An event-based point of view on the control of insulin-dependent diabetes

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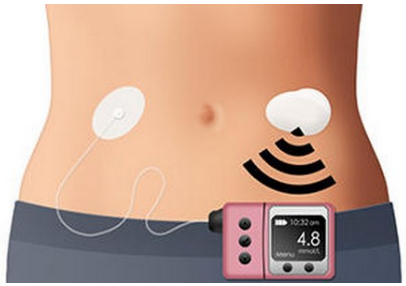
Treatment of insulin-dependent diabetes continuous *vs.* discrete control

The treatment of insulin-dependent diabetes involves the artificial control of the patient's plasma glucose rate via insulin infusion.

- Today's main research: artificial pancreas, which combines a glycaemia sensor and an insulin pump → continuous control.
- Most patients do not have this device.
  The sensor and the control are decoupled.
  Glycaemia measurements and insulin infusions are not continuous in time but triggered at discrete times.
  → discrete control, event- and self-triggered control.



Signal processing *vs.* ODE approach

- Engineering approach: signal processing
  Glycaemia is measured, producing a discrete signal, with a 1 minute sampling time on current devices.
  Its value should be within a target interval $\mathcal{I}_{\text{target}}$.
  When it departs from this target, glycaemia can be pushed back by infusing insulin, or ingesting carbohydrates.
- Mathematical approach: ODEs
  A patient is modeled by a big system of Ordinary Differential Eqs:

$$\dot{Y} = f(Y, P, U)$$

  involving many variables Y, patient-dependent parameters P and a complex control procedure U.
  Only one variable, glycaemia, is observed:

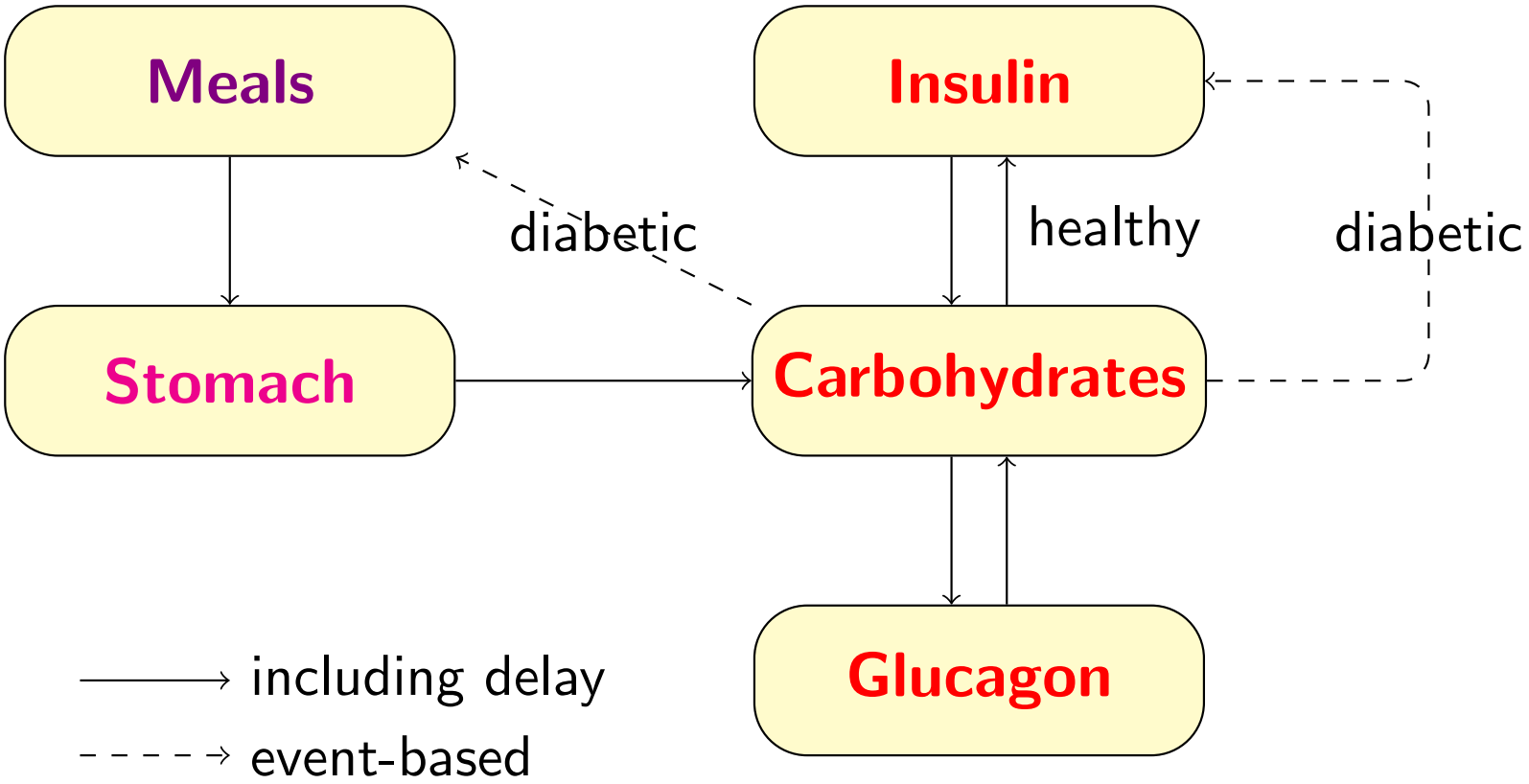
$$y = CY.$$

Model definition

- ODE model based on Cobelli's model ([DM07,DM14]).
- Time evolution of main variables:
  - G: plasma glucose rate,
  - I: plasma insulin rate,
  - H: plasma glucagon rate.
- and secondary variables.
- It involves many patient-dependent parameters.
- It is driven by external outputs (meals M, physical exercise) and control procedures.

[DM07] Chiara Dalla Man, Robert A. Rizza, and Claudio Cobelli, *Meal simulation model of the glucose-insulin system,* IEEE Transactions on Biomedical Engineering 54 (2007), no. 10, 1740–1749.
[DM14] Chiara Dalla Man, Francesco Micheletto, Dayu Lv, Marc Breton, Boris Kovatchev, and Claudio Cobelli, *The UVA/PADOVA type 1 diabetes simulator: New features,* Journal of Diabetes Science and Technology 8 (2014), no. 1, 26–34.

