

Nanofluidic Charged-Coupled Devices for Controlled DNA Transport and Separation

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Abstract

Controlled molecular transport and separation is of significant importance in various applications. In this work, we presented a novel concept of nanofluidic molecular charge-coupled device (CCD) for controlled DNA transport and separation. By leveraging the unique field-effect coupling in nanofluidic systems, the nanofluidic molecular CCD aims to store charged biomolecules such as DNAs in discrete regions in nanochannels and transfer and separate these biomolecules as a charge packet in a bucket brigade fashion. We developed a quantitative model to capture the impact of nanochannel surface charge, gating voltage and frequency, molecule diffusivity, and gating electrode geometry on the transport and separation efficiency. We studied the synergistic effects of these factors to guide the device design and optimize the DNA transport and separation in a nanofluidic CCD. The findings in this study provided insight into the rational design and implementation of the nanofluidic molecular CCD.

Keywords

Nanofluidics, Charge-coupled device, Molecular transport, Molecular separation

1. Introduction

The ionic and molecular transport phenomena in nanoscale channels are much different from those in larger micrometer- and millimeter-scale structures [1-3]. These differences stem from the unique characteristics of nanoscale structures, such as enhanced surface-to-volume ratios, and comparability of nanochannel size to the Debye length in ionic solutions [4, 5]. Over the past decade, these unique characteristics have been leveraged for developing many different nanofluidic devices such as diode [6-8], bipolar junction transistor (BJT) [9, 10], field-effect transistor (FET) [11-19], and energy harvesting device [20-22]. Among these devices, voltage-gated ionic and molecular transport is the most intriguing [23]. It borrows inspiration from its solid-state counterparts, such as metal oxide semiconductor field-effect transistor (MOSFET). Similar to electrons/holes being modulated in the MOSFET device by an external electric field, the cation/anion (positively/negatively charged molecule) population in the nanochannels can be manipulated in a similar fashion in a nanofluidic field-effect transistor. Active modulation of ions and molecules via field-effect gating in nanofluidic channels is attractive for various applications since it offers a unique opportunity to integrate wet ionics with dry electronics. So far, the direct electric field-charge interaction in nanochannels has been used for regulating the ion [24-28], protein [14], DNA [29], and fluid [30] transport. For instance, utilized an array of electrically gated ~200 nm solid-state pores as nanofluidic transistors to manipulate the capture of DNA molecules [29]. In another study, Liu *et al.* introduced reduced the DNA translocation speed across a nanochannel by modulating the channel surface charge through an externally applied gate bias [18].

The solid-state charge-coupled device (CCD), building with an array of metal-oxide-

semiconductor (MOS) capacitors, is now widely used as the image sensor. The seminal work describing the CCD concept envisioned that the device could be used as memory, a delay line, an imaging device, and a shift register [31]. CCDs store charges in discrete regions in a semiconductor and transfer the charges as a packet in a bucket brigade fashion [31]. Based on the field-effect coupling in nanofluidic devices, Stern *et al.* conceptually proposed a sensitive chemical sensor (chemical ionic CCD) with a theoretically predicted ionic detection limit $<1\times10^{-13}$ M [28]. It was an extension of the single-gate ionic FET to multiple-gate structures. It was expected to have the capability of concentrating ions for sensitive detection. While biomolecules manipulation such as DNAs has been achieved by electric field-charge interaction in nanochannels [18, 29], the conceptual CCD mechanism for a bucket brigade transport of charged biomolecules has not been explored in a nanofluidic device.

In this work, we explored the charge-coupled device (CCD) concept for controlled molecular transport and separation, fundamentally different from the conventional passive gel and capillary methods [32, 33]. We numerically studied the transport and separation efficiency in a three-phase nanofluidic molecular CCD. The effects of the nanochannel surface charge, gating voltage and clocking frequency, and molecular diffusion coefficient on the transport efficiency were elucidated. We also explored the feasibility of the nanofluidic molecular CCD for separating the DNA molecules based on their different diffusivities. We believe the proposed nanofluidic molecular CCD concept would open a new avenue for nanofluidic device research and offer a promising approach towards actively-controlled biomolecule transport and separation.

