Centro de Investigación en Matemáticas, A.C. (CIMAT A.C.)

Bayesian Analysis of a model for glucose-insulin dynamics during the Oral Glucose Tolerance Test (OGTT)

Thesis presented by Hugo Alberto Flores Arguedas
to obtain the degree of Maestro en Ciencias con especialidad en Matemáticas Aplicadas

Jury: Dr. Ignacio Barradas Bribieska
Dr. Rogelio Ramos Quiroga
Dr. Marcos A. Capistrán Ocampo (Advisor)

2016

Basic Mathematics

Acknowledgement

I would like to thank

- Conacyt (Consejo Nacional de Ciencia y Tecnología) for sponsoring my studies and stay in Mexico during this master's degree.
- CIMAT (Centro de Investigación en Matemáticas, A.C.) for helping me during this master's degree: administrative staff, researchers, teachers, collegues and especially my advisor Dr. Marcos Capistrán Ocampo.
- Sonia and Marcela.

Abstract

Diabetes Mellitus 2 is a metabolic disorder. Its prevalence has been increasing all over the world. The Oral Glucose Tolerance Test (OGTT) allows to diagnose some anomalies related to the status of the disease. This work presents a model for the dynamics of glucose-insulin-glucagon in the human body and the corresponding qualitative analysis. Measurements of the glucose level during the OGTT supplie observations (data) for the formulation of the inverse problem. Quantifying the uncertainty is the principal objective of the bayesian approach presented. Under specific conditions, the model predicts around 60% of diagnosed patients.

Keywords: OGTT; Diabetes; bayesian; glucose; insulin; uncertainty

Contents

Chapter 1

Introduction

The World Health Organization (WHO) refers to diabetes as a chronic, metabolic disease characterized by elevated levels of blood glucose which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival [WHO]. That means that the economic cost around the treatment and medication of diabetes is growing.

Table 1 Direct, indirect and total costs (in US$) for healthcare service providers attributable to diabetes expected for the year 2010 in Mexico

Costs	Healthcare service provider					Total
	SSA	IMSS	ISSSTE	Other providers	PHI	
Direct costs (US$)						
Consultations/diagnosis	7,101,113	16,029,089	3,750,300	31,061,914	1,792,032	59,734,448
Drugs	15,813,331	35,749,875	8,351,475	69,234,743	3,994,310	133,143,734
Hospitalisation	4,747,670	10,716,748	2,507,381	20,767,414	1,198,118	39,937,331
Retinopathy	1,443,797	3,259,033	762,510	4,593,095	264,986	10,323,421
Cardiovascular disease	1,312,545	2,962,757	66,191	8,037,915	463,726	12,843,134
Nephropathy	9,581,565	21,628,130	5,060,299	43,060,262	2,484,244	81,814,501
Neuropathy	472,515	1,066,592	249,548	918,619	52,997	2,760,271
Peripheral vascular disease	315,010	711,061	166,365	803,792	46,373	2,042,601
Total direct	40,787,547	92,123,384	21,541,070	178,477,754	10,296,786	343,226,541
Indirect costs (US$)						
Mortality	2,267,624	5,326,703	1,217,070	10,811,632	na	19,623,029
Permanent disability	47,188,661	110,847,272	25,326,919	225,842,994	na	409,205,846
Temporary disability	712,395	1,673,432	382,353	3,603,879	na	6,372,059
Total indirect	50,168,680	117,847,407	26,926,342	240,258,505	na	435,200,934
Total costs*	90,956,227	209,970,791	48,467,412	418,736,259	10,296,786	778,427,475

Source: A. Arredondo, E. de Icaza, R. Ramos, A. Zuñiga and C. Carrillo, unpublished results

Exchange rate: January 2009, 1 US$=13.35 Mexican $

*$p<0.05$ (Box–Pierce statistical test) for the difference in expected total costs in 2010 between the different institutions (i.e. SSA, IMSS, ISSSTE, Other providers, PHI)

Figure 1.1: Cost for Healthcare in Mexico, 2010

Since 1965, WHO has published guidelines for the diagnosis and classification of diabetes. Globally in 2013, it is estimated that almost 382 million people suffer from diabetes for a prevalence of 8.3%. North America and the Caribbean is the region with the highest prevalence of 11% having 37 million people with diabetes, followed by the Middle East and North Africa with a prevalence of 9.2% having 35 million people with diabetes. The Western Pacific is the region with the highest number of people living with diabetes (138 million), however its prevalence is 8.6%, close to the prevalence of the World. In Mexico, the situation is worse than worldwide as we can see in the next picture, taken from the International Diabetes Federation [IDF]

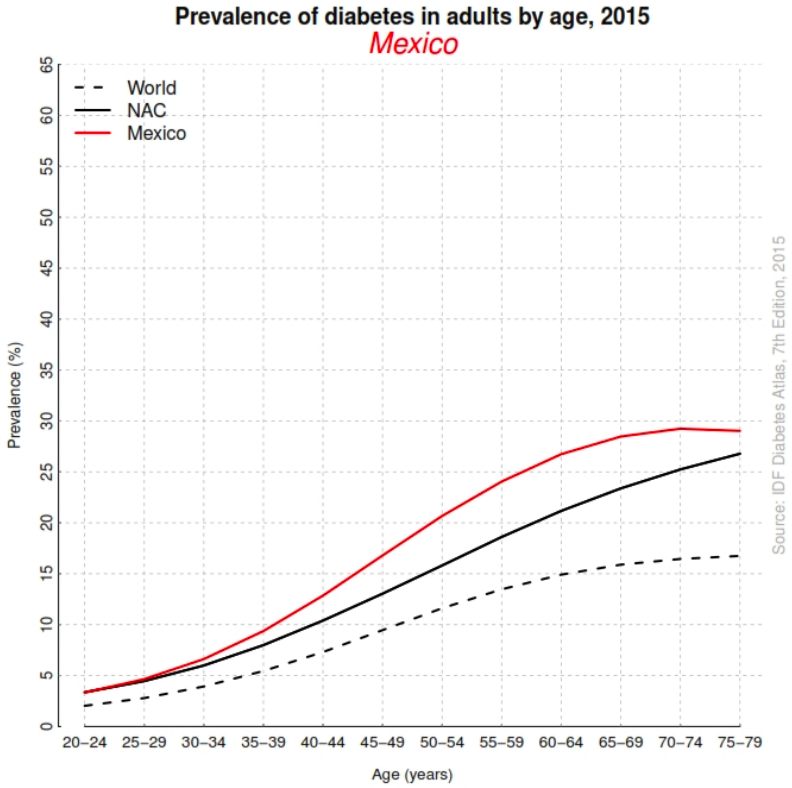


Figure 1.2: NAC(North America and Caribbean)

In the last decades, diabetes has become the principal health problem in Mexico. It is the leading cause of death in women since the year 2000. It is the primary cause of premature retirement, blindness, and kidney failure. By the year 2025, close to 11.7 million Mexicans are expected to be diagnosed with diabetes.

In this work, we will explain the biological situation of the desease, review some mathematical models and describe tests for the diagnose of diabetes, particularly the Oral Glucose Tolerance Test. In the next chapters, we will explain our model, propose the inverse problem and present results from the bayesian approach. The following scheme shows the aspects of this work:

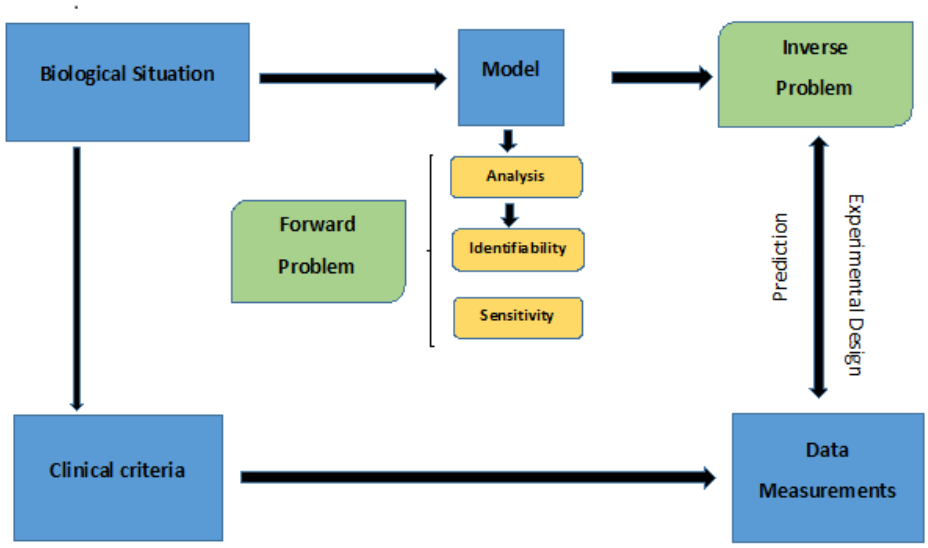


Figure 1.3: Work scheme

1.1 Biological situation

Hormones travel in the bloodstream to tissues and organs. They affect a vast array of bodily functions, such as sexual functions, growth and development, whole-body metabolism and blood glucose levels. The glucose level in the blood is regulated by two main chemical messengers in the body that are created in the endocrine glands, insulin and glucagon. Most tissues and organs need glucose constantly, as an important source of energy. Low blood concentrations of glucose can causes seizures, loss of consciousness, and death. On the other hand, a long-lasting elevation of blood glucose concentration can result in blindness, renal failure, vascular disease, and neuropathy. Therefore, blood glucose concentration needs to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis. [14]

The normal blood glucose level in humans is in a range of 70-110 mg/dl. We can find in [8] an extensive explanation of the endocrine system. Hormones secreted from

cells in the pancreas are responsible for the control of glucose, amino acids, and other molecules that are necessary for metabolism. The pancreas contains a large number of secretory cells. There are three principal secretory cell types: the α-cells secrete glucagon, the β-cells secrete insulin and the δ-cells secrete somatostatin. We are interested in the first two. Glucagon and insulin have complementary actions. A high concentration of glucose in the bloodstream (corresponding to an over-abundance of nutrients) stimulates the production of insulin, which in turn induces storage of excess nutrients and decreases the rate at which nutrients are mobilized from storage areas such as adipose tissue or the liver. Insulin acts principally on three tissues: striated muscle (including the heart), liver, and adipose tissue. All the actions of insulin apparently stem from its interaction with a specific receptor in the plasma membrane of insulin-sensitive cells. How this interaction leads to the many actions of insulin on the cell is not fully understood. In striated muscle and adipose tissue, one important action of insulin is to stimulate the transport of glucose into the cell. In the liver, insulin acts on enzymes to increase glucose storage and decrease mobilization of glucose stores. Exercise and fasting can induce a decrease in the glucose level and glucagon raises this concentration of glucose in the bloodstream. It acts mainly but not entirely on the liver, where it stimulates glycogen breakdown and the formation of glucose. Figure (1.4), found in [9], summarizes the situation.
Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia). A brief classification by type is:

- Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production.

- Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the bodys ineffective use of insulin. It often results from excess body weight and physical inactivity.

- Gestational diabetes is hyperglycaemia that is first recognized during pregnancy.

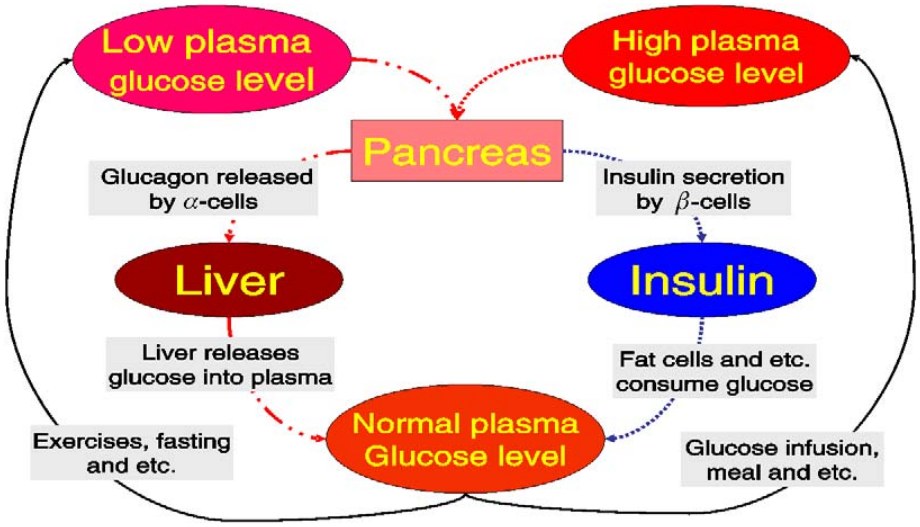


Figure 1.4: Biological situation

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable. The following picture shows the criteria to diagnose these conditions

Table 3. Major Diagnostic Criteria for Diabetes and Prediabetic or At-Risk States.*

Measure	American Diabetes Association		World Health Organization	
	Diabetes	Prediabetes	Diabetes	Impaired Glucose Regulation
Fasting plasma glucose	≥126 mg/dl	100–125 mg/dl (IFG)	≥126 mg/dl	110–125 mg/dl (IFG)
2-Hr plasma glucose (during an OGTT with a loading dose of 75 g)	≥200 mg/dl	140–199 mg/dl (IGT)	≥200 mg/dl	140–199 mg/dl (IGT)
Casual (or random) plasma glucose (in a patient with classic hyperglycemic symptoms)	≥200 mg/dl		≥200 mg/dl	
Glycated hemoglobin	≥6.5%	5.7–6.4%	≥6.5%	

* Data are adapted from the American Diabetes Association,[7,18] Alberti and Zimmet,[12] and the World Health Organization.[19] All listed plasma glucose levels are based on venous sampling. All tests (except for casual plasma glucose in a symptomatic patient) should be repeated and confirmed on a separate day. (The American Diabetes Association allows for glycated hemoglobin testing to be paired with fasting plasma glucose testing on the same day. If the values for both tests are in the diabetic range, the diagnosis is confirmed.) To convert the values for glucose to millimoles per liter, multiply by 0.05551. IFG denotes impaired fasting glucose, IGT impaired glucose tolerance, and OGTT oral glucose-tolerance test.

