The hypoglycaemia free artificial pancreas project

28 january 2020

Claude MOOG, LS2N, Nantes France

Directeur de recherche CNRS

Fellow of the IEEE

Joint work with

- Emeric Scharbarg
- Nicolas Magdelaine
- Eric Le Carpentier
- …

content

- Some history/state of the art
- Mathematical model
- Identification
- Control

- The perspectives (hospital & industry…)

Main message

- Stick to medical practice: FIT, Flexible Insulin Therapy

→ Constraints on the model

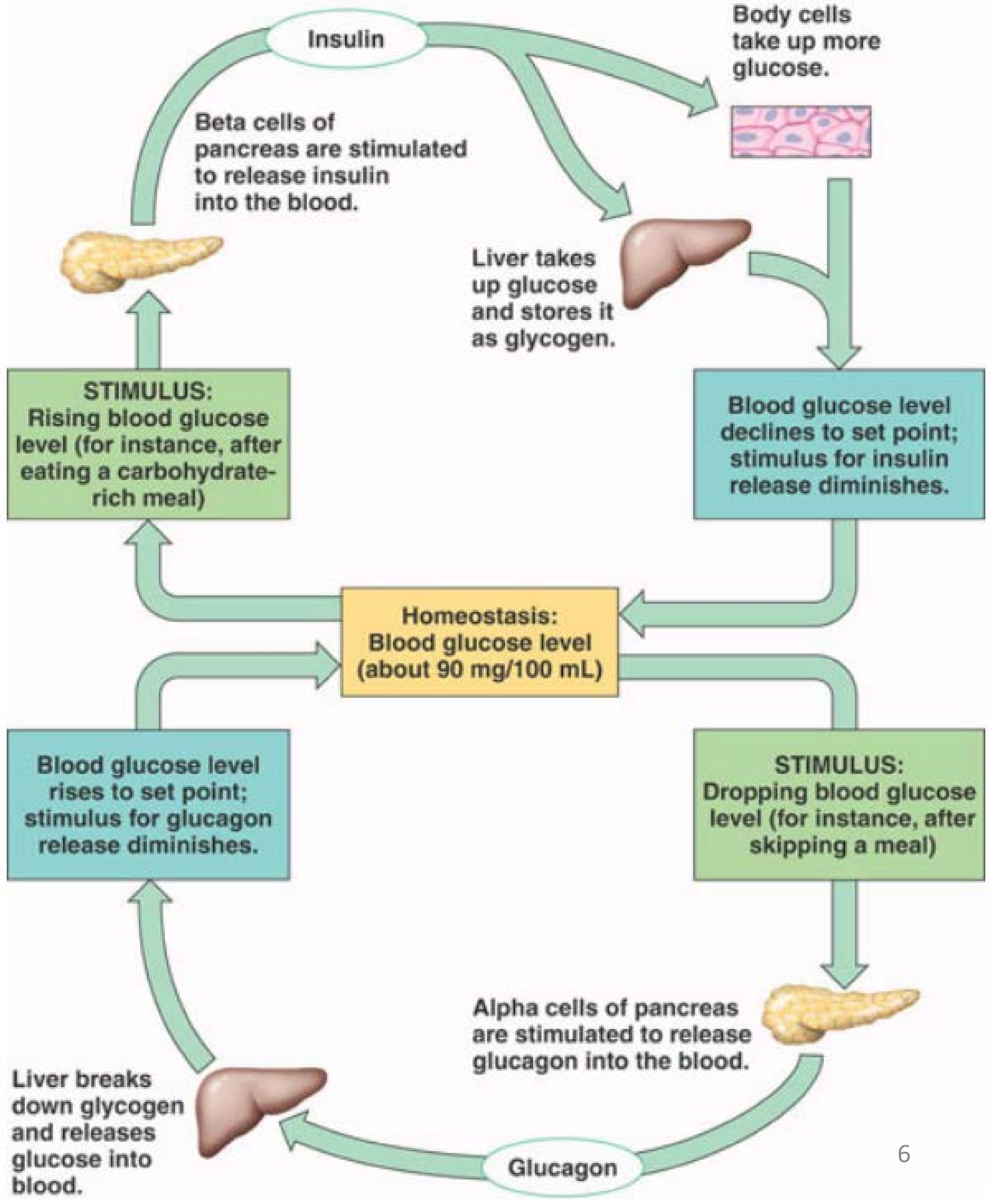
- Avoid hypoglycemia

→ Existing (Medtronic, Diabeloop) solutions may be open loop for up to 30% of the time

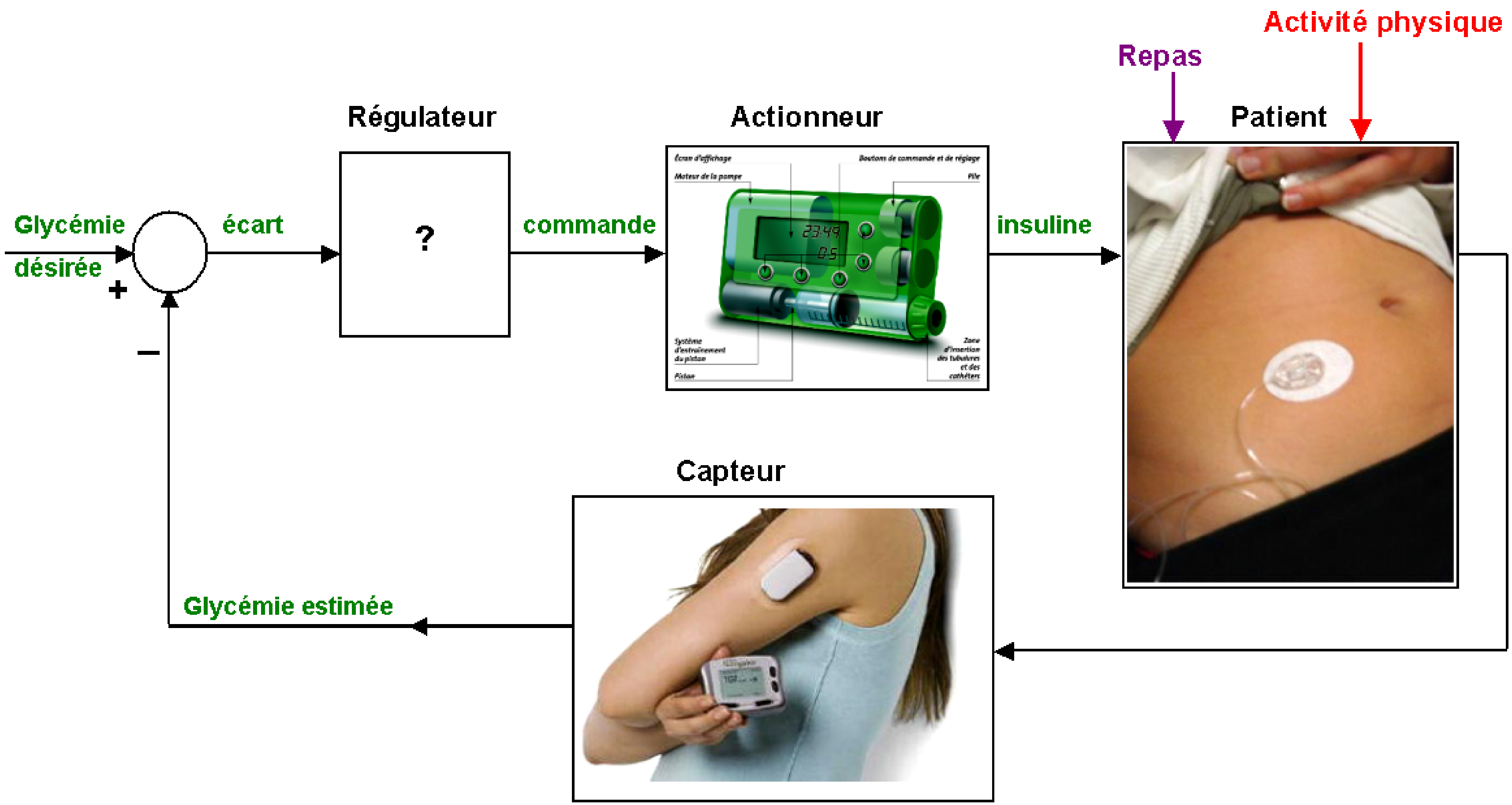
The general population vs Diabetes

- No diabetes
- Type 1 → no insulin production by the pancreas
- Type 2 → aging patients, lack of insulin production, decrease of sensitivity
- diabetis related to pregnancy

Biology – the natural mechanism which regulates glycemia



A challenging control problem



Long standing contributions !

