A Diabetes minimal model for Oral Glucose Tolerance Tests: a three parameter patient-wise multi diagnostic tool

Marcos Capistrán[1] J. Andrés Christen[1] Adriana Monroy[2] Silvia Quintana Vargas[3]

[1]Centro de Investigación en Matemáticas (CIMAT), Guanajuato, Gto., Mexico

[2]Hospital General, Mexico City, Mexico

[3]DIF/Hospital Alta Especialidad, Guanajuato, Mexico

Oct. 2014

Introduction: Context and issues

- La diabetes es un problema de salud pública muy (¡muy!) serio en México.
- Se estima que hasta tal ves 30% de la población en México es diabética (Diabetes B; solo la mitad lo sabe). Y posiblemente la mitad de la poblacin (sí, ¡50%!) tiene síndrome metabólico y/o prediabetes.
- Esto es, 36.000.000 de personas son dibéticas en México!!!

Introduction: Context and issues

- La diabetes es un problema de salud pública muy (¡muy!) serio en México.
- Se estima que hasta tal ves 30% de la población en México es diabética (Diabetes B; solo la mitad lo sabe). Y posiblemente **la mitad** de la poblacin (sí, ¡50%!) tiene síndrome metabólico y/o prediabetes.
- Esto es, 36,000,000 de personas son dibéticas en México!!!

Introduction: Context and issues

- La diabetes es un problema de salud pública muy (¡muy!) serio en México.
- Se estima que hasta tal ves 30% de la población en México es diabética (Diabetes B; solo la mitad lo sabe). Y posiblemente **la mitad** de la poblacin (sí, ¡50%!) tiene síndrome metabólico y/o prediabetes.
- Esto es, 36,000,000 de personas son dibéticas en México!!!

Introduction: Context and issues

- La diabetes es un problema de salud pública muy (¡muy!) serio en México.
- Se estima que hasta tal ves 30% de la población en México es diabética (Diabetes B; solo la mitad lo sabe). Y posiblemente **la mitad** de la poblacin (sí, ¡50%!) tiene síndrome metabólico y/o prediabetes.
- Esto es, 36,000,000 de personas son dibéticas en México!!!

Introduction: Context and issues

- Aunque posiblememte solo 18,000,000 lo saben!!!
- **Si la (pre)diabetes es detectada a tiempo, se puede recobrar la salud prácticamente al 100%**. Se vive sin medicamentos y una vida 100% normal.
- Se necesita seguir dieta adecuada y ejercicio aeróbico.
- Un instrumento para diagnóstico es la prueba de OGTT.

Introduction: Context and issues

- Aunque posiblememte solo 18,000,000 lo saben!!!
- **Si la (pre)diabetes es detectada a tiempo, se puede recobrar la salud prácticamente al 100%**. Se vive sin medicamentos y una vida 100% normal.
- Se necesita seguir dieta adecuada y ejercicio aeróbico.
- Un instrumento para diagnóstico es la prueba de OGTT.

Introduction: Context and issues

- Aunque posiblememte solo 18,000,000 lo saben!!!
- **Si la (pre)diabetes es detectada a tiempo, se puede recobrar la salud prácticamente al 100%**. Se vive sin medicamentos y una vida 100% normal.
- Se necesita seguir dieta adecuada y ejercicio aeróbico.
- Un instrumento para diagnóstico es la prueba de OGTT.

Introduction: Context and issues

- Aunque posiblememte solo 18,000,000 lo saben!!!
- **Si la (pre)diabetes es detectada a tiempo, se puede recobrar la salud prácticamente al 100%**. Se vive sin medicamentos y una vida 100% normal.
- Se necesita seguir dieta adecuada y ejercicio aeróbico.
- Un instrumento para diagnóstico es la prueba de OGTT.

Introduction: Context and issues

For diagnosis of diabetes, methabolic syndrome and other conditions an Oral Glucose Tolerance Test (OGTT) is performed.

