Automated Insulin Dosing (AID) for TDC

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Disclosures

Consultant: Abbott Diabetes Care, Biolinq, Capillary Biomedical, Deep Valley Labs, Gluroo, Morgan Stanley, ProventionBio, Tidepool
My Background (Historical Order)

• Person with diabetes
• Engineer
• Brother
• Physician
• Scientist
Outline

• Introduction
• Algorithm Basics
• Commercial AID
• Open-Source AID
• When predictions are tough
• Goals
Idea Ahead of its Time

• Lot of people show this as the first insulin pump to show how far we have come, but the reality is...

• This is an insulin and glucagon intravenous automated system (Kadish 1964)

• If we are lucky Bionic Pancreas will be doing a bihormonal pivotal trial in 2022 (58 years later)
Automated Insulin Dosing

• Rapid changes in diabetes technology have allowed for *closed-loop* control of insulin delivery.
Rapid Advances

• Every United States pump manufacturer now has an automated insulin dosing system available

• Each system relies on different rules (algorithms) to control the delivery of insulin. Some rely primarily on CGM while others use models to predict the future.

• The designers and/or regulators must balance the interests of glycemic control, safety, personalization, generalizability and adaptation.
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PID Controller

- Target glucose
- CGM glucose

- Error function

- K_p ×
- K_i ×
- K_d ×

+ Insulin change
**Fuzzy Logic (e.g. Mauseth 2013)**

**FIG. 1.** Insulin dosage calculation schemata (version 1.5). The fuzzy logic controller uses current glucose level, rate of change, and acceleration to calculate insulin dosage. This example shows that when the glucose level is normal (N) (red circle), the rate is zero (Z) (blue circle), and the acceleration is positive (P) (green circle), the dose is 0.10 units of insulin (black circle). All of the dosing rules are based on a 5-min glucose sample time. BG, blood glucose; H, high; L, low; N, negative (for rate and acceleration); VH, very high; VN, very negative; VVH, very, very high.

<table>
<thead>
<tr>
<th>BG Level</th>
<th>VN</th>
<th>N</th>
<th>Z</th>
<th>P</th>
<th>VP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Z</td>
<td>P</td>
<td>N</td>
<td>Z</td>
</tr>
<tr>
<td>BG Acceleration</td>
<td>N</td>
<td>Z</td>
<td>P</td>
<td>N</td>
<td>Z</td>
</tr>
<tr>
<td>VVH</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>VH</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>H</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>N</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>L</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Predictive Control

Future Predicted Glucose =
Factors to improve prediction accuracy +

Active Insulin Effect on BG +

Active Carbohydrate Effect on BG +
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<table>
<thead>
<tr>
<th>Available Sensors</th>
<th>Dexcom G6</th>
<th>Medtronic Guardian Connect</th>
<th>Abbott FreeStyle Libre 14 Day*</th>
<th>Senseonics Eversense*</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many parts does it have?</td>
<td>3: transmitter, sensor, and receiver</td>
<td>3: transmitter, sensor, and smartphone used as the receiver</td>
<td>2: sensor and receiver</td>
<td>3: transmitter, implantable sensor, and smartphone/ smartwatch used as the receiver</td>
</tr>
<tr>
<td>Does it offer alerts and alarms?</td>
<td>Yes, can be customized</td>
<td>Yes, can be customized</td>
<td>No</td>
<td>Yes, can be customized</td>
</tr>
<tr>
<td>How do I view data?</td>
<td>On a smartphone (Apple or Android), smartwatch, or the receiver</td>
<td>On an Apple smartphone</td>
<td>On a smartphone (Apple or Android) or on the receiver</td>
<td>On a smartphone (Apple or Android) or smartwatch</td>
</tr>
<tr>
<td>How do I share the data with family members?</td>
<td>Real-time data can be shared using an app</td>
<td>Real-time data can be shared using an app; family members can also receive text message alerts</td>
<td>Data from whenever you scan can be shared using an app</td>
<td>Real-time data can be shared using an app</td>
</tr>
<tr>
<td>How many fingersticks are needed to calibrate the sensor?</td>
<td>None</td>
<td>2 per day</td>
<td>None</td>
<td>2 per day</td>
</tr>
<tr>
<td>How long is the sensor used?</td>
<td>10 days</td>
<td>7 days</td>
<td>14 days</td>
<td>90 days</td>
</tr>
<tr>
<td>How does it attach to the body?</td>
<td>Sensor is inserted in 1 step, and integrated adhesive holds the sensor and transmitter in place</td>
<td>Sensor is inserted with the use of a Medtronic one-press insertion aid, then the sensor and transmitter are held in place by an outer adhesive</td>
<td>Sensor is inserted in 1 step, and integrated adhesive holds it in place</td>
<td>Sensor needs to be inserted by a doctor, nurse practitioner, or physician assistant, then the transmitter sits outside the body and is held in place by an adhesive</td>
</tr>
</tbody>
</table>

