The Quest for the Artificial Pancreas
Clinical and Engineering Studies

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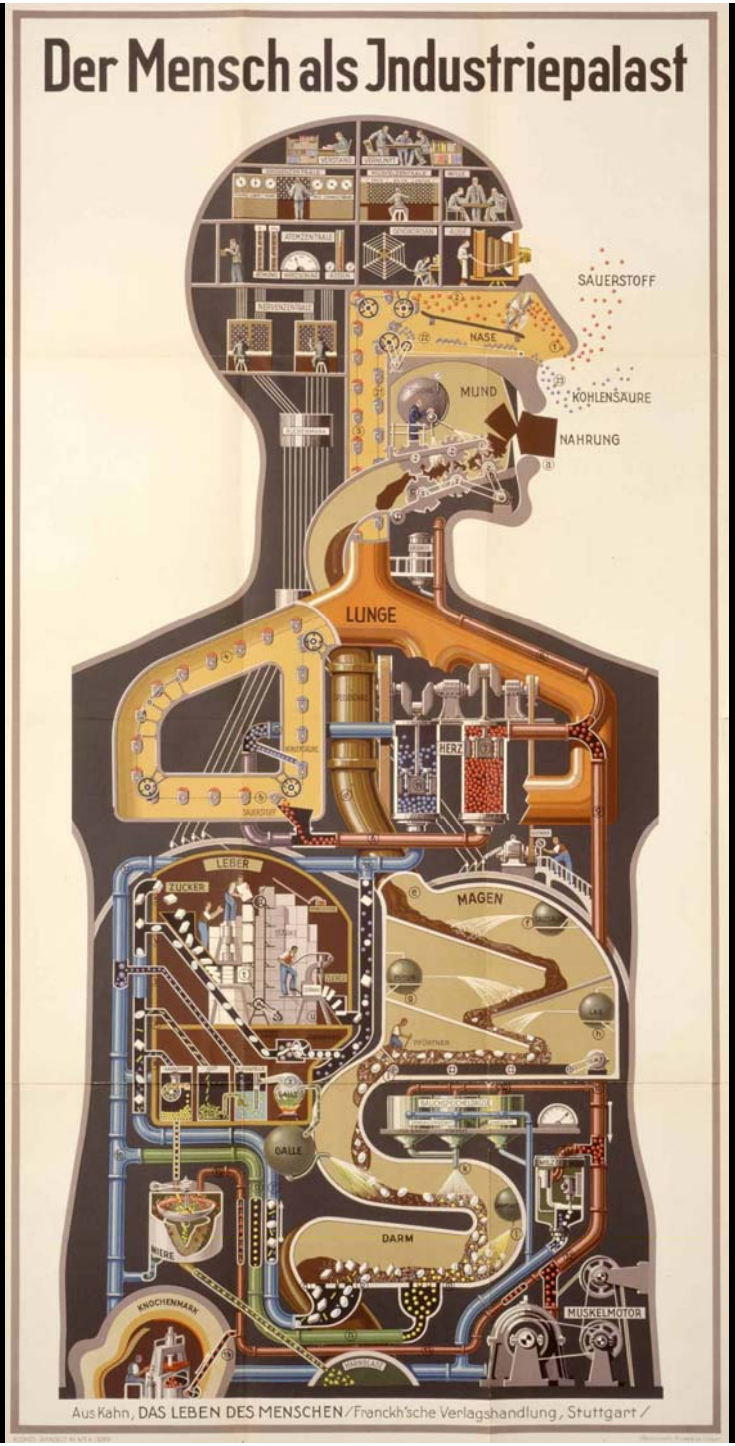
Artificial Organs

- pancreas
- heart
- kidney
- limbs
- cochlear implant
- retinal prosthesis
- proprioception system

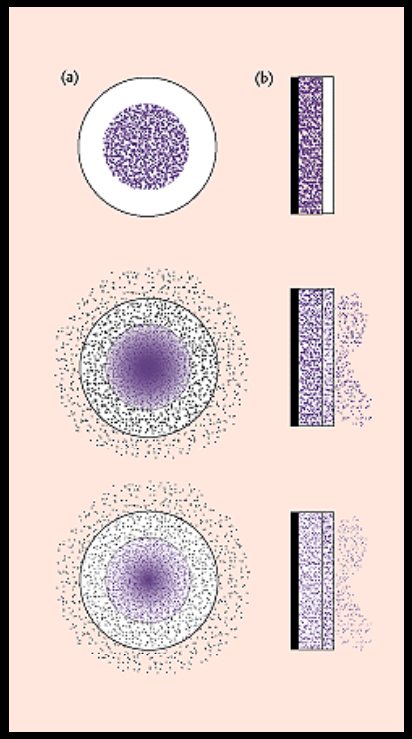


Controlled Drug Delivery

- anesthesia
- blood pressure
- analgesia
- HIV
- cancer
- blood glucose

Controlled Drug Delivery

- Dosing of a therapeutic agent is *dynamic*
  - Constant delivery over time
  - Cyclic or pulsatile or biphasic
  - Triggered by environment
- Design of novel biomaterials to achieve optimal dosing is active area of research
- Control and dynamic systems approach
  - Optimized design of a polymer (e.g., hydrogel)
  - Algorithmic optimization of delivery device

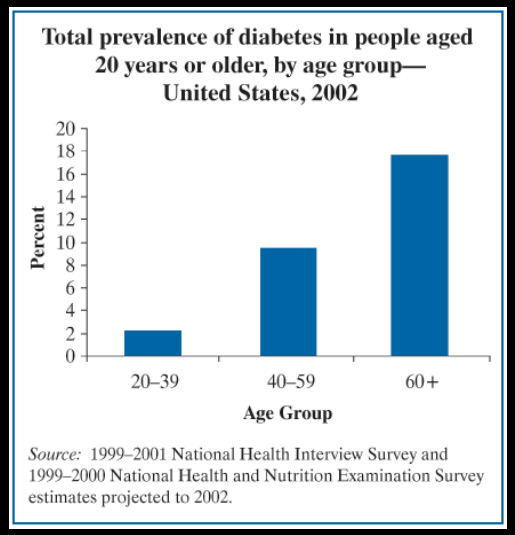


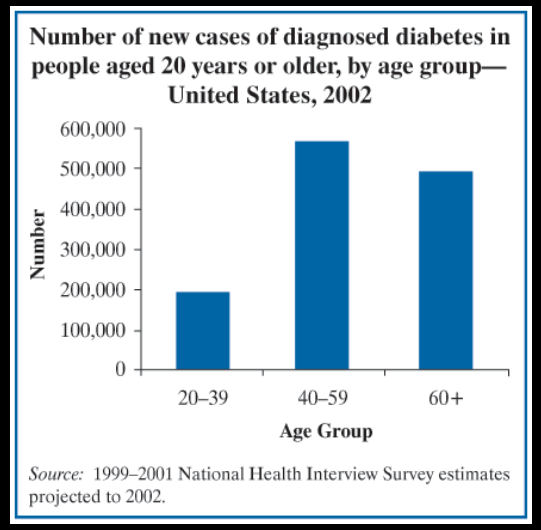
[Brannon-Peppas, 1997]

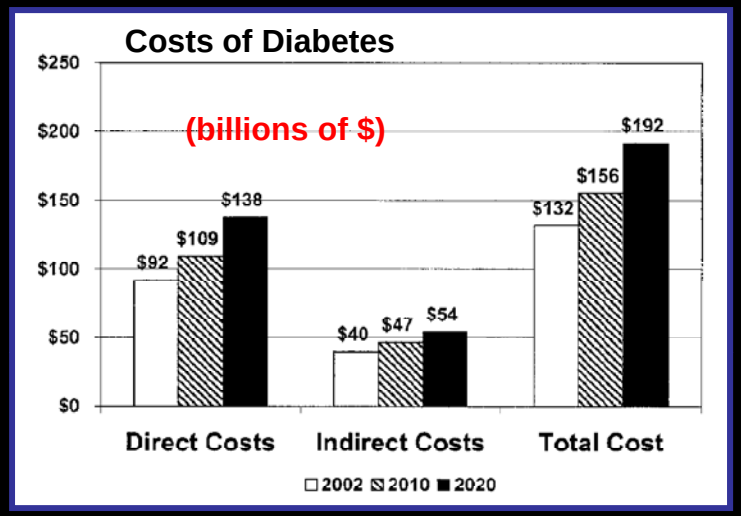
Diabetes Mellitus

- World's most common and costly disease
- 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 ~15 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



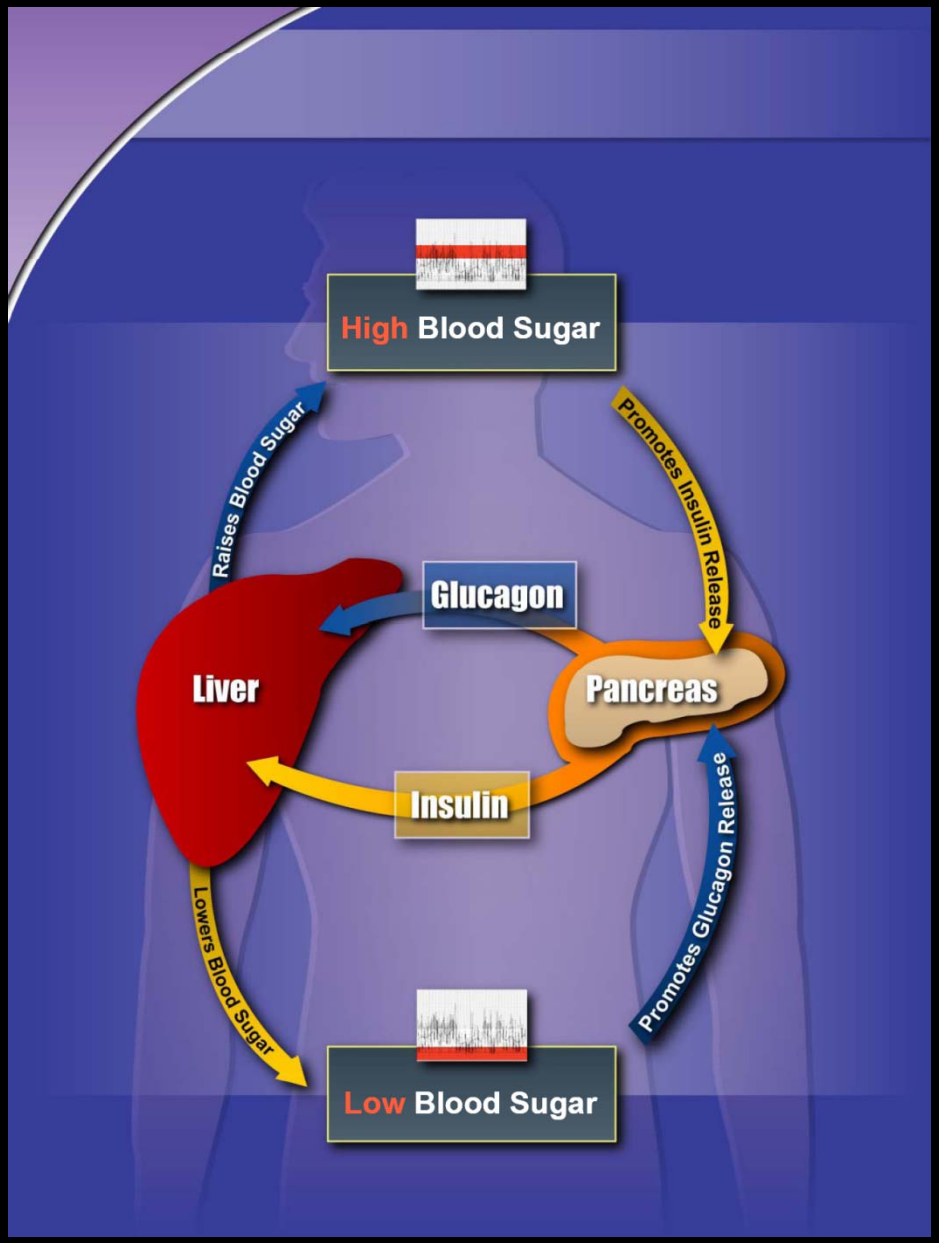




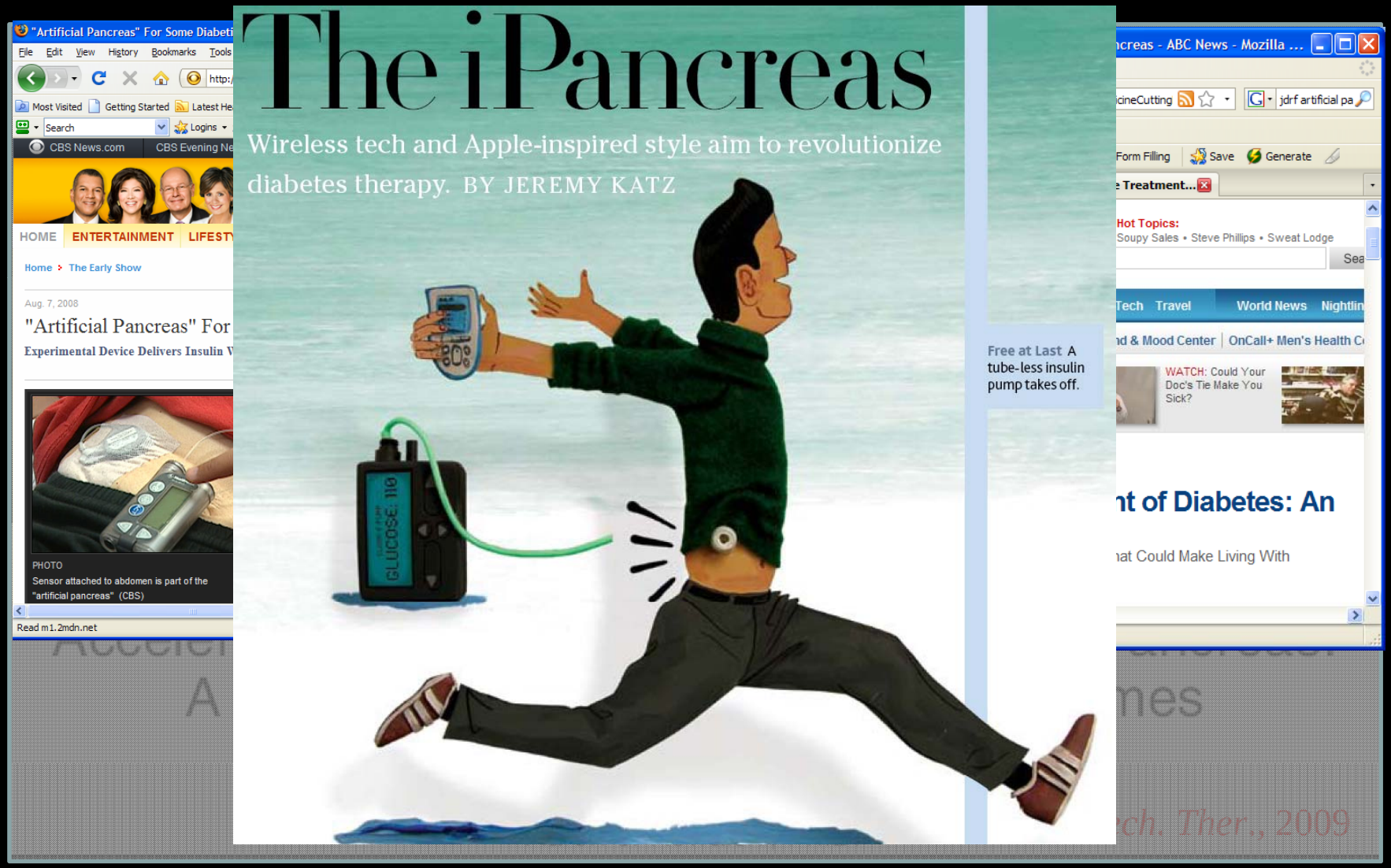
[ADA 2003]

