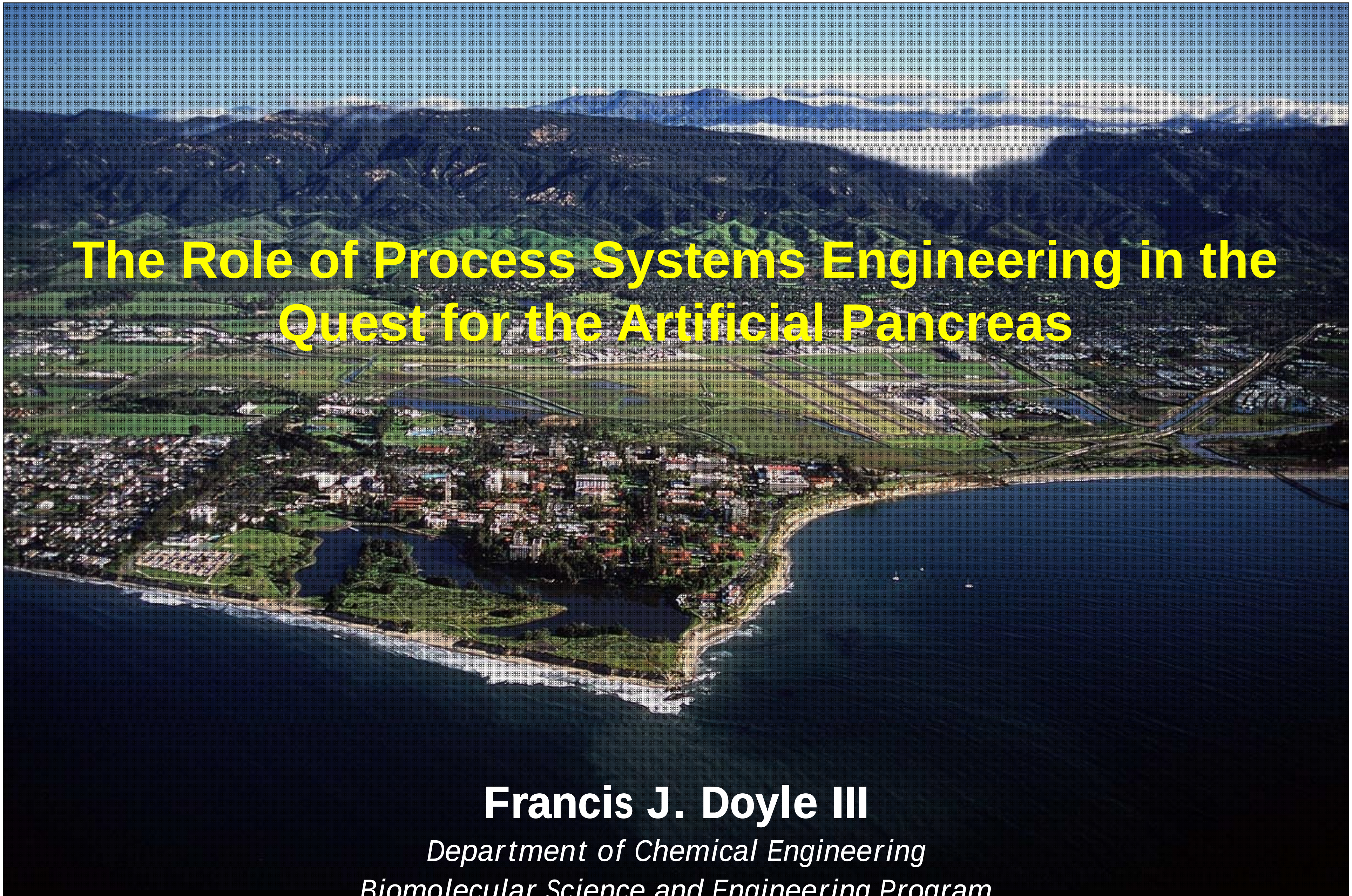

The Role of Process Systems Engineering in the Quest for the Artificial Pancreas

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Biomolecular Science and Engineering Program

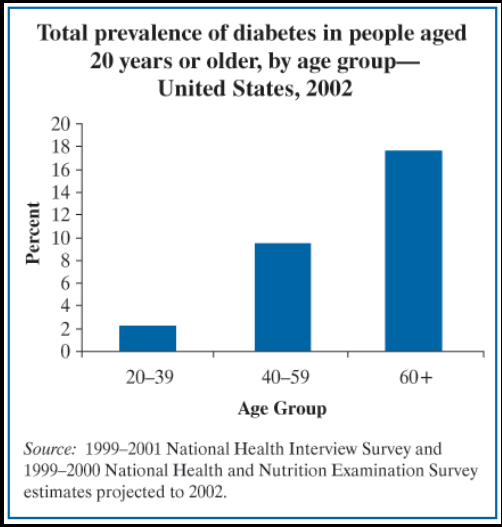
Institute for Collaborative Biotechnologies

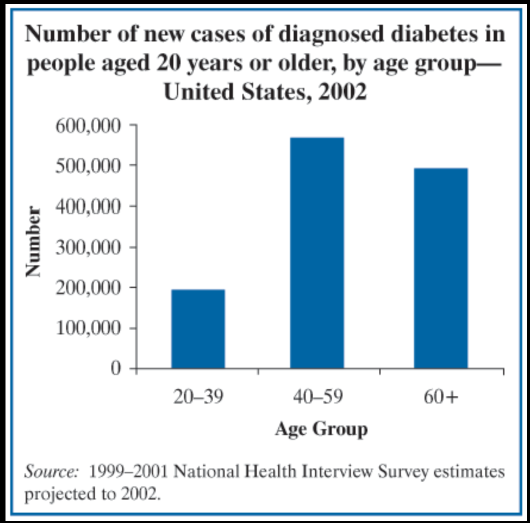
UCSB

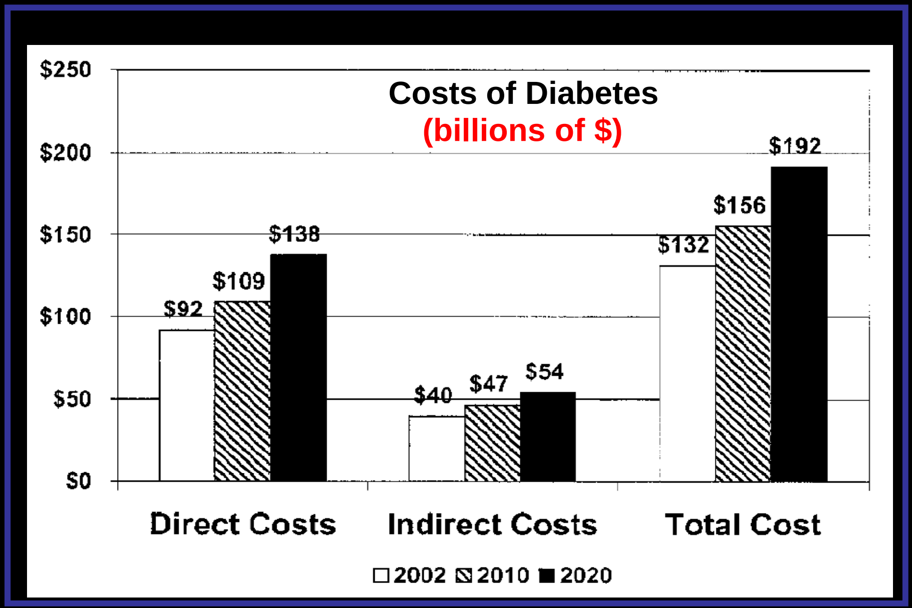
Type 1 Diabetes Mellitus

- About one in every 400 to 600 children and adolescents has type 1 diabetes mellitus (T1DM)
  - *National Diabetes Fact Sheet, 2005, Centers for Disease Control and Prevention*
- Complications of T1DM reduce life expectancy by 20 years through micro- and macro-vascular disease
  - Heart disease and stroke
  - Blindness
  - Kidney disease
  - Nervous system disease
- Evidence that intensive insulin therapy (IIT) reduces complications
  - *Diabetes Control and Complications Trial Research Group, 1993*
- Increased hypoglycemic events with IIT
  - *Diabetes Control and Complications Trial Research Group, 1993*

The Cost of Diabetes

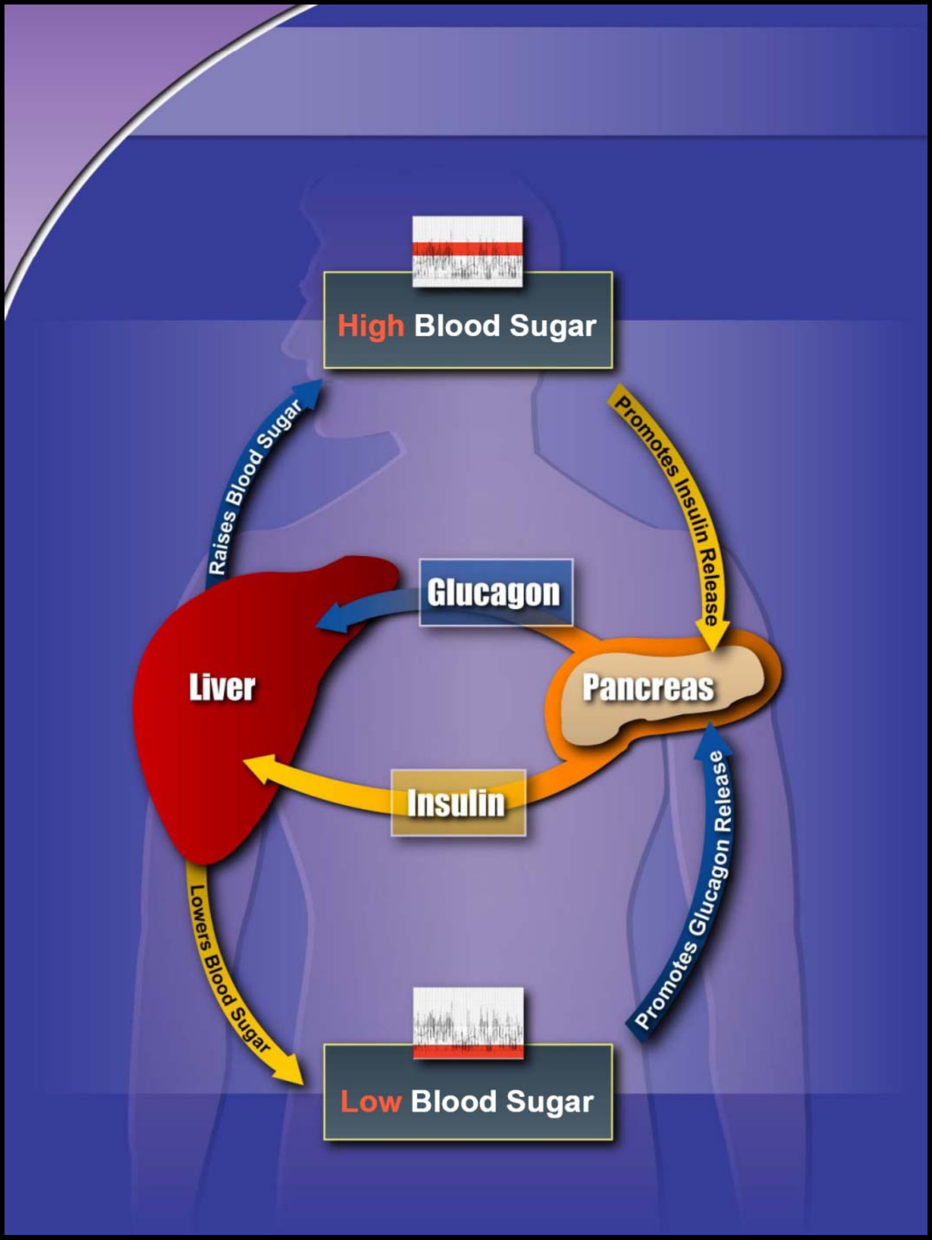






[ADA 2003]

Glucose Homeostasis



The Glucose – Insulin “Loop”

