Modeling a nanocantilever based biosensor using a stochastically perturbed harmonic oscillator

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A nanoscale biosensor most suitable for clinical purposes could be based on the use of nanocantilevers. These microscopic ‘diving boards’ are coated with binding probes that have an affinity to a specific amino acid, enzyme or protein in the body. The binding probes on the silicon cantilever attract target particles, and as target biomolecules bind to the cantilever, it changes the vibrating frequency of the cantilever. The process of target binding is a random process and hence creates fluctuations in the frequency and damping mechanism of the cantilever. The effect of such fluctuations are given in our model calculations to provide a broader quantitative understanding of nanocantilever biosensors.

Keywords: biosensors, stochastic harmonic oscillator, nanocantilever

I. INTRODUCTION

Biosensors are composite devices consisting of biological sensing elements and transducer systems. The working principle of these devices involves the binding of the desired analyte to the biorecognition element fixed on a suitable support matrix connected to a transducer. The binding of analytes cause changes in physical or chemical properties of bioreceptive elements together with a support matrix, which can then be sensed by a transducer to generate an electrical signal. This generated signal quantifies the amount of analyte deposited. Classification of biosensors can be based on either their biorecognition mechanisms or on the methodology of signal transduction.

Nanosensors utilizing nanocantilevers can provide extreme sensitivity in the detection of biomolecules (analytes) down to a single-molecule level. Detecting particular biomolecules can help biomedical researchers recognize pathogens and diseases during clinical monitoring. Like many other detectors, nanoscale biosensors are characterized by a quantity called the dynamic range. The dynamic range is characterized by two extreme points starting at the minimum detection limit for detecting mass concentration (intrinsic to the detector) to the upper limit when saturation occurs in the detector.

Nanocantilever based biosensors are based on the mechanical motion of cantilevers. A cantilever is an oscillating mechanical device whose mass continually changes as biological analytes attach to it. The attachment of analytes leads to a change in the device’s resonant frequency. The amount of mass deposited on such detectors can be estimated by measuring the shift in frequency of the resonator. These detectors possess high sensitivity because their intrinsic mass is small but the sticking of analyte molecules causes significant mass change and hence produces a very large change in frequency. The quality factor of such nanodevices is also large and that further adds to their sensitivity of detection.

Recently, a slightly different kind of nanocantilever has emerged. These nanocantilever biosensors contain microfluidic channels that are used to detect small mass species, e.g., cells, proteins etc. These microfluidic channels allow one to operate under a low pressure background which enhances the quality factor of detector.

In order to measure the change in frequency of nanocantilevers it is required that system parameters should remain unaltered. Ideally speaking, the analyte once attached to nanocantilever should not detach or move. Such attachment-detachment or adsorption-desorption of analyte particles causes fluctuations in resonant frequency along with shifts in frequency. These fluctuations, according to fluctuation-dissipation theorem broaden the spectrum of nanocantilever oscillatory motion.

In order to develop a theoretical model related to detection process for these nanocantilevers it is incredibly important to keep all macroscopic and microscopic factors involved in the detection process in mind. For such a tiny system having dimensions on several tens to hundred nanometers, it is indeed possible to analyze some variables macroscopically, but was critical to recognize the elements that were less obvious and would be negligible if one was not working on the nanoscale. Because amino acids are one of the main bioreceptors used in nanocantilever-based biosensors, the affinity and specificity of amino acid sequences was a very important factor in our analyses. These amino acids are critically dependent on ligands to which they are attached. Ligands play a major role in the determination of geometric dimensions. This change in geometry could cause receptor amino acid sequences to become inactive or even initiate other events like nonlinear expansion or stochastic
motion of the cantilever. These chaotic events need to be noted when mathematically modeling nanocantilever biosensors.

This paper is organized as follows: In section II we give a brief description of how mass deposition causes frequency shifts in the harmonic oscillator. In section III we model nanocantilevers mathematically using a stochastically perturbed harmonic oscillator. We explain how noise introduces measurable random frequency fluctuations in the oscillating nanocantilever that are proportional to the mass deposited on its surface. This feature is used by biosensors as the detecting mechanism. Finally, some concluding remarks are presented in section IV.

II. MASS DEPOSITION AND FREQUENCY SHIFT

Nanocantilevers can be simply modeled as damped, driven harmonic oscillators. The oscillating mechanism we consider in this work consists of a mass-spring system, and its equation of motion will be used to describe the classical behavior of nanocantilevers. As it is well known, this equation includes a damping and a driving terms. Random damping in the oscillator changes its frequency. If these frequency changes can be measured, then the oscillators (nanocantilevers) can be used to detect simple physical phenomena such as mass deposition. For a nanocantilever, it is common to measure changes in its frequency of resonance. This frequency shift is directly proportional to the mass deposited on it as we will see in the following.

