Dynamical Response of Nanomechanical Oscillators in Immiscible Viscous Fluid for \textit{in vitro} Biomolecular Recognition

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Dynamical response of nanomechanical cantilever structures immersed in a viscous fluid is important to \textit{in vitro} single-molecule force spectroscopy, biomolecular recognition of disease-specific proteins, and the detection of microscopic dynamics of proteins. Here we study the stochastic response of biofunctionalized nanomechanical cantilevers beam in a viscous fluid. Using the fluctuation-dissipation theorem we derive an exact expression for the spectral density of the displacement and a linear approximation for the resonance frequency shift. We find that in a viscous solution the frequency shift of the nanoscale cantilever is determined by surface stress generated by biomolecular interaction with negligible contributions from mass loading.

\[ E I \frac{\partial^4 y}{\partial x^4} - S \frac{\partial^2 y}{\partial x^2} + \mu(x) \frac{\partial^2 y}{\partial t^2} = f_h(x,t) + f_{th}(x,t). \] \hspace{1cm} (1)

\( E \) and \( I \) are the Young’s modulus and moment of inertia of the (coated) beam, respectively. \( f_h(x,t) \) is the hydrodynamic loading due to the motion of the fluid around the beam and \( f_{th}(x,t) \) is a Langevin-type force per unit length responsible for the thermalization of the beam. The linear mass (mass per unit length) of the system \( \mu(x) \) consists of the linear mass of the beam \( \mu_b \), and the linear mass of the trapped biomolecules \( \mu_t(x) \). The axial load \( S \) introduced in Eq. \textsuperscript{11} describes the mutual interaction of biomolecules adsorbed on the beam \textsuperscript{11}. The boundary conditions for Eq. \textsuperscript{11} are given by \( y(0,t) = y'(0,t) = 0 \), \( y''(L,t) = 0 \) and \( E I y''''(L,t) = S y'(L,t) \), where primes denote spatial derivatives \textsuperscript{12}.

At higher concentrations, the biomolecules form a uniform layer with mass \( \mu_l \) and thickness \( h \) so that

\[ \mu(x) = \mu_b + \mu_l = \text{constant}. \] \hspace{1cm} (2)

The mutual interaction of biomolecules within the layer is modeled by taking into account the stress \( \sigma \) they generate...
on the coated surface of the beam. As shown in ref. 2, this stress enables the bending of the silicon-nitride microcantilevers with length to thickness ratio \( L/d \), ranging from \( 10^2 \) to \( 10^3 \). The resulting static deflection, on the order of a few tenths of microns, is related to surface stress by Stoney’s formula [10]. However, for the silicon nanomechanical cantilevers under investigation here \( (L/d \sim 50) \), Stoney’s formula typically yields angstrom-level bendings \( (10^{-5}L) \). So these nanocantilevers remain almost straight under the influence of surface stress. Nevertheless, as shown in [11], this stress induces an effective axial load, \( S = \sigma L \), that must be included in Eq. (4). In vacuum, such a model has been studied in ref. 13.

In addition, biomolecular interaction on the surface results in an effective Young’s modulus of the layer \( E_t \) [see ref. 7]:

\[
EI = E_b I_b + E_l I_l \approx E_b d^3 / 12 + E_l h b d^2 / 4. \tag{3}
\]

\( E_b I_b \) and \( E_l I_l \) are the respective bending rigidities of the beam and the layer (the last equality holds when \( h \ll d \)). In the opposite limit, biomolecules with mass \( m \) sparsely scattered over the beam at locations \( x_i \), result in

\[
\mu(x) = \mu_b + \mu_l(x) = \mu_b + m \sum_i \delta(x-x_i), \quad x_i \in [0, L]. \tag{4}
\]

If the average spacing is large compared to their size, their mutual interaction is negligible and \( S = 0 \). Considering that their presence does not substantially affect the moment \( I_b \) of the beam, the bending rigidity of the whole system is the same as for an unloaded beam, \( EI = E_b I_b \).

