Model-based closed-loop control for Type 2 Diabetes

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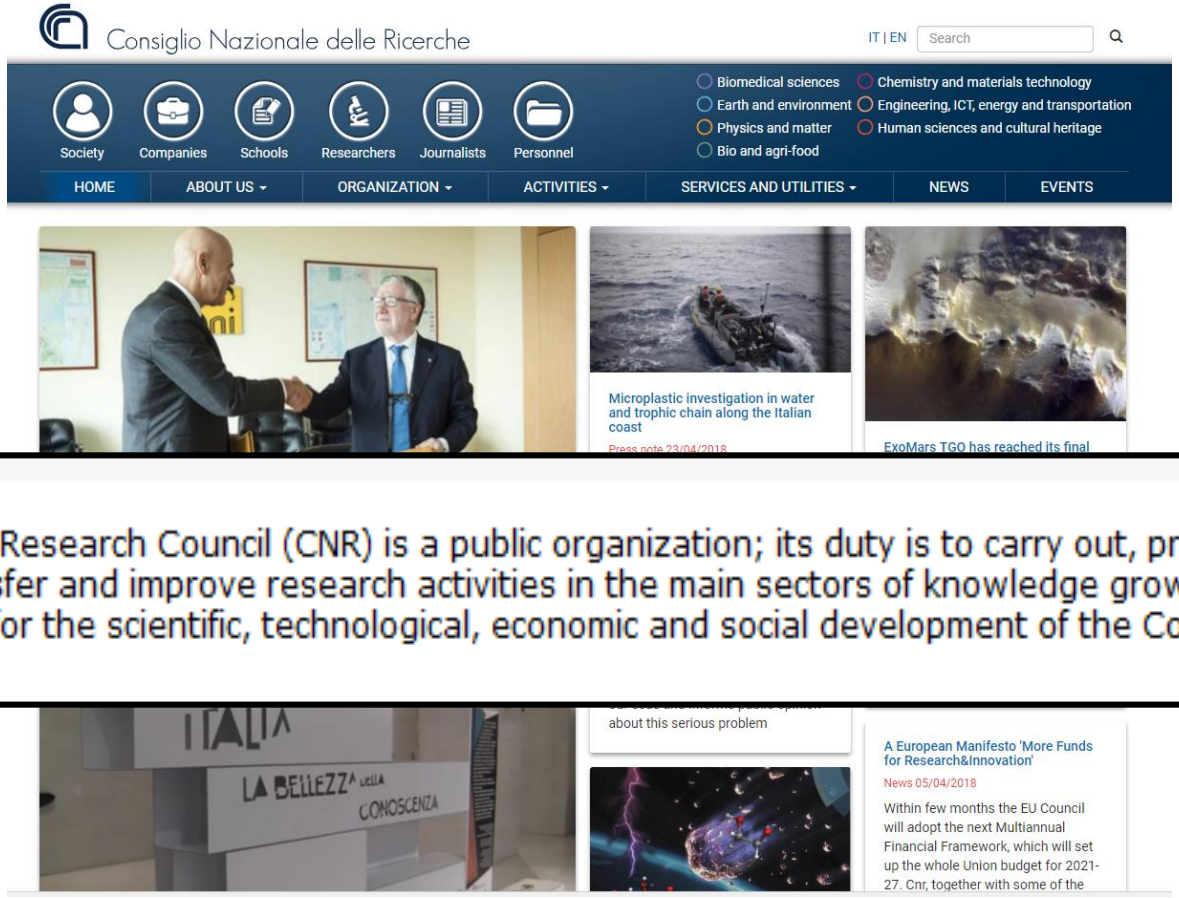
Consiglio Nazionale delle Ricerche

IASI Istituto di Analisi dei Sistemi ed Informatica "Antonio Ruberti"

National Research Council (CNR)

The **National Research Council (CNR)** is the largest public research institution in Italy, the only one under the Research Ministry performing multidisciplinary activities



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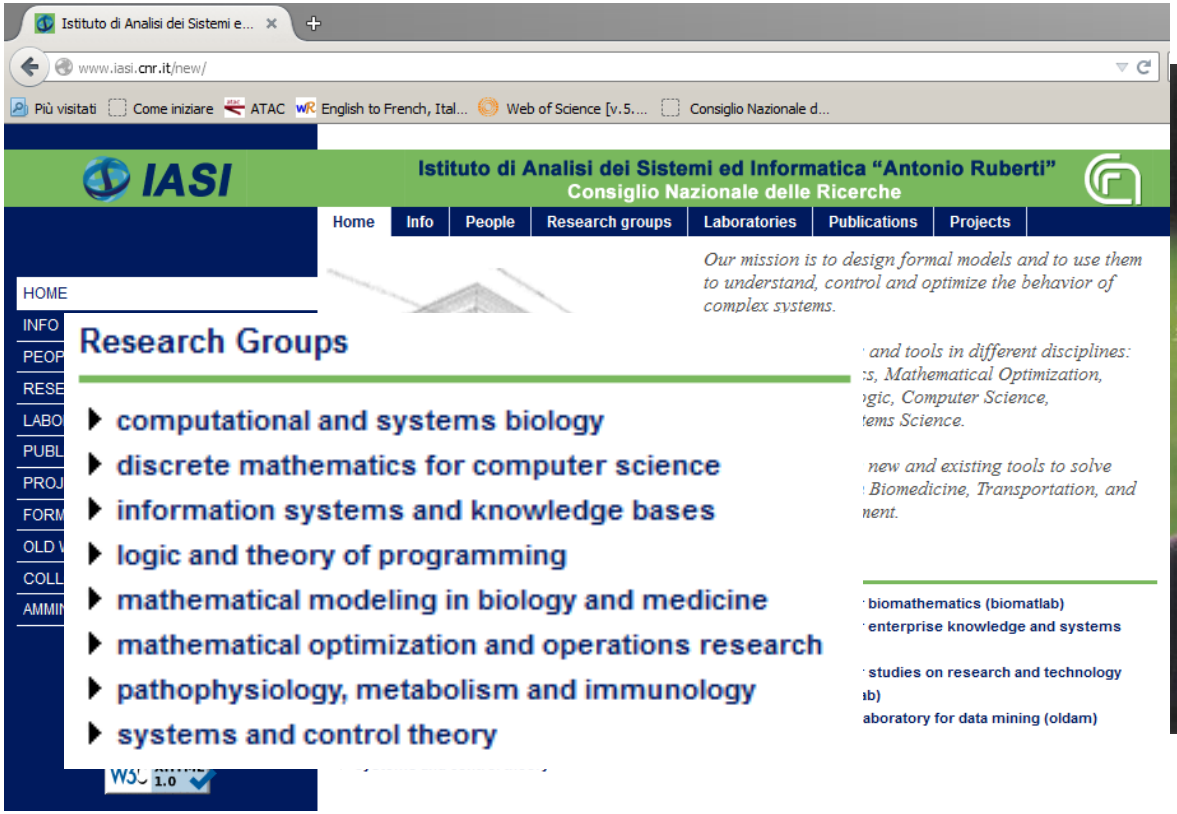


My research activity @ IASI

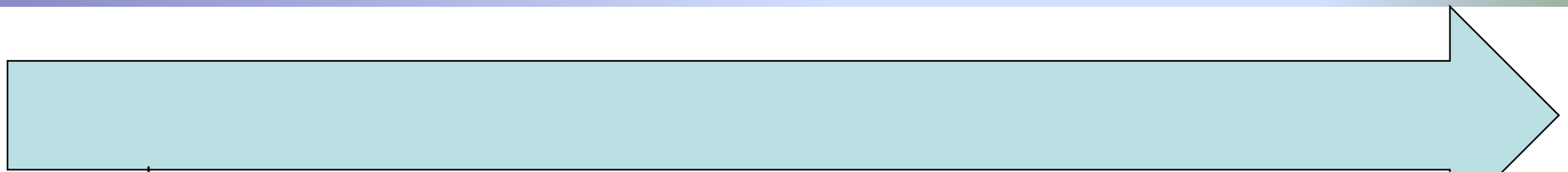
1) **Mathematical Control Theory**
   - ❑ Systems identification, state estimation, nonlinear filtering
   - ❑ Polynomial methods

2) **Modeling and control of the glucose-insulin system**
   - ❑ Short-term models (IVGTT)
   - ❑ Long-term models (diabetes progression)
   - ❑ Pulsatile insulin secretion
   - ❑ Artificial Pancreas

