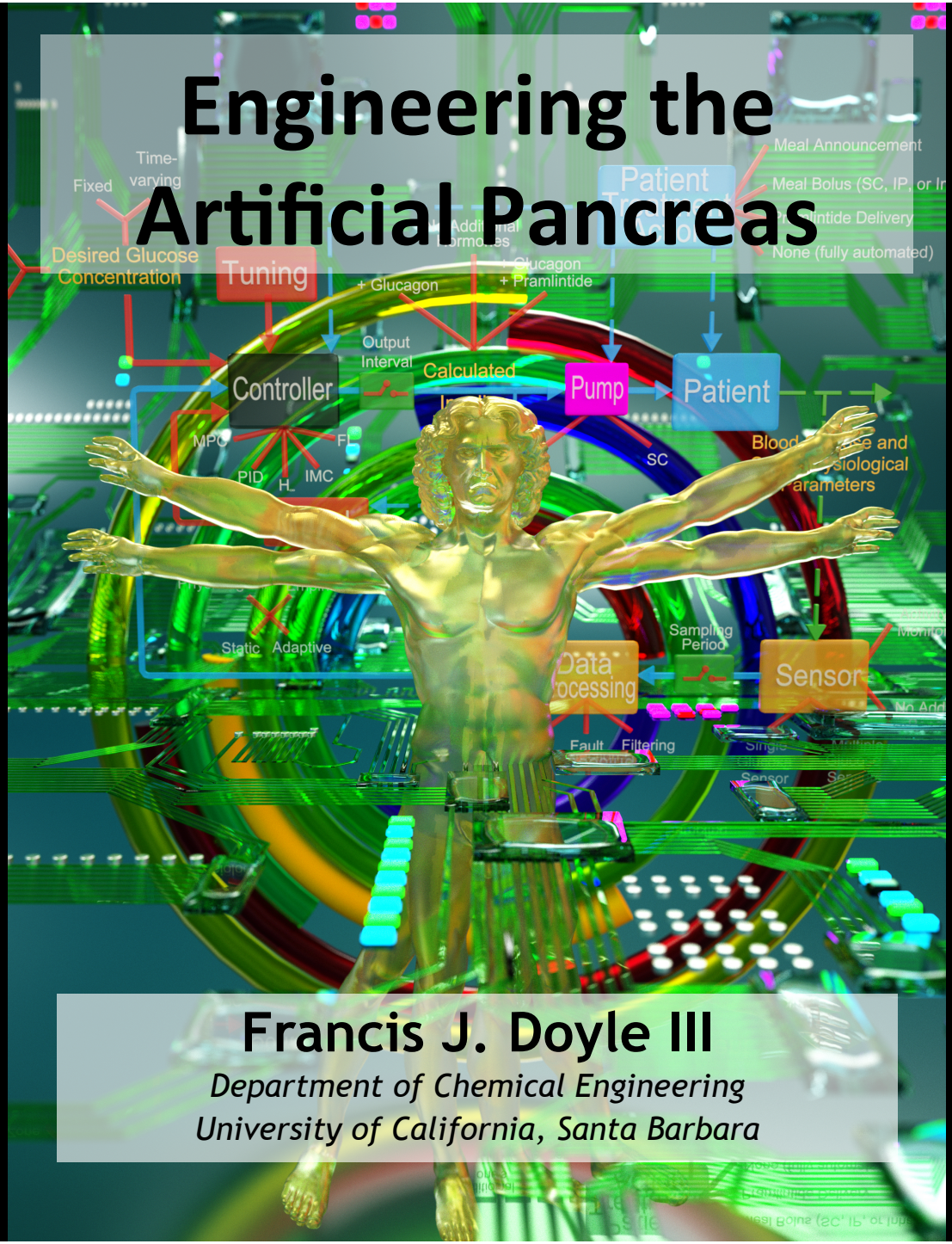
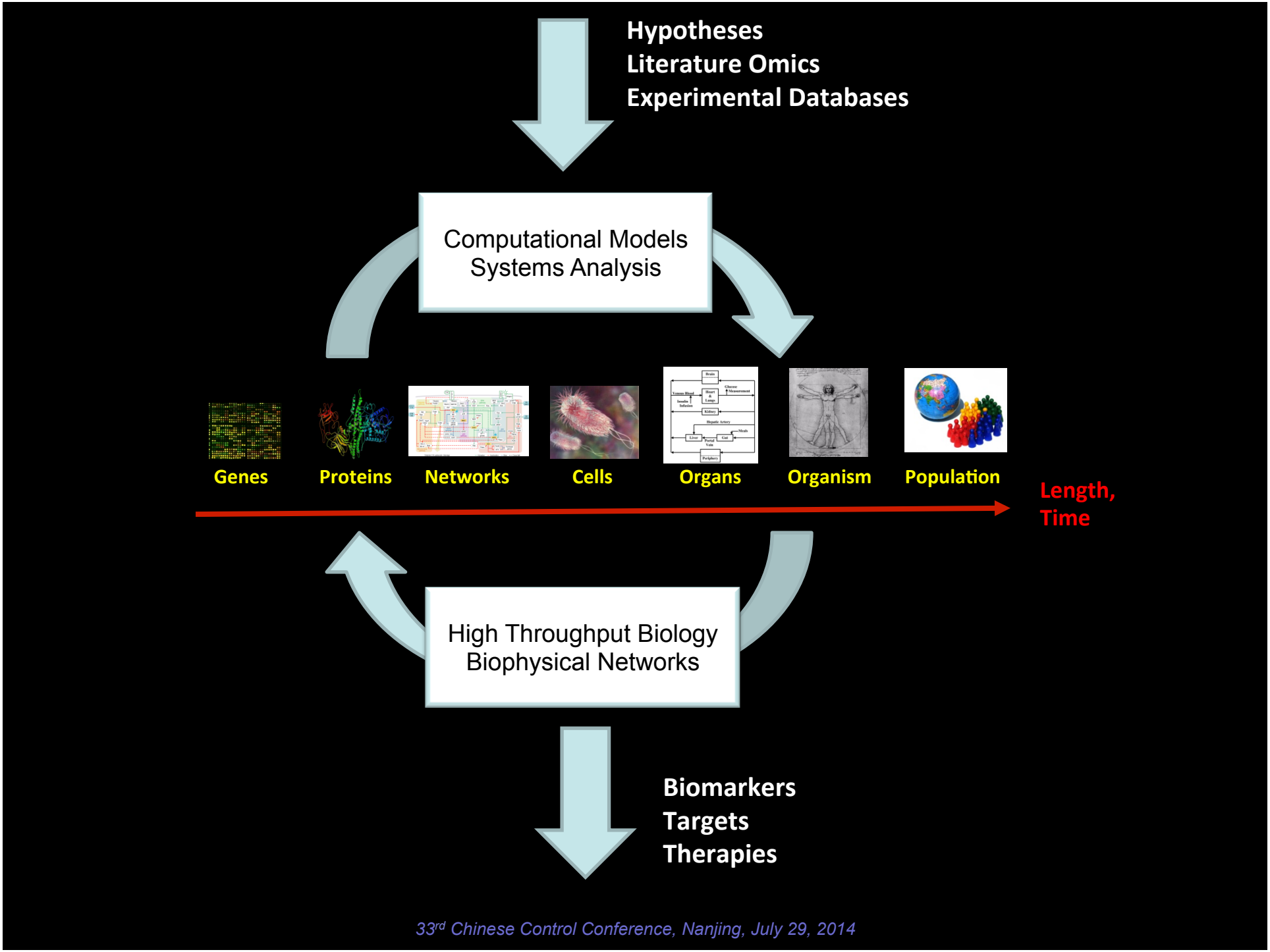
Engineering the Artificial Pancreas



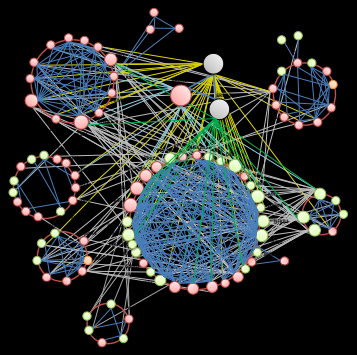
Francis J. Doyle III

Department of Chemical Engineering

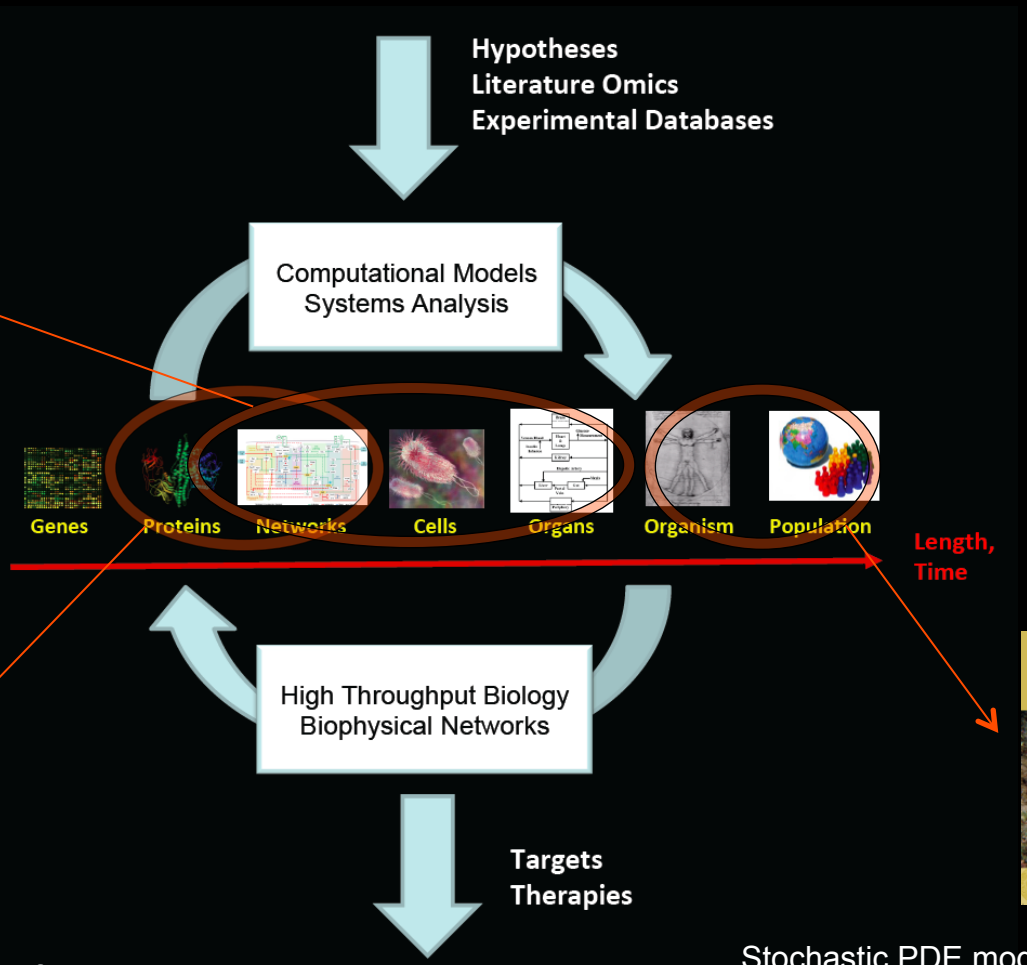
University of California, Santa Barbara

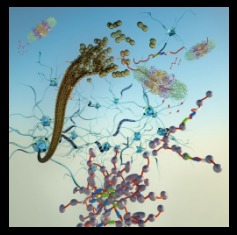

Hypotheses
Literature Omics
Experimental Databases
Computational Models
Systems Analysis
Genes
Proteins
Networks
Cells
Organs
Organism
Population
Length,
Time
High Throughput Biology
Biophysical Networks
Biomarkers
Targets
Therapies

Control Systems Analysis Unravels Biological Circuits

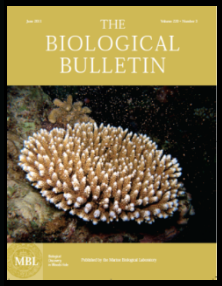


Network module expression identifies biomarkers for PTSD
[Yang et al., *BMC Bioinform.*, 2012]





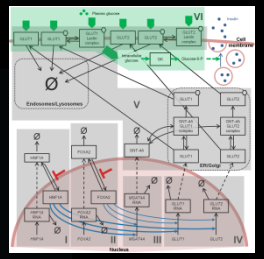
Ultra-sensitivity reveals potential targets for Tau misfolding in Alzheimers
[Yuraszeck et al., *Plos Comp Biol.*, 2010]



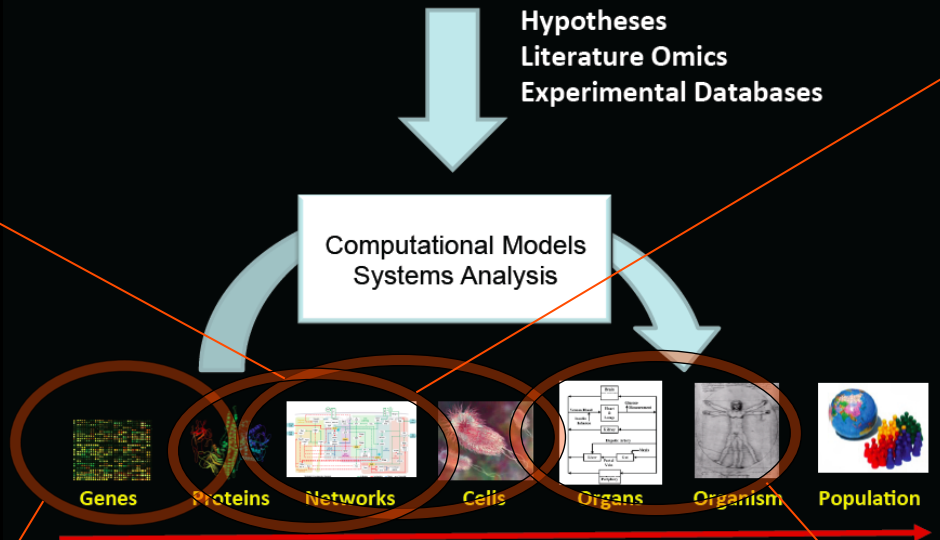
Stochastic PDE model sheds light on circadian timing and spawning synchrony at the eco-scale
[Boch et al., *Biol. Bull.*, 2011]

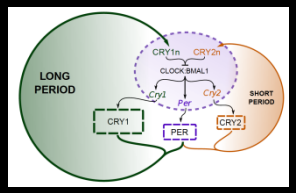
Control Systems Analysis Unravels Biological Circuits

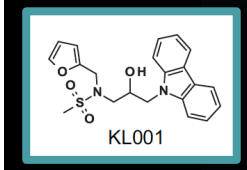
Coupled oscillator control reveals SCN neuron synchrony
[Liu et al., *Cell*, 2007;
Bagheri et al., *Interface*, 2008]



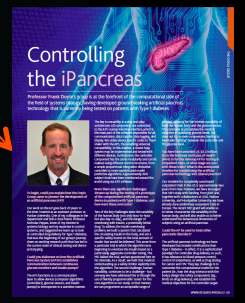
Robust control strategy for multi-target drug design in type 2 diabetes
[Luni et al., *IJRNC*, 2011;
Luni et al., *PLoS One*, 2012]