For a mass-spring system with mass $m$ and spring constant $k$, the characteristic angular frequency under simple harmonic motion is given by $\omega_0 = \sqrt{k/m}$. A small change in the mass of the system due to mass deposition modifies the frequency of oscillation of the system. Taking finite differences of the angular frequency with respect to mass and solving for $\Delta m$, we may get

$$\Delta \omega = -\frac{2m}{\omega_0} \Delta \omega_0.$$

For this equation to make physical sense, we assume that the elastic and geometric properties of the nanocantilever remain unchanged after the small mass deposition.

When analyte molecules are deposited on a nanocantilever, there is a momentum exchange between the oscillator and the particles colliding with it. The process can be called a process of random collisions. These collisions bring a random dragging force that affects the nanocantilever motion. If the concentration of analyte molecules is low, then this dragging force can be attributed to a molecular drag proportional to the molecular velocity and contributing to the dissipative part of the equation of motion of the oscillator. This dragging force can be written as $F_d = b(dx/dt)$ and corresponds to the damping term of the oscillator’s equation. When the concentration of analyte molecules is low, we can say that $F_d$ is proportional to the number of analyte particles $N_a$ striking the nanocantilever per second. However, if the dragging force is random, it can be described by the term $\xi(t)(dx/dt)$. The term brings random damping to the nanocantilever oscillator. Another possible type of dragging is called inertial dragging, and it is proportional to the molecular acceleration. We will not discuss this case here.

Some other type of phenomenon taking place is the adsorption-desorption of the analyte molecules on the nanocantilever surface. Such thermally driven effect produces random frequency fluctuations in the oscillator. The process of adsorption-desorption can be modeled by a molecular flux-dependent adsorption rate and a thermally activated rate of desorption. Another mechanism that produces frequency fluctuations is the one occurring with nanocantilevers having microfluidic channels. In this case, the fluctuations are produced by the diffusion of an adsorbed particle along the microfluidic channel inside the vibrating nanocantilever. All of these fluctuations or random stochastic processes mentioned above can be incorporated as delta-correlated or exponentially correlated noise processes (Ornstein-Uhlenbeck processes) in the modeling equations.

III. STOCHASTICALLY PERTURBED HARMONIC OSCILLATOR

Let us consider the simple case of a nanocantilever described by a damped harmonic oscillator of mass $m$ and spring constant $k$, and driven by a sinusoidal external force. The differential equation describing the motion is

$$m \frac{d^2x}{dt^2} + b \frac{dx}{dt} + kx = F_0 \sin(\omega t), \quad (2)$$

where $F_0$ and $\omega$ are the amplitude and frequency of the external driving force, respectively, and $b$ is a positive damping coefficient.

If a system is subject to both random and periodic forces, the well-known phenomenon of stochastic resonance (SR) may emerge. In the following, we will describe the effects of including random damping and frequency as stochastically perturbations in the equation of evolution of the nanocantilever. They will enter Eq. (2) as multiplicative noise $\xi(t)$, such as the new equations of motion can be written as

$$\frac{d^2x}{dt^2} + 2\beta [1 + \xi(t)] \frac{dx}{dt} + \omega_0^2 x = A \sin(\omega t) \quad (3)$$

for the random damping, and

$$\frac{d^2x}{dt^2} + 2\beta \frac{dx}{dt} + \omega_0^2 [1 + \xi(t)] x = A \sin(\omega t) \quad (4)$$

for random frequency. Here $\beta \equiv b/2m$ is the damping parameter, $\omega_0 = \sqrt{k/m}$ is the characteristic angular frequency in the absence of damping, and $A = F_0/m$. The
The random variable $\xi(t)$ will be considered as both Gaussian white noise with the correlator
\[ \langle \xi(t)\xi(t') \rangle = D\delta(t-t'), \tag{5} \]
and color noise with exponential correlator
\[ \langle \xi(t)\xi(t') \rangle = \alpha^2 e^{-\lambda|t-t'|}. \tag{6} \]
The parameters $D$ and $\alpha$ represent the white and color noise strengths, respectively, and $\lambda$ the correlational decay rate. For color noise, we are only interested in symmetrical dichotomous noise (random telegraph signal) for which $\xi(t)$ can take one of the values $\xi = \pm \alpha$, and the average waiting time for each of these states is $\lambda^{-1}$. Under the following limiting conditions: $\alpha^2 \to \infty$ and $\lambda \to \infty$, Eq. (6) reduces to (5), provided $\alpha^2/\lambda = D$ (see Ref. [10]).