After a night sleep, fasting patients are measured for blood glucose and asked to drink a 75gr of a sugar concentrate. Blood glucose is then measured at the hour, two hours and sometime 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 normal levels in different patterns and MD's resort only to very simple guidelines for diagnosis (mean Glucose, final Glucose at 2 hr, etc.).

Introduction: Context and issues

For diagnosis of diabetes, methabolic syndrome and other conditions an Oral Glucose Tolerance Test (OGTT) is performed.

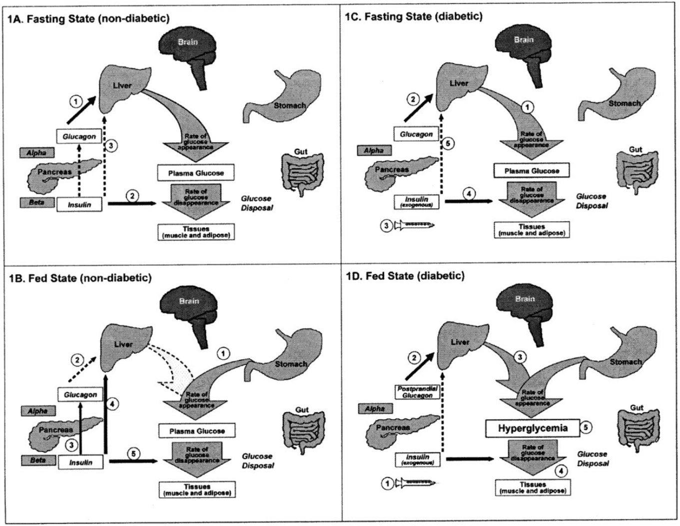
After a night sleep, fasting patients are measured for blood glucose and asked to drink a 75gr of a sugar concentrate. Blood glucose is then measured at the hour, two hours and sometime at three hours, depending on local practices.

A diagnosis tool is needed since there are many scenarios in which blood glucose ranges from low to high to normal levels in different patterns and MD's resort only to very simple guidelines for diagnosis (mean Glucose, final Glucose at 2 hr, etc.).

Introduction: Context and issues

We develop a minimal model for blood glucose-insulin interaction base on a two compartment model, on simple transfer compartment of glucose in the diagestive system and one more complex compartment for blood glucose and interactions with Insulin and other glucose substitution mechanisms. Once having OGTT data, we do a formal statistical analysis using Bayesian analysis.

Glucose homeostasis: roles of insulin and glucagon. 1A.



Aronoff S L et al. Diabetes Spectr 2004;17:183-190

The model

Our Diabetes minimal dynamical model is

$$\begin{aligned}
\frac{dG}{dt} &= -\theta_0 I + \theta_1 L + \alpha \frac{D}{\theta_2} && (1)\\
\frac{dI}{dt} &= k_0^{-1} (G - G_b)^+ - \frac{I}{a} && (2)\\
\frac{dL}{dt} &= k_1^{-1} (G_b - G)^+ - \frac{L}{b} && (3)\\
\frac{dD}{dt} &= -\frac{D}{\theta_2} + \frac{2V}{c} && (4)\\
\frac{dV}{dt} &= -\frac{2V}{c}. && (5)
\end{aligned}$$

All state variables and parameters are positive. Definition of the state variables, parameters and their units are described in Table 2.

The model

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

	Units	Interpretation
G	$\frac{mg}{dL}$	Blood glucose.
I	$\frac{mg}{dL}$ (see text)	Blood Insulin.
L	$\frac{mg}{dL}$ (see text)	Blood Glucagon.
D	$\frac{mg}{dL}$	Glucose in digestive system.
V	$\frac{mg}{dL}$	Glucose in the drinkable solution, to be transferred to the digestive system.

