Numerical study of *in situ* preconcentration for rapid and sensitive nanoparticle detection

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This paper presents a numerical study of a preconcentrator design that can effectively increase the binding rate at the sensor in a real time manner. The particle enrichment is realized by the ac electrothermal (ACET) effect, which induces fluid movement to carry nanoparticles toward the sensor. The ACET is the only electrical method to manipulate a biological sample of medium to high ionic strength (>0.1 S/m, e.g., $0.06\times$ phosphate buffered saline). The preconcentrator consists of a pair of electrodes striding over the sensor, simple to implement as it is electrically controlled. This preconcentrator design is compatible and can be readily integrated with many types of micro- to nanosensors. By applying an ac signal over the electrodes, local vortices will generate a large velocity perpendicular to the reaction surface, which enhances transport of analytes toward the sensor. Our simulation shows that the binding rate at the sensor surface is greatly enhanced. Our study also shows that the collection of analytes will be affected by various parameters such as channel height, inlet velocity, and sensor size, and our results will provide guidance in optimization of the preconcentrator design. © 2010 American Institute of Physics. [doi:10.1063/1.3467446]

I. INTRODUCTION

Preconcentration, separation, and identification of macromolecules such as DNA and proteins play an important role in sample processing and analysis of (bio)chemistry and life sciences. The recent development in nanometer scale sensing elements has enabled biomolecular detection at a level of femtomolar (fM) concentration.¹ By scaling down a sensor, the detection system can increase its signal-to-noise ratio for more sensitive detection. However, as the concentration of a target analyte is lowered, the diffusion and absorption to the sensor take longer and longer to the extent that the detection becomes limited by the absorption of the target analytes to the sensor. A theoretical analysis in Ref. 2 reveals that for diluted biosolution in fM range, the detection is usually a transport-limited process. It is found that if diffusion is the sole mechanism for the delivery of nanoparticles to the sensor, it would take an impractical long incubation time in static fluid, from weeks to months, for the analytes to reach critical mass at the sensor. To speed up the detection, it is necessary to break the diffusion barrier in static fluid, so a flow-through system is often used, in which analytes are flowed past the sensor with a stream of buffer solution. Reference 3 investigates the effects of the surface reaction, convection, and diffusion processes on the binding rate in a flow-through system. Enhancing the diffusion was found to have the most pronounced effect on detection. As the response time of a biosensor is inversely proportional to the local concentration of the analyte in the vicinity of the sensor, replenishing the local analyte rapidly will significantly reduce the sensing response time. The binding rate at the sensor is shown to increase for microsensors² with a low to moderate channel Péclet number ($Pe=LU/D$, where L is the channel characteristic length, U is the flow rate, and D is the diffusivity).⁴ It can also be

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noted that the enhancement is less for smaller sensors still due to the diffusion limit. Because of the small dimensions of the microchannels and the limited flow rates, flow in microchannels is generally confined to the laminar regime, i.e., no mixing. The travel of analytes to the sensor therefore relies on the molecular diffusion to transverse the streamlines. A smaller sensor allows less time for diffusion before the analytes stream past the sensor. As analytes are pumped through the microchannel, the nanoparticles need to diffuse across the height of the channel to reach the sensor on the channel bottom. A protein with $D = 10 \mu\text{m}^2/\text{s}$ takes 10 s to diffuse across a $10 \mu\text{m}$ channel. Given a sensor of $5 \mu\text{m}$ width with $100 \mu\text{m}/\text{s}$ flow velocity, reagents only have 0.05 s passing the sensor, so certainly most of the analytes just flow by. Hence, only a small fraction of available samples can be analyzed, and flow-through provides merely marginal improvement in the binding rate.

Therefore, to improve the detection limits for nano- to microsensors, preconcentration becomes a necessary step to enrich the sample for downstream analysis. A number of strategies are currently available to provide sample preconcentration in liquids, including field-amplified sample stacking, isotachopheresis, chromatographic preconcentration, and membrane preconcentration. Most of them require special buffer arrangements, reagents, or both, which may not be feasible for *in situ* detection. So, in this paper, an electrokinetic method is presented and discussed, which is label-free with minimal requirements on pretreatment of the sample.