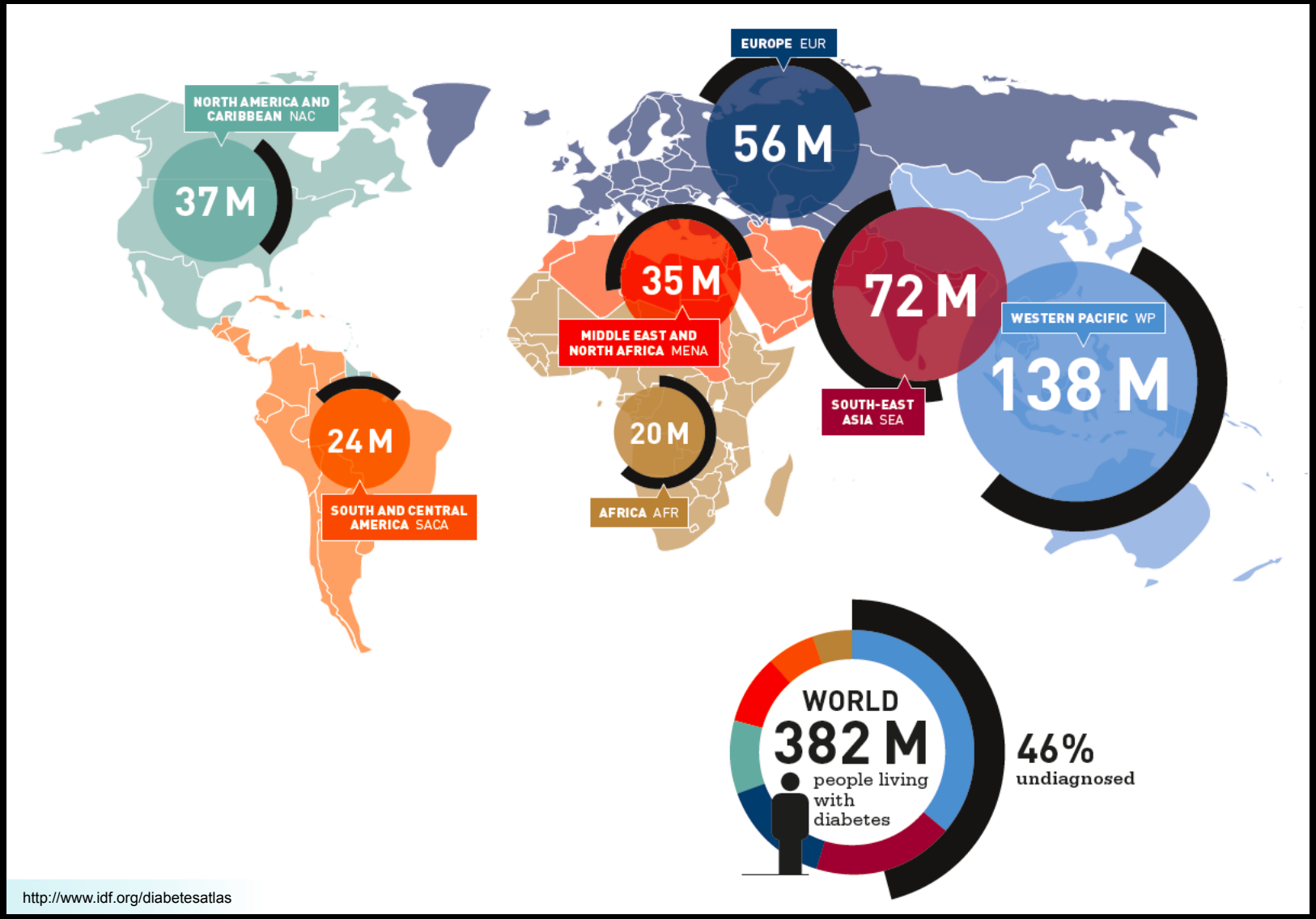


Systems approach identifies novel small molecule that targets circadian period
[Hirota et al., *Science*, 2012
St. John et al., *PNAS*, 2014]



Clinical testing of artificial pancreas for type 1 diabetes
[Dassau et al., *Diabetes Care*, 2012]

Diabetes: A Worldwide Problem



Diabetes Incidence in China

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N ENGL J MED 362;12 NEJM.ORG MARCH 25, 2010

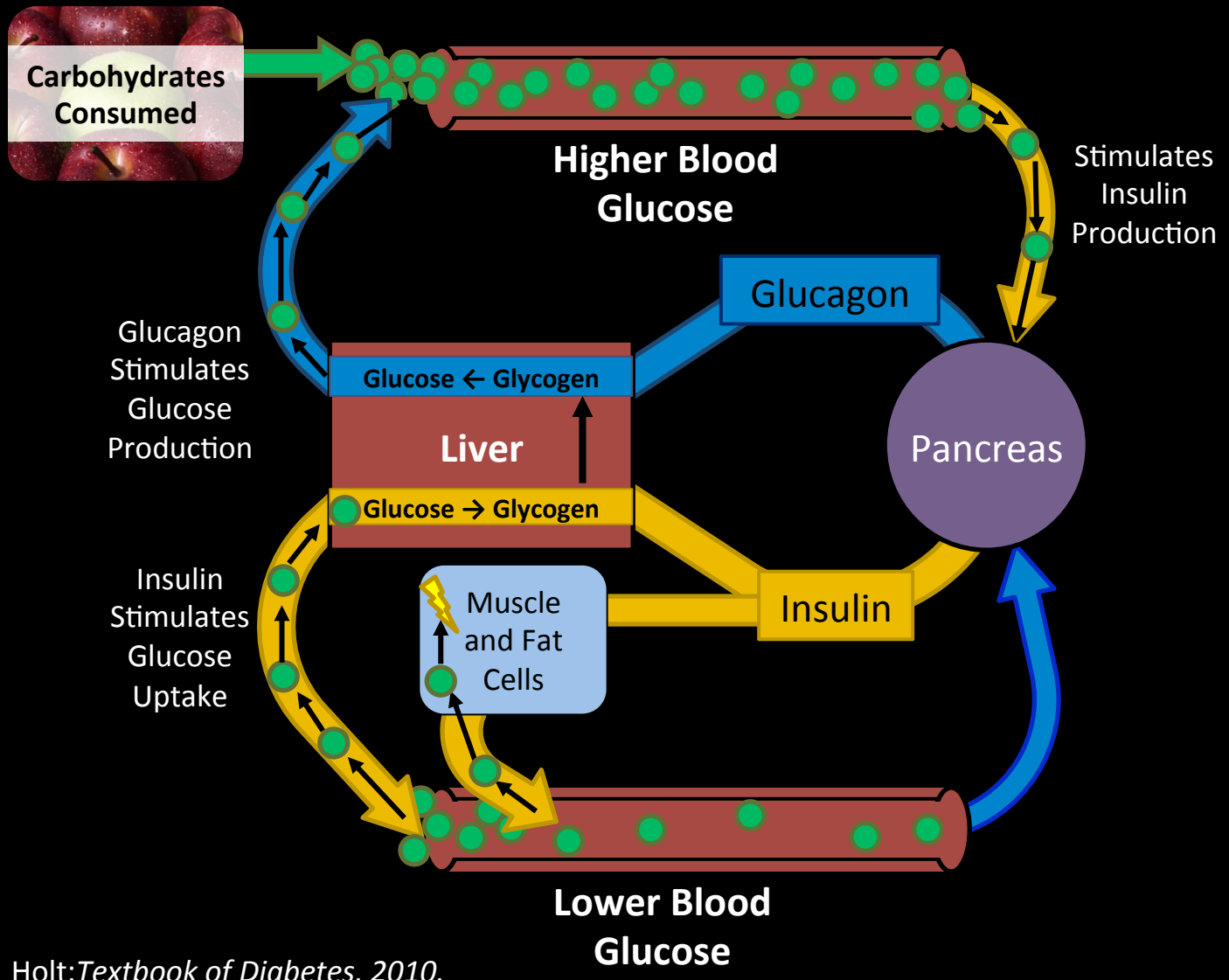
Prevalence of Diabetes among Men and Women in China

Wenying Yang, M.D., Juming Lu, M.D., Jianping Weng, M.D., Weiping Jia, M.D., Linong Ji, M.D., Jianzhong Xiao, M.D., Ph.D., Zhongyan Shan, M.D., Jie Liu, M.D., Haoming Tian, M.D., Qiuhe Ji, M.D., Dalong Zhu, M.D., Jiapu Ge, M.D., Lixiang Lin, M.D., Li Chen, M.D., Xiaohui Guo, M.D., Zhigang Zhao, M.D., Qiang Li, M.D., Zhiguang Zhou, M.D., Guangliang Shan, M.D., Ph.D., and Jiang He, M.D., Ph.D., for the China National Diabetes and Metabolic Disorders Study Group*

- A nationally representative sample of 46,239 adults, 20 years of age or older, from 14 provinces and municipalities participated in the study
- Prevalence of total diabetes = 9.7% (92.4 million) and prediabetes was 15.5% (148.2 million)

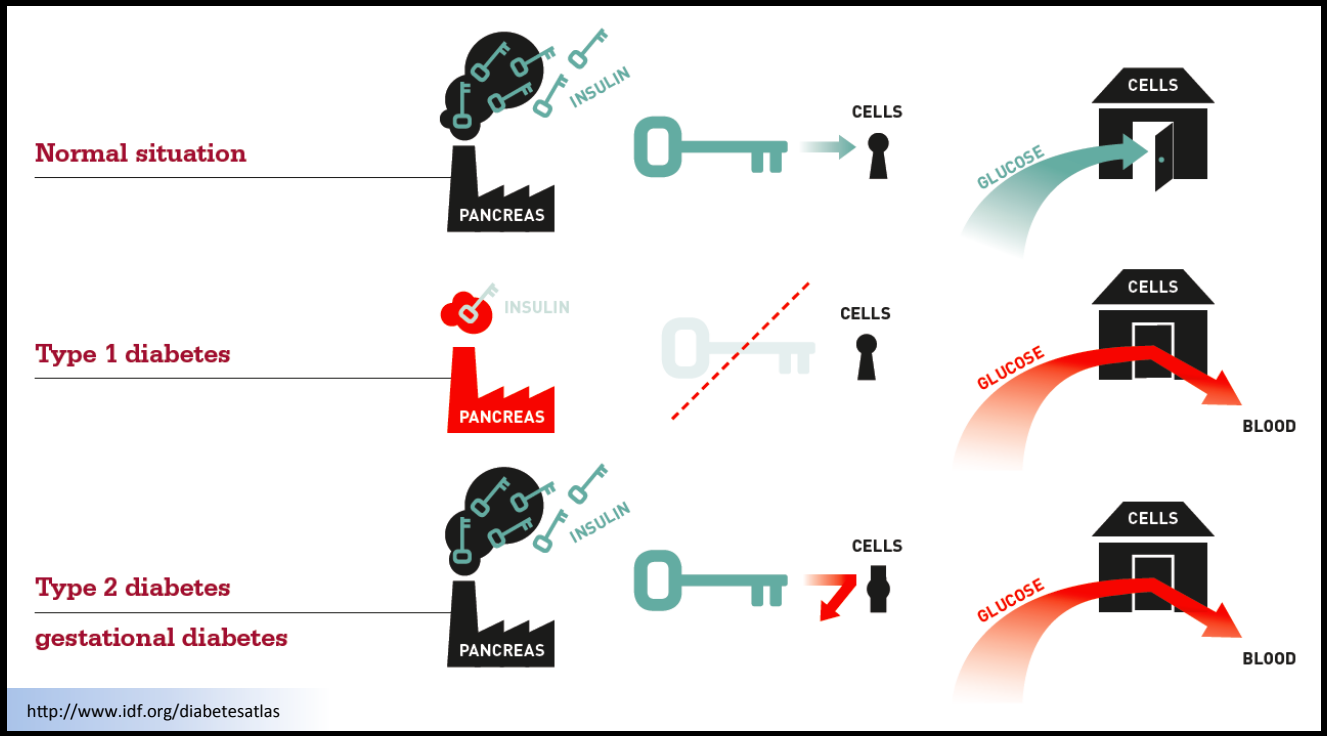
"These results indicate that diabetes has become a major public health problem in China and that strategies aimed at the prevention and treatment of diabetes are needed."

