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

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Education:

- BSc Biotechnology, Grenoble Alpes Univ. (2014 - 2017);
- MSc Bioinformatics, Univ. of Paris-Saclay (2017 - 2019);
- PhD thesis, Univ. of Lille (2019 - ongoing).

Thesis topic:
Computational Models of Intestinal Glucose Absorption for Diabetes Prediction.
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Type 2 Diabetes (T2D)

Definition

Chronic metabolic disease characterized by:

- lack of insulin secretion $\rightarrow$ hypoinsulinemia;
- unability of the body to use insulin $\rightarrow$ hyperglycemia;
- perturbated glucose and insulin homeostasis;
- high prevalence: 400 millions affected $\rightarrow$ 90% of diabetics;
- limited therapeutic solutions.

Challenges

- Type 2 diabetes is a major public health issue.
- Identifying new therapeutic targets.

Type 2 Diabetes (T2D)

Hypothetical Causes

- High-carbonhydrate diet.
- Sedentary lifestyle.
- **Excess of intestinal glucose absorption $\rightarrow$ High rate of glucose appearance.**

Problematic

- How much impact does glucose intestinal absorption have on T2D?

  $\rightarrow$ Hypothesis based on clinical observations.
- How can a standard glucose-insulin model take into account such hypothesis?

  $\rightarrow$ Limits of the standard model.

Roux-en-Y Gastric Bypass (RYGB)

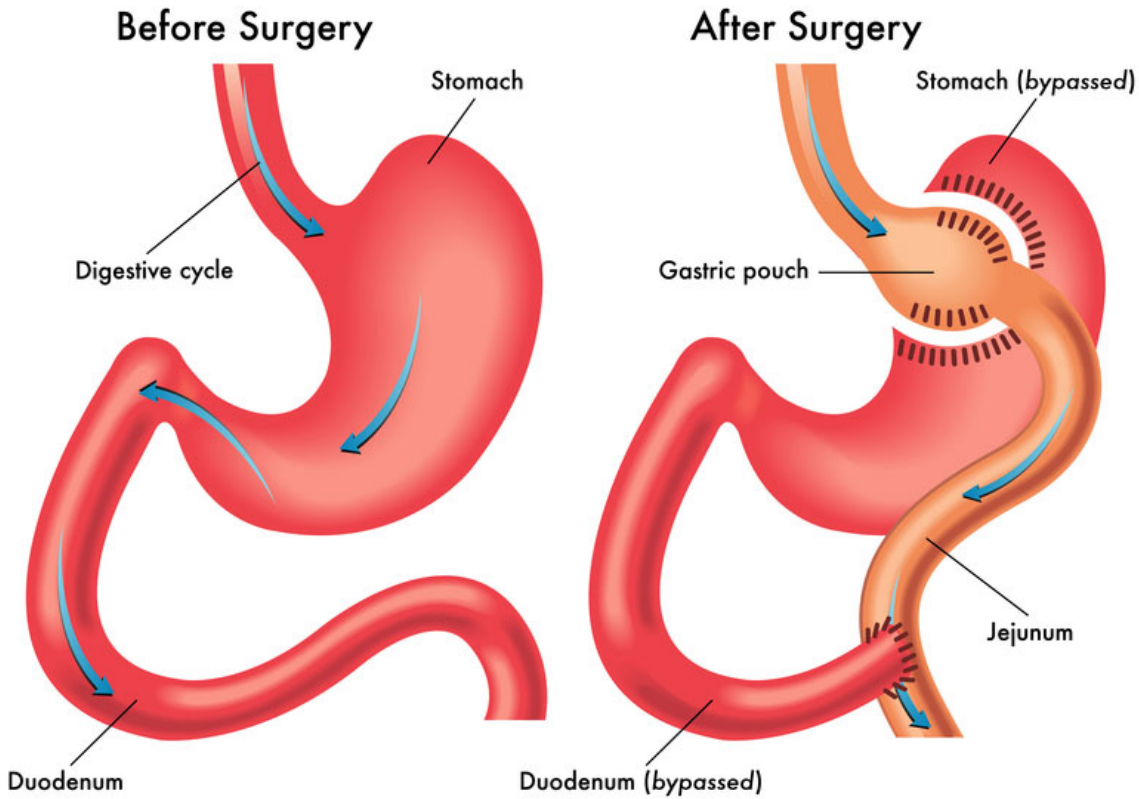


Figure: Roux-en-Y Gastric Bypass (RYGB). UCLA Health: http://surgery.ucla.edu/bariatrics-gastric-bypass

RYGB leads to weight loss and glucose-insulin homeostasis restoration.

