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# UNRAVELING THE PHYSICS OF NANOFUIDIC PHENOMENA AT THE SINGLE-MOLECULE LEVEL

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## Abstract

Despite groundbreaking potential in a broad application space, several nanofluidic phenomena remain poorly understood. Toward advancing the understanding of fluid behavior under nanoscale confinement, we developed a novel, ideal platform for fundamental molecular transport studies, in which the fluidic channel is a single carbon nanotube (CNT). CNTs offer the advantage of simple chemistry and structure, which can be synthetically tuned with nanometer precision and accurately modeled. With combined experimental and computational approaches, we demonstrated that CNT pores with 1-5 nm diameters conduct giant ionic currents that follow an unusual sub-linear electrolyte concentration dependence. The large magnitude of the ionic conductance appears to originate from a strong electroosmotic flow in smooth CNT pores. First-principle simulations suggest that electroosmotic flow arises from localized negative polarization charges on carbon atoms near a potassium ( $K^+$ ) ion and from the strong cation-graphitic wall interactions, which drive  $K^+$  ions much closer to the wall than chlorides ( $Cl^-$ ). Single-molecule translocation studies reveal that charged molecules may be distinguished from neutral species on the basis of the sign of the transient current change during their passage through the nanopore. Together with shedding light on a few controversial questions in the CNT nanofluidics area, these results may benefit LLNL's Security Mission by providing the foundation for the development of advanced single-molecule detection system for bio/chem/explosive analytes. In addition, these experimental and computational platforms can be applied to advance fundamental knowledge in other fields, from energy storage and membrane separation to superfluid physics.

## Background and Research Objectives

When fluids are confined in nanoscale structures approaching the fluid physical length scale, novel physical phenomena are observed, many of which remain poorly understood. Advancing their understanding is critical for their future exploitation in high-performance devices that could provide a groundbreaking step forward in application areas such as ultrasensitive detection systems (S. Howorka and Z. Siwy 2009), nanoporous energy storage/harvesting platforms (H. Daiguji et al. 2004, J. Chmiola et al. 2006, F. H. J. van der Heyden et al. 2007), and separation systems (F. Fornasiero et al. 2008). Methods that allow a direct investigation of ions and single molecule motion in well-defined nanopores and their direct comparison with simulation predictions are critical for a rapid development of the field. Nanopore analytics enables a label-free, direct investigation of the passage of ions and of a single-molecule through nanopores.

However, previous approaches based on biological and solid-state nanopores failed to provide the required pore size control at the nanoscale, simple chemistry and geometry, robustness, and ability of local chemical functionalization in the same fluidic platform (S. Howorka and Z. Siwy 2009). As revealed by MD simulations, ionic transport through nanopores is sensitive even to minute changes in the structure of the same chemical composition (E. R. Cruz-Chu et al. 2009).

In this proposal, we aim to advance the fundamental understanding of transport phenomena in confined nano-scale geometries by a synergistic experimental and theoretical investigation of ionic and molecular transport in an ideal, model nanopore. To this goal, we developed a novel nanofluidic platform that is an advanced Coulter counter with a single, 1-5nm wide CNT as the flow-channel. We chose CNTs as nanopores because of their superior properties for nanopore analytics (S. Howorka and Z. Siwy 2009) and their simple structure known with atomic precision, which enables accurate modeling.

At the same time, we aim to synergistically employ a multiscale computational framework (first principle + classical molecular dynamics + continuum) for modeling transport through a CNT and to provide unique insights into microscopic mechanisms governing nanoscale transport. Classical molecular dynamics simulations (MD) have been used in the past to predict a number of surprising features for fluid transport in narrow CNTs, such as ultrafast fluid flow (G. Hummer et al. 2001, A. I. Skoulidas et al. 2002, C. Dellago et al. 2003), transport rates independent of CNT length (A. Kalra et al. 2003), spontaneous water filling (G. Hummer et al. 2001) and DNA insertion (H. J. Gao et al. 2003). However, only a few of these interesting predictions have been validated experimentally due to the lack of adequate nanofluidic platforms. Moreover, most of the existing MD studies of fluid flow in CNTs have relied on rather simple water models that are fit to reproduce known bulk liquid properties. As such, their applicability to complex interfacial systems characteristic of a fluid-filled CNT is questionable (G. Cicero et al. 2008, P. Huang et al. 2009). Because we adopt here a multiscale approach, potentials used in our simulations will provide an accurate description of fluid properties in confined nanoscale structures.

