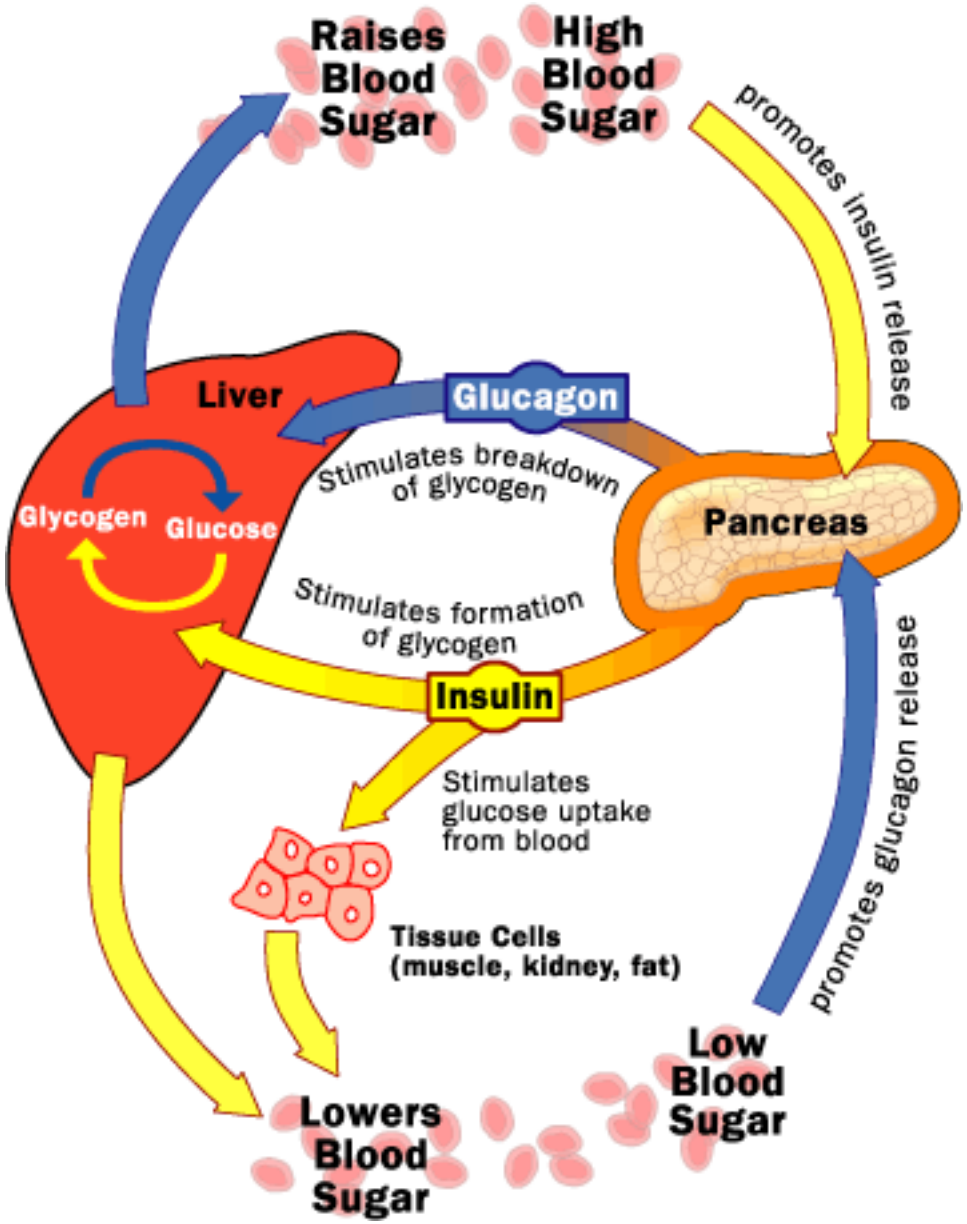
# Systems and Control Applications in Diabetes

- Background
- Type 1 (Juvenile) Diabetes
  - Glucose monitoring
  - Estimation & Hypoglycemia Alarms
  - Glucose Control (Artificial Pancreas)
- Summary of Other Projects

B. Wayne Bequette

Rensselaer

# Healthy Pancreas: Blood Glucose Regulation




Source: howstuffworks.com

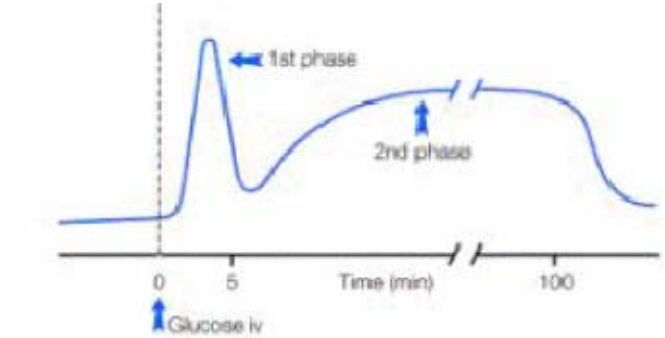
**Two manipulated inputs:**

**Insulin - lowers glucose**

**Glucagon - raises glucose**

**Beta cell:**

**Insulin secretion**



# Diabetes Diagnosis


Diabetes was characterized by Arataeus in the 1st century as a disease which resulted in the "melting down of the flesh and limbs into urine"

# Insulin Therapy


F. G. Banting and C. H. Best, "The internal secretion of the pancreas," *Journal of Laboratory and Clinical Medicine*, vol. 7, pp. 251–266, 1922.

# Diabetes

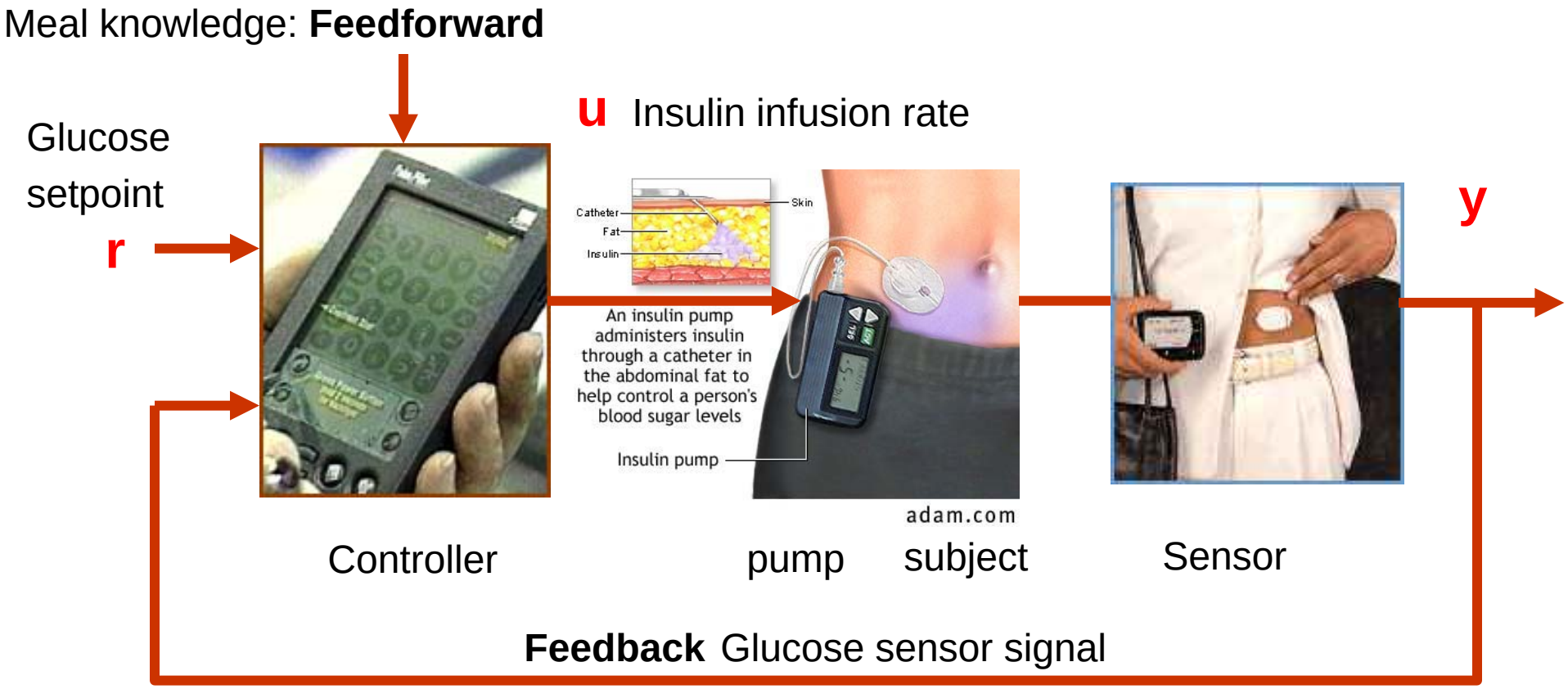
- Type 1 (Juvenile) Diabetes
  - Pancreas Beta cells do not produce insulin
  - Must inject insulin or use insulin pumps
- Type 2 Diabetes
  - Insulin resistance
  - Often associated with age and obesity
  - Oral medications, diet
  - Increasingly: insulin therapy
- Pre-diabetes
  - Insulin resistance

# Type 1 Diabetes: Intensive Insulin Therapy

DCCT (1983-93) 1400 Type 1 volunteers

- Advantages - reduced risk of:
  - Eye disease by 76%
  - Kidney failure by 50%
  - Nervous disease by 60%
- Disadvantages
  - Three times risk of hypoglycemia (low blood glucose)
  - Frequent, painful, “finger stick” capillary blood measurements

# Blood Glucose Control



# Blood Glucose Control

Amount of carbohydrates?

Remember to bolus?

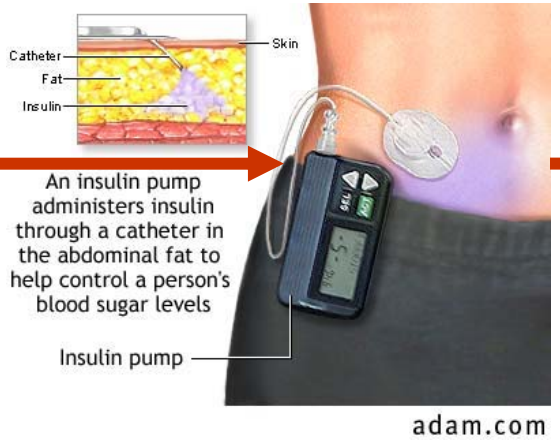
Meal knowledge: **Feedforward**

Insulin pharmacokinetics
& pharmacodynamics (time-lags)

Changes in absorption

Glucose
setpoint
**r**

**u** Insulin infusion rate




**y**

Controller pump subject Sensor

**Feedback** Glucose sensor signal

Sensor noise & calibration uncertainty

# Biostator

IV infusion and
glucose sampling

## Comparison of Algorithms for the Closed-Loop Control of Blood Glucose Using the Artificial Beta Cell

HENRY M. BROEKHUYSE, JILL D. NELSO

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J. D. Nelson is with the Division of Endocrinology and Metabolis Shaughnessy Hospital, Vancouver, B.C., Canada.

B. Zinman is with the Toronto General Hospital, Toronto, On Canada.

**A. M. Albisser** was born in Johannesburg, Union of South Africa, on September 5, 1941. He received the B.E. degree in electrical engineering from McGill University, Montreal, Canada, in 1964, and the M.A.Sc. degree in electrical engineering and the Ph.D. degree in biomedical engineering from the University of Toronto, Toronto, Canada, in 1966 and 1968, respectively.

He is presently a Senior Scientist at the Department of Surgery, Division of Biomedical Research, Research Institute, Hospital for Sick Children, Toronto, Canada, and an Associate Professor, Departments of Medicine, Surgery, and Electrical Engineering, University of Toronto.

