RESONANT MICRO-SENSING PLATFORM FOR ULTRASONIC CHARACTERIZATION OF BLOOD COAGULATION

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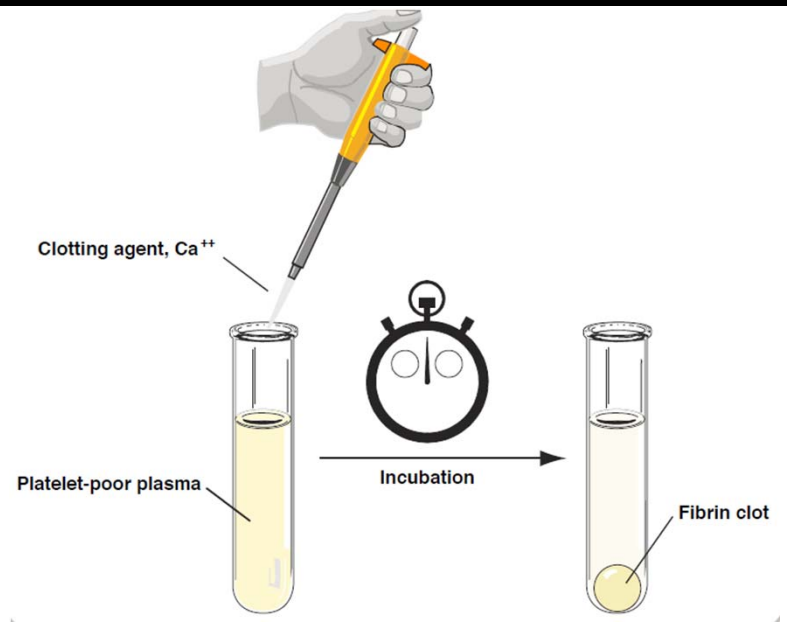
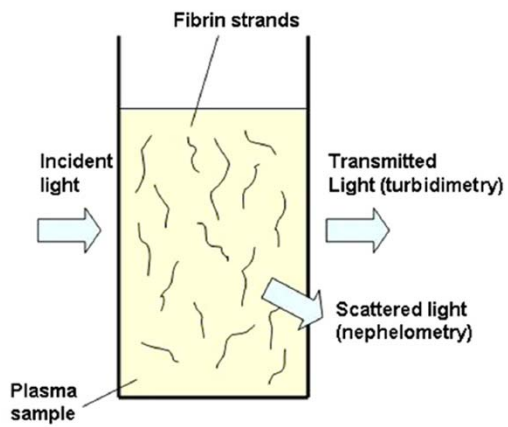
Blood Coagulation: Background

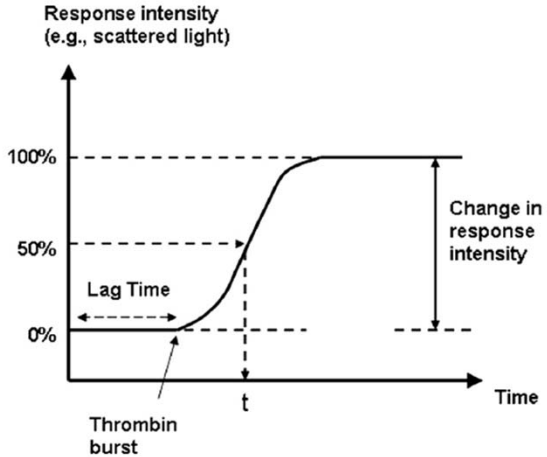
- Since Early 1900 blood clotting disorders have been detected by blood coagulation tests.
- More common tests include:
  - Prothrombin Time (PT) test: measures the tissue factor-induced clotting time of plasma.
  - Thrombin Time test (TT): measures the conversion rate of fibrinogen to insoluble fibrin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







Harris, Leanne F., et al. "Coagulation monitoring devices: Past, present, and future at the point of care." *TrAC Trends in Analytical Chemistry* 50 (2013): 85-95.

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

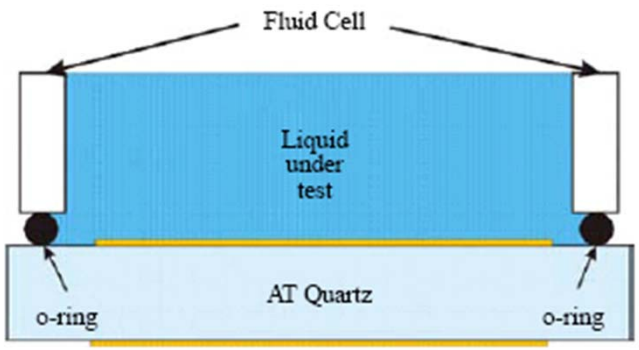
MEMS for Coagulation Test

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

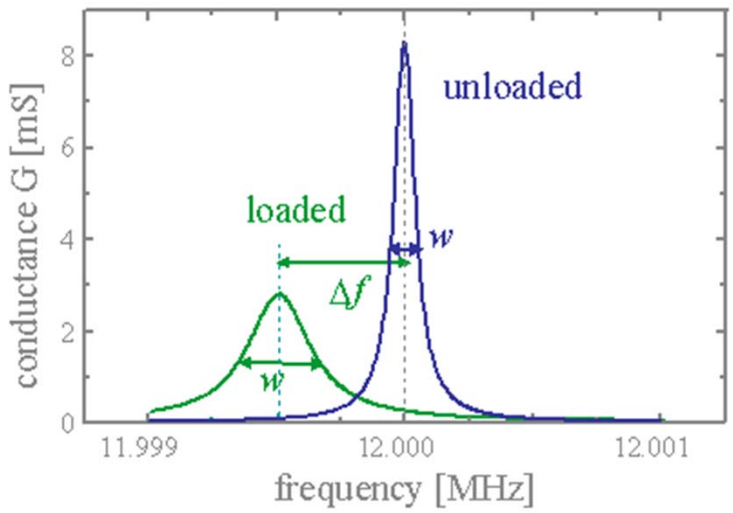
Basics of Resonant Sensing

- 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?



