MAAC/gSc interaction suggests clues regarding recognition of damage by MAAC, and the basis of its holdase activity.

3061-Pos
How well do molecular dynamics simulations model the unfolded states of small proteins?
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Molecular dynamics force fields have been shown to be able to reversibly fold and unfold small proteins. However, it has been documented that certain force fields create unfolded states which are too collapsed when compared to experiment. Thus, it is unknown whether any cooperative substructures formed by the polypeptide chain in the unfolded states of these simulations may be force field artifacts. In this work, we analyze the unfolded states of all-atom trajectories modeled using the Charmm 22* and DES-Amber force fields, performed by Shaw and co workers. We find that the DES-Amber force field is significantly less collapsed and in better agreement with a range of experimental observables. However, despite the differences in overall unfolded state dimensions, we find that the Charmm 22* and desAmber force fields populate similar cooperative substructures in the unfolded state, albeit with different weights. The results suggest that, force fields that result in excessively collapsed unfolded protein structures can still yield local structure in the unfolded state that is qualitatively consistent with that obtained with force fields that give more realistic unfolded state dimensions.

3062-Pos
Establishing the role of structure and dynamics in radiation brightening from super-fluorescent virus-like particles
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Increasing the number of fluorescent dyes conjugated to a nanobead ultimately leads to self-quenching rather than increasing fluorescence signal from the particle. However, protein cages derived from some virus capsids overcome this limitation, and conjugation with many dye copies leads to coherent, ultra-bright radiative emission that is super-fluorescent. Limited examples of room temperature super-fluorescence have been previously reported, making this an exciting discovery with interesting potential biotechnology applications (e.g., high-contrast tumor imaging). However, only certain protein cages have been found to achieve this effect, particularly those based on the T=3 capsid of Brome mosaic virus (BMV), which infects plants. We employ atomistic molecular dynamics (MD) simulations of the intact BMV capsid decorated with Oregon Green 488 to establish the role of structure and dynamics in producing ultra-bright, super-fluorescent emission. Our results indicate that the location of covalent dye attachment and collective motions of the virus-like particle are most pertinent to radiation brightening in the BMV system.

3063-Pos
Advancing G-quadruplex drug targeting through polarizable simulations and SILCS
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Human immunodeficiency virus (HIV) impacts over one million people in the United States alone. While there are antiretrovirals that effectively manage the disease, resistance to current drugs is emerging. Non-canonical nucleic acid structures, such as G-quadruplexes (GQs), are promising targets for small-molecule drug design against viral replication. HIV-1 replication relies on two mutually exclusive GQs, LTR-III and LTR-IV, which are structurally distinct and inversely regulate viral gene expression. Efforts to target GQs have been limited by a lack of selectivity in known binding compounds as they primarily bind to the tetrad core found in all GQs. Here, the LTR-III and LTR-IV GQs serve as a platform to study how compounds can discriminate between distinct GQ structures for improved drug design based on dynamic and electronic properties. We first employed polarizable molecular dynamics simulations to study the dynamic and electronic properties of LTR-III. We observed that Ade4:Thy14 and Gua3:Thy14 base pairs formed at the quadruplex:duplex junction, a common target for GQ-binding ligands. Despite not being present in the NMR ensemble, Ade4:Thy14 fits the NOE data and was observed in prior simulations. Ade4:Thy14 was more prevalent than Gua3:Thy14 and analysis of the intrinsic electric field and the base dipole moments rationalize the preference for Ade4:Thy14. The conformational free energy associated with Ade4:Thy14 states is lower than that of Gua3:Thy14, but the 2–3 kcal/mol energy barriers between these states suggest that Thy14 may readily interact with both bases, modulating the properties and accessibility of a likely drug binding site. We then used site identification by ligand competitive saturation (SILCS) to screen common drug fragments against these states and to determine how this conformational flexibility modulates affinity patterns of drug-like moieties. Our results represent a critical step toward the rational design of selective compounds for LTR-III.

3064-Pos
Investigating potential drug targets in the *PIM1* promoter G-quadruplex
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Triple negative breast cancer (TNBC) is an aggressive disease with poor patient prognoses due to a lack of viable chemotherapeutic targets. However, the genetic profile of TNBC may provide insight into potential targets for managing this disease. Notably, the *PIM1* oncogene, a serine/threonine kinase with roles in cellular growth and apoptosis, is often over-expressed in TNBC and is regulated by two distinct G-quadruplex (GQ)-duplex hybrid structures. Promoter GQs have been demonstrated to have a crucial role in regulating oncogene expression, making them attractive novel drug targets for genes implicated in cancers. The *PIM1* promoter GQs exhibit conformational heterogeneity by adopting two forms. Form 1, the primary topology, maintains a conventional GQ structure, with a guanine tetrad core and a duplex region containing two Watson-Crick base pairs. Form 2 contains a recently identified mixed-tetrad motif composed of guanine and cytosine bases (a ''GCGC mixed tetrad'') within the GQ core, in addition to a duplex region. These distinct structural features may serve as targets for future small-molecule drug design. We conducted conventional and Gaussian-accelerated molecular dynamics (GaMD) simulations to explore the electronic characteristics and conformational landscapes of these GQs. We monitored dipole moments and electric fields to characterize ion coordination and conformational flexibility observed in form 2, specifically focusing on the contributions from the GCGC mixed tetrad, as our previous analyses have demonstrated altered electronic properties of bases in this structural motif. Additionally, site identification by ligand competitive saturation (SILCS) simulations were performed to provide novel insights into how to develop specific chemotherapeutic agents to differentially target the two GQ forms for the regulation of *PIM1* expression on the transcriptional level.

3065-Pos
Computational analysis of photophysical changes of oligomeric P-phenylene ethynylene sensors upon binding to amyloid-β aggregates
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Alzheimer's disease (AD) is an uncurable progressive neurodegenerative disease and is the most common cause of dementia. As current understanding of the disease suggests damage begins accumulating a decade before diagnosable symptoms, preventative treatment strategies will require screenings during the asymptomatic state. The high cost of PET and MRI scans make them challenging for the throughput necessary to screen the large population of 65+ individuals most at risk of developing AD. An alternative is near-IR fluorescence imaging, which is less costly and less invasive. We have reported a small-molecule fluorescent sensor able to selectively detect and oxidize the amyloid-β oligomers and fibrils implicated as pathogenic agents in the early development of AD. In this study, we use computational modeling to gain insights into what changes in sensor-protein binding lead to both turn-on fluorescence and turn-on singlet oxygen generation. We utilize molecular dynamics to model sensor behavior in multiple environments, including sensor complexation and protein binding. Both density functional theory (DFT) and time-dependent DFT *ab initio* calculations are used to monitor intra- and inter-molecular photophysical properties of the molecule. Results show that the structural dynamics of the sensor depends on its binding environment and that the structural changes upon binding are correlated with changes in sensor photophysical characteristics. This investigation contributes to a better understanding of how molecular design gives rise to desirable properties for molecular sensing, leading to improved ability to rationally design near-IR fluorescent sensors for AD.

3066-Pos
Insights into the electronic and structural properties of cellulose and amylose: A comparative force field study
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Cellulose and amylose are fundamental biopolymers with diverse biotechnology and materials science applications. Understanding their structural,