Diabetes: Models, Signals, and Control

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The Diabetes World Epidemic
Millions with Diabetes 2000-2030

Diabetes Prevalence (%) in Persons Aged 35-64:
- <3;
- 3-5;
- 6-8;
- >8;

<table>
<thead>
<tr>
<th>Region</th>
<th>2000</th>
<th>2030</th>
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<tbody>
<tr>
<td>India</td>
<td>31.7</td>
<td>79.4</td>
</tr>
<tr>
<td>China</td>
<td>20.8</td>
<td>42.3</td>
</tr>
<tr>
<td>USA</td>
<td>17.7</td>
<td>30.3</td>
</tr>
</tbody>
</table>

Global
- 366

Americas
- 67 (2000), 33 (2030)

Europe
- 48 (2000), 33 (2030)

Middle East
- 43 (2000), 15 (2030)

Africa
- 18 (2000), 7 (2030)

Asia & Australasia
- 191 (2000), 83 (2030)

(WHO data)
Models

• **Models to Understand/Measure (Minimal)**
  - Whole Body
  - Organ/Tissue

• **Models to Simulate (Maximal)**
  - In Silico Trial
The Glucose-Insulin System

- Production
- Utilization
- Degradation
- Insulin Sensitivity
- B-cell Responsivity

β-CELLS

LIVER

BRAIN

MUSCLE

TISSUES
Glucose Clamp Technique

- Glucose Analyzer
- Insulin Pump
- Glucose Pump
- Computer Algorithm
Dual Clamp Test

**Euglycemic Clamp**
- **insulin sensitivity**

**Hyperglycemic Clamp**
- **B-cell responsivity**

**GLUCOSE**
- Euglycemic Clamp: Stable at around 100 mg/dl.
- Hyperglycemic Clamp: Rises to 250 mg/dl and stabilizes.

**INSULIN**
- Euglycemic Clamp: Increases from baseline to 240 pmol/l.
- Hyperglycemic Clamp: Peaks at 360 pmol/l and stabilizes.

**GLUCOSE INFUSION**
- Euglycemic Clamp: Gradually increases from 0 to 30 mg/kg/min.
- Hyperglycemic Clamp: Begins at 0 and increases to 600 mg/kg/min.

**C-PEPTIDE**
- Euglycemic Clamp: Increases from 0 to 600 pmol/l.
- Hyperglycemic Clamp: Maintains a steady state at 600 pmol/l.

**[min]**
IVGTT Glucose Minimal Model

(Bergman & Cobelli, 1979)

$S_i$: Insulin Sensitivity (liver & periphery)
Young vs Elderly Subjects

N = 59 vs 145 (Basu et al, 2006)

IVGTT

GLUCOSE

INSULIN

C-PEPTIDE

MEAL

GLUCOSE

INSULIN

C-PEPTIDE

MEAL
Oral Glucose Minimal Model
(Dalla Man & Cobelli, 2002)

$S_I$: Insulin Sensitivity (liver & periphery)
Validation

**Ra**

Triple Tracer Method  
(Dalla Man et al., 2004)

**SI**

Euglycemic Clamp  
(Dalla Man et al., 2005)

R = 0.81, p < 0.001
Insulin Sensitivity

59 Y vs 145 E

\[ S_I \]

\[ [10^{-4} \text{dl/kg/min per } \mu \text{U/ml}] \]

* \( p<0.05 \)
Importance of C-peptide

- Cells
- Liver
- Insulin
- C-peptide

Glucose [mmol/l]

Graphs showing glucose, insulin, and C-peptide levels over time.
**β-Cell Responsivity Minimal Model**

(Toffolo et al, Am J. Physiol, 2001; Breda et al, Diabetes, 2001)

- **Glucose**
- **SECRETION**
- **Delay**
- **Static Phase**
- **Dynamic Phase**
- **Releasable Insulin**
- **CP₁**
- **CP₂**

