Resonance fluctuations of a whispering gallery mode biosensor by particles undergoing Brownian motion

D. Keng, S. R. McAnanam, I. Teraoka, and S. Arnold
MicroParticle PhotoPhysics Laboratory, Polytechnic University, Brooklyn, New York 11201
(Received 31 July 2007; accepted 8 August 2007; published online 4 September 2007)

Nanoparticles suspended in the vicinity of a whispering gallery mode (WGM) biosensor are detected from fluctuations in the driving light-guide transmission. These fluctuations are described by Brownian particles perturbing the resonance wavelength in reaction to being polarized by the WGM’s evanescent field. Comparison between the autocorrelation of the measured fluctuations and theory provides a first order approximation for the nanoparticle size and lays the basis for future studies of interfacial dynamics. With this advance, the WGM biosensor goes beyond low-frequency measurements of adsorption and desorption and into a world which has been dominated by fluorescence correlation spectroscopy, but without labels. © 2007 American Institute of Physics.

DOI: 10.1063/1.2778351

There is an extant revolution in label-free biosensing brought on by the use of whispering gallery mode (WGM) resonances. Nanoparticles in the vicinity of a resonator sensitively perturb its characteristics (e.g., resonance wavelength). Already, resonance wavelength shift data have enabled the label-free specific sensing of protein, DNA, and virus, as well as the characterization of nanolayer growth and solvent refractive index changes. These sensing applications have been implemented by simply measuring the dc component of the resonance wavelength shift signal. Herein, we show that the broadband “noise” on this signal provides physical information not available from its dc component. Stochastic effects associated with molecules undergoing Brownian motion near the resonator surface are responsible for this noise. This observation allows this all-photonic sensor to enter a world that has been dominated by total internal reflection fluorescence correlation spectroscopy (TIR-FCS), without the need for fluorescent labels. In what follows, we characterize the noise in resonance wavelength fluctuations of a spherical microwire bathed in a solution containing nanoparticles of viral size, and demonstrate that nanoparticle sizes may be estimated from the analysis of this noise.

Let us consider the situation depicted in Fig. 1(a). A nanoparticle (diameter $d \sim 1–200$ nm) in an aqueous solution just outside a spherical microresonator (radius $R \sim 50–500$ μm) diffuses through the evanescent field of a WGM. The WGM is driven by coupling the microsphere evanescently to light guided through an optical fiber. Each nanoparticle diffusing within the evanescent field near the equator of the microsphere influences the resonance wavelength as a result of polarization by the field. As the free space wavelength $\lambda$ of the laser driving the fiber is swept across the resonance, the WGM is revealed as a dip in the transmitted intensity $T$ through the fiber [Fig. 1(b)]. The resonance wavelength at the center of this Lorentzian dip, $\lambda_r$, fluctuates as a result of the interaction with this particle and others in the surrounding solution. Temporal changes of the resonant wavelength are transduced and amplified by positioning the laser wavelength at $\lambda_{bias}$ on one side at the maximum slope of the dip and recording the intensity, as shown in Fig. 1(b).

In previous studies, we followed the slow variation of the resonance dip position using a scanning approach to record the fiber transmission spectrum. In this way, the dip position was updated every 0.1 s. With the $\lambda_{bias}$ scheme in Fig. 1, we can follow variations in the resonance wavelength at a much faster pace, limited only by our data acquisition system, which samples the transmitted intensity with 16 bit precision at 200 kHz. The noise with Brownian particles present in the surrounding solution will be different in comparison to the neat buffer, as shown in Figs. 1(c) and 1(d). Since the noise is stochastic, it will be characterized by its autocorrelation function (ACF). Below, we describe some experimental details.

