A Diabetes minimal model for Oral Glucose Tolerance Tests

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Abstract

We present a minimal model for analyzing Oral Glucose Tolerance Test (OGTT) data base on system of 5 ODEs. The model has 4 unknown parameters which are inferred using a Bayesian approach. Preliminarily results are shown with three real patient data.

1 Introduction

For diagnosis of diabetes, metabolic syndrome and other conditions an Oral Glucose Tolerance Test (OGTT) is performed. After a night's sleep, fasting patients have their blood glucose measured and are asked to drink a 75 g sugar concentrate. Blood glucose is then measured at the hour, two hours and sometimes at three hours, depending on local practices.

A diagnosis tool is needed since there are many scenarios in which blood glucose ranges from low to high to intermediate levels in different patterns and MD's resort only to simple guidelines for diagnosis.

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Table 1: Minimal model for analysis of OGTT state variables, parameter definition and units. Time is measured in hours (hr) and therefore all derivatives have corresponding units per hr.

	Units	Interpretation	Value
G	$\frac{mg}{dL}$	Blood glucose.	State variable
I	$\frac{mg}{dL}$ (see text)	Blood Insulin.	State variable
L	$\frac{mg}{dL}$ (see text)	Blood Glucagon.	State variable
D	$\frac{mg}{dL}$	Glucose in digestive system.	State variable
V	$\frac{mg}{dL}$	Glucose in the drinkable solution, to be transferred to the digestive system.	State variable
θ_0	hr^{-1}	Insulin tissue sensitivity.	Unknown par.
θ_1	hr^{-1}	Glucagon liver sensitivity.	Unknown par.
θ_2	hr	Glucose digestive system mean life.	Unknown par.
a, b	hr	Insulin and Glucagon clearance mean life.	31 min.
c	hr	Time that the subject took to drink most of the glucose solution (transfer time to D).	5 min max.

We develop a minimal model for blood glucose-insulin interaction based on a two compartment model. A a simple transfer compartment of glucose into the diagestive system and a more complex compartment for blood glucose and interactions with Insulin and other glucose substitution mechanisms.

Once OGTT data is available, we perform a formal statistical analysis using Bayesian inference for the unknown parameters of each patient and predict their glucose level at 3h after the test.

2   The model

Our Diabetes minimal dynamic model is

$$\frac{dG}{dt} = L - I + \frac{D}{\theta_2} \tag{1}$$

$$\frac{dI}{dt} = \theta_0 \left(G - G_b \right)^+ - \frac{I}{a} \tag{2}$$

$$\frac{dL}{dt} = \theta_1 \left(G_b - G \right)^+ - \frac{L}{b} \tag{3}$$

$$\frac{dD}{dt} = -\frac{D}{\theta_2} + \frac{2V}{c} \tag{4}$$

$$\frac{dV}{dt} = -\frac{2V}{c}. \tag{5}$$

All state variables and parameters are positive. Definitions of the state variables, parameters and their units are described in Table 1.

The heuristics behind this model are as follows and are similar to other minimal models following the same heuristics (for example, see Palumbo et al., 2013).

When glucose goes above the normal threshold (G_b), Insulin is produced, ie. its derivative increases, see (2). This, in turn, acts on blood glucose and decreases its concentration, given the $-I$ term in (1), and decreases the derivative of G. The opposite effect is achieved with the Glucagon derivative in (3), increasing blood Glucose levels, with the term L in (1), once Glucose is below the threshold G_b.

$D(t)$ represents the glucose in the digestive system that will be transferred to the blood stream. After the oral sugar intake, glucose in this compartment decreases, increasing the blood glucose $G(t)$; see (1) and (4).

$D(t)$ is measured in the same units as G (mg/dL) and θ_2 (the rate of glucose transfer form D to G) is measured in hr that is the glucose compartment transfer mean life. This Glucose transfer mean life has been estimated at 71 min Anderwald et al. (2011), however it may vary greatly, perhaps from 15 to 60 min, depending on the subject's digestive system, bowel characteristics, gender, etc.

