Wearable Artificial Pancreas

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Presenter Disclosure

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Advisory Panel: Animas, Sanofi-Aventis;

Research Support: BD, Dexcom, LifeScan, Sanofi-Aventis, Tandem Diabetes Care

Stock/Shareholder: TypeZero Technologies

Other: Patents and patent applications related to the study technology
The next generation closed-loop control systems will be:

- Informed by a *body sensor array*;
- *Modular*, distributing tasks across specialized devices—certain processes and patient interaction are available through local devices; other services and analytics are available via Cloud computing;
- *Scalable*, supporting functional expansion, multiple data source configurations, and graceful system degradation to a known state.

**Differences in glycemic targets** (for a particular patient at a particular time) **define different closed-loop control modalities:**

- *Safety first*—an algorithm dedicated to reduction of hypoglycemia, **adjunct to** standard basal-bolus insulin pump therapy;
- *Control-to-range* minimizing both hypo- and hyperglycemic excursions, **adjunct to** standard basal-bolus therapy;
- *Control-to-target* fine-tuning glucose control, **replacement** for basal-bolus therapy.
Example: Artificial Pancreas through Glass
Memo 1: The next generation closed-loop systems will be **mobile medical networks** informed by a body sensor array:
System Configuration A

All closed-loop, interface, and communication functions are run by the insulin pump

Cloud services:
- Remote diagnostics;
- Databases;
- Telemedicine...

AP Hub

Pump:
- Graphical User Interface;
- Safety System;
- Control Algorithm

CGM
System Configuration B

All closed-loop, interface, and communication functions are run by a system hub (e.g. smart phone).

Cloud services:
- Remote diagnostics;
- Databases;
- Telemedicine...

AP Hub (Smartphone):
- Graphical User Interface;
- Safety System;
- Control Algorithm

CGM

Pump
System Configuration C: Modular Design Distributing Tasks Among Devices

Cloud services:
Remote diagnostics;
Databases;
Telemedicine...

Defines a pipeline for feature deployment from the hub to the pump and the sensor when features are established on the hub.

Graphical User Interface;
Control Algorithm

CGM
Signal Processing;
Data Relay

Pump:
Safety Algorithms;
Data Relay;
Default if System Fails
Memo 2: The Artificial Pancreas is not a single product – it is a platform for technology deployment. Closed-loop control is one of many possible applications running on a scalable mobile medical network:

- Control actions depend on the available peripheral devices;
- The system degrades gracefully in case of component failure;
- Key element: Estimation of the state of the patient from available data sources.
Configuration 1: Sensor Companion

Works when only CGM signal is available; Can be deployed with MDI or insulin pen; Default mode of operation in case of pump failure.
Configuration 2: Pump Companion

Works when CGM signal is not available;
Can be deployed with SMBG alone;
Default mode when CGM fails.
Configuration 3: Meter Companion

Works with SMBG alone;
Provides long-term trends for average glycemia, risk for hypoglycemia, or glucose variability.
Configuration 4: Hypoglycemia Minimizer

Uses the same signals as full closed-loop, but limits control action to safety. Preferred deployment directly in sensor-augmented pump. Default mode when the system hub malfunctions.

<table>
<thead>
<tr>
<th>Available Peripheral Devices</th>
<th>Patient and System State Estimation</th>
<th>Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Readings</td>
<td></td>
<td>Trends, Alerts, Advice</td>
</tr>
<tr>
<td>SMBG</td>
<td></td>
<td>Safety; Hypoglycemia prevention</td>
</tr>
<tr>
<td>CGM</td>
<td></td>
<td>Automated closed-Loop control</td>
</tr>
<tr>
<td>Insulin Delivery</td>
<td></td>
<td>Remote monitoring &amp; diagnostics</td>
</tr>
<tr>
<td>MDI/Pen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (e.g. heart rate, accelerometer)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Configuration 5: Closed-Loop Control

Upgrade of Safety that uses the **same signals and the same basic computations**;
Can be user-selectable option on AP systems already running safety.

