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Microcantilever Arrays for Biomedical Applications

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Mexico City

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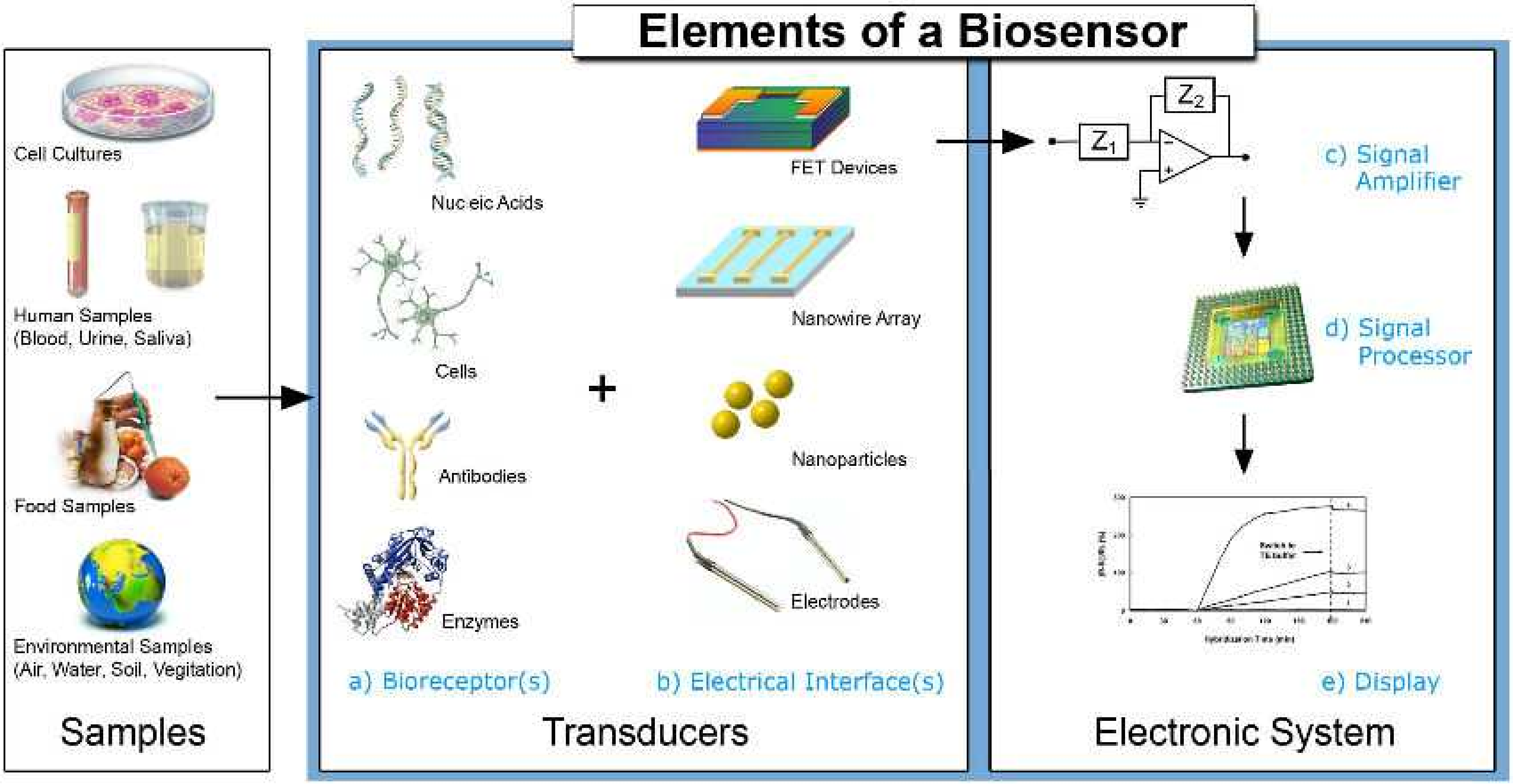
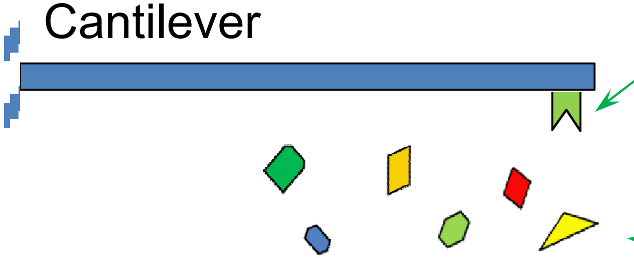
Biosensors use receptors and interfaces



http://upload.wikimedia.org/wikipedia/commons/e/ec/Biosensor_System.jpg

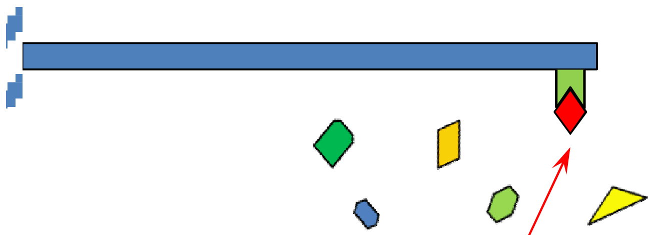
A micro-cantilever can be an interface

Cantilever



Receptor immobilized on cantilever

Analytes in tested sample



Only targeted analyte binds to receptor.

Transducer converts cantilever property to electrical signal.

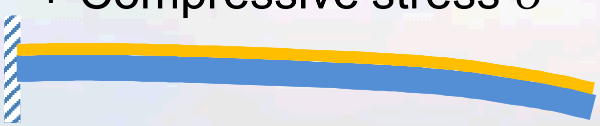
Analyte changes cantilever property.

Analyte causes deflection

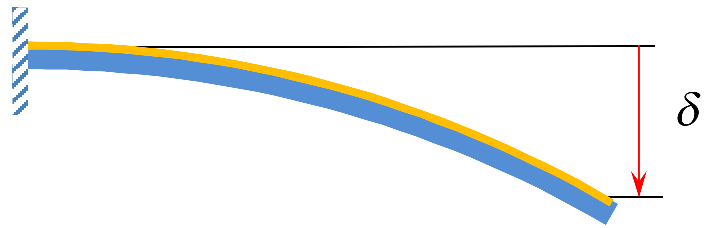
Single-stranded DNA (ss-DNA) coating

Target complementary ss-DNA

Hybridization results in double-stranded DNA (ds-DNA)
+ Compressive stress σ



Stress σ causes a bending radius and deflection δ.



$$\delta = \frac{3(1-\nu)L^2}{Eh^2}\sigma$$

E = Modulus of elasticity
L = Cantilever length
h = Cantilever thickness
ν = Poisson's ratio

Jaccodin RJ and Schlegel WA 1966 Measurement of strains at Si-SiO_2interface *J. Appl. Phys.* 37 2429

Origin of surface stress σ is a subject of research.

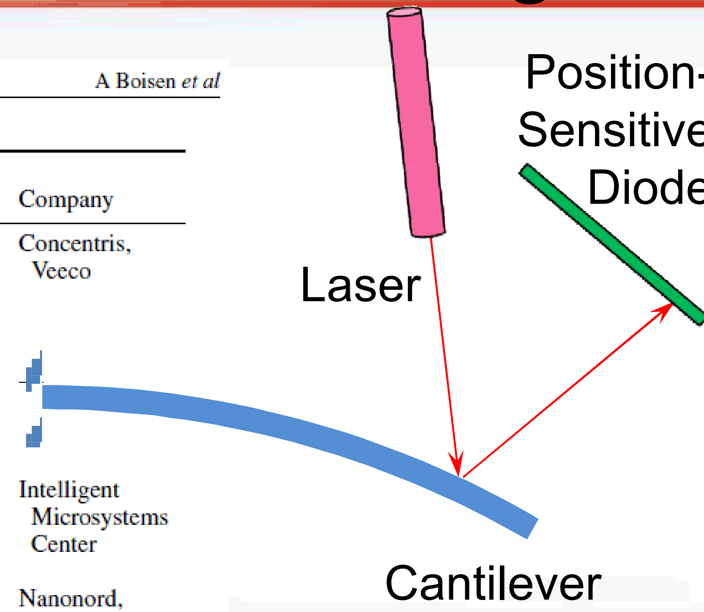
System	Concluded origin of surface stress	Reference
DNA in saline sodium citrate hybridization buffer	Electrostatic, steric and hydrophobic	Fritz et al 2000 *Science* 288 316
DNA in sodium phosphate buffer	Interaction between configurational entropy and inter-molecular energetics	Wu et al 2001 *PNAS* 98 1560
DNA in triethyl ammonium acetate buffer	Electrostatic and steric hindrance effects	McKendry et al 2002 *PNAS* 99 9783
DNA in saline sodium phosphate buffer	Electrostatic; also entropic, hydrophobic, hydration and solvation surface forces	Shu et al 2005 *J. Am. Chem. Soc.* 127 17054
Thiolated alkanechains in sodium phosphate buffer	Electrostatic, ionic hydrogen bonds; effects of counter ions from aqueous solution	Watari et al *J. Am. Chem. Soc.* 2007 129 601
DNA in saline sodium phosphate buffer	Hydration forces in between ss-DNA and ds-DNA	Martens et al 2008 *Nature Nanotechnol.* 3 301
Thiolated alkanechais deposited from gas phase	Intermolecular electrostatics, Lennard-Jones interactions, effect of adsorption-induced changes in the electronic density of the metal film combined with associated electronic charge transfer from gold to thiol bond	Godin et al 2010 *Nanotechnology* 21 075501

Transduction converts deflection into electrical signal.

Rep. Prog. Phys. 74 (2011) 036101 A Boisen *et al*

Table 3. Summary of read-out methods.