Moreover, there is the process of drinking the glucose solution, which may take up to 5min, but an individual may drink the contents in far less time. This is modeled by the additional compartment V, where c is the time where most of the glucose (87%) solution has been drunk. Ideally the health

practictioner would record the total time the patient took to drink the glucose solution. Unfortunately this information is not available and therefore we fix $c = 5/60 hr$.

The Insulin and Glucagon clearance rates are not estimated. It is known that the total Insulin clearance time is approximately 71 min (Duckworth et al., 1998); we therefore set the Insulin half life to 36min, that is $a = 0.6hr$. There is less knowledge regarding clearance rates for Glucagon. We set it equal to the clearance rate of Insulin, that is $b = 0.6hr$.

3 Uncertainty Quantification Using Bayesian Inference

Once the OGTT data is observed we perform the *Inverse Analysis* by inferring the patient's corresponding model parameters using Bayesian statistics (Fox et al., 2013). We have observations $d_0, d_1, \ldots, d_{n-1}$ for the measured Glucose during the OGTT test at times $t_0, t_1, \ldots, t_{n-1}$. Plasma glucose is measured with relative precision, however high frequency fluctuations exist (given the pancreatic beta cells' Insulin delivery mechanisms, idf.org (2015)) and, along with model error itself, we expect Glucose readings d_i to fluctuate around a mean value, modeled here as $G(t_i)$. We impute an independent Gaussian error for these readings, namely

$$d_i = G(t_i) + e_i \quad \text{where} \quad e_i \sim N(0, \sigma); i = 0, 1, \ldots, n - 1.$$

To account for observation errors and, at least informally, model uncertainty we use a $\sigma = 5$. From this a likelihood is constructed.

As mentioned in the previous section the only parameters being inferred are θ_0, θ_1 and θ_2. Moreover, the initial value $G(0)$ is also a parameter to be inferred. These are all positive and as a first choice we select Gamma priors for the parameters θ_0 and θ_1. Since we would like to learn about these two parameters for each patient, we use vague Gamma distributions with shape=2 and rate=$\frac{1}{4}$.

The rest of the initial values are set to $I(0) = 0$ and $L(0) = 0$ since the patient is expected to be in homeostasis (equilibrium) and $D(0) = 0$ fasting. $V(0) = V_0$ is the initial Glucose intake, at the onset of the test.

On the other hand, we do have information regarding θ_2, the glucose transfer mean life. This transfer cannot be arbitrarily fast or slow, given the

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transit through the digestive tract and the fact that the drinkable Glucose solution is basically directly taken into the blood requiring no digestive process. The Glucose half life in the digestive tract has been estimated to be between 40 and 90 min Anderwald et al. (2011).

We use a gamma distribution with mean at 1/2hr (shape= 10 and rate= 20) and truncated at the extreme (but bounded) values $0.16 < \theta_2 < 2$. That is, most sugar will be transferred $(2\theta_2)$ to the blood stream within in a minimum of 20 min and a maximum of 4hr. In fact, since (4) and (5) may be regarded as a separate system of ODEs (forcing the system of (1), (2) and (3) with the term $\frac{D}{\theta_2}$), which in turn may be regarded as a linear nonhomegeneous ODE, it may be solved analytically for D to obtain $D(t) = \frac{V_0}{\frac{c}{2\theta_2}-1}\left(e^{-\frac{2t}{c}} - e^{-\frac{t}{\theta_2}}\right)$. Since D cannot be negative, at $t = 0$ it may only increase, therefore $D'(0) > 0$. From this it is straightforward to see that we most have $\theta_2 > c/2$. The support of θ_2 most start above zero.