3) **Tumor Growth Control**

4) **Systems Biology**
   - ❑ Chemical Master Equations
   - ❑ Pharmacokinetics & Pharmacodynamics
   - ❑ Whole-cell models
   - ❑ Noise propagation in metabolic networks

My intersections with Óbuda University



2005, **Prague, IFAC WC**, Meeting with Levente Kovacs

2012, **Budapest, IFAC BMS**

2012, **Rome, Colloquia@IASI**

2013, **Vezprem**

2014, **San Diego, IEEE SMC**

2015, **Linz, ECC**

2017, **Melbourne, CDC**

2018, **Rome, SIMAI**

2018, **Lisbon, ECMTB**

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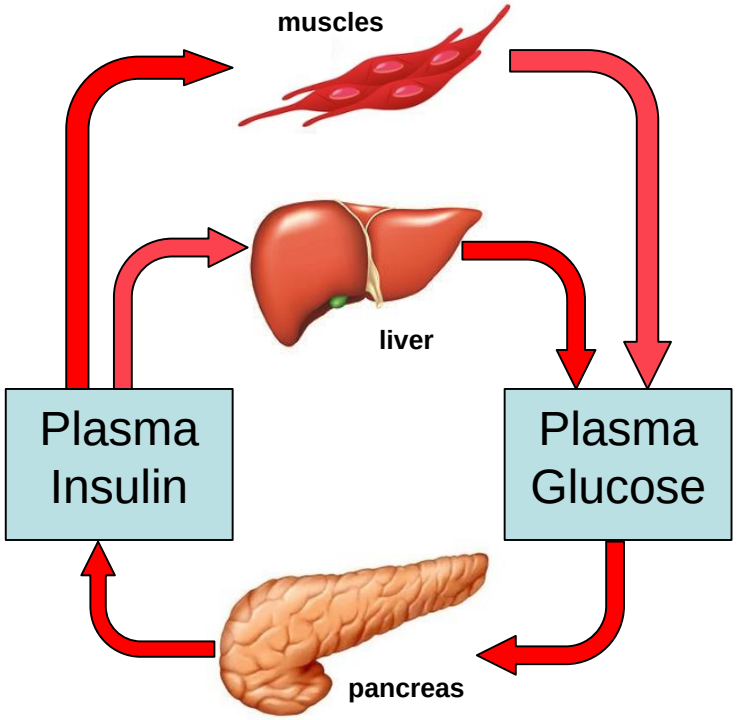
Physiological Glucose Control

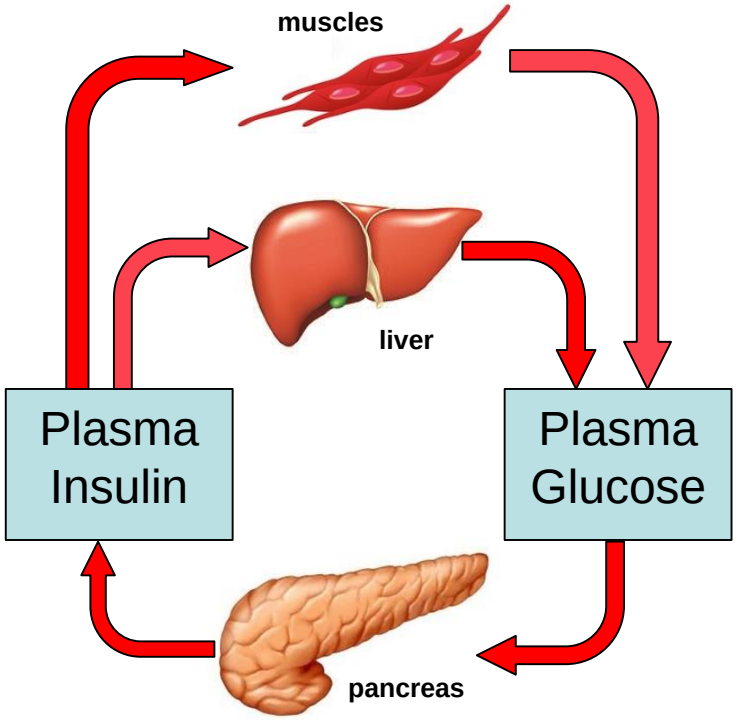


Glucose is the main energy source for the cells

Its basal concentration needs to be constrained within a narrow interval [60-90]mg/dl

Plasma glucose concentration is kept under control (mainly) by means of insulin hormone

Physiological Glucose Control



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Plasma glucose concentration is kept under control (mainly) by means of insulin hormone

High levels of glucose concentration (e.g. after a meal) stimulate **pancreatic insulin release** that:

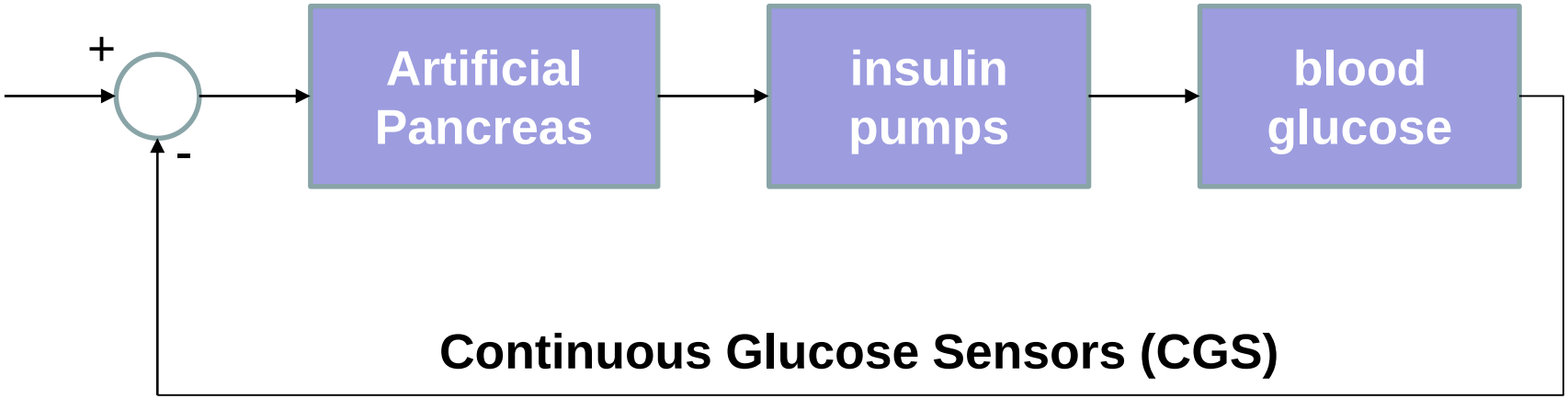
- enhance glucose uptake in muscles
- allows the liver to storage extra glucose (as glycogen)

Diabetes comprises metabolic disorders characterized by hyperglycemia resulting from impaired insulin secretion and/or action

- **Type 1 Diabetes Mellitus (T1DM):** absolute deficiency of insulin secretion
- **Type 2 Diabetes Mellitus (T2DM):** resistance to insulin action and/or inadequate insulin secretory response

Control Theory meets Glucose Control

Artificial Pancreas: refers to the set of glucose control strategies required for diabetic people and delivered by means of exogenous insulin administration



AP task: to close the loop automatically, safely, without any patient operation

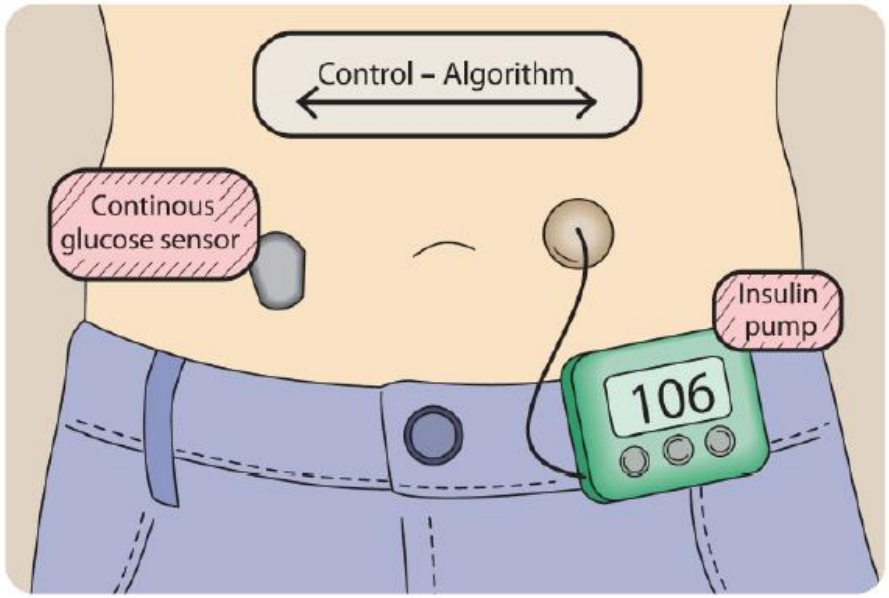
Subcutaneous injections:

- more widespread, since the dose is administered by the patients themselves
- modeling the absorption from the subcutaneous depot

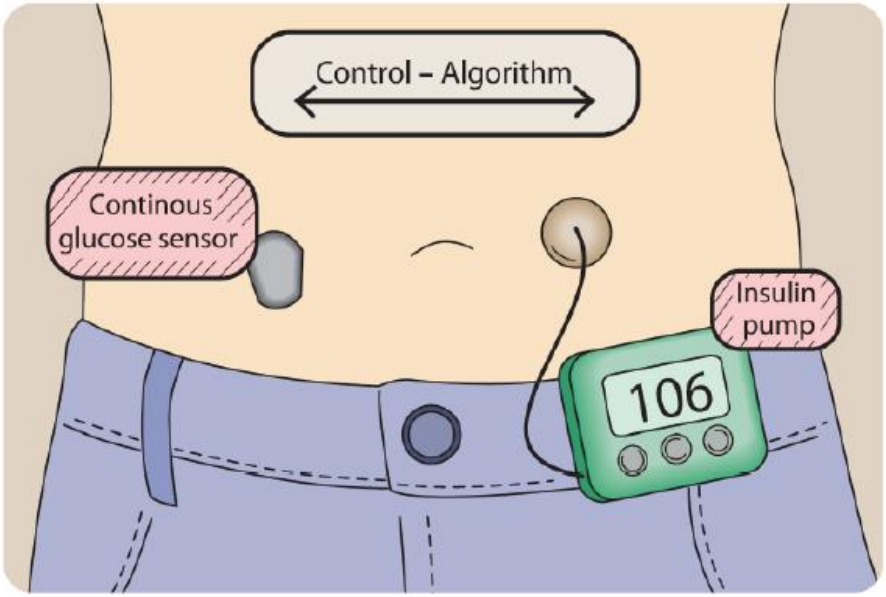
Intravenous infusions:

- rapid delivery with negligible delays
- more technology and a direct supervision of a physician (usually adopted in ICU)

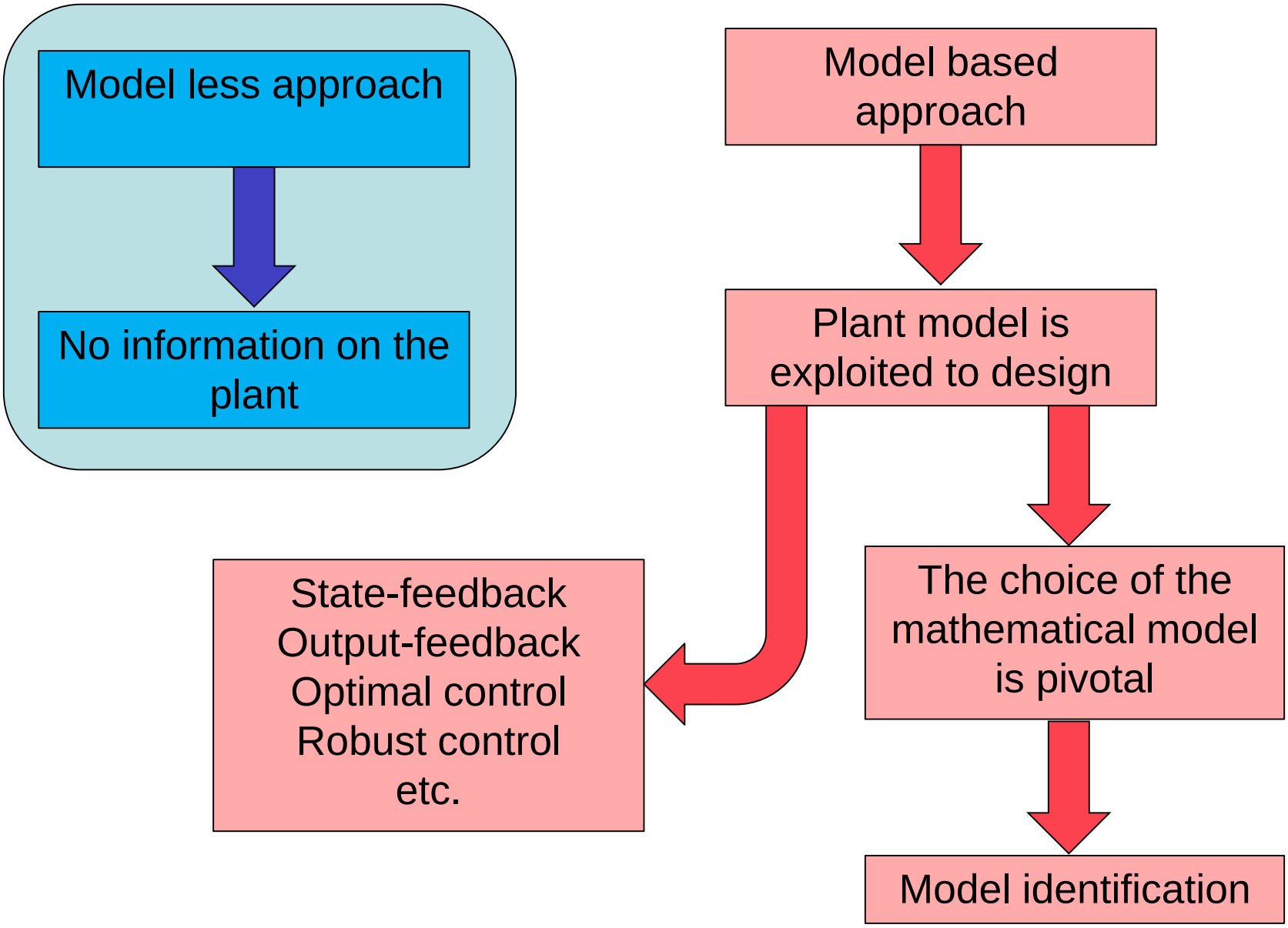
Subcutaneous insulin pumps



Continuous Glucose Sensors (CGS)



“Model less” vs “model based” approach



The AP: State of the art

- **AP for T1DM:**
  - many **model-less** approaches (e.g. PID, Fuzzy Logic, Model Predictive Control), most validated in closed-loop on a T1DM comprehensive model (UVA/Padua simulator, accepted by the FDA as a substitute of animal trials)
    - L. Magni, G. De Nicolao (Pavia), B. Kovatchev (Virginia), J. Doyle III (California)
  - **model-based** approaches, usually exploiting MPC/Robust Control
    - R. Hovorka (UK)
    - L. Kovacs (Hungary)

- **OUR contribute, AP for T2DM:**
  - Though less severe than T1DM, T2DM accounts for 85% to 95% of all cases of diabetes, thus having a relevant impact in worldwide NHS
  - **model-based** approach: we exploit a **Delay Differential Equation (DDE)** system to model the endogenous insulin delivery rate
  - observer-based control: we exploit glucose measurements to infer **real-time estimates** of the plasma insulin concentration
  - the control law is validated by closing the loop on a modified version of the UVA/Padua simulator

DDE models of the glucose-insulin system

- DDE models are known to better attain to glucose-induced pancreatic insulin release
- **De Gaetano, Arino (2000)** – DDE model to explain the Intra-Venous Glucose Tolerance Test (IVGTT)
- **Li, Kuang (2001)** – Introduce a family of DDE models
- … many other DDE models (more or less comprehensive) …
- **De Gaetano, Palumbo, Panunzi (2007)** – A minimal DDE model
- … many other DDE models (more or less comprehensive) …

Since 2008, we have been the only ones to exploit DDE models within the AP framework

Motivation: to design closed-loop control laws also for T2DM patients, for which the endogenous insulin release cannot be neglected