Natural Glucose Regulation



Holt: *Textbook of Diabetes, 2010.*

Glucose Dysregulation



Manual Glucose Control

Higher Blood Glucose

Glucagon

Glucagon Stimulates Glucose Production

Glucose ← Glycogen

Liver

Glucose → Glycogen

Pancreas

Insulin Stimulates Glucose Uptake

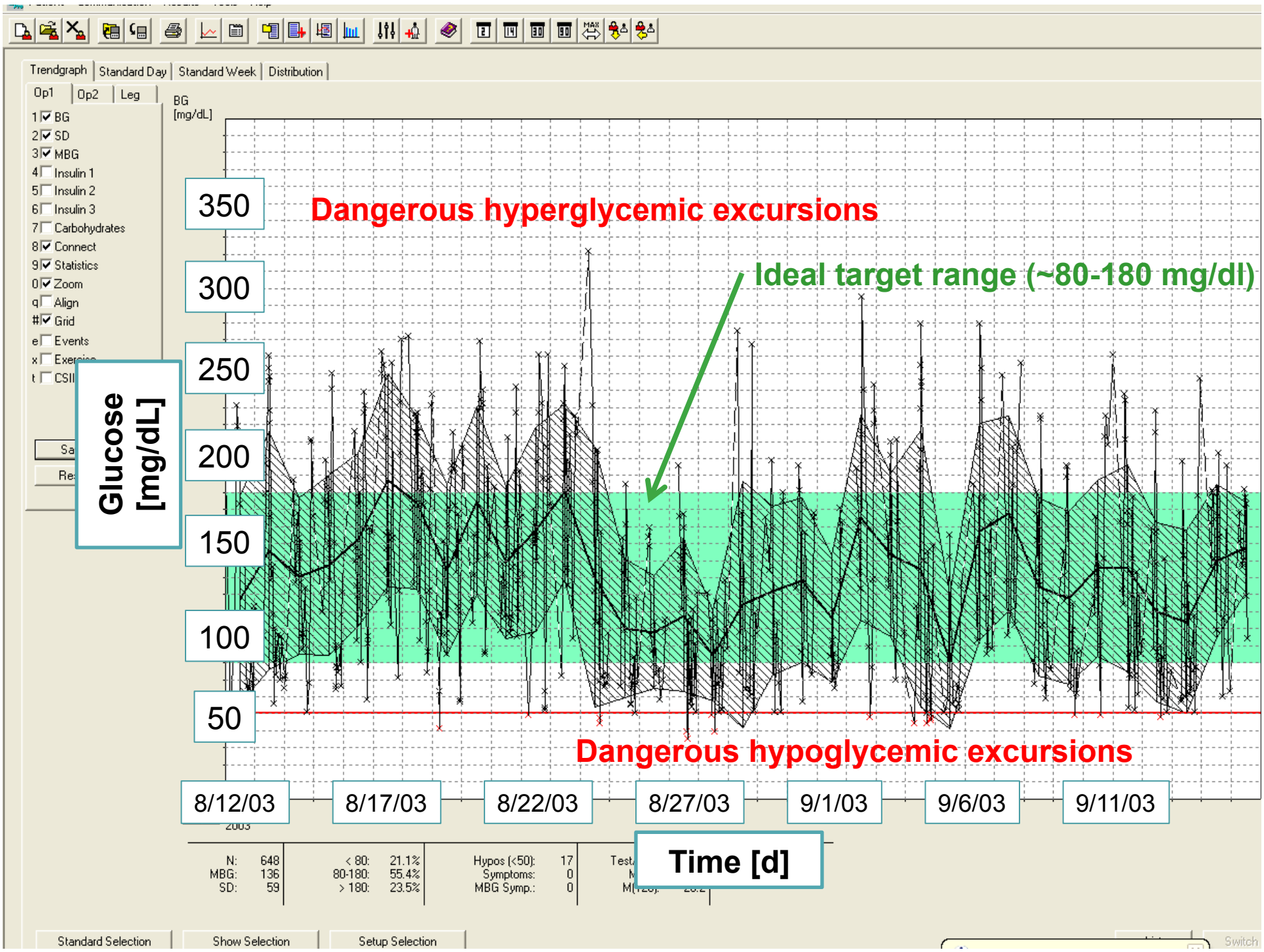
Muscle and Fat Cells

Insulin

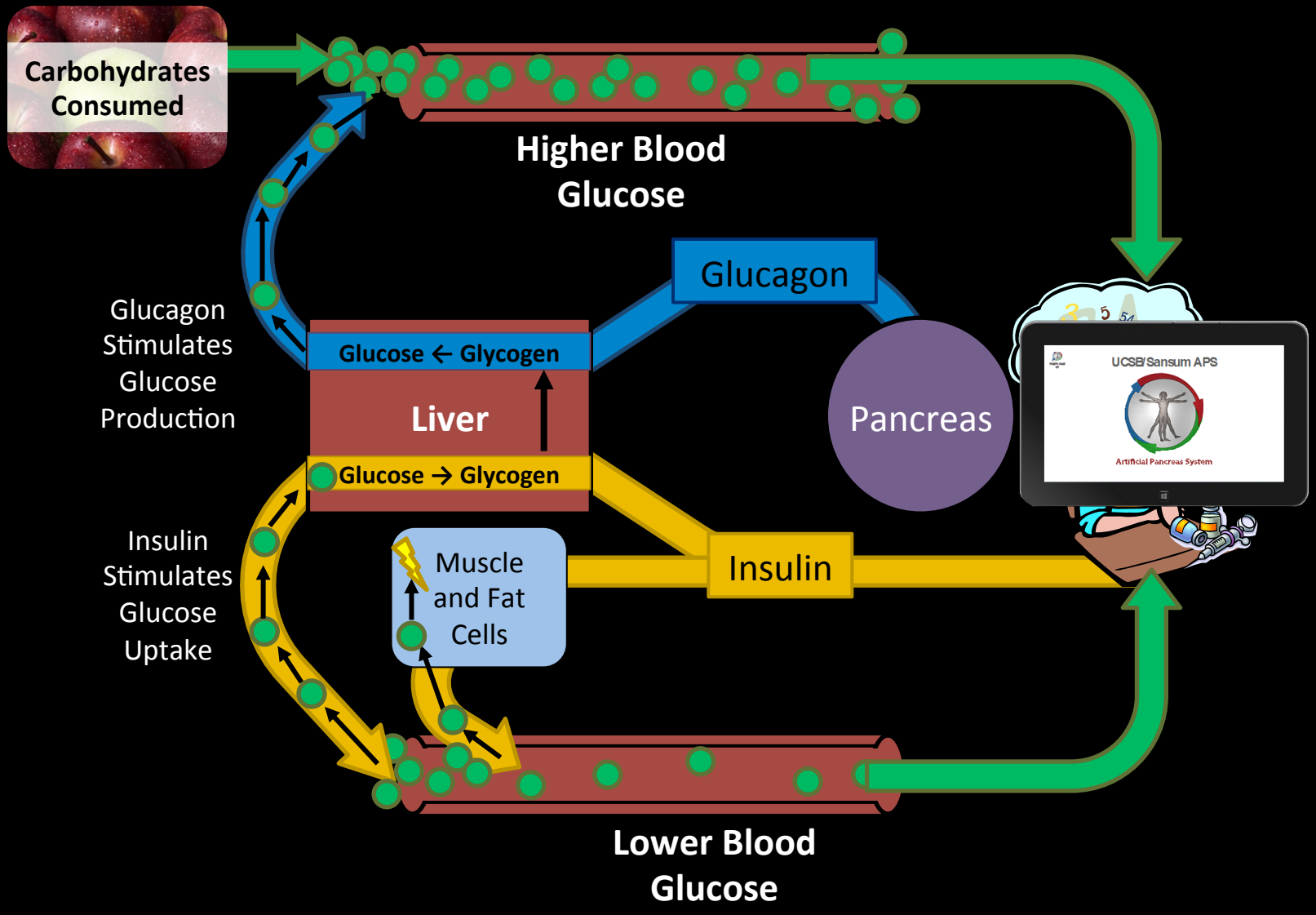
Lower Blood Glucose

Hyperglycemia
Retinopathy
Nephropathy
Neuropathy
Cardiovascular disease
Diabetic ketoacidosis

Hypoglycemia
Trembling/Anxiety
Headache
Confusion/Dizziness
Coma
Death


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
BG [mg/dL]
Glucose [mg/dL]
350
300
250
200
150
100
50
Dangerous hyperglycemic excursions
Ideal target range (~80-180 mg/dl)
Dangerous hypoglycemic excursions
8/12/03
8/17/03
8/22/03
8/27/03
9/1/03
9/6/03
9/11/03
2003
Time [d]
N: 648
MBG: 136
SD: 59
< 80: 21.1%
80-180: 55.4%
> 180: 23.5%
Hypos (<50): 17
Symptoms: 0
MBG Symp.: 0
Standard Selection
Show Selection
Setup Selection

Automated Glucose Control



Control Actuation: Insulin Pumps

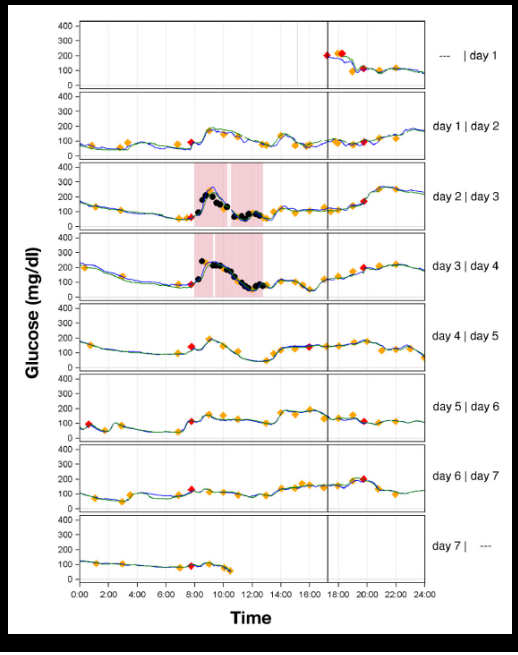
	Implantable cardiac defibrillator	*Insulin pump*	*Mobile phone*	*MP3 player*
End-user interactions	±	++	+++	++++
Cost	$$$$	$$$	$$	$
Design flexibility	+	++	+++	++++
Constituencies	FDA, HCPs	FDA, HCPs, end-users	FCC, end-users	End-users
Nominal lifespan	++++	+++	++	+
Consequence of device failure	Arrhythmia	Dysglycemia	Inconvenience	Peace and quiet

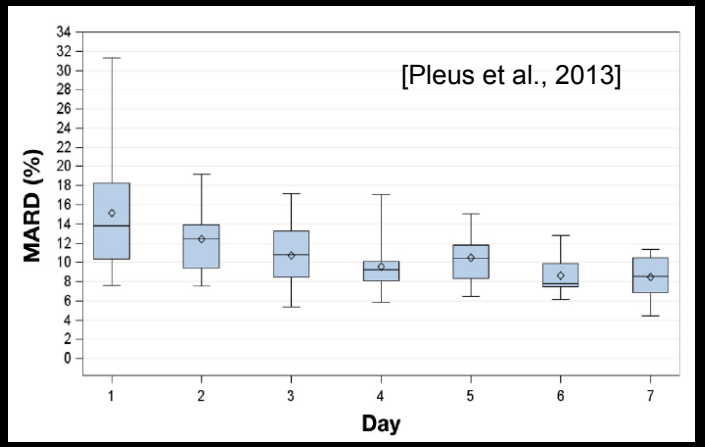
FCC, Federal Communications Commission; FDA, Food and Drug Administration; HCP, healthcare professional.

[Welsh et al., 2010]

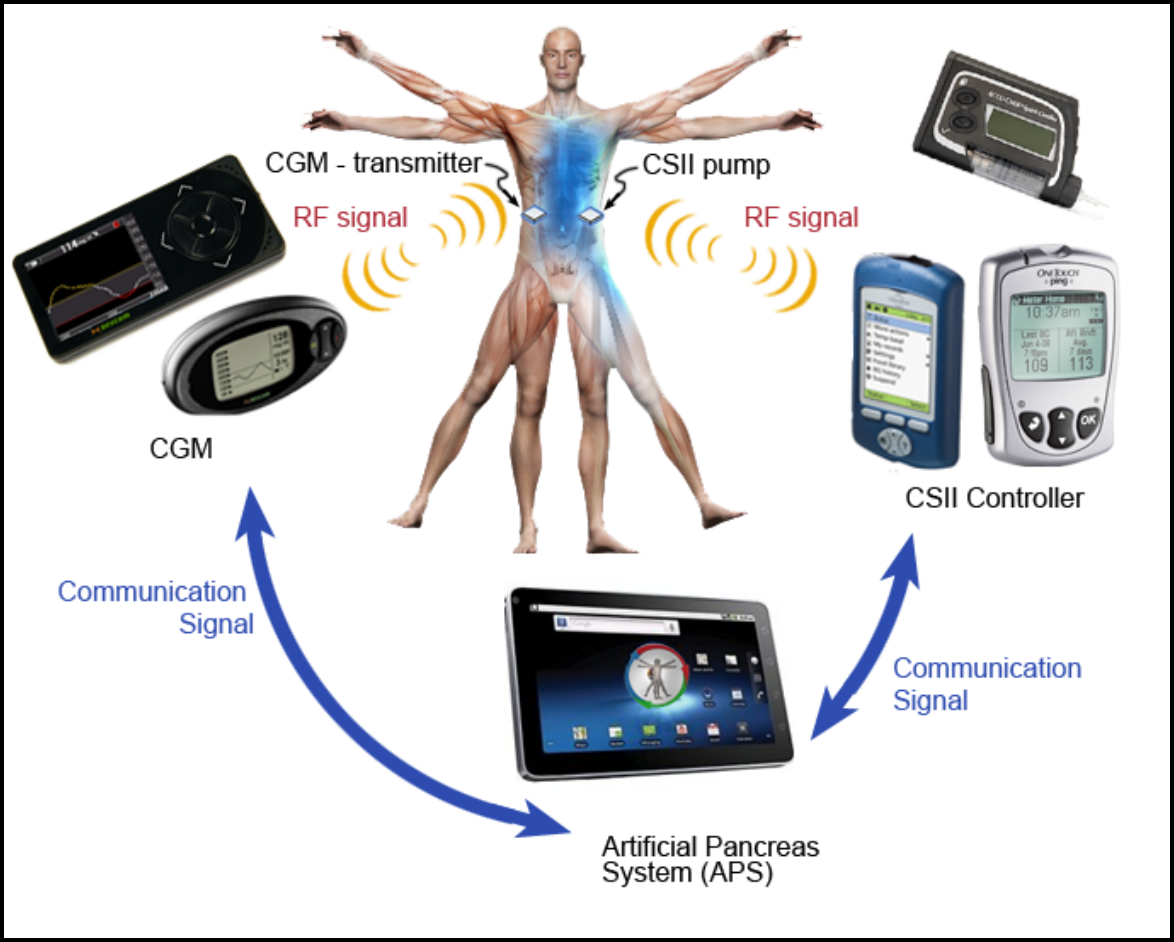
Control Sensor:
Continuous Glucose Measurement (CGM)