- Wire-based sensors rely on glucose oxidase
- Eliminating calibrations requires: (1) identical hardware manufacturing and (2) accurate data
Interstitial limits

- Glucose sensing in the interstitial fluid smooths and delays the blood signal (Burnett 2014)
- More algorithms used to coerce the signal to make it look diabetes-like.
# No Data = No Accuracy Penalty

<table>
<thead>
<tr>
<th><strong>Users</strong></th>
<th><strong>Regulators</strong></th>
<th><strong>Company</strong></th>
</tr>
</thead>
</table>
| ![Sensor Error](image) | • We want to make sure reported data is accurate.  
• But we do not enforce exactly how much needs to be reported. | • We are seeing data we do not trust.  
• If we report it we may adversely effect accuracy metrics. |

Temporary issue. Wait up to 3 hours.

You will not receive alerts, alarms, or sensor glucose readings.
Medtronic 670G/770G

- PID with an internal model of insulin-on-board.
- Received FDA approval in September 2016
- First commercial “hybrid” closed-loop device
Medtronic 780G

• PID with an internal model of insulin-on-board some of the time

• Licensed fuzzy logic from DreaMed but mixed messages on how much it is used.
### Medtronic – Future

**GOAL**
Deliver improved outcomes with less effort

<table>
<thead>
<tr>
<th>TODAY</th>
<th>1 Year</th>
<th>2+ years</th>
</tr>
</thead>
</table>

#### Automated basal
- Performance:
  - 72% Time in Range\(^1\)
  - Mean SG: 150 mg/dL

#### Pediatric labeling (2+ years)

#### Improved handling of highs w/ auto-correction\(^3\)
- >80% Time in Range\(^2\)
- Mean SG: 135 mg/dL\(^2\)

#### Real-time personalized therapy & meal handling\(^3\)
- >85% Time in Range\(^2\)
- Mean SG: <130 mg/dL\(^2\)

#### Lower cost system with high ease of use\(^3\)

#### Connectivity
- Manual data uploads
- Smartphone display
- Care Partner app

#### In-warranty pump software upgrades
- Pump control with phone
- HCP dashboard
- Proactive patient support

#### Sensor
- 2 cals/day

#### Fewer fingersticks:
- 1 cal/day
- Insulin dosing claim\(^2\)

#### Insulin Infusion
- 7-day wear

#### Easy 3-step insertion
- 50% smaller

#### Pump hardware
- Color screen
- Waterproof

#### 7-day wear
- Easy insertion

#### All-in-One: Sensor + insulin infusion
- Fingerstick replacement

#### New pump:
- Lower cost, 50% smaller

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\(^1\) TIDEEPOLL Medtronic
\(^2\) TiPproven handling of highs w/ aut, o-correction
\(^3\) TiPmedtronic
Medtronic Algorithm Questions

• Over what time frame do you perform derivative, integral? Longer could reduce error but also reduce responsiveness.

• How frequently do the \( K_P, K_I, K_D \) get tuned (effects rate of adaptation)?

• When and how much fuzzy logic gets used for 780G? What is the basis for the logic?
Tandem Control-IQ™

- Control-IQ™ received FDA approval in December 2019.
- Estimates glucose and insulin in the body using available pump data and compares it to an internal model.
• Basal modulation: The internal model uses parameters for basal, ICR and ISF that are derived from your total daily dose and **not** your profile settings.

Who are “Some People”
- Low/High Carb
- *Honeymoon
- Outside insulin/Afrezza
- Very young/old
- Organ dysfunction
- Cystic Fibrosis
- Other forms of diabetes (e.g. *T2DM, gestational)
Tandem Algorithm Questions

• What is the rate of adaptation?
• What equations govern inferred settings?
• Auto boluses are based on programmed ISF, but basal modulation based on inferred settings and capped by set basal. For most users is the bulk of automated insulin given by basal modulation or auto boluses?
Insulet

- Loop compatibility over 433MHz
- OmniPod 5 (submitted)
- First pump to support Tidepool Loop
Horizon Algorithm Questions

• What is the rate of adaptation?
• What equations govern inferred settings? What happens if initialized basal settings are way off?
• When to use Horizon algorithm versus Tidepool Loop?
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Loop – Pump Hardware

x15

x23 (FW \leq 2.4A)

x22

x54 - European (FW \leq 2.6A)

x54 – Canadian (FW \leq 2.7A)
Loop – iOS with Bluetooth + RileyLink

Microcontroller (iPhone)  Bluetooth -> Pump bridge
Loop – Where to go for help?

