Smart Technologies for Biomedical and Environmental Applications
A joint DEWS@UNIVAQ – IASI@CNR Laboratory

Model-based control of plasma glycemia: in quest of robustness

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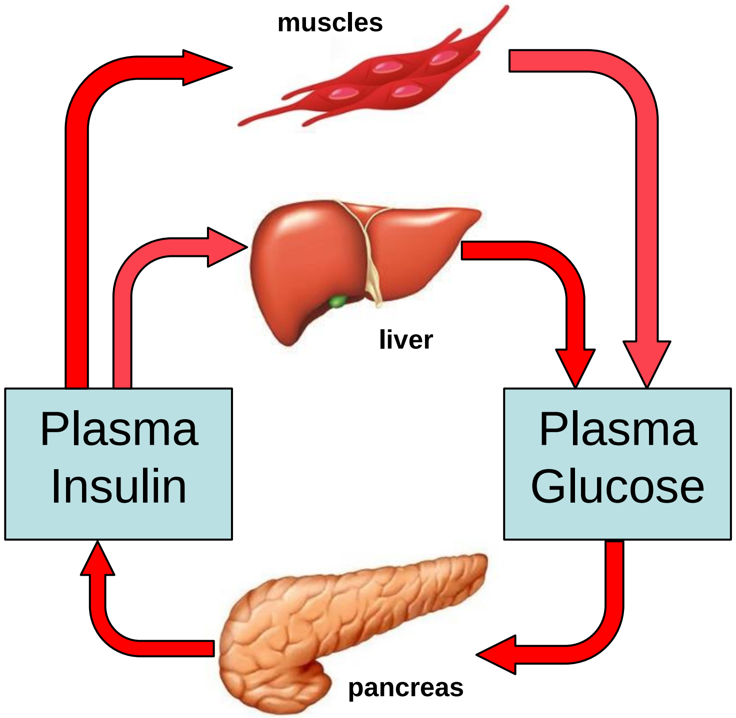
Physiological Glucose Control



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

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

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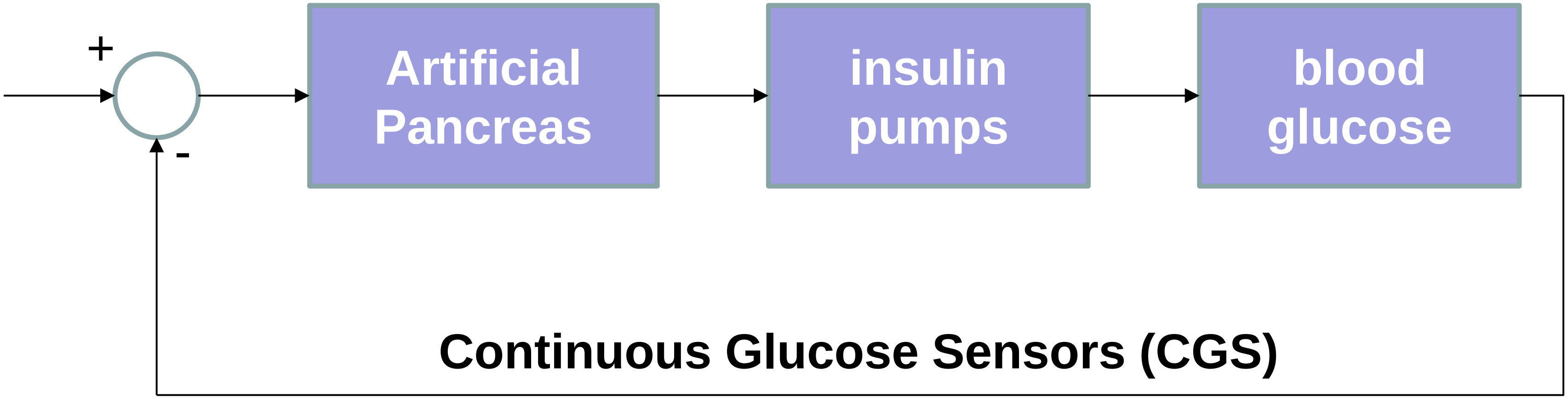
Control Theory meets Glucose Control

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)

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Model-less vs Model-based approach

Model-less approach: no models of the glucose-insulin system are considered to design the control law

- It provides a control rule for the insulin infusion rate mainly based on experimental data
- The controllers mimic the pancreatic glucose response
- Its successful working often relies on human expertise in the adjustments of the algorithm parameters to different patients

Model-based approach: the control law is designed by exploiting the model of the glucose-insulin system.

