approaches, we present a graphics-processing unit (GPU)-optimized coarse-grained Go-type MD simulation approach for protein-nanoparticle interactions, the first in the field. We performed MD simulations of a spherical, negatively charged citrate-covered silver nanoparticle (AgNP), represented by 500 charged beads, interacting with 15 apolipoproteins that are 243 residues in length each. We probed the secondary structural changes of apolipoprotein upon its binding to the AgNP, and we make direct quantitative comparisons of our simulations with experimentally measured CD spectra. Consistent with the CD spectra, we observed a decrease in α-helices coupled with an increase in β-sheets in apolipoprotein upon biocorona formation.

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Biophysical Insights of Neutral and Non-Neutral Sequence Variants in the Human Proteome

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From extraordinary advances in sequencing technologies, it is now clear that each personal exome carries thousands of protein sequence variants, many of which manifest into unique phenotypes involved in disease. Current *in silico* tools being employed to predict phenotypes of these variants yield fairly accurate results at highly conserved positions. However, these tools are based solely on evolutionary data and often fail when evaluating variants that occur at faster evolving positions. Moreover, their performance accuracy is relatively low for neutral variants at highly conserved positions. These shortcomings necessitate the addition of an another metric to provide biophysical insights of these variants, and also to increase the predicting capabilities of *in silico* tools. We employ a novel metric, called the dynamic flexibility index (*dfi*), based exclusively on structural dynamics to evaluate the functional impact of these variants. The *dfi* metric is a mechanistic approach that goes beyond evolutionary data, and probes into the dynamics of each site to measure its contribution to function[1]. Previous studies have shown that *dfi* is related to functional dynamics at the proteome scale[1]. We use a set of over 10,000 laboratory-induced variants of human proteins that have been diagnosed as either neutral or non-neutral from a functional perspective. Interestingly, only ~51% of non-neutral cases are also associated with disease. We evaluate the *dfi* metric for each variant site in this data set and compare our ability to diagnose neutral and non-neutral variants with state-of-the-art computational tools. Moreover, our results will provide insights to a new outlook on phenotypic prediction, which will likely have a broad impact in genomic and personalized medicine.

[1]Gerek, Z. N. *et al.* (2013) Structural dynamics flexibility informs function and evolution at a proteome scale. *Evolutionary Applications*.

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NMR-Restrained Protein Structure Calculations in Implicit Environment

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The aqueous and lipid membrane environments that make up the intra- and extra-cellular compartments of biological organisms are critical for supporting the structural and functional integrity of both soluble proteins and membrane proteins. NMR spectroscopy is extremely versatile and adept at characterizing the structures and functions of both types of proteins in samples that closely resemble the native environment. However, structure calculations in explicit solvent or explicit lipids are computationally expensive. Therefore, even when NMR structural restraints are measured in a native-like protein environment, protein structures are typically calculated using simple repulsive potentials without physically meaningful terms for electrostatics, non-covalent interactions or atom solvation. To facilitate NMR structure calculations in the proper environment we are developing a computationally less demanding implicit solvent potential for the XPLOR-NIH NMR structure refinement package. Here we show that the potential provides significant improvements both in the quality and precision of the calculated structures; it improves the accuracy of structures determined with sparse restraints; it provides numerous physically meaningful hydrogen bonding connections; and it provides correct embedding of membrane proteins in lipid bilayer membranes.

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Benchmarking Collective Motion Predictions of Elastic Network Models

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Elastic Network Models (ENMs) provide approximate descriptions of the collective conformational freedom intrinsically accessible to protein structures. Despite their simplicity, many ENMs have been repeatedly demonstrated to be in qualitative agreement with experimental observations of protein conformational changes. A wide variety of ENMs has been proposed in the last two decades, and they have become a favored approach for elucidating the collective components of protein motion. Since experimental data on the temporal correlations of atoms in proteins are currently unavailable, most attempts at quantitative assessment of ENMs rely on comparisons of predicted atomic fluctuations with crystallographic B-factors. Using such benchmarks, diverse ENMs have been shown to give very similar predictions. In contrast to this, we have revealed consistent differences between ENMs by comparing their inter-atomic covariances with those obtained from Molecular Dynamics sampling.

Some of us recently demonstrated the importance of considering the covariance structure explicitly when comparing the conformational freedom of protein homologs (Fuglebakk et.al., Bioinformatics 2012) . In the same work we developed rigorous means of carrying out such comparisons. I will present results obtained from applying this approach to do a thorough assessment of a selection of ENMs. We find consistent differences between the ENMs. However, the differences do not always follow a priori expectations based on the models complexity. Rather, even some of the simpler ENMs give good approximations to the covariances obtained from Molecular Dynamics. Often this comes at the cost of less reliably predicting the atomic fluctuations that have commonly been used for parameterization and validation. Lastly, we find that the use of B-factors for parameterization or validation warrants particular care, as the common approach for doing this favors ENMs that constrain collective motion.

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PRIMO-M: An Extension of the Coarse-Grained Force Field Primo to the Membrane Environment

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CG models for biomolecules and lipids are widely established but often suffer from a lack of transferability between different systems and to different environments. Furthermore, the combination with atomistic force fields in hybrid AA/CG multiscale models is often challenging. To alleviate these problems, we have previously developed the PRIMO coarse-grained force field. Here, the extension of PRIMO to membrane environments, PRIMO-M, is presented. The membrane environment is modeled implicitly with the heterogeneous dielectric generalized Born methodology that simply replaces the standard generalized Born model in PRIMO without further parameterization. The resulting model was initially validated by reproducing amino acid insertion free energy profiles. Membrane proteins with 148-661 amino acids show stable root-mean-squared-deviation between 2 and 4 Å for most systems. PRIMO-M was able to predict tilt angles of several transmembrane helical peptides that are in good agreement with experimental or other simulation data. The association of two glycophorin A helices was simulated using replica exchange molecular dynamics simulations yielding the correct dimer structure with a crossing angle in agreement with previous studies. Finally, the conformational sampling of influenza fusion peptide also generates structures in agreement with previous studies. Overall, these findings suggest that PRIMO-M can be used to study membrane bound peptides and proteins and validates the transferable nature of the PRIMO coarse-grained force field.

Large-Scale Organization of Domains and Chains

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Single Molecule Study of Rela During the Stringent Response in Live E. Coli Cells

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The stringent response is a physiological response that occurs when bacterial cells encounter nutritional stresses such as amino acid starvation or fatty acid