Using the Medical Logic to Close the Loop
Towards an Artificial Pancreas

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Denver- July, 2011
Disclosure

- Medtronic, Dexcom, Smith Medical – Grants/Research support
- Bristol Myers Squibb, Sanofi Aventis and Bayer – Consultant
- CGM3, D-Medical and Physical Logic – member of the board
Artificial Pancreas – Not So Far Away

Glucose Monitoring

Insulin Delivery


Urine Monitoring

SBGM

CGMS

Open Loop

Closed Loop

Pumps

Pens

Syringes

1983
1979
1921

1920
1980
1999
2000
Artificial Pancreas – The Dream

“Sensing” Hormone Delivery

Continuous Glucose Sensor Insulin Pump Control Algorithm
Design the Controller: The Medical Way of Thinking

Fuzzy-Logic Theory

Precision and Significance in the Real World

A 1500 kg mass is approaching your head at 45.3 m/s

LOO K OUT!!

Precision

Significance
Incorporate diabetes care giver's traditional treatment principles

Individualized patient system

Learning capabilities

Automatic communication between all aspects involved in diabetes management

Both full and hybrid closed-loop system

An encompassing system securing safe management and control

Can be used in the intravascular space
MD-Logic Artificial Pancreas System

- Incorporate diabetes care giver's traditional treatment principles
- Individualized patient system
- Learning capabilities
- Automatic communication between all aspects involved in diabetes management
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## Diabetes Caregivers Traditional Treatment Principles

### Engineering way of thinking

<table>
<thead>
<tr>
<th>System Core</th>
<th>Controllers which have similar characteristics as the physiological blood glucose regulation system</th>
</tr>
</thead>
<tbody>
<tr>
<td>System parameters</td>
<td>Quantitative parameters only</td>
</tr>
<tr>
<td>System implementation</td>
<td>solving a set of equations or optimization problems</td>
</tr>
</tbody>
</table>

### Medical way of thinking

1. Medical Knowledge of blood glucose regulation
2. Trial and error

Quantitative and qualitative parameters

Weighted consideration of what is known
Diabetes Caregivers Traditional Treatment Principles (Cont.)

Control to Range & Control to Target

Table 1. Target indicators of glycemic control

<table>
<thead>
<tr>
<th>Level of control</th>
<th>Ideal (non-diabetic)</th>
<th>Optimal</th>
<th>Suboptimal (action suggested)</th>
<th>High risk (action required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised BG</td>
<td>Not raised</td>
<td>No symptoms</td>
<td>Polyuria, polydipsia, and enuresis</td>
<td>Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications</td>
</tr>
<tr>
<td>Low BG</td>
<td>Not low</td>
<td>Few mild and no severe hypoglycemia</td>
<td>Episodes of severe hypoglycemia (unconscious and/or convulsions)</td>
<td></td>
</tr>
</tbody>
</table>

