The Artificial Pancreas
Convex and Real-Time Optimization for Model Predictive Control in a Cyber-Medical System

John Bagterp Jørgensen

DIACON

DTU STU

REGION
Hvidovre Hospital

CortoOpt
Aalborg University, Aalborg, Denmark, August 23, 2016
DIACON – The Diabetes Control Group in Denmark
www.diacongroup.org
Diabetes is a Global Problem

**World**: 371 M people living with diabetes

**North America and Caribbean**
- 10.5% prevalence
- 29.2% undiagnosed
- More healthcare dollars were spent on diabetes in this region than any other
- 1 in 10 adults in this region has diabetes

**Middle East and North Africa**
- 9.2% prevalence
- 45.5% undiagnosed
- 1 in 9 adults in this region has diabetes
- More than half of people with diabetes in this region don’t know they have it

**Europe**
- 6.7% prevalence
- 38.6% undiagnosed
- 1 out of every 3 dollars spent on diabetes healthcare was spent in this region
- 21.2 million people in this region have diabetes and don’t know it

**Western Pacific**
- 8.0% prevalence
- 57.9% undiagnosed
- 1 in 3 adults with diabetes lives in this region
- 6 of the top 10 countries for diabetes prevalence are Pacific Islands

**South-East Asia**
- 8.3% prevalence
- 50% undiagnosed
- 1 in 5 of all undiagnosed cases of diabetes is in this region
- 1 in 4 deaths due to diabetes occurred in this region

*All estimates are presented as comparative rates*
Diabetes Statistics

More than **371 million** people have diabetes.

Top 10 Countries/Territories for people with diabetes (20-79 years):

- China: 123.0
- India: 118.4
- USA: 26.3
- Brazil: 13.6
- Russian Federation: 12.7
- Mexico: 10.4
- Indonesia: 7.6
- Egypt: 7.5
- Japan: 7.3
- Pakistan: 4.6

The number of people with diabetes is **increasing** in every country.

Top 10 Countries/Territories for prevalence (% of diabetes (20-79 years)):

1. Federated States of Micronesia: 37.2%
2. Nauru: 30.1%
3. Marshall Islands: 27.1%
4. Kiribati: 25.5%
5. Tuvalu: 24.8%
6. Kuwait: 22.9%
7. Saudi Arabia: 22.4%
8. Qatar: 22.3%
9. Bahrain: 22.1%
10. Vanuatu: 22.0%

Half of people with diabetes **don't know** they have it.

Undiagnosed percentage and undiagnosed cases of diabetes (20-79 years) by region:

- 4 out of 5 people with diabetes live in **low- and middle-income** countries.

- Half of people who die from diabetes are **under the age of 60**.

- 4.8 million people died and **471 billion USD were spent** due to diabetes in 2012.

Healthcare Expenditures and deaths per 1,000 due to diabetes by income group:
Conventional Insulin Therapy

5-8 blood glucose measurements per day

Detailed carbohydrate counting & adjustment for other events

Computation of insulin dosage by pen or pump

Insulin administration

Blood glucose concentration for conventional insulin therapy

- Conventional therapy relies on patients’ decisions
- Therapeutic goals are often not achieved
  - Metabolic control (Hb1Ac) too high
  - Late diabetic complications (eyes, kidneys, micro vascular, nerves...)
  - Prevailing risk of mild and severe hypoglycemia
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Goal

Artificial Pancreas
- Closed Loop Control
Insulin and Glucagon
Dual Hormone Artificial Pancreas
Technologies for Diabetes Treatment

(a) Single hormone (insulin) AP.

(b) Dual hormone (insulin and glucagon) AP.

(c) Integrated sensor and smart insulin pens.

(d) Traditional pen based treatment of diabetes.
Artificial Pancreas

Single- (insulin) or dual-hormone (insulin+glucagon)?

Our approach
CLINICAL TEST AND VERIFICATION OF THE ARTIFICIAL PANCREAS

Overnight Clinical Study of the Artificial Pancreas (AP)

Average blood glucose and its variation for all patients in the study.