# Glucose Meter Technology


Urine test strips


1971 – Ames Reflectance Meter

Accu Chek


1993 – 2007 (Wikipedia)

# Insulin Delivery

- Basal
  - Steady-state “non-meal” periods
    - Long-acting insulin (injection)
    - Insulin pump
      - Fast-acting insulin delivered continuously
      - Different rates for different periods during the day
- Bolus
  - Fast-acting insulin
    - Meal time to compensate for meal carbohydrates
    - Correction for high blood glucose

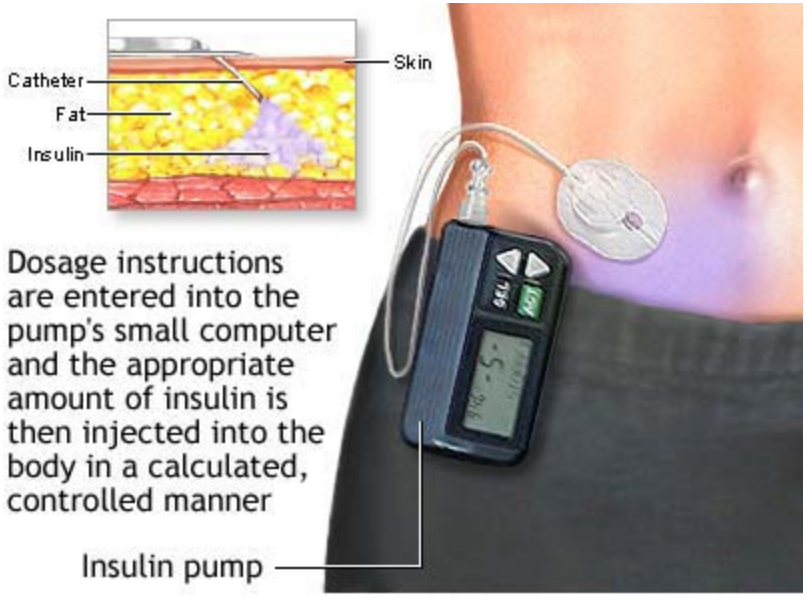
# Insulin Pump Technology

1963 – first pump delivers insulin & glucagon

1980 - Autosyringe

1990s - MiniMed


Medtronic Minimed 512 & Minimed 712



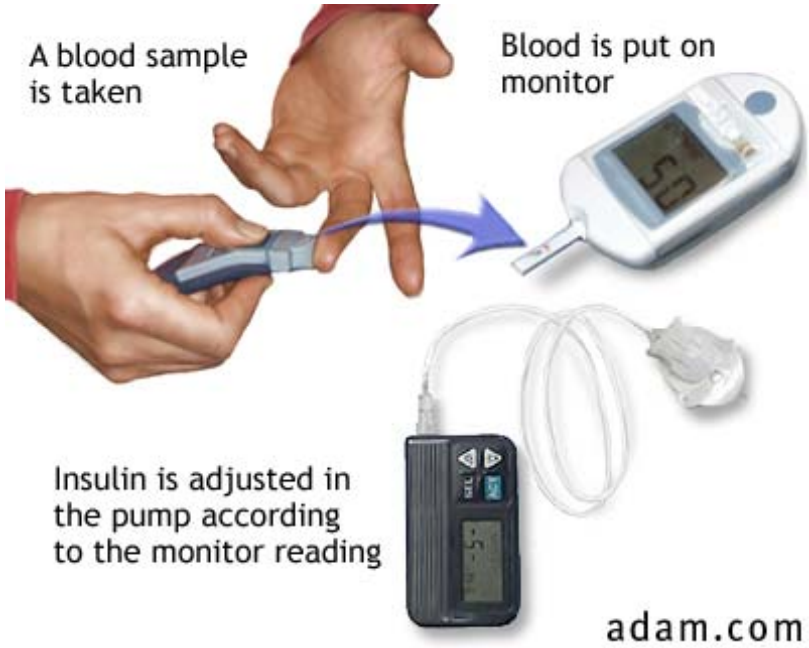

Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner


Animas


Deltec Cozmo

OmniPod

# Current State of Blood Glucose Monitoring




- Infrequent “fingerstick” samples
- Adjust insulin dose
  - Bolus “wizard”
  - Insulin-on-board

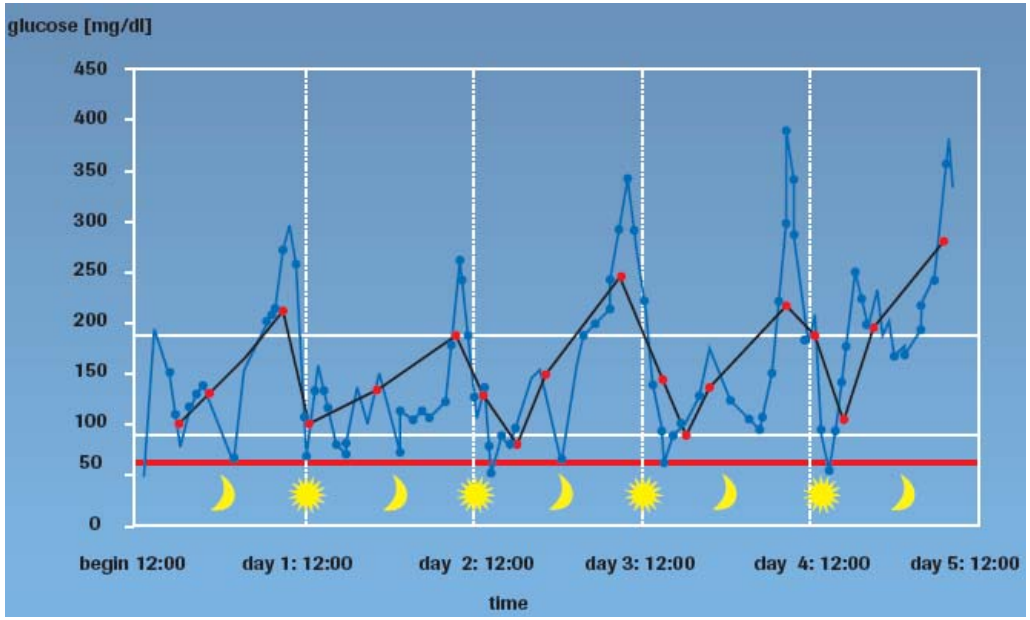
- Many “highs” and “lows” are missed
- Long- & short-term problems

**High BG**

**A1c**
**vascular problems**
**eye disease, etc.**

**Low BG**

**drowsiness,**
**diabetic coma,**
**driving dangers, etc.**




**Roche**

# Continuous Glucose Monitors


**Glucowatch**


**Medtronic MiniMed**

**Abbott (Therasense)**

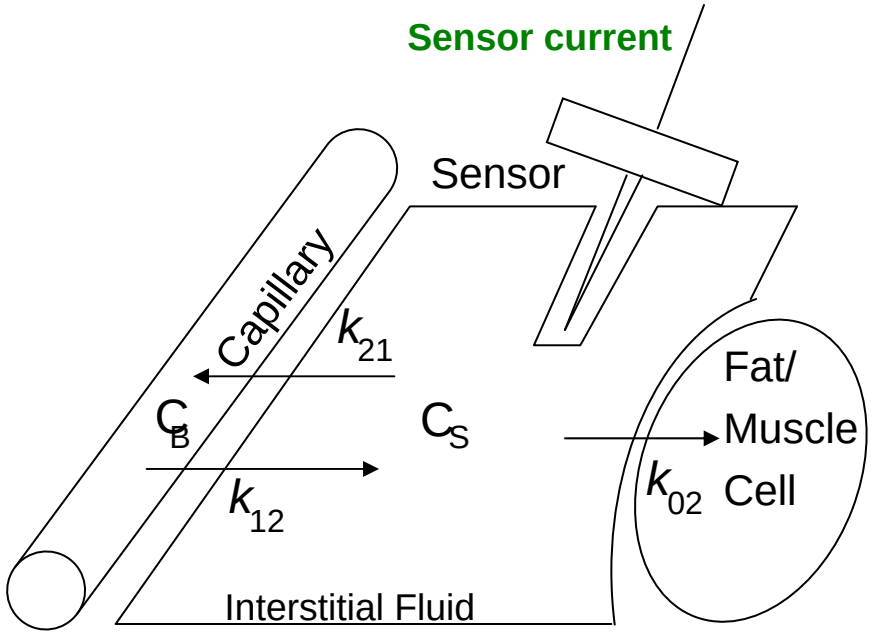

**Dexcom**

Sensor signals are related to subcutaneous glucose values

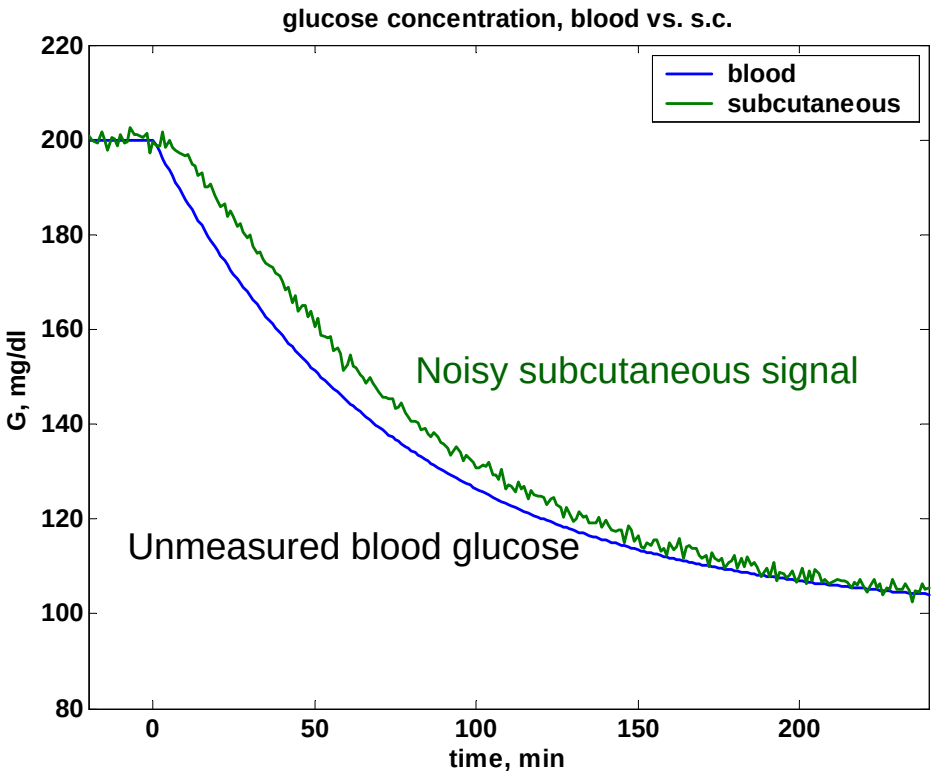
## Goals: blood glucose estimation

- Estimate blood glucose from noisy subcutaneous sensor signal
- Hypoglycemia detection/prediction
- Closed-loop control
- First, need a model…

# Blood/Subcutaneous Dynamics




Rebrin *et al*. *Am. J. Phys*. (1999)




$$\frac{dC_S}{dt} = -(k_{02} + k_{12})C_S + k_{21}\frac{V_1}{V_2}C_B$$

standard first-order form (two parameters)

$$\frac{dy}{dt} = -\frac{1}{\tau}y + \frac{k}{\tau}u$$

where $k = \dfrac{k_{21}(V_1/V_2)}{k_{02} + k_{12}}$ **gain** $\qquad \tau = \dfrac{1}{k_{02} + k_{12}}$ **time constant**

Objective:

From noisy s.c. signal, estimate blood glucose (+ rate-of-change)

