-insulin system dynamics by means of second-order differential equations with four parameters: $\alpha$, $\beta$, $\gamma$ and $\delta$,\textsuperscript{3} where:

$\alpha$: pancreatic insulin sensitivity to elevated insulin concentration
$\beta$: pancreatic insulin sensitivity to elevated glucose concentration
$\gamma$: tissue glycogen storage to elevated insulin concentration
$\delta$: tissue glucose utilization to elevated blood-glucose concentrations.
2.2. Differential equation model of the GIRS (Glucose-insulin regulatory system)

The first-order differential equations of the insulin and glucose regulatory subsystems are given by Bolie:

\[ x' = p - \alpha x + \beta y \]  
\[ y' = q - \gamma x - \delta y \]  

where \( x' \) and \( y' \) denote the first time-derivatives of \( x \) and \( y \):

\( x \): blood insulin concentration output  \( y \): blood glucose concentration output  
\( p \): insulin input-rate  \( q \): glucose input-rate,

all for unit blood-glucose compartment volume (V).

From Eqs. (1) and (2), the differential equation model of second-order in glucose concentration (\( y \)), for \( p \) (insulin infusion rate) = 0 and glucose input inflow rate (\( q \)), is obtained as:

\[ y'' + y' \alpha + y(\alpha \delta + \beta \gamma) = q' + \alpha q \]  

wherein \( y' \) and \( y'' \) denote first and second time derivatives of \( y \).

Also, from Eqs. (1) and (2), the differential equation model of second-order in insulin concentration (\( x \)) is obtained as:

\[ x'' + x' \alpha + x(\alpha \delta + \beta \gamma) = \beta q \]  

wherein \( x' \) and \( x'' \) denote first and second time derivatives of \( x \).

2.3. Laplace transform of the governing equations (3) and (4)

The transfer function of Eq. (3) is obtained by taking Laplace transform on both sides (assuming the initial conditions to be zero):

Thereby, we obtain, for glucose response,

\[ Y(s)/Q(s) = \frac{(s + \alpha)}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)} = G(s). \]  

Similarly, from Eq. (4), we obtain the insulin response as follows:

\[ X(s)/Q(s) = \frac{\beta}{s^2 + s(\alpha + \delta) + (\alpha \delta + \beta \gamma)}. \]  

2.4. OGTT model analysis

The assumption used in the analysis is that a 70 kg normal person’s body is to contain 17.5 L of blood, i.e. 4 kg body-mass approximately 1 L of blood, or 1 g of glucose input/kg of body mass approximately 4 g of glucose input/L of blood.
The OGTT model-simulation response curve is considered to be the result of giving an impulse glucose dose (of 4 g of glucose/L of blood-pool volume) to the combined system consisting of Gastrointestinal (GI) tract and Blood Glucose Control System (BGCS). The glucose-bolus impulse-input at the mouth later on manifests itself as a rectangular-pulse input to the glucose blood-pool compartment (as depicted by Hobbie\(^5\)), as far as the average glucose transport rate is considered.

Now, based on the analysis of Fisher,\(^6\) the transfer-function of the GI tract is \(1/(s + \alpha)\), because the intestinal glucose-concentration output-variation into the blood glucose compartment is an exponential decay, and the exponential parameter value is close to that of the parameter \(\alpha\). Thus, by multiplying the GI tract's transfer function \([1/(s + \alpha)]\) by the transfer function of the blood-pool volume per hour [Eq. (5)], and putting \(Q(s) = G\) (g of glucose per L of blood-pool volume per hr), we obtain:

\[
Y(s) = \frac{G}{s^2 + s(\alpha + \delta) + (\alpha\delta + \beta\gamma)}.
\]  (7)

2.5. Rate control model for OGTT simulation

Even though the transfer-function of the GI tract can be represented by a definite time integrator \((1/s)\), the precise shape of the curve of the glucose-input to the blood pool cannot be said to be known. In order to circumvent this problem, we have considered that the gut and the blood-pool together form one single compartment, with even the glucose bolus \(G\) to be regarded as an unknown (and to be determined) magnitude of the glucose-input impulse function \(G\delta(t)\) of the clinically monitored OGTT data curve representing the system response.

