MEMS in Healthcare (Products?)

Dorian Liepmann

University of California, Berkeley
Berkeley Sensor & Actuator Center
Department of Bioengineering
Existing Products

- **ISSYS**
  - Pressure
  - Force
  - Encapsulated
  - RF powered

- **Medtronic**
  - CareLink Monitor for defibrillator patients

- **CardioMEMS**
  - Implantable pressure sensor
  - Abdominal aneurysm monitoring – EndoSensor
  - Cardiac sensing - HeartSensor
Existing Products (?)

- **All simple devices (Piezo-based)**
  - Pressure
  - Force
  - Displacement

- **ISSYS**
  - Pressure
  - Force
  - Encapsulated
  - RF powered
Microneedles vs. Hypodermic Needles

Stainless Steel Hypodermic Needle
25G5/8, OD: 0.53 mm

Microneedles

500 μm
### Structure of the Skin

#### Target site: Epidermis
- **Interstitial fluid**
- **Above nerve endings**
  - Painless
- **No blood contact**
  - Reduced risk of infections
  - Reduced risk for device contamination

#### Drug injection
- Minimally invasive
- Low risk

#### Biomedical sensing
- Sensing system outside the body (simplifies approval)
- Fluid extraction: very difficult
- Dialysis: complex geometry
- Diffusion: passive (no control over time)
Putting Stuff into the Body

- Hypodermic Syringes
- Current push for different approaches
  - 1.x Billion vaccine doses delivered per year using hypos
  - Lots of accidents and problems
- Needle Free Injection
  - $10.2M in 2002 going to $425M by 2007 (Greystone Assoc. 2003)
  - 54% of sales being insulin-based
- Self-injection Market Growing at 15% per year (B-D)
- Options
  - Safety Needles
  - Jet injectors
  - Active Patch Technologies
  - Microneedles
Microneedle Categories

### Geometry

- **In-plane**
  - Solid: Silicon (1989)

- **Out-of-plane**
  - Solid: Silicon (1991)

### Application

- Electrodes for sensing & stimulation, perforation
- Injection or sampling of compounds

### Advantages

- Integration of electronics in one substrate
- High-density arrays
Complete MEMS Syringe
Drug Injection Through Microneedles

- Sample drug: Methyl Nicotinate
  - Causes dilation of blood vessel
  - Increases blood flow velocity

- Measurement of blood velocity
  - Laser Doppler velocimeter
  - Increase in blood velocity

- Effective drug delivery through microneedles
- Microneedles provide pathway through stratum corneum
- Painless

Shaft of conventional plastic syringe

Microneedles

% increase in blood flow rate

Sivamani et al. 2005
Extension to Diagnostics (Diabetes)

Array of 200 µm long out-of-plane microneedles (ID = 40 µm)

Pyrex bottom
Bond pad
Silicon top

Continuous Glucose Sensor
Increased needs for Sensors

- Healthcare is an obvious need
  - Sick people stay in hospitals mainly to be monitored
  - Chronic illnesses
  - Home healthcare
  - Elder care
  - Rural healthcare

- Monitoring what?
  - Small molecules
  - Physical state (fall sensors, motion data)
  - Overall health parameters (blood pressure, pulse, visual factors)

- Current situation
  - Trained and untrained people have to be around
  - Overall health checked regularly (needs a person around)
  - Occasional biochemical checks
  - High cost, low data rates, no data analysis
Diabetes epidemic

Per Capita medical expenses = $13,243/yr with diabetes and
= $ 2,560 /yr without diabetes

Source: United Nations Population Division,
World Health Organisation
Concept of a microneedle-based monitor

Integrated components:

- **Out-of-plane microneedles**
  - Painless and easy to apply
  - Good mechanical stability
  - Simple fabrication

- **Porous poly-Si dialysis membrane**
  - Improved long-term stability

- **Enzyme-based glucose sensor**
  - Automatic recalibration

*Continuous glucose monitor*
In-device enzyme patterning

1. Anodic bonding
2. Filling of the system with enzyme-polymer solution
3. Crosslinking of the PVA-SbQ\(^1\) under UV light
   \[\Rightarrow \text{Enzymes get entrapped}\]
4. Rinsing out the unlinked solution

\(^1\) PVA-SbQ: Poly(vinyl alcohol)-styrylpyridinium from Toyo Gosei, Japan
The new microneedle design (left) allows easier penetration of the skin due to a longer needle shaft, which causes the skin to stretch more and to break the stratum corneum. However, the longer microneedles reach the capillary bed of the dermis so that blood was sampled through the needles instead of interstitial fluid. The right figure shows the puncture wounds with blood clots after removing the microneedle array from the skin (back of the hand). Thus, significantly sharper needle tips and slim shafts are required.
Patient with type 1 diabetes for 5 years

Continuous glucose monitoring required

Source:
E. Cheyne and D. Kerr, Diabetes Metab Res Rev, 2002
Non-Invasive Measurements

- Need to ‘see’ the Interstitial Fluid
- Optical Approaches can ‘see’ ~1 mm into the skin
  - Near and Mid–Infared (OrSense, Cascade Metrix)
  - Fluorescence via FRET (BioTex)
  - Optical Coherence Tomography (UT Galveston, Penn State)
  - Laser/LED based system (VivaScan)
  - Non-Linear Dielectric Spectroscopy (Crospon)
  - Raman Spectroscopy (C8 MediSensors, DIRAmed)
- Optical Approaches applied to the eye
- Exhaled Methly Nitrate (UC Irvine)
Minimally Invasive Monitoring

