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PUSHING THE LIMITS OF ELECTRICAL DETECTION OF ULTRALOW FLOWS IN NANOFLUIDIC CHANNELS

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ABSTRACT

This paper presents improvements in flow detection by electrical cross-correlation spectroscopy. This new technique detects molecular number fluctuations of electrochemically active analyte molecules as they are transported by liquid flow through a nanochannel. These fluctuations are used as a marker of liquid flow as their time of flight in between two consecutive transducers is determined, thereby allowing for the measurement of liquid flow rates in the picoliter-per-minute regime. Here we show an enhanced record-low sensitivity below 1 pL/min by capitalizing on improved electrical instrumentation, an optimized sensor geometry and a smaller channel cross section.

KEYWORDS

Flow detection, electrochemical sensor, nano-fluidics, cross-correlation, nanochannel, redox cycling

INTRODUCTION

Microfabricated flow sensors are used in a wide range of commercial and research applications, their importance being reflected in the vast number of different types of sensors and measurement concepts [1,2]. Also in nanofluidic systems, the flow rate is a desirable property to quantify, e.g. when measuring liquid slip or investigating the transport of macromolecules through nanochannels [3].

Our group has recently introduced electrochemical cross-correlation spectroscopy as an all-electrical method to detect ultralow picoliter-per-minute flow rates in nanofluidic channels [4]. The basis of this method is nanogap sensors [5], in which electrochemical active molecules undergo redox cycling between two closely spaced electrodes embedded in opposite walls of a nanochannel. The molecules travel back and forth by diffusion and are repeatedly oxidized and reduced at the electrodes, thereby shuttling electrons across the channel and generating an electrical current. This current is directly proportional to the number of molecules in the nanogap sensor. Since the molecules undergo random thermal Brownian motion, their number fluctuates considerably in time in the small femtoliter detection volume – an effect that is reflected in corresponding fluctuations of the electrical current.

To measure liquid flow we detect the time of flight of this diffusion noise in between two consecutive transducers, as shown in Figure 1. The fluctuations are measured by recording current-time traces at the top electrodes of both sensors. The time of flight is then extracted by cross correlation analysis of these traces.

Here, we report a tenfold improvement in the sensitivity of this method and discuss its limits.

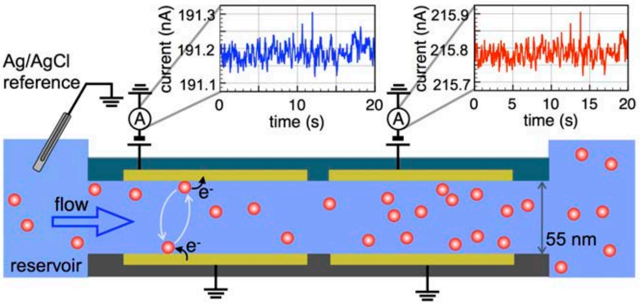

Figure 1: Schematic of the experimental setup. Fluctuations in the number density of electroactive molecules are used as tracers of liquid flow as water is transported through a nanochannel. The fluctuations are detected electrically by redox cycling and their time of flight between the detectors – or, equivalently, the flow velocity – are then determined by cross correlation analysis of current-time traces (curves in the insets are a schematic illustration).

DEVICE FABRICATION

Nanogap devices were fabricated as described previously [6] on an oxidized 4-inch silicon wafer. 20 nm thick Pt bottom electrodes were deposited by electron beam evaporation and patterned by a lift-off process. The nanochannel was defined as a 55 nm thick Cr layer also deposited and defined by electron beam deposition and photolithography, respectively. After deposition of a 100 nm thick Pt top electrode, the whole structure was buried in a passivating SiN layer deposited by chemical vapor deposition. At both ends of the nanochannel, access holes were etched into the passivation layer by reactive ion etching. Schematic cross sections of the device are shown in Figure 2. It consists of a 202 µm long, 5 µm wide and 55 nm high nanochannel. The electrode pairs at the channel floor and ceiling are 100 µm long and are separated by a 2 µm wide gap.