Read-out method	Pros	Cons	Used in	Company
Optical leverage	Simple read-out method, known from AFM; can be used on any cantilever with a good optical quality	Difficult to apply for large arrays; prone to optical artefacts such as change in refractive index; not suitable for nanometre-sized cantilevers	Surface stress; mass; bulk stress	Concentris, Veeco
Capacitive	Useful for nanometre-sized cantilevers; read-out does not affect the mechanical properties of the cantilever	Stray capacitances make pre-amplifications and CMOS integration necessary; this complicates the fabrication	Mass	—
Piezoelectric	The principle can be used for actuation as well as read-out	Many piezoelectric materials are not cleanroom compatible; many piezoelectrical materials are only suitable for dynamic measurements	Surface stress; mass; bulk stress	Intelligent Microsystems Center
Piezoresistive	Facilitates large arrays and system integration; works in all media and in all modes of operation	A piezoresistive layer needs to be integrated into the cantilever which affects the mechanical performance; for operation in liquid, care has to be taken in order to insulate the resistor	Surface stress; mass; bulk stress	Nanonord, Seiko
Hard contact	Offers a 'digital' read-out where a signal is only generated when the cantilever is in resonance; high signal-to-noise ratio	Wear of the counter electrode is a challenge; works only in air	Mass	—
Tunnelling	Potentially very sensitive detection of cantilever bending	Complicated operation and only works in air	Mass	—
Integrated optical methods (waveguides)	Suitable for large scale arrays with the same sensitivity as optical leverage	More complicated fabrication and packaging; prone to optical artefacts, such as changes in refractive index	Surface stress	—
Autonomous devices	Simple device concept with no need for external energy	Difficult to realize the device such that there is no leakage of dye molecules	Surface stress	—



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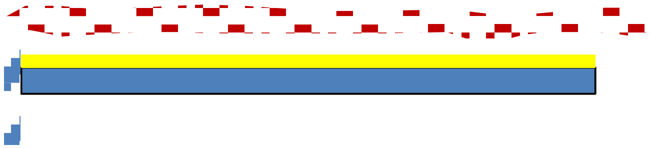
Analyte also changes resonant frequency of cantilever.

Review: Stress-based sensing



DNA hybridization causes stress

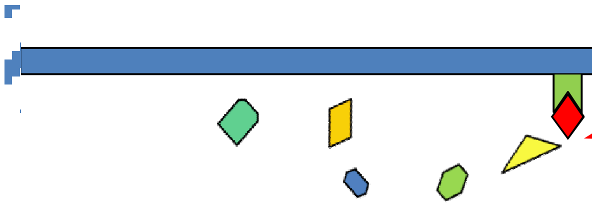
Stress causes deflection

$$\delta = \frac{3(1-\nu)L^2}{Eh^2}\sigma$$

Origin of stress is a research topic.

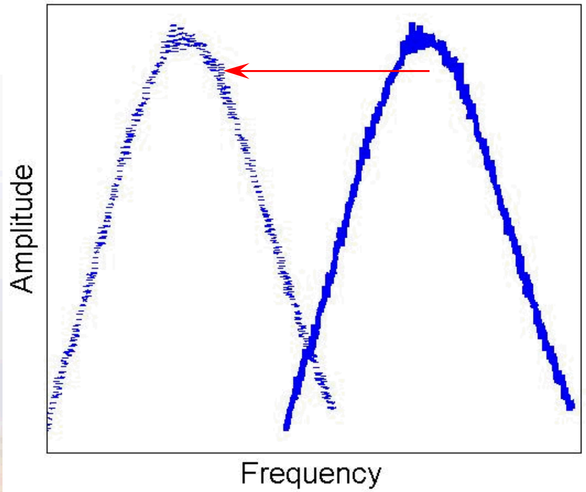
Nano-scale cantilevers are not significantly more sensitive than micro-scale cantilevers.

Resonance-based sensing



Targeted analyte binds to receptor.

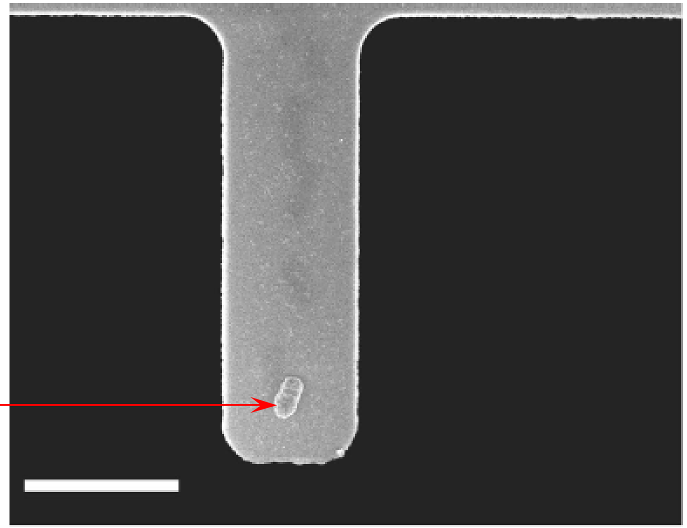
Mass loading lowers cantilever's resonant frequency.



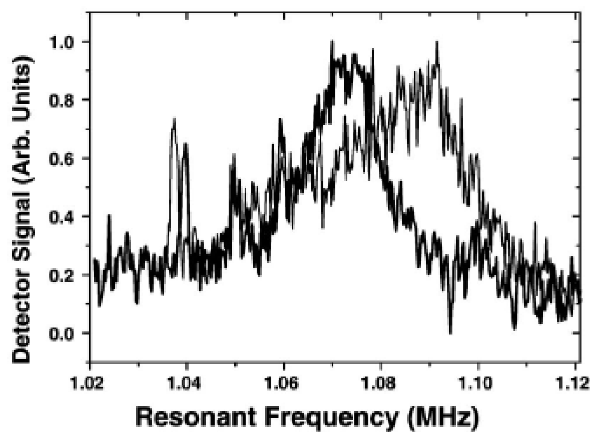
Sensitivity can be increased by reducing cantilever size.

E. coli cell lowers resonant frequency.

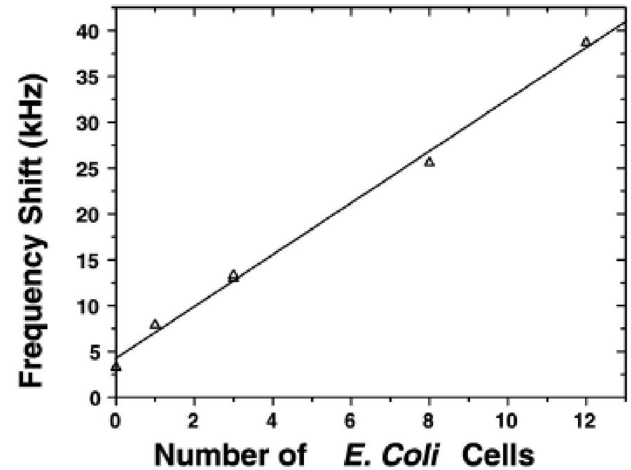
E. coli cell



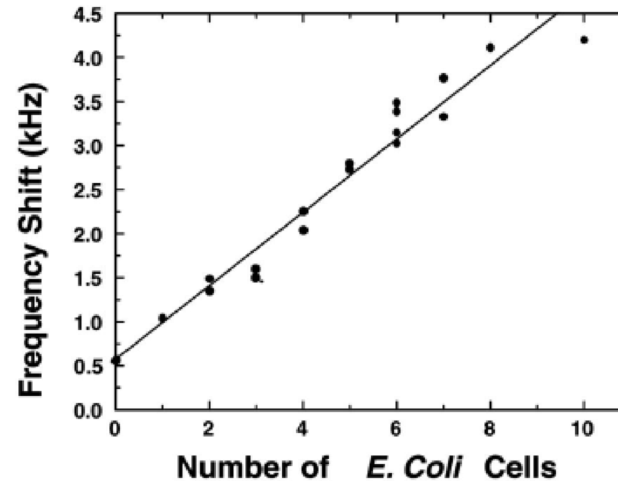
(a)



(b)