Conclusion:
More blood glucose values are in the target range (4-8 mmol/L) with the AP than without.

REGION
Hvidovre Hospital
Average blood glucose and its variation for all patients in the study.

Grey: Without the AP
Dark Grey: With the AP

**Conclusion:**
More blood glucose values are in the target range (4-8 mmol/L) with the AP than without.
PORTABLE ARTIFICIAL PANCREAS
CHALLENGES IN ESTABLISHING THE CLOSED LOOP

Platform:
- Control algorithm
- Data integration
- Hardware

Glucose sensing:
- Accuracy
- Reliability
- Time lag

Insulin infusion:
- Subc. vs iv.
- ”Slow” insulin
- Insulin cannot be withdrawn
CHALLENGES IN ESTABLISHING THE CLOSED LOOP

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O120 Heise et al. Faster-acting insulin aspart improves postprandial glycaemia versus insulin aspart in patients with type 1 diabetes.

Figure: Meal test blood glucose profile.

\[
\Delta AUC_{BG,0-2\, \text{hours}} \text{ ratio [95\% CI]} \frac{\text{FIA(B)}}{\text{IAsp}} = 0.74 \, [0.63; \, 0.87]
\]

\[
\Delta AUC_{BG,0-6\, \text{hours}} \text{ ratio [95\% CI]} \frac{\text{FIA(B)}}{\text{IAsp}} = 0.67 \, [0.45; \, 0.92]
\]
Glucagon

- Not stable in liquid solution
  - Cannot be used in pump

-Glucagon Analogue (Zealand Pharma)
  - Stable in liquid solution
  - Can be used in a pump

-Purposes
  - Safety mechanism in case of low BG
  - Allow addition of more insulin at meals => more efficient treatment
CHALLENGES IN ESTABLISHING THE CLOSED LOOP

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Uses the left CGM for feedback
CHALLENGES 1
# NEWEST SENSOR ACCURACY

<table>
<thead>
<tr>
<th>Performance vs. YSI</th>
<th>CGM</th>
<th>SMBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal matched pairs (N)</td>
<td>2263</td>
<td>994</td>
</tr>
<tr>
<td>Pearson Correlation Coefficient</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean Absolute Relative Difference (ARD)</td>
<td>9.0%</td>
<td>4.6%</td>
</tr>
<tr>
<td>MARD within Day 1</td>
<td>Day 4</td>
<td>Day 7</td>
</tr>
<tr>
<td>Mean Absolute Difference (MAD), at Hypoglycemia BG &lt;= 70 mg/dl</td>
<td>6.4 mg/dL</td>
<td>4.2 mg/dL</td>
</tr>
<tr>
<td>MARD at Euglycemia 70 &lt; BG &lt;= 180</td>
<td>9.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>MARD at Hyperglycemia BG &gt; 180 mg/dl</td>
<td>8.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Overall CEGA+B Zones</td>
<td>A Zone</td>
<td>99.5%</td>
</tr>
<tr>
<td>CG-EGA Zone Accurate Readings</td>
<td>95.6%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Hypoglycemia/Euglycemia/Hyperglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Balo, EASD, Vienna 2014
CHALLENGES IN ESTABLISHING THE CLOSED LOOP

Platform:
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- Hardware

Glucose sensing:
- Accuracy
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- Subc. vs iv.
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INSULIN PUMPS & GGMS & ...
Diabetes and Computational Engineering

Mathematical & Statistical Modeling

Optimization & Model Predictive Control

\[ \min \phi = \int_{t_k}^{t_k+T} g(x(t), u(t)) \, dt \]

s.t. \[ x(t_k) = \tilde{x}_{k|k} \]
\[ \dot{x}(t) = f(x(t), u(t), d(t)) \quad t \in [t_k, t_k + T] \]
\[ c(x(t), u(t)) \geq 0 \quad t \in [t_k, t_k + T] \]

