Conventional Feedback and Model-Based Control of Blood Glucose Level in Type-I Diabetes Mellitus

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Outline

- Model development: Glucosim
- Routes for insulin infusion
- Model characteristics
- Controller characteristics
- Simulation results for single glucose input
- Simulation results for multiple food intakes
- Conclusions

Model Development

- Compartmental model
- Based on mass balances written around each organ for blood glucose and insulin using pharmacokinetic diagrams of glucose and insulin.
- Kinetic parameters chosen to simulate observed behavior of absorption, extraction and uptake of glucose and/or insulin in each organ.
- Revision: No dead-time for insulin activation.
  (Sorensen,1985) (Hillman, 1976)

GLUCOSIM

- A user-friendly, interactive simulation package developed in Matlab
  - Illustration of glucose-insulin interactions in human body at various conditions:
    - change in diet, (i.e. time and CHOM content)
    - change in insulin type,
    - change in exercise,
    - healthy and diabetic subjects
  - Regulation of insulin using insulin pumps
  - Assessment of various types of automatic control systems (PID, IMC, MPC) for operating the pump
- Uncontrolled response simulation available as Matlab files and on the Web:
  www.chee.iit.edu/~cinar/
Physiological Compartments

21 ordinary differential equations representing single organs with variable volumes as a function of the body weight, overall mass balances and subcutaneous insulin transport.

1. Heart (heart, lungs and arteries) [G,I]
2. Brain (central nervous system) [G]
3. Liver [G,I]
5. Gastrointestinal (GI) tract [G,I]
7. Periphery (skeletal muscle and adipose tissue) [G,I]
8. Subcutaneous tissue [I -- diabetic patient only]

Pharmacokinetic Diagrams

Insulin Administration with Feedback Controlled Pump

- Reduced risk of long-term complications with intensive diabetes management
- Potential to reduce risk of hypoglycemia
- Increased risk of hypoglycemia with poorly tuned controllers
- Control algorithms used:
  - Proportional-Integral-Derivative (PID)
  - Internal model control (IMC)
  - Model predictive control (MPC)

Routes for Insulin Delivery

- Subcutaneous Route
  - Currently used for injections and pumps
  - Transportation issues
- Intraperitoneal Route
  - Clinical trials for implantable pumps
  - Physiologically correct method
  - Assumption: Rapid absorption into portal circulation
Model Characteristics (Glucosim)

- Compartmental model with 21 state variables
- Nonlinear
  - 2 bilinear terms
  - 1 exponential term
  - 2 threshold functions
- 30 min dead-time for 2 variables
- Subcutaneous route
  - Time constant: 192 min
  - Time delay: 172 min
- Intraperitoneal route
  - Time constant: 86 min
  - Time delay 32 min

Controller Characteristics

Digital PID, IMC, and MPC controllers

- Input: Blood glucose measurements with white noise (σ² = 2 mg/dl)
- Output: Insulin injection rate
- Sampling time: 5 min

- PID Controller
  - Ciancone correlations (P, I, D settings function of gain, first order lag time constant, and delay values of model)
  - Antireset windup settings

- IMC Controller
  - Ciancone correlations
  - Internal Model: First order plus time delay

MPC controller

- Linear MPC with linear Kalman filter
- 33 state variables
- Objective Function:

$\min_{\Delta u(k)} \sum_{i=1}^{p}[\Gamma_y (y(k+l|k) - r(k+l)]^2 + \sum_{l=1}^{m}[\Gamma_u (\Delta u(k+l) - 0)]^2$

- $p, m = 10$, prediction and control horizons
- $u$: Insulin injection rate ($\Delta u$ change in input) $0 < u < 100$ mU/min
- $y$: Estimates of future glucose level measurements
- $\Gamma_y, \Gamma_u$: Weights
- $r$: 80 mg/dl reference (set-point)

Simulation with Single Glucose Input

- 154 lb (70 kg) Type I diabetic patient
- 15 hours of simulation (900 min)
- System disturbed at $t = 30$ min with 50 g glucose
- Measurements every 5 min with white noise (σ² = 2 mg/dl)
- Regular (fast acting) insulin
Intraperitoneal Route

PID controller performance

- Better control with intraperitoneal route (response characteristics, IAE and ITSE magnitudes)
- Quicker response of blood insulin concentration to injection rate for peritoneal route (difference in mass transport limitations)
Comparison of All Controllers

Intraperitoneal Route

- Glucose concentration within physiological limits.
- Noise amplification for PID and IMC prevents aggressive controller settings.
- Better control with MPC in terms of response characteristics, IAE and ITSE magnitudes.