- Complications
  - Heart disease and stroke
  - High blood pressure
  - Blindness
  - Kidney disease
  - Nervous system disease

Glucose Homeostasis



Artificial Pancreas in the News

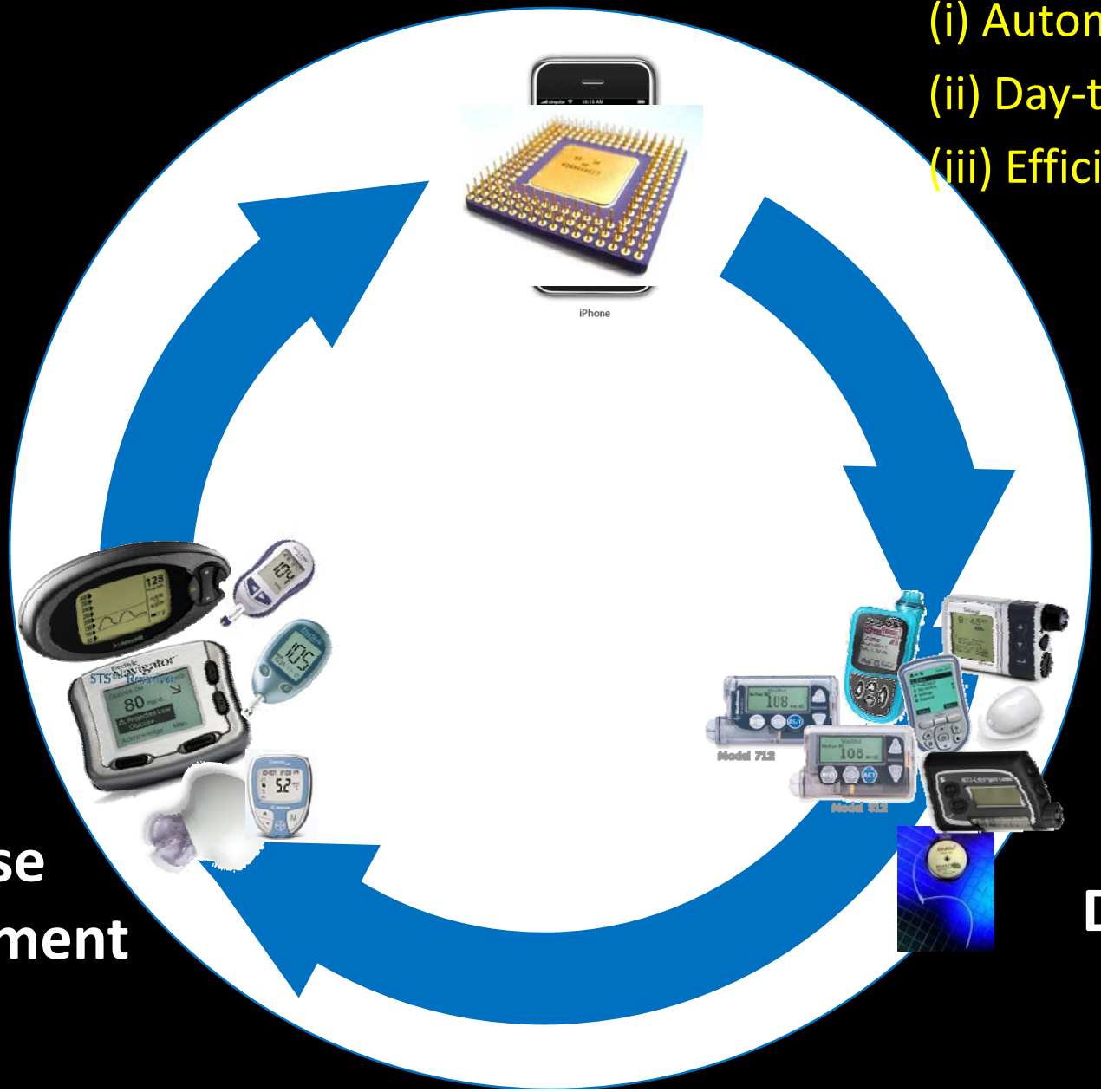


The Glucose – Insulin "Loop"

(i) Automatic Control

(ii) Day-to-day Control

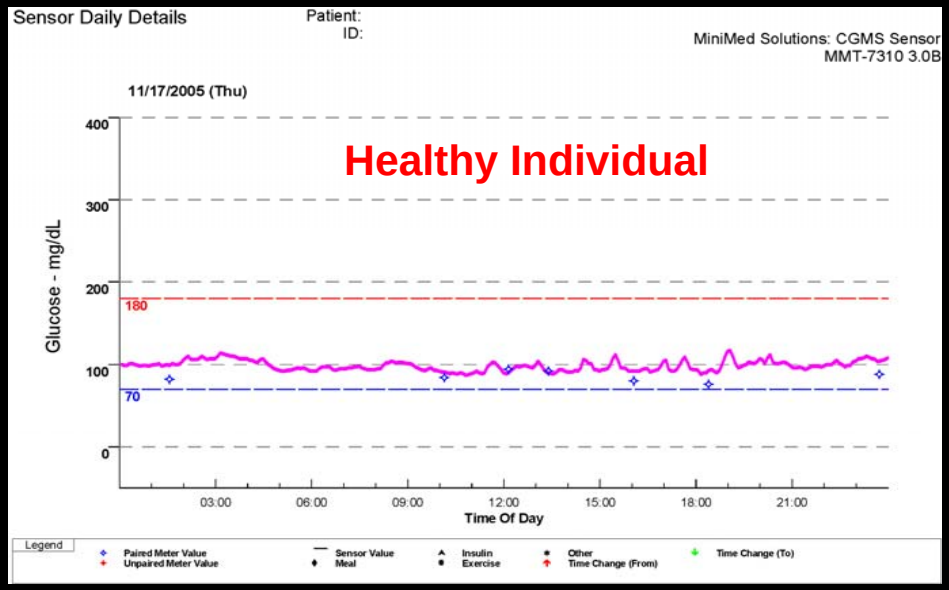
(iii) Efficient Solution

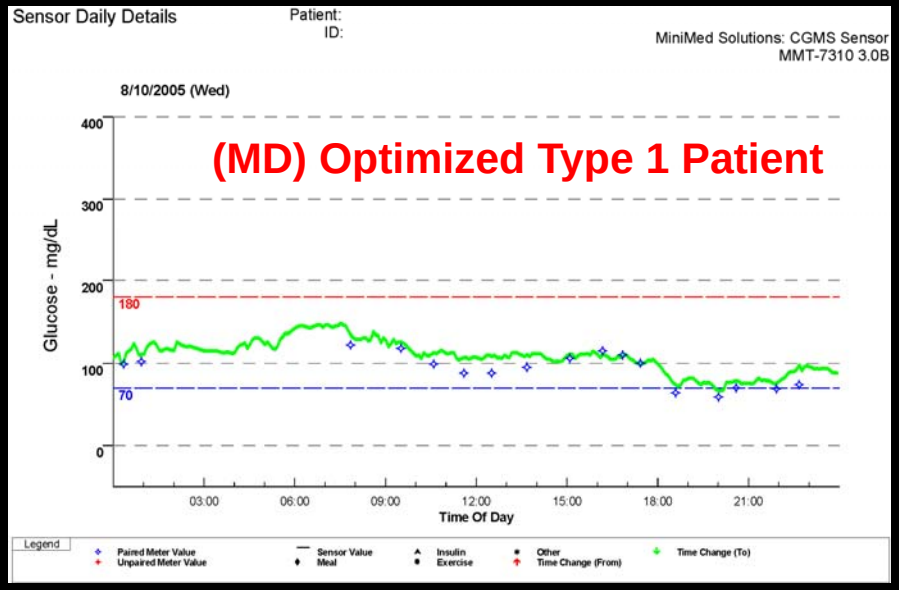


Glucose Measurement

Insulin Delivery

Normalization of Glycemia





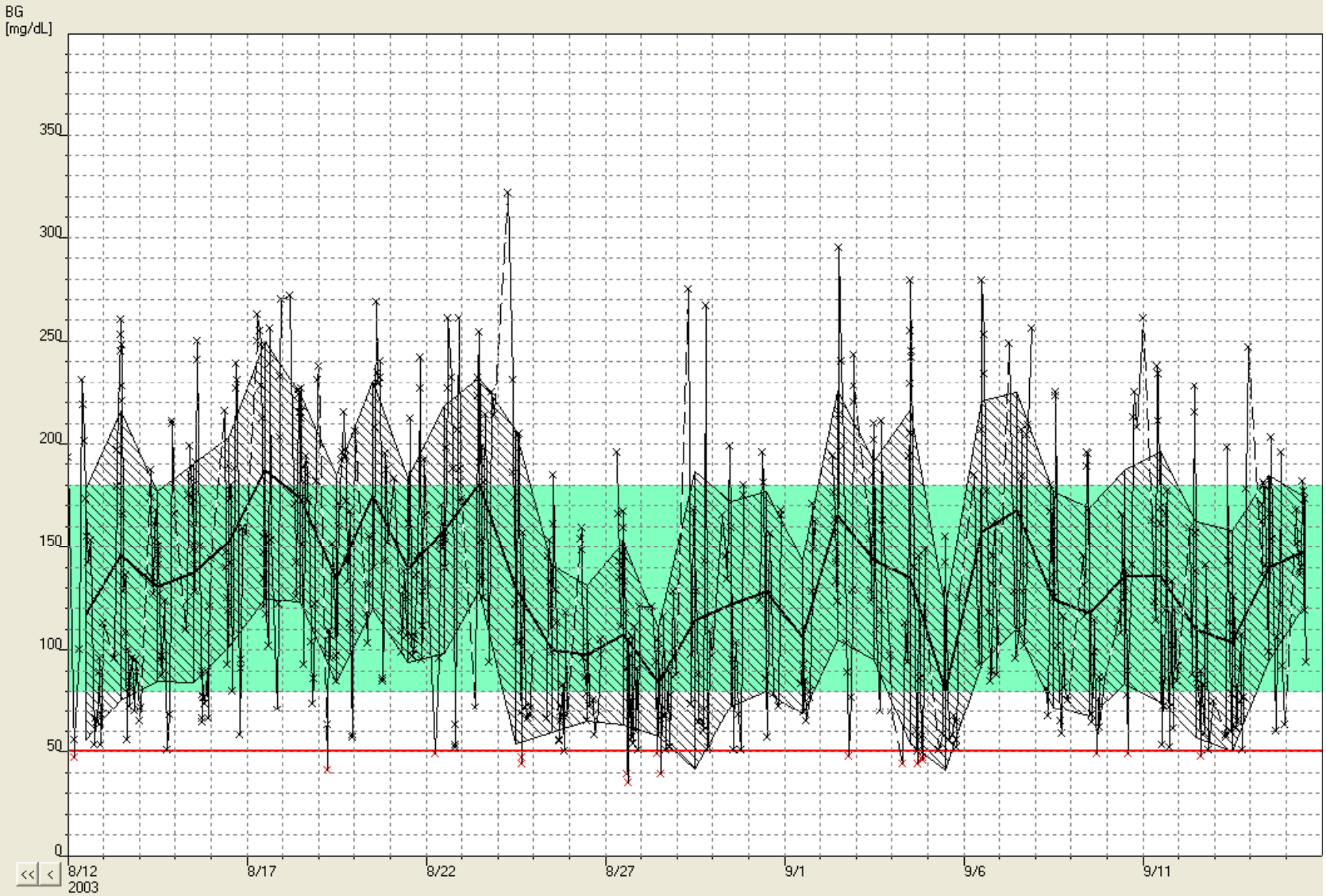
Trendgraph | Standard Day | Standard Week | Distribution

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



N:	648	< 80:	21.1%	Hypos (<50):	17	Test/Day:	18.5	Nr. of Hi:	0
MBG:	136	80-180:	55.4%	Symptoms:	0	M(80):	42.5	Nr. of Lo:	0
SD:	59	> 180:	23.5%	MBG Symp.:	0	M(120):	26.2		

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*

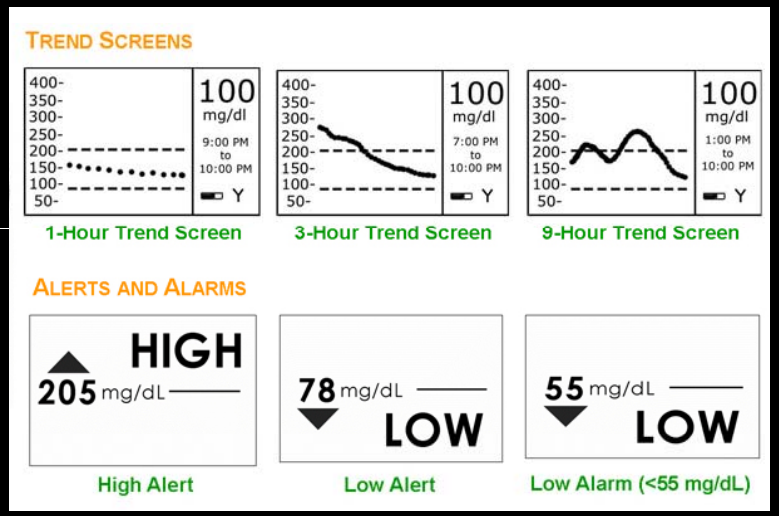
- Iterative learning control
  - Account for intra-subject variations

    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

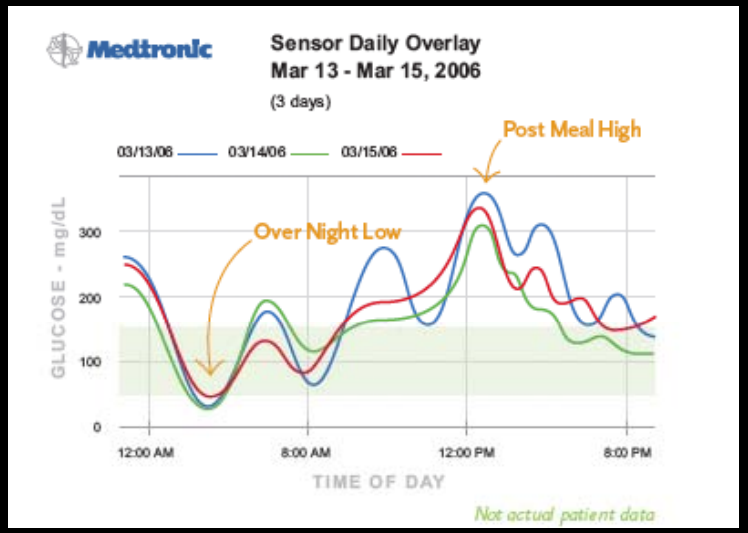
    Dassau et al., 2009, *Diabetes Technol . Ther*

