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

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Outline

Introduction

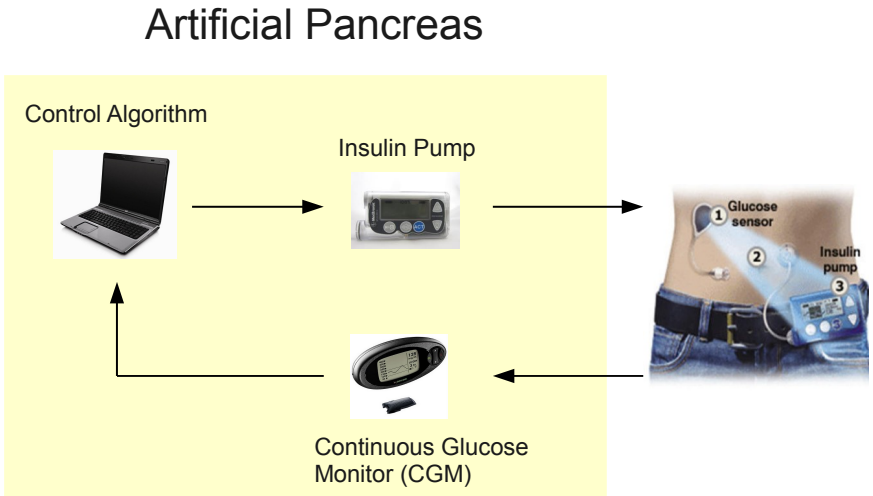
- People with type 1 diabetes must rely on exogenous insulin to regulate blood glucose
- Ideally, try to keep blood glucose (BG) in the range 4-8 mmol/L
  - A too low glucose concentration (hypoglycemia) has immediate effects: seizures, coma, brain damage or even death
  - A too high glucose concentration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

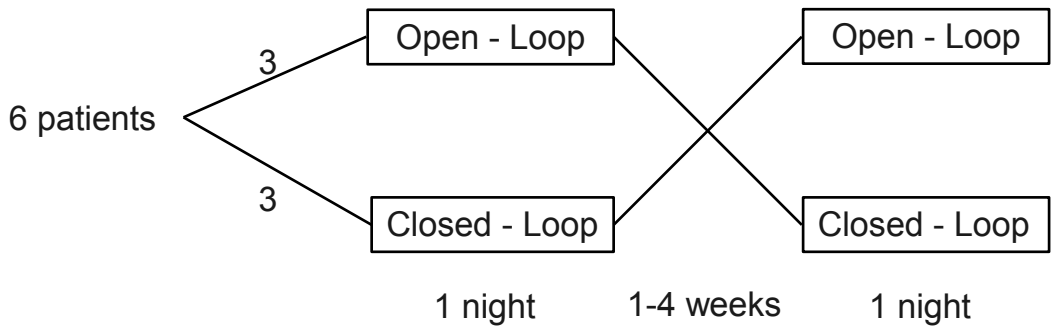
- Closed-loop control of blood glucose (here, using MPC) using a CGM and an insulin pump



