Biophysics at the Dawn of Exascale Computers

Hamburg, Germany | May 16–20, 2022

Biophysical Society Biophysical Journal

Université franco-allemande Deutsch-Französische Hochschule

ASU Center for Biological Physics Arizona State University

ASU School of Molecular Sciences ARIZONA STATE UNIVERSITY

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Organizing Committee

Rommie Amaro, University of California San Diego, USA

Christophe Chipot, Centre National de la Recherche Scientifique (CNRS), France

Rosana Collepardo, University of Cambridge, United Kingdom

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Alberto Perez, University of Florida, USA

Abhishek Singharoy, Arizona State University, USA

Gregory A. Voth, University of Chicago, USA

Thank You to Our Sponsors

May 2022

Dear Colleagues,

We would like to welcome you to the Biophysical Society Thematic Meeting, ***Biophysics at the Dawn of Exascale Computers***, co-sponsored by Arizona State University, University of Florida, Chicago Center for Theoretical Chemistry and Université Franco-Allemande Deutsch-Französische Hochschule. These Thematic Meetings are an opportunity for scientists who might not normally meet together to gather and exchange ideas in different locations around the world. Previous Thematic Meetings have been held in Brazil, Canada, China, France, India, Ireland, Peru, Poland, South Africa, and South Korea, to name a few. Future meetings are scheduled for Sweden, England, Malaysia, Argentina, and Greece.

Our meeting is aimed at bringing together biophysicists to share their perspective on the application of large-scale computations for solving a diverse range of biological problems. Notably, modalities deployed on today's computing resources capture events on scales ranging from small molecules to molecular motors, up to the chemical machinery of an entire cell. Growing from the peta- to the exascale regime, these machines will yield 3-orders of magnitude more data at least an order of magnitude speed-up than available today; the GPUs are optimized particularly for machine-learning optimizations. Already leveraging parallel capabilities, areas of diffraction data and single-particle image processing, hybrid-modeling, molecular dynamics and free-energy simulations, and drug design and discovery are frontrunners in leveraging the prowess of exascale computing. Fortuitously overlapping with the inception of the exascale era, this meeting will prepare the Biophysics community to start advancing the development and implementation of computational algorithms towards the best use of these resources.

We hope that you will all actively take part in the discussions following each talk, in the poster sessions, and in the informal exchanges that will be possible during the coffee breaks, reception, banquet, and during the free time given to explore the city. We also hope that you will enjoy the beautiful surroundings of Hamburg!

The Organizing Committee

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Abhishek Singharoy, Arizona State University, USA
Gregory A. Voth, University of Chicago, USA

Biophysical Society Code of Conduct, Anti-Harassment Policy

The Biophysical Society (BPS) is committed to providing an environment that encourages the free expression and exchange of scientific ideas. As a global, professional Society, the BPS is committed to the philosophy of equal opportunity and respectful treatment for all, regardless of national or ethnic origin, religion or religious belief, gender, gender identity or expression, race, color, age, marital status, sexual orientation, disabilities, veteran status, or any other reason not related to scientific merit.

All BPS meetings and BPS-sponsored activities promote an environment that is free of inappropriate behavior and harassment by or toward all attendees and participants of Society events, including speakers, organizers, students, guests, media, exhibitors, staff, vendors, and other suppliers. BPS expects anyone associated with an official BPS-sponsored event to respect the rules and policies of the Society, the venue, the hotels, and the city.

Definition of Harassment
The term "harassment" includes but is not limited to epithets, unwelcome slurs, jokes, or verbal, graphic or physical conduct relating to an individual's race, color, religious creed, sex, national origin, ancestry, citizenship status, age, gender or sexual orientation that denigrate or show hostility or aversion toward an individual or group.

Sexual harassment refers to unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature. Behavior and language that are welcome/acceptable to one person may be unwelcome/offensive to another. Consequently, individuals must use discretion to ensure that their words and actions communicate respect for others. This is especially important for those in positions of authority since individuals with lower rank or status may be reluctant to express their objections or discomfort regarding unwelcome behavior. It does not refer to occasional compliments of a socially acceptable nature. It refers to behavior that is not welcome, is personally offensive, debilitates morale, and therefore, interferes with work effectiveness. The following are examples of behavior that, when unwelcome, may constitute sexual harassment: sexual flirtations, advances, or propositions; verbal comments or physical actions of a sexual nature; sexually degrading words used to describe an individual; a display of sexually suggestive objects or pictures; sexually explicit jokes; unnecessary touching.

Attendees or participants who are asked to stop engaging in harassing behavior are expected to comply immediately. Anyone who feels harassed is encouraged to immediately inform the alleged harasser that the behavior is unwelcome. In many instances, the person is unaware that their conduct is offensive and when so advised can easily and willingly correct the conduct so that it does not reoccur. Anyone who feels harassed is NOT REQUIRED to address the person believed guilty of inappropriate treatment. If the informal discussion with the alleged harasser is unsuccessful in remedying the problem or if the complainant does not feel comfortable with such an approach, they can report the behavior as detailed below.

Reported or suspected occurrences of harassment will be promptly and thoroughly investigated. Following an investigation, BPS will immediately take any necessary and appropriate action. BPS will not permit or condone any acts of retaliation against anyone who files harassment complaints or cooperates in the investigation of same.

Reporting a Violation
Violations of this Conduct Policy should be reported immediately. If you feel physically unsafe or believe a crime has been committed, you should report it to the police immediately.

To report a violation to BPS:

- You may do so in person at the Annual Meeting at the BPS Business Office in the convention center.

- You may do so in person to BPS senior staff at Thematic Meetings, BPS Conferences, or other BPS events.

- At any time (during or after an event), you can make a report through http://biophysics.ethicspoint.com or via a dedicated hotline (phone numbers listed on the website) which will collect and relay information in a secure and sensitive manner.

Reported or suspected occurrences of harassment will be promptly and thoroughly investigated per the procedure detailed below. Following an
investigation, BPS will immediately take any necessary and appropriate action. BPS will not permit or condone any acts of retaliation against anyone who files harassment complaints or cooperates in the investigation of same.

Investigative Procedure
All reports of harassment or sexual harassment will be treated seriously. However, absolute confidentiality cannot be promised nor can it be assured. BPS will conduct an investigation of any complaint of harassment or sexual harassment, which may require limited disclosure of pertinent information to certain parties, including the alleged harasser.

Once a complaint of harassment or sexual harassment is received, BPS will begin a prompt and thorough investigation. Please note, if a complaint is filed anonymously, BPS may be severely limited in our ability to follow-up on the allegation.

- An impartial investigative committee, consisting of the current President, President-Elect, and Executive Officer will be established. If any of these individuals were to be named in an allegation, they would be excluded from the committee.

- The committee will interview the complainant and review the written complaint. If no written complaint exists, one will be requested.

- The committee will speak to the alleged offender and present the complaint.

- The alleged offender will be given the opportunity to address the complaint, with sufficient time to respond to the evidence and bring his/her own evidence.

- If the facts are in dispute, the investigative team may need to interview anyone named as witnesses.

- The investigative committee may seek BPS Counsel's advice.

- Once the investigation is complete, the committee will report their findings and make recommendations to the Society Officers.

- If the severity of the allegation is high, is a possible repeat offense, or is determined to be beyond BPS's capacity to assess claims and views on either side, BPS may refer the case to the alleged offender's home institution (Office of Research Integrity of similar), employer, licensing board, or law enforcement for their investigation and decision.

Disciplinary Actions
Individuals engaging in behavior prohibited by this policy as well as those making allegations of harassment in bad faith will be subject to disciplinary action. Such actions range from a written warning to ejection from the meeting or activity in question without refund of registration fees, being banned from participating in future Society meetings or Society-sponsored activities, being expelled from membership in the Society, and reporting the behavior to their employer or calling the authorities. In the event that the individual is dissatisfied with the results of the investigation, they may appeal to the President of the Society. Any questions regarding this policy should be directed to the BPS Executive Officer or other Society Officer.

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GENERAL INFORMATION

Registration/Information Location and Hours

On Monday, Tuesday, Wednesday, Thursday, and Friday registration will be in the foyer near Seminar Rooms I, II, and III of the Center for Free-Electron Laser Science (CFEL), Building 99. Registration hours are as follows:

Monday, May 16	15:00 – 18:30
Tuesday, May 17	08:30 – 18:30
Wednesday, May 18	08:30 – 18:30
Thursday, May 19	13:30 – 18:45
Friday, May 20	08:30 – 15:45

Instructions for Presentations

(1) Presentation Facilities:

A data projector will be available in the Seminar Room. Speakers are required to bring their own laptops and adaptors. It is recommended to have a backup of the presentation on a USB drive in case of any unforeseen circumstances. Speakers are advised to preview their final presentations before the start of each session. **Masks are required, however speakers may remove their mask during presentation.**

(2) Poster Session:

1) All poster sessions will be held in the foyer of the of the Center for Free-Electron Laser Science (CFEL), Building 99. **Masks are required during presentation.**

2) A display board measuring 90 cm wide x 130 cm high - Portrait Style (approximately 2.9 feet wide x 4.3 feet high) will be provided for each poster. Poster boards are numbered according to the same numbering scheme as listed in the e-book.

3) Posters should be set up the morning of Tuesday, May 17 and removed by noon Friday, May 20. All posters are available for viewing during all poster sessions; however, there will be formal poster presentations at the following times:

Tuesday, May 17	15:00 – 16:00	Odd-numbered poster boards
Tuesday, May 17	16:00 – 17:00	Even-numbered poster boards
Wednesday, May 18	15:00 – 16:00	Odd-numbered poster boards
Wednesday, May 18	16:00 – 17:00	Even-numbered poster boards
Thursday, May 19	15:15 – 16:05	Odd-numbered poster boards
Thursday, May 19	16:05 – 17:00	Even-numbered poster boards

4) During the assigned poster presentation sessions, presenters are requested to remain in front of their poster boards to meet with attendees.

5) All posters left uncollected at the end of the meeting will be disposed.

Meals and Coffee Breaks

There will be a Welcome Reception on Monday evening from 18:30 – 19:30 in the Foyer.

Coffee Breaks (Tuesday, Wednesday, Thursday, and Friday) will be served in the Foyer.

Lunches (Tuesday, Wednesday, and Friday) will be served in the Foyer.

A banquet will be held on Thursday evening beginning at 20:00 at FISCHclub Blankenese, Strandweg 30a, 22587 Hamburg. More information will be provided at registration. All participants must have confirmed participation to attend.

Smoking

Please be advised that smoking is not permitted at the Center for Free-Electron Laser Science (CFEL), Building 99.

Proof of Vaccination and Masks

All participants are to have had their vaccinations verified through CrowdPass. No exemptions will be permitted. Please be prepared to show your approved vaccination QR code from CrowdPass at registration.

KN95 or FFP2 masks are required and must be worn for the duration of the meeting.

Name Badges

Name badges are required to enter all scientific sessions, poster sessions, and social functions. Please wear your badge throughout the meeting.

Internet

Wi-Fi will be provided at the venue. Attendees will receive information at registration.

Contact

If you have any further requirements during the meeting, please contact the meeting staff at the registration desk from May 16 – 20 during registration hours.

In case of emergency, you may contact the following:

Elena Kornilova, CFEL/DESY Staff (Available 09:00 – 14:00)
elena.kornilova@uni-hamburg.de

Dorothy Chaconas, BPS Staff
dchaconas@biophysics.org

Umi Zhou, BPS Staff
uzhou@biophysics.org

Biophysics at the Dawn of Exascale Computers

Hamburg, Germany
May 16 – 20, 2022

All sessions will be held at Center for Free-Electron Laser Science (CFEL), Building 99 in Seminar Rooms I, II, III unless otherwise noted.

PROGRAM

Monday, May 16, 2022

15:00 – 18:30	**Registration/Information**	Foyer
18:30 –19:30	**Welcome Reception**	Foyer

Tuesday, May 17, 2022

08:30 – 18:30	**Registration/Information**	Foyer
09:00 – 09:05	Abhishek Singharoy, Arizona State University, USA **Welcome & Opening Remarks**	
Session I	**Protein Folding and Assembly I (From Sequence to Structure)**	
09:05 – 09:15	Gregory A. Voth, University of Chicago, USA, Chair	
09:15 – 09:45	Chaok Seok, Seoul National University, South Korea ***Searching Chemical Space and Protein Space in the Era of Accurate Protein Structure Prediction***	
09:45 – 10:15	Henry Chapman, DESY, Germany ***Serial Diffractive Imaging and Crystallography with Intense X-ray Sources***	
10:15 – 10:30	Eliane Briand, MPI for Biophysical Chemistry, Germany* ***Constant PH Molecular Dynamics in Gromacs Using Lambda Dynamics and the Fast Multipole Method***	
10:30 – 11:00	**Coffee Break**	Foyer
Session II	**Dissection of Allosteric Pathways I (Thermodynamics of Allostery)**	
11:00 – 11:15	Alberto Perez, University of Florida, USA, Chair	
11:15 – 11:45	Abbas Ourmazd, University of Wisconsin-Milwaukee, USA ***What Can We Learn from Machine Learning?***	
11:45 – 12:15	Ivet Bahar, University of Pittsburgh, USA ***Using Network Models for Exploring Biomolecular Function at Multiple Scales from Proteins to Chromosomes***	
12:15 – 12:30	Karen Palacio-Rodriguez, Sorbonne Université IMPMC, France* ***Development of Predictive Approaches for Biomolecular Association Kinetics***	
12:30 – 13:30	**Lunch**	Foyer

Session III	**Macromolecular Interactions I (Molecular Recognition)**	
13:30 – 13:45	Rommie Amaro, University of California San Diego, USA, Chair	
13:45 – 14:15	Adrian Mulholland, University of Bristol, United Kingdom ***Cloud-Enabled Dynamical Nonequilibrium Molecular Dynamics Simulations Reveal the Structural Basis for Allostery, Signal Propagation and Networks Involved in Evolution of Catalytic Activity***	
14:15 – 14:45	Gerhard Hummer, Max Planck Institute, Germany ***Molecular Simulations in the Era of AI and Exascale Computing: Ready for Prime Time?***	
14:45 – 15:00	Kumar Gaurav, Johannes Gutenberg University of Mainz, Germany* ***Molecular Recognition by Phase-Separated Condensates in Small RNA Biology***	
15:00 – 17:00	**Coffee Break / Poster Session I**	Foyer
Session IV	**Bottom-Up Structure of Cells I (Soluble Complexes)**	
17:00 – 17:15	Petra Fromme, Arizona State University, USA, Chair	
17:15 – 17:45	Zaida Luthey-Schulten, University of Illinois at Urbana-Champaign, USA ***Simulating a Living Minimal Cell: An Integration of Experiment, Theory, and Simulation***	
17:45 – 18:15	Josh Vermaas, Michigan State University, USA* ***Tracking Photosynthetic Reactant and Product Diffusion Across Cyanobacterial Carboxysomes on Exascale Computing Platforms***	
18:15 – 18:30	Arvind Ramanathan, Argonne National Laboratory, USA* ***Visualizing the SARS-COV-2 Replication Transcription Complex with AI-Driven Adaptive Multiscale Simulations***	

Wednesday, May 18, 2022

8:30 – 18:30	**Registration/Information**	Foyer
Session V	**Macromolecular Interactions II (Protein-Ligand Interactions)**	
09:00 – 09:15	Gregory A. Voth, University of Chicago, USA, Chair	
09:15 – 09:45	Tamara Bidone, University of Utah, USA* ***Structure and Function of Integrin: From Molecular Dynamics to Adhesion Assembly***	
09:45 – 10:15	Greg Bowman, Washington University, USA ***A First Glimpse of Exascale Computing with Folding@Home***	
10:15 – 10:30	Vytautas Gapsys, Max Planck Institute, Germany* ***Large Scale Protein-Ligand Binding Free Energy Calculations in the Cloud and HPC Centers***	
10:30 – 11:00	**Coffee Break**	Foyer
Session VI	**Dissection of Allosteric Pathways II (Kinetics of Allostery)**	
11:00 – 11:15	Arwen Pearson, University of Hamburg, Germany, Chair	