(i) Automatic Control

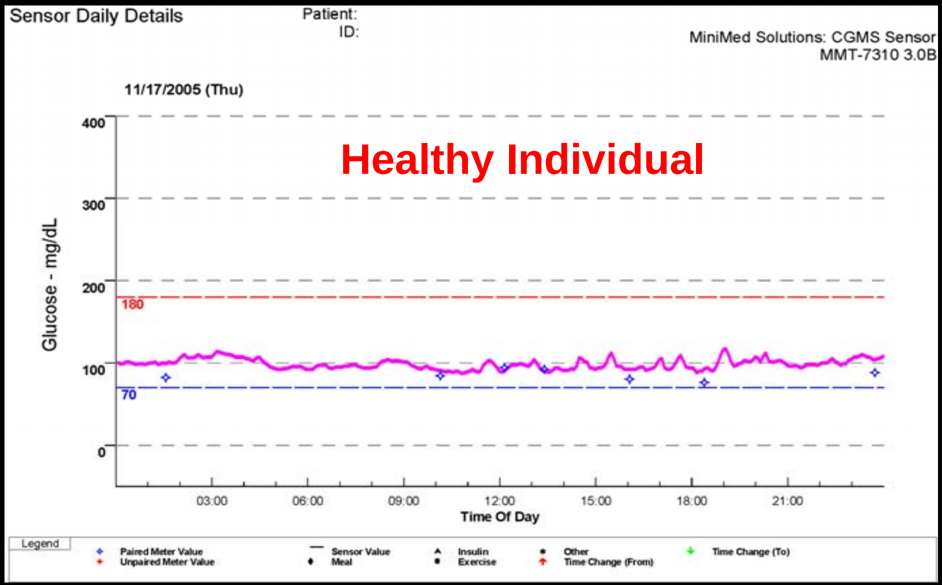
(ii) Day-to-day Control

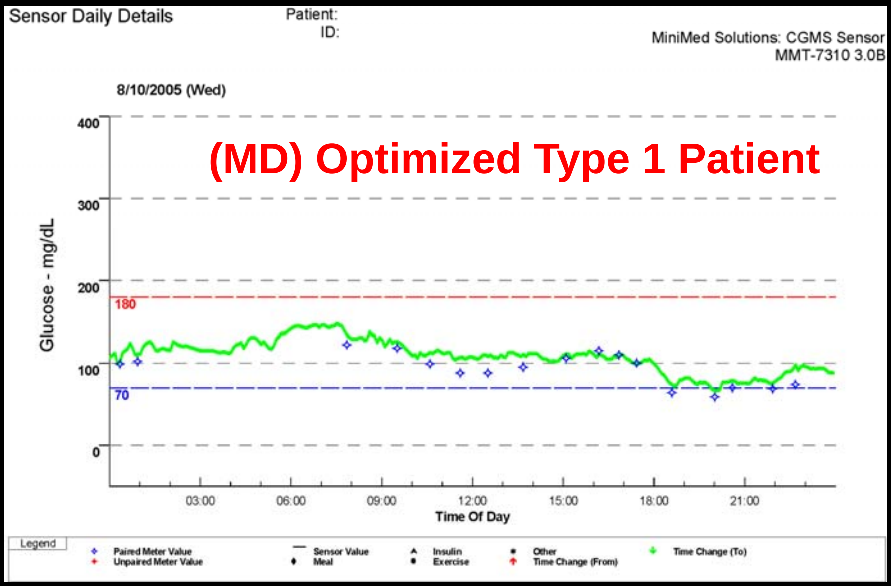
(iii) Efficient Solution

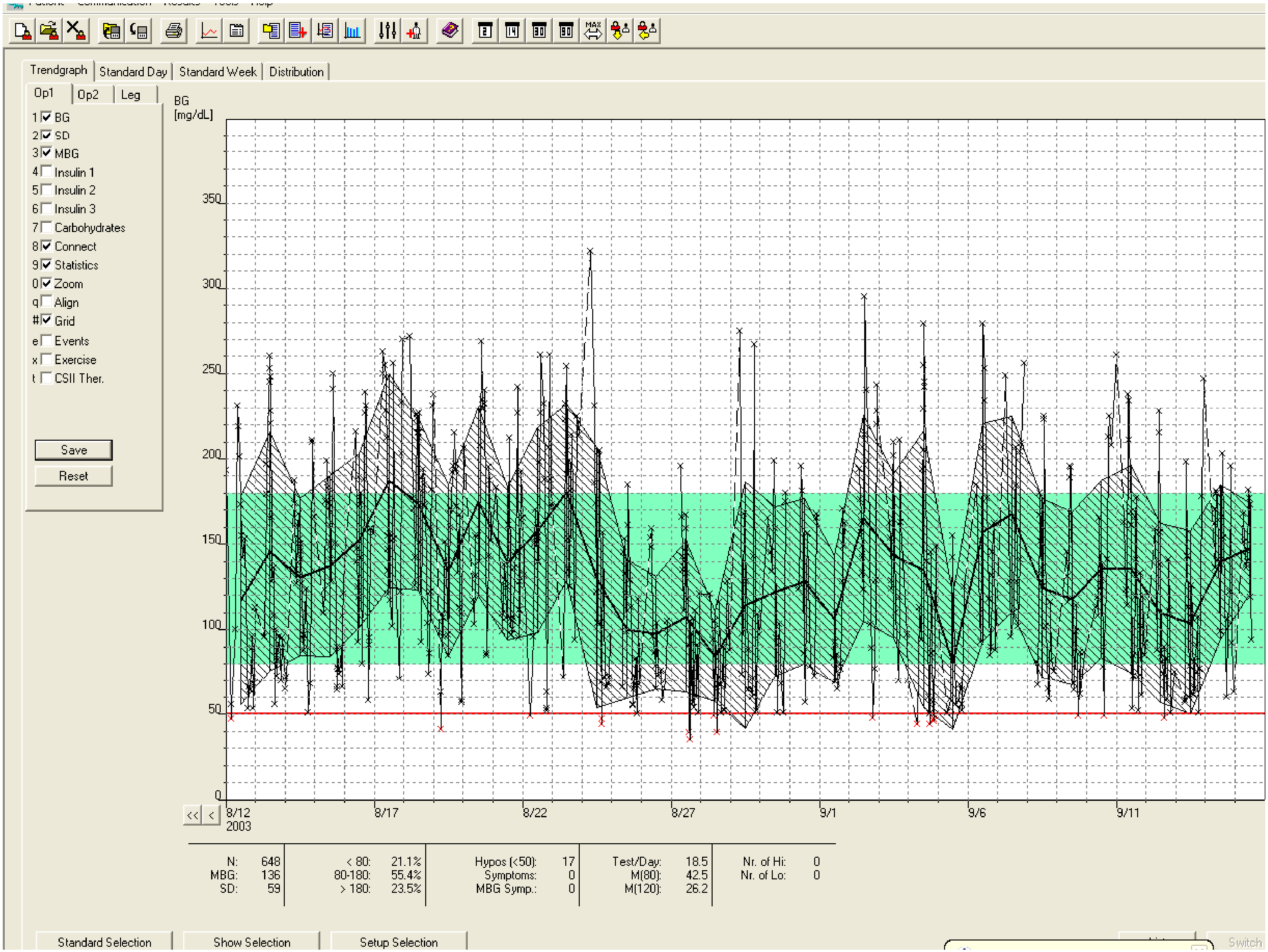
Glucose Measurement

Insulin Delivery

Normalization of Glycemia







Trendgraph
Standard Day
Standard Week
Distribution
Op1
Op2
Leg
1 BG
2 SD
3 MBG
4 Insulin 1
5 Insulin 2
6 Insulin 3
7 Carbohydrates
8 Connect
9 Statistics
0 Zoom
q Align
Grid
e Events
x Exercise
t CSII Ther.
Save
Reset
BG [mg/dL]
350
300
250
200
150
100
50
0
8/12 2003
8/17
8/22
8/27
9/1
9/6
9/11
N: 648
MBG: 136
SD: 59
< 80: 21.1%
80-180: 55.4%
> 180: 23.5%
Hypos (<50): 17
Symptoms: 0
MBG Symp.: 0
Test/Day: 18.5
M(80): 42.5
M(120): 26.2
Nr. of Hi: 0
Nr. of Lo: 0
Standard Selection
Show Selection
Setup Selection
Switch

UCSB/Sansum Approach

- Feedback control algorithm
  - Core insulin delivery algorithm

    Ellingsen et al., 2009, *J. Diabetes Sci. Tech.;* Percival et al., submitted, 2009

- Hypoglycemia prediction
  - Alarms and pump shut-off

    Dassau et al., 2008, *Diabetes*

- Meal detection
  - Augment control algorithm

    Dassau et al., 2008, *Diabetes Care*

- Iterative learning control
  - Account for intra-subject variations

    Zisser et al., 2005 *Diabetes Technol. Ther.*; Wang et al., 2009, *IEEE Trans Biomed Eng*, 2009

- Hardware-in-the-loop trials
  - Testing communication protocols of off-the-shelf devices

    Dassau et al., 2009, *Diabetes Technol . Ther*

Glucose Sensing and Insulin Delivery

Current State of the Art:
Self-Monitoring Blood Glucose Meters (SMBG)

TABLE 9 Cost Comparisons of Blood Glucose Monitors

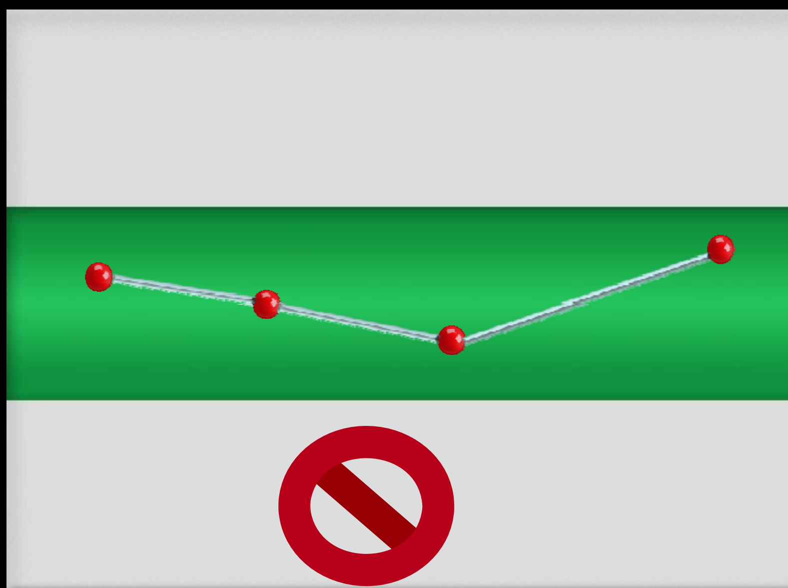
Monitor/Kit	AWP	Strip/Disc Package Size	AWP	Control Solution	AWP
Ascensia® Breeze	$58.75	Ascensia® Autodisc® 50/100	$47.00/$85.00	Low-high 2.5 ml/NL 2.5 ml	$6.30/$11.90
Ascensia® Contour®	$75.00	50/100	$47.50/$87.50	Low-high 2.5 ml/NL 2.5 ml	$6.30/$11.90
Ascensia® Dex® 2	$71.90	Ascensia® Autodisc® 50 (5 x 10)/100 (10 x 10)	$47.00/$85.00	Low-high 2.5 ml/NL 2.5 ml	$6.30/$11.90
Ascensia Elite®	$43.75	25/50/100	$25.00/$46.20/$83.20	Low-high 2.5 ml/NL 2.5 ml	$6.30/$11.90
Ascensia Elite® XL	$56.25	25/50/100	$25.00/$48.20/$83.20	Low-high 2.5 ml/NL 2.5 ml	$6.30/$11.90
Accu-Chek® Active	$18.75	50	$29.69	Low-high	$8.44
Accu-Chek® Advantage	$68.75	50/100	$47.19/$89.69	Level 1 and 2	$8.44
Accu-Chek® Aviva		50		Level 1 and 2	
Accu-Chek® Compact	$75.00	Strip drums; 51 (one drum); 102 (two drums)	$48.44/$92.19	Low-high	$8.44
Accu-Chek® Complete	$118.75	50/100	$47.19/$89.69	Low-high/low-high-mid	$8.44/$9.38
Accu-Chek® Voicemate	$493.75	50/100	$47.19/$89.69	Low-high/low-high-mid	$8.44/$9.38
Advance Intuition	$68.00	50	$38.50	Normal	$10.00
Advance Micro-draw	$68.00	50/100	$38.50/$69.30	Level 1 and 2	$10.00
Assure	$30.00*	50/100	$39.30/$56.00	Level 1 and 2	$11.00
Assure II	$85.00	50/100	$29.25/$53.00	Level 1/level 1 and 2	$6.30/$10.00
Assure 3	$68.00	50/100	$38.50/$69.30	Level 1 and 2	$10.00
BD Logic Blood Glucose Monitor	$73.75	Strips 50/100	$45.50/$87.86	Patient must contact BD for delivery.	Free
FreeStyle®	$75.00 $83.10	50	$46.56	High-low/normal	$7.82/$6.69
FreeStyle Flash™	$73.75	50	$46.56	High-low/normal	$7.82/$6.69
OneTouch™ Basic	$50.00	25/50/100	$25.31/$48.12/$89.38	High-low/normal	$7.38/$7.38
OneTouch™ InDuo	$98.75	25/50/100	$26.25/$49.38 / $92.50	Normal	$7.38
OneTouch™ SureStep	$62.50	50/100	$48.12/$89.38	High-low/normal	$9.38/$9.38
OneTouch™ Ultra	$68.75	25/50/100	$26.25/$49.38/$92.50	Normal	$7.38
OneTouch™ UltraSmart	$92.81	25/50/100	$26.25/$49.38/$92.50	Normal	$7.38
Prestige IQ™	$70.68	50/100	$28.60/$45.99	High control/low control	$4.75/$4.75
Precision QID®	$47.94	50/100	$45.13/$83.08	Normal/mid low/high/normal	$8.28/$10.50
Precision Xtra	$71.94	50/100	$44.47/$83.21	Normal/mid low/high/normal	$8.28/$10.50
QuickTek	$19.95	50/100	$38.50/$69.30	Normal	$10.00
ReliOn® NewTek	$55.90	50/100	$26.12/$52.24	Patient must contact for delivery.	Free
ReliOn® Ultima	$26.40	50/100	$31.20/$62.40	NA	NA
TrackEase™ Smart System	$21.40	50/100	$26.75/$52.00	High/low	$6.90/$6.90
TrueTrack Smart System™	$23.70	50/100	$30.50/$53.50	High/low	$6.90/$6.90

AWP = average wholesale price.
* Standard list price. This monitor will not be manufactured after January 2006.
Data from *Red Book*®, 109th ed. Montvale, NJ: Thomson; 2005.[39]

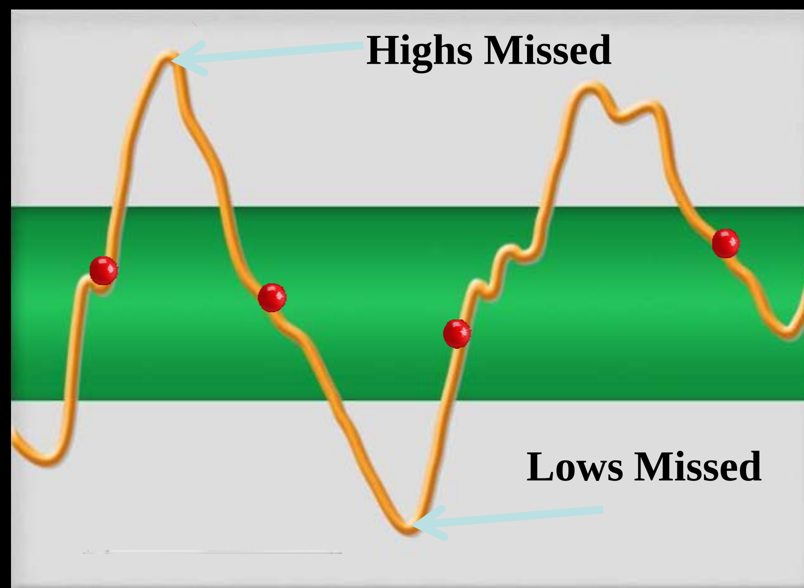
[Graham, P&T, 2005]