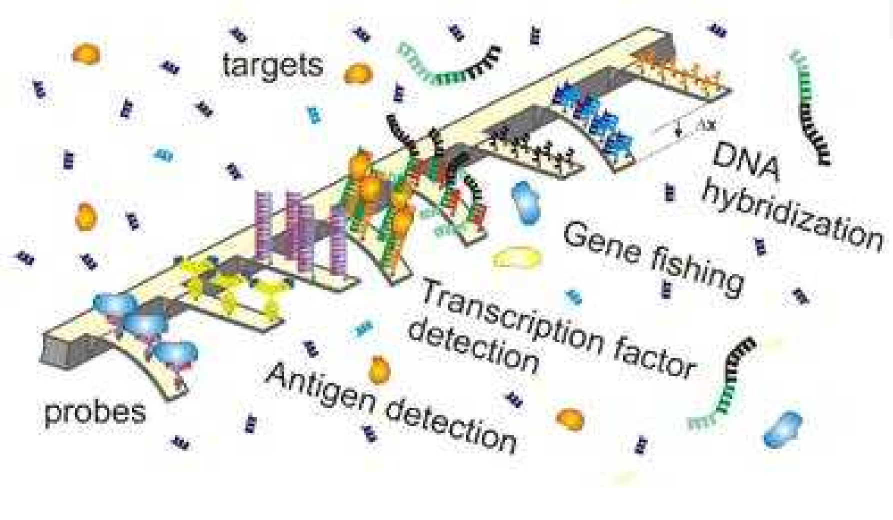
Shorter cantilever



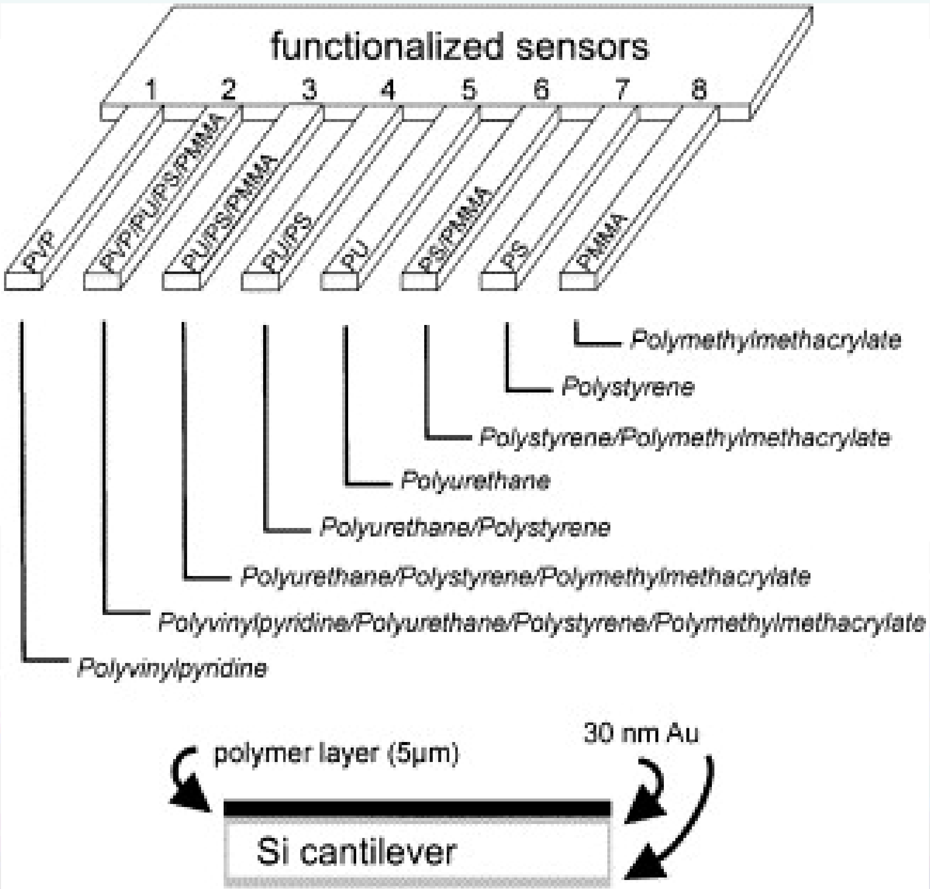
Longer cantilever

Ilic et al 2001 *J. Vac Sci. Technol. B* 19 6

Multi-functionalized cantilever array detect several analytes.



Cantilever arrays detect and quantify the binding affinity of the antibiotic Vancomycin to the drug-target mucopeptide analogs: Lysine-DAlanine-D-Alanine – found in Vancomycin-sensitive bacteria, and Lysine-D-Alanine-D- Lac - found in vancomycin-resistant bacteria.



Cantilever-array-based artificial nose

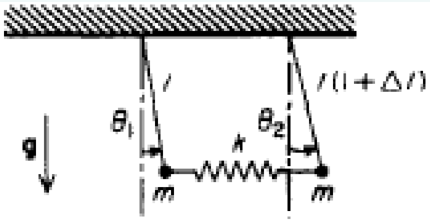
Ndieyira, J. W. et al. 2008 Nature Nanotech. 3, 691-696

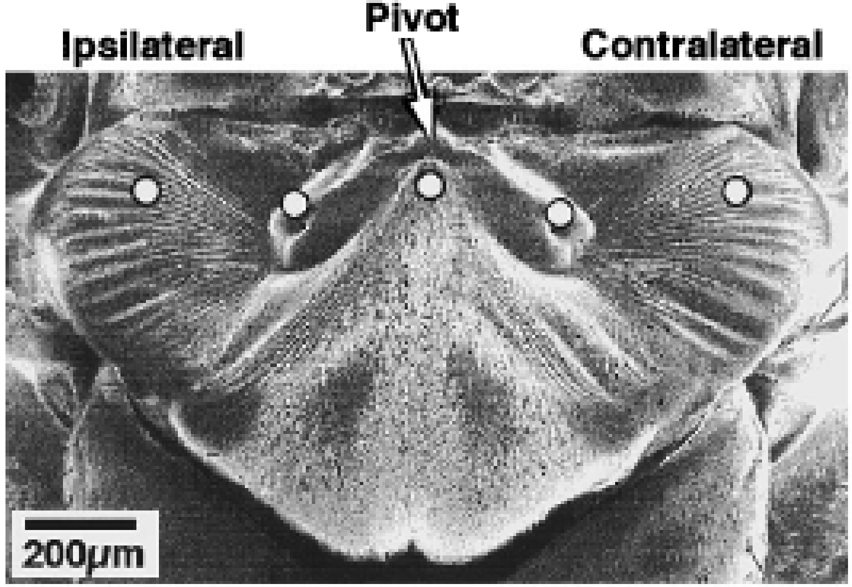
Coupling oscillators results in changing eigenvectors (mode shapes)

- Small perturbations to nominally identical, lightly coupled systems can lead to significant changes in system characteristics
  - Mode localization
  - Eigenvalue veering

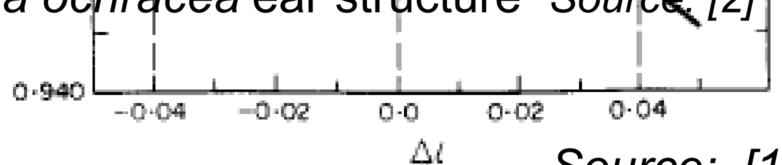
- Coupled systems have been observed in nature
  - *Ormia ochracea* ear structure

- Coupling microcantilevers would allow measurement of eigenmode shifts as well as frequency shifts





Ormia ochracea ear structure *Source: [2]*

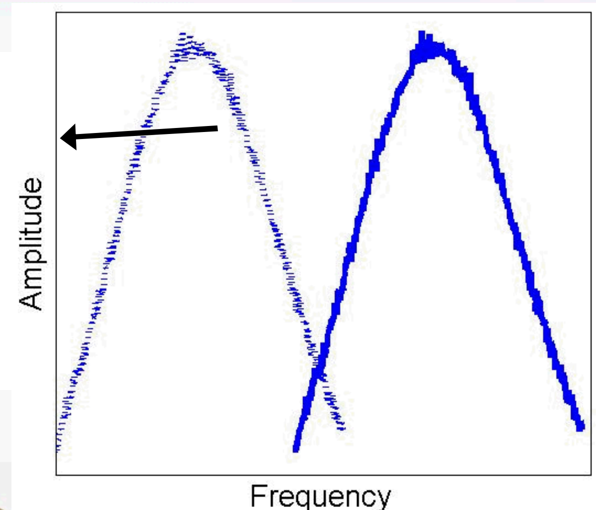


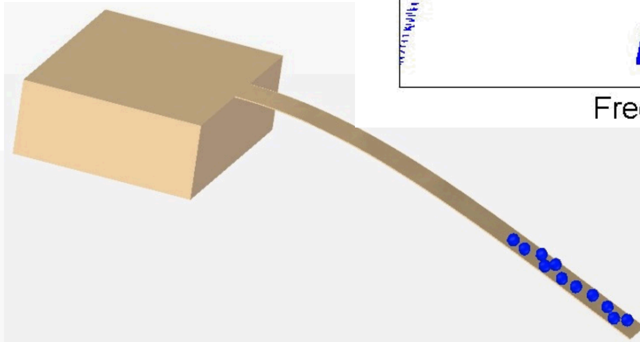
Source: [1]

[1] Pierre et al., J. Sound and Vib. 126(3), 485-502 (1998).
[2] Miles et al., J. Acoust Soc. Am. 98(6), 3059-3070 (1995).

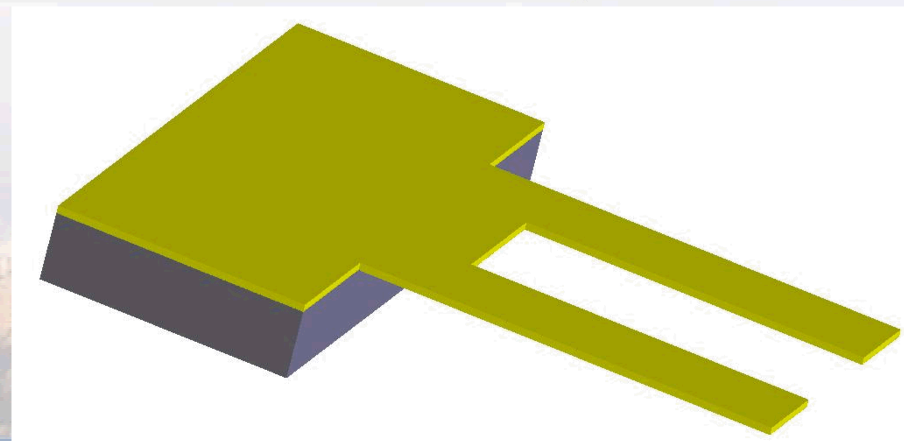
Changes in eigenmodes are more sensitive than frequency shift.

