the complementary bioinformatic tools SIFT, PolyPhen-2, Provean, MutPred2, and FATHMM are also presented. The ability to predict the effects of missense mutation on catalytic function has important implications for protein engineering and for a variety of biomedical questions. This work was supported by the NSF MCB-2147498.

2309-Pos
BPS2025 - Bayesian single-particle tracking using normalizing flows
Jay C. Spendlove, Pedro Pessoa, Weiqing Xu, Steve Pressé.
Department of Physics, Arizona State University, Tempe, AZ, USA.
Single-particle tracking (SPT) describes efforts for developing data-driven methods for tracking experimental particle trajectories of fluorescent molecules imaged over time. However, many SPT methods fail in crowded environments or in situations with low signal to noise ratio. Bayesian methods provide a robust approach to SPT which simultaneously incorporates information from all frames and reliably infers the particle trajectories from the experimental data. One downside of Bayesian methods is the high computational cost. Specifically, the Monte Carlo proposal of particle trajectories requires many samples of the posterior distribution. To decrease the computational cost of proposing particle trajectories in Bayesian methods, we approximate the proposal distribution using normalizing flows, a deep learning based method for constructing complex probability distributions. Here we present initial results adapting normalizing flows to SPT.

2310-Pos
BPS2025 - Bayesian inference of molecular machine kinetic models with incomplete data
Leah Repa[1,2], David L. Stokes[3], Oliver Beckstein[1,2].
[1]Department of Physics, Arizona State University, Tempe, AZ, USA, [2]Center for Biological Physics, Arizona State University, Tempe, AZ, USA, [3]Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, NY, USA.
Molecular machines are macromolecular structures that perform some useful function via physical conformational changes at the single molecule level, such as membrane transporters or motor proteins in muscle cells. While experimental techniques to observe certain aspects of molecular machines do exist, these systems are often extremely difficult to fully characterize experimentally due to their dependence on chemical or physical reactions on the single molecule scale that take place on time scales several orders of magnitude faster than their functional behavior. In order to derive full kinetic models of function from this limited experimental data, we developed a Bayesian framework to infer complete kinetic models by combining this data with computational simulation and constraints from thermodynamic theory. This framework was then successfully applied to infer the rate parameters of a toy membrane antiporter system starting with uninformative prior assumptions and little to no time scale information beyond what could be reasonably obtained from simulation estimates or methods such as FRET. This framework is now also being extended to use other experimental techniques such as non-equilibrium transport current data from solid membrane supported electrophysiology (SSME) towards inferring full kinetic models of membrane transporter function.

2311-Pos
BPS2025 - MDANCE: Flexible and versatile *N*-ary clustering package
Lexin Chen, Ramon Miranda-Quintana.
Department of Chemistry, University of Florida, Gainesville, FL, USA.
Molecular dynamics (MD) simulations offer a computational window into intricate biological processes, yet the challenge lies in extending their scope to encompass longer timescales and larger systems. Unfortunately, the post-processing analysis of MD trajectories has struggled to keep pace with this demand, particularly in the realm of clustering techniques. Clustering is essential for unraveling protein folding dynamics, constructing Markov state models, enhancing replica exchange simulations, and discerning drug binding modes. The predicament arises from a stark trade-off: conventional algorithms such as k-means prove efficient but fall short in identifying subtle metastable states, while more robust methods like density-based clustering incur significant computational overhead. In this contribution, we unveil a transformative solution in the form of molecular dynamics Analysis with N-ary clustering ensembles (MDANCE) software. One of the key novelties in MDANCE is that it provides the tools to quickly implement and test novel clustering algorithms. MDANCE stands as an open-source powerhouse, serving both as a user-friendly tool for analyzing diverse MD simulations and as a versatile platform empowering developers with unparalleled flexibility in crafting and integrating clustering and post-processing tools. MDANCE transcends the limitations of traditional approaches by introducing novel, linear scaling (highly efficient) clustering algorithms and can be highly useful in applications, such as drug design, million-molecule molecular docking, and molecular dynamics analysis.

2312-Pos
BPS2025 - Capturing large conformational changes in proteins by the enhanced GōMartini 3 approach
Adolfo B. Poma[1], Luis F. Cofas-Vargas[1], Gustavo E. Olivos-Ramirez[1], Jesús Antonio Rauda-Ceja[2], Adrián Durán-Vargas[2], Thu Thi Minh Tran[3,4].
[1]Department of Soft Matter and Biosystems, Institute of Fundamendal Technological Research, Polish Academy of Sciences, Warsaw, Poland, [2]Instituto de Química, Universidad Nacional Autónoma de México, Ciudad de México, Mexico, [3]Faculty of Materials Science and Technology, University of Science-Vietnam National University Ho Chi Minh, Ho Chi Minh City, Vietnam, [4]Vietnam National University, Ho Chi Minh City, Vietnam.
Despite the success of the GōMartini approach in capturing large conformational changes in proteins associated with mechanical forces in the order of hundreds of piconewtons and under different biological environments that affect the protein conformations, a systematic comparison is not yet available between the early implementation in Martini 2 coarse-grained (CG) force field and the recent version in the Martini 3 CG force field. The latter approach has been validated against experimental and all-atom molecular dynamics (AAMD) data and currently can be found in the Martini Force Field Initiative. We validate both approaches in two scenarios where large conformational changes are observed: (1) the thermal unfolding of wheat germ agglutinin domains, which has been extensively characterised through both in vitro experiments and AAMD simulations and (2) the nanomechanics of the Cohesin:dockerin-X domain complex, also studied via single-molecule force spectroscopy, which is crucial for understanding the self-assembly of the multi-enzyme cellulosome complex and function in cellulose-degrading bacteria. Moreover, our observations are contrasted with a recent structure-based approach that employs a new set of Gō interactions denoted as OLIVES in the Martini 3. Finally we aim to provide a comparative analysis that focuses on the ability of these CG models to replicate the intricate dynamics and interactions of proteins during non-equilibrium processes at time scales beyond AAMD simulations. Our results will delineate the pros and limitations of each approach in exploring large conformational changes in proteins and they will offer targeted suggestions for refining these approaches, enhancing their accuracy and predictive capabilities in biomolecular simulations.

2313-Pos
BPS2025 - Effects of conformations of gD-Crystallin on distributions of aggregation networks
Elizabeth M. Diessner[1], Carter T. Butts[2,3], J. Alfredo Freites[4], Douglas J. Tobias[4].
[1]Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, CA, USA, [2]Department of Sociology, University of California Irvine, Irvine, CA, USA, [3]Department of Electrical Engineering and Computer Science, Statistics, University of California Irvine, Irvine, CA, USA, [4]Department of Chemistry, University of California Irvine, Irvine, CA, USA.
The mutations to crystallin proteins of the eye lens that lead to cataract formation do so by altering the conformational state space of the proteins. Here, we employ network Hamiltonian models, previously shown to recapitulate the aggregate structures formed by gD-Crystallin WT and its W42R variant, to simulate distributions of aggregates with varying compositions of conformations of the gD-Crystallin proteins. In doing so, we examine the influence of individual protein conformational states on the propensity to form larger aggregate structures, providing insight into the mechanisms by which such mutations promote the formation of cataract.

2314-Pos
BPS2025 - Predicting generalized-born molecular solvation energies using an active-learning neural network ensemble
Vahe M. Grigorian, Ezequiel Donovan, Alexander McMahon, Tyler Luchko.
California State University Northridge, Northridge, CA, USA.
Molecular simulations are used to predict the real-world behavior of candidate drug molecules interacting with protein binding sites. However,