The WGM biosensor consisted of a silica microsphere ($\sim 200$ μm radius) coupled to a phase-matched silica optical fiber. The fiber is aligned to pass light through a silica microsphere that is placed in a solution containing a dispersion of molecules. The laser wavelength is swept to detect the dip in the transmitted intensity. The transmitted intensity is recorded as a function of time, and the autocorrelation function of the transmitted intensity is calculated. The autocorrelation function is analyzed to determine the size of the nanoparticles.
FIG. 2. (Color online) Microfluidic system incorporating a microsphere resonator and a coupling fiber.

fiber\textsuperscript{12} within a microfluidic cell molded from silicone, as shown in Fig. 2. A 1300 nm pigtailed distributed feedback laser was connected to the input end of the fiber, and its wavelength was controlled through the drive current.\textsuperscript{11,10}

Noise associated with nanoparticles was first discerned while sensing bacterial virus. To understand the phenomenon, we chose polystyrene particles having a carboxylated surface and mean diameters of 37, 103, and 219 nm (Poly-sciences, Inc.), as measured by dynamic light scattering (N4Plus, Coulter), as viral simulants.

After recording resonance fluctuations using a filtered phosphate buffered saline (PBS) solution (\(\mathrm{pH}=7.4\)) for 1 s, the ACF of the signal was computed. This procedure was repeated 50 times with each new ACF added to the previous ones in order to form an average. Following this, particles of a given size (suspended in PBS) were injected into the microfluidic channel (Fig. 2) using a digitally controlled syringe pump, and the resonance wavelength was seen to shift toward a longer wavelength, indicative of adsorption. When the wavelength shift stabilized, the ACF of the signal was calculated as in the case of the buffer. Then, the microfluidic channel was washed with the buffer solution using a second digitally controlled pump (Fig. 2). As the particles were removed from the solution surrounding the microsphere, the resonance wavelength changed only slightly, indicative of strong nonspecific binding. The rms value of the resonance wavelength fluctuations essentially returned to its value before the particles were injected into the channel, indicating that the observed fluctuations were principally associated with particles diffusing in solution. Experiments for each new particle size utilized a new microsphere, but otherwise followed the same procedure.

The initial decay in the normalized ACF, \(c(\tau)/c(0)\), for the three particle sizes is shown in Fig. 3 as a function of delay time \(\tau\) for the first 1 ms. Each ACF is seen to fall linearly with time following the empirical equation \(c(\tau)/c(0)=1-\alpha \tau\) for \(\alpha \ll 1\). The inset shows that the decay rate \(\alpha\) is approximately proportional to the inverse diameter of the particles: \(\alpha \approx \beta/d\), with \(\beta=13.1 \times 10^{3} \, \text{nm/s}\).

The results in Fig. 3 may be understood from the Brownian motion of particles in the evanescent field near the surface of the microsphere. A given particle at position \(\mathbf{r}\) causes a resonance wavelength shift (\(\Delta \lambda_r\)) as a reaction to being polarized by the evanescent field \(\mathbf{E}(\mathbf{r}, t)\).\textsuperscript{10} The shift is proportional to the scalar product of the induced dipole and the electric field, and is consequently proportional to the square modulus of the field \(|\mathbf{E}(\mathbf{r})|^2\). The accumulated resonance wavelength shift from many particles is most easily accounted for by utilizing a number density \(\rho(\mathbf{r}, t)\) and performing a simple sum,

\[
\Delta \lambda_r(t) \sim \int \rho(\mathbf{r}, t)|\mathbf{E}(\mathbf{r})|^2 dV. \tag{1}
\]

Before evaluating Eq. (1) it is useful to consider the characteristic lengths of our system. The "ribbon" of intensity near the equator (Fig. 1) has three characteristic lengths; the circumference (~600 \(\mu m\)), the width along a meridian (~3 \(\mu m\)), and the evanescent intensity length \(L \sim 0.2 \, \mu m\). Considering that the time to diffuse through a given length is proportional to its square, the short time behavior demonstrated in Fig. 3 should be overwhelmingly controlled by \(L\). This allows us to pare down the integral in Eq. (1) to essentially one dimension,

\[
\Delta \lambda_r(t) \sim \rho(\mathbf{r}, t)E_{\perp}(\mathbf{r})^2 dV. \tag{2}
\]

The inset of Fig. 3 shows that the decay rate of the ACF for three particle diameters \(d\) follows \(\rho(\mathbf{r}, t)/\rho(0) = 1-\alpha t\), for \(\alpha \ll 1\). The inset plot of \(\alpha\) vs \(1/d\) shows that the decay rate \(\alpha\) is approximately proportional to the inverse diameter of the particles: \(\alpha \approx \beta/d\), with \(\beta=13.1 \times 10^{3} \, \text{nm/s}\).