**Equations of Motion:** To solve equation (4), we expand the deflection \( y(x,t) \) and the force densities \( f_b(x,t) \) and \( f_{th}(x,t) \) in terms of the modes of the bare beam, defined as the beam without the added mass \( (\mu_l(x) = 0) \) though it includes the tension \( S = \sigma L \):

\[
y(x,t) = \sum_{n=1}^{\infty} y_n(t) \phi_n(\xi), \quad \xi = x/L. \tag{5}
\]

Similar expressions hold for the force densities. The eigenmodes \( \phi_n(\xi) \) satisfy the following conditions:

\[
\phi_n^*(\xi) - \alpha \phi_n''(\xi) = \beta_n \phi_n(\xi) : \alpha = \sigma L^3 / EI; \\
\phi_n(0) = \phi_n'(0) = 0; \phi_n''(1) = \alpha \phi_n'(1). \tag{6}
\]

The self-adjointness of (6) makes the modes orthonormal: \( \int_0^1 \phi_n^*(\xi) \phi_n(\xi) d\xi = \delta_{n,l} \). From Eq. (6), the eigenvalues \( \beta_n \) are the successive positive roots of

\[
1 + (1 + \varepsilon_n^2) \cosh \lambda_n \cos \lambda_n + \varepsilon_n \sinh \lambda_n \sin \lambda_n = 0 \tag{7}
\]

where \( \varepsilon_n = \alpha / (2 \beta_n^3) \) and \( \lambda_n = \beta_n [\sqrt{1 + \varepsilon_n^2} \pm \varepsilon_n] \). Note that, for \( \varepsilon_n = \alpha / (2 \beta_n^3) \ll 1 \), Eq. (6) reduces to the usual clamped-free equation, \( 1 + \cos \beta_n \cosh \beta_n = 0 \). As \( \beta_n \propto n \) for large \( n \), eigenvalues for which \( n \gg \sqrt{\alpha} \) are essentially independent of the surface stress.

Let \( \mu(x) = \mu_b + \mu_l(x) \). Using (5), Eq. (5) reduces to

\[
M \ddot{y}_n(t) + k_n y_n(t) + \sum_{j=1}^{\infty} \Phi_{nj} \ddot{y}_j(t) = F_{n,h}(t) + F_{n,th}(t). \tag{8}
\]

\( M = \mu_b L \) is the mass of the beam and \( F_{n,h}(t) = L f_{n,h}(t) \). The effective stiffness of mode \( n \) is

\[
k_n = E \beta_n^4 / L^3. \tag{9}
\]

The real and symmetric matrix \( \Phi \) has components

\[
\Phi_{nj} = L \int_0^1 \mu_i(\xi \xi') \phi_n(\xi') \phi_j(\xi') d\xi'. \tag{10}
\]

If \( \mu_l(x) = \mu_l \), then \( \Phi = M \mathbf{I} \), where \( \mathbf{I} \) is the identity matrix and \( M = L \mu_l \) is the layer mass. Eqs. (8) decouple and the mass of modes \( y_n \) becomes the total mass of the system, \( M + M_l \). But non-uniform mass distributions as in Eq. (4) couple the bare modes of the beam.

Taking the Fourier transform of (8) and using the expression for the hydrodynamic force [8],

\[
\hat{F}_{n,th}(\omega) = M f_\omega \omega^2 \Gamma(\omega) \hat{y}_n(\omega), \tag{11}
\]

where \( M_f = \frac{4}{9} \rho f L \beta^2 \) is the mass of the fluid loading the beam, and \( \Gamma(\omega) = \Gamma_s(\omega) + i \Gamma_i(\omega) \) is a complex “hydrodynamic function” discussed in detail in [6], we obtain

\[
\Lambda(\omega)|\hat{y}(\omega)| = |\hat{F}_{th}(\omega)|. \tag{12}
\]

Kets \(|v\rangle\) are column vectors with components \( v_i, \ i \in \mathbb{N} \). The nonhermitian matrix \( \Lambda(\omega) \) is given by

\[
\Lambda(\omega) = \Lambda_0(\omega) - \omega^2 \hat{\Phi} \tag{13}
\]

where

\[
\Lambda_0(\omega)_{nj} = [k_n - \omega^2(M_f \omega \Gamma(\omega) + M_n)] \delta_{nj} \\
\hat{\Phi}_{nj} = \Phi_{nj}(1 - \delta_{nj}); \quad M_n = M + \Phi_{nn}. \tag{14}
\]