Figure 1.5: Diagnostic Criteria for WHO and ADA

Measurement of glucose in blood remains the mainstay of testing for glucose tolerance status. There are a number of important considerations which can influence this measurement which require careful attention in order to ensure an accurate result.

The OGTT consists of a small sample of fasting-state blood. After giving a blood sample, the patient must drink a concentrated solution of glucose (250 ml. of water with 75 gr. of sucar) within a given amount of time (usually five minutes). Then blood samples are taken each 30 minutes for 2 hours (a total of five samples). By taking several samples of your blood as your body processes the sugary drink, the healthcare professional can deduce how quickly your body can process sugar.

The Intravenous Glucose Tolerance Test (IVGTT) consists of giving a bolus of glucose (300 mg/kg in a 30% solution) within 60 seconds into the antecubital vein. Blood is sampled from the contralateral antecubital vein for assessment of the plasma glucose, insulin, and C-peptide concentrations.

Oral tests necessarily fail to distinguish between effects due to changes in intestinal absorption and those due to alterations in carbohydrate metabolism. Variations in gastric emptying time and in intestinal absorption are in fact known to influence the results of oral tests. Technically, the IVGTT is more difficult, time-consuming and is rarely used.

There is continuing debate about the place of the OGTT for clinical and epidemiological purposes. The test is recommended by the WHO inasmuch as fasting plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed diabetes and is the only means of identifying people with IGT. Although the ADA (American Diabetes Association) acknowledges the OGTT as a valid way to diagnose diabetes, the use of the test for diagnostic purposes in clinical practice is discouraged in favour of fasting plasma glucose for several reasons, including inconvenience, greater cost and less reproducibility.

We can see in ([3]) a brief description of some indices used to "measure" *insulin sensitivity*. The HOMA formula is a simplification of a mathematical model which assesses β-cell response and can be described as the product of fasting glucose and fasting insulin divided by a constant. As insulin secretion follows a pulsatile pattern, the accuracy of the indices is questioned in several cases. That gives a prospect of

tools and limitations possessing the clinical professionals.

1.2 Previous models for glucose-insulin dynamics

1. **Bergman** Bergman's Minimal Model was presented in 1979 and is a model that works during the IVGTT. The model is given by

$$\begin{aligned} \dot{G}(t) &= -p_1\left(G(t) - G_b\right) - X(t)G(t), \qquad G(0) = G_0 \\ \dot{X}(t) &= -p_2 X(t) + p_3\left(I(t) - I_b\right), \qquad X(0) = 0 \\ \dot{I}(t) &= -n\left(I(t) - I_b\right) + \gamma\left(G(t) - h\right)^+ t, \qquad I(0) = I_0, \end{aligned} \tag{1.1}$$

   where $t = 0$ is the glucose injection time and the variables denote the following;

   - $G(t)$: the glucose concentration in plasma at time t.
   - $I(t)$: the insulin concentration in plasma at time t.
   - $X(t)$: the insulin's effect on the net glucose disappearance (remote insulin action).

   See [1] for a bayesian approach with this model. We want to point out that the glucose level as well as the insulin level of the body are modelled with a basal level, G_b and I_b. Moreover, the rate of change for the insulin is characterized by a switch that is on when the glucose is over a threshold value.

2. **Sturis** Based on two negative feedback loops describing the effects of insulin on glucose utilization and production and the effect of glucose on insulin secretion, Sturis et al. (1991) developed a six-dimensional ODE model. A negative feedback is a key regulatory mechanism for physiological function in living things. Negative feedback tends to promote a settling to equilibrium, and reduces the effects of perturbations. Ussually, negative feedback loops occur in a series of steps: There is an stimulus, in which a change occurs. There is a sensor, or the change is detected. There is a control, which is just a response to the change. There is an effector, or the effect of the response for a period of time

until the situation is brought back to normal. This model includes additional variables associated with the delays of the insulin effect on the hepatic glucose production. A brief explanation of this model and references are presented in [9].

3. The next model is presented in [4] and it is a premodel for [5],

$$\begin{aligned} \dot{G} &= (L - I)\, G + \frac{D}{\theta_2} \\ \dot{I} &= \theta_0 \left(\frac{G}{G_0} - 1 \right)^+ - \frac{I}{a} \\ \dot{L} &= \theta_1 \left(1 - \frac{G}{G_0} \right)^+ - \frac{L}{b} \\ \dot{D} &= \frac{D}{\theta_2} \qquad , \end{aligned} \tag{1.2}$$

where $G(t)$ is the blood glucose level at time t, $I(t)$ is the blood insulin level at time t and $L(t)$ the glucagon levels. Also, $D(t)$ is the digestive system "glucose level". This model shows, again, that when $G(t)$ is over a threshold value, G_b, insulin is produced. On the contrary, when $G(t)$ is under that value, glucagon is produced.

In [9] we can find a variety of models for the glucose-insulin system from the ODE models, delay equations, integro-differential equations, PDE models among others.

1.3 The model

We will explain the biological motivation for the following model:

$$\begin{aligned}
\dot{G} &= \lambda_1 L - \lambda_2 I + 0.8\lambda_3 D \\
\dot{I} &= \lambda_4 (G - G_0)^+ - \lambda_5 I \\
\dot{L} &= \lambda_6 (G_0 - G)^+ - \lambda_7 L \\
\dot{D} &= -\lambda_3 D + \lambda_8 V \\
\dot{V} &= -\lambda_8 V \qquad ,
\end{aligned} \tag{1.3}$$

where $G(t)$, $I(t)$ and $L(t)$ are as in (1.2). Also, $D(t)$ is the digestive system "glucose level" due to the supply and finally $V(t)$ is the "glucose level" in the glass. The fifth equation models the glucose level in the glass in an exponential way. The digestive system "glucose level" $D(t)$ is modeled like a tank, all the glucose taken from the glass arrives in the digestive system at a different rate than it desintegrates. Just a fraction of the glucose in the digestive system affects the blood level. Several epidemiological studies reveal sex-specific differences during oral glucose tolerance tests, such as gut glucose absorption. Based on [2], we will work with 0.8 as this fraction. λ_4 and λ_6 are the production rates of insulin and glucagon and λ_5 and λ_7 their desintegration rates respectively. Finally, λ_1 and λ_2 are the effectiveness rates of the glucagon and insulin that affects the blood glucose level.
In the following chapter, we will parameterize this model, analyze its stability, properties of its solutions and propose the inverse problem under the bayesian approach.

Chapter 2

Materials and Methods

Making the following parametrization $\lambda_1 L = L_1$ and $\lambda_2 I = I_1$ in (1.3), we reach the next system

$$\begin{aligned} \dot{G} &= L_1 - I_1 + 0.8\theta_0 D \\ \dot{I}_1 &= \theta_1 (G - G_b)^+ - \lambda_5 I_1 \\ \dot{L}_1 &= \theta_2 (G_b - G)^+ - \lambda_7 L_1 \\ \dot{D} &= -\theta_0 D + \lambda_8 V \\ \dot{V} &= -\lambda_8 V \end{aligned} \qquad , \tag{2.1}$$

equivalent to the one shown in [5].

2.1 Analysis of the ODE system

2.1.1 Equilibrium points and stability

The equilibrium points are found by solving each equation of the system. Fifth equation forces that $V = 0$. Substituting in the fourth equation we get $D = 0$. In the same way, from the first equation, we obtain the condition $L_1 = I_1$. Finally, from the second and third equation, it follows that $G = G_b$, $L_1 = I_1 = 0$. So our unique

equilibrium point is $(G_b, 0, 0, 0, 0)$.

Now we proceed to the calculation of the jacobian matrix for our system. Observe that the jacobian matrix must be determined in two different ways; for G_0^+ and for G_0^-. Thus,

$$J^- = \begin{pmatrix} 0 & -1 & 1 & \theta_0 & 0 \\ 0 & -\lambda_5 & 0 & 0 & 0 \\ -\theta_2 & 0 & -\lambda_7 & 0 & 0 \\ 0 & 0 & 0 & -\theta_0 & 1 \\ 0 & 0 & 0 & 0 & -\lambda_8 \end{pmatrix}.$$

The characteristic polynomial associated to J^- is

$$p^-(\lambda) = (\lambda + \lambda_8)(\lambda + \theta_0)(\lambda + \lambda_5)(\lambda^2 + \lambda\lambda_7 + \theta_2).$$

So, the corresponding eigenvalues are $-\lambda_8, -\lambda_5, -\theta_0, \dfrac{-\lambda_7 \pm \sqrt{(\lambda_7)^2 - 4\theta_2}}{2}$. Note that all have a negative real part.

On the other hand

$$J^+ = \begin{pmatrix} 0 & -1 & 1 & \theta_0 & 0 \\ \theta_1 & -\lambda_5 & 0 & 0 & 0 \\ 0 & 0 & -\lambda_7 & 0 & 0 \\ 0 & 0 & 0 & -\theta_0 & 1 \\ 0 & 0 & 0 & 0 & -\lambda_8 \end{pmatrix}.$$

The characteristic polynomial asociated to J^+ is

$$p^+(\lambda) = (\lambda + \lambda_8)(\lambda + \theta_0)(\lambda + \lambda_7)(\lambda^2 + \lambda\lambda_5 + \theta_1).$$

Since the eigenvalues associated to J^+ are $-\lambda_8, -\lambda_7, -\theta_0, \dfrac{-\lambda_5 \pm \sqrt{(\lambda_5)^2 - 4\theta_1}}{2}$, we can observe that again all possess a negative real part.

Finally, it follows that the equilibrium point $(G_b, 0, 0, 0, 0)$ is asymptotically stable.

2.1.2 An expression for the glucose in the digestive system

We will start with the fifth equation in (2.1). Using separation of variables, we have

$$\frac{dV}{dt} = -\lambda_8 V \Rightarrow \frac{dV}{V} = -\lambda_8 dt$$

$$\Rightarrow \ln V = -\lambda_8 t + C \Rightarrow V(t) = Ke^{-\lambda_8 t}$$

then

$$V(t) = V_0 e^{-\lambda_8 t}. \tag{2.2}$$

With that expression for V, we now solve the fourth equation in (2.1),

$$\dot{D} = -\theta_0 D + \lambda_8 V = -\theta_0 D + \lambda_8 V_0 e^{-\lambda_8 t}.$$

We consider two cases:

(i) $\theta_0 \neq \lambda_8$

For this case, $D(t)$ takes the form $D(t) = K_1 e^{-\theta_0 t} + K_2 e^{-\lambda_8 t}$ and we must determine K_1 and K_2, then

$$\dot{D} + \theta_0 D = -\theta_0 K_1 e^{-\theta_0 t} - \lambda_8 K_2 e^{-\lambda_8 t} + \theta_0 K_1 e^{-\theta_0 t} + \theta_0 K_2 e^{-\lambda_8 t} =$$

$$= -\lambda_8 K_2 e^{-\lambda_8 t} + \theta_0 K_2 e^{-\lambda_8 t} = K_2 e^{-\lambda_8 t}\left(-\lambda_8 + \theta_0\right) = \lambda_8 V_0 e^{-\lambda_8 t}$$

$$\Rightarrow K_2\left(-\lambda_8 + \theta_0\right) = \lambda_8 V_0 \Rightarrow K_2 = \frac{\lambda_8 V_0}{\theta_0 - \lambda_8}.$$

So, $D(t) = K_1 e^{-\theta_0 t} + \dfrac{\lambda_8 V_0}{\theta_0 - \lambda_8} e^{-\lambda_8 t}$ and since $D(0) = 0$ we have

$$D(0) = K_1 + K_2 = K_1 + \frac{\lambda_8 V_0}{\theta_0 - \lambda_8} = 0$$

$$\Rightarrow K_1 = -\frac{\lambda_8 V_0}{\theta_0 - \lambda_8}.$$

Finally,

$$D(t) = \frac{\lambda_8 V_0}{\theta_0 - \lambda_8}\left(e^{-\lambda_8 t} - e^{-\theta_0 t}\right). \tag{2.3}$$

(ii) $\theta_0 = \lambda_8$

For this case, $D(t)$ must be $D(t) = (P_1 + P_2 t)\, e^{-\theta_0 t}$. To determine P_1 and P_2, substituting as before we have

$$\dot{D}+\theta_0 D = P_2 e^{-\theta_0 t} - \theta_0 (P_1 + P_2 t)\, e^{-\theta_0 t} + \theta_0 (P_1 + P_2 t)\, e^{-\theta_0 t} = P_2 e^{-\theta_0 t} = \theta_0 V_0 e^{-\theta_0 t}$$

$$\Rightarrow P_2 = \theta_0 V_0.$$

Again, since $D(0) = 0$, we arrive to

$$D(0) = P_1 = 0.$$

Finally,

$$D(t) = \theta_0 V_0 t e^{-\theta_0 t}. \tag{2.4}$$

Therefore,

$$D(t) = \begin{cases} \dfrac{\lambda_8 V_0}{\theta_0 - \lambda_8} \left(e^{-\lambda_8 t} - e^{-\theta_0 t}\right), & \text{if } \theta_0 \neq \lambda_8, \\ \\ \theta_0 V_0 t e^{-\theta_0 t}, & \text{if } \theta_0 = \lambda_8 \end{cases}. \tag{2.5}$$

For the numerical approach, we will work with the case $\theta_0 \neq \lambda_8$.