In our design of the nanoparticle preconcentrator, a flow-through microchannel is used to stream the particles past the sensor, and a pair of stirring electrodes is placed beside the sensor in the detection channel to enhance the binding. When excited with an ac signal, the ac electrothermal (ACET) effect would generate vortices that will give active guidance of targets toward the sensor. There have been prior research efforts using the ACET effect for particle concentration.^{5,6} References 5 and 6 presented experimental results on concentrating particles in a closed microchamber. In Ref. 5, particles were concentrated onto the electrode surfaces. The particle count increased three times in 2 min. In some applications, such an arrangement may not be applicable since the operation of the sensors and ACET electrodes may interfere with each other. In Ref. 6, the sensor is placed between the ACET electrodes on the bottom of a microchamber. The binding rate increased by a factor of close to 9 with $10 V_{\text{rms}}$ applied ACET voltage. There is also simulation study on combining ACET stirring with a flow-through channel. References 7 and 8 simulated a flow-through microfluidic system in which the sensor and ACET electrodes are located on separate channel walls facing each. Reference 7 predicted a $7\times$ increase in bound antigen after $6 V_{\text{rms}}$ ACET voltage being applied for 100 s. Our past work⁹ showed more improvement in binding if the sensor is placed between the electrodes instead of facing the electrodes on another channel wall. This paper continues that work and offers more detailed discussions with respect to the geometry of the flow-through preconcentrator.

Because fluid convection is used to route the particles, the sensitivity enhancement is independent of the specific type of sensors used. Therefore, the nanoparticle preconcentrator investigated here can be viewed as a generic platform to work with various sensors. It is the objective of this paper, using COMSOL numerical simulation, to study the effects of various parameters on the performance of such a preconcentrator and to seek to maximize its performance. In the following sections, we are going to present ac electrokinetics (ACEK) mechanisms, simulation procedures, results, and discussions on the flow-through preconcentrator.

II. AC ELECTROKINETIC MECHANISMS

There are many technological advantages in favor of using electrokinetics for microfluidic applications. Direct or alternating current (dc or ac) electric fields are relatively easy to implement and control. The characteristics of the electric fields can be adjusted rather elaborately, and high field strength can be easily generated with low voltages by the use of microfabricated electrodes and features. The advances in microfabrication lead to highly reliable and repeatable production of both microelectrodes and microchannels.

Electrical manipulation of particles can be achieved with a dc or ac source. dc electrokinetics typically produces electrical field lines that are parallel to the fluid streamlines, difficult to realize

mixing. ACEK is based on inhomogeneous electric fields produced by microelectrodes. ACEK could produce converging flows at trapping sites, providing efficient delivery of target molecules. By ACEK, the locations where particles are attracted can be manipulated by patterning of electrodes and ac signals. Its effective range can be highly local or global depending on the coverage and configuration of electrodes used. Therefore, ac electrokinetics is more suitable for actively directing particles toward the sensors.

ac electrokinetics mainly includes dielectrophoresis (DEP), ac electro-osmosis (ACEO), and the ACET effect. DEP is a nondestructive method for the manipulation of particles. In a typical DEP concentrator, small electrodes and high voltage are used to generate adequate electric field (of the order of 0.1–1 MV/m). However, DEP techniques are limited by the fact that the DEP force is only effective near the edges of the electrode due to the rapid decay of the electric field gradients with the distance from the electrodes. For spherical particles, DEP velocity can be expressed as

$$\langle u_{\text{DEP}} \rangle = \frac{a^2 \epsilon_m}{6\eta} \text{Re}[f_{\text{CM}}] \nabla |E|^2, \quad (1)$$

where ϵ_m is the permittivity of the medium. f_{CM} is known as Clausius–Mossotti factor, and its real part $\text{Re}[f_{\text{CM}}]$ has a value between -0.5 and 1 . DEP velocity decreases rapidly with the distance from the electrode, and it is size dependent. The order of magnitude estimation shows that $1 \mu\text{m}$ particles will exhibit no more than $0.9 \mu\text{m/s}$ DEP velocity when they are $10 \mu\text{m}$ from the electrode edge at 5 V_{rms} , and 100 nm particles will have less than 9 nm/s DEP velocity. Additionally, if ac electrokinetically induced fluid flow (such as ACEO or ACET flow) is present, the fluid flows could be much stronger than the DEP holding force. So, for nanosized particles, DEP force is negligible unless within a distance very close to electrode edges.

On the other hand, preconcentration of nanoparticles can be realized through ACEO or ACET fluid motion. Preconcentrators of particles, such as cells, virus, proteins, and DNA molecules, have been prototyped in various forms, with ACEO^{10–14} or ACET^{5,6} mechanisms. Flow generated by ACEO and ACET has no dependence on particle size and has a longer effective range as it takes advantage of the hydrodynamic flow as long as the particles stay suspended in the fluid long enough to be focused. These features are particularly advantageous for nanoparticle focusing.