**Rate of Increase of Glucose (first 50-60 minutes)**

Φₖ : Dynamic Beta-Cell Responsivity

Φₛ : Static Beta-Cell Responsivity

Φ : Overall Beta-Cell Responsivity
β-Cell Responsivity Indices

59 Y vs 145 E

Φ_d

[10^{-9} min^{-1}]

Y

E

Φ_s

[10^{-9} min^{-1}]

Y

E

p<0.05

[hr]

0 5 10 15 20 25 30

0 2 4 6 8 10 12 14

0 200 400 600 800

0 10 20 30 40

0 5 10 15 20 25 30 40 50 60

0 10 20 30 40 50 60 70 80 90 100 110 120
The Glucose-Insulin System

- **LIVER**
  - Production
  - Glucose Regulation

- **β-CELLS**
  - Secretion
  - Insulin Sensitivity

- **BRAIN**
  - Utilization

- **MUSCLE**
  - Degradation

- **TISSUES**
  - Insulin Sensitivity
  - B-cell Responsivity

- **GLUCOSE**
  - Production
  - Utilization

- **INSULIN**
  - Secretion
  - Degradation
Efficiency of Control: Disposition Index


Insulin Sensitivity x Beta-Cell Function = Constant

Diagram: 
- Beta-Cell Responsivity
- Insulin Sensitivity
- Therapy
- Normal Tolerance
- Impaired Tolerance

Graph showing the relationship between insulin sensitivity and beta-cell function with therapy options.

Therapy options:
- Increased
- Normal
- Reduced

Therapy points:
- Normal Tolerance
- Impaired Tolerance
Disposition Index

Beta-Cell Responsivity

Insulin Sensitivity

Y: DI = 459
E: DI = 313
What Happens if You Add a Stable Isotope Tracer to the OGTT/Meal?

Tracers Allow Segregation of

Insulin Sensitivity into its

- Disposal Component
- Hepatic Component
Disposal Insulin Sensitivity

“COLD” MINIMAL MODEL

OGTT/MEAL

Gastrointestinal Tract

Liver

Production

Glucose

Utilization

Tissues

Insulin

Remote Insulin

$S_I$: Insulin Sensitivity

(Uutilization + Production)

“HOT” MINIMAL MODEL

OGTT/MEAL

Gastrointestinal Tract

Glucose

Utilization

Tissues

Insulin

Remote Insulin

$S_{ID}^D$: Disposal Insulin Sensitivity

(Uutilization Only)
Hepatic Insulin Sensitivity

From $S_i$ and $S_i^D$  

$$S_i^L = S_i - S_i^D$$

“COLD” MINIMAL MODEL

OGTT/MEAL

Gastrointestinal Tract

Liver → Production → Glucose → Utilization → Tissues

Insulin → Remote Insulin

“HOT” MINIMAL MODEL

OGTT/MEAL

Gastrointestinal Tract

Insulin → Remote Insulin

$S_i^P$ → Remote Insulin

Gastrointestinal Tract

Glucose → Utilization → Tissues
Labelled Meal: Additional Information

**Rate of Appearance**

**Rate of Disappearance**

**Endogenous Production**

$S_{i}^{p}$ * $p<0.01$

$S_{i}^{l}$
Fluxes Validation: Triple Tracer Meal
(Basu et al. Diabetes 2006)

Oral tracer ingested with the meal
mimicking endogenous glucose production

Tracer-to-tracee clamp technique
virtually model-independent glucose fluxes

Endogenous Glucose Production
- Model
- Triple Tracer

Rate of Appearance
- Model
- Triple Tracer
Use in Pathophysiology

1) Role of age and gender (Basu et al, Diabetes 2006)

2) Reduced OGTT & Meal Protocols (Dalla Man et al, Diabetes 2006)

3) Pathogenesis of Prediabetes (Bock et al, Diabetes 2006)