- The control problem may be treated mathematically and optimal strategies may be determined
- It allows to test *in-silico* a control strategy before involving patients
- It requires a preliminary identification step to adapt the model to a given patient

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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 Model Predictive Control
    - R. Hovorka (UK), Moog (CNRS)

- **OUR contribute, AP for T2DM:**
  - model-based approach: we exploit a **Delay Differential Equation (DDE)** system to model the endogenous insulin delivery rate
  - we exploit glucose measurements to infer **real-time estimates** of the plasma insulin concentration (possibly by means of observers)
  - the control law is designed by means of **glucose measurements** (and **insulin estimates**)
  - the control law is **validated** by closing the loop on a modified version of the UVA/Padua simulator

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Challeges in the AP

- ✓ From a control-theoretic viewpoint, insulin is a **non-negative input** (it reduces glycemia)
- ✓ Dealing with secretion **delays**
- ✓ **Food** as a source of **uncertainty**
- ✓ Random variations (hormones, stress, physical activity…)
- ✓ The subcutaneous compartment introduces filtering/delay effects (Insulin On-Board, IOB)
- ✓ Continuous-discrete system

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Minimal DDE model

Model equations Adapted from Panunzi et al. (2007), Palumbo et al. (2007)

Insulin input

Glycemia [mM] $$\frac{dG(t)}{dt} = -k_{xgi}\mathrm{G(t)I(t)} + \frac{T_{gh}}{V_G}$$

Insulinemia [pM] $$\frac{dI(t)}{dt} = -k_{xi}\mathrm{I(t)} + \frac{T_{iGmax}}{V_I}\varphi\left(G\left(t-\tau_g\right)\right) + u(t)$$

Parameters

- k_{xgi}: insulin sensitivity index
- T_{gh}: net balance between hepatic glucose output and insulin-independent zero-order glucose tissue uptake
- V_G, V_I: apparent distribution volume for glucose, insulin
- k_{xi}: first-order disappearance rate constant for insulin
- τ_g: apparent delay with which the pancreas varies secondary insulin
- release in response to varying plasma glucose concentrations
- T_{iGmax}: maximal rate of second-phase insulin release

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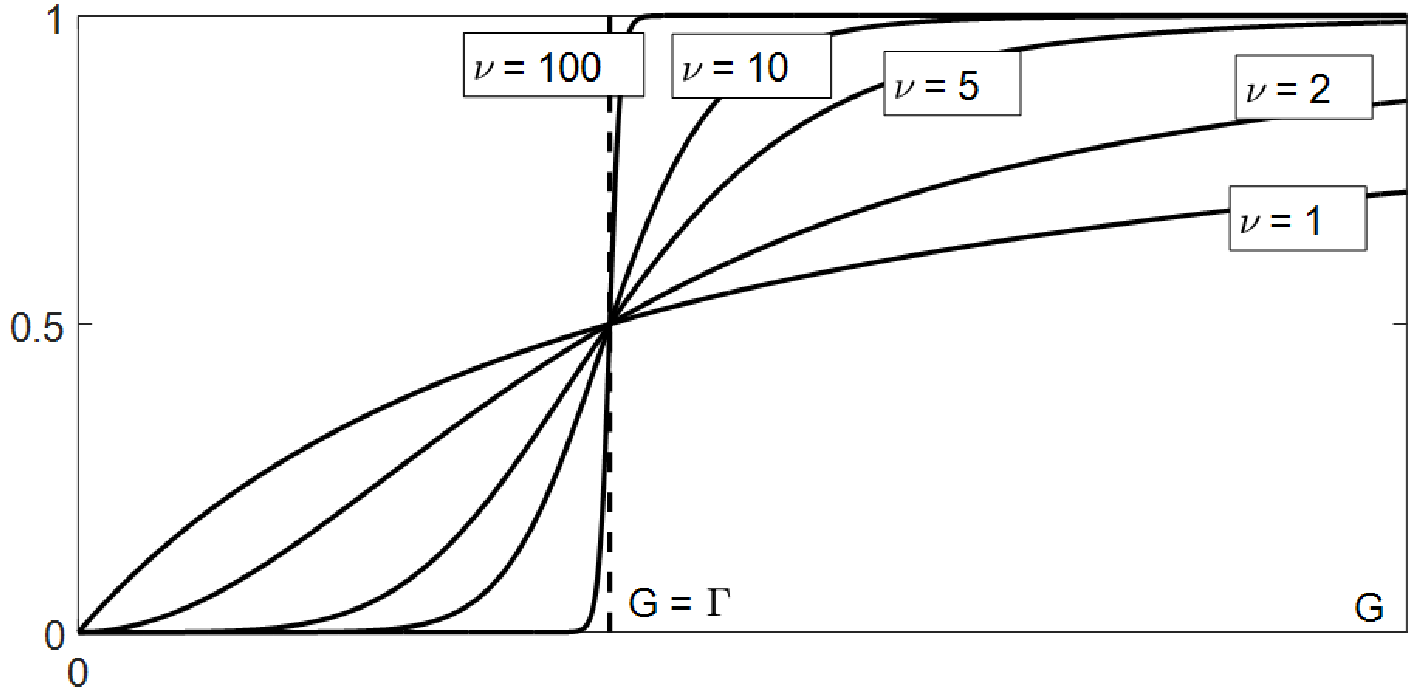