Quartz Shear mode liquid sensor*



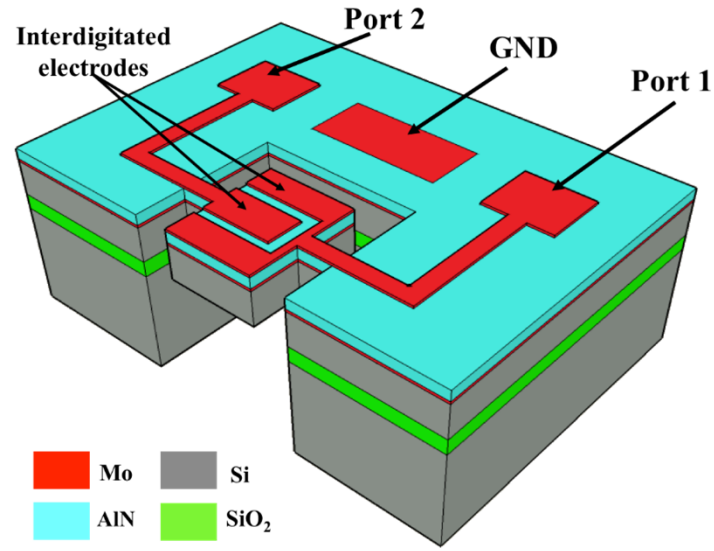
Microbalance principle**

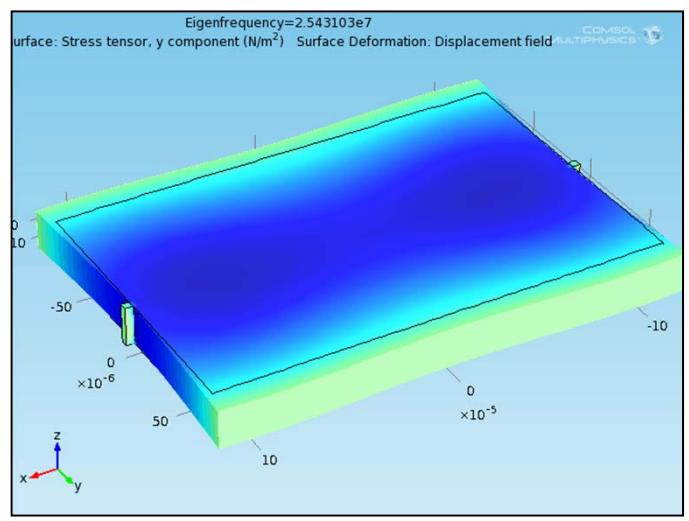
* Sensor Review. Volume 28 · Number 1 · 2008 · 68–73

** http://en.wikipedia.org/wiki/File:QCM_principle.gif[2]

Thin Film-Piezoelectric-on-Substrate Resonators

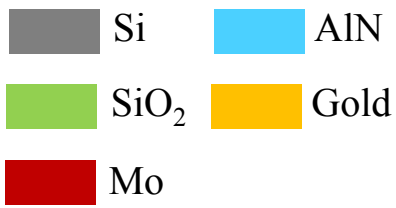
- Piezoelectric transduction
- Low loss substrate (e.g. Si)
- Lithographically-defined frequency
- Advantages:
  - Higher Q relative to piezoelectric resonators
  - Lower R_m relative to capacitive resonator
  - Higher power handling relative to both