2.1.3 A harmonic oscillator

Consider the first three equations in (2.1). Now, we will assume that $\lambda_5 = \lambda_7$ and $\theta_1 = \theta_2$, then (2.1) becomes

$$\dot{G} = L_1 - I_1 + 0.8\theta_0 D$$

$$\dot{I}_1 = \theta_1 (G - G_b)^+ - \lambda_5 I_1 \tag{2.6}$$

$$\dot{L}_1 = \theta_1 (G_b - G)^+ - \lambda_5 L_1$$

Let $w = L_1 - I_1$ so $\dot{w} = \dot{L}_1 - \dot{I}_1$. Since $(G_b - G)^+ - (G - G_b)^+ = G_b - G$ we have that

$$\begin{aligned}\dot{w} = \dot{L}_1 - \dot{I}_1 &= \theta_1(G_b - G)^+ - \lambda_5 L_1 - \theta_1(G - G_b)^+ + \lambda_5 I_1 \\ &= \theta_1\left[(G_b - G)^+ - (G - G_b)^+\right] - \lambda_5(L_1 - I_1) \\ &= \theta_1(G_b - G) - \lambda_5 w\end{aligned}$$

Now, if we choose $x = G - G_b$, then we have $\dot{x} = \dot{G} = L_1 - I_1 + 0.8\theta_0 D$. Then (2.6) becomes

$$\begin{aligned}\dot{x} &= w + 0.8\theta_0 D \\ \dot{w} &= -\theta_1 x - \lambda_5 w\end{aligned} \quad . \tag{2.7}$$

Finally, since $\dot{x} = w + \theta_0 D$, then

$$\ddot{x} = \dot{w} + 0.8\theta_0 \dot{D} = -\theta_1 x - \lambda_5 w + 0.8\theta_0 \dot{D}$$

so

$$\ddot{x} = -\theta_1 x - \lambda_5(\dot{x} - 0.8\theta_0 D) + 0.8\theta_0 \dot{D}.$$

The last equation can be written as

$$\ddot{x} + \lambda_5 \dot{x} + \theta_1 x = 0.8\theta_0 \left(\lambda_5 D + \dot{D}\right) \tag{2.8}$$

and the solution $x(t)$ can be found analytically and is a driven harmonic oscillator, i.e., a damped oscillator with an external force applied.

2.1.4 A third order oscillator

As in the last subsection, let us consider $\theta_1 = \theta_2 + \epsilon$ and $\lambda_5 = \lambda_7 + \eta$ and using (2.6), we have

$$\dot{w} = \dot{L}_1 - \dot{I}_1 = \theta_2(G_b - G)^+ - \lambda_7 L_1 - (\theta_2 + \epsilon)(G - G_b)^+ + (\lambda_7 + \eta) I_1$$

$$= \theta_2\left[(G_b - G)^+ - (G - G_b)^+\right] - \lambda_7(L_1 - I_1) - \epsilon(G - G_b)^+ + \eta I_1 =$$

$$= \theta_2(G_b - G) - \lambda_7 w - \epsilon(G - G_b)^+ + \eta I_1.$$

Now, letting $x = G - G_b$, instead of (2.7) we obtain

$$\begin{aligned} \dot{x} &= w + 0.8\theta_0 D \\ \dot{w} &= -\theta_2 x - \lambda_7 w - \epsilon x^+ + \eta I_1. \end{aligned} \tag{2.9}$$

Differentiating on (2.9) we get an order 2 equation.
Since $\dot{x} = w + 0.8\theta_0 D$ then

$$\ddot{x} = \dot{w} + 0.8\theta_0 \dot{D} = -\theta_2 x - \lambda_7 w - \epsilon x^+ + \eta I_1 + 0.8\theta_0 \dot{D}$$

$$\ddot{x} = -\theta_2 x - \lambda_7 (\dot{x} - 0.8\theta_0 D) - \epsilon (x)^+ + \eta I_1 + 0.8\theta_0 \dot{D}$$

finally, we arrive to

$$\begin{cases} \ddot{x} + \lambda_7 \dot{x} + \theta_1 x = 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right) + \eta I_1, & \text{if } x \geq 0, \\ \\ \ddot{x} + \lambda_7 \dot{x} + \theta_2 x = 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right) + \eta I_1, & \text{if } x < 0 \end{cases} . \tag{2.10}$$

Note that when $\epsilon = \eta = 0$ we have (2.8).
In the next equation, we will use (2.10) to differentiate and eliminate the I_1 term

$$\Rightarrow \begin{cases} x^{(3)} + \lambda_7 \ddot{x} + \theta_1 \dot{x} = 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) + \eta \dot{I}_1, & \text{if } x \geq 0, \\ \\ x^{(3)} + \lambda_7 \ddot{x} + \theta_2 \dot{x} = 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) + \eta \dot{I}_1, & \text{if } x < 0 \end{cases} \tag{2.11}$$

next, using the second equation in (2.6) we have

$$\begin{cases} x^{(3)} + \lambda_7 \ddot{x} + \theta_1 \dot{x} = 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) + \eta \left(\theta_1 x - \lambda_5 I_1\right), & \text{if } x \geq 0, \\ \\ x^{(3)} + \lambda_7 \ddot{x} + \theta_2 \dot{x} = 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) - \eta \lambda_5 I_1, & \text{if } x < 0 \end{cases} \tag{2.12}$$

From (2.10), we can obtain a relation to I_1

$$\Rightarrow \begin{cases} \ddot{x} + \lambda_7 \dot{x} + \theta_1 x - 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right) = \eta I_1, & \text{if } x \geq 0, \\ \\ \ddot{x} + \lambda_7 \dot{x} + \theta_2 x - 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right) = \eta I_1, & \text{if } x < 0 \end{cases}$$

and substituting in (2.12) we have

$$\Rightarrow \begin{cases} x^{(3)} + \lambda_7 \ddot{x} + \theta_1 \dot{x} - \eta\theta_1 x = \\ 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) - \lambda_5 \left(\ddot{x} + \lambda_7 \dot{x} + \theta_1 x - 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right)\right), & \text{if } x \geq 0, \\ \\ x^{(3)} + \lambda_7 \ddot{x} + \theta_2 \dot{x} = \\ 0.8\theta_0 \left(\lambda_7 \dot{D} + \ddot{D}\right) - \lambda_5 \left(\ddot{x} + \lambda_7 \dot{x} + \theta_2 x - 0.8\theta_0 \left(\lambda_7 D + \dot{D}\right)\right), & \text{if } x < 0 \end{cases} \tag{2.13}$$

Finally, simplifying we arrive to

$$\Rightarrow \begin{cases} x^{(3)} + (\lambda_7 + \lambda_5)\ddot{x} + (\theta_1 + \lambda_7\lambda_5)\dot{x} + \theta_1\lambda_7 x = \\ 0.8\theta_0 \left(\ddot{D} + (\lambda_7 + \lambda_5)\dot{D} + \lambda_5\lambda_7 D\right), & \text{if } x \geq 0, \\ \\ x^{(3)} + (\lambda_7 + \lambda_5)\ddot{x} + (\theta_2 + \lambda_7\lambda_5)\dot{x} + \lambda_5\theta_2 x = \\ 0.8\theta_0 \left(\ddot{D} + (\lambda_7 + \lambda_5)\dot{D} + \lambda_5\lambda_7 D\right), & \text{if } x < 0 \end{cases} \tag{2.14}$$

2.1.5 Qualitative features of solutions

(a) **Homogeneous equation solution**

The characteristic equation asociated to the first case in (2.14) is

$$m^3 + (\lambda_7 + \lambda_5)m^2 + (\theta_1 + \lambda_7\lambda_5)m + \theta_1\lambda_7 = 0$$

which we can write as

$$(m + \lambda_7)(m^2 + \lambda_5 m + \theta_1) = 0. \tag{2.15}$$

In an analogous way for the second equation in (2.14), we have

$$(m + \lambda_5)(m^2 + \lambda_7 m + \theta_2) = 0. \tag{2.16}$$

Different behaviours are possible relative to the number $\Delta_1 = \lambda_5^2 - 4\theta_1$ for (2.15) and $\Delta_2 = \lambda_7^2 - 4\theta_2$ for (2.16). We characterize these cases in the following.

Insulin subsystem

(i) $\lambda_5^2 - 4\theta_1 > 0$

The solutions to (2.15) are $m_0 = -\lambda_7$ and

$$m_1 = \frac{-\lambda_5 - \sqrt{\lambda_5^2 - 4\theta_1}}{2} \qquad m_2 = \frac{-\lambda_5 + \sqrt{\lambda_5^2 - 4\theta_1}}{2}$$

Since $0 < \lambda_5^2 - 4\theta_1 < \lambda_5^2$ then $\sqrt{\lambda_5^2 - 4\theta_1} < \lambda_5$. Moreover $-\lambda_5 + \sqrt{\lambda_5^2 - 4\theta_1} < 0$ so, we have that m_1 and m_2 are both negatives.
Therefore

$$x_H(t) = A_1 e^{m_1 t} + A_2 e^{m_2 t} + A_3 e^{-\lambda_7 t}.$$

(ii) $(\lambda_5)^2 - 4\theta_1 = 0$

In this case, the equation (2.15) has solutions $m_0 = -\lambda_7$ and $m = -\dfrac{\lambda_5}{2}$ with multiplicity two. Hence,

$$x_H(t) = e^{-\frac{\lambda_5}{2} t} (B_1 + B_2 t) + B_3 e^{-\lambda_7 t}.$$

(iii) $(\lambda_5)^2 - 4\theta_1 < 0$

The solutions to (2.15) are $m_0 = -\lambda_7$ and

$$m_1 = \frac{-\lambda_5 - i\sqrt{4\theta_1 - \lambda_5^2}}{2} \qquad m_2 = \frac{-\lambda_5 + i\sqrt{4\theta_1 - \lambda_5^2}}{2}$$

Accordingly,

$$x_H(t) = e^{-\frac{\lambda_5}{2}t}\left[C_1\cos\left(\frac{\sqrt{4\theta_1-\lambda_5^2}}{2}t\right)+C_2\sin\left(\frac{\sqrt{4\theta_1-\lambda_5^2}}{2}t\right)\right]+C_3e^{-\lambda_7 t}$$

Glucagon subsystem: For this case, we consider exactly the same cases as in the insulin subsystem.