# Estimate Blood Glucose – Naïve Method

$$\frac{dy}{dt} = -\frac{1}{\tau}y + \frac{k}{\tau}u = -p_2 y + p_3 u$$

Solve for u (blood glucose) based on y (s.c. glucose)

$$u = \frac{\frac{dy}{dt} + p_2 y}{p_3}$$

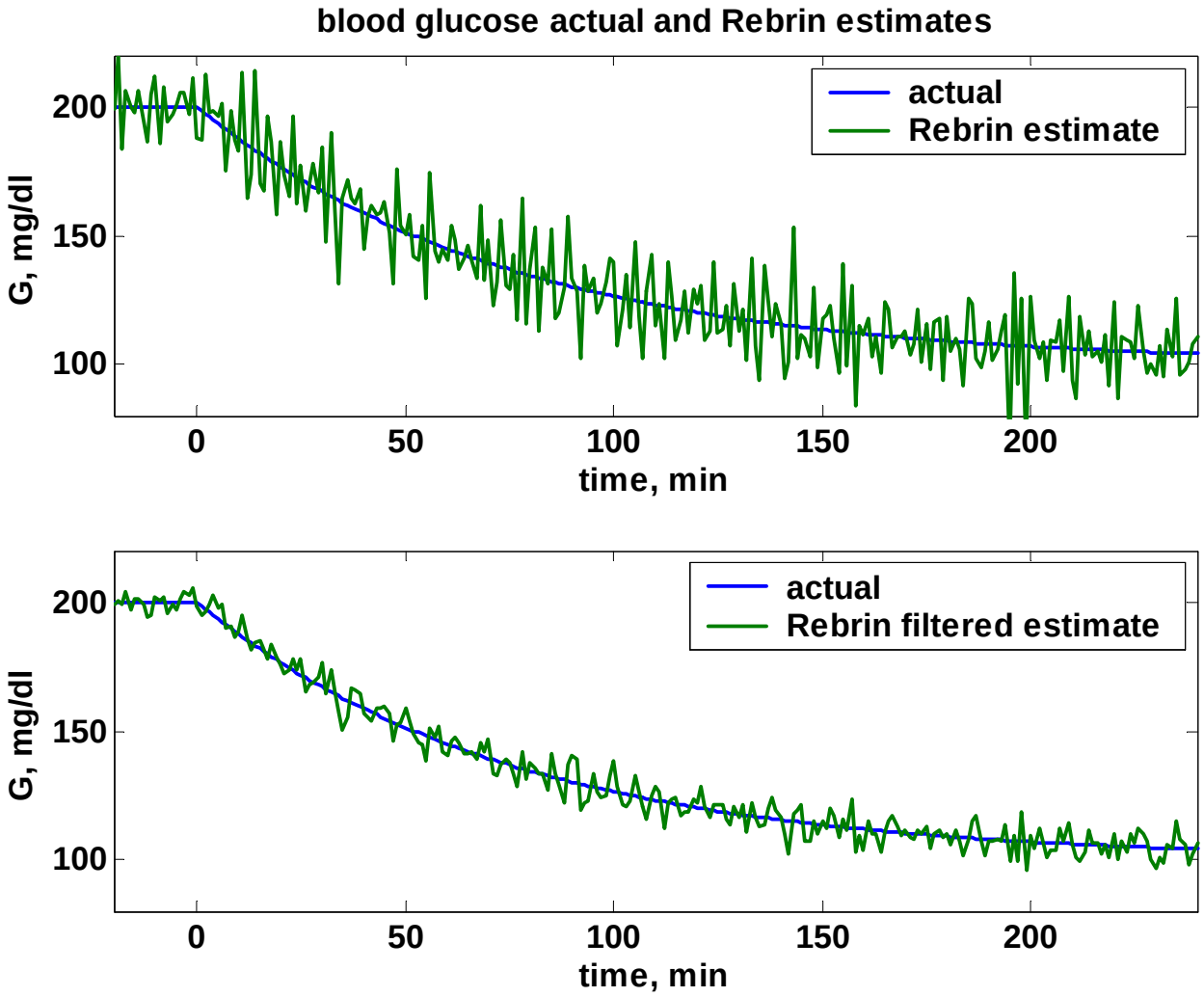
Finite differences

$$u_k = \frac{\frac{y_k - y_{k-1}}{\Delta t} + p_2 y_k}{p_3}$$

$$u_k = \left(\frac{1}{p_3 \Delta t} + \frac{p_2}{p_3}\right) y_k + \left(\frac{-1}{p_3 \Delta t}\right) y_{k-1}$$

Rebrin et al., Am. J. Physiol., 277, E561-E571(1999)

# Sensitivity to Noise




Need to use optimal estimation techniques…

# Optimal Estimation - Kalman Filter

- Trade-off Probability of Measurement noise vs. Process “Noise” (real change in blood glucose)
  - Which is causing a particular measurement change?
- If little measurement noise
  - Trust measurement more than model
- If much measurement noise
  - Trust model more than measurement
- Estimate unmeasured states
  - Estimate blood glucose based on subcutaneous measurement

# State Model

s.c. glucose

blood glucose

change in bg

$$\underbrace{\begin{bmatrix} x_{k+1} \\ u_{k+1} \\ d_{k+1} \end{bmatrix}}_{x^a_{k+1}} = \underbrace{\begin{bmatrix} \Phi & \Gamma & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}}_{\Phi^a} \underbrace{\begin{bmatrix} x_k \\ u_k \\ d_k \end{bmatrix}}_{x^a_k} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}}_{\Gamma^{a,w}} w_k$$

"process" noise

augmented state (includes blood glucose and its rate of change)

measured s.c. glucose

$$y_k = \underbrace{\begin{bmatrix} 1 & 0 & 0 \end{bmatrix}}_{C^a} \begin{bmatrix} x_k \\ u_k \\ d_k \end{bmatrix} + v_k$$

measurement noise

# Predictor-corrector equations:

$$\hat{x}^a_{k|k-1} = \Phi^a \hat{x}^a_{k-1|k-1}$$

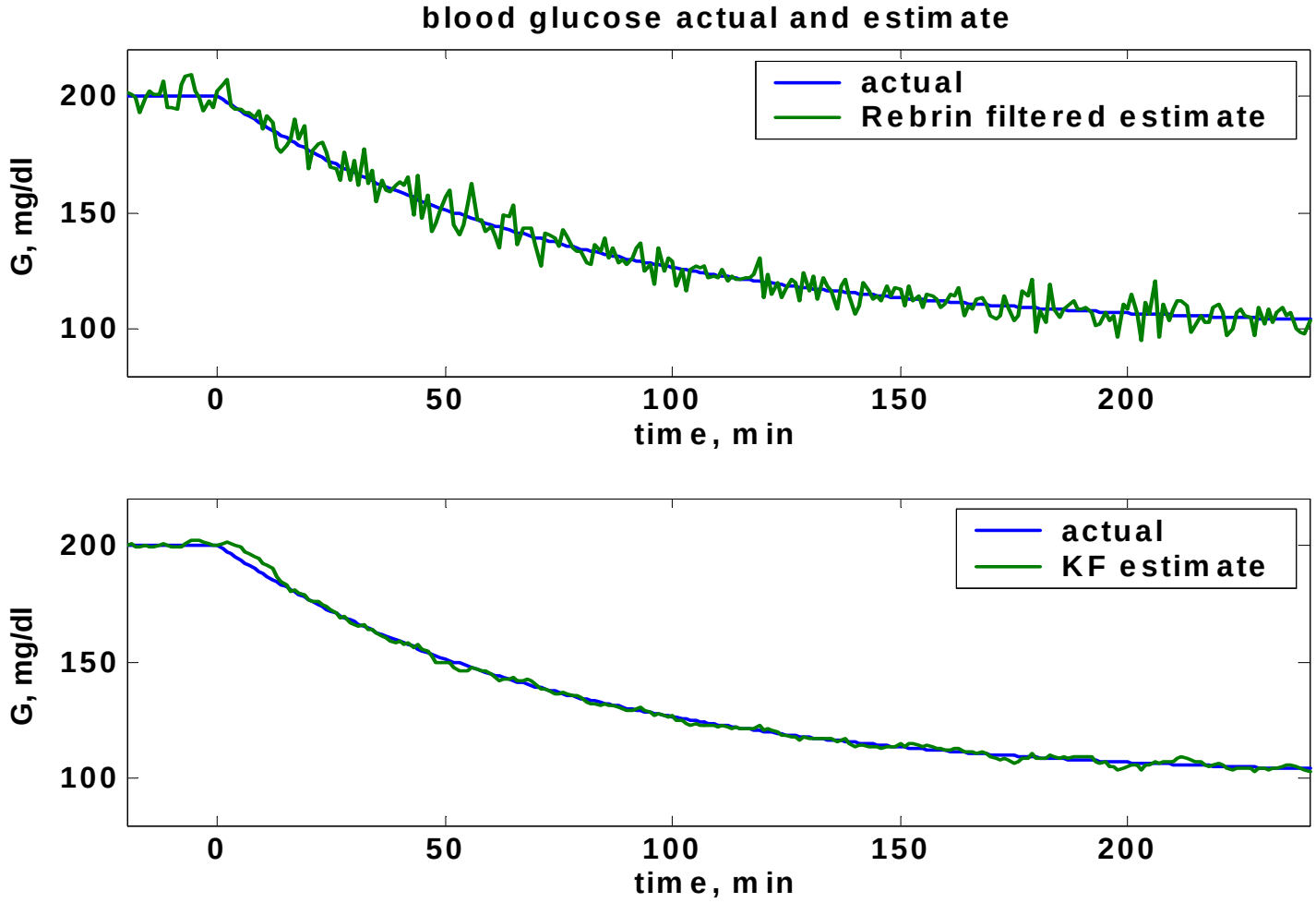
$$\hat{x}^a_{k|k} = \hat{x}^a_{k|k-1} + L_k \left( y_k - C^a \hat{x}^a_{k|k-1} \right)$$

Aug. state estimate

Kalman gain

Measured s.c. glucose

# State Estimation Results




B.W. Bequette, 2004 American Control Conference

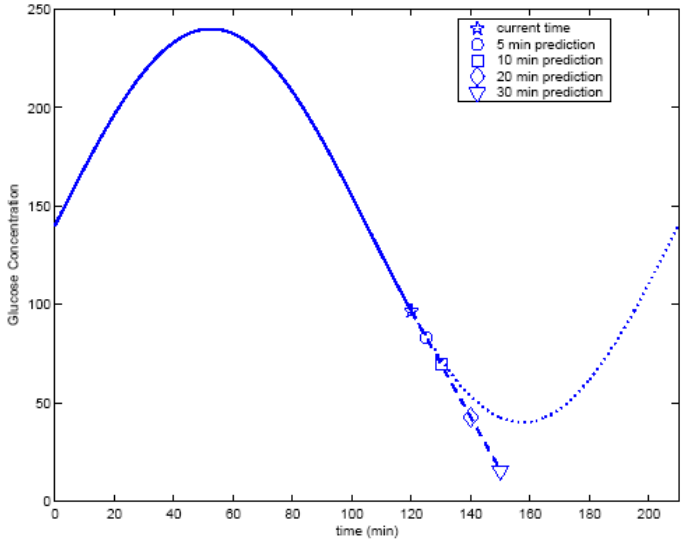
# Hypoglycemia Concerns

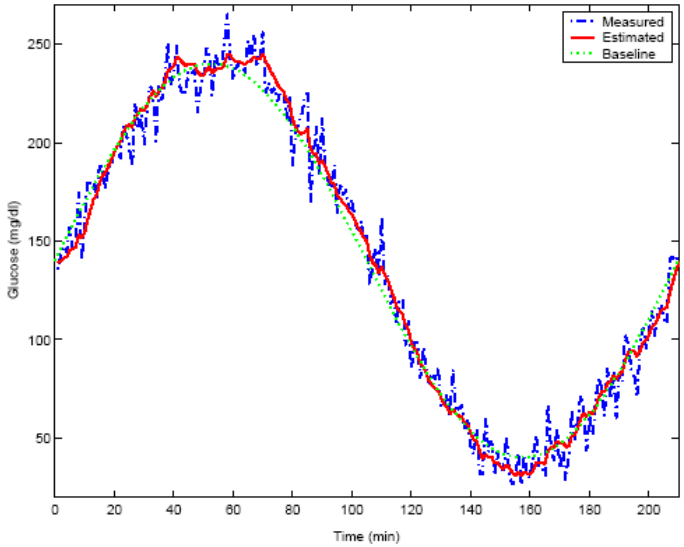
- False alarm rate

DirecNet

Buckingham, American Diabetes Association (2004)

