2025 CBP & GCSC Joint Workshop

Date & Time: 15th December 2025, 13:30 ~ 17:30

Location: Bali Oceanfront Restaurant Luana Lounge lagoon side, Hilton Hawaiian Village Waikiki Beach Resort

Sponsors

ASU Center for Biological Physics
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Program

December 14 (Sun)

18:00~20:00	Round Table Discussion

December 15 (Mon)

13:00 ~ 13:25	Registration
13:25 ~ 13:35	Opening Remark: S. Banu Ozkan
Session 1 - Chair: Jaeyoung Sung	
13:35 ~ 14:00	S. Banu Ozkan (Arizona State Univ.) How Dynamic Allostery Rewires Protein Function: From Distal Mutations to Predictive AI Models
14:00 ~ 14:25	Judith Klein-Seetharaman (Arizona State Univ.) Exposome-targetome interactions probed by large scale protein-ligand docking
14:25 ~ 14:50	Sang-Hee Shim (Korea Univ.) Atomic-resolution Single-molecule Localization Microscopy
14:50 ~ 15:00	Coffee Break
Session 2 - Chair: Sang-Hee Shim	
15:00 ~ 15:25	Dmitry V. Matyushov (Arizona State Univ.) Diffusion dynamics: From water to electrolytes to proteins
15:25 ~ 15:50	Mi Hee Lim (KAIST) Chemical (Bioinorganic) Strategies to Study Multiple Facets in Alzheimer's Disease
15:50 ~ 16:15	Steve Pressé (Arizona State Univ.) Tracking without Localization
16:15 ~ 16:25	Coffee Break
Session 3 - Chair: Steve Pressé	
16:25 ~ 16:50	Matthias Heyden (Arizona State Univ.) Bridging Time- and Length-Scales in Biomolecular Simulations
16:50 ~ 17:15	Jeong-Mo Choi (Pusan Nat. Univ.) Network Structure of Biomolecular Condensates
17:15 ~ 17:30	Jaeyoung Sung (Chung-Ang Univ.) Statistical Thermodynamics of Biological Condensates and Chemical Dynamics of Biological Networks

Oral Session

Abstract

(session 1-1)

How Dynamic Allostery Rewires Protein Function: From Distal Mutations to Predictive AI Models

S. Banu Ozkan[1,2]

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Proteins rely on long-range communication to regulate activity, enabling perturbations at one site to influence distant functional regions. Increasing evidence shows that dynamic allostery, redistribution of thermal fluctuations without major structural change, is a primary mechanism by which proteins achieve this communication. Distal mutations often act by rewiring dynamic coupling networks, shifting hinge regions and altering pathways of rigidity and flexibility that control collective motions. Using metrics such as the Dynamic Flexibility Index (DFI), Dynamic Coupling Index (DCI), and vibrational density of states (VDOS), we have shown that these network rewiring events are central to functional adaptation and underlie the impact of mutations occurring far from active sites. Residues that maintain strong dynamic influence over functional centers form Dynamic Allosteric Residue Couplings (DARC sites) and frequently host evolutionary, disease-associated, or drug-resistant substitutions.

A major challenge is predicting how multiple mutations jointly alter these dynamic networks. Although deep learning can capture single-mutation effects, modeling epistasis, the non-additivity of functional outcomes when mutations interact, requires representing the underlying reorganization of dynamic couplings. To address this gap, we introduce an allosteric graph neural network (GNN) that embeds dynamic communication directly into its architecture. Using the asymmetric Dynamic Coupling Index (DCIasym), which quantifies direction-dependent influence between residue pairs, we link each residue to its distant dynamic influencers, enabling the GNN to learn how mutations propagate through and rewire allosteric networks. This physics-informed design substantially improves prediction accuracy across deep mutational scanning datasets and successfully predicts activities of 37 designed TEM-1 β-lactamase variants in a blind test. Together, these results demonstrate that incorporating dynamic allostery and network rewiring into AI models provides a powerful framework for predicting the functional effects of distal and combinatorial mutations.

