ARTIFICIAL PANCREAS: Technology and Clinical Trials

The UVa Center For Diabetes Technology: Stacey Anderson, MD, Boris Kovatchev, PhD, Marc Breton, PhD, Patrick Keith-Hynes, PhD

Artificial Pancreas Components

- Continuous Glucose Monitor
- Insulin Pump
- Closed-Loop Control Algorithm
**Highlights from the JDRF AP Project**

- 2006: The JDRF Artificial Pancreas Consortium is launched.
- 2008: First human trials begin using a system designed entirely in silico: UVA, Italy, and France.
- 2010: JDRF Multi-Center Trial of inpatient modular control-to-range begins at 7 sites.
- 2012: Multi-site Randomized Cross-Over Efficacy trials of outpatient closed-loop control (UVA, Santa Barbara, Padova, Montpellier).

**Milestones**

- 30 years ago
- 3 years ago
- 3 months ago
Artificial Pancreas: Past, Present, Future
Claudio Cobelli,1, Eric Renard,2,3 and Boris Kovatchev4

The artificial pancreas (AP), known as closed-loop control of blood glucose in diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device. AP developments can be traced back 50 years to when the possibility for hinders their use in subcutaneous systems because of un-avoidable time-lag in subcutaneous glucose sensing and insulin action. Newer controllers, known as model-predictive control (MPC), avoid these limitations by using a mathematical model of the metabolic system of the person being controlled in their calculations. Many of these MPC algorithms are based on another 1979 milestone, the Minimal Model of Glucose Kinetics (17). Thus, since the early years of AP development, glucose sensing and insulin delivery technologies were accompanied by computer modeling of critical problems in AP development and to outline possible solutions and a pathway toward the clinical acceptance of ambulatory closed-loop control.

LIMITATIONS OF CURRENT GLUCOSE SENSORS
CGM technology was introduced 10 years ago, initially as a method for retrospective review of glucose profiles (34–36). Shortly after, real-time devices came about, providing online glucose readings (37). These first devices had lim-ited performance, particularly in the hypoglycemic range (36,38,39). Since then, significant progress has been made toward versatile and reliable CGM, a number of studies

2008: In Silico Model of Type 1 Diabetes
Kovatchev, Breton, Dalla Man & Cobelli, 2008

In Silico Subject

Simulated Sensor

Control Algorithm

Simulated Insulin Pump

Glucose-Insulin Model
**The In Silico “Subjects”**

\[
\begin{align*}
\dot{G}_j &= -k_1G_j + k_2G_j - U_j - E_j + k_{j1}G_j - k_{j2}G_j - k_{fj}I_j + \frac{f_{jmax}Q_{m1}}{BW} \\
\dot{G}_i &= -k_1G_i + k_2G_i - \frac{(U_{m1} + U_{m2} - X)G_i}{k_{m1} + G_i}
\end{align*}
\]

Biometric Characteristics of the Population of N=300 In Silico “Subjects”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.7 (12.8)</td>
<td>52.3</td>
<td>118.7</td>
</tr>
<tr>
<td>Insulin (U/day)</td>
<td>47.2 (15.2)</td>
<td>21.3</td>
<td>98.4</td>
</tr>
<tr>
<td>Carb ratio (g/U)</td>
<td>10.5 (3.3)</td>
<td>4.6</td>
<td>21.1</td>
</tr>
</tbody>
</table>

**Paradigm Change: In Silico Experiments Replacing Animal Trials**

- Concept
- Animal Trials
  - Clinical Trials
  - Treatment
- In Silico Trials
  - Clinical Trials
  - Treatment

Saves Years

FDA Master File MAF 1521, February 2008
2009-2012:

Modular Closed-Loop Control of Diabetes


Control Module 3: Meal Control
Fully automated control action; multi-hormone meal control (e.g. insulin + amylin)

Control Module 2: Range Correction
Acts episodically as needed to correct hyperglycemia

Control Module 1: Safety Supervision
Acts continuously to prevent hypoglycemia by smooth attenuation of insulin delivery and preventative warnings/actions if needed.

