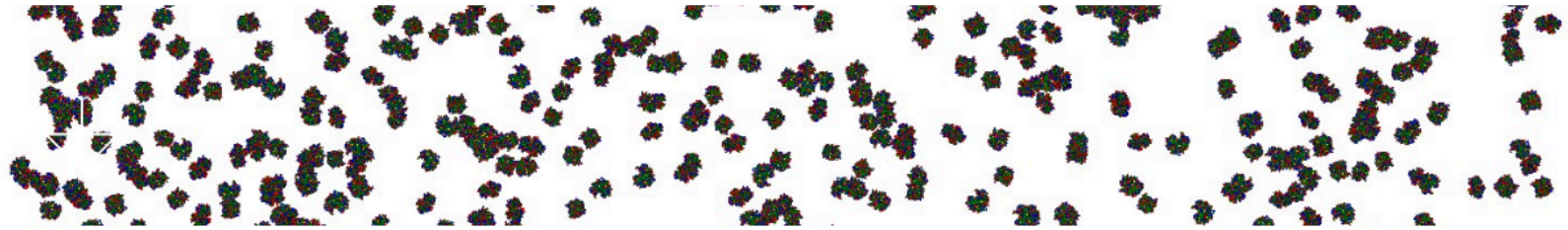

Sixth Biological Diffusion and Brownian Dynamics Brainstorm

Start
11 December 2025

End
12 December 2025

Category
Workshop

Venue
Online via Zoom - please note the different time zones (PDT/CET)!

Pricing
Free

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Description

Biological Diffusion and Brownian Dynamics Brainstorm 6 (BDBDB6) is an online workshop dedicated to exploring and informally discussing the latest experimental and theoretical advances in biological diffusion. This event will emphasize the Brownian Dynamics method and its applications in simulating biological macromolecules. Building on a tradition that began in 2007, the BDBDB series has been held periodically, with the most recent event taking place in 2021.

Confirmed Speakers:

- Maciej Długosz, Faculty of Physics; University of Warsaw, Poland
- Adrian Elcock. Department of Biochemistry and Molecular Biology; University of Iowa, USA
- Sarah Harris, School of Mathematical and Physical Sciences; University of Sheffield, UK
- Tamar Schlick, Department of Chemistry, Mathematics and Computer Science; NY University, USA
- Johannes Schoeneberg, University of California, San Diego, USA

Program

Thursday, 11 Dec 2025

17:00 Welcome

17:10 Keynote 1 – Adrian Elcock: –Brownian dynamics simulations of large biomolecular systems with hydrodynamic interactions–

17:50 Contributed talk 1 – Hender Lopez: –Machine Learning approach to include Hydrodynamics interactions in Brownian Dynamics simulations–

18:10 Keynote 2 – Johannes Schoeneberg

18:50 Break

19:15 Keynote 3 – Maciej Długosz: –Accurate Estimation of Diffusion Coefficients of Confined Molecules with Shape-Based Coarse-Graining and Mobility Scaling.–

19:55 Contributed talk 2 – Debabrata Dey: –Lost in the Cytoplasm: A Journey of Weakly Basic Drugs Through Cellular Crowding–

20:15 Discussion session/software updates

Friday, 12 Dec 2025

17:00 Welcome

17:05 Keynote 4 – Tamar Schlick: –Folding genomes at nucleosome resolution–

17:45 Contributed talk 3 – Parisa Fasihianifard: –Molecular Encounter Efficiency in Cellular Environments: Brownian Dynamics Insights into Molecular Binding–

18:05 Contributed talk 4 – Riccardo Beccaria: –Protein-Ligand Association in Crowded Media: a Multiscale Brownian Dynamics Simulation Approach–

18:25 Discussion and Q&A on Updates

19:00 Break

19:15 Keynote 5 – Sarah Harris: –Multi-meso: Mesoscale modelling of Molecular Machines and MesoSoup–

19:55 Contributed talk 5 – Abraham Muniz Chicarro: – Multiscale approach to predict drug-protein binding kinetics–

20:15 Contributed talk 6 – Lane Votapka: –Multiscale Simulation Approaches To Computational Binding Kinetics with SEEKR–

20:35 Roadmap Discussion: What's next?

