LPV models for the Artificial Pancreas controller design

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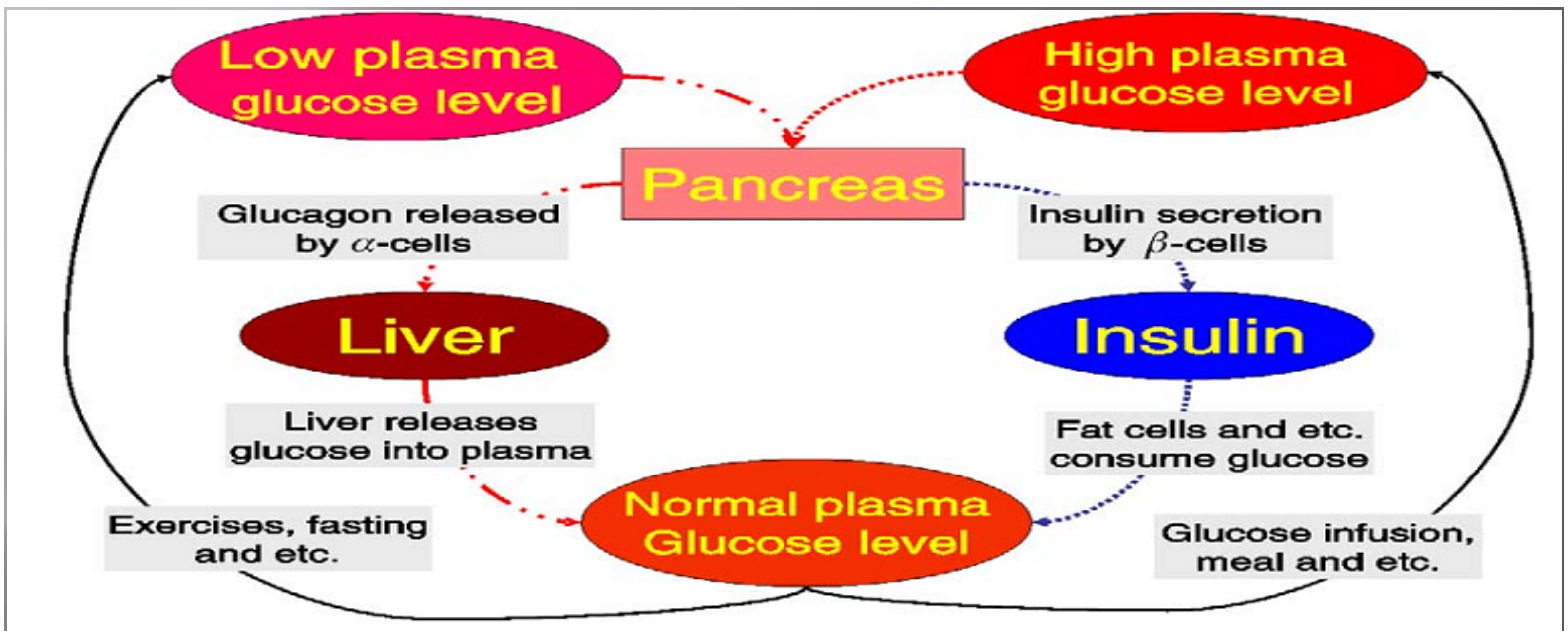
Personnel: CONICET, ITBA, UNQ, UNLP, UVa. Insulin pumps: ROCHE donation

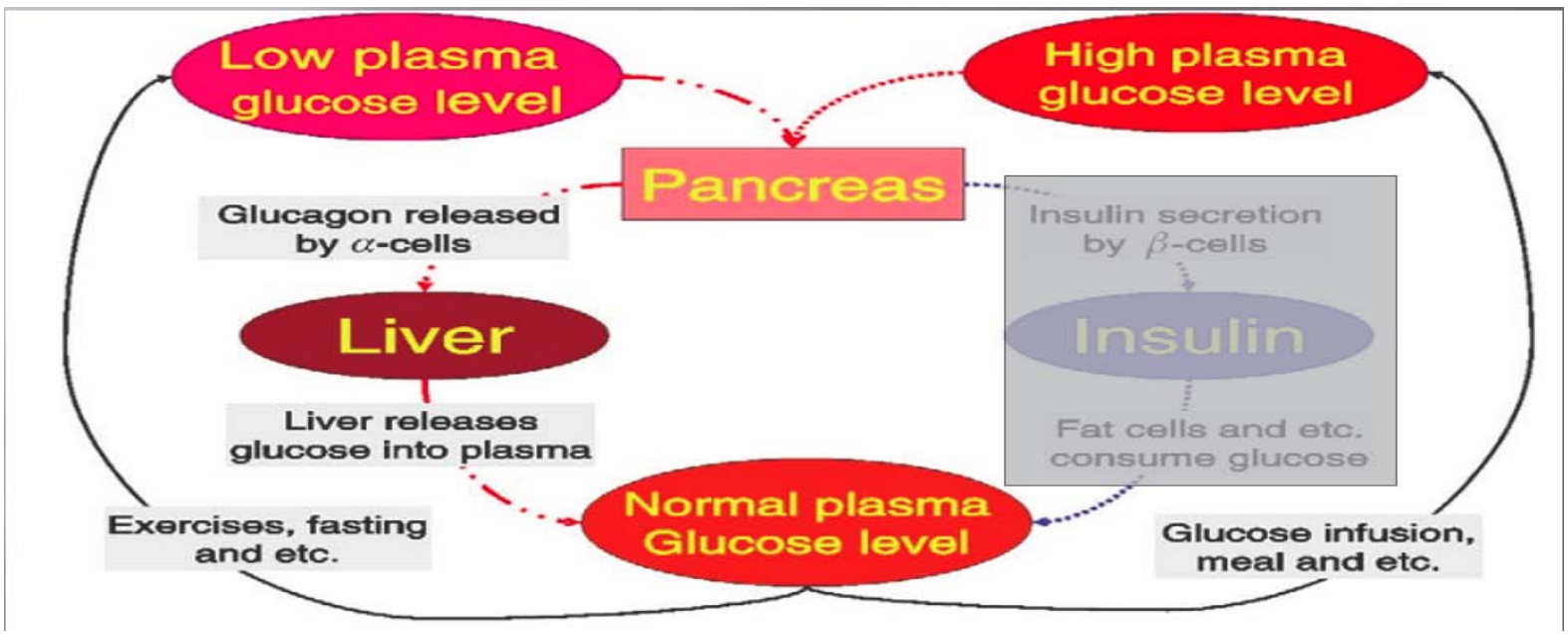
ITBA

CONICET

Diabetes Physiology



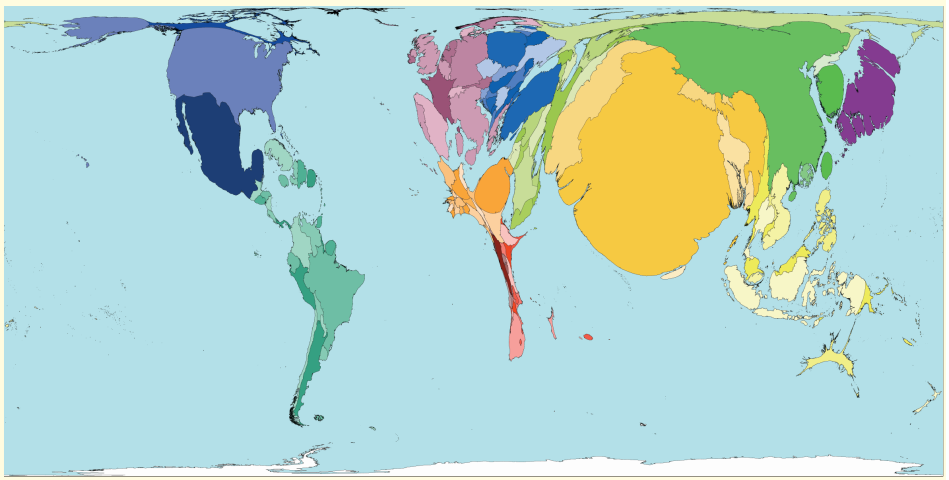
Diabetes Physiology: Type 1 Diabetes Mellitus (T1DM)

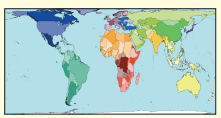


- Usually appears before age 35.
- An autoimmune disease.
- Characterized by the destruction of the pancreatic β-cells.
- An insulin-dependent treatment is essential from the beginning of the disease to prevent dehydration, ketoacidosis, and death.
- Consequences:
  - hyperglycaemia (high sugar) $\longrightarrow$ long-term
  - hypoglycaemia (low sugar) $\longrightarrow$ short-term

Diabetes world distribution

Diabetes Prevalence





Land area

Technical notes
- Data are from the World Bank's 2005 World Development Indicators.
- See website for further information.