Real-time Glucose Measurement



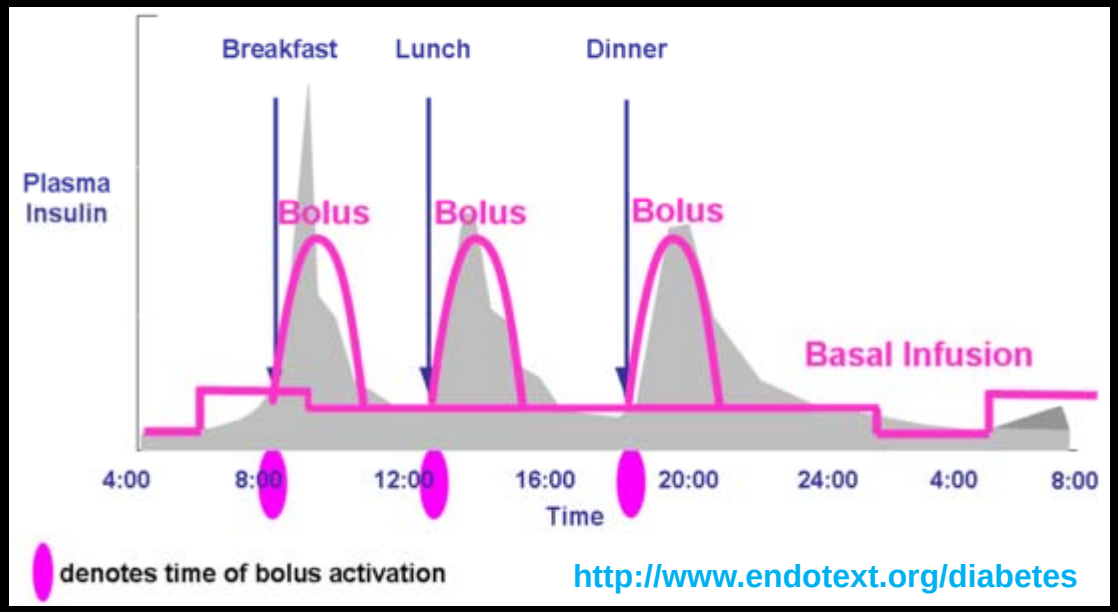
STS™ Receiver

Source: DexCom,Inc.

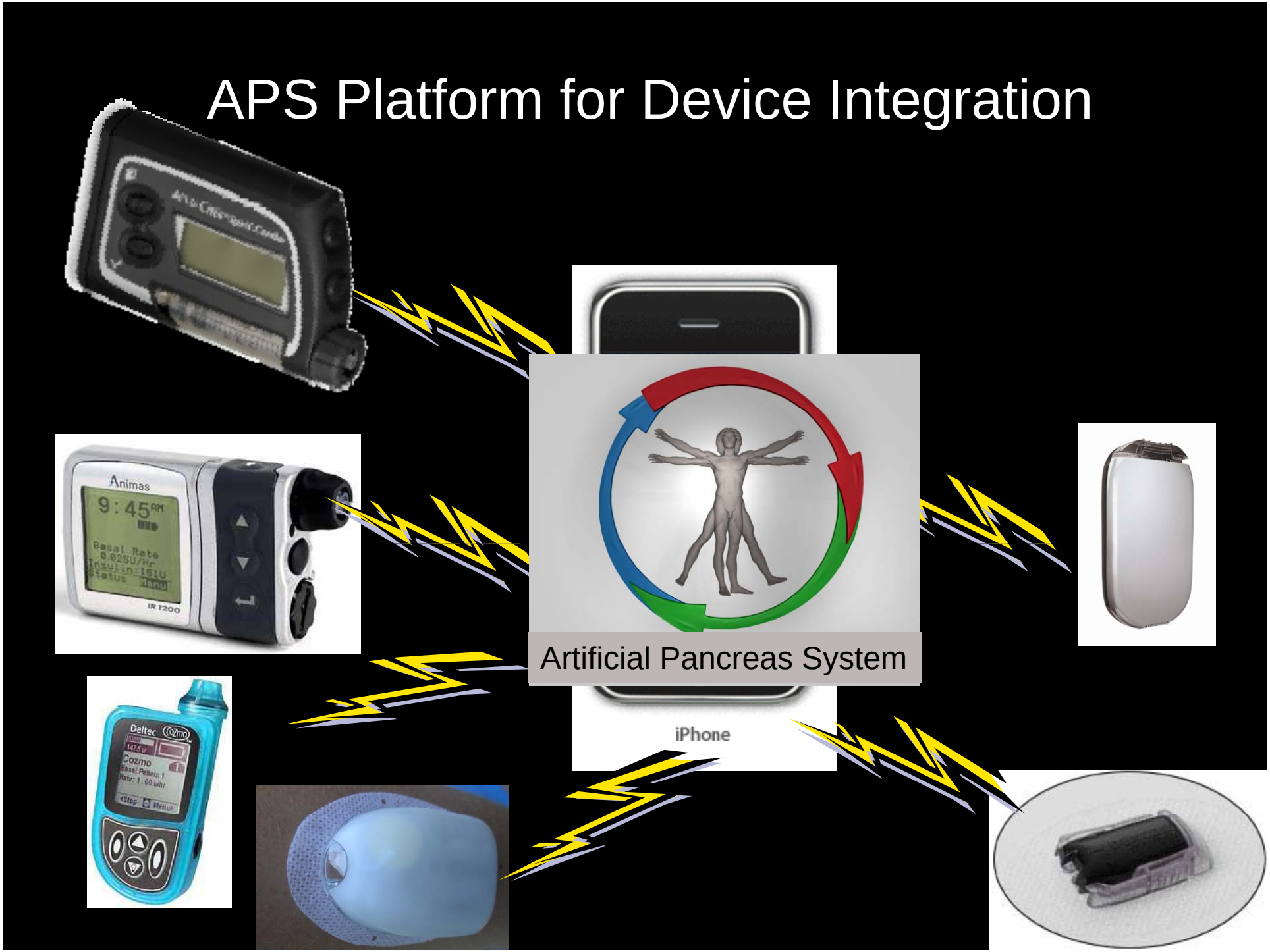


Source: Medtronic Diabetes

Continuous Subcutaneous Insulin Infusion (CSII)

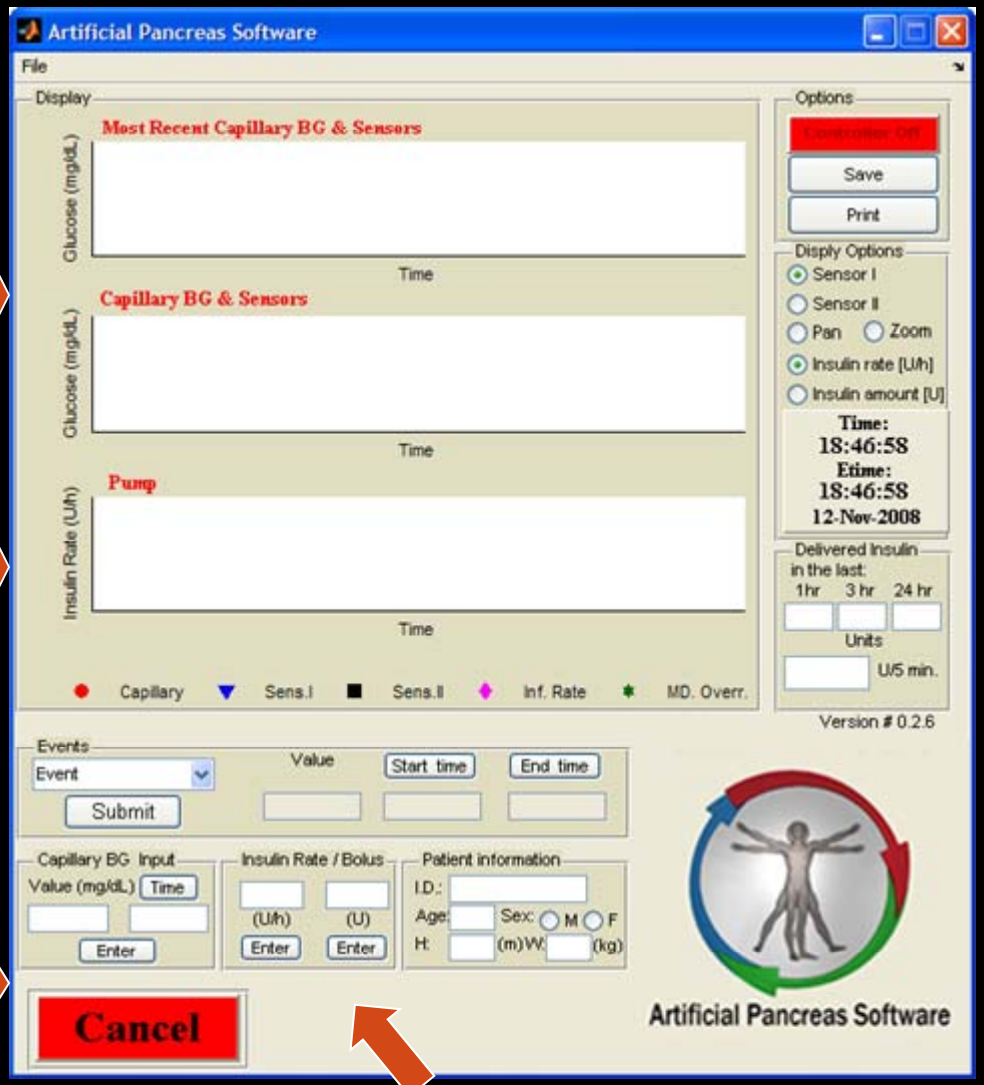


APS Platform for Device Integration



Artificial Pancreas (β-cell) Software

Human Machine Interface



Sensor & Capillary measurements

Insulin delivery

Event log

Capillary BG

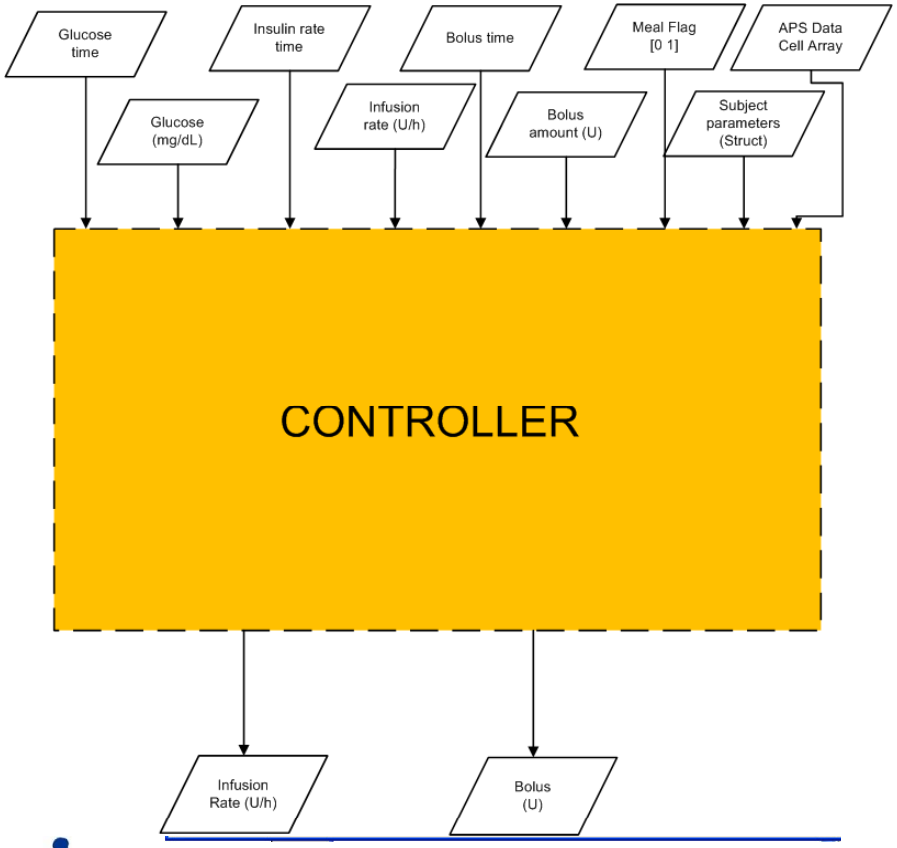
Rate or amount

Delivered insulin

Physician override

Artificial Pancreas Software

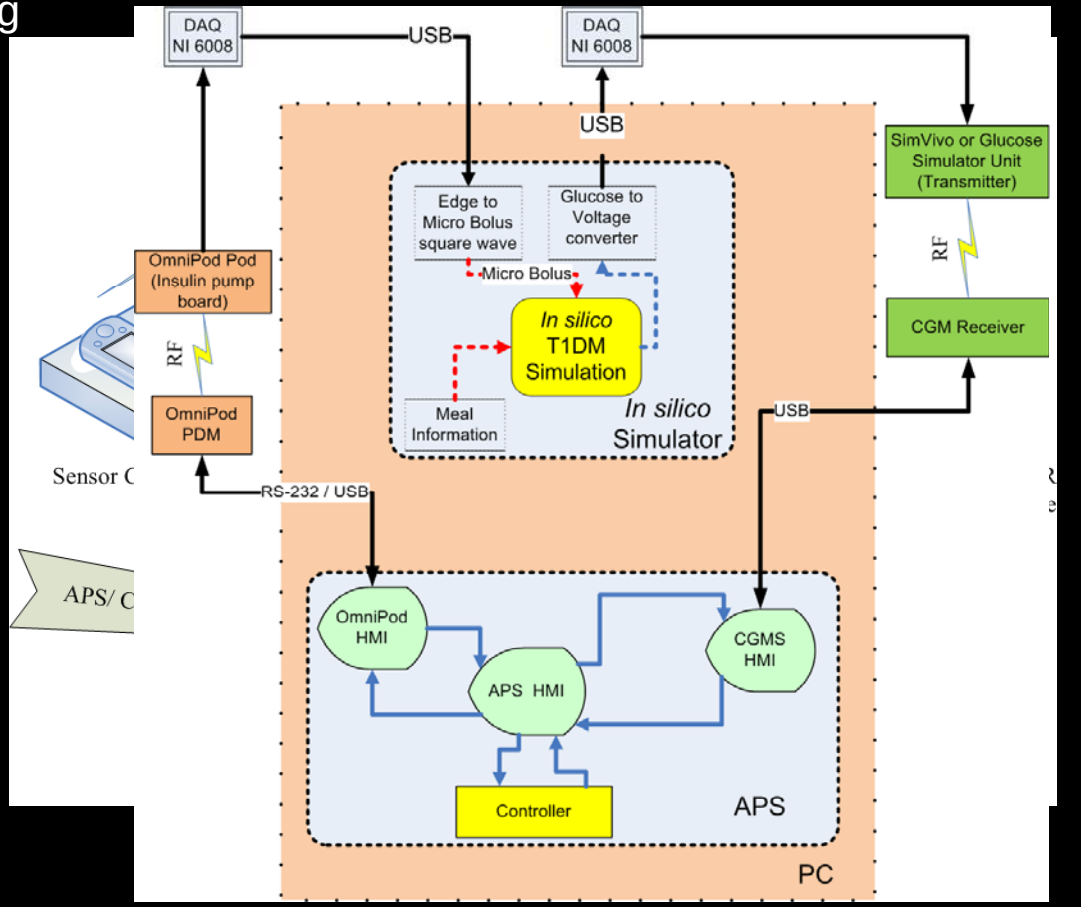
- Clinical Sites with access to the APS:
  - SDRI / UCSB
  - Stanford Medical School
  - Barbara Davis Center
  - University of Virginia
  - University of Padova, Italy
  - University of Montpellier, France
  - Schneider Children's Medical Center of Israel , Israel
  - …