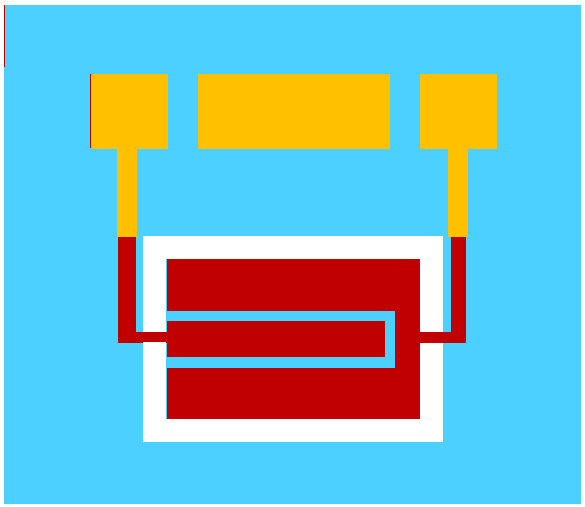




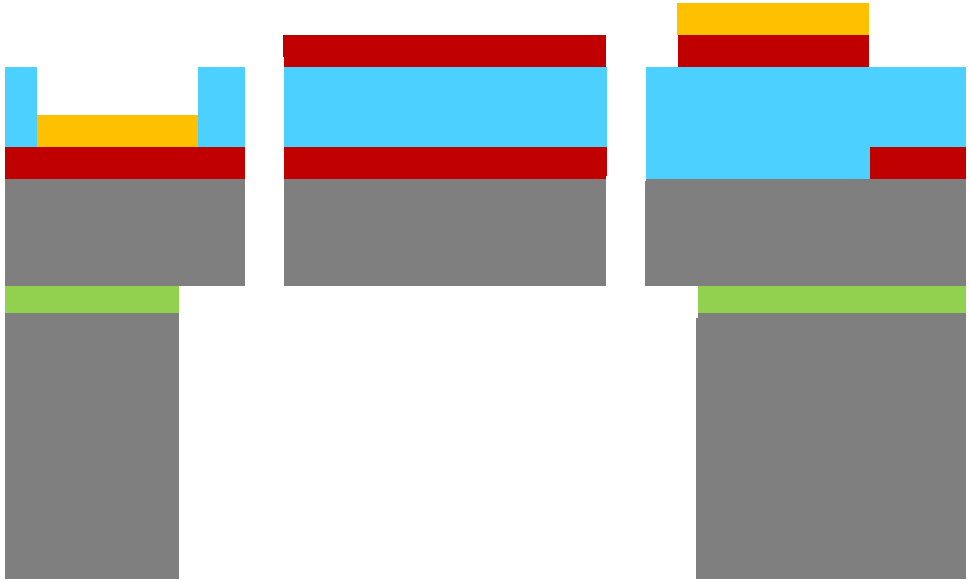
Fabrication

- 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





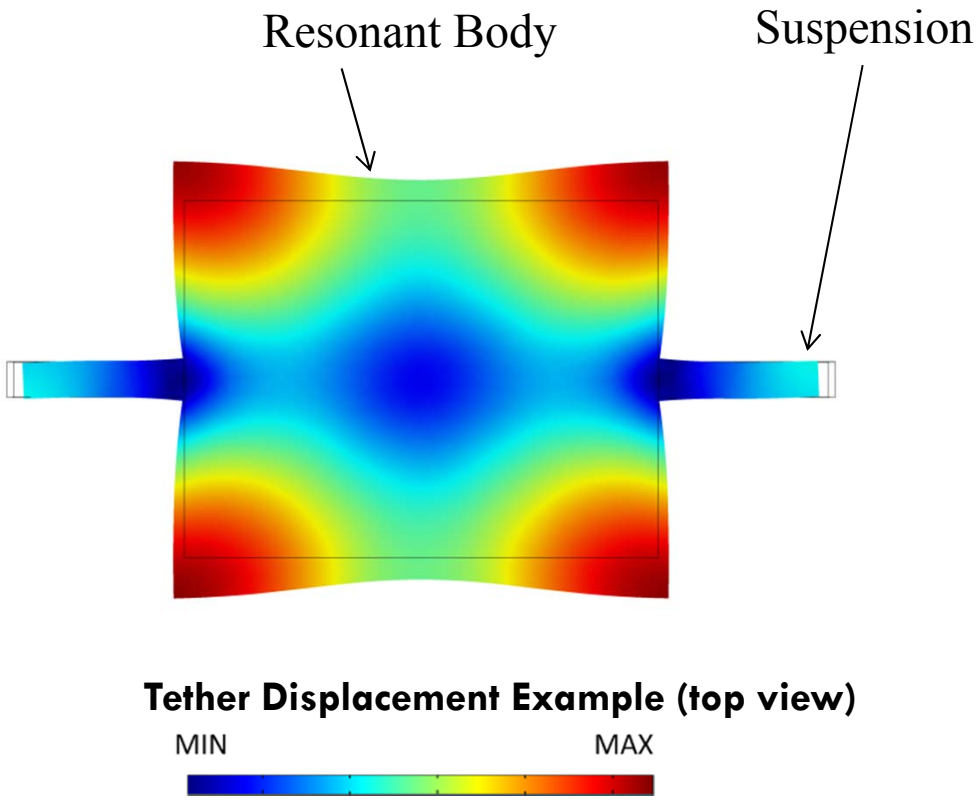
Top View



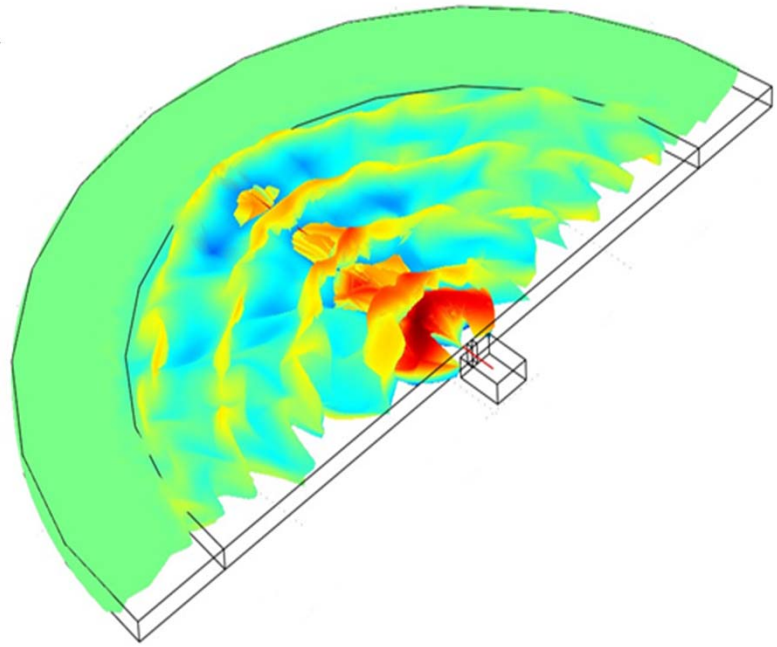
Side View

Anchor/Tether Loss

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



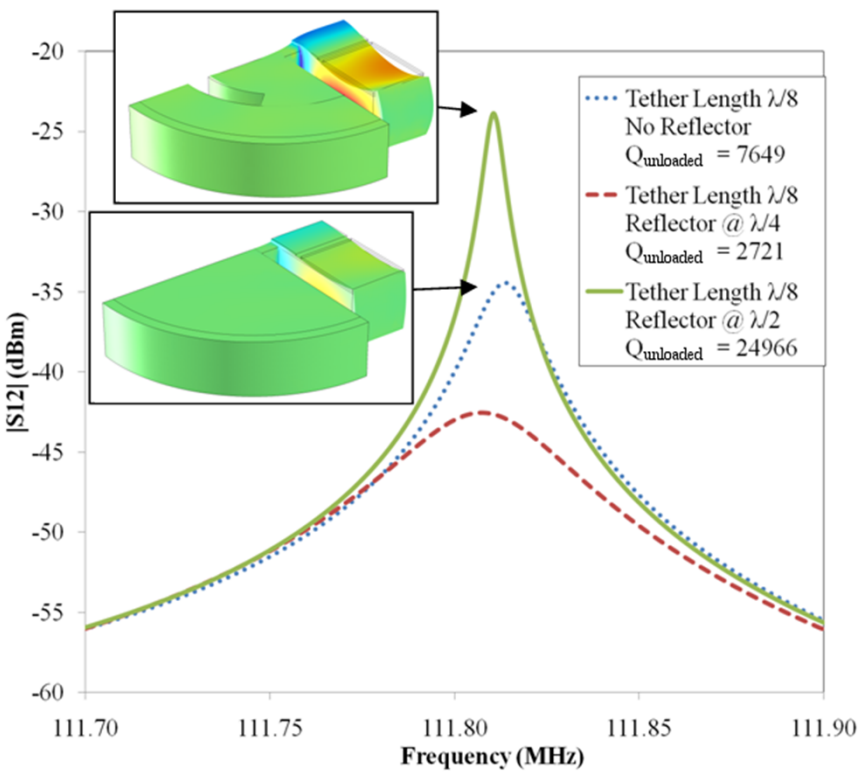
