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Nanomechanical Resonators and Their Potential to Biosensor Applications

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Abstract

Recently, nanomechanical resonators have played a vital role in detecting unprecedented physical phenomena. Also, nanomechanical resonators exhibit ultrahigh sensitivity for detecting molecular mass, quantum mechanical behavior and nonlinear dynamics. In this article, the current achievements of nanomechanical resonators for various sensing applications are reviewed. The fundamental principle of the dynamic behavior of nanomechanical resonators and its implications for design of nanomechanical resonators for biosensor applications are also discussed.

Keywords: NEMS, Resonator, Biosensor

Introduction

Mechanical resonators have gained much attention for their ability to detect the gravitational wave[1] and the quantum ground states of mechanical resonators[2-4]. This indicates that mechanical resonators allow one to understand the physical phenomena and/or verify physics theories from them. The scaling down of mechanical resonator to micro- or nano-scales has resulted in unprecedented physical behaviors to be observed, with the emergence of novel physics theories. For instance, NEMS resonators have succeeded in explaining the transition from classical mechanics to quantum mechanics[5], which has provided an insight into critical length-scales related to classical-to-quantum transitions. Nanomechanical resonators have also been able to verify the mathematical model of Duffing oscillators, that is, a nonlinear oscillator model[6,7]. The behavior of Duffing nanomechanical oscillators has been well understood in the analogy to Landau theory in relation to phase transition[8]. Furthermore, nanomechanical resonators immersed in a gas environment recently enabled Ekinci's group to detect the transition from Newtonian fluid flow to Non-Newtonian fluid flow[9], implying their potential application to nano-fluidics system for understanding nanofluidic phenomena[10]. This indicates that nanomechanical resonators may allow insight into the fundamental physical phenomena and/or nano-scale physics phenomena to be attained.

Recently, nanomechanical resonators have been shown to exhibit unprecedented sensitivity for detecting molecular masses[11,12] and forces[13]. Specifically, Roukes' group was able to detect the molecular mass in the order of zepto (10^{-21})-gram resolution using a nanomechanical resonator[14]. This implies that nanomechanical resonators may ultimately allow the mass of single molecules to be detected in the near future. Moreover, nanomechanical resonators possess high resolution of force sensitivity, which provides potential for the performance of atomic force microscopy to be improved. This indicates that nanomechanical resonators may exhibit great potential in the application of sensors for detecting molecular masses and intermolecular forces. Further, nanomechanical resonators recently allowed Craighead's group to detect biological molecules, such as DNA[15] and virus[16]. Specifically, a nanomechanical resonator allowed a single DNA chain to be detected, implying the enumeration of DNA molecules with the use of a nanomechanical resonator[15]. The detection principle of nanomechanical resonators for *in-vitro* biomolecular detection was recently reported, such that the surface stress induced by biomolecular interactions was found to play a crucial role in the resonant frequency shift of the nanomechanical resonator[17-19]. Until recently, nanomechanical resonators have exhibited restrictions for the *in situ* real-time monitoring of biomolecular interactions in a liquid, as the quality factor was extremely low in the liquid, even though a very high quality factor has been shown in either a vacuum or air[20]. This indicates that nanomechanical resonators may be applicable to biosensors for *in-vitro* biomolecular detection[21,22], although they still possess limitations for the *in situ* detection of biomolecules in a liquid.

As stated above, nanomechanical resonators have great potential for the application to novel devices that allow one to observe unprecedented physical

phenomena and/or detect inorganic molecules as well as the biological molecules with ultrahigh sensitivity. This article summarizes the current research on nanomechanical resonators for various applications, as well as their fundamental principles, which may provide a novel design concept for NEMS devices. This review consists of the following: in section 1, the basic principles of mechanical resonators are reviewed, with the fundamentals for their use in mass sensing illustrated; in section 2, the basic principles of nanomechanical resonators for *in-vitro* biomolecular detection are considered; in section 3, the computational models for nanomechanical resonator are explained, which provides a design concept for nanomechanical resonators. Finally, concluding remarks and the further directions of nanomechanical resonators are provided.