- PADOVA : C. Cobelli et al.
- Montpellier hospital : E. Renard

- …
- > 1960’s

Our choices/constraints

- **Stick to medical practice**: FIT, Flexible Insulin Therapy

→Recover the basal rate from the mathematical model

Definition - the basal insulin rate stabilizes any glucose concentration.

- Avoid hypoglycemia

→ *Positivity of the system*

Mathematical model

- Stick to medical practice: FIT, Flexible Insulin Therapy

If no meal & stable glycemia:

$$\dot{G} = 0$$

Or

$$\dot{G} = \theta(I_{basal} - I)$$

$$\dot{G} = \theta_1 - \theta_2 I$$

If a meal is ingested: $\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$

Mathematical model

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$$

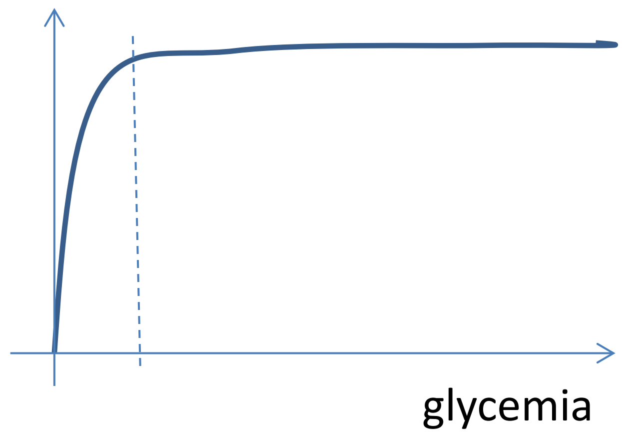
θ_1 : glucose delivery from the liver – consumption by the brain…

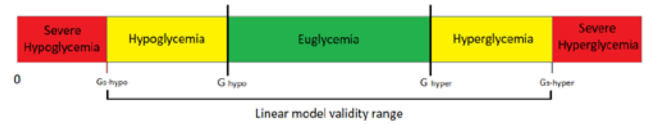
θ_2 : insulin sensitivity factor

θ_3 : sensitivity to digested carbohydrates

$$G \geq 0$$

$$\theta_2 = \theta_2(G)$$





Ref.: Tolic et al.
J. Theor. Biol. (2000) 207, 361-375.

Mathematical model

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$$

$$I_{basal} = \theta_1 / \theta_2$$

Insulin diffusion : may involve several compartments

Digestion of carbohydrates : may involve several compartments.

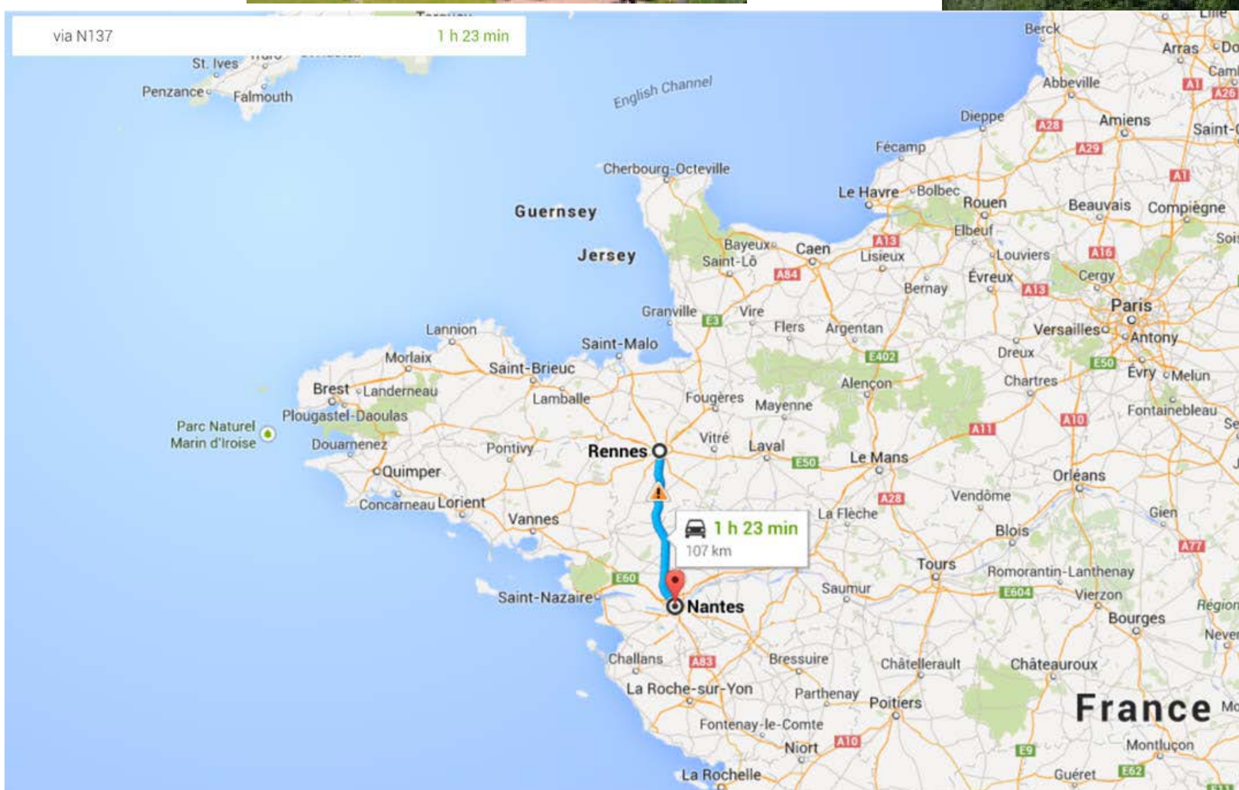
Drawback for identification from clinical data: declared meals are questionable