Comparison of All Controllers

Subcutaneous Route

- First glucose peak hard to handle for subcutaneous route due to transport delay.
- Risk to induce hypoglycemia.

<table>
<thead>
<tr>
<th>Min glucose conc. (mg/dl)</th>
<th>No control</th>
<th>PID</th>
<th>IMC</th>
<th>MPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max glucose conc. (mg/dl)</td>
<td>245</td>
<td>239</td>
<td>230</td>
<td>245</td>
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</tbody>
</table>

Comparison of All Controllers

Subcutaneous Route

<table>
<thead>
<tr>
<th>Min glucose conc. (mg/dl)</th>
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</thead>
<tbody>
<tr>
<td>Max glucose conc. (mg/dl)</td>
<td>245</td>
<td>170</td>
<td>146</td>
<td>127</td>
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</tbody>
</table>

<table>
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<tr>
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<th>MPC</th>
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</thead>
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<tr>
<td>Max glucose conc. (mg/dl)</td>
<td>80</td>
<td>71</td>
<td>72</td>
<td>62</td>
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</table>
Comparison of Controllers Using Integrated Errors Over Time

**Subcutaneous Route**

<table>
<thead>
<tr>
<th></th>
<th>No control</th>
<th>PID</th>
<th>IMC</th>
<th>MPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IAE</strong></td>
<td>60.6 x 10^6</td>
<td>43.8 x 10^6</td>
<td>33.2 x 10^6</td>
<td>54.4 x 10^6</td>
</tr>
<tr>
<td><strong>ITSE</strong></td>
<td>1777 x 10^6</td>
<td>975.5 x 10^6</td>
<td>530.9 x 10^6</td>
<td>1521 x 10^6</td>
</tr>
</tbody>
</table>

**Intraperitoneal Route**

<table>
<thead>
<tr>
<th></th>
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<th>PID</th>
<th>IMC</th>
<th>MPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IAE</strong></td>
<td>60.6 x 10^3</td>
<td>15.1 x 10^3</td>
<td>11.4 x 10^3</td>
<td>3.3 x 10^3</td>
</tr>
<tr>
<td><strong>ITSE</strong></td>
<td>1777 x 10^3</td>
<td>121.3 x 10^3</td>
<td>52.9 x 10^3</td>
<td>7.2 x 10^3</td>
</tr>
</tbody>
</table>

**IAE** integral of absolute error

**ITSE** integral of squared error multiplied by time

### Simulation of Glucose Dynamics With Multiple Food Intakes

- 154 lb (70 kg) Type I diabetic patient
- Intraperitoneal Route
- 15 hours of simulation (900 min)
  - Simulation start: 8:00am
  - Breakfast: 8:30am 400 mg/kg CHOM
  - Exercise: 9:00am to 9:30am
  - Snack: 12:00pm 100 mg/kg CHOM
  - Lunch: 1:30pm 800 mg/kg CHOM
  - Snack: 5:00pm 100 mg/kg CHOM
  - Dinner: 6:30pm 800 mg/kg CHOM
  - Snack: 10:00pm 100 mg/kg CHOM

### Conclusions

- **Intraperitoneal route**
  - Glucose concentration within physiological limits
  - Better control with MPC (response characteristics, IAE and ITSE magnitudes)
- **Subcutaneous route**
  - Risk to induce hypoglycemia with aggressive controller settings
  - Infeasible with the discussed control strategies
Acknowledgments

• NSF

• Prof. Martha Evens and Dr. Cenk Ündey, IIT
• Dr. İnanç Birol, NWU
• Dr. Horacio Rilo, MD, University of Cincinnati Medical School