DDE model exploited for the AP

Discrete-Delay Differential Equation Model

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\,G(t)\,I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\,I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) \end{cases}$$

$$f(x) = \frac{\left(\frac{x}{G^*}\right)^{\gamma}}{1+\left(\frac{x}{G^*}\right)^{\gamma}}$$

- $G(t)$ [mM] plasma glucose concentration
- $I(t)$ [pM] plasma insulin concentration

Glucose kinetics

- K_{xgi} [$\text{min}^{-1}\ \text{pM}^{-1}$] rate of glucose uptake by tissues (insulin-dependent) per pM of plasma insulin concentration
- T_{gh} [min^{-1}(mmol/kgBW)] net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake
- V_G [L/kgBW] apparent distribution volume for glucose

DDE model exploited for the AP

Discrete-Delay Differential Equation Model

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\,G(t)I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\,I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) \end{cases} \qquad f(x) = \frac{\left(\frac{x}{G^*}\right)^{\gamma}}{1+\left(\frac{x}{G^*}\right)^{\gamma}}$$

Insulin kinetics

- K_{xi} [min^{-1}] apparent first-order disappearance rate constant for insulin
- T_{iGmax} [min^{-1}(pmol/kgBW)] maximal rate of second-phase insulin release
- V_I [L/kgBW] is the apparent distribution volume for insulin
- τ_g apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations
- γ [♯] progressivity with which the pancreas reacts to circulating glucose
- G^* [mM] glycemia at which the insulin release is the half of its maximal rate

DDE model exploited for the AP

Discrete-Delay Differential Equation Model

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\,G(t)I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\,I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) \end{cases} \qquad f(x) = \frac{\left(\frac{x}{G^*}\right)^{\gamma}}{1+\left(\frac{x}{G^*}\right)^{\gamma}}$$

- **It conforms to established physiological concepts**:
  - it presents a realistic pancreatic IDR
  - no unobservable states variables are considered
- It may be used for any closed loop control strategy on type 1 or type 2 diabetic patients
- It can be adopted to perform clinical trials on healthy subjects
- It is easy enough to be used to synthesize control laws which are proven to work, at least theoretically

DDE model exploited for the AP: properties

Discrete-Delay Differential Equation Model

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\,G(t)I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\,I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) \end{cases} \qquad f(x) = \frac{\left(\frac{x}{G^*}\right)^{\gamma}}{1+\left(\frac{x}{G^*}\right)^{\gamma}}$$

- **It is statistically robust**, in that its parameters are statistically identifiable with very good precision by means of standard perturbation experiments, such as the Intra-Venous Glucose Tolerance Test (IVGTT):
  - healthy subjects: **Panunzi et al. [2007]**
  - obese, insulin-resistant subjects: **Panunzi et al. [2010]**
- **It is a Minimal Model**, in the sense that according to a "minimal" set of independent parameters, it allows to very well resemble the physiology of the glucose/insulin kinetics: **Panunzi et al. [2007]**
- **It is mathematical coherent**, in that exhibits satisfactory properties of the solutions: **Palumbo et al. [2007]**:
  - positivity, boundedness and persistence of solutions
  - stability of a single positive equilibrium point

Closed-loop control strategy

No approximation, linearization or discretization

→ A geometric approach is exploited to cope with the important model nonlinearities

Dangerous glucose oscillations have to be avoided

→ The control law aims at tracking a desired smooth trajectory

The control law must be feasible (only positive insulin infusions)

→ The control is switched off whenever it requires negative infusions

Only glucose measurements are exploited

→ Insulin is estimated by means of a state observer for DDE systems

The control law is validated onto a different, independent model

→ Massive simulations are carried out to test safety and efficacy onto populations of Virtual Patients built upon the UVA/Padua simulator

Closed-loop control: main steps

1) **Feedback linearization (geometric approach):**
   - the control law is designed according to a state transformation that allows to re-write the system in a linear, ODE form
   - a complete knowledge of the state of the system (glucose and insulin) is assumed
   - *Palumbo, Pepe, Panunzi, De Gaetano, 2009*

2) **Observer-based control law:**
   - a state observer estimates in real-time plasma insulin concentration from glucose measurements
   - *Palumbo, Pepe, Panunzi, De Gaetano, 2012*

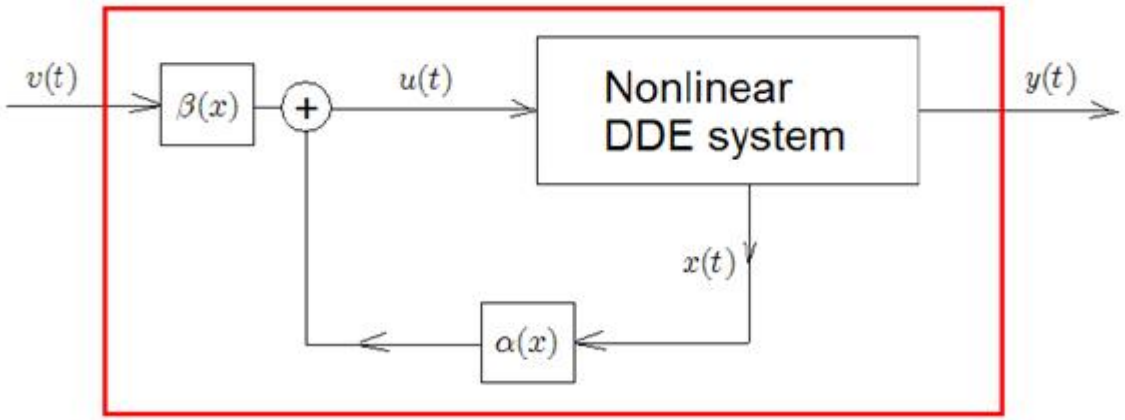
3) **Validation on a population of Virtual Patients (VP)**
   - the UVA/Padua simulator is exploited
   - a virtual IVGTT experiment is carried out to estimate the DDE minimal model parameters that best fit the average VP
   - *Palumbo, Pizzichelli, Panunzi, De Gaetano, Pepe, 2014*

Closed-loop control: feedback linearization

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\, G(t)\, I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\, I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) + u(t) \end{cases}$$

State feedback linearization with delay cancellation

Oguchi et al. [2002] Germani et al. [2003]



- The *red box* system is **linear** w.r.t. a suitably defined coordinate state transformation

Closed-loop control: feedback linearization

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi} G(t) I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi} I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) + u(t) \end{cases}$$

- Coordinate transformation:

$$Z(t) = \begin{bmatrix} Z_1(t) \\ Z_2(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ \dot{G}(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ -K_{xgi} G(t) I(t) + \frac{T_{gh}}{V_G} \end{bmatrix}$$

$$\begin{cases} \dot{Z}_1 = Z_2(t) \\ \dot{Z}_2(t) = S\left(G(t), I(t), G(t-\tau_g)\right) - K_{xgi} G(t) u(t) \end{cases}$$

$$u(t) = \frac{S\left(G(t), I(t), G(t-\tau_g)\right) - v(t)}{K_{xgi} G(t)}$$

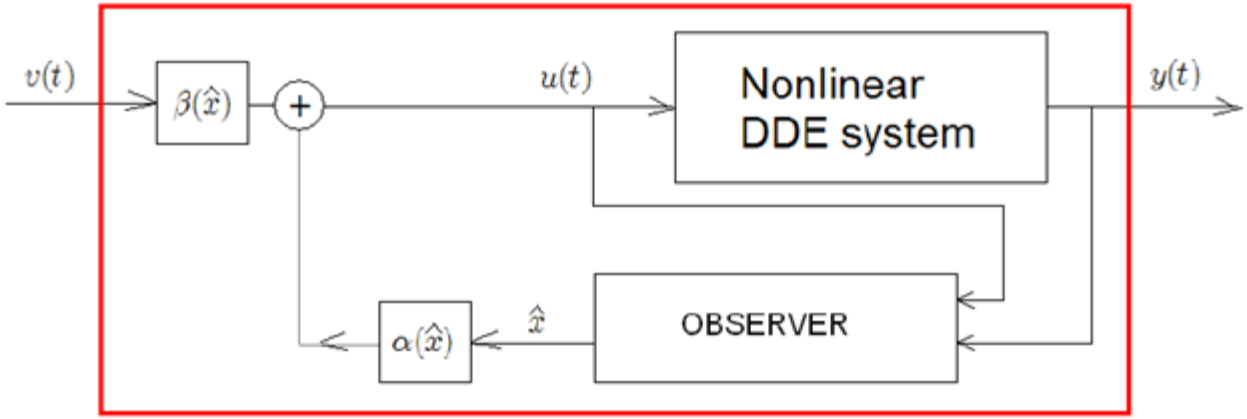
$$\dot{Z}(t) = A_b Z(t) + B_b v(t)$$

Closed-loop control: state observer

$$\begin{cases} \dfrac{dG}{dt} = -K_{xgi}\, G(t)\, I(t) + \dfrac{T_{gh}}{V_G} \\ \dfrac{dI}{dt} = -K_{xi}\, I(t) + \dfrac{T_{iGmax}}{V_I} f\left(G(t-\tau_g)\right) + u(t) \end{cases}$$