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

The clinical protocol

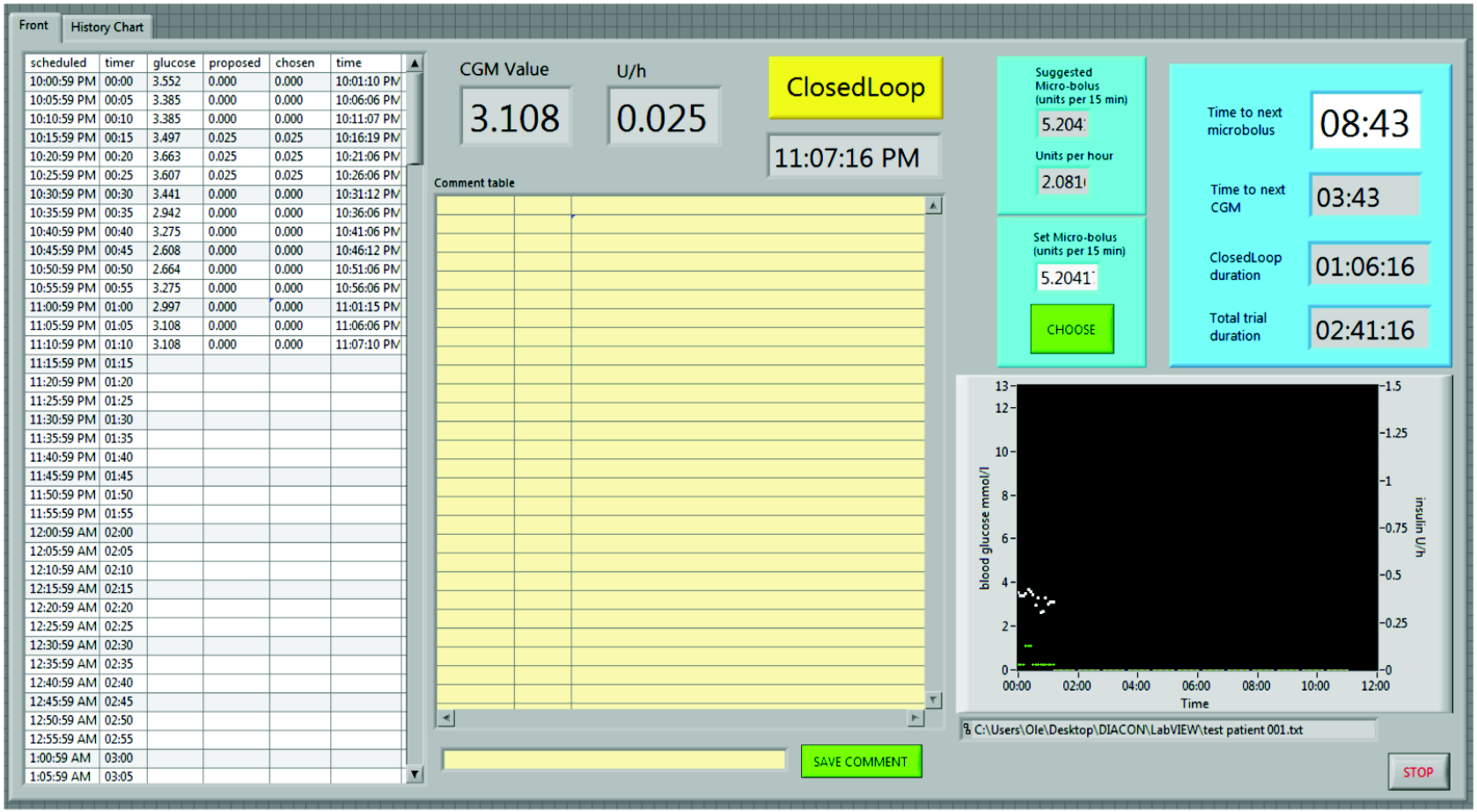
- Overnight $\Longrightarrow$ No meal
- 2 Randomized cross-studies



- 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

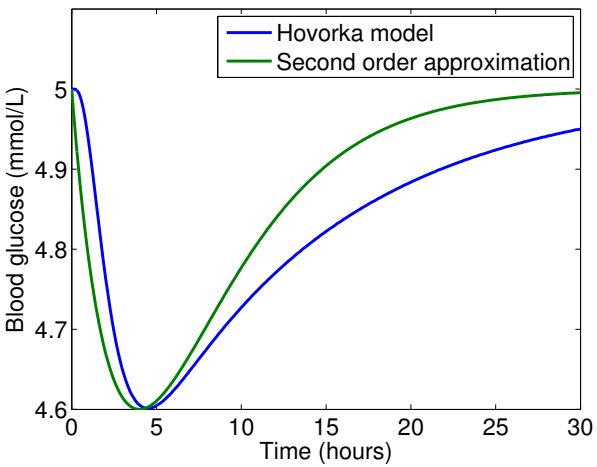


Patient model computation

- No use of prior data
- Instead, use of empirically estimated patient parameters
  - **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