Dassau *et al*., 2008, "Modular Artificial β-Cell System: A Prototype for Clinical Research ", *J Diabetes Sci Technol* 2(5), 863-872
Dassau & Zisser *et al*., 2009, "Sansum / UCSB Artificial Pancreas Software (APS)", Food and Drug Administration Master File,(MAF- 1625)

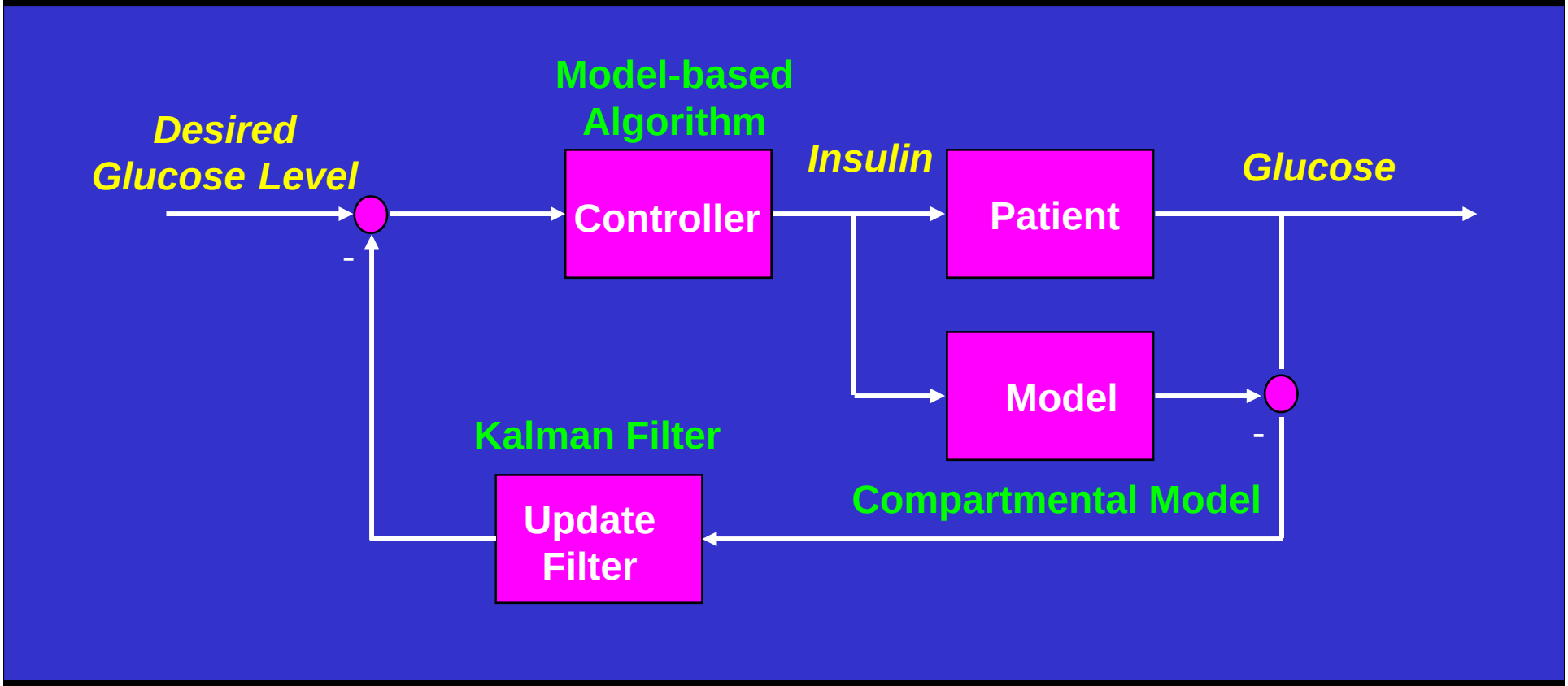
Hardware-in-the-Loop Testing

- 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



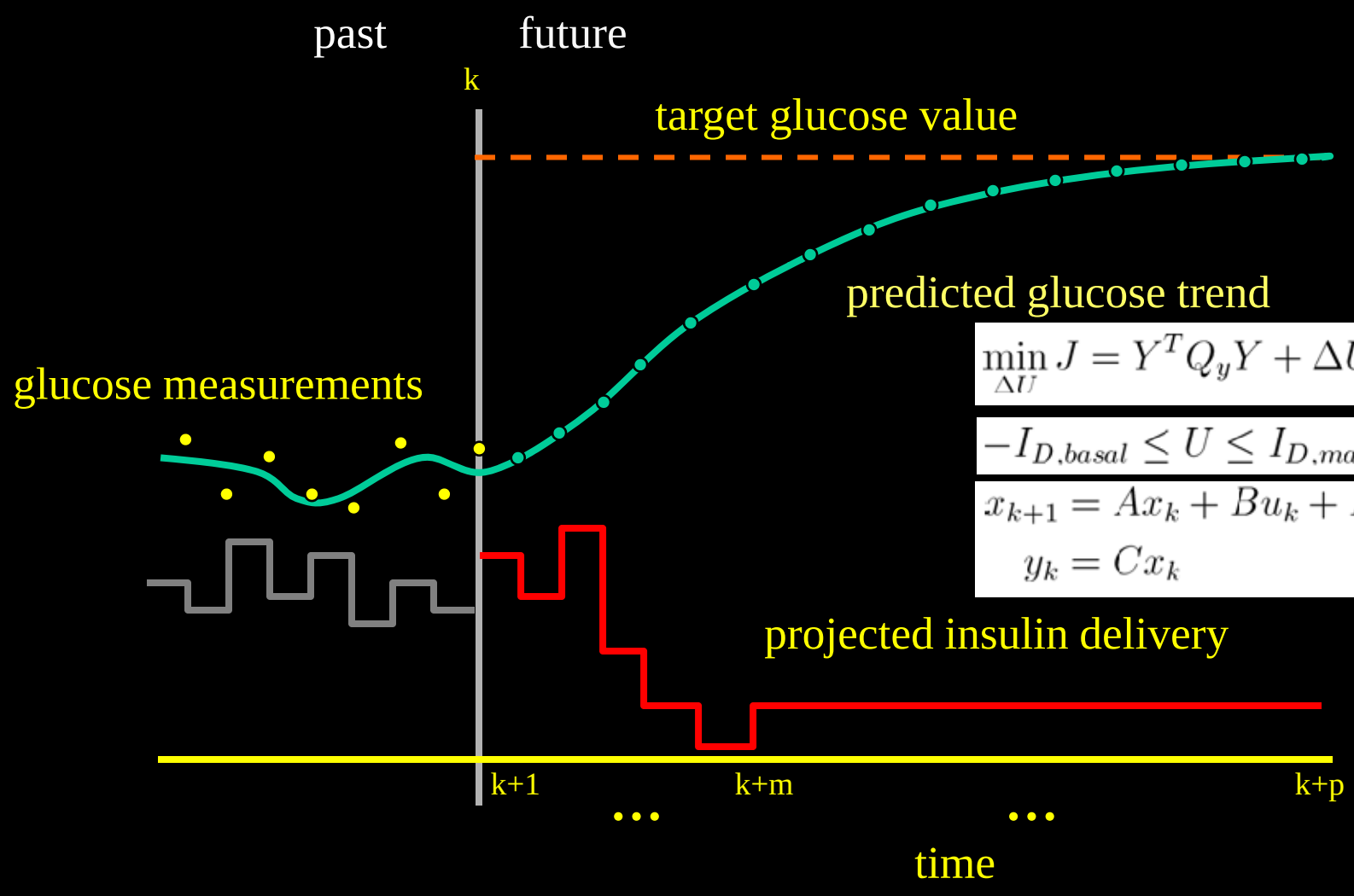
Model-Based Control Approach for Diabetes

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



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

Moving Horizon Concept of MPC

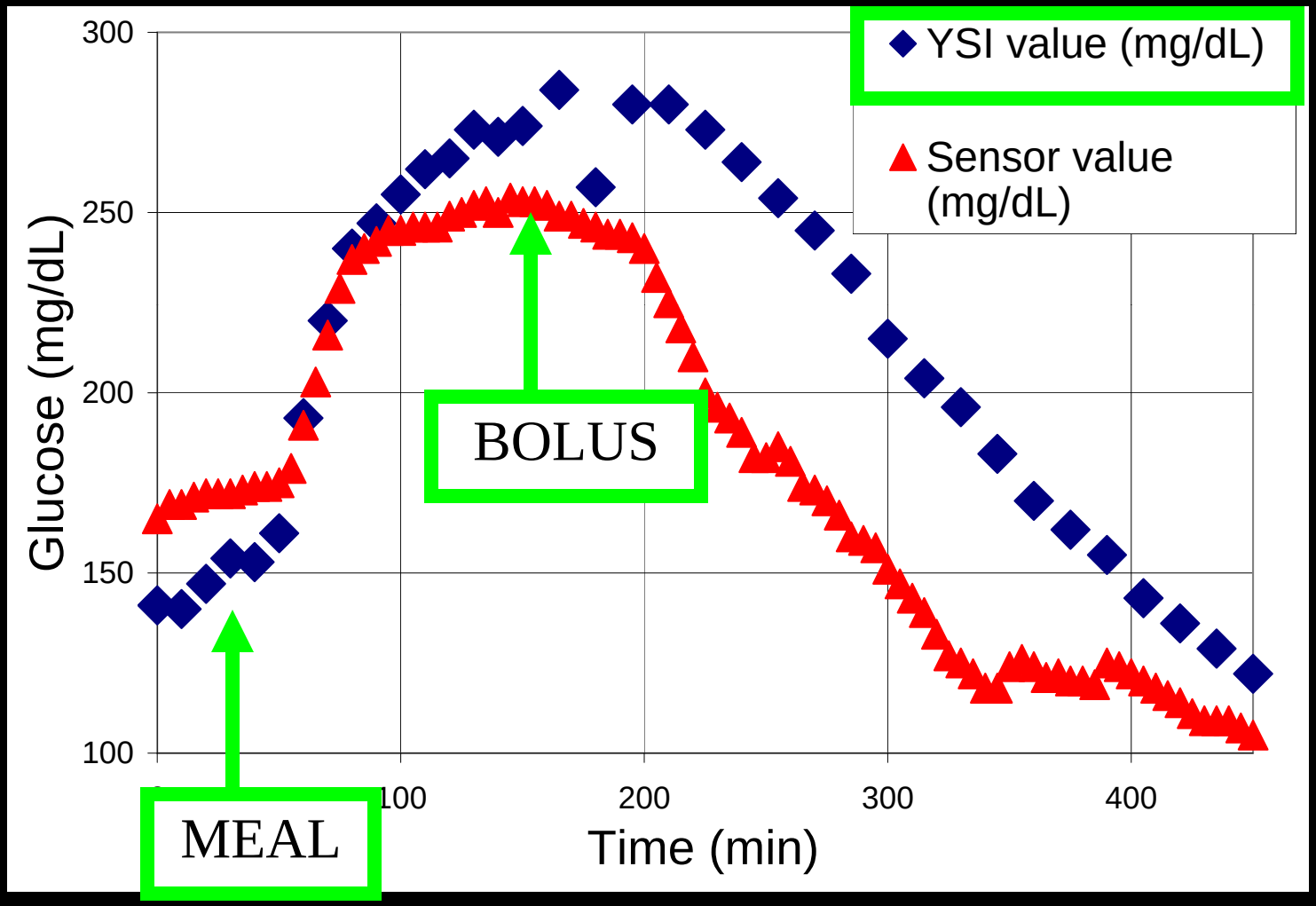


$$\min_{\Delta U} J = Y^T Q_y Y + \Delta U^T R \Delta U$$

$$-I_{D,basal} \leq U \leq I_{D,max} - I_{D,basal}$$

$$x_{k+1} = Ax_k + Bu_k + B_d u_{d,k}$$
$$y_k = Cx_k$$

Individualized Algorithm: Subject Model



Individualized Algorithm: Subject Model

$$\left(1+\sum_{l=1}^{n_A} a_l q^{-l}\right) G(k) = \left(\sum_{m=1}^{n_{B_1}} b_{1,m} q^{-m-k_1}\right) I_D(k) + \left(\sum_{n=1}^{n_{B_2}} b_{2,n} q^{-n-k_2}\right) G_M(k) + e(k)$$

lagged values of blood sugar (2-3)

lagged values of insulin delivered (1-2)

lagged values of CHO consumed (4-5)