A rate-control first-order model was first suggested by Hobbie,\(^5\) but it could not explain the oscillatory features of the OGTT curve. However, all the features of the normal clinical OGTT curve can be satisfied by means of an oral glucose-regulatory model of Dittakavi and Ghista,\(^3\) involving proportional plus derivative feedback-control, i.e. by a second-order system [analogous to Eq. (7)] and represented in Laplace Transform by:

\[
Y(s) = \frac{G}{s^2 + \lambda T_d s + \lambda}.
\]  (8)

wherein

(i) the glucose input-rate, \(G\) in \((g \ L^{-1} \ hr^{-1})\) constitutes the glucose-bolus impulse-input into the combined gut and blood-pool compartment,
(ii) \(\lambda(= \beta y)\) is the proportional-control term which replaces \((\alpha\delta + \beta\gamma)\) of Eq. (7), and
(iii) \(\lambda T_d(dy/dt)\) is the derivative feedback-control term with derivative-time \(T_d\), with \(\lambda T_d\) replacing \((\alpha + \delta)\) of Eq. (7), in the differential equation.
The block diagram of Eq. (8) is displayed in Fig. 1. Equation (8) is now adopted to represent the response of the blood glucose (proportional + derivative) feedback control-system model for simulating glucose metabolism during OGTT.

Equation (8) can also be written as:

\[
Y(s) = \frac{G}{s^2 + 2As + \omega_n^2},
\]

wherein \( G \) is in grams of glucose per liter of blood-pool volume per hour, as the Laplace transform representation of the governing differential equation:

\[
y'' + 2Ay' + \omega_n^2y = G\delta(t) \quad \text{or} \quad y'' + \lambda T_d y' + \lambda y = G\delta(t)
\]

wherein \( \omega_n = \lambda^{1/2} \) is the natural frequency of the system in rad/hr;

\( A \) is the attenuation or damping constant of the system in (hr)^{-1};

\( \lambda = 2A/T_d = \omega_n^2 \) (in hr^{-2}); and

\( \omega = (\omega_n^2 - A^2)^{1/2} \) in rad/hr is the angular frequency of damped-oscillation of the system.

The solution of Eq. (10), for an under-damped response corresponding to that of normal subjects, is given by (3):

\[
y(t) = (G/\omega)e^{-At}\sin \omega t.
\]

The solution for over-damped response, corresponding to that of diabetic subjects, is given by:

\[
y(t) = (G/\omega)e^{-At}\sinh \omega t.
\]
These solutions are employed to simulate the clinical data and to therefrom evaluate the model-system parameters $G$, $A$, $\omega$, $\lambda$ and $T_d$ to differentially-diagnose diabetes subjects as well as to characterize resistance-to-insulin.

3. Clinical Studies

The studies entailed monitoring of blood-glucose concentration response to administered inputs of glucose during the oral glucose tolerance test, as a measure of the ability of the body to use or metabolize glucose.

The OGTT model solutions were matched with the clinical data (of time-based response of blood-glucose concentration), for model parameters identification. There were 47 test subjects in total, of which 26 were normal test subjects and 21 were diabetic subjects.

The blood glucose “normal” values, used for the clinical studies, were:

- Fasting: 70 to 115 mg/dL
- At 30th min.: less than 200 mg/dL
- At 1st hour: less than 200 mg/dL
- At 2nd hour: less than 140 mg/dL

A person is deemed to be diabetic if oral glucose tolerance tests show that the blood glucose level at 2 hours after oral glucose intake is equal to or more than 200 mg/dL. This must be confirmed by a second test on another day.

In order to perform clinical simulation and parametric identification, a normalized data is obtained from the clinical data by subtracting the blood-glucose fasting values from the monitored clinical values of blood glucose. Hence all values of blood glucose level at all time intervals (15 minutes, 30 minutes, 60 minutes, 90 minutes, and 120 minutes after oral glucose intake) have been reduced to their own fasting values in order to obtain the normalized data.