Benefits of Continuous Glucose Monitoring

Standard Blood Glucose Monitoring

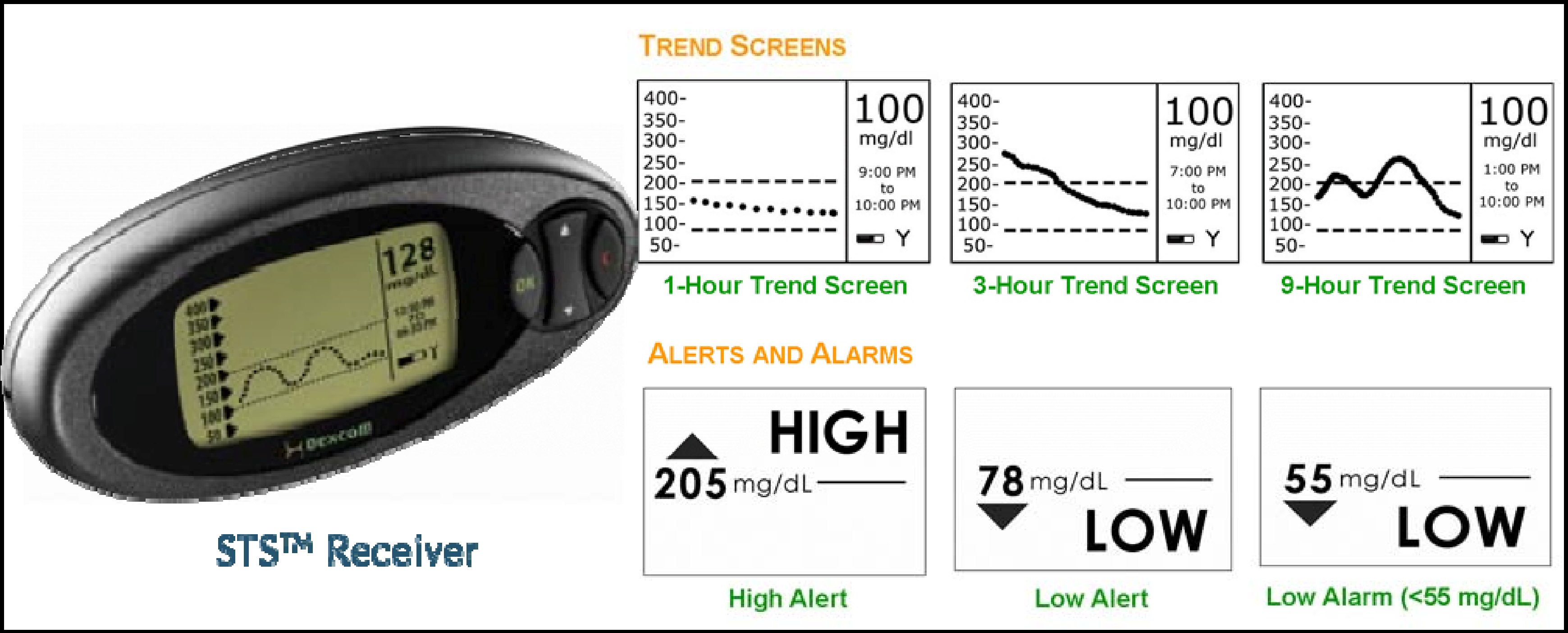


Continuous Glucose Monitoring



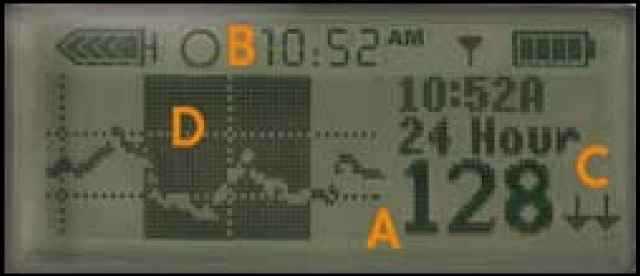
Source: Medtronic Diabetes modified by H. Zisser

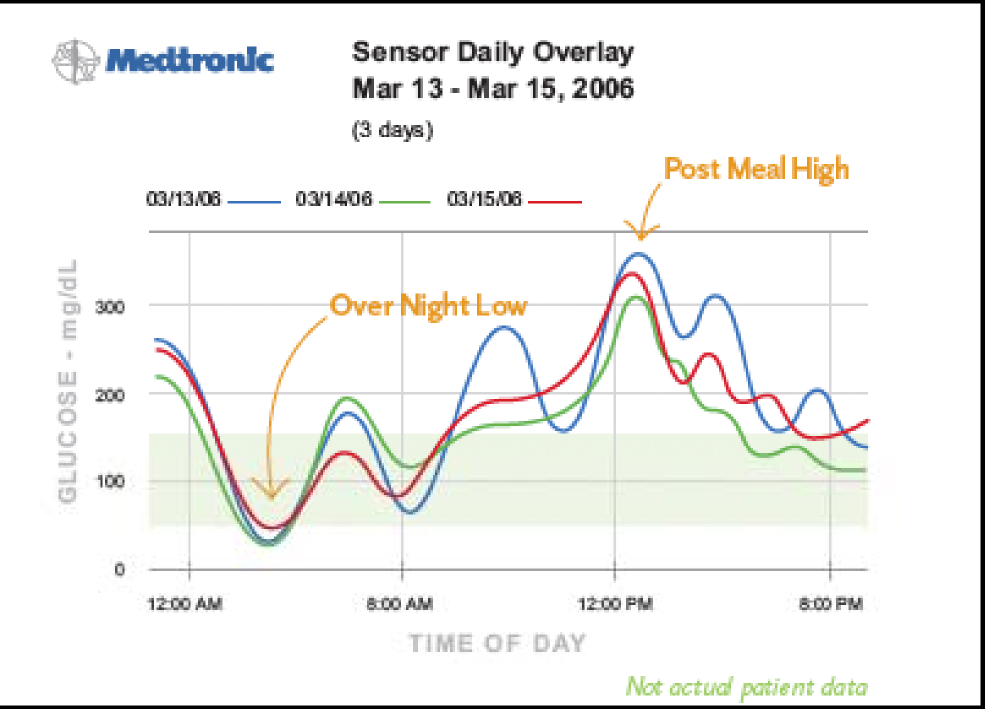
Receiver for Sensor



Source: DexCom,Inc.

Archival Data Analysis

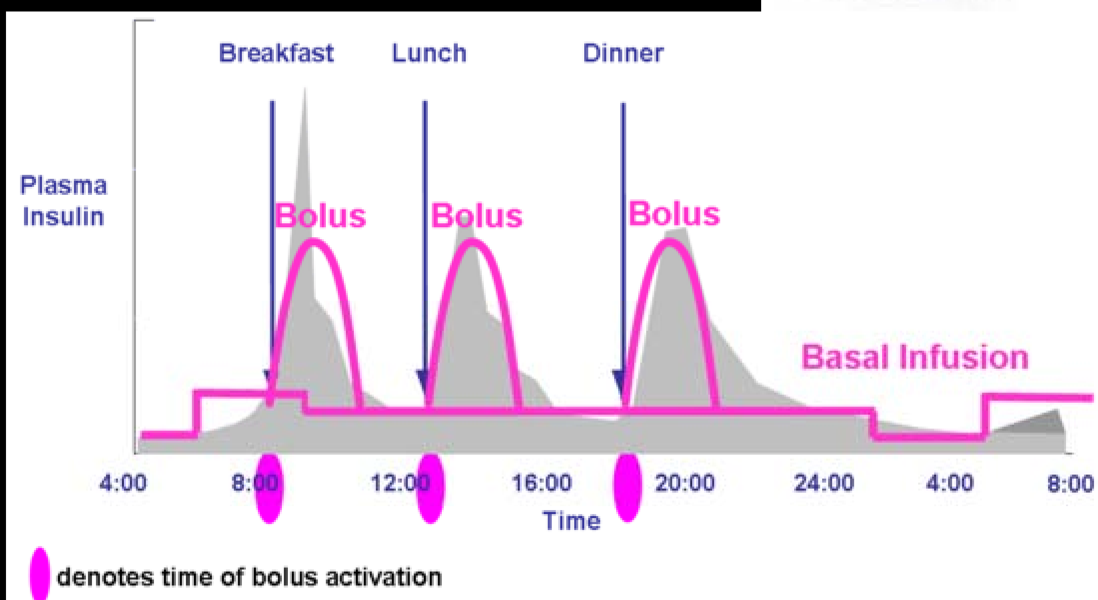




Source: Medtronic Diabetes

Continuous Subcutaneous Insulin Infusion (CSII)

- Patients can easily accommodate metabolic changes
- Set basal rate
- Deliver manual boluses



http://www.endotext.org/diabetes

Opportunities for Process Systems Engineering:

SMBG Systems

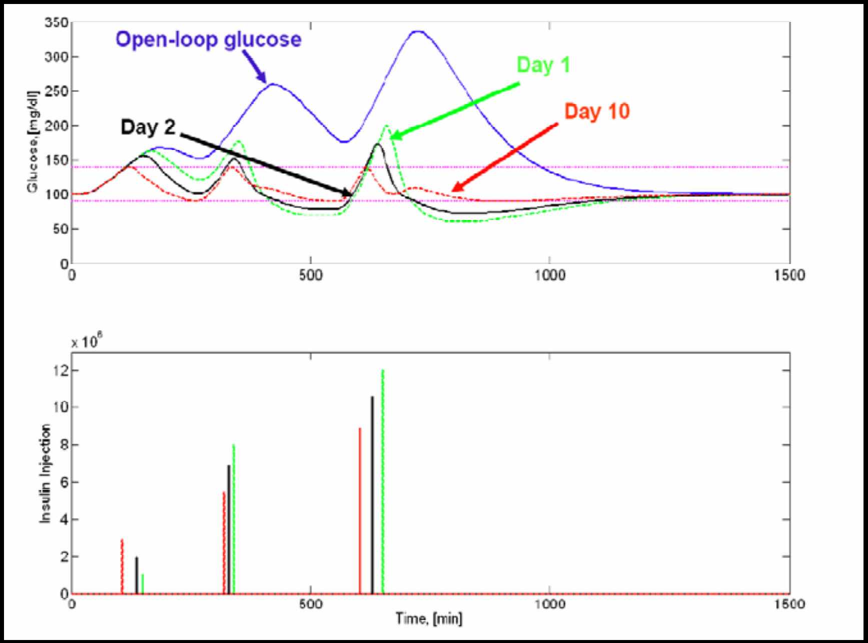
Meal Bolus Dosing Analogy: Run-to-Run Control

[Doyle III *et al*., 2001; Zisser *et al*., 2005; Owens *et al*., 2006]

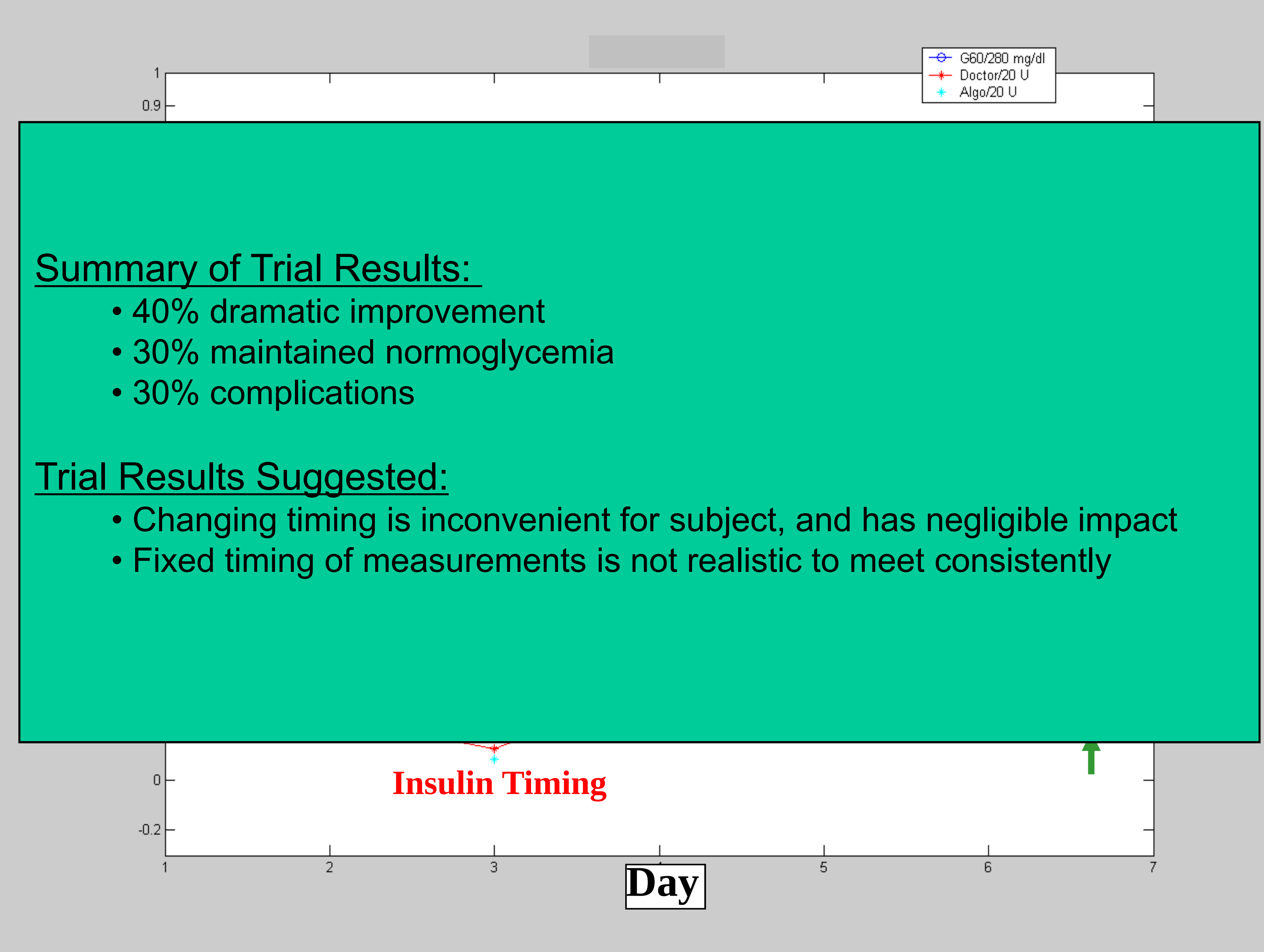
- Emerged from robotics and semiconductor processing problems where "repetition" is key
  - emphasis on measurement-based framework
  - batch-to-batch optimization ⇒ iteratively converge to optimal input profile in fewest number of (sub-optimal) runs
  - terminal constraints (end-conditions) are a critical element of the optimization problem

- **Concept: Use meal cycle (run) to manage diabetes**

$$T(k+1) = T(k) + K_T \min(0, G^r_{\max} - G_{\max}(k))$$
$$Q(k+1) = Q(k) + K_Q \max(0, G^r_{\min} - G_{\min}(k))$$



Clinical Evaluation of Run-to-Run Control



<u>Summary of Trial Results:</u>

- 40% dramatic improvement
- 30% maintained normoglycemia
- 30% complications

<u>Trial Results Suggested:</u>

- Changing timing is inconvenient for subject, and has negligible impact
- Fixed timing of measurements is not realistic to meet consistently