**Spectral Densities:** As the dissipative (complex) part of the hydrodynamic function is frequency-dependent, we apply the generalized fluctuation-dissipation theorem [2] to derive the power spectrum matrix of the stochastic forces \( F_{n,th} \). \( S_\Phi(\omega) = \langle \hat{F}_{th}(\omega) \hat{F}_\omega(\omega') \rangle \) (the over-line denotes thermal averaging, the superscript \( s \) refers to the spectral density and \( \langle \hat{F}_{th} \rangle \) is the hermitian conjugate of \( \langle \hat{F}_{th} \rangle \)):

\[
S_\Phi(\omega) = \frac{k T}{k \omega} \left( \Lambda^\dagger(\omega) - \Lambda(\omega) \right) = 2kT M_f \omega \Gamma_i(\omega) \mathbf{I} \tag{14}
\]

where \( k \) is the Boltzmann constant and \( T \) the temperature. In components, this yields

\[
\overline{F_{n,th}(\omega) F_{p,th}(\omega')} = 2kT M_f \omega \Gamma_i(\omega) \delta_{np} \delta(\omega - \omega'). \tag{15}
\]
Notice that this expression does not depend on $\Phi$. It is the same as for a bare beam. As seen above, the stochastic forces acting on distinct modes are uncorrelated. Nevertheless, their power spectrum cannot be assumed to be constant, contrary to the assumption in ref. 4, as the dissipative part of the hydrodynamic function is frequency-dependent. Eq. (16) is the generalization of the expression derived by Paul and Cross for a single cantilever mode 5. Now, inverting (12), we obtain

$$|\tilde{y}(\omega)| = \chi(\omega) |\hat{F}_{th}(\omega)|, \quad \chi(\omega) = \Lambda^{-1}(\omega)$$  \hspace{1cm} (16)$$
and

$$|\tilde{y}(\omega)|^2 = \chi(\omega)|\hat{F}_{th}(\omega)|^2 |\chi(\omega)|^2.$$  \hspace{1cm} (17)$$
Introducing $\phi_{\xi}$ with components $\phi_n(\xi)$, the Fourier transform of the deflection 6 reads $\tilde{y}(x, \omega) = \langle \phi_{\xi} \rangle \tilde{y}(\omega)$ and using (17), we find its spectral density to be

$$\chi \chi^\dagger = \chi_0 \chi_0^\dagger + \omega^2 \chi_0 \left( \hat{\Phi} \chi_0 + \chi_0^\dagger \hat{\Phi} \right) \chi_0^\dagger + O(\Phi^2)$$  \hspace{1cm} (19)$$
where $\chi_0 = \Lambda_0^{-1}$. Reinstating in (18), we finally get

$$|\tilde{y}(x, \omega)|^2 = 2kT M_\eta \sum_{n=1}^\infty \left[ M_p^2 |\tilde{A}_n|^2 + 2\omega^2 \sum_{n=1}^\infty \sum_{p=1}^\infty \phi_n(\xi) \phi_p(\eta) \tilde{A}_n^p \right] \chi_{\eta} \chi_\eta^\dagger$$  \hspace{1cm} (20)$$
In this expression, $\xi = x/L$, $\Phi_{np}$ is given by 14 and the quantity $A_n = \Lambda_0(\omega)_{nn}/M_\eta$ reads

$$A_n = \omega_n^2 - \omega^2 (1 + \lambda_n/x_n(\omega))$$  \hspace{1cm} (21)$$
where $\omega_n = \sqrt{K_n/M_n}$ is the frequency in vacuum, $\lambda_n = M_f/M_n$ and $Re(A_n)$ is the real part of $A_n$. An expression similar to (20) can be derived for the slope of the deflection provided $\phi_0(\xi)$ is replaced by $\phi'_0(\xi)$ and the overall prefactor is divided by $L^2$.

Expression (20) is valid for any mass distribution $\mu(x)$ along the beam. For a uniform layer with linear mass $\mu$, $\Phi_{np} = L\mu_0 \delta_{np}$, and then $\Phi_{np} = 0$. All modes have the same effective mass, $M_\eta = M + L\mu$, and are decoupled. Reinstating in (20), the second term vanishes and we obtain the exact spectral density of a composite beam consisting of the original beam plus the layer. For molecules trapped on the beam at positions $\xi_i$, the mass profile given in Eq. (14) leads to $\Phi_{np} = m \sum_i \phi_n(\xi_i) \phi_p(\xi_i)$ and Eq. (20) is valid up to first order in $m$ provided the frequency satisfies $M_f \Gamma_\eta(\omega) \gg 4M_\eta$. Interestingly, if we assume $N$ molecules to be randomly scattered along the beam in a uniform way and average $\Phi_{np}$ accordingly, we find $\langle \Phi_{np} \rangle = n \sum_i \phi_n(\xi_i) \phi_p(\xi_i) d\xi_i = N m \delta_{np}$. As the total mass of the trapped molecules is small compared to the mass of the beam, in the first approximation, the average spectral density is the same as the spectral density of their average mass distribution—i.e. the spectral density of a uniform layer of mass $Nm$.