The difference between the two mechanisms of ACEO and ACET is that ACEO is typically limited to fluids with low ionic strength, e.g., de-ionized water. High conductivity compresses the thickness of the double layer, rendering electro-osmosis ineffective. For the same applied voltage, more conductive fluids have a lower peak velocity, and the highest fluid conductivity with which ACEO has been observed is 85 mS/m . Most biological applications involve conductive fluids, up to $1\text{--}2 \text{ S/m}$. To actuate fluid at such high conductivities, a viable option is to use the ACET effect. Recent studies have demonstrated that the ACET effect is a promising technique to manipulate conductive fluids. Its principle is described briefly in the following.

The ac electrothermal effect results from the interactions of ac electric fields and temperature gradients in the fluid. When an electric field E is applied over a fluid of electrical conductivity σ , Joule heating of the fluid will take place according to the energy balance equation,

$$k\nabla^2 T + \frac{1}{2} \langle \sigma E^2 \rangle = 0, \quad (2)$$

where T is the temperature and k is the thermal conductivity. If the electric field is inhomogeneous, the heat generation will be nonuniform as well, which leads to temperature gradients ∇T in the fluid. In turn, the temperature gradient ∇T will produce spatial gradient in fluid conductivity and permittivity $\nabla \epsilon = (\partial \epsilon / \partial T) \nabla T$ and $\nabla \sigma = (\partial \sigma / \partial T) \nabla T$, which induces mobile charges, ρ_e , in the fluid bulk according to $\rho_e = \nabla \cdot (\epsilon E)$ and $\partial \rho / \partial t + \nabla \cdot (\sigma E) = 0$, with $\partial / \partial t = i\omega$ in ac fields.

The electric field will impose a force on the induced charges as

$$F_{\text{et}} = \rho E - \frac{1}{2} |E|^2 \nabla \epsilon. \quad (3)$$

The first term in Eq. (3) is the Coulomb force, and the second term is the dielectric force. The time averaged force is

$$\langle F_{\text{et}} \rangle = -\frac{1}{2} \left(\frac{\nabla \sigma}{\sigma} - \frac{\nabla \varepsilon}{\varepsilon} \right) \cdot \frac{\varepsilon |E|^2}{1 + (\omega \tau)^2} - \frac{1}{4} \nabla \varepsilon |E|^2, \quad (4)$$

where σ and ε are the electrical conductivity and permittivity of the medium, $\tau = \varepsilon / \sigma$ is its charge relaxation time, and $\omega = 2\pi f$ is the radian frequency. Here, sinusoidal waveform is assumed, and E is the magnitude of electric field. For aqueous media at 293 K, we have

$$\begin{aligned} \frac{1}{\varepsilon} \frac{\partial \varepsilon}{\partial T} &= -0.004 \Rightarrow \frac{\nabla \varepsilon}{\varepsilon} = \frac{1}{\varepsilon} \frac{\partial \varepsilon}{\partial T} \nabla T = -0.004 \nabla T \quad \text{and} \\ \frac{1}{\sigma} \frac{\partial \sigma}{\partial T} &= 0.02 \Rightarrow \frac{\nabla \sigma}{\sigma} = \frac{1}{\sigma} \frac{\partial \sigma}{\partial T} \nabla T = 0.02 \nabla T, \end{aligned} \quad (5)$$

giving

$$\langle F_{\text{et}} \rangle = -0.012 \cdot \nabla T \cdot \frac{\varepsilon |E|^2}{1 + (\omega \tau)^2} + 0.001 \cdot \nabla T \cdot \varepsilon |E|^2. \quad (6)$$

It can be seen that the electrothermal force is proportional to ∇T , which can be imposed externally, such as strong illumination, or generated internally by electric currents passing through the fluid.

As electric field will exert volume forces through induced charges, fluid motion will be induced according to the Navier–Stokes equation,

$$\rho \frac{\partial u}{\partial t} + \rho(\nabla \cdot u)u - \eta \nabla^2 u + \nabla P = F_{\text{et}}, \quad (7)$$

where ρ is the fluid density, η is the dynamic viscosity of the fluid, P is the external pressure, and u is the velocity of the fluid. Together with $\nabla \cdot u = 0$ for incompressible fluid, fluid velocity can be found for an electrokinetic microdevice. It needs to point out that ACET flows depend on temperature gradient, not temperature rise. At microscale, it does not need much energy and temperature rise to obtain a high temperature gradient (e.g., 0.1 K/ μm). The temperature rise in the device is usually limited to a few degrees as observed experimentally and verified by simulation.⁵

ACET velocity increases with conductivity, which is expected since energy dissipation increases as $\langle P \rangle = \sigma E_{\text{rms}}^2$. ACET flow has been observed for fluid conductivity up to 700 mS/m. So, ACET is chosen as the stirring mechanism in our preconcentrator. The ACET effect originates from Joule heating and temperature gradient; frequency is chosen, so system impedance is close to resistive nature, when most voltage will drop in the fluid bulk, instead of in electrode/fluid interface. Using ac signals typically above several tens of kilohertz, ACET can effectively avoid the unwanted electrochemical reactions in the fluids. It bypasses the interfacial effects, such as electrode polarization and the related undesirable reaction.