11:15 – 11:45	Florence Tama, Nagoya University, Japan ***Integrative Modeling to Characterize Structure and Dynamics of Biomolecules from Single Molecule Experiments***	
11:45 – 12:15	Holger Stark, University of Göttingen, Germany ***Atomic-Resolution Structure Determination of Proteins by Cryo-EM***	
12:15 – 12:30	Neelanjana Sengupta, IISER Kolkata, India* ***Expectation Maximized Molecular Dynamics: Rapid Estimation of Transition Barriers in Biomolecular Free Energy Landscapes***	
12:30 – 13:30	**Lunch**	Foyer
Session VII	**Protein Folding and Assembly II (From Structure to Complexes)**	
13:30 – 13:45	Petra Fromme, Arizona State University, USA, Chair	
13:45 – 14:15	Yuji Sugita, Riken, Japan ***Conformational Dynamics and Functions of Proteins in Crowded Cellular Environments***	
14:15 – 14:45	Sarah Rauscher, University of Toronto, Canada ***Molecular Simulations of Disordered and Flexible Proteins***	
14:45 – 15:00	Dagmar Klostermeier, University of Muenster, Germany* ***Dissecting Structure, Function and Dynamics of the Dead-Box Helicase EIF4A by Single-Molecule Fret Microscopy: Regulation of Translation Initiation Through Modulation of Kinetic Competition Between Alternative Conformational Cycles***	
15:00 – 17:00	**Coffee Break / Poster Session II**	Foyer
Session VIII	**Bottom-up Structure of Cells II (Membrane-Bound Complexes)**	
17:00 – 17:15	Christophe Chipot, Centre National de la Recherche Scientifique (CNRS), France, Chair	
17:15 – 17:45	Syma Khalid, University of Southampton, United Kingdom ***Molecular Simulations of Gram-Negative Bacterial Cell Envelopes: A Complex Picture is Emerging***	
17:45 – 18:15	Oliver Beckstein, Arizona State University, USA ***Molecular Mechanisms of Transporter Membrane Proteins***	
18:15 – 18:30	Karolina Mikulska, Nicolaus Copernicus University in Torun, Poland* ***The Role of PE-Binding Protein 1 in the Ferroptosis Process***	

Thursday, May 19, 2022

08:30 – 13:30	**Free Time**	
13:30 – 18:45	**Registration/Information**	Foyer
Session IX	**Dissection of Allosteric Pathways III (Controlling Induced-Fit)**	
13:30 – 13:45	Alberto Perez, University of Florida, USA, Chair	
13:45 – 14:15	Banu Ozkan, Arizona State University, USA ***Protein Dynamics and Function Through the Lens of Evolution***	

14:15 – 14:45	Nathalie Reuter, University of Bergen, Norway ***Deciphering the Energetics of Peripheral Protein-Membrane Interactions***	
14:45 – 15:00	Luise Jacobsen, University of Southern Denmark, Denmark* ***Introducing the Automated: Ligand Searcher (Alise)***	
15:00 – 15:15	An Ghysels, Ghent University* ***Pushing the Time Scale of Membrane Permeability Calculations***	
15:15 – 17:00	**Coffee Break / Poster Session III**	Foyer
Session X	**Macromolecular Interactions III (Confined Environments)**	
17:00 – 17:15	Abhishek Singharoy, Arizona State University, USA, Chair	
17:15 – 17:45	Helmut Grubmüller, Max Planck Institute, Germany ***Single Molecular Structure and Function at the Dawn of Exascale Computers***	
17:45 – 18:15	Emad Tajkhorshid, University of Illinois at Urbana-Champaign, USA ***Novel Modeling Tools and Simulation Approaches for Exascale Structural Biology***	
18:15 – 18:30	Kush Coshic, University of Illinois at Urbana-Champaign, USA* ***The Structure and Physical Properties of a Bacteriophage Genome Resolved Through Atomistic Molecular Dynamics Simulation***	
18:30 – 18:45	Benedikt Rennekamp, Heidelberg University, Germany* ***Hybrid Simulations of Collagen Failure***	
20:00 – 23:00	**Banquet**	Fischclub Blankenese

Friday, May 20, 2022

08:30 – 15:45	**Information**	Foyer
Session XI	**Protein Folding and Assembly III (Supercomplexes and Beyond)**	
09:00 – 09:15	Raimund Fromme, Arizona State University, USA, Chair	
09:15 – 09:45	JC Gumbart, Georgia Tech, USA ***Combatting Microbial Infections with Leadership-Class MD Simulations***	
09:45 – 10:15	Ulrich Kleinekathöfer, Jacobs University Bremen, Germany* ***Insight from Advanced Molecular Simulation Approaches into Transport Across Bacterial Membranes***	
10:15 – 10:45	Ryan Cheng, Rice University, USA ***A Physicochemical Basis for Chromosome Organization and Structural Heterogeneity Across Human Cell Types***	
10:45 – 11:15	**Coffee Break**	Foyer
Session XII	**DNA, Nucleosomes, and Chromatin**	
11:15 – 11:30	Rosana Collepardo, University of Cambridge, United Kingdom, Chair	

11:30 – 12:00	Modesto Orozco, IRB-Barcelona, Spain ***New Advances in Molecular Simulations of Nucleic Acids***	
12:00 – 12:30	Tamar Schlick, New York University, USA ***Trajectory of a Prospering Field: Biomolecular Modeling in the Age of Technology***	
12:30 – 12:45	Vlad Cojocaru, Hubrecht Institute, The Netherlands* ***Breaths, Twists, and Turns of Free and Interacting Atomistic Nucleosomes***	
12:45 – 13:00	Sergio Cruz-Leon, Max Planck Institute, Germany* ***Twisting DNA with Salt***	
13:00 – 14:00	**Lunch**	Foyer
Session XIII	**Bottom-Up Organization of Cells III (Minimal Cell)**	
14:00 – 14:15	Rommie Amaro, University of California San Diego, USA, Chair	
14:15 – 14:45	Rebecca Wade, Heidelberg Institute for Theoretical Studies, Germany ***Computing Protein Binding Kinetics: Challenges in Bridging Timescales***	
14:45 – 15:00	Peter Tieleman, University of Calgary, Canada ***Computer Simulations of Lipid-Protein Interactions***	
15:00 – 15:15	Rajat Punia, Indian Institute of Technology Delhi, India* ***Damped Elastic Network Model in Thermal Bath Accurately Describes Lipid Bilayer Collective Dynamics***	
15:15 – 15:45	**Closing Remarks and *Biophysical Journal* Poster Awards**	
15:45	**Departure**	Foyer

**Short talks selected from among submitted abstracts*

SPEAKER ABSTRACTS

SEARCHING CHEMICAL SPACE AND PROTEIN SPACE IN THE ERA OF ACCURATE PROTEIN STRUCTURE PREDICTION

Chaok Seok[1,2]; Jiho Sim[1]; Sohee Kwon[1]; Changsoo Lee[1]; Jonghun Won[2];
[1]Seoul National University, Department of Chemistry, Seoul, South Korea
[2]Galux Inc, Seoul, South Korea

Protein structure prediction has become highly accurate by the big sequence and structure data and the recent advances in deep learning techniques. The extensive repertoire of predicted protein structures provides a new opportunity for discovering new chemicals and proteins that regulate the physiological functions of proteins that were not explored by structure-based computations before. We have been developing tools for searching chemical space and protein space for such purposes. We have predicted small-molecule binding sites and corresponding chemicals for all proteins in the human proteome using a similarity-based docking method. We have also developed a technique for predicting putative binding proteins in human proteome and corresponding binding poses for a given chemical by combining similarity-based and ab initio prediction methods. However, more accurate methods for predicting protein-chemical and protein-protein interactions are necessary for more effective functional studies and drug discovery. We thus discuss our ongoing efforts to improve protein-chemical and protein-protein docking accuracy using machine-learned energy.

SERIAL DIFFRACTIVE IMAGING AND CRYSTALLOGRAPHY WITH INTENSE X-RAY SOURCES

Henry Chapman
DESY, Germany

No Abstract

CONSTANT PH MOLECULAR DYNAMICS IN GROMACS USING LAMBDA DYNAMICS AND THE FAST MULTIPOLE METHOD

Eliane Briand[1]; Bartosz Kohnke[1]; Carsten Kutzner[1]; Helmut Grubmüller[1];
[1]Max Planck Institute for Multidisciplinary Sciences, Department of Theoretical and Computational Biophysics, Göttingen, Germany

The residue protonation state of biomolecules is usually treated as fixed in molecular dynamics (MD) simulations: this is equivalent to a time-varying pH. Numerous approaches are found in the literature to obtain a more realistic constant pH by dynamically altering protonation, however these tend to be too slow or too complicated for routine use. Building upon the established λ-dynamics method with Hamiltonian interpolation, we aim to make constant pH MD (CPH-MD) accessible to the non-expert by an intuitive interface, a user-oriented documentation, and a performance high enough for use beyond small proteins through FMM electrostatics. To illustrate practical usages of our implementation as well as sketch an accuracy profile, we present titration results for small histidine and glutamate-containing peptides with pKa shifted by their proximate environment, as well as the usual CPH-MD benchmark protein lysozyme.

WHAT CAN WE LEARN FROM MACHINE LEARNING?

Abbas Ourmazd[1];
[1]University of Wisconsin-Milwaukee, Physics, Milwaukee, WI, USA

The advent of high repetition-rate XFELs is generating a torrent of data. Will machine learning conquer the deluge? Machine learning, a branch of Artificial Intelligence, perform tasks typically reserved for humans. Most machine-learning tasks involve some kind of "recognition". Examples include recognizing individuals (facial recognition), obstacles (self-driving vehicles), or patterns (stock-market fluctuations).Recognition tasks are, in essence, labeling exercises. Recognizing a face, for example, involves attaching a name to it. Most machine-learning approaches, such as "Deep Learning", provide little or no insight into the principles by which the labels are generated. The ability to perform a task does not require understanding the underlying processes. You do not have to understand the workings of the brain to recognize your spouse. Scientific knowledge, in contrast, entails understanding the underlying processes. A deep understanding of facial recognition, for example, must elucidate the structures and processes by which the brain recognizes faces. Traditionally, scientific understanding proceeds by assimilating a few experimental clues into a (mathematically sound) theory. This theory is then buttressed by a succession of carefully designed observations. Such discovery processes are designed to make the best use of limited data. The data deluge is undermining this approach. I will describe how machine learning can help extract scientific understanding from the data deluge. This work was supported by the US Department of Energy, Office of Science, Basic Energy Sciences under award DE-SC0002164 (underlying dynamical techniques), and by the US National Science Foundation under award STC 1231306 (underlying data analytical techniques).

USING NETWORK MODELS FOR EXPLORING BIOMOLECULAR FUNCTION AT MULTIPLE SCALES FROM PROTEINS TO CHROMOSOMES

Ivet Bahar; Ivet Bahar[1];
[1]University of Pittsburgh, Computational and Systems Biology, Pittsburgh, PA, USA

Network models proved useful in the last two decades in improving our understanding of the coupled dynamics of biomolecules, from individual proteins to supramolecular. Among network models that have been developed for biological applications, elastic network models (ENMs) found wide usage in molecular biology[1]. The global motions predicted by ENMs have proven in numerous applications to provide a good description of molecular machinery and allosteric behavior, opening the way to designing allosteric modulators of protein function. Application to supramolecular structures, including cryo-EM structures, has been a major utility. A major advantage of ENMs is their simplicity and computational efficiency, which enables proteome-scale analyses, applications to large systems such as the entire chromatin, and/or combination with machine learning (ML) algorithms. Such a recent ML approach that incorporates ENM predictions in addition to sequence and structure data proved to yield an accurate assessment of the effect of mutations on function, compared to those based on sequence and structure exclusively[2,3]. Another recent adaptation to modeling human chromosomal 3D dynamics showed the close correspondence between the spatial mobilities of gene loci and the expression levels of the corresponding genes[4]. These recent developments and future directions will be discussed. References 1 1. Krieger JM, Doruker P, Scott AL, Perahia D, Bahar I. (2020) Towards Gaining Sight of Multiscale Events: Utilizing Network Models and Normal Modes in Hybrid Methods. Curr Opin Struct Biol 64:34-41. 2. Ponzoni L, Bahar I. (2018) Structural dynamics is a determinant of the functional significance of missense variants. Proc Natl Acad Sci USA 115: 4164-4163. Ponzoni L, Penaherrera DA, Oltvai ZN, and Bahar I (2020) Rhapsody: Predicting the pathogenicity of human missense variants. Bioinformatics 36:3084-3092. 4. Zhang S, Chen F, Bahar I. (2020) Differences in the Intrinsic Spatial Dynamics of the Chromatin Contribute to Cell Differentiation. Nucleic Acids Res 48, 1131-1145.

DEVELOPMENT OF PREDICTIVE APPROACHES FOR BIOMOLECULAR ASSOCIATION KINETICS

Karen Palacio-Rodriguez[1,2]; Hadrien Vroylandt[3]; Lukas S Stelzl[4]; Gerhard Hummer[5,6]; Pilar Cossio[2,7]; Fabio Pietrucci[1];
[1]Sorbonne Université, Institut de Minéralogie, de Physique des Matériaux et de Cosmochimie, IMPMC, Paris, France
[2]University of Antioquia, Biophysics of Tropical Diseases Max Planck Tandem Group, Medellín, Colombia
[3]Sorbonne Université, Institut des Sciences du Calcul et des Données, ISCD, Paris, France
[4]Johannes Gutenberg University Mainz, Faculty of Biology, Mainz, Germany
[5]Max Planck Institute of Biophysics, Department of Theoretical Biophysics, Frankfurt, Germany
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Atomistic computer simulations of rare events have three paramount goals: predicting detailed mechanisms, free energy landscapes, and kinetic rates. In real-life applications, all of these tasks are cumbersome and require intensive human and computer effort, especially the calculation of rates. We developed two efficient methodologies for the prediction of transition rates from molecular dynamics simulations. Both strategies only require sets of short simulations, which allows exploiting the parallel capabilities of current supercomputers. On one side, transition path sampling trajectories are the golden standard to access mechanistic information: we demonstrate that they also encode accurate thermodynamic and kinetic information, that can be extracted by training a data-driven Langevin model of the dynamics projected on a collective variable [1]. We use fullerene dimers as a proxy system to protein-protein interactions and recover free energies, position-dependent diffusion coefficients, and rates. On the other side, we use metadynamics, an enhanced sampling technique that allows accelerating the sampling of rare events but distorts the dynamics. We overcome this limitation by developing a method based on Kramers' theory for calculating the barrier-crossing rate when a time-dependent bias is added to the system [2]. We tested this method in a double-well potential and in the fullerene dimers, showing that we are able to extract the rate and measure at the same time the quality of the collective variables. Finally, we apply the method to a complex protein-ligand interaction (CDK2-03K) reproducing the experimental unbinding rate up to an order of magnitude discrepancy. Overall, these new theoretical tools make efficient use of computing resources providing simple procedures to accurately predict kinetic rates and could be suitable for applications far beyond the field of biomolecular association.References:1. Palacio-Rodriguez, K., & Pietrucci, F. (2021). Free energy landscapes, diffusion coefficients and kinetic rates from transition paths. arXiv preprint arXiv:2106.05415.2. Palacio-Rodriguez, K., Vroylandt, H., Stelzl, L. S., Pietrucci, F., Hummer, G., & Cossio, P. (2021). Transition rates, survival probabilities, and quality of bias from time-dependent biased simulations. arXiv preprint arXiv:2109.11360.

CLOUD-ENABLED DYNAMICAL NONEQUILIBRIUM MOLECULAR DYNAMICS SIMULATIONS REVEAL THE STRUCTURAL BASIS FOR ALLOSTERY, SIGNAL PROPAGATION AND NETWORKS INVOLVED IN EVOLUTION OF CATALYTIC ACTIVITY

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Simulations have helped to identify important features of SARS-CoV-2 proteins, such as the effects of linoleic acid on the viral Spike protein. Dynamical-nonequilibrium molecular dynamics (D-NEMD) simulations reveal allosteric coupling of the fatty acid binding site to distant functional regions in the Spike, such as the furin cleavage site. They also show significant differences between viral variants (Alpha, Delta and Omicron). They have identified coupling between allosteric sites and the active site in beta-lactamase enzymes; the pathways identified contain positions that differ between clinically relevant variants, indicating that allosteric effects modulate the spectrum of activity. The D-NEMD approach can effectively combine cloud-based and other HPC resources. Increasingly, simulations are contributing to the engineering of natural enzymes and de novo biocatalysts. Simulations are also contributing to the emerging evidence that activation heat capacity is an important factor in enzyme evolution and thermoadaptation. Directed evolution of a designed Kemp eliminase unexpectedly introduced curvature into the temperature dependence of reaction, showing the emergence of an activation heat capacity. The dynamical networks involved provide targets for mutation. QM/MM methods can identify mechanisms of reaction (e.g. for covalent inhibitors such as ibrutinib, and for the SARS-CoV-2 main protease, Mpro) determinants of catalytic activity and predict the activity of bacterial enzymes against antibiotics. Virtual reality offers new ways interact with simulations, and new ways to collaborate. Interactive MD simulation in virtual reality (iMD-VR) allows fully flexible docking of drugs into protein targets. The COVID-19 pandemic has highlighted the need for effective tools for virtual collaboration. Groups of researchers can work together, using iMD-VR for molecular problems such as structure-based drug design. Using the cloud, researchers in different physical locations can work together in the same virtual molecular environment. Simulations, including iMD-VR, with sharing of models, have been used to design peptide inhibitors of the SARS-CoV-2 Mpro.

MOLECULAR SIMULATIONS IN THE ERA OF AI AND EXASCALE COMPUTING: READY FOR PRIME TIME?