Typical subject model has ~8 coefficients

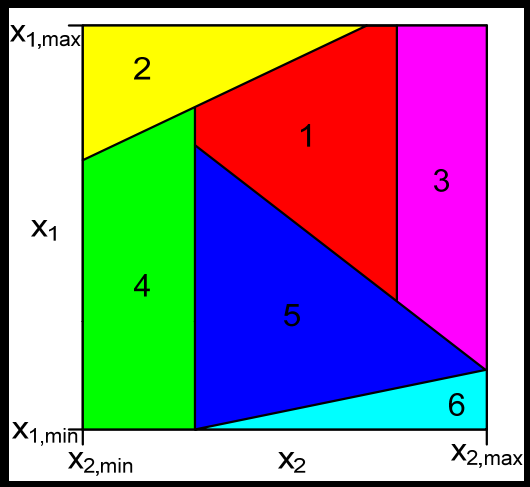
Algorithm Engineering MPC for Diabetes

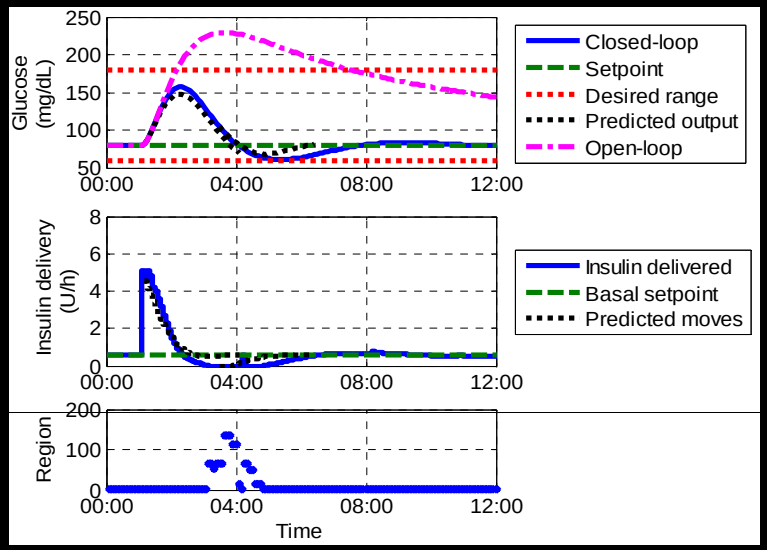
- “Traditional” MPC has been employed in petroleum refineries for ~4 decades
- Application to T1DM requires algorithm customization
- UCSB/Sansum innovations:
  - Discrete event disturbance estimation (i.e., meals)
  - Efficient programming implementation (mpMPC)
  - Safety constraints (Insulin-on-Board)

Multi-Parametric Programming Implementation

[Percival et al., AIChE, 2008]

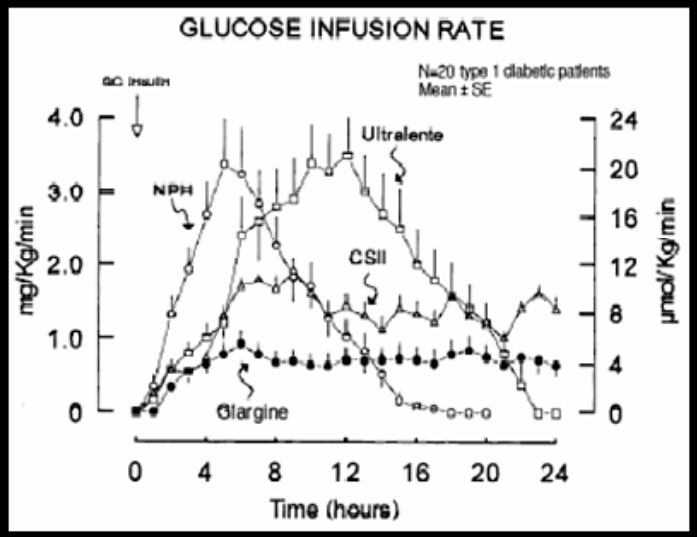
- Biomedical devices are subject to stringent FDA regulation
  - Limitations on on-line optimization
  - Prior risk analysis mandatory
- MPC can be transformed into a multi-parametric program (mpMPC)
  - Offline optimization over state-space region
    - Lookup table of optimal control laws
  - Online optimization
    - Determine *critical region* in state-space
    - Evaluate an affine function of the state vector
- *In silico* response to an 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



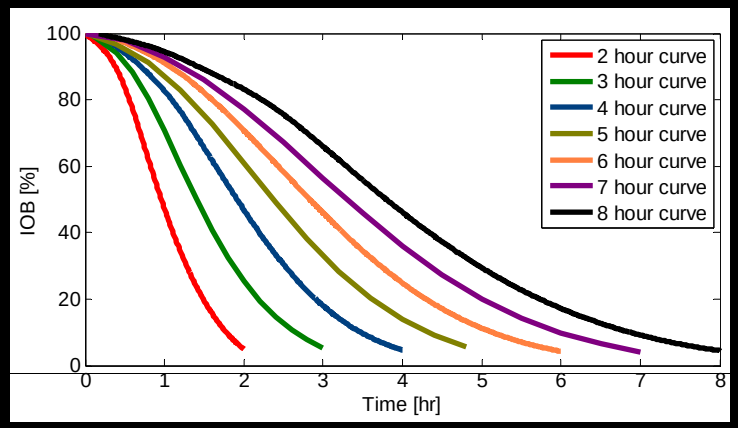


Safety Constraints – Insulin on Board (IOB)

- 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



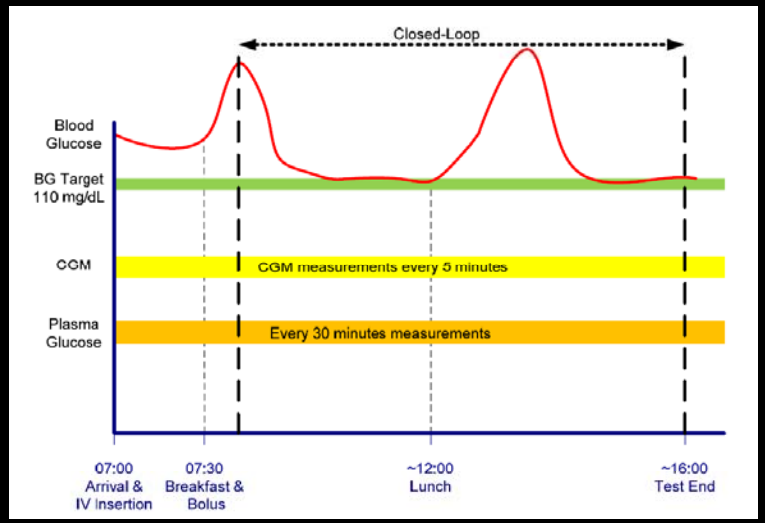
Time–Action Profile Of Insulin Glargine Following Subcutaneous Injection. Glycemic clamp study. [Taken from Lepore et al, *Diabetes* 49:2142–2148, 2000]



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

Clinical Evaluation

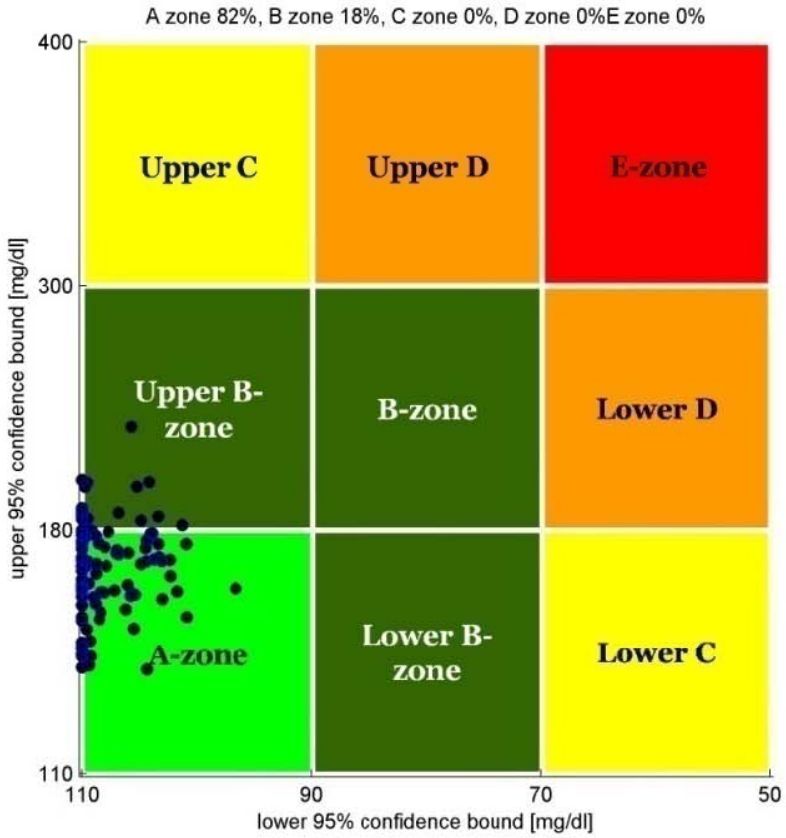
- FDA requirements
  - Investigational Device Exemption (IDE)
  - Detailed proof of safety of protocol/software
  - Master file already acknowledged for APS
- Phase I – *in silico trial*
  - UVa-Padova simulation platform
  - 300 virtual subjects
  - Master file already acknowledged
  - Evaluate same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

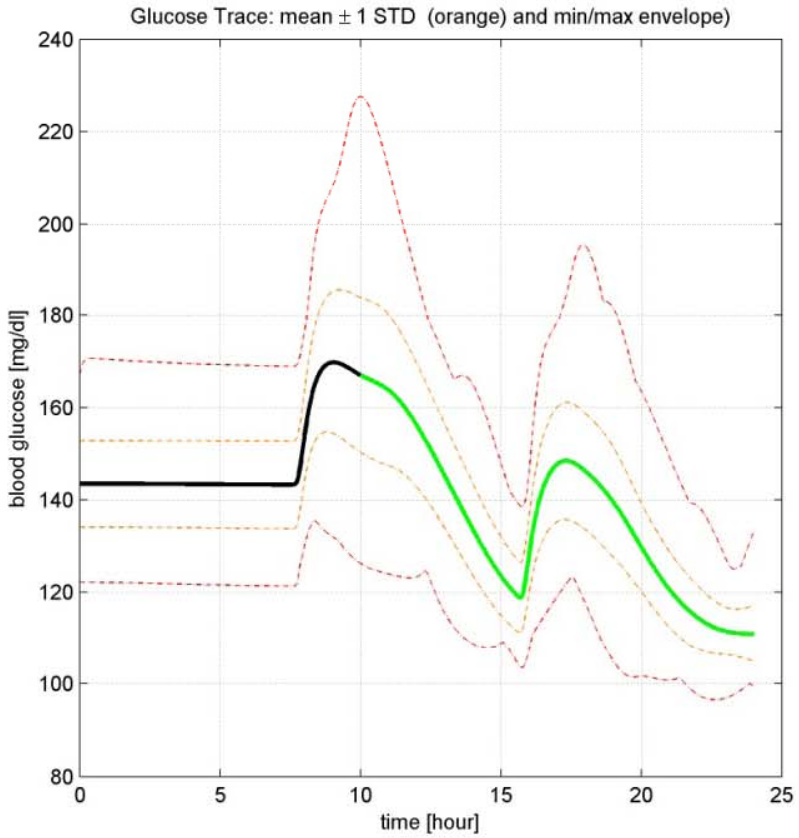


- Phase II – *human subject studies*
  - Initial studies underway in Israel
  - Planned studies in Santa Barbara in late 2009
  - Large international trial (multi-site) planned for 2010

In Silico Trial Results

[100 adult subjects]





Clinical Trial Results

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

Sansum / UCSB Presents:

Closed-Loop Insulin Delivery using Multi-Parametric MPC with Insulin-on-Board

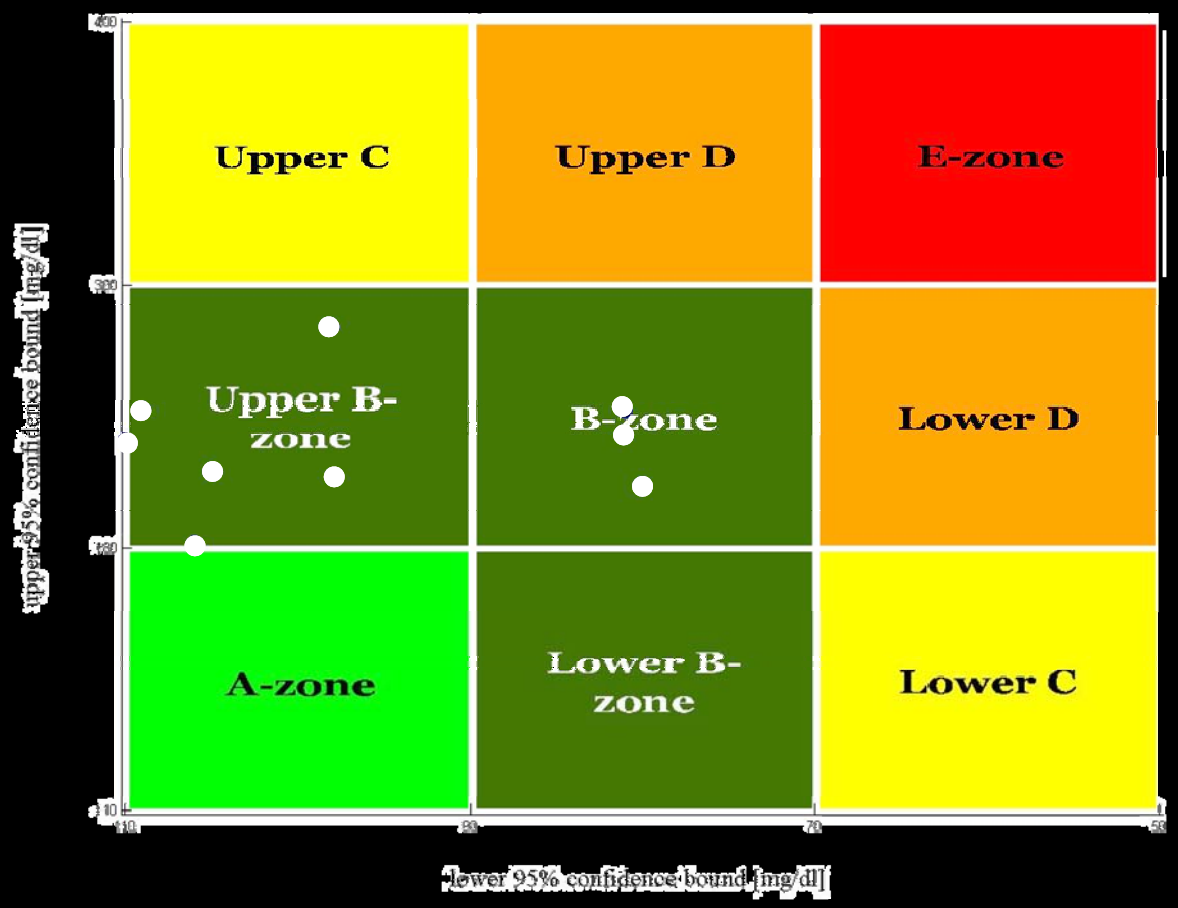
Schneider Children's Medical Center, Israel

March 2, 2009

DIABETES TECHNOLOGY CENTER
INSTITUTE FOR ENDOCRINOLOGY AND DIABETES
NATIONAL CENTER FOR CHILDHOOD DIABETES
SCHNEIDER CHILDREN'S MEDICAL CENTER OF ISRAEL

Clinical Trial Results Summary

- Starting point in Upper B-zone
- Time in range (80 -180 mg/dL): ~70%
- No hypoglycemia episodes
- CVGA : all in A+B zone
  (Including meal time)



