Limits of a Glucose-Insulin Model to Investigate Intestinal Absorption in Type 2 Diabetes

Work in progress

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***Abstract*—Abnormal regulation of glucose absorption in the small intestine is an important cause of Type 2 Diabetes (T2D). Even if this hypothesis is clinically well-known, it has not been fundamentally validated yet, mainly due to a lack of reliable metabolic knowledge on the glucose regulation. The main objective of this paper is to test this hypothesis on a highly referenced model composed of ordinary differential equations. This model is tested on an original dataset featuring the observations of obese diabetic patients. It shows its limits to predict our post-prandial glycemia and insulinemia time series especially with regard to the crucial complexity of gastro-intestinal regulation.**

***Keywords*—Ordinary Differential Equation; Systems Biology; Type 2 Diabetes; Intestinal Glucose Absorption.**

I. Introduction

Diabetes is a chronic metabolic disease characterized by a lack of insulin secretion and a decreased peripheral insulin response. Insulin is a hormone that down-regulates blood sugar concentration. Consequently, the balance of glucose and insulin concentrations in different tissues, called *homeostasis*, is pathologically perturbed: hyperglycemia is observed both during fasting and post-prandial periods. It gradually leads to tissues damages and subsequent diseases, i.e., a high rate of comorbidity [6].

More precisely, *Type 2 Diabetes* (T2D) results from the body's ineffective use of insulin. Most patients ($\sim 90\%$) with diabetes have T2D. Around 400 millions of people are affected worldwide by the disease representing a major public health issue in most developed countries [7]. It is commonly accepted that this type of diabetes is largely caused by physical inactivity combined with an high-carbohydrate diet. However, through bariatric surgery, obese patients with T2D have seen their physiological glycemia immediately restored, independently to their weight loss [1]. This observation leads us to consider *Intestinal Glucose Absorption* (IGA) as a critical cause of T2D, among others. Bariatric surgery, and more precisely *Roux-en-Y Bariatric Surgery* (RYGB), anatomically leads to the decrease of the glucose absorption surface, which would explain, at least partially, this unexpected clinical benefit. Furthermore, the gastro-intestinal tract includes:

- enzymatic and mechanical transformation of starch (amylopectine and amylose) into absorbable glucose,
- incretin secretion and effects on the blood sugar,
- and the small intestine microbiota, which may modulate dietary responses.

This landscape of hypothetical causal factors shows that fundamental research effort on T2D must continue despite precise clinical understanding of the disease. However, all representations of glucose-insulin homeostasis largely underestimate the importance of the gastro-intestinal tract into the blood sugar consequences. Instead, they tend to model with increasing details the interaction of insulin with its related tissues (pancreas, liver and insulino-dependent tissues). We want to investigate the contribution of IGA to glucose homeostasis and its potential role in diabetes. To this aim, and as a preliminary work, we consider a typical and state of the art homeostasis glucose-insulin model [5] formalized as a system of *Ordinary Differential Equations* (ODEs). Our objective is twofold:

- test if this model can predict a significant improvement of glucose homeostasis by simulating RYGB as is observed experimentally,
- test if this model can predict the time-course data of an original dataset of diabetic patients.

In Section 2, we briefly describe the model. In Section 3, we present our parameter fitting results both from the original parameters of [5] and for our own dataset We discuss the partial results in Section 4 and present the on-going and future work in Section 5.

II. Model

Many simulation models of the glucose-insulin system for the postprandial period have been developed [8]. In this work, we consider a highly cited model, proposed in [5], to simulate the postprandial physiological events of their own cohorts of normal subjects and T2D patients. This model is made of 12 ODEs and 36 parameters describing fluxes of glucose and insulin between physiological compartments: gastro-intestinal tract, plasma, liver, pancreas, muscle and adipose tissues (Figure 1). We recall in the following, in informal terms, how the physiological modules interact.