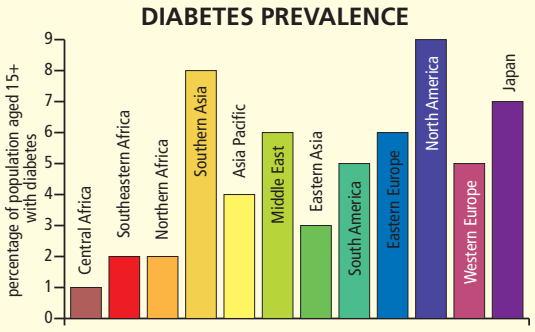
HIGHEST AND LOWEST DIABETES PREVALENCE

Rank	Territory	Value	Rank	Territory	Value
1	Mexico	14	190	Congo	0.9
2	Trinidad & Tobago	14	192	Cote d'Ivoire	0.8
3	Saudi Arabia	12	192	Senegal	0.8
4	Mauritius	12	192	Uganda	0.8
4	Hong Kong (China)	12	192	Cameroon	0.8
6	Papua New Guinea	12	196	Nigeria	0.4
7	Cuba	12	196	Ghana	0.4
8	Puerto Rico	11	198	Mali	0.3
8	Singapore	11	198	Gambia	0.3
10	Jamaica	11	198	Togo	0.3

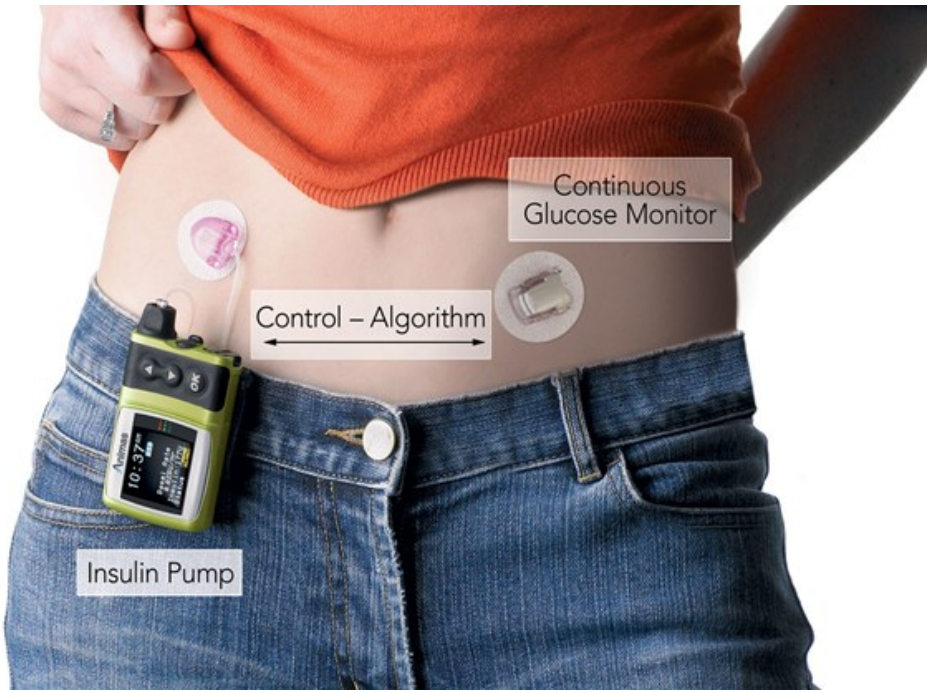
percentage of people aged over fifteen with diabetes, in 2001

The highest diabetes prevalence is in North America. Of the total North American cases, 4% are in Canada, 33% are in Mexico, and 62% are in the United States. The largest population of diabetics in 2001 was in India: 56 million people.

Territory size shows the proportion of all people in the world living with diabetes who live there.



Artificial Pancreas



Sensor: CGM (Continuous Glucose Monitoring) meter.

Actuator: CSII (Continuous Subcutaneous Insulin Infusion) pump.

The control algorithm is usually designed based on a mathematical model of the insulin-glucose dynamics

Insulin-Glucose Dynamics for Controller Design

Simulation models

Sorensen **UVA/Padova** Cambridge	Provide good glucose prediction, but mathematically complex

+

Most of well established theory of control law design accommodates only simpler models, and simplifications are generally considered at the controller design phase

$\Downarrow$

Control-oriented models represents the underlying dynamics, but with a much simpler mathematical formulation

Problem challenges and controllers

Challenges

- Intra- and inter-patient uncertainty
- Subcutaneous-intravenous delays in CGM and insulin injection
- Nonlinear, time-varying dynamics

Popular control methodologies

- Proportional-integral-derivative (PID): since Fisher (1991): most popular industrial (model-less) method.
- Model Predictive Control (MPC): comes from process control.

Our design methodologies

- Robust control: includes model uncertainty restrictions, mainly for Linear Time Invariant (LTI) models, could be conservative
- Linear Parameter Varying (LPV) control: includes nonlinear/time-varying dynamics
- Switched LQG/LPV: ideal to focus on normo/hypo/hyperglycaemias

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Challenges and solutions adopted

Control-oriented model: challenge # 1

- **Inter-patient variations**:
  - Cover uncertainty and apply Robust control
  - Tune model to patient (model personalization) using clinical data without going through an Identification process

Control-oriented model: challenge # 2

- **Intra-patient variations, nonlinearities, simplicity**:
  - LPV model (possibly affine)

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Model Personalization

Model personalization and the 1800 rule

For a given patient, the underlying insulin-glucose model must be tuned to patient-specific characteristics [1]

⇓

Problem

It is not possible to estimate the values of all system parameters from *in vivo* dynamic data [2]

⇓

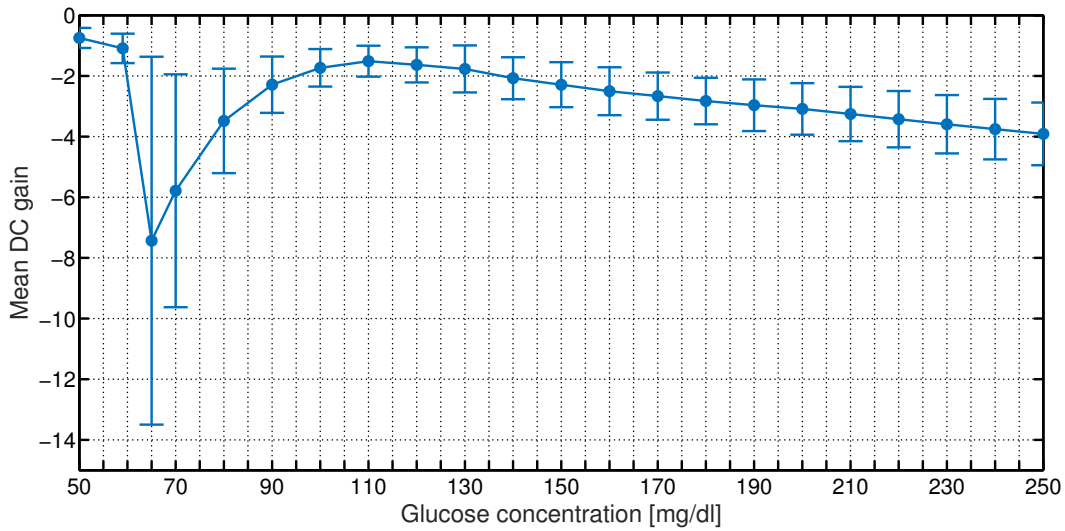
Control-oriented solution

Adapt a low-order model structure based on *a priori* patient information, e.g. the 1800 rule: 1800/TDI.

[1] S. Patek *et al.*, "*In Silico Preclinical Trials: Methodology and Engineering Guide to Closed-Loop Control in T1DM*", 2009.
[2] C. Cobelli *et al.*, "*Diabetes: Models, Signals and Control*", 2009.