Biochemical assessment*

<table>
<thead>
<tr>
<th>SBGM values</th>
<th>AM fasting or preprandial</th>
<th>Postprandial PG†</th>
<th>Breakfast PG†</th>
<th>Nocturnal PG†</th>
<th>HbA1c (%) (DCCT standardized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGGM values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM fasting or preprandial</td>
<td>3.6—5.6 (&lt;5–100)</td>
<td>4.5—7.0 (&lt;90–126)</td>
<td>4.0—5.6 (&lt;80–100)</td>
<td>3.6—5.8 (&lt;85–100)</td>
<td>&lt;6.05</td>
</tr>
<tr>
<td>Preprandial PG†</td>
<td>5—10 (&lt;90–180)</td>
<td>6.7—10 (&lt;120–190)</td>
<td>&lt;8.7 or 10—11 (&lt;120 or 180—200)</td>
<td>4.5—9 (&lt;80—162)</td>
<td>&lt;7.5†</td>
</tr>
<tr>
<td>Breakfast PG†</td>
<td>10—14 (&lt;180–250)</td>
<td>&lt;8.7 or 10—11 (&lt;120 or 180—200)</td>
<td>&lt;4.4 or &gt;11 (&lt;80 or &gt;200)</td>
<td>&lt;4.2 or &gt;9 (&lt;75 or &gt;162)</td>
<td>&gt;7.5—9.0†</td>
</tr>
<tr>
<td>Nocturnal PG†</td>
<td>&gt;8 (&gt;145)</td>
<td>10—14 (&lt;180–250)</td>
<td>&lt;8.7 or 10—11 (&lt;120 or 180—200)</td>
<td>&lt;4.2 or &gt;9 (&lt;75 or &gt;162)</td>
<td>&gt;7.5—9.0†</td>
</tr>
<tr>
<td>HbA1c (%) (DCCT standardized)</td>
<td>&gt;9 (&gt;102)</td>
<td>&gt;14 (&gt;250)</td>
<td>&lt;4.4 or &gt;11 (&lt;80 or &gt;200)</td>
<td>&lt;4.0 or &gt;11 (&lt;70 or &gt;200)</td>
<td>&gt;9.0†</td>
</tr>
</tbody>
</table>

Basal / Bolus Therapy

ISPAD Guidelines, Pediatric Diabetes 10(Suppl. 12):71-81, 2009
MD-Logic Artificial Pancreas System

- Incorporate diabetes care giver's traditional treatment principles
- Individualized patient system
- Learning capabilities
- Automatic communication between all aspects involved in diabetes management
- Both full and hybrid closed-loop system
- An encompassing system securing safe management and control
- Can be used in the intravascular space
Individualized Patient System with Automatic Learning

The Diabetes Team
- Physician
- Nurse specialist
- Dietitian
- Social Worker
- Psychologist
Individualized Patient System with Automatic Learning

- Learning Algorithm
  - Initial Learning of Patient Profile
  - Real-time update of patient profile
Individualized Patient System with Automatic Learning

**In Silico** adolescents (N=100) – Constant simulation parameters

**Time spent Below 70 mg/dl**
- Home Care: 9%
- First CL Day: 0.5%
- 6th CL Day: 1.9%

**Time spent Within 70-180 mg/dl**
- Home Care: 58%
- First CL Day: 66%
- 6th CL Day: 77%

NSD – No Statistical Difference

Miller et al, Diabetes Technol Ther – Accepted
MD-Logic Artificial Pancreas System

- Incorporate diabetes care givers traditional treatment principles
- Individualized patient system
- Learning capabilities
- Automatic communication between all aspects involved in diabetes management
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- Can be used in the intravascular space
Automatic MDLAP system

MD-Logic Artificial Pancreas

Patient

Controller Laptop
MD-Logic Artificial Pancreas System

- Incorporate diabetes care giver's traditional treatment principles
- Individualized patient system
- Learning capabilities
- Wireless communication between all aspects involved in diabetes management
- Both full and hybrid closed-loop system
- An encompassing system securing safe management and control
- Can be used in the intravascular space
We need **BOTH!**

<table>
<thead>
<tr>
<th></th>
<th>Meaning</th>
<th>Why do we need an artificial pancreas?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full closed-loop</strong></td>
<td>1. No information about meal size and time</td>
<td>Missed bolus scenario</td>
</tr>
<tr>
<td></td>
<td>2. Insulin is delivered only by the system</td>
<td></td>
</tr>
<tr>
<td><strong>Hybrid Closed-loop</strong></td>
<td>Patient delivers pre-prandial bolus to cover meal</td>
<td>MDLAP will support meal treatment, i.e. add or decrease insulin delivery as needed</td>
</tr>
</tbody>
</table>
Total of 31 closed-loop sessions

- Short visit (8 Hours) – full closed-loop
  - Meal and fasting conditions (12 sessions)

- Long visit (24 hours) – full closed-loop
  - Rest state
  - Three mixed meals
  - Sleep of about 7 hours
  - 7 sessions