Modified Algorithm

$$\nu_{k+1} = \nu_k + K\left(\psi^r - \psi_k\right)$$

$$\psi_k = \begin{bmatrix} G(T_{B_1}) - G(T_{B_2}) \\ G(T_{L_1}) - G(T_{L_2}) \\ G(T_{D_1}) - G(T_{D_2}) \end{bmatrix}$$

rate of postprandial glucose rise

$$\nu_k = \begin{bmatrix} Q_B & Q_L & Q_D \end{bmatrix}^T$$

insulin meal bolus

- Only changing insulin dose, timing always fixed to the beginning of the meal
- Still require two post-meal measurements
  - First measurement 60-90 minutes after the start of the meal
  - Second measurement 30-60 minutes after the first
  - For each meal, denote these times as:
    T_{B1}, T_{B2}, T_{L1}, T_{L2}, T_{D1}, T_{D2}

$$\begin{aligned} e_{k+1} &= \psi^r - \psi_{k+1} \\ &= \psi^r - S\nu_{k+1} \\ &= \psi^r - S\left(\nu_k + Ke_k\right) \\ &= \psi^r - \psi_k - SKe_k \\ &= \left(I - SK\right)e_k \end{aligned}$$

$$e_{k+1} = \left(I - S\left(I + \Delta\right)K\right)e_k$$

- **Specific uncertainties:**
  - **Measurement timing**
    $$\Delta = \operatorname{diag}\begin{pmatrix} -0.064 & -0.070 & -0.119 \end{pmatrix}$$
  - **Measurement noise**
    $$\Delta = \operatorname{diag}\begin{pmatrix} -0.236 & -0.382 & -0.260 \end{pmatrix}$$
  - **Meal timing**
    $$\Delta = \operatorname{diag}\begin{pmatrix} -0.194 & -0.450 & -0.473 \end{pmatrix}$$
  - **Meal carbohydrate content**
    $$\Delta = \operatorname{diag}\begin{pmatrix} -0.281 & -0.496 & -0.414 \end{pmatrix}$$
  - **Meal estimate**
    $$\Delta = \operatorname{diag}\begin{pmatrix} -0.184 & -0.415 & -0.395 \end{pmatrix}$$

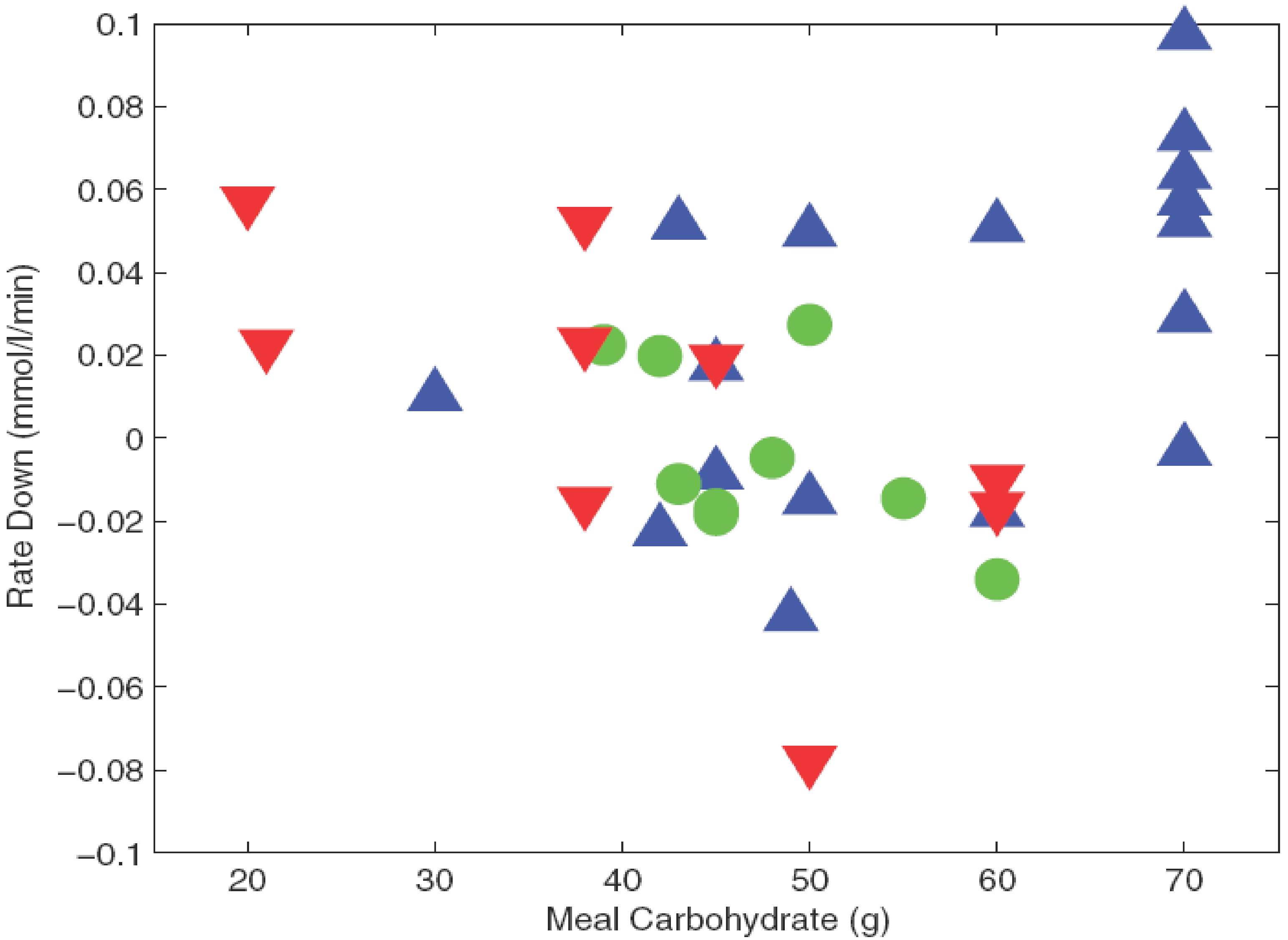
Clinical Evaluation of New Algorithm

- *11 subjects with type 1 diabetes & CSII pumps*

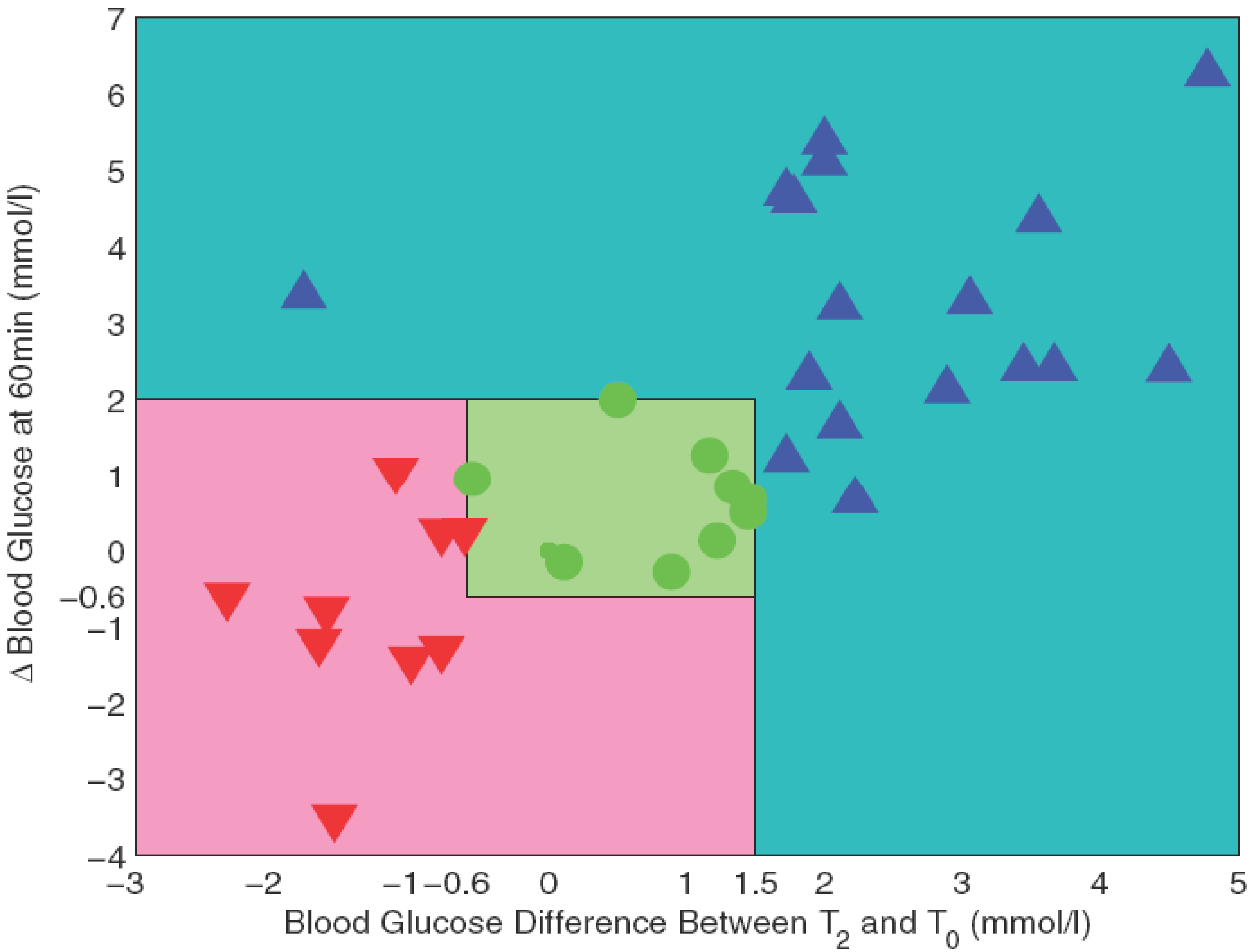
- **Phase 1**
  - Optimized basal rates
  - Brought out of control (1h post-prandial 170–200 mg/dl)
  - Lunch only
  - Carbohydrate content kept constant
  - Algorithm adjusted dosing over 2 weeks

- **Phase 2**
  - All three meals
  - Carbohydrate content varied
  - Algorithm adjusted dosing over 2–3 weeks