State-feedback would require also insulin measurements

On the other hand, we use a **state-observer**, by means of only glucose measurements: Germani, Manes, Pepe 2001



Closed-loop control: Validation

A **minimal model** of the glucose-insulin system to design the insulin therapy, and a **different, more detailed, comprehensive model** to test in silico the control scheme

The crucial point to ensure attainable experiments is to make the two models consistent each other

Steps of the validation algorithm

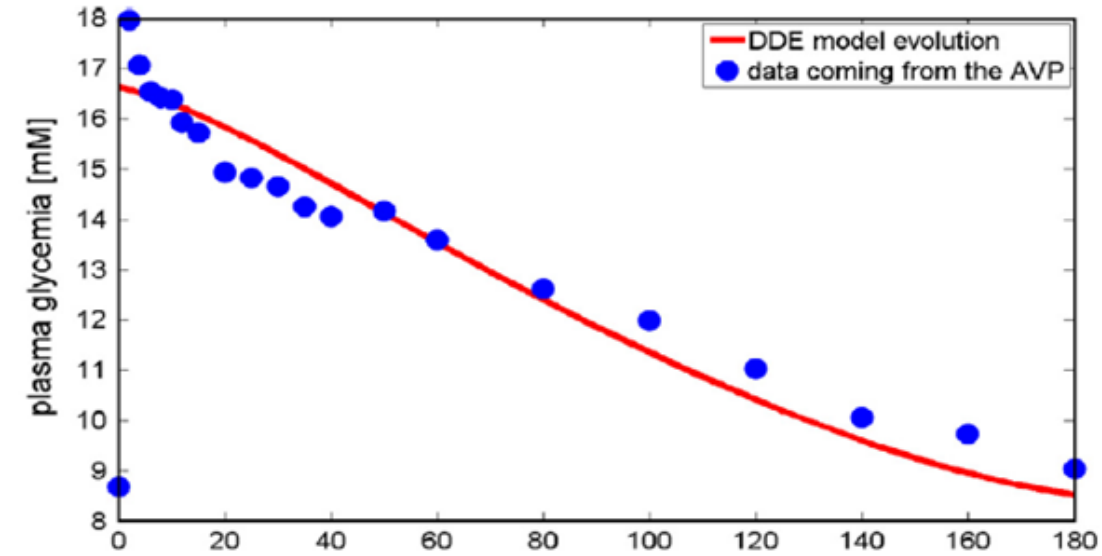
1. A Virtual Patient (VP) is chosen by setting the comprehensive model parameters
2. The DDE minimal model is fitted on the VP by implementing *in silico* an IVGTT
3. The control law parameter are tuned on the DDE minimal model
4. The control law is closed on the VP

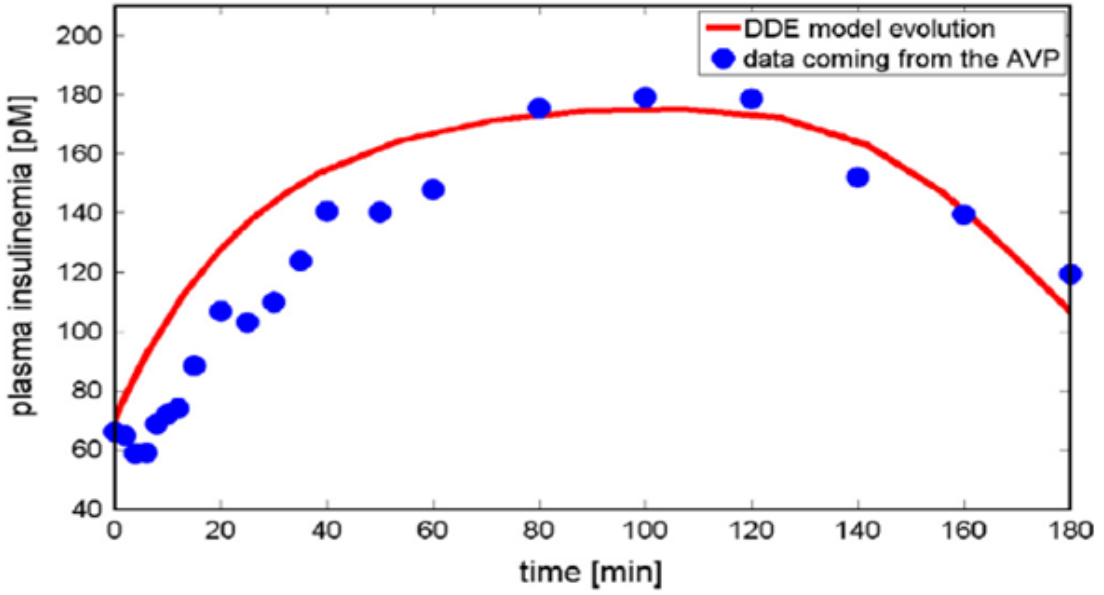
Validation: *in silico* IVGTT

The **IVGTT** consists in administering intra-venously a glucose bolus after an overnight fasting and then sampling plasma glucose and insulin concentrations during the following 3 hours

$$G(0) = G_b + \frac{D_g}{V_G} \qquad I(0) = I_b + I_\Delta \frac{D_g}{V_G}$$

Once the DDE minimal model is identified, the control law is designed and control parameters are tuned upon DDE simulations





Validation: discretization + failures

We need a discrete control scheme because:

- **glucose sensors** provide quite reliable measurements of plasma glycemia at given sample times, whose frequency is limited by the time needed to analyze plasma glucose on a bed-side analyzer
- **insulin pumps** are used to administer insulin by means of piecewise constant infusions

The virtual environment accounts for:

- glucose measurement errors

$$G_m(k\Delta) = G(k\Delta) + C_g G(k\Delta) N_k$$

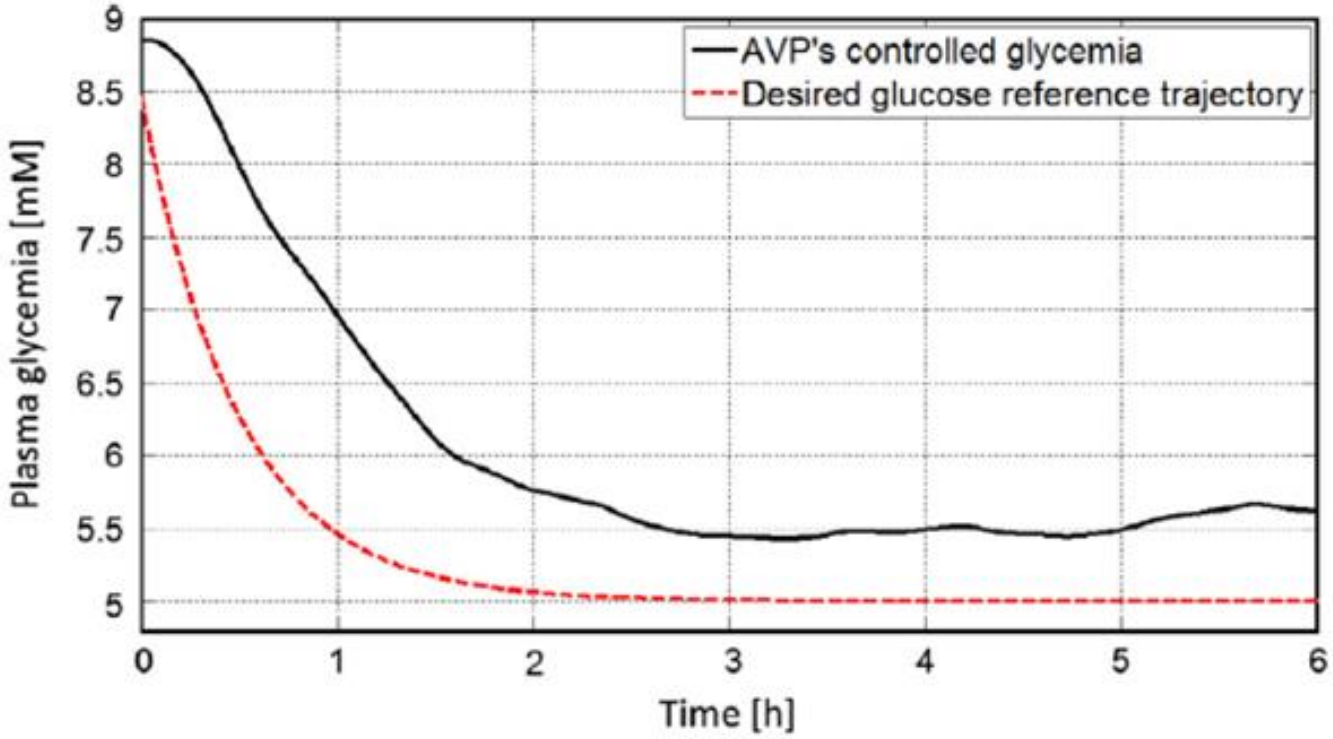
$C_g = 5\%$

- insulin pump malfunctioning

$$u_m(k\Delta) = u(k\Delta) + C_u u(k\Delta) M_k$$

$C_u = 15\%$

Validation: simulations on the Average VP

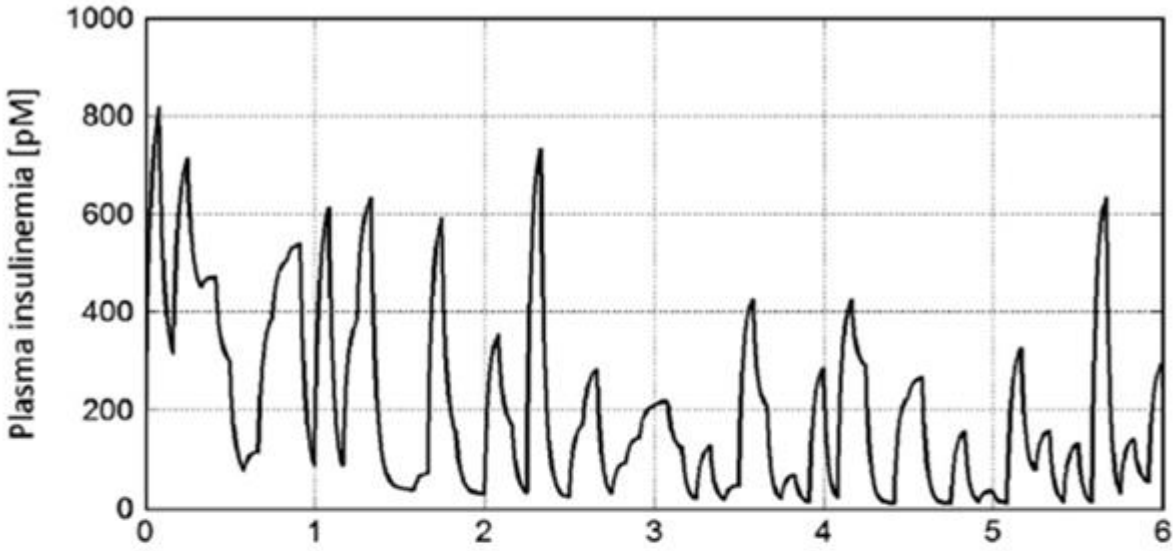


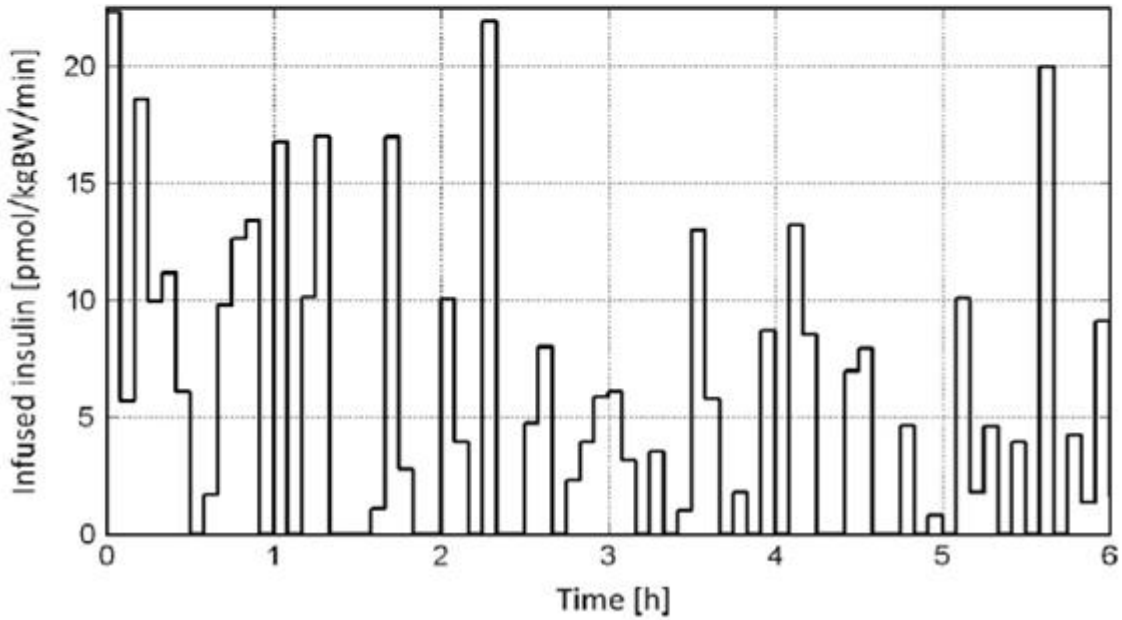
Patient at rest

No meals

Δ = 5min

Validation: simulations on the Average VP





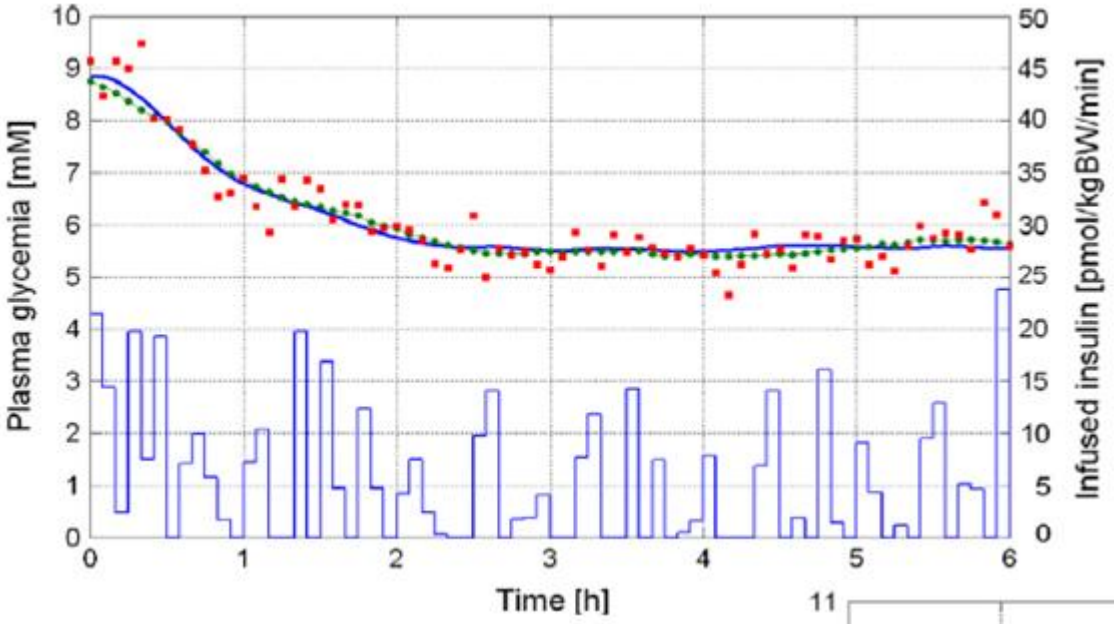
Patient at rest

No meals

Δ = 5min

