Electrokinetic effects on detection time of nanowire biosensor

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We develop a multiphysics model to study the contribution of electrokinetics on the biomolecular detection process and provide a physical explanation of the two to three orders of magnitude difference in detection time between experimental results and theoretical predications at ultralow concentration. The electrokinetic effects, including electrophoretic force and electroosmotic flow, have been systematically studied under various sensor design and test conditions. In a typical single nanowire-based sensor, it is found that electrokinetic effects could result in a reduction of detection time over 90 times, compared with that induced by pure biomolecular diffusion. The detection time difference is further enhanced by increasing the applied gate voltage or the number of nanowires. It is proposed that accelerated biomolecular detection at ultralow concentration could be achieved by appropriate combinations of electrokinetic effects and nanowire sensor design.

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Nanoscale sensors such as Si nanowires (SiNWs) carbon nanotubes and metal oxide nanotubes, due to their ultrasensitivity, label-free, and real-time detection capabilities, are emerging as a promising tool in quantification and analysis of biochemical processes.^{1,2} In the past decades, SiNW sensors have been widely used in detecting DNA, proteins, virus, gas molecules, and many other biomolecules, and ultrafast detection of biomolecules at femtomolar (fM) concentration has been achieved in several minutes experimentally.^{3,4} However, theoretical calculations based on diffusion theory indicate that it would need several hours or days to detect a few biomolecules at such low concentration,^{5,6} which are two to three orders of magnitude larger than experimental results. Various possible factors such as fluid flow⁷ and statistical variance,⁸ contributing to the formation of this detection time discrepancy, have been characterized. But satisfactory explanations on this puzzling phenomenon are rarely achieved, which hinders the understanding of experimental results as well as biosensor design.

In this letter, the influence of electrokinetic effects on biomolecular detection process is characterized. Previous studies have already shown the significant acceleration of biomolecular detection speed due to electrokinetics in selectively manipulating, driving, and directing biomolecules.⁹ For example, Fixe *et al.* applied single and square voltage pulses in the microsecond timescale to study the electric-field-assisted DNA immobilization and hybridization and observed that immobilization and hybridization rates are 10^9 and 10^7 times faster, respectively, than those in passive assays without applying any electric pulse.¹⁰ Heller *et al.* developed a simple and rapid electrophoretic (EP) method that allows detection of degradative enzyme activity directly in blood using charge-changing fluorescent peptide substrates, and a detection limit of about 10–20 pg was achieved

for chymotrypsin and trypsin.¹¹ Due to applied voltage on solution gate, electrokinetic effects also widely exist in SiNW sensing devices. However, these electrokinetic effects, which are proposed to be the leading reason for the large detection time discrepancy at ultralow concentration, have not yet been considered in theoretical analysis or numerical calculations.

In what follows, a multiphysics model is developed to study the influence of electrokinetic effects on biomolecular detection process in SiNW sensors. First, a mathematical model is described. The response time of biomolecules in a typical SiNW sensor with a single nanowire of diameter 100 nm and length 20 μm is studied. The influences of number of SiNW nanowires and applied voltage on solution gate are also investigated under electrokinetic effects. The goal of our work is to provide a framework for understanding the fundamental science governing biosensing at ultralow concentration and optimizing current biosensors for better performance.

In traditional diffusion-reaction theory, the movement of biomolecules is determined by Brownian motion (BM), given as

$$m\dot{\mathbf{v}}_i = \mathbf{f}_i^B, \quad (1)$$

where m is the mass of each biomolecule, $\dot{\mathbf{v}}_i$ the acceleration of the i th biomolecule, and $\mathbf{f}_i^B$ the force due to Brownian motion. This equation works well for analyzing the detection of biomolecules at regular concentrations above μM for SiNW sensors, but the accuracy vanishes at low concentrations below nM. The voltage applied on solution gate would induce electrokinetic effects and influence the behavior of biomolecules. Assume a DC voltage is applied on the solution gate, the EP force and electroosmotic flow (EOF) should be included in Eq. (1), given as

$$m\dot{\mathbf{v}}_i = -\zeta(\mathbf{v}_i - \mathbf{u}) + \mathbf{f}_i^B + q\mathbf{E}_i, \quad (2)$$