4) Role of Race (Petersen et al, Proceedings of the National Academy of Science 2006)


6) Type 2 Diabetes (Basu et al Diabetes Care 2009)

7) Effect of DPP-4 Inhibitors (Dalla Man et al, Diabetes Care 2009)

8) Children and Adolescent (Cali et al, Diabetes Care 2009, Sunehag et al, Obesity 2009)
Models

• **Models to Understand/Measure (Minimal)**
  - Whole Body
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• **Models to Simulate (Maximal)**
  - In Silico Trial
The Glucose-Insulin System

- **Liver**: Production
- **Muscle**: Utilization
- **β-cells**: Secretion

**Stimulation of glucose transport**: Exercise

**Insulin Sensitivity**: Increases with exercise-responsive GLUT-4-containing vesicles

**Tissues**: Degradation

**Brain**: ATP consumption

**Insulin**: Secretion, insulin response, glucoregulation, and tissue sensitivity

**Glucose**: Production, degradation, muscle utilization, liver secretion, and brain uptake
Muscle Glucose Metabolism

- Plasma
- Interstitium
- Cell

Glucose

Glucose-6-phosphate
Using PET to Study Insulin Action on Glucose Delivery, Transport and Phosphorylation
Basal & Insulin Study

$[^{11}\text{C}]$-3-OMG

$[^{18}\text{F}]$FDG
The 5K model
(Bertoldo et al., Diabetes 2006)

$C_p \xrightarrow{k_1} C_i \xrightarrow{k_2} C_e \xrightarrow{k_4} C_m$

$C_e \xrightarrow{k_3} C_i$

Transport

Phosphorylation

Graph showing the rates of Transport in ($k_3$), Transport out ($k_4$), and Phosphorylation ($k_5$) under Basal and Insulin conditions.
Models

• Models to Understand/Measure (Minimal)
  - Whole Body
  - Organ/Tissue

• Models to Simulate (Maximal)
  - In Silico Trial
Background

- **Models to Simulate:**
  often not possible, appropriate, convenient or desirable to perform experiments in humans, e.g. testing of glucose sensors and insulin infusion algorithms for closed loop control during normal life condition

- Can **Models to Measure** be used as **Models to Simulate** for in Silico Trial?
  No

**Models to Measure** need to be Minimal (parsimonious)
**Models to Simulate** need to be Maximal (large scale)
New Generation of Simulation Models

Fluxes, in addition to concentrations, available through Triple Tracer Meal

(N=204 Normals)
Healthy State Meal Simulator

(Dalla Man et al, 2007)

Meal

GASTRO-INTESTINAL TRACT

Plasma Glucose

Rate of Appearance

Renal Excretion

Production

Utilization

LIVER

GLUCOSE SYSTEM

MUSCLE AND ADIPOSE TISSUE

BETA-CELL

INSULIN SYSTEM

Secretion

Plasma Insulin
Identification: System Decomposition & Forcing Function Strategy
Muscle and Adipose Tissue Model

- Plasma Insulin (I)
- Glucose Production (EGP)
- Glucose Rate of Appearance (Ra)
- MUSCLE AND ADIPOSE TISSUE
- Plasma Glucose (G)
- Glucose Utilization (U)

Model:
- Insulin Action (X)
- Plasma Glucose (G_p)
- Tissues Glucose (G_t)
- U(t)
- V_m(X_1), V_m(X_2), V_m(X_3)

Equations:
\[ G(t) = \frac{K_m(X_3)}{K_m(X_3) + V_m(X_3)} \]
\[ G(t) = \frac{K_m(X_2)}{K_m(X_2) + V_m(X_2)} \]
\[ G(t) = \frac{K_m(X_1)}{K_m(X_1) + V_m(X_1)} \]

Conditions:
\[ X_1 < X_2 < X_3 \]
Inter-Subject Variability
Generation of In Silico Normal Subjects