# Simulation Studies




Palerm, Bequette, Desemone, Willis
Diabetes Technology & Therapeutics (2005)

# 3-State vs. 2-State Models

glucose

change in glucose

change in change

$$\underbrace{\begin{bmatrix} g_{k+1} \\ d_{k+1} \\ f_{k+1} \end{bmatrix}}_{x_{k+1}} = \underbrace{\begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}}_{\Phi} \underbrace{\begin{bmatrix} g_k \\ d_k \\ f_k \end{bmatrix}}_{x_k} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}}_{\Gamma^w} w_k$$

noise

variance = Q

measured glucose

$$y_k = \underbrace{\begin{bmatrix} 1 & 0 & 0 \end{bmatrix}}_{C} \begin{bmatrix} g_k \\ d_k \\ f_k \end{bmatrix} + v_k$$

measurement

noise

variance = R

---

glucose

change in glucose

$$\underbrace{\begin{bmatrix} g_{k+1} \\ d_{k+1} \end{bmatrix}}_{x_{k+1}} = \underbrace{\begin{bmatrix} 1 & 1 \\ 0 & 1 \end{bmatrix}}_{\Phi} \underbrace{\begin{bmatrix} g_k \\ d_k \end{bmatrix}}_{x_k} + \underbrace{\begin{bmatrix} 0 \\ 1 \end{bmatrix}}_{\Gamma^w} w_k$$

noise

variance = Q

measured glucose

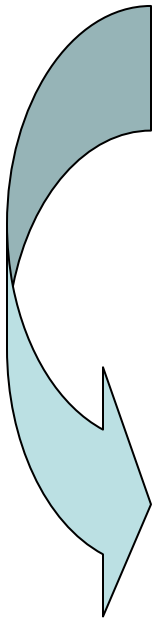
$$y_k = \underbrace{\begin{bmatrix} 1 & 0 \end{bmatrix}}_{C} \underbrace{\begin{bmatrix} g_k \\ d_k \end{bmatrix}}_{x_k} + v_k$$

measurement

noise

variance = R

# State Estimation: Kalman Filter



$$\hat{x}_{k|k-1} = \Phi \ \hat{x}_{k-1|k-1}$$

prediction

$$\hat{x}_{k|k} = \hat{x}_{k|k-1} + L\left(y_k - C \ \hat{x}_{k|k-1}\right)$$

correction
(measurement update)

$$\underbrace{\begin{bmatrix} \hat{g}_{k|k-1} \\ \hat{d}_{k|k-1} \\ \hat{f}_{k|k-1} \end{bmatrix}}_{\hat{x}_{k|k-1}} = \underbrace{\begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}}_{\Phi} \underbrace{\begin{bmatrix} \hat{g}_{k-1|k-1} \\ \hat{d}_{k-1|k-1} \\ \hat{f}_{k-1|k-1} \end{bmatrix}}_{\hat{x}_{k-1|k-1}}$$

prediction

$$\underbrace{\begin{bmatrix} \hat{g}_{k|k} \\ \hat{d}_{k|k} \\ \hat{f}_{k|k} \end{bmatrix}}_{\hat{x}_{k|k}} = \underbrace{\begin{bmatrix} \hat{g}_{k|k-1} \\ \hat{d}_{k|k-1} \\ \hat{f}_{k|k-1} \end{bmatrix}}_{\hat{x}_{k|k-1}} + \underbrace{\begin{bmatrix} L_1 \\ L_2 \\ L_3 \end{bmatrix}}_{L} \left(y_k - \hat{g}_{k|k-1}\right)$$

correction
(measurement update)

function of Q/R

# Simple Outlier Detection/Compensation

- Measurement invalid if

$$\left|y_k - y_{k-1}\right| > \delta$$

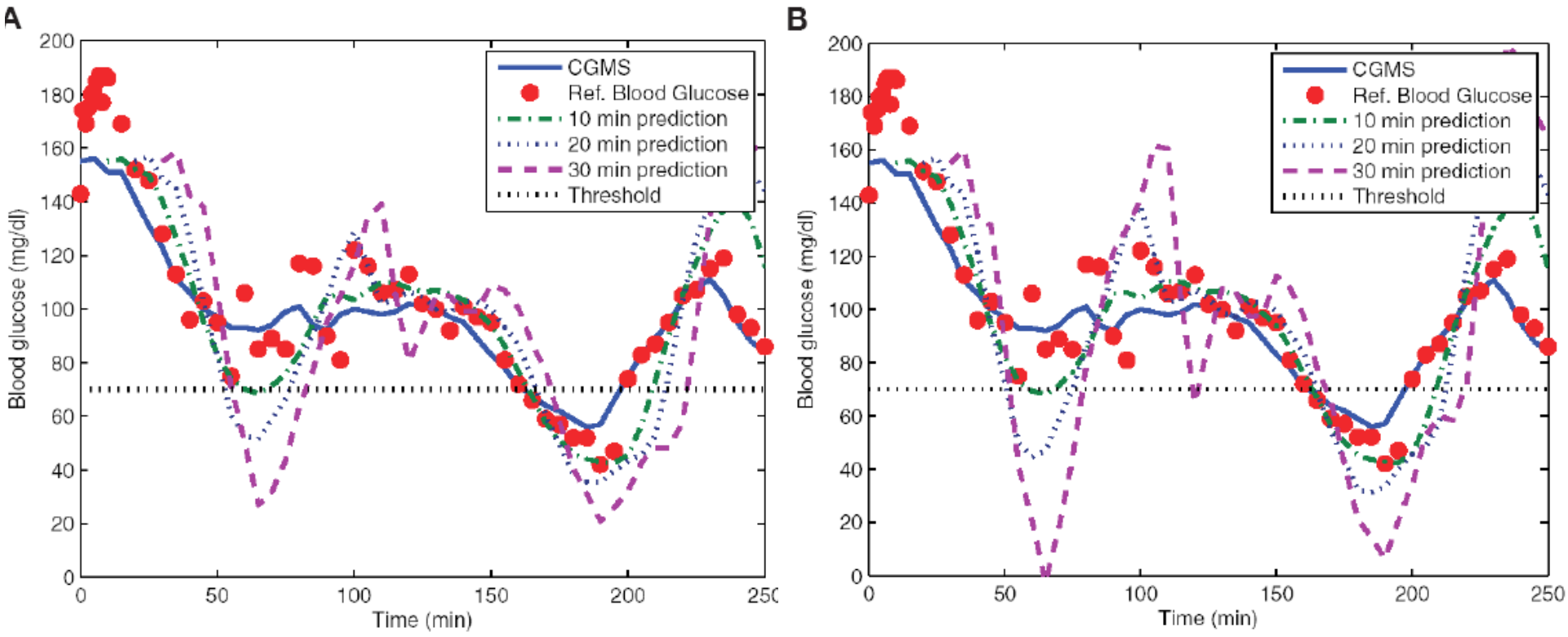
$$y_k < \varepsilon$$

- If measurement is invalid, then simply use the **prediction** & not the measurement update

$$\hat{x}_{k|k-1} = \Phi\ \hat{x}_{k-1|k-1}$$

$$\hat{x}_{k|k} = \hat{x}_{k|k-1}$$

# Comparison 2-state vs. 3-state



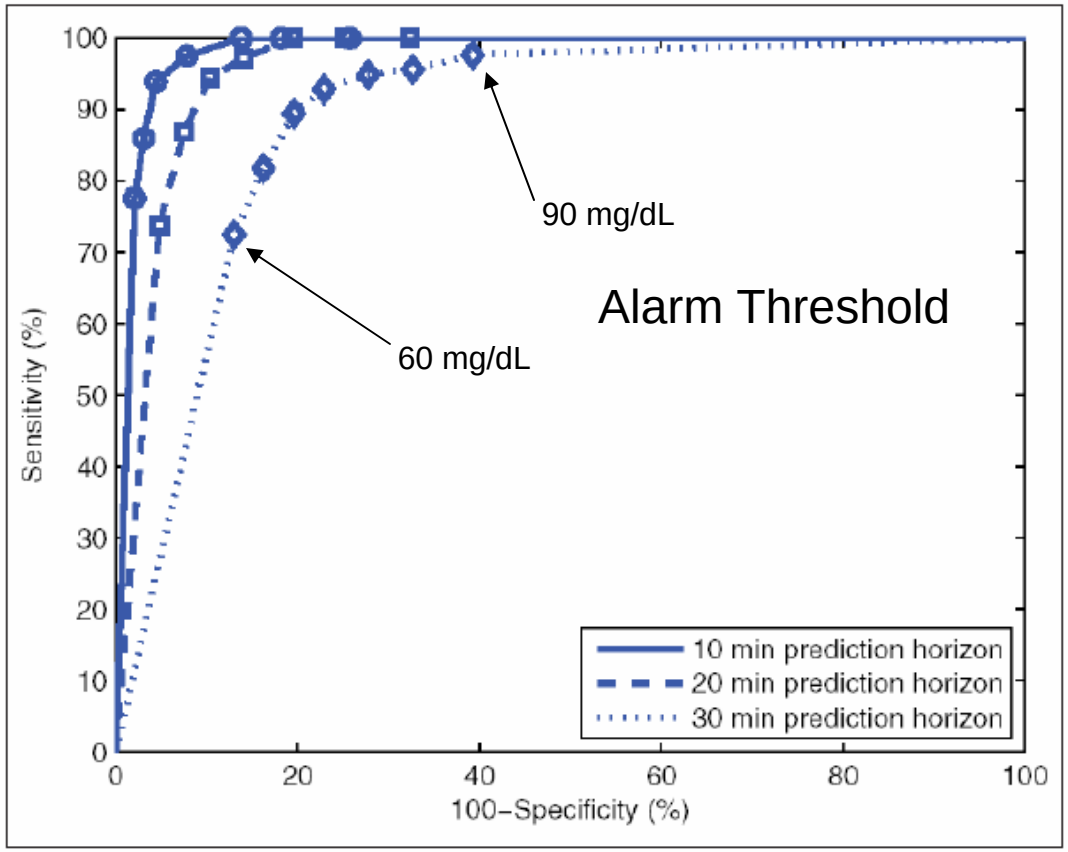

Assumes constant first derivative for predictions

Assumes constant second derivative for predictions

Palerm, C.C., B.W. Bequette *Journal of Diabetes Science and Technology*, **1**(5), 624-629 (2007).