MPC Cost Function Formulation

$$J(\underline{u}) = \sum_{j=1}^{P} \left\| \left(y_{k+j} - y_{k+j}^{r} \right) \right\| Q_j + \sum_{j=0}^{M-1} \left\| \left(u_{k+j} - u_s \right) \right\| R_j$$

$$s.t.$$

$$x_{k+j} = f\left(x_{k+j-1}, u_{k+j-1} \right) \ \forall j = 1, P$$

$$y_{k+j} = g\left(x_{k+j}, u_{k+j} \right) \ \forall j = 1, P$$

$$u_{\min} \le u_{k+j} \le u_{\max} \ \forall j = 1, M$$

$$\Delta u_{low} \le \Delta u_{k+j} \le \Delta u_{up} \ \forall j = 1, M$$

Set-point MPC keeps the reference at a constant value that is the target of the optimization

However, a *precise* reference is **not** consistent with medical practice

Zone-MPC Formulation

$$J(\underline{u}) = \sum_{j=1}^{P} \left\| y_{k+j}^{range} \right\| Q_j + \sum_{j=0}^{M-1} \left\| \left(u_{k+j} - u_s \right) \right\| R_j$$

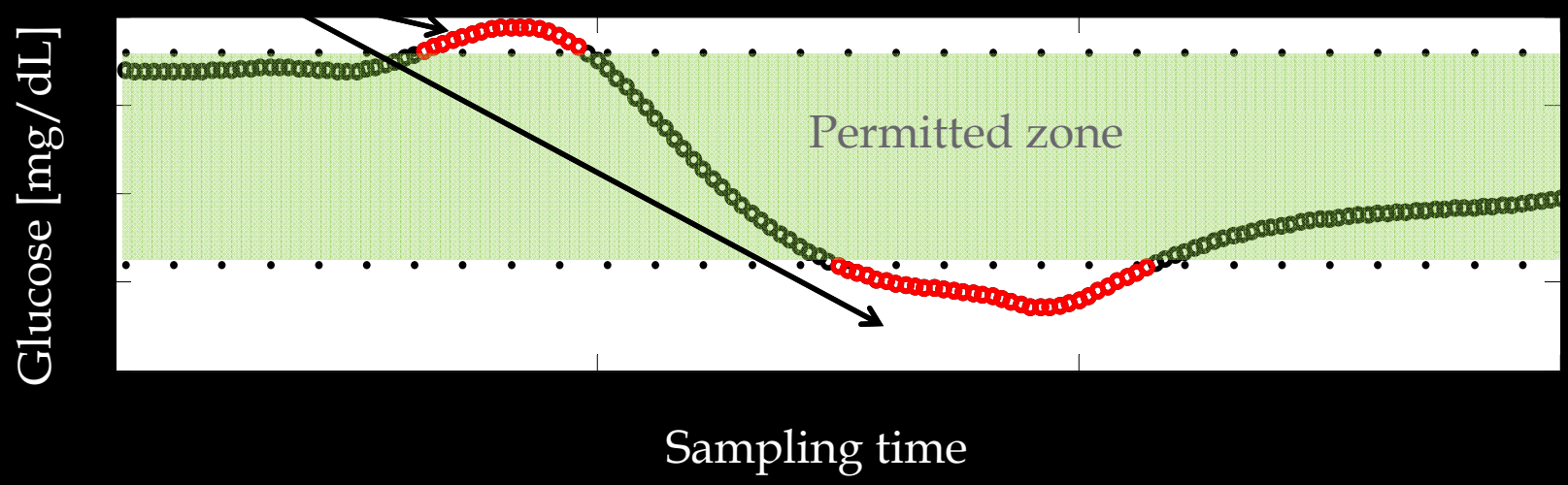
$$s.t.$$

$$y_{k+j} = f\left(y_{k+j-1}, u_{k+j-1} \right) \ \forall j = 1, P$$

$$0 \le u_{k+j} \le u_{\max} \ \forall j = 1, M$$

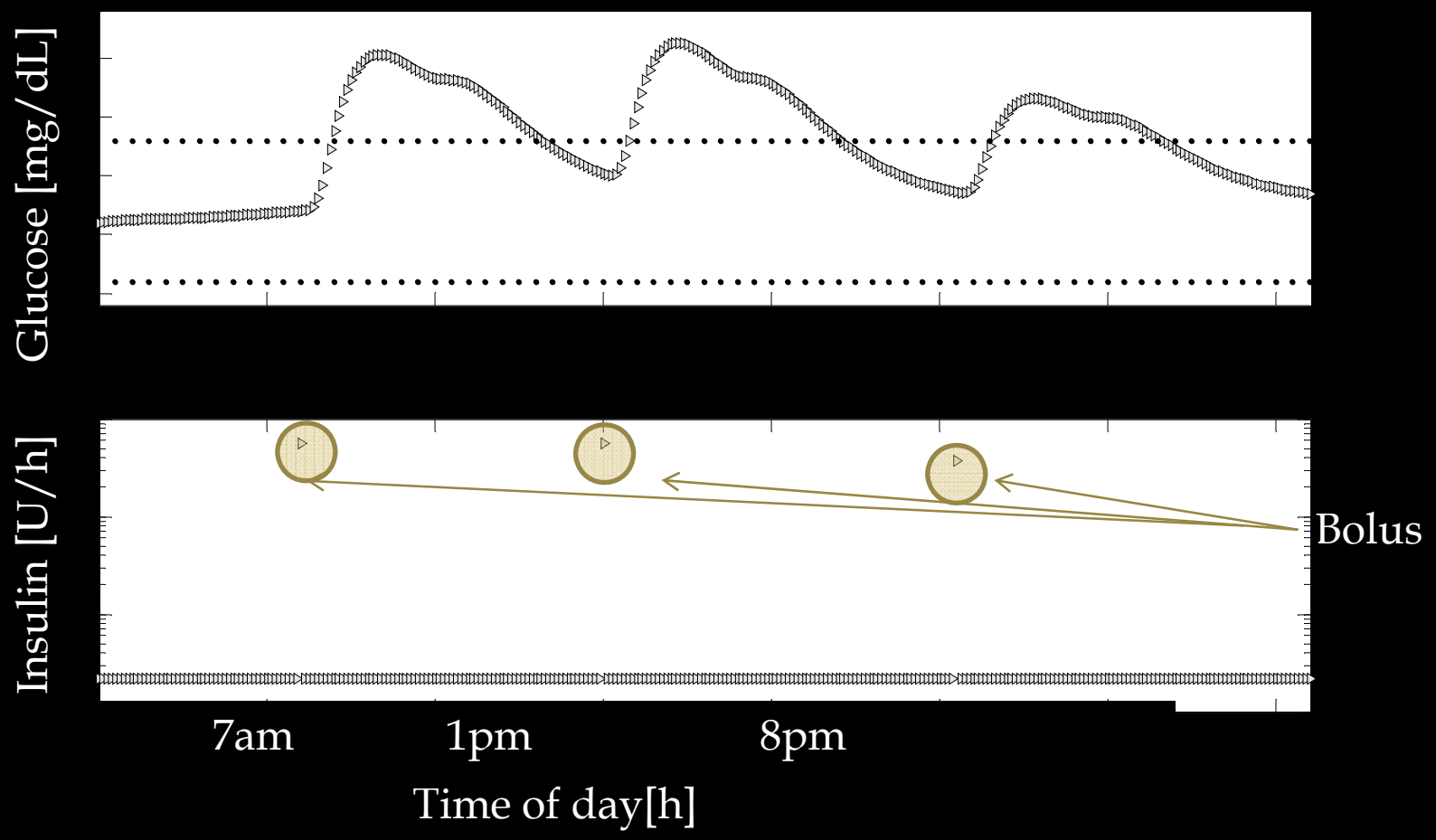
Zone-MPC optimizes future predictions into a predefined range