Clinical Observations After a Meal

Dataset

Clinical datasets collected and provided by Inserm collaborators, from obese patients, before and after surgery.

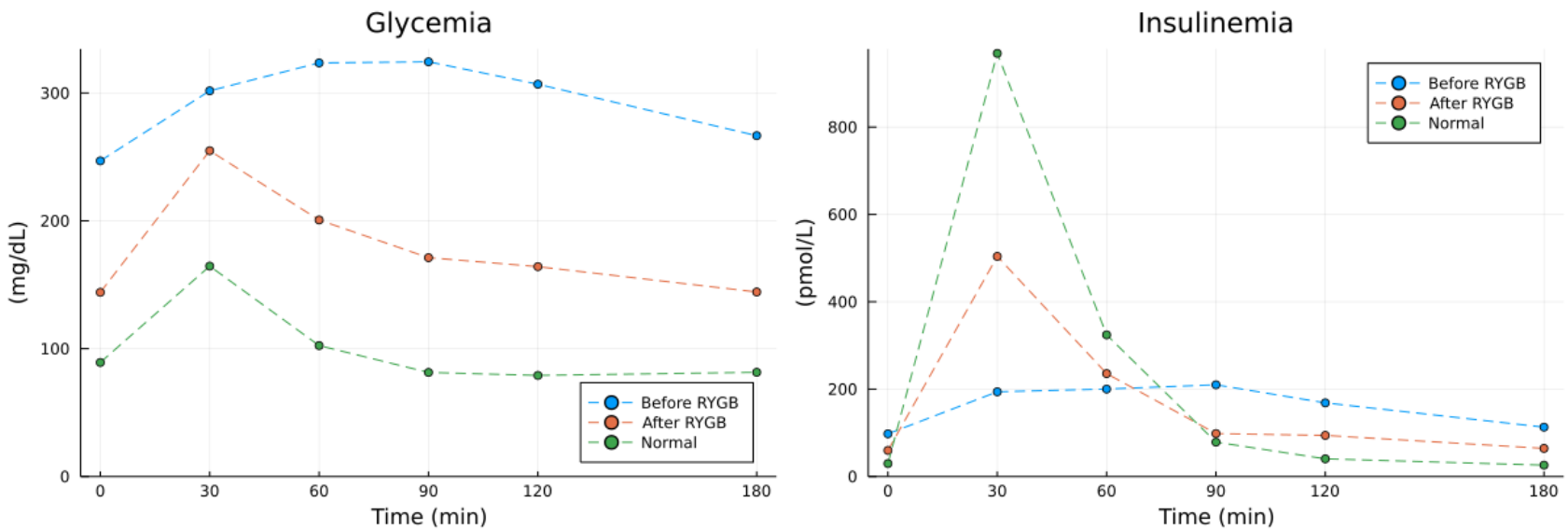


Figure: Average glycemia and insulinemia on 180 minutes, after a meal.

$\Longrightarrow$ **After surgery: good glucose and insulin homeostasis restoration.**

