# Control of Blood Glucose for People with Type 1 Diabetes: an in Vivo Study

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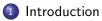
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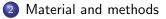
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### Outline





#### 3 Controller design



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#### Introduction

- People with type 1 diabetes must rely on exogenous insulin to regulate blood glucose
- Ideally, try to keep blood glucose (BG) in the range 4-8 mmol/L
  - A too low glucose concentration (hypoglycemia) has immediate effects: seizures, coma, brain damage or even death

• A too high glucose concentration (hyperglycemia) has long-term effects: blindness, nerve disease, kidney disease etc.

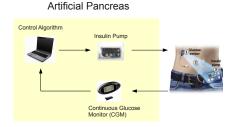
#### Introduction

- Continuous Subcutaneous Injection of Insulin (CSII)
  - Continuous Glucose Monitor (CGM) to measure subcutaneous glucose
  - Insulin pump injects insulin subcutaneously
  - The patient decides on the insulin dosage: preset continuous insulin injections (basal rate) + bigger discrete insulin injections before mealtimes, or if the BG is too high (boluses)

- Main issues:
  - Sensor accuracy, even if correctly calibrated
  - Insulin action time
  - Daily variations in physiology
  - Human factor

#### The artificial pancreas

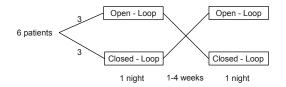
 Closed-loop control of blood glucose (here, using MPC) using a CGM and an insulin pump



 Test our closed-loop controller for two "pilot" studies on the same patient at Hvidovre Hospital

### The clinical protocol

- Overnight  $\Longrightarrow$  No meal
- 2 Randomized cross-studies



• Compare overnight CSII therapy vs. closed-loop control ability to

- Stabilize blood glucose
- Bring blood glucose to target
- Scenario:
  - The patient arrives at 16:00.
  - A meal is consumed at 18:00 and an insulin bolus is administrated.
  - The loop is closed at 22:00 (for closed-loop studies only).
  - The closed-loop ends at 07:00 the following day (for closed-loop studies only).

### The Graphical User Interface

- Glucose measurement from CGM provided to the software every 5 minutes (if available)
- Discrete insulin injection every 15 minutes implemented by hand

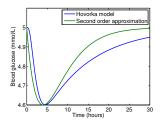
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#### Patient model computation

- No use of prior data
- Instead, use of empirically estimated patient parameters
  - $\bullet\,$  Basal insulin (in U/hr): Insulin needed to keep BG constant
  - Insulin sensitivity factor (ISF) (in mmol/L/U): Decrease in BG per unit of insulin
  - Insulin action time (in hours): Time to reach the minimum BG
- Second order transfer function model from insulin to glucose

$$Y(s) = G(s)U(s), \quad G(s) = rac{K}{( au s + 1)^2}$$

• Example: Impulse response for a simulated patient (Bolus size: 0.1U)



Basal insulin: 0.4 U/hr ISF: 4 mmol/L/U Insulin action time: 4 hours

### ARMAX model

$$Y(s) = G(s)U(s), \quad G(s) = rac{K}{( au s + 1)^2}$$

Discretization of the previous transfer function model

$$\bar{A}(q^{-1})y(t) = q^{-n_k}\bar{B}(q^{-1})u(t) + \xi(t)$$

where

$$ar{A}(q^{-1}) = 1 + ar{a}_1 q^{-1} + ar{a}_2 q^{-2} \ ar{B}(q^{-1}) = ar{b}_1 q^{-1} + ar{b}_2 q^{-2}$$

Offset-free description

$$A(q^{-1})y(t) = B(q^{-1})u(t) + (1 - \alpha q^{-1})e(t)$$

in which

$$\begin{split} & A(q^{-1}) = (1 - q^{-1})\bar{A}(q^{-1}) \\ & B(q^{-1}) = (1 - q^{-1})\bar{B}(q^{-1}) \\ & 0 \leq \alpha \leq 1 \end{split}$$

may be realized as a stationary state space model in innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k$$
$$y_k = Cx_k$$

### MPC with soft output constraints

$$\min_{\{u_{k+j}, v_j\}_{j=0}^{N-1}} \phi = \frac{1}{2} \sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 + \lambda \|\Delta u_{k+j}\|_2^2 + \kappa \|v_{k+j}\|_2^2$$