The model

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

	Units	Interpretation
θ_0	hr^{-1}	Insuline tissue sensitivity.
θ_1	hr^{-1}	Glucagon liver sensitivity.
θ_2	hr	Glucose digestive system mean life.
a, b	hr	Insulin and Glucagon clarence mean life, respectively. Set to 0.6, 71 min for nearly total clearance.
c	hr	Time that took the subject to drink most of the glucose solution (transfer time to D); 5min.
α	no units	Proportion of Glucose transferred to the blood (0.8).
k_0, k_1	hr	Arbitrary constants to calibrate the normal values for θ_0 and θ_1, respectively.

The model

The heuristics behind this model is as follows and is losely based on **??**. 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 to decrease its concentration, given the $-\theta_0 I$ term in (1), to decrease the derivative of G. The contrary effect is achieved with the Glucagon derivative in (3), increasing blood Glucose levels, with the term $\theta_1 L$ in (1), once Glucose is below the threshold G_b.

The model

$D(t)$ represents the glucose in the digestive compartment that will be transferred to the blood stream. After the sugar oral intake, glucose in this compartment decreases, increasing the blood glucose $G(t)$; see (1) and (4). An estimate of 80% of the glucose taken gets transferred to the blood (see **?**), and therefore we commonly set $\alpha = 0.8$ in (1). $D(t)$ is measured in the same units as G (mg/dL) and θ_2 (the speed 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 **?**, however it may vary greatly, perhaps from 15 to 60 min, depending on the subject digestive system, bowel characteristics, gender,

The model

Moreover, there is the process of drinking the glucose solution, which may take up to 5min, but each 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.

Qualitative Analysis

In an asymptotic analysis V and D tend to zero (all glucose gets transferred to the blood). We may think $G(t_1) > G_b$, $I(t_1) > 0$ and $L(t_1) = 0$.

The only relevant equations are therefore (setting $k_0 = k_1 = 1$)

$$\begin{aligned}\frac{dG}{dt} &= -\theta_0 I + \theta_1 L \\ \frac{dI}{dt} &= (G - G_b)^+ - \frac{I}{a} \\ \frac{dL}{dt} &= (G_b - G)^+ - \frac{L}{b}.\end{aligned}$$

Note that, given $\theta_0 \neq 0$ and $\theta_1 \neq 0$ the only limit is $G = G_b$.

If G remains above G_b, $L = 0$ and $\frac{dG}{dt} < 0$. The Glucose decreases monotonuos to G_b. If G goes below G_b, $\frac{dG}{dt}$ may change sign; G oscillates to G_b.

Inverse Problem

We have observations $d_0, d_1, \ldots, d_{n-1}$ for the measured Glucose during the OGTT test at times $t_0, t_1, \ldots, t_{n-1}$:

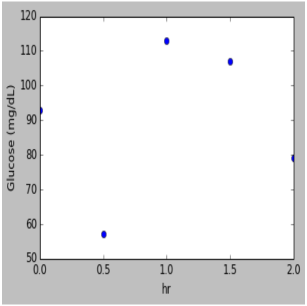


Figure: Data from a "healthy" subject OGTT.

We need to set the parameters θ_0, θ_1 and θ_2 ...is an inverse problem! **Is an inference problem!, given data we want to infer the parameters.**

Inverse Problem

We have observations $d_0, d_1, \ldots, d_{n-1}$ for the measured Glucose during the OGTT test at times $t_0, t_1, \ldots, t_{n-1}$:

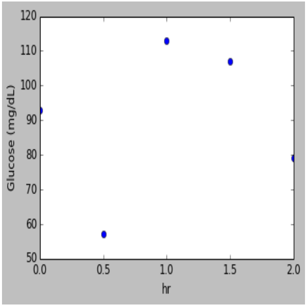


Figure: Data from a “healthy” subject OGTT.