# 1
Glucose

# 2
Glucose

# 3
Glucose

# 100
Glucose
In Silico Meal Model

Simulated Subject

In silico experiments with Metabolic Demand

Liver

BETA CELL

GLUCOSE SYSTEM

INSULIN SYSTEM

Muscle and Adipose Tissue

Renal Excretion

Rate of Appearance

Plasma Glucose

Production

Secretion

Plasma Insulin

Artificial pancreas development:

In silico testing of closed-loop control algorithms

Simulated Clinical Trials

In silico experiments with Metabolic Demand

Artificial pancreas development:

In silico testing of closed-loop control algorithms
Continuous Monitoring Systems

**DexCom Seven Plus**

**Abbott FreeStyle Navigator**

**Medtronic Guardian® Real-Time**
Self Monitoring Blood Glucose (SMBG) vs Continuous Glucose Monitoring (CGM)

• Glucose concentration: process in time
• Close observation of trends and variability can provide actionable clinical information
CGM Signal Processing

- On-line noise removal

- Real-time forecast of trends and glycemic events, e.g. hypo & hyperglycemia
Signal-to-Noise Ratio (SNR) characteristics:

• SNR may change from sensor to sensor (e.g. Abbott vs Medtronic vs DeXCom vs …) (sensor-to-sensor variability)

• Having fixed the sensor, SNR may change from individual to individual (inter-individual variability)

• Having fixed the subject, SNR may change during the monitoring (intra-individual variability)
Signal-to-Noise Ratio (SNR) Variability

Sensor-to-Sensor Variability

Intra-individual Variability

“low” SNR

“high” SNR

Glucose (mg/dl)
CGM Signal Denoising

Signal-to-Noise Ratio (SNR) characteristics:

• SNR may change from sensor to sensor (e.g. Abbott vs Medtronic vs DeXCom vs ...) (sensor-to-sensor variability)

• Having fixed the sensor, SNR may change from individual to individual (inter-individual variability)

• Having fixed the subject, SNR may change during the monitoring (intra-individual variability)

• Because of SNR variability the Moving Average filter implemented in commercial devices is suboptimal

• Idea: to develop a filter with simple structure but able to automatically adapt its parameters on line
CGM model:
\[ y(t) = u(t) + v(t) \]

- variances \( \sigma^2(t) \) and \( \lambda^2(t) \) unknown and change during monitoring
- \( \sigma^2(t) \) and \( \lambda^2(t) \) estimated by maximum likelihood
- glucose level \( \hat{u}(t) \) estimated via Kalman filtering (recursive equations \( \Rightarrow \) on-line implementations with low-cost hardware)

Integrated Random Walk:
\[ u(t + 1) = 2u(t) - u(t - 1) + w(t) \]
\[ w(t) = N(0, \lambda^2) \]
Results: Simulated Data

Simulated subject

- CGM more noisy
- CGM less noisy
- Burn in
- True CGM
- Noisy CGM
- True $\sigma^2$

- Higher noise variance
- Lower noise variance

- Time (hours)
- Glucose (mg/dl)
- $\sigma^2$
Results: Simulated Data

Simulated subject
Results: Real Data

Menarini Glucoday Subject #14

Estimated noise variance changes significantly during monitoring
CGM Signal Processing

- On-line noise removal
- Real-time forecast of trends and glycemic events, e.g. hypo & hyperglycemia
Prediction of future glucose levels

*Graph showing past and future glucose levels.*
Based on:

- mathematical models (Polynomial, AR, ARMA)
- past data weighting via forgetting factor
Autoregressive Modeling

Sensor CGM

Hypo-threshold

105 mg/dl at time 78

77.1 mg/dl at time 171

70.1 mg/dl at time 201

Parameters:

- a1
- a2
- a3
A First Attempt on Prediction

Glucoday 24-48 h home monitoring in 28 Type 1 diabetics
(Sparacino et al, IEEE Trans BME, 2007)