III. CONVECTION, DIFFUSION, AND REACTION AT THE SENSOR

Much prior research has been done for flow-through microfluidic devices, and both analytical and numerical analyses of transport phenomenon have been performed.^{4,15–17} The discussions presented here simply follow well-established formulas.

The distribution (convection and diffusion) of the target molecules within the microchannel can be described as

$$\frac{\partial c}{\partial t} + \vec{u} \cdot \nabla c = D \nabla^2 c, \quad (8)$$

where c is the molecule concentration, u is the fluid velocity, and D is the diffusivity of the antigen. When a target molecule strikes the sensor surface, it will be immobilized by surface modification such as antigen-antibody docking. On the sensor surface, we assume a first order reaction profile

FIG. 1. Schematic of the preconcentrator (2D side view). Sensor is placed between two stirring electrodes. Fluid with a given target concentration flows in from left boundary and exits on the right boundary.

$$\frac{\partial B}{\partial t} = k_{\text{on}} c_s (b_m - B) - k_{\text{off}} B, \quad (9)$$

where b_m is the surface concentration receptors on the sensor. c_s is the target concentration on sensor surface, and k_{on} and k_{off} are the reaction and dissociation constants, respectively. The binding rate of the molecules to the sensor surface must be balanced by the diffusive flux of molecules at the binding surface. This boundary condition along with Eqs. (8) and (9) determines the molecule distribution in the channel and on the sensor.

Whether the system is diffusion limited or reaction limited can be determined by sensor and channel characteristics, represented as Damköhler number Da (reaction velocity over diffusion velocity). Our model applies to a strongly diffusion limited case since calculated Da ($k_{\text{on}} b_m H / D$, where H is the characteristic channel height) is much greater than 10, which is in agreement with other groups' results.

IV. SIMULATION OF *IN SITU* FLOW-THROUGH NANOPARTICLE PRECONCENTRATOR

The proposed preconcentrator consists of a flow-through microchannel with a pair of microstirring ACET electrodes integrated on its bottom. The sensor is to be placed in the gap between the two electrodes. The two-dimensional (2D) side view of the preconcentrator is shown in Fig. 1.

The characteristics of the designed preconcentrator were studied with finite-element analysis software COMSOL MULTIPHYSICS. The height of the microchannel, H , will vary in the simulation to study their effects on the performance of the preconcentrator. The sensor width is denoted as L , which can vary from micron to submicron sizes. The two stirring electrodes are $20 \mu\text{m}$ in width, and the spacing between them is set at $5 \mu\text{m}$, which is sufficient to accommodate most nano- to microsensors. Sample solution at a concentration of 1 fM is pressure-driven in from the left boundary, assuming a parabolic profile with a mean velocity of u_{in} (peak velocity in the middle of the channel with $1.5 \times u_{\text{in}}$) at the inlet. The flow exits the chamber at the right boundary.

The simulation of ACET stirring involves several physical modules including electrostatics, heat transfer, Navier–Stokes, and convection-diffusion models. Parameters used in the simulation are comparable to the values in a real world setting, as given in Table I. For the boundary conditions in electrostatics module, electrodes are given electrical potential, while other boundaries are electrically insulated. For thermal boundaries (convection and conduction modules), metal electrodes are set at room temperature as they are good thermal conductor, while the top and bottom of the channels are assumed thermal insulation (bottom glass substrate and top polymer

TABLE I. Device parameters used in the simulation.

Parameter	Value (unit)	Description
ϵ_r	80.2	Relative permittivity of fluid
k	0.598 [W/(m K)]	Thermal conductivity of fluid
ρ	1000 [kg/m ³]	Density of fluid
C_p	4.184 [kJ/(kg K)]	Heat capacity of fluid
η	1.08×10^{-3} (Pa s)	Dynamic viscosity of fluid
σ	0.36 (S/m)	Electric conductivity of fluid (BSA in PBS)
D	10^{-11} (m ² /s)	Diffusion coefficient of analyte
f	100 (kHz)	ac signal frequency
c	10^{-12} (mol/m ³)	Analyte concentration at the inlet (1 fM)
k_{on}	10^8 [m ³ /(mol s)]	Association rate constant
k_{off}	0.02 (1/s)	Dissociation constant
b_m	1.67×10^{-8} (mol/m ²)	Total surface concentration of antibody ligand
V	Variable	Electric potential (rms value)
u_{in}	Variable	Average flow velocity at the inlet

channel wall). Although very small, convective heat flux boundary conditions are applied to the inlet and outlet boundaries. For fluid dynamics (incompressible Navier–Stokes module), both top and bottom channel walls assume no-slip boundaries. Parabolic pressure-driven flow profile is applied to the left inlet boundary. Fluid exits the outlet boundary with zero normal stress. In the simulation, electric field is solved first, and then thermal field and flow velocity field are solved simultaneously since they are coupled in the equations.