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Rapid growth in raw computing power and advances in artificial intelligence are ushering in a new era in biomolecular modeling and simulation. On the one hand, a massive expansion in aggregate computing allows us to tackle ever larger biomolecular systems; on the other hand, the development of sophisticated artificial intelligence frameworks provides critical support in the design, operation, and analysis of these simulations. In my presentation, I will showcase our efforts to tackle the tripe challenges of system size, complexity and time scale. I will highlight our push towards cell-scale molecular simulations and our efforts to develop a self-learning AI framework to resolve second-scale dynamics in microsecond-scale simulations and reveal the underlying mechanisms.

MOLECULAR RECOGNITION BY PHASE-SEPARATED CONDENSATES IN SMALL RNA BIOLOGY

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Trans-generational epigenetic inheritance (TEI) is the transmission of epigenetic information across generations via small RNAs or proteins present in the sperm or eggs. In many organisms including humans, small RNAs play an essential role in TEI. In C. elegans, TEI is facilitated by a small RNA. Small RNA-based molecular mechanisms are often choreographed in non-membraneous organelles called bio-molecular condensates. The formation of these condensates is orchestrated by the liquid-liquid phase separation of the proteins containing intrinsically disordered regions (IDR) or by multivalent proteins. Experiments have shown that PEI granules need to specifically recognise their native binding partners to mediate TEI and ensure that correct RNAs are inherited. To understand how PEI granules achieve their biological function by specific molecular recognition we are studying PEI granules and their biological patterns with multi-scale simulations. Coarse-grained simulations with implicit solvent enabled us to investigate the co-phase separation of PEI-granules proteins and their binding partners and thus the possible roles of inherent sequence-encoded affinities for the recognition of disordered proteins by phase-separated PEI-granules. In these simulations, we explored the possible roles of post-translational modifications such as phosphorylation and proteolytic cleavage on modulating the recognition by PEI granules. To better understand the molecular driving forces of PEI granule phase behaviour and molecular recognition by these granules we employ large-scale coarse-grained simulations (> 1 Million particles and hundreds of proteins) with near-atomic resolution and explicit solvent. Back-mapping to atomistic representations and simulations of sub-systems will enable us to ultimately understand with an atomic resolution how PEI granules ensure TEI of the correct RNAs.

SIMULATING A LIVING MINIMAL CELL: AN INTEGRATION OF EXPERIMENT, THEORY, AND SIMULATION

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We present a whole-cell fully dynamical kinetic model (WCM) of JCVI-syn3A, a minimal bacterial cell with a reduced genome of 493 genes that has retained few regulatory proteins or small RNAs. Cryo-electron tomograms provide the cell geometry and ribosome distributions. Time-dependent behaviors of concentrations and reaction fluxes from stochastic-deterministic simulations over a cell cycle reveal how the cell balances demands of its metabolism, genetic information processes, and growth, and offer insight into the principles of life for this minimal cell. The energy economy of each process including active transport of amino acids, nucleosides, and ions is analyzed. WCM reveals how emergent imbalances lead to slowdowns in the rates of transcription and translation. Integration of experimental data is critical in building a kinetic model from which emerges a genome-wide distribution of mRNA half-lives, multiple DNA replication events that can be compared to qPCR results, and the experimentally observed doubling behavior. Simulations are carried out using our GPU-based Lattice Microbes software for the spherical cells approximately 500 nm in diameter. References: Thornburg et al. “Fundamental behaviors emerge from simulations of a living minimal cell” , 2022, Cellhttps://doi.org/10.1016/j.cell.2021.12.025Gilbert et al. “Generating Chromosome Geometries in a Minimal Cell from Cryo-Electron Tomograms and Chromosome Conformation Capture Maps” 2021, Frontiers in Molecular Biosciences, https://doi.org/10.3389/fmolb.2021.644133T. M. Earnest, J. A. Cole, and Z. Luthey-Schulten. Simulating Biological Processes: Stochastic Physics from Whole Cells to Colonies Reports on Progress in Physics, 2018, doi:10.1088/1361-6633/aaae2cM. J. Hallock, J. E. Stone, E. Roberts, C. Fry, Z. Luthey-Schulten Simulation of reaction diffusion processes over biologically-relevant size and time scales using multi-GPU workstations Parallel Comput. 2014, 40, 86-99, doi: 10.1016/j.parco.2014.03.009.

TRACKING PHOTOSYNTHETIC REACTANT AND PRODUCT DIFFUSION ACROSS CYANOBACTERIAL CARBOXYSOMES ON EXASCALE COMPUTING PLATFORMS

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Molecular simulation algorithms depend on rapidly evaluating Newton's equations of motion across a moderate number of particles for a large number of timesteps. Advances in modern high performance computing architectures have driven algorithmic changes to develop GPU-resident molecular simulation engines. These advances have had a profound impact on the types of questions that can be addressed by molecular simulation at low cost. One example from our group are explicit solvent simulations for a model cyanobacterial carboxysome. The carboxysome is an organelle found in photosynthetic bacteria that locally concentrates carbon dioxide to improve the efficiency for RuBisCO, the key enzyme in photosynthetic carbon fixation. The carboxysome encapsulates RuBisCO and carbonic anhydrase, which is an enzyme that converts soluble bicarbonate into lipophilic carbon dioxide, increasing local carbon dioxide concentration for RuBisCO. Leveraging these new GPU-resident molecular simulation engines, we determine the permeability for the carboxysome to RuBisCO reactants and products through unbiased simulation. We find that the carboxysome itself is not selectively permeable to bicarbonate over carbon dioxide, as originally hypothesized. Instead, the carboxysome shell proteins form a general barrier to maintain the carbon dioxide gradient generated by carbonic anhydrase activity within the carboxysome. We highlight that the multimillion atom scale for this system would have required substantial computational resources as recently as a few years ago. However, utilizing new GPU architectures, systems at this scale achieve excellent performance that offer new opportunities for molecular simulation as it moves into the exascale regime.

VISUALIZING THE SARS-COV-2 REPLICATION TRANSCRIPTION COMPLEX WITH AI-DRIVEN ADAPTIVE MULTISCALE SIMULATIONS

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) replication transcription complex (RTC) is a multi-domain protein responsible for replicating and transcribing the viral mRNA inside a human cell. Attacking RTC function with pharmaceutical compounds is a pathway to treating COVID-19. Conventional tools, e.g., cryo-electron microscopy and all-atom molecular dynamics (AAMD), do not provide sufficiently high resolution or timescale to capture important dynamics of this molecular machine. Consequently, we develop an iterative workflow that bridges the gap between these resolutions, using mesoscale fluctuating finite element analysis (FFEA) continuum simulations and a hierarchy of AI-methods that continually learn and infer features from simulations while maintaining consistency between AAMD and FFEA resolutions. We further leverage a multi-site distributed workflow manager to orchestrate AI, FFEA, and AAMD jobs, providing optimal resource utilization across HPC centers. Our AI-enabled multiscale simulations provides mechanistic insights into how the SARS-CoV-2 RTC machinery operates, in terms of backtracking the bound RNA across two different enzyme complexes, including the viral RNA-dependent RNA polymerase (RDRP) and the non-structural protein-13 (nsp13). The intrinsic correlations between the two rather large subunits points to a cooperative mechanism that can be potentially exploited to devise novel small molecules that can target the RTC. Further, the insights from this study also points to potentially 'missing' links between other RTC experimental datasets -- complementing knowledge from across multiple studies. We posit that such AI-informed multiscale simulation techniques hold promise in gaining fundamental insights into the mechanism of how large molecular machines function while complementing experimental observations and potentially providing feedback in improving their overall quality and accessibility.

STRUCTURE AND FUNCTION OF INTEGRIN: FROM MOLECULAR DYNAMICS TO ADHESION ASSEMBLY

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Integrin is a transmembrane adhesion protein that undergoes long range conformational transitions associated with its functional conversion from inactive (low affinity) to active (high affinity). Its inactive/bent and active/extended conformations have been described, however interconversion between these conformations necessarily involves intermediate states that are less well studied. Elucidating the properties of these intermediates at the atomistic level and characterizing their contributions to the assembly of adhesions at the mesoscale is important for understanding how cells form adhesions with the extracellular environment, change shape, and move. My lab develops algorithms that combine molecular simulations, analysis of the principal components of the atomistic motions, and mesoscale modeling to understand how integrin conformations govern the assembly of cell adhesions. Our studies reveal that the structural deformations of the bent and intermediate conformations are directed towards elongation of the headpiece away from the legs, and destabilization of the transmembrane helices; the open state presents high flexibility, with correlated motions between headpiece and legs. At the mesoscale, bent integrins cannot form stable adhesions, but intermediate or open conformations stabilize the adhesions. These effects are due to small variations in ligand binding affinity and ligand-bound lifetime in the presence of actin retrograde flow. Collectively, our results demonstrate how integrin receptors stabilize nascent adhesions through changes in atomistic motions that underlie differences in conformation, ligand-binding affinity, and ligand-bound lifetime. These findings are conceptually important because they identify new functional relationships between integrin conformation and cell function.

A FIRST GLIMPSE OF EXASCALE COMPUTING WITH FOLDING@HOME

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What would you do with an exascale computer if you were given access to one at this very moment and had to use it at full capacity to the best of your ability? While absurd sounding, this hypothetical situation is exactly where the Folding@home community found itself in the spring of 2020 as citizen scientists from around the world pooled their computational resources to drive research on SARS-CoV2. Our response was to go big in every possible dimension, simulating large systems (e.g. the spike), many different proteins (e.g. most of the SARS-CoV-2 proteome), many different homologs (e.g. from across extant coronaviruses), and long timescales using a combination of goal-oriented adaptive sampling and the extreme parallelism of Folding@home. The results are a powerful demonstration of the predictive power of modern simulations when taken to a massive scale, and include both fundamental insights and a potent inhibitor of the main protease that is advancing towards clinical trials.

LARGE SCALE PROTEIN-LIGAND BINDING FREE ENERGY CALCULATIONS IN THE CLOUD AND HPC CENTERS

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Rational drug design benefits from molecular dynamics based protein-ligand binding free energy calculations which offer a remarkable accuracy in guiding ligand optimization process. While such calculations are computationally expensive, the advances in simulation engines, compute infrastructures and specialized software for the free energy calculation setup have now substantially reduced the barriers for using these methods in everyday projects. Here, I will present several large scale ligand screening studies illustrating how these calculations can be efficiently performed in HPC facilities and in the AWS cloud setting. Relying on the open source software (GROMACS and PMX) we can set up, perform and analyze large scale free energy calculations for hundreds of compounds in a matter of days. The use case of the simulations in an HPC center illustrates the ease with which such type of calculations can be scaled up: the throughput is limited only by the available resources. The cloud based services offer a possibility to scale up in a virtually unlimited manner, yet it is important to carefully select the compute architectures for the cost efficient calculations. The results obtained from the performed scans provide valuable information on the current state of the field in predicting free energy differences for pharmaceutically relevant targets.

INTEGRATIVE MODELING TO CHARACTERIZE STRUCTURE AND DYNAMICS OF BIOMOLECULES FROM SINGLE MOLECULE EXPERIMENTS

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X-ray free electron laser (XFEL) is an exciting new technology that could significantly extend our structural knowledge of biological systems. One of the experimental approaches that are currently pursued is called "single particle analysis", in which strong laser light from XFEL is used to observe single molecular complexes. Since it does not require crystallization, it could be applied to a wider variety of systems under various physiological conditions. However, applications to biological systems are still challenging due to their low diffraction power and require further developments of experimental as well as computational analysis techniques. Therefore, we have been developing programs to perform three-dimensional reconstruction from a large data set of diffraction patterns by adopting algorithms used in cryo-EM 3D reconstruction to handle XFEL diffraction patterns. This approach was successfully tested with X-ray tomography experimental data. Using synthetic data, we have also estimated the experimental conditions that are necessary to achieve subnanometer resolutions for ribosomes. Finally, after data processing of nanoparticles experimental diffraction patterns to reduce background noise, we have obtained a 3D shape consistent with scanning electron microscope images.

ATOMIC-RESOLUTION STRUCTURE DETERMINATION OF PROTEINS BY CRYO-EM

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No Abstract

EXPECTATION MAXIMIZED MOLECULAR DYNAMICS: RAPID ESTIMATION OF TRANSITION BARRIERS IN BIOMOLECULAR FREE ENERGY LANDSCAPES

Neelanjana Sengupta[1]; Pallab Dutta[1];
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Modern-day efforts towards uncovering emergent protein structure-function relationships incorporate methods that leverage data from both experiments and computational studies. A large part of such efforts is devoted to capturing the infrequent transitions that control complex biophysical processes over long timescales. Such efforts, however, are often challenged by the lack of objective definitions of system-specific slow modes, and sometimes by lack of access to high-end computational resources. This talk will present our recently proposed novel algorithm termed 'Expectation Maximized Molecular Dynamics' (EMMD) that incorporates a statistical inference-based approach in estimating free energy barriers related to rate-limiting transitions. The method bypasses conventional thermodynamic sampling by connecting metastable basins using Bayesian likelihood maximization. Furthermore, the method incorporates a tunable self-feedback protocol to prevent unnecessary sampling that does not effectively contribute to the underlying distributions of metastable states. Termed 'Expectation Maximized Molecular Dynamics' (EMMD), this algorithm has demonstrated significant efficacy in predicting the experimentally known free energy barriers in putative biomolecular systems. Ongoing efforts are geared towards leveraging the method to unravel key descriptive features that accompany conformational changes during the catalytic activity of a tyrosine kinase. Finally, as we step into the era of ‘exascale computing’, a glimpse of the emergent possibilities from integration of EMMD with other state of the art machine learning and enhanced sampling schemes will be discussed. Reference: P. Dutta and N. Sengupta, J. Chem. Phys. 153, 154104 (2020)

CONFORMATIONAL DYNAMICS AND FUNCTIONS OF PROTEINS IN CROWDED CELLULAR ENVIRONMENTS

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Recent advances of molecular dynamics (MD) simulations of biomolecules have allowed us to study protein dynamics and functions in realistic cellular environments. The cellular cytoplasm contains a large number of proteins, RNAs, metabolites, ions, and waters, suggesting that specific protein-ligand or protein-protein interactions are competing with many other off-target molecular interactions. If we include such interactions explicitly, larger number of atoms are required in the calculations, reducing the simulation time significantly. Therefore, we need to accelerate MD simulation on massively supercomputer by software optimization or parallelization. In addition, the increase of a time step to integrate the equation of motions is very effective. By introducing a theoretically accurate definition of temperature and a new hydrogen mass repartitioning scheme, we succeeded to use a 5 fs time step in the velocity Verlet integrator and a 3.5 fs fast motion time step in the multiple time step integrator without losing the stability and accuracy. These new methods were implemented into GENESIS software (https://www.r-ccs.riken.jp/labs/cbrt/) and are used now in the simulations of macromolecular crowding.

MOLECULAR SIMULATIONS OF DISORDERED AND FLEXIBLE PROTEINS

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The STAT (signal transducer and activator of transcription) protein family is an important therapeutic target in leukemia and lymphoma. However, the lack of structural and dynamic information on STAT proteins limit drug design efforts. Cancer activating mutations located in the SH2 domain of STAT5B, including N642H, are observed clinically and the molecular basis for their increased oncogenicity is not currently known. Additionally, patients with the N642H mutation are reported to have increased drug resistance and poor response to chemotherapy. Here, we used molecular dynamics simulations to elucidate the dynamics of the wild type and an oncogenic mutant of human STAT5B protein, and to provide a molecular basis for the increased oncogenicity. We carried out extensive atomistic simulations of the wild type and mutant STAT5B proteins. The N642H mutation (i) led to a more rigid SH2 domain; (ii) significantly affected the size and dynamics of the peptide binding pockets; and (iii) increased the intra-SH2 domain interactions. The structural and dynamic information uncovered in this work may facilitate the design of small molecule drugs targeting the cancer activating mutants of STAT5B.

DISSECTING STRUCTURE, FUNCTION AND DYNAMICS OF THE DEAD-BOX HELICASE EIF4A BY SINGLE-MOLECULE FRET MICROSCOPY: REGULATION OF TRANSLATION INITIATION THROUGH MODULATION OF KINETIC COMPETITION BETWEEN ALTERNATIVE CONFORMATIONAL CYCLES

Alexandra Z Andreou[1]; Ulf Harms[1]; **Dagmar Klostermeier**[1];
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Translation initiation is a tightly regulated step in eukaryotic protein biosynthesis. Deregulation leads to altered gene expression, tumor formation, and cancer. Initiation requires unwinding of secondary structures in the 5'-untranslated region (5'-UTR) of mRNAs by the DEAD-box helicase eIF4A, an RNA-dependent ATPase and ATP-dependent helicase. The activities of eIF4A are stimulated by the translation factors eIF4B and eIF4G, and are linked to switching of eIF4A between open and closed conformations. Single-molecule FRET by confocal microscopy on eIF4A in solution shows that eIF4B, eIF4G, and the RNA itself modulate eIF4A activity by promoting formation of the closed state. Single-molecule experiments on surface-immobilized eIF4A by total internal reflection microscopy reveals that eIF4B and eIF4G jointly stimulate eIF4A activities by accelerating its conformational changes. The RNA substrate also influences eIF4A conformational dynamics: Short RNAs or RNA duplexes with short 5'-single-stranded regions only partially stimulate the ATPase activity, and closing is rate-limiting for the conformational cycle. Longer RNAs or RNA duplexes with a longer 5'-single-stranded region maximally stimulate ATP hydrolysis and promote closing of eIF4A. However, the rate constants of unwinding do not correlate with the length of a single-stranded region preceding a duplex. Instead, they reach a maximum for RNA with a single-stranded region of only six nucleotides. We propose a kinetic partitioning model where eIF4B, eIF4G, and the 5'-UTR of the respective mRNA affect eIF4A activity and translation initiation by modulating its partitioning between alternative conformational cycles: futile cycles (ATP hydrolysis without RNA unwinding), unproductive cycles (neither ATP hydrolysis nor duplex unwinding), and productive cycles (ATP hydrolysis coupled to duplex unwinding). Computational modeling of the flux of eIF4A through the different conformational cycles should enable predictions of translation efficiencies of mRNAs.

