**1074-Pos Board B829**

**Quantifying Short-Lived Events in Multi-State Ionic Channel Measurements**

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We present a new technique that considerably improves the resolution and accuracy of single molecule measurements with nanopores. Molecular interactions with nanopores are characterized by electrical measurements of discrete changes in the channel conductance. By representing physical components of the system with electrical equivalents, we used circuit theory to model response of the system to a stimulus (e.g., a molecule entering the channel). This allowed us to characterize short-lived events where the ionic current does not reach a steady state value, and were previously not analyzed. Applying this technique to measurements of poly(ethylene glycol) (PEG) molecules with the $\alpha$-hemolysin ($\alpha$HL) nanopore resulted in remarkable improvements in accuracy and the number of detected events. When measuring polydisperse PEG (mean molecular weights of 400 g/mol and 600 g/mol), the new method recovered $\approx$ 18-fold more events per unit time, compared with existing techniques, and discriminated molecules with as few as 8 monomers (PEG8). We validated the measurement of PEG with an $\alpha$HL nanopore using results from a recently published study (Balijepalli et. al, J Am Chem Soc, 135: 7064, 2013) that refined a previous analytical theory with molecular dynamics simulations. Fitting this model to the newly obtained experimental data resulted in excellent agreement of both the blockade depth (the ratio of the ionic current when a molecule occupies the pore to the open channel current) and the residence times of the molecule in the channel, over the entire measurement range (PEG8 to PEG19). Finally, we applied the new analysis technique to recover the sequence of a known DNA strand with 26 bases, from a published ionic current trace (Manrao et. al, Nat. Biotechnol. 30: 349, 2012). The technique detected systematic fluctuations in the ionic current that were as small as $0.9 \pm 0.04$ pA.

**1075-Pos Board B830**

**Fast, Label-Free Force Spectroscopy of Histone-DNA Interactions in Individual Nucleosomes using Nanopores**

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Eukaryotic DNA is packaged into nucleosomes, each comprised of ~147 base pairs of DNA wrapped 1.7 turns around histone octamers. Nucleosome organization inherently limits the accessibility of regulatory proteins to genes, which serves as a sophisticated mechanism to control transcription, replication, and repair processes in a cell. While it is known that dynamic modulation of nucleosomal structures is achieved via epigenetic modifications of histone proteins and DNA and by ATP-dependent remodelers, the mechanisms by which these enzyme-assisted modifications affect intranucleosomal interactions remain elusive. Forster resonance energy transfer (FRET), atomic force microscopy, and optical tweezers, all of these methods, though have provided valuable insight, require time-consuming sample labeling and/or surface immobilization. Herein we report a novel approach for fast, label-free probing of DNA-histone interactions in individual nucleosomes. We use small 3 nm diameter solid-state nanopores to unravel individual DNA/histone complexes for the first time. Three force regimes can be distinguished: (1) at low voltages no nucleosome-related events are detected; (2) at moderate voltages nucleosome collisions with the pore are observed, although force is insufficient for nucleosome unraveling; (3) at voltages above the critical nucleosomes are captured and unraveled by the pore. We also find that the unraveling time depends on the applied electrophoretic force, and our results are in line with previous studies that employ optical tweezers. Our approach for studying nucleosomal interactions can greatly accelerate the understanding of fundamental mechanisms by which transcription, replication, and repair processes in a cell are modulated through DNA-histone interactions, as well as in diagnosis of diseases with abnormal patterns of DNA and histone modifications.

**1076-Pos Board B831**

**Controlling the Mechanism of DNA transport through Synthetic Nanopores**

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Solid-state nanopores have emerged as a useful tool for studying biopolymers. The ability to map regions of interest along stretched biopolymers, as well as to detect subtle changes in conformation, makes nanopores attractive single-molecule sensors. Using solid-state nanopores with diameters in the range of 3-10 nm, DNA transport has been too fast but seems to be more regulated. In contrast, transport through smaller pores in the 3-5 nm range is noticeably slower, yet sticking and other interactions complicate the transport dynamics. Therefore, a full understanding of the translocation process requires exploring regimes where polymer linearization is coupled to regulated transport. In this study, we report on an interesting nanopore geometry regime that allows for regulated DNA transport process, while slowing down DNA in order to achieve true detection from individual base pairs. We will show that transport matches theoretical prediction in this geometric regime, and that these results allow us to obtain quantitative information on polymer length with unprecedented detail.

**1077-Pos Board B832**

**Hydrophobic Interactions Retard Proteins upon Translocation through Silicon Nitride Nanopores**

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Over the last years, translocation experiments with proteins through solid-state nanopores have consistently produced anomalously long residence times that are far beyond a ballistic passage process. It has been suggested that attractive interactions to the pore wall might cause a retardation of the protein, but the origin of these interactions has remained elusive up to now.

Here we present experimental evidence that this interaction is of hydrophobic nature: We quantitatively compared the translocation times of a variety of different proteins from our own experiments as well as from other authors and analyzed the hydrophobicity of the respective protein surfaces from available atomic structure data. We found that the occurrence of very long translocation times correlates with the existence of large hydrophobic patches on the protein surface. This strongly suggests that hydrophobic interactions are a dominant factor in determining the passage time of proteins through artificial nanopores, and that it is necessary to engineer the hydrophobicity of artificial nanopores in order to control the passage of proteins through the pore.

**1078-Pos Board B833**

**Direct and Simultaneous Force and Current Measurements of Single-Stranded DNA in Synthetic Nanopores**

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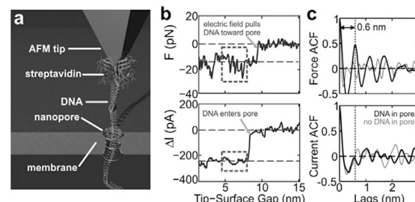
We report direct and simultaneous measurements of the forces and currents associated with the translocation of a single-stranded DNA molecule tethered to an AFM cantilever (Figure a) through synthetic pores 1.2 to 3.5 nm in diameter in $8 \pm 2$ nm thick silicon nitride membranes. These measurements were performed to determine the force required and the electrical signal available for sequencing a single molecule of DNA in a pore small enough to affect the configuration of the molecule. The measurements revealed that ssDNA either translocated the nanopore in a ‘‘stick-slip’’ motion characterized by multiple stretching and rupture events or slid with a relatively constant net force between 10 and 60 pN (Figure b). While the tip moved at a constant velocity, minute $<1$ pN and $<20$ pA fluctuations in the force and current, respectively, were observed every 0.35-0.60 nm (Figure c) in homo/heteropolymers of ssDNA, which were attributed to individual nucleotides translating through the nanopore in a turnstile-like motion. These results indicate that synthetic nanopores $<2$ nm in diameter may offer the resolution to sequence individual bases of DNA, provided the molecule slides through the pore.




**1079-Pos Board B834**

**Osmotically-Driven Transport through Carbon Nanotube Pores**

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