AP Operating System: Specific built of mobile OS that allows a system to function as a Class 3 medical device; Comm drivers and patient-oriented user interface.

Safety First!

- **Adjunct to** sensor-augmented pump therapy;
- Supervises the **safety of insulin delivery** to prevent hypoglycemia;
- Supervises the **accuracy of the sensor** to detect sensor failure.

Safety Supervision System
(works continuously to prevent hypoglycemia, improve the safety of insulin pump and the accuracy of CGM)

Safety Action System State Estimation Data Retrieval

Open-loop physician-prescribed basal and meal control

Hardware Interface

Insulin Pump CGM
Defining Control-to-Range

- **Adjunct to** sensor-augmented pump therapy;
- **Silent** if open-loop therapy is optimal.

**Post-Meal Correction Algorithm**
(worked when needed in advisory or automatic mode to correct postprandial hyperglycemia)

**Safety Supervision System**
(worked continuously to prevent hypoglycemia, improve the safety of insulin pump and the accuracy of CGM)

**Hardware Interface**

- Insulin Pump
- CGM

2011: Portable Artificial Pancreas Platform

**DiAs** (the Diabetes Assistant) introduced by Patrick Keith-Hynes

**Key specifications:**

- Based on smartphone;
- Runs various control algorithms, open-loop, or sensor-alone modes;
- Connects to remote monitoring site through WiFi or 3G;
- Android OS modified to meet medical application standards.
The Technology to Date

- In silico experiments replaced animal trials;
- Modular architecture enabled easy configuration of control algorithms;
- Medical Android OS was designed to run artificial pancreas applications;
- DiAs was introduced by UVA as the first portable outpatient artificial pancreas system;
- Total outpatient use of DiAs so far: 2,600 hours in the U.S. and Europe.

2008-2013: An International Consortium

The JDRF AP Project at UVA-Padova-Montpellier (2008-2010)

The JDRF Multi-Center Trial of Control-to-Range (2009-2012)

The NIH Bio-Behavioral AP Project (2009-2014)

The European AP@Home Project (2010-2014)

The JDRF CTR at Home Project (2011-2013)

The NIH DP3 AP Project (2011-2016)
Fully Integrated Artificial Pancreas in Type 1 Diabetes

Modular Closed-Loop Glucose Control Maintains Near Normoglycemia

Marc Breton, Anne Farret, Daniela Breuttmesser, Stacey Anderson, Lali Magi, Stephen Patik, Chiara Della Man, Jerome Phare, Sasan Benishli, Simone Del Farerro, Chiara Toscani, Colleen Hughes-Karvetski, Eyal Dassau, Howard Zisser, Francis J. Doyle III, Giuseppe De Nicolai, Angelo Avogaro, Claudio Cobelli, Eric Renard, and Boris Kovatchev, on behalf of The International Artificial Pancreas (IAP) Study Group

2008-2011 In-Clinic Feasibility Studies:

60 Subjects – 48 Adults and 12 Adolescents
UVA (N=30); Montpellier, France (N=18); Padova, Italy (N=12)
Randomized Cross-Over Design; Moderate Exercise (2 Studies)

# Hypoglycemic episodes /subject <70mg/dl
Percent time within target range 70-180 mg/dl
Average Glucose (mg/dl)
(Translates into A1c change 7.0-9.36)