Model Personalization and the 1800 rule

The 1800 rule indicates the maximum drop in glucose concentration, measured in mg/dl, after a 1 U injection of rapid-acting insulin

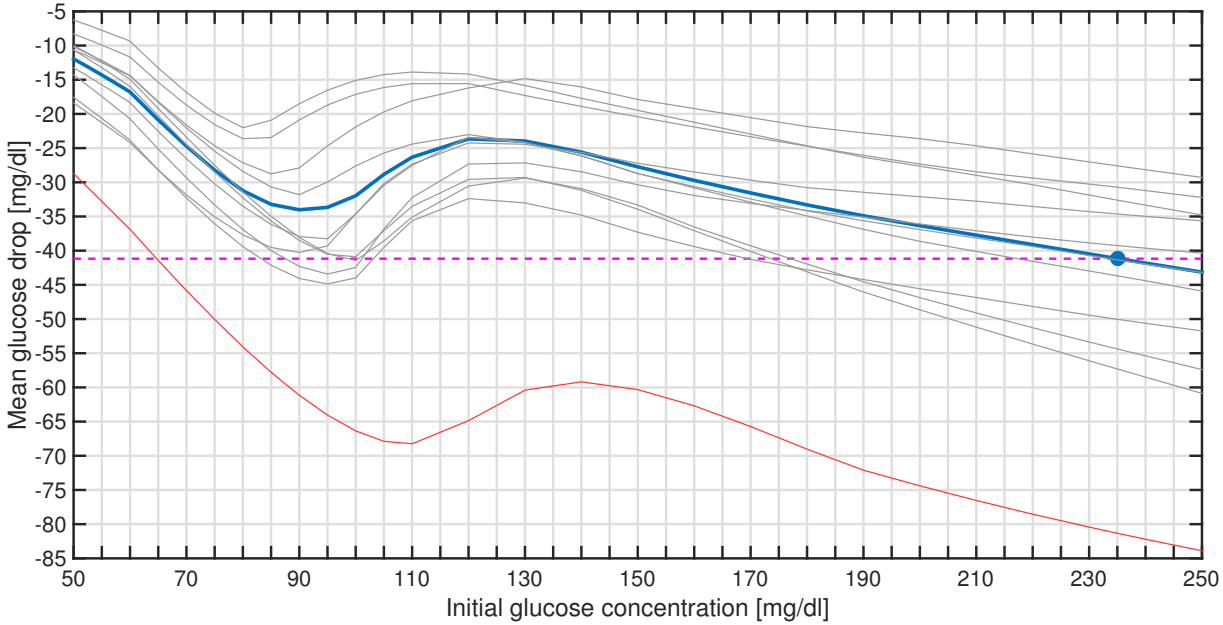


Mean DC gain for the adult patients of the distribution version of the UVA/Padova simulator, linearized at different glucose concentrations

Patient's insulin sensitivity depends, amongst other factors, on the glucose concentration, therefore... at which glucose concentration does it work best, or is it most appropriate?

Model Personalization and the 1800 rule

A 1 U insulin bolus was applied to each *in-silico* adult of the distribution version of the UVA/Padova simulator at a large number of different steady-state glucose concentrations (operation conditions), and the maximum glucose decrease was captured in each case.



Glucose drop for each *in-silico* adult (gray lines: Study patients, red line: Adult #007) and the mean values excluding Adult #007 (blue line) at different operation conditions after a 1 U insulin bolus. The magenta dashed line indicates the average value of the 1800 rule.

The (average) 1800 rule is only rendered correct at 235 mg/dl

Control-oriented model objectives

1. Determine a low order model that copes with the previous challenges and can be used on well-known controller design methods.
   - LPV structure with delay
2. Define a method to personalize the model based on the 1800 rule.
   - Identify an average model based on previous structure
   - Fix all parameters except for two: p_1 to adjust with glucose in real-time (LPV) and k to personalize a particular patient using the 1800-rule
3. Quantify the quality of the model in open– and closed–loop.
   - RMSE for OL and ν-gap for CL

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Average Model Definition

According to control-oriented models previously presented:

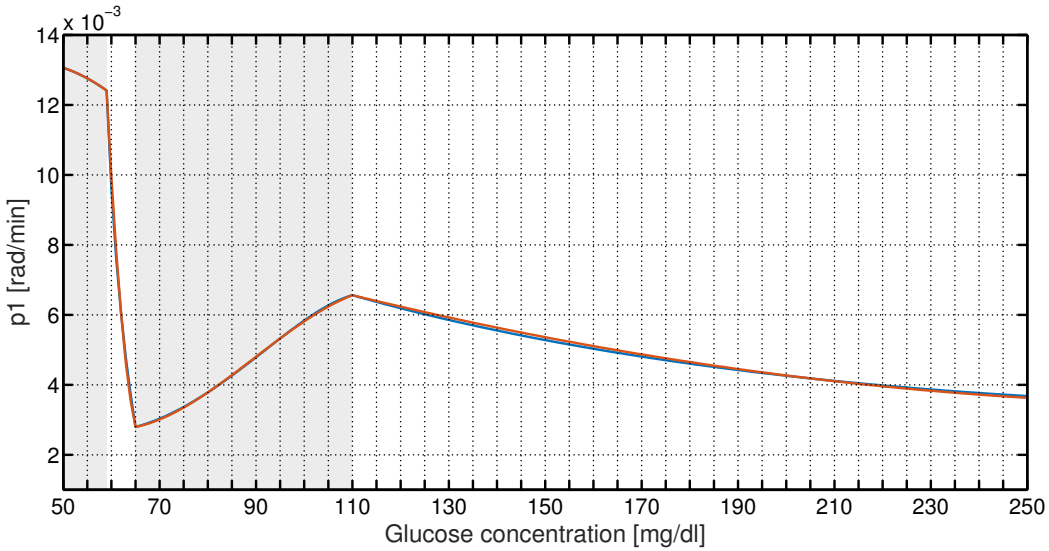
- **Model 1:** K. van Heusden *et al.*, "Control-relevant models for glucose control using *a priori* patient characteristics," IEEE Trans. Biomed. Eng., 2012.
- **Model 2:** J. Lee *et al.*, "Model-based personalization scheme of an artificial pancreas for type 1 diabetes applications," in ACC, 2013.
- **Model 3:** P. Colmegna *et al.*, "Switched LPV glucose control in type 1 diabetes," IEEE Trans. Biomed. Eng., 2016.

the following model structure from the subcutaneous insulin delivery (pmol/min) to the subcutaneous glucose concentration deviation (mg/dl) is proposed:

$$G(s) = k\frac{s+z}{(s+p_1)(s+p_2)(s+p_3)}\mathrm{e}^{-15s} \tag{1}$$

Parameter p_1

Parameter p_1 computed at different values of glucose concentration g (light-blue), and piecewise polynomial function $p_1(g)$ (orange).



$$p_1(g) = q_i g^3 + r_i g^2 + s_i g + t_i$$

i	g region [mg/dl]	q_i	r_i	s_i	t_i
1	$110 \leq g$	0	9.0580×10^{-8}	-5.3562×10^{-5}	1.1357×10^{-2}
2	$65 \leq g < 110$	-4.2382×10^{-8}	1.1402×10^{-5}	-9.1676×10^{-4}	2.5849×10^{-2}
3	$59 \leq g < 65$	0	1.7321×10^{-4}	-2.3080×10^{-2}	7.7121×10^{-1}
4	$g < 59$	0	-2.9126×10^{-6}	2.4514×10^{-4}	8.0865×10^{-3}

Fitting achieved: 97.24%

Average LPV Model

$$\dot{x}(t) = A(p_1)x(t) + Bu_\Delta(t)$$
$$y_\Delta(t) = Cx(t)$$

with

$$A(p_1) = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & -p_2p_3 & -(p_2+p_3) \end{bmatrix} + p_1 \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ -p_2p_3 & -(p_2+p_3) & -1 \end{bmatrix}$$
$$B = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}^T$$
$$C = k \begin{bmatrix} z & 1 & 0 \end{bmatrix}$$

A delay of 15 min should be added to the output.