- Delay significantly lower than Prediction Horizon
- Gain of nearly 25 min for alert generation

<table>
<thead>
<tr>
<th>Positive trends</th>
<th>Negative trends</th>
</tr>
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<tbody>
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<td>3.8 min</td>
<td>5.3 min</td>
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Sensor CGM
Prediction 30 min ahead
Delay
Delay

AVERAGE DELAY
Diabetes

- Physiology & Pathophysiology
- System Biology
- Health Care Delivery & Economics
- Patient Management
- Artificial Pancreas
- Drugs
- Technology & Devices (Sensors, Pumps)
- Islet Transplantation

- Models
- Signals
- Control
What is an Artificial Pancreas?
The JDRF Artificial Pancreas Consortium

Eight Centers:

- Cambridge (UK), P.I. Roman Hovorka, Ph.D.
- Colorado, P.I. Peter Chase, M.D.
- Santa Barbara, P.I. Lois Jovanovich, M.D.
- Stanford, P.I. Bruce Buckingham, M.D.
- Virginia, P.I. Boris Kovatchev, Ph.D.
- Yale, P.I. Stuart Weinzimer, M.D.
- Boston, P.I. Ed Milano, Ph.D.
- Portland, P.I. Ken Ward, Ph.D.

Coordinating Center: Jaeb Center for Health Research, Tampa, FL
University of Virginia:

- Diabetes Technology: Boris Kovatchev, Marc Breton, Pam Mendosa
- Medicine/Endocrinology: Stacey Anderson
- Pediatrics: William Clarke, Laurissa Kashmer
- System Engineering: Stephen Patek

University of Padova:

- Bioengineering: Claudio Cobelli, Chiara Dalla Man, Simone Del Favero
- Medicine: Angelo Avogaro, Alberto Maran, Daniela Bruttomesso, Silvana Costa

University of Pavia:

- Control Engineering: Lalo Magni, Giuseppe De Nicolao, Chiara Toffanin

University of Montpellier:

- Eric Renard, Anne Farret, Jerome Place
Traditional vs. Accelerated Development

Concept

Animal Trials

Clinical Trials

Product

Concept

In Silico Trials

Clinical Trials

Product

Saves Years
Tested against, and showing excellent agreement with:

- Adult & Children Pathophysiology
- Accepted Clinical Care Standards
- Field data of children with T1DM
- Healthy population variability retained
January 18, 2008: T1DM Simulator accepted by FDA as substitute to animal trials (Master file #1521)
Model Predictive Control

past

future

k

k+1

... k+m

... k+p

time

target value

(courtesy Frank Doyle)
Moving Horizon Concept of MPC

- Past archived measurements
- Future target value and model prediction
- Calculated Insulin infusion

(courtesy Frank Doyle)
In Silico Closed-Loop Trial on 100 Subjects

- Admission
- Dinner & Insulin Bolus
- Breakfast & Insulin Bolus
- Lunch & Insulin Bolus

BG target 100 mg/dl
- plasma insulin (Total & Free)
- CGM
- plasma glucose

- every 30 minutes measurements
- frequent measurements*

21:30 Dinner & Insulin Bolus

12:00 Breakfast & Insulin Bolus

6:00 Lunch & Insulin Bolus

16:00 Admission

plasma insulin (Total & Free)
CGM
plasma glucose

Closed-Loop
January 18, 2008: Simulation accepted by FDA as substitute to animal trials (Master file #1521)

Traditional vs. Accelerated Development

Concept -> Animal Trials -> Clinical Trials -> Product

Concept -> In Silico Trials -> Clinical Trials -> Product

January 18, 2008: Simulation accepted by FDA as substitute to animal trials (Master file #1521)

Regulatory Approval for clinical trials based entirely on in silico testing:
April 17, 2008 (UVA IDE);
May 20, 2008 (Padova EC)
Study Design