Tether Displacement Example (top view)

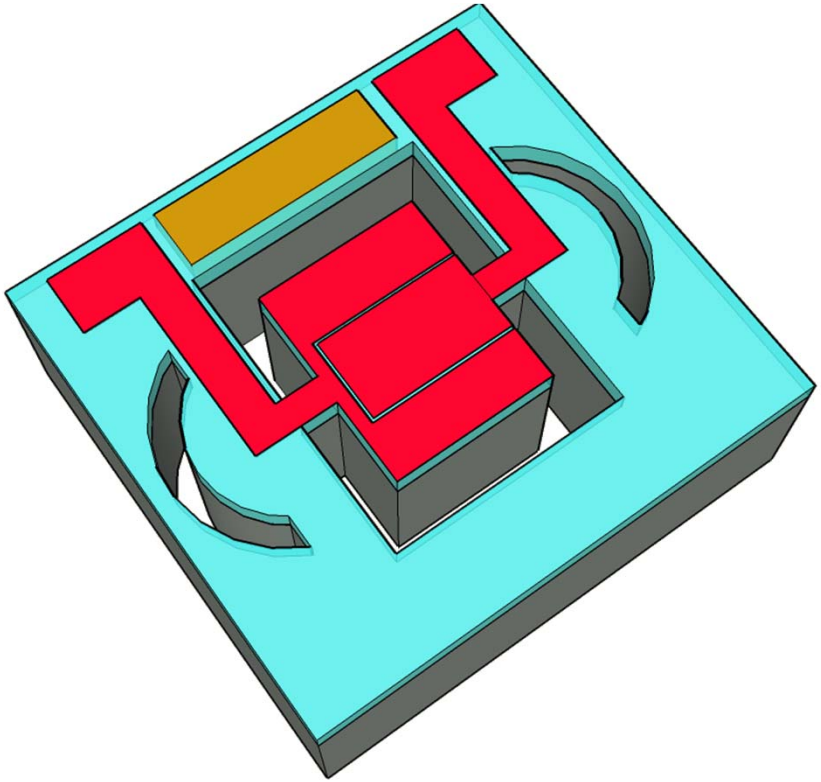


3D acoustic propagation simulation

In-Plane Acoustic Reflectors

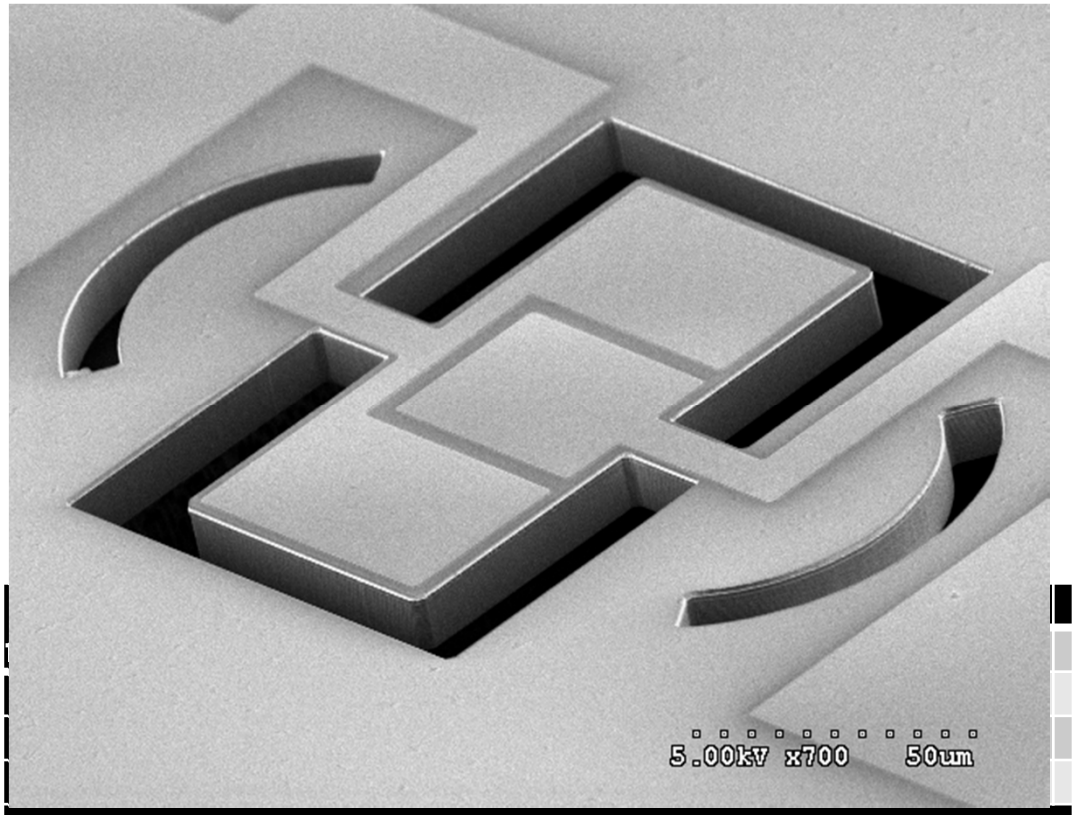
- A circular trench in the substrate serves as a very efficient reflector
- Location of the trench is expected to be critical
- Finite Element Modeling predicts the enhancement of Q for a device with properly designed reflector