Liquid flow is generated in the nanochannel by a syringe pump (Harvard Apparatus Pump 11 Pico Plus Elite). Since ultralow flow rates cannot be driven directly, the pump flow is reduced via Parallel Flow

Control [7]. Tubing is connected to the nanofluidic device via an additional layer in polydimethylsiloxane (PDMS), which was formed by molding on an SU-8/silicon master and bonded to the SiN surface after surface activation in an oxygen plasma. In this layer, four 200 µm long, 5 µm wide and 3 µm high microchannels connect both access holes of the nanochannel. The flow is then divided in between the parallel nano- and microchannels according to the ratio of their hydraulic resistances. Since the resistances change cubically with the channel height the nanochannel flow rate is reduced by a factor of approximately 400 000 with respect to the syringe pump flow rate. A micrograph of the device is shown in Figure 3.

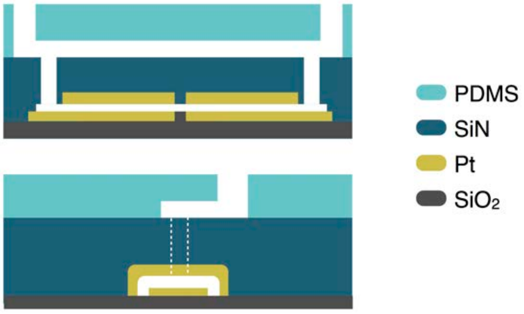

Figure 2: Schematic cross section of the device along the longitudinal (top) and lateral axis (bottom).

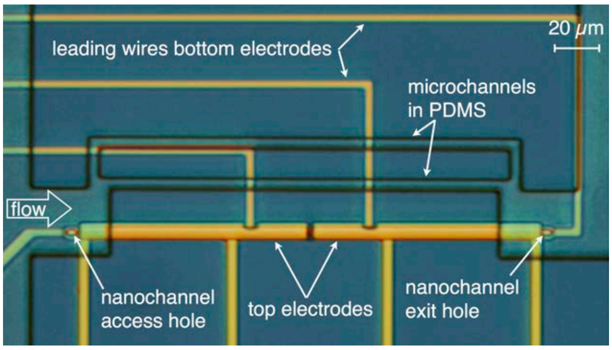

Figure 3: Top view micrograph of a 202 µm long nanofluidic device bonded to a PDMS microchannel layer (only two out of four microchannels running in parallel to the device are shown).

EXPERIMENTAL

Ferrocenedimethanol (Fc(MeOH)$_2$ from Acros, diffusion coefficient $D = 6.7 \cdot 10^{-10}$ m^2/s) was chosen as redox-active species and prepared as a 1 mM solution in Milli-Q water with 0.1 M KCl (Sigma-Aldrich) added as background electrolyte together with 5 mM H_2SO_4 (Sigma-Aldrich) to prevent electrode degradation. Directly before a measurement, the Cr sacrificial layer was removed and the nanochannel was formed by purging the microchannels with a chromium etchant solution (Selectipur, BASF). The redox active solution was then driven through the channel with varying syringe pump flow rates of up to 60 µL/h.

Both the bottom and top electrodes of the device were connected to a CH Instruments 842B bipotentiostat. Both top electrodes were biased at an oxidizing potential of 0.45 V while the bottom electrodes were short-circuited to a Ag/AgCl reference electrode that was connected by tubing downstream of the device (reducing potential). The whole setup except for the bipotentiostat was shielded from interference in a Faraday cage. Current-time traces of up to 600 s length were recorded at 10 ms sampling intervals at both top electrodes. We used high pass filtering to remove slow instrumental drift (see below).