2. Device principle and modeling

2.1. Nanofluidic molecular CCD principles

The schematic layout for the nanofluidic molecular CCD and its enlarged nanofluidic channel with multiple gate structures is illustrated in **Figure 1a**. It consists of a long nanochannel in between two chambers: *cis* (reservoir chamber) and *trans* (outlet chamber). Two electrodes are placed in the chambers for applying the driving voltage V_{tc} . An array of gate electrodes with a fixed pitch size (L_G) is placed above the nanochannel with a three-phased biasing design (every three gating electrodes form a set). An output control gate is adopted immediately before the *trans* chamber to prevent the molecules from flowing back into the nanochannel. The analyte molecules are initially added into the *cis* chamber. **Figure 1b** shows the three-phase clocking scheme for gate electrodes (G1-G3) and the control gate (CG). Each clocking cycle can be divided into six distinct periods (T1-T6). **Figure 1c** illustrates the distribution of the DNA molecules at each of these different time spots. At the time of T1, a positive bias V_G is applied to each set's first gate electrode, which forms a packet of negatively charged DNAs under that electrode. By positively biasing the consecutive electrodes, DNA packets can be moved through the nanochannel sequentially (T2-T5). The molecular flux through the nanochannel is the outcome of diffusion and drift forces. At the time of T6, a negative voltage ($-V_G$) is applied to the control gate (CG) to prevent the molecules' backflow into the nanochannel. This process is periodically repeated. In each cycle, a portion of the molecules in the *cis* chamber will be transferred to the *trans* outlet. This working principle is very much like that in the solid-state CCD [31].

2.2. Device modeling

Diffusion and electrophoresis are the two mechanisms that determine the molecular translocation through the nanofluidic molecular CCD. To capture the DNA translocation, we need to compute these two motions. The Poisson-Nernst-Planck equations were used to capture the time-varying electric field, ionic, and molecules concentration as follows:

$$\nabla^2 V(t) = -\rho_e(t)/\varepsilon_0 \varepsilon_r \quad (1)$$

$$\frac{\partial c_i(t)}{\partial t} + \nabla \cdot J_i(t) = 0 \quad (2)$$

in which $V(t)$ is the electric potential, and $\rho_e(t) = eN_A(\sum_i z_i c_i(t))$ is the charge density of mobile ions. ε_0 , and ε_r are the vacuum and relative permittivity, respectively. Note that the molecules' charge density was not considered for calculating the potential distribution since their concentration (\sim nM) is often negligible compared to that of ions (\sim mM). In addition, the intermolecular interaction was not taken into consideration. The time-varying molecular and ionic flux density $J_i(t)$ is given by:

$$J_i(t) = -D_i \nabla c_i(t) - c_i(t)(z_i \mu_i \nabla V(t)) \quad (3)$$

where D_i , μ_i z_i and c_i are the diffusivity, mobility, valance, and concentration of each species (ions and molecules). Electrophoretic mobility of DNAs after exceeding a certain length (\sim 100 bp) is identical. In this study, we did not consider shorter DNAs and fixed the electrophoretic mobility of the molecules as $4 \times 10^{-8} \text{ m}^2/(\text{V.s})$.

The coupled mathematical model was numerically solved by COMSOL Multiphysics. A two-dimensional computational domain was developed based on the nanofluidic molecular CCD

concept, and suitable boundary conditions were applied to capture the transient operation of the nanofluidic molecular CCD (**Supplementary Figure S1** and **Table S1**). In addition, **supplementary note S1** presents the model details in terms of grid size and quality and convergence criteria.