(i) $\lambda_7^2-4\theta_2>0$

The solutions to (2.16) are $m_0=-\lambda_5$ and

$$m_1=\frac{-\lambda_7-\sqrt{\lambda_7^2-4\theta_2}}{2} \qquad m_2=\frac{-\lambda_7+\sqrt{\lambda_7^2-4\theta_2}}{2}.$$

Since $0<\lambda_7^2-4\theta_2<\lambda_7^2$ then $\sqrt{\lambda_7^2-4\theta_2}<\lambda_7$. Therefore $-\lambda_7+\sqrt{\lambda_7^2-4\theta_2}<0$ and we have that m_1 and m_2 are both negative. Hence,

$$x_H(t)=A_1e^{m_1t}+A_2e^{m_2t}+A_3e^{-\lambda_5 t}.$$

(ii) $\lambda_7^2-4\theta_2=0$

In this case, the equation (2.16) has solutions $m_0=-\lambda_5$ and $m=-\dfrac{\lambda_7}{2}$ with multiplicity two. Hence,

$$x_H(t)=e^{-\frac{\lambda_7}{2}t}\left(B_1+B_2t\right)+B_3e^{-\lambda_5 t}.$$

(iii) $\lambda_7^2-4\theta_2<0$

The solutions to (2.16) are $m_0=-\lambda_5$ and

$$m_1=\frac{-\lambda_7-i\sqrt{4\theta_2-\lambda_7^2}}{2} \qquad m_2=\frac{-\lambda_7+i\sqrt{4\theta_2-\lambda_7^2}}{2}.$$

Accordingly,

$$x_H(t) = e^{-\frac{\lambda_7}{2}t}\left[C_1\cos\left(\frac{\sqrt{4\theta_2-\lambda_7^2}}{2}t\right)+C_2\sin\left(\frac{\sqrt{4\theta_2-\lambda_7^2}}{2}t\right)\right]+C_3e^{-\lambda_5 t}.$$

(b) **Particular solution**

From (2.5) and since $F(t) = 0.8\theta_0\left(\ddot{D}+(\lambda_7+\lambda_5)\dot{D}+\lambda_7\lambda_5 D\right)$ we can conclude that $F(t)$ will be given by

$$\begin{cases} \dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\left[e^{-\lambda_8 t}\left(\lambda_5-\lambda_8\right)\left(\lambda_7-\lambda_8\right)-e^{-\theta_0 t}\left(\lambda_5-\theta_0\right)\left(\lambda_7-\theta_0\right)\right], & \text{if } \theta_0\neq\lambda_8, \\ 0.8\theta_0^2 V_0 e^{-\theta_0 t}\left[\left(\lambda_5+\lambda_7-2\theta_0\right)+\left(\lambda_5-\theta_0\right)\left(\lambda_7-\theta_0\right)t\right], & \text{if } \theta_0=\lambda_8 \end{cases} \tag{2.17}$$

From (2.17) we deduce that a particular solution for system (2.14) can be for $\theta_0 \neq \lambda_8$

$$x_p(t) = K_1e^{-\theta_0 t}+K_2e^{-\lambda_8 t}.$$

Our aim is to determine the constants K_1 and K_2. Note that

$$\dot{x}_p(t) = -\theta_0K_1e^{-\theta_0 t}-\lambda_8K_2e^{-\lambda_8 t}$$

$$\ddot{x}_p(t) = \theta_0^2K_1e^{-\theta_0 t}+\lambda_8^2K_2e^{-\lambda_8 t}$$

$$x_p^{(3)}(t) = -\theta_0^3K_1e^{-\theta_0 t}-\lambda_8^3K_2e^{-\lambda_8 t}.$$

Next substituting on (2.15) we have

$$K_1e^{-\theta_0 t}\left(-\theta_0^3+(\lambda_5+\lambda_7)\theta_0^2-(\theta_1+\lambda_7\lambda_5)\theta_0+\theta_1\lambda_7\right)$$

$$+K_2e^{-\lambda_8 t}\left(-\lambda_8^3+(\lambda_5+\lambda_7)\lambda_8^2-(\theta_1+\lambda_7\lambda_5)\lambda_8+\theta_1\lambda_7\right) = F(t)$$

$$\Rightarrow \begin{cases} K_1(-\theta_0+\lambda_7)(\theta_0^2-\lambda_5\theta_0+\theta_1) = -\dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}(\theta_0-\lambda_5)(\theta_0-\lambda_7) \\ \\ K_2(-\lambda_8+\lambda_7)(\lambda_8^2-\lambda_5\lambda_8+\theta_1) = \dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}(\lambda_8-\lambda_5)(\lambda_8-\lambda_7) \end{cases} \tag{2.18}$$

$$\Rightarrow \begin{cases} K_1 = \dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\dfrac{\theta_0-\lambda_5}{\theta_0^2-\lambda_5\theta_0+\theta_1} \\ \\ K_2 = -\dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\dfrac{\lambda_8-\lambda_5}{\lambda_8^2-\lambda_5\lambda_8+\theta_1} \end{cases} \tag{2.19}$$

In the same way, but substituting

$$x_p(t) = L_1 e^{-\theta_0 t} + L_2 e^{-\lambda_8 t}$$

in (2.16) we have

$$\Rightarrow \begin{cases} L_1 = \dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\dfrac{\theta_0-\lambda_7}{\theta_0^2-\lambda_7\theta_0+\theta_2} \\ \\ L_2 = -\dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\dfrac{\lambda_8-\lambda_7}{\lambda_8^2-\lambda_7\lambda_8+\theta_2}. \end{cases} \tag{2.20}$$

(c) **General solution**

In the following, we just consider the case $\lambda_8 \neq \theta_0$

(i) $\lambda_5^2 - 4\theta_1 < 0$ and $\lambda_7^2 - 4\theta_2 < 0$.

In this case, the solution is given by

$$x(t) = \begin{cases} A_1 e^{-\lambda_7 t} + e^{-\lambda_5 t/2}\left[A_2 \cos\left(\frac{\sqrt{4\theta_1 - \lambda_5^2}}{2}t\right) + A_3 \sin\left(\frac{\sqrt{4\theta_1 - \lambda_5^2}}{2}t\right)\right] \\ +\frac{0.8\theta_0\lambda_8 V_0}{\theta_0 - \lambda_8}\left(\frac{\theta_0 - \lambda_5}{\theta_0^2 - \lambda_5\theta_0 + \theta_1}e^{-\theta_0 t} - \frac{\lambda_8 - \lambda_5}{\lambda_8^2 - \lambda_5\lambda_8 + \theta_1}e^{-\lambda_8 t}\right), \\ \text{if } x \geq 0, \\ \\ B_1 e^{-\lambda_5 t} + e^{-\lambda_7 t/2}\left[B_2 \cos\left(\frac{\sqrt{4\theta_2 - \lambda_7^2}}{2}t\right) + B_3 \sin\left(\frac{\sqrt{4\theta_2 - \lambda_7^2}}{2}t\right)\right] \\ +\frac{0.8\theta_0\lambda_8 V_0}{\theta_0 - \lambda_8}\left(\frac{\theta_0 - \lambda_7}{\theta_0^2 - \lambda_7\theta_0 + \theta_2}e^{-\theta_0 t} - \frac{\lambda_8 - \lambda_7}{\lambda_8^2 - \lambda_7\lambda_8 + \theta_2}e^{-\lambda_8 t}\right), \\ \text{if } x < 0 \end{cases} \tag{2.21}$$

Since the solution must satisfy the conditions

$$x(0) = 0, \qquad x'(0) = 0, \qquad x''(0) = 0.8\theta_0\lambda_8 V_0$$

we must solve the system

$$\begin{pmatrix} 1 & 1 & 0 \\ \lambda_7 & \frac{\lambda_5}{2} & -\frac{\sqrt{4\theta_1 - \lambda_5^2}}{2} \\ \lambda_7^2 & \frac{\lambda_5^2}{2} - \theta_1 & -\frac{\lambda_5\sqrt{4\theta_1 - \lambda_5^2}}{2} \end{pmatrix} \begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} = \tilde{K}$$

where

$$\tilde{K} = \frac{0.8\theta_0\lambda_8 V_0}{(\theta_0^2 - \lambda_5\theta_0 + \theta_1)(\lambda_8^2 - \lambda_5\lambda_8 + \theta_1)} \begin{pmatrix} \lambda_5^2 + \theta_0\lambda_8 - \theta_0\lambda_5 - \theta_1 - \lambda_5\lambda_8 \\ \theta_1(\lambda_5 - \theta_0 - \lambda_8) \\ \theta_1(\theta_1 - \theta_0\lambda_8) \end{pmatrix}$$

Finally, we have

$$A_1 = 0$$

$$A_2 = \frac{0.8\theta_0\lambda_8 V_0\left[\lambda_5(\lambda_5-\theta_0-\lambda_8)-(\theta_1-\theta_0\lambda_8)\right]}{\left(\theta_0^2-\lambda_5\theta_0+\theta_1\right)\left(\lambda_8^2-\lambda_5\lambda_8+\theta_1\right)}$$

$$A_3 = \frac{0.8\theta_0\lambda_8 V_0\left[2\lambda_7(\lambda_5^2+\theta_0\lambda_8-\theta_0\lambda_5-\theta_1-\lambda_5\lambda_8)-(\lambda_5^2+2\theta_1)(\lambda_5-\theta_0-\lambda_8)\right]}{\sqrt{4\theta_1-\lambda_5^2}\left(\theta_0^2-\lambda_5\theta_0+\theta_1\right)\left(\lambda_8^2-\lambda_5\lambda_8+\theta_1\right)}+$$
$$+\frac{0.8\theta_0\lambda_8 V_0\left[\lambda_5(\theta_1-\theta_0\lambda_8)\right]}{\sqrt{4\theta_1-\lambda_5^2}\left(\theta_0^2-\lambda_5\theta_0+\theta_1\right)\left(\lambda_8^2-\lambda_5\lambda_8+\theta_1\right)}$$

Since we are in the oscillatory regime, and (2.1) is not C^1 for every t then we need to solve another system for B_1, B_2, B_3 with different initial conditions.

(ii) $\lambda_5^2-4\theta_1>0$ and $\lambda_7^2-4\theta_2>0$

In this case, the solution is given by

$$x(t)=\begin{cases} C_1e^{-\lambda_7 t}+C_2e^{m_1 t}+C_3e^{m_2 t} \\ +\dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\left(\dfrac{\theta_0-\lambda_5}{\theta_0^2-\lambda_5\theta_0+\theta_1}e^{-\theta_0 t}-\dfrac{\lambda_8-\lambda_5}{\lambda_8^2-\lambda_5\lambda_8+\theta_1}e^{-\lambda_8 t}\right), \\ \text{if } x\geq 0, \\ \\ D_1e^{-\lambda_5 t}+D_2e^{n_1 t}+D_3e^{n_2 t} \\ +\dfrac{0.8\theta_0\lambda_8 V_0}{\theta_0-\lambda_8}\left(\dfrac{\theta_0-\lambda_7}{\theta_0^2-\lambda_7\theta_0+\theta_2}e^{-\theta_0 t}-\dfrac{\lambda_8-\lambda_7}{\lambda_8^2-\lambda_7\lambda_8+\theta_2}e^{-\lambda_8 t}\right), \\ \text{if } x<0 \end{cases} \tag{2.22}$$

where

$$m_1=\frac{-\lambda_5-\sqrt{\lambda_5^2-4\theta_1}}{2} \qquad m_2=\frac{-\lambda_5+\sqrt{\lambda_5^2-4\theta_1}}{2}$$

and

$$n_1=\frac{-\lambda_7-\sqrt{\lambda_7^2-4\theta_2}}{2} \qquad n_2=\frac{-\lambda_7+\sqrt{\lambda_7^2-4\theta_2}}{2}.$$

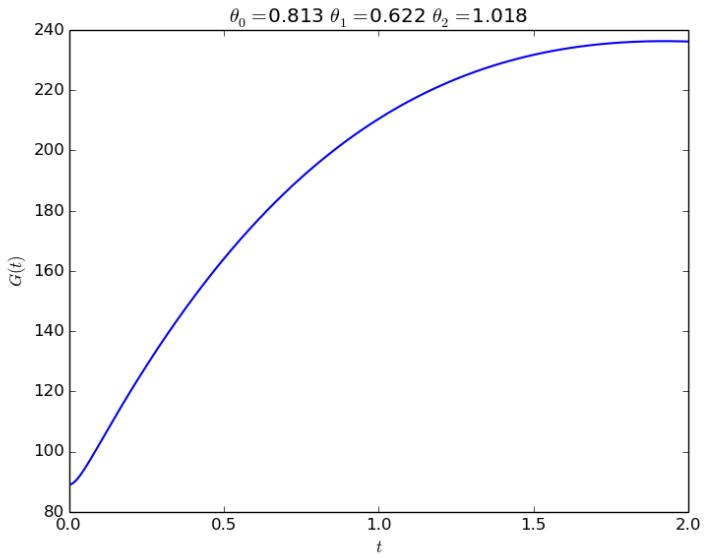
The system that we obtain from substituting and using the initial condi-

tions is

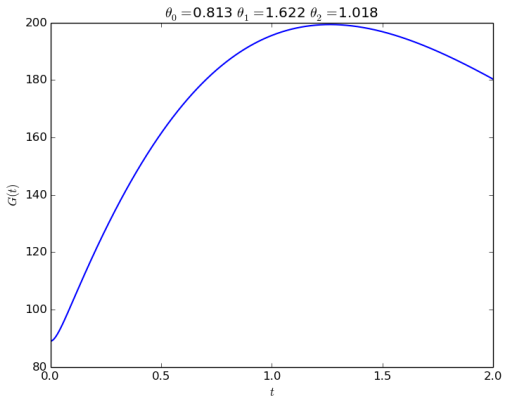
$$\begin{pmatrix} 1 & 1 & 1 \\ -m_1 & -m_2 & \lambda_7 \\ m_1^2 & m_2^2 & \lambda_7^2 \end{pmatrix} \begin{pmatrix} C_1 \\ C_2 \\ C_3 \end{pmatrix} = K \begin{pmatrix} \lambda_5^2 + \theta_0\lambda_8 - \theta_0\lambda_5 - \theta_1 - \lambda_5\lambda_8 \\ \theta_1(\lambda_5 - \theta_0 - \lambda_8) \\ \theta_1(\theta_1 - \theta_0\lambda_8) \end{pmatrix},$$

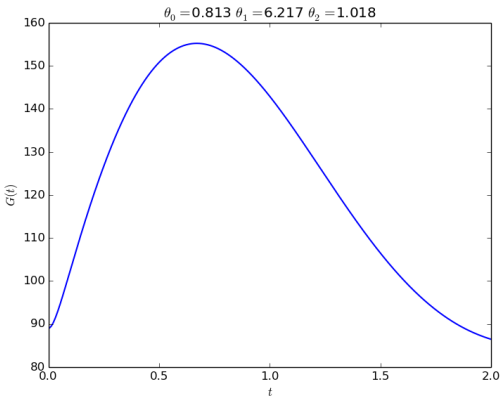
where again $K = \dfrac{0.8\theta_0\lambda_8 V_0}{(\theta_0^2 - \lambda_5\theta_0 + \theta_1)(\lambda_8^2 - \lambda_5\lambda_8 + \theta_1)}$.