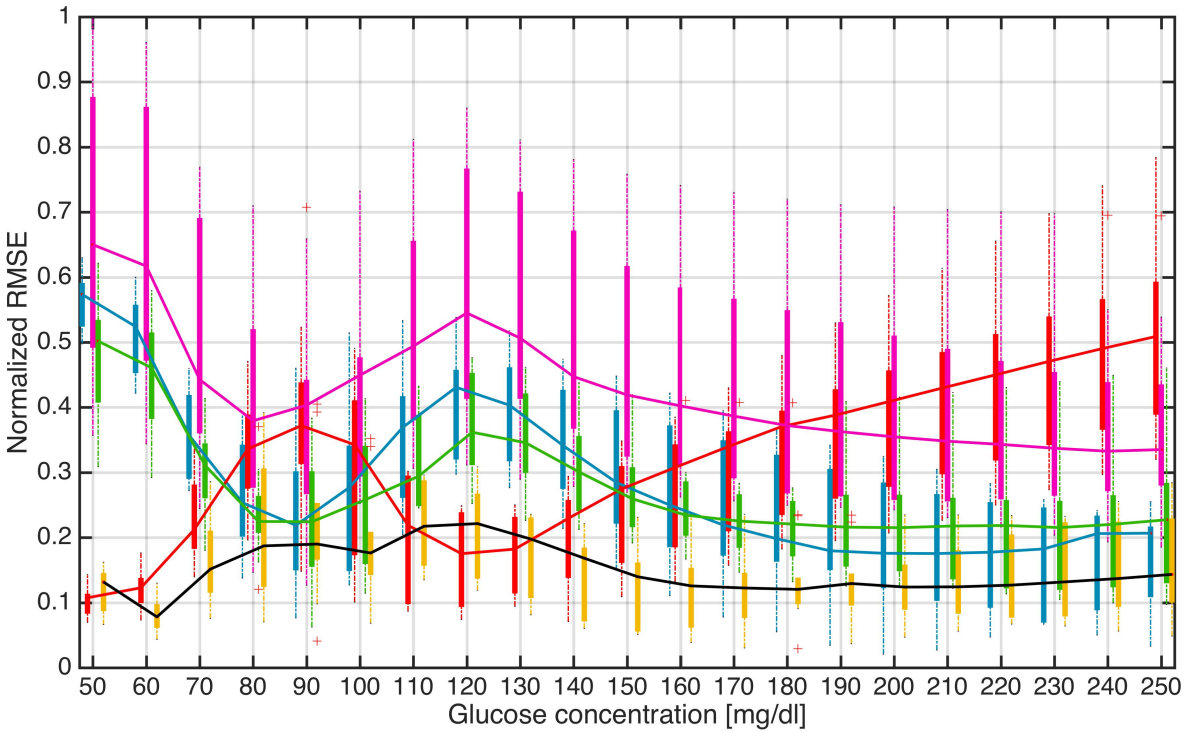
The (average) LPV model is affine in the parameter p_1

Model quality

Performance Analysis	
Open-Loop	Closed-Loop
Is a particular model capable of providing a good fit to the UVA/Padova model? **Measure:** RMSE	Is a particular model capable of providing a good closed-loop performance? **Measure:** ν-gap metric

Open-Loop Comparison

Normalized RMSE between the time-response of the control oriented models and the nonlinear UVA/Padova model to a 1 U insulin bolus at different operation conditions

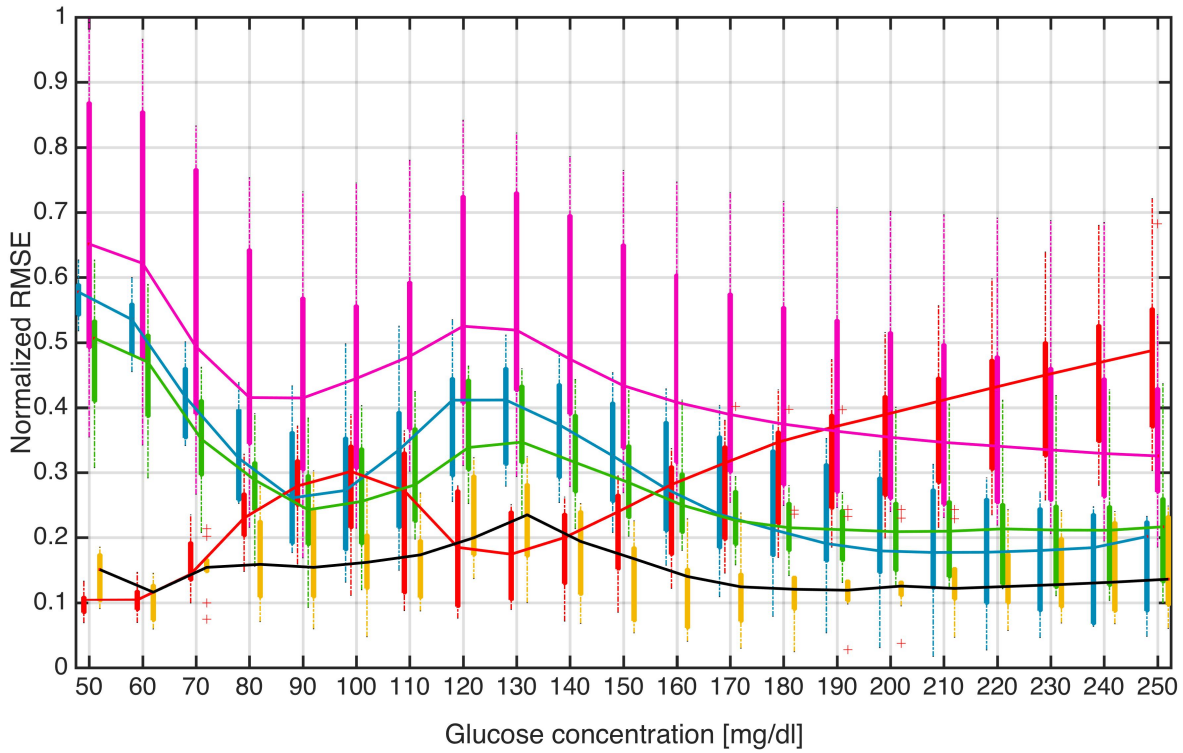


Personalized LPV model
Average LTI model
Model 1
Model 2
Model 3

The personalized LPV model has the best fit for most of the glucose concentration values that were considered (average improvement $\geq$ 81%)

Open-Loop Comparison

Normalized RMSE between the time-response of the control oriented models and the nonlinear UVA/Padova model to a 1.5 U insulin bolus at different operation conditions



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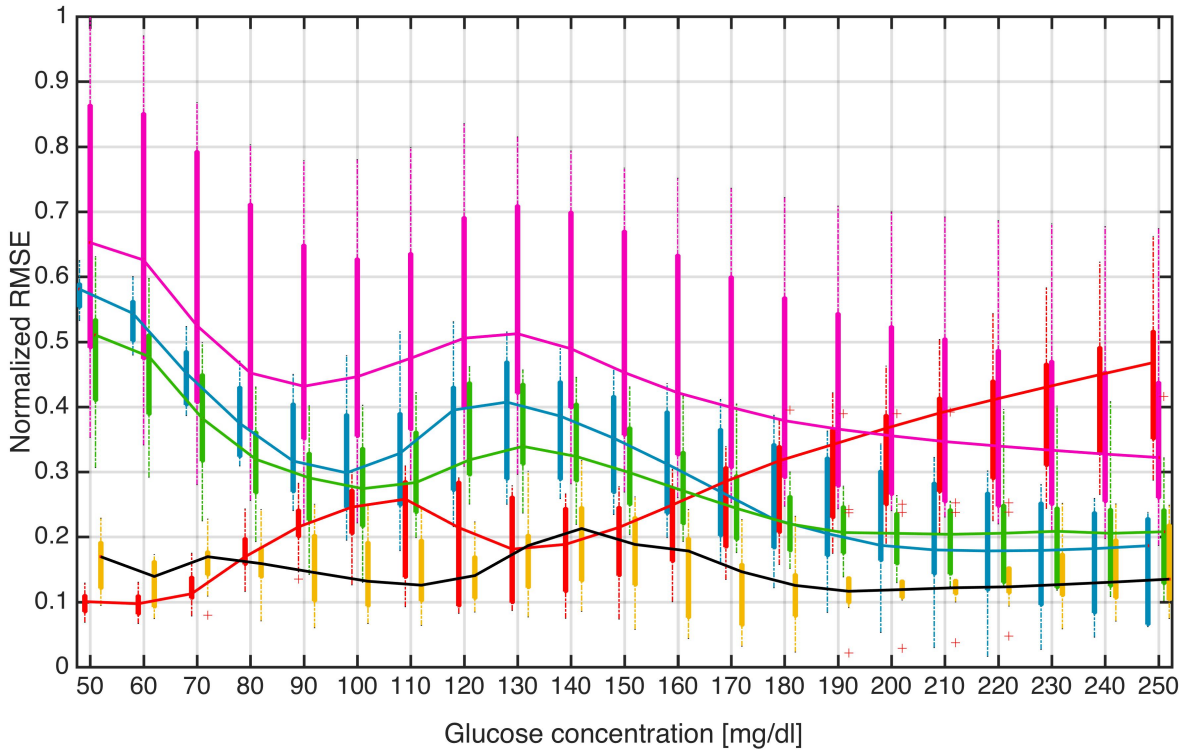
Average LTI model
Model 1
Model 2
Model 3