The *Gastro-Intestinal Tract* module describes the digestion process, from the stomach to the gut, and can be considered as the input of the whole system. It includes the complexity of

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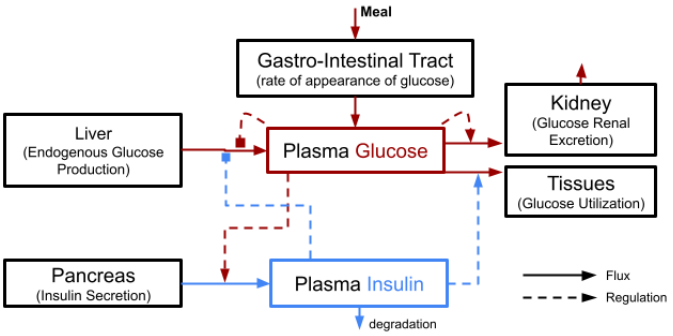

Figure 1: Simplified interaction graph of physiological compartments describing the model of [5].

the gastric emptying depending on the proportion of the solid and liquid phases of the alimentary bolus [4]. Only the liquid phase that ends up in the gut is absorbed by the intestine and discharged to the peripheral blood. Incretins are not modeled. The *Liver* module describes the hepatic activity responsible for the endogenous glucose production down-regulated by the insulin. The glucagon hormone is not modeled. The *Pancreas* secretes insulin, which is up-regulated with the amount of glucose in the blood. The uptake of glucose by the (muscle and adipose) *Tissues* is regulated by the insulin. The *Kidney* is responsible for the glucose excretion-reabsorption. The insulin degradation is due to its lifespan and liver clearance. Even though the insulin independent glucose uptake by the brain is modeled (not in shown in Figure 1) the regulation of the glucose by the brain is neglected in [5].

Using tracer-to-tracee ratio clamp technics [3], the authors of [5] measured the time course of the glucose concentration in various compartments. This was done following a mixed-meal received by several normal and diabetic subjects. The parameters were estimated to fit this experimental data, which resulted in two sets of parameter values modeling respectively normal and T2D behaviors. For practical reasons, we fully reimplemented the model in the *Julia* programming language (version 1.5.3) with the *DifferentialEquations* package (version 6.17.0).

III. Results

A. From T2D to normal model

In the following, we call *normal model*, resp. *T2D model*, the model instantiated with the normal, resp. diabetic, parameter values given in [5] (Table 1). We consider several parameter subsets corresponding to the previous modules: gastro-intestinal tract (also denoted as Ra in [5]), liver (EGP), tissues (GK+U), pancreas (IK+S) and kidney (RE).

Starting from the T2D model, we re-estimated, in turn, each of these subsets of parameters, while leaving the other parameters fixed, in order to fit the plasma glucose dynamics of the normal model. Based on the data of [5], our first objective is to evaluate the capability of the model to predict, for each module alone, its capability to restore a normal glycemia. We estimate the parameters twice: with and without estimation of the basal values for insulin secretion by the pancreas, glucose production by the liver and utilization by the tissues. From the resulting 10 inferred models, we plotted the time course of the observed variables.

In this short paper, we only report (Figures 4a to 4d) the most relevant plots for our purpose: plasma glucose (G), plasma insulin (I) and the rate of intestinal absorption (Ra) for the two models obtained from the estimations of the gastro-intestinal tract and pancreas compartments, with and without basal estimation. In order to compare the models' performance in fitting the normal model, we collect in a bar plot (Figure 3) the residual sum of squares for each model.

B. Parameter estimation of obese diabetics and RYGB

Our second objective is to test whether the model of [5] can predict the time course concentrations of glucose and insulin obtained from our own dataset of diabetic patients who underwent RYGB surgery. For each patient, we use data before (hereafter referred to as *visit A*) and 3 months after (*visit B*) surgery. We first estimate all the parameters in order to fit the time course data of glucose and insulin from the *visit A* dataset. The model that we obtain is called the *visit A* model. Figure 2 shows the glucose and insulin plasma concentrations predicted by this model as well as the fitted data points. Then, as previously, we estimate each subset of parameters in order to fit the *visit B* dataset. Here, we only consider the case where we also estimate the basal concentrations, which indeed changed 3 months after surgery. We report in Figure 4 the time course of G, I and Ra after estimation of the parameters of the gastro-intestinal tract and pancreas.