- Overnight (12 hours) – hybrid closed-loop
  - After dinner (6 sessions)
  - After physical activity + dinner (6 sessions)
  - Free meal scenario (on going)
Results – 24-hour Full Closed-loop Sessions

<table>
<thead>
<tr>
<th>N = 7</th>
<th>Episodes of below 63 mg/dl</th>
<th>Time within 70-180 mg/dl per 24 hours</th>
<th>Time Below 70 mg/dl per 24 hours</th>
<th>Mean BG Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0</td>
<td>70.7 [60.7-80]</td>
<td>0.3 [0-1.78]</td>
<td>153</td>
</tr>
<tr>
<td>[ Range]</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>
Results – Overnight Glycemic Control under MDLAP System

- 90 - 180 mg/dl
- 70 - 90 mg/dl
- 50 - 70 mg/dl

<table>
<thead>
<tr>
<th></th>
<th>N = 20</th>
<th>Time Below 70mg/dl [%]</th>
<th>Time Within 70-140 mg/dl [%]</th>
<th>Time Within 80-120 mg/dl [%]</th>
<th>Mean BG level [mg/dl]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2300h – 0700h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0</td>
<td>85 14</td>
<td>56 25</td>
<td></td>
<td>118 11</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0</td>
<td>87 (81-93)</td>
<td>62 (39-72)</td>
<td></td>
<td>118 (111-129)</td>
</tr>
</tbody>
</table>
## Results – Meal Treatment under MDLAP Closed-loop Control

<table>
<thead>
<tr>
<th>Closed-loop method</th>
<th># Meals</th>
<th>Peak Post Pradial BG [mg/dl]</th>
<th># Meals, BG&lt;180mg/dl at 3hrs</th>
<th># Meals, BG&lt;180mg/dl at 4hrs</th>
<th># Meals, BG stable in 71-140 mg/dl at 4hrs</th>
<th># Meals, BG stable in 71-140 mg/dl at 5hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full CL</td>
<td>22</td>
<td>229 35</td>
<td>50%</td>
<td>91%</td>
<td>23%</td>
<td>60%</td>
</tr>
</tbody>
</table>
To reduce the risk of nocturnal hypoglycaemia

- Most of the severe hypoglycemic events occur at night \(^1\)
  - 75% of hypoglycemic seizures in children \(^2\)
  - 6% of the deaths (T1DM aged <40 yr) were due to “dead-in-bed” syndrome \(^3\)

- Hypoglycemia occurred during 8.5% of nights on open CGM \(^4\)
  - 71% of youth didn’t respond to glucose sensor alarms during the night \(^5\)

---

1. The DCCT , NEJM; 329(14):977-86,1993
4. JDRF CGM Study group , Diabetes Care; 33:1004-8, 2010
5. Buckingham et al, Diabetes Technol Ther; 7:440-7,2005
The diabetes wireless artificial pancreas consortium (DREAM)
DREAM Project Aim

To Evaluate the Efficacy and Safety of the MD-Logic Artificial Pancreas System in Controlling the Blood Glucose Levels of Patients with T1DM During the Night at Home
DREAM Project – 3 Step Plan

1. Validation
   - Develop insulin pump / sensor – PC communication
   - Closed-loop startup with double click
   - Preliminary safety system
   - Feasibility studies (hybrid meal, after physical activity)

2. Inpatient Study
   Randomized, cross over study comparing the MDALP to regular treatment during overnight in the CRC

3. Outpatient Study
   - Develop patient device
   - Home safety system (including status from pump/sensor & local safety monitor for house members)
   - Develop remote monitoring and control system
   - Randomized, cross over study comparing the MDALP to regular treatment during overnight at home
Overview of Glycemic Control under MDLAP

Homecare Overnight
(N=15, 7 Patients)

MDLAP Overnight
(N=12, 7 Patients)

Sensor Glucose [mg/dl]

Time [HH:MM]

