MEMS FOR DRUG DISCOVERY APPLICATIONS

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Problem Statement

Combinatorial chemistry: synthesize many new compounds

many possible biomolecules

Combinatorial Chemistry

Need a rapid low cost method to identify effective “drugs”

Q: How can we screen the new drugs?
Q: Where is there a hit?
MEMS As A Screening Tool

- batch fabrication
- low cost
- disposable
- rapid testing
Approach

Vibrating Structures

- cantilever
- bridge

Challenges
- fabrication
- surface chemistry
- sensitivity
- operation in a fluid

Principle: Frequency shift when new compounds attached to the biomolecule

\[ \omega = C \sqrt{\frac{k}{m}} + \Delta m \rightarrow \omega \downarrow \]
Overview

- Design Details
- Surface Treatment
- Performance Measures
- Device Performance
- Current Focus
- Overview of Performance in Liquid
- Conclusion
Design Details

Two layers PZT, for sensing and actuating
Cross Section of Cantilever
SEM Picture — Cantilever
SEM Picture — Cantilever Vibrating
SEM Picture — Cantilever Vibrating
Cantilever Vibration
SEM Picture — Bridge
SEM Picture — Bridge With Dam
### Hysteresis Loop – Top PZT

<table>
<thead>
<tr>
<th>Charge 2.2</th>
<th>RT-66A</th>
<th>4/27/1999 8:55</th>
<th>Hysteresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>X div=2.5000</td>
<td>Y div=6.6312</td>
<td>Offset=12.909</td>
<td>+Ps=26.525</td>
</tr>
<tr>
<td>uC/cm²</td>
<td>Virtual Ground Mode</td>
<td>+Pr=14.515</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Pr=-14.668</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+Vc=2.886</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Vc=-1.566</td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P*'=36.528</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P*r=27.501</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P^'=16.791</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P^r=7.229</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(nF)=11.0059</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kef=1657</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I=3.0641-09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-I=-1.4724-09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R=3.2619+09</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>-R=6.7933+09</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ry=2.4464+11</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-Ry=5.0950+11</td>
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<td></td>
</tr>
<tr>
<td>Sample: su201</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area(cm)=3.00E-03 Thick(μ)=0.400 Vmax=10.000 #Pts=500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse=2.0293ms Hyst=545.00ms Resist=250.155ms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Hysteresis Loop — Bottom PZT

## Hysteresis

<table>
<thead>
<tr>
<th>CHARGE 2.2</th>
<th>RT-66A</th>
<th>4/27/1999  8:58</th>
<th>Hysteresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>X div=2.5000</td>
<td>Y div=10.3319</td>
<td>Offset=17.652</td>
<td></td>
</tr>
</tbody>
</table>

Sample: su201

<table>
<thead>
<tr>
<th>Volts</th>
<th>uC/cm²</th>
</tr>
</thead>
</table>

Ymax=5.1660E+01
Ymin=-5.1660E+01
Xmax=1.2500E+01
Xmin=-1.2500E+01

## Hysteresis

<table>
<thead>
<tr>
<th>Virtual Ground Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>+Ps=41.328</td>
</tr>
<tr>
<td>+Pr=20.214</td>
</tr>
<tr>
<td>-Pr=20.520</td>
</tr>
<tr>
<td>+Vc=1.955</td>
</tr>
<tr>
<td>-Vc=1.364</td>
</tr>
</tbody>
</table>

## Pulse

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P*=57.756</td>
</tr>
<tr>
<td>P*r=39.167</td>
</tr>
<tr>
<td>P^=25.741</td>
</tr>
<tr>
<td>P^r=8.300</td>
</tr>
<tr>
<td>C(nF)=17.3848</td>
</tr>
<tr>
<td>Kef=2618</td>
</tr>
</tbody>
</table>

## Resistivity

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I=1.3387-09</td>
</tr>
<tr>
<td>-I=1.7946-09</td>
</tr>
<tr>
<td>R=7.4648+09</td>
</tr>
<tr>
<td>-R=5.5738+09</td>
</tr>
<tr>
<td>Rx=5.5986+11</td>
</tr>
<tr>
<td>-Ry=4.1804+11</td>
</tr>
</tbody>
</table>