Compartments



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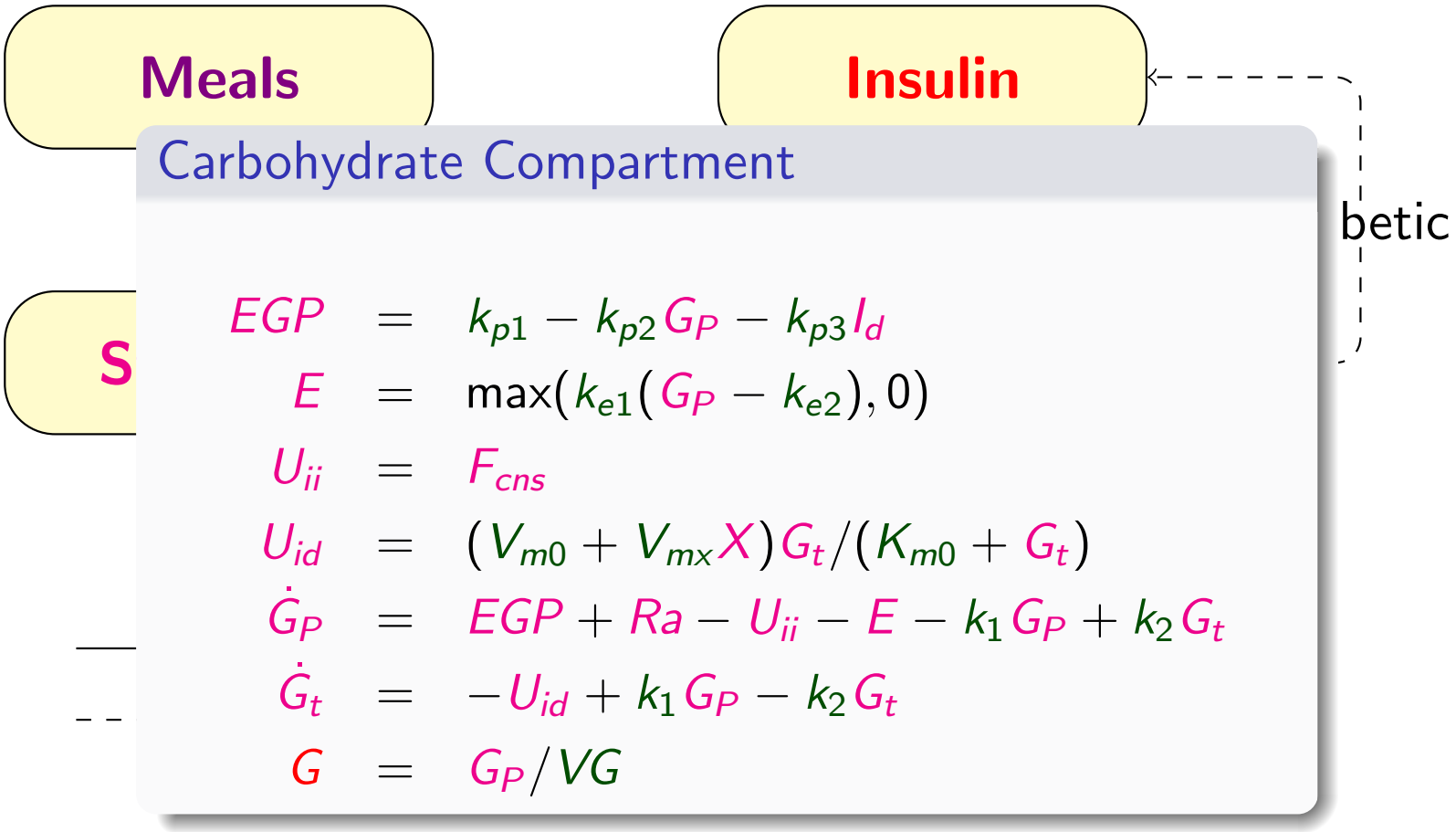
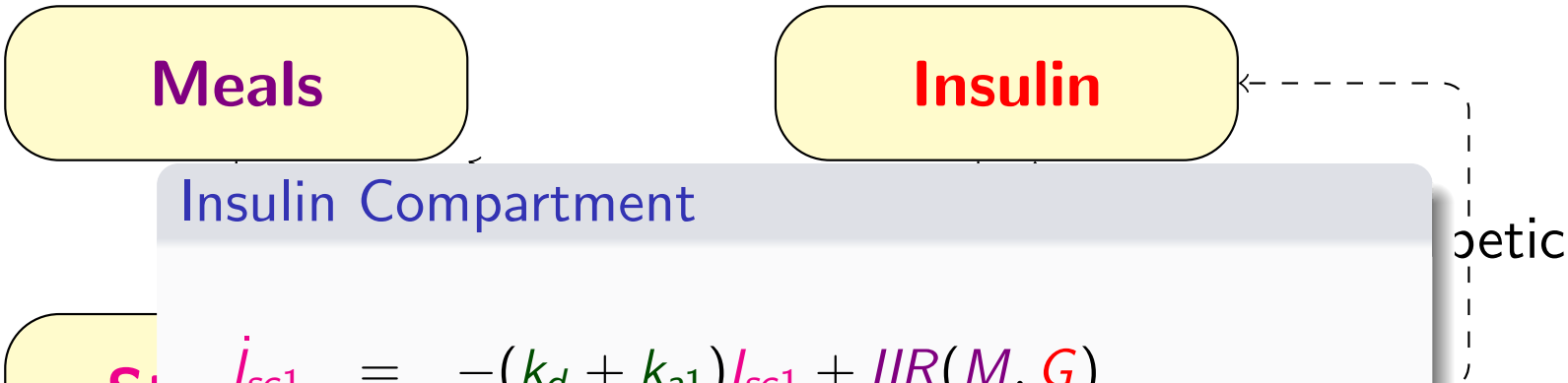


Carbohydrate Compartment

$$
\begin{aligned}
EGP &= k_{p1} - k_{p2} G_P - k_{p3} I_d \\
E &= \max(k_{e1}(G_P - k_{e2}), 0) \\
U_{ii} &= F_{cns} \\
U_{id} &= (V_{m0} + V_{mx} X) G_t / (K_{m0} + G_t) \\
\dot{G}_P &= EGP + Ra - U_{ii} - E - k_1 G_P + k_2 G_t \\
\dot{G}_t &= -U_{id} + k_1 G_P - k_2 G_t \\
G &= G_P / VG
\end{aligned}
$$

Compartments



Insulin Compartment

$$
\begin{aligned}
\dot{I}_{sc1} &= -(k_d + k_{a1})I_{sc1} + IIR(M, G) \\
\dot{I}_{sc2} &= k_d I_{sc1} - k_{a2} I_{sc2} \\
\dot{I}_l &= -(m_1 + m_3)I_l + m_2 I_p \\
\dot{I}_p &= -(m_2 + m_4)I_p + m_1 I_l + k_{a1} I_{sc1} + k_{a2} I_{sc2} \\
I &= I_p / VI \\
\dot{I}_1 &= -k_i(I_1 - I) \\
\dot{I}_d &= -k_i(I_d - I_1) \\
\dot{X} &= -p_{2U} X + p_{2U}(I - I_b)
\end{aligned}
$$

Parameter definition

Parametrization of the model in many steps.