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

- 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

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

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

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

Offset-free description

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

in which

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

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

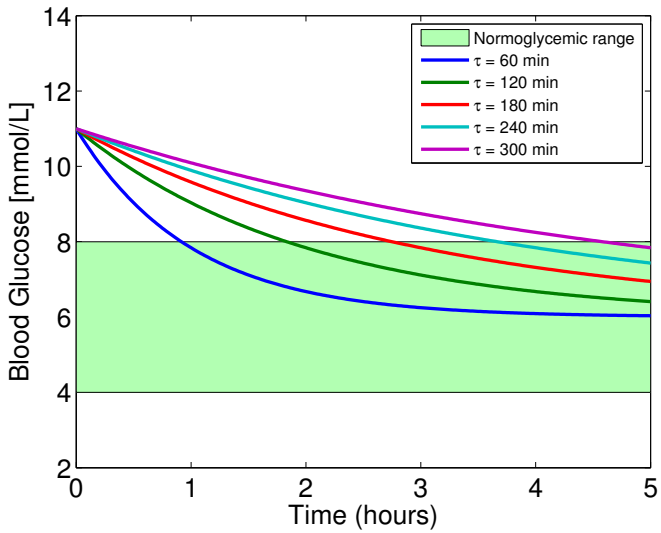
$$\min_{\{u_{k+j}, v_j\}_{j=0}^{N-1}} \phi = \frac{1}{2} \sum_{j=0}^{N-1} \|\hat{y}_{k+j+1|k} - \hat{r}_{k+j+1|k}\|_2^2 + \lambda \|\Delta u_{k+j}\|_2^2 + \kappa \|v_{k+j}\|_2^2$$

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

- $\hat{y}_{k+j+1|k}$ j+1 step ahead predictions of glucose
- $\hat{r}_{k+j+1|k}$ glucose setpoint
- u_{k+j} predicted insulin injections
- Penalize low BG, ie. $\hat{y}_{k+j+1|k} \leq G_{\min}$