MOLECULAR SIMULATIONS OF GRAM-NEGATIVE BACTERIAL CELL ENVELOPES: A COMPLEX PICTURE IS EMERGING

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No Abstract

MOLECULAR MECHANISMS OF TRANSPORTER MEMBRANE PROTEINS

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Transport of ions and small molecules across the cell membrane against electrochemical gradients is catalyzed by integral membrane proteins that use a source of free energy to drive the energetically uphill flux of the transported substrate. Secondary active transporters couple the spontaneous influx of a "driving" ion such as sodium ions or protons to the flux of the substrate. The fact that these transporters operate out of equilibrium and change their conformation between an inward-facing and outward-facing conformation in a cyclical fashion, called the alternating access mechanism, has been recognized as the general principle underlying secondary transporter function. We have been using molecular dynamics simulations (long equilibrium MD, free energy calculations, enhanced sampling for rare events, constant pH simulations) in combination with experimental techniques such as X-ray crystallography, cryo-electron microscopy, and functional measurements to better understand the mechanism of secondary active transport in a wide range of transporters such as sodium/proton antiporters, bile acid/sodium symporters, the major facilitator superfamily, nucleobase-sodium symporters, and zinc transporters. We have been following a research program to dissect key steps in the transport cycle, namely identification of binding sites of ions and substrates, delineation of the moving elements of the alternating access transition, and sampling of the transitions themselves. We employ an analytical multi-scale rate model to combine estimates of rates and free energies from simulations to arrive at a bottom-up computational estimate for the transporter turnover number as function of the external gradients. Experiments and simulations taken together allow us to understand the fundamental physiological process of ion-driven transport across the membrane at the molecular scale.

THE ROLE OF PE-BINDING PROTEIN 1 IN THE FERROPTOSIS PROCESS

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Recent years have brought attention to ferroptosis, an iron- and lipid peroxidation-dependent form of regulated cell death implicated in a broad range of diseases, including Alzheimer and Parkinson disease, acute brain injury, kidney damage, and asthma. Active research shows that ferroptosis may become a new strategy in the treatment of cancers. Its characteristic feature is the enhanced lipid peroxidation where abstraction of H-atoms from polyunsaturated phospholipids drives the entire peroxidation process causing membrane damage. We demonstrated that a protein complex composed of 15-lipoxygenase and PEBP1 (Cell 2017), is a master promoter of ferroptotic cell-death signaling regulated by several enzymatic mechanisms occurring independently or concertedly. Our objective is to unearth the enzymatic mechanisms underlying the ferroptosis process at the molecular level. Using molecular dynamics simulations, elastic network models, and bioinformatic tools together with the experimental verification, we explained the previously unknown mechanisms and factors that affect ferroptosis, thus providing molecular insights of the catalytic processes involved (JACS, J Clin Invest 2018, JCIM 2019). Our recent studies also revealed a critical role of iNOS/nitric oxide (Nature Chem Biol 2020, IJMS 2021) and phospholipase iPLA2beta (Nature Chem Biol 2021) in the regulation of ferroptosis. We also resolved an apparent paradox related to the most common ferroptosis inhibitor, Ferrostatin 1. We demonstrated that its anti-ferroptotic action is not limited to radical scavenging but also includes suppression of peroxidation of arachidonoyl-phosphatidylethanolamine catalyzed by the 15-lipoxygenase-PEBP1 complex (Redox Biol 2021). Our studies showed that the presence of PEBP1 is essential for the generation of the ferroptotic cell death signal. Acknowledgments: This work was supported by NIH (HL114453, U01AI156924, U01AI156923, CA165065, NS076511, NS061817, P41 GM103712) and by Polish National Science Centre no. 2019/35/D/ST4/02203.

PROTEIN DYNAMICS AND FUNCTION THROUGH THE LENS OF EVOLUTION

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Proteins are the most efficient nano-machines. Not only they perform a broad range of functions, but they exquisitely adapt and evolve. Thus, inferring evolutionary record of extant proteins offers a tractable and highly effective solution protein design. We have developed a physics-based metrics called the Dynamic Flexibility Index (DFI) to study protein evolution. DFI quantifies the resilience of a given position to the perturbations occurring at various parts of a protein using linear response theory, mimicking the multidimensional response when the protein's conformational space is probed upon interaction with small molecules or other cellular constituents. In this talk we will discuss our structural dynamics analysis on TEM-1 enzymes. TEM-1 is a class A β-lactamase produced by gram negative bacteria as their defense against β-lactam antibiotics through hydrolysis of β-lactam ring. Modern TEM-1 have evolved from gram negative common ancestral, GNCA β-lactamase about 2 billion years ago. Resurrection studies of GNCA have revealed that evolution has preserved their 3-D fold, but surprisingly several remarkable changes have been observed in their biophysical properties. Ancestral GNCA exhibit promiscuity albeit moderate efficiency, which enables it to provide resistance against several β-lactam antibiotics. This is in contrast with TEM-1 β-lactamase which is more specific enzyme hydrolyzing only penicillin with a higher efficiency. Moreover, TEM-1 has functionally evolved by substituting about 50% of its residue positions while conserving not only the fold but also its catalytic sites residues. Are there minimum number substitutions that are required for modulating the evolution from promiscuity to substrate specificity? If so, what are their biophysical characteristics? Here we answer these questions by exploring conformation dynamics of ancestral and modern TEM-1 through a set of position specific dynamics metrics. Our analysis not only provides the mechanism of evolution of resistance but also allows us to predict the location of substitutions required to evolve from a promiscuous β-lactamase to degrade a specific antibiotic with a better efficiency.

DECIPHERING THE ENERGETICS OF PERIPHERAL PROTEIN-MEMBRANE INTERACTIONS

Emmanuel E Moutoussamy[1]; Hanif M Khan[1]; Qaiser Waheed[1]; Anne Gershenson[4]; Mary F Roberts[3]; Chris Chipot[2]; **Nathalie Reuter**[1];
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Peripheral membrane proteins (PMPs) bind temporarily to cellular membranes and play important roles in signalling, lipid metabolism and membrane trafficking. Obtaining accurate membrane-PMP affinities using experimental techniques is more challenging than for protein-ligand affinities in aqueous solution, and molecular dynamics (MD) simulations have the potential to fill that gap. The phosphatidylinositol-specific phospholipase C from Bacillus thurigiensis (BtPI-PLC), reduces host innate immunity by catalyzing the cleavage of GPI-anchored proteins at the surface of the cell, thereby contributing to bacterial virulence. The availability of detailed experimental data for BtPI-PLC binding to lipid vesicles makes it a convenient choice to evaluate computational approaches. Apparent dissociation constants (K_D) for BtPI-PLC on small unilamellar POPC vesicles have been determined experimentally for an array of membrane compositions and protein variants. Using free energy perturbation calculations, we computed the energetic cost of alanine substitution for five interfacial aromatics. The obtained values were in good agreement with experimental data (Waheed et al, J Phys Chem Lett, 2019) showing that FEP calculations provide a computationally inexpensive way to dissect the roles of interfacial amino acids. Calculation of standard protein-membrane binding free energy using MD simulations remains a daunting challenge owing to the size of the biological objects at play, the slow lipid diffusion and the large variation in configurational entropy that accompanies the binding process. To overcome these challenges, we used a computational framework relying on a series of potential-of-mean-force (PMF) calculations including a set of geometrical restraints on collective variables (Gumbart et al., JCTC, 2013). We computed a standard binding free energy of -8.2±1.4 kcal/mol, in reasonable agreement with the reported experimental values (-6.6±0.2 kcal/mol). In light of the 2.3-μs separation PMF calculation, we could gain insights into the mechanism whereby BtPI-PLC disengages from interactions with the lipid bilayer during separation (Moutoussamy et al, ChemRxiv, 2022).

INTRODUCING THE AUTOMATED LIGAND SEARCHER (ALISE)

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The elaborate and automated drug discovery tool, the Automated Ligand Searcher (ALISE), is introduced. ALISE applies a three-stage workflow with each stage applying an increasingly sophisticated computational method: molecular docking, molecular dynamics simulations, and free energy perturbation simulations, respectively, to approximate the binding free energy of ligands binding to a receptor. Poorly performing ligands are gradually segregated to narrow down the number of potential ligands. Two exemplary case studies of ALISE focusing on the polymerase basic protein 2 in influenza A virus and the main protease of SARS-CoV-2 as drug targets demonstrated that each of ALISE's three stages provides increasingly refined and valuable information on assessing the energetics between the drug candidates and a receptor. Ultimately, the automation and comprehensiveness of ALISE make it a valuable tool for improved and faster drug development workflows.

PUSHING THE TIME SCALE OF MEMBRANE PERMEABILITY CALCULATIONS

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Membrane permeability is a crucial property for the delivery of chemical compounds, nutrients, and drug molecules. For instance, the last barrier for oxygen to reach its final destination, the binding site located on the cytochrome c oxydase in the mitochondrial membrane, is the entrance into the bilayer.[1,2] While this step cannot be observed directly in experiment, oxygen trajectories can be generated with molecular dynamics simulations. A methodology based on the Smoluchowsky equation was derived to extract the dynamics of oxygen permeation from these trajectories using Bayesian analysis (BA).[3] The results of the methodology are the free energy across the membrane, and the diffusion profiles normal and parallel to the membrane surface. From these profiles, the permeability and the characteristic entrance, transit, and escape times as well as characteristic lengths have been derived for a model of the inner mitochondrial membrane. Analysis of other saturated and unsaturated phospholipid membranes in the liquid phase show little difference, while a noticeable reduction of the permeability is found in liquid ordered phases.[4]The described BA methodology has the advantage that radial diffusion can be analyzed. More importantly, multiple short trajectories can be used for the permeability calculation, whereas a strategy of counting membrane transitions would need very long trajectories for a simple hydrophilic molecule like oxygen. For a hydrophobic molecule like water, however, the BA methodology has also convergence issues. Therefore we explore a new methodology, where the intrinsic kinetics may be retrieved from an accelerated molecular dynamics simulation. Moreover, we present another new methodology based on a divide-and-conquer strategy using sampling that can assess the exact kinetics of the permeation event, i.e. without assuming diffusive kinetics in the membrane.[5]References[1] Riistama et al. Biochim. Biophys. Acta, Bioenerg. 1-4, 1 (1996).[2] Wikstrom et al. Chem. Rev. 115, 2196-2221 (2015).[3] Ghysels et al. J. Chem. Theory Comput. 13, 2962-2976 (2017).[4] Ghysels et al. Nat. Commun. 10, 5616 (2019).[5] Riccardi et al. J. Phys. Chem. B, 125, 1, 193-201 (2021).

SINGLE MOLECULAR STRUCTURE AND FUNCTION AT THE DAWN OF EXASCALE COMPUTERS

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Exascale computing will have a profound impact on biophysics, both for the experimental and the theoretical/simulation side. Progress will be essential along three lines. First, it will allow for experiments that are optimized more for maximum information gain than for straightforward analysis and interpretation. Second, it will make Bayesian approaches numerically manageable for a much larger scope than today. Third, it will allow atomistic and mesoscopic simulations to access larger spatial and longer time scales. We will provide examples for all three lines: Atomistic biomolecular structures from single molecule femtosecond XFEL diffraction experiments, dynamic single molecule atomic force spectroscopy over 11 orders of magnitude, thermodynamics of programmed ribosomal frameshifting, and the molecular mechanism of ribosomal antibiotics.

NOVEL MODELING TOOLS AND SIMULATION APPROACHES FOR EXASCALE STRUCTURAL BIOLOGY

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The viral pandemic and its huge impact on all societal aspects of human life, and in particular the power of vaccination in its control, continue to remind us of the key importance of molecular research in handling major health conditions facing humanity. Tremendous advances have been achieved in molecular and structural biological research of the SARS-CoV2 viral components presenting potential drug targets against the infection, as well as in obtaining structural information on the entire viral particle (e.g., through cryoEM studies). In parallel, a major objective in computational studies has been the development of complete models for the viral components and particle, at various desired resolutions, with the goal of completing the step needed for simulating the behavior of the whole virus in different media, and modeling its interaction, fusion, and penetration into the host cell. Such models could also provide details on the interaction of biologics such as antibodies with the virus, as well as a structural framework to develop novel strategies against the virus. Modeling such large molecular assemblies as the viral particle at a sufficiently high quality for detailed simulation and structural studies, however, poses major challenges. In this talk, I will share our latest efforts in developing a robust protocol to assemble a very large number of lipids (100,000s) and proteins (10,000s) into viral envelopes robust and stable for simulation studies. The protocol employs several advanced modeling techniques, interleaved with simulations at different resolutions, to construct optimally packed arrangements of lipids and proteins at any desired densities. In addition to spherical membranes representing viral envelopes, the protocol can be used to construct lipid-protein molecular assemblies of any shape. Along with lessons learnt and solutions to challenges during the process, I will also discuss the results of the simulations performed on whole viral envelope structures.

THE STRUCTURE AND PHYSICAL PROPERTIES OF A BACTERIOPHAGE GENOME RESOLVED THROUGH ATOMISTIC MOLECULAR DYNAMICS SIMULATION

Kush Coshic; Christopher M Maffeo[2]; David Winogradoff[2]; Aleksei Aksimentiev[1,2];
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[2]University of Illinois, Urbana-Champaign, Physics, Urbana, IL, USA

While atomic structures of protein capsids have been resolved for several viruses, the structural organization of their genomes still remains largely unknown. One such viral species is HK97 bacteriophage, for which experiments have characterized the packaging mechanism and resolved its protein capsid with atomistic resolution. Here, we report a computational reconstruction of a complete bacteriophage HK97 viral particle at atomistic resolution, including its genome, obtained from a series of simulations gradually increasing in resolution. In a typical simulation, a 37 kb DNA was forced into a viral capsid by local force, mimicking the action of the packaging motor, with or without an additional torque that twisted the molecule as it was packaged. The assembled particle was simulated at several resolutions, including a 26 million atom explicit-solvent model of a complete virion that contained both the protein capsid and the DNA. Measurements of the internal pressure throughout the simulations were consistent with experimental data whereas the SAXS profile derived from the resulting structures matched the corresponding experiment. The results of all-atom simulations revealed the pattern of DNA-protein capsid interactions and striking DNA mobility within the packaged virion. The complete atomistic structure of a packaged virion uncovers the detailed genome-capsid interactions, offering exciting new avenues for the development of antiviral drugs.

HYBRID SIMULATIONS OF COLLAGEN FAILURE

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[1]Heidelberg Institute for Theoretical Studies (HITS), Molecular Biomechanics, Heidelberg, Germany
[2]Heidelberg University, Interdisciplinary Center for Scientific Computing, Heidelberg, Germany

Structural proteins such as collagen and many other force-bearing biological materials have important functions such as carrying load and providing stability, but also in signaling. For example, we recently found that excessive mechanical load can lead to covalent bond scissions and the creation of mechanoradicals inside collagen fibrils. The implications for the hierarchical structure and subsequent biochemical reactions therein are yet to be determined on the molecular scale. We therefore developed a hybrid Kinetic Monte Carlo / Molecular Dynamics (KIMMDY) simulation scheme featuring bond ruptures that allows to investigate this link between mechanical stress, breakages, and the subsequent dynamical response. Here, bond rupture rates are calculated in the spirit of a transition state model based on the interatomic distances in the MD simulation and then serve as an input for a Kinetic Monte Carlo step. This hybrid approach bridges various time scales between MD and the rupture processes in such complex hierarchical materials, which are - even at the Dawn of Exascale Computers - otherwise not reachable. With this new technique, we investigated bond ruptures in a multi-million atom system of tensed collagen. Our simulations show a clear concentration of homolytic bond scissions near chemical crosslinks in collagen. Having a higher rupture propensity on this molecule side, crosslinks located there can act as a mechanical buffer by releasing additional length of the stressed strands. These breakage sites are located in the vicinity of redox-active amino acids, thereby also acting as a chemical buffer for the arising oxidative stress.