http://www.diabetesmanager.pbworks.com

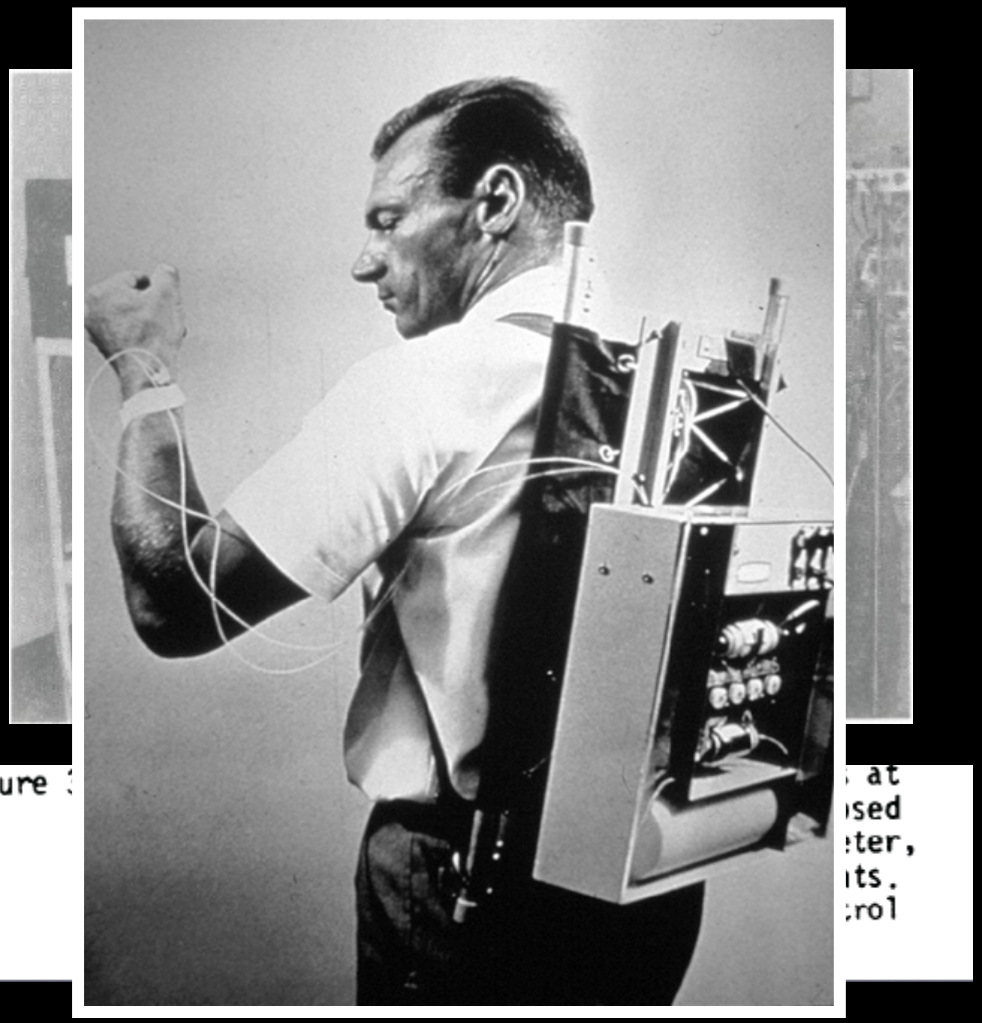




Control Feedback Loop



Artificial Pancreas circa 1960s/1970s



Static control law

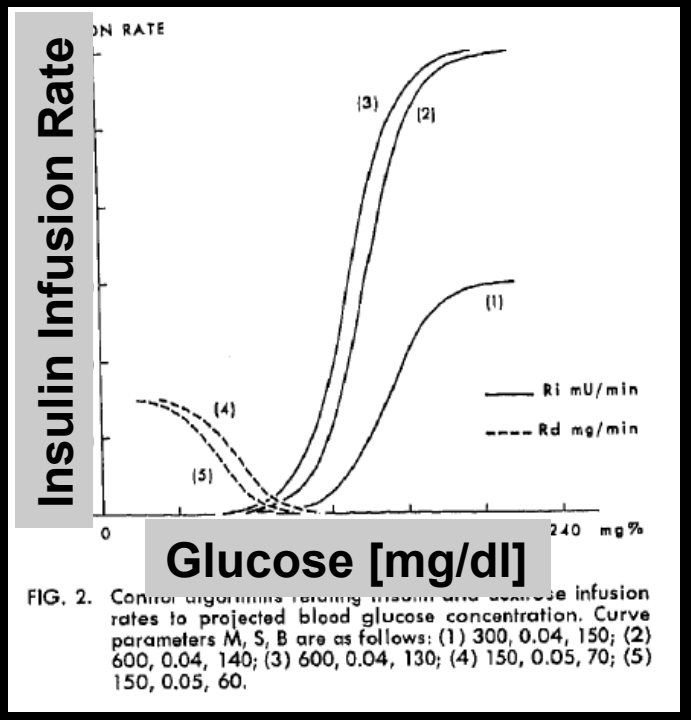


FIG. 2. Control algorithms relating insulin and glucose infusion rates to projected blood glucose concentration. Curve parameters M, S, B are as follows: (1) 300, 0.04, 150; (2) 600, 0.04, 140; (3) 600, 0.04, 130; (4) 150, 0.05, 70; (5) 150, 0.05, 60.

[Albisser et al., 1974]

Artificial Pancreas Today

NEWSFOCUS

Rest easy. An artificial pancreas will protect diabetics from low blood sugar while sleeping.

MEDICINE

A Pancreas in a Box

Sophisticated sensors, insulin pumps, and algorithms may help give type 1 diabetics a more normal life while researchers work on a cure

One morning last April, a woman named Jane checked out after an overnight stay in Addenbrooke's Hospital in Cambridge, U.K. She had spent 24 hours connected by tubes to several medical devices—mostly bored, she says, but also "mildly apprehensive." Now, she was taking them home to do something she hadn't done for 3 decades, something that she and the rest of the world's 30 million type 1 diabetics are never able to do: forget about her diabetes.

The devices—an insulin pump, a blood glucose sensor, and a computer about the size of a paperback book—make up a prototype of what researchers call an artificial pancreas. Together, they replicate the function of the pancreas that is lacking in diabetics: producing insulin in response to rises in blood glucose level. Groups in Europe, the United States, and elsewhere are now testing such systems in small groups of patients, hoping to show that the technology can work efficiently and safely. If so, it could transform the lives of diabetics, improving their health and allowing them something closer to an ordinary life. After controlling her diabetes with blood tests and injections for most of her life, having an artificial pancreas "would be magical," Jane says.

With its tubes and needles and gadgets, an artificial pancreas is not an elegant solution to the problem of diabetes. But researchers say it could provide a valuable stopgap until effective biological treatments—or even cures—come along. The principle is simple: Connect a commercially available glucose sensor to a commercially available insulin pump via a computer programmed to interpret the sensor readings and decide how much of the drug is needed. But implementing it has turned out to be far from straightforward. Controlling the level of sugar in the blood from outside the body is fiendishly difficult because sensors are slow and error-prone, while injected insulin can take hours to have an effect and overdoses can be fatal. For a person with diabetes, used to calculating insulin doses multiple times every day and dealing with the consequences, handing over that responsibility to a computer is daunting. Patients may be clamoring for such a solution, but researchers will have to convince them that it is safe.

Glucose, ingested in the form of sugar and other carbohydrates, is the body's energy source. But without the hormone insulin to help glucose out of the bloodstream and into cells, muscle and brain can't consume it, and liver and fat tissue can't store it for later use. Type 1 diabetics, whose condition develops early in life, lack insulin because their own immune system has attacked insulin-producing cells in their pancreas known as β cells. (Another form of diabetes, type 2, usually affects older people and results from insensitivity to insulin rather than a lack of it.)

Before the discovery of insulin in the early 1920s, type 1 diabetics would simply wither away, fall into a coma, and die within months or years. In the developed world at least, today's diabetics (including the writer of this article) can live a relatively normal life—although one dominated by a never-ending round of blood sugar tests, usually achieved with a finger prick to draw blood and an electronic meter, insulin injections, and meals carefully weighed to estimate how much carbohydrate is being eaten.

The consequences of getting it wrong can be severe. Give slightly too much insulin and glucose in the blood drops to low levels. Starved of fuel, the brain first shows symptoms similar to drunkenness, followed by unconsciousness and even death. Allow sugar levels to get too high and the syrupy blood can damage delicate blood vessels, leading to long-term complications that include heart disease, blindness, kidney failure, and limb amputation. Completely uncontrolled blood sugar leads to a coma and a trip to the hospital by ambulance, which is how many type 1 diabetics find out that they have the disease. So living with diabetes is a continual balancing act: trying to keep blood sugar levels close to those of a normal person using sporadic and erratic information (finger-prick tests) and inadequate tools (injected insulin).

"We're trying to do this invisibly and automatically. But we need faster insulin and we need faster [sensors]."

—FRANK DOYLE, UC SANTA BARBARA

Researchers worldwide are working on biological

Science, January 2014

News & Analysis

Medical News & Perspectives

Fully Automated Artificial Pancreas Finally Within Reach

Tracy Hampton, PhD

Even with increasingly effective treatments and glucose monitors, most individuals with type 1 diabetes still cannot achieve recommended glucose control goals. Many experts believe that the best near-term solution for patients will be a system that can independently restore insulin and glucose balance.

"Artificial pancreas systems will be the most revolutionary advance in diabetes care since the discovery of insulin," said Aaron Kowalski, PhD, a vice president at the Juvenile Diabetes Research Foundation (JDRF), a global organization that funds type 1 diabetes research.

An artificial pancreas is based on a simple concept: an automated system to dispense insulin and other pancreatic hormones based on real-time changes in blood sugar levels. But researchers face numerous challenges in turning the concept into reality.

"Some of us have been working in this field for more than 20 years, and these days most of us would say that a true automated device is maybe 3 to 5 years in the future," said Frank Doyle, PhD, chair of the chemical engineering department at the University of California, Santa Barbara. "But there will be evolution and continual improvement, as with any piece of technology."

Stages of Development

According to the US Food and Drug Administration (FDA), an artificial pancreas can be entirely mechanical, entirely biological (such as islet transplantation), or a mechanical-biological hybrid. "I don't think there is only one definition of an artificial pancreas—and furthermore, parts of the artificial pancreas are already showing up in devices in the market," said Doyle.

A first-generation model of an artificial pancreas system is now available in many countries. Last fall, the FDA approved an insulin delivery system made by Medtronic that can automatically stop insulin release when sensor glucose values reach a preset level and when the patient does not respond to a low-glucose alarm. The company says that the device's sensor detects up to 93% of hypoglycemia episodes when predictive and threshold alerts are on. Still, the system does not mimic the full biological function of the pancreas, and it requires the patient to take actions such as eating or drinking to correct low glucose levels.

Based on a road map created by JDRF, the Medtronic device is at step 1 of a 6-step process toward generating an artificial pancreas (http://bit.ly/1jYiknJ). Each step represents incremental advances, beginning with devices that shut off insulin delivery to prevent low blood sugar and progressing ultimately to a fully automated system that maintains blood glucose at a target level without the need to manually take insulin for meals or adjust for exercise. First-generation products focus on preventing unsafe blood sugar levels and aim to maintain blood sugar between approximately 70 and 180 mg/dL.

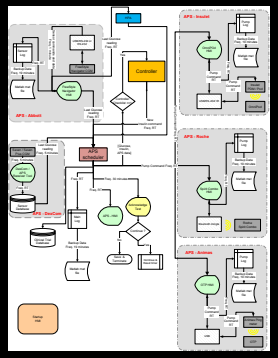
While a step 1 product like Medtronic's continuously monitors glucose levels and suspends insulin delivery when such levels become low, a step 2 product can predict when a user will reach the bottom threshold and automatically suspend or reduce insulin delivery before reaching that point. Such a device, called a predictive low glucose suspend system, can be created by adding controlling software to currently marketed pumps and sensors. Medtronic has developed a version that is expected to be approved in Europe first. "Device makers have to go through a different review process for each country where they plan to offer their products," said Kowalski. "The timing of each [review] for a single product is different, so there are often lags in availability from one country to the next."

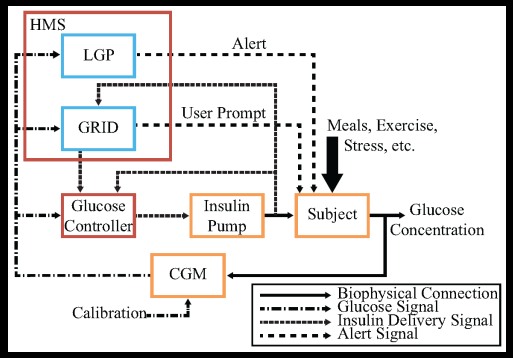
A step 3 product, called a hypoglycemia/hyperglycemia minimizer, prevents unsafe high blood sugar levels as well as low ones. Step 4, a hybrid closed-loop product, adjusts for both upper and lower thresholds and targets a specific blood sugar level instead of a range, while step 5 eliminates manual administration of insulin before meals. Finally, a step 6 product adds the ability to dispense additional hormonal drugs to more closely mimic the way the body maintains blood sugar levels. For example, glucagon may be administered to counter the effects of insulin and increase blood glucose levels if they become too low. This is crucial because hypoglycemia can cause seizures, coma, or death, and it can strike at

Howard Zisser, MD, and Frank Doyle, PhD, of the department of chemical engineering at the University of California, Santa Barbara, monitor the performance of an artificial pancreas system during a clinical trial.

JAMA, May 2014

Control Design





$$J_{zone}(u) = \sum_{i=1}^{n_p} Q\left(y_z(k+i\,|\,k) - r(k+i)\right)^2 + \sum_{i=1}^{n_u} Ru(k+i-1)^2$$

$$y_z(k+i\,|\,k) = \begin{cases} y(k+i\,|\,k) - y_{ub} & if\ y(k+i\,|\,k) > y_{ub} \\ 0 & if\ y_{lb} \le y(k+i\,|\,k) \le y_{ub} \\ y_{lb} - y(k+i\,|\,k) & if\ y(k+i\,|\,k) < y_{lb} \end{cases}$$

$$x(k+1\,|\,k) = Ax(k\,|\,k) + B^u u(k) + B^u u(k) + \hat{d}_1(k)$$

$$y(k+1\,|\,k) = Cx(k+1\,|\,k) + \hat{d}_2(k)$$

$$u_{\min}^{pump} \le u(k) \le u_{\max}^{pump}$$

$$\Delta u_{\min}^{pump} \le u(k) - u(k-1) \le \Delta u_{\max}^{pump}$$

$$u(k) \le u_{\max}^{safety} = F_{PK}\left(u(k-1), \ldots, u(k-h)\right)$$

Challenges for Feedback Control

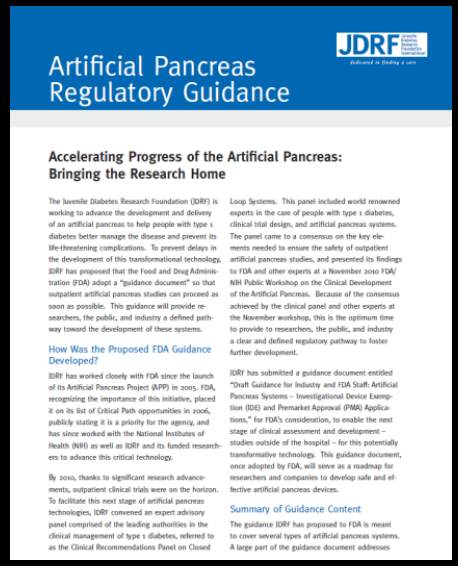
- CGM sensors lag blood glucose by 5-15 mins [sensor lag]
- CGM systems have an average absolute error of 10-15% (95% confidence limit of ± 30-40%) [sensor accuracy]
- Insulin (rapid acting analogs) have a lag of 60-90 mins in their peak action after subcutaneous administration [actuator lag]
- Natural response exploits neurally mediated cephalic phase [no feedforward]
- Time-varying nature of human body (stress, activity, etc.)
  - Insulin absorption from subcutaneous sites has a variability of 20-35% (95% confidence limit of ± 50-87%)
  - Insulin sensitivity may vary as much as 50% during the day

→ Overall errors related to CGM and insulin absorption is 24-37% with a lag of 70-110 mins

Regulatory Process

- FDA is playing an active role in supporting the development of the artificial pancreas
  - Critical Path Initiative
  - Convened multiple workshops [July 2008, Nov. 2010]

- Clinical studies (incl. academic) require Investigational Device Exemption
  - ***Clinical studies using investigational devices, that have the potential for significant risk***
  - Elements
    - Protocol
    - Risk analysis
    - Monitoring procedures
    - IRB review



JDRF

Artificial Pancreas Regulatory Guidance

Accelerating Progress of the Artificial Pancreas: Bringing the Research Home

The Juvenile Diabetes Research Foundation (JDRF) is working to advance the development and delivery of an artificial pancreas to help people with type 1 diabetes better manage the disease and prevent its life-threatening complications. To prevent delays in the development of this transformational technology, JDRF has proposed that the Food and Drug Administration (FDA) adopt a "guidance document" so that outpatient artificial pancreas studies can proceed as soon as possible. This guidance will provide researchers, the public, and industry a defined pathway toward the development of these systems.

How Was the Proposed FDA Guidance Developed?

JDRF has worked closely with FDA since the launch of its Artificial Pancreas Project (APP) in 2005. FDA, recognizing the importance of this initiative, placed it on its list of Critical Path opportunities in 2006, publicly stating it is a priority for the agency, and has since worked with the National Institutes of Health (NIH) as well as JDRF and its funded researchers to advance this critical technology.

