RESONANT MICRO-SENSING PLATFORM FOR ULTRASONIC CHARACTERIZATION OF BLOOD COAGULATION

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Blood Coagulation: Background

- Since Early 1900 blood clotting disorders have been detected by blood coagulation tests.
- More common tests include:
  - Prothrombin Time (PT) test: measures the tissue factor-induced clotting time of plasma.
  - Thrombin Time test (TT): measures the conversion rate of fibrinogen to insoluble fibrin
  - Activated Partial Thromboplastin Time (aPTT)
  - Activated Clotting Time (ACT)
Coagulation Test: Earlier Techniques

- Initially, based on visual detection of clot formation
- Later, optical and mechanical detections replaced the visual detection

PoC Coagulation Test

- The drive:
  - Faster result
  - Very small blood sample size (less painful)
  - Potential for patient self-test (more data points)

- Mainly categorized in two classes based on the measured property:
  - Mechanical: measuring change in viscosity or flow (e.g. microINR, iLine Microsystems)
    - Relatively complicated measurement technique
  - Electro-chemical: measuring change in impedance (e.g. INRatio, Alere)
    - Prone to error resulted from interfering properties

CoaguCheck XS from Roche
MEMS for Coagulation Test

- Motivation: Directly measuring mechanical properties at very small scales and lower lost
- Pioneered by Microvisk Company
Basics of Resonant Sensing

- Commonly liquid placed in direct contact with the resonant body
- Resulting change is observed
  - Wave damping
  - Frequency
- Excessive damping of acoustic waves: shear mode preferred
- Measuring highly viscous liquids gives near zero output
- Electrical interference

- Is a contact-free method viable?

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* Sensor Review. Volume 28 · Number 1 · 2008 · 68–73
Thin Film-Piezoelectric-on-Substrate Resonators

- Piezoelectric transduction
- Low loss substrate (e.g. Si)
- Lithographically-defined frequency

Advantages:
- Higher Q relative to piezoelectric resonators
- Lower $R_m$ relative to capacitive resonator
- Higher power handling relative to both
Fabrication

- 6 mask process
- Mo patterned by dry etching in SF$_6$ & O$_2$ plasma
- AlN is etched by wet and dry etching in Cl$_2$ plasma
- Silicon is etched in DRIE (Topside and Backside)
- Devices are released in BOE
Anchor/Tether Loss

- Finite displacement at tether/substrate boundary
- Pressure waves are radiated into the substrate

![Image of Tether Displacement Example (top view)](image1)

![Image of 3D acoustic propagation simulation](image2)
In-Plane Acoustic Reflectors

- A circular trench in the substrate serves as a very efficient reflector
- Location of the trench is expected to be critical
- Finite Element Modeling predicts the enhancement of $Q$ for a device with properly designed reflector
Experimental Validation

- Devices with properly designed reflector show >%400 improvement in Q
- Multiples devices of the same design are measured and Q’s are averaged

<table>
<thead>
<tr>
<th>Tether length (μm)</th>
<th>No acoustic reflector</th>
<th>Reflector distance to tether (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 (λ/4)</td>
<td>36 (λ/2)</td>
<td>54 (3λ/4)</td>
</tr>
<tr>
<td>9 (λ/8)</td>
<td>3492</td>
<td>1475 15531 4676</td>
</tr>
<tr>
<td>27 (3λ/8)</td>
<td>1818</td>
<td>3326 12042 1969</td>
</tr>
</tbody>
</table>

*Lengths expressed in acoustic wavelength are given in parentheses.*
Sensor Design

- Sample collection site
- Capillary-based microfluidics
- Electrode pads for I/O measurement
- Transmission signal measurement
Preliminary Data

- Q is monitored as the liquid is injected in the channel.
- Change in the Q is a measure of acoustic impedance of the filling.
Ultrasonic Blood Analyzer

- Using the same device the change in $Q$ is monitored for different fluids
- The goal is to characterize blood properties based on its acoustic signature

![Graph showing dynamic output response with PR drying](image)

**Initial $Q = 6100$ (in air)**

**Device Response to Fillers**

- $\sigma = 32$, $N = 6$
- $\sigma = 34$, $N = 10$
- $\sigma = 35$, $N = 2$

![Bar chart showing decrease in $Q$ for different liquid fillers](image)

**Quality factor dependence on sample liquid (different device)**
Transmission Signal

- Transmission response is measured for liquid with variable glycol in water concentration.
- Transmission response increases with increased glycol concentrations.
- Q decreases ($\Delta Q = 550$) with increased glycol concentration.

Transmission signal collected with filled channel

Transmission signal and Q for different glycol solutions
Simple Capping Techniques

- Polymer based capping of the channels and device is examined
- Bonded PDMS films and deposited parylene films yield inexpensive covers

Polymer channel covering

Polymer device cover
Final Test: PT monitoring

- IntegSense Inc. recently received funding to do a feasibility study on using this platform for PT monitoring.
- Results are due in a few months.
I would like to acknowledge my former group members whose contribution was presented in this talk:

- Brandon Harington (now with Knowles)
- Mohsen Shahmohammadi (now with Qualtre)
- Jonathan Gonzales (now with IntegSense)

Thank you for your time!