BioMEMS Overview and Introduction

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Topics to be Covered

- What is BioMEMS?
  - Scaling in the biological world
  - A brief history
- BioMEMS Devices
  - Biosensors
  - Microactuators
  - Microfluidics*
- Major categories of BioMEMS
  - Surgical
  - Implants
  - Transdermal biofluids sampling
  - Imaging
- Examples of BioMEMS for Major Diseases
  - Cardiovascular disease
  - Cancer
  - Stroke
  - Diabetes (covered elsewhere)

- Future trends –
  - Diagnostics and treatment
  - Minimally-invasive
  - Implanted
  - Bionanotechnology
    - Nanomedicine
    - Programmable biomolecular devices
  - The convergence of bio:info:nano technologies
What is Bio-MEMS?

1. The development of MEMS for biomedical and biotechnological applications

2. The application of MEMS in medicine and bioinstrumentation

MEMS:
- In Vivo MEMS (Biomedical)
  - Minimally-invasive therapies
  - Precision surgery
  - Biotelemetry
  - Physical sensors

BioMEMS:
- Merge early detection, diagnostics with treatment, therapeutics
- Gene sequencing
- Proteomics
- Drug discovery/testing
- Diagnostics
- Pathogen detection/ID

The best market for BioMEMS is a New One!
Deals with samples from the host
Deals with the host anatomy

Customers

- Military
- Pharmaceutical industry
- Environmental monitoring
- Medical devices
- Instrumentation
- Food monitoring
**BioMEMS Market Studies**

- NEXUS predicts $19B market in 2005
- Technology for Industry Ltd. (UK) $11B in 2005
  - [http://www.combichem.net/acatalog/Technology_Networks_Market_Reports_49.html](http://www.combichem.net/acatalog/Technology_Networks_Market_Reports_49.html)
- MEMS Consortium in Pittsburgh (approx. $2-3B in 2005)
- Market for Microfluidic systems is forecast to grow from $77M in 2002 to top US$395M by 2004. (Frost & Sullivan)
- Worldwide market for micro-array, micro-fluidics devices and other biochips is expected to grow at 65% annual rate and reach $3.3B by 2004. (Technical Insights, San Antonio, TX)
- The cost of pharmaceutical development ($800 million per approval) is dominated by the expenses and failures experienced in clinical trials.

The ever-increasing aging population, the general acceptance of technology to improve healthcare, the third world epidemic crisis, and perhaps bioterrorism will drive up the need for BioMEMS

**Chip-Scale Integration:**
*From MEMS to BioMEMS*

- μelectronics
- μphotronics
- MEMS
- Biochips/BioMEMS

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*Abraham P. Lee, Ph.D.*
Nano “feelers” (resonators, probes, grabbers) will function inside a microfluidic chip much like an ion channel functions in a biological cell. The INBIT vision is to further advance the integration of the micro and nano devices with the biological counterparts.

**History of MEMS-BioMEMS**

- **the 60's:**
  - 1960: Richard Feynman "There's Plenty of Room at the Bottom.
  - 1965: Nathanson and Wickstrom Resonant gate transistor, the first "MEMS" actuator.
- **the 70's:**
  - 1970: Richard White at UC Berkeley started working on surface acoustic wave (SAW) devices that were fabricated by bulk silicon micromachining.
  - 1978-79: Ken Wise at University of Michigan and Wen Ko at Case Western Reserve University led the way in the development of pressure transducers, both piezoresistive and capacitive. Fabrication technologies employed include thin film doped membranes, and doped polysilicon piezoresistive sensing schemes and capacitive membrane sensing.
- **the 80's:**
  - 1982: Kurt Petersen at IBM published "Silicon as a Mechanical Material" described applications in sensors and actuators. Important devices were ink jet nozzles, accelerometers, and microrelays. Pointed out 3 major advantages of silicon-based micromachining:
  1) provide functions not easily duplicated by conventional analog and digital circuit.
  2) satisfactorily solve inherent problems of mechanical reliability and reproducibility.
  3) fabrication process compatible with standard IC processes. Low cost, high yield technologies are preferred only if well-established batch fabrication processes are employed.
**BioMEMS History (continued)**

- **1982**: Masayoshi Esashi at Tohoku presents work on catheter-tip pressure sensors. Many packaging techniques [Esashi 1993] are also developed by Esashi’s group for microvalves and pressure transducers.
- **1984**: Roger Howe at U.C. Berkeley presents a chemical vapor sensor, which initiates the polysilicon surface micromachining era. This transforms into the micromotor and lateral resonators that launched the explosion of MEMS and inspired the imagination of many researchers today.
- Other 1980s: the LIGA process by Germans, Wise and Ko continued development of biomedical sensors.