3. Results and discussion

3.1. Controlled DNA transport in nanofluidic CCD

To illustrate the transient transport and the distribution of the molecules in each time segment, we simulated the transfer of DNAs with a typical diffusivity [34] of $2 \times 10^{-12} \text{ m}^2/\text{s}$ through one set of nanofluidic molecular CCD for 10 cycles. **Figure 1d** shows the distribution of the molecules across the channel at different cycles. At each time spot, the number of molecules across the channel was normalized by the total number of starting molecules (n/n_{total}). At the beginning (0T), all the molecules are at the *cis* ($n_{cis}/n_{total}=1$). As the gating voltage cycles, the movement of DNA packets from the left (*cis*) to the right (*trans*) can be clearly observed. A discrete portion of the molecules was transferred to the *trans* chamber at the end of each cycle when the control gate switched from $-V_G$ to 0 V. As the cycling continues, the transferred DNA molecules to the *trans* chamber were decreased. This is due to the fact that the difference between the *cis* and *trans* molecular concentration is reducing as the cycles continue, and consequently, the diffusion term of the molecular flux decreases. After about 10 cycles in this one set CCD, DNAs in the *cis* were almost entirely transferred to the *trans*.

3.2. Impact of surface charge on the transfer efficiency

It is well known that the nanochannel surface charges will significantly affect the electrokinetic transport of ions, fluids, and molecules in nanofluidic devices due to the effect of the electrical double layer (EDL)[35, 36]. To study the effect of surface charge on the transport process in a CCD, we defined the transfer efficiency as the number of transported molecules to the *trans* as a percentage of the total number of molecules ($\eta = n_{trans}/n_{total}$). We studied the transfer efficiency of DNAs with a fixed diffusivity ($2 \times 10^{-12} \text{ m}^2/\text{s}$) and gating voltage (1.2 V) for 100 cycles at different surface charges. In this study, we examined the device with one set of gates (three gates and one control gate). The gating frequency was set at 0.1 Hz, and a lateral driving voltage V_{tc} of 50 mV was applied between *cis* and *trans*. **Figure 2a** shows the transfer efficiency as the function of time. We observed that the transfer efficiency was decreased as we increase the negative surface charge magnitude for fixed operation time. This stems from the fact that the induced electric field by the negative surface charge and gating electrodes have opposite directions. The more negative surface charge we have, the more opposing forces will be applied to the negatively charged DNA molecules. The nanofluidic CCD will thus have less transfer efficiency. A neutral nanochannel surface charge is preferred towards higher transfer efficiency [37-39]. It should be noted that the transfer efficiency was not continuously increased as the operation time went by. This happened because only a discrete portion of the molecules was transferred to the trans chamber at the end of each cycle.

3.3. Impact of gating voltage magnitude on the transfer efficiency

The gating voltage not only alters the transverse electric field distribution in the nanochannel

due to the double layer effect [40] but also impacts the lateral electric field and thus the electrophoretic force. Consequently, varying the gating voltage magnitude would have an impact on the molecular flux and transfer efficiency.

To capture the effect of gating voltage magnitude, we studied the transfer efficiency of DNAs with a fixed diffusivity ($2 \times 10^{-12} \text{ m}^2/\text{s}$) at different gating voltages for 100 cycles. In all these cases, we selected the gating frequency at 0.1 Hz, the surface charge of the nanochannel at -2 mC/m^2 , and lateral driving voltage V_{tc} as 50 mV. **Figure 2b** shows the transfer efficiency as the function of time. The transfer efficiency improved with increasing the gating voltages. This is not surprising since a larger gating voltage would create a higher lateral electric field, ∇V , and thus a higher electrophoretic flux ($\mu c \nabla V$).

3.4. Impact of clocking frequency and molecular diffusivity on the transfer efficiency

While gating voltage magnitude impacts the electrophoretic force's magnitude, gate clocking frequency would affect the transient dynamics of this force. To study the effect of the gating frequency on the transfer dynamics, we studied the transfer efficiency of DNAs with a fixed diffusivity ($3.5 \times 10^{-12} \text{ m}^2/\text{s}$) and gating voltage (1.3 V) at different frequencies. **Figure 3a** shows the transfer efficiency as a function of time under various gating frequency scenarios. The transfer efficiency was improved when the frequency was increased from 0.1 to 1 Hz. However, increasing the frequency from 1 to 10 Hz reduced the transfer efficiency. This could be understood by the comparison between the clocking period ($\sim 1/f$) and the time for a given molecule to diffuse to the adjacent electrode ($\sim L_G^2/D$). If the clocking occurs too fast ($1/f \ll L_G^2/D$), some of the molecules in each packet will be left behind and later localized in a trailing packet, reducing the transfer

efficiency.