RESULTS AND DISCUSSION

The times of flight of molecular number concentrations were extracted from the detected current-time traces by cross-correlation analysis [4]: the traces $I_{1,2}(t)$ exhibit diffusion noise $\delta I(t) = I(t) - \langle I(t) \rangle$, from which a normalized cross-correlation function $G(\tau)$ is evaluated:

$$G(\tau) = \langle \delta I_1(t) \delta I_2(t+\tau) \rangle / \langle \delta I_{1,2}^2 \rangle.$$

$G(\tau)$ peaks at the time τ_{Peak}, which is – in a first approximation – identical to the time of flight of Fc(MeOH)$_2$ molecules from the center of the first transducer to the center of the second one located 102 µm downstream. In Figure 4 cross-correlation functions are shown as a function of the syringe pump flow rate.

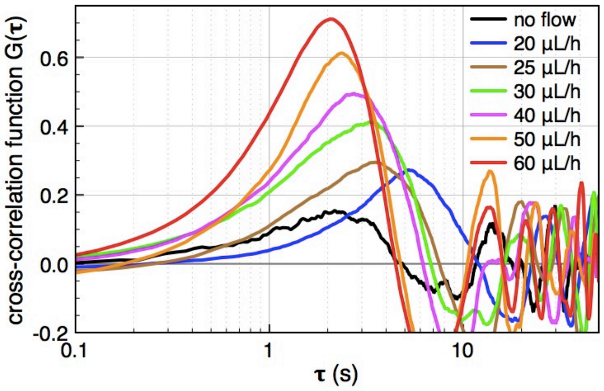

Figure 4: Cross-correlation functions for different syringe pump flow rates determined from current-time traces recorded at both 100 µm long top electrodes of a 202 µm long nanofluidic device.

The curves are defined exclusively by longitudinal advection and diffusion. The increasing influence of diffusion for decreasing flow rates leads to peak broadening and loss of correlation. It prohibits the detection of times of flight longer than approximately 8 s because the number fluctuations decay entirely during the flight.

The liquid flow rate in the nanochannel was determined by multiplying the center-to-center distance Δx of the transducers with the channel cross section and dividing by τ_{Peak}. It is shown in Figure 5 as a function of pump flow (orange diamonds).

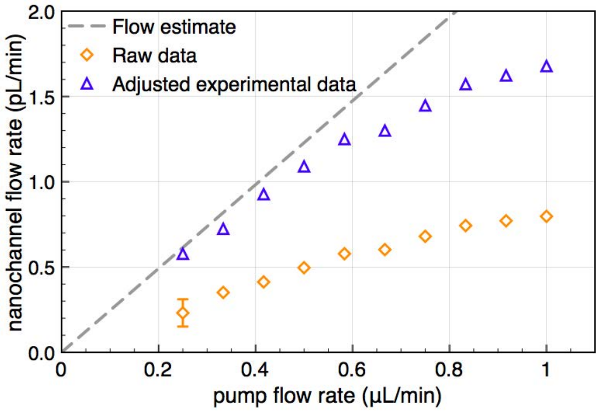

Figure 6: Nanofluidic flow rates as a function of syringe flow. The adjusted experimental data points are corrected for the shift of the peak times as well as for dynamic adsorption. The dashed line's slope corresponds to the ratio of the micro- and nanochannels' resistances of 1/400 000.

However, two effects need to be accounted for for a more accurate flow detection.

First, due to the high surface-to-volume ratio of the nanochannel of $2 \cdot 10^{7}$ m^{-1}, the $\mathrm{Fc(MeOH)_2}$ molecules undergo pronounced dynamic reversible adsorption at the electrodes and nanochannel walls, which slows down their average transport with respect to the fluid. We estimate the relative number of adsorbed molecules $N_{\mathrm{ads}}/N_{\mathrm{tot}}$ by stochastic chrono-amperometry [8]. Its magnitude exhibits considerable scatter but amounts approximately to $N_{\mathrm{ads}}/N_{\mathrm{tot}} = 0.5$, i.e., the molecules are slowed down to 50% of the mean liquid flow velocity.