By 2010, thanks to significant research advancements, outpatient clinical trials were on the horizon. To facilitate this next stage of artificial pancreas technologies, JDRF convened an expert advisory panel comprised of the leading authorities in the clinical management of type 1 diabetes, referred to as the Clinical Recommendations Panel on Closed Loop Systems. This panel included world renowned experts in the care of people with type 1 diabetes, clinical trial design, and artificial pancreas systems. The panel came to a consensus on the key elements needed to ensure the safety of outpatient artificial pancreas studies, and presented its findings to FDA and other experts at a November 2010 FDA/NIH Public Workshop on the Clinical Development of the Artificial Pancreas. Because of the consensus achieved by the clinical panel and other experts at the November workshop, this is the optimum time to provide to researchers, the public, and industry a clear and defined regulatory pathway to foster further development.

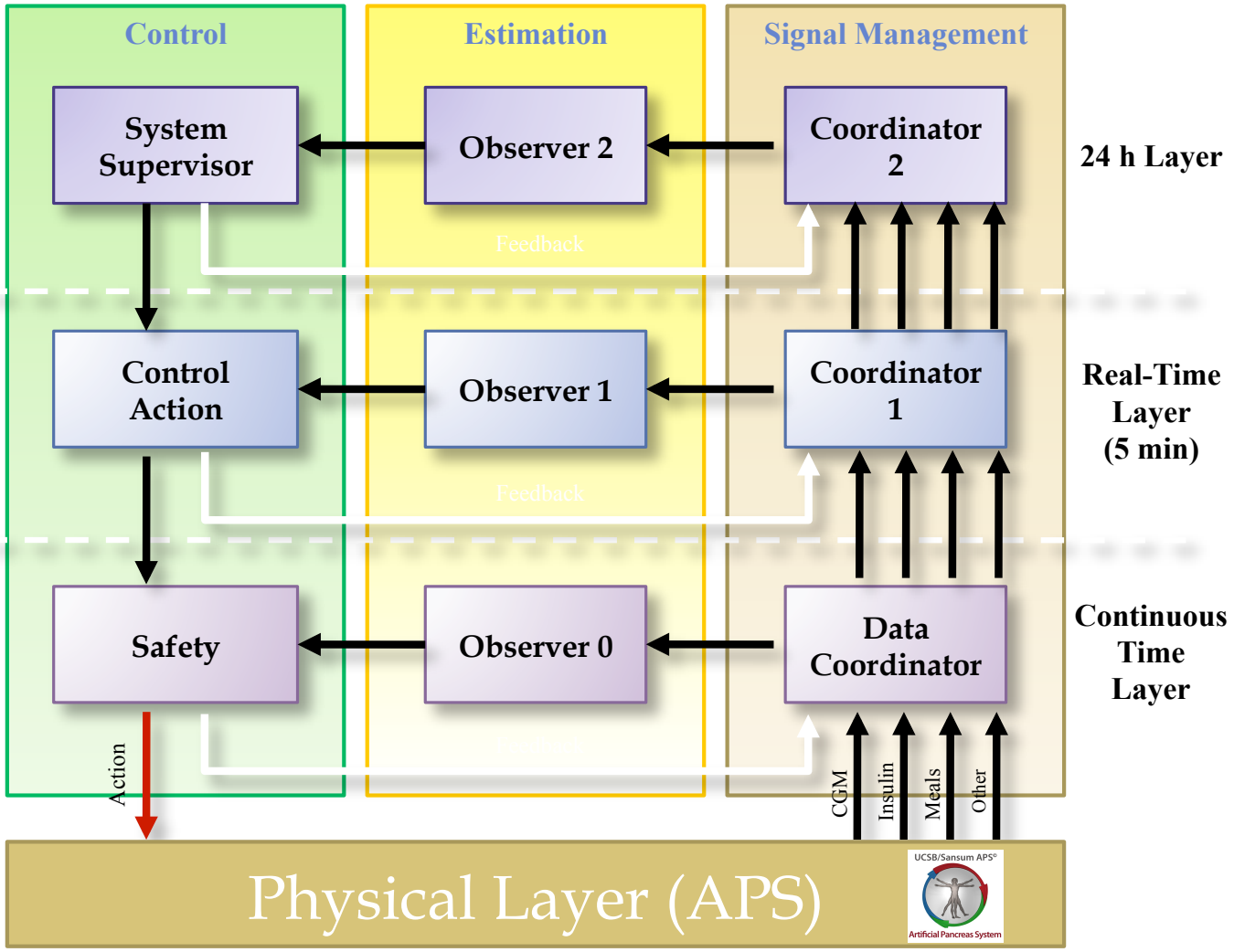
JDRF has submitted a guidance document entitled "Draft Guidance for Industry and FDA Staff: Artificial Pancreas Systems – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications," for FDA's consideration, to enable the next stage of clinical assessment and development – studies outside of the hospital – for this potentially transformative technology. This guidance document, once adopted by FDA, will serve as a roadmap for researchers and companies to develop safe and effective artificial pancreas devices.

Summary of Guidance Content

The guidance JDRF has proposed to FDA is meant to cover several types of artificial pancreas systems. A large part of the guidance document addresses

Modular Control Architecture

[Dassau *et al*., 2008; Kovatchev *et al*., 2009; Patek *et al*., 2012]

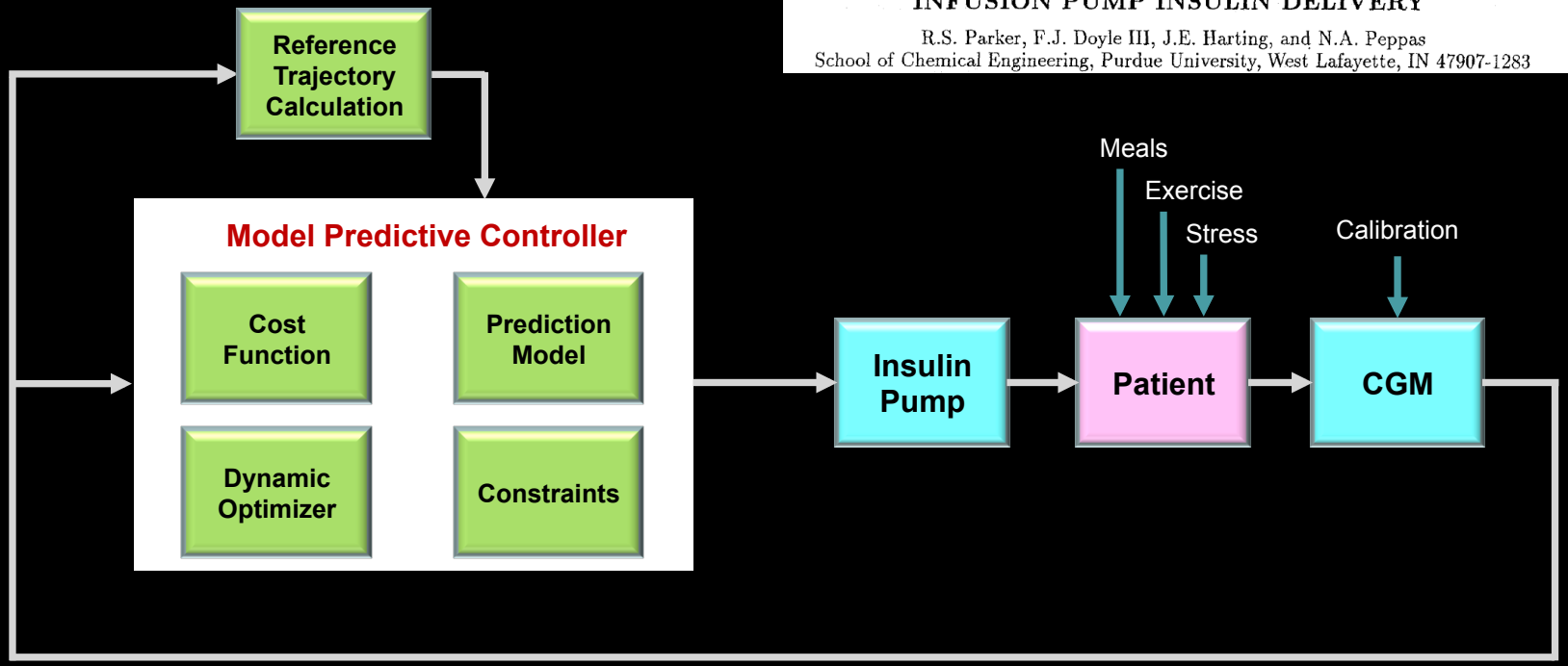


Core Algorithm Summary

18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Amsterdam 1996
6.3.4: Physiological Modelling - Glucose

MODEL PREDICTIVE CONTROL FOR INFUSION PUMP INSULIN DELIVERY

R.S. Parker, F.J. Doyle III, J.E. Harting, and N.A. Peppas
School of Chemical Engineering, Purdue University, West Lafayette, IN 47907-1283



Core Algorithm Summary

18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Amsterdam 1996
6.3.4: Physiological Modelling - Glucose

MODEL PREDICTIVE CONTROL FOR INFUSION PUMP INSULIN DELIVERY

R.S. Parker, F.J. Doyle III, J.E. Harting, and N.A. Peppas
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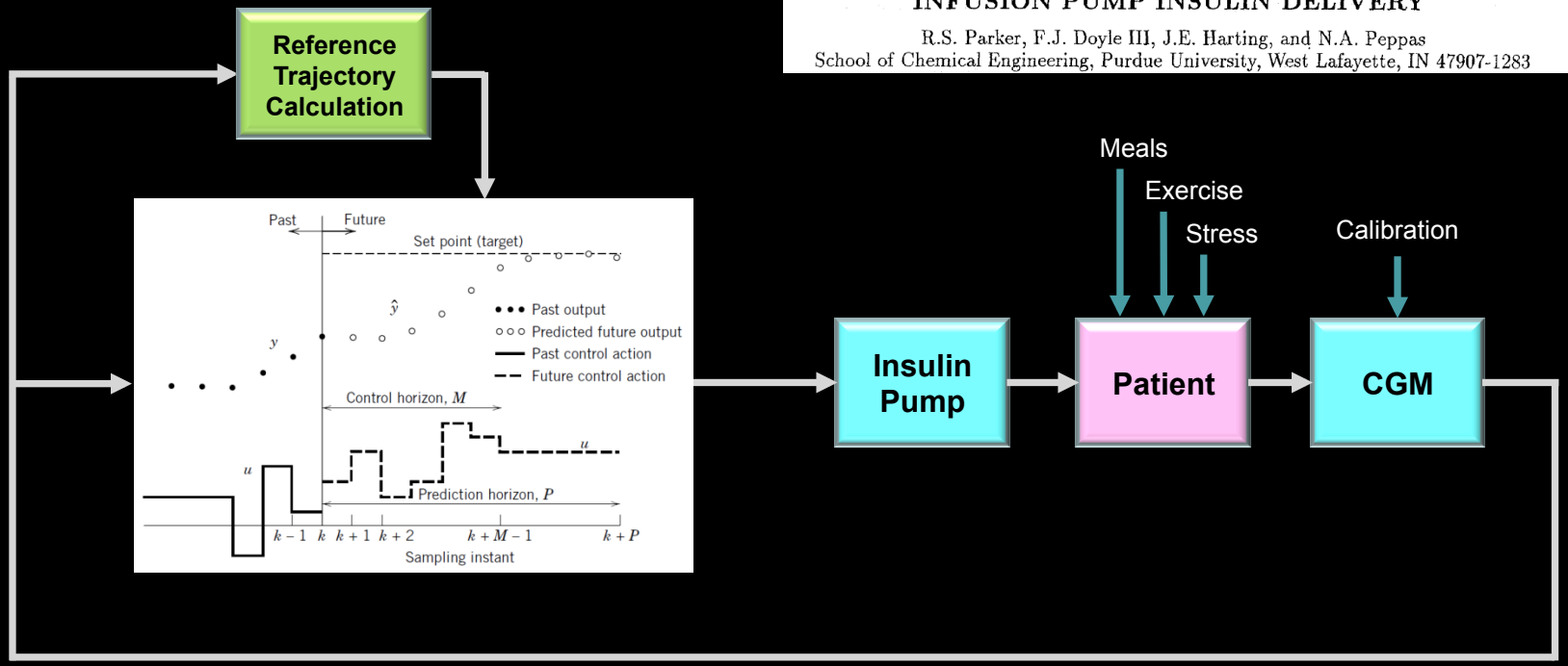


System (Patient) Identification

- Wide variety of models employed in theoretical studies:
  - Pharmacokinetic/pharmacodynamic [Bergman et al., 1981; Cobelli et al., 1995; Kovatchev et al., 2008]
  - Subspace identification [Ståhl and Johansson, 2008; Lee et al., 2009]
  - Time series (ARX, ARMA, etc.) [Parker et al., 1999; Desai et al., 2002; Finan et al., 2006; Eren-Oruklu et al., 2009]
  - Transfer functions [Percival et al., 2010]
  - Volterra models [Florian and Parker, 2002; Mitsis et al., 2009]
  - Artificial neural networks [Trajanoski et al., 1997]
- Limitations for clinical testing:
  - Short patient records
  - Limited excitation for inputs (incl. cancellation/identifiability)
  - Sensor accuracy
- Current work:
  - Personalized *a priori* patient models

Personalized *a priori* Patient Models

[van Heusden et al., *IEEE Trans. Biomed. Eng.*, 2012]

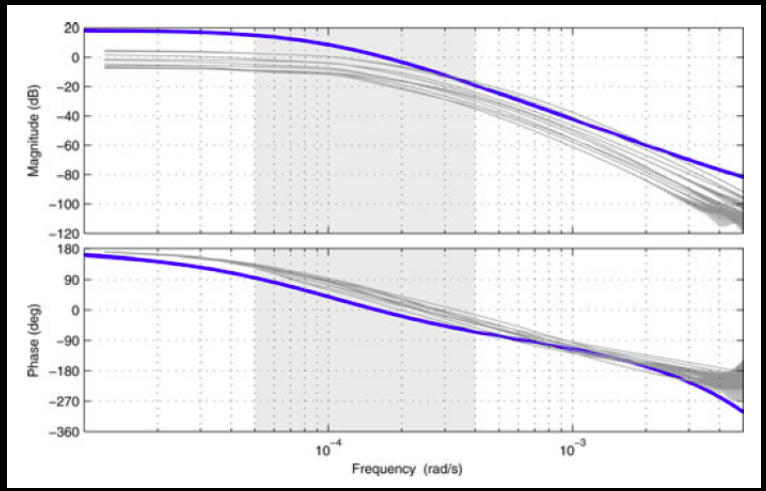
$$\frac{G_i(z)}{I_D(z)} = F_s K_i \frac{Cz^{-3}}{(1-0.98z^{-1})(1-0.965z^{-1})(1-0.965z^{-1})},$$

K_i **Individual gain based on the correction factor**

F_s **Safety factor**

Universal Dynamics

- A parametric model is estimated using the output-error approach from the UVa/Padova FDA accepted metabolic simulator
- The safety factor leads to (further) underestimation of the system phase and overestimation of system gain

