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NANOCHANNELS WITH TWO PORES IN SERIES FOR SINGLE PARTICLE SENSING AND CHARACTERIZATION

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We report for the first time the fabrication and use of nanochannels with multiple nanopores in series for resistive-pulse sensing and characterization of virus capsids. Having two pores in series permits single particles to be probed multiple times to improve counting statistics and to determine physical properties.

Conventional resistive-pulse sensing has been demonstrated in a variety of applications, including analysis of virus capsids [1], but the technique is generally limited in scope to the counting and sizing of particles [2]. Our device expands the utility of resistive-pulse sensing by allowing physical properties, e.g., electrophoretic mobility, zeta potential, and charge, of single particles to be determined from the transit time between two or more pores in series. In addition, having multiple pores in the device permits a single particle to be probed multiple times and, consequently, improves the precision of the measurement by the square root of the number of measurements made. To fabricate the nanochannels, we combined electron beam lithography with reactive ion etching to confine both the channel width and depth to the nanoscale.

In **Figure 1a**, conventional photolithography and reactive ion etching are used to fabricate two V-shaped microchannels in a silicon wafer. The two microchannels have a small gap (~40 µm) between them across which a nanochannel with one, two, or five pores is fabricated. The double thermal oxidation method is used to create the nanochannels [3]. After developing the e-beam patterns, the nanochannels are etched into the first SiO_2 layer by reactive ion etching with the Si wafer as the etch stop. The channels are then tuned to a final depth of 50 nm by a second thermal oxidation step. A schematic of the nanochannel cross-section is depicted in **Figure 1b**, and a scanning electron microscope image in **Figure 2a** shows a nanochannel with two pores in series that are each 50 nm wide and 50 nm deep.

Our application is to characterize hepatitis B virus (HBV) capsids, which are ~37 nm in diameter. Between each nanopore, the channel is expanded to 1-µm wide to lower the resistance between each pore used for sensing. COMSOL Multiphysics was used to model the behavior of the nanochannel (**Figure 2b**). **Figure 3** shows the variation of current with time and clearly depicts three two-pulse events, where the current decreases each time a HBV capsid transits one of the two pores. At low concentrations, a single capsid enters the series of nanopores and is counted, whereas at higher concentrations, particles are tracked by correlating the frequency of resistive-pulse events. Nanochannels with up to five pores in series are tested. In addition, the pore-to-pore transit time is measured to determine the electrophoretic mobility of single virus capsids (e.g., $\mu_{ep} = 7.2 \times 10^{-6}$ $cm^2V^{-1}s^{-1}$). The impact of the applied potential on the pore-to-pore transit time is demonstrated in **Figure 4**. As expected, the transit time scales linearly with potential and makes determination of mobilities straightforward. Future work will be directed toward monitoring self-assembly of single virus capsids.

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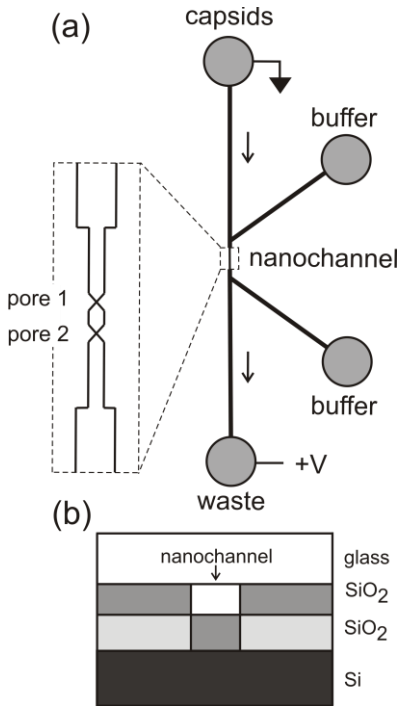

Figure 1. (a) Schematic of two V-shaped microchannels bridged by a nanochannel with two nanopores in series. Inset is expanded view of nanochannel. (b) Cross-section of the device layers fabricated by e-beam lithography, reactive ion etching, and two thermal oxidation steps.