Results and Discussion

Dynamics of Mechanical Resonator

The dynamic behavior of mechanical resonators has been well described by the Euler-Bernoulli beam model, which delineates the resonant frequency of a mechanical resonator in the form of[23]:

$$\omega_i = \left(\frac{\lambda_i}{L}\right)\sqrt{\frac{\xi}{\mu}} \quad (1)$$

Here, ω_i is the resonant frequency for the i-th mode, L the length of a resonator, ξ the bending stiffness of the resonator, given as $\xi = EI$, where E is Young's modulus and I the second moment of inertia of a cross-section for a resonator, μ the mass per unit length of a resonator, and λ_i a constant depending on the boundary conditions, e.g. $\cos\lambda_i \cosh\lambda_i + 1 = 0$ for cantilever boundary conditions. Upon molecular adsorption, the resonant frequency of a resonator shifts as the result of a mass change due to molecular adsorption[14,23,24].

$$\Delta\omega \simeq \frac{\partial\omega}{\partial m}\Delta m = \frac{1}{2}\frac{\omega_0}{m}\Delta m \quad (2)$$

where, $\Delta\omega$ is the resonant frequency shift, ω_0 the reference resonant frequency (without any molecular adsorption), m the mass of a resonator, and Δm the mass of adsorbed molecules. This indicates that the resonant frequency shift due to molecular adsorption is linearly proportional to the mass of the adsorbed molecules. The principle dictated by Eq. 2 has been satisfactorily applied to mass sensing of inorganic molecules, thin film layers and organic molecules and/or particles. For instance, Figure 1 shows the resonant frequency shift induced by an adsorbed Au thin layer in comparison with the theoretical resonant

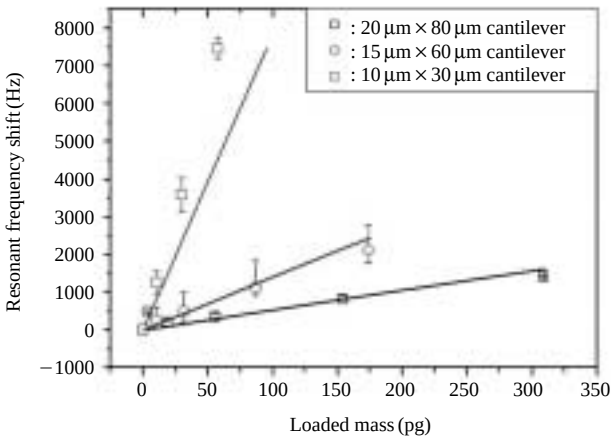

Figure 1. Resonant frequency shift of microcantilever upon mass loading of Au thin layer. The solid lines indicate the theoretical predictions of resonant frequency shift upon mass loading[23].

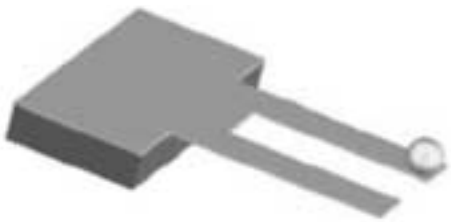

Figure 2. Schematic of coupled micromechanical resonator with mass loading on the end of one cantilever.

shift from Eq. 2.

In recent years, nanomechanical resonators have been considered for understanding nonlinear dynamics, such as synchronization[25-27], which play a role in gaining an insight into biological physics, such as molecular systems (e.g. protein structure)[28]. Moreover, the coupled resonator has been suggested as a sensitive device which takes into account variations in the eigen-mode in response to molecular adsorption[29]. For convenience, the coupled resonator reviewed here was assumed to consist of two resonators, with coupling between two resonators. The two resonators were also assumed to be identical cantilevers, one of which allows the analyte to be loaded at the end of it (see Figure 2). The oscillation motion of such a system is described by the eigenvalue problem[28,29].

$$\begin{bmatrix} 1+k & -k \\ -k & (1+k)/(1+\delta) \end{bmatrix}\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = \alpha\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \quad (3)$$