In Fig. 1, we compare the bare beam ($\Phi = 0$) spectral density of the deflection slope at the tip of a rectangular silicon nanocantilever ($E = 160$ Gpa, $\rho = 2.33 \times 10^3$ kg/m$^3$) to Sader’s result 24 in air and water. The beam dimensions are $b \times d \times L = 0.2 \times 0.2 \times 10$ (μm). From 24, at $T = 27^\circ$ C, the viscosities are $\eta_{water} = 1.86 \times 10^{-5}$, $\eta_{water} = 8.59 \times 10^{-4}$ (kg/m/s) and the densities, $\rho_{air} = 1.18$, $\rho_{water} = 997$ (kg/m$^3$). Although different, Sader’s formula can be shown to reduce to (20) provided $\lambda(\Gamma(\omega)) \ll 1$. This explains why the results are very similar in air ($\lambda(\Gamma(\omega)) \approx 0.06$ at resonance) while they start to differ in water ($\lambda(\Gamma(\omega)) \approx 25$ at resonance).

**Frequency Shift:** As stated earlier, when trapped molecules form a uniform layer, the exact spectral density of the beam deflection is given by

$$|\tilde{y}(x, \omega)|^2 = \frac{4kT M_\eta \Gamma_\eta(\omega)}{(M + M_f)^2} \sum_{n=1}^{\infty} \frac{\phi_n^2(\xi)}{|A_n|^2}$$  \hspace{1cm} (22)$$
where $M_\eta$ is the mass of the layer and where $A_n$ is given in Eq. (21) with $M_n = M + M_f$. When the peaks of Eq. (22) are sharp enough, the hydrodynamic function is almost constant in their vicinity and the resonant frequency sat-
versus the dimensionless surface stress \( \sigma \) and compared to its linear approximation (24). The layer shift is evaluated from the spectral density (22) and \( \ln(25) \) has been obtained from (7) in perturbation. It is 

\[
\omega_{R,n}^2 = f(\omega_{R,n}, M_n) k_n, \quad f = \frac{1}{3} \left( R + \frac{4R^2 + 3T^2}{R^2 + T^2} \right)
\]

where \( R = M_n + M_I \Gamma_{r,i} \), I = M_I \Gamma_1, and \( \Gamma_{r,i} \equiv \Gamma_{r,i}(\omega_{R,n}) \). From the expression (23), the mass and stiffness variations due to the layer, \( \delta M \) and \( \delta k_n \), induce a relative frequency shift between a bare and a loaded beam:

\[
\frac{\delta \omega_{R,n}}{\omega_{R,n}} = \frac{1}{2 - \omega_{R,n} \frac{\partial f}{\partial M}} \left[ \frac{\delta \omega_{R,n}}{\omega_{R,n}} + \frac{\partial \ln f}{\partial M} \delta M \right]. \quad (24)
\]

Here, \( \delta M = M_l \) and its prefactor in (24) takes into account dissipative \( (M_l \Gamma_I) \) and fluid mass loading \( (M_I \Gamma_r) \) effects. According to (7), the two contributions to the stiffness \( \delta k_n \) come from the bending rigidity, \( E_b I_b \rightarrow E_b I_b + E_I I_I \), and from the surface stress through the eigenvalue \( \beta_n(\alpha) \). From (14) and (17), we find

\[
\frac{1}{k_n} \frac{\delta \omega_{R,n}}{\omega_{R,n}} = \frac{3 \hbar E_b}{2 \omega_{R,n} + 2 T_n + \beta_0(n) (T_n - T_n)}, \quad (25)
\]

where \( \beta_{0,n} \) is the nth root of \( \cosh(\beta) \cos(\beta) + 1 = 0 \) and where \( T_n = \tanh \beta_{0,n}, \; t_n = \tan \beta_{0,n} \). The last term of (26) has been obtained from (7) in perturbation. It is valid when \( \alpha \ll n^2 \) and vanishes as \( n \to \infty \).