Mean

Mean 2SDErr

70-140mg/dl
1. Validation

- Develop insulin pump / sensor – PC communication
- Closed-loop startup with double click
- Preliminary safety system
- Feasibility studies (hybrid meal, after physical activity)

2. Inpatient Study

Randomized, cross over study comparing the MDALP to regular treatment during overnight in the CRC

3. Outpatient Study

- Develop patient device
- Home safety system (including status from pump/sensor & local safety monitor for house members)
- Develop remote monitoring and control system
- Randomized, cross over study comparing the MDALP to regular treatment during overnight at home
Step 2: Study Design

Screening

- Age ≥ 10 yrs
- CSII duration > 3 months
- HbA1c ≥ 7 and < 10
- BMI SDS < 97th

Baseline Assessment

- Download iPRO data, insulin pump, glucose meter and collect meal diary

Session 1

- Standard treatment with CSII
- MD-Logic closed loop control

Session 2

- Standard treatment with CSII
- MD-Logic closed loop control

Meal Bolus – According to patient regular routine (carb. count + insulin calc.)

During CSII nights – patients allowed to measure and correct glucose levels
Step 2: Inpatient Study Patient Demographic

Intermediate Analysis:

7 patients with Type 1 DM participated in 14 sessions

<table>
<thead>
<tr>
<th></th>
<th>N=7</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [yrs]</td>
<td></td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Sex [F/M]</td>
<td></td>
<td>5 / 2</td>
<td></td>
</tr>
<tr>
<td>Duration of Diabetes [yrs]</td>
<td></td>
<td>15.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Duration on Pump Therapy [yrs]</td>
<td></td>
<td>6.5</td>
<td>5</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td></td>
<td>23.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Total Daily Dose [U/kg]</td>
<td></td>
<td>0.64</td>
<td>0.2</td>
</tr>
<tr>
<td>HbA1C [%]</td>
<td></td>
<td>8.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Step 2: Results – intermediate Analysis

From Dinner Time

<table>
<thead>
<tr>
<th>Time [HH:MM]</th>
<th>MDLAP Arm</th>
<th>CSII Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinner</td>
<td>IQR</td>
<td>IQR</td>
</tr>
<tr>
<td>Median</td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Dinner</td>
<td>Dinner</td>
<td>Dinner</td>
</tr>
</tbody>
</table>
### Step 2: Summary of Glucose Variables – Intermediate Analysis - From Dinner Time

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>CL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=7, 19:00 – 07:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Within 63-140 [%]</td>
<td>27 [15-40]</td>
<td>65 [42-78]</td>
<td>0.03</td>
</tr>
<tr>
<td>Time Within 63-180 [%]</td>
<td>45 [30-81]</td>
<td>96 [80-100]</td>
<td>0.006</td>
</tr>
<tr>
<td>Total Number of Events &lt;63mg/dl</td>
<td>2</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Mean SD [mg/dl]</td>
<td>169 48</td>
<td>133 22</td>
<td>0.02</td>
</tr>
<tr>
<td>HBGI$^{1,2}$</td>
<td>8 6</td>
<td>2 2</td>
<td>0.011</td>
</tr>
<tr>
<td>LBG$^{1,2}$</td>
<td>1 2</td>
<td>0 1</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Kovatchev B et al., Diabetes Care 29: 2433-2438, 2006
2 McCall A et al., Diabetes Technol Ther 8: 644-653, 2006
Step 2: Results – intermediate Analysis

Overnight

Sensor Glucose [mg/dl]

Time [HH:MM]

MDLAP Arm

CSII Arm

IQR

Median

IQR

Median
### Step 2: Summary of Glucose Variables – Intermediate Analysis - Overnight