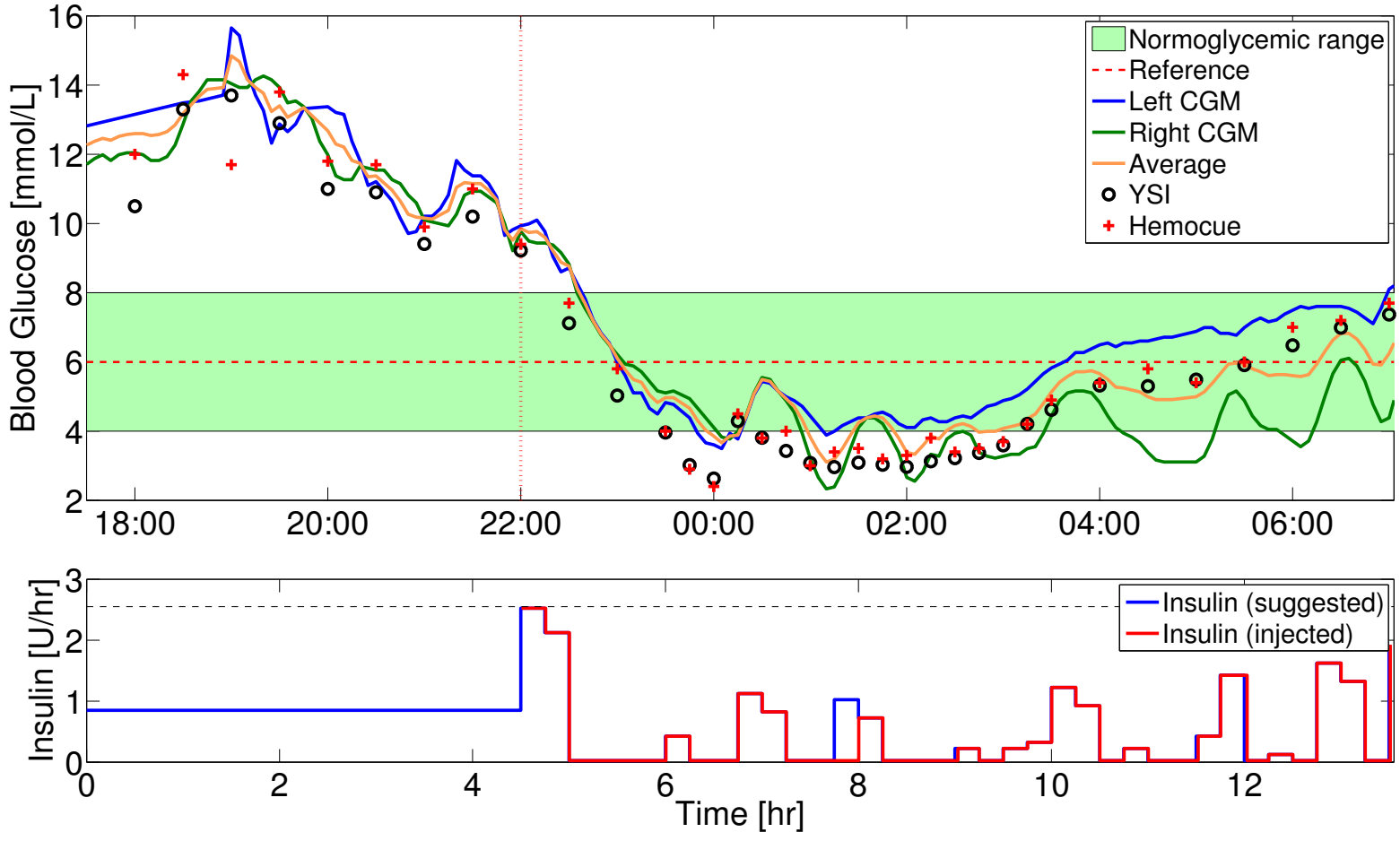
Glucose reference signal

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



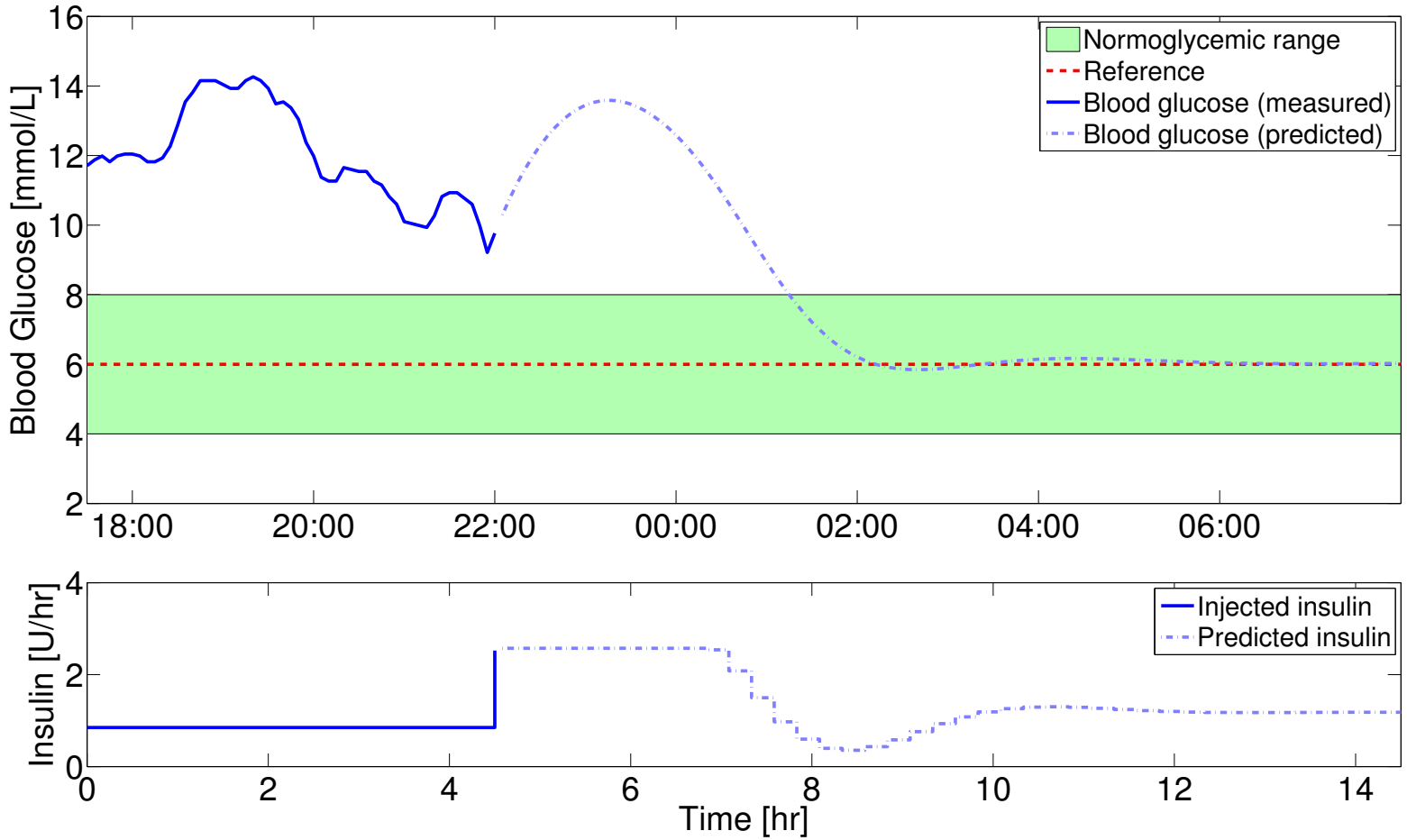
Results

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



Example of prediction

- Only based on the 2 last observations



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

$$\begin{aligned} x_{k+1} &= Ax_k + Bu_k + K\varepsilon_k \\ y_k &= Cx_k \end{aligned}$$