Using the same data as in Fig. 1 we display in Fig. 2 the relative frequency shift in air (left) and water (right) versus the dimensionless surface stress \( \alpha \). The exact shift is evaluated from the spectral density \( \omega_{R,n}^2 \) and compared to its linear approximation (24). The layer mass has been arbitrarily fixed to 1\% of the beam mass and \( E_b \) set to zero, hence the negative offset observed in air at \( \alpha = 0 \). For typical values of the surface stress, \( \sigma \sim 10^{-2} \text{Jm}^{-2} \) (see Wu et al. in ref. 2), \( |\alpha| \lesssim 1 \). In air, \( \alpha^2 \Gamma(\omega_{R,n}) \ll 1 \), and \( f \sim M_1 \omega_{R,n} \). Then, \( \frac{\partial \ln f}{\partial M} \sim -1/M \), \( \frac{\partial \ln f}{\partial \omega_{R,n}} \sim 0 \), and we recover the usual frequency shift for a linear oscillator in vacuum. As seen on the left panel, the first peak is the most sensitive to \( \alpha \). The deviation of the data from the linear result (24) indicates that the condition \( \alpha \ll n^2 \) with \( n = 1 \) becomes violated. This effect disappears for the second and third peaks that are less sensitive to \( \alpha \). In water (right panel), a single broad peak occurs. Eq. (24) loses its accuracy but the frequency shift (24) derived from it is still acceptable. The contribution of \( \frac{\partial \ln f}{\partial M} \) becomes negligible while \( \frac{\partial \ln f}{\partial \omega_{R,n}} \sim -\frac{\partial \ln \Gamma_I}{\partial \omega_{R,n}} \) becomes important, hence the increase in the slope of the relative frequency shift versus \( \alpha \) in water compared to air.

In conclusion, we treat the stochastic response of bio-functionalized nanomechanical cantilevers with a generalized fluctuation-dissipation relation. In a viscous fluid like water, the resonance frequency shift for a continuous distribution of biomolecules on the cantilever surface is dominated by surface stress rather than mass loading.

[1] M.B. Viani et al., Jour. Appl. Phys. 86, 2258 (1999).
[2] G. Wu et al., Nature Biotechnology 19, 856 (2001). G. Wu et al., PNAS 98, 1560 (2001).
[3] E.M. Purcell, Am. J. Phys. 45, 3 (1976).
[4] J.E. Sader, J. Appl. Phys., 84, 64 (1998); C.P. Green and J.E. Sader, Jour. Appl. Phys. 98, 114913 (2005).
[5] J.W.N. Chon and P. Mulvaney, J. Appl. Phys. 8, 3978 (2000).
[6] M.R. Paul and M.C. Cross, Phys. Rev. Lett. 92, 235501 (2004). In Eq. (5) of the above paper, \( m_2 \) should be replaced by \( m \). The extra factor 2 contained in this equation as compared to our equation (15) is due to our convention to work with double-sided Fourier transform.
[7] J.P. Gere and S.P. Timoshenko, Mechanics of Materials, (PWS Publishing Company, 1997).
[8] L. Rosenhead, Laminar Boundary Layers, p.391 (Clarendon, Oxford, 1963). We assume here that the presence of a layer of molecules binding to the beam does not affect the hydrodynamic force.
[9] N. Smith, J. Appl. Phys., 90 (11), 5768 (2001); J. Appl. Phys., 92 (7), 3877 (2002).
[10] G. Stoney, Proc. Roy. Soc. of London, Series A, 82, 553 (1919); G.E. Sader, J. Appl. Phys., 89 (5), 2911 (2001).
[11] G.Y. Chen et al. J. Appl. Phys., 77 (8), 3618 (1995). P. Müller and R. Kern, Surf. Sci. 301 (1-3), 386 (1994).
[12] J.H. Amar, Dynamics of Structures, p. 654 (Prentice Hall, New Jersey, 1990).
[13] P. Lu et al., Mater. Phys. Mech. 4, 51 (2001). Q. Ren and Y.-P. Zhao, Microsystem Technologies 10, 307 (2004).
[14] As \( \Gamma_I(\omega) \to 0 \) when \( \omega \to \infty \), \( M_I \Gamma_I(\omega) \gg 4M_1 \) is violated at some critical frequency beyond which Eq. (19) does not hold. A “non-perturbative” treatment of the inversion of \( \Lambda(\omega) \) is then in order. It can be done approximately by analytically inverting the \( 2 \times 2 \) or \( 3 \times 3 \) sub-block of \( \Lambda(\omega) \) surrounding the small diagonal element.