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>CL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=7, 23:00 – 07:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Within 63-140 [%]</td>
<td>29 [0-31]</td>
<td>77 [48-86]</td>
<td>0.018</td>
</tr>
<tr>
<td>Total Number of Events &lt;63mg/dl</td>
<td>2</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Mean SD [mg/dl]</td>
<td>182 56</td>
<td>126 21</td>
<td>0.014</td>
</tr>
<tr>
<td>HBGI&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>11 9</td>
<td>2 2</td>
<td>0.019</td>
</tr>
<tr>
<td>LBGI&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>1 2</td>
<td>0 1</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>1</sup> Kovatchev B et al., Diabetes Care 29: 2433-2438, 2006
<sup>2</sup> McCall A et al., Diabetes Technol Ther 8: 644-653, 2006
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The Need For Safety Measures -
Our Solutions

Sensor drift: We are in the process of developing an algorithm that will detect sensor drift.

In order to treat unexpected and unpreventable hypoglycemia we are considering the use of a rescue glucagon infusion.

The safety and alarm system is currently undergoing effectiveness testing.
Incorporate diabetes care givers traditional treatment principles

Individualized patient system

Learning capabilities

Automatic communication between all aspects involved in diabetes management

Both full and hybrid closed-loop system

An encompassing system securing safe management and control

Can be used in the intravascular space
Subcutaneous route - Why not?

S.C sensing-S.C delivery is not ideal due to:

✓ S.C Insulin Absorption
  o Delay
  o Unpredictable

✓ S.C Glucose sensor
  o Delay
    o Interstitial fluid
    o Sensor response
  o Accuracy
Intravascular route
The long run solution

- I.V-I.V closed loop has several advantages over the S.C-S.C route:
  - Measuring blood glucose level and not interstitial fluid
  - More physiological insulin infusion
  - Allows for faster response to events, such as meals

Therefore, we expanded the MDLAP system to allow I.V-I.V closed loop

The MDLAP system also uses glucagon as contra regulator arm to insulin
Counter Regulatory Delivery

Insulin

Glucagon

Hot

Cold
Closed Loop - Study Protocol

Induction of Diabetes
Interim treatment
18h Fasting/ no insulin 8 am
Elevated FBG
Meal
BG stabilization
Meal consumption
BG stabilization
~ 5pm
Components of the CL System

Sensing arm

- IV BG samples every 5 min
  - Glucometer
    - FreeStyle
  - Sensor

Delivery arm

- Insulin Pump
  - Human Regular insulin
    - Eli Lilly
- Glucagon Pump
  - GlucaGen HypoKit
    - Novo-Nordisk

Controller

- IV MD Logic
Full Closed - Loop in Diabetic swine

Pig- #1665, 34Kg

Blood Glucose [mg/dL]

09:00 09:30 10:00 10:30 11:00 11:30 12:00 12:30 13:00 13:30 14:00 14:30 15:00

0 100 200 300

Ensure Meal

Treatment

Rate [Units/Hour]

09:00 09:30 10:00 10:30 11:00 11:30 12:00 12:30 13:00 13:30 14:00 14:30 15:00

0 0.2 0.4 0.6 0.8

IV Blood Glucose

Insulin Infusion Rate

Ensure Meal

Bolus Insulin

Glucagon

1 2 3 4

Bolus [Units]
• Closed-loop using the MDLAP is a feasible and safe solution to overnight glycemic control

• Some safety issues relating to the whole system need to be addressed before moving on to the home setting

• Step 2 – Inpatient multi-center multi-national study will be finished in a few weeks
Thank You!

Moshe Phillip, MD
Revital Nimri, MD
Eran Atlas, M.Sc
Shahar Miller, B.Sc
Eli Grunberg, B.Sc
Tal Oron, MD
Michal Ajzensztejn, MD
Rachel Naveh
Sharon Demol, MD
Tal Ben Ari, MD
Nitzan Dror, MD
Alona Hamou, M.Sc
Orna Hermon, B.A.

Tadej Battelino, MD
Nataša Bratina, MD
Magdalena Avbelj, MD
Ana Gianini, nurse

Thomas Danne, MD
Olga Kordonouri, MD
Torben Biester, MD