Here, k is the ratio of the spring constant for coupling to that of a cantilever, i.e. $k = K_c/K$, where K_c

and K represents the spring constants for coupling and the cantilever, respectively. A parameter, δ, indicates the ratio of the mass of analyte to that of the cantilever, i.e. $\delta=\Delta M/M$, where ΔM and M are the masses of the analytes and cantilever, respectively. A vector, $\mathbf{u}=[u_1\ u_2]^T$, represents the deflection eigen-mode of each cantilever; whereas, α is the eigenvalue or resonant frequency. The changes in eigen-modes and eigenvalues for adsorption of an analyte onto a coupled resonator are given by:

$$\frac{\Delta\alpha}{\alpha_0}=-\frac{\delta}{2}$$
$$\frac{\Delta u_i}{u_i^0}=\frac{1}{4}\left(1+\frac{1}{k}\right)\delta \quad (4)$$

where the index, 0, indicates the reference state before the analytes are adsorbed. This indicates that the resonant frequency shift due to the mass of analytes is independent of the spring constant, K_c, for coupling, while the change in the eigen-mode depends on the dimensionless spring constant, k, for coupling. This implies that the mass sensitivity of a nanomechanical resonator can be improved by detecting the eigen-mode change for a coupled resonator in response to analyte adsorption (i.e. $k \ll 1$).

In-vitro Biomolecular Detection

Recently, nanomechanical resonators for *in-vitro* biomolecular detection have been reported[18,19,21,30, 31]. The detection principle is one of direct transduction of biomolecular interactions (e.g. protein antigen-antibody interaction, DNA hybridization, etc.) into change of the mechanical properties, such as the resonant frequency of a resonator. As stated earlier in section 2, the resonant frequency shift due to molecular adsorption is ascribed to the mass of adsorbed molecules. However, it was recently found that the resonant frequency shift induced by biomolecular adsorption is attributed to not only the mass of adsorbed molecules, but also the biomolecular interactions described by the surface stress.

The dynamic motion of a nanomechanical resonator with biomolecular adsorption is represented in the form[18,19]:

$$\xi\frac{\partial^4 w(x,t)}{\partial x^4}+\frac{\partial}{\partial x}\left[N(x)\frac{\partial w(x,t)}{\partial x}\right]+\mu\frac{\partial^2 w(x,t)}{\partial t^2}=f(x,t) \quad (5)$$

Here, w(x, t) is the deflection of a resonator, x the coordinate along the longitudinal direction of a resonator, t the time, N(x) the axial loading due to surface stress describing the biomolecular interactions and f(x, t) the Gaussian white-noise force due to thermal fluctuation. In general, for a micron-scale resonator, thermal fluctuation does not play a crucial role in the dynamic behavior of a resonator. For the oscillation motion of a resonator, the deflection, w(x, t), is described by $w(x,t)=u(x)\cdot\exp(i\omega t)$, where ω is the resonant frequency and u(x) its corresponding deflection Eigen-mode. Consequently, the oscillation motion of a resonator with biomolecular adsorption is delineated by the eigenvalue problem.

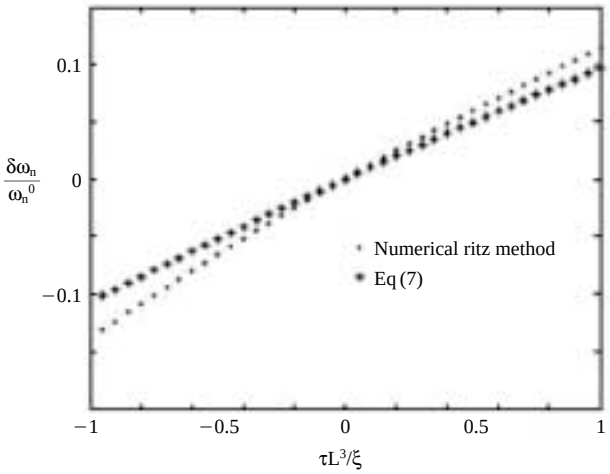

Figure 3. Resonant frequency shift vs. surface stress driven by biomolecular interactions, computed by numerical method (Ritz method)[18].