Since the impact of the molecule diffusivity on the transfer dynamic depends on the gating frequency, we set out to study the effect of the molecule diffusivity on the transfer efficiency at different clocking frequencies. We studied the transfer efficiency of molecules with different diffusivities (2×10^{-12} to 4×10^{-12} m²/s) and a fixed gating voltage of 1.3 V at various frequencies. **Figure 3b** illustrates the transfer efficiency as a function of clocking frequency at different diffusivities. We observed two features. One is that the transfer efficiency was always improved by increasing the molecule diffusivity (D) at a fixed clocking frequency. This is not surprising since increasing the molecule diffusivity would increase the diffusion term of the molecular flux ($D\nabla c$). The other feature was that for a fixed molecular diffusivity, the transfer efficiency went up with increasing the frequency until reaching a peak, after which the transfer efficiency reduced when further increasing the frequency. We defined the frequency at which the transfer efficiency was maximized as optimal frequency. **Figure 3c** presents the optimal frequencies as a function of DNA diffusivities. It is clear that the optimized clocking frequency goes up when increasing the DNA diffusivities. This is due to the fact that the maximal transfer efficiency will happen when the clocking period matches the time required for the molecules to diffuse to the next electrode ($1/f \sim L_G^2/D$).

3.5. Use of nanofluidic CCD for diffusivity-based separation

Since the transfer efficiency strongly depends on the molecule diffusivities, nanofluidic CCD can be implemented for molecular separation based on their diffusivities. **Figure 4a** illustrates the schematic of nanofluidic CCD utilization for separating a mixed DNA sample consisting of two

subpopulations A and B . Assuming population B has a higher diffusivity than A , more molecules B would be transferred to the *trans* outlet after operating the nanofluidic CCD for a particular time. As a result, we would be able to separate two subpopulations in a nanofluidic CCD. To quantify the separation efficiency, we defined the relative abundance (RA) of population A and B as $\frac{n_{A,trans}/n_{B,trans}}{n_{A,total}/n_{B,total}}$, in which $n_{A,total}$ and $n_{B,total}$ are the total number of molecules A and B respectively, $n_{A,trans}$ and $n_{B,trans}$ are the number of molecules A and B in the *trans* outlet after a certain operation time.

{Figure 4b} shows the relative abundance of population A and B at different combinations of diffusivities after 50 s of operation. A fixed gating voltage of 1.2 V with a frequency of 0.1 Hz was applied, and $V_{tc} = 50$ mV was considered across the channel. Not surprisingly, for cases where the diffusivities of the two populations are similar (the diagonal), we were not able to separate the samples ($RA = 1$). For cases where diffusivity of population B was larger than sample A , RA was larger than 1 which means we can separate population B from population A . At a constant diffusivity for population A , as we increased the diffusivity of population B , higher RA was achieved. In an extreme case, where diffusivities of the population A and B were 1×10^{-12} and 4×10^{-12} m²/s, respectively, population B in the *trans* was almost 1000 times more than population A in the *trans*. These results show that the nanofluidic molecular CCD can sensitively separate DNA molecules based on their diffusivities.

3.6. Impact of gating set numbers on separation performance

To evaluate the effect of the number of gating sets on the separation performance, we studied the separation of two DNA subpopulations with different diffusivities (2×10^{-12} and 3×10^{-12} m²/s)

through the nanofluidic CCD with a different number of sets (1 to 6). The gating voltage was fixed at 1.2 V with a frequency of 0.1 Hz. Since the nanochannel length increases as we increase the number of sets, we scaled up the voltage across the channel to make the transverse electric field constant. **Figure 5a** presents the transfer efficiencies of the two populations through the nanofluidic molecular CCD with a different number of sets over 1000s (100 cycles). As shown, increasing the number of sets would decrease the transfer efficiency in a fixed time frame. This is not surprising since as the number of sets is increased, the channel length would be increased, and consequently, more time is required to transfer the molecules to the *trans*.