Goal: Choose α, β_1 and β_2 which are the roots of the characteristic polynomial of $A - KC$

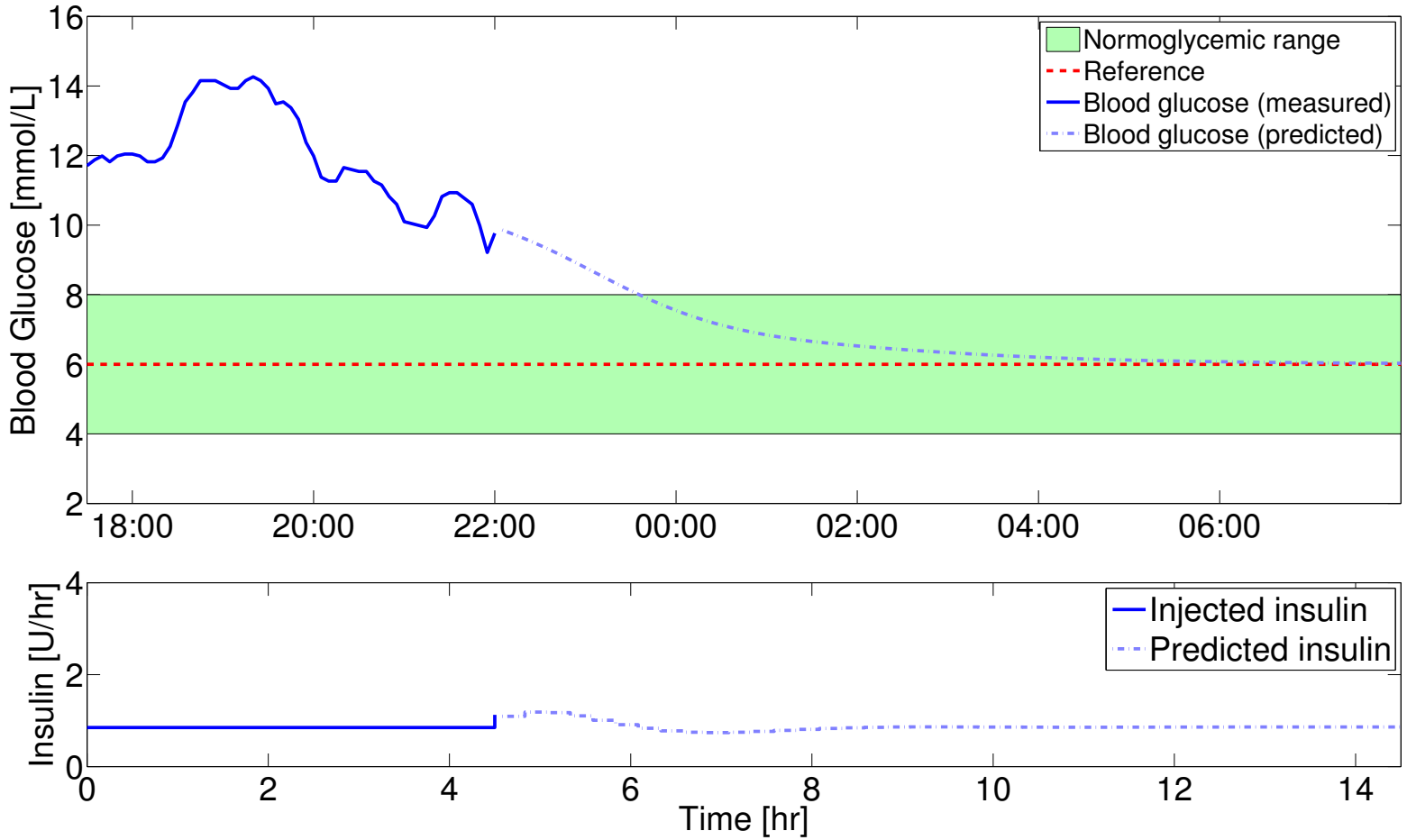
$$\chi(z) = z^3 + c_1 z^2 + c_2 z + c_3$$