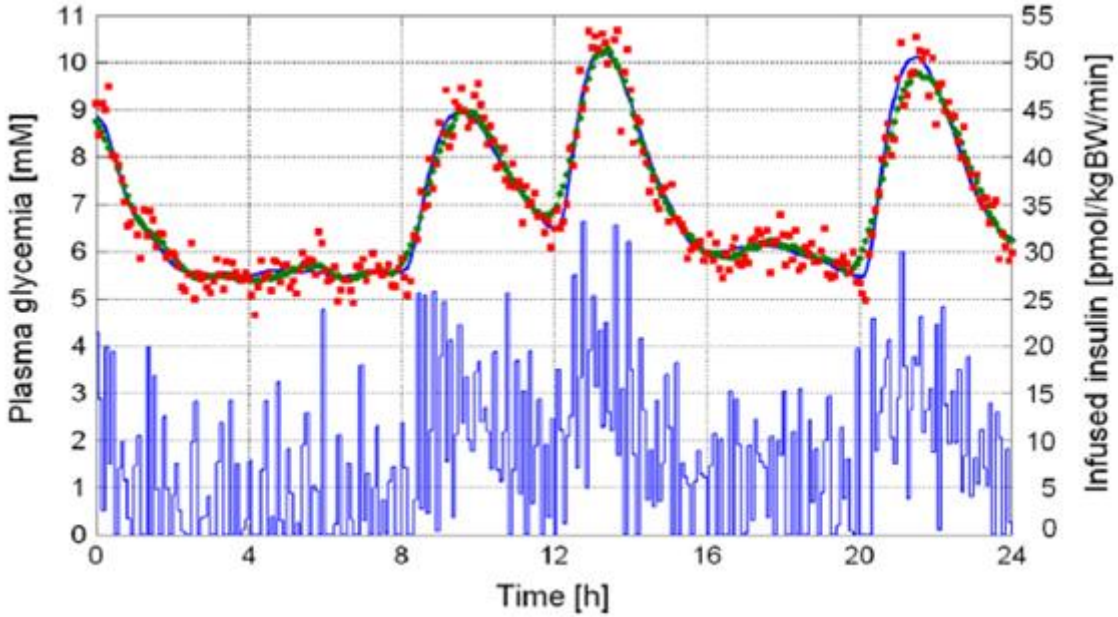
Whenever the required input becomes negative, the control law is switched off

Validation: simulations on the Average VP



Red squares are noisy measurements

24h simulation, including three meals



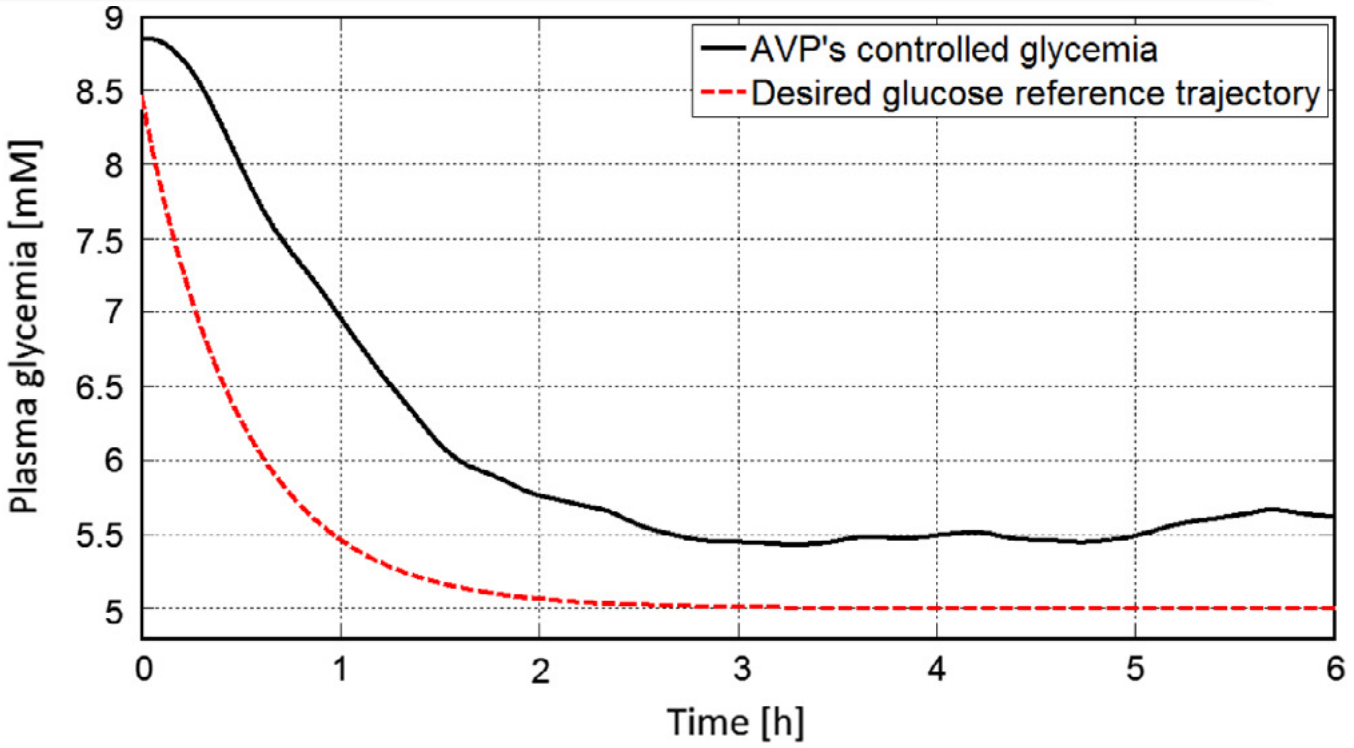
Validation: safety criteria

Safety

- **severe hypoglycemia**, when plasma glycemia falls to 2 mM or lower, within the simulation period
- **hypoglycemia**, when plasma glycemia falls to 3.3 mM or lower, but always remains above 2 mM, within the simulation period