We have already mentioned that different behaviours can be obtained and depend on the numbers $\Delta_1 = \lambda_5^2 - 4\theta_1$ and $\Delta_2 = \lambda_7^2 - 4\theta_2$. For example, a possible scenario for the exponential regime is:



On the other hand, possible scenarios for the oscillatory regime are





Our aim is to find a scenario that models the glucose level for a patient for two hours. That scenario will be *chosen* through blood samples. The next subsection allows us to formulate an approach to make that choice.

2.1.6 Identifiability

We begin this subsection by giving a definition from [11]. Consider a dynamical system given by

$$\dot{x}(t) = f(t, x(t), u(t), \theta) \tag{2.23}$$

$$y(t) = h(t, x(t), u(t), \theta) \tag{2.24}$$

where $x(t)$ is a vector of state variables, $y(t)$ is the measurement vector, $u(t)$ is a known system input vector and θ is a parameter vector. Then

Definition 1. *The dynamical system given by (2.23) and (2.24) is identifiable if θ can be uniquely determined from the given system input $u(t)$ and the measurable system output $y(t)$; otherwise, it is said to be unidentifiable.*

A way of verifying system identifiability is through exploration of the system structure, that is, the model itself. We refer to that as *structural identifiability*. Denis-Vidal and Joly-Blanchard proposed to verify the identifiability of uncontrolled and autonomous systems by directly comparing the function f in (2.23). In this

case, $f(t, x(t), u(t), \theta) = f(x, \theta)$. Therefore, the problem is to determine when

$$f(x, \theta) = f(x, \theta') \Rightarrow \theta = \theta'. \tag{2.25}$$

We will call this technique the **Direct Test**. Getting back to (2.1), and applying the last test, from the fourth equation we have that

$$-\theta_0 D + \lambda_8 V = -\theta_0' D + \lambda_8 V.$$

Then if we partially differentiate with respect to D on both sides of the equation, we conclude that $\theta_0 = \theta_0'$. For the second equation, we have

$$\theta_1 (G - G_b)^+ - \lambda_5 I_1 = \theta_1' (G - G_b')^+ - \lambda_5 I_1.$$

Then

$$\theta_1 (G - G_b)^+ = \theta_1' (G - G_b')^+.$$

If $G_b \neq G_b'$ then $\theta_1 = \theta_1' = 0$, but we need that $\theta_1 > 0$, so we conclude that $G_b = G_b'$. Then, differentiating again with respect to G, we conclude that $\theta_1 = \theta_1'$. In an analogous way, we have $\theta_2 = \theta_2'$.
Finally, the model is identifiable.

2.1.7 Sensitivity analysis

The sensitivity analysis is the study of how the uncertainty in the output of a mathematical model can be apportioned to different sources of uncertainty in its inputs. This study can be made determining *sensitivity indices*, which according to [12], are used for estimating the influence of individual variables or groups of variables in the model output. Given a model of the form

$$Y = f(X_1, X_2, ..., X_k) \tag{2.26}$$

with Y a scalar, a variance based first order effect for a generic factor X_i can be written as

$$V_{X_i} \left(E_{X \sim i}(Y | X_i) \right)$$

where $E_{X\sim i}(\cdot)$ is the mean of argument $(\cdot)$ taken over all factors but X_i and $V_{X_i}(\cdot)$ is the variance of argument $(\cdot)$ taken over X_i. The meaning of the inner expectation operator is that the mean of Y is taken over all possible values of $X \sim i$ while keeping X_i fixed. The outer variance is taken over all possible values of X_i. The associated sensitivity measure (first order sensitivity coefficient) is written as:

$$S_i = \frac{V_{X_i}\left(E_{X\sim i}(Y|X_i)\right)}{V(Y)} \tag{2.27}$$

In our case, Y will be the glucose level given by $G(t)$ at $t = 2$. That is, the level glucose after two hours of starting the OGTT.
In the following, we justify our election of values for some constants.

(a) $V(0)$
Consider the case when $\theta_1 = 0$. Then $G(t)$ is a monotone increasing and bounded function. It can be shown that

$$\sup_{t\in(0,\infty)} G(t) = G(0) + 0.8V(0).$$

For that reason, considering the values of the data and because the process in the body that converts food to blood glucose is unknown, we decide to choose $V(0) = 300$.

(b) The OGTT establishes 5 minutes at most to drink the sweetened solution. So we will use this information to estimate λ_8. We want that at 5 min $= \frac{1}{12}$h, 95% of the solution was taken. That is

$$V\left(\frac{1}{12}\right) = 0.05V(0)$$

where $V(t) = V(0)e^{-\lambda_8 t}$. We must solve the equation

$$e^{-\frac{\lambda_8}{12}} = 0.05 \tag{2.28}$$

Then, we use $\lambda_8 \approx 35.948$.

(c) λ_5 and λ_7

For both, we use estimates provided by Dr. Adriana Monroy. Since $\frac{1}{\lambda_5} \approx 31\text{min}$ then $\lambda_5 = \lambda_7 = 60/31$.

(d) $G(0)$
Our initial value for the glucose level will be $G_0 = 90$. However, we know that the glucose level, after 8 hours fasting will vary in different ranges relative to the health state of the patient.

(e) $I_1(0) = L_1(0) = 0$
We are working for a level of Insulin and Glucagon with respect to the basal level. That means that $I(0) = L(0) = 0$ in (1.3). Since $L_1 = \lambda_1 L$ and $I_1 = \lambda_2 I$, then $I_1(0) = L_1(0) = 0$.

We have used SALib for this analysis. SALib is an open source library written in Python for performing sensitivity analysis, [SALib]. The range for the parameter are given in the following:

$$\theta_0 \in [0, 2] \qquad \theta_1 \in [0, 100] \qquad \theta_2 \in [0, 100] \qquad G_b \in [50, 300].$$

These are the results of the sensitivity indices with 100000 vector parameters values: S1 is the column for the first-order index, ST is the column for the total-order index.

Parameter	S1	ST
θ_0	0.050386	0.085926
θ_1	0.332847	0.230311
θ_2	0.504080	0.288524
G_b	0.366470	0.491858

The parameters θ_1, θ_2 and G_b exhibit first-order sensitivity, especially θ_2. The output model is not sensitive to θ_0. If ST is considerably bigger than S1, there will be high-order interactions ocurring, like for G_b for our case.
Now, with 500000 vector parameters values we have

Parameter	S1	ST
θ_0	0.058373	0.084982
θ_1	0.340894	0.228474
θ_2	0.510008	0.282305
G_b	0.366677	0.488995

.

The increase in the sample do not change significantly the indices values. The high sensitivity on G_b is reflex of the meaning of this value. As we explain above, G_b is the equilibrium value for $G(t)$ and we expect that a two hours, $G(2)$ will be close to G_b, that means that changes in G_b will affects directly $G(2)$.

2.2 Bayesian formulation for the inverse problem

To consider an inverse problem we need first to determine a direct one. In our case the forward problem is

Given θ_0, θ_1, θ_2 and G_b in (2.1) determine the solution $G(t)$

For this description, we will follow [7]. First, we find the characterization

Inverse problems are encountered typically in situations where one makes indirect observations of a quantity of interest

Statistical inversion theory reformulates inverse problems as problems of statistical inference by means of Bayesian statistics. In Bayesian statistics all quantities are modeled as random variables. The randomness, which reflects the observers uncertainty concerning their values, is coded in the probability distributions of the quantities. From the perspective of the statistical inversion theory, the solution to an inverse problem is the probability distribution of the quantity of interest when all information available has been incorporated in the model. This distribution, called the posterior distribution, describes the degree of confidence about the quantity after the measurement has been performed.

Assume we have observations of some quantity $y \in \mathbb{R}^m$ with the aim of obtaining information about another quantity $x \in \mathbb{R}^n$. These two variables are connected through a model, for example, one with the form

$$y = f(x, e),$$

where $f : \mathbb{R}^n \times \mathbb{R}^k \to \mathbb{R}^m$ is the observation operator and $e \in \mathbb{R}^k$ is the vector with all unknown parameters, including the noise.

The classic approach to inverse problems is to make a formulation as an optimization problem, formulated as

$$\min_{e \in \mathbb{R}^k} ||y - f(x, e)||$$

This problem is *ill-posed* in the sense of Hadamard. Recall that we said that a problem is well posed, in the sense of Hadamard, if and only if

(i) The solution exists.

(ii) The solution is unique.

(iii) The solution depends continuously on the data.

In our case, we have an observation operator $\mathcal{G} : \mathbb{R}^4 \to C[0,2]$. It is clear that the $\mathcal{G}$ is not onto. Nevertheless, the main problem is that the observations are contaminated with noise and the formulation does not take into account the randomness of the measurements and other possible errors sources.
The philosophy behind the statistical inversion methods is to recast the inverse problem in the form of a statistical quest for information. We have directly observable quantities and others that cannot be observed. In inverse problems, some of the unobservable quantities are of primary interest. The objective of the statistical inversion theory is to extract information and assess the uncertainty about the variables based on all available knowledge of the measurement process as well as information and models of the unknowns that are available prior to the measurement.

2.2.1 Bayes' Theorem

In the following we call the observable random variable Y *the measurement* and its realization, *the data*. The primary interest random variable X will be called *the unknown*. Those variables that we can not observe or are not of primary interest will be called *parameters* or *noise*.
Assume that before taking the measurements of Y, we have some information about X. The bayesian framework assumes that this information can be codified under a probability density, $x \to \pi_{\text{pr}}(x)$ called *the prior density*.
Now, suppose that there exists a joint propabibility distribution for X and Y, denoted by $\pi(x, y)$. Then, the marginal density for the unknown X is given by the formula

$$\int_{\mathbb{R}^m} \pi(x, y)dy = \pi_{\text{pr}}(x).$$

On the other hand, if we want the value of the unknown, then the conditional probability density of Y given X will be given by

$$\pi(y|x) = \frac{\pi(x, y)}{\pi_{\text{pr}}(x)}, \qquad \text{if } \pi_{\text{pr}}(x) \neq 0.$$

We call the conditional probability of Y the *likelihood function* because it expresses the likelihood of differents posibles measurements given that $X = x$.
Finally assuming that the observations $Y = y$ are given the conditional probability distribution

$$\pi(x|y) = \frac{\pi(x,y)}{\pi(y)}, \qquad \text{if } \pi(y) = \int_{\mathbb{R}^n} \pi(x,y)dx \neq 0$$

will be called *the posterior distribution* of X. This distribution expresses what we know about X after the realization of observation $Y = y$.
Under the bayesian approach, the inverse problem is expressed in the following way: *Given the data $Y = y$, find the conditional probability distribution $\pi(x|y)$ of the variable X*. The following result represents the main result of the theory

Theorem 1 (Bayes' Theorem)**.** *Assume that the random variable $X \in \mathbb{R}^n$ has a known prior probability density $\pi_{pr}(x)$ and the data consists of the observed value y of an observable random variable $Y \in \mathbb{R}^k$ such that $\pi(y) > 0$. Then, the posterior probability distribution of X, given the data y is*

$$\pi_{post}(x) = \pi(x|y) = \frac{\pi_{pr}(x)\pi(y|x)}{\pi(y)} \tag{2.29}$$

2.2.2 Likelihood and prior

In this section, we establish our assumptions for $\pi(y|x)$ and $\pi_{\text{pr}}(x)$. According to (2.29), we have

$$\pi(x|y) \propto \pi(y|x)\pi_{\text{pr}}(x). \tag{2.30}$$

The likelihood function $\pi(y|x)$ refers to the probability of the data given the parameters and is directly related with the observation operator. For our problem, we assume that

$$y = G(x) + \epsilon, \tag{2.31}$$

where G is the solution of the glucose level of (2.1) and ϵ represents an additive noise distributed as $\mathcal{N}(0, \sigma^2 I)$. Moreover , we have measurement y_i for $i \in \{0, 1, \cdots, 4\}$. Note that, formally $G(x) \equiv G(t, x)$, where x represents our parameter vector and t denote the time dependence of the function. Recall that $t \in [0, 2]$ and it is measured in hours. Under the assumption that ϵ and x are independent, we have that $y_i \sim$