Talks

Brownian Dynamics Simulations of Large Biomolecular Systems with Hydrodynamic Interactions

Adrian Elcock (adrian-elcock@uiowa.edu)
University of Iowa

In this talk I will describe some recent work from our lab aimed at developing Brownian dynamics methods suitable for modeling large biomolecular systems. I will describe some algorithmic developments that allow hydrodynamic interactions to be rapidly approximated, and I will show some current applications of the methods in our lab.

Machine Learning Approach to Include Hydrodynamics Interactions in Brownian Dynamics Simulations

Dr. Hender Lopez (hender.lopezsilva@tudublin.ie)
Technological University Dublin

Hydrodynamics interactions (HIs) are known to heavily influence the slow-down of the mobilities of colloids in crowded environment. For example, we have recently used Brownian dynamic simulations to study the diffusion of proteins in crowded environment and found that HIs are a major contributor to the slow down of proteins under these conditions [1, 2]. From a computational point of view, the inclusion of HIs in implicit solvent simulation (as in Brownian Dynamics) can be highly costly in terms of computer time. To address this limitation, a common strategy is to use a mean-field approximation to include HIs [3]. In this approach, HIs are modeled as corrections to the diffusion coefficients of the colloids. For this, expressions of how the diffusion coefficients depend on the occupied volume fraction are used, but this approach does not completely account for the local distribution of colloids. In this work, we introduce a data driven model that predicts the diffusion coefficient of colloids and includes far field and lubrication HIs [4]. We will also discuss how this approach can reduce the computational cost compared to other methodologies (e.g. Stokesian Dynamics) and how polydispersity (which is normally ignored) can be also addressed with this methodology.

[1] Grimaldo M., Lopez H., et al. (2019) J. Phys. Chem. Lett. 10, 1709–1715
[2] Beck C., Hirschmann F., Lopez H., et al. (in preparation)
[3] Mereghetti P., Wade R. C. (2012) J. Phys. Chem. B 116, 8523–8533
[4] Lopez H. (in preparation)

Accurate Estimation of Diffusion Coefficients of Confined Molecules with Shape-Based Coarse-Graining and Mobility Scaling.

Maciej Długosz (Maciej.Dlugosz@fuw.edu.pl)
Institute of Experimental Physics, Faculty of Physics, University of Warsaw

The diffusion of geometrically confined molecules plays a fundamental role in many areas of physics, biophysics, and chemistry. Under geometric confinement, translational and rotational mobilities of arbitrarily shaped molecules become complex functions of their position and orientation relative to nearby boundaries. This complexity arises from hydrodynamic interactions with confining surfaces. A variety of numerical approaches exist that can be used, in principle, to evaluate diffusion coefficients of rigid bodies with arbitrary shapes under confinement, including boundary integral methods, finite element and immersed boundary methods, fluctuating hydrodynamics, and mesoscopic molecular dynamics. Other techniques approximate molecular geometries using rigid assemblies of spherical subunits, either incorporating analytical corrections to account for boundary effects or modeling the boundaries themselves as assemblies of spheres. However, these techniques can be computationally demanding. While coarse-graining molecular shapes improves their computational efficiency, it typically introduces errors into the calculated mobility functions. In this talk, I will present a recent approach applicable to creeping (Stokes) flows that enables accurate estimation of translational and rotational diffusion coefficients for arbitrarily shaped molecules in bounded viscous fluids. The method uses low-resolution, shape-based coarse-graining combined with a low-level hydrodynamic description based on the Rotne–Prager–Yamakawa tensor. Accuracy is restored by scaling the components of the computed mobility matrix using factors derived from energy-dissipation arguments in Stokes flow. This approach significantly reduces computational cost while maintaining high accuracy, offering a practical tool for modeling diffusion in confined geometries.

