MASS SENSING OF MICROBEADS USING A WEAKLY-COUPLED CANTILEVER

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Abstract

Recently, the measurement of biological molecules using a microcantilever is attracting much interest. In the measurements as DNA detection with a microcantilever, the mass is usually identified from the eigenfrequency shift in a resonator. Such a way relies on the frequency response curve under the external or forced excitation and requires a low viscosity environment like air or vacuum. However, the sensing of biological molecules including the reaction between antibody and antigen needs to be performed in active and the measurement in a liquid environment is essential. We detect small biological masses in a liquid environment using a self-excited oscillation produced by the velocity feedback control. We use a weakly coupled cantilever and carry out a mass sensing based on the change of an amplitude ratio. We form a gold pattern on one of the cantilevers to fix the biological masses. We obtained the time history about the amplitude ratio to show the process of the biological reaction of the molecules.

Key words

Biological mass sensing, MEMS, Self-excited oscillation, Velocity feedback, cantilever

1 Introduction

Measurement of biological masses using a microcantilever is attracting interest recently. As shown in DNA detection in the low concentration solution[Su et al., 2003], ultrasensitive detection of a virus[Ilic et al., 2004] and detection of growth of colon bacillus[Gfeller et al., 2005], a mass is usually detected from the eigenfrequency shift of a resonator. Because such a way requires high Q-factor, it is difficult to measure a mass in viscous environment. To avoid the effect of viscous environment and keep Q-factor high, detailed analysis of the shape of a resonator was investigated[Van Eysden and Sader, 2007]. On the other hand, our research group has proposed self-excited coupled cantilevers, which keeps high accuracy indepedent of the effect of the scale and avoid the viscosity in measuring environments. In this article, we report the measurement of microbeads fixed on a cantilever with biological bonding.

2 Mass measurement method

As shown in [Spletzer et al., 2006], coupled cantilevers can be modelized as a 2-degrees spring mass damper system shown in figure 2. The characters in

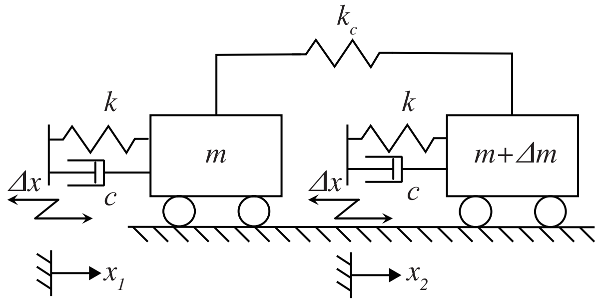

Figure 1. Analytical model of a coupled cantilevers.

figure 2 represent these parameters:

Δm : Mass value of a measurement target.

m : Equivalent mass value of the cantilever.

k : Equivalent spring stiffness of the cantilever.

k_c : Coupling stiffness between the cantilevers.

c : Equivalent damping of a viscous environment.

Δx: External excitation

Here we show the equation of motion of the model with coordinate transformation as $X_1 = x_1 - \Delta x$, $X_2 = x_2 - \Delta x$ and set Δx as $\Delta x = \alpha \int X_1 \mathrm{dt}$ to produce self-excited oscillation. Dot represents time derivative. The equations of motion are expressed as follows:

$$m\ddot{X}_1 + (c + m\alpha)\dot{X}_1 + (k + k_c)X_1 - k_c X_2 = 0 \tag{1}$$

$$(m + \Delta m)\ddot{X}_2 + (m + \Delta m)\alpha\dot{X}_1 + c\dot{X}_2 - k_c X_1 + (k + kc)X_2 = 0. \tag{2}$$

To make the parameters dimensionless, Substituting dimensionless parameters like below. * means dimensionless parameter.

$$t = Tt^* = \sqrt{\frac{m}{k}}t^*,\ X = LX^*\ \kappa = \frac{kc}{k},\ \delta = \frac{\Delta m}{m} \tag{3}$$

Substituting them into eq. (1), eq. (2). Since now, dot represents dimensionless time derivative.

$$\ddot{X}_1^* + (\frac{c}{\sqrt{mk}} + \alpha\sqrt{\frac{m}{k}})\dot{X}_1^* + (1+\kappa)X_1^* - \kappa X_2^* = 0 \tag{4}$$

$$\ddot{X}_2^* + \alpha\sqrt{\frac{m}{k}}\dot{X}_1^* + \frac{c}{\sqrt{mk}}\frac{1}{1+\delta}\dot{X}_2^* - \frac{\kappa}{1+\delta}X_1^* + \frac{1+\kappa}{1+\delta}X_2^* = 0 \tag{5}$$