Meal Simulation Model of the Glucose-Insulin System

Reference Model

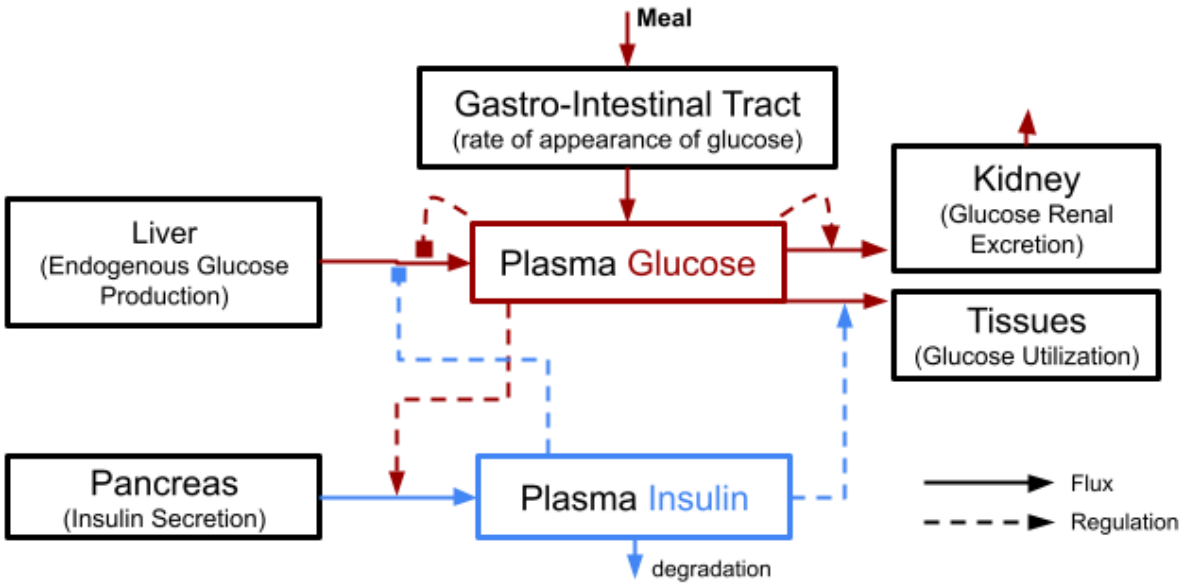
Standard, highly cited model from:

Meal Simulation Model of the Glucose-Insulin System, Dalla Man et al., 2007.

System of *ordinary differential equations* (ODEs):

- **12 dependent ODEs**, functions of time;
- **36 pairs of parameters values**:
  - non-diabetics;
  - diabetics.
- **No original dataset provided by the modellers** $\rightarrow$ low reproductibility $\rightarrow$ model validation from our dataset.
- Equations distributed in **7 biological modules** corresponding to biological functions: gastro-intestinal tract, liver, pancreas, etc.

Graph representation of the reference model



RYGB simulation $\Longleftrightarrow$ Modifying gastro-intestinal parameters values

1. How much does each biological module contribute to glucose-insulin homeostasis restoration?
2. Can the model predict our own dataset of diabetic patients?
3. Can the model predict glucose-insulin homeostasis restoration after RYGB?

Parameters Estimation Methods

Parameters estimation (optimization problem):

- **Estimated parameter values**: all or parts;
- **Fitted variables**: Glycemia and Insulinemia.
- **Objective function**: maximum likelihood or MSE etc.

$$\text{initial parameters} \xRightarrow{\text{estimation}} \text{inferred parameters} \xRightarrow{\text{model}} \text{inferred variables.}$$