Lost in the Cytoplasm: A Journey of Weakly Basic Drugs Through Cellular Crowding

Dr. Debabrata Dey (ddey@amity.edu)
Amity University, UP, India

For drugs to exert their biological effects, they must reach their intracellular targets, requiring efficient membrane permeation, diffusion, and distribution. We examined the intracellular diffusion and distribution of small-molecule fluorescent drugs in comparison with proteins using fluorescence microscopy and fluorescence recovery after photobleaching (FRAP). While proteins diffused freely, small molecules showed a strong dependence of diffusion behavior on their pK_a. Weakly basic drugs exhibited markedly reduced fractional recovery and 10–20-fold slower diffusion in cells than in aqueous solution. As most pharmaceutical drugs are weak bases, their protonation in the cytoplasm forms membrane-impermeable ionic species, leading to ion trapping and reduced mobility under crowded intracellular conditions. Imaging revealed substantial accumulation of these molecules in acidic organelles, particularly lysosomes. Inhibition of lysosomal import slightly improved diffusion, whereas preventing protonation through N-acetylation greatly enhanced both diffusion and recovery. These findings indicate that N-acetylation may be an effective strategy to improve the intracellular availability and distribution of weakly basic small-molecule drugs.

Folding Genomes at Nucleosome Resolution

Tamar Schlick (Schlick@nyu.edu)
New York University

Molecular modeling and simulation is now recognized as a field on its own right capable of making key mechanistic insights into biomolecular processes. Notable successes include prediction of conformational transitions and mechanisms; generation of new insights into biomolecular activity; and thriving collaborations between modeling and experimentation, including experiments driven by modelinghemical. As examples from my lab, I will describe mesoscale and multiscale modeling applications of genome folding, showing how we use tailored algorithms like DiSCO (Discrete Surface Charge Optimization) and Brownian dynamics to fold genes, recover chromosome conformations from Hi-C maps, and solve frontier problems in the epigenetic regulation of the genome and its relation to human disease.

Molecular Encounter Efficiency in Cellular Environments: Brownian Dynamics Insights into Molecular Binding

Parisa Fasihianifard (pfasi002@ucr.edu)
University of California Riverside

Molecular encounters in the cell are governed by diffusion, crowding, and spatial organization, all of which shape how efficiently substrates bind their targets. To understand these principles, we used Brownian dynamics simulations (BD) to model the association of 1-(o- carboxyphenylamino)-1-deoxyribulose 5-phosphate (CdRP) in the tryptophan biosynthesis pathway of Escherichia coli, focusing on the bifunctional enzyme TrpCF (fused PRAI:IGPS) under both in test-tube and in cell-like environments. We quantified how interenzyme distance, active-site orientation, macromolecular crowding, and side-reactions influence substrate binding. In test-tube conditions, reducing interenzyme distances below 50 Å improved binding, but fused TrpCF offered no advantage over optimally spaced, freely diffusing enzymes, indicating that proximity alone is insufficient without favorable orientation. Under diluted conditions, direct binding probabilities ranged from 1.5% to 17.2%, with the 0° orientation yielding an 11.5- fold improvement, highlighting the importance of active-site alignment. In cell-like environments, crowding and side reactions slowed substrate diffusion and reduced CdRP availability. Even TrpCF could not maintain high binding efficiency, showing that intermediate transfer remains vulnerable to spatial interference, though mechanisms such as electrostatically steered diffusion could enhance association. Specific local arrangements, including crowder positioning near both PRAI and IGPS, modestly increased direct binding, suggesting that spatial geometry can still support productive encounters.