Introducing dimensionless damping coefficient $\gamma = \frac{c}{2\sqrt{mk}}$ and dimensionless feedback gain $\beta = \alpha\sqrt{\frac{m}{k}}$. Expressing the equations above into matrix form. * is omitted from here.

$$\begin{bmatrix}\ddot{X}_1 \\ \ddot{X}_2\end{bmatrix} + \begin{bmatrix}2\gamma+\beta & 0 \\ \beta & \frac{2\gamma}{1+\delta}\end{bmatrix}\begin{bmatrix}\dot{X}_1 \\ \dot{X}_2\end{bmatrix} + \begin{bmatrix}1+\kappa & -\kappa \\ -\frac{\kappa}{1+\delta} & \frac{1+\kappa}{1+\delta}\end{bmatrix}\begin{bmatrix}X_1 \\ X_2\end{bmatrix} = \begin{bmatrix}0 \\ 0\end{bmatrix} \tag{6}$$

Now eigenvaluesλ_1 λ_2 and eigenvectors$\boldsymbol{p_1}$ $\boldsymbol{p_2}$ of stiffness matrix are derived.

$$\lambda_1 = \frac{1}{2(1+\delta)}\left\{(1+\kappa)(2+\delta) - \sqrt{(1+\kappa)^2\delta^2 + 4\kappa^2(1+\delta)}\right\} \tag{7}$$

$$\lambda_2 = \frac{1}{2(1+\delta)}\left\{(1+\kappa)(2+\delta) + \sqrt{(1+\kappa)^2\delta^2 + 4\kappa^2(1+\delta)}\right\} \tag{8}$$

$$\boldsymbol{p_1} = \begin{bmatrix}1 \\ \frac{\kappa}{1+\kappa-(1+\delta)\lambda_1}\end{bmatrix} = \begin{bmatrix}1 \\ -\frac{1}{2}\frac{\delta}{\kappa}(1+\kappa) + \frac{1}{2}\sqrt{(1+\kappa)^2(\frac{\delta}{\kappa})^2 + 4\kappa^2(1+\delta)}\end{bmatrix} \tag{9}$$

$$\boldsymbol{p_2} = \begin{bmatrix}1 \\ \frac{\kappa}{1+\kappa-(1+\delta)\lambda_2}\end{bmatrix} = \begin{bmatrix}1 \\ -\frac{1}{2}\frac{\delta}{\kappa}(1+\kappa) - \frac{1}{2}\sqrt{(1+\kappa)^2(\frac{\delta}{\kappa})^2 + 4\kappa^2(1+\delta)}\end{bmatrix} \tag{10}$$

Considering the case Δm is much smaller than m. This condition can be written as $\delta << 1$ by $\delta = \frac{\Delta m}{m}$. Also, k_c is assumed to be smaller than k. This condition can be written as $\kappa < 1$ by $\kappa = \frac{k_c}{k}$. $\boldsymbol{p_1}$ $\boldsymbol{p_2}$ are approximated as follows:

$$\boldsymbol{p_1} \approx \begin{bmatrix}1 \\ \frac{1}{1-\frac{1}{2}\frac{\delta}{\kappa}}\end{bmatrix} \tag{11}$$

$$\boldsymbol{p_2} \approx \begin{bmatrix}1 \\ -\frac{1}{1+\frac{1}{2}\frac{\delta}{\kappa}}\end{bmatrix} \tag{12}$$

These expresses the amplitude ratio of the model. From modal analysis of (6), eigenvalue of first mode $\lambda_0^{(1)} = \pm i\omega_1$ and eigenvalue of second mode $\lambda_0^{(2)} = -\gamma \pm \sqrt{\gamma^2 - \omega_2^2}$ $(-\gamma \pm i\sqrt{\omega_2^2 - \gamma^2})$ are acquired. So second mode will disappear and first mode keeps oscillating and not sure it will have self-excited oscillation. From higher order analysis of parameter smaller than 1, self-excited oscillation nondimentionalized feedback gain $\beta = \alpha\sqrt{\frac{m}{k}}$ is in the range of equation (13)[Yabuno et al., 2013].

$$\beta < -2\gamma - \frac{\delta}{\kappa}\frac{\gamma(\omega_2^2 - \omega_1^2)^2}{8\gamma^2\omega_1^2 + 2(\omega_2^2 - \omega_1^2)^2} \tag{13}$$

When the cantilevers oscillate with first mode, the amplitude ratio is expressed as equation (14).

$$\begin{bmatrix}X_1 \\ X_2\end{bmatrix} = \begin{bmatrix}1 \\ \frac{1}{1-\frac{1}{2}\frac{\delta}{\kappa}}\end{bmatrix} \tag{14}$$

κ can be derived from first and second eigenfrequency and m can be derived from the first eigenfrequency. Therefore, according to equation (14), Δm can be derived from amplitude ratio[Spletzer et al., 2006].

