mean-field theory with the PB equation, which under low field condition be further simplified to the linearized Poisson-Boltzmann equation (LPBE). A variety of analytical and numerical techniques have been developed to solve the PB equation. Our group has achieved a fundamental result in deriving the first completely general analytical solution to the linearized Poisson-Boltzmann equation (LPBE) for computing the screened (salty) electrostatic interaction between arbitrary numbers of nanoscale spheres of arbitrarily complex charge distributions, separated by arbitrary distance (or concentration), adapted from the generalized Kirkwood PBE solution. This analytical solution in turn serves as the foundation of a full-numerical approach to solving the LPBE for any nanoscale shape (PB-SAM). We have recently incorporated PB-SAM into a Brownian Dynamic approach to create a robust coarse-grained simulation tool to study a range of biological systems, including a recent study of Barnase/Bastar association under crowded conditions. We have developed a highly parallelized version of PB-SAM that is competitive with current PBE software, and are exploring 3-body implementations to further increase PB-SAM efficiency.

**2083-Pos Board B813**

**Simple Method for Hybrid All-Atom and Coarse-Grained Molecular Dynamics Simulations and Its Applications**

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Hybrid all-atom (AA) and coarse-grained (CG) simulation has the possibility of overcoming the limitations of both AA and CG molecular dynamics (MD) simulations. Hybrid AA/CG systems are practicable to simulate microscopic time scale and to convey detailed information for molecular structures. Many existing methods for hybrid AA/CG simulations tend to require heavy parameterizations that complicate multiscale simulations. We test a simple scheme for simulating hybrid AA/CG systems using standard AA and CG force fields, together with four small proteins as test cases for the scheme. Our method uses virtual sites for interactions between CG and AA resolution as reported earlier (Rzepiela et al. Phys. Chem. Chem. Phys. 2011, 13, 10437-10448) and we add distance restrained FG water layer to improve the reliability of the hybrid simulation. We observe that the addition of distance restrained FG water layer in the hybrid simulation results in close accord with the structure from the atomistic simulations. However, there are also digressions from correct behaviors that need to be addressed in future developments. We show such various results in detail and discuss the prospects of our scheme.

**Biosensors I**

**2084-Pos Board B814**

**Nanopore Quantitation of Cancer BRAF Driver Mutation Facilitated by a DNA Interstrand MercuLock**

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Driver mutations are a special type of genetic alterations that are causally correlated with malignancies. Accurate detection of the presence of driver mutations is extremely useful for early cancer diagnosis. BRAF Serine/threonine-protein kinase B-Raf) has a predominant driver mutation V600E, which occurs with the highest incidence mainly in melanoma, colorectal and thyroid cancers, and in other cancers. Currently the BRAF pathway has become a drug target for molecular therapy. Here we devise a novel nanopore single-molecule assay to accurately detect this driver mutation. The BRAF V600E gene involves a single-nucleotide transversion T1799A in the sense strand, and A1799T in the antisense strand. We selected the antisense strand as the target. Upon hybridization with an optimized probe that contains a thymine at the mutation site, the targeted probe complex can form a T-T mismatch. The nanopore single-molecule sensor can be used to visually discriminate this T-T mismatch bound with a mercury ion (Hg(2+)). This is because the Hg(2+) binding creates a reversible interstrand lock, called MercuLock, which enhances the hybridization strength by two orders of magnitude. Such MercuLock cannot be formed in A-T base pair between the normal BRAF gene and the same probe, suggesting that the MercuLock acts as a fingerprint of the mutant DNA. By counting the frequency of MercuLock blocking events in the nanopore, we can quantitate trace amount of mutant DNA in the mixture. This approach can be adapted to the detection of any thymine-involved driver mutations and single nucleotide polymorphisms (SNPs) for cancer detection.

**2085-Pos Board B815**

**Constructing CPG Site-Specific Interstrand Locks for Single-Molecule Epigenetic Detection with Nanopore**

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DNA methylation is an important epigenetic regulation of gene transcription. Locus-specific DNA methylation can be used as biomarkers in various diseases including cancer. Most current methods are for genome-wide methylation analysis, but clinical diagnostics demands simple, low cost and quantitative approach for determining methylation at individual CpG sites in a gene fragment. The nanopore is providing an excellent single-molecule platform for genetic and epigenetic exploration. Using the nanopore single-molecule sensor, we identified that divalent Mercury ion (Hg(2+)) can selectively bind a single uracil-thymine mismatch (U-T) in a dsDNA. The Hg(2+) binding creates a reversible interstrand lock, called MercuLock, which enhances the hybridization strength by two orders of magnitude. Such MercuLock cannot be formed in a 5-methyl-cytosine-thymine mismatch (mC-T). By nanopore detection of dsDNA stability, single bases of uracil 5-methylcytosine can be distinguished. Since uracil is converted from cytosine by bisulfite treatment, cytosine and 5-methylcytosine can be discriminated. We have demonstrated multiple CpG methylation analysis of a CpG island in the cancer-derived p16 gene. This single-molecule assay has potential in detection of epigenetic cancer biomarkers in biofluids, with an ultimate goal for early diagnosis of cancer.

**2086-Pos Board B816**

**Novel Nanopore Dielectrophoresis Mechanism for Selective Microrna Detection in Clinical Set**

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The nanopore can electropheretically trap single DNA/RNA molecules for genetic/epigenetic detections. However, low selectivity for complex samples (extracts from plasma) remains the challenge to clinical applications. We report an novel biophysical mechanism – Carrier-guided-Nanopore-Dielectrophoresis (CND) – for selective nucleic acids detection. We invented a polycationic micro-carrier. Upon hybridization with the target, the target-carrier forms a moment-tunable dipole, which can be attracted into the nanopore by dielectrophoresis from a huge electric field gradient (10^11 V/m/nm) outside the nanopore entrance. In contrast, any non-target species without carrier hybridization carries negative charge and would electropheretically migrate away from the nanopore. Consequently only the target-carrier nanopore signatures can be identified; any interference signal from non-target nucleic acids is completely eliminated. Unlike electrophoresis that lacks selectivity, the nanopore dielectrophoresis can selectively drive target nucleic acids of any size by using a universal micro-carrier. This represents the first and substantial step in translating the nanopore-sensor into a clinically-usable tool for molecular diagnostics. We demonstrate how to utilize this mechanism to accurately quantify cancer-derived microRNA biomarkers in patient plasma.

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**2087-Pos Board B817**

**Detection of Single Biopolymers at High Current Bandwidth with Hafnium Oxide Nanopores**

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Hafnium oxide (HfO2) is a chemically and mechanically stable insulator that may be deposited via atomic layer deposition. These properties make it an ideal material for ultrathin, free-standing membranes. We fabricate these membranes by depositing HfO2 on a low stress silicon nitride (SiN) film, and then locally removing the SiN. We then fabricate a nanopore in this HfO2 membrane with a diameter of 200 nm. We then fabricate a nanopore in this HfO2 membrane with a 200 kV transmission electron beam. Coupled with a megahertz-bandwidth