Closing the Loop: From Sensor Integrated Pumps to the Artificial Pancreas

David Ahn, MD
Outline

• Need for a Closed Loop
• Definitions and Terms
• Pathway toward a Closed Loop
• Medtronic 670G Hybrid Closed Loop
• Overview of the Competition
• Barriers and Future Directions
Current State of T1D

Miller, Diabetes Care 2015
The Mental Burden of Diabetes

- Managing medications, activity, nutrition, mood, etc
- Constant monitoring
- Unexpected variables
- “It’s like driving a car…”
“Managing diabetes is like driving a car, but with the caveat that you can never leave the car”

-Mark Wilson (@warkmilson), PWD
Why a Closed Loop?

1. Present methods of diabetes treatments are largely unsuccessful in helping patients meet glycemic targets.

2. Intensive management is burdensome and can negatively impact the quality of life for those living with diabetes and their loved ones.
Definitions

- **Open Loop (OL)** - system requiring manual input
  - Sensor Augmented Pump (SAP)
  - Sensor Integrated Pump
  - Multiple Daily Injections (MDI)

- **Closed Loops (CL)** - fully automated system
  - Bionic Pancreas
  - Artificial Pancreas (AP)
Closing the Loop…

- Usual Care: Full OL SAP
- Insulin Suspension: Threshold Predictive
- Insulin Delivery: Overnight Hybrid CL
- The goal: Full CL Bihormonal CL

Automation
System Complexity
First Generation

1. Very-Low-Glucose Insulin Off Pump
   - Pump shuts off when user not responding to low-glucose alarm

2. Hypoglycemia Minimizer
   - Predictive hypoglycemia causes alarms, followed by reduction or cessation of insulin delivery before blood glucose gets low

3. Hypoglycemia/ Hyperglycemia Minimizer
   - Same product as #2 but with added feature allowing insulin dosing above high threshold (e.g. 200 mg/dL)

Second Generation

4. Automated Basal/Hybrid Closed Loop
   - Closed loop at all times with mealtime manual-assist bolusing

5. Fully Automated Insulin Closed Loop
   - Manual meal-time bolus eliminated

Third Generation

6. Fully Automated Multihormone Closed Loop
The Components of a Closed Loop System

- Insulin pump
- Control algorithm device
- CGM receiver
- CGM sensor

[Image of a smartphone displaying carbohydrate and glucose levels]
Progress

- Type Zero (University of Virginia)
- Florence System (Hovorka Group)
- Beta Bionics iLet Pump
- Bigfoot Biomedical
- Omnipod
- Animas
- Tandem
- Medtronic
- And more…

Where we started

Cell Phones

Where we are today

Insulin Pumps
Closed Loops in Development

- Type Zero (University of Virginia)
- Florence System (Hovorka Group)
- Beta Bionics iLet Pump
- Bigfoot Biomedical
- Omnipod
- Animas
- Tandem
- Medtronic
- And more…
Control Algorithms

- Proportional Integral Derivative (PID)
  - Responds to measured glucose levels
- Model Predictive Control (MPC)
  - Model to predict glucose levels in the near future
  - Can account for meals, delayed insulin action
Control Algorithms

- Fuzzy Logic (FL)\(^1\)
  - Uses “fuzzy” rules to express empirical knowledge
  - Similar to how DM providers might manage
- Bio-Inspired\(^2\)
  - Uses a model of how pancreatic beta cells produce insulin in response to changes in glucose

\(^1\)Atlas, Diabetes Care 2010  
\(^2\)http://www.imperial.ac.uk/bio-inspired-technology/research/metabolic/bionicpancreas/
Closing the Loop…

Usual Care: Full OL SAP
Insulin Suspension: Threshold Predictive
Insulin Delivery:
- Overnight
- Hybrid CL
The goal:
- Full CL
- B-hormonal CL