FIG. 3. (Color online) Normalized autocorrelation of resonance wavelength fluctuations for several particle diameters \(d\). Each follows \(c(\tau)/c(0)=1-\alpha \tau\), for \(\alpha \ll 1\). Inset: plot of \(\alpha\) vs \(1/d\).
\[ \Delta \lambda_{i}(t) \sim \int \rho(\xi,t) \exp[-\xi/L] d\xi, \]  

(2)

where \( \xi \) is the distance from the surface. The normalized ACF is then

\[ \frac{c(\tau)}{c(0)} = \frac{\langle \Delta \lambda_{i}(\tau) \Delta \lambda_{i}(0) \rangle}{\langle \Delta \lambda_{i}(0)^2 \rangle} \]

\[ = \int_{0}^{\infty} d\xi \int_{0}^{\infty} d\xi' \langle \rho(\xi,\tau) \rho(\xi',0) \rangle \exp[-(\xi + \xi')/L]. \]

(3)

Fortunately, this integral has been worked out for a self-similar problem in TIR-FCS.\(^8\) It is the problem of fluorescence fluctuations from particles diffusing in the evanescent field at the back of a prism. The solution involves deriving the density autocorrelation \( \langle \rho(\xi,\tau) \rho(\xi',0) \rangle \) from the diffusion equation under a prescribed boundary condition, and carrying out the integration. For a reflecting boundary, consistent with having saturated the surface with particles having the same charge as those diffusing, the solution is\(^{13}\)

\[ \frac{c(\tau)}{c(0)} = (1 - 2R_e \tau) \exp(R_e \tau) \text{erfc}[(R_e \tau)^{1/2}] + 2 \left( \frac{R_e \tau}{\pi} \right)^{1/2}, \]

(4)

where \( R_e = D/L^2 \), with \( D \) being the diffusion coefficient. For short times \( (\tau \ll 1/R_e) \), \( c(\tau)/c(0) \approx 1 - R_e \tau \) allowing us to identify our experimental \( \alpha \) with \( R_e \). The approximate proportionality found between \( \alpha \) and \( 1/d \) would also be expected based on bulk diffusion for which \( D \) follows the Stokes-Einstein (S-E) relation \( D = k_B T/(3\pi \eta d) \), where \( k_B T \) is the thermal energy and \( \eta \) the solvent viscosity. The assumption of S-E diffusion also allows us to calculate \( \beta = k_B T/(3\pi \eta L^2) \), from which we can estimate the evanescent field length without using optics; \( L = [k_B T/(3\pi \eta \beta)]^{1/2} \).

Using our experimental value for \( \beta = 13.1 \times 10^7 \) nm/s, we extract \( L = 193 \) nm. Optical calculations based on a microsphere of 200 \( \mu \)m in radius with a refractive index for silica of 1.452 and water of 1.32 for the first order radial mode\(^{14}\) gives \( L = 188 \) nm, in good agreement with the estimate produced by comparing fluctuation theory with experiment.

Although S-E diffusion is a good approximation for describing our experimental results, it is wanting. This is best seen by inverting our previous discussion and asking how accurately we can determine nanoparticle diameters from the simple S-E based equation,

\[ d = \left[ \frac{k_B T}{3\pi \eta L^2} \right]^{1/2}. \]

(5)

With \( L \) taken as before to be 188 nm, the diameters arrived at from Eq. (5) for our three standard diameters of 37, 103, and 219 nm are 39, 111, and 309 nm, respectively. Here, we see good agreement for the smallest size and a progressive deviation as the nanoparticle size is increased. This is likely due to hydrodynamic effects near the phase boundary.\(^{13}\) Diffusion is expected to slow as one approaches an interface, and this effect increases with particle size.\(^{15}\)

This letter should leave little doubt concerning the role of Brownian motion in the resonance wavelength fluctuations of a WGM. It may be considered a harbinger for using the WGM biosensor for studying the dynamics of nanoparticles near interfaces.

This research was supported by NSF through Division of Bioengineering and Environmental Systems Grant No. 0522668. The authors thank Steve Holler of Novawave Technologies Inc. and Ralph v. Baltz of Universität Karlsruhe for valuable discussions.

References