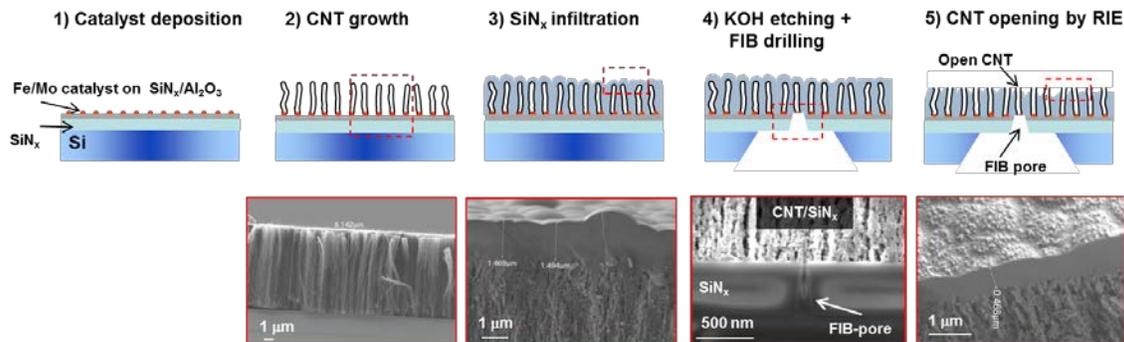
Together with the development of the experimental nanofluidic platform, specific objectives of this work include: 1) quantifying the magnitude of electric-field-driven ionic transport in CNTs, identifying primary charge carriers, and understanding which transport mode dictates the giant ion conductance claimed to be sustained by these nanochannels; 2) demonstrating detection of nanosized molecules; 3) unraveling the relationship between chemical and physical properties of the analytes and their molecular transport under confinement. Objectives 1 and 2 were demonstrated and we made substantial progress on objective 3 by addressing an open question in the literature on the sign of the current modulation during single molecule translocation.

# Scientific Approach and Accomplishments

## Methods

### a) Experiments

The solid-state nanofluidic devices were fabricated following the steps in Figure 1. We first produced 3-10  $\mu\text{m}$  vertically aligned CNT forests by chemical vapor deposition and then infiltrated the CNTs with a low-pressure silicon-nitride ( $\text{SiN}_x$ ) deposition. After forming a window on the back side of silicon chip, focused ion beam (FIB) nanomachining was used to open a single CNT for fluid transport on one surface of the aligned-CNT/ $\text{SiN}_x$  thin film, whereas all CNTs were opened using reactive ion etching (RIE) on the other surface. Measurements of ion current with voltage and in time were performed in KCl solutions with two Ag/AgCl electrodes using the Axopatch 200B and 1550 Digidata system (Molecular Devices, Inc.). Data analysis was performed with Clampfit 10.4 and Origin 9.0.



**Figure 1.** Microfabrication steps of the nanofluidic devices: 1) Deposition of  $\sim 30$  nm  $\text{Al}_2\text{O}_3$  barrier layer and of  $5.5 \text{ \AA}$  Fe/ $0.5 \text{ \AA}$  Mo catalyst layer onto Si wafer; 2) Growth of vertically aligned CNTs by chemical vapor deposition; 3) Conformal LPCVD  $\text{SiN}_x$  deposition to fill the gaps between CNTs; 4) KOH etching to form 250-nm thick  $\text{SiN}_x$  window, and FIB sculpting of a  $>20$  nm hole on the  $\text{SiN}_x/\text{Al}_2\text{O}_3$  layer to open one (or a few) CNT tips on the patterned side of the membrane; 5) Removal of excess  $\text{SiN}_x$  and opening of all CNTs by RIE on the opposite side of the membrane. SEM images below steps 2-5 show cross-sections of the device region enclosed by the dashed red square at that specific fabrication step: 2) Vertically-aligned CNT array; 3)  $\text{SiN}_x$ /CNT composite with a  $\text{SiN}_x$  overlayer; 4) Nanopore drilled by FIB; 5) Etched top-surface of the  $\text{SiN}_x$ /CNT composite showing exposed CNT tips.