### A. Nanocantilever with random damping

In the absence of an external driving force ($A = 0$) the equation of motion (3) takes the form
\[ \dot{O}_D \{ x \} = -2\beta \xi(t) \frac{dx}{dt}, \tag{7} \]
where the operator $\dot{O}_D$ is defined by the following expression
\[ \dot{O}_D \equiv \frac{d^2}{dt^2} + 2\beta \frac{d}{dt} + \omega_0^2. \tag{8} \]
If the random damping is produced by the delta-correlated white noise [9], then (3) reduces to
\[ \frac{d^2}{dt^2}(x) + 2\beta(1-2\beta D) \frac{d}{dt}(x) + \omega_0^2(x) = 0. \tag{9} \]
Here, we have use the fact that averages split in the form [11],
\[ \langle \xi(t)\xi(t') \frac{dx(t')}{dt} \rangle = \langle \xi(t)\xi(t') \rangle \langle \frac{dx(t')}{dt} \rangle. \tag{10} \]
Equation (9) models the collisional damping produced by analytes getting stuck on the nanocantilever. If $2\beta D < 1$, the presence of white noise will lead to a damping decrease (weak noise). On the other hand, if $2\beta D > 1$, the effective damping turns negative increasing the amplitude of oscillation $\langle x \rangle$ and leading to instabilities in the dynamics of the nanocantilever (strong noise). [10]

When the nanocantilever is driven by an external force, a solution to (9) can be written as
\[ \langle x \rangle = B \sin(\omega t + \varphi). \tag{11} \]
Upon substituting (11) into (9), we can solve for the amplitude $B$ and get the following expression
\[ B = \frac{A}{[(\omega^2-\omega_0^2)^2 + 4\beta^2\omega^2(1-2\beta D)^2]^{1/2}}. \tag{12} \]

The presence of noise in the system brings fluctuations in the nanocantilever frequency, resulting in spectral broadening. Hence it becomes necessary to determine the minimum measurable frequency shift that can be observed in this noisy environment. The spread in the frequency $\delta\omega_0$ can be obtained by integrating the spectral density of frequency fluctuations $S(\omega)$
\[ \delta\omega_0 \approx \left[ \int_{-\Delta\omega_0}^{\omega_0+\Delta\omega_0} S(\omega) d\omega \right]^{1/2}. \tag{13} \]
Here, we assume that a measurement of the nanocantilever frequency was done with a square-shaped transfer function over the bandwidth $2\Delta\omega_0$, and centered at $\omega_0$. Equation (13) is an estimate for any real system. The spectral density $S(\omega)$ is determined by the nature of the noise present in the system, and can be determined by taking the Fourier transform of the white noise correlator [2]
\[ S(\omega) = \int_{-\infty}^{\infty} \langle \xi(t)\xi(0) \rangle e^{-i\omega t} dt. \tag{14} \]

At resonance, the second moment of the nanocantilever displacement, $\langle x^2 \rangle$, satisfies the relation
\[ \frac{1}{2}m\omega_0^2 \langle x^2 \rangle = \frac{1}{2}\kappa T, \tag{15} \]
where $\kappa$ is the Boltzmann constant and $T$ is the absolute temperature at resonance. By using (14), we can find the spectral density corresponding to these displacement fluctuations
\[ S\langle x^2 \rangle = \frac{\text{const} \times S(\omega)}{[(\omega^2-\omega_0^2)^2 + 4\beta^2\omega^2(1-2\beta D)^2]^{1/2}}. \tag{16} \]

There are two damping mechanisms present in Eq. (16): The thermo-mechanical fluctuations governed by the damping parameter $\beta$, and the momentum exchanged with white noise, whose spectral density is proportional to $\beta D$. In particular, that momentum exchange is responsible for taking the system into resonant states.

The spectral density for the fluctuations in the nanocantilever displacements turns out to be a resonance frequency curve in the parameter $D$ (the noise strength) which shows a maximum at $D = (4\beta)^{-1}$. This behavior resembles the stochastic resonance phenomenon (see Fig. 1).