Simulation

Blood Glucose Concentration

Carbohydrates in meals

Insulin injections by a pump

Implementation on Different Computing Platforms

Cluster of high performance computers

Laptops & Workstations

Mobile computing devices
The Artificial Pancreas

Prototype Artificial Pancreas – Beta Cell
Insulin Pump + Glucose Sensor
Laptop computer with control algorithm (MPC)

Portable Artificial Pancreas – Beta Cell
Insulin Pump + Glucose Sensor
Smartphone computer with control algorithm (MPC)

Portable Artificial Pancreas
Insulin Pump + Glucagon Pump + Glucose Sensors
Smartphone computer with control algorithm (MPC)

Picture from the Boston Group (Damiano, Russe)
SINGLE HORMONE ARTIFICIAL PANCREAS
MPC

Objective function

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

- \( \hat{y}_{k+j+1|k} \): \( j+1 \) step ahead predictions of glucose
- \( \bar{r}_{k+j+1|k} \): glucose setpoint
- \( u_{k+j} \): predicted insulin injections

\[ \min \{ u_{k+j} \}_{j=0}^{N-1} \phi \]

s.t.

\[ \hat{x}_{k+1|k} = A \hat{x}_{k|k-1} + B \hat{u}_{k|k} + K e_k \]
\[ \hat{y}_{k+1|k} = C \hat{x}_{k+1|k} \]
\[ \hat{x}_{k+j+1|k} = A \hat{x}_{k+j|k} + B \hat{u}_{k+j|k} \]
\[ \hat{y}_{k+j|k} = C \hat{x}_{k+j|k} \]
\[ u_{\text{min}} \leq u_{k+j} \leq u_{\text{max}} \]
\[ C_{\text{min}} - \hat{y}_{k+j+1|k} \leq v_{k+j} \]
\[ v_j \geq 0 \]
The two parameters in the model for each individual can be computed from the insulin action time and the insulin sensitivity factor.
SINGLE HORMONE MPC – OVERNIGHT
SINGLE HORMONE MPC – OVERNIGHT
DUAL HORMONE 
ARTIFICIAL PANCREAS
Why Glucagon?

What it may provide

- Rescue from hypoglycemia after insulin overdose
- Intensive exercise without carbohydrate interventions
- Prevent hypoglycemia during overnight control

Practical issues

- **Stability in liquid form**
- Glucagon dosing
- Infusion system
  - Two pumps or one dual-chamber pump
  - Infusion sets

New glucagon analogues (e.g. Zealand Pharma’s)
Overview of the Control System

Dual-hormone AP

Meal announcement

Target

Insulin / Glucagon Infusion Control System

Insulin

Glucagon

Patient

Measurement (CGM)
Control Structure

Prandial insulin controller

- Meal announcement
- Bolus calculator

Microbolus insulin & glucagon controller

- Target
- Reference trajectory
- Insulin MPC
- Glucagon MPC
- Controller switching
- Safety rules

Estimator

- Kalman filter
- Measurement (CGM)

Patient
Deterministic Prediction Model

**Glucose-Insulin dynamics**

\[ G_{s1}(s) = \frac{K_{u1}}{(\tau_1 s + 1)^2} \]

**Glucose-Glucagon dynamics**

\[ G_{s2}(s) = \frac{K_{u2}}{(\tau_2 s + 1)^2} \]

Stochastic Prediction Model

- Discretized model (ARMAX) with an augmented stochastic part:

\[
y(t) = \frac{B_1(q^{-1})}{A_1(q^{-1})} u_1(t) + \frac{B_2(q^{-1})}{A_2(q^{-1})} u_2(t) + \frac{C(q^{-1})}{A_1(q^{-1})} \epsilon(t)
\]

- Polynomial \( C \) was identified from measurement data for a real patient; constant for all patients*