We need to set the parameters θ_0, θ_1 and θ_2 ...is an inverse problem! **Is an inference problem!, given data we want to infer the parameters.**

Inverse Problem

We have observations $d_0, d_1, \ldots, d_{n-1}$ for the measured Glucose during the OGTT test at times $t_0, t_1, \ldots, t_{n-1}$:

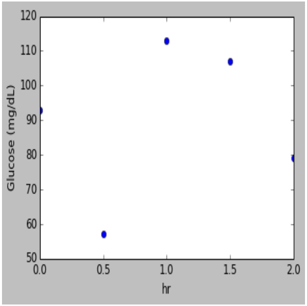


Figure: Data from a "healthy" subject OGTT.

We need to set the parameters θ_0, θ_1 and θ_2 ...is an inverse problem! Is an inference problem!, given data we want to infer the parameters.

Inverse Problem

We have observations $d_0, d_1, \ldots, d_{n-1}$ for the measured Glucose during the OGTT test at times $t_0, t_1, \ldots, t_{n-1}$:

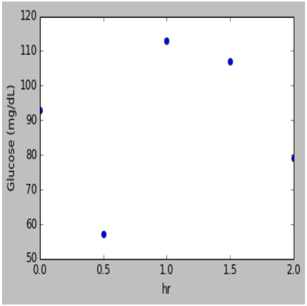


Figure: Data from a "healthy" subject OGTT.

We need to set the parameters θ_0, θ_1 and θ_2 ...is an inverse problem! **Is an inference problem!, given data we want to infer the parameters.**

Bayesian Inference

Three ““simple”” steps:

1. Establish your stochastic observation functional ... that is, your observation error model. Example

$$d_i = G_{\boldsymbol{\theta}}(t_i) + e_i \quad \text{where} \quad e_i \sim N(0, \sigma),$$

and $G(0) = d_0$ the initial condition. From this a likelihood is constructed, ie. the joint distribution of data given the unknown parameters, $f(D|\boldsymbol{\theta})$.

2. Establish the (a priori) distribution, $\pi(\theta)$, of the unknown parameters θ to code relevant information regarding θ.

3. Calculate all needed probabilities, eg. $P(G(3) > 120|D) = \int 1(G_\theta(3) > 120)\pi(\theta|D)d\theta$, using the posterior probability

$$\pi(\theta|D) = \frac{f(D|\theta)\pi(\theta)}{\int f(D|\theta')\pi(\theta')d\theta'}$$

Bayesian Inference

Three ""simple"" steps:

1. Establish your stochastic observation functional ... that is, your observation error model. Example

$$d_i = G_{\boldsymbol{\theta}}(t_i) + e_i \quad \text{where} \quad e_i \sim N(0, \sigma),$$

   and $G(0) = d_0$ the initial condition. From this a likelihood is constructed, ie. the joint distribution of data given the unknown parameters, $f(D|\boldsymbol{\theta})$.
2. Establish the (a priori) distribution, $\pi(\boldsymbol{\theta})$, of the unknown parameters $\boldsymbol{\theta}$ to code relevant information regarding $\boldsymbol{\theta}$.
3. Calculate all needed probabilities, eg. $P(G(3) > 120|D) = \int 1(G_{\boldsymbol{\theta}}(3) > 120)\pi(\boldsymbol{\theta}|D)d\boldsymbol{\theta}$, using the posterior probability

$$\pi(\boldsymbol{\theta}|D) = \frac{f(D|\boldsymbol{\theta})\pi(\boldsymbol{\theta})}{\int f(D|\boldsymbol{\theta}')\pi(\boldsymbol{\theta}')d\boldsymbol{\theta}'}$$

Bayesian Inference

Three ""simple"" steps:

1. Establish your stochastic observation functional ... that is, your observation error model. Example

$$d_i = G_{\boldsymbol{\theta}}(t_i) + e_i \quad \text{where} \quad e_i \sim N(0, \sigma),$$

   and $G(0) = d_0$ the initial condition. From this a likelihood is constructed, ie. the joint distribution of data given the unknown parameters, $f(D|\boldsymbol{\theta})$.