$\mathcal{N}(G(t_i, x), \sigma^2)$, where $t \in \{0, 0.5, 1.0, 1.5, 2.0\}$. So, getting back to (2.31), we have

$$y = \begin{pmatrix} y_0 \\ y_1 \\ y_2 \\ y_3 \\ y_4 \end{pmatrix}, \qquad \epsilon = \begin{pmatrix} \epsilon_0 \\ \epsilon_1 \\ \epsilon_2 \\ \epsilon_3 \\ \epsilon_4 \end{pmatrix}, \qquad G(x) = \begin{pmatrix} G(t_0, x) \\ G(t_1, x) \\ G(t_2, x) \\ G(t_3, x) \\ G(t_4, x) \end{pmatrix}. \tag{2.32}$$

Finally,

$$\pi(y|x) = \exp\left(-\frac{1}{2\sigma^2}||y - G(x)||_2^2\right). \tag{2.33}$$

In relation with the prior distribution, the qualitative information that we have of θ_0, θ_1 and θ_2 is that they are rates, so we must establish the condition $\theta_i > 0$. Moreover, the basal glucose level G_b must also be positive. Nevertheless, the following two graphs can show the importance of the choice for the prior:

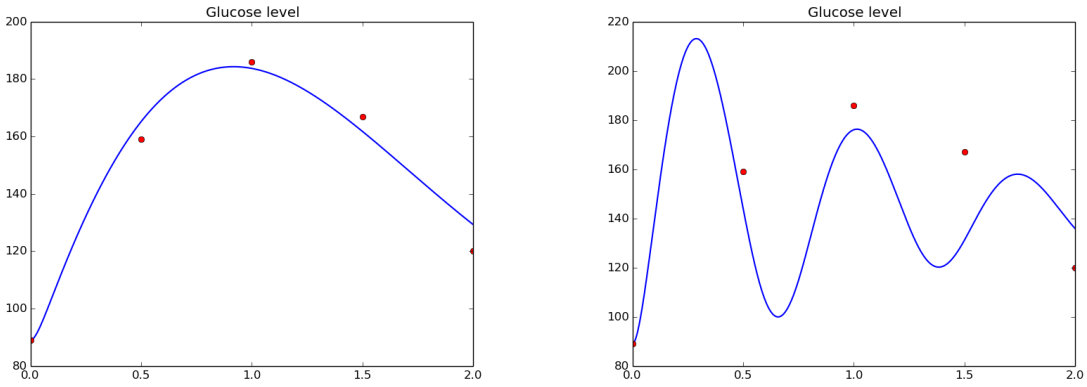


Figure 2.1: Possible glucose level for the same patient data

It is clear that the insulin sensitivity, θ_1, is completely different in both scenarios. We have an oscillatory regime in the right and an exponential regime on the left. Moreover the basal glucose level on the left is lower than on the right, this implies that glucagon sensitivity, θ_2, is representative for the figure on the right and it is not on the left. Our choice of the prior can affect what regime the stationary status would be.

2.2.3 MCMC

Being guaranteed the existence of the posterior density, we need to explore it. We use a Markov Chain Monte Carlo (MCMC) method, which has the advantage of sampling from a probability measure only known up to a normalizing constant. As in [13], the basic idea is to design a Markov chain with the property that a single sequence of output for the chain $\{x_n\}_{n=0}^{\infty}$ is distributed according to the posterior measure μ associated to $\pi(x|y)$. This Markov Chain, with $x \in E$, is aperiodic and irreducible and has stationary distribution $\pi(x|y)$. E is called the support of x and is directly related with the support of our prior. Nevertheless, if $E \subset \mathbb{R}^n$, we need to determine *representative* points since, in practice, we can not sample all the domain. That selection will be made by the density itself.

The way that the chain *jumps* from a state x_i to the next state x_{i+1} is determined by a transition kernel. As the explanation in [7], let P be a probability transition kernel. P is a map from $\mathbb{R}^n \times \mathcal{B} \to [0,1]$, where $\mathcal{B}$ denotes the Borel sets of $\mathbb{R}^n$. Then $P(x_i, A_{i+1})$ is the probability that the chain $X \in A_{i+1}$ conditioned that the state of X is x_i. P is related with the measure μ by

$$\mu_{X_{j+1}}(A_{j+1}|x_1, \ldots, x_j) = \mu_{X_{j+1}}(A_{j+1}|x_j) = P(x_j, A_{j+1}) \tag{2.34}$$

If $P^{(k)}(x_j, B_{j+k})$ denotes the transition kernel that propagates k steps forward in time, we will say that P is *irreducible* if for each $x \in \mathbb{R}^n$ and $A \in \mathcal{B}$, with $\mu(A) > 0$, there exists $k > 0$ such that $P^{(k)}(x, A) > 0$.

On the other hand, for stating the property of aperiodicity, we will define what a periodic kernel is. P is *periodic* if for some integer $m \geq 2$, there is a set of disjoint nonempty sets $\{E_1, \ldots, E_m\} \subset \mathbb{R}^n$ such that for all $j = 1, \ldots, m$ and all $x \in E_j$, $P(x, E_{j+1(\mathrm{mod}\ m)}) = 1$. A kernel P is aperiodic if it is not periodic.

The construction of this transition kernel can vary relating to the observation operator, prior and noise distributions. To make our exploration, we will use *twalk*, [6], which is a MCMC sampling that can sample from target distributions with arbitrary scale and correlation structure.

2.2.4 Data

The data used in this work was provided by Dr. Adriana Monroy Guzmán from the Hospital General in Mexico City. There are data from five different categories of patients(A total of 80 patients):

1. Healthy patients.
2. Patients with Impaired Fasting Glucose (IFG): Fasting blood glucose level ≥ 100.
3. Patients with Impaired Glucose Tolerance (IGT): Blood glucose level ≥ 140 at $t = 2$.
4. Patients with IFG and IGT (BA: both alterations).
5. Patients with Diabetes Mellitus 2 (DM2): Fasting blood glucose level ≥ 126 and blood glucose level ≥ 200 at $t = 2$.

In the next figures, the data presented are five blood glucose measurements at $t = 0$, the first in a fasting status, and the other four at $t = 0.5, 1, 1.5$ and 2 hours.
In Figure (2.2), the image at the left shows that there is a wide range for the glucose level at 2 hours. All the data are lower that 200. The figure on the right shows oscillations for many patients. Although all these patients are healthy, there is a variety of behavior during two hours.

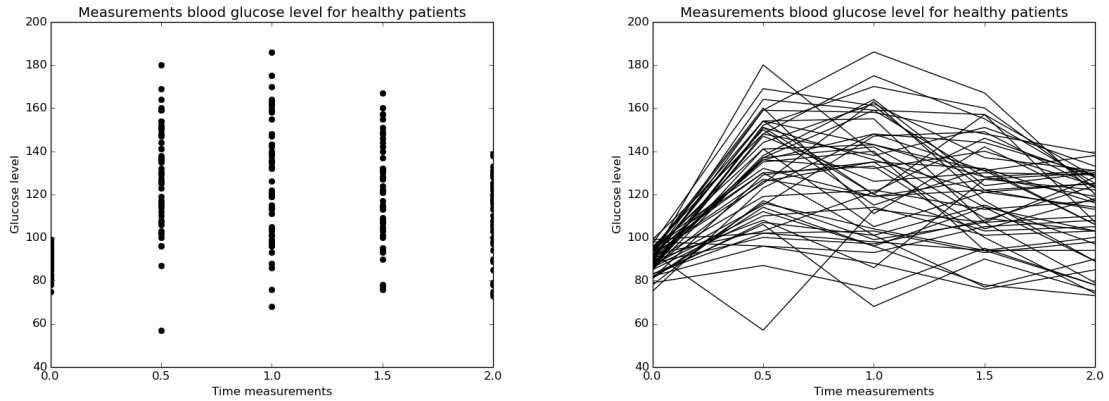


Figure 2.2: Data for healthy patients

Figure (2.3) shows data for patients diagnosed with an alteration. The image in the bottom right corner shows that patients with DM2 have higher blood glucose levels that other patients and they can not bring back their blood glucose to a normal level at 2 hours.

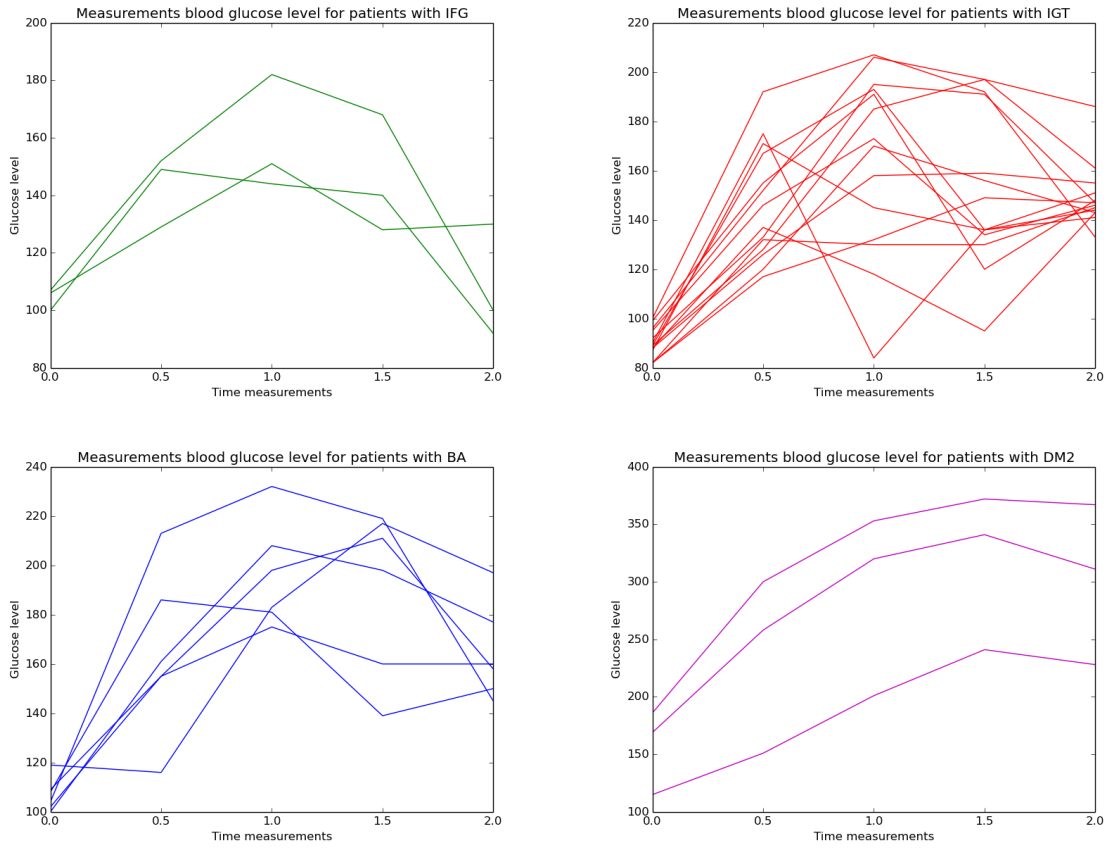


Figure 2.3: Data for unhealthy patients

Chapter 3

Results and discussion

This discussion will follow the terminology introduced in [5]. We work with the following conditions for the prior distributions of the parameters:

$$\begin{array}{ll} \theta_0 \sim \Gamma(1,1) & \theta_1 \sim \Gamma(1,1) \\ \theta_2 \sim \Gamma(1,1) & G_b \sim \Gamma(y_0^2/20, 20/y_0) \end{array} \tag{3.1}$$

where y_0 is the fasting glucose data.
Figure 3.1 shows some simulations for data corresponding to a healthy patient. Furthermore, the estimators for the function $G(t)$, solution of the ODE system in (2.1), given by the MAP and the CM are shown. Also, in grey, we show the last 1000 more probably simulations.