Experimental Validation

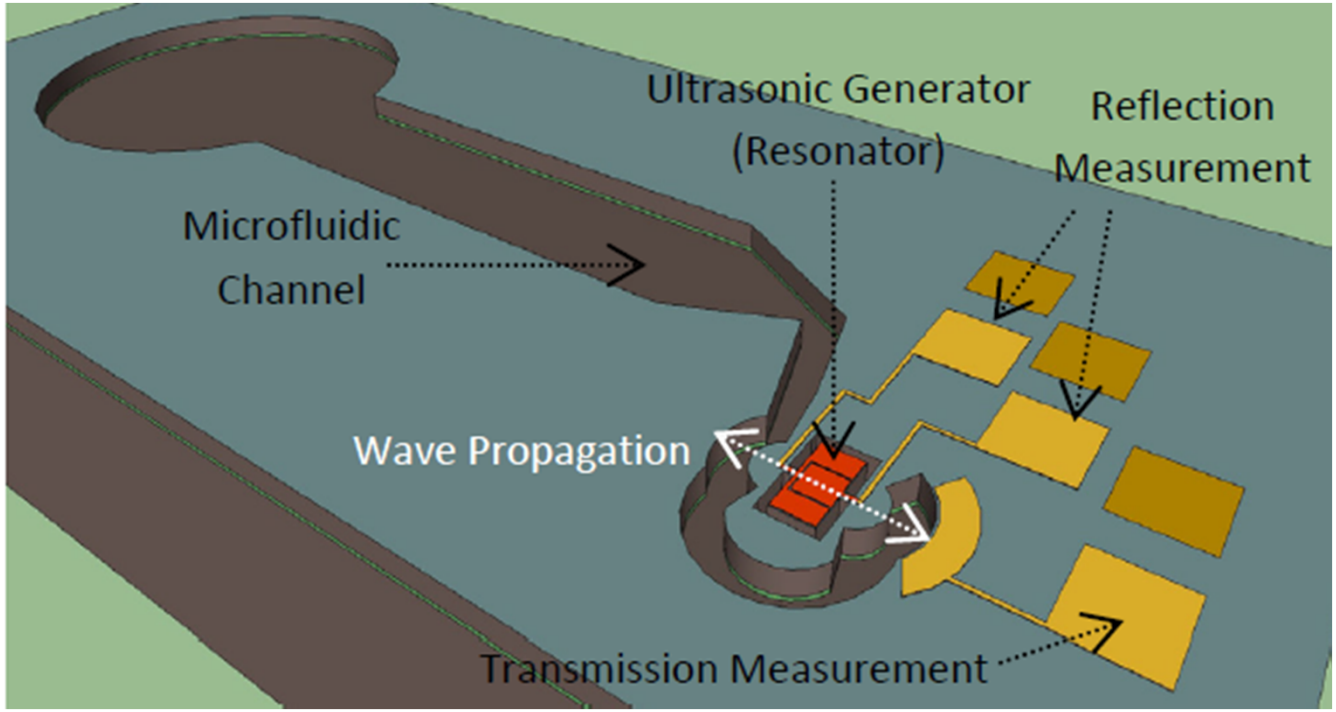
- Devices with properly designed reflector show >%400 improvement in Q
- Multiples devices of the same design are measured and Q's are averaged



[a] Lengths expressed in acoustic wavelength are given in parentheses.