- Implanted minimal stuff: put part of system under the skin
  - Make measurement *in situ* and avoid transport issues
  - Minimize energy requirements for pumping, etc.
  - Smaller devices
  - Faster response

- RFID technology (no batteries)
  - Power supplied from outside for both analysis and communication

- Implanted physical sensors
  - Micro-Rheometry (EPFL, Columbia Univ.)
  - Micro-Dialysis techniques (Penn State)

- High-Tech Tattoos (La Tech, Smart Holograms)
  - Optically based systems
  - Measure result of a reaction

- Issues
  - Long term characteristics
  - Fouling, etc.
Intensive Insulin Therapy in the ICU

- Reduced Mortality by a factor of 2
  - 4.6% with intensive insulin therapy
  - 8.0% in the conventional therapy

- ICU Problems reduced
  - Blood stream infections requiring dialysis or prolonged hemofiltration
  - Critical illness polyneuropathy
  - Transfusion requirements
  - Prolonged mechanical ventilation

- Reduced the number of deaths from multiple-organ failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia

Portland Data for ~4000 By-Pass Surgeries

Fig. 5. Mortality among 3,959 patients with diabetes who underwent coronary artery bypass grafting between 1987 and 2003, stratified by 3 day average postoperative blood glucose sextile.

# My recent ER trip

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>H 198 mg/dL</td>
<td>70-99</td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>H 27 mg/dL</td>
<td>5-26 F</td>
</tr>
<tr>
<td>Creatinine</td>
<td>H 1.54 mg/dL</td>
<td>0.61-1.24</td>
</tr>
<tr>
<td>Sodium</td>
<td>L 127 mmol/L</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium</td>
<td>L 3.2 mmoll/L</td>
<td>3.5-5.1</td>
</tr>
<tr>
<td>Chloride</td>
<td>L 95 mmoll</td>
<td>95-110</td>
</tr>
<tr>
<td>Carbon Dioxide</td>
<td>L 21 mmoll/L</td>
<td>22-32</td>
</tr>
<tr>
<td>Amylase 59 U/</td>
<td>L 30-140 F</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>L 8.4 mg/dL</td>
<td>8.6-10.5</td>
</tr>
<tr>
<td>AST(SOOn)</td>
<td>44 U/L</td>
<td>15-45</td>
</tr>
<tr>
<td>ALT(SGPT)</td>
<td>46 U/L</td>
<td>10-63</td>
</tr>
<tr>
<td>Alk Phosphatase</td>
<td>H 272 UIL</td>
<td>35-115</td>
</tr>
<tr>
<td>Bilirubin-Total</td>
<td>H 1.71 mg/dL</td>
<td>0.00-1.30</td>
</tr>
</tbody>
</table>
ICU Tools for Tight Glycemic Control

- Firmly established for both home and hospital use for diabetics
- Devices perform well for these intended applications
- Virtually 100% of hospitals use BGT

Selected problems remain
1. Intensive glucose monitoring (Portland protocol)
2. Reliable patient identification
3. Interferences: Ketoacidosis, xylose, galactose, etc
4. Nagging issues with test strips
5. Connectivity/data management

Timing, Strip Wiping, No Connectivity

Kent Lewandrowski, MD, Associate Chief Of Pathology, Mass General Hospital
Advanced Technology in the ICU – Bar Codes

Error rate reduced by a factor of 10!

Interface problems for different sites

Kent Lewandrowski, MD, Associate Chief Of Pathology, Mass General Hospital
POCT in the future?

POC device with built in RFID reader

Wireless access point

Data management system

LIS → HIS

Lot number M878, Exp 7/2005

Operator ID card

Operator ID

Test strip

Patient wristband

Patient ID, billing number, patient name, patient DOB

Kent Lewandrowski, MD, Associate Chief Of Pathology, Mass General Hospital
MEMS Possibilities – Biosensing

- MEMS creates platform technologies
  - Will work with any enzyme or reactant
  - Can measure a wide range of medically significant molecules

- People simply refuse to sample data often enough
  - Painful and/or difficult
  - Invasive

- Application for drug development is potentially huge
  - System could monitor in-vivo drug concentration
  - Increase effectiveness of clinical trials (e.g. cancer therapies)

- Future systems will be continuous for every-day use
  - Currently continuous sensors are used for occasional monitoring
  - Hospitals are an example of the current need
  - Eventually will be deployed in ambulances

- Continuous data will become standard of care
  - Data for improved health care (e.g. glucose control in ICU)
  - Improved monitoring in surgery
  - Data for legal protection

- Acceptance of continuous sensing will take a few years
  - Too much information
  - Doctors are not used to it
Problems for getting MEMS into Market

- Research Side
  - **Funding**
    - DARPA is great: 10% chance of success
    - NIH requires 95% chance of success
    - NIH does not like “Design-based” research
  - **Identifying application area**
    - Need to work with an MD
    - QB3 is helping
    - Many needs are not high volume

- Jump to Products
  - Long-lead times from R&D to market (10 – 15 yrs)
  - Insurance reimbursement problems
  - Companies often cannot afford such long lead-times
  - Adoption by doctors – becoming standard of care
The Sci-Fi Future of Medicine

Fantastic Voyage

Ken Gilleo, ET-Trends
Ken@ET-Trends.com