COMBATTING MICROBIAL INFECTIONS WITH LEADERSHIP-CLASS MD SIMULATIONS

James C. Gumbart;
[1]Georgia Tech, Physics, Atlanta, GA, USA

The cell envelope in Gram-negative bacteria comprises two distinct membranes with a cell wall between them. There has been a growing interest in understanding how these layers, namely the inner membrane (IM), outer membrane (OM), and peptidoglycan cell wall (PG), are coupled to and interact with one another to carry a number of critical cellular functions, such as mechanically resisting turgor pressure, importing nutrients, and exporting drugs. To begin addressing these uncertainties, we have developed accurate, atomistic models of all the components, which can then be used as input to molecular dynamics (MD) simulations of envelope-spanning complexes. In this talk, I will highlight a few examples of our work on these complexes, including the multi-drug efflux pump AcrAB-TolC, which exports harmful compounds before they can accumulate, the Lpt system, which traffics lipopolysaccharides to the OM, and the BAM complex, which inserts ß-barrel proteins into the OM.

INSIGHT FROM ADVANCED MOLECULAR SIMULATION APPROACHES INTO TRANSPORT ACROSS BACTERIAL MEMBRANES

Abhishek Acharya[1]; Jigneshkumar D Prajapat[1]; **Ulrich Kleinekathöfer**[1];
[1]Jacobs University Bremen, Dept. of Physics and Earth Sciences, Bremen, Germany

Channels in the outer membrane of Gram-negative bacteria provide essential pathways for the controlled and unidirectional transport of ions, nutrients and metabolites into the cell. At the same time the outer membrane serves as a physical barrier for the penetration of noxious substances such as antibiotics into the bacteria. In this presentation the simulation of ion and substrate transport across such bacterial channels will be detailed. As examples, the translocations of the antibiotics fosfomycin, ciprofloxacin and enrofloxacin have been computed recently [1-3] and will be briefly reviewed. Moreover, we investigated a variety of substrates and their free energy surfaces along the Pseudomonas aeruginosa outer membrane channel OprO using the well advanced metadynamics and umbrella sampling free energy methods. The free energy calculations have been performed to illustrate the difference of computed free energies by virtue of increasing the substrate complexity along with the involved asymmetry of the outer membrane channels during the substrate translocation process. Thus, the resulting comparative analysis helps us to choose the most appropriate method for future calculations of similar case studies.[1] J. D. Prajapati, U. Kleinekathöfer and M. Winterhalter, How to Enter a Bacterium: Bacterial Porins and the Permeation of Antibiotics, Chem. Rev. 121, 5158–5192 (2021).[2] A. Acharya, J. D. Prajapati and U. Kleinekathöfer, Improved Sampling and Free Energy Estimates for Antibiotic Permeation through Bacterial Porins, J. Chem. Theory Comput. 17, 4564–4577 (2021). [3] V. K. Golla, J. D. Prajapati and U. Kleinekathöfer, Millisecond-Long Simulations of Antibiotics Transport through Outer Membrane Channels, J. Chem. Theory Comput. 17, 549–559 (2021).

A PHYSICOCHEMICAL BASIS FOR CHROMOSOME ORGANIZATION AND STRUCTURAL HETEROGENEITY ACROSS HUMAN CELL TYPES

Ryan R. Cheng[1]; Jose N Onuchic[1];
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We use a combination of polymer physics, machine learning, and computer simulations to predict the chromosome structural ensembles for different human cell types in the interphase. Our computational predictions for chromosome organization are not only quantitatively consistent with DNA-DNA ligation and fluorescence in situ hybridization (FISH) experiments across multiple human cell types, but also remarkably capture the types of structures and the degree of structural variability observed in recent microscopy experiments.

NEW ADVANCES IN MOLECULAR SIMULATIONS OF NUCLEIC ACIDS

Modesto Orozco;
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Nucleic acids are long, heavily charged polymers which display a large conformational freedom depending on environmental conditions. Simulations of nucleic acids have been challenging due to: i) the complexity of the interactions modulating the structure and energetics of the molecule (dispersion, solvation, electrostatic, bonded terms,…) and ii) the length of the polymer, which can reach cm in eukarya organisms. I will summarize work done in Barcelona to improve nucleic acids simulations by increasing the quality of the Hamiltonian used to reproduce nucleic acids interactions, and the length of the polymer to be considered.

TRAJECTORY OF A PROSPERING FIELD: BIOMOLECULAR MODELING IN THE AGE OF TECHNOLOGY

Tamar Schlick
New York University, USA

No Abstract

BREATHS, TWISTS, AND TURNS OF FREE AND INTERACTING ATOMISTIC NUCLEOSOMES

Vlad Cojocaru[1,2,3]; Jan Huertas[2]; Caitlin MacCarthy[2]; Hans Schoeler[2];
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[2]Max Planck Institute for Molecular Biomedicine, Department of Cell and Developmental Biology, Muenster, Germany
[3]Babes Bolyai University, Faculty of Geology and Biology, Cluj Napoca, Romania

Nuclear chromatin is a dynamic structure made of arrays of nucleosomes with different sizes and degrees of compaction. Structural rearrangements in chromatin rely on inter and intra nucleosome dynamics and are essential for gene regulation and cell fate transitions. Understanding these rearrangements requires elucidating nucleosome structural flexibility and how different factors affect it. In the nucleosome, 145-147 base pairs of DNA are wrapped around an octamer formed by four histone proteins. The histones have a structured core region and terminal disordered tails. Intra nucleosome dynamics in complete nucleosomes with genomic sequences are still poorly understood. Our recent data from a total of 25 μs atomistic molecular dynamics simulations revealed how the interplay of two histone tails mediate breathing motions of native nucleosomes by transient interactions with different DNA segments. Moreover, when the tails were removed, the DNA sequence determined the amplitude of nucleosome breathing. The nucleosomes we studied are bound by the transcription factor Oct4, a master regulator of stem cell pluripotency, during the conversion of somatic cells to pluripotent stem cells. Therefore, we further aimed to understand how the binding of Oct4 impacts intra nucleosome dynamics. From additional 30 μs of atomistic simulations and experiments, we found that Oct4 requires some nucleosome opening to bind at some locations on the nucleosome and stabilizes partially open nucleosome conformations. Under certain conditions defined by the binding site position and the configuration of the histone tails, the binding of Oct4 induces a large opening of the nucleosome. This open conformation is stable after Oct4 removal for at least 2 μs. The closing of the nucleosome in the presence and absence of Oct4 depends on how fast the interactions between the histone tails and the linker DNA are re-established.

TWISTING DNA WITH SALT

Sergio Cruz-Leon[1]; Willem Vanderlinden[2]; Peter Müller[2]; Tobias Forster[2]; Georgina Staudt[2]; Yi-Yun Lin[2]; Jan Lipfert[2]; Nadine Schwierz[1];
[1]Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany
[2]LMU Munich, Department of Physics and Center for Nanoscience (CeNS), Munich, Germany

The structure and properties of DNA change with the environment, in particular with the ionic atmosphere. In this work, we resolve how cations influence the helical twist of DNA -one of its central properties- by combining single-molecule magnetic tweezer experiments with extensive all-atom molecular dynamics simulations for monovalent alkali and divalent alkaline earth cations. Two interconnected trends emerged: First, DNA twist strongly depends on cation identity. For example, at 50 mM concentration, DNA twist increases as $Na^+ < K^+ < Ba^{2+} < Rb^+ < Li^+ \approx Cs^+ < Sr^{2+} < Mg^{2+} < Ca^{2+}$. Second, DNA twist increases with increasing concentration for all ions investigated. MD simulations reveal a preferential binding of the cations to the DNA backbone or nucleobases, which have an opposite effect on DNA twist and provide an atomic explanation of the overall effect. Simultaneously, the quantitative comparison between MD simulation and high-resolution experimental twist measurements provides a stringent test for the existing simulation force fields and reveals their shortcomings. The comprehensive view obtained from our integrated approach provides the foundation for understanding and predicting DNA changes induced by the ionic environment in nature and nanotechnology.

COMPUTING PROTEIN BINDING KINETICS: CHALLENGES IN BRIDGING TIMESCALES.

Rebecca C. Wade[1,2];
[1]Heidelberg Institute for Theoretical Studies, Heidelberg, Germany
[2]Heidelberg University, Heidelberg, Germany

The rates at which molecules associate and dissociate are important determinants of biological function. Such rates are challenging to compute as they often on timescales far beyond those accessible to classical atomic-detail molecular dynamics simulations. Growing evidence that the efficacy of a drug can be correlated to target binding kinetics has however led to the development of many new methods aimed at computing rate constants for receptor-ligand binding processes [1,2], see also kbbox.h-its.org. Here, I will describe our recent studies to explore the determinants of structure-kinetic relationships and to develop computationally efficient methods - employing multiresolution molecular simulations and machine learning - to estimate protein-ligand and protein-protein binding kinetic parameters. [1] Bruce NJ, Ganotra GK, Kokh DB, Sadiq SK, Wade RC. New approaches for computing ligand-receptor binding kinetics. Curr Opin Struct Biol. 2018, 49: 1-10.[2] Nunes-Alves A, Kokh DB, Wade RC. Recent progress in molecular simulation methods for drug binding kinetics Curr Opin Struct Biol. 2020, 64:126-133

COMPUTER SIMULATIONS OF LIPID-PROTEIN INTERACTIONS

Peter D. Tieleman;
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Membrane proteins and membranes in general have been simulated for almost 3 decades, during which the scope of simulations has expanded by 6-8 orders of magnitude. At the most expensive end of the scale, atomistic simulations of systems containing > 100 million atoms are become feasible [1], although they pose serious scientific and philosophical challenges. A somewhat more practical approach is the use of coarse-grained simulations, where in particular the Martini model has become very popular [2], which can again be pushed to the most expensive end of the scale by simulations copies in an effort to generate enough data for machine learning analysis [3]. At a more modest scale, questions on individual proteins often use a combination of Martini and atomistic simulations, e.g. [4]. I will highlight some recent applications in the area of membrane simulations, including challenges that can be addressed with the next generation (or the next 6-8 generations) of supercomputer capabilities. [1] C. Gupta et al. The ugly, bad, and good stories of large-scale biomolecular simulations. Curr. Opin. Struct. Biol. 73, 102338, 2022[2] P.C.T. Souza et al. Martini 3: a general purpose force field for coarse-grained molecular dynamics. Nature Methods 18, 382-388, 2021[3] H. Ingolfsson et al. Machine Learning-driven Multiscale Modeling Reveals Lipid-Dependent Dynamics of RAS Signaling Proteins, Proc. Natl. Acad. Sci. 119 (1) e2113297119[4] W.E. Miranda et al. Lipid regulation of hERG1 channel function. Nature Comm. 12, 1-10, 2021

DAMPED ELASTIC NETWORK MODEL IN THERMAL BATH ACCURATELY DESCRIBES LIPID BILAYER COLLECTIVE DYNAMICS

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Collective dynamics in lipid bilayers, the major constituent of biological membranes, plays important role in membrane transport, pore formation, dynamics of membrane proteins and inter-bilayer interactions including membrane fusion. Elastic network models (ENM) has shown numerous successes in describing the collective dynamics of globular and membrane proteins, polynucleotides and large protein assemblies. We show that direct application of standard ENMs to lipid-bilayer fails to describe its collective dynamics accurately and highlight the importance of system (lipid-bilayer)-environment (water) interactions, interactions across periodic boundaries and frictional effects. We present a method to construct and parameterize a lipid-bilayer ENM incorporating these important interactions. Three properties of lipid-bilayers namely (A) relative fluctuations of lipid atoms, (B) lipid bilayer undulations structure factor and (C) velocity autocorrelation of lipid atoms, all determined using molecular dynamics simulations, are used to obtain ENM parameters and friction coefficients along normal modes. The model is able to accurately describe both static and dynamic, in-plane and out-of-plane collective fluctuation properties (density and height fluctuations) of lipid bilayer at varying length scales. Material properties of DMPC lipid bilayer estimated using ENM, such as bending modulus (8.2×10^{-20} J), lipid tilt modulus (3×10^{-20} J nm^{-2}) and thermal diffusivity (9.6×10^{-6} cm^2 s^{-1}) are in close agreement with corresponding experimental values. Finally, we show the application of this model to predict transition pathway of two functional collective motions: (1) transient formation of water pore channels and (2) cell-penetrating peptides induced membrane pore formation. The predicted transition pathways using this model are further refined using path-metadynamics simulations to obtain transition intermediates and free energy profile along these functional transitions.

POSTER ABSTRACTS

TUESDAY, MAY 17
POSTER SESSION I
15:00 – 17:00
Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Tuesday. Presenting authors with odd-numbered poster boards should present from 15:00 – 16:00 and those with even-numbered poster boards should present from 16:00 – 17:00. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Odd-Numbered Boards 15:00 – 16:00 | Even-Numbered Boards 16:00 – 17:00

Acharya, Abhishek	**1-POS**	**Board 1**
Aponte-Santamaría, Camilo	**4-POS**	**Board 4**
Beckett, Daniel	**7-POS**	**Board 7**
Brandner, Astrid	**10-POS**	**Board 10**
Changiarath Sivadasan, Arya	**13-POS**	**Board 13**
Cruz, Matthew	**16-POS**	**Board 16**
Grothaus, Isabell Louise	**19-POS**	**Board 19**
Horvath, Ferdinand	**22-POS**	**Board 22**
Jung, Hendrik	**25-POS**	**Board 25**
Kopec, Wojciech	**28-POS**	**Board 28**
Kutzner, Carsten	**31-POS**	**Board 31**
Maity, Sayan	**34-POS**	**Board 34**
Pandey, Mayank	**40-POS**	**Board 40**
Pöhnl, Matthias	**43-POS**	**Board 43**
Schäfer, Stefan	**46-POS**	**Board 46**
Thakur, Deeksha	**49-POS**	**Board 49**
Valia Madapally, Hridya	**52-POS**	**Board 52**
Wankowicz, Stephanie	**55-POS**	**Board 55**
Woodbury, Dixon	**58-POS**	**Board 58**
Zwolak, Michael	**61-POS**	**Board 61**

Posters should be set up the morning of May 17 and removed by noon May 20.

1-POS Board 1

COMPREHENSIVE EXPLORATION OF FLUROQUINOLONE PERMEATION PATHWAYS THROUGH THE BACTERIAL OMPF CHANNEL

Abhishek Acharya; Jigneshkumar D Prajapati[1]; Ulrich Kleinekathöfer[1];
[1]Jacobs University Bremen, Department of Physics and Earth Sciences, Bremen, Germany

Several antibiotics cross the outer membrane of Gram-negative bacterial cells using diffusion channels called porins. While a host of experimental and simulation studies have provided useful insights into the general mechanism of permeation, this is limited to a few antibiotics. Moreover, a quantitative comparison of permeation mechanisms for different antibiotics is needed for a better understanding of how variations in antibiotic and channels affect the permeation rates. Previously, we described how temperature accelerated sliced sampling (TASS) can be employed for an improved estimation of free energies for antibiotic permeation [1]. Here, we employ the TASS scheme for investigating and comparing the permeation mechanism of two fluroquinolone antibiotics – ciprofloxacin and enrofloxacin - through the Escherichia coli OmpF channel to better understand how a slight modification in an antibiotic influences the respective permeation paths through the channel. Our simulations results support previously reported experimental observations of a slower permeation rate and significantly longer dwell time for enrofloxacin. This is attributable to differences in the permeation paths accessible to the two antibiotics because of terminal different amino groups.

4-POS Board 4

COARSE-GRAINED MODELS FOR INTRINSICALLY DISORDERED DOMAINS PORTED INTO GROMACS: HOW PHOSPHORYLATION SHIFTS IDP CONFORMATIONAL ENSEMBLES

Camilo Aponte-Santamaría[1]; Isabel Martin[1]; Adel Iusupov[1,2,4]; Frauke Gräter[1,3,4];
[1]Heidelberg Institute for Theoretical Studies, Molecular Biomechanics Group, Heidelberg, Germany
[2]University of Göttingen, Göttingen, Germany
[3]Heidelberg University, Interdisciplinary Center for Scientific Computing, Heidelberg, Germany
[4]Max Planck School Matter to Life, Heidelberg, Germany

Determination of the dynamics of intrinsically disordered proteins (IDPs) is essential to understand their function. Although all-atom molecular dynamics (MD) simulations have enabled a quantitative monitoring of the dynamics of these types of proteins at an unprecedented and valuable level of detail, they are still limited to relatively small and individual IDPs. Several coarse-grained models have been recently proposed to efficiently and accurately simulate complete single IDP chains and IDP condensates. These models treat each aminoacid as one particle and involve non-bonded interactions which are different than the conventionally used-ones in standard biomolecular MD simulations. Implementations of these models exist in MD packages such as LAMMPS or HOOMD. Here, we report the port of three recent models HPS, CALVADOS, and MPIPI into the widely used MD software GROMACS. The port is applied to study the dynamics of the intrinsically disordered region of the inner centromere protein (INCENP), a part of the chromosome passenger complex playing a key role during mitosis. The disordered fragment of INCENP is about 440 aminoacids long and our coarse-grained simulations allowed us to systematically study the effect of the phosphorylation on this disordered region, backed up by all-atom simulations of individual short INCENP fragments (Martin, Aponte-Santamaría, et al. J Mol Biol. 434: 167387, 2022). Overall, we expect this port to complement other existing implementations of IDP coarse-grained models and to facilitate their use into a unifying MD framework within the GROMACS package.