# Receiver Operating Characteristic Curve

True Positive Rate




False Positive Rate

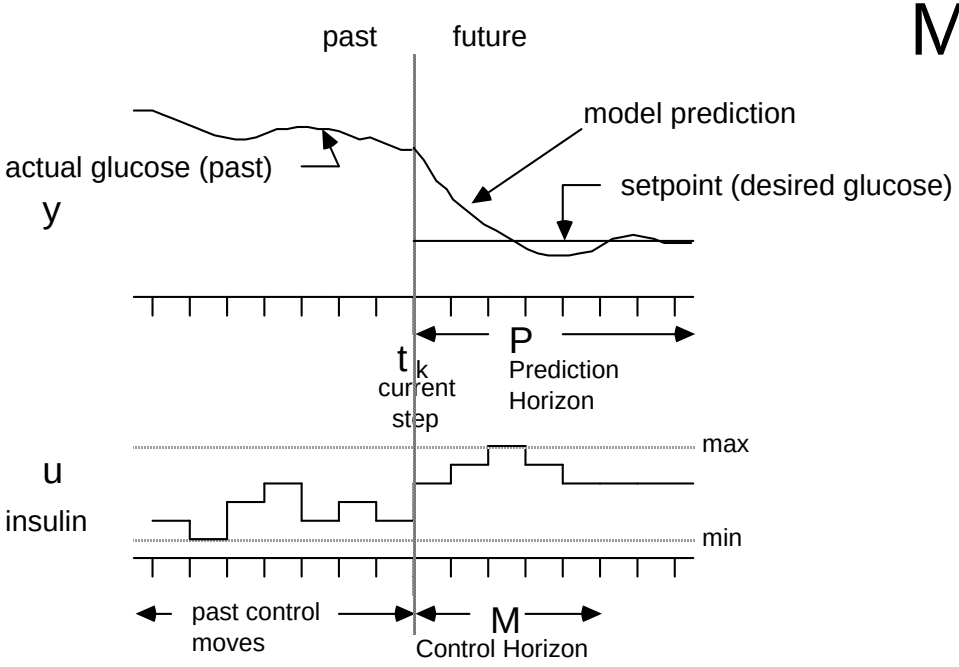
Hypoglycemia defined as < 70 mg/dL

Palerm, C.C., B.W. Bequette *Journal of Diabetes Science and Technology*, **1**(5), 624-629 (2007).

# Control Challenges

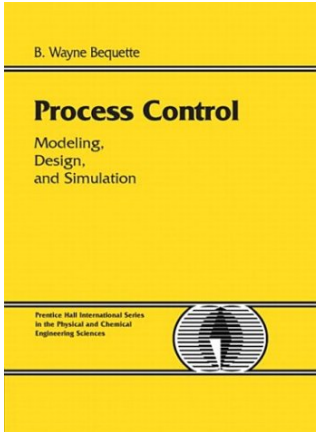
- Meal glucose
  - Variability in rate of absorption into circulation
- Subcutaneous insulin delivery
  - Variability in absorption. Lag in peak effect
  - Need for insulin bolus at meal-time
- Varying insulin sensitivity (“gain”)
  - Dawn phenomenon
  - Effect of exercise
- Sensor issues
- Model “Identification”
  - Clinical data often not rich enough

# Model Predictive Control



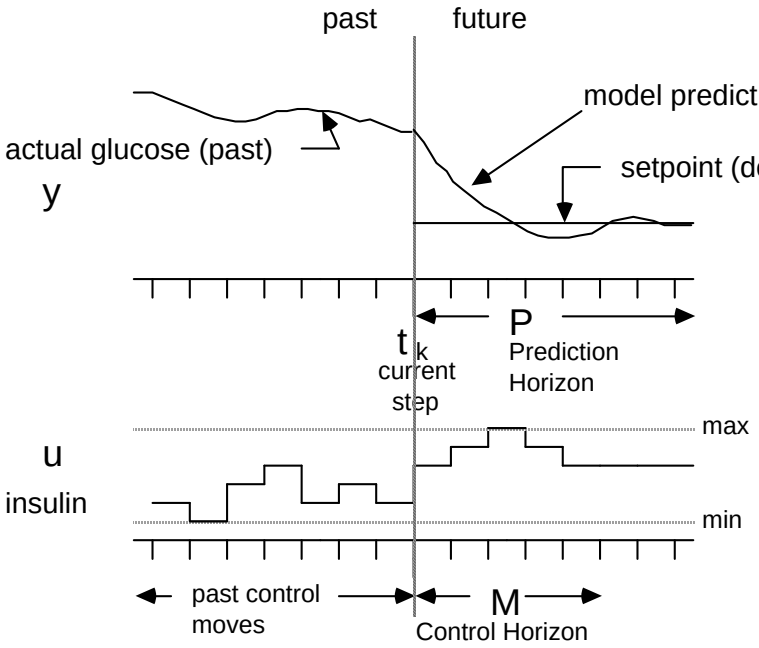

Find current and future insulin infusion rates that best meet a desired future glucose trajectory. Implement first “control move” (infusion rate).

- Type of model for predictions?
- Information needed at step k for predictions?
- Objective function and optimization technique?
- Correction for model error?




**(Chapter 16…)**

# Model Predictive Control




Find current and future insulin infusion rates that best meet a desired future glucose trajectory. Implement first “control move” (infusion rate).

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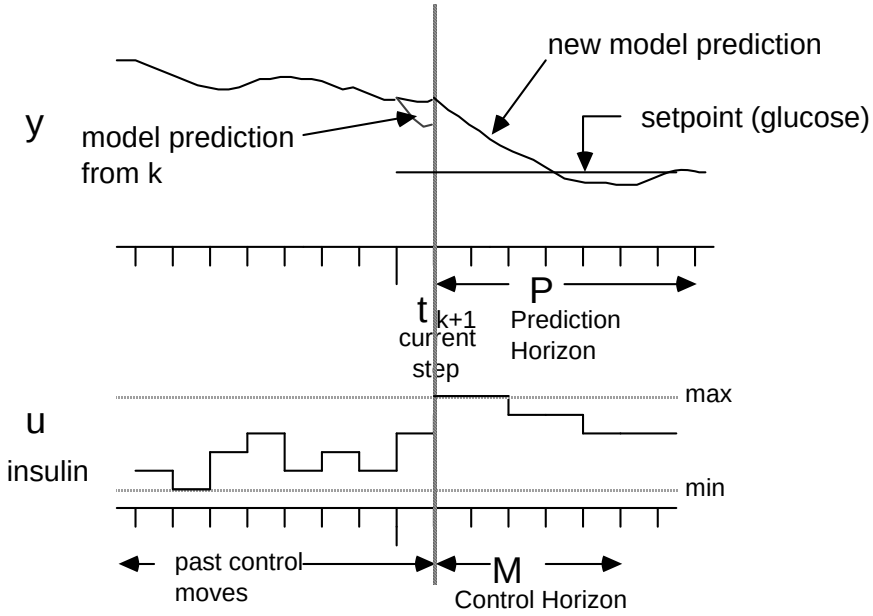



**At next sample time:**

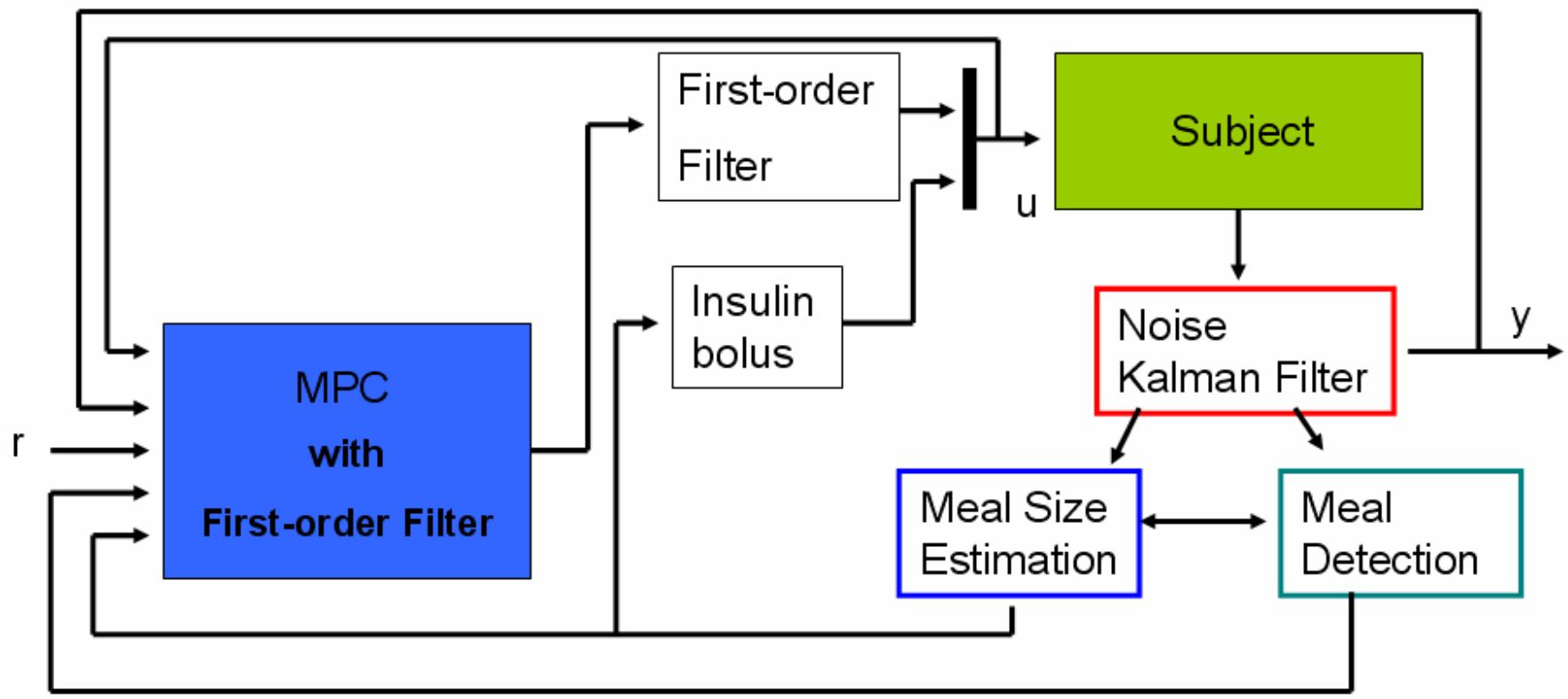
Correct for model mismatch, then perform new optimization.

Disturbances vs. model uncertainty

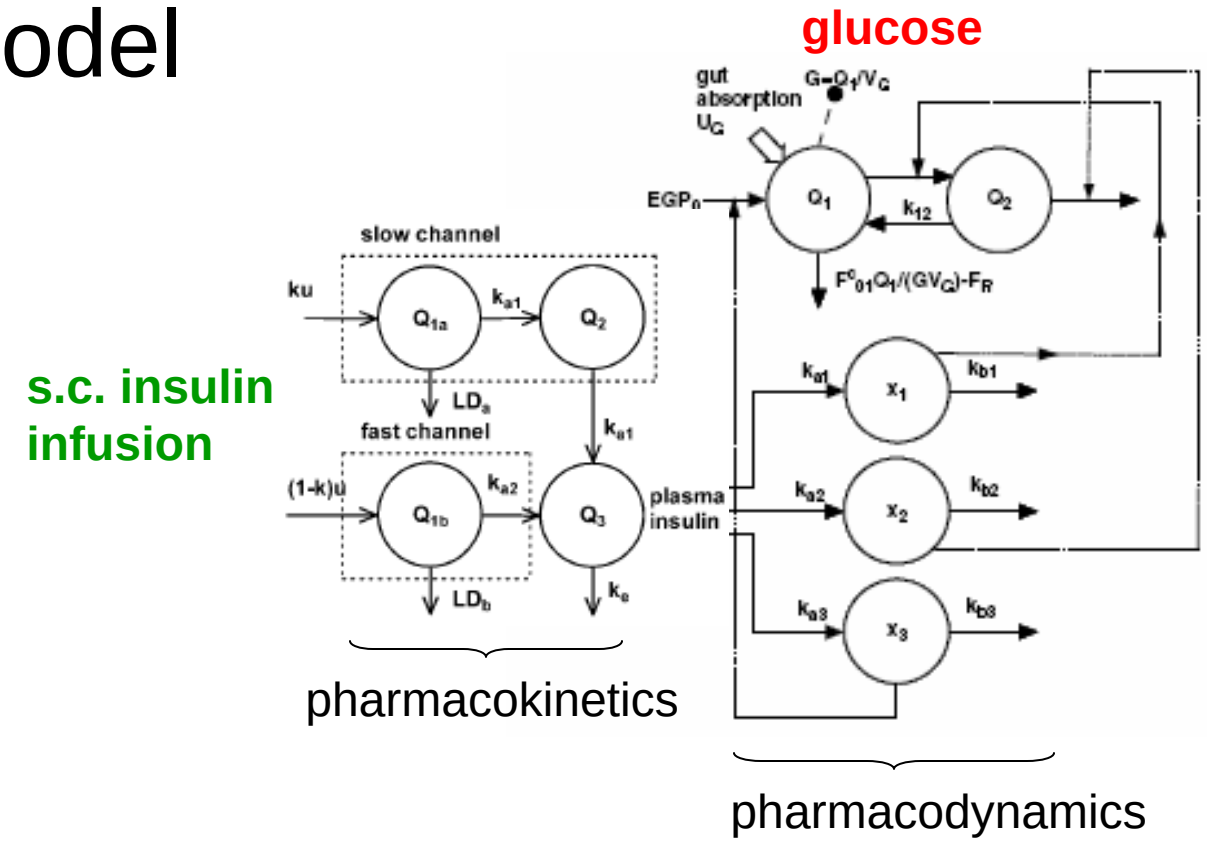
# Concise Review of MPC-AP Applications

- Doyle, Parker, Peppas (IEEE TBME, 1999)
- Lynch, Bequette (ACC 2002)
- Hovorka et al. (Phys. Meas., 2004)
- Damiano, El-Khatib (DTM, 2008)
- Cobelli, Kovatchev, Patek et al. (DTM, 2008)
- Doyle, Dassau, Zisser et al. (IFAC, 2008; DTM, 2008)
- Lee, Bequette (IFAC, 2008; JDST 2009)