**1990-2002**

**key technologies developed:**

- integration of surface and bulk micromachining through wafer bonding and deep reactive ion etching (RIE) of silicon.
- Polymer microfabrication is foundation of many microfluidics/biochip companies, medical microdevices still use a lot of silicon
- Monolithic and hybrid integration of MEMS and electronics
- New materials integrated in silicon-based processes for sensing and actuating advances (soft lithography, SMA, PZT, smart polymers, porous silicon, etc.)

**BioMEMS History (continued)**

- **1990-2002 cont’d**
  - MEMS foundry processes for standard micromachining (surface, bulk, LIGA, polymers)
  - MEMS is truly integrated in academics, as almost every disciplinary are getting involved (EE, ME, CHE, Mat. etc)
  - An explosion of MEMS-based companies; many major industries start exploring MEMS (medical, automotive, biotech, computer, displays, etc.) particularly in the optical switch business
  - Biochips and Microfluidic companies appear (many sprung out of academia): Affymetrix, Nanogen, Caliper, Aclara, Fluidigm, Nanostream, Orchid, Biotrove, Surface Logix,
  - BioMEMS drug delivery companies, e.g. iMEDD, MicroCHIPS, Therafuse
  - NEXUS estimates $19B BioMEMS market by 2005
Requirements of Transducers for Medical Instrumentation [after Ko 1989]

A. Convenience of Use:
   - Of small size and weight.
   - Consume minimal power (µW to mW).
   - User-friendly, no frequent adjustment needed.
   - Long-term stability and compensation for environmental changes.
   - Can be easily interfaced with other parts of the system; interchangeable from unit to unit.

B. Safety to User
   - Packaged with biocompatible material, and with the proper smooth surface.
   - No toxic substance generated when failure occurs due to heat or mechanical forces; does not give out toxic gases and materials when overheated, burned, or crushed.
   - Can be sterilized
   - The mechanical impedance of the device interface with the body should closely match that of the body tissues.

C. Low Cost

Oftentimes the MEMS requirements and the biomed industry don’t match
### Transducers Required for Closed Loop Systems: [Ko 1989]

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prosthesis</th>
<th>Sensors Needed</th>
<th>Actuators Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Arrhythmia</td>
<td>Physiological Pacemakers</td>
<td>Pressure, Flow, and Chemical Sensors</td>
<td>Stimulating Electrodes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Automatic Insulin Infusion Pump</td>
<td>Glucose Sensor</td>
<td>Controlled Pump</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Cerebellar Stimulation System</td>
<td>Electrical Signal Sensors</td>
<td>Stimulating Electrodes Drug Pumps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biochemical Sensors</td>
<td>with Stimulating Electrodes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Automatic Blood Pressure Control Device</td>
<td>Implantable Blood Pressure Sensors</td>
<td>Stimulating Electrodes</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Automatic CSF and Ventricular Size Systems</td>
<td>Pressure and Volume Sensors, Control Valves</td>
<td>Stimulating Electrodes</td>
</tr>
<tr>
<td>Paraplegia and Quadriplegia</td>
<td>Control of Limbs with Nerve bypass System</td>
<td>Electrodes: Position, Touch, and Angle Sensors</td>
<td>Stimulating Electrodes</td>
</tr>
<tr>
<td>Respiratory Apnea</td>
<td>Diaphragm Pacer</td>
<td>Air Pressure and Flow Sensors</td>
<td>Stimulating Electrodes</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Bladder Control System</td>
<td>Pressure or Volume Sensors</td>
<td>Stimulating Electrodes Drug Pump</td>
</tr>
</tbody>
</table>

### Artificial Organs and Drug Delivery

#### Artificial Organs

<table>
<thead>
<tr>
<th>Artificial Organs</th>
<th>Treatment</th>
<th>Sensors Needed</th>
<th>Actuators Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Blood Pump and Control</td>
<td>Pressure, Flow, pO2, pCO2</td>
<td>Electrode stimulators</td>
</tr>
<tr>
<td>Kidney</td>
<td>Dialysis Machine</td>
<td>Uric Acid and Flow</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>Body Controlled</td>
<td>EMG Sensors</td>
<td>EMG Actuators</td>
</tr>
<tr>
<td>Ear</td>
<td>Hearing Aids</td>
<td>Microphones</td>
<td>Electrodes Vibration &amp; Sound Actuators</td>
</tr>
</tbody>
</table>

