The Physician's Perspective of Diabetes and Novel Diabetes Therapies

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Topics To Be Covered

- Continuous Glucose Monitoring
- Augmented alarms for Nocturnal Hypoglycemia
- Partial Closed Loop
- Full Closed Loop
Interstitial Fluid (ISF) Measurement

- With Rapid Glucose Changes, the Sensor Glucose Lags the Blood Glucose
- Physiological Delay
  - With rapid glucose changes this is ≈ 6 minutes
- Sensor Software Filtering Lag
  - With rapid glucose changes this introduces ≈ 12 minute lag

The Devices

- Paradigm® 722 System
- Guardian® RT
- Dexcom® STS
- Navigator
DexCom STS Sensor
Medtronic Paradigm REAL-Time
Side View Showing Needle Sensors

CGMS - 722  Navigator  Dexcom
<table>
<thead>
<tr>
<th>Device Feature</th>
<th>Paradigm 722</th>
<th>DexCom</th>
<th>Navigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of change arrows</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Programmable Threshold Alarm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Projected low alarm</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Days of wear</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Ability to download</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ability to integrate with pump</td>
<td>Yes (MiniMed)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
# Accuracy of Sensors

*Kovatchev, electronic preprint, Diabetes Care, 2008*

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>Guardian</th>
<th>Dexcom</th>
<th>Navigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy 70-180 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ARD%</td>
<td>15</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>% within 20%</td>
<td>73</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td><strong>Accuracy &lt; 70 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ARD%</td>
<td>14</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>% within 15 mg/dl</td>
<td>77</td>
<td>53</td>
<td>79</td>
</tr>
</tbody>
</table>
Glucose Trends: CT

Post-breakfast excursion

Nocturnal lows
Missed meal bolus

Glucose (mg/dL)

Insulin Delivery

Carbohydrates and Exercise
17 yo Female, A1c 6.2
Daily Details 2-2-06

Glucose (mg/dL)

Insulin Delivery

Seizure
17 yo Female, A1c 6.2, in Study 3 Months
Daily Detail 2-1-06
Drill Bit Through Thumb
Drill Bit Through Thumb

Glucose (mg/dL)

Insulin Delivery
Topics To Be Covered

- Continuous Glucose Monitoring
- Augmented alarms for Nocturnal Hypoglycemia
- Partial Closed Loop
- Full Closed Loop
HYPOGLYCEMIA

- 657 children followed for 3 years
- 8.5% had severe (seizure or coma) and 27% moderate (required assistance) hypos
- < 6 y.o. = 40/100 patient yrs
- >6 y.o. = 17/100 patient yrs
- 75% of seizures occurred at night
17 yo Female, A1c 6.2
Daily Details 2-2-06

Glucose (mg/dL)

Insulin Delivery

Seizure
14 y.o. male A1c = 6.6%, Crews (rowing team) in PM
### Response to Navigator Alarms

<table>
<thead>
<tr>
<th>Threshold</th>
<th># of nights wearing a sensor</th>
<th># of episodes</th>
<th>Average duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 mg/dl</td>
<td>138</td>
<td>30</td>
<td>72 minutes</td>
</tr>
<tr>
<td>&lt;70 mg/dl</td>
<td>138</td>
<td>53</td>
<td>80 minutes</td>
</tr>
</tbody>
</table>
Possible Project

- We need an economical alarm that would work with all devices
- All of the devices vibrate and/or beep
- Sensor would need to detect beep or vibration and then
  1) Turn on a light
  2) Relay the alarm to another room, such as the parents bedroom
Topics To Be Covered

- Continuous Glucose Monitoring
- Augmented alarms for Nocturnal Hypoglycemia
- Partial Closed Loop
- Full Closed Loop
Partial closed loop

- Use Real Time CGM to stop insulin delivery for predicted hypoglycemia
- A safety measure
- Sensor is not used to delivery insulin, only to withhold insulin
- FDA has given a Mona Lisa smile to this endeavor
Graph of results from a first admission

Time in Minutes

Basal Insulin

Navigator Glucose
FreeStyle Glucose
Basal Insulin
SP Alarm
LP Alarm
Graph of results from second admission

Time in Minutes

Navigator Glucose
FreeStyle Glucose
Basal Insulin
SP Alarm
LP Alarm
Effectiveness Of Prediction Alarms In Preventing Hypoglycemia (< 60 mg/dl) During 90 Minutes Of Pump Suspension