![Diagram of Configuration 5: Closed-Loop Control]

- **Available Peripheral Devices**
  - **Glucose Readings**
    - SMBG
    - CGM
  - **Insulin Delivery**
    - MDI/Pen
    - CSII
  - **Other** (e.g. heart rate, accelerometer)

- **Patient and System State Estimation**

- **Services**
  - Trends, Alerts, Advice
  - Safety; Hypoglycemia prevention
  - Automated closed-Loop control
  - Remote monitoring & diagnostics
Memo 3: Different glycemic targets (for a particular patient at a particular time) define different closed-loop control modalities

Modular Closed-Loop Control Systems


Abstract—Modularity plays a key role in many engineering systems, allowing for plug-and-play integration of components, enhancing flexibility and adaptability, and facilitating standardization. In the control of diabetes, i.e., the so-called “artificial pancreas,” modularity allows for the step-wise introduction of (and regulatory approval for) algorithmic components, starting with subsystems for assured patient safety and followed by higher layer components that serve to modify the patient’s basal rate in real time. In this paper, we introduce a three-layer modular architecture for the control of diabetes, consisting in a sensor/pump interface module (IM), a continuous safety module (CSM), and a real-time control module (RTCM), which separates the functions of insulin recommendation (postprandial insulin for mitigating hyperglycemia) and safety (prevention of hypoglycemia). In addition, we provide details of instances of all three layers of the architecture: the APS® serving as the IM, the safety system serving as the CSM, and the range control module serving as the RTCM. We evaluate the performance of the system via in silico preclinical trials, investigating the ability of the system to reduce the incidence of hypoglycemia and improve glycemic variability.

Index Terms—Artificial Pancreas System (APS), diabetes, hardware/software integration, in vitro/in vivo model predictive control (MPC), safety.

Patients with diabetes do not have an insufficient supply of insulin produced by the beta cells of the pancreas. Insulin can also be used as a fuel by the liver, muscles, and adipose tissue in the body. When insulin is deficient or absent, a host of disorders arises, characterized by a complex multifaceted spectrum of hyperglycemia. Intensive treatment regimens have been designed to maintain nearly normal levels of blood glucose, which are protective against chronic complications [1–3], but the risk of hypoglycemia and potentially life-threatening hypoglycemia. Thus, hypoglycemia has been identified as a major clinical challenge and a barrier to intensive diabetes management [4]. People with type 1 and type 2-dependent patients face a life-long long-termization of hypoglycemia and strict glycemic control without increasing their risk for hypoglycemia. The struggle
Safety First!

- **Adjunct to** sensor-augmented pump therapy;
- Supervises the *safety of insulin delivery* to prevent hypoglycemia;
- Responsible for alarms or automated rescue actions (e.g. glucagon);
- Supervises the *accuracy of the sensor* to detect sensor failure.

**Safety Supervision Algorithm**

(works continuously to prevent hypoglycemia and improve the safety of the insulin pump)

**Hardware Interface**

CGM, Insulin Pump, Other Sensors and Data-generating devices
**Example: Multi-site Randomized Crossover Safety Trial of Outpatient Closed-Loop Control**

- **Clinical Sites:** UVA, Padova, Montpellier, and Sansum;
- **Engineering Sites:** UVA, Pavia, Montpellier, UC Santa Barbara
- **N=5 subjects per clinical site; Two 40-hour outpatient sessions;**
- **Randomized Cross-Over Design:** Open vs. Closed-Loop Control
- **Primary Outcome:** Reduction in risk for hypoglycemia as measured by the Low BG Index; planned effect size=0.4.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Open Loop</th>
<th>Closed Loop</th>
<th>p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent time in the target range of 70-180 mg/dl</td>
<td>70.7%</td>
<td>66.1%</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Average Blood Glucose</td>
<td>152.1 mg/dl</td>
<td>161.3 mg/dl</td>
<td>0.042</td>
</tr>
<tr>
<td>Percent time below 70mg/dl</td>
<td>1.25%</td>
<td>0.70%</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Number of hypoglycemic episodes/person/session requiring carbohydrate treatment</td>
<td>2.39</td>
<td>1.22</td>
<td>0.021</td>
</tr>
<tr>
<td>Grams of carbohydrate/person/session used for treatment of hypoglycemia</td>
<td>39.7g</td>
<td>17.6g</td>
<td>0.022</td>
</tr>
</tbody>
</table>