- Direct model: Define a first model with mean patient parameters:

$$\dot{Y} = f(Y, P, U).$$

Three types of patients: healthy, insulin-dependent diabetic, non insulin-dependent diabetic.

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- Control parameters: Adapt the control procedures to this specific patient :

$$\dot{Y} = f(Y, P, U).$$

Parameter estimation

The model's parameters can be classified in many categories:

- a few known, and constant, subject parameters
  - weight
  - ...
- a whole bunch of not exactly known and/or variable subject parameters
  - rate constants for intestinal glucose absorption
  - liver responsiveness to glucagon
  - ...

There are also time-dependent inputs

- physical activity
- emotions
- growth hormones for children
- ...

Numerical simulation

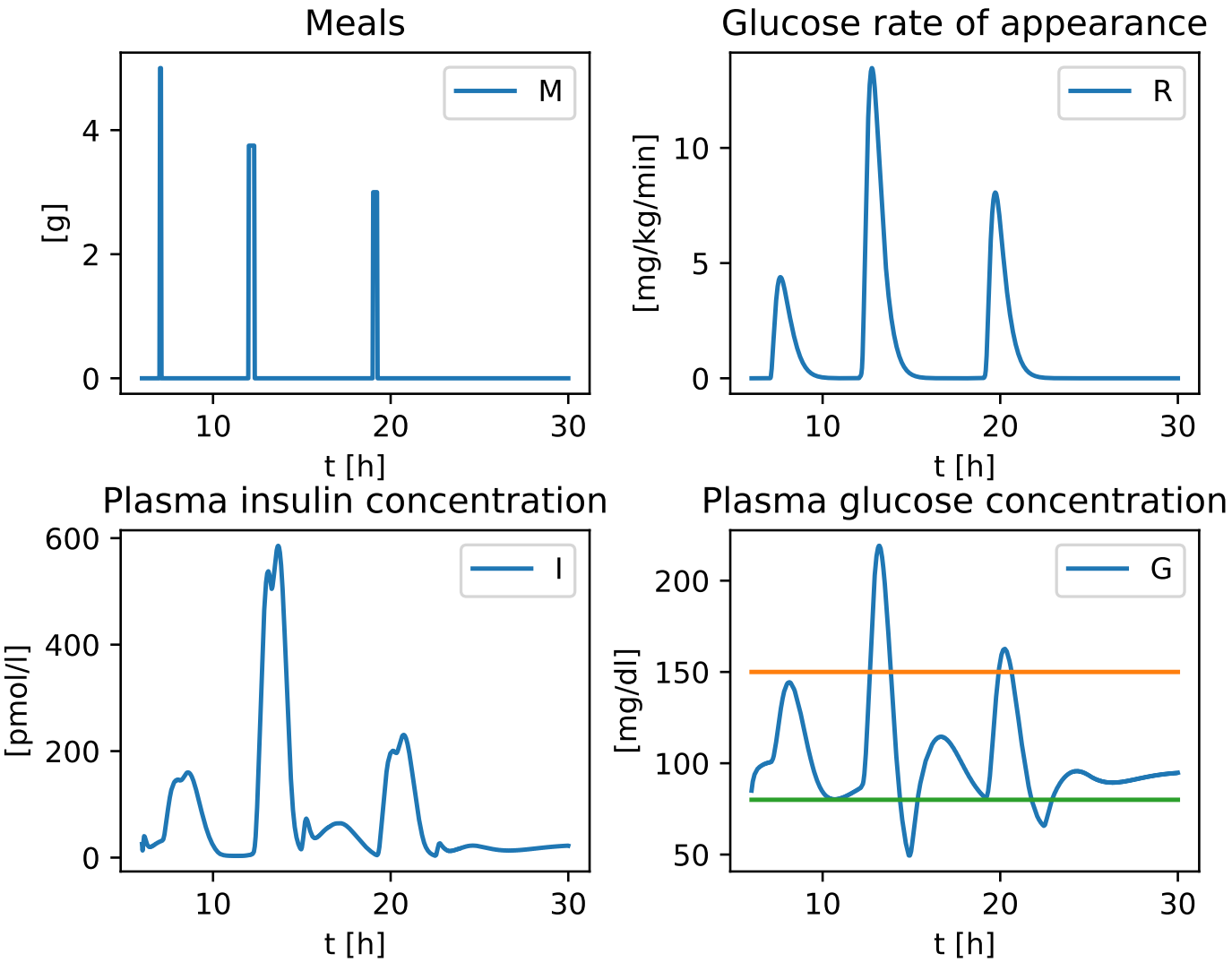
Numerical scheme:

- simple forward Euler scheme
- time step 1 min
- works fine! (as good as more sophisticated schemes)
- 1 min is also the data sampling time obtained from usual glucose subcutaneous sensors.
- good feature for parameter estimation.

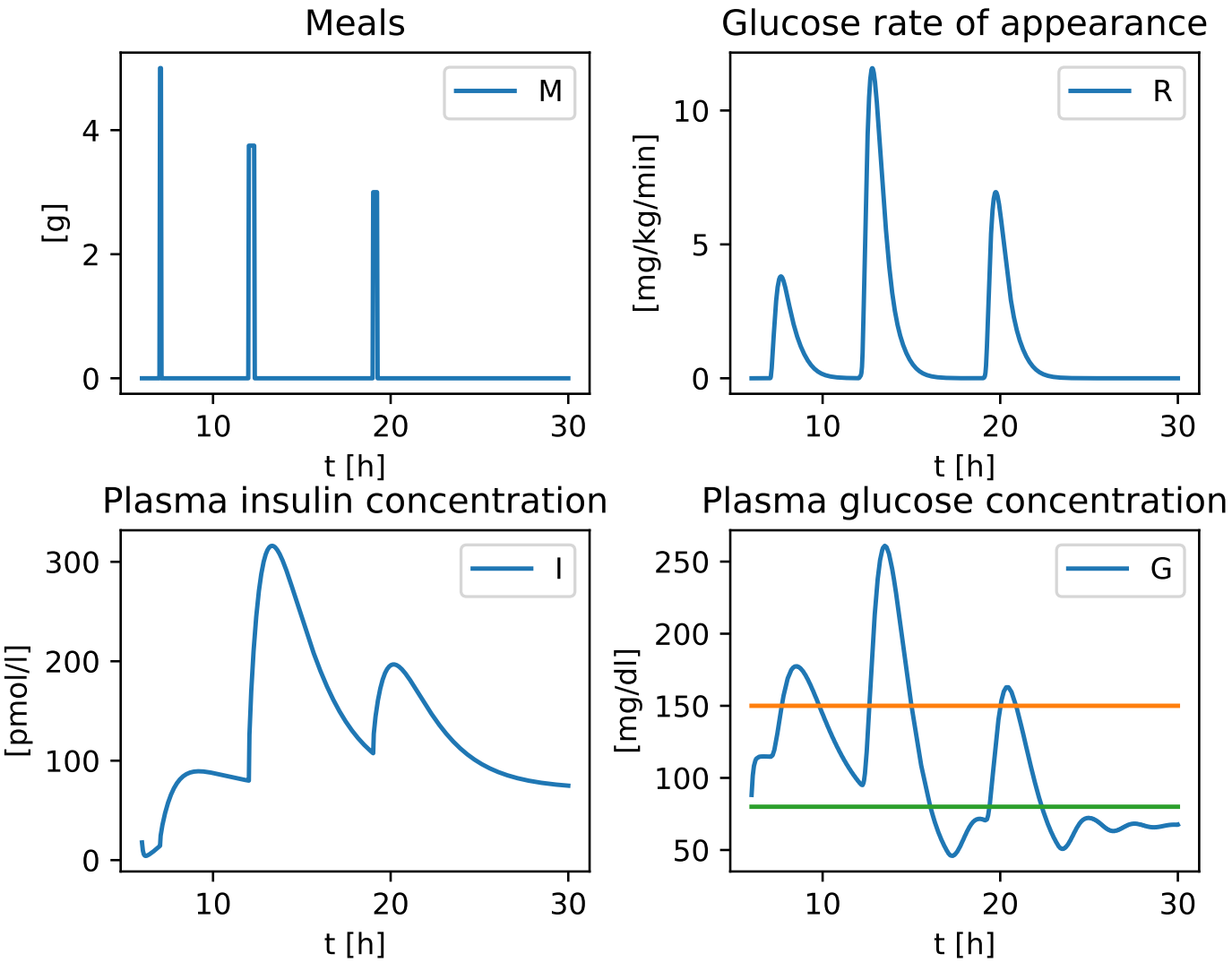
Displayed results: 30 hours of

- Meals