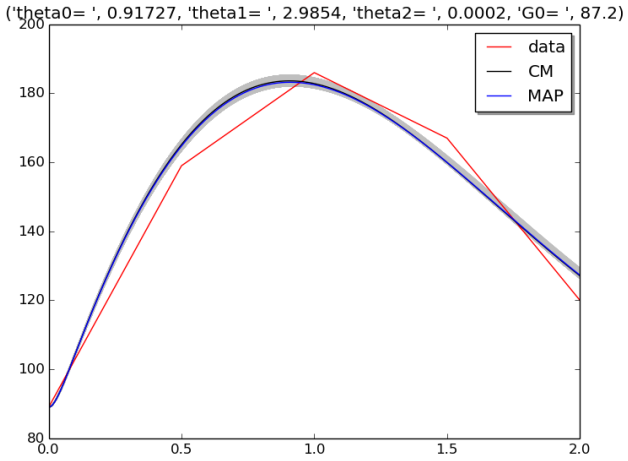


Figure 3.1: Healthy Patient

Figure 3.2 shows the probability distributions, through histograms, of prior and posterior for each of the parameters for the same patient. We can note that all observations are higher than y_0, so the data does not give us information about the reaction of the organism related to glucagon. That is, the parameter θ_2 does not have relevance in this case. Also, the blood glucose level according to the measurements does not reach a high enough level. That means, the estimation of the basal level of glucose for this patient, G_b, is not modified by the data. This last point becomes precise through the fact that the posterior distributions for the parameters θ_2 and G_b match the prior distribution, that is, the data are not informative toward these two parameters.

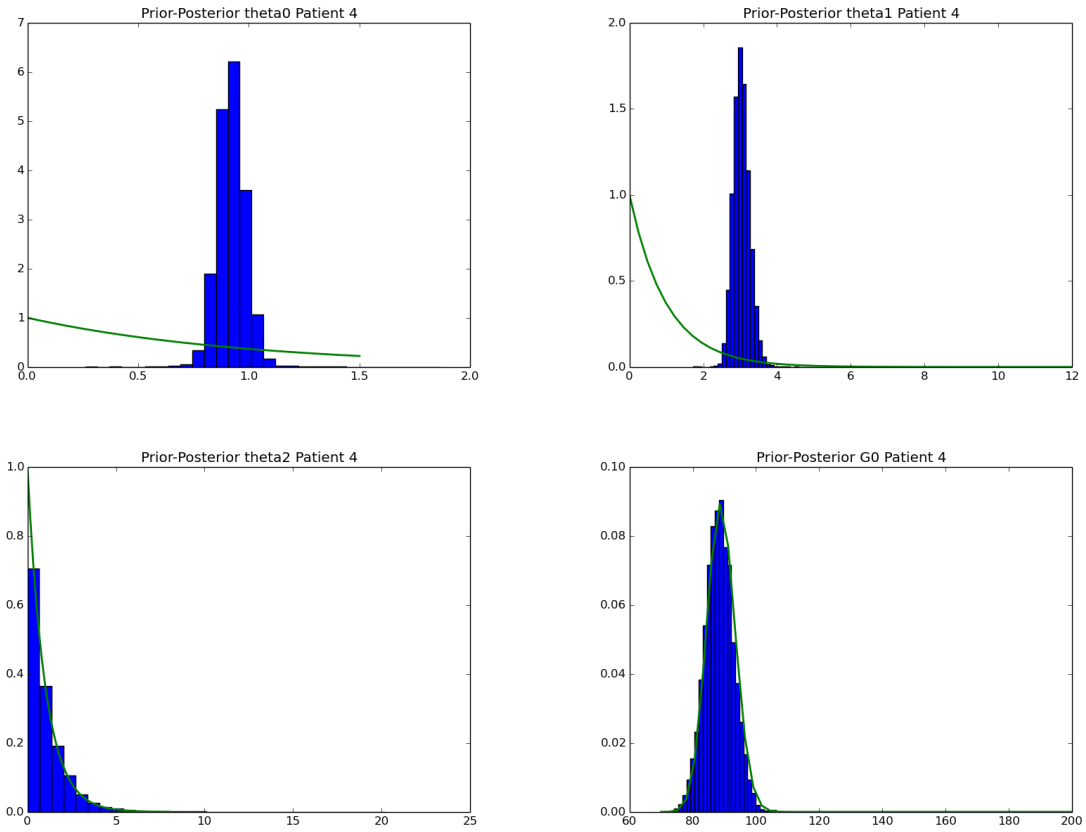


Figure 3.2: Prior and posterior distributions for a healthy patient

However, under conditions (3.1), we have bad approximations for some data as Figure 3.3 shows. On the left, note that the amplitude of data are very small and constant oscillations are not identified by the model. On the right, the model can not reproduce the last oscillation in the data.

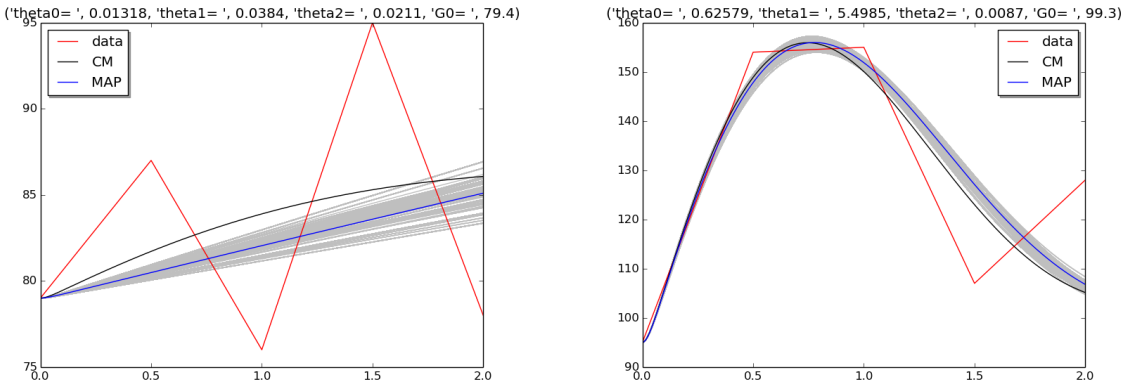


Figure 3.3: Bad approximations for healthy patients

Comparison of prior

We realize a change in the prior for the kind of data shown in Figure (3.3). So, we work with uniform priors for the parameters θ_0, θ_1 and θ_2 and G_b prior stay like in (3.1).

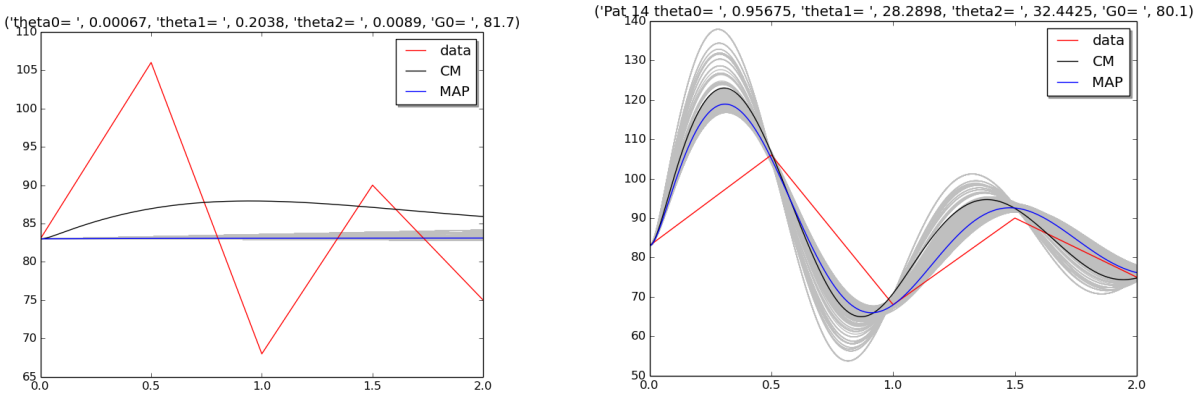


Figure 3.4: Prior distributions $\Gamma(1,1)$ (left) and Uniform (right) for parameters θ_0, θ_1 and θ_2 in a healthy patient with constant oscillations.

Note that in Figure 3.4, on the right, the solutions of the system recognize the oscillations of the data. The MAP and the CM are shown with differences but they

match close the measurement times. The estimation of the insulin and glucagon sensitivity are bigger than the previous cases because of the oscillations in the data. However, in grey we can see a high variance in the trajectories of the solutions especially in the time between measurements. This situation leads us to the question, *which criteria were used in the decision about the time and the number of measurements for the test?*

Prediabetic and diabetic diagnosed patients

In [10] the authors suggest *that the OGTT can be used effectively to define insulin sensitivity and secretory defects in individuals with impaired glucose homeostasis.* Also, they propose an index of whole-body insulin sensitivity derived from the OGTT. This index represents a composite of both hepatic and peripheral tissue sensitivity to insulin.

In a technical report of the World Health Organization and the International Diabetes Foundation, the OGTT is recommended as a diagnostic test because of the following reasons:

- Fasting plasma glucose alone fails to diagnose approximately 30% of the cases of previously undiagnosed diabetes.
- An OGTT is the only means of identifying people with IGT.
- An OGTT is frequently needed to confirm or exclude an abnormality of glucose tolerance in asymptomatic people.

Recall that the category IGT(Impaired Glucose Tolerance) is a state of increasing risk of progressing to diabetes. In the data supplied by Dr.Monroy, we find 29 female patients diagnosed with one of the following conditions:

$$\begin{aligned} &\text{Impaired Fasting Glucose (IFG): Fasting Glucose} \geq 100 \\ &\text{Glucose Intolerance (GI): Glucose level at 2 hours} \geq 140 \\ &\text{Both alterations (BA: IFG and GI)} \\ &\text{Diabetes mellitus 2 (DM2): FG} \geq 126 \text{ and Glucose level at 2 hours} \geq 200 \end{aligned} \tag{3.2}$$

We find individuals with BMI (Body Mass Index) from 23.6 to 53.83 where 69% of

them are obese (BMI≥30). The model recognizes almost 60% of the cases. Some examples are shown in Figures 3.5 and 3.6.

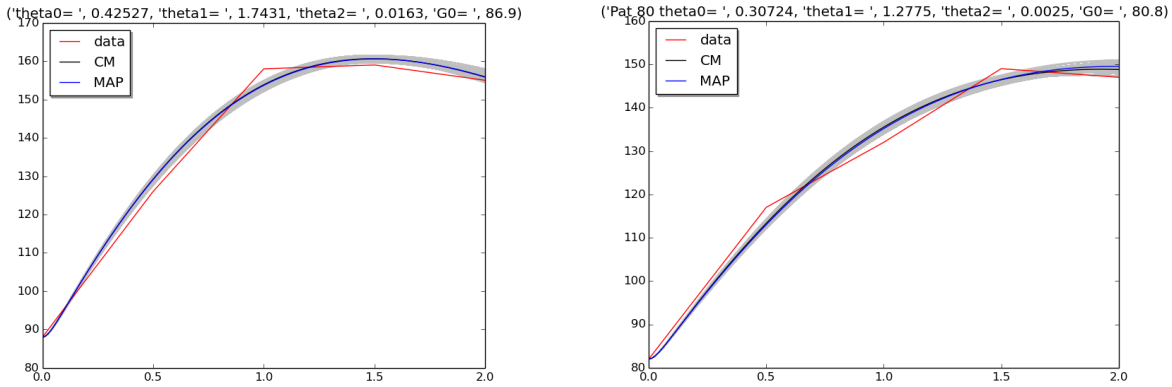


Figure 3.5: Patients with Glucose Intolerance

In patients with Glucose Intolerance, the digestive indicator is smaller than for diabetic patients. That is, the mean life glucose in the digestive system and the insuline sensitivity are lower in diabetic patients. Again, the parameters θ_2 and G_b are not relevant for this patient.

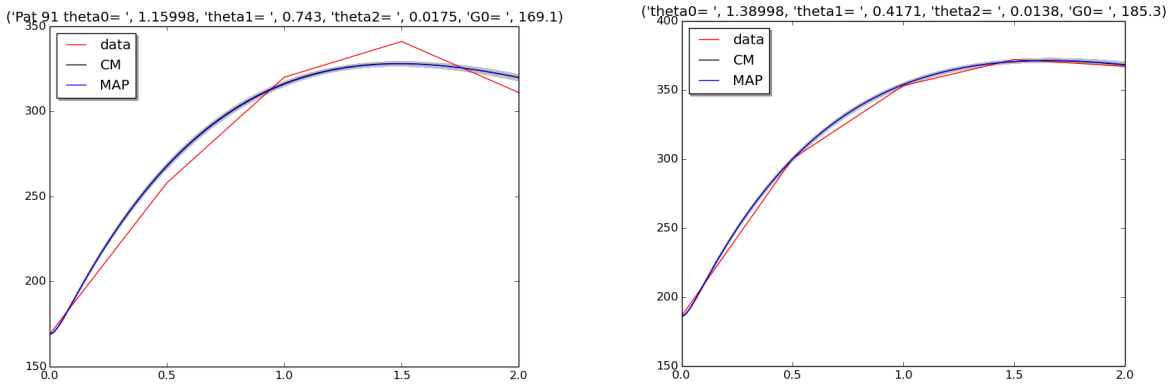


Figure 3.6: Diabetic Patients

In Figure 3.7, we can see a classification of diagnosed patients as in (3.2). Note

that for diabetic patients, the estimation of θ_1 is lower than the other cases and G_b bigger. That is, the insuline sensitivity are lowest than the others.