- **Single cantilever gravimetric sensors**
  - Added mass→resonance frequency drop
  - Added mass resolution is limited by quality factor
  - Current minimum mass resolution is in the pico-femtogram range under ambient conditions





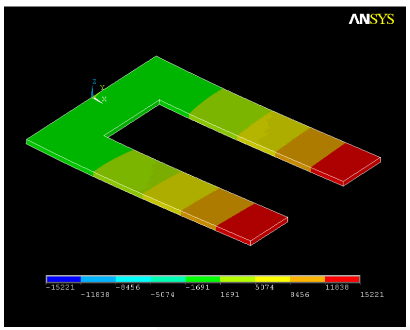
- **Multiple cantilever sensors**
  - Two or more nominally identical cantilevers are mechanically coupled
  - Added mass→change in eigenmodes



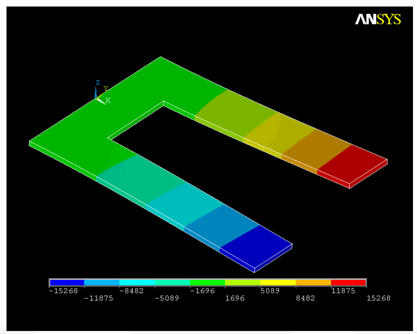
- **Do eigenmode shift-based sensors have an advantage over resonance frequency-based sensors?**

Two cantilevers can be coupled by a coupling spring.

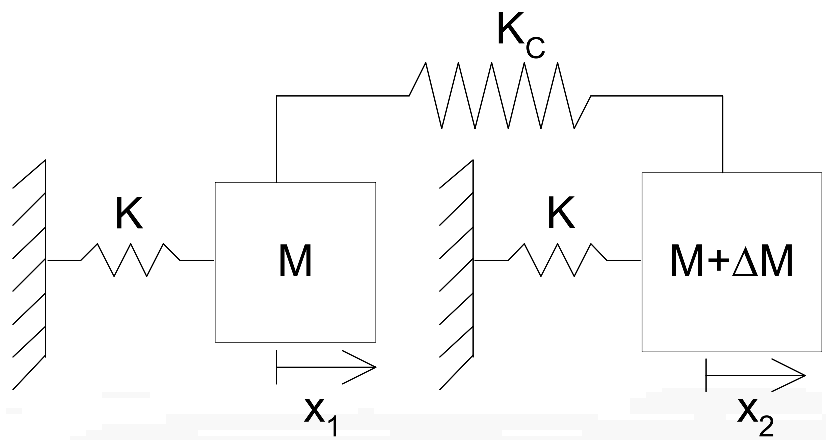
- Assume the cantilevers are identical
  - Finite element analysis predicts symmetric and antisymmetric eigenmodes



Symmetric Mode
f=13837 Hz



Antisymmetric Mode
f=13899 Hz



- Perturbation analysis can be used to predict eigenmode changes with added mass in the lumped parameter system
  - Eigenmode changes depend strongly on cantilever coupling

$$|\Delta\phi| = \frac{|\phi - \phi_0|}{|\phi_0|} = \left(\frac{1}{4} + \frac{1}{4\kappa}\right)\delta \qquad \kappa = \frac{K_C}{K} \sim 10^{-2} \qquad \delta = \frac{\Delta M}{M} \qquad \frac{\Delta f}{f_0} = \frac{-\delta}{2}$$

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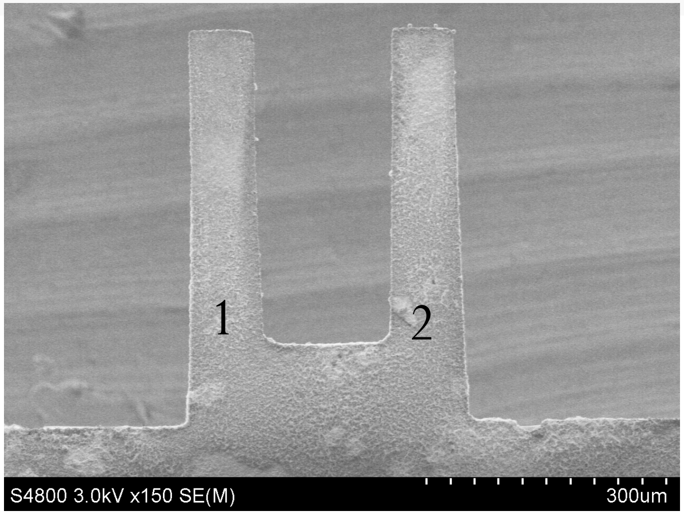
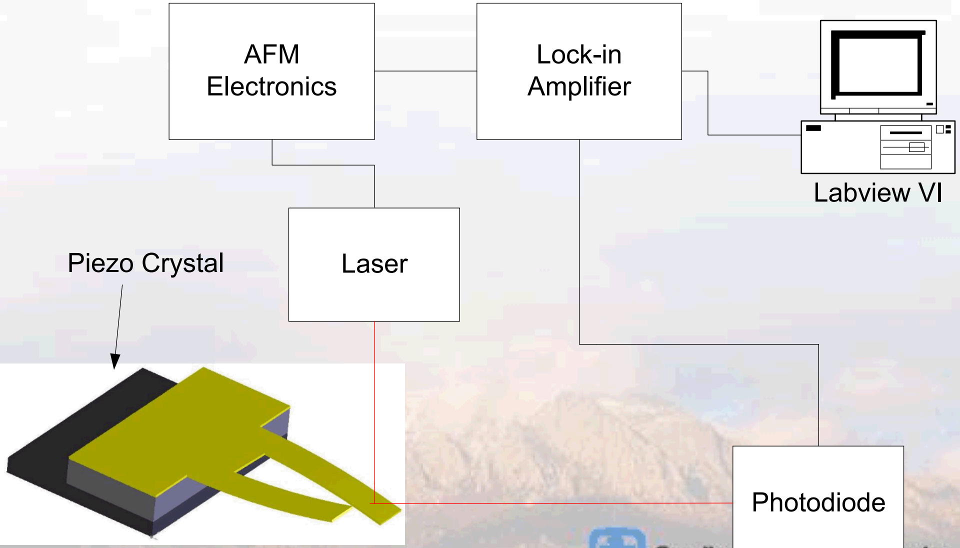
Coupled double-cantilevers were fabricated and tested.

- Gold foil is attached to a silicon base
- A Ti:sapphire femtosecond laser controlled by CNC software machines the arrays

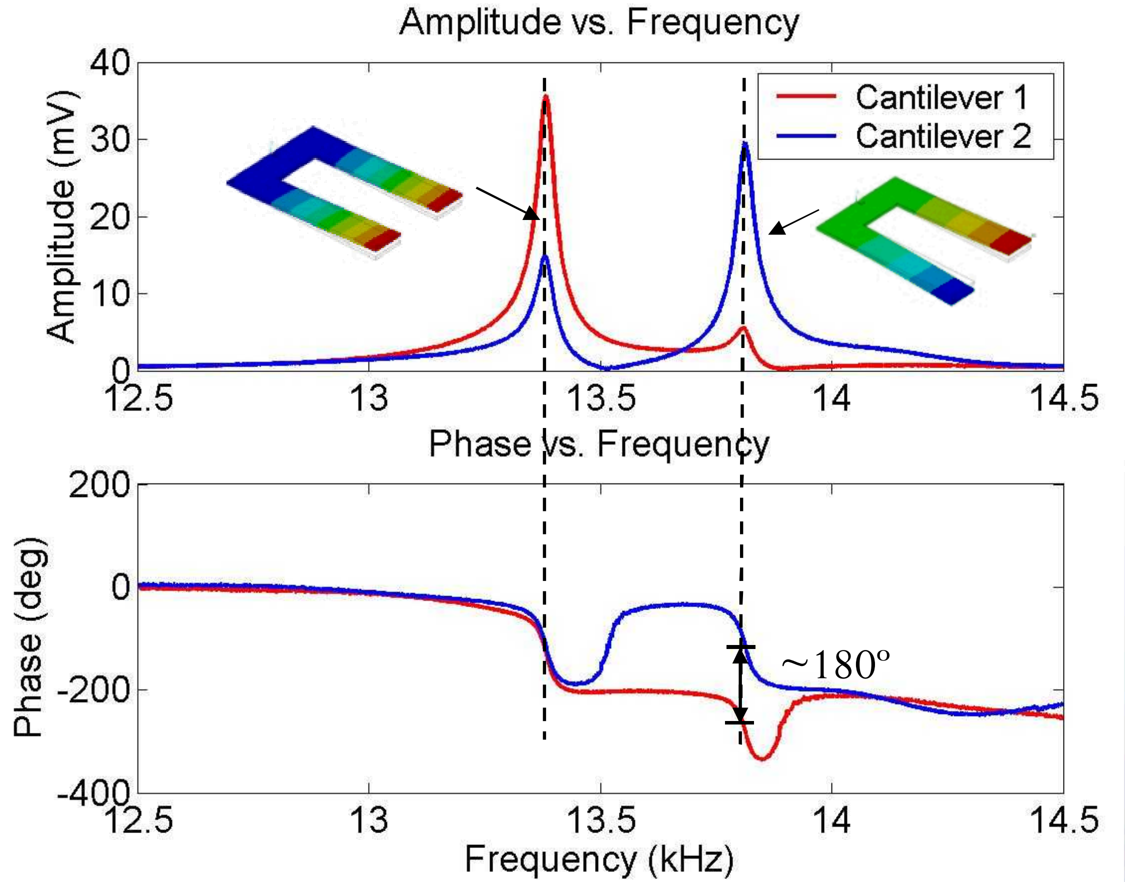


- Array vibrations are measured using an optical lever setup
- A piezo crystal provides a base excitation to the array at a range of frequencies
- Amplitude and phase data are measured with a lock- in amplifier



Two modes were characterized.