With solved flow velocity field, diffusion and convection module and surface reaction module are solved for the concentration effect on the sensor. At the left inlet boundary, concentration is fixed at 1 fM. The outlet boundary is set as convective flux. On the sensor surface, according to Eq. (9), first order reaction is assumed, with $k_{\text{on}}=10^8$ m³/(mol s), $k_{\text{off}}=0.02$, and the total receptors on the sensor is $b_m=1.67 \times 10^{-8}$ mol/m². The diffusivity of the target molecule is 10^{-11} m²/s, which is typical for single stranded DNA. The total concentration accumulated can be found by integration unit point concentration over the whole sensor surface.

In the simulation, external forces on the particle have been considered, and the particle size is assumed to be 0.1 μm in diameter. The forces include dielectrophoretic force [Eq. (1)], for which positive DEP is assumed with a Clausius–Mossotti factor of 1. No difference in simulation results is observed between the models with DEP and without DEP effect. So, it is safe to conclude that DEP force does not play any appreciable role in nanoparticle trapping. Another force considered is the Saffman lift force. Small particles in shear flow experience a lift force that is originated from the pressure variations around the particle, and this is called Saffman force. Its expression,

$$F_{\text{sa}} = |u_f - u_p| \left[6.64 \eta R^2 \sqrt{\frac{\rho_f}{\eta} \nabla (u_f - u_p)} \right], \quad (10)$$

indicates that Saffman force is a function of fluid viscosity η , density ρ_f , particle size R , and velocity difference between particle (u_p) and fluid (u_f). This force is always perpendicular to the direction of flow, which means velocity gradient of horizontal flow will result in the vertical lift force. The effect of the force is taken into account in the simulation. With 8 V_{rms} ACET voltage and 1000 $\mu\text{m/s}$ inlet velocity, concentration on the sensor is reduced by 0.0012% for nanoparticles. The calculation reveals that Saffman force is not a significant factor under our simulation conditions.

(a) 6Vrms 100 μ m/s inlet velocity (b) 10Vrms 100 μ m/s inlet velocity

FIG. 2. Simulated ACET flow fields for guiding biomolecules. Electrode gap is 5 μ m, and channel height is 40 μ m. Pump in velocity is 100 μ m/s. (a) Applied voltage is 6 V_{rms}. Color shows electrical potential, and arrow shows microflows and their relative magnitudes. (b) Applied voltage is 10 V_{rms}. Color shows temperature distribution, and arrow shows microflows and their relative magnitude. Dots and lines in both plots show molecule traces, which are indications of ACET stirring effect.

V. RESULTS AND DISCUSSIONS

Many parameters will contribute to the trapping of nanoparticles on the sensor, such as ACET signal strength, inlet velocity, channel height, and diffusivity of target particles. In the following, the effect of each factor will be discussed.

A. Effect of ACET and proof of concept

From Eq. (4), we can see that the ACET effect is a function of signal frequency and strength. Figure 2 gives a qualitative view of how ACET stirring would guide biomolecules. Pseudocolors in Figs. 2(a) and 2(b) show electrical potential and thermal distribution in the channel, respectively. When excited by ac signal, a nonuniform electric field is generated by the electrode pair,

FIG. 3. Binding rate as a function of time. With ACET stirring at 10 V_{rms} , concentration increased by $9\times$ than with flow-through alone. Channel height $H=20\ \mu\text{m}$, and inlet velocity $u_{in}=100\ \mu\text{m/s}$. The unit of the ordinate is the average concentration of bonded molecules on the sensor (point concentration on 2D model) taken at the end of 300 s.

giving rise to the ACET effect. At a fluid conductivity of 0.36 S/m and 10 V_{rms} signal [Fig. 2(b)], the total temperature rise is around 7.6 K (shown in color bar), while the maximum temperature gradient can reach as high as 20 K/ μm .