Figure 5b presents the relative abundance (RA) of the two populations for the different numbers of sets. For all cases, after an initial increase, RA declines over time. Eventually, after two populations were completely transferred to the *trans*, RA will become 1. However, as we increase the number of sets, the rate of decline is lower, which means the separation becomes less operation time-sensitive. This is because the transfer of the molecules through the nanochannel occurs at a lower rate as we increase the number of sets. For instance, in the case of 1 set, after 1000 s both populations of the molecules were transferred to the *trans*, and consequently, the relative abundance became 1 (no separation anymore). These results suggest that while increasing the number of sets would decrease the transfer efficiency; it would improve the separation stability (less operation time-sensitive).

4. Conclusions

In summary, we presented the nanofluidic charged-coupled device and evaluated its performance towards controlled DNA transport and separation. This study aims to provide useful

and practical insight to establish the design parameters for the nanofluidic charged-coupled devices. We developed a device model to explore the effect of surface charge, gating voltage and frequency, molecules diffusivity, and the number of gate sets on the transport and separation efficiency. The result of the surface charge effect on the transfer efficiency revealed that increasing the negative surface charge magnitude would decline the transfer efficiency. We found that increasing the gating voltage and diffusivity of the molecules enhances the transfer efficiency of the nanofluidic CCD. We also found that the optimized transfer efficiency occurs when the clocking period matches the time required for the molecules to diffuse to the next electrode ($1/f \sim L_G^2/D$). We demonstrated that nanofluidic CCD could separate two populations based on their diffusivities. Although the results presented in this work were computed using DNA electrophoretic mobility and diffusivity, the principle could be well extended to other charged biomolecules such as RNAs and proteins. In this study, we only consider one dimension of gates in our simulations. However, a 2D array of gates could be the next step for the nanofluidic CCD design, giving us more options for molecule manipulation. While the fabrication of a prototype device and experimental realization is crucial for exploring the nanofluidic CCD, we anticipate these findings would provide insight into the future design of molecular CCD and biomolecular transport and separation.