- Glucose rate of appearance
- Plasma insulin concentration
- Plasma glucose concentration
- $\mathcal{I}_{\text{target}}$

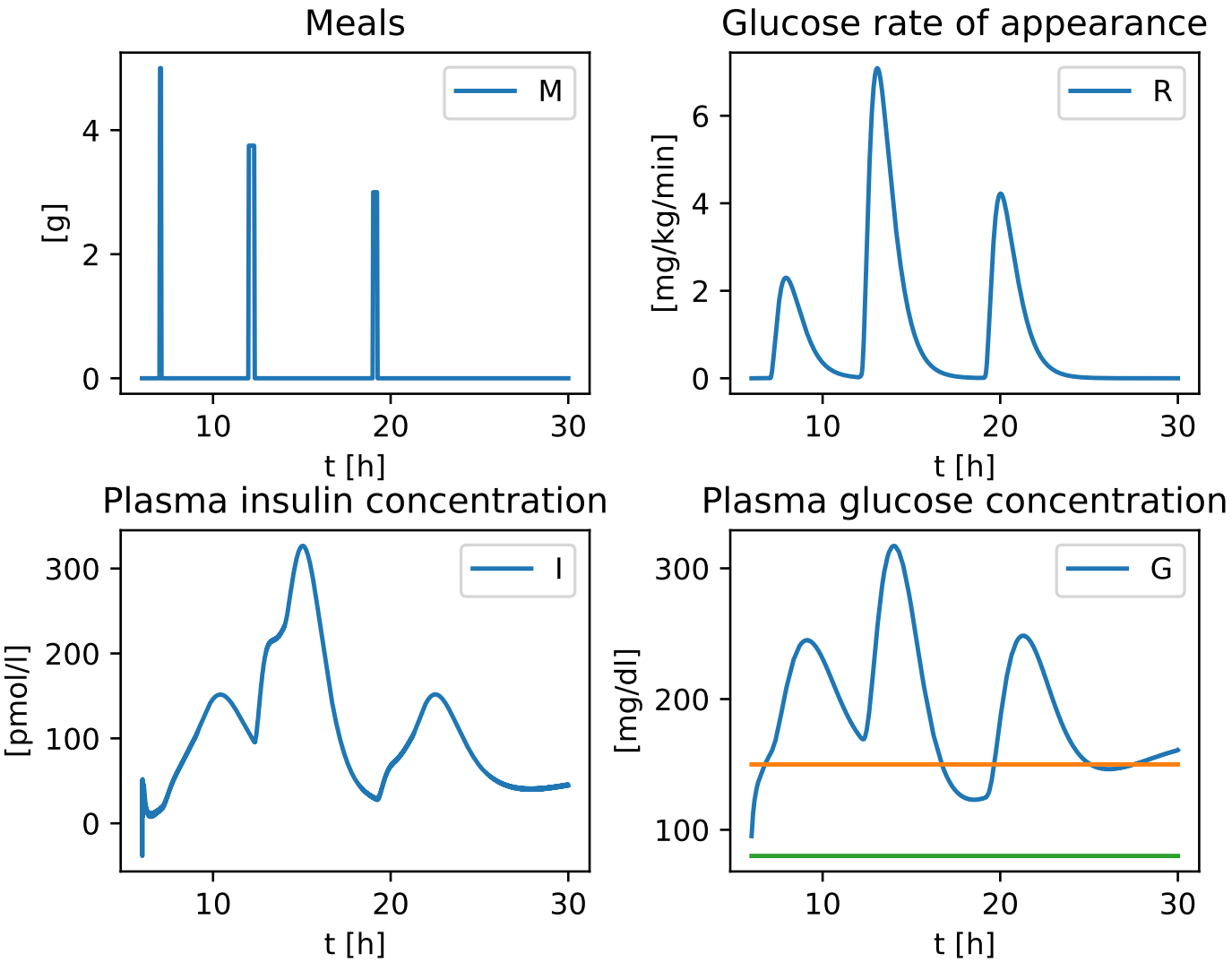
In silico healthy patient



In silico insulin-dependent diabetic patient



In silico non-insulin-dependent diabetic patient



Target and secure intervals

Control goal:

- Keep the plasma glucose rate within a target range $\mathcal{I}_{\text{target}}$ (typically $[80, 150]$ mg/dl).
- There is a larger secure range $\mathcal{I}_{\text{secure}} = [40, 350]$ mg/dl, out of which the subject is in immediate danger (hypo- or hyperglycemia).

Mathematical issues to address:

- Under which conditions can $\mathcal{I}_{\text{secure}}$ be ensured while using $\mathcal{I}_{\text{target}}$ to generate events?
- Can self-triggered control delays be designed to ensure that most time is spent in $\mathcal{I}_{\text{target}}$?

Trade-off between event-based control and an "expensive" continuous control.

Self-triggered control

- When a control is applied a decision is made on the next time the subcutaneous glucose rate will be measured: self-triggered control. Typical values:
  - 3 hours after an insulin infusion,
  - 1 hours after glucose ingestion.
- The presence of a control and its type (insulin infusion or glucose ingestion) triggers the time of the next measure and possibly the next control.
- The value of the control depends on the new state of the system (glycaemia).

This prescribed time delay can of course can be interrupted by an other event (event-triggered control).

Event-triggered control

Events:

- Theoretically: crossing the $\mathcal{I}_{\text{target}}$ boundaries.
  Usually not detected if alarms are disabled.
- Symptoms of hypo-/hyper-glycaemia.
- Meals, sporting activities or other events that can strongly impact the glucose rate.

Actions:

- a measure of glycaemia is done,
- the proper control is applied (insulin infusion or carbohydrate ingestion).

The control algorithm is very simple and only depends on the measured glycaemia, and the quantity of ingested carbohydrates if a meal is involved.

An example: insulin infusion rate

The control is far from continuous in terms of its variables, M and G:

$$\mathrm{IIR} = \mathrm{IIR}_c + \alpha(t)M + \beta(t)\lfloor\frac{G - G_{\max}}{G_{\text{step}}}\rfloor^+ - \beta(t)\lfloor\frac{G_{\min} - G}{G_{\text{step}}}\rfloor^+,$$

- G_{step} and $\lfloor\cdot\rfloor^+$: because computations are made with a tabulated values, and infusion can only be made in integer multiples of a given amount of insulin.
- $\alpha(t)$ and $\beta(t)$ are only nonzero close to meal times.

It is delayed, since it is infused not directly in blood:

$$\dot{I}_1 = -\gamma_1 I_1 + \mathrm{IIR}(t, M, G),$$

$$\dot{I}_2 = -\gamma_2 I_2 + \delta_1 I_1,$$

$$\dot{I} = -\gamma I + \epsilon_1 I_1 + \epsilon_2 I_2.$$

(All the coefficients are patient dependent.)

Work in progress

Still many things to do:

- Parameter sensitivity study.
- Parameter estimation.
- Response to mathematical questions.

Challenging issues:

- The control is both event- and self-triggered.
- The value that is measured by sensors (sub-cutaneous glucose rate) is not the one that we want to keep in a predefined range (blood glucose rate), but reflects its value a few minutes before.
- What in the case of capillary blood measures which cannot be done more than a few times a day (not enough to ensure a proper control)?

A toy model: minimal glucose-insulin model

Only three variables and equations.

$$\begin{aligned}
\partial_t G(t) &= -S_g(G(t) - G_b) - X(t)G(t), & G(t_0) &= G_0,\\
\partial_t X(t) &= k_3(S_i(I(t) - I_b) - X(t)), & X(t_0) &= 0,\\
\partial_t I(t) &= \gamma(G(t) - G_t)^+(t - t_0) - kI(t), & I(t_0) &= I_0.
\end{aligned}$$

Very few and easy to interpret parameters.

- Test sensitivity
- Control analysis

Conclusion

- The treatment of insulin-dependent diabetes can be modeled as a controlled ordinary differential system.
- This approach, contrarily to purely automation approaches, needs to carefully estimate the numerous parameters of the model.
- The analysis as an event-based control will help better understand and calibrate the treatment of diabetic subjects.