- https://loopkit.github.io/loopdocs/
- https://loop.zulipchat.com
- https://www.facebook.com/groups/TheLoopedGroup
- https://github.com/LoopKit/Loop
- https://getrileylink.org/
OpenAPS – Pump Hardware

- x12
- x15
- x22
- x23 (FW ≤ 2.4A)
- x54 - European (FW ≤ 2.6A)
- x54 – Canadian (FW ≤ 2.7A)
OpenAPS – Hardware Controller

Microcontroller (Edison or Pi) + 900MHz Explorer Board ± Display

- Unicorn, “for scale”
- @DanaMLewis
- American chapstick
- European chapstick
- Next round prototype of Explorer HAT (with Pi0W underneath)
- Battery that happened to look and be sized like a chapstick
- Yup, this HAT is smaller than the first prototype.
- One of the first prototype Explorer HATs (with Pi0W underneath)
OpenAPS – CGM

NIGHTSCOUT
#WeAreNotWaiting
OpenAPS – Algorithm

- Issue increasing/decreasing boluses every 5 minutes based on CGM data if glucose stable or rising. Once glucose falling IOB drops quickly, due to 0 basal, until BG stable or more insulin warranted.
OpenAPS – Where to go for help?

• https://openaps.readthedocs.io/en/latest/
• https://gitter.im/nightscout/intend-to-bolus
• https://gitter.im/openaps/autotune
• https://www.facebook.com/groups/TheLoopedGroup
AndroidAPS
AndroidAPS – Where to go for help?

• https://androidaps.readthedocs.io/en/latest/EN/
• https://www.facebook.com/groups/1900195340201874/
• https://gitter.im/MilosKozak/AndroidAPS
• https://github.com/MilosKozak/AndroidAPS/issues
• developers@androidaps.org
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Let’s start at the beginning

- Vicious circle: Initial β cell loss $\rightarrow$ ↑ glucose $\rightarrow$ oxidative stress $\rightarrow$ Glucose toxicity $\rightarrow$ ↓ β cell function $\rightarrow$ 0 insulin state $\rightarrow$ DKA

- When we start treatment with insulin we remove the glucose toxicity and whatever β cells remain start producing some insulin again

- The amount of insulin produced is a function of the residual beta cell mass and secretory capacity (itself glucose dependent).
Endogenous insulin secretion

• Because the number of beta cells and their ability to secrete is in constant flux, it becomes challenging to model and treat.

• There is often adequate insulin secretion overnight when there is no food intake and low levels of counter-regulatory hormones that increase glucose.

• Hard to compensate when you don’t know about insulin.
It all seems so simple…

Time to Peak Insulin Level

Data from different studies
The reality (El-Khatib 2010)

Plasma insulin and glucagon (#122–1)

- Measured insulin
- Predicted insulin
- PK fit ($t_{\text{max}} = 191 \text{ min}$, $t_{95\%} = 19.1 \text{ hr}$)

Fast Insulin Model

Plasma insulin and glucagon (#122–2)

- Measured insulin
- Predicted insulin
- PK fit ($t_{\text{max}} = 127 \text{ min}$, $t_{95\%} = 12.7 \text{ hr}$)

Slow Insulin Model
Ever had this happen?

- An underlying assumption is that what we deliver gets into our body.
- There are adults who might need a longer or angled cannula compared to when they were younger.
Insulin Sensitivity Factor (ISF)

1500 TDD ← 1700 TDD → 1900 TDD

- Very resistant
  - Corticosteroid use
- Resistant
  - Sepsis
  - Trauma
  - Morbid obesity
- Normal
  - Type 2 diabetes
  - Type 1 diabetes
- Sensitive
  - Low body weight
- Very sensitive
  - Renal failure
What can change your ISF?

- Cortisol, Epinephrine, Growth Hormone, Testosterone, Estrogen, Glucagon
- Age/Puberty
- Body composition
- Blood sugar
- Illness/Stress
- Medications
- Exercise
## Activity Tracking?

<table>
<thead>
<tr>
<th>Exercise Type</th>
<th>Description</th>
<th>Blood Glucose Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td>Lower intensity, longer duration</td>
<td>Expect a drop in glucose levels</td>
</tr>
<tr>
<td><strong>Anaerobic</strong></td>
<td>Higher intensity, shorter duration</td>
<td>Expect spikes in glucose levels</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>Combination of aerobic and anaerobic activity</td>
<td>Expect glucose levels to fluctuate, can drop or spike</td>
</tr>
</tbody>
</table>

- Accelerometer ≠ Glucose effect
- Activity doesn’t change a BG target, it changes your glucose utilization and sensitivity
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What are your goals?

• Setting the high score vs living your life without complications so you can do what you actually want

• The best controlled participant in DCCT was mid-70% time-in-range. The average TIR for people who did not develop retinopathy or microalbuminuria was 44 ± 15%.

• Tighter control when consuming a normal carbohydrate diet can come with weight gain, which can cause more cardiovascular risk than your blood sugars.
Conclusions

• More choices than ever
• Until we get the “perfect” system knowing how it functions is important
• Commercial systems often require difficult decisions by designers and regulators
• Open source systems offer unparalleled transparency and personalization
Acknowledgements

• Thanks to the endocrinology teams at Stanford and my mentor Dr. Bruce Buckingham.

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References


Thank You! Any questions?

Just checking my insulin dose!