### b) Multiscale simulations

First-principles and classical MD simulations were carried out to investigate the structure of KCl solution under confinement. The simulation set-up consists of 1.0 M concentration salt solution with the bulk water density inside a 1.4 nm diameter (19,0) CNT. Inter-atomic forces were derived from density functional theory (DFT) in first-principles simulations, while non-polarizable and polarizable empirical force fields were employed in classical simulations. To understand the effect of the interaction between  $\text{K}^+$  and carbon diffusive pi orbitals on the structure of the solution, we also considered polarizable force fields with and without the inclusion of cation-pi interaction.

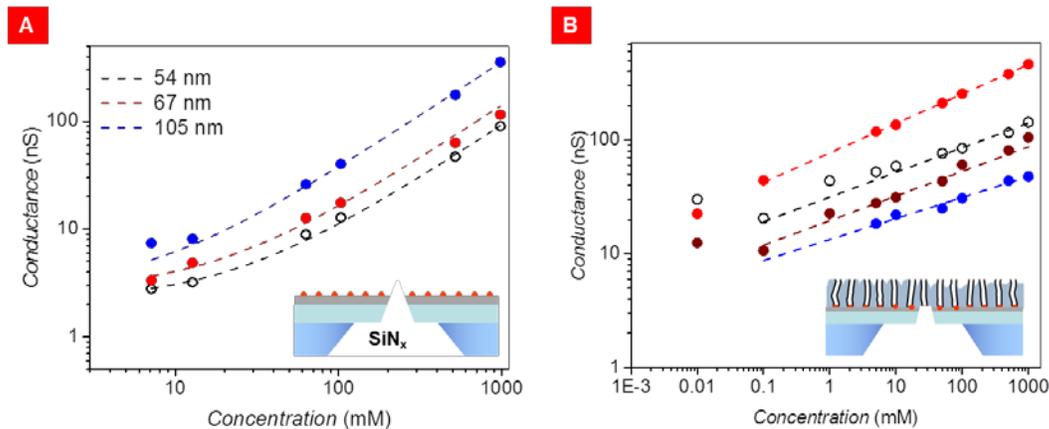
Ionic conductances in nanopore structures mimicking the actual nanofluidic devices

were calculated by numerically solving coupled Poisson equation, Nernst-Planck equation, and Navier-Stokes equations using COMSOL Multiphysics 4.3 package, with and without slip boundary conditions at the CNT inner wall.

## Results

We first demonstrated the successful fabrication of the nanofluidic device by providing evidences of transport through a single CNT-pore. These include a) the recording of a significant (nA range) KCl ionic current only after the last pore-opening step, and b) the detection of transient current blockades with a single current level after introducing a small particle with size comparable to the CNT diameter (Figure 5).

Once we validated the nanofluidic platform, we addressed open questions about ionic conductance in CNTs. Several MD studies have been published about electric-field driven ionic transport through a single CNT, but only a few initial experimental investigations with conflicting results have been reported (S. Guo et al. 2015). While Strano et al. (C. Y. Lee et al. 2010, W. Choi et al. 2013) suggests stochastic pore blocking by the cations ( $K^+$ ,  $Na^+$ ) in solution and  $H^+/OH^-$  as primary charge carriers, other reports did not observe current blockades for KCl solutions (H. T. Liu et al. 2010, J. Geng et al. 2014). Moreover, Lindsay et al. indicated a possibility of a strongly enhanced KCl transport by electroosmosis (H. T. Liu et al. 2010, P. Pang et al. 2011), whereas others measured conductivities in CNT similar to bulk values (J. Geng et al. 2014). To unravel the physics behind electric-field-driven ion transport in CNTs, we thoroughly investigated the current-voltage characteristics of the CNT channel as a function of the solution concentration, pH, and field strength.