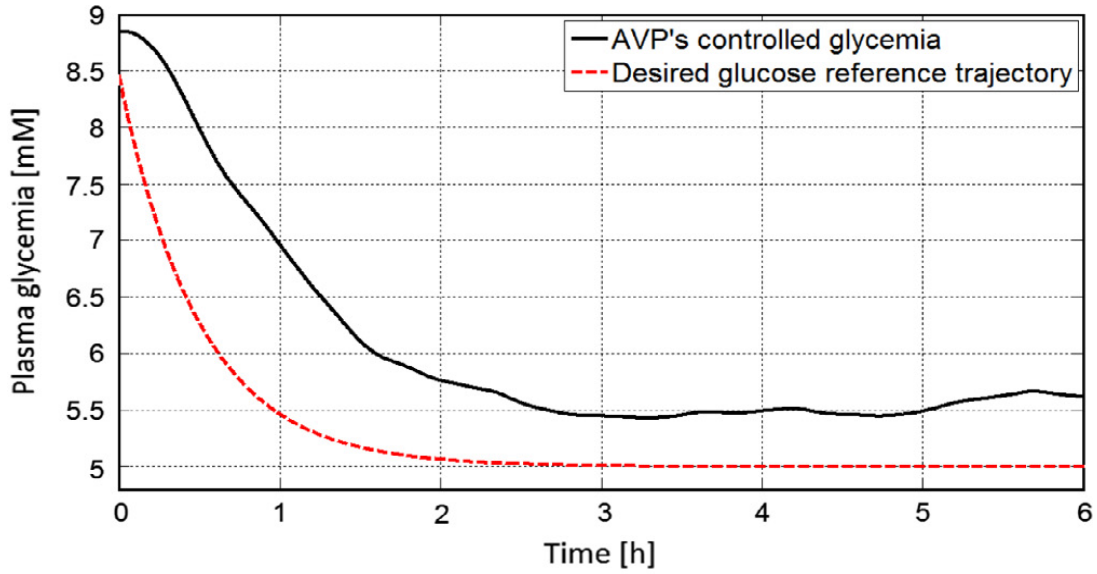
Patient at rest

No meals



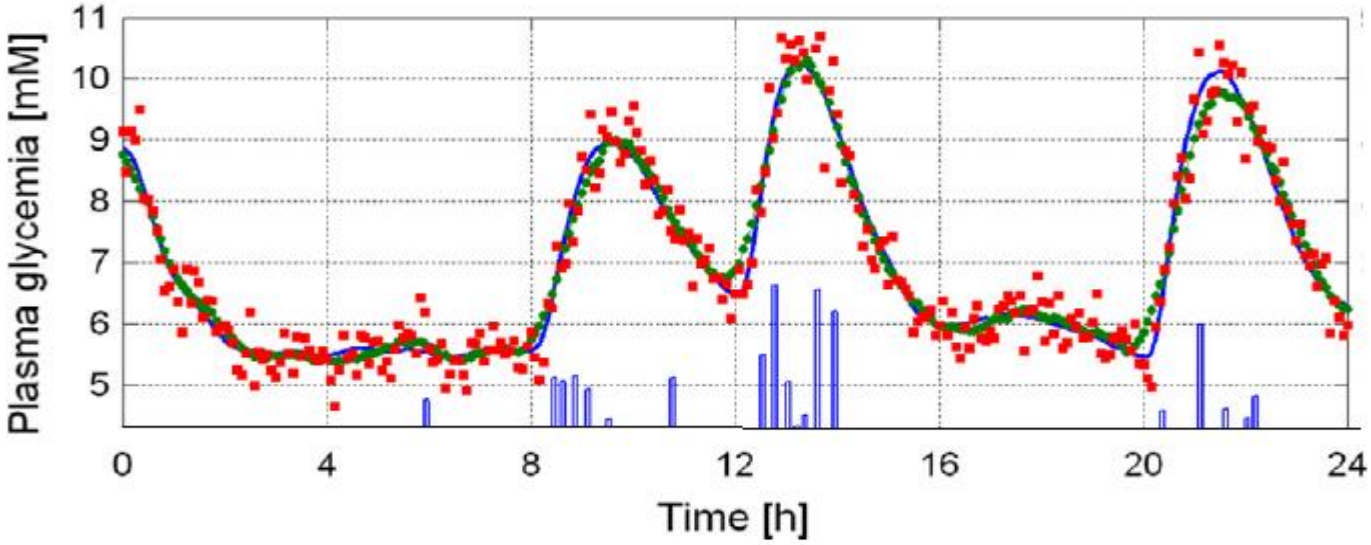
Validation: efficacy criteria at rest

- **excellent efficacy**, when plasma glycemia is constrained below 6mM within the first 3 h of treatment
- **good efficacy**, when plasma glycemia is constrained below 7 mM (but not below 6 mM) within the first 3 h of treatment
- **satisfactory efficacy**, when plasma glycemia is constrained below 8 mM (but not below 7 mM) within the first 3 h of treatment
- **unsatisfactory efficacy**, when plasma glycemia is not constrained below 8 mM within the first 3 h of treatment



Validation: efficacy criteria during meals

- **excellent** efficacy when, for each meal, within 2 h from the meal administration and during the period before the successive meal, glycemia is constrained below 8 mM
- **satisfactory** efficacy when excellent efficacy fails but, for each meal, within the 2 h from the meal administration and during the period before the successive meal, glycemia is constrained below 11 mM
- **unsatisfactory** efficacy when, at least for one meal, after the 2 h from the meal administration, glycemia is not constrained below 11 mM



Validation: efficacy criteria results

Label and fractional efficacy results on a population of fasting 10,000 VPs.

Efficacy	Δ (min)	Label (%)	Fractional (%)
Excellent	5	69.37	93.16
Good	5	30.47	6.83
Satisfactory	5	0.16	0.01
Unsatisfactory	5	0.00	0.00
Excellent	15	65.69	94.37
Good	15	34.29	5.63
Satisfactory	15	0.02	0.00
Unsatisfactory	15	0.00	0.00

Fasting population

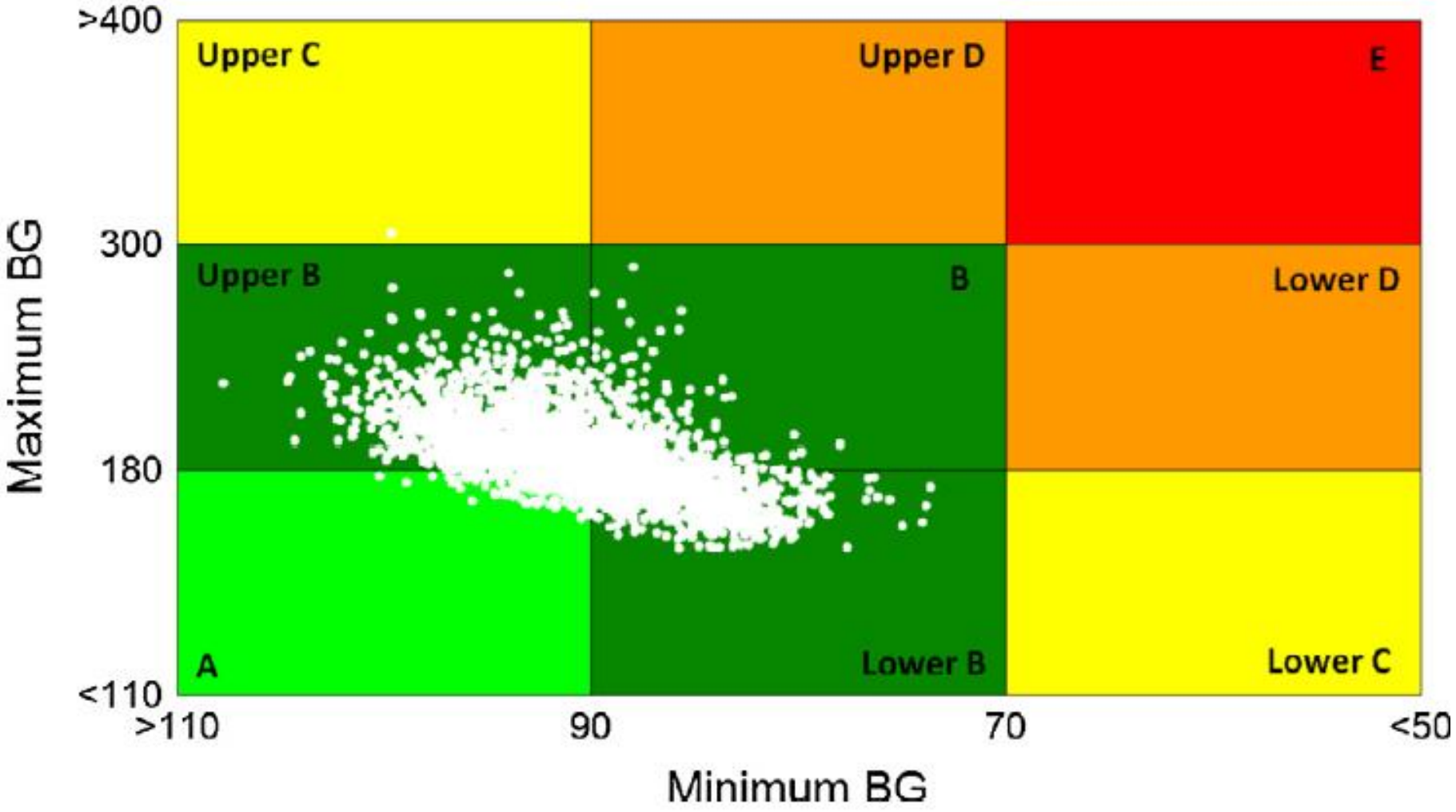
Label and fractional efficacy results on population of 10,000 VPs, during meals administration.

Efficacy	Δ (min)	Label (%)	Fractional (%)
Excellent	5	5.07	83.72
Satisfactory	5	92.47	16.22
Unsatisfactory	5	2.46	0.06
Excellent	15	2.85	82.82
Satisfactory	15	92.63	17.03
Unsatisfactory	15	4.52	0.15

24h simulation, with meals

Validation: Control Variability Grid

ΔT = 15min



Conclusions (AP)

- The present AP research investigates glucose control strategies for T2DM
- A minimal DDE model-based approach is considered
- No approximation, linearization are considered to simplify the model nonlinearities
- An observer-based control law is designed that exploits plasma glucose measurements and insulin estimates
- Validation is carried out on a population of Virtual Patients built up on a different comprehensive model of the glucose-insulin system

Ongoing research

- Continuous-discrete control
- Robustness design (symbolic approach)
- ‘‘Big Glucose’’: ghrelin, leptin, etc.

References

DDE Minimal Model

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- S. Panunzi, P. Palumbo, A. De Gaetano, "*A discrete single-delay model for the Intra-Venous Glucose Tolerance Test*", Theor Biol Med Model, 4(35), 2007

Observer-based glucose control

- P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, "*Robust closed-loop control of plasma glycemia: a discrete-delay model approach*", Discrete Cont Dyn-B, 12(2), 455-468, 2009
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