IV. Discussion

Estimating the basal values for insulin secretion, endogenous glucose production and insulino-dependent glucose utilization, can be interpreted as a prediction of the "long-term" effect of the parameter changes *in the best case* (since the model does not incorporate any long-term recovery mechanisms). Thus, not estimating these basal values can be interpreted as a "short-term" (or worst case) prediction.

A. From T2D to normal model

Our re-estimations of the parameters based on the data of [5] predict (Figure 3) that the best performing compartments to restore a normal glycemia are pancreas and tissues, and then the intestinal tract. As expected, estimating the basal concentrations (i.e., long-term effect) improves the performance especially for the intestinal tract (see also G curve in Figures 4b and 4c), which is consistent with experimental observation. However, the performance of the pancreas should be modulated. Indeed, Figures 4b and 4a show that, in order to improve the glycemia, a very high plasma insulin concentration is necessary if only the pancreas parameters are modified. This seems physiologically unrealistic, meaning that the good performance of this compartment is over-estimated. Similarly, the estimation of the gastro-intestinal tract parameters on the short term (Figure 4d) indicates an unrealistic decrease of

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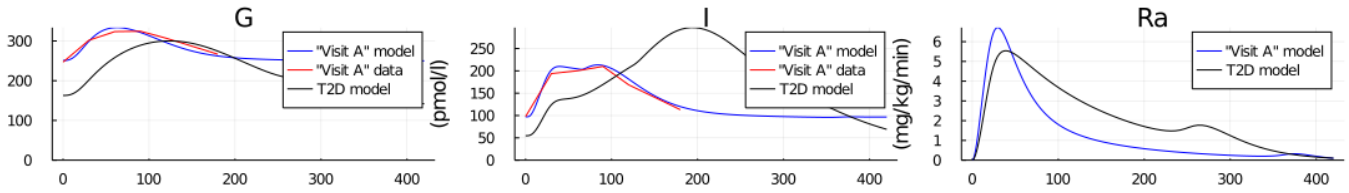

Figure 2: Parameter estimation of all parameters, including basal concentrations, to fit "Visit A" data.

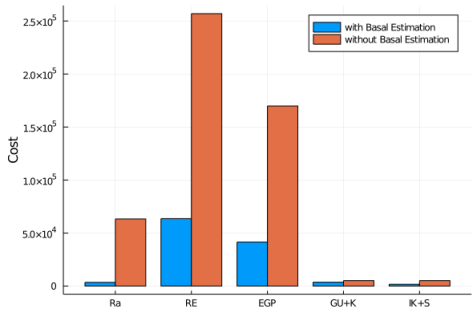

Figure 3: Loss from the parameters estimation applied on the different compartments.

plasma insulin concentration. Finally, the "long-term" estimation of the gastro-intestinal tract parameters (Figure 4c) allows a good improvement of the glycemia with a realistic concentration of insulin and a decrease of intestinal absorption, which is consistent with observation.

B. Parameter estimation of obese diabetics and RYGB

From Figure 2, it is primarily interesting to notice that the T2D data of [5] is significantly different from ours. Indeed, glucose in *visit A* is higher than in *T2D model* whereas insulin in *visit A* is lower than in *T2D model*. Despite this difference, the fitting is satisfying with all parameters set as free. This fitting is sensitive to the parameters estimation methods.

In Figures 4e and 4f, the parameters are set free for the pancreas (IK+S) and the gastro-intestinal tract (Ra), respectively. Such process can be interpreted as surgery simulations targeting respectively the pancreas and the gastro-intestinal tract. No fitting attempt seems satisfying. On the one hand, freeing IK+S parameters seems to be satisfying for fitting the glycemia but clearly overestimates the insulinemia (cf. Figure 4e). On the other hand, by freeing Ra parameters, the rate of appearance is decreased as observed in experimental data (based on our D-xylose data, an alimentary glucose marker). Still, the parameter estimation fails completely to fit *visit B* glycemia and insulinemia (cf. Figure 4f).