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Figures and Captions

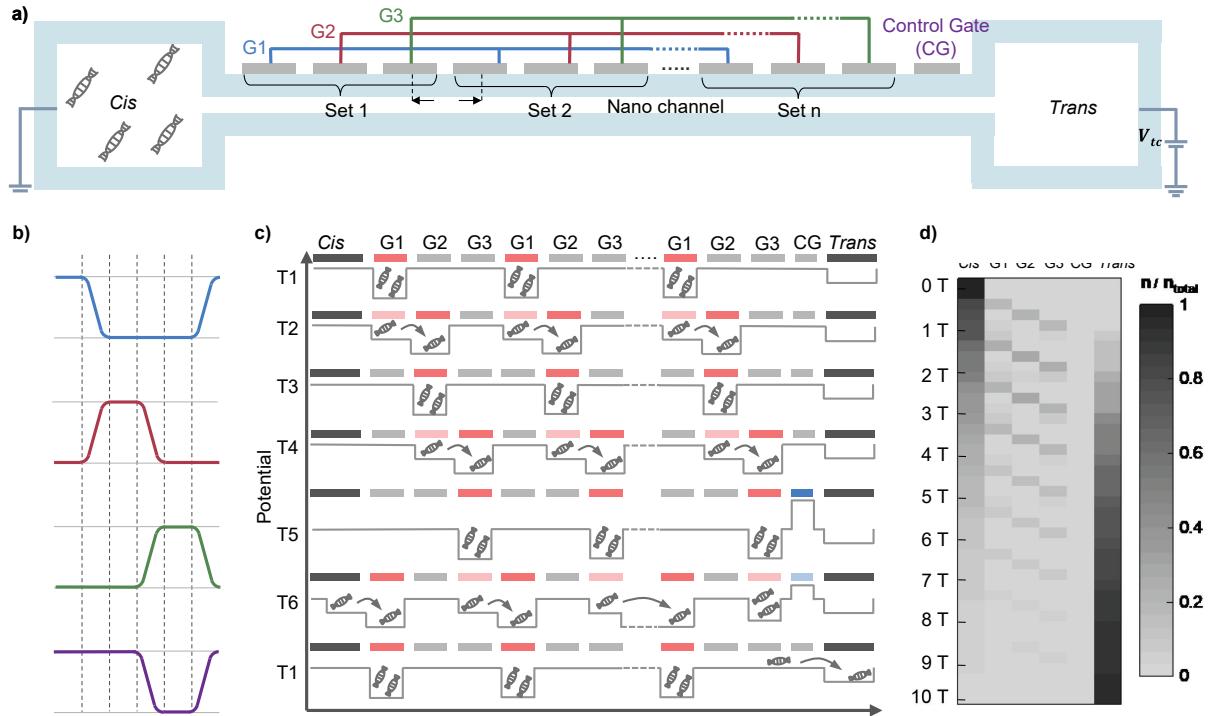


Figure 1. Overview of the nanofluidic charge-coupled device (CCD). **a)** Schematic layout for nanofluidic CCD and its enlarged nanofluidic channel with multiple gate structures. **b)** A three-phase clocking scheme for gate electrodes. T1 to T6 are different time spots. **c)** Illustrative distribution of DNAs under a clocking gate voltage at different time spots (T1-T6). **d)** Simulation results of DNA transport through the nanofluidic molecular CCD with one set of gates. The diffusivity of the DNA is $2 \times 10^{-12} \text{ m}^2/\text{s}$. A 1.5 V voltage with a frequency of 0.1 Hz was applied to the gates. The gate electrode pitch size is 4.5 μm . The surface charge of the nanochannel is -2 mC/m². V_{tc} of 50 mV was applied across the channel.