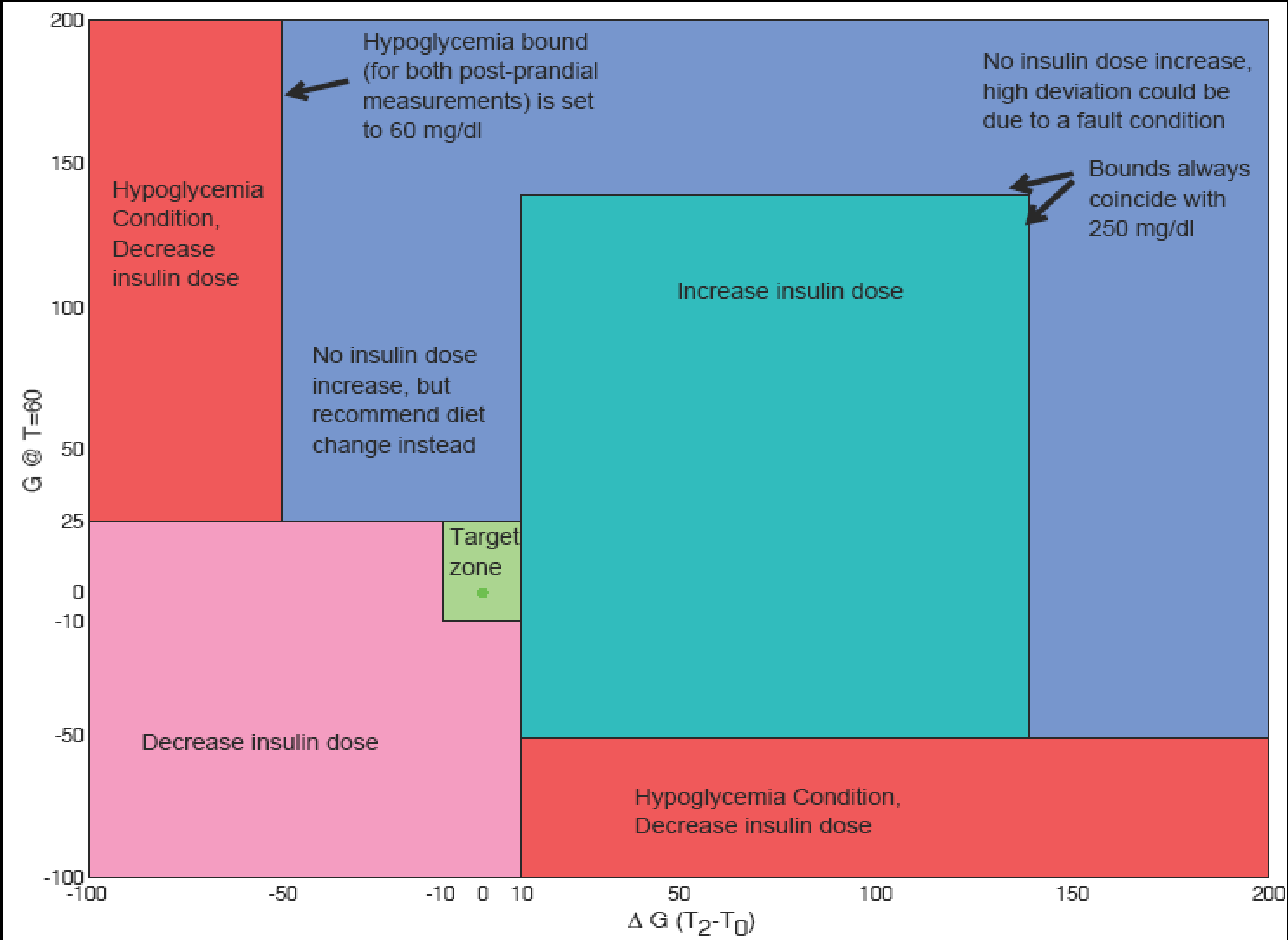
Challenge in Data Clustering



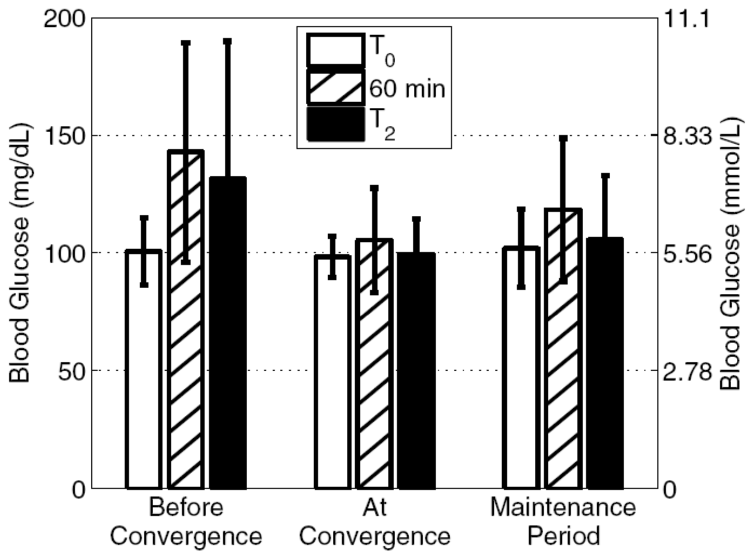
Medically-Inspired Performance Measure



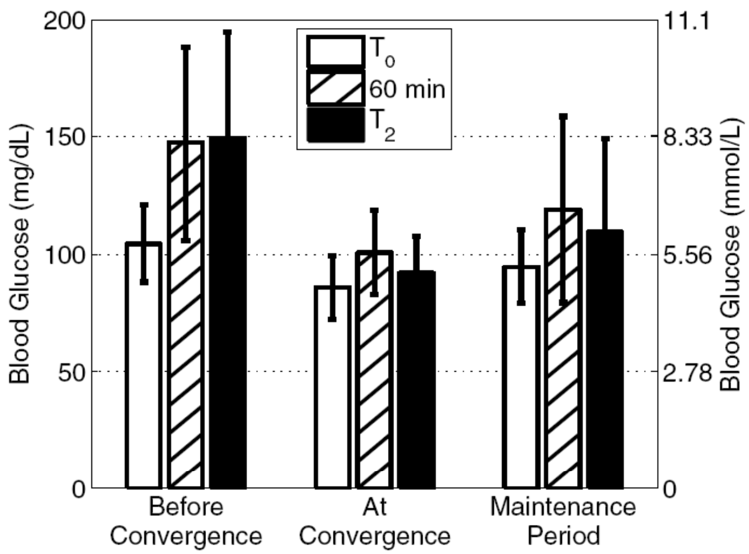
Modifications for Phase 2



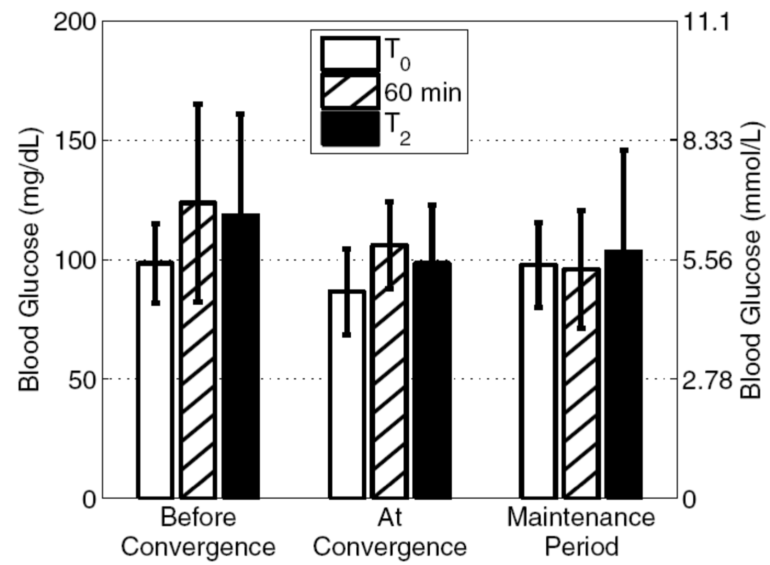
Clinical Results



(a) Breakfast



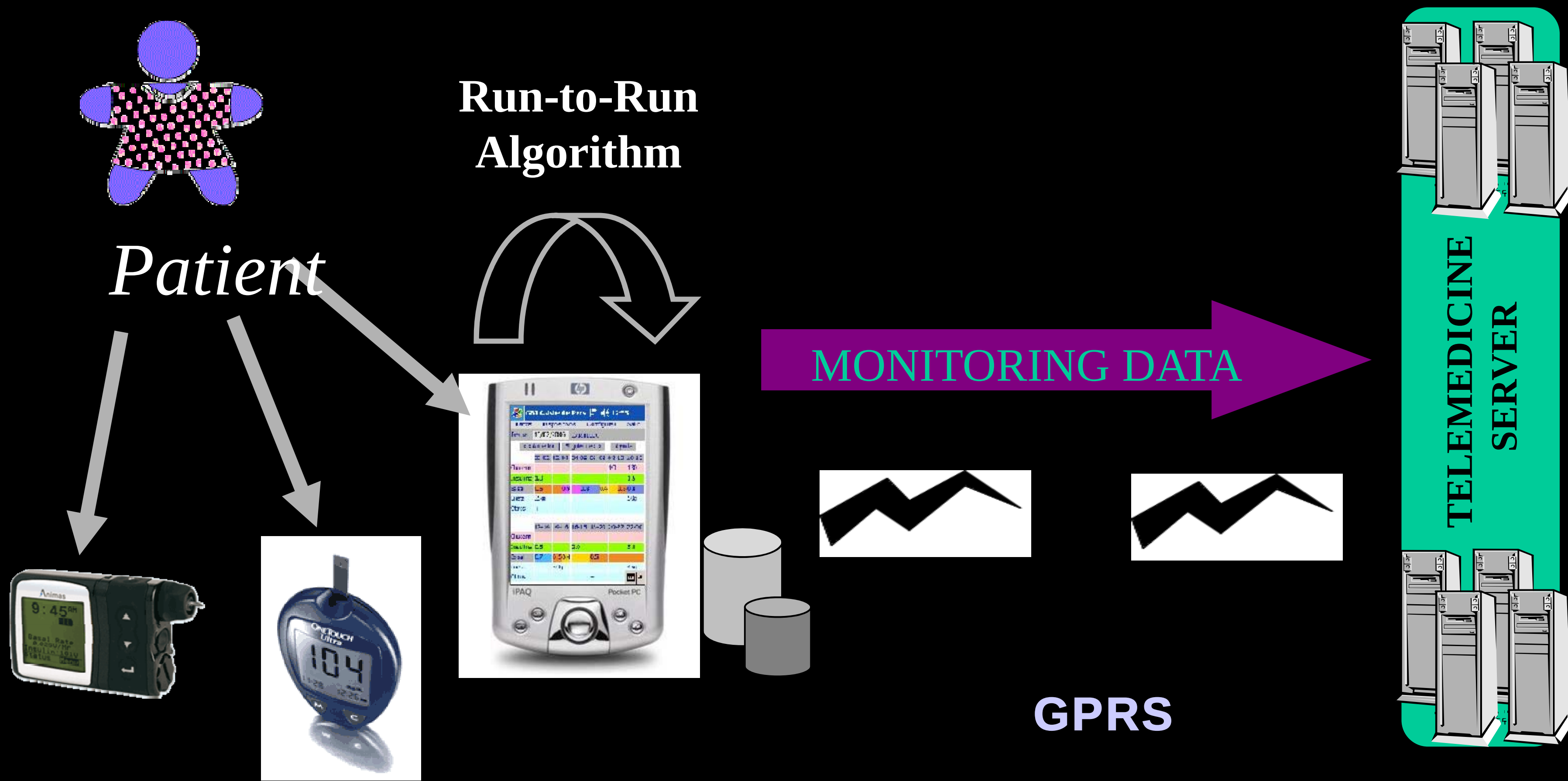
(b) Lunch



(c) Dinner

Implementation of Run-to-Run Controller on PDA Platform

[Gema Garcia Saez and colleagues]

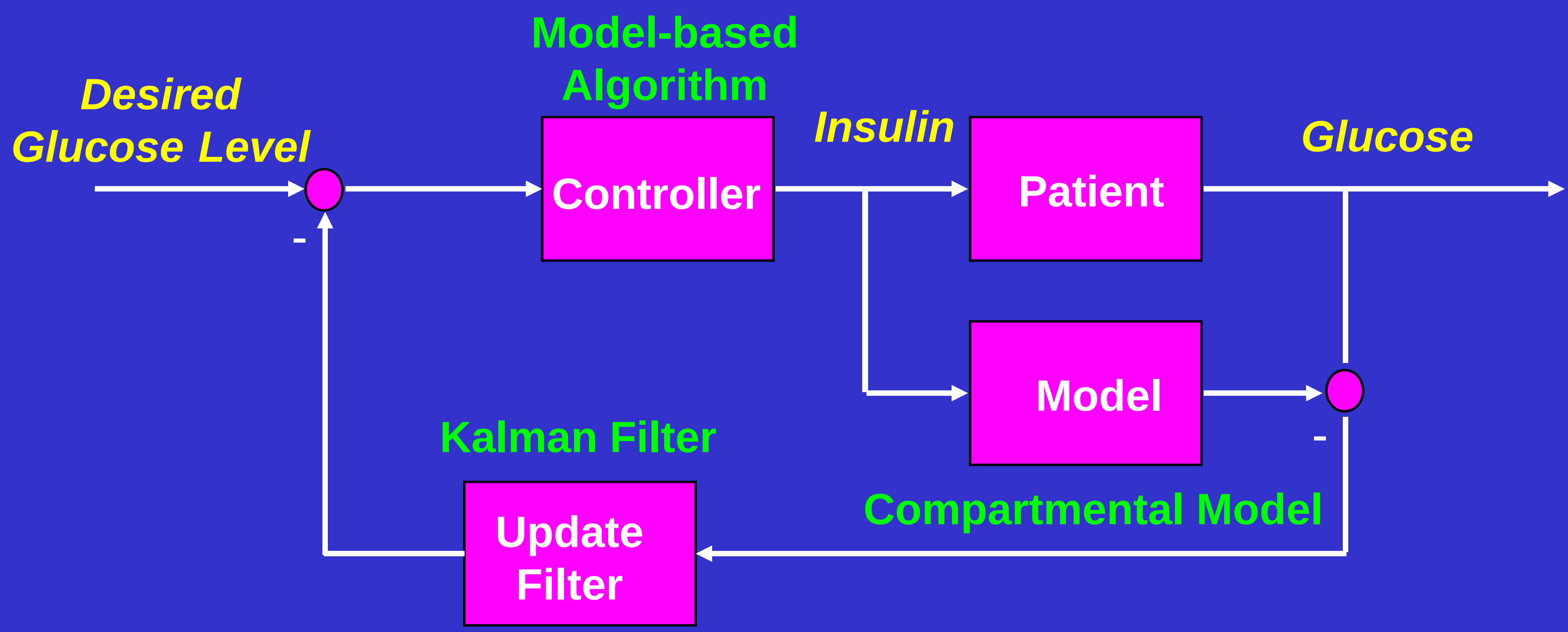


Opportunities for Process Systems Engineering:

CGM Systems

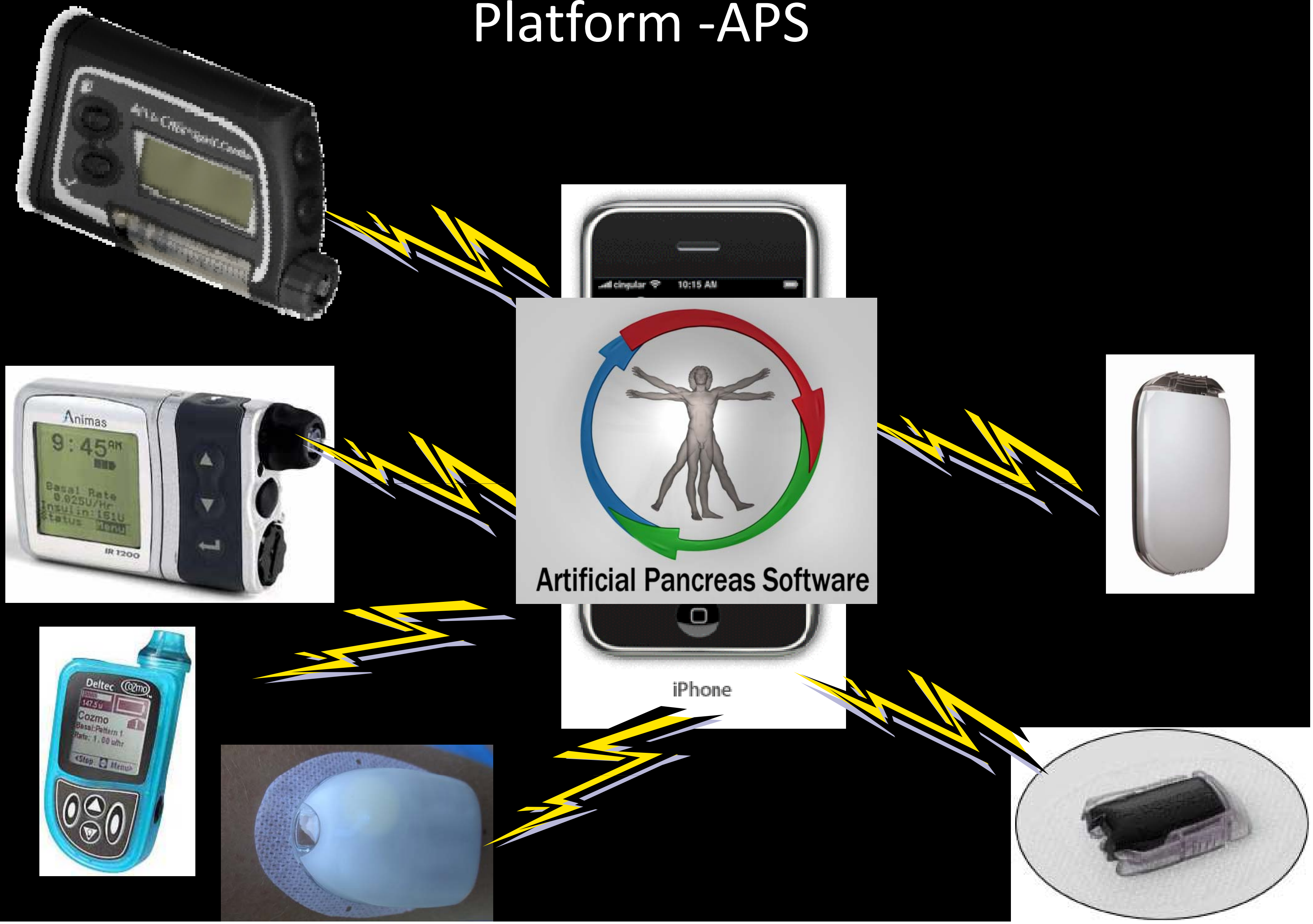
Model-Based Control Approach for Diabetes

[Parker, Doyle III, Peppas, *IEEE Trans. Biomed. Eng.*, 1999]



Key tenet of Robust Control Theory:
Achievable performance is directly tied to model accuracy

