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

Dimitri Boiroux\textsuperscript{1}, Signe Schmidt\textsuperscript{2}, Anne Katrine Duun-Henriksen\textsuperscript{1}, Laurits Frøssing\textsuperscript{2}, Kirsten Nørgaard\textsuperscript{2}, Sten Madsbad\textsuperscript{2}, Ole Skyggebjerg\textsuperscript{1}, Niels Kjølstad Poulsen\textsuperscript{1}, Henrik Madsen\textsuperscript{1}, John Bagterp Jørgensen\textsuperscript{1}

\textsuperscript{1}DTU Informatics
Technical University of Denmark
\textsuperscript{2}Department of Endocrinology
Hvidovre Hospital

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Outline

1. Introduction
2. Material and methods
3. Controller design
4. Conclusion
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 $\implies$ No meal
- 2 Randomized cross-studies

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<table>
<thead>
<tr>
<th></th>
<th>Open - Loop</th>
<th>Closed - Loop</th>
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<tbody>
<tr>
<td>6 patients</td>
<td>3</td>
<td>3</td>
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<tr>
<td>1 night</td>
<td>1-4 weeks</td>
<td>1 night</td>
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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)

![Graph showing blood glucose levels over time](image)

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

\[ \bar{A}(q^{-1})y(t) = q^{-nk} \bar{B}(q^{-1})u(t) + \xi(t) \]

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

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

s.t. 
\begin{align*}
\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{align*}

- \(\hat{y}_{k+j+1|k}\) 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

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

and its reformulation in the innovation form

\[ x_{k+1} = A x_k + B u_k + K \varepsilon_k \]
\[ y_k = C x_k \]

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:

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