Protein-ligand Association in Crowded Media: a Multiscale Brownian Dynamics Simulation Approach

Riccardo Beccaria (riccardo.beccaria@h-its.org)
HITS

Intracellular crowding plays a crucial role in the behaviour of proteins, influencing their motion, kinetic and equilibrium properties. In this work, we present an adaptive model to simulate the association process between two biomolecules in a crowded environment by Brownian dynamics, and thereby compute the bimolecular association rate constant. In this model, interactions are represented with atomistic resolution when crowder molecules are nearby and with a coarser force field when they are farther away. We applied this model to two contrasting protein-ligand systems with varying crowder types and densities. Markov State modelling of the encounter trajectories was used to analyse the binding pathways. The results reveal competing effects resulting in a non-monotonic dependence of the association rate on crowder concentration. While the presence of the crowders can hinder binding by reducing the translational diffusion of the molecules in the medium and obstruction of binding sites, the crowders can also enhance association via caging, channeling, and other mechanisms. We are currently working on incorporating physics-informed machine learning to improve the calculation of short-range intermolecular forces, to increase the accuracy of our simulations. Authors: Riccardo Beccaria, Abraham Muñiz Chicharro, Rebecca Wade

Multi-meso: Mesoscale Modelling of Molecular Machines and Mesosoup

Prof. Sarah Harris (sarah.harris@sheffield.ac.uk)
University of Sheffield

Modelling the mesoscale is arguably the next major challenge for biomolecular simulations, especially given the huge breakthroughs ongoing in bioimaging at the mesoscale. I will describe our own Fluctuating Finite Element Analysis (FFEA) method for performing simulations of molecular motors such as dynein, and the challenges we face. I will then speak more generally about efforts to build a community for biomolecular simulation at the mesoscale, and ask whether people like the idea of MesoSoup, or if there are alternative suggestions.

Multiscale Approach to Predict Drug-Protein Binding Kinetics

Dr. Abraham Muñiz Chicharro (abrahanmuniz@gmail.com)
HITS

Molecular binding rate constants are important parameter for assessing drug efficacy in vivo. In this work, we present a computationally efficient multiscale pipeline designed to predict protein–drug association rate constants and to provide mechanistic insights into the determinants of these rates, such as conformational gating or induced fit. To apply this pipeline in an automated and user-friendly manner, we developed SDAMD, a new software tool integrated into the SDA7 software. SDAMD combines Brownian and molecular dynamics simulations to exploit the advantages of both simulation techniques while reducing their limitations. Brownian dynamics is used to efficiently simulate the diffusional movement of molecules to compute the diffusional association rates and to generate diffusional encounter complexes, with optional evaluation of conformational selection effects when ensembles of protein conformers are available. Subsequently, molecular dynamics refine the generated encounter complexes by simulating internal motions and induced-fit effects. SDAMD results have been validated for a set of proteins and ligands that are diverse in their chemical nature, range of size and flexibility. The predicted association rates show good agreement with experimentally determined values, demonstrating the potential of this multiscale framework to guide molecular design.

Multiscale Simulation Approaches To Computational Binding Kinetics with Seekr

Lane Votapka (l1votapka@ucsd.edu)
University of California San Diego

Understanding and predicting molecular binding kinetics remains one of the central challenges in computational biophysics and drug discovery. The Simulation-Enabled Estimation of Kinetic Rates (SEEKR) framework provides a powerful multiscale approach that integrates molecular dynamics (MD) and Brownian dynamics (BD) simulations to model key biomolecular processes. By leveraging both atomistic and continuum regimes, SEEKR enables accurate and efficient estimation of association and dissociation rate constants (kon and koff) for protein–ligand systems. SEEKR has demonstrated strong performance across diverse targets, including kinases and chaperone proteins such as Janus Kinase, Heat Shock Protein 90, and Threonine Tyrosine Kinase. Crucially, its multiscale design circumvents the limitations of traditional BD simulations, replacing the empirical "reaction criteria" with collective variables and MD-based sampling that reveal realistic binding pathways. Ongoing work focuses on addressing challenges such as charge polarization upon binding, defining optimal MD/BD interface placement, and refining the representation of complex reaction pathways. Together, these developments continue to expand SEEKR's potential as a general framework for simulating and understanding molecular recognition dynamics.

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