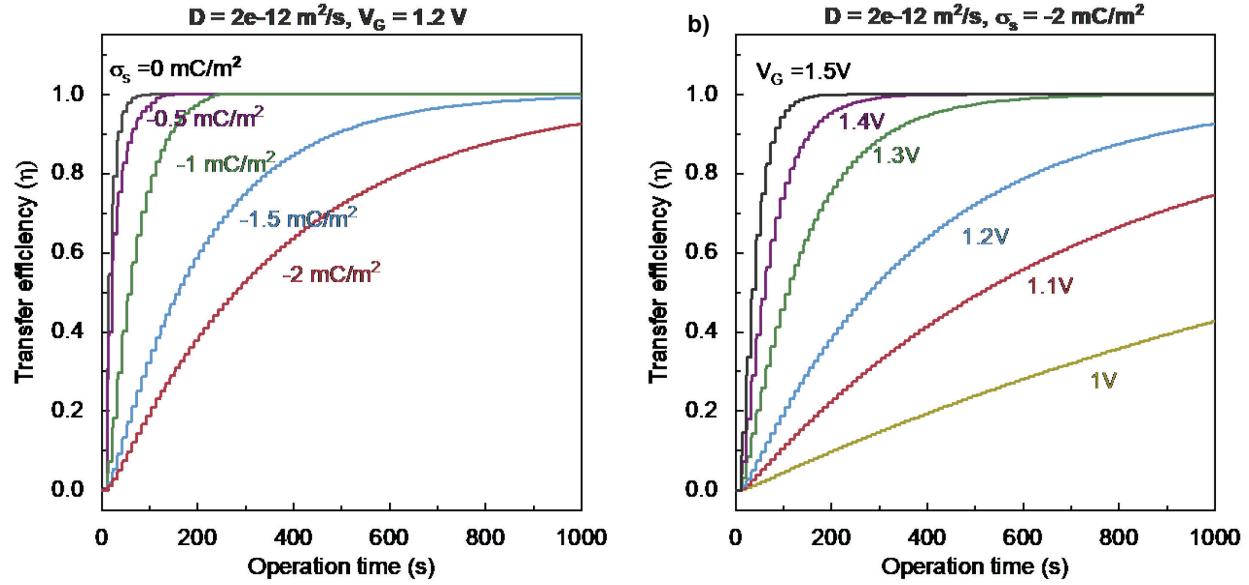


Figure 2. a) Transfer efficiency of DNA with diffusivity of $2 \times 10^{-12} \text{ m}^2/\text{s}$ at different surface charges for 1000 s. A gating voltage of 1.2 V at the frequency of 0.1 Hz was applied, and a lateral driving voltage V_{tc} of 50 mV was set between *cis* and *trans*. In all cases, we set up the simulation in one set of gates (three gates and one control gate). **b)** Transfer efficiency of DNA with diffusivity of $2 \times 10^{-12} \text{ m}^2/\text{s}$ at different gating voltages for 1000 s. The frequency was fixed at 0.1 Hz, and $V_{tc} = 50 \text{ mV}$ was applied across the channel. In all cases, the surface charge of -2 mC/m^2 was used at nanochannel walls.

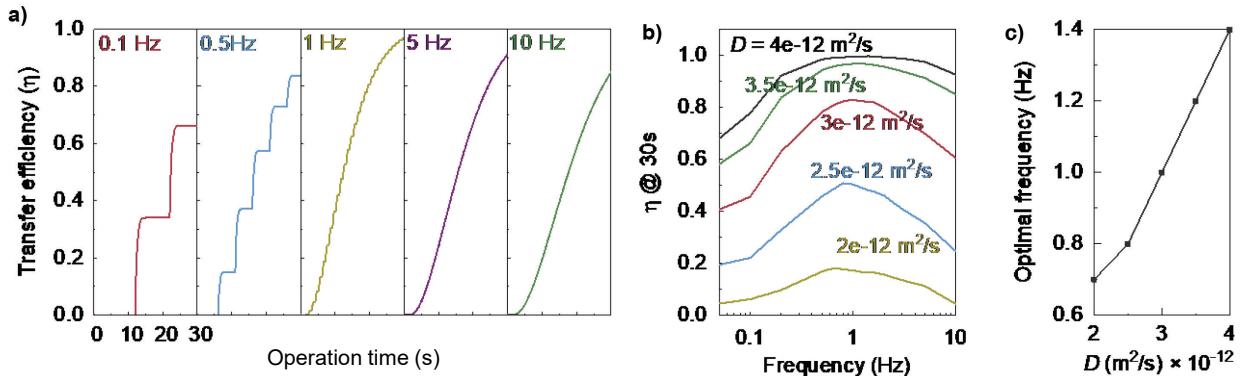


Figure 3. **a)** Transfer efficiencies versus time at different frequencies (0.1, 0.2, 1, 5, 10 Hz). In all cases, the diffusivity and voltage were fixed at $3.5 \times 10^{-12} \text{ m}^2/\text{s}$ and 1.3 V, respectively. $V_{tc} = 50 \text{ mV}$ was applied across the channel to reduce the effect of the surface charge. **b)** Transfer efficiency of DNA with distinct diffusivities at a fixed gating voltage (1.3 V), and different frequencies. In all cases, the surface charge was fixed at -2 mC/m^2 , and $V_{tc} = 50 \text{ mV}$ was applied across the channel. **c)** Optimal frequency as a function of molecular diffusivity.