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$$

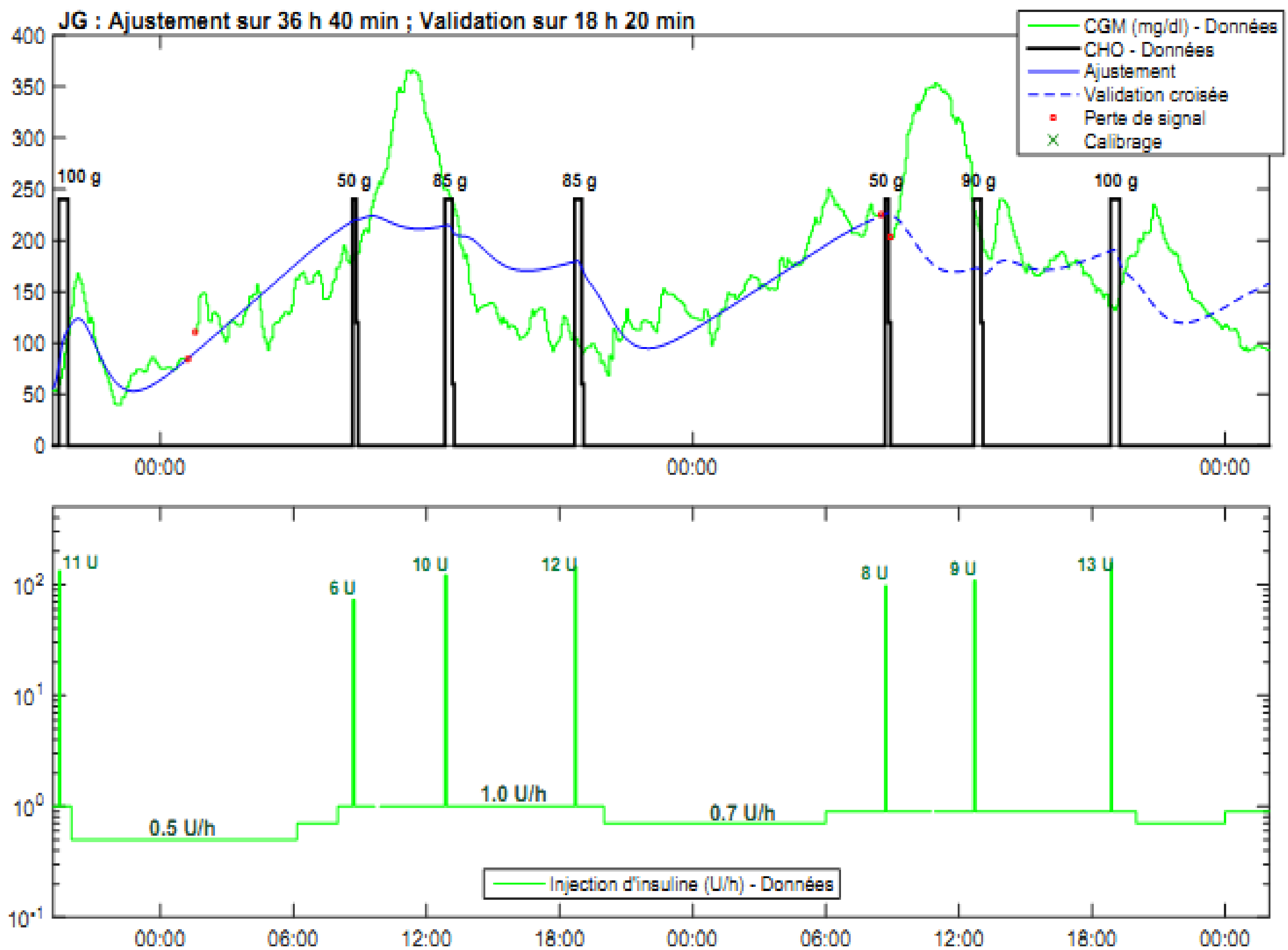
→ Option 1 :
Redefine the time when meals occur, their amplitude…

What is a linear model good for ?

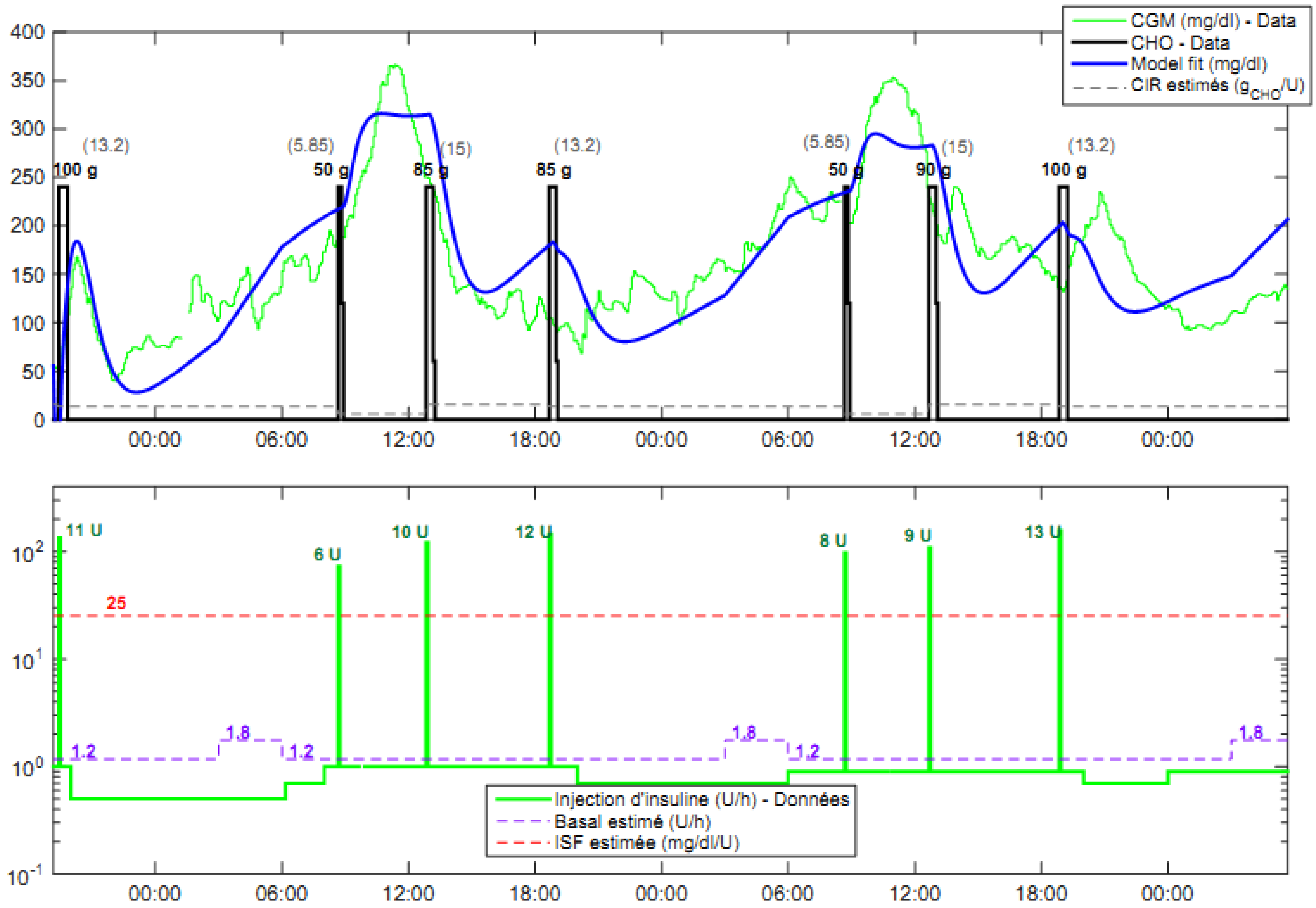
Clinical data from Nantes hospital and Rennes hospital