7-POS Board 7

THE MULTISCALE PROBLEM OF MICROTUBULE CATASTROPHE AND ITS EXASCALE CHALLENGES

Daniel Beckett[1]; Gregory A. Voth[1];
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Microtubules (MTs) constitute the largest components of the eukaryotic cytoskeleton and facilitate a plethora of cellular functions. During mitosis, microtubules form the mitotic spindle, making them a potent drug target for many successful chemotherapeutic agents that interfere with dynamic instability (DI): the ability of microtubules to rapidly switch from polymerizing to depolymerizing states (known as catastrophe) and vice-versa. MT catastrophe is heralded by the hydrolysis of guanosine triphosphate (GTP) bound by the tubulin heterodimer which induces conformational and dynamical changes in MT structure that are still not fully understood. Unravelling the mystery of MT catastrophe is a multiscale problem with exascale challenges at each level and the objective of these studies is a complete molecular picture of the processes underlying catastrophe. Results will be presented for a suite of MT catastrophe-related simulations. First, the catalytic mechanism of GTP hydrolysis in the MT lattice is derived from quantum mechanics/molecular mechanics (QM/MM) hybrid simulations paired with metadynamics free energy sampling. These are long timescale (>100 ps) simulations for the computationally intensive QM portion with relatively large system sizes that require advances in processing speed to be practically tractable, with the presented results requiring millions of CPU hours to acquire. Second, all-atom (AA) molecular dynamics (MD) studies describing the release pathway of inorganic phosphate post-GTP hydrolysis will be presented. These require multiple replicas of >100 ns MD trajectories across multiple systems to converge. Lastly, AA MD studies of a full MT segment will be presented as well as progress on the classification of MT dynamics using a coarse-grained/machine learning approach. These full MT simulations require both very large system size and long timescales. Future studies required to understand MT dynamics will be discussed, as well as their exascale demands.

10-POS Board 10

EFFECT OF SEROTONIN ON SPONTANEOUS MEMBRANE DOMAIN FORMATION

Astrid F Brandner[1]; Anna Bochicchio[1]; Oskar Engberg[2]; Daniel Huster[2]; Rainer A Böckmann[1,3];
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Biomembranes exist in a variety of lipid and protein composition and have a dynamical behaviour to respond to different stimuli. The existence of defined regions or domains with specific structural and dynamical properties were shown to be associated with protein receptor localisation and signalling. Despite their importance e.g. in immune signalling, only little is known about the composition and dynamics of membrane domains. Their transient existence and nanometre scale make them methodologically challenging to identifying highly dynamic domains on the nanometer scale. In this work, by means of atomistic molecular dynamic simulations, we characterized the unbiased spontaneous formation of nanodomains in a plasma membrane model containing phosphatidylcholine, palmitoyl-sphingomyelin and cholesterol at different temperatures in presence or in absence of the neurotransmitter serotonin[1,2]. We show that serotonin binding to the membrane decreases the phase transition temperature. It affects domain composition and domain ordering as well as results in a decreased membrane elasticity. Our results suggest a novel mode of action of neurotransmitters in neuronal signal transmission. We followed the initial steps of nanodomains formation at the microsecond scale starting from a random mixture of lipids. Upon serotonin binding to the membrane, the domain order and composition was affected, resulting in a PC-enrichment of the disordered domains and a decreased membrane elasticity. Overall, we show that binding of serotonin to the membrane decreases the phase transition temperature as well as a modified lipid composition in the domains. Our simulations suggest a novel mode of action of neurotransmitters in neuronal signal transmission. [1] Engberg, O., Bochicchio, A., Brandner, A., Gupta, A., Dey, S., Böckmann, R. Huster, D. (2020). Serotonin Alters the Phase Equilibrium of a Ternary Mixture of Phospholipids and Cholesterol. Frontiers in Physiology, 11. [2] Bochicchio, A., Brandner, A., Engberg, O., Huster, D., & Böckmann, R. (2020). Spontaneous Membrane Nanodomain Formation in the Absence or Presence of the Neurotransmitter Serotonin. Frontiers in Cell and Developmental Biology, 8.

13-POS Board 13

LIQUID-LIQUID PHASE SEPARATION IN GENE TRANSCRIPTION

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Liquid-Liquid phase separation plays an important role in the formation of localized nuclear hubs of RNAP II during the transcription process. Recent experimental studies revealed that the Carboxy terminal domain (CTD), the largest subunit of RNAP II, is a low complexity domain, and has a very strong tendency to phase separate. Our research is focused on understanding the molecular basis of phase separation of CTD using multiscale molecular dynamics simulation methods. CTD is conserved in eukaryotes with the repeats of the heptapeptide sequence. However, there are small differences in CTD sequences of different species. We investigated how the CTD phase separation is affected by such differences in CTD sequences using coarse-grained molecular dynamics simulations. Our investigations indicate that deviation from the ideal heptapeptide sequence has less tendency to phase separate, which suggests that these deviations from the ideal heptapeptide repeats are important for responsive regulation of transcription. Also, the effects of temperature on CTD phase behavior and the influence of polymer length on critical temperature are as expected from Flory-Huggins theory. Moreover, we are looking at how phosphorylation of CTD and the presence of other biomolecules that can influence CTD phase behavior and regulate gene transcription. Hyper-phosphorylation prevents phase separation as the negatively charged phosphate groups repel each other. However CTD is hyper-phosphorylated in transcription elongation. We show how hyper-phosphorylated CTD might co-phase separate in elongation with HRD of Cylin T1 in accordance with experiment. To explore more on this, we studied the phase behavior of CTD and phosphorylated CTD in the presence of HRD and the results show that they co phase separate into a large cluster, but do not mix, which may help to physically distinguish between the initiation and elongation stages of transcription. A precise understanding of the molecular basis of interactions that leads to phase separation could be possible by employing atomistic simulations and this will, in turn, lead to improved coarse-grained simulation models.

16-POS Board 16

A CRYPTIC POCKET IN EBOLA VP35 ALLOSTERICALLY CONTROLS RNA BINDING

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Many proteins are difficult to target with drugs because their primary function is to participate in protein-protein interactions (PPIs) and protein-nucleic acid interactions (PNIs) through flat interfaces that are less conducive to small molecule binding. These interactions are found in many viral proteins that interact with host factors and viral nucleic acids in order to evade the host immune system. We focused our study on viral protein 35 (VP35), from the highly lethal Ebola virus. VP35 plays essential roles in Ebola's replication cycle, including binding the viral RNA genome to block a host's innate immunity. However, there are no FDA approved drugs targeting VP35. One promising opportunity for discovering and designing new drugs is cryptic pockets, or pockets that are absent in available protein structures but form due to protein dynamics. Identifying and exploiting cryptic pockets remains challenging as most known pockets were discovered alongside the identification of a small molecule effector. Here, we applied adaptive sampling simulations to sample states in VP35's conformational landscape with large pocket volumes which revealed a potentially druggable cryptic pocket. Then, using allosteric network detection algorithms, we predicted that VP35 harbors a cryptic pocket that is allosterically coupled to its RNA-binding interface. Thiol labeling experiments along with dsRNA binding experiments suggest the VP35 cryptic pocket is present and that stabilizing this pocket in its open form allosterically disrupts RNA binding. We then conducted an experimental high throughput screen for dsRNA binding inhibitors targeting VP35 that yielded a number of hits. These results demonstrate the potential of cryptic pockets to allosterically affect PPI and PNIs presenting new therapeutic opportunities for targeting these prevalent interactions.

19-POS Board 19

TACKLING THE CONVERGENCE ISSUE OF N-GLYCAN CONFORMER DISTRIBUTIONS IN MOLECULAR DYNAMICS SIMULATION

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Branched polysaccharides, called N-glycans, represent the most diverse post-translational modification of proteins. Their fundamental role in proteins' structure and function is becoming more recognized in molecular dynamics simulation only in recent years. N-glycans harbor an intrinsic flexibility due to their glycosidic linkages and monosaccharide ring dynamics, resulting in difficult-to-converge conformer populations in standard molecular dynamics simulation. We show that an enhanced-sampling metadynamics scheme based on enhancing transitions over all relevant barriers with concurrent one-dimensional energy potentials can in fact capture effectively all biologically relevant conformers of N-glycans. The framework can be applied to free and protein-bound glycans in solution, opening up new possibilities for the investigation of N-glycans in computational studies. Additionally, machine-learning based dimensionality reduction approaches are employed for an unambiguous representation of N-glycan conforms in a two-dimensional space. This visualization facilitates different kinds of analyses, such as force field or experimental parameter comparisons. The combination of presented techniques achieves converged N-glycan conformer populations in a reasonable time frame, dissecting the most varying and therefore important variables in the system, and hence allows to draw conclusions about force field accuracy or differences with respect to other N-glycan systems.

22-POS Board 22

VOLTAGE SENSING IN PROTEIN-CONDUCTING CHANNEL SECYEG

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The bacterial channel SecYEG is responsible for translocating proteins across the plasma membrane. It resides in an energized membrane subjected to the proton motive force (PMF). Experimental reports have shown that the PMF's electrostatic component allows SecYEG to remain impermeable to ions. When the absolute value of the transmembrane electrostatic potential drops below a certain threshold, however, the channel becomes leaky to ions. The precise mechanism behind this voltage-dependent ion channel activity is still unclear. We employ molecular dynamics simulations to study SecYEG's mechanical response to transmembrane voltages. Although electric fields induce only minute displacements of secondary structure elements within the channel, detailed analysis of intramolecular forces reveals a complex pattern of voltage-dependent stress inside the channel. Using force distribution analysis, we discern voltage-sensitive elements in the channel and highlight networks of interacting residues that constrict the channel pore in the presence of electric fields. We find that, depending on the sign of the transmembrane potential, either helices TM5 and TM7 or TM2 and the plug domain are the most voltage-sensitive elements of the channel.

25-POS Board 25

ARTIFICIAL INTELLIGENCE FOR MOLECULAR MECHANISM DISCOVERY

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We develop a machine learning algorithm to extract the mechanism of collective molecular phenomena from computer simulations. Our algorithm combines transition path sampling (TPS), deep learning, and statistical inference to simulate the dynamics of complex molecular reorganizations while simultaneously learning how to predict their outcome. TPS is a Markov Chain Monte Carlo method to sample the rare trajectories showing between states. We iteratively train a deep learning model on the outcomes of the shooting moves used in TPS. In this way, we increase the efficiency of the rare-event sampling while gradually revealing the underlying mechanism of the transition dynamics. The AI can learn from and steer multiple TPS simulations simultaneously, becoming increasingly effective in learning the transition dynamics with increasing degree of parallelization, and is therefore well-suited for highly parallel computing infrastructures. With this algorithm, we study the oligomerization of a transmembrane alpha helix involved in membrane sensing, using a MARTINI simulation model. In less than 20 days of walltime with minimal human intervention, the algorithm accumulates a total of 5 ms simulation time distributed over 10000 trajectories, collecting approximately 4000 transition paths with almost optimal efficiency. We estimated the dissociation rate as approximately 1/s, making it unlikely that even a single dissociation event would be observed in much longer equilibrium simulations. Additionally, the simplified mathematical model helps understanding the mechanism by highlighting the presence of two distinct reaction channels. In conclusion, our algorithm enables researchers to make full use of highly parallel computing resources by autonomously driving many parallel simulations and subsequently aiding in the interpretation of the amassed data.

28-POS Board 28

IN SILICO ELECTROPHYSIOLOGY OF SMALL MOLECULE REGULATION OF POTASSIUM CHANNELS

Wojciech Kopec[1]; Marcus Schewe[3]; Aytug K Kiper[2]; Mauricio Bedoya[4]; Stefanie Marzian[2]; David Ramirez[4]; Elena B Riel[3]; Annemarie Köhler[3]; Rinné Susanne[2]; Niels Decher[2]; Bert L de Groot[1]; Gonzalez Wendy[4,5]; Thomas Baukrowitz[3];
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Potassium channels are essential proteins playing key roles in a multitude of physiological functions. These channels conduct potassium ions down their electrochemical gradient and undergo complex conformational changes between ‘open’, ‘closed’ and ‘inactivated’ states, in so-called gating transitions. Both of these features (ion conduction and gating) can be affected by interactions of a channel with small molecules, opening a way for designing new therapeutic agents targeting potassium channels. In recent years, Molecular Dynamics (MD) simulations of potassium channels matured to the level allowing for near-quantitative comparison with functional data. Therefore, simulations can now be used to study the effect of small molecules on these channels, explaining functional data and generating hypotheses on their molecular mechanism of action. Here, we will present two recent investigations of small molecules interacting with potassium channels. In the first one, we focused on the arachidonic acid (AA), a lipid molecule that targets the elusive C-type inactivation process occurring at the selectivity filter (SF) of voltage-gated potassium channels. Our simulations reveal how binding of AA from the membrane phase allosterically affects the stability of the channel SF. In the second investigation, we studied the effect of the TASK-1 channel activator ONO. In MD ONO binds to the computationally generated open state of the channel and increases its conductance. Simultaneously, the presence of ONO in the channel cavity prohibits the re-formation of the channel X-gate, leading to an enhanced open probability. Both studies are tightly related to functional investigations and show good agreement with mutational and functional observations.

31-POS Board 31

GROMACS IN THE CLOUD: HIGH THROUGHPUT LIGAND SCREENING ON A GLOBAL SUPERCOMPUTER

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Biomolecular simulation is a challenging example of a compute-heavy scientific application that spans the whole range from high performance computing (HPC) to high throughput computing (HTC), depending on the questions addressed. We assess costs and efficiency of state-of-the-art high performance cloud computing and compare the results to a typical in-house cluster for molecular dynamics (MD) simulations carried out with the GROMACS MD software. We set up an HPC cluster in the Amazon Web Services (AWS) cloud that incorporates various different instances with Intel, AMD, and ARM CPUs, some with GPU acceleration. Using representative biomolecular simulation systems we benchmark how GROMACS performs on individual instances (for HTC) and across multiple instances (for HPC scenarios). Thereby we assess which instances deliver the highest performance and which are the most cost-efficient ones for MD. We find that, in terms of total costs including hardware, personnel, room, energy and cooling, producing MD trajectories in the cloud can be about as cost-efficient as an in-house cluster given that optimal cloud instances are chosen. Further, we find that high-throughput ligand-screening can be accelerated dramatically by using global cloud resources. For a ligand screening study consisting of 20,000 independent simulations or 200 microseconds of combined simulation trajectory, we used all the hardware that was available in the cloud at the time of the study. Using more than 4,000 instances, 140,000 cores, and 3,000 GPUs around the globe, our simulation ensemble that would normally take weeks to complete on a typical in-house cluster consisting of several hundred nodes, finished in about two days in the cloud. We demonstrate that the costs of such and similar studies can be drastically reduced with a checkpoint-restart protocol that allows to use cheap Spot pricing and by using instance types with optimal cost-efficiency.

34-POS Board 34

PROTEIN ENVIRONMENT GUIDES THE ENERGY TRANSFER IN THE LIGHT-HARVESTING COMPLEX OF DIATOMS

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The electrostatic protein environment of pigment molecules controls the excitation energy transfer (EET) process in the biological light-harvesting complexes. During the EET process, the excitation energies also known as site-energies of the pigment molecules are regulated by the fluctuating protein surroundings. In this work, we have performed a structure-based investigation of the fucoxanthin and chlorophyll-binding proteins (FCP) of diatoms [1, 2] to figure out the impact of the protein matrix on the site-energies of individual Chl-a and Chl-c1/c2 molecules in the complex. For this purpose, we have employed a multiscale analysis by combining molecular dynamics (MD) simulations and quantum chemistry (QC) calculations within quantum mechanics/molecular mechanics (QM/MM) framework [3]. We found that the QM/MM equilibrium geometry of Chl-c2 has the lowest site-energy within the protein environment for different QC methods. Moreover, the site-energy energies distributions of the FCP complex maintained the same trend for this pigment molecule along a QM/MM MD trajectory. These findings indicate that the energy transfer within the complex ends at this particular pigment. This finding is surprising since the lowest excitation energies of Chl-c molecules are known to be blue-shifted with respect to the Chl-a molecules in vacuum or in organic solvents. We conclude that the local protein solvation is responsible for creating a large electrostatic effect at the position of Chl-c2 leading to an unexpected energy shift.1. Wang et al. Science 2019, 363, eaav0365.2. Nagao et al. Nat. Plants 2019, 5, 890–901.3. Maity et al. J. Phys. Chem. Lett. 2020, 11, 20, 8660–8667.