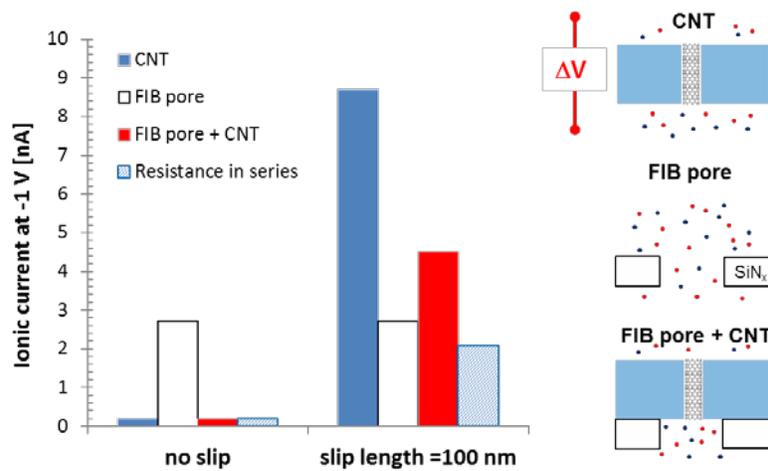


**Figure 2.** Ionic conductance dependence on concentration. A) Reference devices with a single nanopore nanomachined with FIB in the  $SiN_x$ /alumina layer (no CNTs) display a classical conductance behavior: conductance is linearly increasing with electrolyte concentration,  $C$ , at high molarity and reaches a plateau at low concentrations. B) CNT nanochannels show anomalous ionic conductance, with a magnitude exceeding predictions based on pore size and bulk conductivity by orders of magnitude and with a sub-linear power-law dependence on electrolyte concentration at all molarities ( $G \sim C^n$ ,  $n=0.18-0.26$ ).

These tests revealed that (S. Guo et al. 2015):

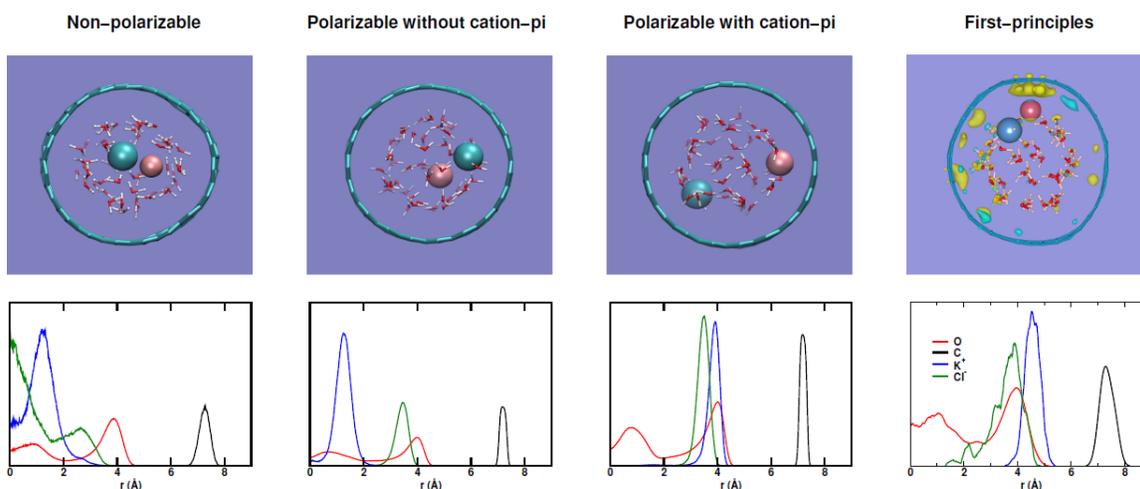
- Ionic conductance ( $G$ ) is weakly dependent on solution pH, thus excluding protons as primary charge carriers;
- $G$  in CNT pores is orders of magnitude larger than expected on the basis of the pore dimensions and bulk conductivities (Figure 2);
- This giant conductance follows an unusual, sub-linear power-law dependence on KCl concentration (Figure 2.B) with an exponent in the range 0.18-0.26, in agreement with the finding from Lindsay's group (H. T. Liu et al. 2010, P. Pang et al. 2011);
- Reference devices without CNTs (i.e., a FIB pore in a silicon nitride film) show the expected magnitude and concentration dependence of KCl conductivity.