$$\xi\frac{d^4u}{dx^4}+\frac{d}{dx}\left[N\frac{du}{dx}\right]=\mu\omega^2 u \quad (6)$$

The resonant frequency, ω_i, of a resonating cantilever with biomolecular adsorption is obtained from solving the eigenvalue problem (Eq. 6) using the Ritz method.

$$\omega_i=\omega_i^0\left(1+\frac{2}{\pi^2}\frac{\tau L^3}{\xi}\right)^{1/2} \quad (7)$$

where ω_i^0 is the resonance of a cantilever without biomolecular adsorption, and τ the surface stress attributed to the biomolecular interactions. Thus, the resonant frequency shift for the biomolecular interactions of a small-scale cantilever is given by:

$$\frac{\Delta\omega}{\omega^0}\simeq\frac{L^3}{\xi}\tau \quad (8)$$

Figure 3 shows the relationship between the resonant frequency shift and the surface stress induced by biomolecular interactions by solving the numerical model.

Even though nanomechanical resonators exhibit unprecedented sensitivity, they also possess restrictions with regard to *in-vitro* biomolecular recognition

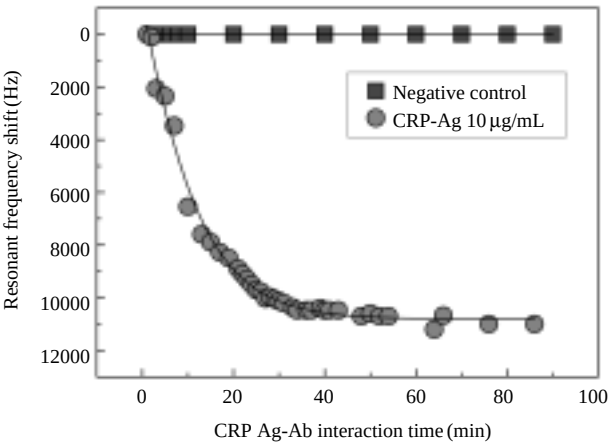

Figure 4. Resonant frequency shift, measured in the liquid environment, during protein antigen-antibody interactions[31].

in a liquid environment, such that they have an extremely low quality factor in liquid[20]. In contrast, until recently, *in-vitro* biomolecular detection in a liquid environment was implemented by micromechanical resonators[31,32]. For such devices, the detection principle for *in-vitro* biomolecular detection were quite different from that for a nanomechanical resonator operated in normal air and/or under vacuum. Specifically, the surface stress effect may not play a vital role in the resonance behavior of a micromechanical resonator. Furthermore, the resonance behavior of micromechanical resonators depends on the hydrodynamic loading arising from the surrounding fluid acting on a resonator[33]. The resonance, ω_i, of a micromechanical resonator operated in a viscous fluid is given by: ω_i, $\omega_i^0\sqrt{\theta}$ where ω_i^0 is the resonance of a resonator operated in normal air and θ a dimensionless parameter, given as[33]:

$$\theta=\frac{m_l}{m_c}=\left(\frac{w}{t_c}\right)\left(1+\frac{4}{(\lambda_i w/L)\sqrt{w^2\omega_i^0/v}}\right)\left(\frac{\rho_l}{\rho_c}\right) \qquad (9)$$

Here, m_c and m_l are the mass of the micromechanical resonator and the hydrodynamic loading arising from the surrounding fluid acting on the resonator, respectively, w the with of the resonator, t_c the thickness of the resonator, v the kinetic viscosity, ρ_l the density of the fluid, and ρ_c the density of the resonator. The resonant frequency shift due to biomolecular interactions (e.g. antigen-antibody interactions, e.g. Figure 4) for a micro-scale resonator was recently ascribed to the change of hydrodynamic loading, driven by the change in the hydrophilicity due to biomolecular interactions, as well as the mass of adsorbed biomolecules[31].

$$\frac{\Delta\omega}{\omega}=\frac{1}{2}\frac{\Delta m_l}{m_l}(1-\theta)+\frac{1}{2}\frac{\Delta m}{m_c}\theta \qquad (10)$$

Here, ω and $\Delta\omega$ are the resonant frequency of a resonator operated in a viscous fluid and the resonant frequency shift, measured in a viscous fluid, due to biomolecular interactions, Δm_l the change of hydrodynamic loading caused by biomolecular interactions in a liquid environment, and Δm the mass of adsorbed biomolecules.