The personalized LPV model has the best fit for most of the glucose concentration values that were considered (average improvement $\geq$ 83%)

Open-Loop Comparison

Normalized RMSE between the time-response of the control oriented models and the nonlinear UVA/Padova model to a 2 U insulin bolus at different operation conditions

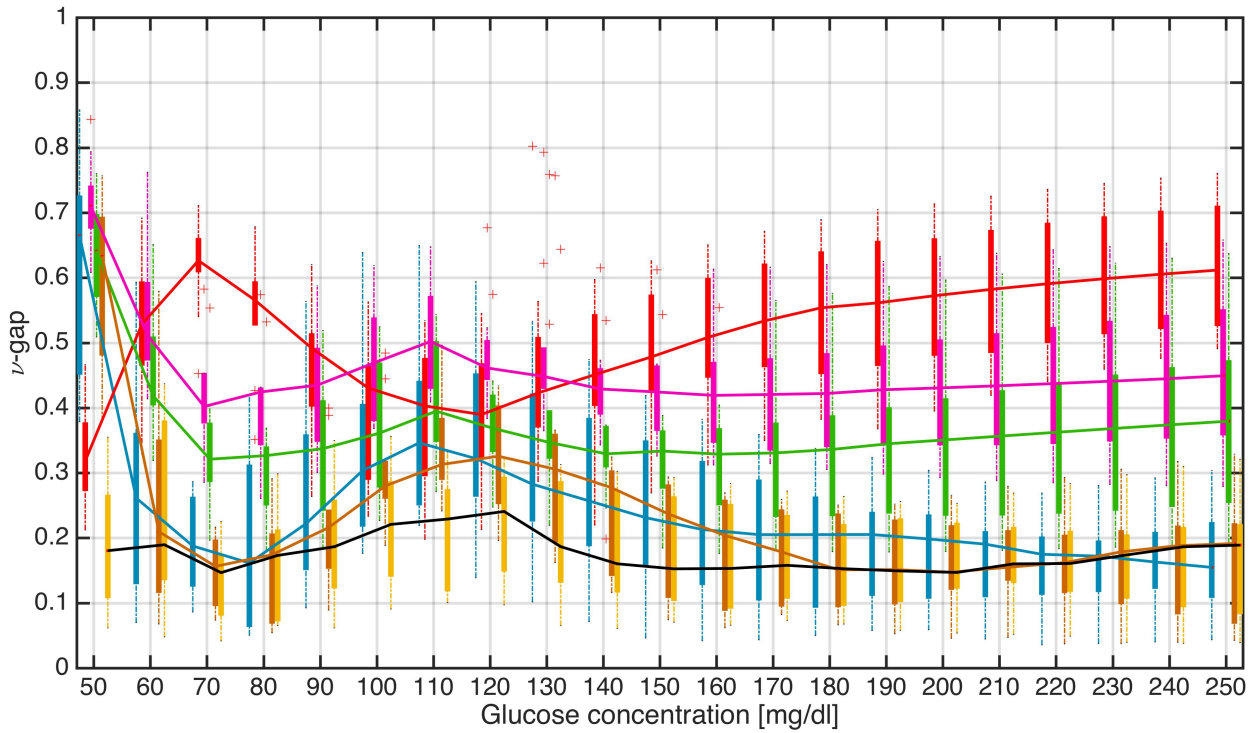


Personalized LPV model
Average LTI model
Model 1
Model 2
Model 3

The personalized LPV model has the best fit for most of the glucose concentration values that were considered (average improvement $\geq$ 72%)

Closed-Loop Comparison

ν-gap δ_ν between the UVA/Padova model linearized at different glucose concentrations and the control-oriented models



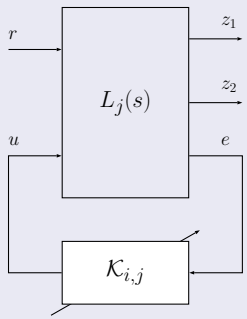
	Model	Average δ_ν	Improvement (%)
	Personalized LPV model	0.1803	38.3
	Personalized LTI model	0.2261	10.3
	Average LTI model	0.2493	0
	Model 1	0.3739	-33.3
	Model 3	0.4619	-46.0
	Model 2	0.5087	-51.0

Remarks on the nominal control-oriented LPV model

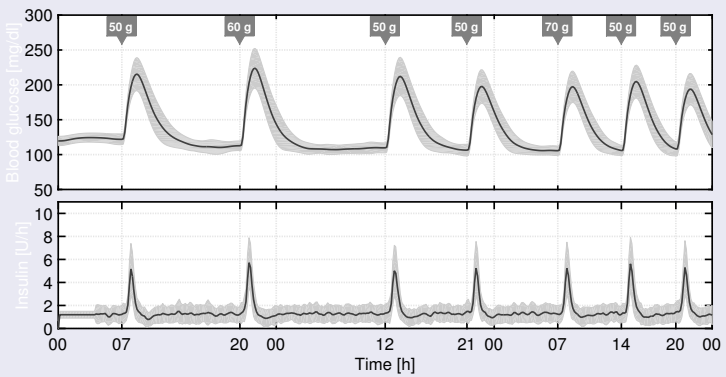
- A control-oriented model of insulin-glucose dynamics that includes problem challenges was characterized.
- The proposed LPV model is affine in the parameter p_1 (suitable for controller design).
- Parameter p_1 is itself a polynomial function of the glucose level (real-time measurable).
- The ν-gap metric was employed as a quantification of CL performance.
- The RMSE and the ν-gap metric indicate that the personalized LPV model achieves smaller errors compared to previous control-oriented models.