Sensor Design

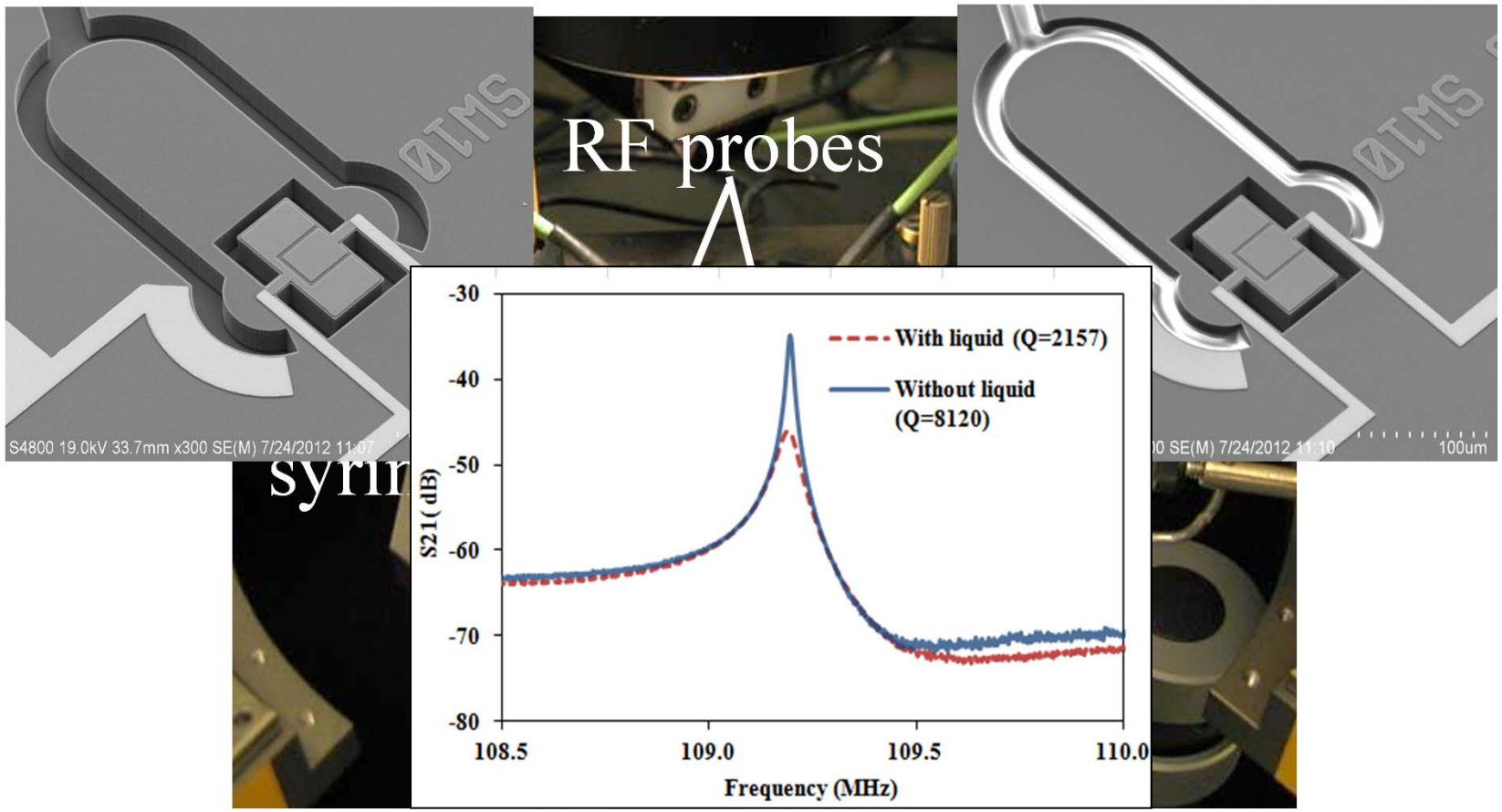
- Sample collection site
- Capillary-based microfluidics
- Electrode pads for I/O measurement
- Transmission signal measurement