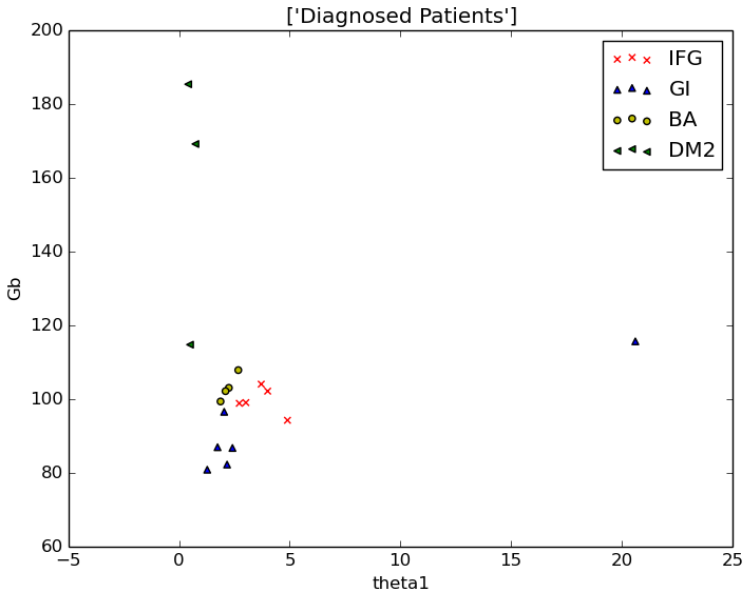
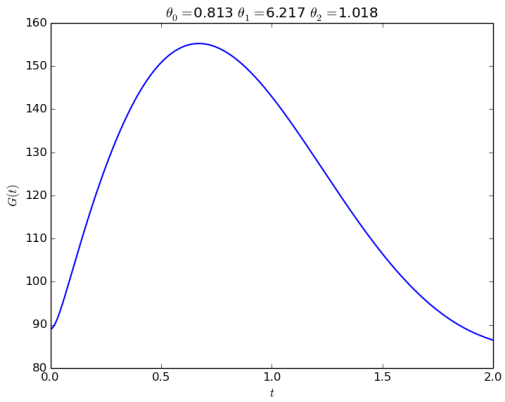


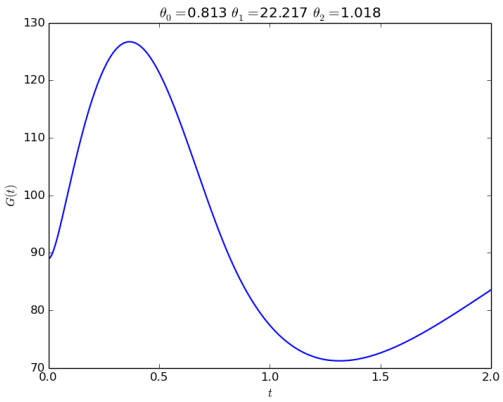
Figure 3.7: Classification by parameters on MAP estimator

Chapter 4

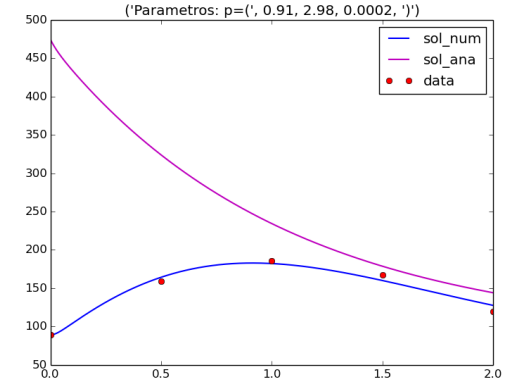
Conclusions

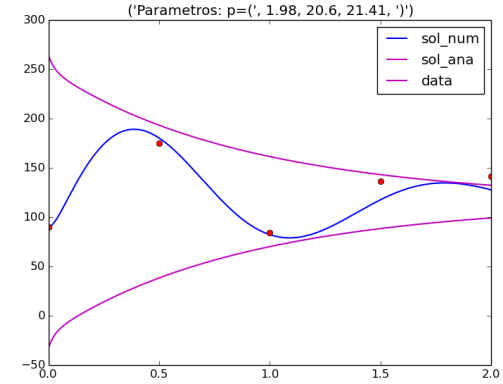
In this work, we have explain the biological situation for the dynamics of the glucose-insulin(-glucagon) system. The human body posseses a basal blood glucose level between 70 and 110 mg/dL. Recall that food increases this level and insulin is the hormone charge to bring down it. On the other hand, usually after a long fasting, the glucagon is the hormone charge to increase it. We introduce a model based on these biological ideas. Our qualitative analysis for the model allows us to identify two main regimes that we associate with their corresponding biological situations. This behaviour, together with the identifiability and sensitivity analysis of the model enables us to introduce a formulation to the inverse problem. The chosen approach was bayesian which furnishes the basis for quantifying the uncertainty associated to the data from the OGTT. The next figure shows two trajectories beginning at 89, at $t = 0$, and finishing between 80 and 90, at $t = 2$.





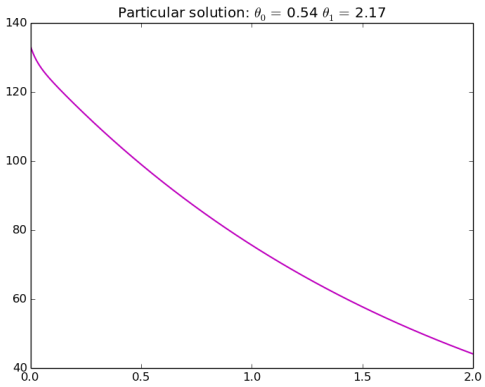
The modeling during two hours can describe different escenarios between this two patients. Instead, estimating the glucose level at two hours can not. If the interest remains to estimate the glucose blood level at 2 hours, there is another path to follow. Depending on the parameters, we think that there is a curve that envelops multiple oscillating escenarios with different frequencies as is shown in the next pictures

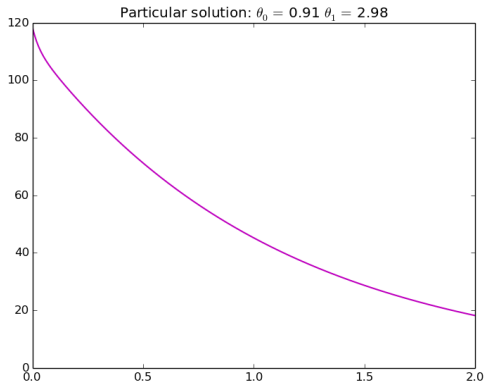


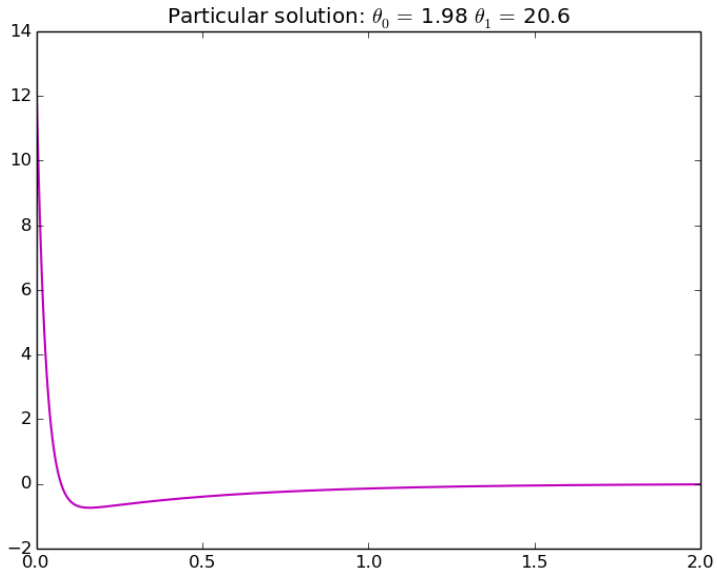


The level of *this envelope* at $t = 2$ satisfies these interest.

The qualitative analysis shows that the dynamic of the model is rule by a third order oscillator with an impulse, which correspond to effects of the solution on the glass. The next figure shows the graphs of this impulse for different values of the parameter







These three different cases depend on the parameters of the model and the estimate value for the rate at which the patient consumes the solution on the glass. This last rate may be an uncertainty source that for this work is negligible.

Even though there are sets of data that the model can not identify, working with data from diagnosed patients, we find that the model is almost 60% predictive. This percentage, besides the probability given by the bayesian approach, result very important as a possible tool on the health system. Moreover, this information leads us to think in a higher percentage if *appropiate data* were provided. Recall that

experimental design is the design of any task that aims to describe or explain the variation of information under conditions that are hypothesized to reflect the variation. Well chosen experimental designs maximize the amount of information that can be obtained for a given amount of experimental effort. Future work can follow this direction: *which criteria were used to determine the time measurement for the test?*

One of our assumptions is the additive form of the noise in the data. Again, future work can consider another approach. For example, suppose that there is an *error measurement* directly related to the time measures t_k. In that case, it will be need to suggest another random structure for that noise and also for the likelihood.

The principal advantage of the bayesian approach is the quantification of uncertainty. Another way to quantify uncertainty is *spectral methods*, that is, orthogonal decomposition methods in which a random variable is expanded with respect to an appropiate orthogonal basis for $L^2[0,2]$. An example of this approach is the K-L expansion used for a Gaussian measure. Using the posterior distribution found with the MCMC, a possible perspective to follow is by the following path. Choose a distribution for one of the parameters and keep the others fixed. The polynomial chaos analyze the propagation of uncertainty only in the direction of the parameter chosen. This approach can be followed in [15].

The formalism about the inversion of the observation operator $\mathcal{G}$ is not developed. We have mentioned that $\mathcal{G}$ is not onto but the existence of an open subset in $C[0,2]$ contained in the image of $\mathcal{G}$ is needed to ensure conditions for inversion. Nevertheless, the identifiability justifies our numerical work.

Another option for quantifying the uncertainty is to review the formulation of the model. There are a wide range of models for the dynamics of glucose-insulin and as we have already mentioned, a very complete review of them is provide by ([9]). Nevertheless, we think that the power prediction of another model will not improve substantially unless the provided data are reconsidered.

Chapter 5

Bibliography

[1] K. E. Andersen , M. Hojbjerre *A Bayesian approach to Bergman's minimal model*, Insulin, 50(100), 200., 2002.

[2] C. Anderwald et al. *Mechanism and effects of glucose absorption during an oral glucose tolerance test among females and males*, The Journal of Clinical Endocrinology & Metabolism, 96(2), 515-524, 2010.

[3] B. Antuna-Puente et al. *How can we measure insulin sensitivity/resistance?*, Diabetes & metabolism, 37(3), 179-188, 2011.

[4] M. Capistran, J. A. Christen & S. Donnet *Bayesian Analysis of ODE's: solver optimal accuracy and Bayes factors*, arXiv preprint arXiv:1311.2281, 2013.

[5] J. A. Christen, M. Capistran et al. *A Diabetes minimal model for Oral Glucose Tolerance Tests*, arXiv:1601.04753, 2016.

[6] J. A. Christen, C. Fox *A general purpose sampling algorithm for continuous distributions (the t-walk)*, Bayesian Analysis, 5(2), 263-281., 2010.

[7] J. Kaipio & E. Somersalo, *Statistical and computational inverse problems*, Springer Science & Business Media, Vol. 160, 2006.

[8] J. P. Keener & J. Sneyd, *Mathematical physiology*, (Vol. 2). New York: Springer, 1998

[9] A. Makroglou, J. Li and Y. Kuang, *Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview*, Elsevier, Applied Numerical Mathematics 56, 559-573, 2006.

[10] M. Matsuda and R. A. DeFronzo, *Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp*, Diabetes care, 22(9), 1462-1470, 1999.

[11] H. Miao et al., *On identifiability of nonlinear ODE models and applications in viral dynamics.*,SIAM review, 53(1), 3-39, 2011.

[12] I. M. Sobol *Global sensitivity indices for nonlinear mathematical models and their Monte Carlo estimates*, Mathematics and computers in simulation, 55(1), 271-280, 2001.

[13] A.M. Stuart *Inverse problems: A Bayesian perspective*, Acta Numerica,19,pp 451-559, 2010.

[14] L. Szablewski *Glucose homeostasis-mechanism and defects*, INTECH Open Access Publisher, 2011.

[15] D. Xiu and G. E. Karniadakis *The Wiener–Askey polynomial chaos for stochastic differential equations*, SIAM journal on scientific computing, 24(2), 619-644, 2002.

[IDF] IDF, *International Diabetes Federation* //www.who.int/mediacentre/factsheets/fs312/es/

[SALib] SALib, *SALib - Sensitivity Analysis Library in Python* //salib.readthedocs.org/en/latest/index.html

[WHO] WHO, *World Health Organization* //www.who.int/mediacentre/factsheets/fs312/en/