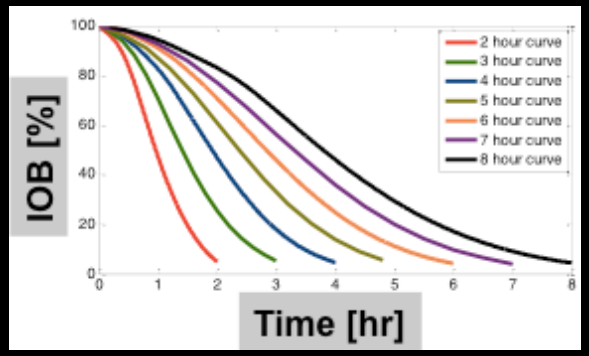


Designing MPC Constraints for Patient Safety

[Ellingsen et al., *JDST*, 2009; Gondhalekar, *et al.*, *DTM*, 2012]

Hard constraints on Insulin

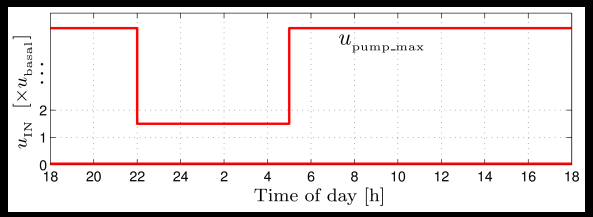
- Insulin on Board (IOB) Curves
- Periodic (diurnal) Pump Constraints



$$x_{IOB}(k) = \sum_{i=1}^{h} f_i \cdot u(k-i)$$

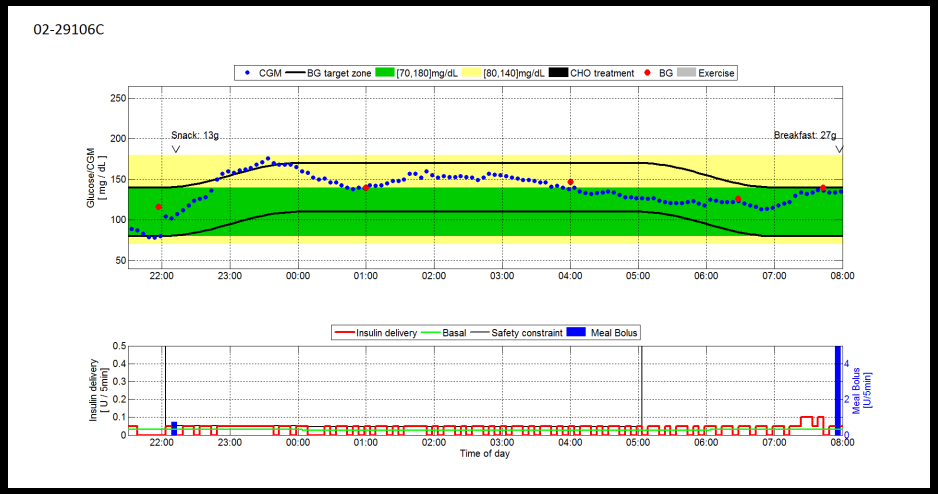
$$u_{\max}^{safety} = \max\left(0, K_{CF} \bullet y_m(k) + K_{IC} \bullet d_m(k) - x_{IOB}(k)\right)$$

$$u(k) \le u_{\max}^{safety} = F_{PK}\left(u(k-1), \mathrm{K}, u(k-h)\right)$$



"Soft" constraints on Glucose

- Zone MPC
- Periodic (diurnal) Zones



Multi-Parametric Programming Implementation

[Bemporad et al., *Aut.*, 2002; Pistikopoulos et al., *Comp. Chem. Eng.*, 2002; Dua et al., *IEEE TBME*, 2006]

- Motivation:
  - Early studies focused on computational limitations
  - Current research motivated by regulatory review
- Transform QP-MPC into mpMPC

$$\min_{U} \quad \tfrac{1}{2} U^T H U + x_t^T F U + \tfrac{1}{2} x_t^T Y x_t$$

$$s.t. \quad GU \le W + Ex_t$$

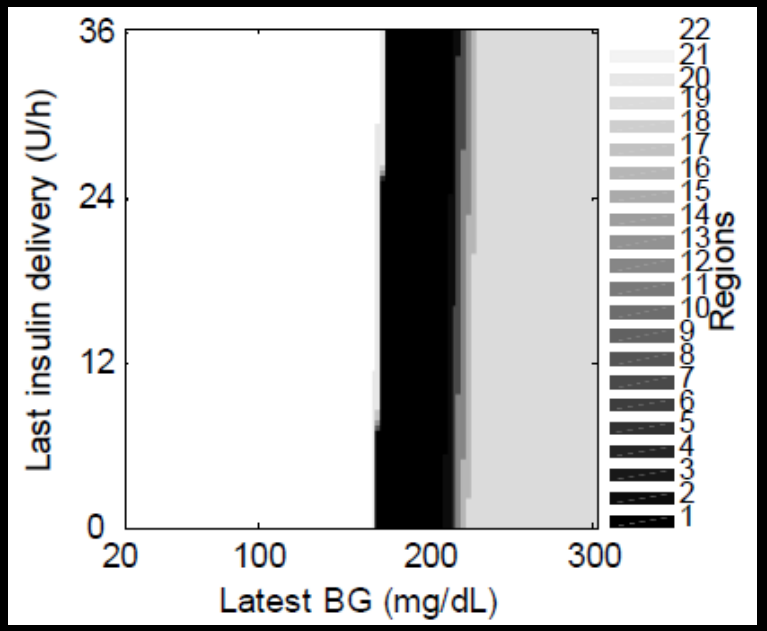
$$\Downarrow$$

$$V_z(x) = \min_{z} \quad \tfrac{1}{2} z^T H z$$

$$s.t. \quad Gz \le W + Sx_t$$

$$\Downarrow$$

$$U = z - H^{-1} F^T x_t$$



- Formulation for Artificial Pancreas
  - ARX model (past measurements)
  - Low dimensional model+constraints
    - **~200-300 regions**

Summary – Core Algorithm

- LTI model: $x_{i+1} = Ax_i + Bu_i \quad , \quad y_i = Cx_i$
- Zone boundaries: $\check{z}_i \quad , \quad \hat{z}_i$ (want $y_i \in [\check{z}_i, \hat{z}_i]$)
- Input constraints: $u_i \in \mathbb{U}_i$

Zone MPC problem: Determine

$$\{\mathbf{u}_0^*, \ldots, \mathbf{u}_{N_\mathrm{u}-1}^*\} := \underset{\{\mathbf{u}_0, \ldots, \mathbf{u}_{N_\mathrm{u}-1}\}}{\arg\min} \sum_{k=1}^{N_\mathrm{y}} \mathbf{z}_k^2 + R \sum_{k=0}^{N_\mathrm{u}-1} \mathbf{u}_k^2$$

subject to

$$\begin{aligned}
\mathbf{x}_0 &:= x_i \\
\mathbf{x}_{k+1} &:= A\mathbf{x}_k + B\mathbf{u}_k && \forall k \in \mathbb{Z}_0^{N_\mathrm{y}-1} \\
\mathbf{y}_k &:= C\mathbf{x}_k && \forall k \in \mathbb{Z}_0^{N_\mathrm{y}-1} \\
\mathbf{z}_k &:= \arg\min_\alpha \left\{ \alpha^2 \mid \mathbf{y}_k - \alpha \in [\, \check{z}_{i+k},\ \hat{z}_{i+k}] \right\} && \forall k \in \mathbb{Z}_0^{N_\mathrm{y}-1} \\
\mathbf{u}_k &\in \mathbb{U}_{i+k} && \forall k \in \mathbb{Z}_0^{N_\mathrm{u}-1} \\
\mathbf{u}_k &:= 0 && \forall k \in \mathbb{Z}_{N_\mathrm{u}}^{N_\mathrm{y}-1}
\end{aligned}$$

MPC law: $u_i = \kappa(x_i, i) := \mathbf{u}_0^*$

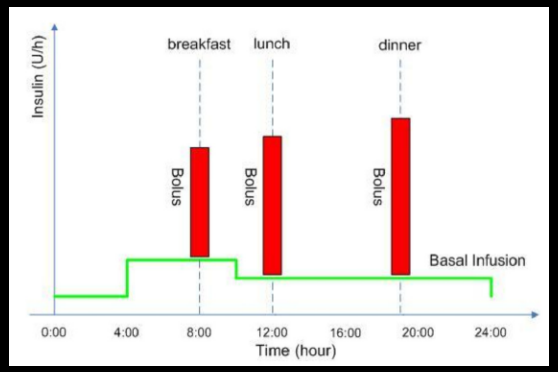
Adaptation: Iterative Learning Control

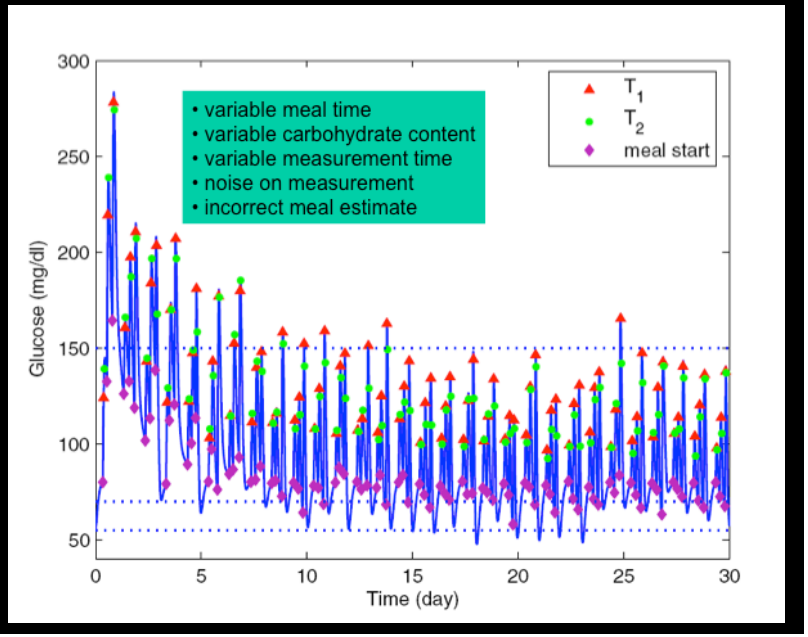
[Doyle III *et al*., 2001; Zisser *et al*., 2005; Owens *et al*., 2006; Wang *et al*., 2009; Wang *et al*., 2010]

- Common in 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: Exploit recurrent cycles (meals, basal profiles, etc.)**

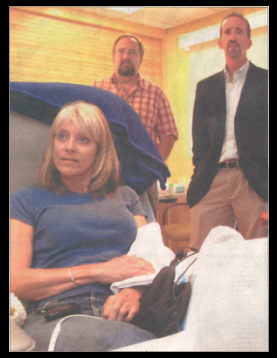
$$T(k+1) = T(k) + K_T \min(0, G^r_{\max} - G_{\max}(k))$$
$$Q(k+1) = Q(k) + K_Q \max(0, G^r_{\min} - G_{\min}(k))$$