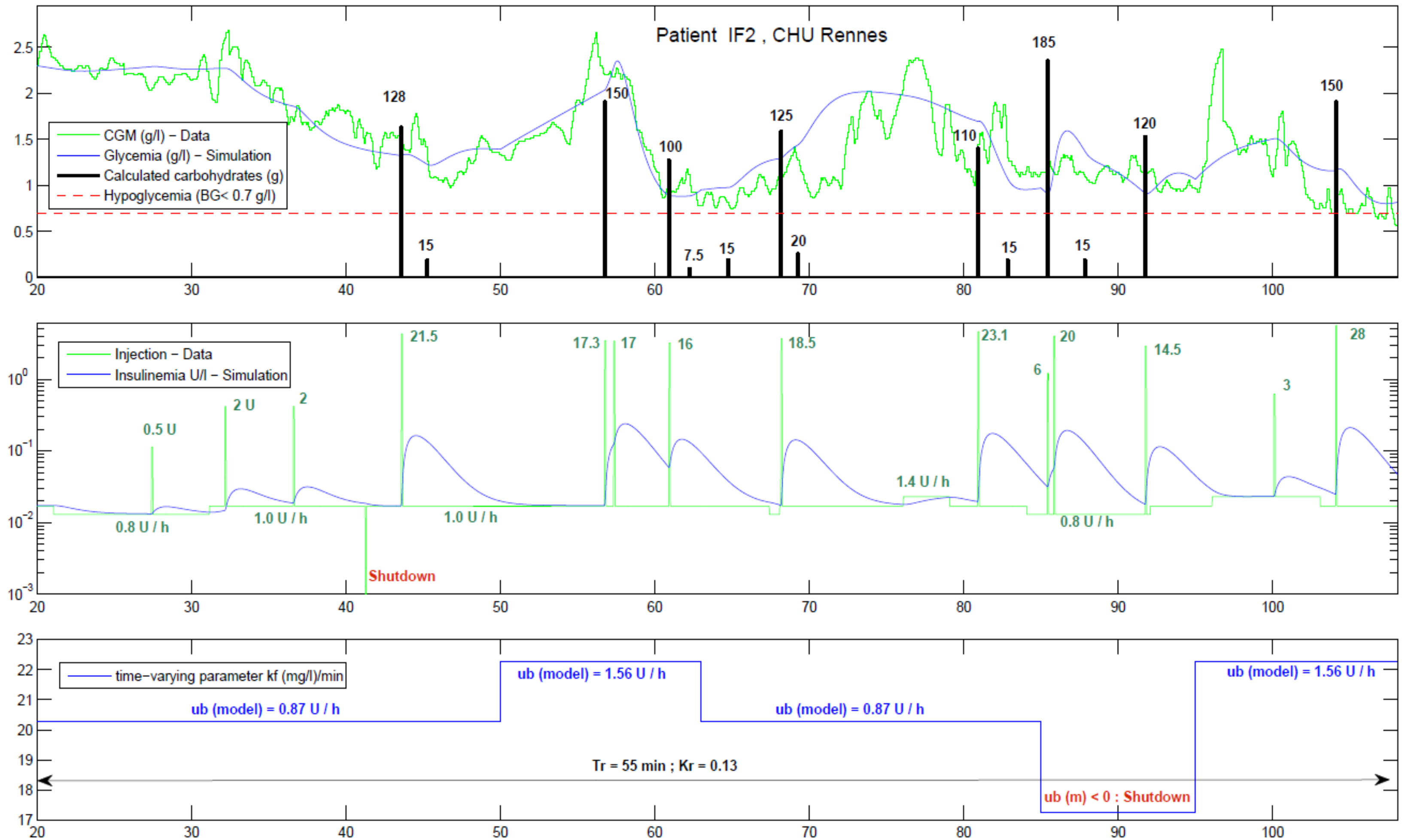
Identification with constant parameters (and re-positionning of meals)



Identification with varying parameters (and re-positionning of meals)