- State space model in the innovation form:

\[
\begin{align*}
x_{k+1} &= A x_k + B u_k + K \epsilon_k \\
y_k &= C x_k + \epsilon_k 
\end{align*}
\]

\[
\begin{align*}
u_k &= [u_{1k} \quad u_{2k}]^T \\
u_{1k} &= u_{1m_k} + u_{1bol_k} \\
u_{1k} &= \text{insulin infusion} \\
u_{2k} &= \text{glucagon infusion}
\end{align*}
\]

Kalman Filter

• Central part of the Control System
• The innovation of the state space realization is

\[ e_k = y_k - C\hat{x}_{k|k-1} \]

• Due to correlated process and measurement noise in the model in innovation form, we can compute the predictions as

\[
\begin{align*}
\hat{x}_{k|k} &= \hat{x}_{k|k-1} \\
\hat{x}_{k+1|k} &= A\hat{x}_{k|k-1} + Bu_k + Ke_k \\
\hat{y}_{k+1|k} &= C\hat{x}_{k+1|k}
\end{align*}
\]

1-step prediction

\[
\begin{align*}
\hat{x}_{k+1+j|k} &= A\hat{x}_{k+j|k} + Bu_{k+j|k} \\
\hat{y}_{k+1+j|k} &= C\hat{x}_{k+1+j|k}
\end{align*}
\]

j-step predictions

Controller Switching

- Switching is based on the Kalman filter predictions
- Insulin controller is suspended and glucagon controller is activated whenever the Kalman filter predicts hypoglycemia
Microbolus Insulin MPC

- **Objective function**

\[
\phi = \frac{1}{2} \sum_{j=0}^{N-1} \left( \left\| \hat{y}_{k+1+j|k} - r_{k+1+j|k} \right\|^2 + \gamma \left\| \hat{\eta}_{k+1+j|k} \right\|^2 + \lambda_I \left\| \Delta u_{1m,k+j|k} \right\|^2 \right)
\]

\[
\text{Glucose penalty function} \quad \text{Regularization term}
\]

- **Convex QP problem**

\[
\min_{\{u_{1m,j}, \eta_{j+1}\}_{j=0}^{N-1}} \phi
\]

\[
\begin{aligned}
\dot{x}_{k+1|k} &= A \hat{x}_{k|k-1} + B_1 u_{1m,k|k} + K e_k \\
\dot{y}_{k+1|k} &= C \hat{x}_{k+1|k} \\
\dot{x}_{k+1+j|k} &= A \hat{x}_{k+j|k} + B_1 u_{1m,k+j|k} \\
\dot{y}_{k+1+j|k} &= C \hat{x}_{k+1+j|k} \\
\min u_{1m} \quad & \leq u_{1m,k+j-1|k} \leq \max u_{1m} \\
\dot{y}_{k+j|k} & \geq y_{\min} - \hat{\eta}_{k+j|k} \\
\dot{y}_{k+j|k} & \leq y_{\max} + \hat{\eta}_{k+j|k} \\
\hat{\eta}_{k+j|k} & \geq 0
\end{aligned}
\]

1-step ahead prediction

\[
\text{j-step ahead predictions} \quad \text{Input constraints} \quad \text{Soft output constraints}
\]

\[
N_0 = \{1, \ldots, N\}, \quad N_1 = \{1, \ldots, N - 1\}
\]
Algorithm Modifications

- Asymmetric time-varying reference signal

\[ r_{k+j|k}(t) = \begin{cases} 
(G - G_{ss})e^{-t/\tau_r} & \text{if } (G - G_{ss}) \geq 0 \text{ (mmol/L)} \\
0 & \text{if } (G - G_{ss}) < 0 \text{ (mmol/L)}
\end{cases} \]

- Additional safety rules – safeguard against aggressive control moves

\[ u_{1m \ max} = \begin{cases} 
2u_1b & \text{if } G \geq 10 \text{ (mmol/L)} \\
u_1b & \text{if } 5.5 \leq G < 10 \text{ (mmol/L)} \\
0 & \text{if } G < 5.5 \text{ (mmol/L)}
\end{cases} \]
Microbolus Glucagon MPC