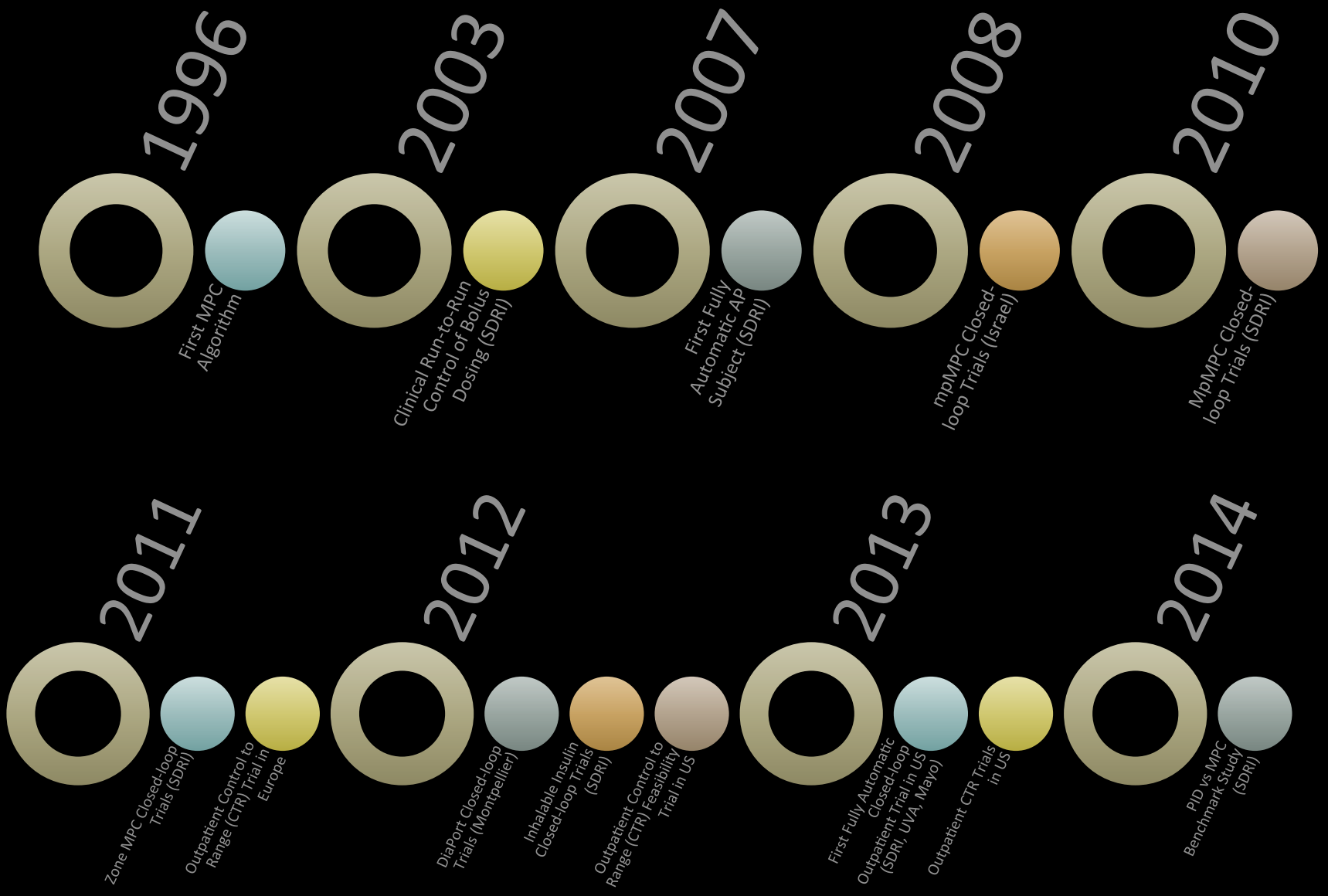


Clinical Testing



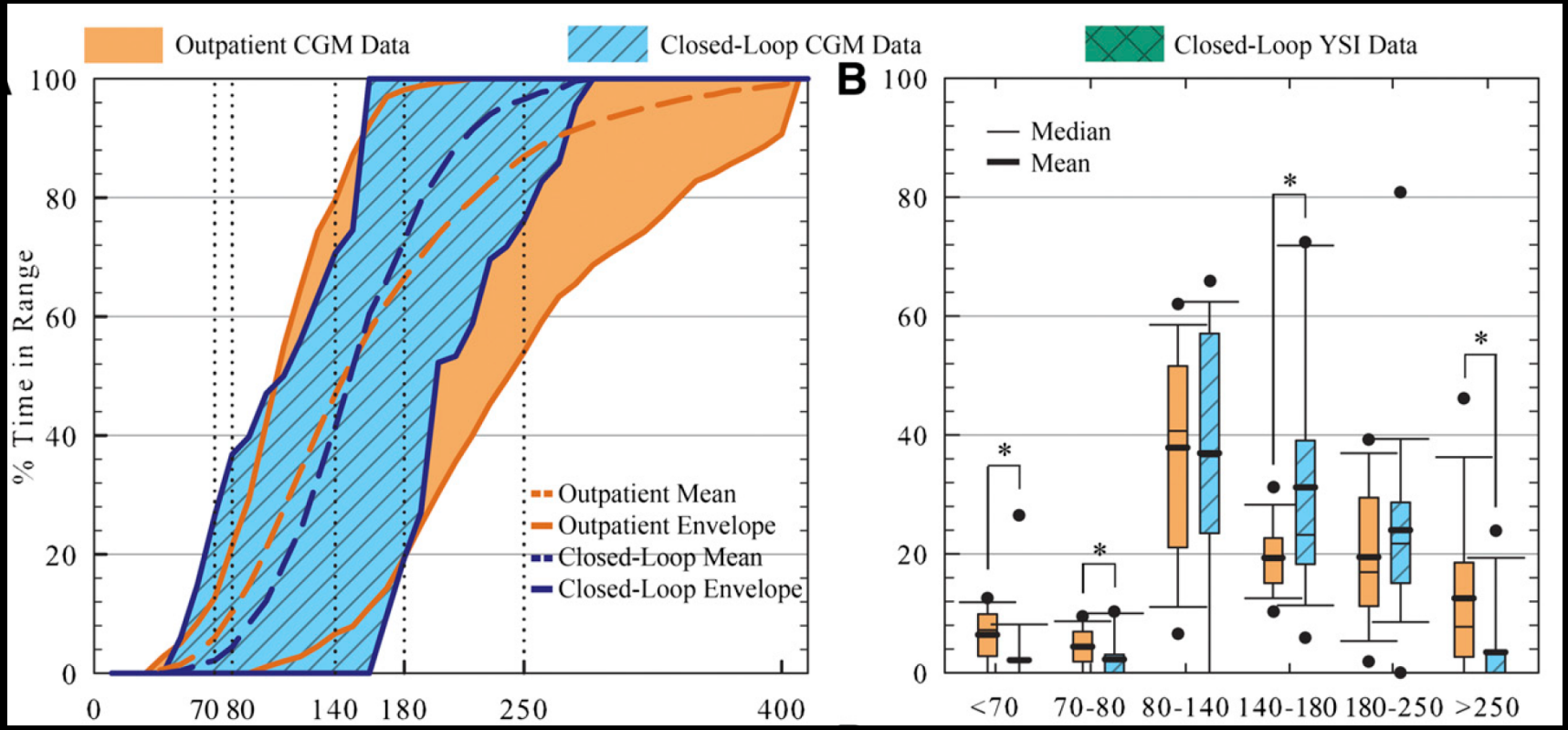



AP Timeline @ UCSB



Control to Target Trial [*Israel & Santa Barbara*]

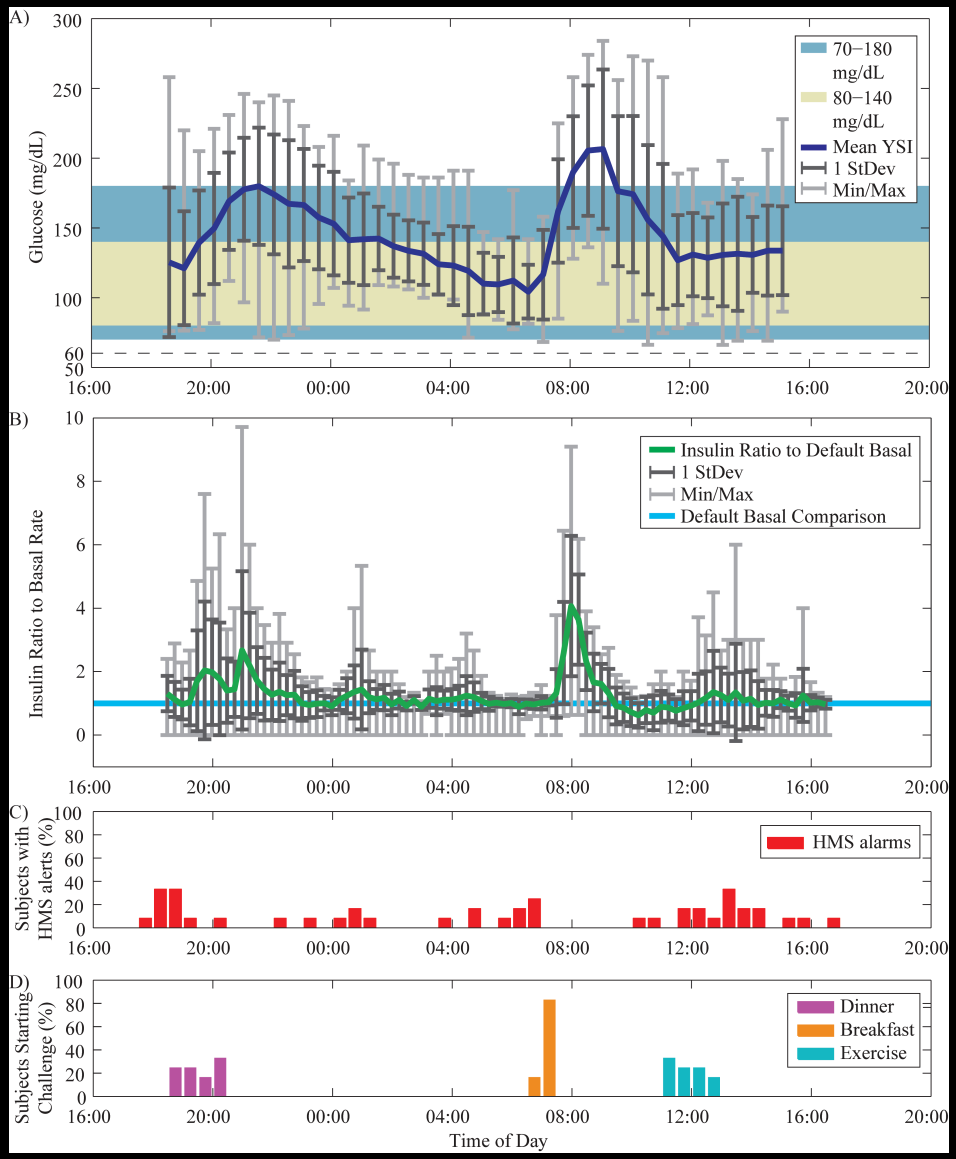
mpMPC, IOB constraints, Tailored ARX Model

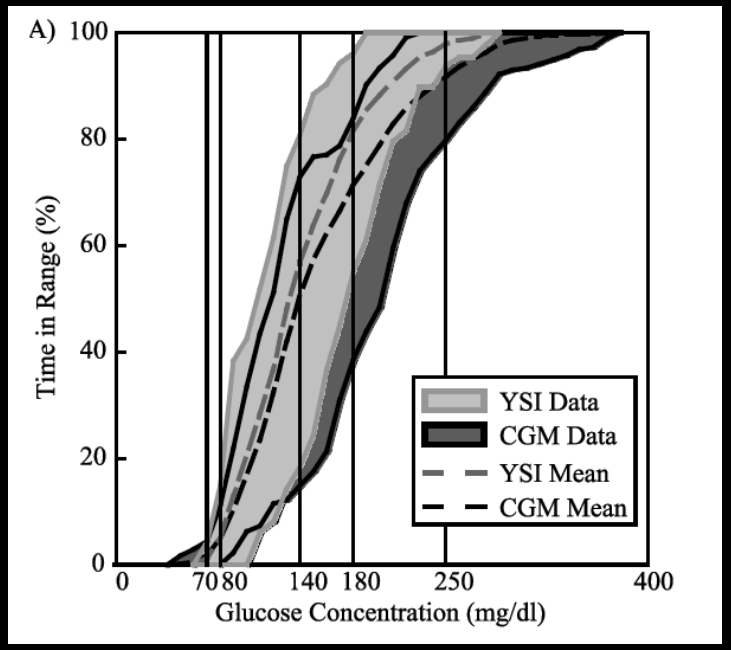


[Dassau et al., *Diabetes Care*, 2013]

Control to Zone Clinical Trial

zone MPC, HMS, IOB constraints, *a priori* Model





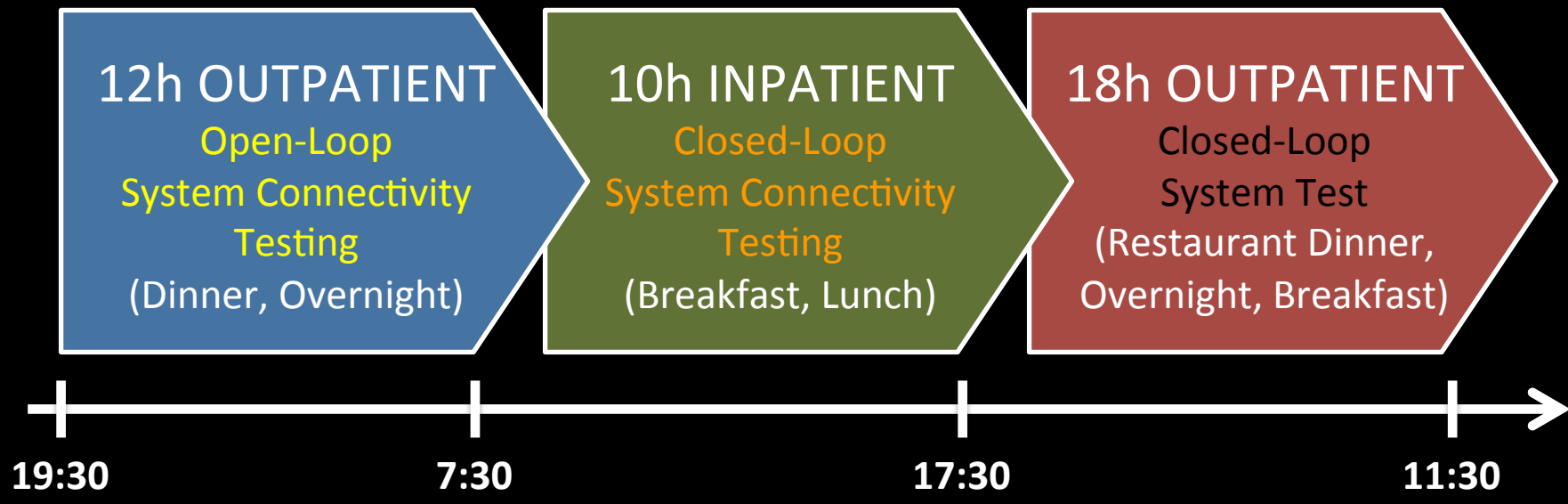
[Harvey et al., *Diab. Tech. Ther.*, 2014]

Getting Outside the Clinic



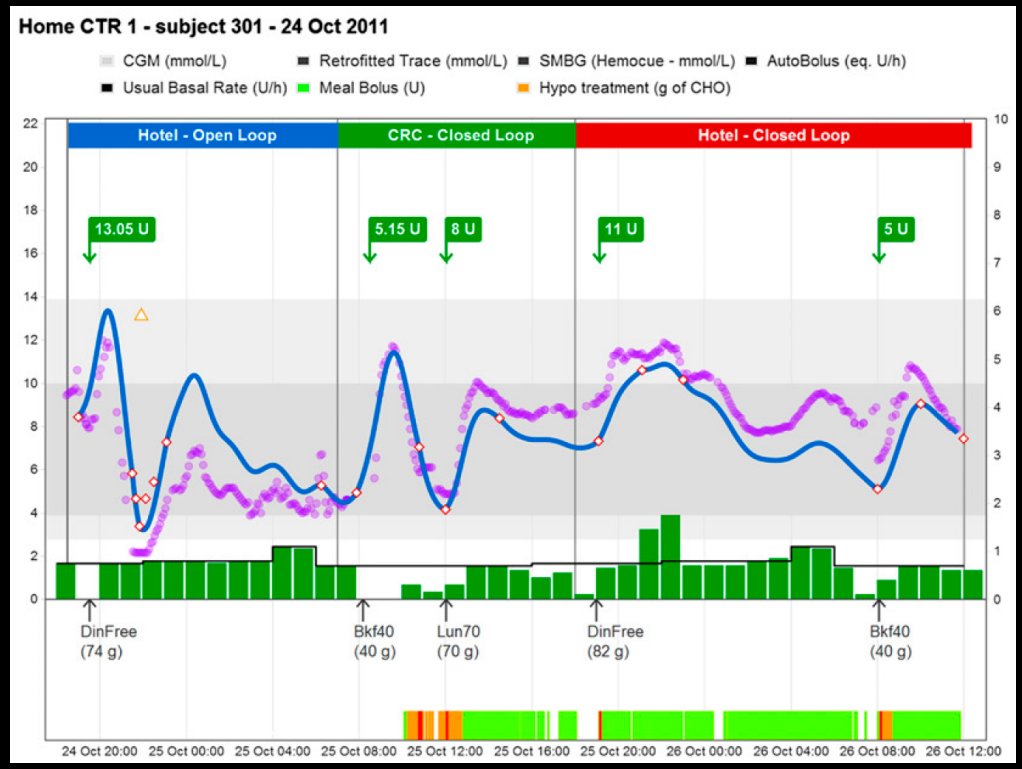

JDRF: First Outpatient Closed-Loop Control Study in Europe

Padova and Montpellier, October 24-26, 2011
(n=1) (n=1)



[Cobelli et al., *Diabetes Care*, 2012]