40-POS Board 40

GTP IS A BETTER HYDROTROPE THAN ATP

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Hydrotropes are small amphiphilic compounds that increase the aqueous solubility of hydrophobic molecules. Recent evidence suggests that adenosine triphosphate (ATP), which is the primary energy carrier in cells, also assumes hydrotropic properties to prevent the aggregation of hydrophobic proteins. Here, we show that guanosine triphosphate (GTP) has superior hydrotropic properties than all other nucleoside triphosphates (NTPs). We compare the hydrotropic behaviour of all four biological NTPs using molecular dynamics (MD) simulations. We launch all-atom MD simulations of aqueous solutions of NTPs (ATP, GTP, CTP and UTP) with pyrene, which acts both as a model hydrophobic compound, and a spectroscopic reporter for aggregation. GTP prevents pyrene aggregation and dissolves pre-formed pyrene clusters effectively. Dissolution is not achieved in the presence of CTP and UTP. The higher stability of base stacking in guanine is responsible for the higher hydrotropic efficiency of GTP. Consistent with the simulations, spectroscopic measurements also suggests that the hydrotropic activity of GTP is higher than ATP. Our results can have broad implications for hydrotrope design in the pharmaceutical industry, as well as the possibility of cells employing GTP as a hydrotrope to regulate hydrophobic protein aggregation in membrane-less biological condensates.

43-POS Board 43

LIPID BICELLES AS A TOOL TO UNLOCK MEMBRANE DYNAMICS

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Cholesterol is a major constituent of membranes in all animals and able to flip between leaflets on timescales orders of magnitude faster than other lipids. But both the distribution of cholesterol between the leaflets as well as the interplay between the distribution and other membrane properties is largely unknown. Difficulties in resolving the particular role of cholesterol for biomembrane characteristics are connected to the limited spatial and temporal resolution in experiments and challenges in studying asymmetric membranes and connected domain formation in simulations [1-2]. In a previous work we were able to show that lipid bicelle systems are a viable tool in simulations to investigate protein-induced membrane curvature [3]. Here, we developed a bicelle model that prevents diffusive lipid exchange between the leaflets, thus allowing for the study of defined asymmetric membrane compositions. While key membrane properties like area per lipid and membrane thickness are unmodified as compared to membranes constrained by periodic boundary conditions, bicelle systems allow for fluctuations with an increased amplitude. Interestingly, the addition of cholesterol substantially further increases these fluctuations accompanied by cholesterol flips between the membrane leaflets. This suggests a role of cholesterol in membrane remodeling processes, e.g in fusion. References [1] van Meer G., Cold Spring Harb. Perspect. Biol., 2011, 3(5) [2] Murate M. et al., Chem Phys Lipids, 2016, 194, 58-71 [3] Kluge C. et al, Biophys J., 2022

46-POS Board 46

FORMATION OF RING AND SLIT SHAPED GASDERMIN-D PORES IN PLASMA MEMBRANES

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Gasdermins execute the final step in pyroptosis, a highly regulated form of lytic cell death associated with inflammation. After activation by caspases, the N-terminal domain of gasdermin-D ($GSDMD^{NT}$) binds to the plasma membrane, assembles into large homo-oligomers and inserts a β-sheet into the membrane. The hydrophobic face of the β-sheet faces the plasma membrane and the hydrophilic face repels the hydrophobic core of the membrane to facilitate pore formation. The exact sequence of events and the detailed mechanisms of membrane binding, conformational rearrangements, assembly, and insertion of the β-sheet remain elusive. To gain insight into the dynamics and stability of the large gasdermin complex with an outer diameter of more than 30 nm, we performed multi-microsecond atomistic molecular dynamics simulations of the $GSDMD^{NT}$ in its 33-mer pore and prepore conformations. Both structures tightly interacted with the acidic phospholipids of the intracellular leaflet. Whereas $GSDMD^{NT}$ in pore conformation maintained a nearly perfect circular shape and was stable in a flat membrane, the ring in prepore conformation deformed the membrane. Motivated by atomic force microscopy (AFM) images, we also performed simulations of $GSDMD^{NT}$ monomers and differently sized oligomers in pore conformation. In all cases, the β-sheets stayed stably inserted in the membrane and formed water-filled membrane pores. Larger oligomers transitioned into the slit and ring shaped pores seen in AFM experiments. We conclude that already small oligomers can sustain stable membrane insertions, and that the oligomers can reorganize into slits and robust circular pores.

49-POS Board 49

SUBSTRATE PROMISCUITY A CONTINUUM FEATURE OF ENZYMES

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Enzyme promiscuity is the ability of (some) enzymes to perform alternate reactions or catalyse non-cognate substrate(s). The latter is referred to as substrate promiscuity, widely studied for its biotechnological applications and understanding enzyme evolution. Insights into the structural basis of substrate promiscuity would greatly benefit the design and engineering of enzymes. Previous studies on some enzymes have suggested that flexibility, hydrophobicity, and active site protonation state could play an important role in enzyme promiscuity. However, it is not known yet whether substrate promiscuous enzymes have distinctive structural characteristics compared to specialist enzymes (specific for a substrate). In pursuit to address this, we have systematically compared substrate/catalytic binding site structural features of substrate promiscuous with those of specialist enzymes using a carefully constructed dataset. Surprisingly, we found that substrate promiscuous and specialist enzymes are similar in various binding/catalytic site structural features such as flexibility, surface area, hydrophobicity, depth, and secondary structures. Even flexibility, arguably the most important factor in controlling the substrate preference of any enzyme, turns out to be similar (analysed through multiple independent measures) for both the enzyme groups. Recent studies have also alluded that promiscuity is widespread among enzymes. Based on these observations, we propose that substrate promiscuity could be defined as a continuum feature that varies from narrow (specialist) to broad range of substrate preferences. Moreover, diversity of conformational states of an enzyme accessible for ligand binding may possibly regulate its substrate preferences.

52-POS Board 52

UNDERSTANDING ION SELECTIVITY OF THE GASTRIC PROTON PUMP H^+, K^+-ATPASE

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H^+, K^+-ATPase protein is an ATP-powered ion pump that maintains acidity of the stomach by electroneutral exchange of H^+ and K^+ ions across the gastric lumen. Though Na^+ is present in higher concentration in the stomach than K^+, H^+, K^+-ATPase binds to K^+ ions with high specificity. One of the main hypotheses attributes the selectivity of K^+ over Na^+ to the protonation states of specific negatively charged amino acids present at the binding site of the protein. Current experimental methods are incapable of accurately identifying the protonation states of these residues at the binding site. Hence, mutation of residues to mimic protonation were employed and the activity of the mutated proteins at different concentration of K^+ and Na^+ ions were measured. We also use free energy perturbation methods to find the potential protonated sites at the binding site that would favour K^+ binding over Na^+ binding. We perform alchemical transformations of K^+ ion at the binding site to Na^+ ion with different combinations of the protonated amino acids at the binding site to measure the free energy difference in binding of the two ions. We identify that the glutamic acid residues E343, E795 and E936 are protonated and preferentially ensures K^+ binding.

55-POS Board 55

LIGAND BINDING REMODELS PROTEIN SIDE CHAIN CONFORMATIONAL HETEROGENEITY

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While protein conformational heterogeneity plays an important role in many aspects of biological function, including ligand binding, its impact has been difficult to quantify. While macromolecular X-ray diffraction is commonly interpreted with a static structure, it can provide information on both the anharmonic and harmonic contributions to conformational heterogeneity. Here, we took advantage of the time- and space-averaged electron density of X-ray structures and applied qFit, an automated and parsimonious multiconformer modeling software. Through using multiconformer models, we were able to more accurately measure conformational heterogeneity of 743 stringently matched pairs of crystallographic datasets that reflect unbound/apo and ligand-bound/holo states. When comparing the conformational heterogeneity oF side chains, we observe that when binding site residues become more rigid upon ligand binding, distant residues tend to become more flexible, especially in non-solvent exposed regions. Among ligand properties, we observe increased protein flexibility as the number of hydrogen bonds decrease and relative hydrophobicity increases. Across a series of 13 inhibitor bound structures of CDK2, we find that conformational heterogeneity is correlated with inhibitor features and identify how conformational changes propagate differences in conformational heterogeneity away from the binding site. Collectively, our findings agree with models emerging from NMR studies suggesting that residual side chain entropy can modulate affinity and point to the need to integrate both static conformational changes and conformational heterogeneity in models of ligand binding.

58-POS Board 58

A NEED FOR EXASCALE MODELING OF MEMBRANE FUSION IN THE PRESENCE OF GENERAL ANESTHETICS

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General anesthetics have been used for over 175 years, and many cellular targets have been identified as possible sites of action. Most modes of action assume that anesthetics enter the membrane and either act directly by loosely binding to a membrane protein (Hemmings, et al., 2019. Trends Pharmacol Sci. 40:464-481), or act indirectly by increasing the lateral pressure that the membrane's hydrophobic core applies to membrane proteins (Cantor, 1997. Biochemistry 36:2339-2344). Either way, it is assumed that loss of synaptic function is due to modulation of critical protein functions. Using a protein-free assay for exocytosis, we have reported a possible mode of anesthetic action that does not fit with the protein model (Paxman et al., 2017. Biophysical J. 112:121-132). The data with short-chain alcohols suggest that alcohols alter the activation energy of membrane-membrane fusion. This could be by promoting dehydration of the fusing membranes (loose-to-tight docking) or by enhancing lipid tail splay (leading to hemifusion) (Witkowska et al., 2021. Nat Commun 12:3606). Both are mechanisms whereby synaptic transmission could be modulated by anesthetics in a protein-independent way. Few experimental systems lend themselves to study this process in vitro, and no in vivo system can be made free of proteins. Therefore, an all-atom simulation appears to be one of just a few paths forward to identify the mechanism of action for alcohols on membrane fusion. To model correctly the effect of different alcohols and anesthetics on the dehydration process, the system would likely need 1000's of lipids. Coarse-grain simulations cannot be used, since the data show that ethanol and methanol had opposite effects on membrane fusion. Calculations on the exascale will likely be required to study this process with sufficient atoms and over 100's of microseconds.

61-POS Board 61

TOPOLOGY, LANDSCAPES, AND BIOMOLECULAR ENERGY TRANSPORT

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The objective of our work is to employ transient data, such as that given by ultrafast spectroscopic measurements of energy transport, to extract features of biomolecular landscapes and topology. We use replica-exchange and non-equilibrium molecular dynamics to study a large set of structural conformations within the microcanonical ensemble. Internal energy transport exhibited a new phenomenon - nonlinear localization - due to what is in essence an impedance mismatch of different regions of the biomolecular landscape. [Nature Communications 10, 4662 (2019)]

While ubiquitous, energy redistribution remains a poorly understood facet of the nonequilibrium thermodynamics of biomolecules. At the molecular level, finite-size effects, pronounced nonlinearities, and ballistic processes conspire to produce behavior that diverges from the macroscale. Here, we show that transient thermal transport reflects macromolecular energy landscape architecture through both (i) the topological characteristics of the conformational ensemble and (ii) the nonlinear processes that mediate dynamics. While the former determines transport pathways via molecular contacts, the latter reflects the ruggedness of the landscape for local motion of atoms and molecular fragments. Unlike transport through small-molecule systems, such as alkanes, nonlinearity dominates over coherent processes at even quite short time- and length-scales. Our exhaustive all-atom simulations and novel local-in-time and space analysis, applicable to both theory and experiment, permit dissection of energy migration in biomolecules. The approach demonstrates that vibrational energy transport can probe otherwise inaccessible aspects of macromolecular dynamics and interactions that underly biological function.

WEDNESDAY, MAY 18
POSTER SESSION II
15:00 – 17:00
Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Wednesday. Presenting authors with odd-numbered poster boards should present from 15:00 – 16:00 and those with even-numbered poster boards should present from 16:00 – 17:00. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Odd-Numbered Boards 15:00 – 16:00 | Even-Numbered Boards 16:00 – 17:00

Agrahari, Ashish Kumar	**2-POS**	**Board 2**
Araki, Mitsugu	**5-POS**	**Board 5**
Berdychowska, Julia	**8-POS**	**Board 8**
Bremer, Peer-Timo	**11-POS**	**Board 11**
Chatzimagas, Leonie	**14-POS**	**Board 14**
de Buhr, Svenja	**17-POS**	**Board 17**
Hanic, Maja	**20-POS**	**Board 20**
Hub, Jochen	**23-POS**	**Board 23**
Kasparyan, Gari	**26-POS**	**Board 26**
Kubo, Shintaroh	**29-POS**	**Board 29**
Leidner, Florian	**32-POS**	**Board 32**
Mallimadugula, Upasana	**35-POS**	**Board 35**
Michelarakis, Nicholas	**38-POS**	**Board 38**
Pang, Yui Tik	**41-POS**	**Board 41**
Ramírez-Martínez, Marco	**44-POS**	**Board 44**
Skóra, Tomasz	**47-POS**	**Board 47**
Trebesch, Noah	**50-POS**	**Board 50**
Verma, Paras	**53-POS**	**Board 53**
Wilm, Matthias	**56-POS**	**Board 56**
~~**Zhang, Zijian**~~	~~**59-POS**~~	~~**Board 59**~~ **CXL**

Posters should be set up the morning of May 17 and removed by noon May 20.

2-POS Board 2

SARS-COV-2 ENVELOPE PROTEIN ATTAIN KAC MEDIATED DYNAMICAL INTERACTION NETWORK TO ADOPT "HISTONE MIMIC" AT BRD4 INTERFACE

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Background Identification of structural determinants which hold the critical residues is the basis of the molecular recognition process, mapping them is essential for mechanistic understanding as well as can help to design therapeutic strategies. Interface mimicry, achieved by recognition of host–pathogen interactions, is the basis by which pathogen protein can hijack the host machinery by attaining the essential wiring via residual network. The envelope (E) protein of SARS-CoV-2 is known to mimic the histones at BRD4 surface via establishing the structural mimicry. However, it is still elusive as to how E protein is able to achieve the stable adduct competing with endogenous regulators such as histones. Experimental approach The extensive protein-peptide docking, followed by 7.3 micro-second MD simulations and its multifaceted post-processing analysis, we have done a comparative mapping of H3/H4/E over BRD4 surfaces. Results We identified that E protein is able to perform an “interaction network mimicry” as it attains the similar orientation of acetylated lysine (Kac) and residual wiring including water-mediated interactions at BRD4 surface. The multiple trajectories confirm the stability of E similar to histones, however, the comparable thermodynamics quantification rules out the possibility of E to outcompeting the histones in a competitive manner. Moreover, due to similar interaction network mimicry, stability of complex and comparable thermodynamics between E and histones, strengthen the possibility that E protein could hijack the host BRD4 surface. Conclusion Overall, this current study has opened up a new avenue for researchers to establish the mechanistic understanding and can be explored for therapeutic intervention by perturbing the interaction network mimicry.

5-POS Board 5

HYPERSOUND-PERTURBED MOLECULAR DYNAMICS TO ACCELERATE SLOW BIOMOLECULAR INTERRACTION PROCESSES.

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Capturing the dynamic processes of biomolecular systems in atomistic detail remains difficult despite recent experimental advances. Although molecular dynamics (MD) techniques enable atomic-level observations, simulations of "slow" biomolecular processes (with timescales longer than submilliseconds) are challenging because of current computer speed limitations. Therefore, we developed a method to accelerate MD simulations by high-frequency ultrasound (hypersound) perturbation. The binding events between the protein CDK2 and its small-molecule inhibitors were nearly undetectable in 100-ns conventional MD, but the method successfully accelerated their slow binding rates by up to 10-20 times. Hypersound-accelerated MD simulations revealed a variety of microscopic kinetic features of the inhibitors on the protein surface, such as the existence of different binding pathways to the active site. Moreover, the simulations allowed the estimation of the corresponding kinetic parameters and exploring other druggable pockets. This method can thus provide deeper insight into the microscopic interactions controlling biomolecular processes.

8-POS Board 8

TOWARDS RATIONAL DESIGN OF BIOTECHNOLOGICAL ENZYMES: IS EXASCALE NEEDED FOR COMPUTATIONAL ANALYSIS OF NITRILE HYDRATASE IN NON-CLASSICAL SOLVENTS?