Area(cm)=3.00E-03  Thick(H)=0.400  Vmax=10.000  #Pts=500

Pulse=2.0293ms  Hyst=545.00ms  Resist=250.155ms
Surface Treatment

1. 4-step
   SAM — Biotin — Blocker — Avidin

2. 1-step
   Avidin — BCIP

- Avidin-Biotin: strong protein-ligand bond
- Blocker: prevent “non-specific” bonding
- BCIP: verification of avidin, amplify response
Performance Measures

- Resonant Frequency
- Resonant Frequency Shift
- Q factor
Resonance Frequency: Cantilever Plate

$$\text{frequency} = f_n = \frac{k_n}{b^2 \sqrt{\frac{D}{w}}}$$

$$D = \frac{Et^3}{12(1 - \nu^2)}$$

$W =$ mass density per unit area

$E =$ composite modulus

$b =$ width

$\nu =$ Poisson’s ratio

<table>
<thead>
<tr>
<th>n</th>
<th>$f_n$ [Hz]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1463</td>
</tr>
<tr>
<td>2</td>
<td>9149</td>
</tr>
<tr>
<td>3</td>
<td>9959</td>
</tr>
<tr>
<td>4</td>
<td>25683</td>
</tr>
</tbody>
</table>
Resonance Frequency: Bridge Plate

\[ f_n = \frac{k_n \sqrt{D}}{b^2 \sqrt{w}} \]

\[ D = \frac{E t^3}{12(1 - \nu^2)} \]

\( W \) = mass density per unit area
\( E \) = composite modulus
\( b \) = width
\( \nu \) = Poisson’s ratio
Resonance Frequency Shift: Mass Of Biomolecules

molecule weight = 1.7 e-20 g/mol

molecule density = 40000 mol/µm^2

weight/area = 6.641 e-16 g/µm^2
Resonance Frequency Shift: Theoretical Shift in Frequency in Air

\[ \frac{\Delta f}{f} = \sqrt{\frac{w_1}{w_2}} - 1 \]

\[ w_1 = \text{weight / area of plate} = 2.555 \times 10^{-11} \text{ g/µm}^2 \]

\[ w_2 = \text{weight / area of plate and biomolecules} = 2.555 \times 10^{-11} + 6.641 \times 10^{-16} \text{ g/µm}^2 \]

<table>
<thead>
<tr>
<th>Design</th>
<th>1st Found Freq.</th>
<th>Shift(Δf)</th>
<th>Shift(Δf/f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantilever</td>
<td>1463Hz</td>
<td>0.0019Hz</td>
<td>0.0013%</td>
</tr>
<tr>
<td>Bridge</td>
<td>9387Hz</td>
<td>0.1220Hz</td>
<td>0.0013%</td>
</tr>
</tbody>
</table>

If biomolecules on both sides, shift = 0.0026%
Quality Factor

Definition:

\[ Q = \frac{2\pi \text{(stored vibration energy)}}{\text{dissipated energy per period}} = \frac{2\pi U_i}{U_d} \]

The quality factor, along with the resonance frequency, is an important parameter that affects the responsiveness expectable from the feedback circuit.
Measurement Of Q

Root-mean-square amplitude curve as a function of frequency for a one-dimensional oscillator with damping $g$.

An example of an experimental diagram.
Data: Resonant Frequency in Air

- Devices without surface treatment
- Devices with surface treatment
Cantilevers Without Biomolecules

Total in sample: 28 cantilevers
Total in sample: 35 bridges
Effect Of Adding Biomolecule

2-step process, bridge design

![Graph showing frequency response with labeled data points and gain for different conditions.]