Reference

[1] Campitell et al., Dynamic Allostery: Evolution's Double-Edged Sword in Protein Function and Disease, J. Mol Biol. 9, 169175 (2025);
[2] Huynh et al., A protein dynamics–based deep learning model enhances predictions of fitness and epistasis, Proc.Natl Acad. Sci. USA 122, e2502444122 (2025)

(session 1-2)

Exposome-targetome interactions probed by large scale protein-ligand docking

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The human body continuously encounters and processes large and complex mixtures of small molecule compounds through food, air, water, medicines, skin contact, infections and modulated by life-style and microbiome actions, collectively referred to as the exposome. The effects of the exposome on the human body typically involve the binding to proteins. We refer to the entirety of proteins inside an organism as the targetome. Because it is not feasible to experimentally determine all exposome-protein interactions, we need reliable methods for predicting them. The large-scale availability of human protein structures (experimentally determined and predicted with reasonable accuracy) and increasing compute power provide an opportunity to begin building a wholistic picture of all the interactions inside cells. We can borrow methods developed for drug discovery applications such as molecular docking but interprotein noise limits its accuracy for target identification. Here, we report the comparison of docking results of 187 diverse biomolecules encountered in the exposome using structure-based reverse docking to the 7,600 human proteins. These docking results were used as feature input in a target identification setting formulated as a binary classification task (interact or not). We show that combining predicted affinity with its ranking in the list of all proteins in a given organism (here human) improves model performance; e.g., logistic regression improves in accuracy from 0.64 to 0.71, precision from 0.64 to 0.68, recall from 0.64 to 0.78 and F1 score from 0.65 to 0.73. Upon addition of protein-only based features performance improved further and the better classifiers were random forest and gradient boosting with best accuracy 0.77, precision 0.75, recall 0.87, F1 0.78. This quantitative demonstration of the utility of protein docking features opens the door to using them in other prediction tasks such as clinical trial outcomes and adverse or synergistic side effects and exposome interactions in the future.

(session 1-3)

Atomic-resolution Single-molecule Localization Microscopy

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Single-molecule localization microscopy surpasses the optical resolution limit of conventional fluorescence microscopy by more than an order of magnitude. This is achieved by switching fluorophore molecules between emissive and dark states, allowing the sequential separation of images of individual molecules across many camera frames and enabling their precise localization of the centroid positions. In DNA-PAINT, for instance, short fluorescent DNA strands (~10 base pairs) transiently hybridize with complementary docking strands attached to target biomolecules. Despite this remarkable improvement, the resulting spatial resolution still exceeds the molecular dimensions, limiting the ability to faithfully reconstruct biomolecular architectures at the true molecule scale.

Resolution Enhancement by Sequential Imaging (RESI) achieves angstrom-scale resolution by performing sequential DNA-PAINT imaging on sparsely labeled, DNA-barcoded target subsets [1]. However, its current implementation is constrained by the limited number of available barcodes composed of repeated docking sequences, which are essential for accelerating data acquisition. To overcome this limitation, we previously introduced an alternative approach to accelerate DNA-PAINT by applying reductive caging, in which fluorescent DNA probes are chemically reduced into a photoactivatable dark state by a strong reducing agent [2]. Here, we extend this concept to RESI, enabling the use of the conventional, non-repeating docking strands and successfully obtaining RESI reconstruction of cellular structures. This caged RESI strategy is expected to further enhance imaging speed, spatial resolution and molecular density.

Reference

[1] Reinhardt et al., Ångström-resolution fluorescence microscopy, Nature 617, 711-716 (2023);

[2] Jang et al. Reductively Caged, Photoactivatable DNA-PAINT for High-Throughput Super-resolution Microscopy, Angewandte Chemie International Edition, 59, 11758-11762 (2020)

(session 2-1)

Diffusion dynamics: From water to electrolytes to proteins

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This talk will discuss diffusional dynamics caused by combined effect of random electrostatic and van der Waals forces in application to proteins [1], aqueous electrolytes.[2], and bulk water [3,4]. Standard algorithms to calculate the diffusion constant from molecular velocities or displacements do not address physical forces kicking the tagged particle into motion. Memory functions are required to calculate diffusivity from forces. We find the force route to be more reliable for diffusion constants of proteins from simulations since it shows a much weaker system-size dependence [1]. Very accurate compensation relations between electrostatic and van der Waals forces apply to all system studied. For concentrated electrolytes, strong slowing down of diffusion is observed experimentally for ions and water in solution, which is traced back to slowing down of the memory relaxation time [3]. Non-Gaussian translational dynamics in water are driven by dipole-dipole interactions [3]. Finally, we find a strong match between single-dipole and collective memory functions of dipolar rotations. This empirical result allows one to calculate the dielectric function of a liquid solely from single-particle dynamics.

Reference

[1] S. M. Sarhangi and D. V. Matyushov, “Memory function for protein diffusion”, J. Chem. Phys. 163, 095101 (2025).

[2]. T Huang, et al, “Aqueous ion mobility over a broad concentration range”, Phys. Rev. Lett. 135, 028002 (2025).