<table>
<thead>
<tr>
<th>Triggering Alarm</th>
<th>Threshold (mg/dl)</th>
<th>Projection Horizon</th>
<th># studied</th>
<th>Hypoglycemia Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP</td>
<td>80</td>
<td>30 min</td>
<td>15</td>
<td>60%</td>
</tr>
<tr>
<td>LP</td>
<td>80</td>
<td>30 min</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>LP</td>
<td>80</td>
<td>45 min</td>
<td>5</td>
<td>80%</td>
</tr>
</tbody>
</table>

SP = Statistical Prediction
LP = Linear Prediction
Topics To Be Covered

- Continuous Glucose Monitoring
- Augmented alarms for Nocturnal Hypoglycemia
- Partial Closed Loop
- Full Closed Loop
Requirements to Create an Artificial Pancreas

- Insulin Pump
- Continuous Glucose Sensor
- Algorithm (control program):
Need for a closed loop

• Diabetes is a demanding, chronic disease
• 65% of pump users miss more than 1 bolus/week raising their A1c by 0.8% (Burdick, Chase, et.al)
• Even with a sensor augmented pump, 20% of adolescents in poor control did not modify their diabetes management and remained in poor control
13 y.o. male, A1c=8.8, Daily Summary

Glucose (mg/dL)

Insulin Delivery

Carbohydrates and Exercise
Insulin Pumps (SQ)

- Subcutaneous
  - Advantages
    - Easy access
    - Little risk of infection
    - Reliable pumps are available today
  - Disadvantages
    - 10-15 minute delay in onset of insulin action
    - Infusion site needs changing every 3-4 days
    - Always wearing a device
Insulin Action after an Insulin Pump Bolus
Important distinction between Pharmacokinetics & Pharmacodynamics

Pharmacokinetics:
Insulin levels

Pharmacodynamics:
Insulin bioactivity

Aspart (NovoLog) insulin

Østerberg, 2003
Infusion Pumps (Intraperitoneal)

- Implanted
  - Advantages
    - Rapid onset of insulin action if insulin delivered to:
      - portal (liver) circulation
      - intravenously
    - Not wearing an external device
    - No infusion set sites to be changed
  - Disadvantages
    - Surgically implanted
    - Size of implanted device (hockey puck)
Response to a Meal

- β-cell response portal delivery
- Feedback of predicted insulin $I_p$
- Adjusted $K_p$, $K_i$, $K_D$
- β-cell response SC delivery
Microneedle Arrays
To deliver Insulin

**FIG. 4.** **Left panel:** A 200-μm-wide nitinol superelastic microneedle next to a 20-gauge standard stainless steel needle tip. **Middle panel:** Microneedles assembled into a nine-needle array. **Right panel:** Needle array next to a U.S. quarter.
Continuous Glucose Sensors (CGS)

- Subcutaneous needle-like sensors
  - Advantages
    - Easy to self-insert
    - Available today
    - Can function 5-6 days
  - Disadvantages
    - 10-15 minute delay in subcutaneous glucose compared to blood glucose
    - Are calibrated to meters with a 5-10% error
    - Accuracy is about 10-18% of actual blood glucose
    - Sensors need to be reinserted every 3-6 days
    - Wearing an external device
Challenges with a SQ Glucose Sensor

- The readings have measurement “noise”
  - Their accuracy is generally 10-15%
- Are calibrated to meters with 5-10% accuracy
- There is a 10-15 minute lag between changes in the blood and Subcutaneous glucose concentrations
Continuous glucose sensors

- Intravascular
  - Advantages
    - No external device
    - Direct measurements from blood
  - Disadvantages
    - Need to be surgically implanted
    - A risk for a potential blood clot forming around the sensor or the sensor becoming a source for an infection
    - To last for over 1 year requires a thick biocompatible membrane causes delays in blood glucose sensing
SQ compared to IV glucose sensor
Steil, Adv Drug Delivery 56: 125, 2004
Closed-Loop setup for “artificial pancreas” dog studies

MiniMed Telemetered Glucose Monitoring System (TGMS)

Diabetic dog with vest

External insulin pump

Computer with control algorithms and telemetry

K. Rebrin, MD-PhD, MiniMed personal communication (May 2001)
Prototypic closed-loop system

- Sensor signals transmitted to a laptop computer that displays the sensor glucose and calculates rate of insulin delivery
- Rate of insulin delivery is transmitted to the insulin pump
Artificial External Pancreas