- **Gain (Cleaned)**
- **Gain2 (Avidin)**
- **Gain3 (BCIP)**

Data points:
- \(124700 \pm 14\)
- \(125993 \pm 12\)
- \(126825 \pm 0\)
Independent Measure of Performance

Avidin → Biotin with Fluorescein

Frequency Shift vs. Shift in Fluorescence

Intensity of Fluorescein

-2.5 -2 -1.5 -1 -0.5

Frequency Shift (%)
Summary of Performance
With Biomolecule: Cantilevers

4-step Process

13 devices tested
5 devices shifted down
7 devices shifted up
-1.1% average down shift
Summary of Performance With Biomolecule: Bridges

4-step Process
- 13 devices tested
- 6 devices shift down
- 5 devices shifted up
- -0.65% average down shift

2-step Process
- 9 devices tested
- 5 devices shift down
- 0 devices shifted up
- -1.47% average down shift
Current Focus

- Performance in a Liquid
- Secondary Verification of Avidin mass or Thickness
- Packaging
Frequency Shift in Liquid

The resonance frequencies in water are much lower than in air, due to the mass of water dragged along with the cantilever.

\[
f_n^M = \frac{f_n^V}{\sqrt{1 + \left(\frac{L}{t}\right)\frac{\rho_M}{\rho_{Beam}}}k_n}
\]

\[f_n^M = \text{res.freq.in liquid}\]
\[f_n^V = \text{res.freq.in vacuum}\]

The motion of the lever affects a layer of fluid which is approximately half a wavelength \(\lambda_n\) thick:

\[
\lambda_n \approx \frac{4L}{(2n - 1)}
\]

Source: Weigert et al., Frequency shifts of cantilevers vibrating in various media, 1996
Schematic of cantilever oscillating in a fluid. The virtual mass of the cantilever includes an induced mass caused by the fluid being carried along. Viscous damping must also be considered to determine the resonant frequency and width.
Calculation Of Q In Liquid

From theoretical model:

\[ Q = \frac{k_n^2 b t^2 (\rho_b E / 12)}{6\pi \mu R L (1 + R / \delta)} \]

where:
- \( k_n \) = modal constant
- \( b \) = beam width
- \( t \) = beam thickness
- \( L \) = beam length
- \( \rho_b \) = beam density
- \( E \) = Young's modulus

\[ \delta = \left( \frac{\rho}{\rho_0 \pi f} \right)^{1/2} \]

\( \mu \) = fluid viscosity
\( r \) = sphere radius
\( \rho_0 \) = fluid density
\( f \) = frequency
Both resonance frequencies and quality factors drop down when the beams are immersed in the liquid.

Source: Walters et al., Short Cantilevers for atomic force microscopy, 1996
Liquid Test(1)
Liquid Test(3)
Concepts for Liquid Test
— Channel

Inlet

Outlet

Glass
Concepts for Liquid Test
— Reservoir 1
Concepts for Liquid Test
— Reservoir 2

Drop in Liquid

O Ring
Conclusions

- Bridge devices are more repeatable
- Device sensitivity is adequate

**Future Work**

- New set of bridge devices nearly completed
- Additional verification of surface treatment and sensitivity required
- Complete study of performance in a liquid
Resonance Frequency: Finite Element Model

<table>
<thead>
<tr>
<th>mode (n)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>analytical model [kHz]</td>
<td>9.387</td>
<td>22.601</td>
<td>25.73</td>
<td>50.984</td>
<td>52.763</td>
<td>84.352</td>
</tr>
</tbody>
</table>
Behavior in Liquid: Damping Force

\[ \beta = \frac{4}{3\pi} \frac{\rho_{\text{fluid}}}{\rho_{\text{comp}}} \frac{C_D A}{\omega t_{\text{comp}}} \]

\[ \beta_{\text{water}} = 3 \times 10^{-8} \]
Behavior in Liquid: Finite Element Results

Middle-node displacement

\[ \beta_{\text{water}} \]
Conclusions

• Resonance frequencies have been predicted with analytical and numerical models
• Shift in resonance frequency due to added biomolecule has been evaluated
• Behavior in liquid has been studied
• Results from analytical and numerical (Finite Element) approaches have a good agreement
• Experiments performed in a related work confirm the obtained results