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

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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.

Compartmental model for diabetes includes compartments for Meals, Stomach, Carbohydrates, Insulin, Glucagon, healthy, diabetic, including delay, event-based control.
Compartments

**Carbohydrate Compartment**

\[
\begin{align*}
\dot{E}_G &= k_p_1 - k_p_2 G_P - k_p_3 I_d \\
E &= \max(k_e_1( G_P - k_e_2), 0) \\
U_{ii} &= F_{cns} \\
U_{id} &= (V_{m0} + V_{mx} X) G_t / (K_{m0} + G_t) \\
\dot{G}_P &= EGP + Ra - U_{ii} - E - k_1 G_P + k_2 G_t \\
\dot{G}_t &= -U_{id} + k_1 G_P - k_2 G_t \\
G &= G_P / VG
\end{align*}
\]
**Compartment**

**Meals**

**Insulin**

**Insulin Compartment**

\[
\begin{align*}
\dot{i}_{sc1} &= -(k_d + k_{a1})i_{sc1} + IIR(M, G) \\
\dot{i}_{sc2} &= k_d i_{sc1} - k_{a2} i_{sc2} \\
\dot{i}_l &= -(m_1 + m_3) i_l + m_2 i_p \\
\dot{i}_p &= -(m_2 + m_4) i_p + m_1 i_l + k_{a1} i_{sc1} + k_{a2} i_{sc2} \\
i &= i_p / V I \\
\dot{i}_1 &= -k_i (i_1 - i) \\
\dot{i}_d &= -k_i (i_d - i_1) \\
\dot{X} &= -p_2 u X + p_2 u (i - i_b)
\end{align*}
\]
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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- **Parameter estimation**: Identify the parameters with real patient glycaemia measures, when knowing the inputs and controls (meals, insulin infusions):

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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
- $I_{\text{target}}$
**In silico healthy patient**

- **Meals**
  - Graph showing the consumption of meals over time in grams (g).
  - **M** represents meals.

- **Glucose rate of appearance**
  - Graph showing the rate of glucose appearance in mg/kg/min.
  - **R** represents the glucose rate.

- **Plasma insulin concentration**
  - Graph showing the concentration of insulin in pmol/l.
  - **I** represents insulin.

- **Plasma glucose concentration**
  - Graph showing the concentration of glucose in mg/dl.
  - **G** represents glucose.

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In silico insulin-dependent diabetic patient

Cobelli’s model

Three types of in silico patients

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In silico non-insulin-dependent diabetic patient

Cobelli’s model

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Target and secure intervals

Control goal:

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

Mathematical issues to address:

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

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-based and self-triggered controls

Event-triggered control

Events:

- Theoretically: crossing the $I_{\text{target}}$ 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 $G$:

$$IIR = IIR_c + \alpha(t) M + \beta(t) \left[ \frac{G - G_{\text{max}}}{G_{\text{step}}} \right]^+ - \beta(t) \left[ \frac{G_{\text{min}} - G}{G_{\text{step}}} \right]^+,$$

- $G_{\text{step}}$ and $[\cdot]^+$: 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:

$$\dot{i}_1 = -\gamma_1 i_1 + IIR(t, M, G),$$
$$\dot{i}_2 = -\gamma_2 i_2 + \delta_1 i_1,$$
$$\dot{i} = -\gamma i + \epsilon_1 i_1 + \epsilon_2 i_2.$$

(All the coefficients are patient dependent.)
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.

\[
\begin{align*}
\partial_t G(t) &= -S_g(G(t) - G_b) - X(t)G(t), & G(t_0) &= G_0, \\
\partial_t X(t) &= k_3(S_i(I(t) - I_b) - X(t)), & X(t_0) &= 0, \\
\partial_t I(t) &= \gamma(G(t) - G_t)(t - t_0) - kl(t), & I(t_0) &= I_0.
\end{align*}
\]

Very few and easy to interpret parameters.

- Test sensitivity
- Control analysis
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.