Pumps and Sensors Communicate to a Shared Platform -APS



Artificial Pancreas (β-cell) Software

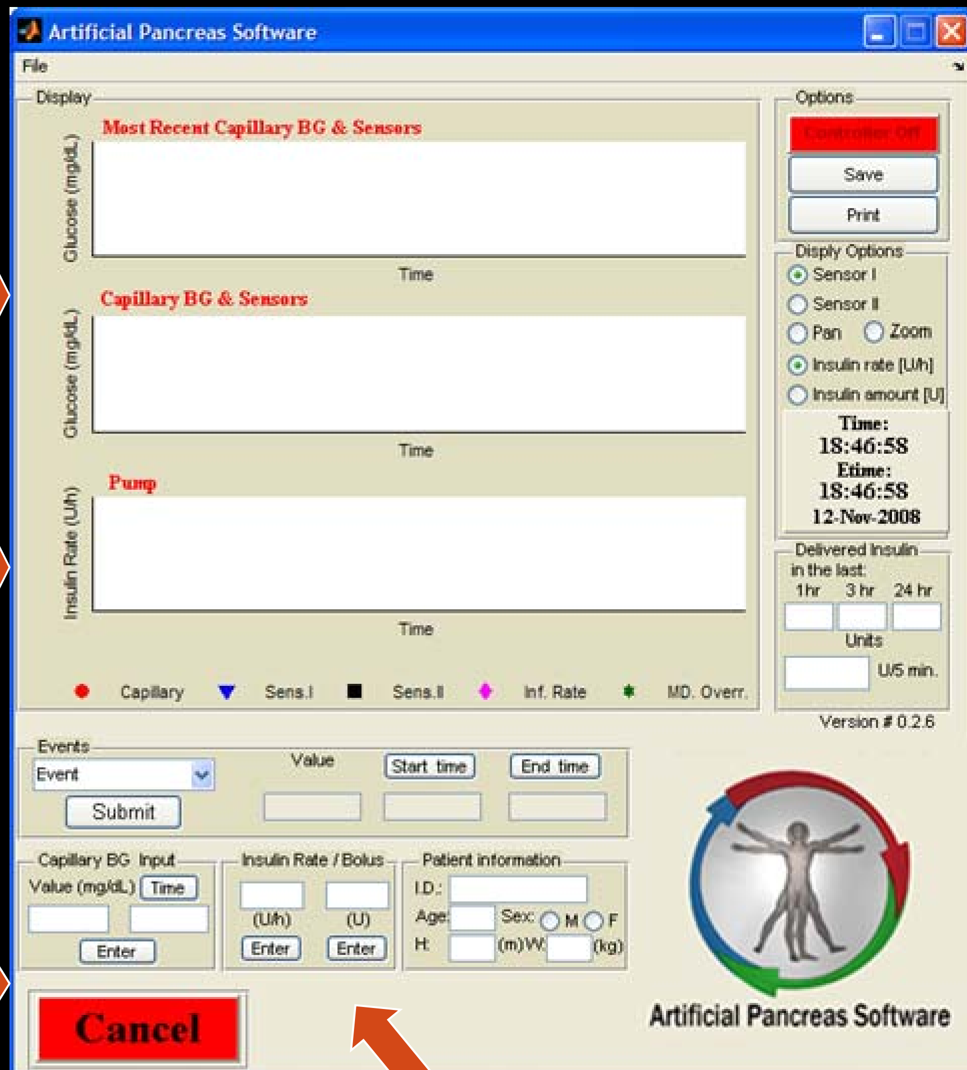
Human Machine Interface

Sensor & Capillary measurements

Insulin delivery

Event log

Capillary BG



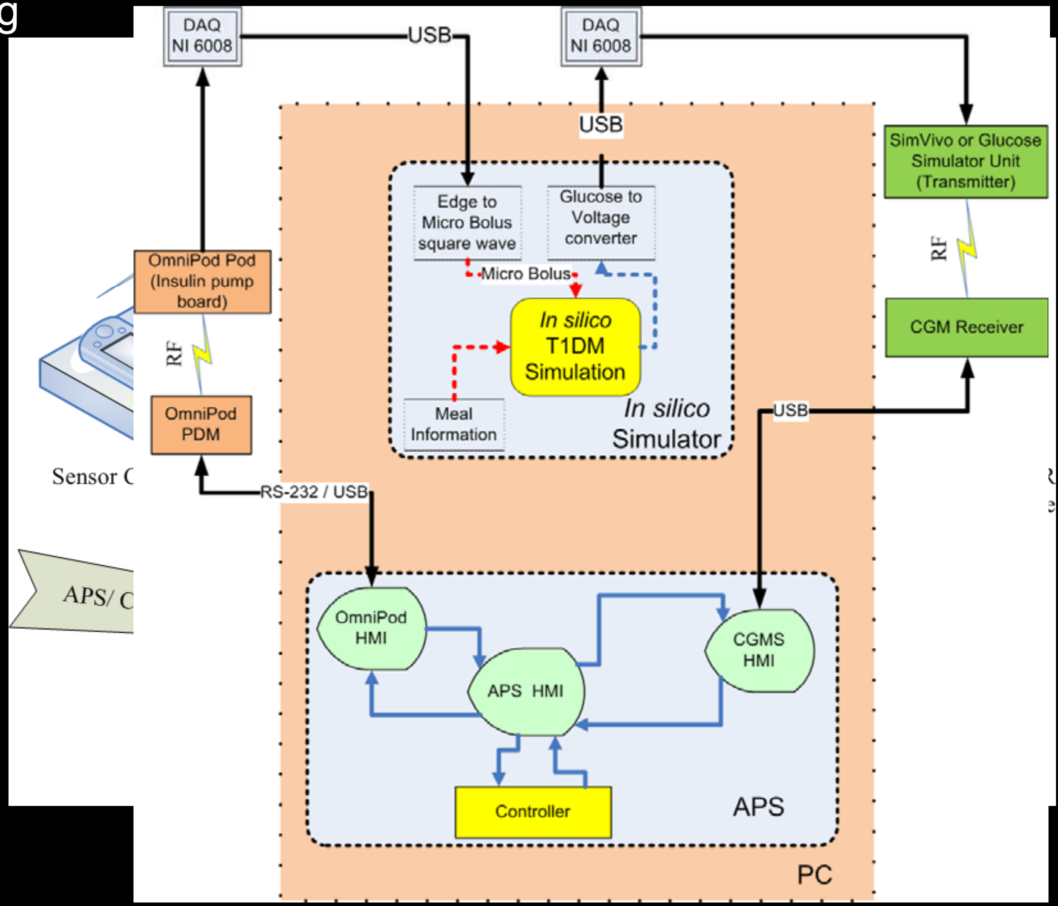
Rate or amount

Delivered insulin

Physician override

Hardware-in-the-Loop Testing

- A complete artificial β-cell system testing platform, allowing:
  - Systematic analysis
  - Component Verification and Validation
  - Complete system V&V
  - PnP for *in silico* patients
  - PnP for control algorithms
- Realistic virtual clinical trial



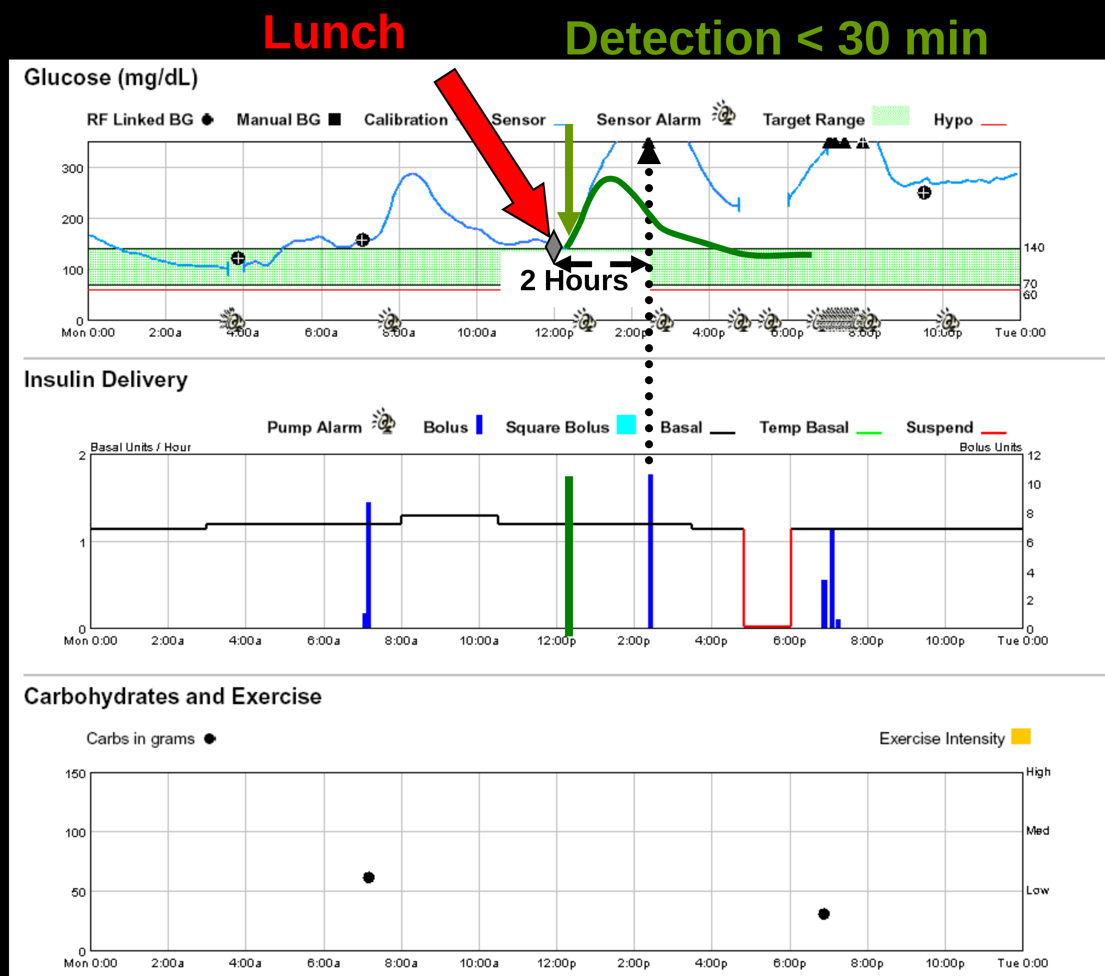
Dassau *et al*., 2007, 7th DTM, San Francisco CA, USA

Dassau *et al*., 2008, "*In Silico* Evaluation Platform for Artificial Pancreatic β–Cell Development – a Dynamic Simulator for Closed-Loop Control with Hardware-in-the-Loop." *Diabetes Technol Ther.*, 2009

Algorithm Engineering MPC for T1DM

- Patient Model Identification
- Disturbance Estimation (i.e., meals)
- Programming Implementation (mpMPC)
- Safety Constraints (Insulin-on-Board)

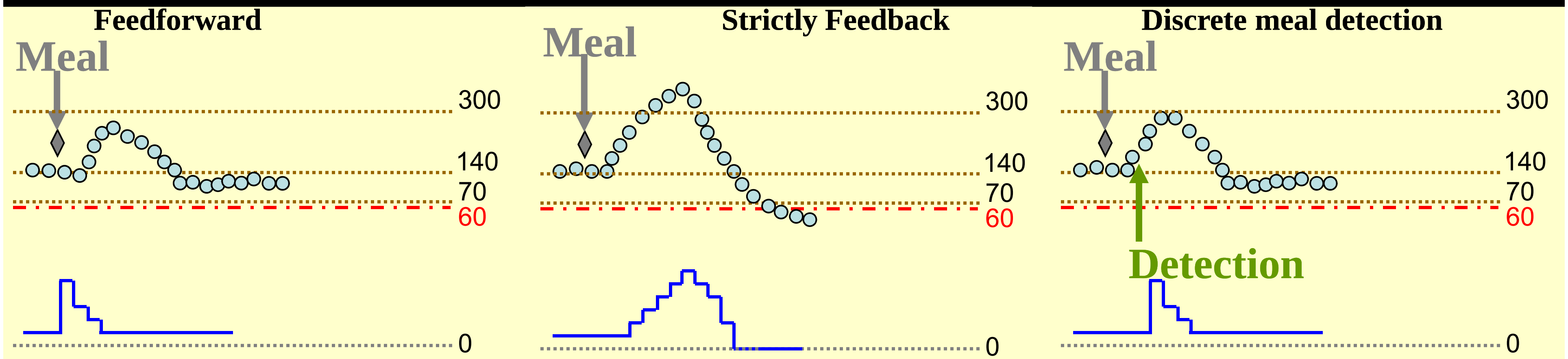
Meal Detection



13 y.o. male, A1c=8.8

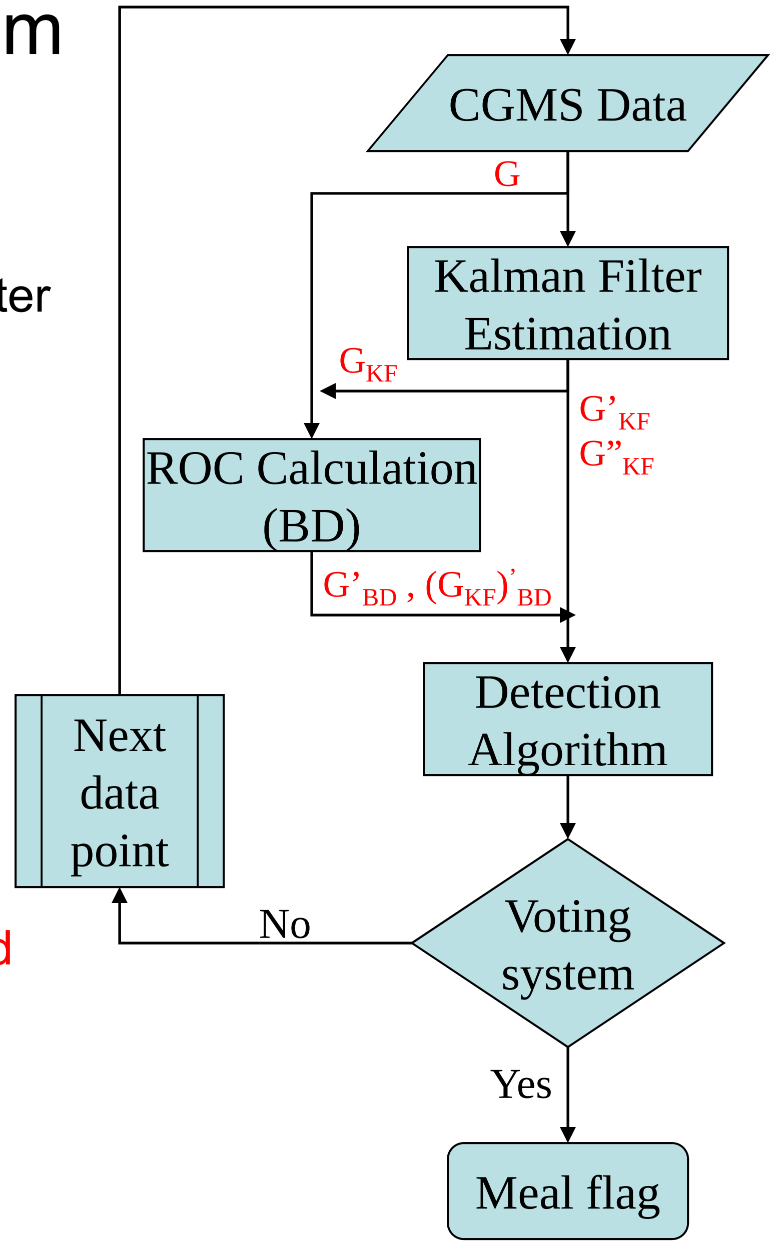
Classes of Control Action for Meals

- Feedforward control
  - User intervention: clicking a button, thus initiating an insulin bolus
- Strictly feedback method
  - Totally automated: the algorithm will respond only after a sufficiently large rise in glucose
- Discrete meal detection
  - Safety net: this will trigger an insulin bolus as part of an algorithm using continuous feedback from a CGM