Computational Model on Nanomechanical Resonator

Nanomechanical and/or biological materials (e.g. protein) have been satisfactorily analyzed by molecular models, such as molecular dynamics (MD) simulation and coarse-grained models[34]. Specifically, MD simulations have allowed many research groups to understand the dynamic behavior of CNT resonators[35], the buckling behavior of CNTs[36,37], bending behavior of CNTs[38], dynamic crack propagation in nano-material[39], protein folding kinetics[40-42], protein dynamics[43-46] and single-molecule mechanics[47-51]. Despite their ability to accurately describe the molecular motions of nanomaterials and biological materials, MD simulations have restrictions, in that the time-scale accessible by a MD simulation is much smaller than that relevant to the dynamic motion of large nano-structures[52]; also, a large nano-structure entails very expensive computational cost in estimating the stiffness matrix based on an anharmonic potential field[53]. The potential field prescribed to a nano-structure is represented in the form[40,54]:

$$V=\frac{1}{2}\sum_i k_i(r_i-r_i^0)^2+\frac{1}{2}\sum_i k_{\theta,i}(\theta_i-\theta_i^0)+\sum_{i,j}U(r_{ij})+L \qquad (11)$$

where k_i is the stiffness of a covalent bond, r_i the distance for a covalent bond consisting of two atoms, i and i+1, $k_{\theta,i}$ the stiffness of the bending angle, θ_i, U(r) the van der Waals interaction and r_{ij} the distance between two non-bonded atoms, i and j, where the superscript 0 indicates the equilibrium position. Such a potential field, known as Tersoff-Brenner's potential[55], to CNT and/or graphene allows the stiffness matrix, **K**, to be estimated using a second derivative of potential field, V. The dynamic behavior of a CNT resonator and/or a graphene sheet is described by the following equation of motion:

$$\mathbf{M\ddot{u}+Q\dot{u}+Ku=f} \qquad (12)$$

where **M** is the mass matrix, **Q** the matrix representing the damping effect due to the surrounding gas (or liquid) acting on the nano-structure, **K** the stiffness matrix, **f** the Gaussian white-noise force due to the

thermal effect, and **u** the displacement fields for all atoms. For oscillating CNTs and/or graphene sheets, the equation of motion becomes the eigenvalue problem[56-58].

$$\mathbf{Ku}=\omega^2\mathbf{Mu} \quad (13)$$

Here, ω is the resonant frequency of a nanostructure and **u** its corresponding eigen-mode.

Conclusions

In this paper, the current work on nanomechanical resonators and their potential to sensor applications are reviewed. As stated earlier, nanomechanical resonators exhibit ultrahigh mass-sensitivity for the detection of molecular mass, even with zepto-gram resolution. Although nanomechanical resonators are able to be applied to ultra-high sensitive sensors, an understanding of the fundamental dynamic behavior of nanomechanical resonators and their response to molecular adsorptions and/or molecular interactions are required for the effective design of resonator-based sensors. This review summarizes the fundamental principles of nanomechanical resonator for various applications, such as *in-vitro* biomolecular detection, molecular mass detection and quantum measurement. Moreover, the theoretical models, such as the molecular model, are briefly reviewed with respect to nanomechanical resonators. The theoretical model may play a crucial role in the fundamental physics of nanomechanical resonators, which may allow insight into how to design a nanomechanical resonator for applications to a sensor for the detection of various physical phenomena. In summary, the experimental and theoretical (computational) work on the nanomechanical resonators are reviewed, but further work will be required to gain an understanding of the unprecedented physical phenomena of nano-scale structures.

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