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);
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Thesis topic:

*Computational Models of Intestinal Glucose Absorption for Diabetes Prediction.*

Directors: Cedric Lhoussaine (Prof.), François Pattou (Prof.)

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Type 2 Diabetes (T2D)

Definition

Chronic metabolic disease characterized by:

- lack of insulin secretion $\rightarrow$ hypoinsulinemia;
- inability 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-carbohydrate diet.
- Sedentary lifestyle.
- Excess of intestinal glucose absorption → High rate of glucose appearance.

Problematic

- How much impact does glucose intestinal absorption have on T2D?
  → Hypothesis based on clinical observations.

- How can a standard glucose-insulin model take into account such hypothesis?
  → 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.

⇒ **After surgery:** good glucose and insulin homeostasis restoration.
Meal Simulation Model of the Glucose-Insulin System

Reference Model

Standard, highly cited model from:

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** → low reproductibility → 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 $\iff$ 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 (optimization problem):

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

initial parameters $\xrightarrow{\text{estimation}}$ inferred parameters $\xrightarrow{\text{model}}$ inferred variables.
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.
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)
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).
⇒ good fitting despite very different diabetic population than [DallaMan2007].
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 (simulation of RYGB).

⇒ bad fitting.
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 → rate of glucose appearance
   * C-peptide → 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?