2. Establish the (a priori) distribution, $\pi(\boldsymbol{\theta})$, of the unknown parameters $\boldsymbol{\theta}$ to code relevant information regarding $\boldsymbol{\theta}$.

3. Calculate all needed probabilities, eg. $P(G(3) > 120|D) = \int 1(G_{\boldsymbol{\theta}}(3) > 120)\pi(\boldsymbol{\theta}|D)d\boldsymbol{\theta}$, using the posterior probability

$$\pi(\boldsymbol{\theta}|D) = \frac{f(D|\boldsymbol{\theta})\pi(\boldsymbol{\theta})}{\int f(D|\boldsymbol{\theta}')\pi(\boldsymbol{\theta}')d\boldsymbol{\theta}'}$$

Bayesian Inference

Gamma priors are assumed for the parameters θ_0, θ_1 and θ_2.

We do have information on θ_2, the glucose transfer mean life; this is a truncated gamma such that $0.1 < \theta_2 < 2$. That is, most sugar will be transferred ($2\theta_2$) to the blood stream within in a minimum of 6 min and a maximum of 2hr.

We have less informative priors on θ_0 and θ_1.

Bayesian Inference: The posterior Dustribution

$$\pi(\boldsymbol{\theta}|D) = \frac{f(D|\boldsymbol{\theta})\pi(\boldsymbol{\theta})}{\int f(D|\boldsymbol{\theta}')\pi(\boldsymbol{\theta}')d\boldsymbol{\theta}'}.$$

Therefore:

$$\pi(\boldsymbol{\theta}|D) \propto \exp\{-0.5\sum_{i=1}^{n}(d_i - G_{\boldsymbol{\theta}}(t_i))^2 + \log\pi(\boldsymbol{\theta})\}$$

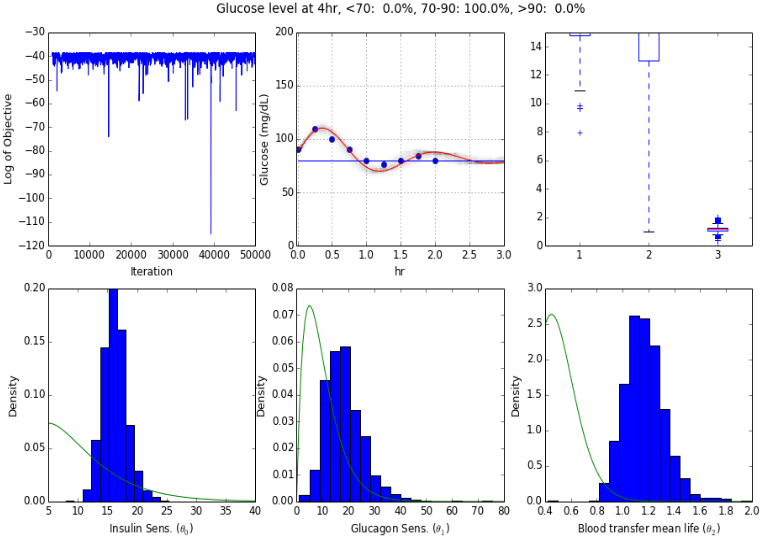
$(\log\pi(\boldsymbol{\theta}) = ||\boldsymbol{\theta}||^2$?????).