- Objective function

\[
\phi = \frac{1}{2} \sum_{j=0}^{N-1} \left( \| \hat{y}_{k+1+j|k} - r_{g\, k+1+j|k} \|_2^2 + \gamma \| \hat{\eta}_{k+1+j|k} \|_2^2 \right) + \lambda_G \| \Delta u_{2;k+j|k} \|_2^2
\]

Glucose penalty function

Regularization term

- Convex QP problem

\[
\min_{\{u_{1m,j}, \eta_{j+1}\}^{N-1}_{j=0}} \phi
\]

s. t.

1-step ahead prediction

\[
\hat{x}_{k+1|k} = A \hat{x}_{k|k-1} + B_2 u_{2|k} + K e_k
\]

\[
\hat{y}_{k+1|k} = C \hat{x}_{k+1|k}
\]

\[
\hat{x}_{k+1+j|k} = A \hat{x}_{k+j|k} + B_2 u_{2|k+j|k} \quad j \in \mathcal{N}_1
\]

\[
\hat{y}_{k+1+j|k} = C \hat{x}_{k+1+j|k} \quad j \in \mathcal{N}_1
\]

\[
u_{2} \geq 0 \quad j \in \mathcal{N}_0
\]

Input constraint

\[
\hat{y}_{k+j|k} \geq y_{\min} - \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0
\]

\[
\hat{y}_{k+j|k} \leq y_{\max} + \hat{\eta}_{k+j|k} \quad j \in \mathcal{N}_0
\]

Soft output constraints

\[
\hat{\eta}_{k+j|k} \geq 0 \quad j \in \mathcal{N}_0
\]

\[\mathcal{N}_0 = \{1, \ldots, N\}, \mathcal{N}_1 = \{1, \ldots, N - 1\}\]
Bolus Calculator

- Calculation includes correction for the current glucose level

\[ \text{Bolus} = \text{CHO} \cdot IC + \hat{y}_k|_k / ISF \]

- CHO – carbohydrate content in the meal (g)
- IC – insulin to carbohydrate ratio [U/g]
- ISF – insulin sensitivity factor [mmol/L/U]
- \( \hat{y}_k|_k \) is deviation from the target [mmol]
INSULIN ADMINISTRATION STRATEGIES

NMPC
Pre-meal Insulin Allowed

NMPC
No Pre-meal Insulin

MDI (Pen Based) Insulin Treatment

\[
\begin{align*}
\min \phi &= \int_{t_k}^{t_k+T} g(x(t), u(t)) \, dt \\
\text{s.t.} \quad x(t_k) &= \hat{x}_{k|k} \\
\dot{x}(t) &= f(x(t), u(t), d(t)) \quad t \in [t_k, t_k + T] \\
c(x(t), u(t)) &\geq 0 \quad t \in [t_k, t_k + T]
\end{align*}
\]
Effect of Insulin prediction

Effect of glucagon prediction

CONTROLLER PRINCIPLE

\[
\min_{\{u_{1m, j}\}_{j=0}^{N-1}} \phi = \frac{1}{2} \sum_{j=0}^{N-1} \|\tilde{y}_{k+1+j|k} - \bar{r}_{k+1+j|k}\|^2 + \lambda_1 \|\Delta u_{1m, k+j|k}\|^2 + \gamma \|\tilde{h}_{k+1+j|k}\|^2
\]

s. t.
\[
\begin{align*}
\tilde{x}_{k+1|k} &= A\tilde{x}_{k|k-1} + B_1 u_{1m, k|k} + Ke_k \\
\tilde{y}_{k+1|k} &= C\tilde{x}_{k+1|k} \\
\tilde{y}_{k+1+j|k} &= A\tilde{x}_{k+1+j|k} + B_1 u_{1m, k+j|k} \\
\hat{y}_{k+1+j|k} &= C\tilde{x}_{k+1+j|k} \\
u_{1m, \min} \leq u_{1m, k+j|k} &\leq u_{1m, \max} \\
\bar{h}_{k+j|k} &\geq \bar{h}_{k+j|k} \\
\tilde{h}_{k+j|k} &\leq \tilde{h}_{k+j|k} \\
\hat{h}_{k+j|k} &\geq 0
\end{align*}
\]