#### Drug Delivery

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>Sensors Needed</th>
<th>Actuators Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Drug or Stimulation</td>
<td>Drug Delivery Sensor</td>
<td>Drug Level Actuators</td>
</tr>
<tr>
<td>Cancer and Other Diseases</td>
<td>Drug with Sensor for Monitoring</td>
<td>Drug Level Sensor</td>
<td>Drug Level Actuators</td>
</tr>
</tbody>
</table>
Categorization of Biosensors by Applications

- In vivo realtime monitoring of chronic signals for disease management
  - Examples: Glucose sensors, cancer product blood sensors, blood pressure, heartbeat sensors, or neural prosthesis probes.
- In vivo realtime monitoring of acute signals for emergency medicine and triage (e.g. combat casualty care)
  - Examples: oxygen sensors, PH sensors during surgery, blood pressure, heartbeat sensors, blood gas sensors, and other vital signs.
- Sensors for biological processing stations:
  - Examples: Temperature sensors for PCR devices, optical sensors for monitoring biochemical reactions, in vitro molecular/neural cell interaction electric sensors.
- Sensors for environmental monitoring
  - Examples: sensors for bio-hazards, food processing monitoring, agriculture sensors, pharmaceutical sensors, and petrochemical sensors, etc.

MEMS Biosensors:
- Advantages: Cost, size.
- Applications: Pressure sensors, Practical Examples in literature and in market.
- MEMS Biosensor Examples:
  - Glucose Sensor
  - Neural Probes
  - Tactile
  - Pressure Sensors
  - Temperature
  - Flow
  - Force/Stress/strain
  - Inertial
  - PH
  - Optical Fiber
  - Blood Gas Sensors, O2, CO2
  - Immunosensors
**Minimally-Invasive Therapy and Diagnostics**

- **Types:** laparoscopic surgery, catheterization
- **Advantages:**
  - reduced trauma to patient, reduced hospitalization, potential for remote surgery → reduced health care cost.
- **Disadvantages:**
  - constraints on instrument maneuverability, visibility, and reduced tactile sensation
  → MEMS have great potential to improve MIT
- **Examples:**
  - catheter steering, endoscope steering
  - micromanipulation
  - pressure sensors
  - imaging

**Ultraminiature catheter pressure sensor**

- **Size, Assembly, and Packaging:**
  - Mounted on 0.5 mm OD catheter with only 2 leads
  - 290x550x1.5µm diaphragm with 2 µm gap
  - Three chips integrated, glass substrate, interface circuit chip, and silicon transducer chip
- **Sensing:**
  - Capacitive sensing allows low power requirements
  - Intravascular coronary artery pressure sensing
  - Multiple pressures sensors can be mounted to measure pressure gradient and even act as flow sensor
  - Temperature compensation by interface circuit
  - Sensitivity 850 ppm/mmHg @ \( P_{\text{applied}} = 0 \)
  - Pressure range 500 mmHg
  - Pressure resolution 1 mmHg
  - Pressure accuracy 2 mmHg
  - Signal bandwidth 40 Hz
  - Signal format: supply current pulse rate
  - Capacitance at zero-pressure is 490 fF at 37°C

A Passive Implantable Pressure Sensor for Continuous Intraocular Pressure Monitoring [Rosengren et al. 1993]

Monitoring and detection of Glaucoma.

- **Fabrication:**
  - Oxide fusion bonding, KOH wet etching with manual V-groove etch stop
- **Size, Assembly, and Packaging:**
  - Assembled external coil wrapped around device
  - External detector coil
  - 1.8mm square diaphragm
  - Total device size: 5mm x 2mm
- **Sensing:**
  - LC circuit forms passive RF resonator
  - In vitro sensitivity 4 mV/mmHg
  - Resonator pressure sensitivity 1 kHz/mmHg
  - Pressure range 80 mmHg
  - No leakage at 75 mmHg through the surgery cut

![Fabrication Cross-section of Passive Intraocular Pressure Sensor](image1)

In Vivo experiment test setup

![Rabbit Eye](image2)

Microturbines for Minimally-Invasive Therapy

- LIGA fabricated gears and shaft with 100 µm wall thickness and 20:1 aspect ratio
- Driving fluid normal to turbines
- Improvement over current atherectomy or a rotablator since microturbine could be attached to tip which eliminates the need for stiff staff throughout catheter
- Projected torque 30 µN•m at 2000 rev/sec (40 mW) comparable to current rotablator
- Expected pressure drop is sufficient

![Microturbines](image3)