The basis of Bayesian analysis is the posterior distribution for all parameters. This results in

$$f(\boldsymbol{\theta}|D) \propto \exp\left\{\frac{1}{2\sigma^2}\sum_{i=0}^{n-1}(d_i - G_{\boldsymbol{\theta}}(t_i))^2\right\}\prod_{j=0}^{2}\theta_i^{a_j-1}\exp(-b_j\theta_j)I_{S_j}(\theta_j),$$

where a_j and b_j are the Gamma hyper parameters for the prior of θ_j, $S_1 = S_2 = (0, \infty)$ and $S_3 = [1/6, 2]$. To obtain Monte Carlo samples from this (unnormalized) posterior distribution, an MCMC is performed using the t-walk (Christen and Fox, 2010). This is a self-adjusting MCMC algorithm and the resulting sampler is efficient in most cases for this low dimensional (3) problem. In the next Section we present some examples of how our model and inference works on some real OGTT data.

4   Examples and Results

Figures 1, 3 and 5 show how real OGTT data is adjusted by our model. The red dots are the measured data points, and the grey lines are elements of a posterior sample of glucose curves.

Figure 1 is a healthy patient, figure 2 shows the marginal priors of θ_0, θ_1 and θ_2 corresponding to this patient, overlaid with a histogram of the marginal posteriors. Figure 3 is a patient with strange oscillating blood glucose measurements (previous diagnosis technique would classify this patient
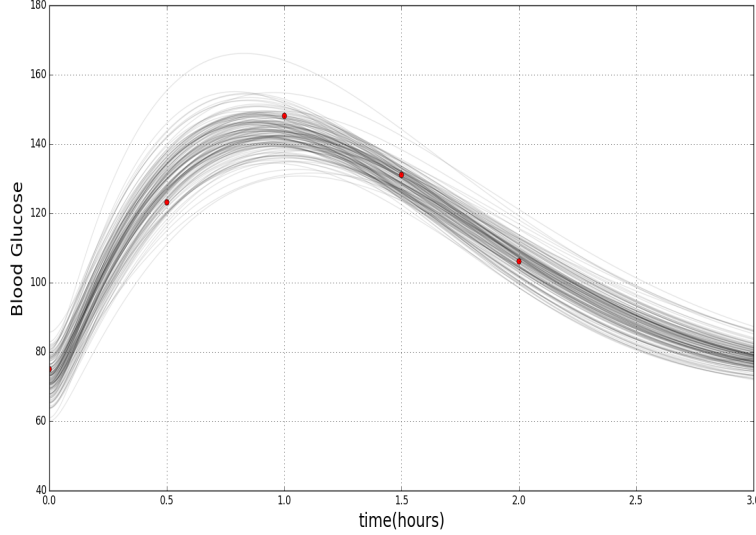
Figure 1: A nice decaying OGTT, belonging to a healthy patient

as "normal"), and figure 4 shows the corresponding priors and posteriors. Figure 5 is a considered and Impaired Glucose Tolerant patient (IGT, currently considered an pre diabetic condition) and figure 6 shows the corresponding posteriors for this patient.

As can be seen in all three cases, the model has strong descriptive power for the times contained in the measurement interval. It also has reasonable predictive power for times beyond the interval before the patient returns to a fasting glucose level. After that the predictive power tapers off because the uncertainty in θ_1 is typically very high – usually matching the uncertainty in the prior for this parameter, except in the case of the oscillating data.

