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

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/

Model Development

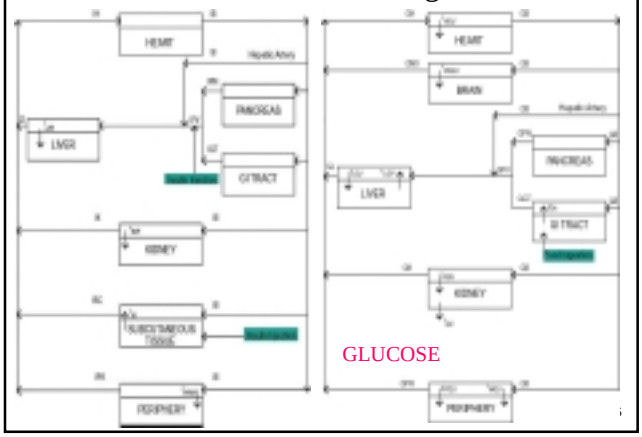
- Compartmental model
- Based on *mass balances* written around each organ for blood glucose and insulin using *pharmacokinetic diagrams* of glucose and insulin.
- *Kinetic parameters* chosen to simulate observed behavior of absorption, extraction and uptake of glucose and/or insulin in each organ.
-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

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]
4. **Pancreas** [G,I]
5. **Gastrointestinal** (GI) **tract** [G,I]
6. **Kidney** [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 ($\sigma^2 = 2$ *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

Controller Characteristics

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

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

p, m = 10, prediction and control horizons

u : Insulin injection rate (Δu change in input) 0 < u < 100 *mU/min*

y: Estimates of future glucose level measurements

Γ_y , Γ_u : Weights

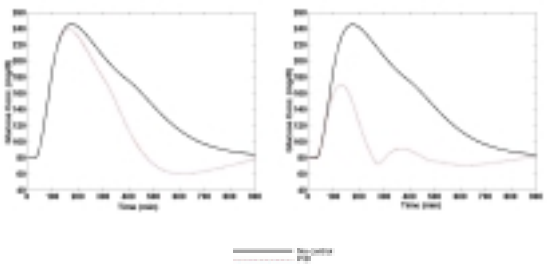
r: 80 *mg/dl* reference (set-point)

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 ($\sigma^2 = 2$ *mg/dl*)
- Regular (fast acting) insulin

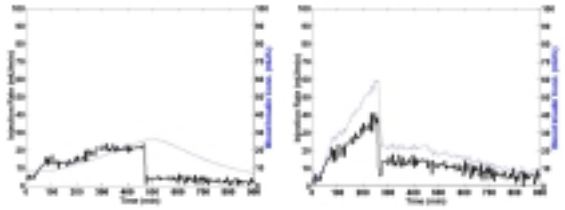
PID control

Subcutaneous Route | Intraperitoneal Route



PID controller

Subcutaneous Route | Intraperitoneal Route

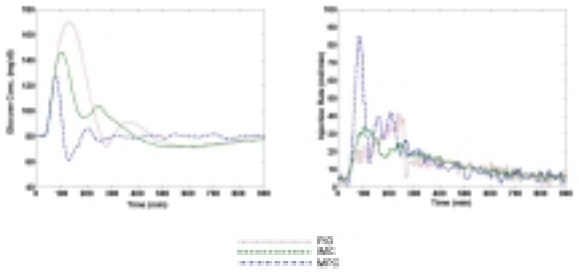


PID controller performance

- 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

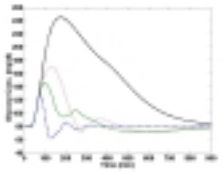


Comparison of All Controllers

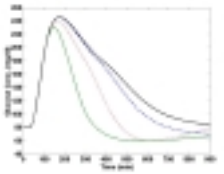
Intraperitoneal Route

- 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.

Intraperitoneal

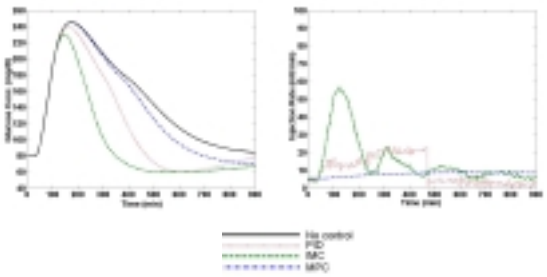


Subcutaneous



Comparison of All Controllers

Subcutaneous Route



Comparison of All Controllers

Subcutaneous Route

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

Comparison of All Controllers

Subcutaneous Route

	No control	PID	IMC	MPC
Max glucose conc. (mg/dl)	245	239	230	245
Min glucose conc. (mg/dl)	80	60	60	70

Intraperitoneal Route

	No control	PID	IMC	MPC
Max glucose conc. (mg/dl)	245	170	146	127
Min glucose conc. (mg/dl)	80	71	72	62

Comparison of Controllers Using Integrated Errors Over Time

Subcutaneous Route

	No control	PID	IMC	MPC
IAE	60.6 x 10^3	43.8 x 10^3	33.2 x 10^3	54.4 x 10^3
ITSE	1777 x 10^6	975.5 x 10^6	530.9 x 10^6	1521 x 10^6

Intraperitoneal Route

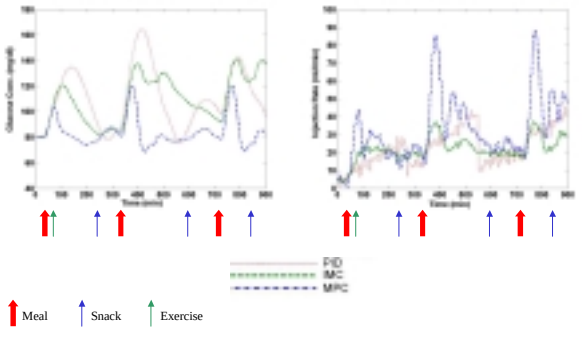
	No control	PID	IMC	MPC
IAE	60.6 x 10^3	15.1 x 10^3	11.4 x 10^3	3.3 x 10^3
ITSE	1777 x 10^6	121.3 x 10^6	52.9 x 10^6	7.2 x 10^6

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: 13:30pm 800 mg/kg CHOM
  - Snack: 18:00pm 100 mg/kg CHOM
  - Dinner: 20:00pm 800 mg/kg CHOM
  - Snack: 22:00pm 100 mg/kg CHOM

Simulation with All Controllers



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

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