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Minimal DDE model

- **It is mathematically well-posed**
  - Single locally attractive equilibrium (basal conditions)
  - Positive, limited solutions
  - Global stability guaranteed under conditions on parameters
  - Physiologically limited pancreatic secretion ability

- **It is statistically robust**
  - Parameters statistically identifiable with very good precision via standard perturbation experiments, such as IVGTT

- **It is a Compact Model**
  - “minimal” set of independent (physiological) parameters

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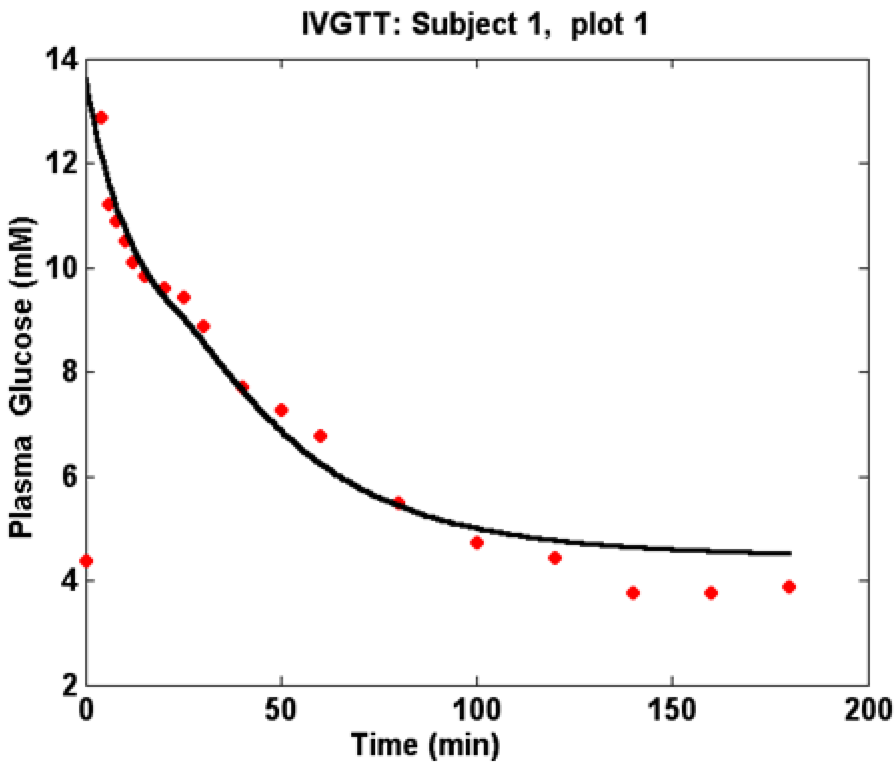
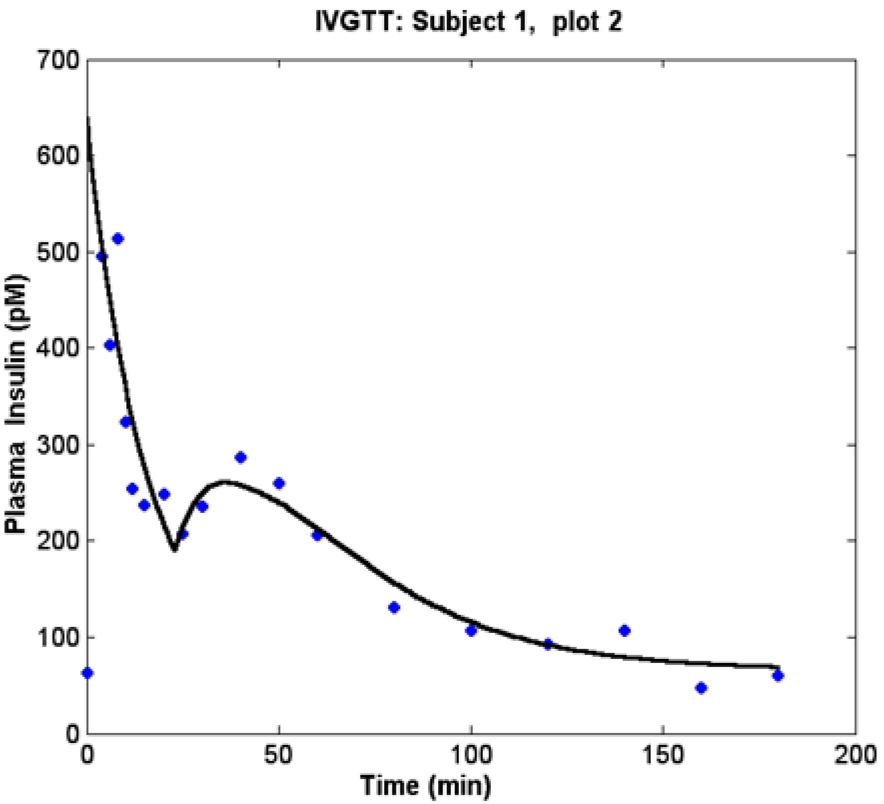
Minimal DDE model