V. Conclusion and Future Works

The parameter estimation performed by the authors of [5] is based on training data generated by tracer-to-tracee clamp technique [3], which, despite its efficiency, remains an uncommon and complex method to monitor exogenous solutes. In practice, plasma glycemia and insulinemia are usually the only accessible clinical data. However, and as our model assessment suggests, this may raise parameter identifiability issues. To overcome this problem, we first plan to use the available additional D-xylose data, a marker that can be used to fit the rate of appearance (Ra) [2]. We also plan, by exploiting profile likelihood and sensitivity analysis, to study model reduction in order to eliminate the potential sources of non-identifiability. Other original datasets are currently used for the parameter estimation, generated from experiments on minipigs. Such biological models allow for more experiments and reproducibility, and decreased individual variabilities thus improving the reliability of parameter estimation. In this direction, another possibility, is to use publicly available datasets.

It should be noted that the failure of parameter estimation may be due to structural problems inherent to the model of [5] which sub-model of IGA is largely simplified. For instance, it ignores the spatial none uniform glucose absorption rate along the intestin and the secretion of incretins. We plan to extend the model of [5] with these aspects while simplifying the others to overcome identifiability issues that could emerge from additional parameters related to the gastro-intestinal tract.

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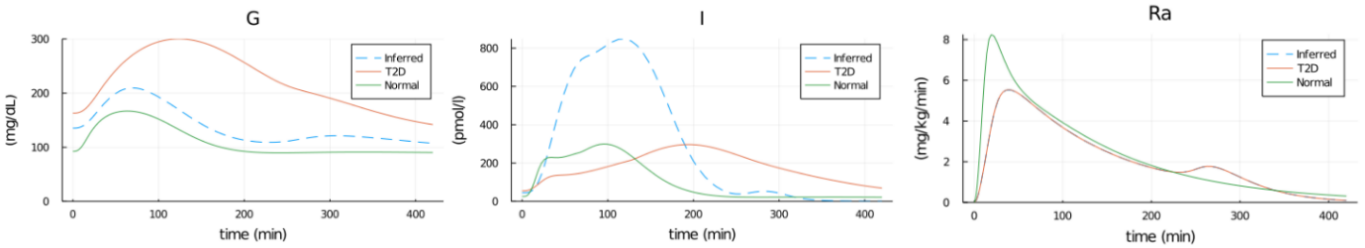
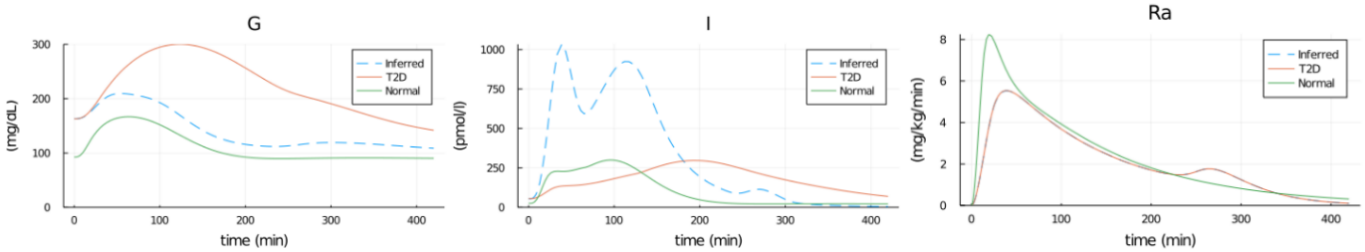
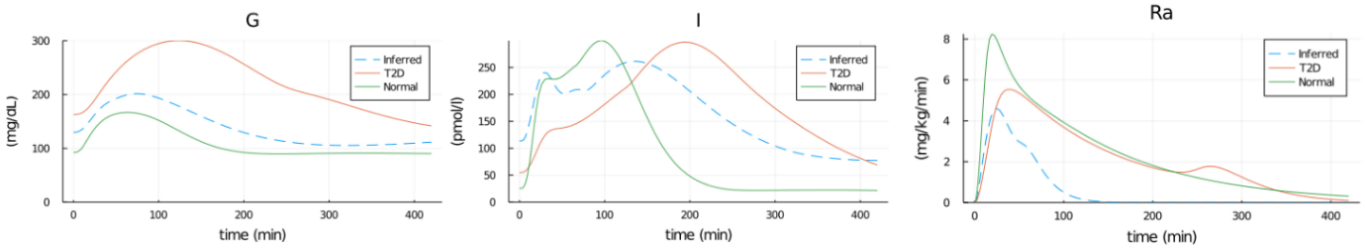