Secondly, the increasing influence of diffusion shifts the cross-correlation peak time τ_{Peak} away from the actual times of flight for slow flow rates. This shift is determined from the known analytical cross-correlation function [4] and is shown in Figure 6 for the molecular diffusion coefficient $D = 6.7 \cdot 10^{-10}$ m^2/s (green curve) and an adjusted effective $D_{\mathrm{eff}} = 0.5\,D$, which takes into account the reduction of diffusive transport by the dynamic adsorption.

Nanochannel flow rates adjusted for both effects are shown as blue triangles in Figure 6. (The nonlinear decrease in nanochannel flow for higher pump flow rates is caused by PDMS bulging at high pressures [9].) We are able to detect flow rates below 1 pL/min, which is a factor of ten smaller compared to our previous measurements [4].

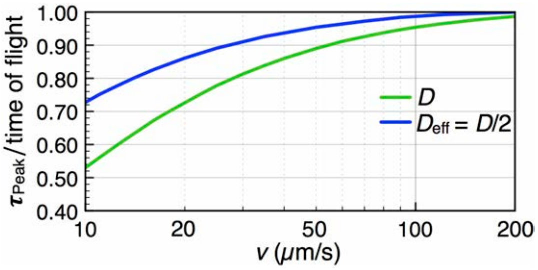

Figure 6: Analytically determined deviation of the cross-correlation function's peak time τ_{Peak} from the time of flight as a function of flow velocity. The blue curve is corrected for an effectively slower diffusion of the molecules due to dynamic adsorption. Experimental flow rates range from 15 µm/s to 50 µm/s.

This increase in sensitivity is achieved for three reason:

1) The nanochannel has a height of 55 nm instead of 130 nm, thereby simply reducing the flow rate for the same average flow velocity.

2) The length of each electrode is increased from 50 µm to 100 µm. The correlation or fluctuation in a longer plug of fluid is measured, thereby directly increasing the signal strength. Also, in a longer plug it takes more time for the fluctuations to decay by diffusion.

3) Since our method relies on the detection of purely stochastic noise, sensitivity is increased by sampling longer traces or employing faster sampling rates. Our previous instrumentation (Keithley 6430 sub-femtoamp source meters) limited the current-time traces to a length of 25 s at a fast 100 s^{-1} acquisition rate. The instrumentation used here allowed extending the measurement period to up to 600 s at the same sampling interval.

Diffusion sets the limit of the slowest resolvable velocity in the nanochannel to $v \geq 2D/\Delta x$. However, for our current setup, the sensitivity is ultimately limited by instrumental drift of the measured current of about 0.5% or 1 nA peak-to-peak, most likely caused by temperature drift. This external noise occurs at time scales of up to several 10's of mHz and can be reduced by high-pass filtering (4th order Butterworth filter) with a $f = 100$ mHz cutoff frequency. The drift essentially prohibits detection of slower flow rates with corresponding times of flight longer than about 10 s. For longer times, the diffusion noise is lost in the instrumental drift, which occurs at the same time scales but exhibits a larger amplitude.

CONCLUSION AND OUTLOOK

We have used all-electrical cross-correlation spectroscopy of mesoscopic number fluctuations to detect record-low liquid flow rates below 1 pL/min in electrochemical nanogap sensors. This is comparable to the sensitivity achieved by the related method of determining the autocorrelation function of a single current-time trace as a function of flow in a 100 µm long and 50 nm high sensor [10].

We emphasize that the determined nanochannel flow rates are subject to error due to uncertainties in channel height, τ_{Peak}, and adsorption. Thus, while detection in the sub-picoliter-per-minute range is possible, we do not claim a precision measurement in this regime.

Our method is the direct electrical analogue to optical fluorescence correlation spectroscopy [11]. Therefore we envision its application not exclusively for flow detection but as a tool to investigate properties of smallest quantities of analyte molecules such as adsorption, concentration or electrochemical reaction kinetics.

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