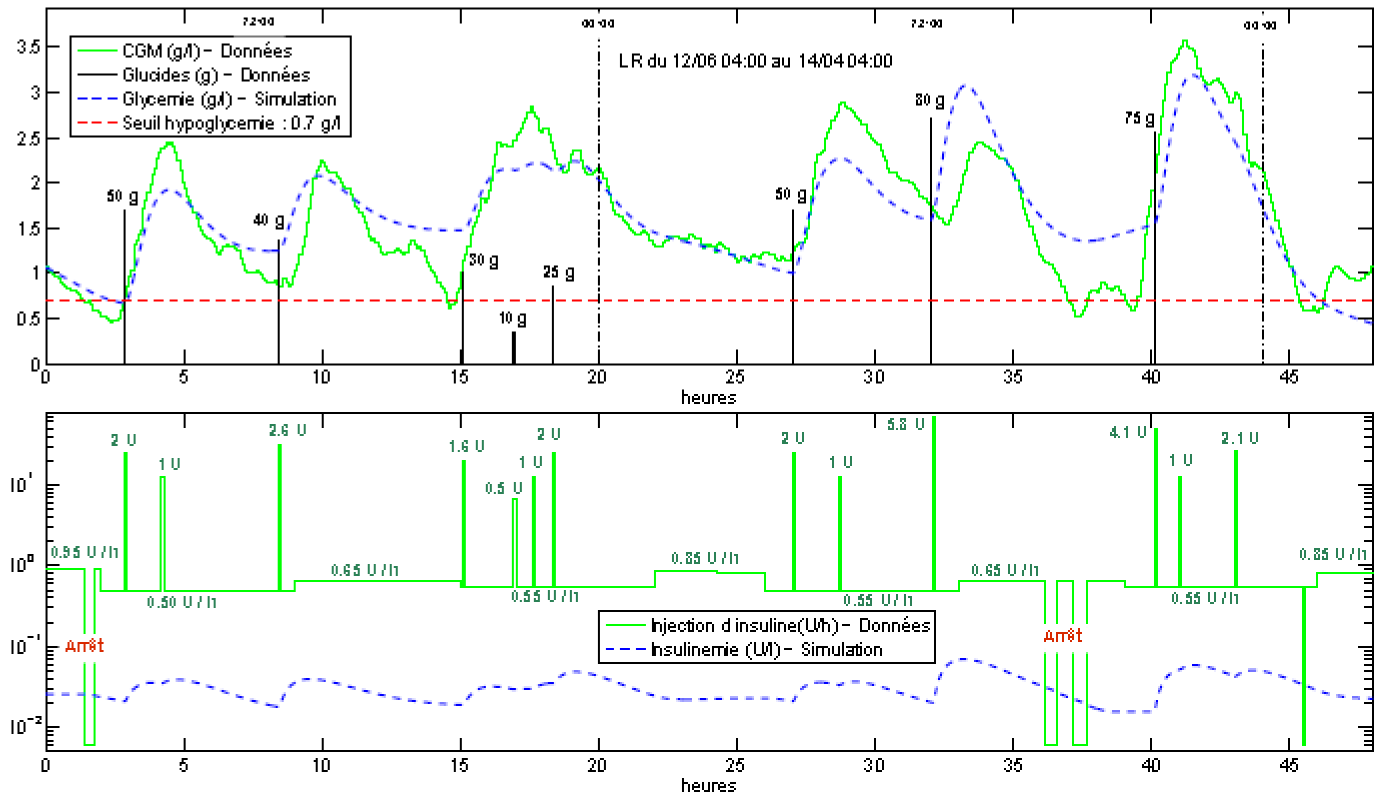


Patient IF2



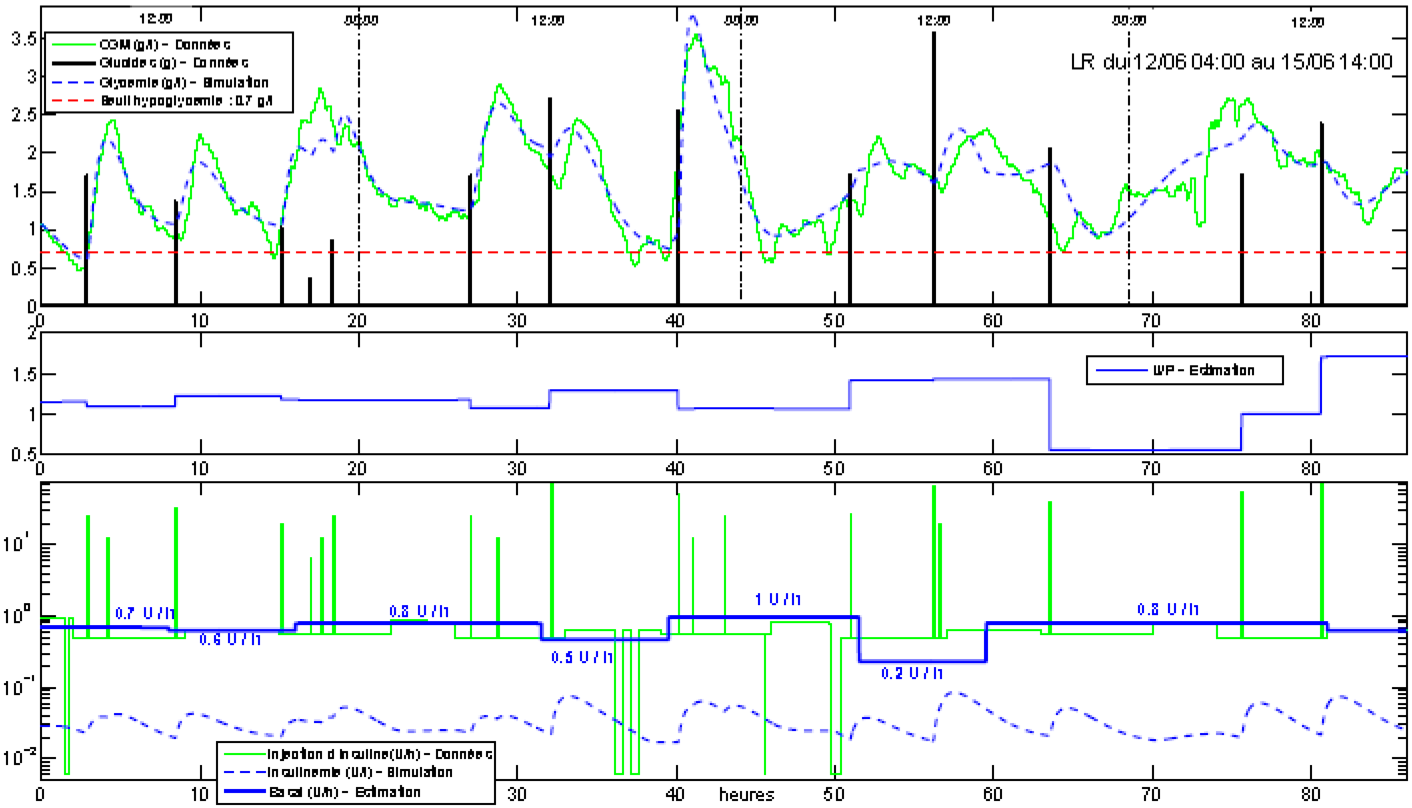
Patient IF2 , CHU Rennes
CGM (g/l) – Data
Glycemia (g/l) – Simulation
Calculated carbohydrates (g)
Hypoglycemia (BG< 0.7 g/l)
128
15
150
100
7.5
15
125
20
110
15
185
15
120
150
Injection – Data
Insulinemia U/l – Simulation
0.5 U
2 U
2
21.5
17.3
17
16
18.5
23.1
6
20
14.5
3
28
0.8 U / h
1.0 U / h
1.0 U / h
1.4 U / h
0.8 U / h
Shutdown
time-varying parameter kf (mg/l)/min
ub (model) = 0.87 U / h
ub (model) = 1.56 U / h
ub (model) = 0.87 U / h
ub (model) = 1.56 U / h
Tr = 55 min ; Kr = 0.13
ub (m) < 0 : Shutdown

Patient LR



CGM (g/l) - Données
Glucides (g) - Données
Glycemie (g/l) - Simulation
Seuil hypoglycemie : 0.7 g/l
LR du 12/06 04:00 au 14/04 04:00
50 g
40 g
30 g
10 g
25 g
50 g
80 g
75 g
heures
2 U
1 U
2.6 U
1.6 U
0.5 U
1 U
2 U
2 U
1 U
5.8 U
4.1 U
1 U
2.1 U
0.95 U / h
0.50 U / h
0.65 U / h
0.55 U / h
0.85 U / h
0.55 U / h
0.65 U / h
0.55 U / h
0.85 U / h
Arrêt
Arrêt
Injection d insuline(U/h) - Données
Insulinemie (U/l) - Simulation
heures

Patient LR: adaptive estimation



Criticism:

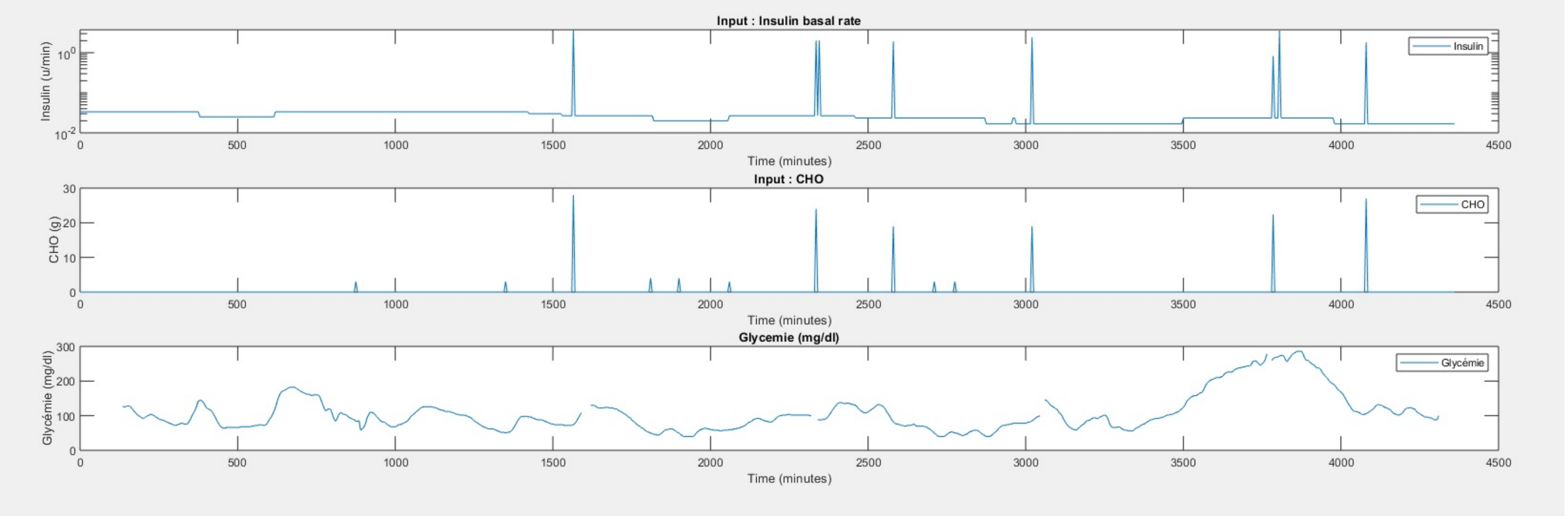
the sequence of meals is used an extra « tuning » for the best fit