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where ξ is the drag coefficient, $\mathbf{u}$ the bulk fluid velocity induced by EOF, and $\mathbf{E}_i$ the electric field of the i th biomolecule. The EOF is introduced as a slip boundary for the fluid on the sensor surface, given as¹²

$$\mathbf{u}_{\text{slip wall}} = \frac{-\varepsilon_f \psi_0 \mathbf{E}}{\mu}, \quad (3)$$

where ε_f is the fluid permittivity, ψ_0 the zeta potential, and μ the fluid viscosity.

Equation (2) is solved numerically to track the motion of biomolecules under various conditions. The multiphysics model developed for a typical SiNW sensor is illustrated in Fig. 1. A given number of biomolecules, determined by analyte concentration, are randomly distributed in a channel of height $200\ \mu\text{m}$ and width $370\ \mu\text{m}$ (a typical set-up of our experiments).^{3,4} A finite length of channel $200\ \mu\text{m}$ is adapted to simplify the simulation. The SiNW is treated as a semi-cylinder of diameter $100\ \text{nm}$ and length $20\ \mu\text{m}$ on the bottom surface of the model, and the solution gate is assumed to be a cylinder of length $100\ \mu\text{m}$ and radius $10\ \mu\text{m}$ attached to the top wall. A voltage of $1\ \text{V}$ is applied on the solution gate. The surfaces of nanowire are assumed to be ground, and other surfaces are assumed to be electric insulation. The bottom surface is assumed to be wall with electroosmotic flow. Other surfaces are assumed to be wall without slip. The solvent fluid is set to be water with a density of $10^3\ \text{kg/m}^3$ and a dynamic viscosity of $10^{-3}\ \text{Pa}\cdot\text{s}$. The zeta potential is set to be $-35\ \text{mV}$.¹³

The electric field is solved first and then the slip wall boundary conditions are applied to resolve the velocity field. These electrokinetic effects are combined together with the Brownian motion to solve Eq. (2) numerically.

Before coupling the electrokinetic effects and Brownian motion force together to study the biomolecular detection process, a benchmark is performed based on pure Brownian dynamics, to demonstrate the accuracy of our model in describing the biomolecular diffusion process. In this case, the diameter of biomolecules is assumed to be $10\ \text{nm}$ with a diffusion coefficient of $4.36 \times 10^{-11}\ \text{m}^2/\text{s}$. The movement of biomolecules is dominated by Brownian motion, and interactions among biomolecules are ignored due to low analyte concentration. Biomolecules are assumed to firmly bind with conjugate receptors in contact with the nanowire surface,

FIG. 1. A Brownian dynamics model for SiNW sensors, with randomly distributed biomolecules (red dots) in the fluid domain.

which means the biosensing process is a diffusion-limited problem with binding constant $k_{on} \rightarrow \infty$. Furthermore, a bonded biomolecule density of $10\ \mu\text{m}^{-2}$ (Refs. 5 and 6) is assumed to be enough to trigger an electronic signal. All the simulations are repeated 10 times, and the average of response time for these 10 trails is treated as the detection time of SiNW sensors at that concentration.