**Micro Active Forceps for Intra-Ocular Microsurgery [Ikuta et al. 1996]**

- Fabricated using stereolithography [Ikuta et al. 1993]
- Laparoscopic on the eye
- Optical fiber scope is 2000 µm in diameter
- Prototype tested on a pig eye

**Active Catheter by SMA and Smart Polymer Actuator**

- Remote control of tip steering by 3 SMA links, power 80 mW with 13° bending, 0.8 Hz response time; signal processing IC to minimize lead wires
- Electroosmosis by ion current and water current in water, Na+ ions move to the cathode side and become water rich to swell towards the anode

Source: Lim et al., MEMS 1995

Source: S. Sewa, MEMS 1998
**Micromachined Confocal Microscope**

- Fiber optic real-time imaging system with scanning micromirrors in x- and y-directions.
- Process: bulk silicon micromachining fiber optic grooves, scanning chamber, polish to 25 µm mirror thickness
- Characteristics: electrostatic actuation, off-axis binary lens, NA=0.25, 1 µm resolution over 100 µm field of view


**Implants: Retinal Prosthesis**

- Development of functional microdevices that fit in the human eye to restore vision
- Two types: EPI-RET (stimulates the ganglion cells) and MPD Array (subretinal, replaces photoreceptors)

- Review article: J.-Uwe Meyer, "Retinal Implant – A BioMEMS challenge"
**MEMS to Tackle Stroke**

“The No. 3 killer of Americans and No. 1 cause of serious disability”

- Catheter technology reduce healthcare costs by eliminating long hospital stays and recovery times associated with treating aneurysms today
- Cost for treatment and rehabilitation account for more than $40 billion/year in the U.S.

![Image of catheter technology](image1.png)

**MEMS for Cerebrovascular Diseases**

- Micromechanical delivery System
- Micro cauterizer
- Micro biopsy tool
- Optical acoustic thrombolysis
- Micromechanical devices for ischemic stroke therapy
- Drug delivery microfluidic system

**MEMS for Ischemic and Hemorrhagic stroke treatment**
Design of Micromechanical Release Mechanism – An In Vivo Example

Design parameters:
- gripping force (30gm required by physicians)
- rigidity, torquability
- size
- temperature
- voltage

SMA-Silicon Microgripper and Test Cantilever

- NiTiCu
- Au-Si
- 1 mm
- SMA
- poly-Si
- SiO2
- substrate

Power Consumption 0.14 watts (water) to 0.032 watts (air)
**SMA Actuation of Microgripper**

- Stress measured by substrate curvature measurements and translating the curvature to stress through Stoney’s equation:
  \[
  \sigma_f = \frac{E \cdot d^2}{6(1 - v)rt}
  \]
- Displacement from SMA film induced stress (375 MPa) is calculated to deflect 53 \(\mu\)m by bimorph theory (Timoshenko)
- Experiment results show 55x2 \(\mu\)m = 110 \(\mu\)m total displacement
- Equivalent force \(F\) applied at the tip is calculated to be 13mN for 55 \(\mu\)m displacement

**Shape Memory Polymer (SMP) Release Mechanism**

- Transition temperature \(T_g\) between glassy and rubbery phases
- Glassy phase elastic modulus \(\approx\) GPa
- Shown to be biocompatible in systemic, in vitro, intracutaneous cell toxicity tests
Optical Feedback Mechanism

Biosystems-on-a-Chip Merges Diagnostics with Treatment

BioMEMS Market Forecast: $19B by 2005 (NEXUS)
Creating Biomolecular Sensors to Enable Integrated Cancer Care

Microfluidic Chips as the Bridge from the Host Response to in vivo Molecular Signatures

Two emerging biofluids technologies:

- **Sampling**: GlucoWatch™ from Cygnus (Redwood City) can non-invasively monitor glucose levels continuously through the skin via reverse iontophoresis.
- **Delivery**: Microneedles, Skin Patches (contraceptive, smoke quitting), Chemical Osmosis, Electroporation, Sonphoresis, Thermal poration.
**Transdermal Sampling of Biofluids**

- Continuous monitoring of physiological status and delivery of drugs
- Small, unobtrusive, integrated patch-type sensor Periodic, precise and minimally invasive sampling of body fluids
- One key application is for detection of stress, leading to appropriate “first response” for maintenance of war-fighter’s health.
- Leading research institutes: UC Davis, U of Cincinnati, UC Berkeley, Georgetown U.
- Companies: Redeon, Kumetrix