Lack of methodology for a suitable processing of the meal data ☹

Towards a methodology for identification

Option 2 :

Select some identifiable events in clinical data as:

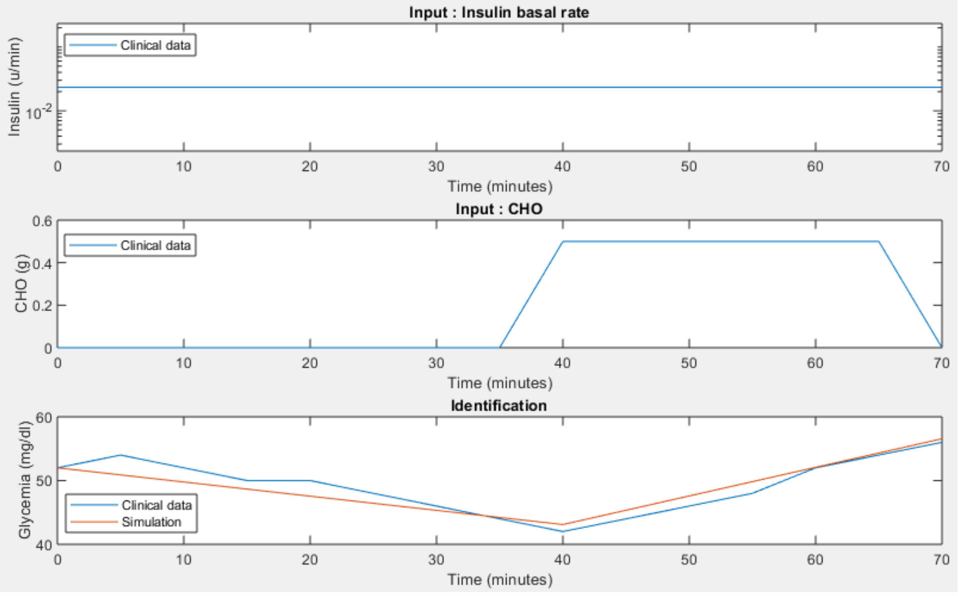


Towards a methodology for identification

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$$

identification of θ_3

Special event: when glycemia is too low, $I = I_{basal} = \theta_1 / \theta_2$ and $D \neq 0$



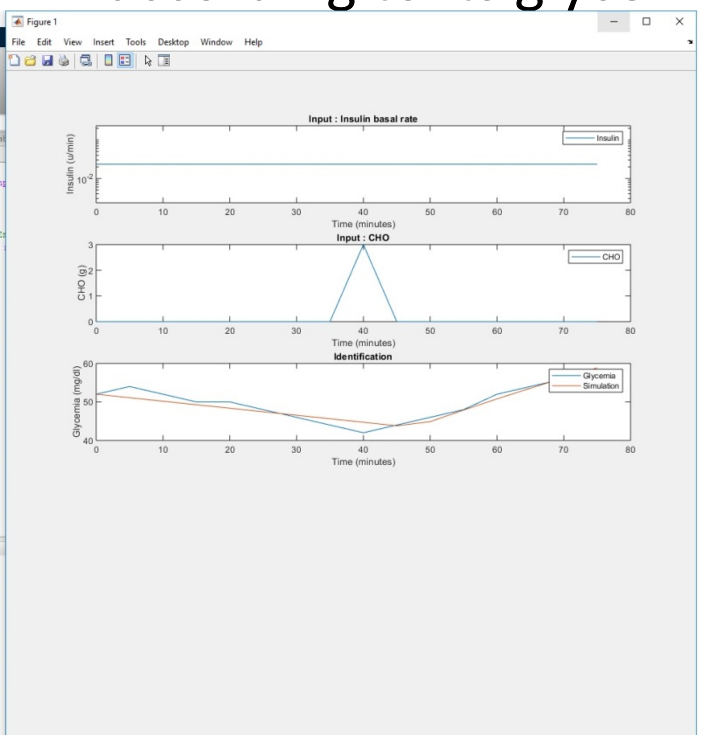
Towards a methodology for identification

$$\dot{G} = \theta_1 - \theta_2 I + \theta_3 D$$

identification of θ_3

The inclusion of digestion dynamics $\dot{D} = -\theta_4 D + \theta_4 M$

allows to identify the « duration » of the effect of the meal M, according to its glycemic index



Type of the model

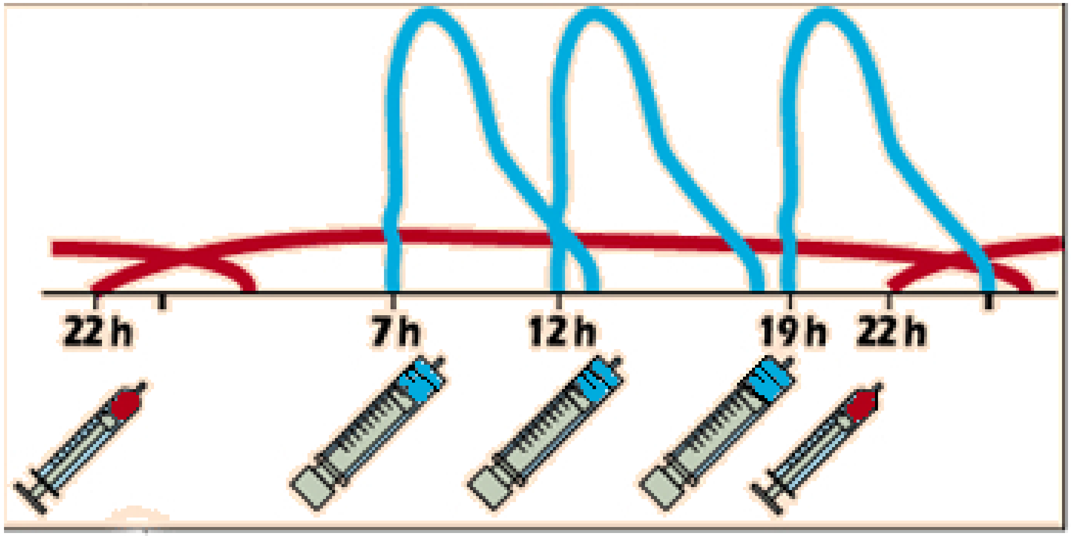
up to some insulin compartments and some digestion compartments:

$$\dot{G} = \theta_1 - \theta_2(G).I + \theta_3 D$$
$$\dot{D} = -\theta_4 D + \theta_4 M$$