Fig. 2 shows the results obtained from Brownian dynamics simulations of biomolecular detection process. The detection time for biomolecular concentration varying from $1\ \text{fM}$ to $1\ \text{picomolar (pM)}$ are calculated. Four different types of sensors, a nanosphere sensor of diameter $1\ \mu\text{m}$, a SiNW sensor of diameter $100\ \text{nm}$ and length $20\ \mu\text{m}$, a small planar sensor of width $20\ \mu\text{m}$ and length $200\ \mu\text{m}$, and a large planar sensor of width $370\ \mu\text{m}$ and length $200\ \mu\text{m}$, are investigated. The response time decreases dramatically with the increase of biomolecular concentration, with a slope of around -1 , -1.5 , and -2 in logarithm for nanosphere, nanowire, and planar sensors, respectively. This is consistent with theoretical prediction from diffusion-reaction theory.⁶ Specifically, at analyte concentration of $1\ \text{fM}$, the response time for planar sensor is 200 times as large as that of SiNW sensor, which indicates the advantage of SiNW sensor in biomolecular detection at ultralow concentration. In addition, as illustrated in Fig. 2, it would need more than 1 day for a typical SiNW sensor to detect target biomolecules at concentration of $1\ \text{fM}$, which is far beyond the time limits in clinical diagnosis and lab experiments. However, experimental results^{3,14-17} plotted as black crosses in Fig. 2 imply that nanosensors could always present a clear signal of detection process at fM concentration within several minutes, which means a two- to three-orders magnitude of detection time gap between theoretical predictions and experimental results.

Compared with the diffusion-reaction modeling, Brownian dynamics simulations have the advantage of capturing the statistical variances. The statistical variances are plotted as error bars in Fig. 2. The length of error bars is proportional to the magnitude of the variances in logarithm. As the analyte concentration decreases, the statistical variance increases. In other words, the more sensitive the biosensor is, the larger the response time variance is. This is because while the binding of individual biomolecule is random, the

FIG. 2. Response time of various nanosensors at different concentrations. Error bars are plotted to show the statistical variances of numerical calculations. Experimental reported values for NW sensors are also shown as black crosses.

collective binding results of a large number of biomolecules are determinant and described well by diffusion-reaction theory. However, the variance in response time for a single SiNW sensor is limited and is less than half of the response time. Such small statistical variances cannot give satisfactory descriptions of the biosensing process at ultralow concentration.

In the following parts, electrokinetic forces are considered in the biomolecular detection process and the corresponding detection time at different concentrations is shown in Fig. 3. If only Brownian motion of biomolecules is considered, the response time decreases with the increase of concentrations with a slope -1 in logarithm at sub-fM concentration. The slope changes to be around -1.5 at high concentration. This phenomenon may be due to the decrease of average distance between biomolecules and nanowire surfaces. At high concentration, the distance between nanowire surfaces and biomolecules is short, especially for the first few biomolecules binding with the nanowire surface. The closer the biomolecules are to the nanowire surface, the more likely that SiNW sensors will perform like planar sensors, and the slope would keep decreasing until it approaches the limit -2 , which is the slope in logarithm between the detection time and the analyte concentration in 1D planar sensor.

Significant reduction in response time is observed after introducing electrokinetic effects. At concentration 1 fM, the response time difference with and without electrokinetic forces is around 41 for uncharged biomolecules and around 93 for charged biomolecules. This is because the movement of biomolecules under Brownian motion is random and stochastic, which is the main reason for the long detection time for transporting biomolecules toward the nanowire surface. However, due to electrokinetic forces induced by the existence of solution gate, the random motion of biomolecules would become suppressed to some extent, especially at the region where electrokinetic forces overwhelm the Brownian motion force. The electroosmotic flow would transport biomolecules along the vortex flow pattern and concentrate them near sensing region. If strong electrophoretic force exists near the nanowire surface, when the biomolecule cir-

culates close to the sensing region, the biomolecule would be quickly attracted to the nanowire surface, thus significantly reduces the detection time.

Such difference in detection time induced by electrokinetic effects vanishes at high concentration of around 1 μ M. This is because the distance for biomolecules to travel and bind with the sensor surface decreases as the concentration increases. Beyond a certain analyte concentration, the Brownian motion becomes the dominant factor to transport biomolecules toward the nanowire surface. Such observation indicates that the diffusion-reaction theory is only valid at medium to high concentration while electrokinetic effects should be taken into account at ultralow concentration.