Subjects
Total of 18 subjects who use insulin pumps
(21 years of age or older with Type 1 Diabetes for at least 2 years)

- University of Virginia: N=9
- University of Padova: N=6
- University of Montpellier: N=3

Protocol
Repeated Measures design: Each patient serves as his/her own control

- Inpatient Admission 1: Baseline Physician-Supervised Open-Loop Control
- Inpatient Admission 2: Closed-Loop Control, which begins at 21:30
The AP System

Study Participant

FreeStyle Navigator™ (Abbott Diabetes Care)

Navigator™ cradle enables real-time data transfer to PC

Attending Physician

Frequent YSI provides reference BG

OmniPod Insulin Management System

PC running Model Predictive Control
Blood Glucose during Closed-Loop

Breakfast 50g CHO
Five-Fold Reduction in nocturnal hypoglycemia with better overall glucose control within target range

**Primary Outcome**

- Overnight % time within the target range of 70-140 mg/dl:
  - Open-Loop: 64
  - Closed-Loop: 78

- Nocturnal hypoglycemic episodes (BG<70 mg/dl):
  - Open-Loop: 23
  - Closed-Loop: 5
Glucose System

Signal & Control Algorithms

Minimal Models

Maximal Models

Models to Control

Patient Behavior

Insulin System

Hypoglycemia

Signal & Control Algorithms

Minimal Models
Diabetes: Models, Signals, and Control

Claudio Cobelli, Chiara Dalla Man, Giovanni Spagnuolo, Lalo Magni, Giuseppe De Nicolao, and Bertis P. Kovatchev

Methodological Review

Abstract—The control of diabetes is an interdisciplinary endeavor, which includes a significant biomedical engineering component, with traditions of success beginning in the early 1960s. It began with modeling of the insulin-glucose system, and progressed to large-scale in silico experiments, and eventually closed-loop control (artificial pancreas). Here, we follow these engineering efforts through the last almost 50 years. We begin with the new classic minimal modeling approach and discuss a number of subsequent models, which have recently resulted in the first in silico simulation model accepted as a substitute to animal trials in the quest for optimal diabetes control. We then review metabolic modeling, with a particular emphasis on the new continuous glucose sensors, on the analysis of their time-series data, and on the opportunities that they present for automation of diabetes control. Finally, we review control strategies that have been successfully employed in vivo or in vitro, presenting a procedure for the development of a future artificial pancreas and, in particular, discuss a modular architecture for building closed-loop control systems, including insulin delivery and safety supervision layers. We conclude with a brief discussion of the unique interactions between human physiology, behavioral events, engineering modeling and control relevant to diabetes.

Index Terms—Artificial pancreas, automatic control, identification, parameter estimation, physiological systems, sensors, signal processing.