0.1 ISF
Constrained Extended Linear Quadratic Optimal Control Problem

The constrained extended linear quadratic optimal control problem

\[
\min_{\{x_{k+1}, u_k\}_{k=0}^{N-1}} \phi = \sum_{k=0}^{N-1} l_k(x_k, u_k) + l_N(x_N)
\]

s.t. \[x_{k+1} = A'_k x_k + B'_k u_k + b_k, \quad k = 0, 1, \ldots, N - 1\]

\[C'_k x_k + D'_k u_k + c_k \geq d_k, \quad k = 0, 1, \ldots, N - 1\]

with stage costs

\[
l_k(x_k, u_k) = \frac{1}{2} (x'_k Q_k x_k + 2x'_k M_k u_k + u'_k R_k u_k) + q'_k x_k + r'_k u_k + f_k
\]

\[
l_N(x_N) = \frac{1}{2} x'_N P_N x_N + p'_N x_N + \gamma_N
\]
Convex Quadratic Program

\[
\begin{align*}
\min_x \quad & \phi = \frac{1}{2} x' G x + g' x \\
\text{s.t.} \quad & A' x = b \\
& C' x \geq d
\end{align*}
\]

Principal solution methods

- Primal active set method \cite{GillMurray1978} (Gill and Murray, 1978)
- Dual active set method \cite{GoldfarbIdnani1983} (Goldfarb and Idnani, 1983)
- Primal-dual interior point methods \cite{Wright1997} (Wright, 1997)
KKT Systems

- **Primal active set method**

\[
\begin{bmatrix}
G & -A & -F \\
-A' & 0 & 0 \\
-F' & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
p \\
\pi \\
\lambda \\
\end{bmatrix} = -
\begin{bmatrix}
Gx + g \\
0 \\
0 \\
\end{bmatrix}
\]

\[F = [c_i]_{i \in \mathcal{W}}\]

- **Dual active set method**

\[
\begin{bmatrix}
G & -A & -F \\
-A' & 0 & 0 \\
-F' & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
p \\
w \\
v \\
\end{bmatrix} = \begin{bmatrix}
c_r \\
0 \\
0 \\
\end{bmatrix}
\]

\[F = [c_i]_{i \in \mathcal{W}}\]
Schur Complement Solution Method

The KKT equation (5) and an associated Schur complement, $S$, is

$$
\begin{bmatrix}
  G & -A & -F \\
  -A' & 0 & 0 \\
  -F' & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
  p \\
  s \\
  u \\
\end{bmatrix}
= -
\begin{bmatrix}
  h \\
  0 \\
  0 \\
\end{bmatrix}
$$

(5)

$$
S = \begin{bmatrix}
  F' & 0 \\
\end{bmatrix}
\begin{bmatrix}
  G & -A \\
  -A' & 0 \\
\end{bmatrix}^{-1}
\begin{bmatrix}
  F \\
  0 \\
\end{bmatrix}
= LL'
$$

Then (5) may be solved by

$$
\begin{bmatrix}
  G & -A \\
  -A' & 0 \\
\end{bmatrix}
\begin{bmatrix}
  p_0 \\
  s_0 \\
\end{bmatrix}
= -
\begin{bmatrix}
  h \\
  0 \\
\end{bmatrix}
$$

$$
LL'u = -F'p_0
$$

$$
\begin{bmatrix}
  G & -A \\
  -A' & 0 \\
\end{bmatrix}
\begin{bmatrix}
  p \\
  s \\
\end{bmatrix}
= -
\begin{bmatrix}
  h - Fu \\
  0 \\
\end{bmatrix}
$$
Summary of the Solution of the QPs