Tables 1 and 2 show the normalized OGTT results for normal and diabetic test subjects, respectively.

4. Model Simulation Results

4.1. Parametric identification

The analysis for computing the values of the parameters (for both normal and diabetic test subjects) is illustrated for one normal test subject.

4.1.1. Sample calculation for normal test subject No.5

Calculations for an under-damped response corresponding to that of normal subjects based on Eq. (11), are as follows:

At $1/2$ hour: $y(t) = 34 \text{ mg/dL} = 0.34 \text{ g/L}$
At 1 hour: $y(t) = 24 \text{ mg/dL} = 0.24 \text{ g/L}$
At 2 hour: $y(t) = -9 \text{ mg/dL} = -0.09 \text{ g/L}$. 
Table 1. Normalized blood glucose level for normal test subjects.

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*N/A means not available.

From Eq. (11), the following can be obtained:

\[
y(1/2) = \frac{G}{\omega} e^{-A/2} \sin \omega/2 = 0.34
\]

(13.1)

\[
y(1) = \frac{G}{\omega} e^{-A} \sin \omega = 0.24
\]

(13.2)

\[
y(2) = \frac{G}{\omega} e^{-2A} \sin 2\omega = -0.09.
\]

(13.3)

Using the trigonometric identity \(\sin 2\theta = 2 \sin \theta \cos \theta\), we obtain from Eqs. (13.1) and (13.2),

\[
2e^{-A/2} \cos \omega/2 = 0.24/0.34 = 0.7059.
\]

(13.4)

from Eqs. (13.2) and (13.3),

\[
2e^{-A} \cos \omega = (-0.09/0.24) = -0.375.
\]

(13.5)

Squaring Eq. (13.4):

\[
4e^{-A} \cos^2 \omega/2 = 0.4983.
\]

(13.6)

Employing trigonometric identity \(2 \cos^2 \omega/2 = 1 + \cos \omega\), we obtain from Eqs. (13.5) and (13.6):

\[
\frac{(2 \cos^2 \omega/2) / (\cos \omega)} = (1 + \cos \omega) / (\cos \omega) = -1.3287
\]

(13.7)
Table 2. Normalized blood glucose level for diabetic test subjects.

<table>
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* N/A means not available.

and hence,

$$\omega = 2.0146 \text{ rad/hr.} \quad (13.8)$$

Putting $\cos \omega = -0.4294$ in Eq. (13.5), we obtain:

$$A = 0.8287 \text{ hr}^{-1} \quad (13.9)$$

$$\lambda = \omega_n^2 = A^2 + \omega^2 = (0.82875)^2 + (2.0146)^2 = 4.7455 \text{ hr}^{-2}, \quad (13.10)$$

$$T_d = 2A/\lambda = 0.3492 \text{ hr.} \quad (13.11)$$

Upon substituting the above values of $\lambda$ and $T_d$ in Eq. (13.2), the value of the third parameter, $G = 1.2262 \text{ g(L)}^{-1} \text{ hr}^{-1}$. Similar calculations for an over-damped response, corresponding to that of diabetic subjects, based on Eq. (12) was also performed to obtain the relevant parameters.

It was found from these calculations that not all of the normal test subjects’ clinical data could be simulated as under-damped response as identified by Eq. (11). Similarly, not all the diabetic test subjects’ clinical data corresponded to over-damped response, as represented by Eq. (12). However, it was found that the clinical data of these test subjects (both normal and diabetic), which could not be simulated by means of Eqs. (11) or (12), could indeed be fitted by a critically-damped glucose-response solution of the governing Eq. (10), as given by:

$$y(t) = Gte^{-At}. \quad (14)$$
It can be seen from Eq. (14) that for a critically damped response:

\[ \omega = 0 \quad \text{and} \quad \omega^2_n = A^2 = \lambda. \]  

(15)

Therefore, by using the relationship in Eq. (15), we obtain:

\[ T_d = 2A/\lambda = 2. \]  

(16)

Now, the only parameters that need to be identified in Eq. (14) are \( A \) and \( G \) for this category of subjects. Similar calculations as those illustrated for the one normal test subject were performed using Eq. (14), and the relevant model parameters (for both normal and diabetic test subjects) were evaluated.