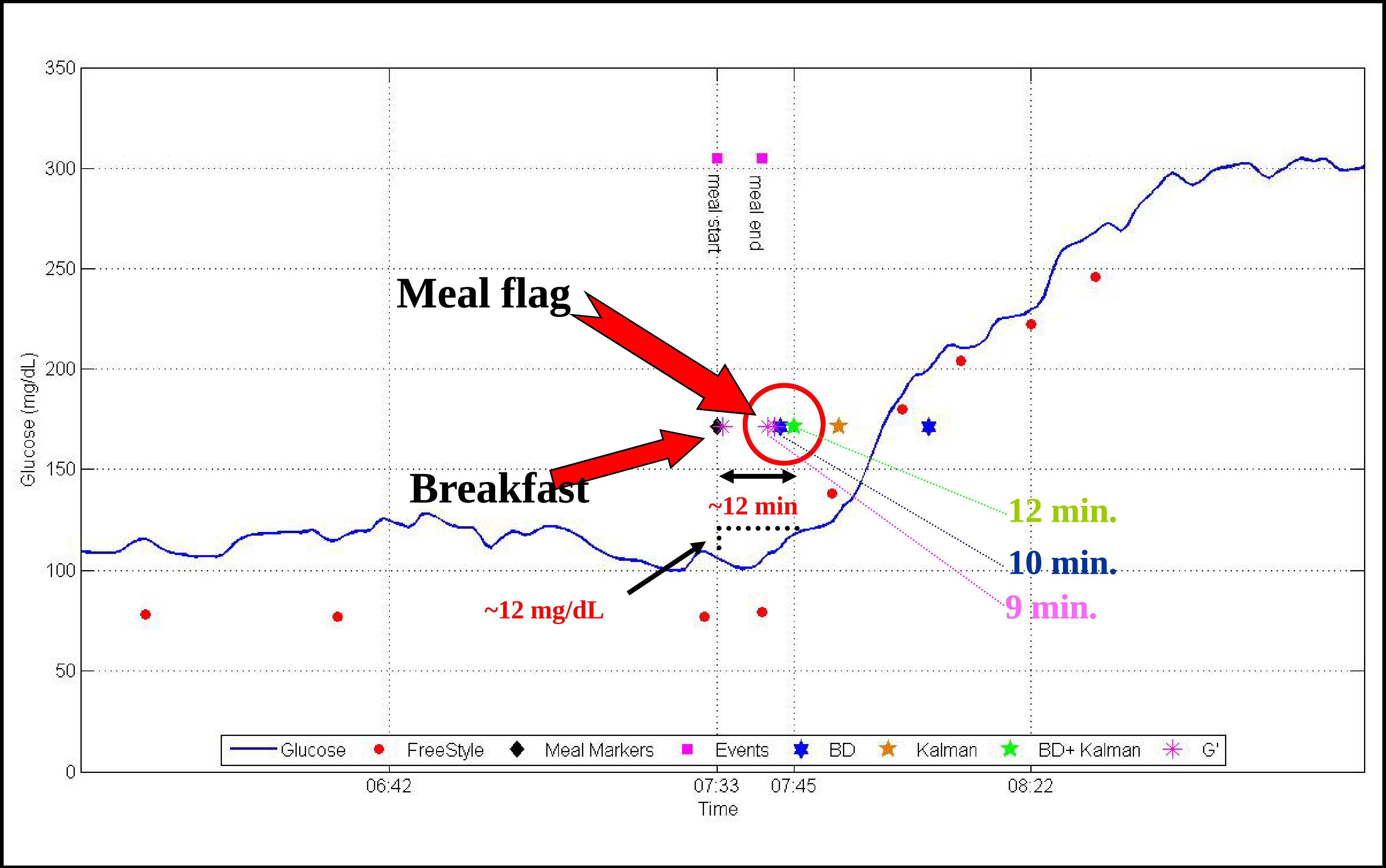
Meal Detection – Voting Algorithm

- Data acquisition
- Algorithms:
  - Glucose profile estimation by Kalman Filter (KF), G_{KF}
  - Glucose rate (velocity) estimation using Backward Difference G'_{BD} & KF ,G'_{KF} , $(G_{KF})'_{BD}$
  - Glucose velocity rate (acceleration) estimation by KF, G''_{KF}
- Detection procedure:
  - Satisfying threshold conditions
  - Heuristics
  - Tradeoff between speed of response and accuracy in flagging a meal
- Voting algorithm
  - Minimizing false detections
- Meal flag to the controller



[Dassau et al., *Diabetes Care*, 2008]

Detection of a Single Meal



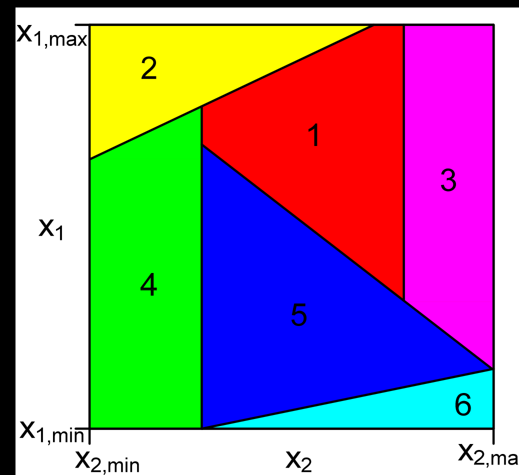
Multi-Parametric Programming Implementation

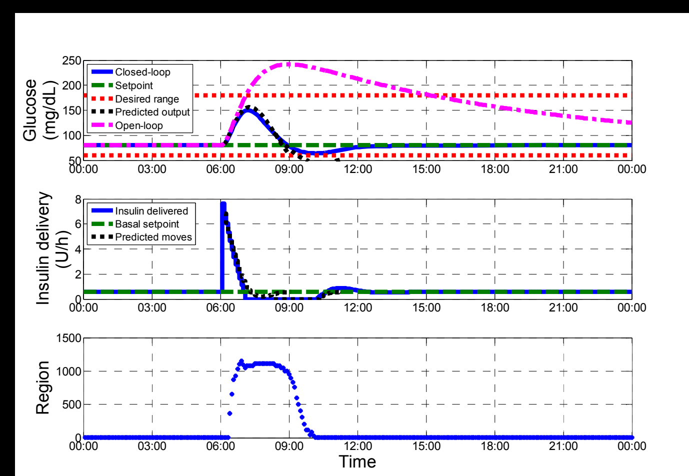
[Percival et al., AIChE, 2008]

- Biomedical devices are subject to stringent FDA regulation
  - Restrictions on online optimization permissible
  - Prior risk analysis mandatory

- MPC is transformed into a multi-parametric program (mpMPC)
  - Offline optimization over state-space region of interest
    - Lookup table of optimal control laws
  - Online optimization
    - Determine *critical region* in state-space
    - Evaluate an affine function of the state vector

- Simulated response to announced 60 g CHO meal
  - Bolus-style controller response
  - Hyperglycemia and hypoglycemia avoided
  - Euglycemia restored in under three hours
  - Variations in the state vector change the *critical region* used to evaluate the control law





Controller Derivation

[Dua, Doyle III, Pistokopoulos, *IEEE TBME*, 2006]

$$\min_U J(U, x(t)) = x^T_{t+N_y|t} P x_{t+N_y|t} + \sum_{k=0}^{N_y-1} \left[x^T_{t+k|t} Q x_{t+k|t} + u^T_{t+k} R u_{t+k} \right]$$

$$\begin{aligned} s.t.\ x_{\min} &\le x_{t+k|t} \le x_{\max}, k = 1, \ldots, N_c \\ u_{\min} &\le u_{t+k} \le u_{\max}, k = 1, \ldots, N_c \\ x_{t+k+1|t} &= A x_{t+k|t} + B u_{t+k}, k \ge 0 \\ u_{t+k} &= K x_{t+k|t}, N_u \le k \le N_y \end{aligned}$$

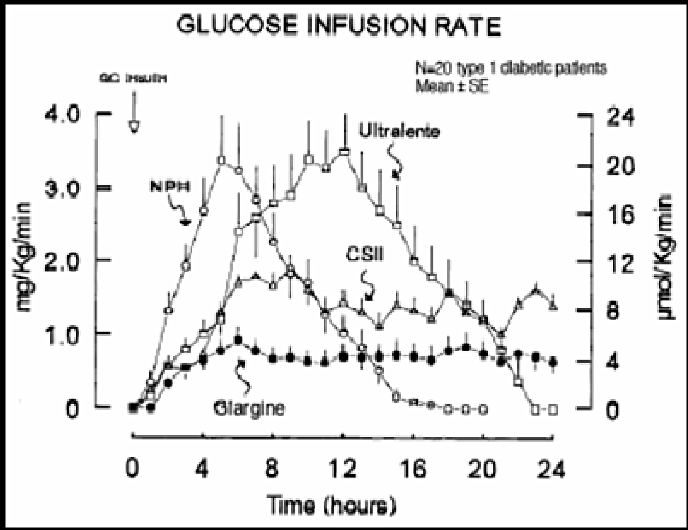
$$\min_U \frac{1}{2} U^T H U + x_t^T F U + \frac{1}{2} x_t^T Y x_t$$
$$s.t.\ GU \le W + E x_t$$

$$V_z(x) = \min_z \frac{1}{2} z^T H z$$
$$s.t.\ Gz \le W + S x_t$$

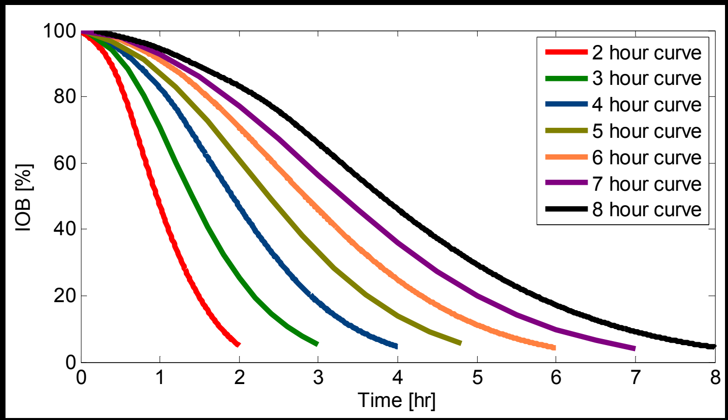
where $z = U + H^{-1} F^T x_t$, $z \in R^s$, and $S = E + G H^{-1} F^T$

Safety Constraints – Insulin on Board (IOB)

- Residual insulin (IOB) remains active for up to 8 hours
- Clinicians and bolus "wizards" factor in IOB
- Constraint formulation
  - Choose IOB curve
  - Calculate IOB
  - Allow insulin for correction
  - Allow insulin for meals
  - Constrain control algorithm



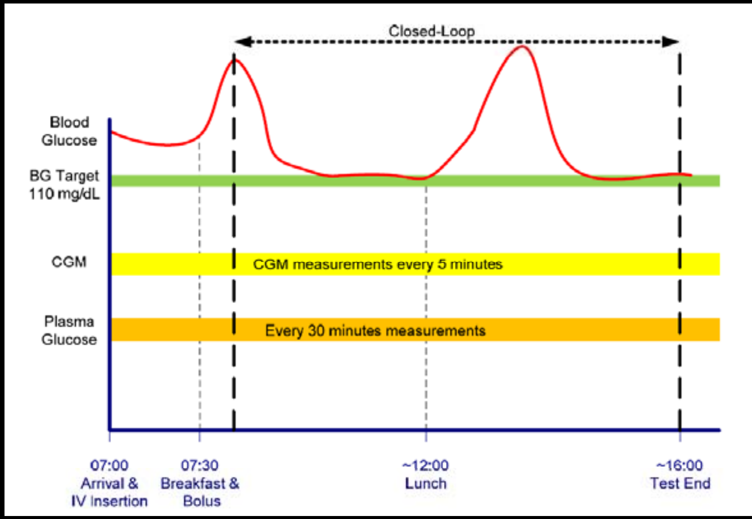
Time–Action Profile Of Insulin Glargine Following Subcutaneous Injection. Glycemic clamp study. [Taken from Lepore et al, *Diabetes* 49:2142–2148, 2000]



Walsh and Roberts, *Pumping Insulin*, 2006
Zisser et al., *Diabetes Technol Ther*, 2008
Ellingsen et al., *J Diabetes Sci Technol*, 2009