The total flow pattern in the channel is a combination of pressure-driven flow and the induced ACET microflows. Figure 2 also shows simulated flow patterns for two different applied voltages (indicated by arrows in plots). The parameters used are $H=40\ \mu\text{m}$ and $u_{in}=100\ \mu\text{m/s}$. In the simulation, particles representing biomolecules are introduced to reveal the flow traces. It is obvious that the ACET effect induces vortices that generate a vertical velocity component right above the sensor surface, and this can effectively convey particles toward the sensor. As a result, the binding rate at the reaction surface is greatly enhanced.

The induced ACET vortices function as an adjustable aperture to constrict the target molecule streamlines to very close vicinity of the sensor surface so as to enhance binding. According to Eq. (4), ACET velocity increases rapidly with applied voltage ($\sim V^4$), so the vortices increase in size with voltage as well. As a result, the sample streams become more confined as they are squeezed by the vortices, and the aperture becomes smaller with increasing ac voltage. At a higher voltage [e.g., 10 V_{rms} in Fig. 2(b), compared with 6 V_{rms} in Fig. 2(a)], most of the target particles are routed through the narrow pathway pinched by two vortices toward the sensor surface, and even those at the other side of the channel become captured. So, increasing the voltage will enhance the molecule count on the sensor.

The cumulative concentration of bonded molecules can be integrated over time. Figure 3 shows the concentration effect by ACET stirring as a function of time. Channel height $H=20\ \mu\text{m}$; inlet flow-through velocity $u_{in}=100\ \mu\text{m/s}$. With the ACET effect, the binding rate is shown to be increased by nine times compared with flow-through alone. Note that the y-axis shows average concentration of bonded molecules on the sensor (point concentration on 2D model). The total concentration can be obtained by multiplying it with the sensor area [width (L) $\times$ length]. Note that the concentration on the sensor increases linearly since the con-

FIG. 4. Concentration effect at different signal levels against inlet velocity. The data points are normalized against the value at 0 V_{rms} and 0.1 $\mu\text{m/s}$ inlet velocity. A reference velocity is given at each signal level in the legend showing a representative downward velocity generated by the ACET effect.

centration on the sensor is far from saturation (available trapping site $b_m = 1.67 \times 10^{-8} \text{ mol/m}^2$). For real time detection, ACET stirring would greatly reduce incubation time, in the case above, by nine times.

B. Effect of flow-through velocity

In the following, the combined effect of flow-through velocity and ACET stirring is studied, and the results are shown in Fig. 4. The parameters used here are 20 μm channel height, 5 μm spacing between the ACET electrodes, and 5 μm sensor width. Convection, diffusion, and reaction processes are solved for 300 s using time-dependent solver. With given parameters, the calculated Da number ($k_{on}b_mH/D$) is 3.3×10^6 , which indicates strong diffusion limited nature. For easy comparison, the data points are normalized against the value at 0 V_{rms} and 0.1 $\mu\text{m/s}$ inlet velocity. Reference velocities shown in the legend are the averaged downward (V_y) velocities in the middle of the channel above the sensor surface as an indicator of ACET velocity.

When there is no ACET stirring (0 V), increasing the inlet velocity by 1000 times (from 0.1 to 100 $\mu\text{m/s}$) only increases the concentration on the sensor by a factor of ~ 5.6 . The preconcentration effect increases to above $10\times$ at extreme high velocity such as 1000 $\mu\text{m/s}$, which, however, is difficult to maintain due to the high pressure required for small channels. This indicates that flow-through alone only has a limited effect on the concentration. From Fig. 4, it can be seen that ACET stirring and flow-through will work together to increase the binding on the sensor. A higher ACET voltage will increase the binding rate. When the stirring is weak (2 V_{rms} ACET signal), the increase of concentration against inlet velocity is minimal. The 2 V_{rms} curve almost overlaps with the 0 V_{rms} curve. At the same 100 $\mu\text{m/s}$ fluid velocity, a 6 V_{rms} ACET signal will provide a gain of 20, and a 10 V_{rms} signal can reach a gain of 46, indicating the benefits of adding the ACET stirring mechanism.

However, the improvement in concentration flattens out at high flow-through velocities. The concentration starts to saturate at 30 and 100 $\mu\text{m/s}$ of flow-through velocities, for 6 and 10 V_{rms}

FIG. 5. The effect of channel height on the sensor concentration with (a) ACET voltage at 0 V, (b) at 4 V_{rms} , and (c) at 10 V_{rms} . The unit of the ordinate is point concentration (2D) accumulated on sensor surface.

ac signal, respectively. At very high flow-through velocity, ACET flows can only carry the molecules into the compressed depletion region around the sensor to a limited extent. At increasing flow-through velocity, most of molecules simply get carried down the stream. So, with ACET stirring, only a moderate flow-through velocity is needed, easing the requirements on pumping pressure and the strength of device bonding.