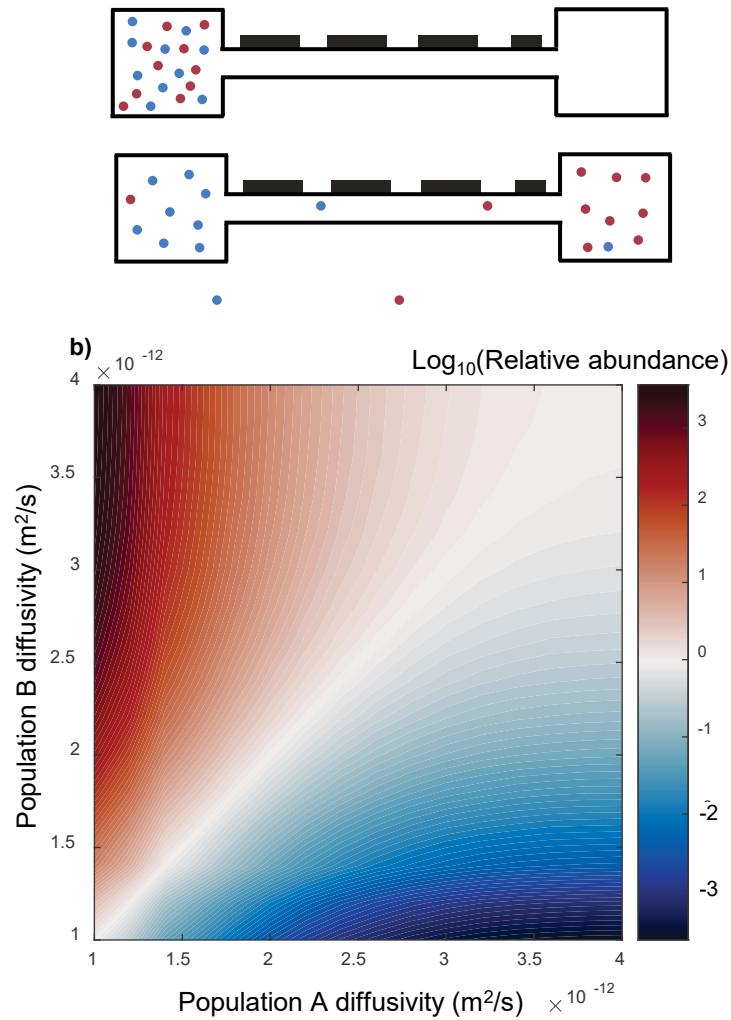


Figure 4. **a)** Schematic of the nanofluidic CCD separation, where two samples can be separated based on their diffusivities. **b)** The relative abundance of two populations based on their diffusivities (1×10^{-12} to $4 \times 10^{-12} \text{ m}^2/\text{s}$) after 50 s. In all cases, a fixed gating voltage of 1.2 V with a frequency of 0.1 Hz was applied, and $V_{tc} = 50 \text{ mV}$ was considered across the channel.

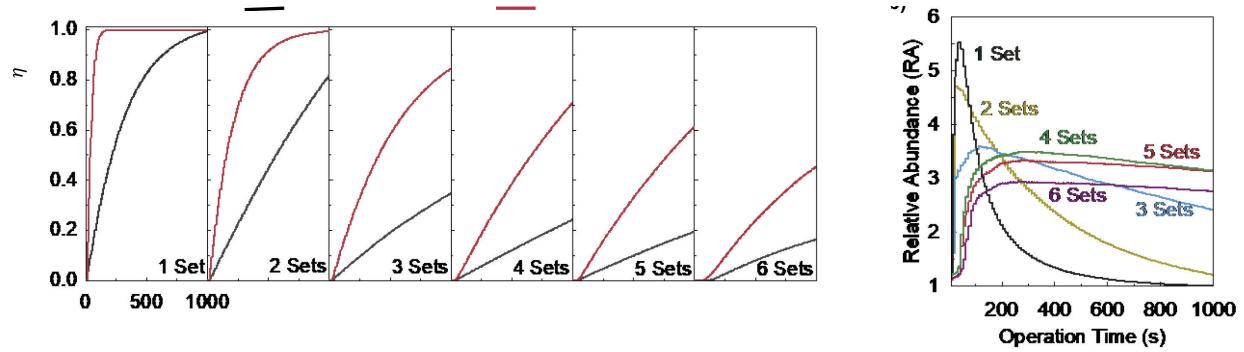


Figure 5. **a)** Transfer efficiencies of the two populations with different diffusivities (2×10^{-12} and 3×10^{-12} m²/s) through the nanofluidic molecular CCD with a different number of sets (1 to 6) over 1000s (100 cycles). In all cases, we applied a voltage of 1.2 V with a frequency of 0.1 Hz. **b)** The relative abundance of the two populations through the nanofluidic molecular CCD with a different number of sets over 1000s (100 cycles). In all cases, we applied a voltage of 1.2 V with a frequency of 0.1 Hz.

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