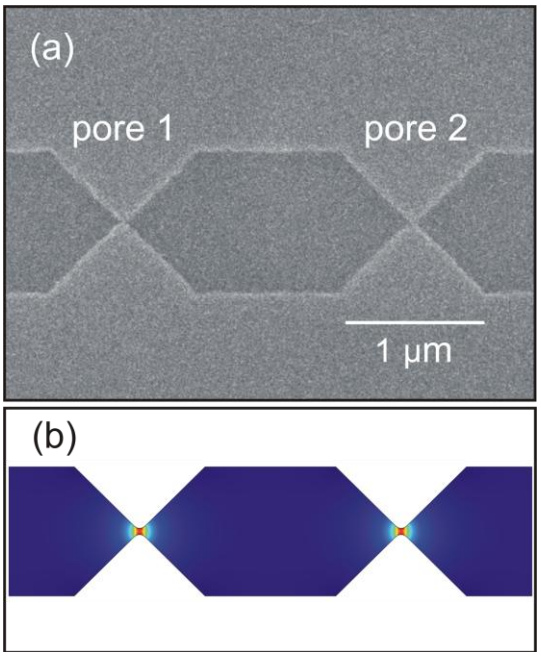

Figure 2. (a) Scanning electron microscope image of a nanochannel with two nanopores in series and (b) a COMSOL simulation of the electric field. The nanochannel is designed to minimize the resistance between the two nanopores.

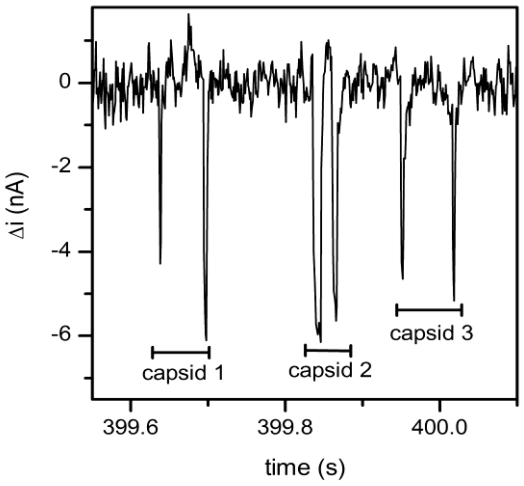

Figure 3. Variation of current with time for hepatitis B virus (HBV) capsids transiting through a nanochannel with two pores in series. Two-pulse events are shown for three HBV capsids.

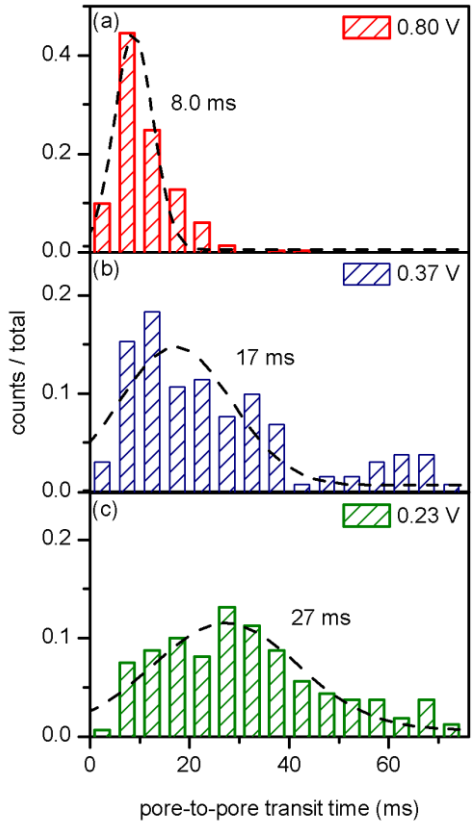

Figure 4. Histograms of the pore-to-pore transit time of HBV capsids through a nanochannel with two pores in series. The potential drops between the two pores are (a) 0.80 V, (b) 0.37 V, and (c) 0.23 V. The fits to the histograms are Gaussian functions. Transit times scale linearly with the applied potential.