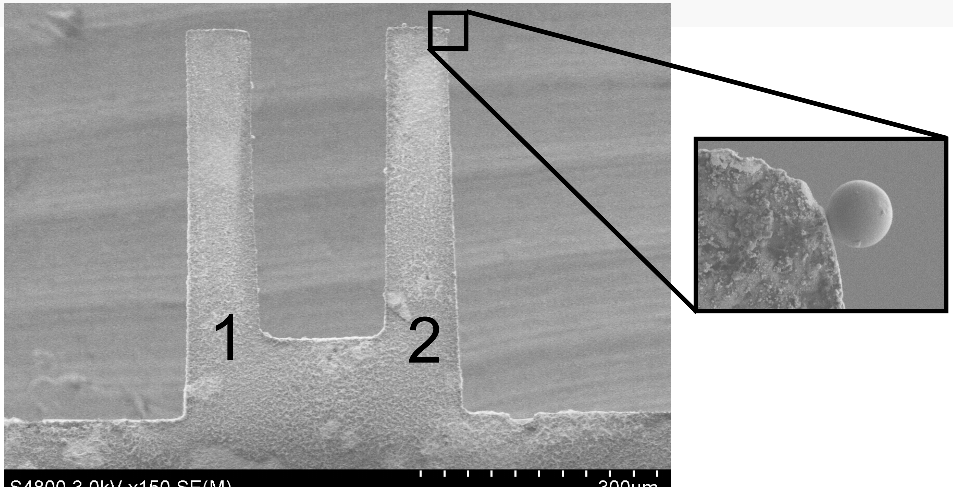
- Frequency sweeps show two clear peaks
- Phase difference indicates the first peak is the symmetric eigenmode, second peak is the antisymmetric eigenmode
  - Initial imperfections cause both peaks to appear in the frequency sweeps
- The components of each eigenmode are given by the peak amplitudes

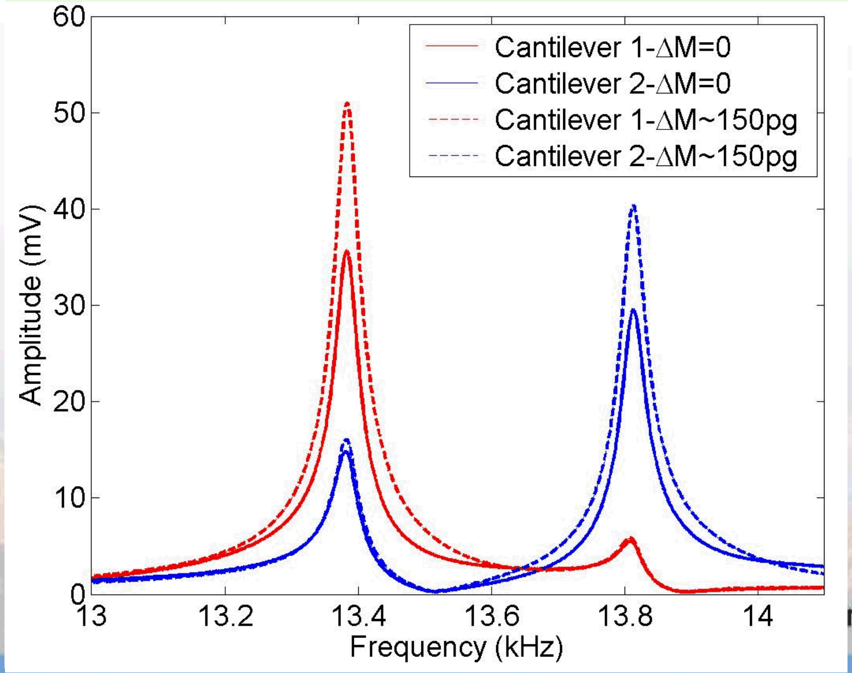


ΔM~150 pg changed the mode shapes significantly

- The symmetric eigenmode changes by 7%, while the antisymmetric eigenmode changes by about 5%

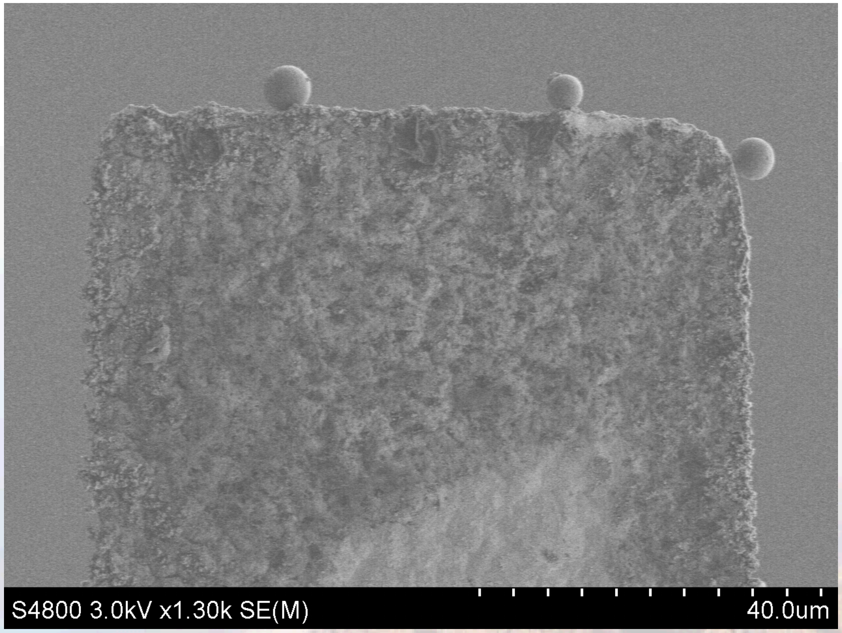
- The resonance frequencies are expected to shift by about 0.01% due to added mass
  - Under ambient conditions, resonance frequencies drift by up to 0.1%

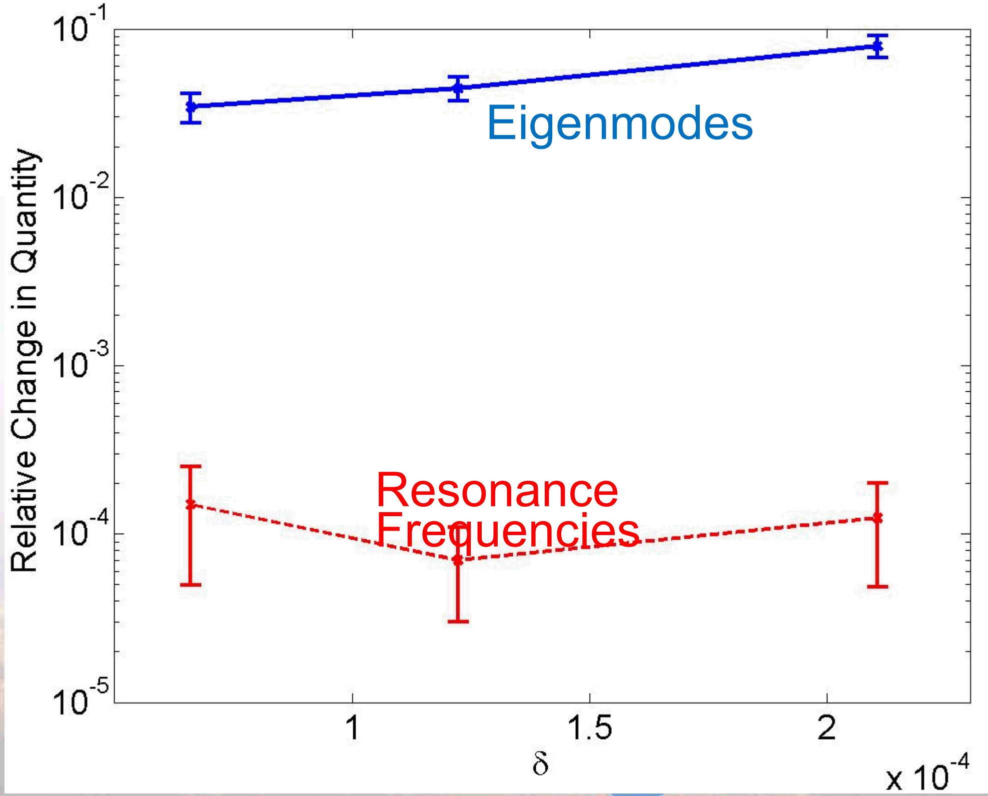




Multiple masses were detected.

- Adding multiple masses causes the relative shift in eigenmodes to increase
  - The relative shifts in resonance frequencies again fall within the expected drift of the system under ambient conditions





Two cantilever array-summary

- **Eigenmode shifts are two orders of magnitude more sensitive to added mass than resonant frequency shifts**
  - Eigenmodes are sensitive only to differences between cantilevers (common mode rejection)
- **Added mass resolution is limited by measurement system**
  - Minimum detectable mass is comparable to resonance-frequency based sensors
  - Improvements in amplitude measurement would lower minimum detectable mass
- **How could this sensor be improved?**
  - Decrease coupling
  - Use a larger array with the potential to detect multiple analytes
  - Increased number of eigenmodes provides additional verification of analyte binding and decreases false positive chances

Featured work

APPLIED PHYSICS LETTERS **92**, 114102 (2008)

Highly sensitive mass detection and identification using vibration localization in coupled microcantilever arrays