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

$$\beta_{1,2} = 0.8 \pm 0.15i$$

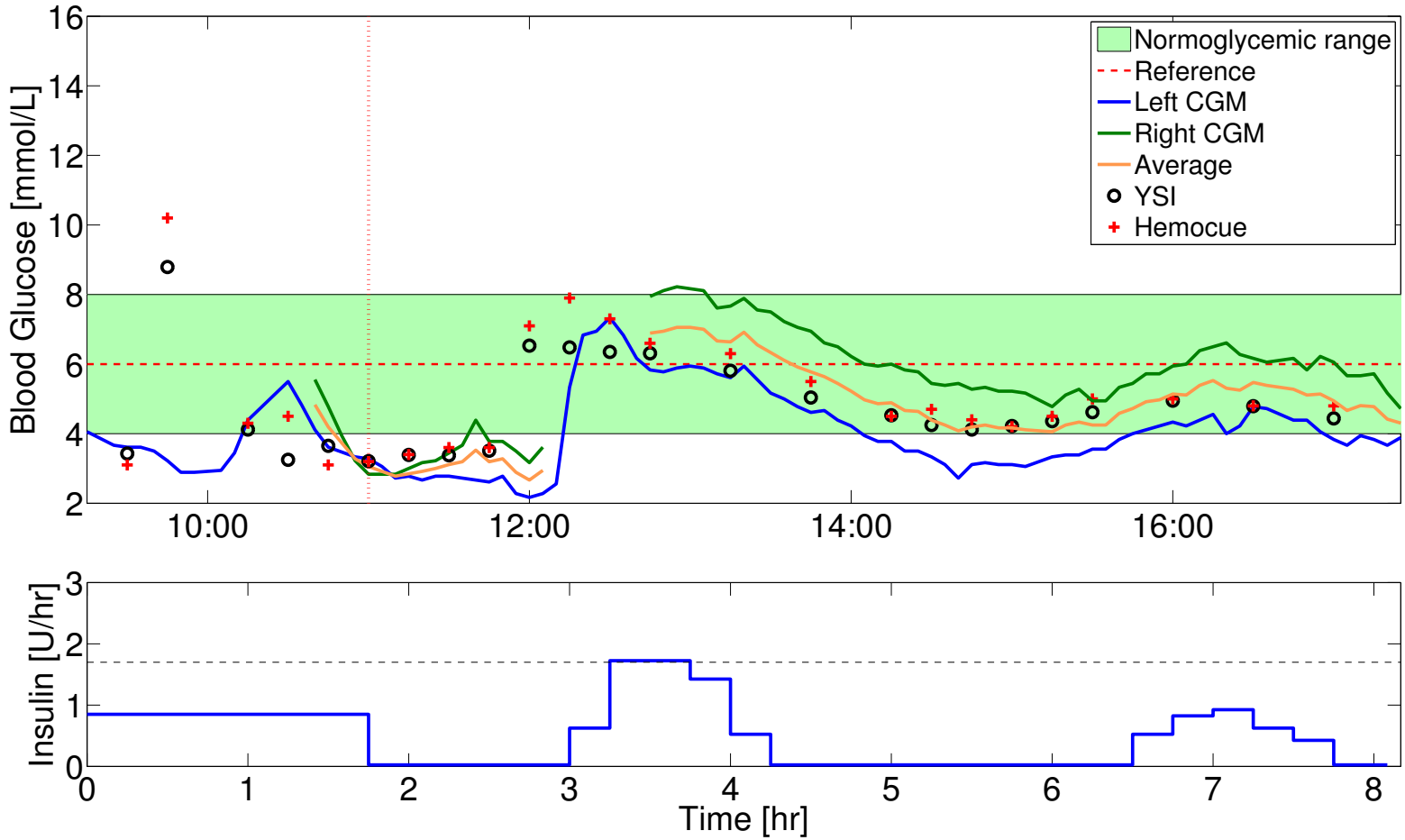
Example of prediction with the redesigned observer

- More taking the global trend of BG into account



Results - 2nd study

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



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