In this problem, however, the phenomenon of stochastic resonance is somehow counterintuitive. The reason is that the “unwanted” noise coherently adds up to the external force signal, increasing the signal to noise ratio instead of reducing it [2]. From Fig. 1 it is clear that, for these nanocantilever based biosensors, the resonance peak is not sharp but has a finite width. The peak width is determined by the intrinsic damping ($\beta$) of the nanocantilever, and the stochastic fluctuations caused by analyte molecules sticking on it. To measure the precise
shift in the resonance frequency of the nanocantilever, the sharpest possible peak from the figure should be the appropriate choice. Therefore, knowing precise values of $\beta$ and $D$ parameters, and estimating the mass deposition correctly becomes critical in designing suitable nanocantilever based biosensors.

**B. Nanocantilever with random frequency**

In the absence of an external driving force ($A = 0$) equation (11) takes the form

$$\frac{d^2 x}{dt^2} + 2\beta \frac{dx}{dt} + \omega_0^2 [1 + \xi(t)] x = 0. \quad (17)$$

Here, the multiplicative noise $\xi(t)$ introduces random fluctuations in the nanocantilever frequency. It can be shown that, if the noise is white with correlator $[\xi(t)\xi(t')] = 0$, the first moment of the oscillator is not affected by the noise and $(x(t)) = x(t)$. On the other hand, for the exponentially correlated noise $[\xi(t)\xi(t')] = \lambda \exp(-|t-t'|)/\tau_\xi$, the first moment $(x)$ satisfies the following equation in accordance with the cumulative expansion of van Kampen\(^{\text{12}}\)

$$\frac{d^2}{dt^2} \langle x \rangle + (2\beta - \omega_0^2 q_1) \frac{d}{dt} \langle x \rangle + \omega_0^2 q_2 \langle 1 - \omega_0 q_2 \rangle \langle x \rangle = 0, \quad (18)$$

where the parameters $q_1$ and $q_2$ are given by\(^{\text{13}}\)

$$q_1 = 2 \int_0^\infty \langle \xi(t)\xi(t-\tau) \rangle [1 - \cos(2\omega_0\tau)] d\tau', \quad (19a)$$

$$q_2 = 2 \int_0^\infty \langle \xi(t)\xi(t-\tau) \rangle \sin(2\omega_0\tau') d\tau'. \quad (19b)$$

In the limit of white noise both parameters $q_1$ and $q_2$ vanish. In other words, white noise does not change the width of the resonance profile of the frequency. So the rate at which the frequency of the nanocantilever changes due to mass deposition remains simple to calculate.

With random frequency, the mathematical expression used to find the spectral densities of noise fluctuations becomes a bit more complicated than that used in random damping (see Eq. (14)). Hence, the analytical solution (11) for the first moment in random damping can not be used to obtain a solution for random frequency. However, for dichotomous color noise, the amplitude associated with the first moment shows a stochastic resonance-like feature in $\alpha$ and $\lambda$ similar to that observed in (13). Therefore, a similar analysis can be applied to get the resonance profile and find the change in frequency of the nanocantilever due to analyte deposition.

The adsorption-desorption of noise by the nanocantilever gives rise to fluctuations in its frequency. This is caused mostly by the constant bombardment of analyte molecules on its surface. This noise mechanism can be understood from the following perspective. The analyte molecules are adsorbed due to their affinity to the nanocantilever substrate and are desorbed because of a finite temperature change. This creates some fractional frequency noise. It is interesting to note that this process of adsorption-desorption of analyte molecules does not produce a damping mechanism per se. The randomness in the sticking and releasing particles on the cantilever does not contribute to the average change in the energy, but it changes the frequency of the nanocantilever in a nondeterministic manner. This process introduces a different parametric noise that does not culminate into dissipation.

The nanoscale cantilevers are quite sensitive to the adsorption-desorption of noise when compared with conventional scale cantilevers. The reason is the difference between the surface to volume ratio for each type. This explains why the number of adsorption locations in nanocantilevers is bigger than those on the counterpart.

The frequency fluctuations caused by noise can also be described using some basic considerations different from those discussed in (13). We describe this method briefly for the sake of completeness, closely following Refs. (6) and (7). Let the adsorption rate be $R_a$, which is dependent on the sticking coefficient of the nanocantilever surface, and $R_d$ the temperature dependent desorption rate. The probability of molecular occupation in a particular area is given by $p = R_a/(R_a + R_d)$, and the corresponding variance in the occupation probability $\sigma^2_v = \sqrt{R_a R_d/(R_a + R_d)}$. The correlation time $\tau_c$ of absorption-desorption noise is also given by $\tau_c = (R_a + R_d)^{-1}$. The spectral density of noise in this case can be written as

$$S_v(\omega) = \frac{2\pi \omega_0^2 N_a \sigma_v^2 \tau_c}{[1 + (\omega - \omega_0)^2 \tau_c^2]} \frac{(\Delta m/m)^2}{\omega^2}, \quad (20)$$

where $\Delta m$ is the mass of the molecules attached on the cantilever surface. The shift in frequency follows equation (14). The noise variance is a maximum when the probability of occupation is 1/2, that is the adsorption rate equals the desorption rate. On the other hand, the noise is a minimum when the occupation probability is either 0 or 1. This noise will be superimposed on the