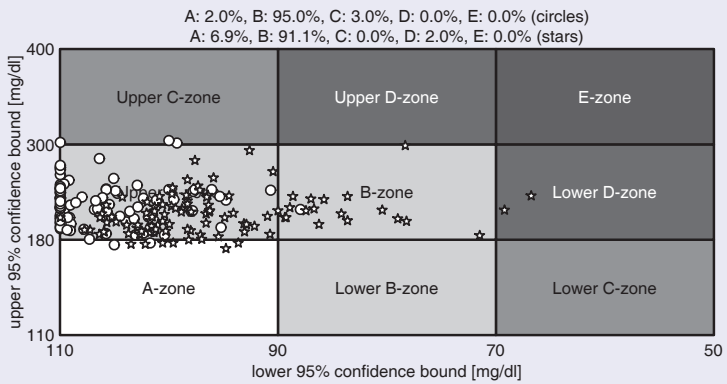
Designs: Switched LPV controller

Controller structure



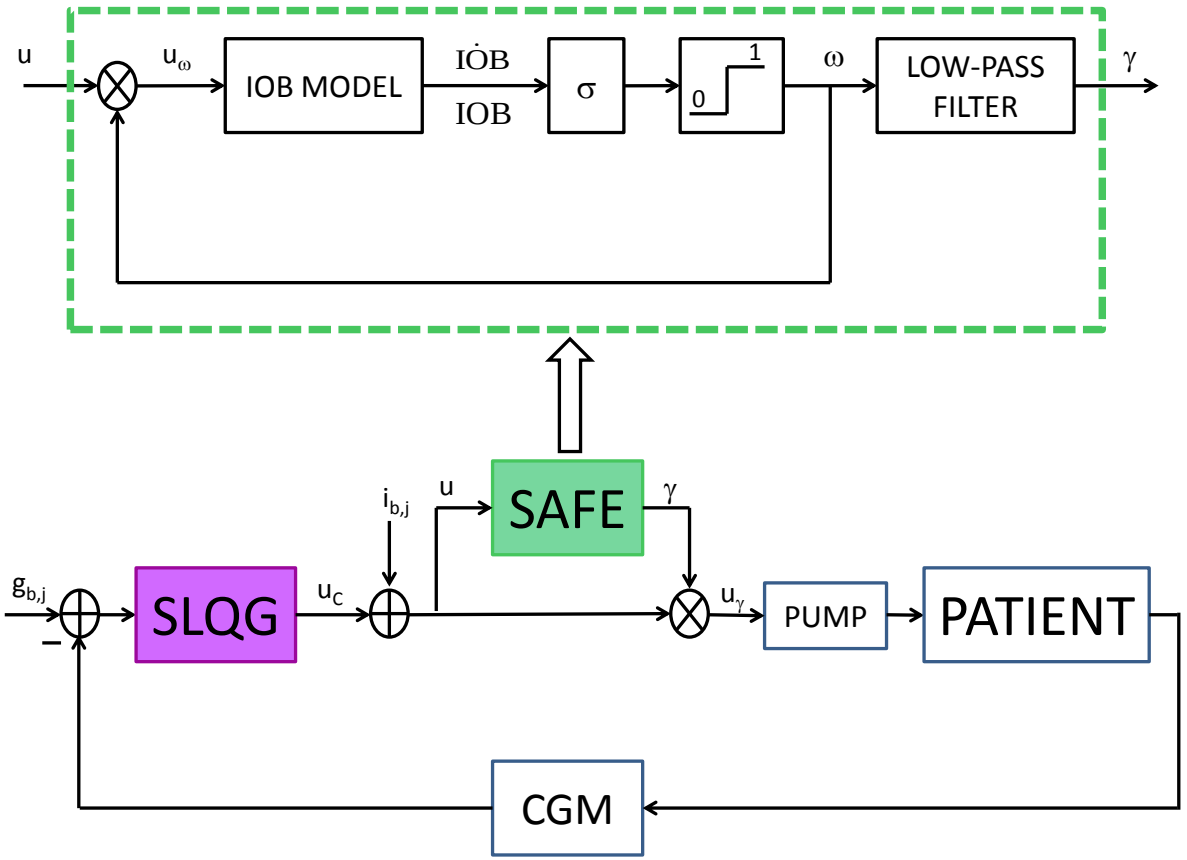
Results (complete UVA/Padova simulator)





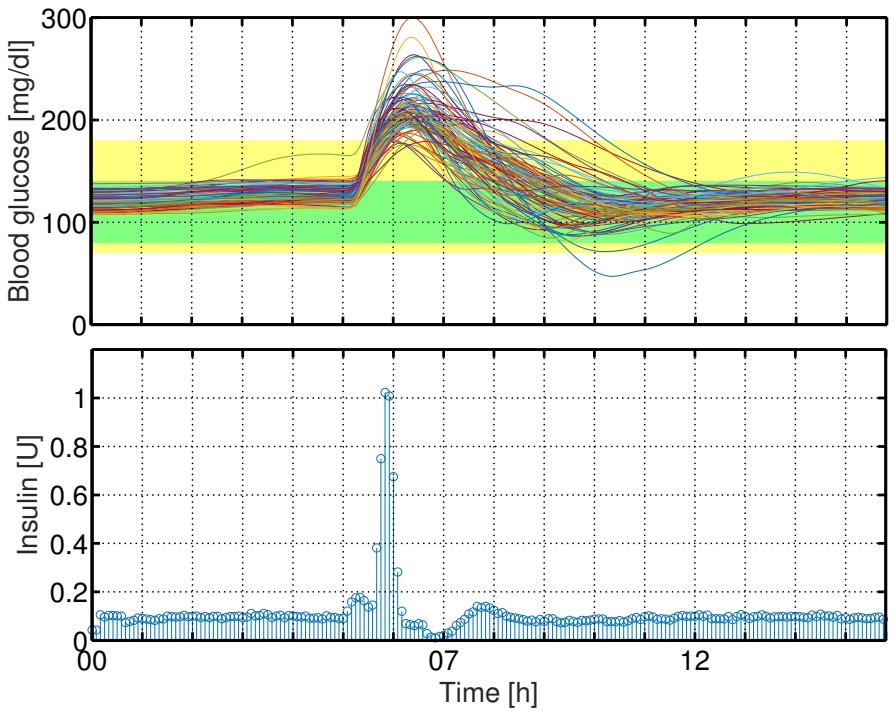
Colmegna, Sánchez-Peña, Gondhalekar, Dassau, Doyle III, *Switched LPV Glucose Control in T1DM*, IEEE Transactions on Biomedical Engineering, 63(6), 2016

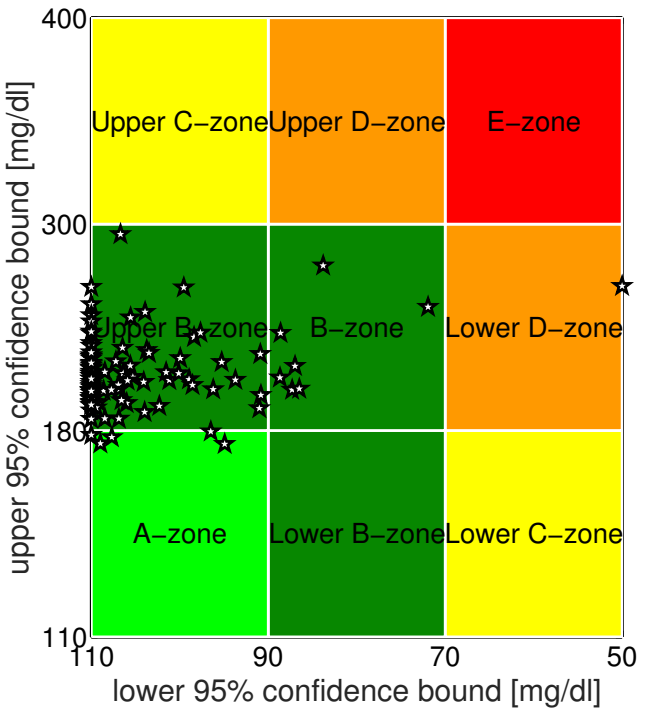
Designs: Switched LQG controller – ARG algorithm



Switched-LQG + SAFE controller: ARG (Automatic Regulation of Glucose) algorithm

pre-Clinical test results



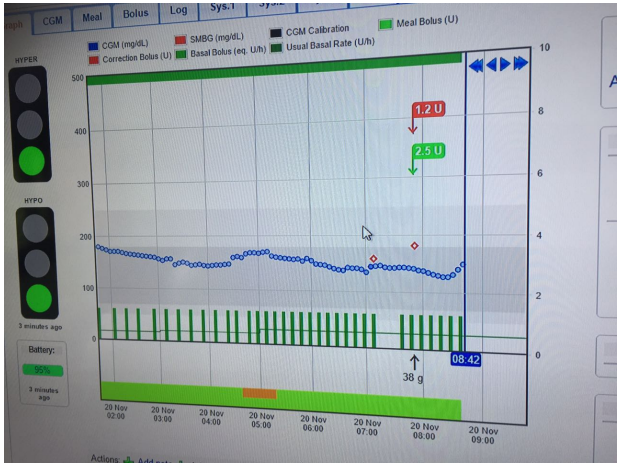


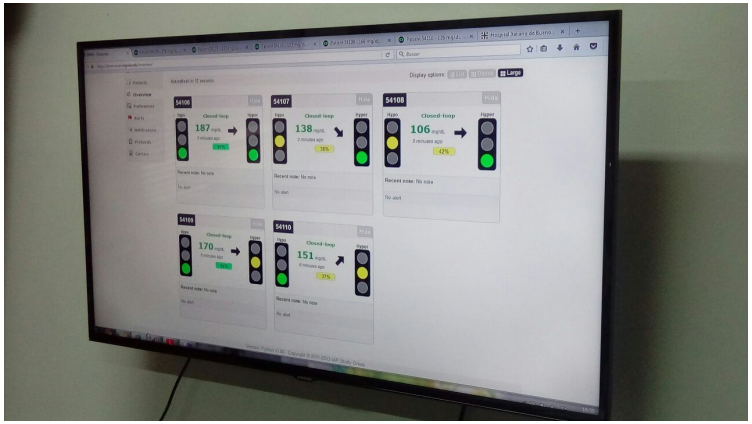
101 *in-silico* adult patients in the complete UVA/Padova simulator, considering a 50g meal.