# Closed-Loop Artificial Pancreas Framework



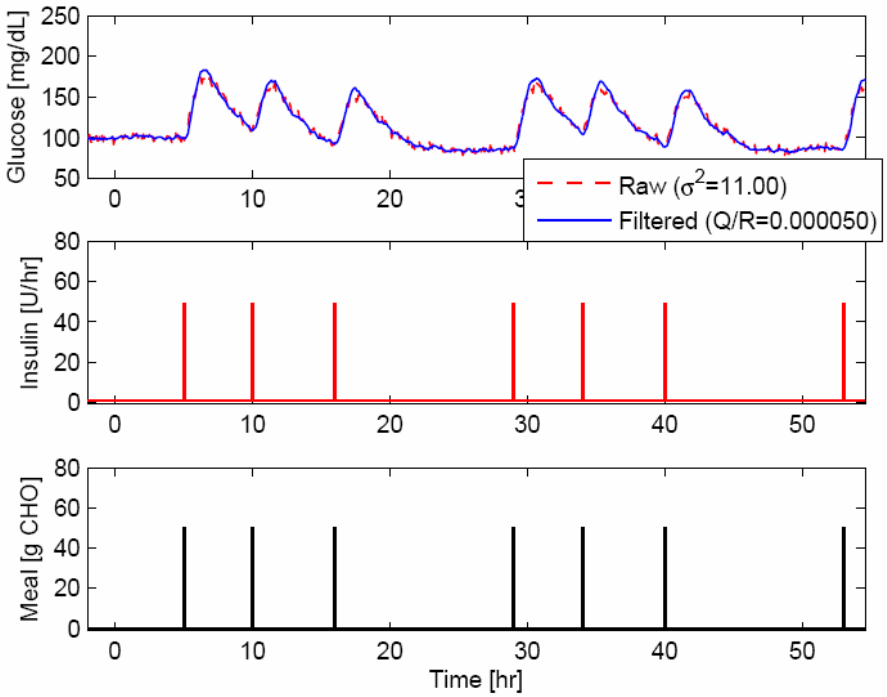
# Simulation Model



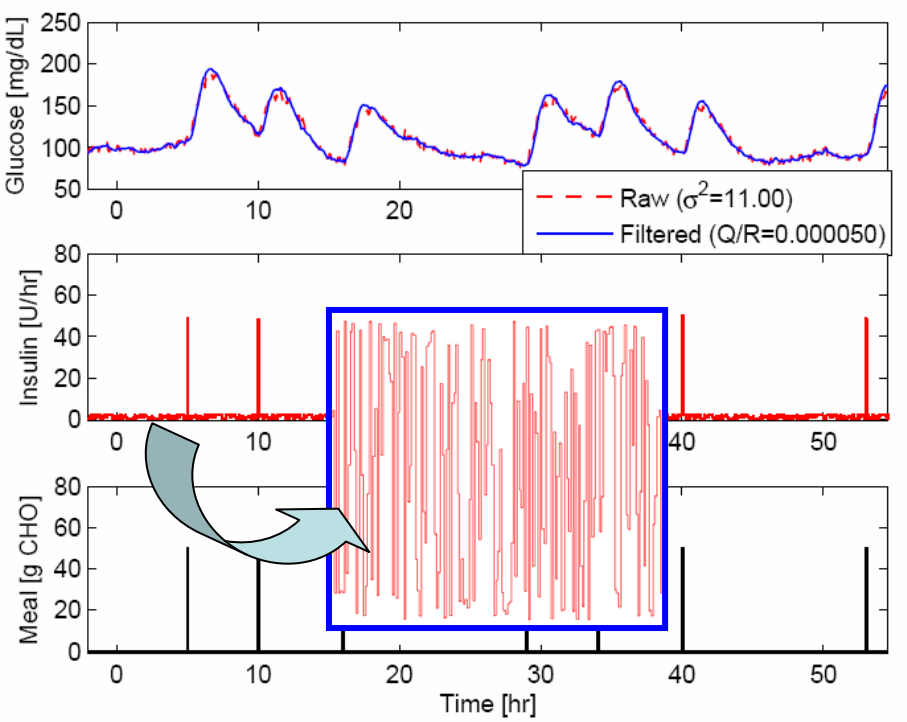

- Compartment-based
  - Hovorka: includes s.c. insulin kinetics
  - Dawn phenomena and time-dependent variations

Figure from Hovorka *et al*. *Physiol. Meas*. (2004); Wilinksa et al. *IEEE TBME* (2005)

# Modeling Experiments



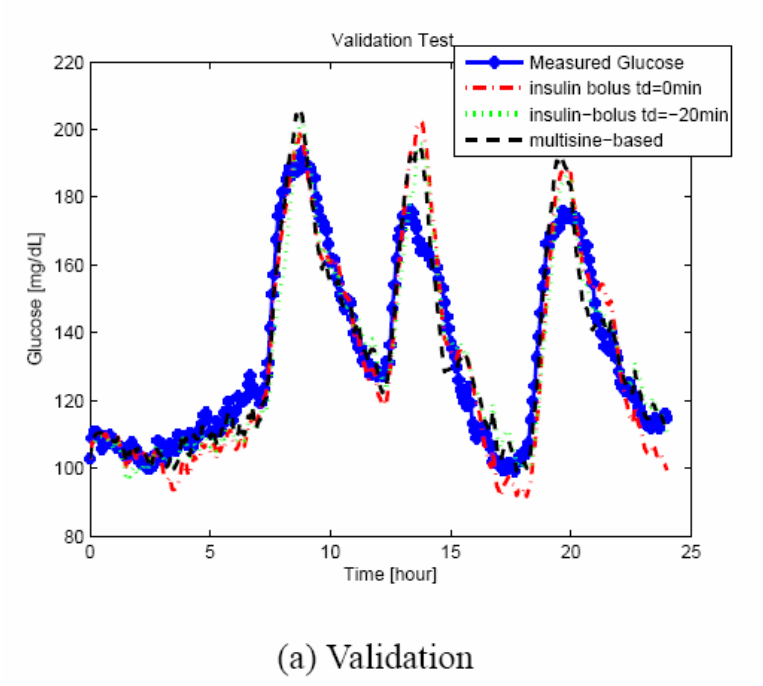

Traditional Insulin Injection



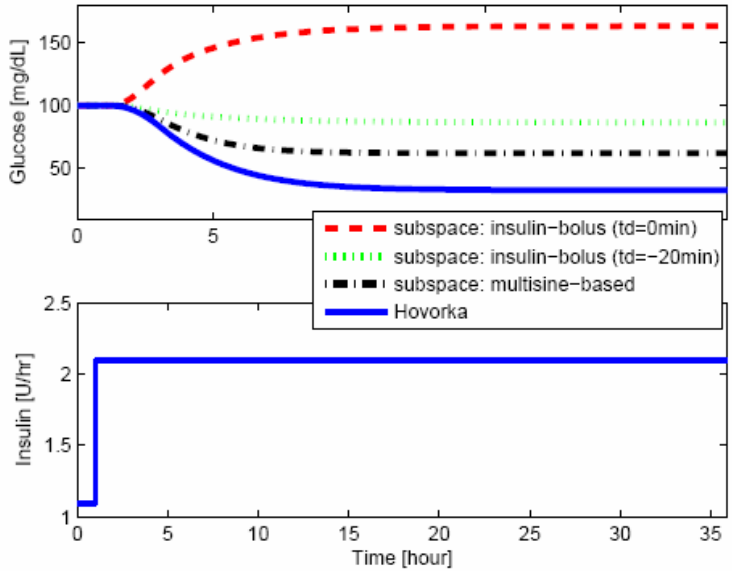

Multisine-basal rate Injection

Approach of “Plant Friendly ID”
(Lee and Rivera, 2005)

# Model Validation




(a) Validation




(b) Step Test

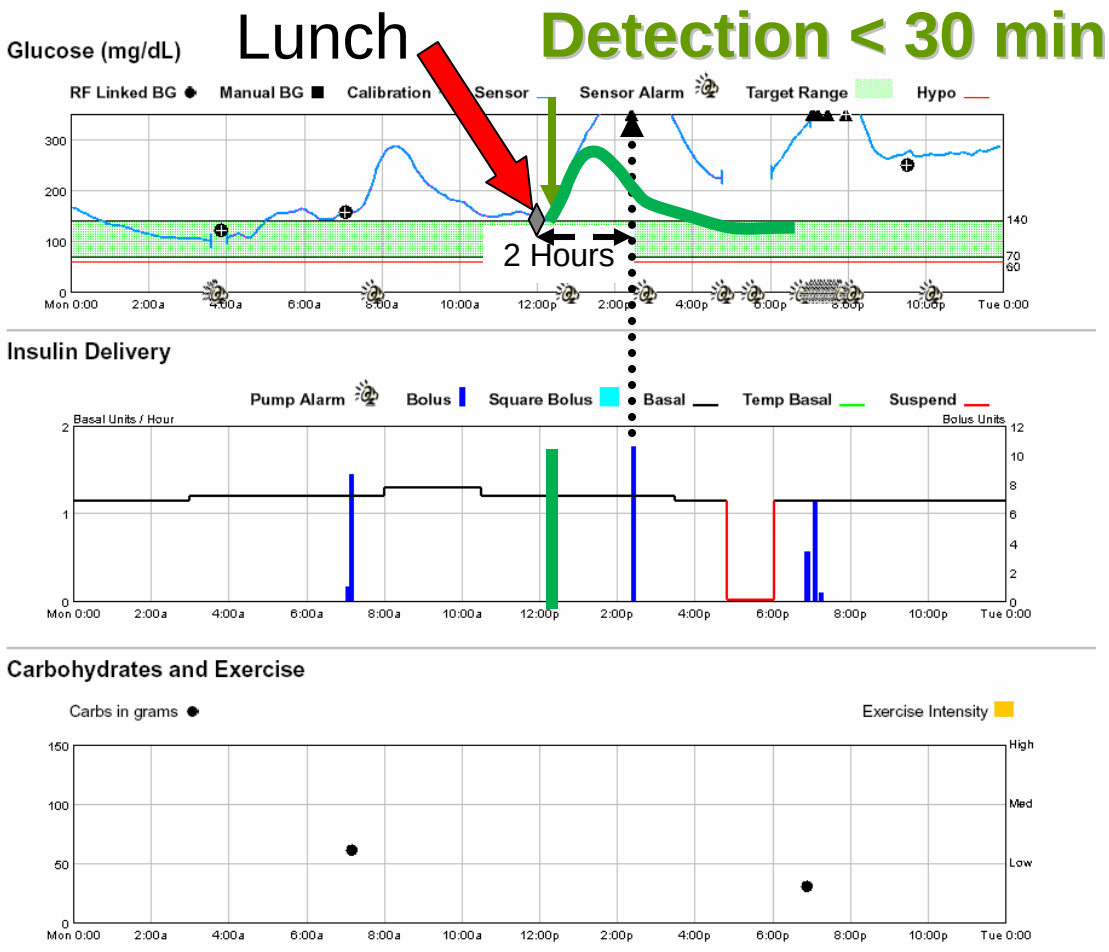
| Test Ahead-of-Time Prediction (FIT(%)) | 30 min | 1 hour | 3 hour |
|---|---|---|---|
| Insulin-bolus (*dt*=0 min) | 74.9 | 64.2 | 43.8 |
| Insulin-bolus (*dt*=-20 min) | 74.9 | 65.3 | 49.7 |
| Multisine (*dt*= 0 min) | 77.8 | 69.3 | 64.2 |