Open Loop Closed Loop
Open Loop Closed Loop
Open Loop Closed Loop

Open Loop: physician-directed control
Closed-Loop Control

Integrated closed-loop control (CLC), combining continuous glucose monitoring (CGM) with insulin pump (continuous subcutaneous insulin infusion, CSII), known as artificial pancreas, can help achieve glycemic control in diabetes. We report a randomized cross-over study comparing CLC and physician-directed control in 60 subjects – 48 adults and 12 adolescents, at UVA (N=30), Montpellier, France (N=18), and Padova, Italy (N=12). Subjects randomized were stratified by HbA1c and baseline needs. All subjects had moderate level of exercise. Open Loop: physician-directed control. CLC: automated control of glucose, proposed to be superior to physician-directed control. Preliminary results show that CLC can maintain glycemic control at 70-180 mg/dl (72% vs. 53% for Open Loop and Closed Loop). Average glucose levels were lower in Closed Loop (136 vs. 154 mg/dl for Open Loop and Closed Loop). However, in the Open Loop, only 2 cases of hypoglycemia (55 mg/dl) were recorded compared to 1.15 cases in the Closed Loop. These results suggest that CLC is superior to physician-directed control in maintaining glycemic control and reducing hypoglycemia risk.
**2010-2012 In-Clinic Exercise Feasibility Studies:**

Enabling exercise during closed loop control using heart rate.
UVA Center for Diabetes Technology;

**Study Design:**
- N= 12 subjects;
- Low intensity exercise
- Portable AP system + Heart Rate monitor
- Randomized cross-over sessions, heart rate enhanced- vs. standard closed-loop control;
- Each session continues for 24h;
- DiAs runs both open- and closed-loop;
- Patient in charge of system communications.

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**2011: Outpatient Artificial Pancreas**

User Interface Designed to be Operated by the Patient

Android OS modified to meet medical application requirements (FDA Master File MAF 2109)
13h Open Loop run by DiAs - System Connectivity Testing (Dinner, Overnight)

16h Closed Loop Control-to-Range (Breakfast, Lunch, Restaurant Dinner)

8h Closed Loop Safety Mode (Overnight)

5h Closed Loop Control-to-Range (Breakfast)

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**2011-2012: Early Feasibility Studies of Outpatient Closed-Loop Control**

- UVA, Padova, Montpellier, Santa Barbara;
- N=5 subjects per site;
- 42-hour outpatient sessions;
- No meal restrictions (e.g. restaurant meals).

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**Pilot Studies of Wearable Outpatient Artificial Pancreas in Type 1 Diabetes**

- Day 3—At 8:00, the patients had breakfast at the hotel. At 11:00, they had low intensity exercise (30-min walk in town). Throughout the study, the clinical team remotely observed the system operation and reference blood glucose was measured using HemoCue (HemoCue AB, Angelholm, Sweden) pre- and post-meals, at bedtime, and upon physician judgment.

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**Complete Results:**

*Diabetes Care, In Press*
The DiAs Remote Monitoring System

Simultaneous Real-Time Remote Monitoring of Several Patients
LAST SUMMER: Remote Monitoring

Stanford, UVA:
Three camp sessions, N=20 children / camp
N=10 Dexcom G4 + DiAs remote monitoring
N=10 Dexcom G4 only (control group)

• For the control group, hypoglycemia treatment based on standard diabetes camp night-time SMBG;
• For the remote monitoring group, hypoglycemia treatment initiated at 70 mg/dl observed on the remote monitor.

2012-2013: Efficacy of Outpatient Artificial Pancreas

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

Study Design:
• N= 5 subjects per site;
• Randomized cross-over sessions, open-vs. closed-loop control;
• Each session continues for 40h;
• DiAs runs both open- and closed-loop;
• Patient in charge of system communications.
System Configuration

3G or WiFi Connection for remote monitoring

DiAs Smart Phone

USB

Dexcom G4 Receiver

Devices near the subject

Low Power Bluetooth

Wireless connection

Tandem t:slim insulin pump

Dexcom G4 Sensor

Devices worn by the subject

Pilot Trial: October 30-31, 2012

Graph showing glucose levels and insulin doses over time.
Plans for 2013-2014

Multi-Site Home Trials of Control-to-Range (UVA, Padova, Montpellier, Santa Barbara, Stanford, other)

GOAL:
Design and execute a definitive multi-center trial that will establish the artificial pancreas as viable treatment for type 1 diabetes.

Anticipated System Configuration:

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