C. Effect of channel height

Channel height can affect ACET preconcentration in two ways. First, the ACET velocity is determined by electric field strength and thermal gradient, so it is the strongest near the electrode edges (arrows in Fig. 2). The ACET flow gets weaker with its distance away from the electrodes. So, beyond a certain height in the channel, ACET vortices cannot effectively guide the target molecules down toward the sensor. Besides, small channel diameter will reduce the distance that analytes are required to travel to the sensor. On the other hand, ACET flows can get suppressed at small hydraulic diameter. Therefore, the effect of channel height on the concentration needs to be investigated.

Simulation results on the effect of channel height are shown in Fig. 5, with three different signal strengths. The electrode separation is 5 μm , and the sensor is also 5 μm wide, i.e., completely filling up the electrode gap. In almost all cases, concentration on the sensor increases with inlet velocity. Also, there are two regimes. One regime is at low flow-through velocity where a larger channel will produce a higher binding rate, and the other regime is at high flow-through velocity where a smaller channel will lead to a higher binding rate.

Without ACET guidance (0 V), the capture of an analyte molecule is dominated by diffusion. So, above a reasonable flow-through velocity ($>2 \mu m/s$), a smaller channel height produces higher concentration on the sensor since the channel constrains the sample solution to be closer to

FIG. 6. Cross-sectional fluid velocity along the centerline between the two electrodes through the channel height. Vertical velocity is shown as the blue square line, and horizontal velocity is shown as the red circle line. Inlet velocity is $100 \mu\text{m/s}$, and voltage is fixed at $10 V_{\text{rms}}$ for all cases.

the sensor. While at very low inlet velocity ($< 2 \mu\text{m/s}$), the fluid is almost at rest, the target molecule has sufficient time to diffuse to the sensor. So the sample depletion region above the sensor becomes thicker, and a higher channel will lead to a slightly higher concentration.

With ACET stirring (4 and $10 V_{\text{rms}}$), it seems that the low velocity regime is extended to higher velocities with increasing ACET voltages [cf. Figs. 5(b) and 5(c)]. With $4 V_{\text{rms}}$, the transition between the two regimes happens at $100\text{--}200 \mu\text{m/s}$. Below $200 \mu\text{m/s}$, a larger channel permits more effective mixing, hence higher capture rate at the sensor. At higher flow-through

FIG. 7. The ACET concentration effect as molecular diffusivity changes. Calculation assumes $100 \mu\text{m/s}$ inlet velocity and $20 \mu\text{m}$ channel height.

FIG. 8. Concentration effect for a submicron sensor ($0.5 \mu\text{m}$ wide) in a $2 \mu\text{m}$ high channel. No benefit from ACET stirring can be observed compared with its $10\times$ larger microsized sensor.

velocities, the data points start to coincide with those without ACET mixing [e.g., data at $1000 \mu\text{m/s}$ in Fig. 5(b)], and the binding rate is dictated by the flow-through velocity. As the mixing strengthens rapidly with ACET voltage, at $10 V_{\text{rms}}$, the binding process is dominated by the ACET effect for most of the velocity range until above 1 mm/s .

It can also be observed that there is a plateau region for concentration, where the binding rate is almost independent of the flow-through velocity. For example, at $4 V_{\text{rms}}$ with $60 \mu\text{m}$ channel, the binding rate stays almost the same from 30 to $1000 \mu\text{m/s}$, and the similar is true with $10 V_{\text{rms}}$ ACET voltage. So, by incorporating an ACET mixing mechanism, a larger channel and a slower flow rate can be used, which will reduce the pressure that microchannels have to sustain and ease the difficulty in fabrication.

The effect of channel height on concentration can be understood by studying the velocity profile at the center line between the two electrodes, indicated by a dotted line in Fig. 1. The horizontal component V_x and vertical component V_y are plotted over the span of channel height for several sizes of channel, namely, 2 , 5 , 10 , 20 , and $40 \mu\text{m}$. V_x is a superposition of inlet velocity and V_x of ACET flows, and V_y , the guiding flow for the targets, is solely attributed to the y -component of ACET flows. For all the curves in Fig. 6, the inlet velocity is set at $100 \mu\text{m/s}$, which always exhibits a parabolic profile with peak velocity ($1.5u_{\text{in}} = 150 \mu\text{m/s}$) in the middle of the channel. The applied voltage is fixed at $10 V_{\text{rms}}$ with an electrode gap of $5 \mu\text{m}$; if Eq. (4) or Eq. (6) alone is considered, the ACET velocities for all five heights would be the same.