Clinical Evaluation

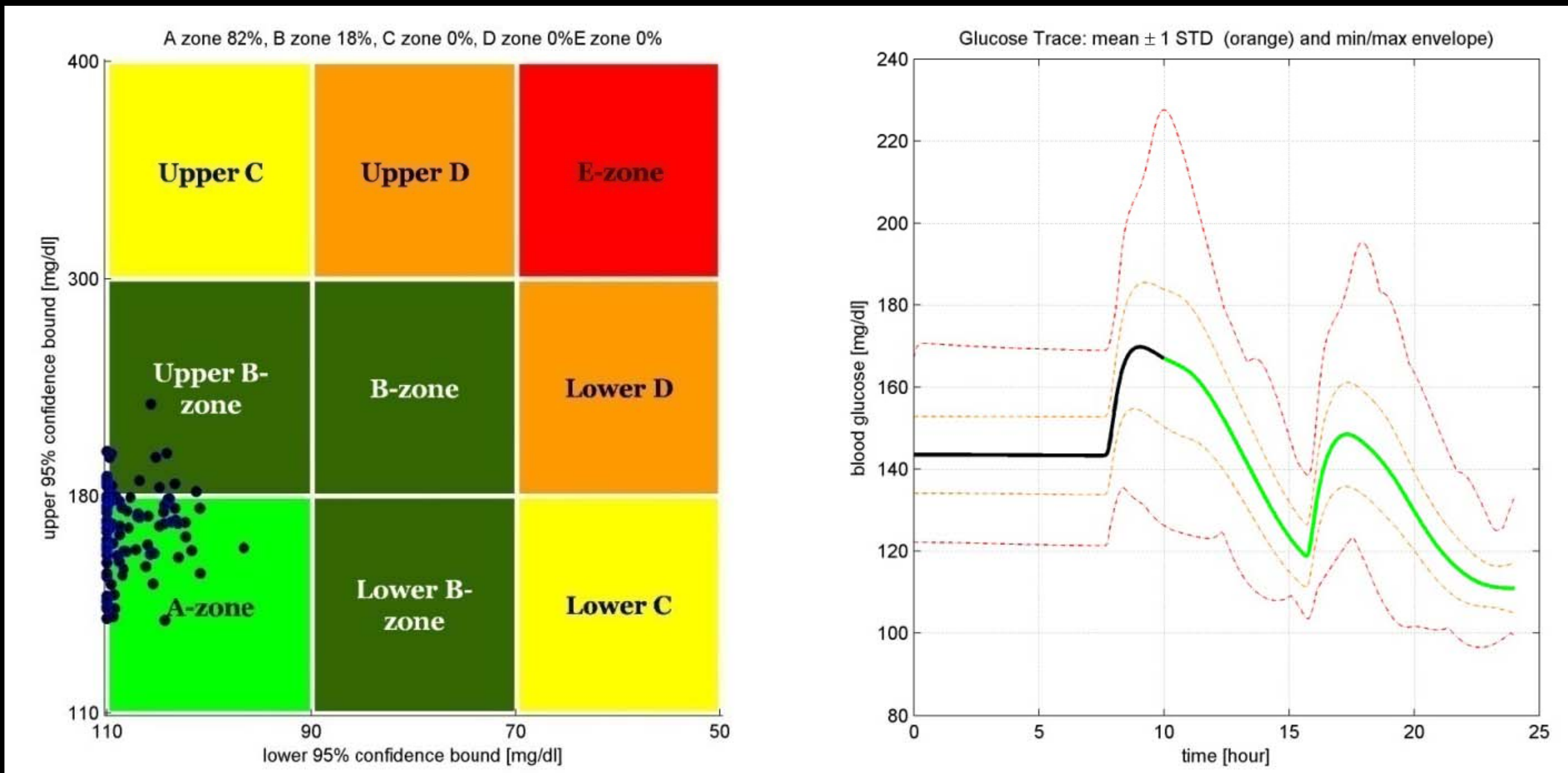
- FDA requirements
  - Investigational Device Exemption (IDE)
  - Detailed proof of safety of protocol/software
  - Master file already acknowledged for APS
- Phase I – *in silico trial*
  - UVa-Padova simulation platform
  - 300 virtual subjects
  - Master file already acknowledged
  - Evaluate same clinical protocol



- Phase II – *human subject studies*
  - Initial studies underway in Israel
  - Planned studies in Santa Barbara in late 2009
  - Large international trial (multi-site) planned for 2010

In Silico Trial Results

[100 adult subjects]



Clinical Trial Results

[Schneider Children's Medical Center of Israel, Tel Aviv]

Pieces of the Puzzle Are Coming Together

Looking Towards the Future:

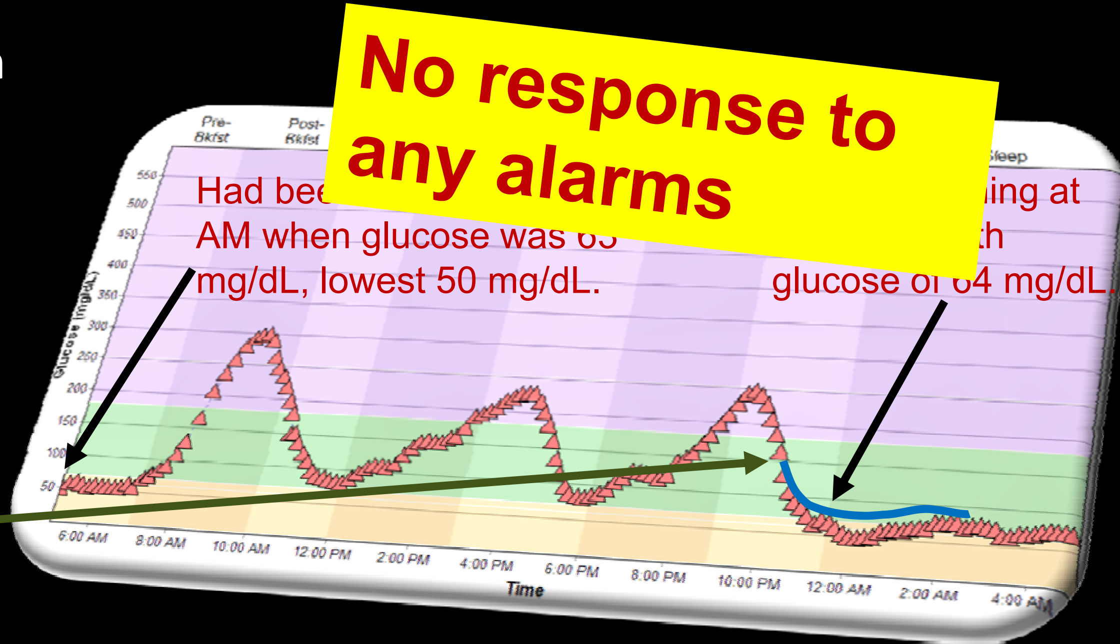
Safety Issues

Human Variability

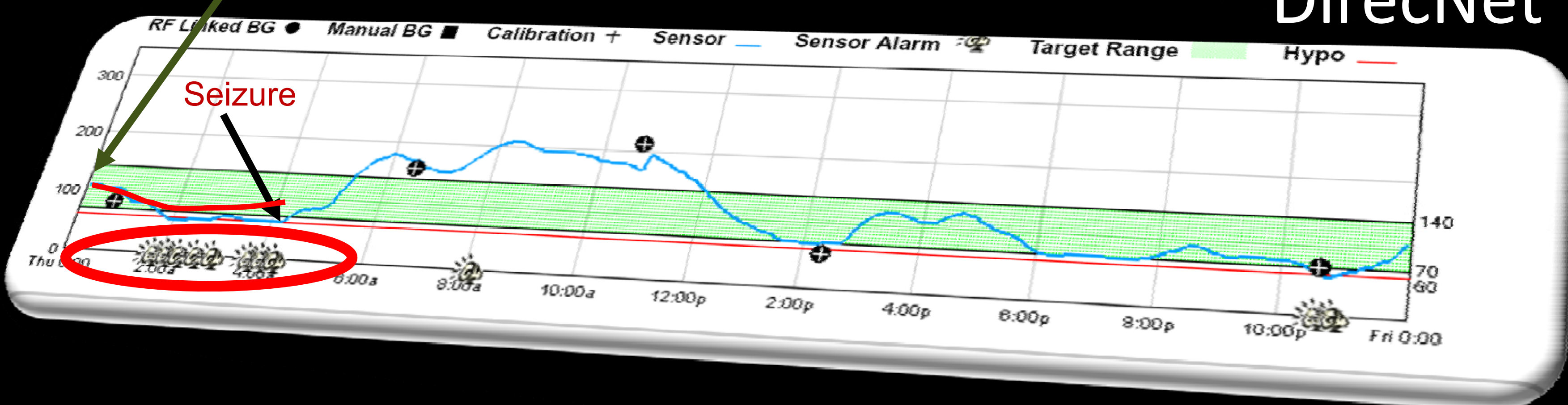
Hypoglycemia Prediction

- Intensive insulin therapy has an inherent risk of nocturnal hypoglycemia
  - No response to any alarm
  - Threshold alarms are insufficient

Prediction of pending hypoglycemic event & pump suspension



DirecNet



Dassau et al. 68th ADA meeting San Francisco CA, 06.08.08

Hypoglycemia Prediction System

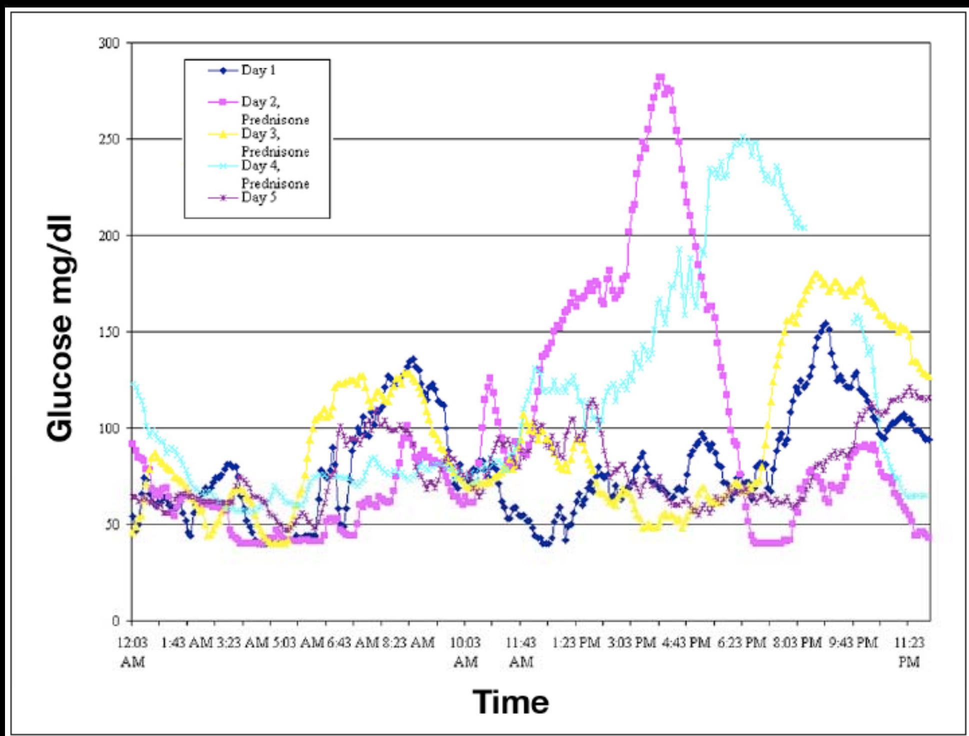
[collaboration w/ Bruce Buckingham, Stanford Medical]

- A Hypoglycemia Prediction System (HPS) was developed using data derived from 21 Navigator studies which assessed Navigator function over 24 hours in children with Type 1 diabetes in clinical research centers (CRC)*

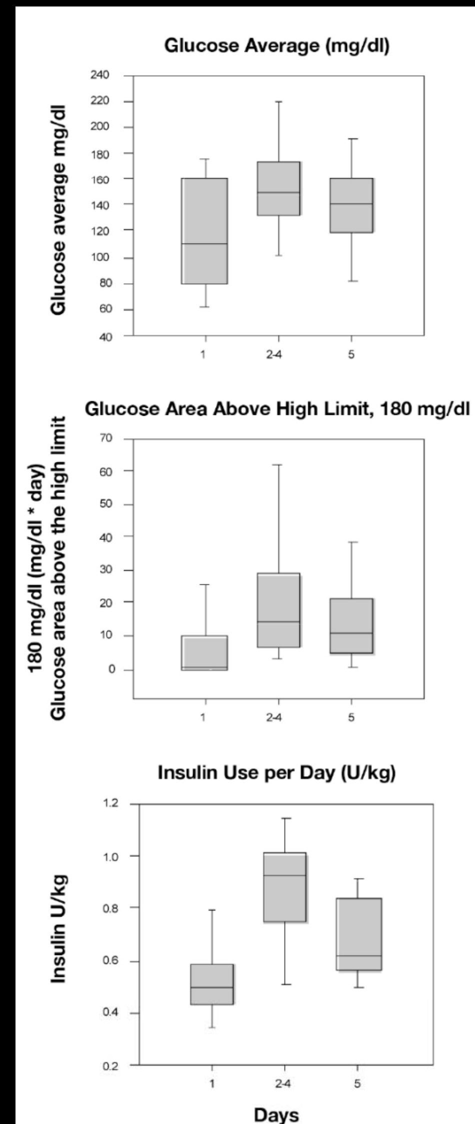
- The HPS functionality was confirmed using a separate dataset from 22 CRC admissions of T1DM subjects
  - mean age = 20 years (range 6 -38)
  - hypoglycemia was induced by gradual increases in the basal insulin infusion rate by a mean of 180%
  - 18 of the 22 subjects (82%) reached a glucose value of ≤ 60 mg/dL

*DirecNet, Diabetes Care

Variability in the Human Body: Stress Effects



Clinical evaluation of the effect of Prednisone [Bevier, et al., 2007]

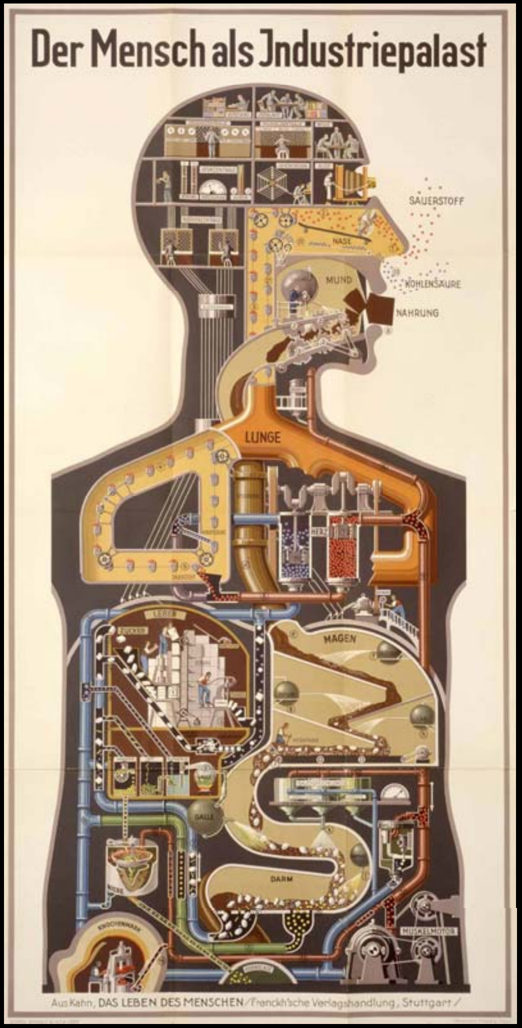


Summary

- **Process systems engineering offers tremendous capability to enable the artificial pancreas**

- Promising technologies:
  - Run-to-run control
  - Model predictive control
  - Parametric programming implementation

- Many challenges still remain:
  - Patient model identification
  - Reliable (long-term) sensors
  - Transport and site issues
  - Patient variability (incl. stress, activity, etc.)
  - Regulatory issues



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