[3]. M. M. Pirnia and D. V. Matyushov, “Dynamics of low-temperature water are driven by electrostatics”, unpublished.

[4] D. N. Asthagiri and D. V. Matyushov, “Rotational memory function of SPC/E water”, unpublished.

(session 2-2)

Chemical (Bioinorganic) Strategies to Study Multiple Facets in Alzheimer's Disease

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Alzheimer's disease (AD), associated with degeneration of neurons and synapses in the brain, leads to motor impairment and eventual fatality. Neurodegeneration could be related to various interconnected features, including (i) plaque formation from amyloid- (A) peptide fragments, (ii) metal ion dyshomeostasis and miscompartmentalization, as well as (iii) inflammation and increased oxidative stress due to overproduction of reactive oxygen species (ROS). The inter-relations between some of these pathological factors have been investigated. Metals are found entangled in the A plaque and likely contribute to A neurotoxicity and oxidative stress. ROS have been shown to increase the rate of A plaque formation. Our understanding of the correlation between these elements and AD neuropathogenesis has been very limited, however. There is currently no cure for AD; therapies are focused on symptomatic relief targeting the decrease in the levels of acetylcholine, only one of the multiple factors causing the disease [1-4]. To find a cure for AD, we require a better understanding of the relationship between various causative factors of this devastating disease. Towards this goal, we have been developing suitable chemical tools capable of targeting and regulating multiple underlying factors or identifying the pathogenic networks composed of their direct interactions and reactivities [5-9].

References

[1] Chem. Soc. Rev. 2012, 41, 608; Chem. Soc. Rev. 2017
[2] Acc. Chem. Res. 2014, 47, 2475; Acc. Chem. Res. 2021, 54, 3930.
[3] Chem. Rev. 2019, 119, 1221.
[4] Coord. Chem. Rev. 2023, 478, 214978.
[5] Proc. Natl. Acad. Sci. USA 2010, 107, 21990; Chem. Sci. 2015, 6, 1879; Nat. Commun. 2016, 7, 13115; Proc. Natl. Acad. Sci. USA 2020, 117, 5160.
[6] J. Am. Chem. Soc. 2014, 136, 299; J. Am. Chem. Soc. 2015, 137, 14785; J. Am. Chem. Soc. 2020, 142, 8183.
[7] Nature Chem. 2022, 14, 1021.
[8] Adv. Sci. 2024, 11, 2307182.
[9] Nature Chem. Biol. 2025, 21, 1709.

(session 2-3)

Tracking without Localization

Steve Pressé[1,2]

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We'll be talking about two fundamental problems and their solution. The title reflects the first problem.

Problem 1 [1]: As you try to track increasingly fast molecules, you normally increase your frame rate to avoid motion blur and eventually recover a smattering of photons in each frame. At this point, it is impossible to localize molecules in each frame in order to track, let alone link their positions frame to frame to form trajectories. This raises the question: given a smattering of photons in each frame, how do you leverage this information to determine molecular tracks while circumventing the localization and linking paradigm inherent to tracking? Put differently, we propose a new paradigm appropriate for molecular tracking.
Collaborators: Lance W.Q. Xu, Nathan Ronceray, Marianna, Fanouria Mitsioni, Titouan Brossy, David Šťastný, Radek Šachl, Martin Hof, Aleksandra Radenovic.

Problem 2 [2]: Looking at a bright cell, with fluorescence reporting on the activity of a gene, we ask the question: what fraction of the labeled protein of interest is inherited from the mother cell versus being produced by the current cell? Answering this question immediately presents a mathematical barrier: if inherited, the amount of protein depends on the cell's division history. Put differently, this seemingly simple inference question becomes mathematically pathological. Here, concretely, we answer this question by proposing a solution through AI- assisted simulation based inference to perform inference on arbitrarily non-Markov processes.
Collaborators: Pedro Pessoa, Juan Andres Martinez, Vincent Vandenbroucke, Frank Delvigne.

Reference

[1] Xu et al., "Single-Photon Single-Particle Tracking" https://www.biorxiv.org/content/10.1101/2025.01.10.632389v2 (2025)

[2]. Pessoa et al., "Inherited or produced? Inferring protein, production kinetics when protein counts are shaped by a cells division history" https://arxiv.org/abs/2506.09374 (2025)

(session 3-1)

Bridging Time- and Length-Scales in Biomolecular Simulations

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Biomolecular structure, dynamics and function is closely tied to interactions with specific molecular environments: 1) interactions with the solvent stabilize the folded state, 2) ligand binding modulates the equilibrium between conformations, 3) solvent fluctuations modulate dynamics, and 4) interactions with the biomolecular matrix further shape the conformational free energy landscape. For proteins, our ability to predict structures and conformational ensembles based on amino sequence information has seen drastic recent improvements. However, understanding the modulation of protein properties via interactions with varying environments remains a challenge that is critical for our understanding of biomolecular function in vivo.