From the development of V_y , it can be seen that channel height less than $20 \mu\text{m}$ will suppress ACET vortices, as the peak value of V_y keeps increasing until the channel height reaches $20 \mu\text{m}$. This explains why in Fig. 5(c), the $10 \mu\text{m}$ curve produces a noticeably lower binding rate than the other larger channels. Calculations show that ACET vertical velocity V_y has a peak value around $4 \mu\text{m}$ above the bottom, and the peak can be as high as $5800 \mu\text{m/s}$ if given enough channel height to develop the vortices. This peak velocity is orders of magnitude higher than inlet flow-through velocity, which ensures the guiding ability of the vortices.

FIG. 9. Fluid velocity distribution along the electrode centerline as a function of channel height for the scaled-down device ($0.5 \mu\text{m}$ wide sensor and $2 \mu\text{m}$ channel height). Vertical velocity is shown as the blue square line, and horizontal velocity is shown as the red circle line. Inlet velocity is $10 \mu\text{m/s}$, and voltage is $1 V_{\text{rms}}$.

D. Effect of molecular diffusivity

For all the above discussions, target diffusivity is fixed at $10^{-11} \text{ m}^2/\text{s}$, which is a typical value for a single stranded DNA sample. We have also studied the effect of diffusivity on ACET preconcentration, and the result is shown in Fig. 7. Equation (8) indicates the diffusivity will affect the distribution of concentration. Over a wide range of diffusivity from 10^{-13} to $10^{-9} \text{ m}^2/\text{s}$, improvement in the binding rate can still be observed with ACET stirring, as shown in Fig. 7, with 4 and $10 V_{\text{rms}}$, compared with flow-through alone ($0 V_{\text{rms}}$). It is noticed that the ACET stirring effect is most effective when diffusivity of analytes is very low, especially for large molecules such as proteins. With $10 V_{\text{rms}}$ signal at diffusivity of $10^{-13} \text{ m}^2/\text{s}$, the improvement of concentration gain can reach 50. As diffusivity increases, stirring becomes less effective and necessary. $4 V_{\text{rms}}$ signal could not improve concentration further at diffusivity of $10^{-9} \text{ m}^2/\text{s}$.

E. Scaling down ACET devices

For the above discussion, sensor length is set at $5 \mu\text{m}$, which is also the electrode gap size. What would happen if the sensor size is reduced to submicron? Is it feasible to construct a preconcentrator for nanosensors by scaling down everything proportionally? The answer looks like a “yes” at first glance. Simulation was performed for which all dimensions were reduced by a factor of 10, i.e., a preconcentrator with a $0.5 \mu\text{m}$ gap between $2 \mu\text{m}$ electrodes, $0.5 \mu\text{m}$ wide sensor, and $2 \mu\text{m}$ channel height. The voltage applied to electrodes thus changes from 10 to $1 V_{\text{rms}}$ in order to keep the same electric field strengths. The concentrator effect for such a preconcentration is shown in Fig. 8, which indicates no benefit from ACET mixing. A look at its velocity profiles (Fig. 9) reveals that scaling down the device size to a length scale of a micron produces very different velocity profiles. Even though the electric field strength remains the same, flow resistance increases by 10 000 times due to a $10\times$ smaller channel size. For the same electric field strength, ACET flow velocity as indicated by V_y is about $6 \mu\text{m/s}$, while the corresponding velocity is $\sim 6000 \mu\text{m/s}$ for its $10\times$ larger counterpart (Fig. 6).

FIG. 10. ACET concentration effect for a submicron sensor ($0.5 \mu\text{m}$ wide) in a $20 \mu\text{m}$ channel.

With lower channel height, ACET vortices are compressed. To improve the binding rate of nanosensors, one possible solution is to use a large channel in which ACET flows can be effectively generated. Figure 10 shows improvement in the binding rate when a larger $20 \mu\text{m}$ channel is used.

VI. CONCLUSIONS

This paper presents a preconcentrator design that can achieve fast and *in situ* concentration of nanoparticles for enhanced detection. Using ACET mixing, vortices can be generated locally to provide active guidance of an analyte such as DNA and protein toward the sensor. The configuration is simple yet effective, and it is easy to implement and integrate with the detection system.

Numerical simulation is used to study the effects of various design parameters on the binding rate at the sensor, including signal strength, flow velocity, channel height, sensor size, and molecule diffusivity. With sufficient advection from vortices generated by the ACET effect, channels larger than $20 \mu\text{m}$ are more effective in trapping targets. Optimized preconcentrator design will also reduce the required flow rate so that sample consumption can be reduced. While scaling down the device may not be viable for nanoscale sensors, it is possible to improve the nanosensor binding rate by carefully choosing channel size and sensor locations.

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