Parameters Estimation Results

1. How much does each biological module contribute to glucose-insulin homeostasis restoration?

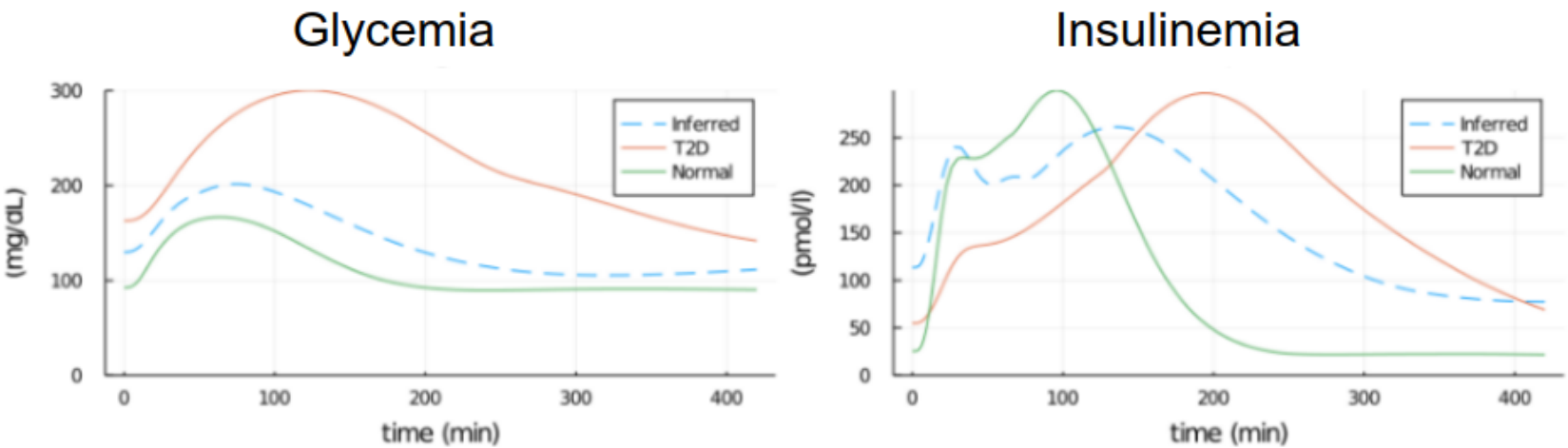
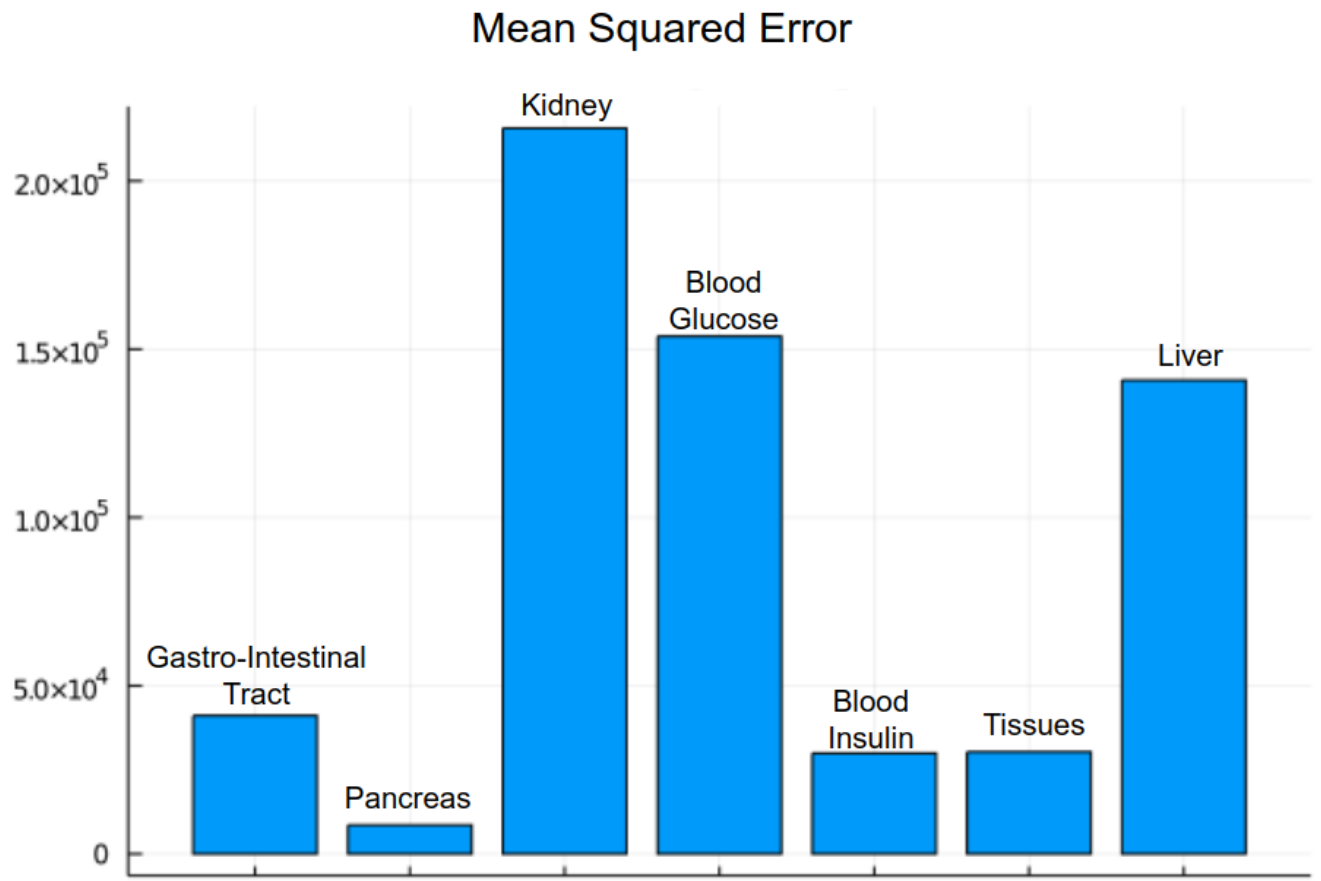