Since the applied voltage on solution gate has direct influence on the strength of electrokinetic forces, we report the response time for nanosensors with different solution gate voltages at 10 fM concentration, as shown in Fig. 4. For voltage smaller than 0.01 V, response time of BM&EO and BM&EO&EP is similar, which means electrokinetic force has little influence on response time. This is because for low applied voltage, electrokinetic forces are negligible compared with Brownian force, whereas as the applied voltage increases, the response time under both BM&EO and BM&EO&EP decreases significantly. This is because increased applied voltage would enhance both EOF and EP, which begin to dominate in the multiphysics model instead of BM, thus making biomolecules bind on nanowire surface faster and reducing detection time. The Peclet number, which characterizes the relative importance of convection and diffusion, is plotted under different applied voltages and biomolecule concentrations in Fig. 1A in the supplementary material.¹⁸

One emerging design factor about SiNW sensor is the number of nanowires.⁴ Nanowire array could be used for detecting of multiple disease marker proteins simultaneously in a single, versatile detection platform.³ In addition, the use of multiple nanowires instead of a single nanowire as sensing elements enables high device uniformity and stability in buffer solutions and selective detection of bovine serum albumin at concentration as low as 0.1 fM.⁴ SiNW sensing devices with a large number of nanowires could provide

FIG. 3. Response time of NW sensors with electrokinetic effects as a function of analyte concentration. The inset shows the statistical variations of detection time.

FIG. 4. Response time under electrokinetic effects for NW sensors with different solution gate voltages at concentration 10 fM. Statistical variations are plotted as error bars.

FIG. 5. Response time under electrokinetic effects for nanowire array with 1, 2, 10, 20, and 50 nanowires at concentration 10 fM. Solid, dashed, and dotted lines represent response time of nanowire array with separation distance 1 μm , 2 μm , and 4 μm , respectively. The inset shows the statistical variations of detection time.

more available sensing surfaces for target biomolecules reacting with receptors, and thus require less time to accumulate enough binding events to trigger detection signal. As shown in Fig. 5, in a sensor array with 50 nanowires of 1 μm separation distance, the detection time difference between BM and BM&EO remains almost the same, which is around 30 times, whereas the gap between BM and BM&EO&EP is around 100 times as the nanowire number increases from 1 to 50. Similar phenomenon happens to the arrays with separation distances from 2 μm to 4 μm . This indicates the significant advantage of nanowire arrays in acceleration of biomolecular detection process. In addition, increasing the separation distance leads the reduction of detection time, since large separation distance could spread out nanowire pattern and provide more chance for biomolecules binding with nanowire surfaces. However, the ratio of detection time between BM and BM&EO or BM&EO&EP increases slower as the separation distance increases. It is found that the detection time is subject to around 1.5 and 2 times reduction for the arrays with separation distance 2 μm and 4 μm , respectively. This is reasonable because the influence of separation distance among nanowires on biomolecular detection is limited. Let us consider two special cases: one with separation distance of two nanowires approaches infinite, the other with two closely packed nanowires. Obviously, the detection time for the first case would be half of the second case, due to two times larger available sensing surfaces. For a finite separation distance, the detection time difference would be less than two times due to the inter-correlations among nanowires.

Central to this letter is the question as to where the two- to three-orders of magnitude detection time difference

between theoretical calculations experimental results comes from. In Fig. 3, we examine the contribution of electrokinetic effects on a single-nanowire sensor and over ninety times detection time difference is observed at 1 fM concentration. The difference is further increased if a higher solution gate voltage is applied or multiple nanowires are used. Thus, the detection time gap between theoretical predictions and experimental demonstration could be well explained by the electrokinetic effects and experimental configurations.

In summary, we have numerically investigated the influence of electrokinetic effects on biomolecular detection process at sub-femtomolar concentration in SiNW sensing devices. It is revealed that the two to three orders of detection time difference existing in diffusion-reaction theory and corresponding experiments is due to the transport speed acceleration by electrokinetic effects. The combined effects of electroosmotic flow, electrophoretic force, applied voltage, and nanowire array could lead to the orders of magnitude shorter detection time than that predicted by diffusion theory.

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