Published work attributed the enormous KCl conductance to large electroosmotic flow, which stems from the negative charge and the large slip at the CNT walls (P. Pang et al. 2011). However, the origin of this charge remains unclear and no direct evidence of electro-osmotic flow was given. Comparison of our data in Figure 2 reveals that devices with CNTs in series with the FIB pore ( $d \sim 54$  nm) have conductance comparable or even larger than the reference devices with only a FIB pore with the same diameter, which is in apparent contradiction with the resistance-in-series model prediction. This unexpected result can be explained with a large electroosmotic flow in CNTs and CNT-containing platforms. Electroosmotic enhancement of ionic transport is negligible in the reference devices lacking nanotubes and is not accounted for by the traditional resistance-in-series models. Thus, our experiments provide strong evidence that electroosmotic flow is dominant in CNTs. To further validate this claim, we performed continuum calculation and quantified ionic conductance for a single FIB pore, a charged 4-nm CNT with and without slip, and a FIB pore + charged CNT with and without slip. Results confirmed that, for sufficiently large slip lengths and with a charged CNT wall, the system combining both FIB and CNT pores can sustain currents that are comparable or larger than those of the reference FIB pore (Figure 3).



**Figure 3.** Ionic current at  $V = -1$  V for a) a charged ( $1 \text{ e/nm}^2$ ), 4-nm diameter CNT pore with and without slip; b) a neutral, 30-nm diameter FIB pore drilled in a 280-nm  $\text{SiN}_x$  membrane; c) the FIB pore and CNT pore of a-b in series; and d) predicted by the resistance-in-series model.

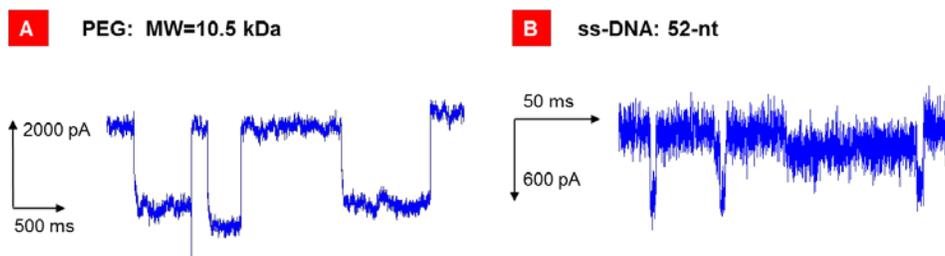
Clues on the mechanistic origin of this electro-osmotic flow were obtained with first principle simulations. The radial distribution function of KCl solution in a CNT (Figure 4) shows the propensity of both ions to reside near the interface with  $K^+$  being noticeably closer to the CNT wall. The radial density distribution of  $K^+$  is rather narrow and indicates strong interaction between  $K^+$  and the CNT wall, as well as the tendency of the ion to be desolvated. In addition, the electronic density difference extracted from the MD trajectory (Figure 4) reveals the formation of localized negative polarization charges on carbon atoms near  $K^+$ , which reinforces the interaction between the CNT and  $K^+$ . These interfacial effects in confined pores, particularly the charge rearrangement at the interface, may explain the origin of electro-osmotic flow in CNTs. Note also, that typical force fields used in classical MD simulations cannot capture correctly the ion structure in CNT pores, and that the inclusion of polarizability and cation- $\pi$  interactions is critical to obtaining a structure of KCl solution in qualitative agreement with first-principles simulations (T. A. Pham et al. 2015).