Figure: Inferred glycemia and insulinemia for gastro-intestinal tract

Initial parameters: diabetic parameters of [DallMan2007];
Fitted variables: non-diabetic glycemia and insulinemia of [DallMan2007];
Inferred parameters: only gastro-intestinal tract
Errors computed between healthy objective model and best estimated fit.

Parameters Estimation Results

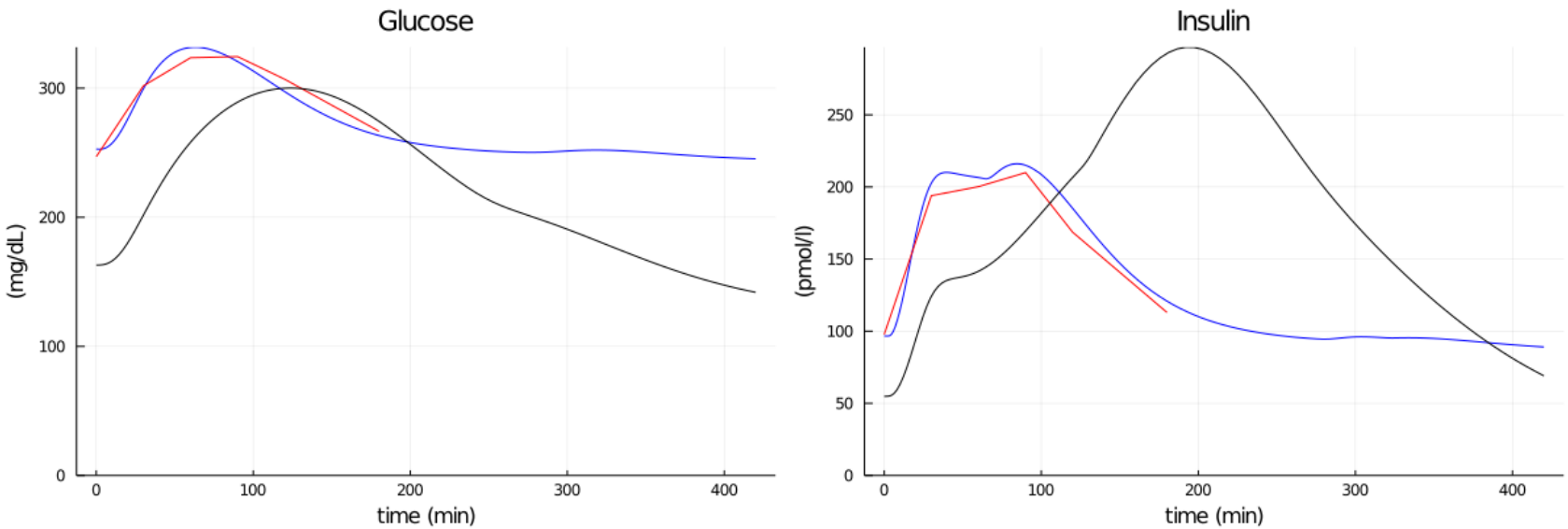
1. How much does each biological module contribute to glucose-insulin homeostasis restoration?