Depends on the glycemic index

Control

Real life « manual » control

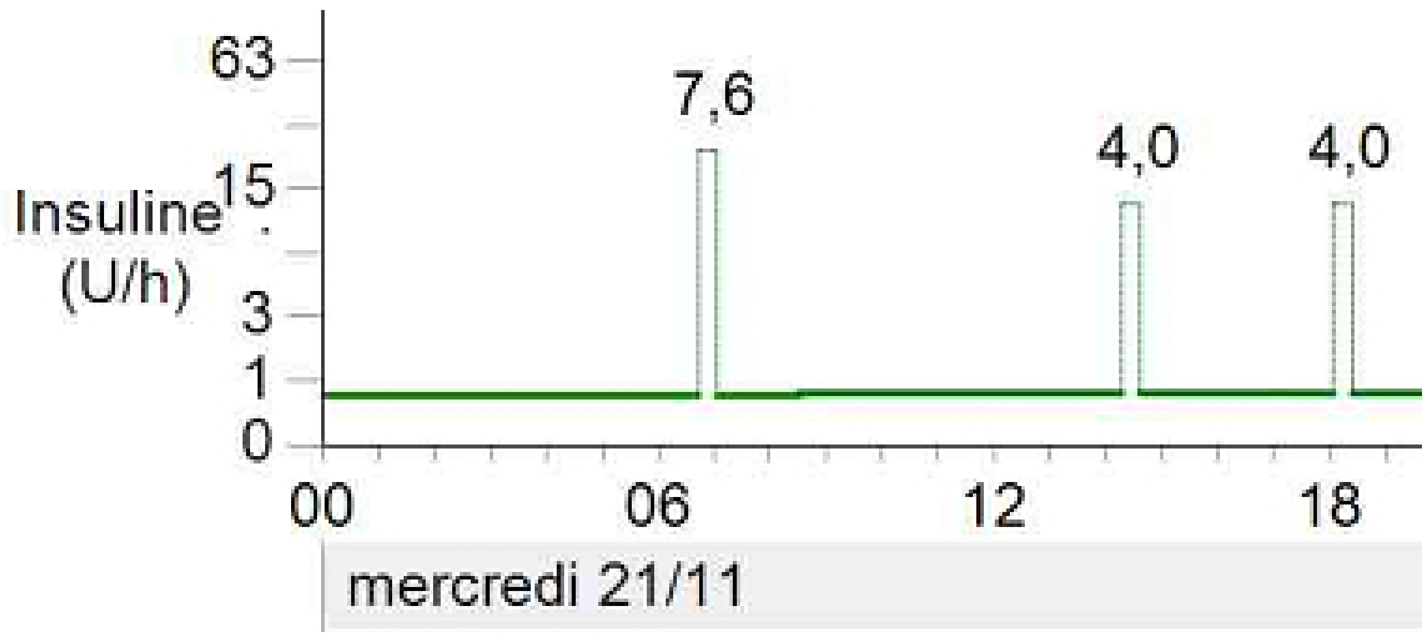


Insulinothérapie
schéma Basal/Bolus

Slow action insulin
Fast action insulin

Insulin pump

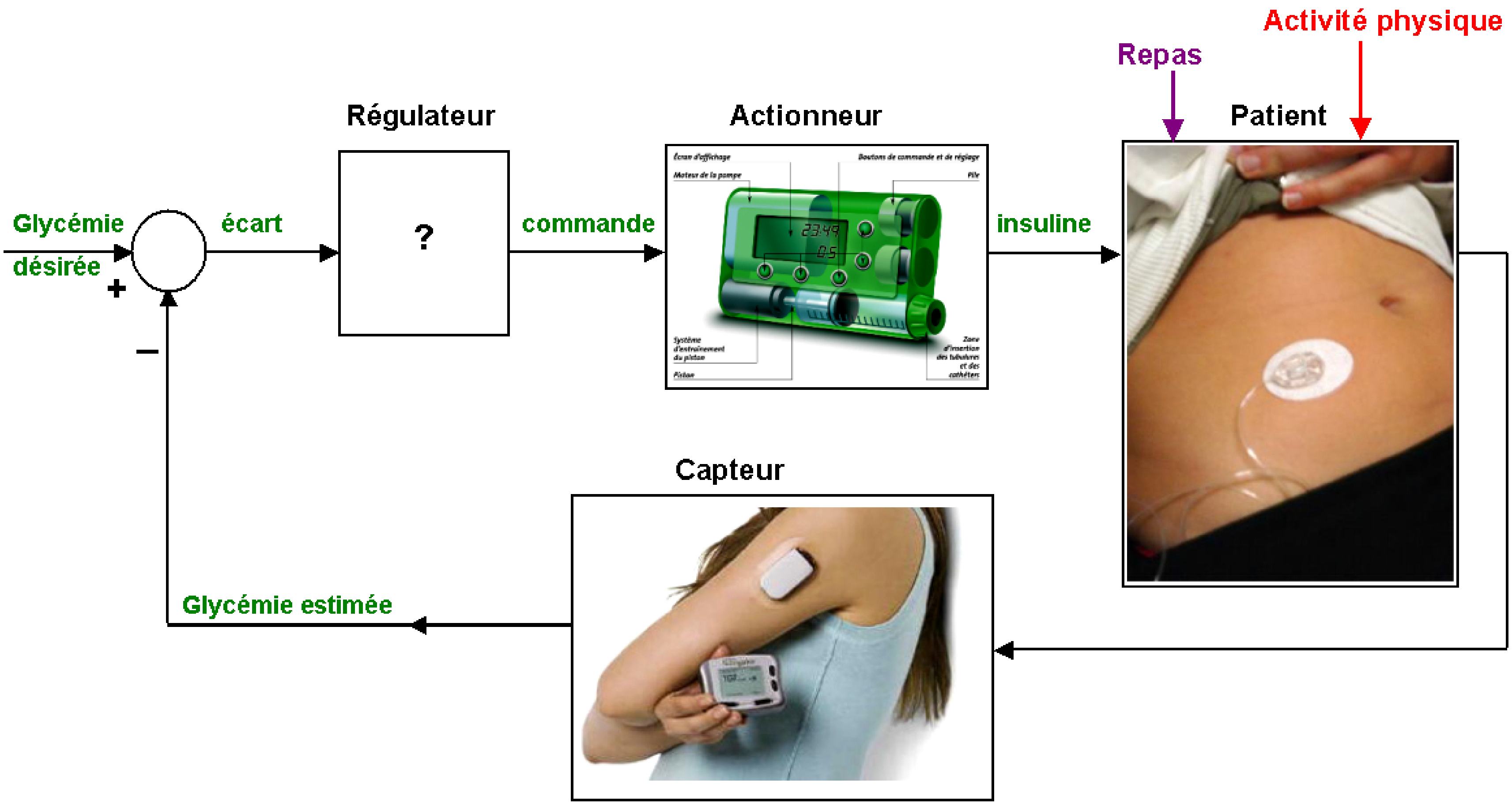
With a single type of insulin



Continuous flow: basal rate

Impulse-like control: bolus

Closing the loop ?



Closing the loop ?

- Mainstreams:

Model predictive control (Diabeloop)

PID (Medtronic)

Control

Dynamic Bolus calculator

derived from the expertise of practioners

Bolus calculator

- Derived from real life devices

Bolus calculator

- Reduces to a state feedback:

Insulin to be injected = insulin required – insulin already injected

$$u = u_{BG} - u_{IoB}$$

$$u = k_1 G - k_2 (I_{SC} + I_P)$$

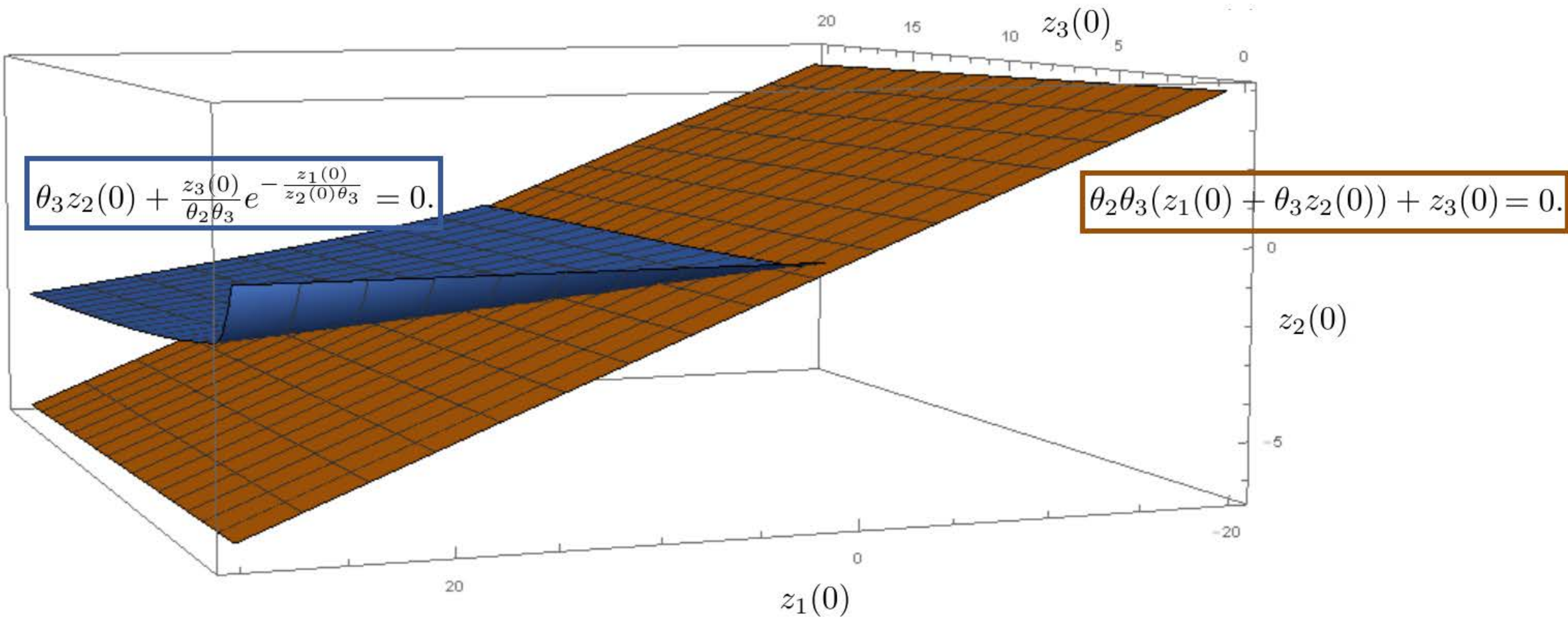
G = glycemia
Isc = sub sutaneous Insulinemia
Ip = Insulin in plasma

Bolus calculator properties

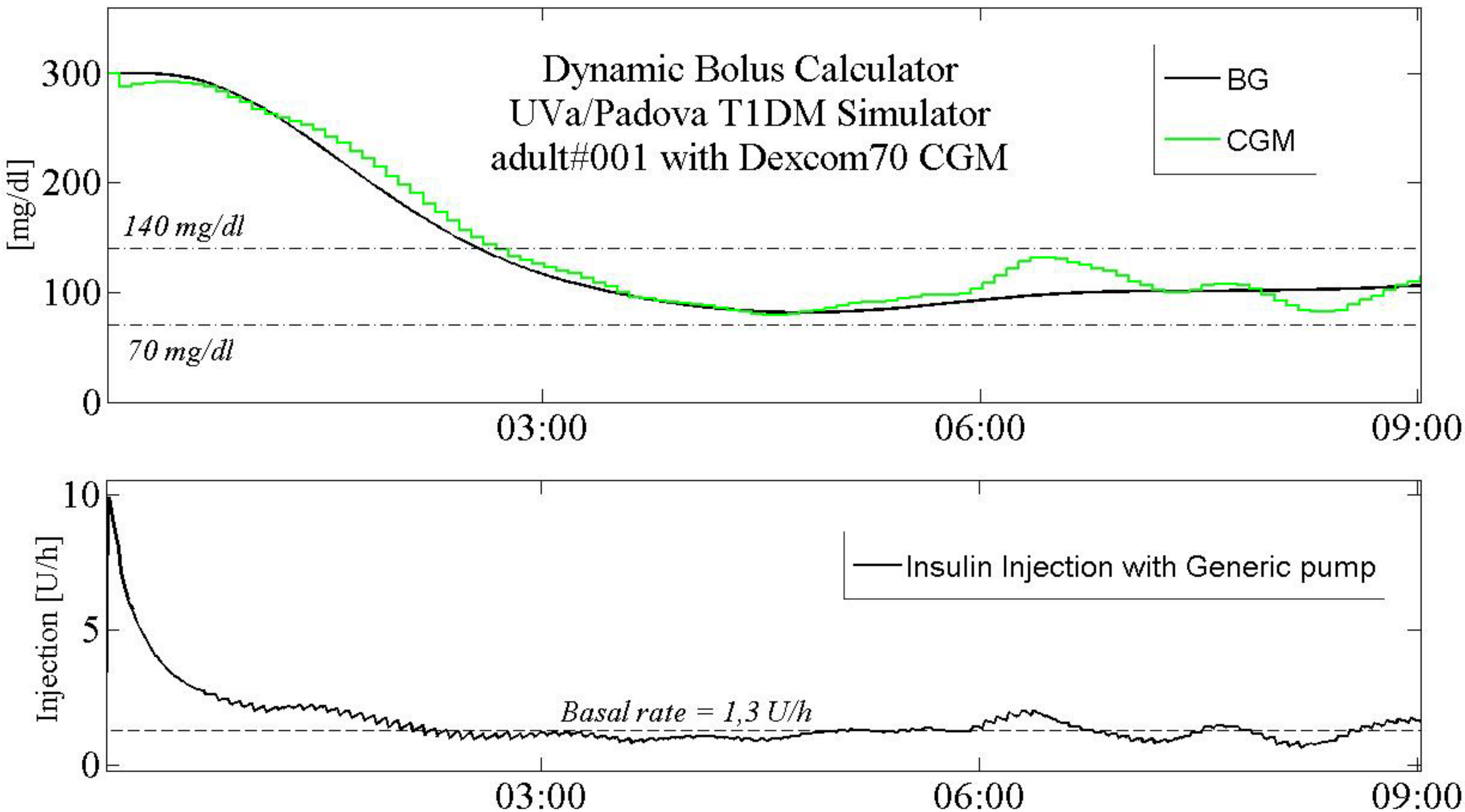
- state feedback: $$u = k\left[\frac{1}{\theta_2}G - \frac{1}{\theta_3}(I_{SC} + I_P)\right]$$
- Defines the largest positively invariant subset !
- Under any other state feedback, the largest PIS shrinks

G = glycemia
Isc = sub sutaneous Insulinemia
Ip = Insulin in plasma

Positively Invariant Set



Dynamic Bolus Calculator



reference

N. Magdelaine, P.S. Rivadeneira, L. Chaillous, A.L. Fournier-Guilloux, M. Krempf, T. MohammadRidha, M. Aït-Ahmed and C.H. Moog,

The Hypoglycaemia-Free Artificial Pancreas Project,

IET Systems Biology, 2020, vol. 14, pp. 16-23.

Conclusions and perspectives

- **What is specific:**
- Recover the FIT parameters from the model
- Positive control (hypoglycemia avoidance)
- **Coming next:**
- Methodology for identification of the basal, CIR,…
- Clinical trial of identification
- Prototype

Conclusions and perspectives

- Main achievement: modelling

N. Magdelaine, L. Chaillous, I. Guilhem, J.Y. Poirier, M. Krempf, C.H. Moog and E. Le Carpentier,

A Long-term Model of the Glucose-Insulin Dynamics of Type I Diabetes,

IEEE Transactions on Biomedical Engineering, (2015).

Conclusions and perspectives

- Main achievement: modelling
- Implementation of the state feedback (OpenAPS)