**Figure 4.** First principle and classical MD predictions of the structure of KCl solution inside a 14 Å single-walled CNT. From left to right: classical MD with non-polarizable, polarizable, polarizable + cation- $\pi$  force field, and first-principle MD simulations. Bottom row: radial distribution functions for water (oxygen),  $K^+$  and  $Cl^-$  ions. Top row: snapshots of the MD trajectories; light blue =  $Cl^-$ ; violet =  $K^+$ ; red = oxygen; white = hydrogen. Negative and positive polarization charges on the CNT are represented by the yellow and blue surfaces, respectively.

After investigating ionic transport in CNTs, we turned our attention toward single molecule translocation in these nanochannels. A recent publication (H. T. Liu et al. 2010) experimentally validated the MD prediction (I. C. Yeh and G. Hummer 2004) that oligonucleotide strands can translocate through narrow CNT nanochannels. In this work DNA translocation events were associated to unusual positive current spikes, and the underlying physics remains poorly understood. To elucidate single-molecule transport events in a nanofluidic channel, we considered single-molecule translocation for charged (ss-DNA) and neutral analytes (PEG). Our experiments revealed that, while neutral molecule translocation transiently blocked the ionic flow of the supporting electrolyte as expected, an ionic current increase (spike) was recorded with negatively

charged ss-DNA. Tests performed with smaller negatively charged dyes gave qualitative similar results. While unusual, a transient current enhancement may occur when the counter-ions accompanying a translocating charged molecule dominate over the steric blockage effect, thus resulting in a greater number of current-carrying ions inside the pore (R. M. M. Smeets et al. 2006, S. W. Kowalczyk and C. Dekker 2012, D. M. Vlassarev and J. A. Golovchenko 2012, K. E. Venta et al. 2014). The markedly different signals we recorded for charged or neutral molecules support this explanation.



**Figure 5.** Particle translocation through a CNT nanochannel. A) Passage of a neutral polymer, PEG, induces a single-level current blockade, while B) translocations of negatively charged oligomers, ss-DNA, generate spikes (increases) in the ionic current recording.

## Impact on Mission

This work helped unravel novel transport phenomena induced by nanoscale confinement. Reported findings are critical for a range of civilian, military, and national security needs, from nanofluidic energy-storage/harvesting devices to protective fabrics and membranes. In particular, this work benefits the Chemical and Biological Security Mission Focus Area by providing the fundamental science for the development of advanced single-molecule detection system for bio/chem/explosive analytes. This project supported the hire of a new post-doc at LLNL and also attracted a graduate student from UC Irvine, now working in the Laboratory within the Lawrence Graduate Scholar Program.

## Conclusion

We developed a novel nanofluidic platform for the investigation of ionic and molecular transport in a model, robust nanochannel with tunable dimensions. The chosen nanochannel (a CNT) can be accurately modeled thanks to its simple chemistry and structure. With nanopore analytics techniques, we demonstrated giant ionic conductances in these pores that follow an anomalous power-law concentration dependence. Synergistic molecular dynamic and continuum simulations revealed that this large conductance is likely caused by a strong electroosmotic flow, which is due to the formation of localized negative polarization charges on the CNT walls near  $K^+$  ions. The latter tend to station very close the graphitic walls because of cation- $\pi$  interactions. Single-molecule translocations studies support the idea that the passage of charged molecule through a nanochannel can produce current spikes, whereas neutral molecule

transport induces the expected current blockades. Thus, charged and uncharged molecules can be distinguished on the basis of the shape of the ionic current recording. Future work will be directed toward examining the potential of the platform for detection of molecules differing by other chemico-physical properties. The developed platform will be also employed for fundamental understanding of confinement effects on supercapacitor performances, and for cutting-edge studies of superfluid transport (a proposal with Prof. Peter Taborek at UC Irvine was submitted to NSF).

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