5   Conclusions

In general, the main indicator of the status of a patient is θ_0. For normal patients, θ_0 is around 2. Significantly lower values indicate that a patient may have diabetes and higher values may indicate that a patient has some other complication. The data is almost always very informative for θ_0. More over, the bayesian inference allows for prediction, and we are able to predict
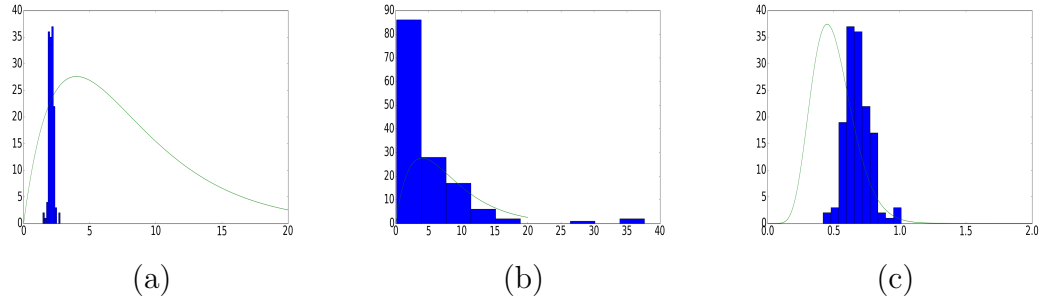
Figure 2: Priors and posteriors for the normal patient (used to generate figure 1). In green are the priors of θ_0(a), θ_1(b), and θ_2(c). In blue are histograms of the corresponding posterior samples.
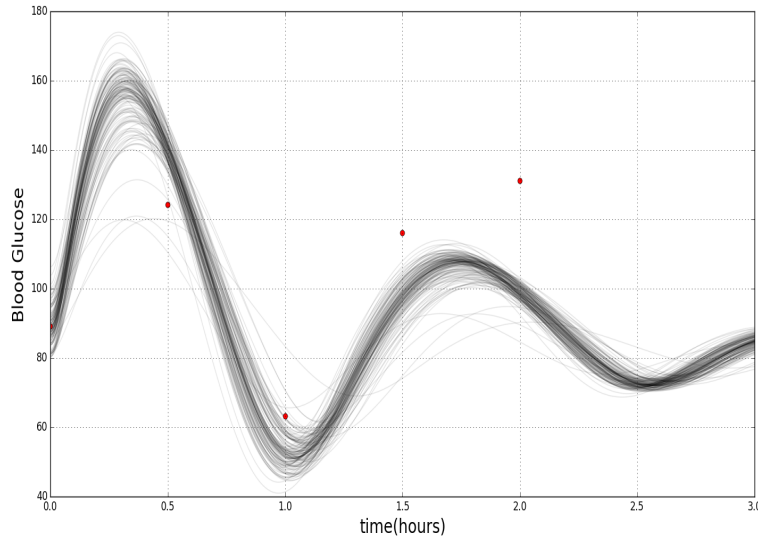

Figure 3: Data with an oscillating fit. Older diagnostic techniques would have called this patient "normal".
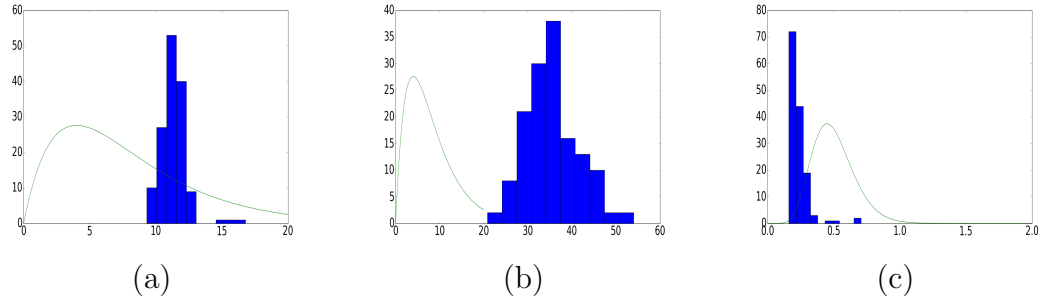
Figure 4: Priors and posteriors for the patient with oscillating data (used to generate figure 3). In green are the priors of θ_0(a), θ_1(b), and θ_2(c). In blue are histograms of the corresponding posterior samples.
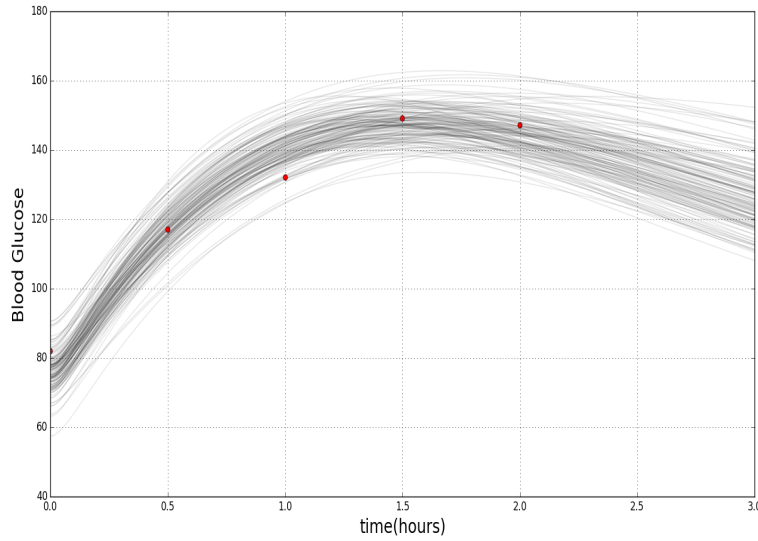