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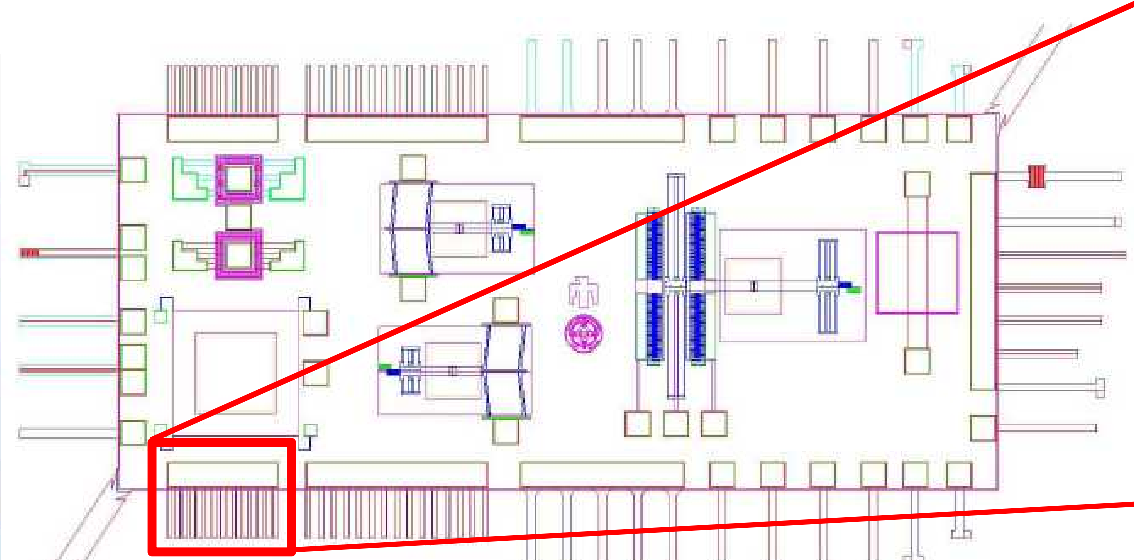
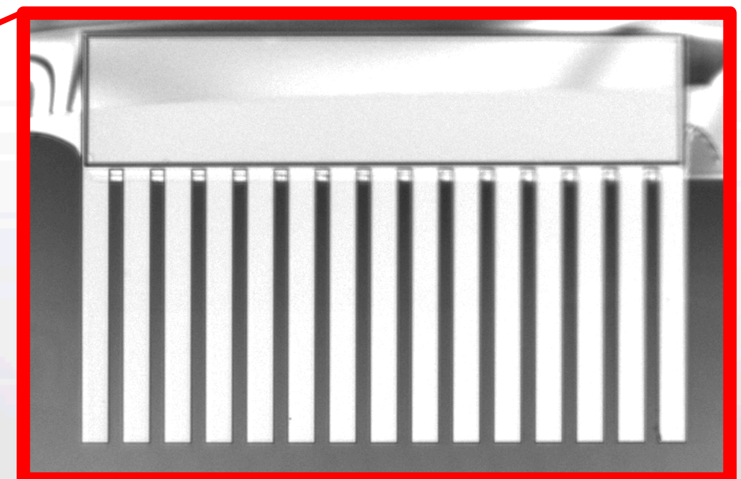
We study the use of vibration localization in large arrays of mechanically coupled, nearly identical microcantilevers for ultrasensitive mass detection and identification. We demonstrate that eigenmode changes in such an array can be two to three orders of magnitude greater than relative changes in resonance frequencies when an analyte mass is added. Moreover, the changes in eigenmodes are unique to the cantilever to which mass is added, thereby providing a characteristic "fingerprint" that identifies the particular cantilever where mass has been added. This opens the door to ultrasensitive detection *and* identification of multiple analytes with a single coupled array. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2899634]

A fifteen-cantilever array was investigated.

- Designed and fabricated at CINT.
- Focusing on an array of 15 coupled cantilevers on Chip 1
- Measurements performed using the Polytec MSA-400 system at Sandia's Microdynamics Lab.
  - Dual laser setup





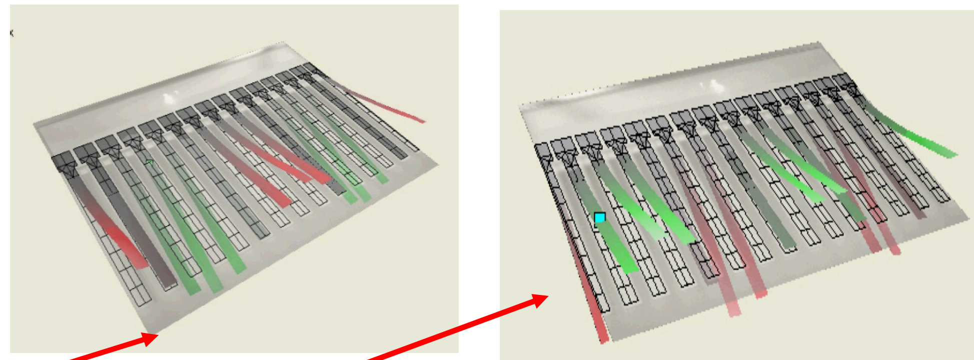
Schematic: J. Sullivan, CINT, SNL

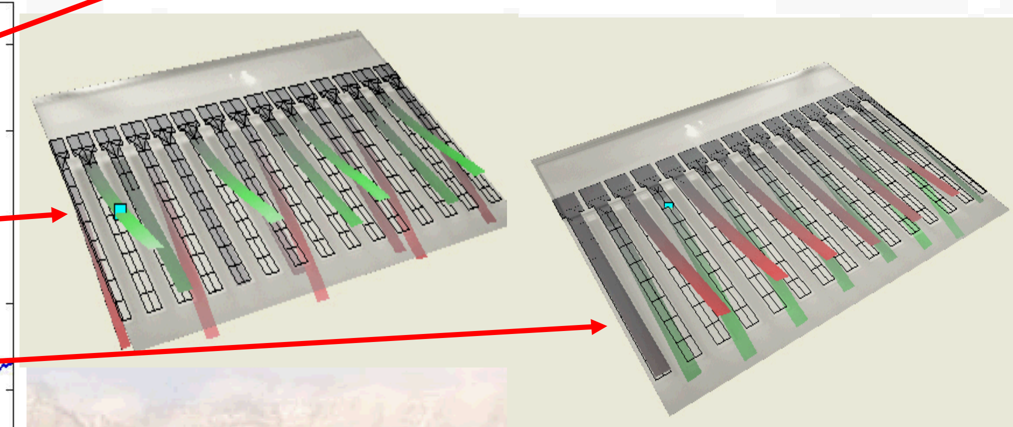
L=200μm w=20μm

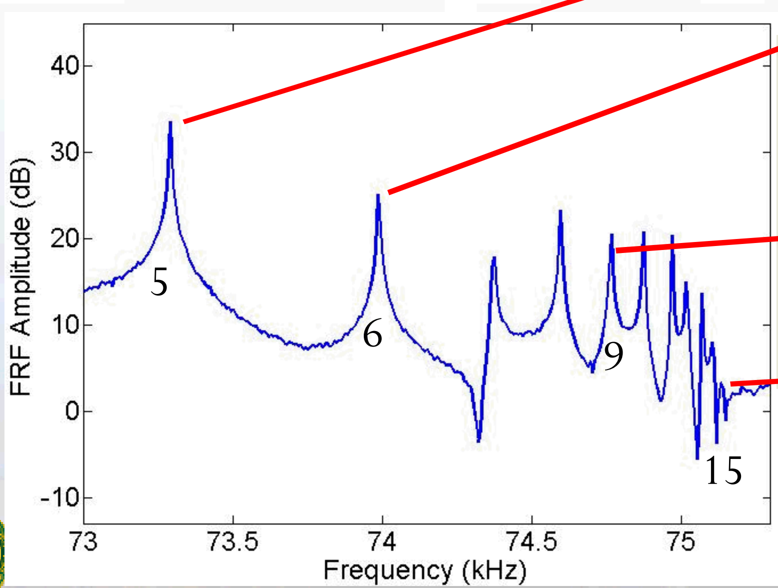
h=2.25μm 10μm gaps

The mode shapes were as predicted.

- Many array modes are very closely spaced
  - At low pressures, the peaks are well separated
- Presence of initial disorder affects the mode shapes