- 10 adults
- Subcutaneous insulin infusion pump
- Insulin infusion controlled by real time glucose levels from subcutaneous glucose sensor (CGMS)
- Studied for 28 hours in a clinical research center
FIG. 1. Simulated response of the *PID* algorithm to a hyperglycemic clamp. Delivery is comprised of a component, *P*(*n*), that is proportional to the difference between SG and target; a component, *I*(*n*), that increments a basal rate in proportion to the difference between SG and target; and a component, *D*(*n*), that adjusts insulin delivery in proportion to the rate of change of SG. The response is shown for *K*_p = 0.025 units/h per mg/dl, *T*_i = 150 min, and *T*_d = 66 min (see text for equations).
PID Controller
Steill, Diabetes 55:3344–3350, 2006

A

GLUCOSE (mg/dl)

Meals
Plasma Glucose
Sensor Glucose

B

SUBJECT

Suplemental Carbohydrate

TIME (h)
Mean glucose levels in first 5 subjects
Augmented Closed Loops

- Small pre-meal bolus given by patient
Closed-loop vs. hybrid control

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Nocturnal</th>
<th>Peak PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full CL</td>
<td>156 (149-163)</td>
<td>109 (87-131)</td>
<td>232 (208-256)</td>
</tr>
<tr>
<td>Hybrid</td>
<td>135 (129-141)</td>
<td>114 (98-131)</td>
<td>191 (168-215)</td>
</tr>
</tbody>
</table>
Results: Increased Time in Normal Range from 58 to 82%

Home CSII
- < 70: 33
- 70-180: 58
- > 180: 8

Closed-Loop
- < 70: 15
- 70-180: 82
- > 180: 3

p < 0.002
Moving Horizon Concept of MPC

- Past
- Future

- Target value

- Time

- k

- k+1

- k+m

- k+p
Moving Horizon Concept of MPC

Chess Analogy
A time-series model is constructed allowing for real-time prediction of glucose fluctuations, in particular hypo- and hyperglycemia.
Length of Wear of System

- Sensors commonly last 5-7 days
- How about infusion sets?
Definition of Infusion Set Failure

- A blood sugar over 300 mg/dl that fails to decrease by at least 50 mg/dl one hour following a correction dose.
- Presence of blood ketones greater than 0.6 mmol/l in the blood associated with a blood glucose over 250 mg/dl.
- Infusion site infection, more than 5 mm of redness or firmness
DC shaft
111-114 tip
1111-116 tip
Possible Project

- Design a set of studies to minimize the tissue reaction around an insulin infusion cannula
  - 1) Changes to insulin
  - 2) Changes to catheter
    - Flexibility
    - Biocompatibility
    - Eluting anti-inflammatory
The Human Interface

- The real estate of skin
  - All want to wear just one device (as sensor and pump)
Skin Issues

- The heavier the device, the stronger the adhesive
- Sensor insertion speed and local trauma are critical
  - Speed decreases pain
  - Local trauma delays a stable environment for sensor readings
Navigator on Toddler
722 Tape Reaction
For Subcutaneous Sensing and Insulin Delivery

- **Size Matters**

- **One Device**
  - Insulin Pump
  - Glucose Sensor
    - Second Sensor?

- **Second Pump for Other Hormones?**
  - Incretin - slows rise in post prandial glucose levels
  - Glucagon - prevents hypoglycemia or rescues from hypoglycemia
Possible Project

- To determine how close an infusion set can be inserted to a glucose sensor
  - Can they be on the same needle/catheter
  - If not, how far apart do they need to be
Issues with Device Communications

- Data for Each Device is stored in its unique file structure
- There is no common structure for RF communications
- Each device only speaks to its own proprietary software
Issues with Device Communications

- Each Device has its own download dongle
The Human Interface

- The real estate of skin
  - All want to wear just one device (as sensor and pump)
- Wearing/carrying controllers/receivers
  - Want a single device to control pump and receive sensor signal
    - Cell phone
    - PDA
    - MP3
    - Games
Pumps and Sensors Communicate to a Shared Platform
The All-In-One Device
Possible Project

- Working on communication between devices
  - Allowing an iPhone or a chip for a PDA/phone to have the code to communicate with both a sensor and a pump
    - What RF signals to use – “medical device” bands
      - Able to penetrate the body
      - Able to be transmitted over distances
Dexcom – Reaction to Taping for a Shower
System Should

- Detect the onset of eating
- Detect Sensor Failure
- Detect Infusion Set Failure
- Prevent Hypoglycemia
- Be small and lightweight
- “Auto-insertion” of sensors and infusion sets
- Be user friendly (an iPhone)
Questions of Redundancy

- How many glucose sensors?
- Several on the same needle probe?
- Different types?
  - Needle (high specificity, some noise)
  - Fluorescence based (now becoming very specific)
  - Optical (poor specificity to date)
- Different sites?
Thank you

- Questions?