**Primary Outcome - Observed Effect Size = 0.64, p=0.003.**

*Outcomes Related to Hypoglycemia*
Control-to-Range

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

**Open-loop physician-prescribed meal control**

**Post-Meal Correction Algorithm**
*works when needed* to correct postprandial hyperglycemia

**Safety Supervision Algorithm**
*works continuously* to prevent hypoglycemia and improve the safety of the insulin pump

**Hardware Interface**
CGM, Insulin Pump, Other Sensors and Data-generating devices

Sensor array data

Output to pump
Example: Control-to-Range after Missed Meal Boluses in Adolescents with Type 1 Diabetes

UVA (Daniel Chernavvsky, Mark DeBoer, Marc Breton)

Study Results:

N=16 participants in outpatient study;

Two 8-hour daily sessions (8AM-4PM);
Randomized cross-over design;

Control condition: Sensor-augmented pump therapy; subjects correcting on their own;

Experimental condition: Closed-Loop Control;

9AM snack without insulin (30g CHO) followed by underbolused lunch;

Closed-loop control reduced significantly postprandial glucose excursions:
Control-to-Target

Open-loop physician-prescribed meal control

• Replacement of sensor-augmented pump therapy, so far overnight;
• Designed to bring the patient to 120mg/dl by the morning.

Basal Rate Modulation Algorithm
(works continuously to bring the patient within range after dinner and then slide to a target glucose level by the morning)

Post-Meal Correction Algorithm
(works when needed to correct postprandial hyperglycemia)

Safety Supervision Algorithm
(works continuously to prevent hypoglycemia and improve the safety of the insulin pump)

Hardware Interface
CGM, Insulin Pump, Other Sensors and Data-generating devices

Sensor array data
Output to pump
Example: Bedside Control-to-Target

**UVA** (Sue Brown, Stacey Anderson, Molly McElwee, Marc Breton, Boris Kovatchev);
**Padova** (Daniella Bruttomesso, Simone Del Favero, Claudio Cobelli)

- 50 nights of closed-loop vs. 50 nights of open-loop SAP;
- BG level achieved by 7AM = 119.3mg/dl;
- Average glucose reduced by >30mg/dl, from 170 to **139mg/dl**;
- Percent time in target increased by >25%, from 59% to **85%**;
- Hypoglycemia reduced from 1.6% to 0.6%;
- Improved overnight control resulted in better control on the **next day**.
In Conclusion:

- The next generation wearable closed-loop systems will be mobile medical networks informed by a body sensor array;
- The Artificial Pancreas is not a single product – it is a platform for technology deployment: closed-loop control is one of many possible applications running on a scalable mobile medical network;
- Different glycemic targets (for a particular patient at a particular time) define different closed-loop control modalities ranging from safety supervision alone to control-to-range and control-to-target;
- A prototype exists – the Diabetes Assistant (DiAs) mobile medical platform developed at UVA.
So far, the DiAs platform was and used in U.S. and European outpatient studies at:

University of Virginia; Stanford University; UC Santa Barbara/Sansum Diabetes Research Institute; Virginia Commonwealth University, Richmond;
University of Montpellier, France; University of Padova and University of Pavia, Italy; Academic Medical Center, Amsterdam.

Coming up: Mount Sinai Medical School, New York; Mayo Clinic, Rochester, MN; Schneider Children’s Medical Center, Israel.

Latest News:

• Right Now, 16 patients in Europe and in the U.S. are on overnight closed-loop control at home;
• FDA approved 1-monght home trial of day-and-night closed-loop control, which will begin in 5 centers within a month.

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