The inequality constrained QP

$$\min_{x} \phi = \frac{1}{2} x' G x + g' x$$

s.t. $A' x = b, \ C' x \geq d$

is solved by solving systems of the type

$$\begin{bmatrix} G & -A \\ -A' & 0 \end{bmatrix} \begin{bmatrix} p \\ s \end{bmatrix} = - \begin{bmatrix} h \\ 0 \end{bmatrix}$$

$$\begin{bmatrix} \tilde{G} & -A \\ -A' & 0 \end{bmatrix} \begin{bmatrix} \Delta x \\ \Delta \pi \end{bmatrix} = - \begin{bmatrix} \tilde{r}_G \\ r_A \end{bmatrix}$$

which correspond to equality constrained QPs
\[
\min_{\{x_k, u_k\}_{k=0}^{N-1}} \phi = \sum_{k=0}^{N-1} \ell_k(x_k, u_k) + l_N(x_N)
\]

\[
s.t. \quad x_{k+1} = A_k'x_k + B_k'u_k + b_k, \quad k = 0, 1, \ldots, N - 1
\]

with stage costs
\[
\ell_k(x_k, u_k) = \frac{1}{2}(x_k'Q_kx_k + 2x_k'M_ku_k + u_k'R_ku_k) + q_k'x_k + r_k'u_k + f_k
\]
\[
l_N(x_N) = \frac{1}{2}x_N'P_Nx_N + p_N'x_N + \gamma_N
\]

1. **Riccati recursions.** Solve for \(k = N - 1, N - 2, \ldots, 0\)

\[
K_k = -(R_k + B_kP_{k+1}B_k')^{-1}(M_k' + B_kP_{k+1}A_k')
\]
\[
a_k = -(R_k + B_kP_{k+1}B_k')^{-1}(r_k + B_k(P_{k+1}b_k + p_{k+1}))
\]
\[
P_k = Q_k + A_kP_{k+1}A_k' + (M_k + A_kP_{k+1}B_k')K_k
\]
\[
p_k = (A_k' + B_k'K_k)'(P_{k+1}b_k + p_{k+1}) + q_k + K_k'r_k
\]

2. **Compute primal solution.** Solve for \(k = 0, 1, \ldots, N - 1\)

\[
u_k = K_kx_k + a_k
\]
\[
x_{k+1} = A_k'x_k + B_k'u_k + b_k
\]

3. **Compute dual solution.** Solve for \(k = N - 1, N - 2, \ldots, 1\)

\[
\pi_{N-1} = P_Nx_N + p_N
\]
\[
\pi_{k-1} = A_k\pi_k + Q_kx_k + M_ku_k + q_k
\]
DUAL HORMONE MPC – CORRECT BOLUS
DUAL HORMONE MPC – CORRECT BOLUS

Graph showing glucose concentration over time with target and predicted profiles, insulin and glucagon infusion profiles.
DUAL HORMONE MPC - OVERBOLUS
DUAL HORMONE MPC - OVERBOLUS
DUAL HORMONE MPC - UNDERBOLUS
DUAL HORMONE MPC – MISSED BOLUS
Conclusion

• Dual-hormone AP Benefits
  – Glucagon - safety feature of the AP systems
  – Prevention/rescue from hypoglycemia after insulin overdose
  – Reduction of psychological burden

• Remaining challenges
  – Glucagon infusion activation
    • Accurate prediction model (short term)
    • Avoid unwanted injection (sensor noise, erroneous estimates)
  – Potential glucagon side effects
DIACON AMBITION

Objective:
Patients in Denmark must have access to Artificial Pancreas Technology in 2020

Safe and efficient Artificial Pancreas System

1. Portable
2. Dual CGMs
3. Ultra Fast Acting Insulin
4. Glucagon Analogue
5. Remote Monitoring
DIACON – The Diabetes Control Group in Denmark
www.diacongroup.org
Thank you for your attention!