Clinical tests: first trials in Latin America (Nov. 2016/June 2017)

- Sánchez-Peña, Colmegna, ..., Cherñavvsky, *Artificial Pancreas: First clinical trials in Argentina*, IFAC World Congress, Toulouse, 2017
- ..... *First clinical trials in Latin America without CHO counting*, J. of Diabetes Science & Tech., 2018.
- Colmegna, Garelli, DeBattista, Sánchez-Peña, *ARG algoritm*, Control Eng. Practice, 2018

Clinical tests: patients monitoring during test





Patient monitoring during clinical test (left) glucose curve of a patient, (right) traffic light indication for all patients.

Clinical tests: some results

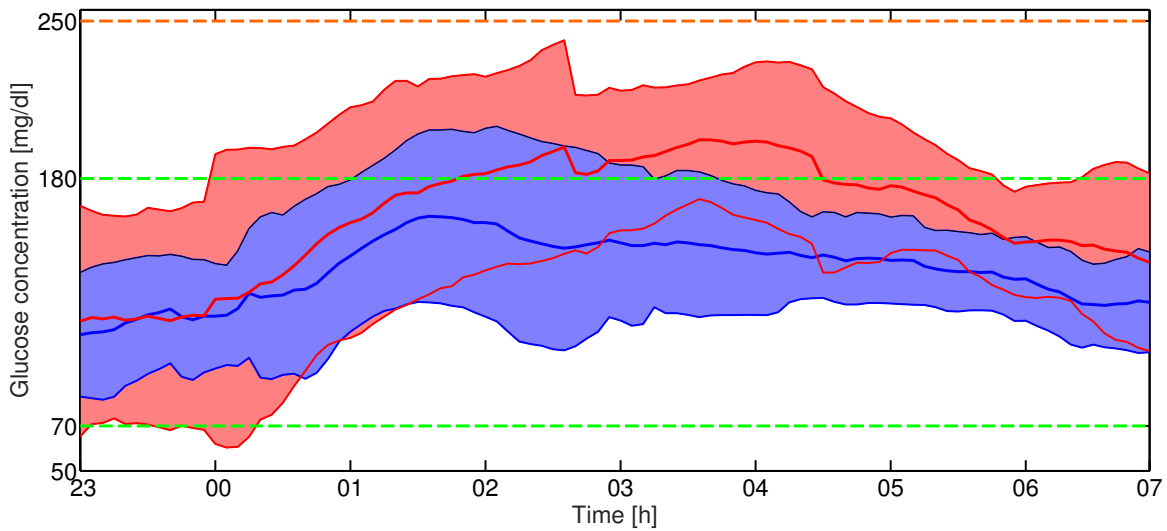


Figure: *(left) Average value of Dexcom G4 in open-loop (red) and closed-loop (blue) during the night. The filled areas represent ± 1 STD. Dashed lines (green and orange) indicate glucose concentration limits (70-180 and 70-250 mg/dl).*

What's next?

- Invalidate the data vs. nominal LPV model
- Produce an LPV (control-oriented) *model set*
- Design a robust controller (switched-LPV)
- Compare both designs: nominal *vs* robust

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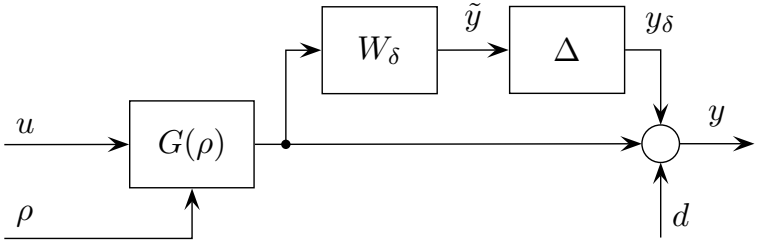
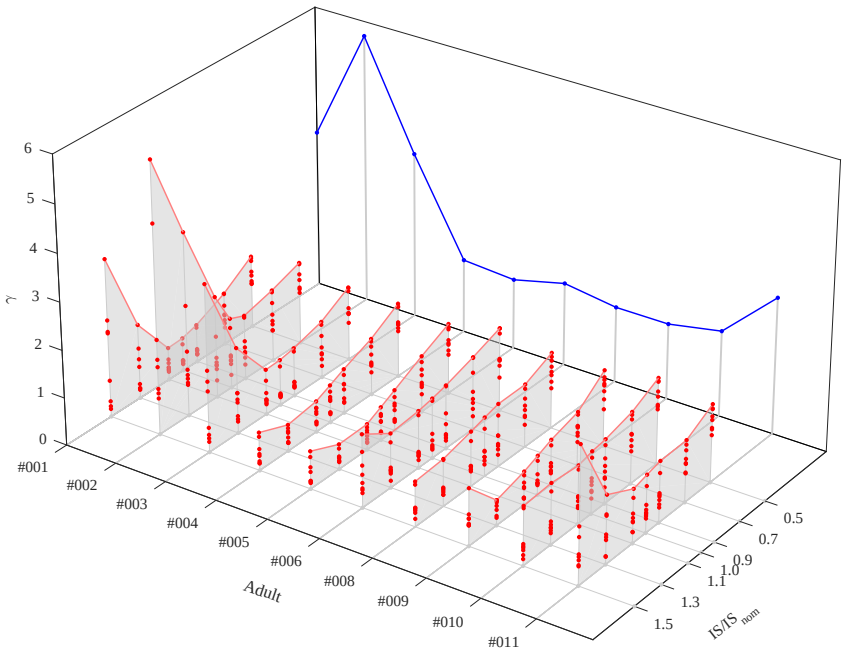
Invalidation results [1]



$$
\begin{aligned}
W_\delta(s) &= 0.2\,\frac{500s+1}{50s+1} \\
\|\Delta\|_\infty &< \gamma \\
\|d\|_2 &< 0.05
\end{aligned}
$$

solve

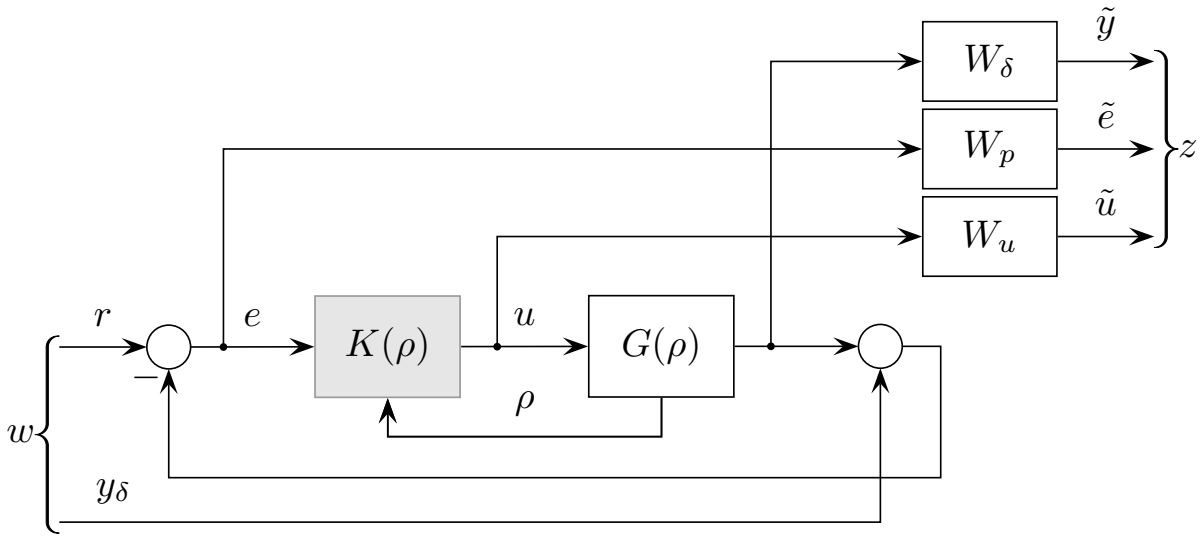
$$
\begin{aligned}
&\min_{d,w} \gamma \\
w &= y - d - G(\rho) * u \\
G(\rho): &\quad \text{nominal model}
\end{aligned}
$$