![Plot](image-url)  
**FIG. 1.** Plot of $S(\omega)/S(\omega)$ as a function of the driving field frequency $\omega$, with parameter conditions: $\omega_0 = 50$ and $\beta = 0.35$. Curves A, B, C, D, and E are for $D = 5, 10, 20, 30$ and 40, respectively.
frequency change of the biosensor and hence becoming critical in estimating the analyte mass deposition as we discuss in the following.

Integration over the spectral density $S_a(\omega)$ provides some change in the nanocantilever frequency

$$\Delta \omega_0 \approx \left[ \int_{\omega_0 - \pi \Delta f}^{\omega_0 + \pi \Delta f} S_a(\omega) d\omega \right]^2$$

$$= \frac{\omega_0 \sigma_v \Delta m}{2\pi m} [N_a \tan^{-1} (2\pi \Delta f \tau_c)]^{1/2},$$

(21)

(22)

where $\Delta f$ defines the width of passband. Hence, the change in mass on the nanocantilever is given by

$$\delta m \approx \Delta m \sigma_v [N_a \tan^{-1} (2\pi \Delta f \tau_c)]^{1/2}.$$  

(23)

Note that this expression for the frequency shift (due to mass deposition) may be more realistic than that obtained in (I).

IV. SUMMARY

In this work, we presented a realistic model for a nanocantilever biosensor based on the description of a stochastically perturbed harmonic oscillator. These biosensors work by mass sensing the analytes through shifts in the characteristic frequency of the oscillator. When analytes are deposited on the nanocantilever, they bring a variety of noises on this vibrating system which gives rise fluctuations in damping as well as frequency of the cantilever. The estimation of such fluctuations on the spectral response of cantilever is important in finding out the exact amount of analyte deposition for clinical diagnostic purposes. In this work we considered frequency fluctuations according to different type noise models and their effect on the mass deposition on the cantilever.

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1 J. Kumar and S. F. D’Souza, “Biosensors for environmental and clinical monitoring,” BARC Newsletter 324, 34–38 (2012)
2 L. M. Bellan, D. Wu, and R. S. Langer, “Current trends in nanobiosensor technology,” NANOMED-NANOTECHNOL BIOL MED 3, 229–246 (2011)
3 J. Fritz, “Cantilever biosensors,” Analyst 133, 855–863 (2008)
4 T. P. Burg, M. Godin, S. M. Knudsen, W. Shen, G. Carlson, J. S. Foster, K. Babcock, and S. R. Manalis, “Weighing of biomolecules, single cells and single nanoparticles in fluid,” Nature 446, 1066–1069 (2007)
5 J. Atalaya, A. Isacsson, and M. I. Dykman, “Diffusion-induced dephasing in nanomechanical resonators,” Phys. Rev. B 83, 045419 (2011)
6 A. N. Cleland and M. L. Roukes, “Noise processes in nanomechanical resonators,” J. Appl. Phys. 92, 2758 (2002)
7 K. L. Ekinci, Y. T. Yang, and M. L. Roukes, “Ultimate limits to inertial mass sensing based upon nanoelectromechanical systems,” J. Appl. Phys. 95, 2682 (2004)
8 M. I. Dykman, M. Khasin, J. Portman, and S. W. Shaw, “Spectrum of an oscillator with jumping frequency and the interference of partial susceptibilities,” Phys. Rev. Lett. 105, 230601 (2010)
9 L. Gammatoni, P. Hänggi, P. Jung, and F. Marchesoni, “Stochastic resonance,” Rev. Mod. Phys. 70, 223–287 (1998)
10 M. Gittermann, “Classical harmonic oscillator with multiplicative noise,” Physica A 352, 309334 (2005)
11 R. C. Bourret, U. Frisch, and A. Pouquet, “Brownian motion of harmonic oscillator with stochastic frequency,” Physica 65, 303–320 (1973)
12 N. G. van Kampen, Stochastic Processes in Physics and Chemistry, 3rd ed. (North Holland, Hungary, 2007)