### 4.2. Clinical simulation

Having computed the values of the model parameters, using Eqs. (11), (12) and (14), we then employed Matlab 5.3 to plot the model-solution response graphs of blood glucose-concentration of the test-subjects. The graphs of test subjects belonging to each category are put on the same graph. These computed blood glucose responses of normal and diabetic subjects, with underdamped or critically damped or overdamped characteristics, are shown in Figs. 2 to 9.

### 5. Non-Dimensional Number for Diagnosis of Diabetes

So far, the test subjects have been classified into four categories:

\[
\begin{align*}
\text{Normal-test subjects based on Eq. (11) (under damped, model-response)} \\
\text{Normal test-subjects based on Eq. (14) (critical-damped model-response)} \\
\text{Diabetic test-subject based on Eq. (14) (critical damped model-response)} \\
\text{Diabetic test-subject based on Eq. (12) (over damped model response)}
\end{align*}
\]

(17)

Based on the knowledge gained from the model clinical simulation and parametric identification, we decided to develop a unique diabetes index number (DIN) to facilitate differential diagnosis of normal and diabetic states as well as diagnose supposedly normal but high (diabetic) risk patients and diabetic patients in early stages of the disorder.

\[
\text{DIN} = \frac{y^{(\text{max})}}{G} \times A \times \frac{T_d}{T^{(\text{max})}}
\]

(18)

wherein,

\[ y^{(\text{max})} = \text{maximum blood glucose value in g/L} \]
\[ G = \text{glucose administered to the system in g/L hr} \]
\[ A = \text{attenuation constant in 1/hour} \]
\[ T_d = \text{derivative-time (} \alpha + \delta \text{) in hour} \]
\[ T^{(\text{max})} = \text{the time at which } y^{(\text{max})} \text{ is attained in hour.} \]
Fig. 2. Blood glucose response of normal subjects (5, 6, 13, 17, 19, 24) with underdamped characteristics based on Eq. (11).

Fig. 3. Blood glucose response of normal subjects (13, 17, 19, 24, 25, 26) with underdamped characteristics based on Eq. (11).
Fig. 4. Blood glucose response of normal subjects (1, 3, 4, 7, 8, 10) with critically-damped characteristics based on Eq. (14).

Fig. 5. Blood glucose response of normal subjects (8, 10, 12, 15, 18, 23) with critically-damped characteristics based on Eq. (14).
Fig. 6. Blood glucose response of diabetic subjects (2, 3, 4, 6, 7, 9) with critically-damped characteristics based on Eq. (14).

Fig. 7. Blood glucose response of diabetic subjects (11, 13, 14, 15, 16, 17) with critically-damped characteristics based on Eq. (14).
Fig. 8. Blood glucose response of diabetic subjects (14, 15, 16, 17, 19, 20) with critically-damped characteristics based on Eq. (14).

Fig. 9. Blood glucose response of diabetic subjects (1, 16, 21) with overdamped characteristics based on Eq. (12).
This non-dimensional number DIN consists of all the three important model parameters. The DIN values for all four categories were computed from Eq. (17). A distribution plot of the DIN is plotted in Fig. 10. For this purpose, the DIN is classified into sections with 0.2 increments (for all the four categories of subjects), and the number of subjects which fall into these sections (frequency) is determined. Then, all this data is combined with the distribution plot shown in Fig. 10. The DIN values 0–0.2 is designated as range 1, the DIN 0.2–0.4 is range 2, 0.4–0.6 is range 3, and so on up to DIN 2.2–2.4, which is range 12.