Uncertainty bound γ *vs* subject # *vs* Insulin sensitivity (IS) factor

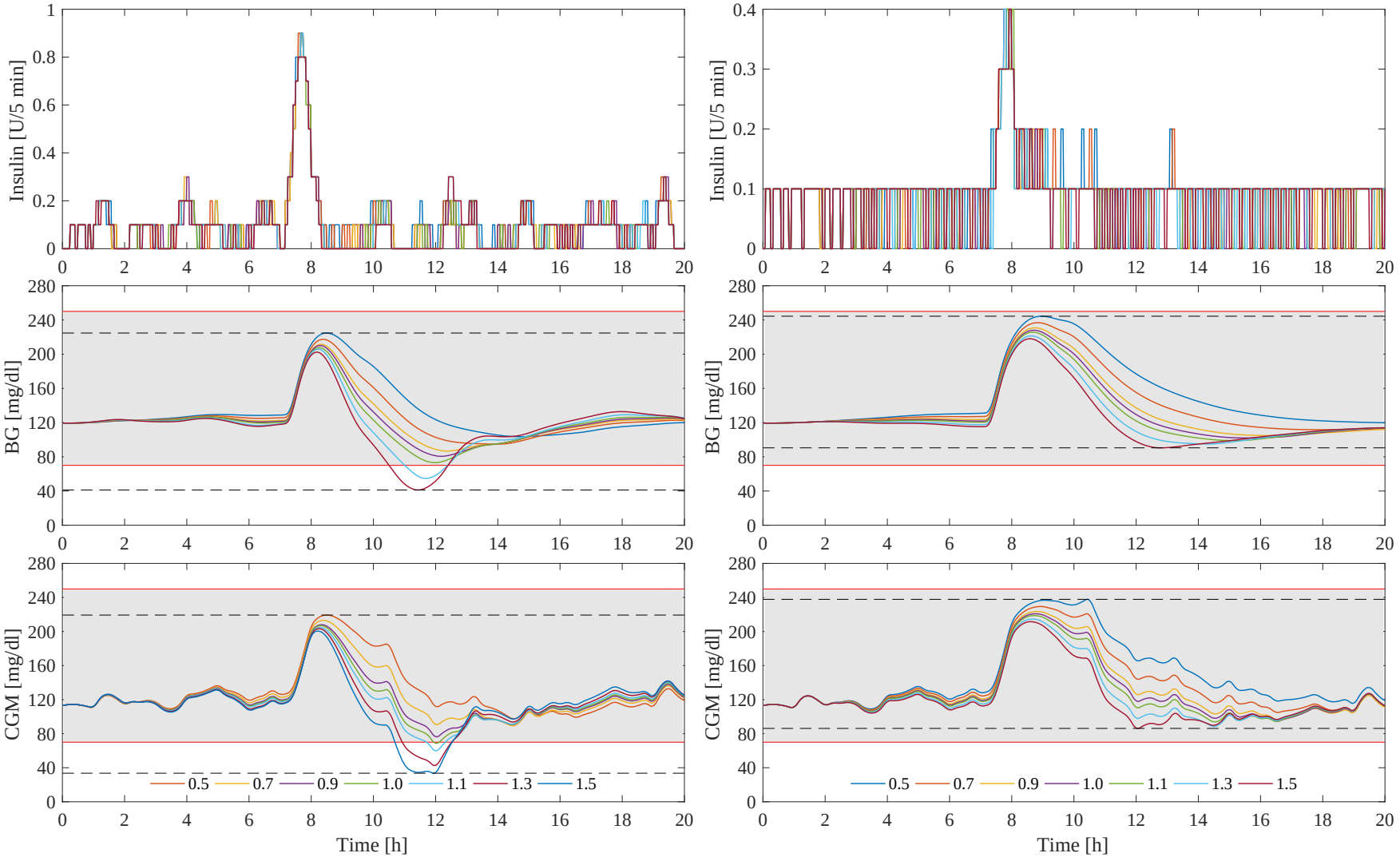
[1] M. Sznaier, M. C. Mazzaro, *An LMI approach to control-oriented identification and model (in)validation of LPV systems*, IEEE Trans Automat Contr 48 (9), 2003.

Controller design



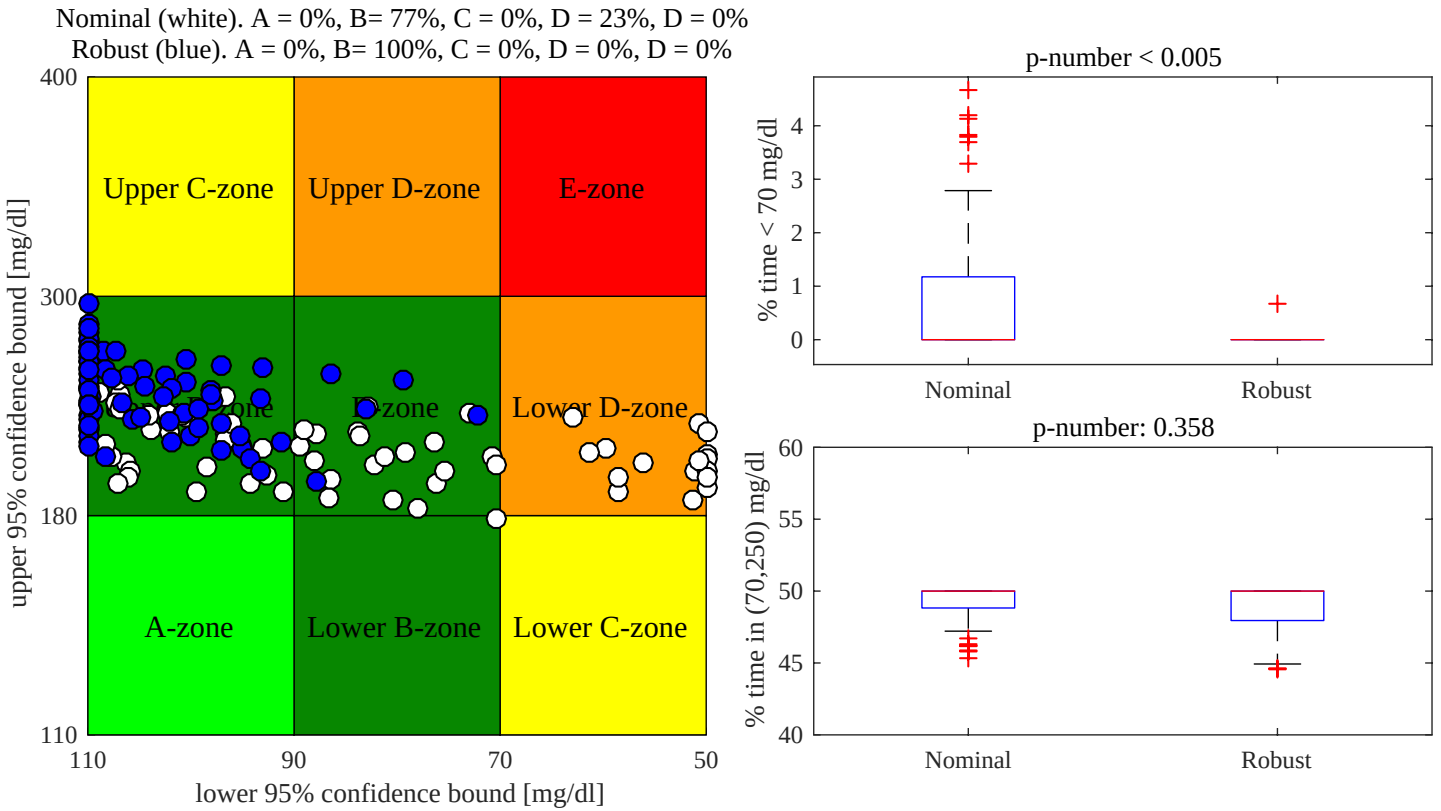
with $W_p(s)$ and $W_u(s)$, the tracking and control action weights, respectively. The robust design also includes $W_\delta(s)$.

Controller comparison



(left) nominal, (right) robust controller

Controller comparison



nominal *vs* robust controller comparison for all subjects and IS variations. (left) CVGA and (right) time-in-range.

Conclusions & Future research

1. A low-order, control-oriented *model set* provides an adequate coverage of several dynamic and parametric uncertainties, e.g. intra-patient variations.
2. An LPV or switched-LPV controller provides a robust design procedure.
3. Next step: augment the nominal LPV model with an extra parameter (real-time measured/estimated) in order to (nominally) represent the intra-patient variations $\longrightarrow$ invalidate $\longrightarrow$ refine LPV *model set* $\longrightarrow$ (hopefully) improve performance.
4. Next clinical trials: children (Hospital Garrahan)

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THANKS FOR YOUR ATTENTION

QUESTIONS?