3D schematic of sensor

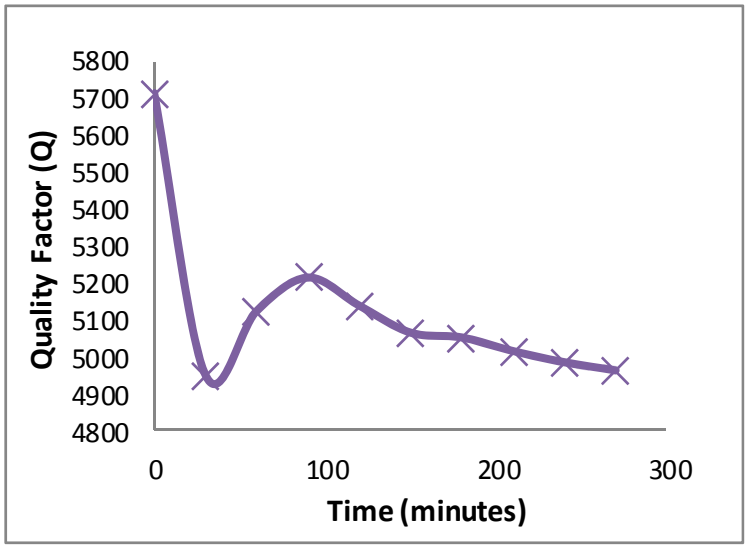
Preliminary Data

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



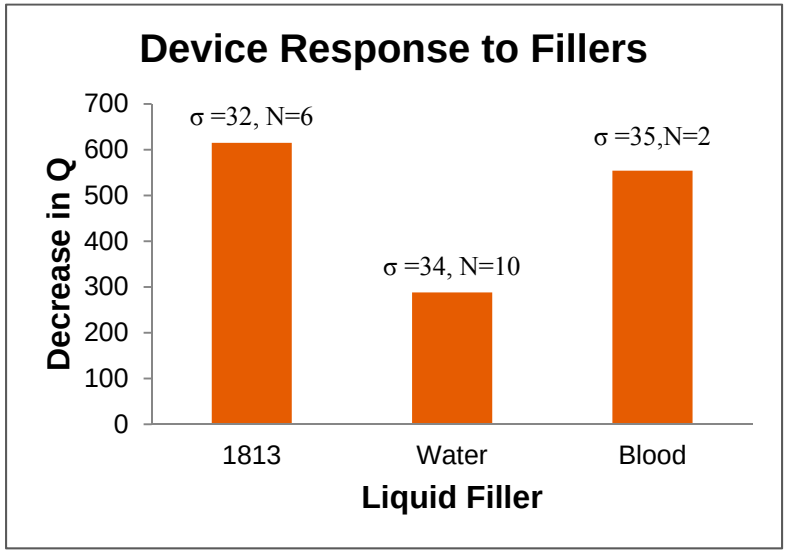
Ultrasonic Blood Analyzer

- 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



Dynamic output response with PR drying

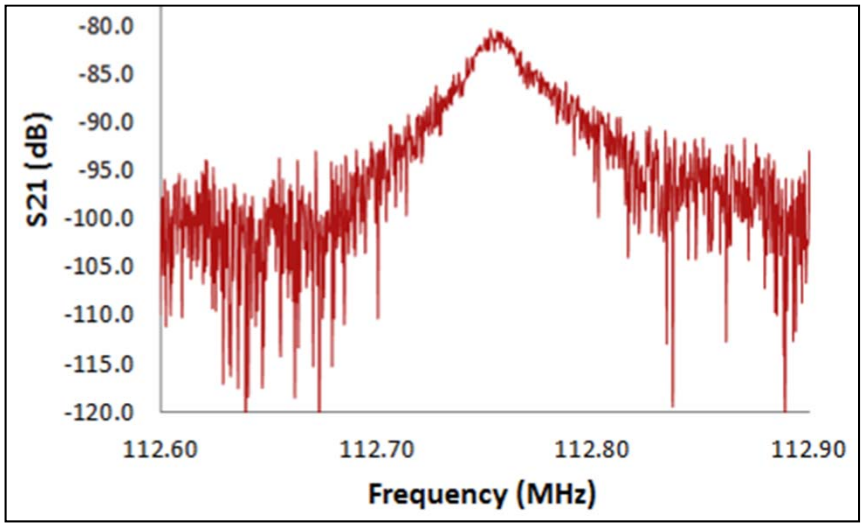
Initial Q = 6100 (in air)



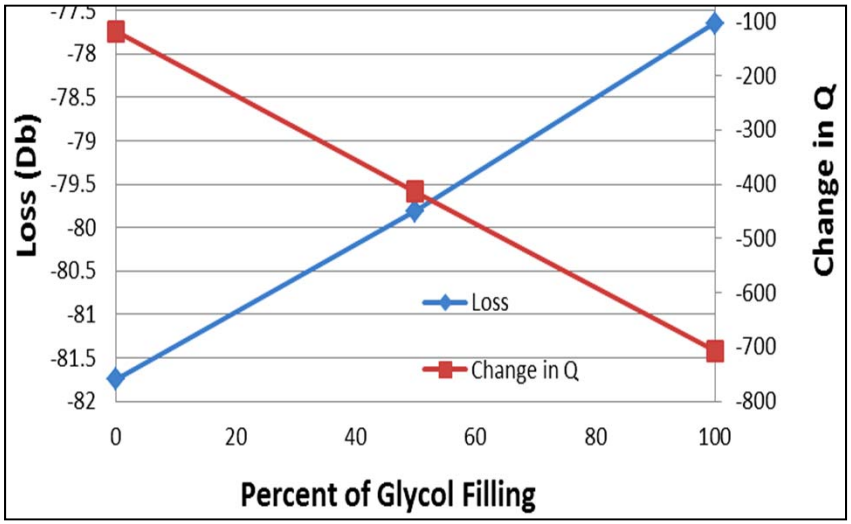
Quality factor dependence on sample liquid (different device)

Transmitted 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



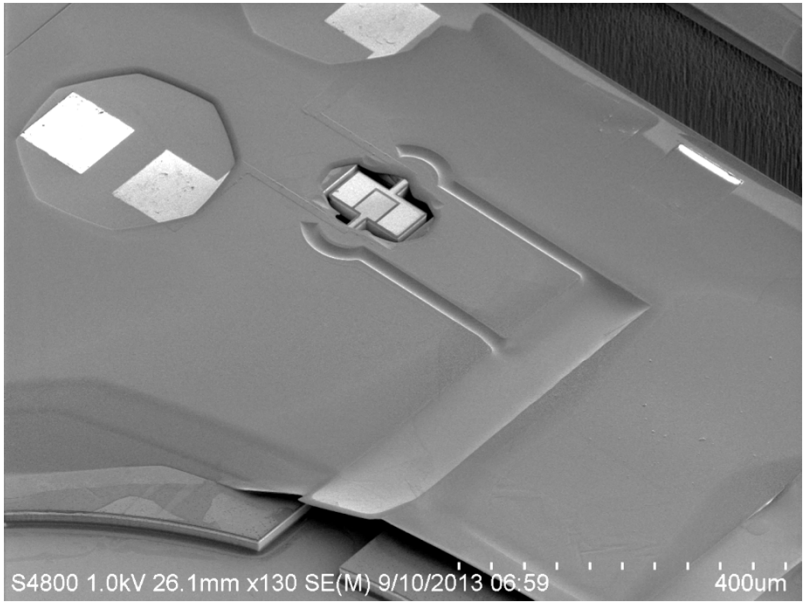
Transmission signal collected with filled channel