Contribution of each functional module to glucose homeostasis (low error = good contributor)

Parameters Estimation Results

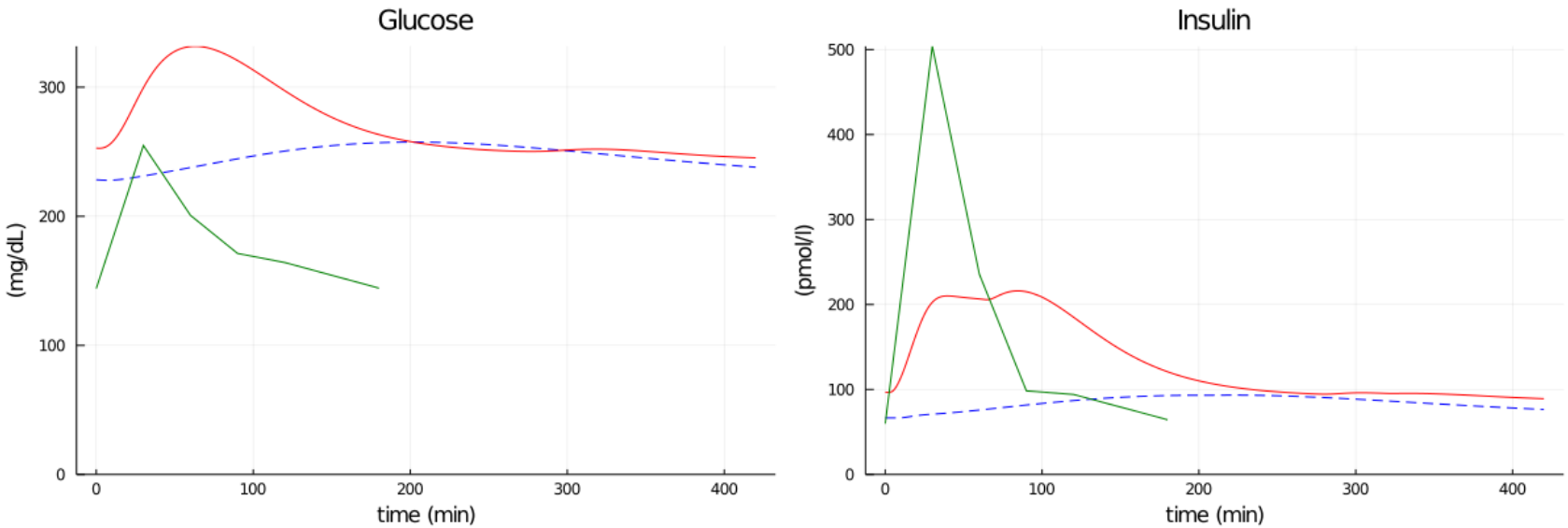
2. Can the model predict our own dataset of diabetic patients?



Initial parameters: diabetic parameters from [DallaMan2007];
Fitted variables: own dataset of pre-surgery glycemia and insulinemia;
Inferred parameters: all parameters (36).
$\Longrightarrow$ **good fitting despite very different diabetic population than [DallaMan2007].**

Parameters Estimation Results

3. Can the model predict glucose-insulin homeostasis restoration after RYGB?



Initial parameters: previous pre-surgery estimated parameters;
Fitted variables: own dataset of post-surgery glycemia and insulinemia;
Inferred parameters: only gastro-intestinal tract ($\Longrightarrow$ simulation of RYGB).
$\Longrightarrow$ **bad fitting.**

Work in Progress

1. From *Inserm* collaboration: animal datasets (Mini Pigs). Exploring populations dataset, **before** and **after** different experiments:
    * Pancreatectomy
    * Small bowel resection
    * Metabolic modulation for obesity

    More homogenous values. Better reproductibility for model validation.
2. New variables to fit
    * D-xylose $\rightarrow$ rate of glucose appearance
    * C-peptide $\rightarrow$ insulin secretion

    Would increase the parameters identifiability.

Discussion

- Struggle to fit our datasets.
- Shifting model validation criteria: from accurate fitting to qualitative validation.
- Building up a new model based on experimental data: more qualitative and explicative for the glucose intestinal absorption on type 2 diabetes prediction.
- Integrating more equations in a new model to explain intestinal glucose absorption.

Questions?