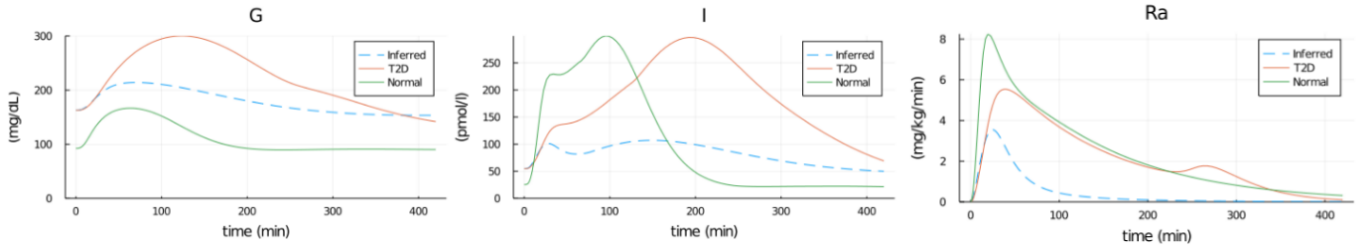
(a) Parameter estimation of IK+S compartment and basal concentration to fit the normal model for the T2D model.



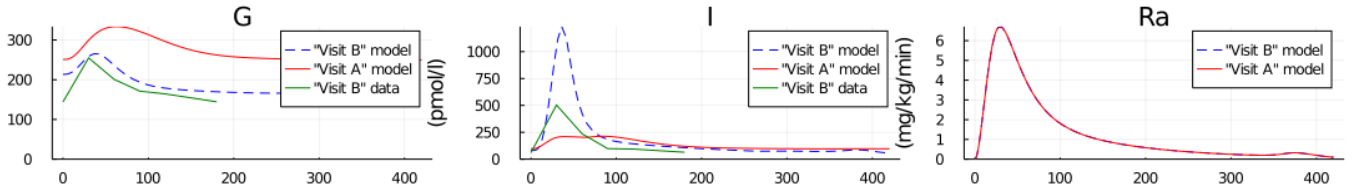
(b) Parameter estimation of IK+S compartment only to fit the normal model for the T2D model.



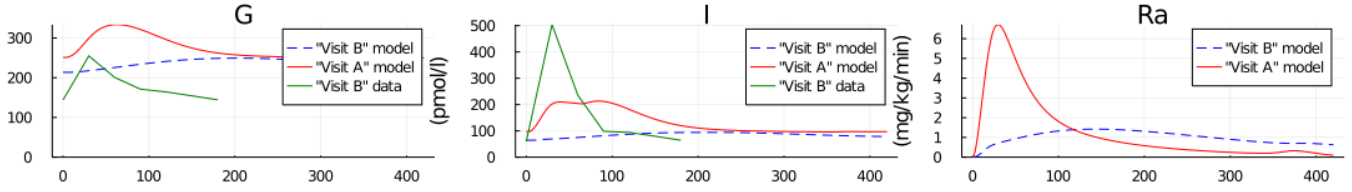
(c) Parameter estimation of Ra compartment and basal concentration to fit the normal model for the T2D model.



(d) Parameter estimation of Ra compartment only to fit the normal model for the T2D model.



(e) Parameter estimation of IK+S compartment and basal concentrations, to fit *visit B* model from *visit A* model.



(f) Parameter estimation of Ra compartment and basal concentrations, to fit *visit B* model from *visit A* model.

Figure 4: Glucose (*G*), insulin (*I*), and rate of appearance (*Ra*) after parameter estimation, with and without basal concentrations, of pancreas (a, b), gastro-intestinal tract (c, d) compartment for fitting normal model from TD2 model and for fitting *visit B* from *visit A* model (e, f).

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