# Major Concerns

- Hypoglycemia (low blood glucose)
  - Short-term problems
- Hyperglycemia (high blood glucose)
  - Long-term problems
- Missed meal boluses
  - More than 65% of adolescents miss one or more meal boluses each week
  - Two missed meal boluses each week increases the A1c by 0.5

**Need a Meal Detection Algorithm**

# Meal Detection Algorithm




E. Dassau, B.W. Bequette, B.A. Buckingham, F.J. Doyle III, *Diabetes Care*, 31(2), 295-300 (2008)

# MPC-based Glucose Control Cases

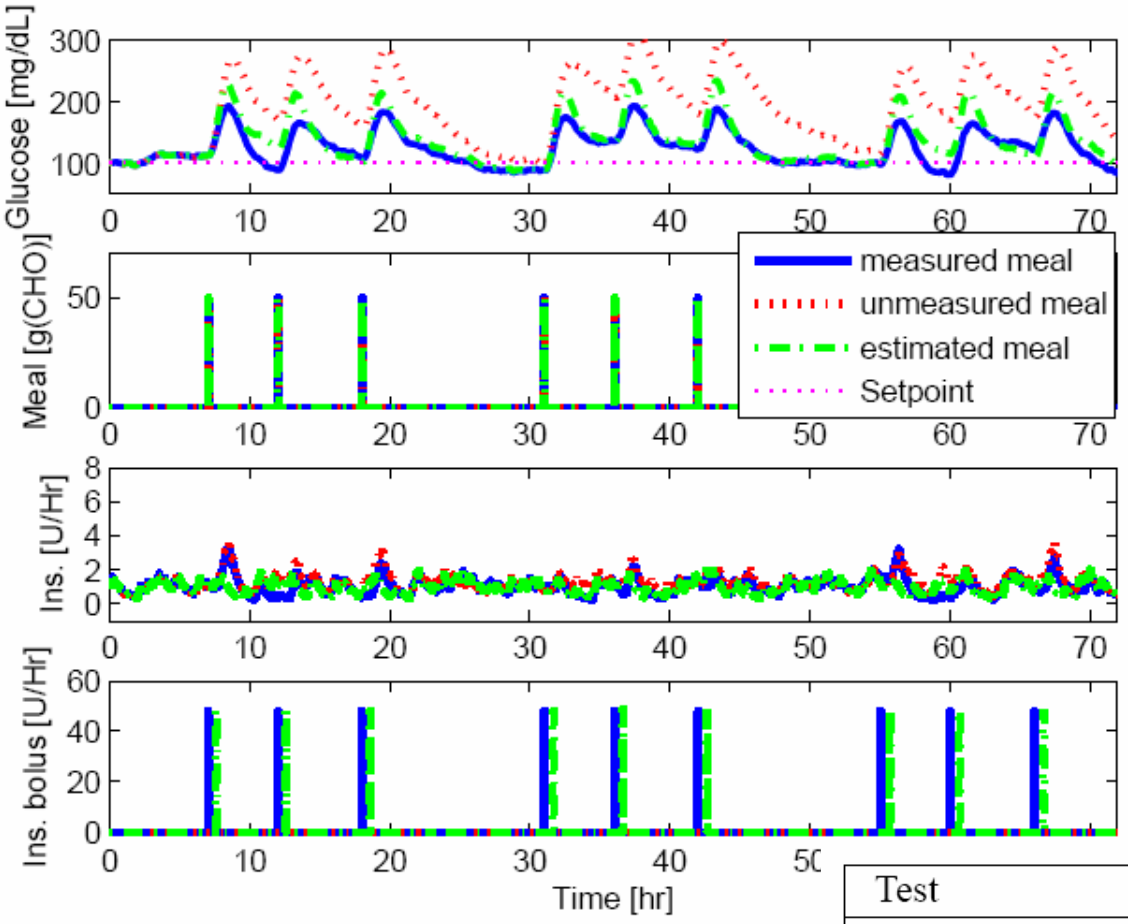
- Case 1: measured meal case considers all meal announcement for exact carbohydrates sizes of meal contents.

- Case 2: unmeasured meal case considers all unmeasured meal disturbances without any meal announcement.

- Case 3: estimated meal case uses the meal size estimation algorithm to allow automatic meal bolus whenever meal announcement is not given.

# *In Silico* Closed-loop Evaluation

under constant insulin sensitivity




Unmeasured meal case shows highest values for MAD, Mean, Min and Max.

**Estimated meal case produces improved closed-loop glucose control compared to the unmeasured case.**

Three meals [50 50 50]g are considered per day.

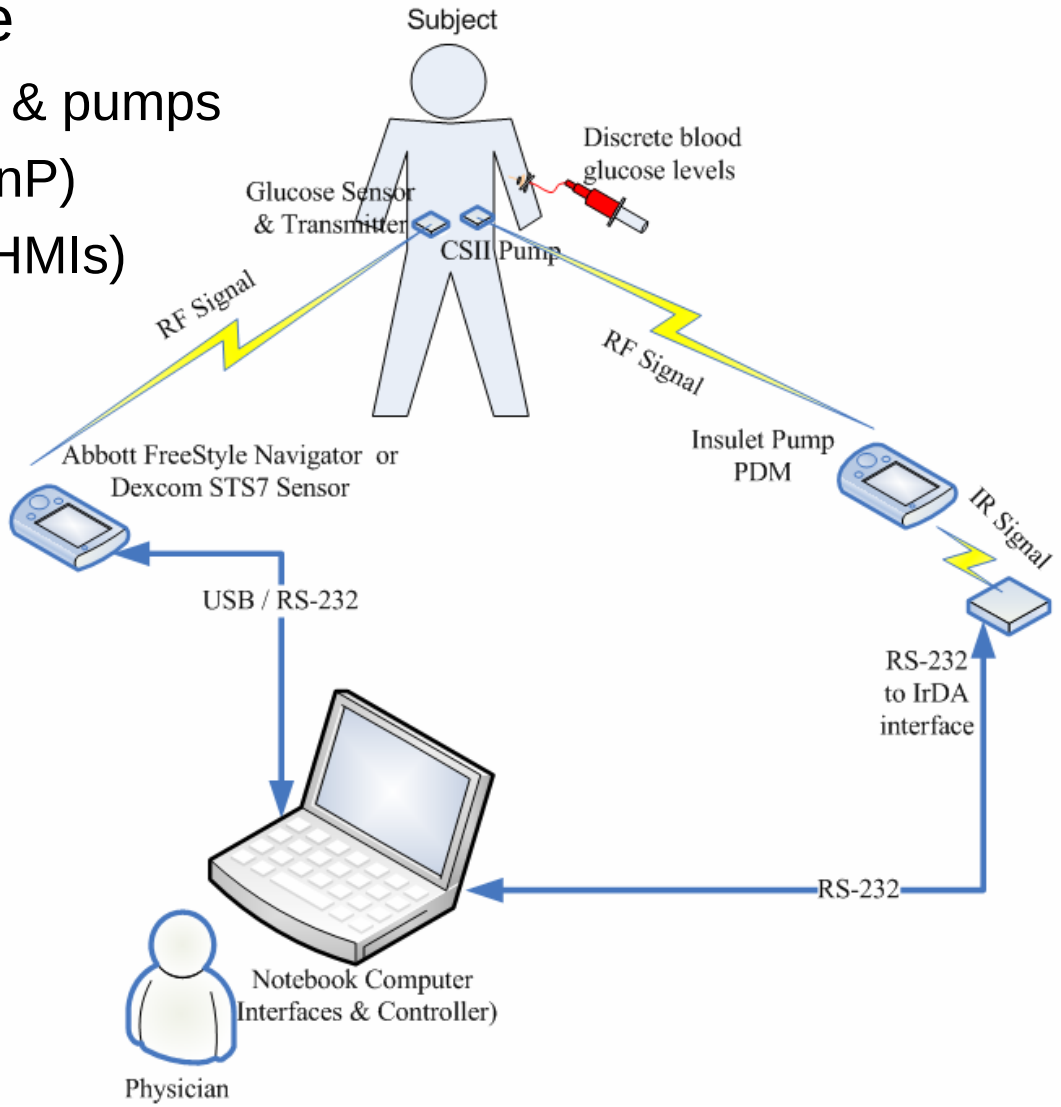
MPC Tuning & Constraints:

P=36, M=3, Wy=1, Wu=5, Umax=4.4U/hr, umin=0 U/hr, dumax=2.2 U/hr

| Test | MAD | Mean | Min | Max |
|---|---|---|---|---|
| Measured meal case | 28.8 | 125.8 | 81.4 | 193.9 |
| Unmeasured meal case | 91.0 | 191.0 | 96.6 | 311.4 |
| Estimated meal case | 38.6 | 137.4 | 87.3 | 234.9 |

# Clinical Studies: Artificial Pancreas

- Artificial Pancreas Software
  - Communication with sensors & pumps
  - Modularity, Plug-and-Play (PnP)
  - Human Machine Interfaces (HMIs)
  - Physician control
  - Data storage
  - Audio & Visual alarms
  - Standalone application
  - Data recording
  - Safety and redundancy



