Digital Health in Diabetes Care: a Computational Journey from Minipigs to Humans

Master research project / internship

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(This project will be supervised in collaboration with François Pattou from CHU Lille, INSERM U1190)

Context

Type 2 Diabetes (T2D) is one of the main epidemics of this century. One of the hypothesis of medical research is that an important cause of T2D may be the abnormal regulation of intestinal glucose absorption (IGA) [1]. Early detection of IGA disorders, and, more generally, precision medicine, may help to prevent the risk of T2D. This could be achieved by *predictive models of glucose dynamics in blood following an oral ingestion*. More precisely, given a dose of sugar, the model should be able to predict the timed evolution of glucose concentration (Figure 1) in blood over a period of about 6 hours (average time necessary to a return to fasting glucose level). In addition, for our question of interest, it should also predict how the glucose dynamics is impacted by a modification of the IGA characteristics. Such computational model is complex because, as illustrated in Figure 2a, it involves the liver (that can store and deliever glucose if needed), adipose and muscle tissues (that uptake the glucose) and regulatory hormones among which insulin is one of the most important.

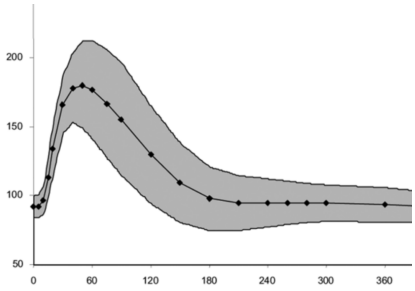

Fig. 1: Timed evolution of glucose concentration in blood.

Even though many such models have been proposed, either the mechanisms of the gastro-intestinal trac are neglected, or, when these mechanisms are carefully modeled, their calibration requires the use of data obtained from complex and invasive clinical protocols that make them unusable on a daily basis. The question is how can we overcome this issue ? One solution is to use a glucose analogue called *DXylose*. Indeed, DXylose is a sugar that has intestinal absorption mechanisms similar to the glucose but it is immediately eliminated by the kidney with negligeable utilization by the tissues. Thus, contrary to glucose, its dynamics in blood only results from gastric emptying, intestinal absorption and elimination by the kidney.

In previous work [2], we investigated a simple model of DXylose dynamics in blood after oral ingestion. We showed that a multi-compartment model (Fig. 3) of intestinal absorption can fit very well DXylose data obtained from different experimental conditions on minpigs and be a good qualitative estimate of

Problematic

In our paper, for the model calibration, we used experimental data that involves Göttingen minipig datasets. For our problematic, different experiments have been performed to monitor blood DXylose concentration after an intake of a bolus of DXylose using 3 different types of administration: oral, intestinal and intravenous. The oral bolus dataset allows to monitor blood DXylose in the normal state, that is after an oral administration of the meal. In the intestinal (or jejunal) bolus dataset the stomach is bypassed and the meal is directly administrated in the small intestine. Using several experimental datasets is crucial not only to estimate but also to *identify* the parameter values of the model. *Identifiability* [3] refers to the existence of a unique set of parameter values capable of fitting the data.

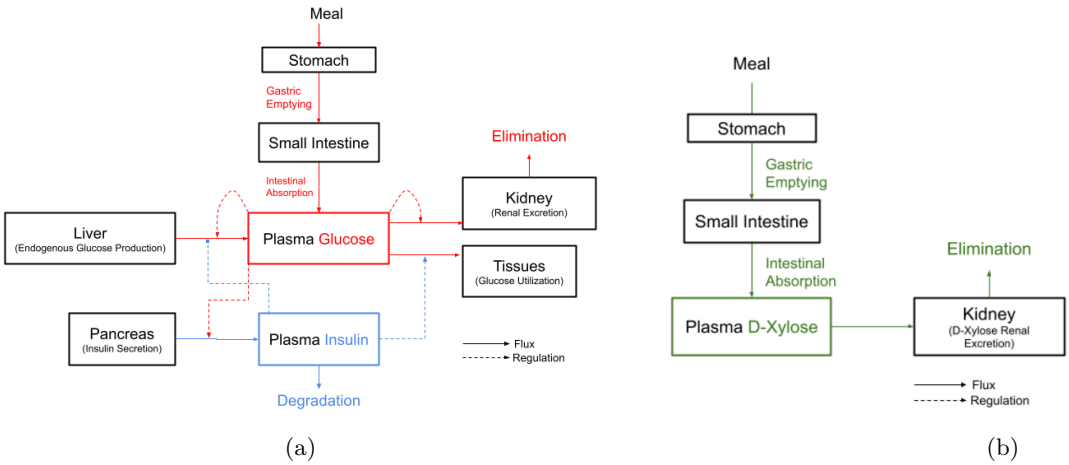

Fig. 2: Glucose (a) and Dxylose (b) fluxes and regulations

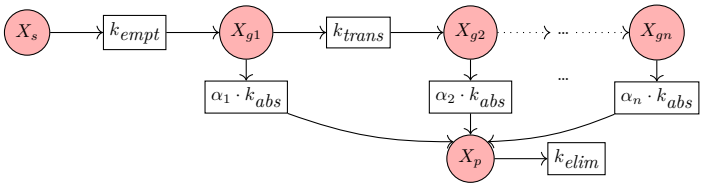

Fig. 3: Multi-compartment reaction model of XDylose dynamics

This characteristic of the model is usually contingent upon the interplay between the number of parameters and the number of experimentally observable variables. Given that we combined a rich experimental dataset with a simple model, we showed that the parameters are identifiable. In the clinical context, human datasets are obviously more limited compared to animal experimental datasets. In particular, no intestinal dataset is available and this one is crucial to distinguish the effect of gastric emptying from the effect of intestinal absorption (which we are interested in) on the blood DXylose dynamics. **The objective of this project is to investigate the extent to which our model is applicable to clinical human datasets.** The implementations will be done in the julia programming language [4].

Project work

The project plan is the following

- learn julia language,
- get familiar with the packages that allows for parameter estimation,
- get familiar with the notion of parameter identifiability and in particular with the profile likelihood method [5],
- practice these methods on the current model,
- investigate how *sensivity analysis* and, in particular the Sobol indices [6], could be used to reduce the number of parameters to estimate for clinical data,
- apply these methods to our clinical dataset of obese diabetes and non diabetes patients to estimate their rate of intestinal absorption,
- find, if any, a correlation between the intestinal rate of absorption and diabetes status of patients.

References

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