Molecular simulations can provide access to atomic level detail on protein structure, dynamics and thermodynamics given that simulations can be performed on the necessary timescales. However, achieving such timescales remains non-trivial for all but the smallest biomolecular systems. Here, we explore how information on biomolecular solvation and conformational dynamics can be extracted efficiently using a combination of picosecond timescale fluctuations and enhanced sampling simulations and how this information can be used to explore their effects in a crowded biomolecular matrix.

(session 3-2)

Network Structure of Biomolecular Condensates

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There is growing interest in uncovering the fundamental principles of liquid-liquid phase separation (LLPS) of multivalent proteins with intrinsically disordered regions, given the direct relevance to the reversible formation/dissolution of biomolecular condensates. However, despite recent advances in the field, achieving multiscale structural characterization of these liquid condensates remains an outstanding challenge. Nucleophosmin (NPM1) stands out as a key component of the liquid-like granular component (GC) within the nucleolus. To gain insight into these systems, a minimal model of NPM1, designated as N130, has been developed. This minimal model, N130, encompasses the N-terminal fragment of NPM1, retaining two acidic tracts and the ability to oligomerize into homopentamers. Notably, N130 has the capacity to induce LLPS in the presence of arginine-rich (R-rich) peptides.

In this presentation, I will discuss our recent investigation on phase separation involving various combinations of N130 and R-rich peptides. Our study aimed to decipher the structural nuances of the resulting phase-separated condensates, employing small-angle neutron scattering (SANS) measurements. Additionally, we employed theoretical models and multiscale computer simulations to unveil the intricate molecular characteristics underlying the experimental structural profiles. Collectively, these experimental and theoretical insights not only contribute to our current understanding but also pave the way for a quantitative comprehension of the liquid-like attributes within the NPM1-rich GC region of the nucleolus in the future.

References

[1] Dar, F. *et al*. Biomolecular Condensates Form Spatially Inhomogeneous Network Fluids. *Nat. Commun.* (2024).

(session 3-3)

Statistical Thermodynamics of Biological Condensates and Chemical Dynamics of Biological Networks

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We will introduce recently proposed nucleation and phase separation theory that provides a unified, quantitative explanation of growth dynamics and size distributions of various biological condensates and nanomaterial systems [1,2]. This theory explains why most nucleus systems exhibit unimodal size distributions and predicts the existence of a critical supersaturation degree at which nuclei undergo phase separation. We will show that the chemical potential of small nuclei strongly deviates from the Gibbs-Thomson equation, which underlies the classical nucleation theory and its modern generalizations, and explain its relationship to the nonclassical growth dynamics and the size distribution of various nuclei. We will also show that the largest cluster size (LCS) is an important state variable that determines the critical supersaturation degree. The supersaturation degree decreases with the LCS, approaching unity in the macroscopic limit. If time permits, we will also talk about new transport equation and chemical dynamics theory that are useful for quantitative investigations into dynamics of complex networks in living cells [3,4]. Combined with modern high throughput experiments and cutting-edge computational methods, including machine learning, these works enable quantitative predictions regarding probabilistic dynamics of living systems on the basis of fundamental principles in physics and chemistry.

References

[1] Kang et al., Supersaturation, Nucleation, and Phase Separation of Mesoscopic Systems, J. Am. Chm. Soc. (in press) (2025).

[2] Kim et al., Multiphasic size-dependent growth dynamics of nanoparticle ensembles, Proc. Nat. Acad. Sci. U.S.A. 122, e2424950122 (2025).

[3] Park et al., The Chemical Fluctuation Theorem governing gene expression, Nature Communications 9, 297 (2018); Song et al., Frequency spectrum of chemical fluctuation: a probe of reaction mechanism and dynamics, PLoS Comp. Biol. 15, e1007356 (2019); Kang et al., Stochastic kinetics of Nanocatalytic Systems, Phys. Rev. Letters 126, 126001 (2021).

[4] Song et al., Transport Dynamics of Complex Fluids, Proc. Nat. Acad. Sci. 116, 12733 (2019); Kang et al., Real-space imaging of nanoparticle transport and interaction dynamics by graphene liquid cell TEM, Sci. Adv. 7, 49 (2021); Lee et al., Transport dynamics of water molecules between lipid membranes J. Phys. Chem. Letters 15, 4437 (2024).