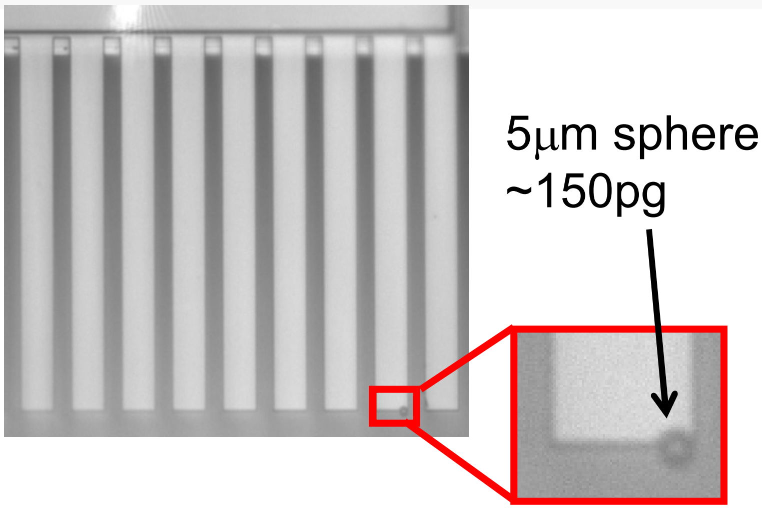


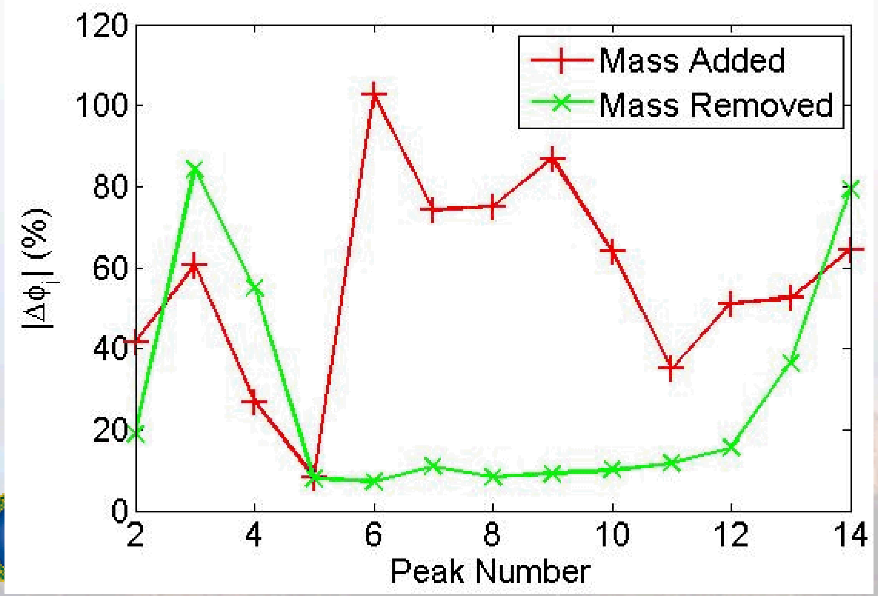


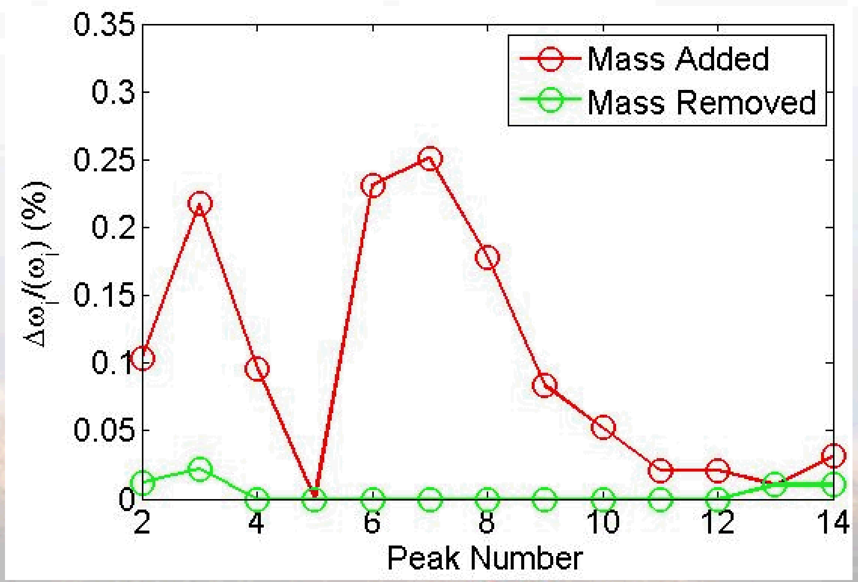


Mass attached to cantilever 14 changed mode shapes dramatically.

- Both frequency shifts and eigenmode shifts were visible
- Frequencies returned to initial values after mass removal
- Most mode shapes returned to initial values
- Smallest relative mode shape shift (35%) was 2 orders of magnitude larger than the largest relative frequency shift (0.25%)

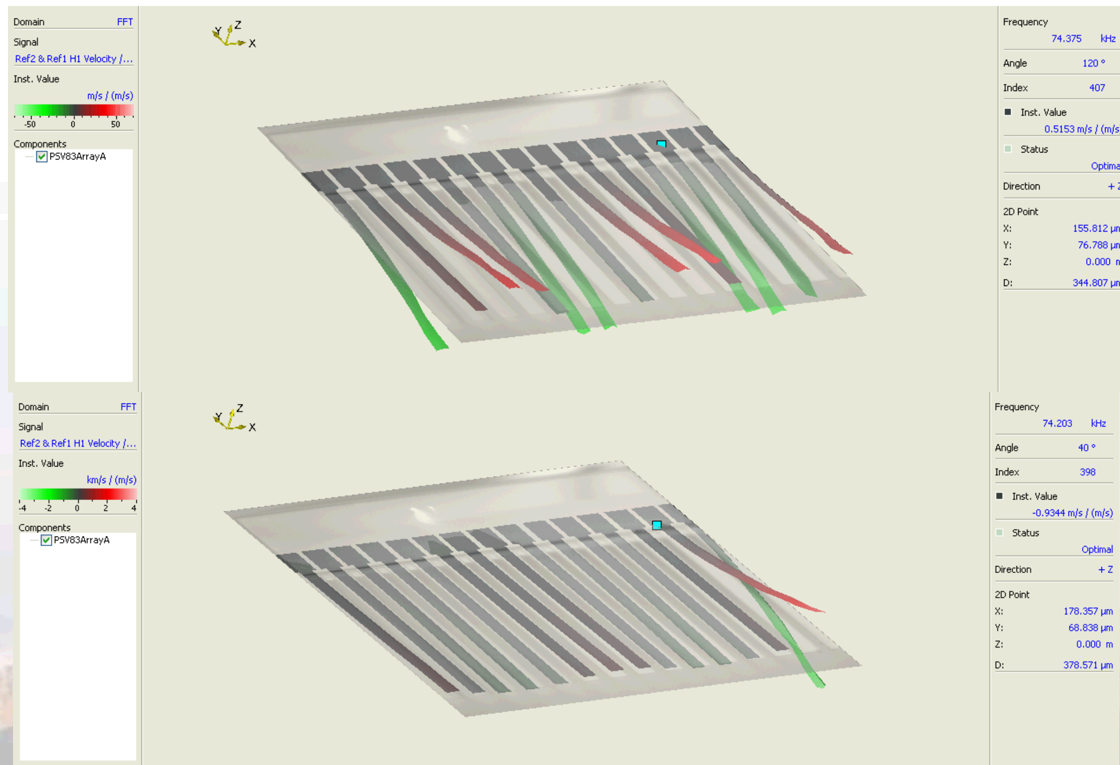






Mass causes mode localization.

- Adding mass to cantilever 14 causes the 6th eigenmode of the array to become localized
  - Vibrations are confined to cantilevers 14 and 15
  - Eigenmode returns to its initial state after mass removal



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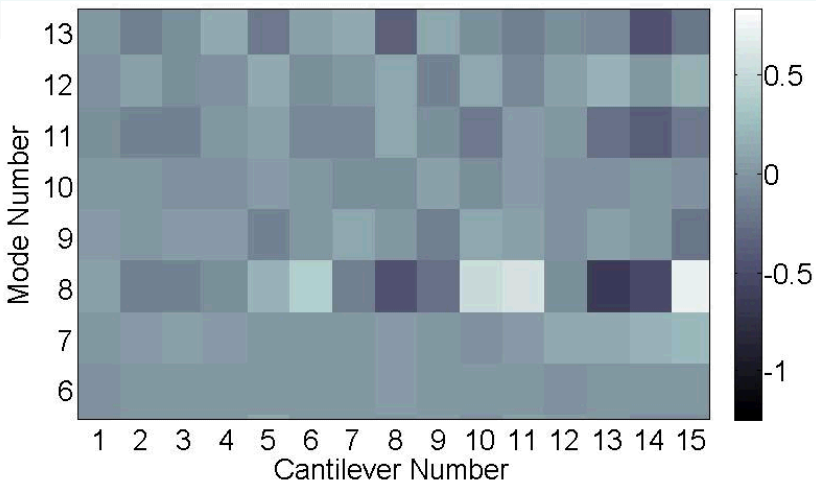
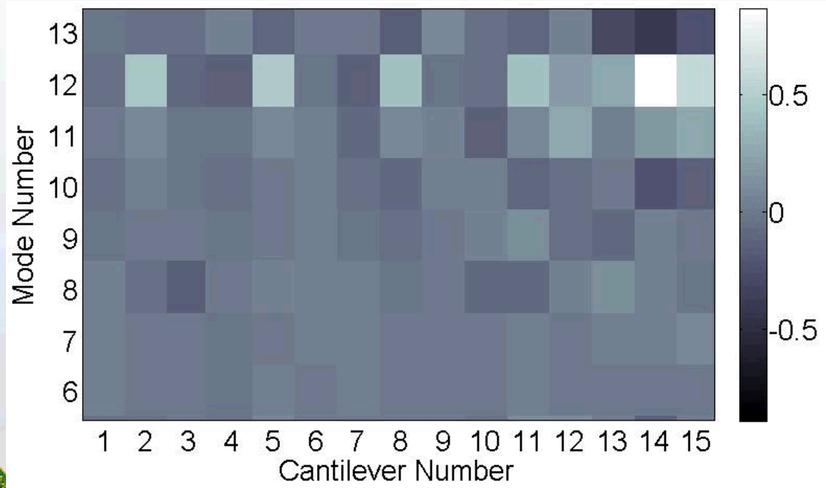
Masses were attached to different cantilevers.