JDRF: First Outpatient Closed-Loop Control Study in Europe

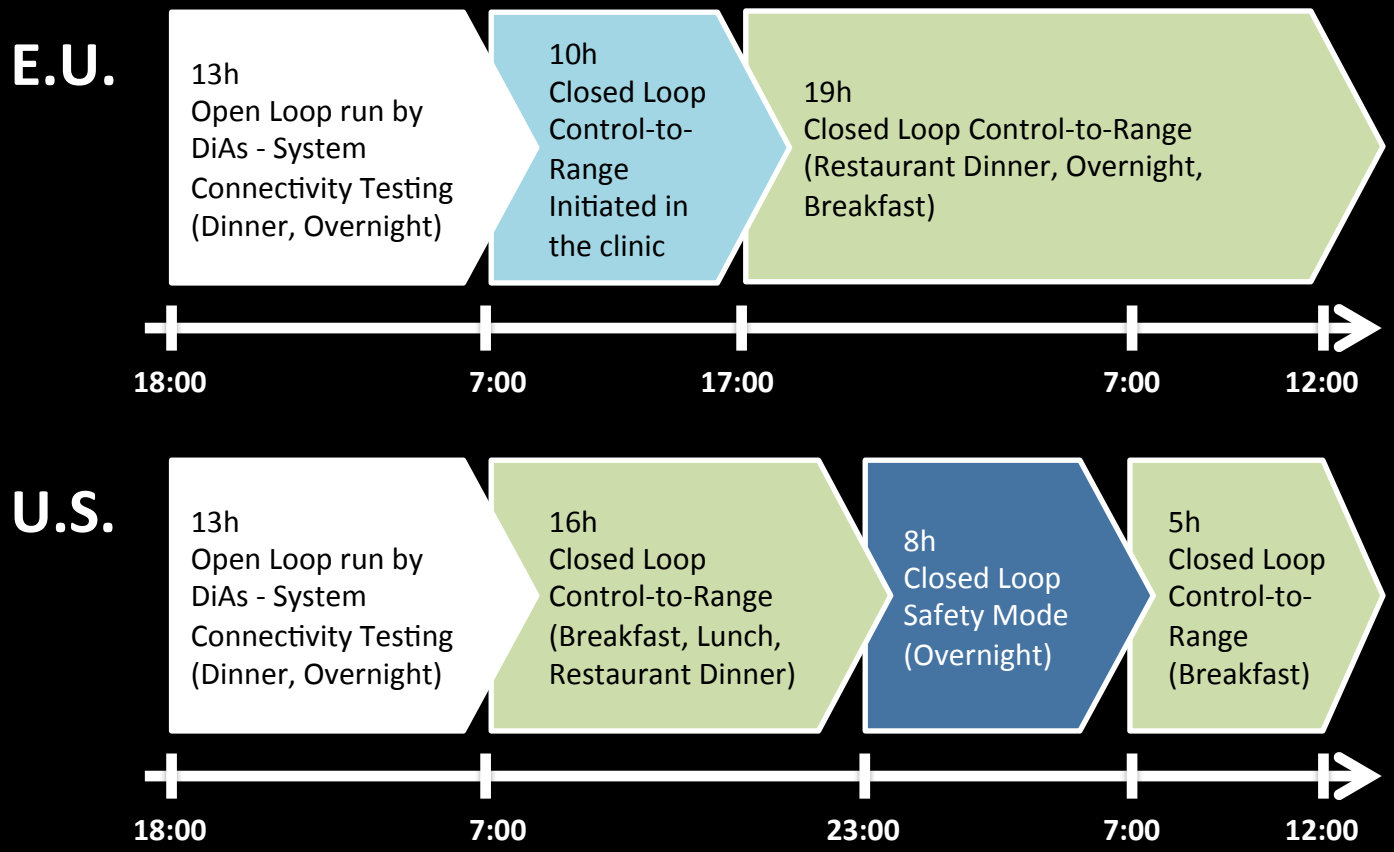


[Cobelli et al., *Diabetes Care*, 2012]

JDRF: Feasibility Study for Outpatient Control in US and Europe

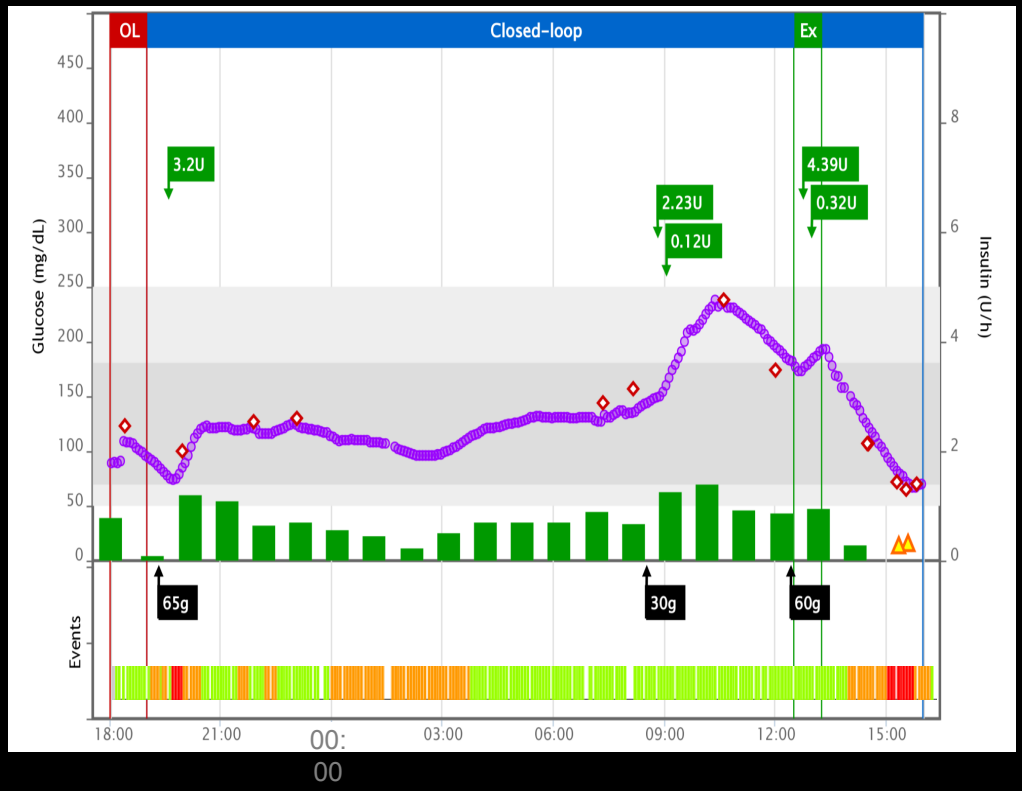
UVA Center for Diabetes Technology
Padova (Italy)
Montpellier (France)
Sansum Diabetes Research Institute / UC Santa Barbara

n = 5 per site



[Kovatchev et al., *Diabetes Care*, 2013]

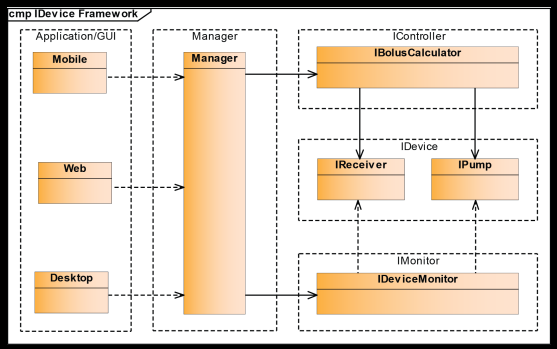
JDRF: Feasibility Study for Outpatient Control in US and Europe



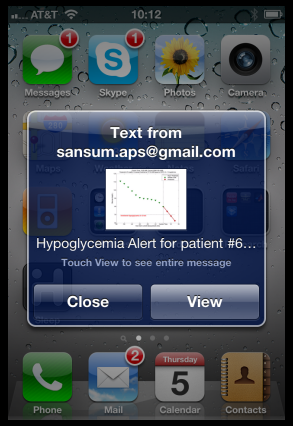
[Kovatchev et al., *Diabetes Care*, 2013]

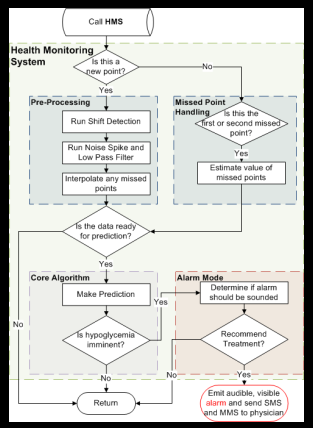
Additional Developments for Outpatient Studies

- Modular APS™ iDevice Framework

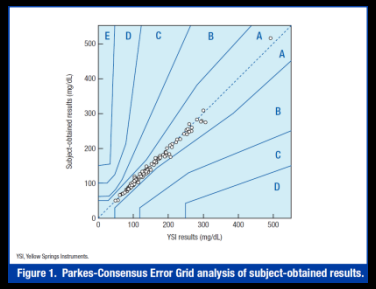


- Health Monitoring Systems (HMS™)



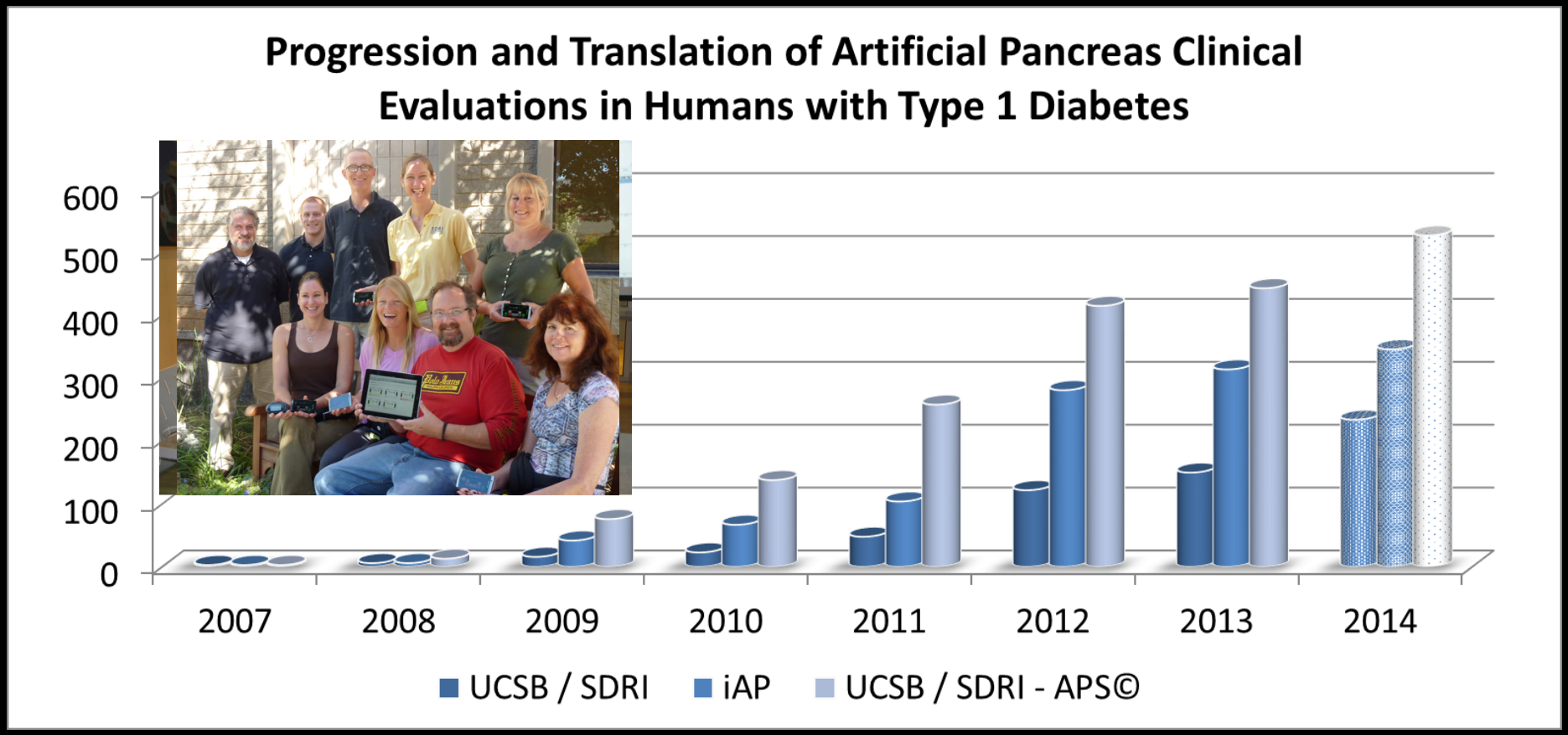


- Reduced measurement requirements
  (IDE approved for TI protocol using new Bayer BG meter)

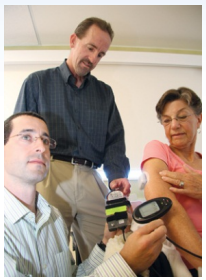


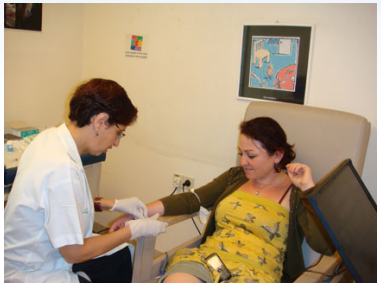
[Bailey et al., ADA, 2012]

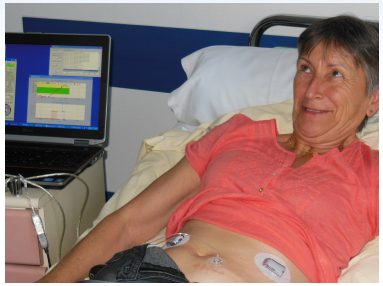
Clinical Trial Summary



Global Clinical Testing of the Artificial Pancreas Around the Globe





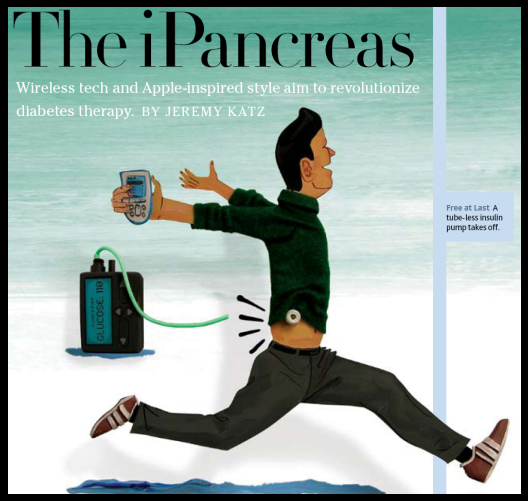


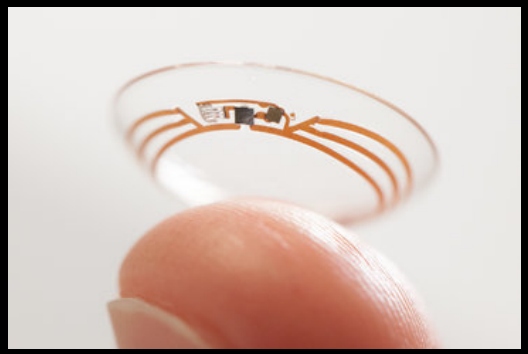
Summary

- **Control engineering has put the artificial pancreas within reach**

- Enabling technologies:
  - (zone) Model Predictive Control
  - Tailored patient models
  - Safety constraints

- Many challenges still remain:
  - Technical
    - State estimation
    - Patient customization
    - Reliable (long-term) sensors (Google lens?)
  - Medical
    - Transport and site issues
    - Patient variability (incl. stress, activity, etc.)
  - Regulatory





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DP3 Consortium: [UVA, Mayo, Padova, SDRI, UCSB]

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