3 Devices used in the experiment

We used the acrylic case shown in figure 2. The cantilever is fixed in the acrylic case. External excitation for the cantilevers is carried by a piezo actuator attached to the case. The case is filled with phosphate buffered saline.

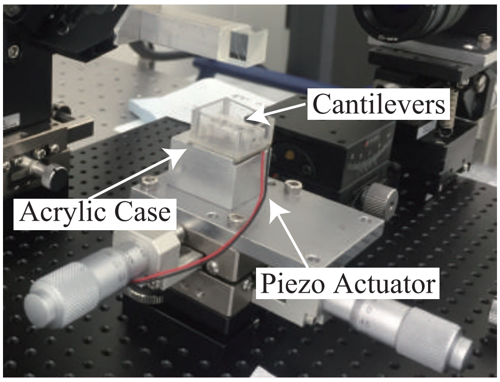

Figure 2. Acrylic case for the experiment.

The signal flow about the laser sensor, the piezo actuator, and the integral circuit to make the suitable control signal is shown in figure 3. The weakly-coupled cantilevers shown in figure 4 is fabricated using deep-reactive ion etching process. Thin gold pattern is formed on one of the cantilevers for chemical bonding between gold and thiol. The measurement targets are polystyrene microbeads (08-18-124, micromod). Its diameter is 12μm and weight is 950 pg approximately and surface is coated with biotin.

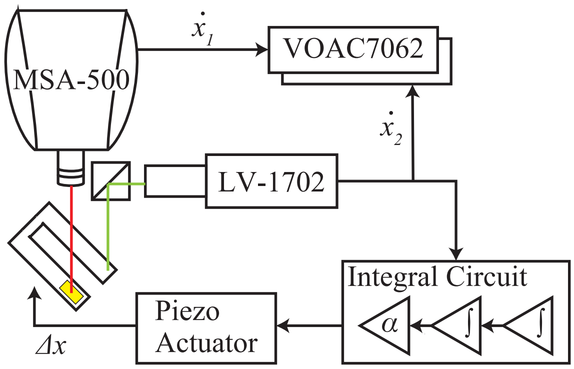

Figure 3. Relationship between the devices used in the experiment. Amplitudes of the cantilevers are measured with two laser doppler vibrometers. The one with red laser is MSA-500 (Polytec) and the another one with green laser is LV-1710 (Ono Sokki). Datas from the vibrometers are stored in two digital multimeters (VOAC7062, IWATSU).

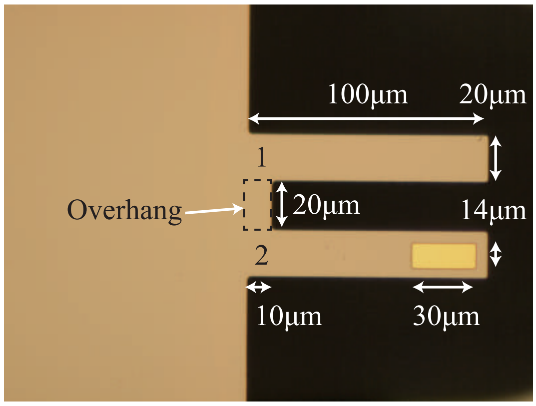

Figure 4. Schemetic diagram of a weakly-coupled cantilevers. Overhang part works as coupling spring stiffness k_c.

4 Chemical bonding between the cantilever and beads

To fix the beads on the cantilever, we prepare for two layers. First layer is biotin-labeled alcane thiol SAM. This layer is fixed on the gold pattern because of the covalent bonding between gold and thiol. Second layer is streptavidin. This layer is fixed on the first layer because of the chemical reaction between avidin and biotin. This reaction is also used for fixing the beads on the second layer. These procedures are preparation for the experiment. We will report the result at PHYSCON 2017.

5 Conclusion

We confirmed that [Yabuno et al., 2013] is effective in viscous environment and realized the measurement of the microbeads with a weakly-coupled microcantilevers.

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