I. INTRODUCTION

DIABETES is a common metabolic disorder characterized by chronic hyperglycemia that leads to microvascular and macrovascular complications [1–5]. These complications include retinopathy, blindness, ischaemic heart disease, and end-stage renal disease. Diabetes is broadly classified into two categories: type 1 diabetes and type 2 diabetes. Both arise from complex interactions between genes and the environment, whereas their pathogenesis is distinct. Type 1 diabetes is the result of immune-mediated destruction of the beta-cells in the islets of Langerhans—the site of insulin secretion and production. In general, the disease occurs in childhood and adolescence (although it can occur at any age) and is characterized by absolute insulin deficiency. Consequently, affected individuals require insulin therapy to control hyperglycemia and maintain life. Acute hyperglycemia does not play a part in the pathogenesis of type 1 diabetes, although obesity in type 2 diabetes is associated with the development of cardiovascular complications. In contrast, type 2 diabetes occurs because insulin secretion in inadequate and cannot overcome the prevailing defects in insulin action, resulting in hyperglycemia. Excess caloric intake, inactivity, and obesity all play parts in the pathogenesis of type 2 diabetes. In general, it is a disease that occurs with increasing frequency with increasing age and is uncommon before age 40 (although there are important exceptions). In addition, people with type 2 diabetes are more likely to have associated adverse cardiovascular risk factors such as dyslipidemia and hypertension. Prediabetes, i.e., impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is an intermediate condition in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable. Both type 2 diabetes and prediabetes are recognized risk factors for overt cardiovascular disease and related metabolic complications and are major components of health care spending [6–7]. Rapid urbanization and societal affluence of global migrating populations has been suggested as major risk factors for the observed exploding prevalence of prediabetes and type 2 diabetes with consequent rising trends in cardiovascular risk [8]. IGT is a rapidly emerging form of prediabetes with a 20%–30% risk of progression to diabetes over 5–10 years. This risk is even greater if individuals have both IFG and IGT. Furthermore, both IFG and IGT are linked to increased risk for cardiovascular events [6, 7] in the Caucasian population. Ninety percent of the world population with diabetes is type 2 with type 1 diabetes comprising between 5%–10%. It is plausible that the relative frequency of type 1 and type 2 diabetes will change with rising trends in the prevalence of type 2 diabetes, obesity, and prediabetes in the developing world.

Over time, diabetes leads to complications, in particular: diabetic neuropathy, which leads to bladescia; diabetic nephropathy, which increases the risk of foot ulceration and limb loss; and diabetic nephropathy leading to kidney failure. In addition, there is an increased risk of heart disease and stroke with 50% of people with diabetes dying of cardiovascular disease and stroke. Finally, the overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.
Triple-Tracer PET Imaging

1. **Plasma**
   - **Glucose**

2. **Interstitium**
   - **Glucose**

3. **Cell**
   - **Glucose**
   - **Glucose-6-phosphate**

- **$[^{15}O]H_2O$: delivery**
- **$[^{11}C]3$-OMG: transport**
- **$[^{18}F]FDG$: phosphorylation (with LC)**
Basal & Insulin Study

$[^{11}C]-3\text{-OMG}$

- Basal
- Insulin

$[^{18}F]\text{FDG}$

- Basal
- Insulin
Weight Loss Impact on Glucose Transport & Phosphorylation in Obesity & Type 2 Diabetes

(Williams et al., Diabetes 2003)
Generation of In Silico Type 1 Subjects

Glucose

# 1

# 2

# 3

# 4

Glucose

Glucose

Glucose

Glucose

... ... ...
Model Predictive Control (MPC)

- Model: derived from the FDA accepted large-scale nonlinear model via linearization, discretization, model reduction and input-output transformation.

- Real-time optimization is not required

- Only one parameter, $q$, “the aggressiveness of control” must individualized for each patient with the two-step procedure:

  **Step 1:** *in silico* determination of the relation between $q$ and clinical parameters
  - Body weight ($BW$); Basal Insulin ($BI$); Carbohydrate Ratio ($CR$)
  
  $q = f(BW, BI, CR)$

  **Step 2:** Use $f$ to compute $q$ for the real patient
Artificial Pancreas Initiatives

- JDRF Artificial Pancreas Consortium
  - Project EU AP@Hope, 7th Framework
- NIH Artificial Pancreas Grants
  - Project EU DIAdvisor, 7th Framework

Insulin Advisor Initiative
A 10.5 M€ European project that involves 6 universities, 2 clinical centers and 4 industrial partners.

Duration: 4 years
Started: 1st February 2010
Artificial Pancreas Initiatives

- JDRF Artificial Pancreas Consortium
- Project EU AP@Home, 7\textsuperscript{th} Framework

Insulin Advisor Initiative

- Project EU DIAdvisor, 7\textsuperscript{th} Framework
A **9.3 M€** European project that involves 4 universities, 3 clinical centers and 7 industrial partners.

**Duration:** 4 years

**Started:** 1st March 2009