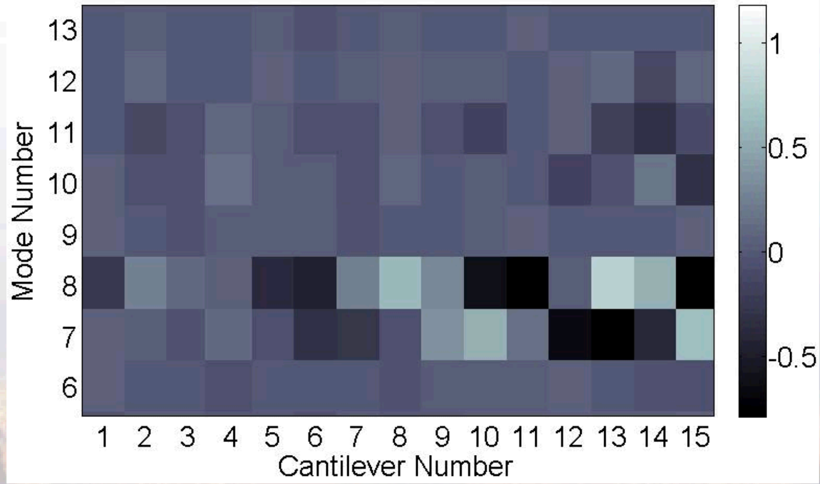
- Adding mass (10 pg) to two different cantilevers creates a unique pattern of eigenmode shifts $\Delta\phi_i$
- The measurement of multiple eigenmodes reduces the chance of false positives



Cantilever 10



Cantilever 14



Cantilever 15

Conclusions

- **Lightly coupling two or more cantilevers improves sensitivity to a target mass**
  - Relative eigenmode shifts are 2-3 times greater than resonance frequency shifts
  - Eigenmode shifts are relatively independent of Q-factor
  - Decreasing the coupling increases relative eigenmode shifts
  - Mode localization is observed

- **Pattern of eigenmode shifts changes with added mass location**
  - Measurement of multiple eigenmodes reduces the chance for false positives

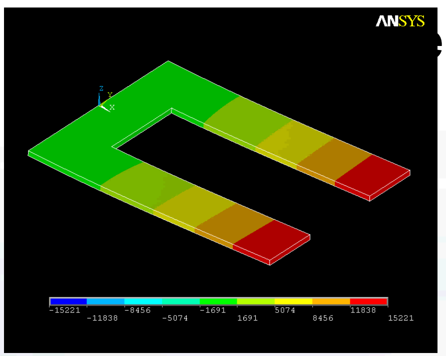
Acknowledgements

- Purdue University: Prof. A. Raman, Prof. R. Reifenberger, Prof. X. Xu, A.Q. Wu
- CINT: J. Sullivan
- NASA Institute for Nanoelectronics and Computing
- National Science Foundation

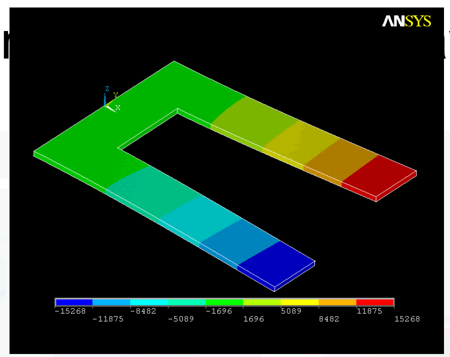
Supplemental Slides

Two Cantilever System

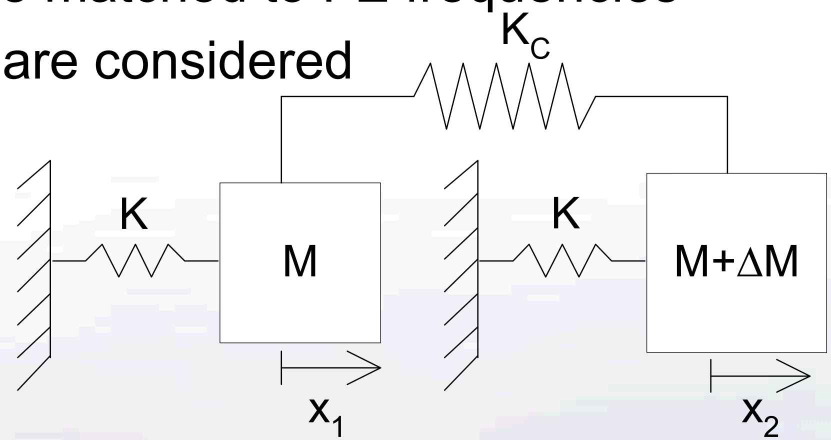
- **Initially, a finite element model of the cantilever array was created**
- **Cantilevers are then modeled as lumped parameter systems**
  - Lumped parameter frequencies are matched to FE frequencies
  - y are considered



Symmetric Mode
f=13837 Hz



Antisymmetric Mode
f=13899 Hz



- Free, undamped oscillations for two identical cantilevers

$$\begin{bmatrix} M & 0 \\ 0 & M+\Delta M \end{bmatrix}\begin{bmatrix} \ddot{x}_1 \\ \ddot{x}_2 \end{bmatrix} + \begin{bmatrix} K+K_C & -K_C \\ -K_C & K+K_C \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = 0 \qquad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \phi e^{i\lambda t}$$

Sensitivity of Initially Symmetric System

- **The eigenvalue problem can be nondimensionalized as follows:**

$$\overbrace{\begin{bmatrix} 1+\kappa & -\kappa \\ -\kappa & (1+\kappa)/(1+\delta) \end{bmatrix}}^{A}\phi = \lambda\phi \qquad \delta = \frac{\Delta M}{M} \qquad \kappa = \frac{K_C}{K}$$

- **Write the problem as a perturbation expansion in terms of δ**

$$A\phi = \lambda\phi \qquad \lambda = \lambda_0 + \lambda_1\delta + O(\delta^2)$$

$$A = A_0 + A_1\delta + O(\delta^2) \qquad \phi = \phi_0 + \phi_1\delta + O(\delta^2)$$

- **The relative change of the eigenmodes to added mass is given by the magnitude of the difference between the perturbed and unperturbed eigenmodes**
  - A similar expression can be defined for the natural frequency of a single cantilever

$$\frac{|\phi-\phi_0|}{|\phi_0|} = \left(\frac{1}{4}+\frac{1}{4\kappa}\right)\delta \qquad \frac{\Delta f}{f_0} = \frac{-\delta}{2}$$

Without optimization, $\kappa \sim 10^{-2}$ for the gold arrays!

Lowering κ produces higher sensitivity

Eigenvalue Problem

- **Perturbation Expressions**

$$\phi^{(1)} = \frac{1}{\sqrt{2}}\begin{bmatrix}1\\1\end{bmatrix} + \frac{1}{\sqrt{2}}\left(\frac{-1-\kappa}{4\kappa}\right)\begin{bmatrix}1\\-1\end{bmatrix}\delta$$

$$\phi^{(2)} = \frac{1}{\sqrt{2}}\begin{bmatrix}1\\-1\end{bmatrix} + \frac{1}{\sqrt{2}}\left(\frac{1+\kappa}{4\kappa}\right)\begin{bmatrix}1\\1\end{bmatrix}\delta$$

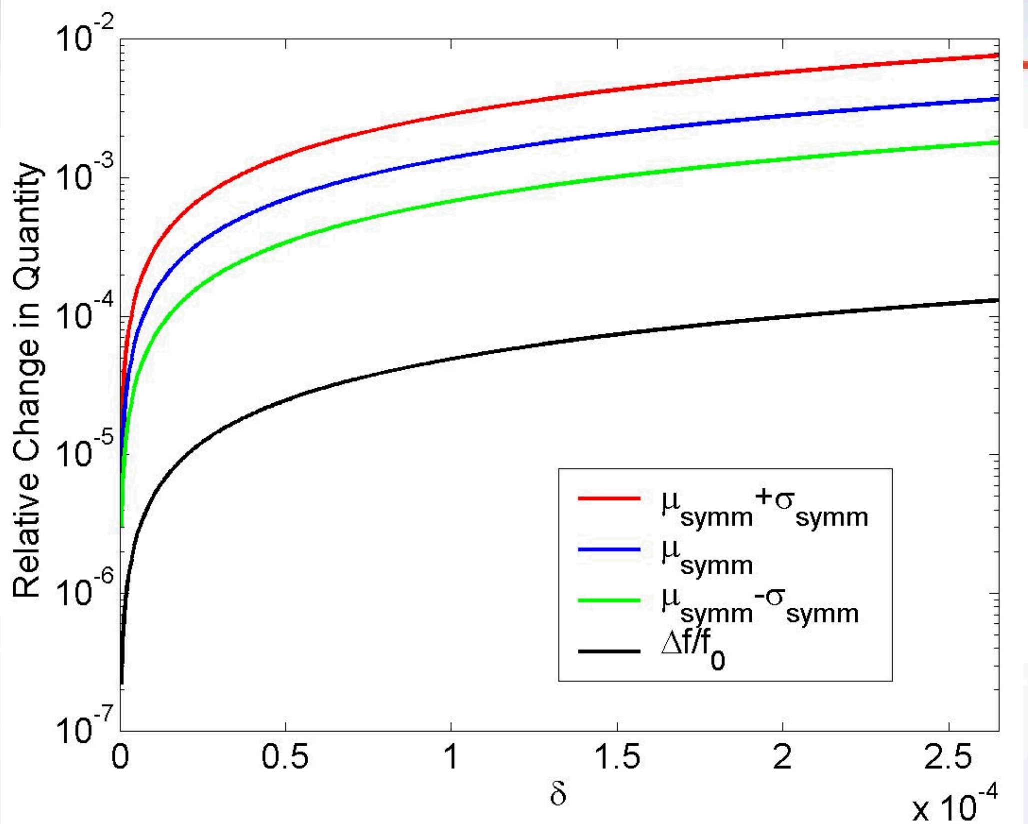
$$\lambda^{(1)} = 1 - {}^{1}\!/_{2}(1+\kappa)\delta$$

$$\lambda^{(2)} = 2\kappa + 1 - {}^{1}\!/_{2}(1+\kappa)\delta$$

- **Other nondimensional quantities**

$$\omega_0 = \sqrt{\frac{K}{M}} \qquad \tau = \omega_0 t$$

Effects of Initial Disorder



- **Manufacturing tolerances will prevent the two cantilevers from being perfectly identical**
  - Small variations in the dimensions of each cantilever will occur
- **Introducing disorder into the dimensions of the cantilevers decreases the sensitivity slightly**
  - Hundreds of simulations were performed using varied length, width, and thickness values for each cantilever