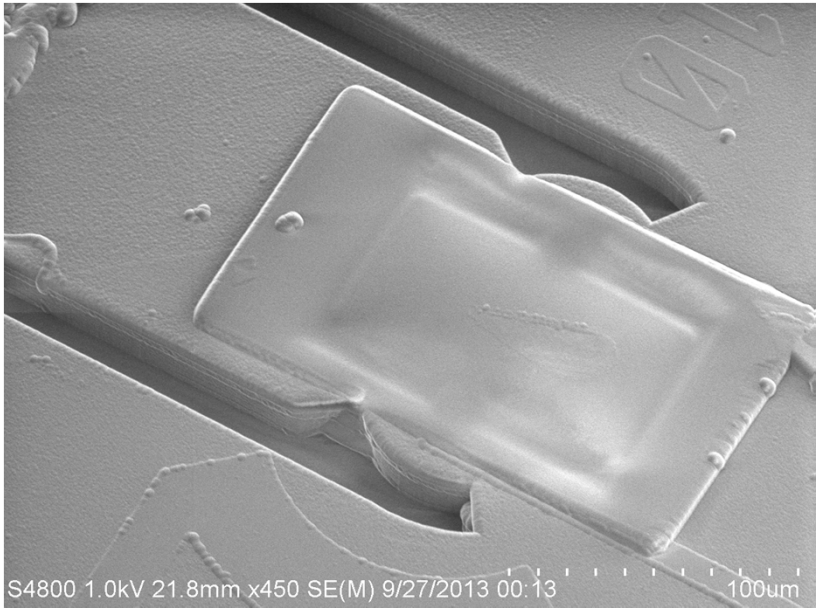
Transmission signal and Q for different glycol solutions

Simple Capping Techniques

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



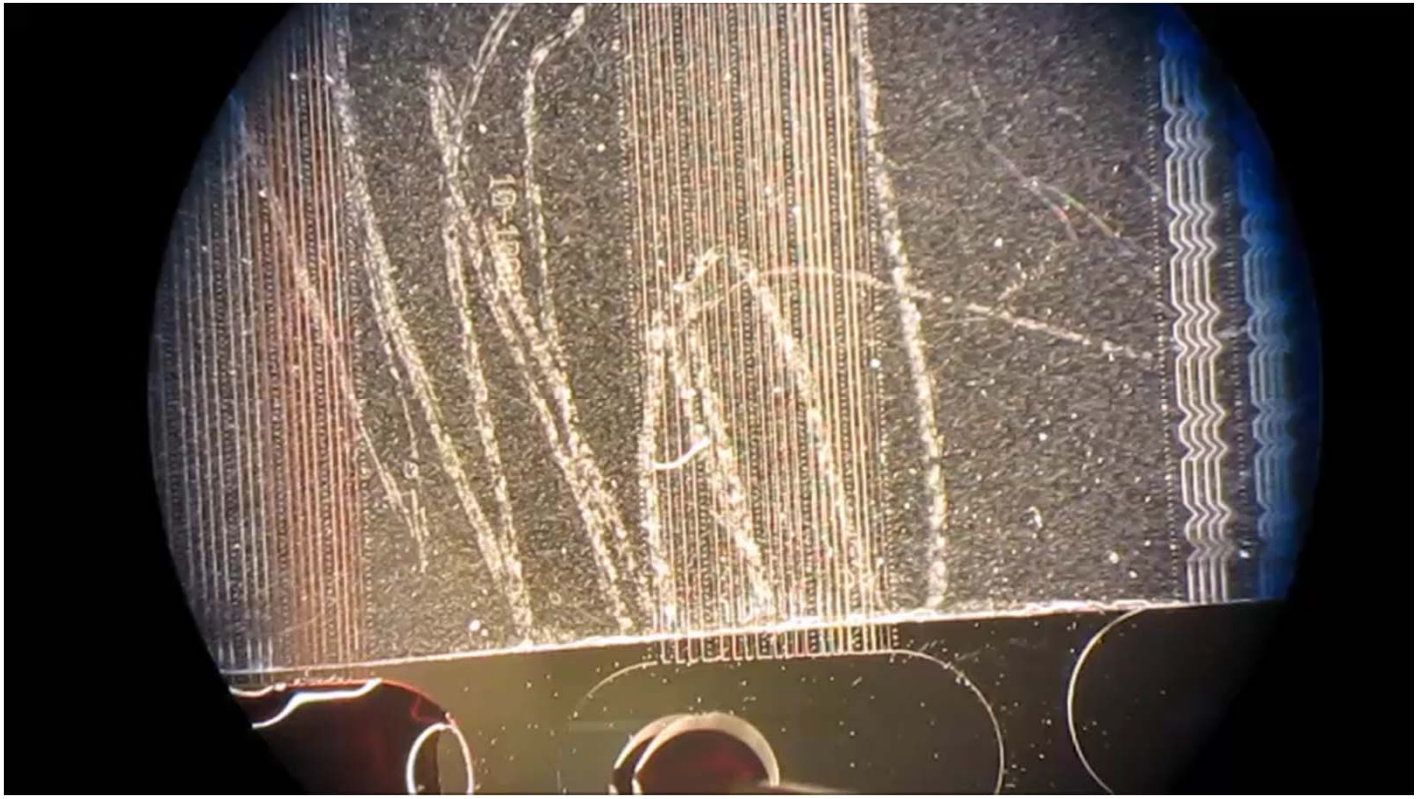
Polymer channel covering



Polymer device cover

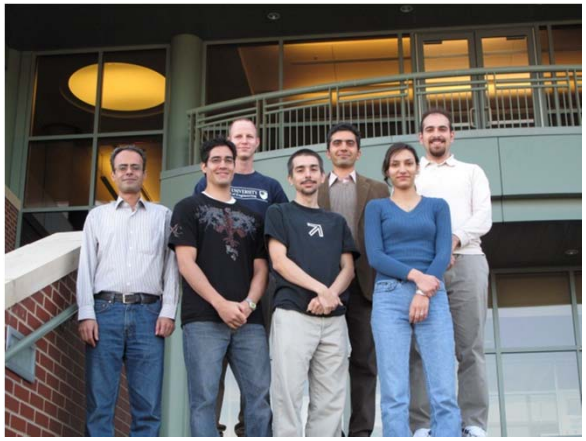
Final Test: PT monitoring

- IntegSense Inc. recently received funding to do a feasibility study on using this platform for PT monitoring
- Results are due in a few month



Acknowledgement

- 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!