# First Step: Automated Pump Shut-off

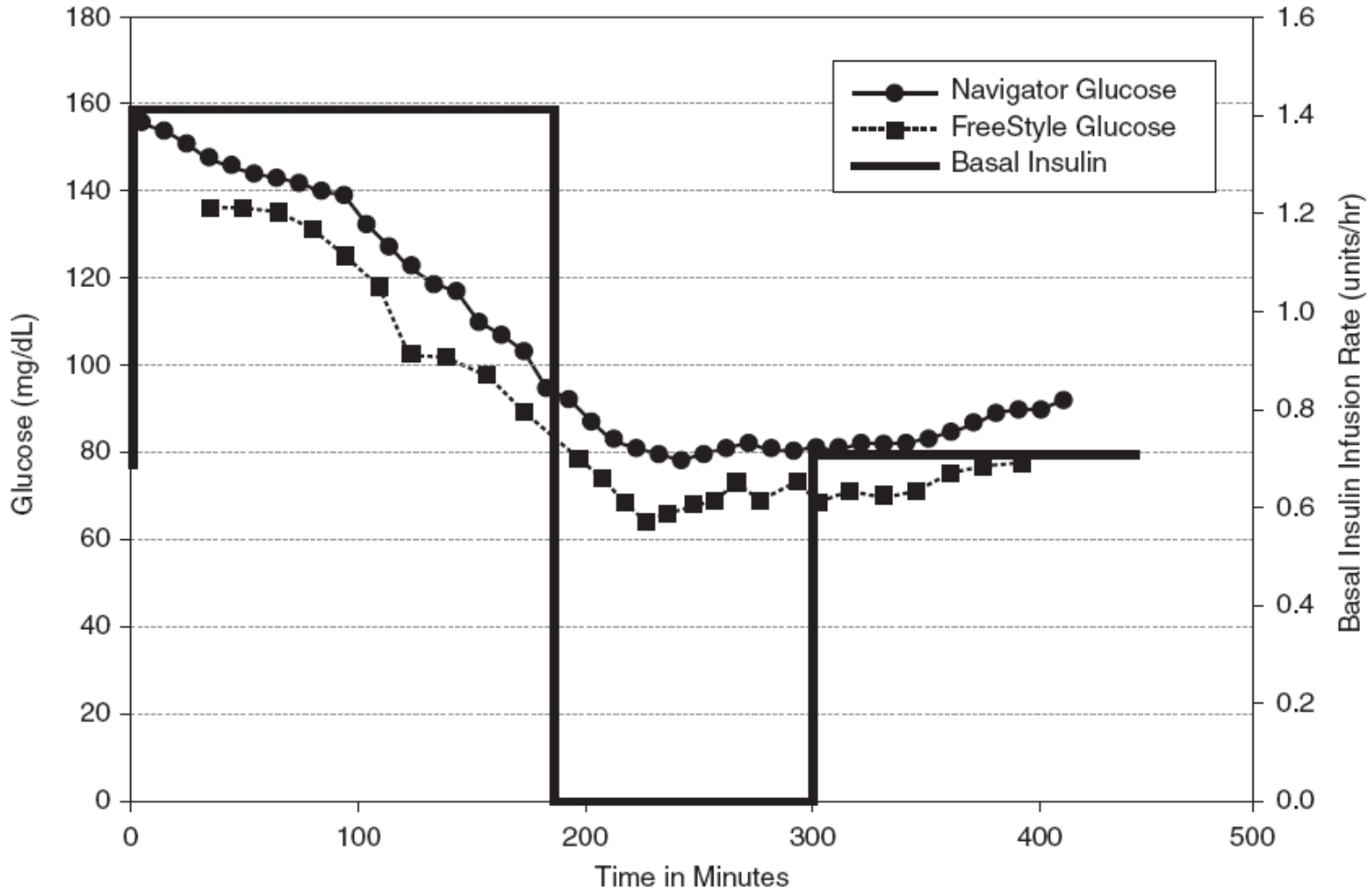
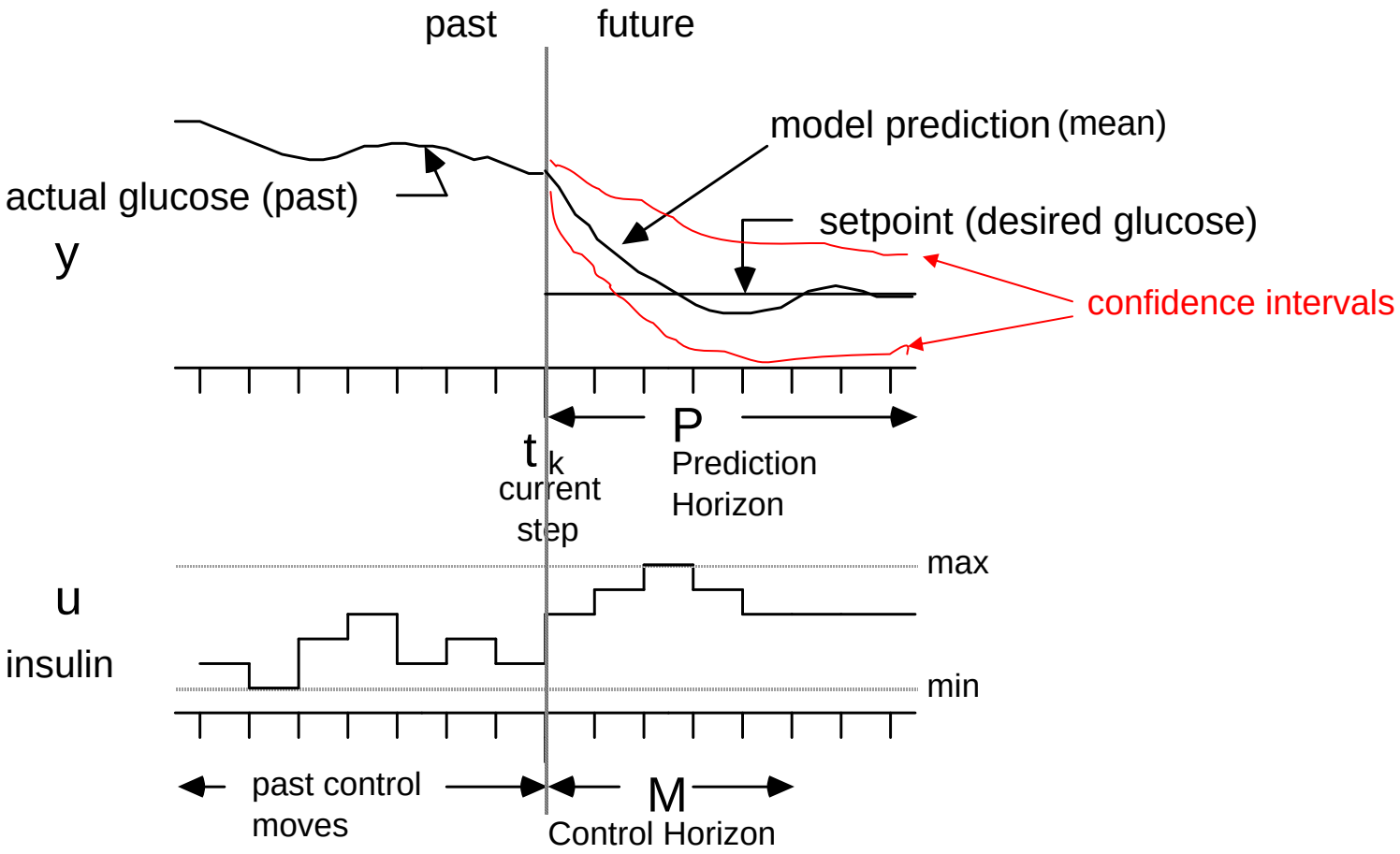



FIG. 2. Second admission with pump shutoff on projected alarm.

Buckingham, B.A., E. Cobry, P Clinton, K Caswell, V. Gage, N. Forghani, B. Vanderwel, E. Dassau, F Cameron, H. Lee, F.J. Doyle III, B.W. Bequette, G. Niemeyer, H.P. Chase “Preventing Nocturnal Hypoglycemia Using Predictive Algorithms and Pump Suspension,” Diabetes, 58(S1), A6 (2009).

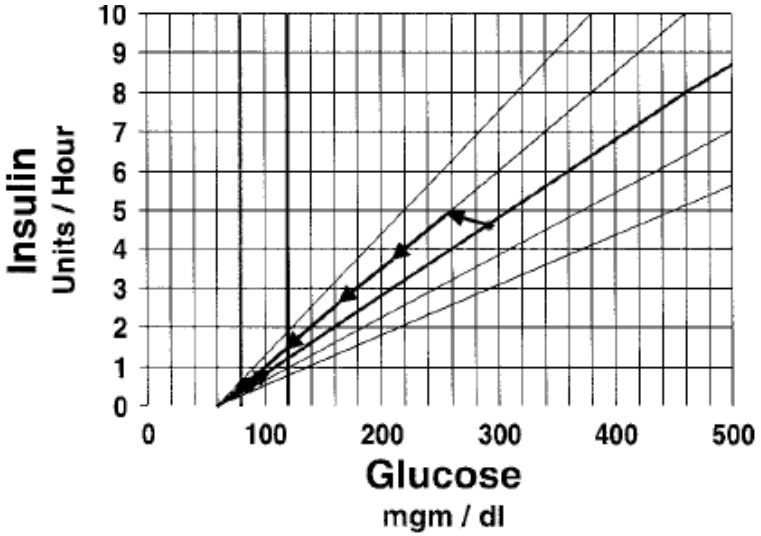
# Current Effort:
# Multiple Model Probabilistic Predictive Control



# Related Topic: ICU Glucose Control

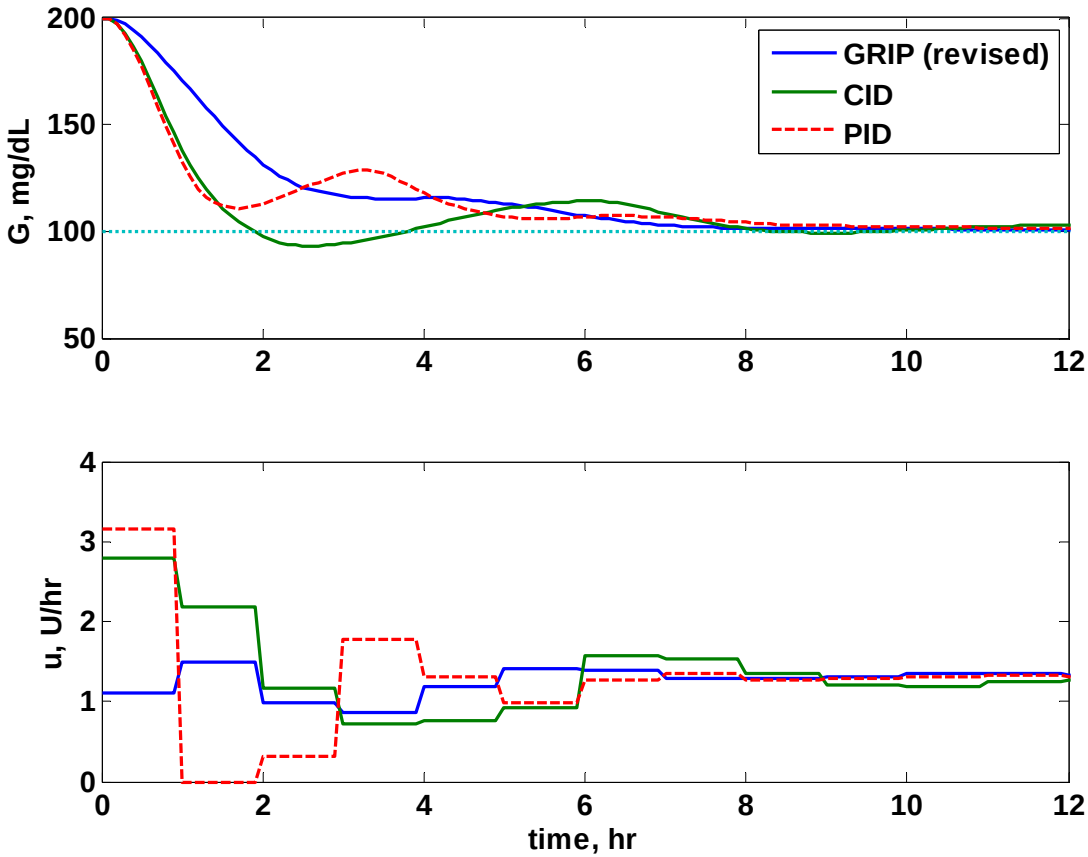
- Critical Illness & Hyperglycemia
  - Independent of Diabetes
- Insulin Infusion to Regulate Glucose
  - i.v. delivery
- Current State:
  - Sample blood every 1-4 hours
  - Table look-up for Insulin Infusion
- Closed-loop algorithms

# ICU Algorithms




Davidson et al., Diabetes Care, 28(10), 2418-23 (2005)

Table look-up and related algorithms are often proportional-controllers




Bequette BW “Analysis of Algorithms for ICU Blood Glucose Control,” *J. Diabetes Sci. Tech*, 2007;1(6),813-824

# Summary Diabetes and Glucose Control

- Overview and current state of technology
- Continuous glucose monitoring
- Hypoglycemic prediction/detection
- Meal detection & meal size estimation
- Closed-loop control
  - Model development: “Human-friendly” and changes in clinical procedures
- Intensive Care Unit (ICU) blood glucose control

# JDRF Team & Acknowledgement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**Algorithms working group** New York, Aug, 2006

# Other Projects

- Model-based Control
  - Nonlinear Systems
- Circadian Effects & Physiology
- Energy
  - Fuel Cell Systems
  - IGCC Power Plants
- Pharma/Biochemical
  - Process scale-up: operability
  - Microbial reactors