Model-based control

Nonlinear feedback control for time-delay systems

The aim of control is to **reduce a high basal glycemia** to a lower level, according to a **reference glucose trajectory**, by means of intravenous/subcutaneous insulin administration

We **do not** want:

- dangerous glucose oscillations: avoid hypoglycemias
- not physically implementable control laws (avoid negative insulin infusions)

Therefore:

- the reference glucose trajectory needs to be slow enough
- in-silico simulations are essential to synthesize/validate an effective control law

Need for **robustness** (relying on fitting the model on a patient)

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Publication/results

European Journal of Control (2012)6:591–606

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European Journal of Control

Time-Delay Model-Based Control of the Glucose–Insulin System, by Means of a State Observer

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Publication/results

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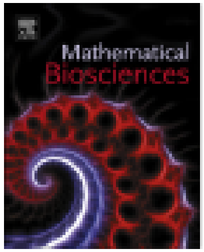

Model-based control of plasma glycemia: Tests on populations of virtual patients

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Publication/results

Luenberger-Like Observers for Nonlinear Time-Delay Systems with Application to the Artificial Pancreas

THE ATTAINMENT OF GOOD PERFORMANCE

ALESSANDRO BORRI, FILIPPO CACACE,
ANDREA DE GAETANO, ALFREDO GERMANI,
COSTANZO MANES, PASQUALE PALUMBO,
SIMONA PANUNZI, and PIERDOMENICO PEPE

Publication/results

16 IEEE TRANSACTIONS ON CONTROL SYSTEMS TECHNOLOGY, VOL. 28, NO. 1, JANUARY 2020

Semiglobal Sampled-Data Dynamic Output Feedback Controller for the Glucose–Insulin System

Mario Di Ferdinando, Pierdomenico Pepe, Pasquale Palumbo, Simona Panunzi, and Andrea De Gaetano

2019 18th European Control Conference (ECC)
Napoli, Italy, June 25-28, 2019

Symbolic models approximating possibly unstable time–delay systems with application to the artificial pancreas

Giordano Pola, Alessandro Borri, Pierdomenico Pepe, Pasquale Palumbo and Maria D. Di Benedetto