Accounted cost dynamics

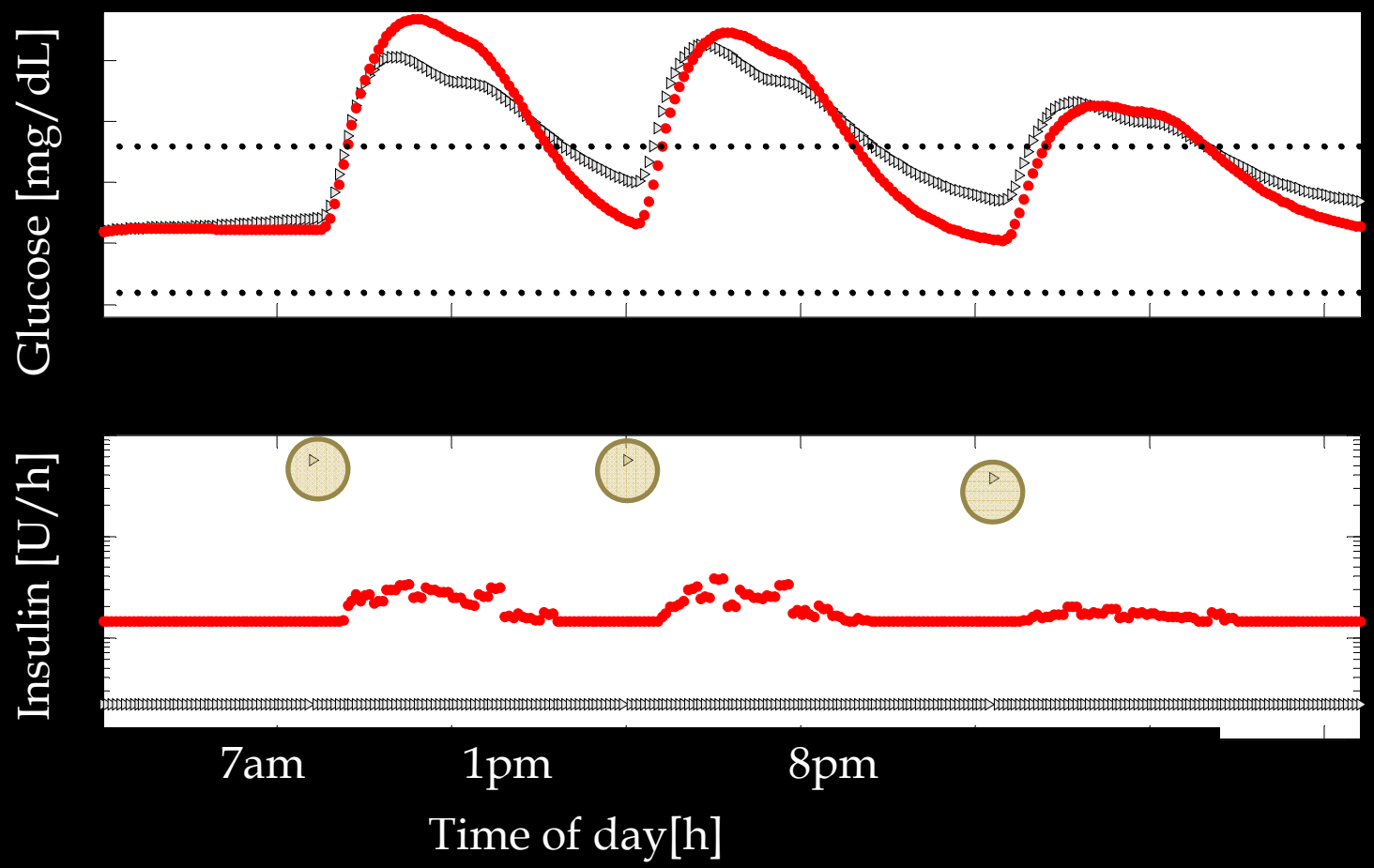


Unannounced Meal

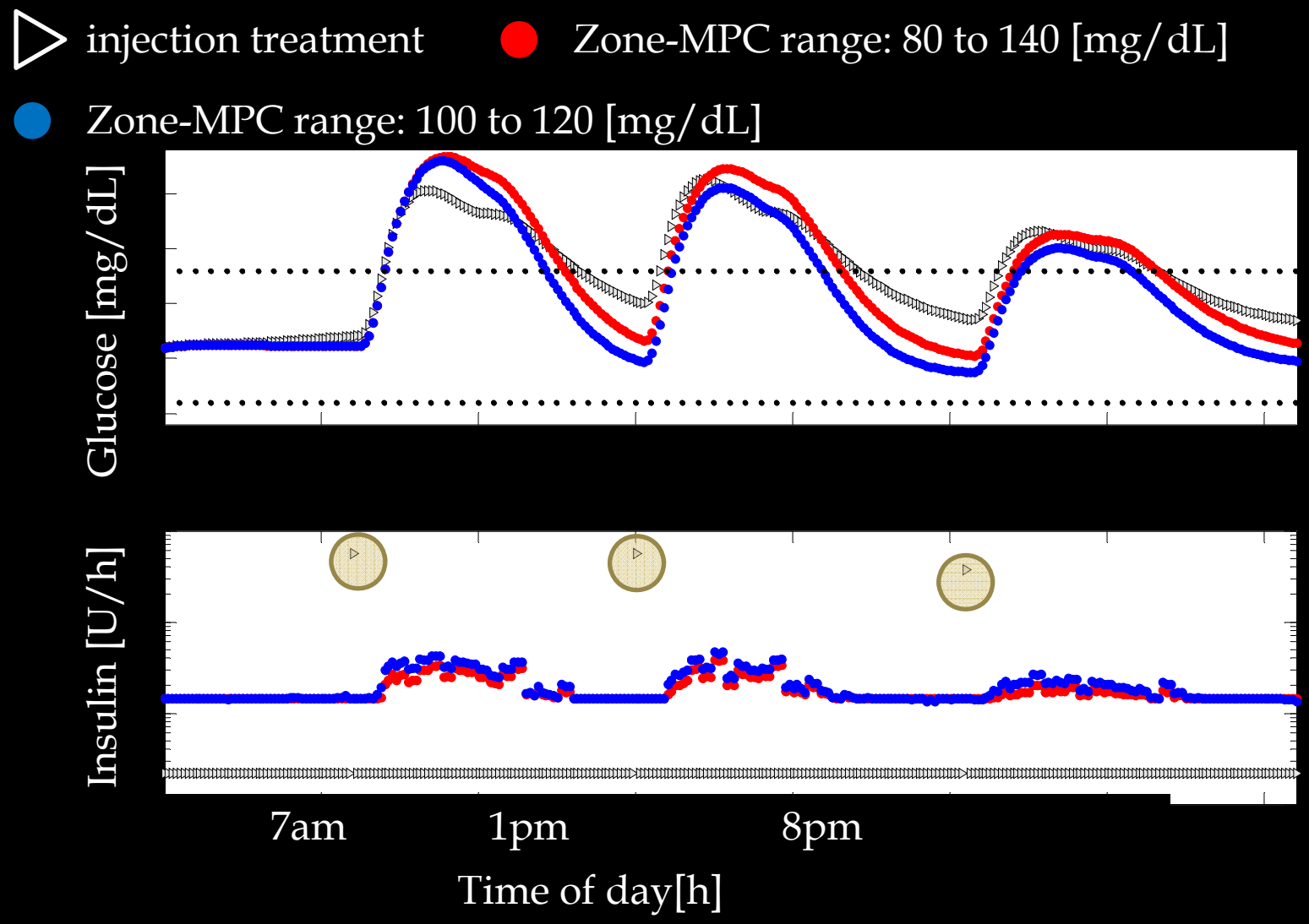
▷ injection treatment



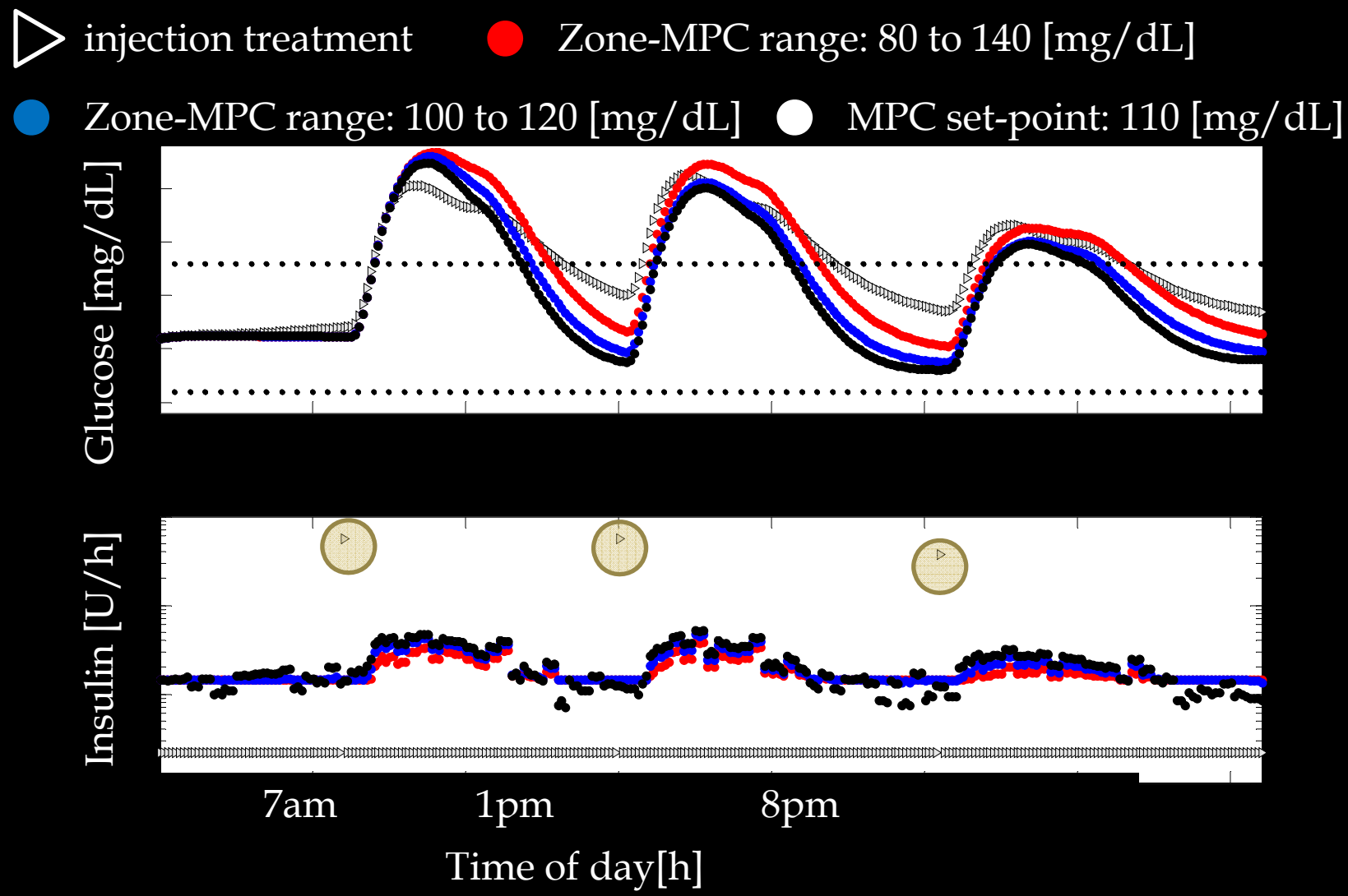
Unannounced Meal



Unannounced Meal



Unannounced Meal

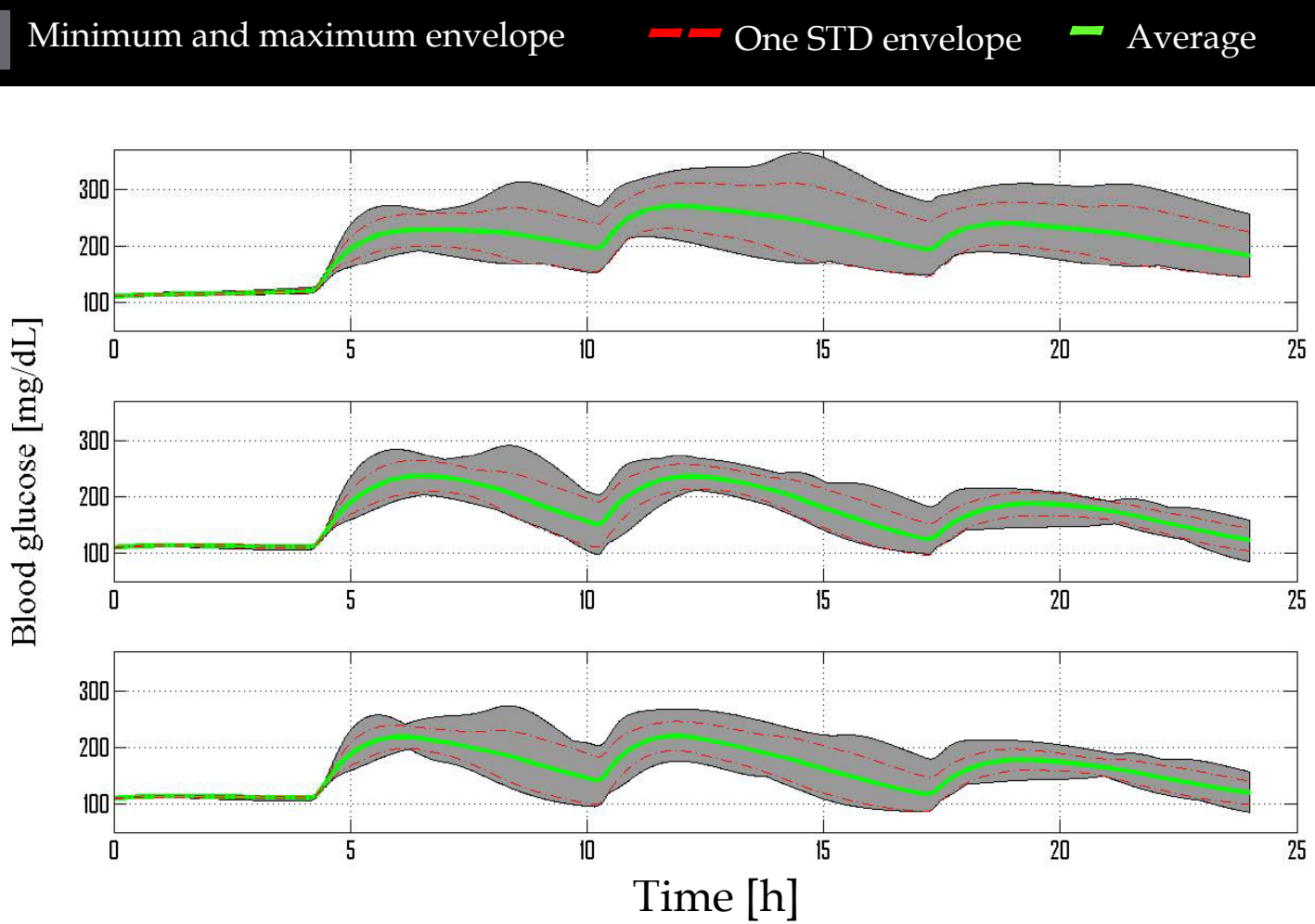


The tighter the range becomes, the higher the variability in control moves

Summary Statistics – Nominal Case

Meal	Controller mode	% of time in range between 70 and 180 mg/dL	% in zone A and B of the control variability grid analysis	Low blood glucose index (LBGI)	High blood glucose index (HBGI)
Unannounced	Zone 80-140 mg/dL	56	100	0	8.1
	Zone 100-120 mg/dL	66	100	0	6.3
	Set-point 110 mg/dL	68	100	0.1	5.6
Announced	Zone 80-140 mg/dL	72	90	0.2	5.1
	Zone 100-120 mg/dL	79	80	0.5	3.8
	Set-point 110 mg/dL	82	80	0.6	3.3
“Optimal” injection treatment		50	90	0	9.2

Comparison between Injection Treatment and Zone-MPC with -40 % Meal Uncertainty



Injection treatment

Zone-MPC with range: 80 to 140 [mg/dL]; Unannounced

Zone-MPC with range: 80 to 140 [mg/dL]; Announced

Looking Towards the Future:

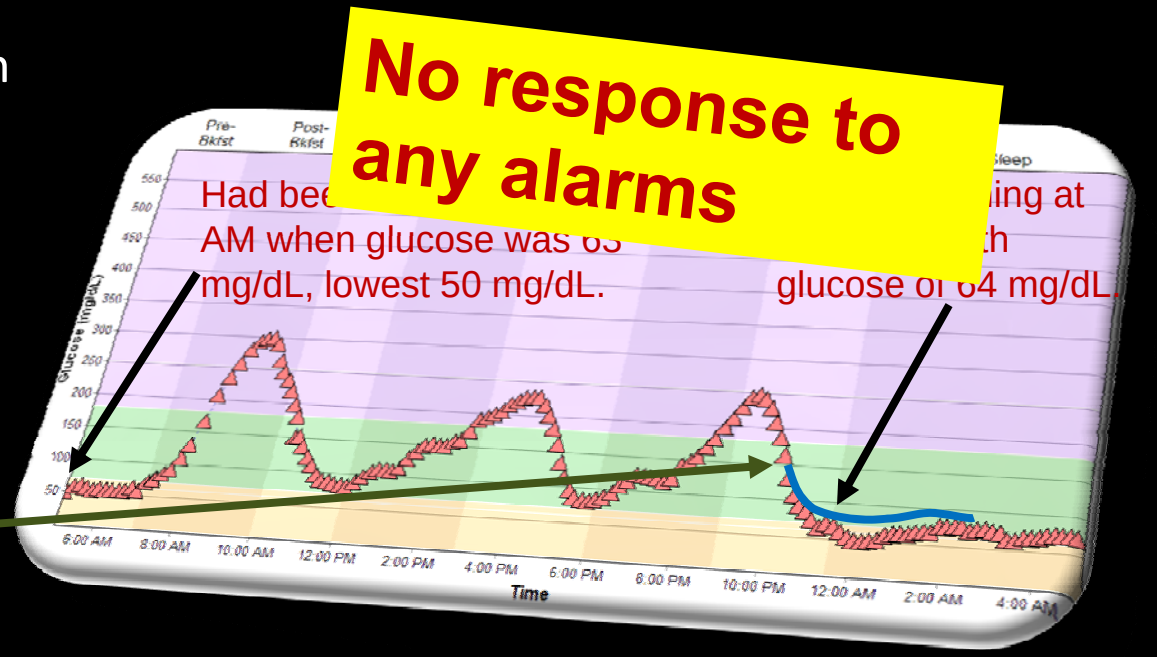
Safety Issues

Human Variability

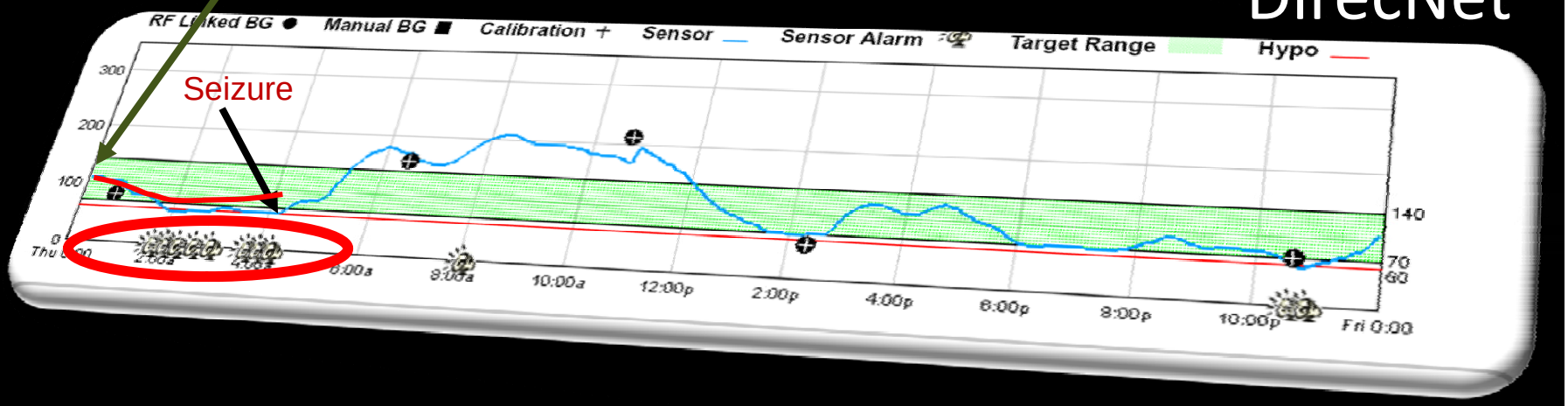
Hypoglycemia Prediction

- 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

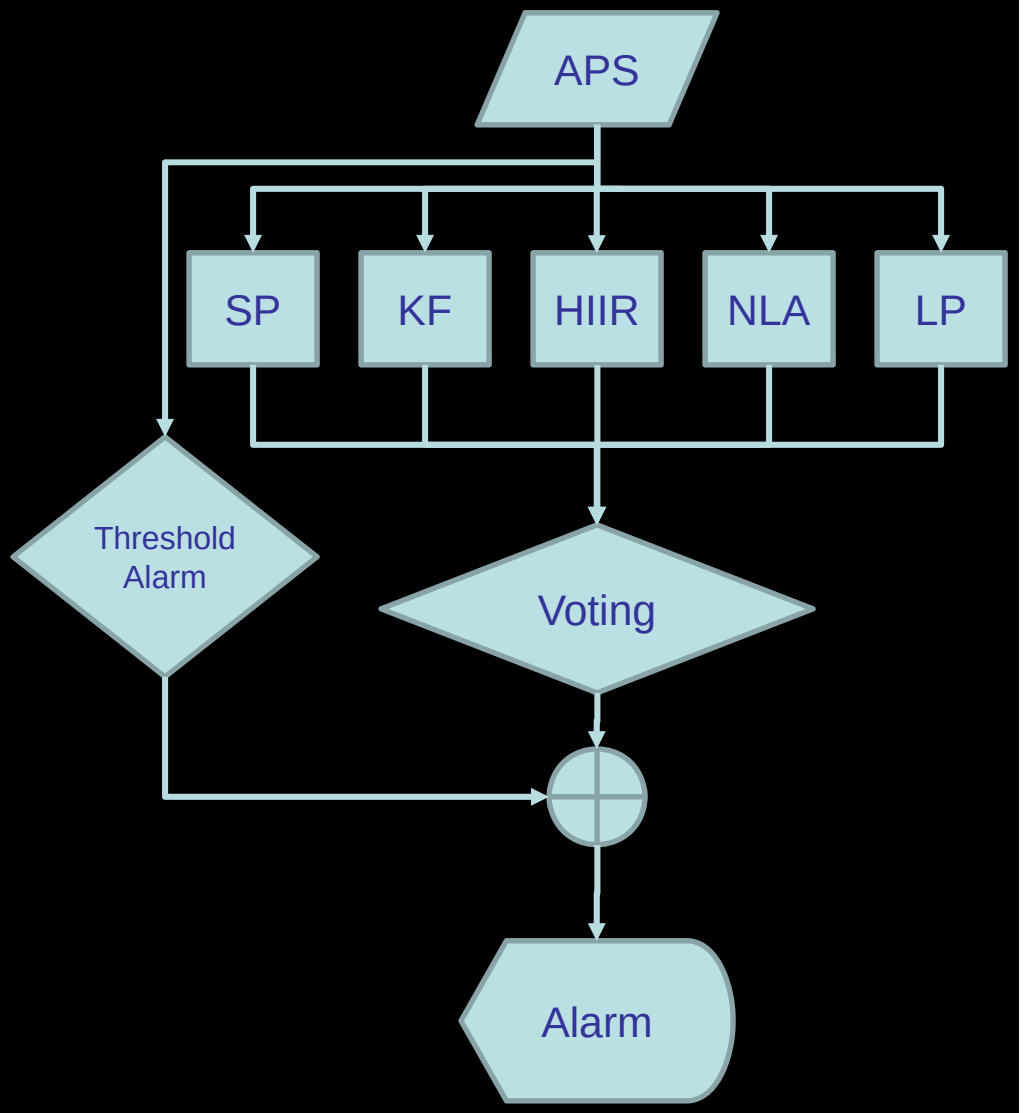


Dassau et al. 68th ADA meeting San Francisco CA, 06.08.08

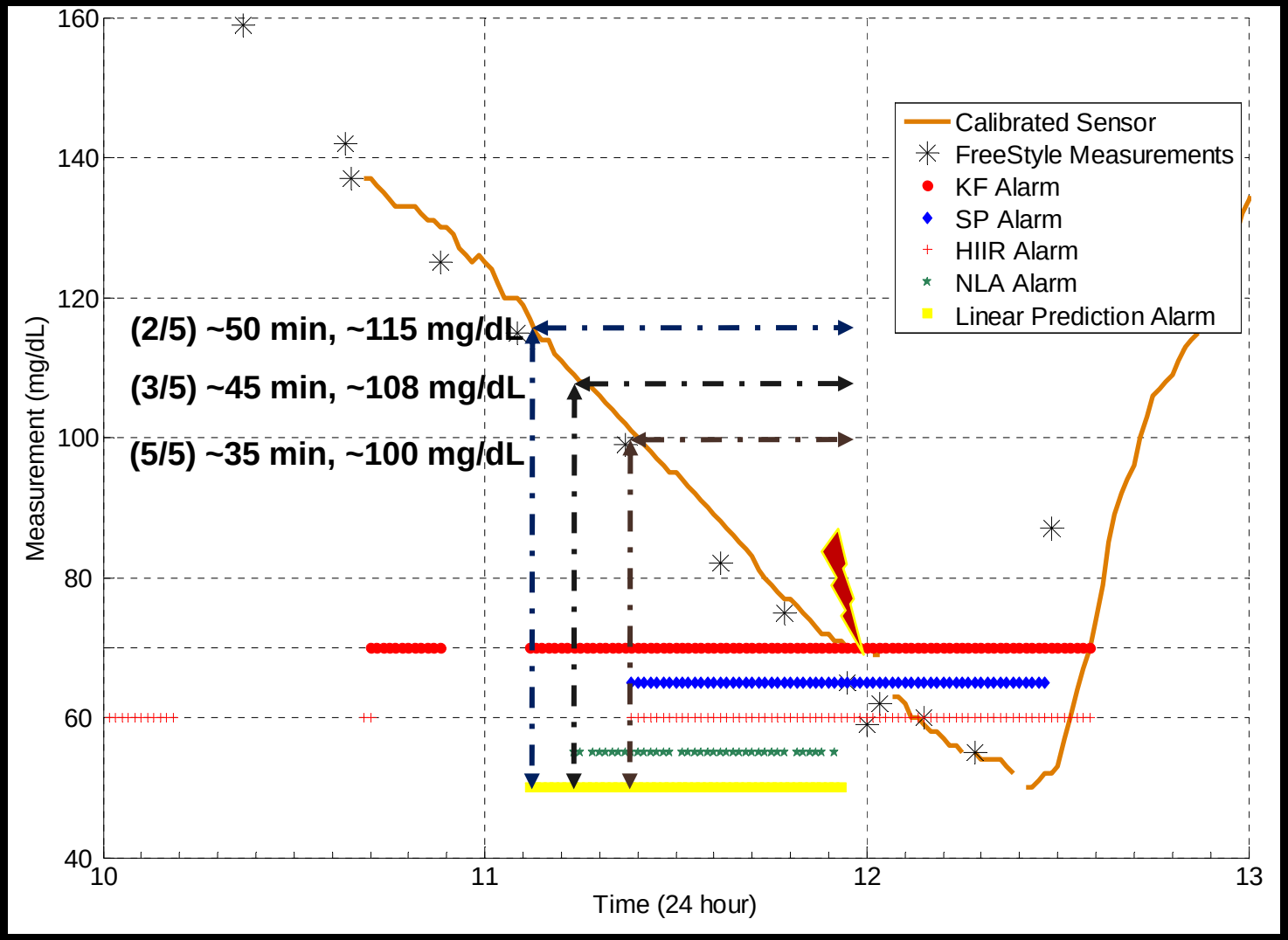
Hypoglycemic Predictive Algorithms

[collaboration with Stanford, RPI]

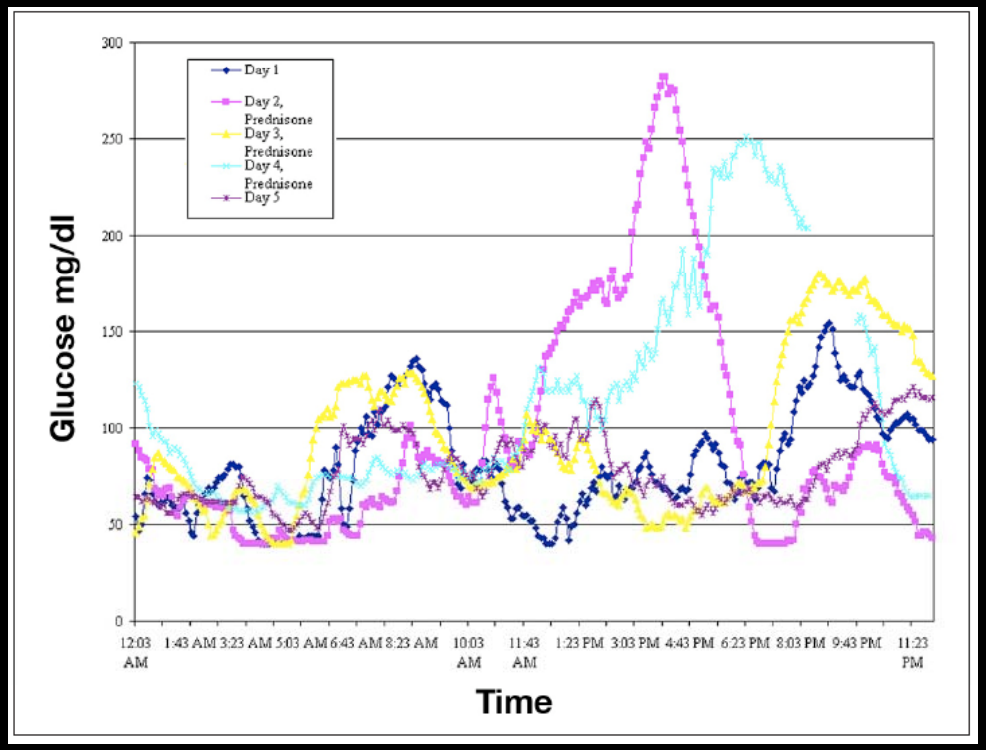
- SP: Statistical linear prediction: multiple empirical, statistical models are used to estimate future blood glucose values and their error bounds
- KF: Kalman filter to estimate glucose and its rate-of-change (ROC), which are then used to predict future glucose levels
- HIIR: Hybrid Infinite Impulse Response filter that generates glucose predictions using previous CGM data
- NLA: Numerical logical algorithm that predicts by numerical estimation of the ROC and a set of logical expressions
- LP: Linear projection based on a short term linear extrapolation of the glucose trend

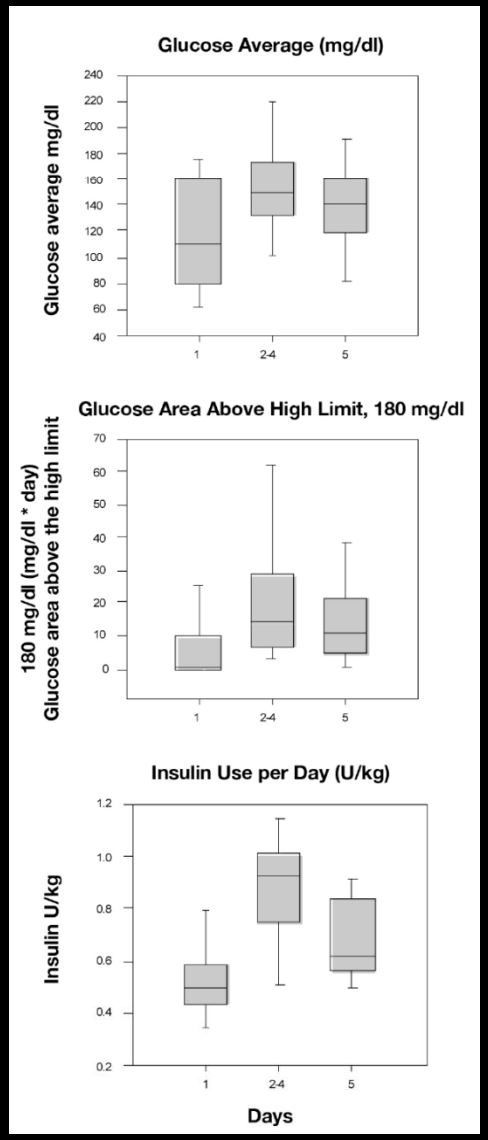


Results – Hypoglycemia Prediction



Variability in the Human Body: Stress Effects



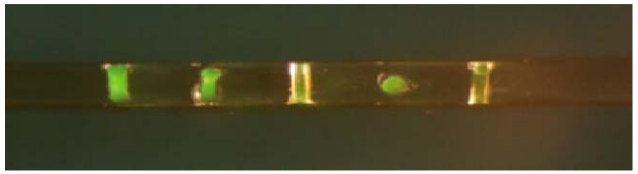


Clinical evaluation of the effect of Prednisone [Bevier, et al., 2007]

✓Progress has been made by several companies in developing fluorescent glucose sensors

Electrochemical sensor

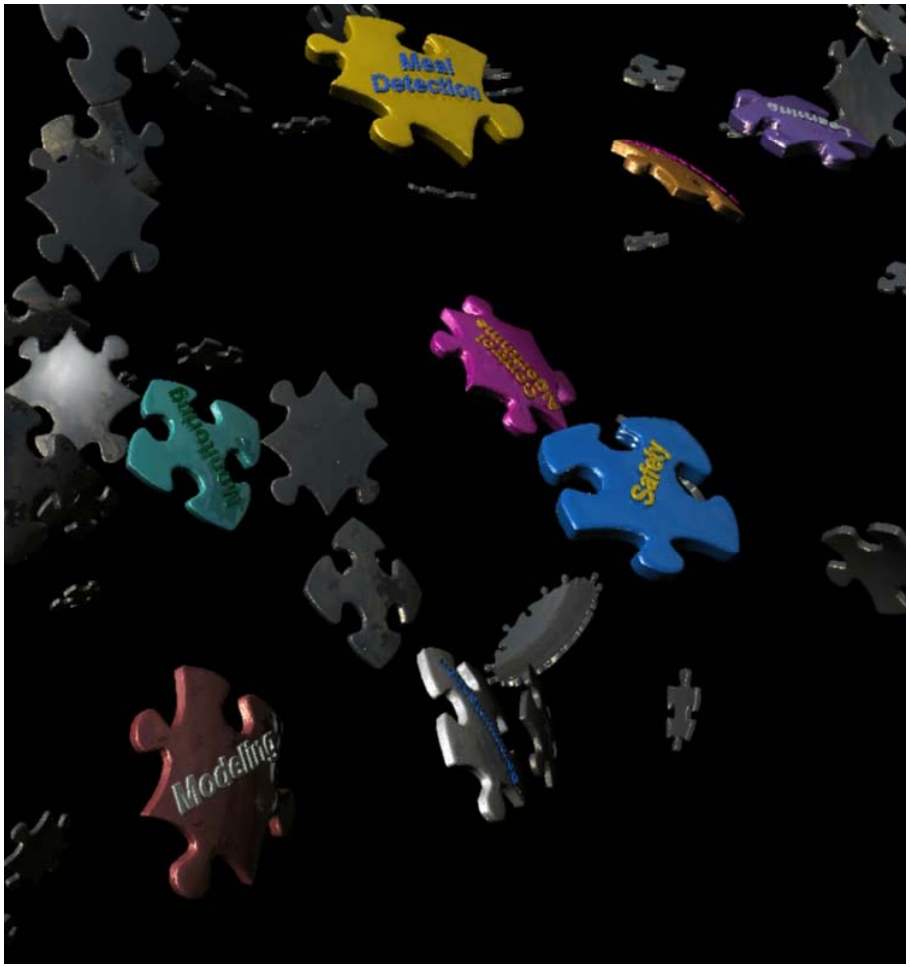
GluMetrics fluorescent sensor



"…two independent and redundant sensor systems operating simultaneously…."

Kowalski A J "Can We Really Close the Loop …" *Diabetes Technol. and Ther.,* 11 Suppl. 113-119 (2009)

- Programming Implementation (mpMPC)
- Safety Constraints (Insulin-on-Board)



- Many challenges still remain:
  - Patient model identification
  - Reliable sensors & number of sensors
  - Transport and site issues
  - Patient variability (incl. stress, activity, etc.)
  - Regulatory issues
- Next
  - More clinical trials

Upcoming: JDRF Multi-Center Trial of Control-to-Range

All centers will use in silico testing and modular design of the control algorithm including: Hardware interface (the APS) developed in Santa Barbara; Safety Supervision Module developed at UVA / UCSB, and Range Correction Module developed in Padova.

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