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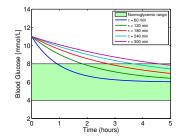
s.t.  

$$\begin{aligned} \hat{x}_{k+1|k} &= A\hat{x}_{k|k-1} + Bu_k + K\varepsilon_k \\ \hat{y}_{k+1|k} &= C\hat{x}_{k+1|k} \\ \hat{x}_{k+j+1|k} &= A\hat{x}_{k+j|k} + Bu_k \\ \hat{y}_{k+j+1|k} &= C\hat{x}_{k+j+1|k} \\ u_{\min} &\leq u_{k+j} \leq u_{\max} \\ G_{\min} - \hat{y}_{k+j+1|k} \leq v_{k+j} \\ v_j &\geq 0 \end{aligned}$$

- $\hat{y}_{k+j+1|k}$  j+1 step ahead predictions of glucose
- *u*<sub>k+j</sub> predicted insulin injections
- Penalize low BG, ie.  $\hat{y}_{k+j+1|k} \leq G_{\min}$

### Glucose reference signal

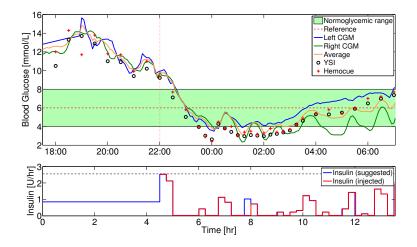
- Reduce the risk of low BG
- Improve the stability of the controller
- The time constant determines the aggressiveness of the controller



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#### Results

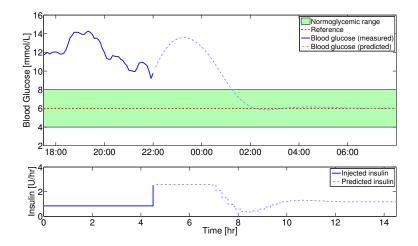
- Use the right CGM for control
- Insulin overdose followed by severe hypoglycemia



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#### Example of prediction

• Only based on the 2 last observations



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#### Observer design

We consider an ARMAX model

$$A(q^{-1})y(t) = B(q^{-1})u(t) + C(t)e(t)$$

where

$$\begin{aligned} A(q^{-1}) &= 1 + a_1 q^{-1} + a_2 q^{-2} + a_3 q^{-3} &= (1 - q^{-1})\bar{A}(q^{-1}) \\ B(q^{-1}) &= b_1 q^{-1} + b_2 q^{-2} + b_3 q^{-3} &= (1 - q^{-1})\bar{B}(q^{-1}) \\ C(q^{-1}) &= 1 + c_1 q^{-1} + c_2 q^{-2} + c_3 q^{-3} &= (1 - \alpha q^{-1})(1 - \beta_1 q^{-1})(1 - \beta_2 q^{-1}) \end{aligned}$$

and its reformulation in the innovation form

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k$$
$$y_k = Cx_k$$

Goal: Choose  $\alpha$ ,  $\beta_1$  and  $\beta_2$  which are the roots of the characteristic polynomial of A - KC

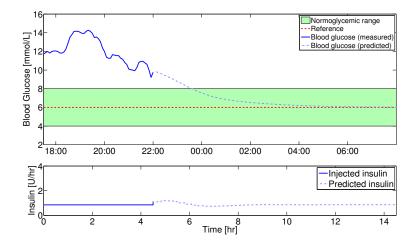
$$\chi(z) = z^3 + c_1 z^2 + c_2 z + c_3$$

based on data from the previous study (ie. estimate process and output noise variances), such that the reconstruction error vanished less rapidly. Here:

$$\beta_{1,2}=0.8\pm0.15i$$

## Example of prediction with the redesigned observer

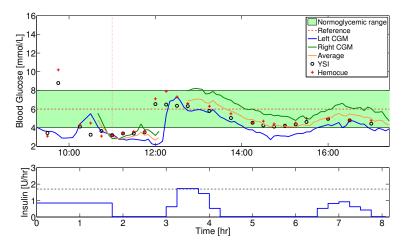
• More taking the global trend of BG into account



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#### Results - 2nd study

- Use the left CGM for control
- Still some insulin overdose



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### Conclusion and discussion

- Overnight closed-loop control of BG
- Importance of observer design for control
- Still few issues related to insulin overdosing
- Need to handle more carefully parameter variability for further trials

- Do not inject insulin if the BG is too low
- Overestimate the gain
- Underestimate the time constant