**What to Sense**

- Time response critical – pulse + fever is a late response
- (10min) Tumor Necrosis Factor (TNF) may be the first response to infection
  - cascade for this has not been identified
  - Pre-TNF response has not been explored
- (1 hour) NO in breath, ionic Calcium, and heart beat variation may be effective although slower
- (1 hour +) ILG, Coagulation, WBLT, Immune activation
- (1 hour +) Pulse rate and fever
- (1000 min) blood pressure
Biochip for Clinical Diagnostics

Fully integrated stand-alone plastic microfluidic biochips

- Inlet ports
- Multiplexing channels with passive valves & mixers
- Biochemical sensors (underneath)
- Liquid sample/buffer reservoirs
- Localized heater “Detonator”
- Pressurized air bladders
- Microneedle array
- Watch & Display cap
- Wrist watch band
- Action buttons

Metabolic Parameters: pH, pCO₂, Hct

BioMEMS
University of Cincinnati

Monitoring the Warfighter's Health Parameters

Bio Defense Applications
- Combat casualty care, triage
- Battle readiness
- Human responses during testing
- Controlled drug delivery
- Presymptomatic, early detection of infections
- Distributed, covert deployment of bio-detectors
- Rapid indication of CBW incident

Abraham P. Lee, Ph.D.

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Biological Systems

- Specified by
  - $4 \times 10^9$ base pairs ($2^{32}$)
  - $10^5$ proteins ($2^{17}$)
- Features
  - Regulation & adaptation
  - Hierarchical self-assembly
  - Repair and maintenance
  - Parallel processing
  - “Just-in-time” processes
  - Non-linear dynamics
  - Asynchronous control and signaling
  - Multicellular systems
  - Scalability

The Software!!!!
The Complexity of Biological Signaling Pathways

- Signaling pathways allow the cell to receive, process, and respond to information.
- Different signaling pathways interact resulting in signaling networks.

Bhalla and Iyengar, Science 283, 15, Jan 1999

Fig. 1. Reaction schemes and parameters for library of pathways in simulations. Reversible reactions are represented as bidirectional arrows, and irreversible reactions as unidirectional arrows. Enzyme reactions are drawn as an arrow with two heads, where the enzyme is located on the middle segment. For clarity, the same reaction may be represented multiple times in a given reaction scheme, but it is modeled only as a single reaction. Details of parameters for the thermodynamic and kinetic values are available at our web site.
**Info vs. Bio in the Speed Domain**

- Mutation rates of proteins
- Organism lifetimes
- Macromolecular rates (e.g., heart)
- H-exchange inside proteins
- Thermal dissociation
- Conformational changes
- Reflex times (nerve impulses, mechanical responses, eye)
- Protein ligand recombination
- Diffusion limited reactions
- Rotation times
- Fluorescence lifetimes
- Primary processes in photosynthesis, purple membrane and hemoglobin
- Molecular relaxation time

**Info**
- Adaptive algorithms
- Robotic control systems
- Spectral and Bayesian Decoding
- Hybrid control architectures
- Single-cell signaling architectures

**High performance computing**

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**Bionanotechnology**

They are stronger than steel, but the most important use for these threadlike molecules may be in fashion more efficient and more durable electronic devices.

*Philip G. Collins and Panchal Arteke*

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*Nanotubes for Electronics*

*Courtesy: Arun Majumdar, UC Berkeley*
MEMS Bioassays for Cancer Diagnostics

- Bioassay of prostate-specific antigen (PSA) using microcantilevers
- Cantilever motion originates from the free-energy change induced by specific biomolecular binding (protein-protein) that can be optically detected
- May offer a common platform for high-throughput label-free analysis of protein–protein binding, DNA hybridization, and DNA–protein interactions, as well as drug discovery.

Wu et al., Nature Biotechnology, vol. 19, Sep 2001
Courtesy of A. Majumdar

Nanoscale Synthesis and Self Assembly of Artificial Cells

- Microfluidics to control nanoscale interfaces (droplet emulsions) and self-assemble cellular machinery into artificial vesicles

Light-dependent generation of ATP

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Nanodevices Using the Cellular Machinery

Neuronal signaling at a synapse

On-chip mimicking of synapse signaling

Research at the Bio:Info:Micro|Nano Interface

New IT and MT to determine equivalent of device physics for technology platforms where biology can communicate with info and micro

- Create a feedback loop among bio, info, & micro to create new knowledge, teams, approaches, and systems
- Leveraging mutual opportunities, challenges will lead to revolutionary technologies
Summary

- BioMEMS market is diverse and looking up
- Two major categories of BioMEMS: in vitro and in vivo
- Integration of diagnostics and treatment
- Integration of molecular scale to organ scale