Automation
System Complexity
Medtronic 670G

- Hybrid Closed Loop System
  - Auto-adjusts basal rate
  - Target blood sugar: 120mg/dl
- Mealtime boluses required
- Now available (in limited release)
- Guardian Sensor 3
  - 3-4x/day: MARD 9.64%
  - 1-2x/day: MARD 10.55%
670G Pivotal Study

- Participants
  - 124 patients for 3 months
  - Aged 14-75 years
  - 10 sites

- Study Design
  - Baseline data collection using sensor augmented pump x 2 wks
  - 3 months with brief intensive evaluation (5 day hotel stay)
  - 24 hr admission for frequent sensor analysis
- Results:
  - Increased time in range
  - Reduced time spent low and high
  - Reduced variability
  - Less post-prandial excursion

Bergenstal, JAMA 2016
<table>
<thead>
<tr>
<th></th>
<th>Adolescents</th>
<th></th>
<th>Adults</th>
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<tbody>
<tr>
<td></td>
<td>Run-In</td>
<td>Study Phase</td>
<td>Run-In</td>
<td>Study Phase</td>
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<tr>
<td>Average Sensor Glucose</td>
<td>163±19</td>
<td>159±12</td>
<td>146±22</td>
<td>148±14</td>
</tr>
<tr>
<td>Time in Target (71-180)</td>
<td>61±11</td>
<td>67±8</td>
<td>69±12</td>
<td>74±8</td>
</tr>
<tr>
<td>Time &lt;70mg/dL</td>
<td>4.3±2.9</td>
<td>2.8±1.3</td>
<td>6.4±4.3</td>
<td>3.4±2.1</td>
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Auto Mode vs Manual Mode

Pump mode

Sensor Augmented Pump

Hybrid Closed Loop/ Auto mode
Manual Mode

Auto Mode
Tandem Diabetes

- Tandem X2 Platform - Software Upgradeable
- PLGS: if anticipates <80mg/dL in 30 min OR <70mg/dL
  - Optional suspend alerts
- Pivotal trials now, Launch Summer 2018?
- HCL: TypeZero InControl MPC + Dexcom G6
  - Does not require active insulin time settings
  - No exiting auto mode due to hyperglycemia
Omnipod Horizon

- Tubeless Insulin Pump + Dexcom Sensor
- Algorithm integrated onto Pod
- MPC-based controller; configurable
  - Can do temp basals, wave bolus etc
- Customizable set points (100-150mg/dL)
- Market Goal: 2020
Bigfoot Biomedical

- Insulin Pump + Freestyle Libre Gen2
- Smartphone UI
- “Model-based” Control
- Meal announcements
- Monthly service fee
- Pivotal Trial 2018
iLet Beta Bionics

- MPC-Based
- Insulin-Only System:
  - Pivotal trial planned for 2018 2H
  - Possible launch in 2019
- Bi-Hormonal System:
  - Pivotal trial depends on Glucagon formulation
Medtronic

- Incorporates DreaMed Diabetes Algorithm
  - Fuzzy Logic
- “Advanced hybrid closed loop” with auto correction boluses
- Little known at this time
<table>
<thead>
<tr>
<th>Barriers</th>
<th>Potential Solutions</th>
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<tr>
<td>CGM Accuracy</td>
<td>Calibration-free CGM</td>
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<tr>
<td>Delayed Insulin Action</td>
<td>Faster Aspart</td>
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<tr>
<td></td>
<td>Co-infusion of Pramlintide/GLP-1</td>
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<td></td>
<td>Warming of local injection site</td>
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<td>Glucagon Instability</td>
<td>Multiple products coming to market</td>
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<tr>
<td>Device Bulk</td>
<td>Implantable Sensors</td>
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<td>Combined sensor/infusion site</td>
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Take-Home Points

• Despite CGM/Pumps, most T1D’s do not meet targets

• Closed loops have been shown to increase time in target, especially overnight

• The hybrid closed loop is here, and is the first of a wave of exciting new developments

• Significant barriers remain, with many potential solutions
Stay Up to Date

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