Artificial Pancreas

Improved blood glucose regulation using
(i) frequent subcutaneous and
(ii) infrequent blood glucose measurements

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Overview

- Motivation
- Sensor/Pump/Control state of the art
- Feedback control
  - State estimation
  - Model predictive control
- Simulation results
  - Single-rate (subcutaneous glucose only)
  - Multi-rate (s.c. & capillary blood glucose)
- Future work
Motivation

DCCT (1983-93) Intensive Therapy Regimen
- 1400 IDDM volunteers

- Advantages - reduced risk of:
  - Eye disease by 76%
  - Kidney failure by 50%
  - Nervous disease by 60%

- Disadvantages
  - Three times risk of hypoglycemic incidences
Feedback Control: Basic Idea

desired glucose concentration ➔ controller ➔ pump ➔ patient ➔ blood glucose concentration

pump speed ➔ pump

insulin flowrate ➔ patient

measured glucose concentration ➔ sensor ➔ controller
Current Practice

- Patient serves as “feedback controller”
- Several “finger pricks”/day for capillary blood glucose measurement
- Multiple injections/day, or continuous infusion
Pump & Sensor Technology

- External (worldwide) & internal (Europe) pumps available
- Many sensors under development
  - Glucose electrodes, microdialysis, non-invasive
- Minimed - FDA approval for 3-day use
  - Glucose electrode
  - Re-calibrate daily w/blood glucose
  - Return to physician for analysis
Control Background

- Many simulation studies
  - IV and s.c. (sensor and infusion)

- Experiments
  - Human - s.c. sensor, s.c. & i.v. infusion, PD control (Shimoda et al., 1997)
  - Animal - venous blood, adaptive control (Fisher et al., 1987)

- Medical Research Group (Shah et al., 2000)
  - Animal - IV sensor and implantable pump

- Our focus - s.c. infusion, s.c. glucose sensor
Motivation for Our Multi-rate MPC Research

- Experience with anesthesia & classical chemical process control
- New/improved sensors (Moussy)
  - Long-term implantable electrode
- State estimation-based model predictive control
  - Frequent samples - s.c. glucose
  - Infrequent samples - capillary blood glucose
- Estimate blood glucose and meal disturbances (frequently), and s.c. sensor sensitivity (infrequently)
Subcutaneous measurements

- Subcutaneous glucose measurement available at frequent intervals
- Use model to:
  - Estimate meal disturbance
  - Estimate blood glucose
Estimation - Basic Idea

Meal disturbance

Insulin infusion rate

IDDM Patient

Sensor

Blood glucose

Measured subcutaneous glucose

Model Feedback

Patient Model

Predicted subcutaneous glucose

Sensor Model

Estimates:
- Blood glucose
- Subcutaneous glucose
- Glucose meal disturbance

Estimator

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Discrete-time Model

$$x_{k+1} = \Phi x_k + \Gamma u_k + \Gamma^d d_k$$

$$d_{k+1} = d_k + w_k$$

$$y_k = C x_k + v_k$$

Form an augmented state description to perform disturbance estimation
Estimation: Basic idea of Kalman Filter

- Based on expected measurement and process noise, estimate the “maximum likelihood” values for the state variables
- Original formulation is for perfectly modeled systems
- Technique extended for parameter or disturbance estimation (Extended Kalman Filter)
Kalman Filter w/Augmented States

Predictor-corrector equations:

\[ \hat{x}^a_{k|k-1} = \Phi^a \hat{x}^a_{k-1|k-1} + \Gamma^a u_{k-1} \]

\[ \hat{x}^a_{k|k} = \hat{x}^a_{k|k-1} + L_k \left( y_k - C^a \hat{x}^a_{k|k-1} \right) \]

Augmented state (includes meal disturbance)

Aug. state estimate

Kalman gain

Measured s.c. glucose

Insulin infusion

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Model Predictive Control

Find current and future insulin infusion rates that best meet a desired future blood glucose trajectory. Implement first "move."

Correct for model mismatch (estimate states), then perform new optimization.
Model Predictive Control

- **Simulation**
  - Neural model - Trajonoski *et al.*
  - Linear model (various) - Parker *et al.*
    - I.V. sensor and infusion

- **Experiment**
  - Linear (GPC) - Kan *et al.*
    - Insulin & glucose infusion, venous blood sampling
Simulation Study Using S.C. Sensor

- Simulated Type I Diabetic
  - 19 State (Sorenson, 1985)
  - Also studied by Parker et al. (1999), among others

- Model for Estimator/Controller
  - Modified Bergman “minimal model”
  - Parameters fit to Sorenson step response
  - Augmented state for meal disturbance
Simulation Results: S.C. Sensor

50 g glucose meal disturbance

5% measurement noise (s.d. = 3.8 mg/dl)

Estimator model assumes first-order lag between blood and s.c. glucose
Simulation Results - S.C. Sensor Degradation

50% sensor sensitivity decrease over 3 days

Motivates additional blood capillary measurement for s.c. sensor calibration
Estimation: Improved (Multi-Rate)

- Problem with s.c. glucose measurement
  - Sensor sensitivity changes
- Solution: Incorporate infrequent blood capillary measurements
- Use model to:
  - Estimate meal disturbance (5 min)
  - Estimate blood glucose (5 min)
  - Update s.c. sensor sensitivity at infrequent intervals (~4 times/day)
Simulation results:
Multirate

5% s.c. noise
(s.d. = 3.8 mg/dl)

2% capillary blood noise
(s.d. =1.6 mg/dl)
Simulation results: Multirate

- Sensor degradation (50% over 3 days)
- Sensitivity estimate

5% s.c. noise
(s.d. = 3.8 mg/dl)
2% capillary blood noise
(s.d. = 1.6 mg/dl)
Proposed Work

- Additional simulation-based studies
- Develop sensor/computer/pump interconnections
  - Glucose sensor
  - Estimation/control algorithms
  - External insulin infusion pump
- Experimental studies
  - Dogs
Implantable Sensor

Figure 4: Implantable Glucose Sensor

Schematic diagram of the sensor's membranes with their functions. Not to scale.

WORKING ELECTRODE:
Coiled Pt wire coated with:
- poly(o-phenylenediamine) film
- GO/albumin/glutaraldehyde

REFERENCE ELECTRODE:
Coiled Ag/AgCl wire

entire sensor coated with Nafion

0.5 mm

Platinum electrode  PPD  Glucose oxidase/albumin/glut.
Nafion

small electrochem. interferences

H₂O₂

glucose

oxygen

negat. + large mol.
Summary

- State estimation-based model predictive control
- Frequent s.c. glucose measurements
  - Estimate blood glucose and meal disturbance
- Infrequent blood capillary glucose measurements
  - Estimate (update) s.c. sensor sensitivity
- Simulation results
- Future experimental work
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