Bayesian Inference: The posterior Dustribution

$$\pi(\boldsymbol{\theta}|D) \propto \exp\left\{-0.5\sum_{i=1}^{n}(d_i - G_{\boldsymbol{\theta}}(t_i))^2 + \sum_{j=1}^{3}(a_i - 1)\log\theta_i + b_i\theta_i\right\}$$

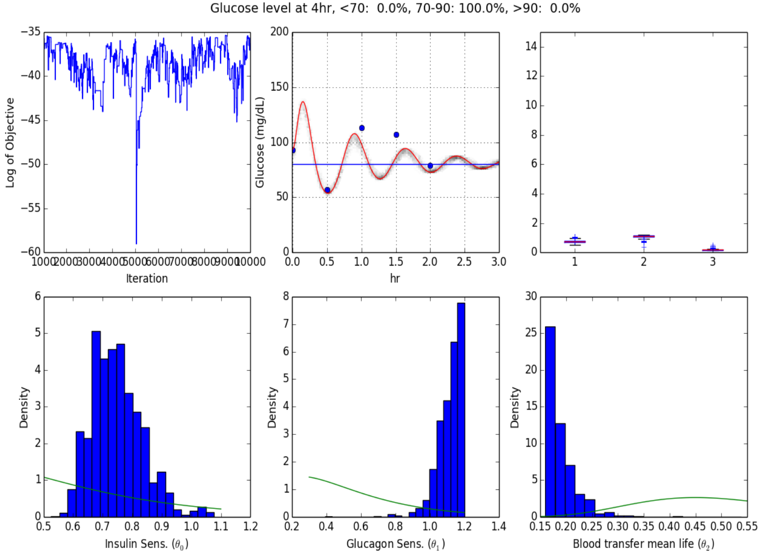
We do an MCMC for these parameters using the t-walk **?**.

Results



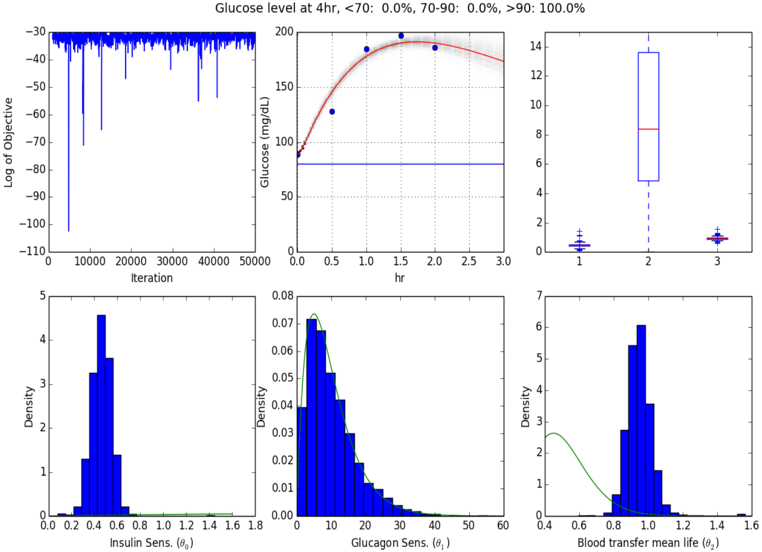
Glucose level at 4hr, <70: 0.0%, 70-90: 100.0%, >90: 0.0%
Log of Objective
Iteration
Glucose (mg/dL)
hr
Density
Insulin Sens. (θ_0)
Glucagon Sens. (θ_1)
Blood transfer mean life (θ_2)

Results



Glucose level at 4hr, <70: 0.0%, 70-90: 100.0%, >90: 0.0%
Log of Objective
Iteration
Glucose (mg/dL)
hr
Density
Insulin Sens. (θ_0)
Glucagon Sens. (θ_1)
Blood transfer mean life (θ_2)

Results


Glucose level at 4hr, <70: 0.0%, 70-90: 0.0%, >90: 100.0%
Log of Objective
−30
−40
−50
−60
−70
−80
−90
−100
−110
0
10000
20000
30000
40000
50000
Iteration
Glucose (mg/dL)
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
hr
14
12
10
8
6
4
2
0
1
2
3
Density
5
4
3
2
1
0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
Insulin Sens. (θ0)
Density
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
10
20
30
40
50
60
Glucagon Sens. (θ1)
Density
7
6
5
4
3
2
1
0
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Blood transfer mean life (θ2)

Results