In Fig. 10, the subjects belonging to range 1, with DIN values of 0–0.2, are non-diabetic and have the least possibility to becoming diabetic. This risk keeps on increasing up to ranges 10 and 12 for severely diabetic subjects. For example, those belong to range 6 have higher risk to become diabetic than those belonging to range 2.

As can be seen from Fig. 10, normal (i.e., non-diabetic) subjects with no risk of becoming diabetic, will have DIN value less than 0.4, or be in the 1–2 range. Distinctly diabetic subjects will have DIN value greater than 1.2, or be in the 7–12 range categories. Supposedly, clinically-identified normal subjects who have DIN values between 0.6 and 1.0, or are in the 3–5 range, are at risk of becoming diabetic. On the other hand, clinically-identified diabetic subjects with DIN value between 0.6–1.2, or in the 3–6 range category are border-line diabetics, who can become normal (with diet control and treatment).

### Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$ or $t$</td>
<td>time</td>
<td>hr</td>
</tr>
<tr>
<td>$V$</td>
<td>extra-cellular fluid volume</td>
<td>L</td>
</tr>
<tr>
<td>$I'$</td>
<td>rate of insulin injection</td>
<td>unit/hr</td>
</tr>
</tbody>
</table>
Clinical Simulation of OGTT Glucose Response Model

\[ G' \]  rate of glucose injection  \( \text{g/hr} \)
\[ X \]  extra-cellular insulin concentration  \( \text{unit/L} \)
\[ Y \]  extra-cellular glucose concentration  \( \text{g/L} \)
\[ X_0 \]  mean physiological value of \( X \)  \( \text{unit/L} \)
\[ Y_0 \]  mean physiological value of \( Y \)  \( \text{g/L} \)
\[ x \]  insulin output \( = X - X_0 \)  \( \text{unit/L} \)
\[ y \]  glucose output \( = Y - Y_0 \)  \( \text{g/L} \)
\[ x' \]  first time-derivatives of \( x \)  \( \text{unit/L hr} \)
\[ y' \]  first time-derivatives of \( y \)  \( \text{g/L hr} \)
\[ p \]  insulin input \( = (I')/V \)  \( \text{unit/L hr} \)
\[ q \]  glucose input \( = (G')/V \)  \( \text{g/L hr} \)
\[ F_1(X) \]  rate of insulin destruction  \( \text{unit/hr} \)
\[ F_2(X) \]  rate of insulin production  \( \text{unit/hr} \)
\[ F_3(X) \]  rate of liver accumulation of glucose  \( \text{g/hr} \)
\[ F_4(X) \]  rate of tissue utilization of glucose  \( \text{g/hr} \)
\[ \alpha \]  pancreatic insulin sensitivity to elevated insulin \( = (1/V)(2F_1/2X)@X_0 \)  \( 1/\text{hr} \)
\[ \beta \]  pancreatic insulin sensitivity to elevated glucose \( = (1/V)(2F_2/2Y)@Y_0 \)  \( \text{unit/g hr} \)
\[ \gamma \]  tissue glycogen storage to elevated insulin \( = (1/V)[(2F_3/2X) + (2F_4/2X)]@X_0 \)  \( \text{g/unit hr} \)
\[ \delta \]  tissue glucose utilization to elevated blood-glucose \( = (1/V)[(2F_3/2Y) + (2F_4/2Y)]@X_0 \)  \( 1/\text{hr} \)
\[ y(t) \]  time dependent function of \( y \)  \( \text{g/L hr} \)
\[ G \]  the to-be-determined value of glucose administered to the system in \( \text{g/L hr} \)
\[ A \]  attenuation constant  \( 1/\text{hr} \)
\[ \omega \]  damped frequency of the system in \( \text{radian/hr} \)
\[ \omega_n \]  natural frequency of the system in \( \text{radian/hr} \)
\[ \lambda \]  proportional-control term \( = (\alpha \delta + \beta \gamma) \)  \( 1/\text{hr}^2 \)
\[ T_d \]  derivative-time \( = (\alpha + \delta) \)  \( \text{hr} \)

References

Bibliography