Figure 5: A diabetic patient with normal fasting OGTT and an Insulin resistance profile.
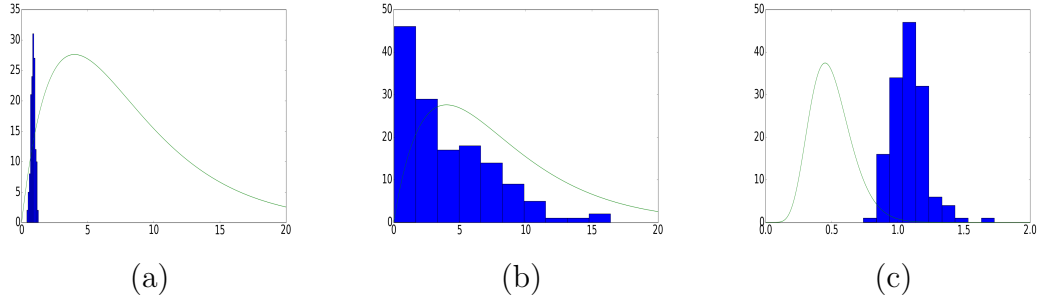
Figure 6: Priors and posteriors for the insulin resistant patient (used to generate figure 5). In green are the priors of θ_0(a), θ_1(b), and θ_2(c). In blue are histograms of the corresponding posterior samples.

Glucose levels beyond the length of the test (shown in figure 1, 3 and 5 up to 3 h). In particular, for figure 5 the prediction is that the patient will still have a high glucose level (above 120 $\frac{mg}{dL}$) and yet current diagnosis standards classify her/him as IGT (a pre diabetic condition).

θ_1, on the other hand, depends on measurements found below fasting glucose levels. For healthy patients and also for diabetics, it is uncommon for such data to become available for the duration of the test.

θ_2 is an important element of inference, and often data provide information for it however, as yet, there is no clear relationship between the value of θ_2 and a patient diagnosis.

We intend to provide a tool for proper diagnosis using OGTT. For this very important public health issue, there is a need for a more sophisticated tool than the direct recording of values read during the test.

Covariates (weight, age, etc.) will be used to help in the analysis, creating a hierarchical model embedded into the ODE model, in more population based studies, using ideally a large sample of patients with a range of health conditions to tune the model parameter value ranges to establish a more comprehensive diagnosis tool than what is currently available.

A more extensive validation of the model, and model parameters, is needed in order to have an effective diagnosis tool. This will necessarily involve the OGTT tests, and their further analysis using our model, in a wide range of healthy individuals and individuals with a various prediabetic and diabetic conditions to establish a more comprehensive diagnosis tool than what is currently available.

We are in the course of such research and our results will be published elsewhere.

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