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Green chemistry uses enzymes, and one of the most successful examples is the application of nitrile hydratase (NHase) to convert nitriles into amides [1]. The main question is how to optimize it further for industrial purposes [2, 3]. Some NHases lose their activity in the product concentration from 20% to 40% [4]. The current variant, extracted from Pseudonocardia thermophila, works at 30% of product concentration but loses activity when a product concentration reaches 50%. In order to gain insight into the mechanism of this effect and to propose modifications in the enzyme (1IRE.pdb) we performed molecular dynamics simulations (3x200 ns for each solution, 300 K) with increasing concentration of acrylamide (0%, 20%, 50% m/m respectively). We were able to observe that acrylamide molecules enter the active center of the enzyme. We could clearly see changes in hydrogen-bond patterns, new distribution of salt bridges and some changes in the first solvation shell induced by the increasing amount of the catalytic product. The problem of industrial enzyme optimization is well suited for massive all-atom simulations, since much longer time scales are necessary to model fully conformational all enzymatic reaction steps, that happen above millisecond timescale and conformational changes that happen in the protein. Acknowledgement: This research is funded by IDUB N. Copernicus #MEMOBIT grant. ICNT UMK computer facilities are acknowledged. 1. Cheng, Z., Y. Xia, and Z. Zhou, Front in Bioeng Biotechnol, 2020. 8(352): p.1. 2. Cheng, Z., Peplowski L. et al., Molecules, 2020. 25(20): p. 4806. 3. Guo J., Berdychowska J., Peplowski L. et al., Int J Biol Macromol, 2021. 181: p. 444. 4. Yamada, H. and M. Kobayashi, Biosci Biotechnol Biochem, 1996. 60(9): p. 1391

11-POS Board 11

EXASCALE READY MACHINE LEARNING DRIVEN MULTISCALE INFRASTRUCTURE TO EXPLORE RAS-RAF BIOLOGY

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Biophysical simulations at various scales can provide important insights into biological mechanisms. These can range from continuous macro-scale simulations that approach common experimentally observable length and timescales and resolve phenomena, such as protein clustering, to atomistic molecular dynamics simulations resolving pheonomena, such as bonding or signaling. However, understanding a complex process such as RAS-RAF signaling requires information at all scales and more importantly an understanding how scales interact. We will present recent results from the MuMMI multiresolution framework that uses advanced machine learning to directly couple massively parallel simulation ensembles at three computing scales – continuum, coarse-grain MD, and atomistic MD – to provide unprecendented insights into RAS-RAF interactions. In particular, we will report results from a large-scale simulation campaign of RAS-RAF proteins on a complex plasma membrane performed on and scalled across all of Summit, the worlds 2nd largest supercomputer.

14-POS Board 14

SIMULATION OF LIQUID JET EXPLOSIONS AND SHOCK WAVES INDUCED BY X-RAY FREE-ELECTRON LASERS

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X-ray free-electron lasers (XFELs) produce X-ray pulses with very high brilliance and short pulse duration. These properties enable structural investigations of biomolecular nanocrystals, and they allow resolving the dynamics of biomolecules down to the femtosecond timescale. To deliver the samples rapidly into the XFEL beam, liquid jets are used. The impact of the X-ray pulse leads to vaporization and explosion of the liquid jet, while the expanding gas triggers the formation of shock wave trains traveling along the jet, which may affect biomolecular samples before they have been probed. Here, we used atomistic molecular dynamics simulations to reveal the structural dynamics of shock waves after an X-ray impact. Analysis of the density in the jet revealed shock waves that form close to the explosion center and travel along the jet. A trailing shock wave formed after the first shock wave, similar to the shock wave trains in experiments. Although using purely classical models in the simulations, the resulting explosion geometry and shock wave dynamics closely resemble experimental findings, and they highlight the importance of the jet surface in shock wave propagation and attenuation.

17-POS Board 17

MECHANICAL FORCE CAN ENHANCE C-SRC KINASE ACTIVITY

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Mechano-sensing proteins are crucial for cellular function since they translate physical cues from the environment to biochemical signaling cascades. Src kinase is involved in a plethora of pathways including cell proliferation and migration. It is a well known player in force transduction pathways and we asked whether it is directly activated by force. In its resting state the kinase domain is auto-inhibited by the SH2 and SH3 domains. Src can be tethered to the cellular membrane through an N-terminal myristoylation and to the cytoskeleton by binding to the adaptor protein p130Cas. We used Molecular Dynamics simulations to mimic forces transmitted to the N-terminus of the SH3 domain and a Src-bond p130Cas peptide to investigate a possible mechano-activating mechanism. Force resulted in partial unfolding of the SH3 domain and therefore enhances kinase activity by impeding re-binding of the SH3/SH2 domains. Furthermore, we tested the mechanical stability of membrane binding, for which electrostatic interactions between negatively charged lipids and positively charged residues on the myristoyl linker are essential. The forces required to rupture the Src membrane anchor are similar or slightly higher than those needed for SH3-domain unfolding. Thus, Src is an intriguing candidate for a mechano-sensing protein, which might be tuned by factors such as cellular ion or membrane composition.

20-POS Board 20

STUCTURAL AND DYNAMIC CHARACTERIZATION OF AVIAN CRYPTOCRHOME 4

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It is remarkable that the inclination angle of the Earth's magnetic field vector can be used by birds as a source of a geomagnetic compass. Since the geomagnetic field penetrates biological materials the sensor for the magnetic field could be located anywhere inside an animal's body. Protein that is believed to be involved in magnetic field sensing is called cryptochrome (Cry). Crys are photoreceptors that are known to regulate the entrainment of the circadian clock in plants and animals. Cry4 in particular was found in the outer segment of double cone cells and long wavelength single cones of birds' eye and was shown to possess unique biochemical properties, unlike other members of the cryptochrome family, making it the best candidate for a magnetic field receptor in migratory birds. To understand the foundation of cryptochrome magnetic field sensing and unravel its biophysics it is imperative to have the structure of the protein. Currently the only Cry4 crystal structure available is that of a non-migratory bird, pigeon (Columba livia). Homology modeling is a computational process in which a 3D protein structure can be constructed by using the structure of another, similar protein, as a template. In this investigation homology models of birds' Cry4 from migratory birds (European robin and Blackcap) and non-migratory bird species (Chicken and Zebra finch) have been constructed and studied. The comparison reveals little structural and dynamical difference of various Cry4, and we try to explain why in spite of these similarities some cryptochromes of migration birds show a stronger magnetic sensing ability. With this investigation we hope to get a deeper insight into the structural differences that are important for magnetic sensing in migratory birds vs. non-migratory birds.

23-POS Board 23

LIPIDOMICS VIEW ON FREE ENERGIES OF PORE AND STALK FORMATION IN AND BETWEEN MEMBRANES

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Many biological membranes are asymmetric and exhibit complex lipid composition, comprising hundreds of distinct chemical species. Identifying the biological function and advantage of this complexity is a central goal of membrane biology. We use MD simulations at atomic and coarse-grained resolution to reveal how complex lipid compositions control the free energy landscape of topological transitions of membranes, including the formation of fusion stalks or trans-membrane pores. We find that the inner leaflet of a typical plasma membrane is far more fusogenic than the outer leaflet, which is likely an adaptation to evolutionary pressure. To rationalize these findings by the distinct lipid compositions of the membrane leaflets, we computed ~200 free energies of stalk formation between membranes of different lipid content, providing a comprehensive fusogenicity map of many biologically relevant lipid classes. In addition, we investigate how lipid-protein interactions and transmembrane potentials shape the landscape of membrane transitions. We find that membrane-binding proteins motifs from viral fusion proteins may control membrane fusion; their impact, however, greatly depends on geometry of the membrane-interacting peptide and on lipid composition. Together, our simulations provide a quantitative view on the role of lipid content and lipid-protein interactions during topological transitions of membranes.

26-POS Board 26

FREE ENERGY SIMULATIONS OF ELECTROPORATION

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Biological cells are defined as the volume enclosed by a semi-permeable lipid membrane. Forming pores in those membranes plays a role in processes such as membrane fusion and fission, increasing the permeability of the membrane, and others. Electroporation is a method used for decades to help introduce drugs and genetic material in cells or generally as a pore forming modality. Although pores are heavily studied with a variety of methods, the free energy landscape of the initial stages of the pore formation is still not fully understood. We use molecular dynamics simulations to study the mechanisms and energetics of electroporation. We overcome the challenge of exploring the free energy landscape using umbrella sampling along a recently developed reaction coordinate[1, 2]. The potentials of mean force (PMFs) show that electric fields greatly stabilize open pores and lower the barrier for pore formation (as expected). An unexpected discovery is the way in which the pore formation energy barrier is influenced by the applied potential. As a result of that discrepancy between simulations and existing continuum models we propose a novel continuum model of electroporation. To verify our findings we compare two methods for establishing transmembrane potential in an MD simulation – external electric field and charge imbalance. [1] J. Hub and N. Awasthi, J. Chem. Theory Comput. 2017, 13, 2352-2366[2] J. Hub, J. Chem. Theory Comput. 2021, 17, 1229−1239

29-POS Board 29

POST-TRANSLATIONAL MODIFICATION OF MICROTUBULES CAN CONTROL DYNEIN-2'S ABILITY TO WALK ON A-TUBULES

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The microtubules (MTs) that form the cytoskeletons of eukaryotic cilia and flagella are doublet MTs composed of A- and B-tubules. It is known that dynein-2 and kinesin-2, responsible for the transportation in cilia and flagella, walk on A-tubules and B-tubules, respectively. However, it is unknown how dynein-2 and kinesin-2 select A-tubules and B-tubules, respectively, while both A- and B-tubules are composed of the same alpha- and beta-tubulin dimer. Recent studies indicate that tubulin post-translational modifications (PTMs) are mostly enriched in the B-tubules. We hypothesized that the MT selection is based on the PTMs. In this study, we performed a molecular dynamics (MD) simulation to reveal how the movement of dynein-2 changes depending on the PTMs. For the effective sampling trajectories, we use a coarse-grained model for MD simulations. In the end, we found poly-glutamylation, one of the PTMs, can inhibit dynein-2 walking on MTs. Interestingly, the key residues of dynein-2 which have contact with poly-glutamylation are well reserved in many species' dynein-2.

32-POS Board 32

TOWARDS UNDERSTANDING THE FUNCTIONAL DYNAMICS OF ACYL CARRIER PROTEIN MEDIATED SUBSTRATE TRANSPORT IN THE FUNGAL FATTY ACID SYNTHASE

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Fatty acid biosynthesis is a central pillar of metabolism providing essential molecules for energy storage, signal transduction and cell wall integrity. In eukaryotes the multiple enzymes required for the synthesis of fatty acids are combined in large multifunctional enzyme complexes. The nascent fatty acid is shuttled between enzymatic domains by an integral acyl carrier protein (ACP). This transfer process is assumed to be stochastic, regulated primarily by steric occlusion and the spatial organization of active sites within the multienzyme complex. In addition, recent studies have identified a regulatory subunit, which can alter the enzymatic activity of the fungal fatty acid synthase (FAS). Cryo-electron microscopy shows that this change in activity is concomitant with a conformations rearrangement of the ACP domain. Yet it is unclear how the presence of this subunit alters the dynamics of substrate transport. Here we show the effect of the regulatory subunit on the dynamics of ACP following initiation of fatty acid biosynthesis. Advances in high performance computing have made it possible to simulate even large systems such as the yeast FAS (approx. 200.000 heavy atoms) at biologically relevant timescales. We modeled the 2.5 MD complex based on cryo-electron microscopy structures. Important functional regions, such as the intrinsically disordered linker region connecting ACP with the FAS were modeled into the complete complex following extensive molecular dynamics simulations. We used the GROMACS software package to investigate the dynamics of ACP in the presence and absence of the regulatory subunit. Based on these simulations we correlate changes in the dynamics of the carrier domain with changes in enzymatic activity. Overall, our work provides insights into carrier mediated transport in multifunctional enzyme complexes. This process is pivotal to the function of the FAS and presents a key component in optimizing the enzyme for biotechnological application.

35-POS Board 35

DIFFERENCES IN CONFORMATIONAL ENSEMBLES OF HUMAN APOLIPOPROTEIN E ISOFORMS PROVIDE INSIGHT INTO ALZHEIMER'S DISEASE MECHANISMS

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Alzheimer's disease (AD) is a proteinopathy which results in severe cognitive impairment, loss of motor control, and death. Mutations in the APOE gene, which encodes the lipid transporting protein, apolipoprotein E (ApoE), are one of the strongest genetic risk factors for AD. ApoE occurs in three common isoforms ApoE2, ApoE3 and ApoE4, and homozygotes of ApoE4 have a 15-fold greater risk of developing the disease when compared to homozygotes of ApoE3. While the monomeric form of ApoE is proposed to be the disease relevant and lipid binding competent form, it is highly dynamic and prone to oligomerization at low concentrations. Together, these two facts have hindered traditional approaches towards obtaining structural data about the pathogenic forms of the protein. We hypothesized that the point mutations between the isoforms shift the conformational ensemble towards pathogenic conformations. Identifying such conformations would open up avenues for designing therapeutics that can shift the ensemble towards non-pathogenic conformations. We use the Folding@Home distributed computing network to perform Molecular Dynamics simulations of the isoforms in order to quantify the differences in their conformational ensembles. We combine our computational results with single molecule Forster Resonance Energy Transfer experiments performed on monomeric ApoE4 to understand the structural biology of this important class of proteins. We find that ApoE4 is considerably more dynamic than has been thought of based on previous structural data. We also identify allosteric effects between the regions of the polymorphisms between the isoforms and putative lipid-binding regions which could contribute to the differences in the pathogenicity of the isoforms.

38-POS Board 38

AVIDITY OF THE MALARIA ADHESIN VAR2CSA IS MECHANO-CONTROLLED BY EXPOSURE OF A SECOND CRYPTIC CSA SUGAR BINDING SITE

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Plasmodium falciparum (Pf) is responsible for the most lethal form of malaria. VAR2CSA is the adhesin protein expressed by the parasite at the membrane of the infected erythrocytes for attachment on the placenta, leading to pregnancy-associated malaria. Accordingly, this protein is a target of vaccines against placental-malaria. VAR2CSA is a large, 350 kDa multidomain protein composed of nine extracellular domains, a transmembrane helix, and an intracellular domain. Chondroitin Sulphate A (CSA) serves as the substrate and anchor point of VAR2CSA. Shear flow, as the one occurring in blood, has been shown to enhance VAR2CSA adhesion on the CSA-matrix. However, the underlying molecular mechanism by which mechanical force influences the adhesivity of this protein still remains elusive. Here, we shed light on this question through the use of million-atom equilibrium and force-probe molecular dynamic simulations, with a cumulative sampling time of more than 2.5 μs. We subjected the VAR2CSA protein-CSA sugar complex to a force mimicking the elongational tension arising from the shear of the flowing blood. We show that upon this force exertion, the CSA sugar chain dissociates from the protein, but before that, the VAR2CSA protein undergoes a large opening conformational transition, exposing a secondary CSA binding site. Molecular docking followed by extensive equilibrium molecular dynamics relaxation suggest that a dodecameric CSA molecule can stably accommodate to the force-exposed binding site. Our results thus suggest that mechanical force increases the avidity of VAR2CSA by uncovering a secondary cryptic CSA binding site. The mechanism provided here paves the way to understanding the molecular mechanism governing the shear enhanced VAR2CSA-CSA interaction. It highlights the mechano-enhanced protein-sugar avidity employed by Pf during malaria-infected erythrocyte adhesion.

41-POS Board 41

SARS-COV-2 SPIKE OPENING DYNAMICS AND ENERGETICS REVEAL THE INDIVIDUAL ROLES OF GLYCANS AND THEIR COLLECTIVE IMPACT

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The trimeric spike (S) glycoprotein, which protrudes from the SARS-CoV-2 viral envelope, is responsible for binding to human ACE2 receptors. The binding process is initiated when the receptor binding domain (RBD) of at least one protomer switches from a "down" (closed) to an "up" (open) state. Here, we used molecular dynamics simulations and two-dimensional replica exchange umbrella sampling calculations to investigate the transition between the two S-protein conformations with and without glycosylation. We show that the glycosylated spike has a higher barrier to opening than the non-glycosylated one with comparable populations of the down and up states. In contrast, we observed that the up conformation is favored without glycans. Analysis of the S-protein opening pathway reveals that glycans at N165 and N122 interfere with hydrogen bonds between the RBD and the N-terminal domain in the up state. We also identify roles for glycans at N165 and N343 in stabilizing the down and up states. Finally, we estimate how epitope exposure for several known antibodies changes along the opening path. We find that the epitope of the BD-368-2 antibody remains exposed irrespective of the S-protein conformation, explaining the high efficacy of this antibody.

44-POS Board 44

CHARACTERIZING THE ENERGY LANDSCAPE OF CRE RECOMBINASE CATALYTIC DOMAIN THROUGH MOLECULAR DYNAMICS SIMULATIONS

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Site-specific tyrosine recombinases are proteins that promote scission or insertion of DNA sequences, being the Cre-loxP system one of the most studied. It acts by forming a tetramer, in which two active and two inactive recombinase monomers bind and recombine two loxP sequences. The complex is stabilized by the interaction of the last catalytic (CAT) domain helix (helix N) with a pocket formed in the adjacent subunit. Despite its extensive use in genetic engineering, there is still missing information regarding target selection, intasome formation, and structural changes associated with the recombination reaction. Here we used molecular dynamics simulations to characterize the energy landscape of the two states of CAT domain from Cre recombinase with the helix N in three different positions (cat-delN: no helix N; cat-trans: helix N in the intasome pocket; and cat-cis: helix N in a proposed auto-inhibitory pocket). All simulations were carried out using GROMACS, the charmm36m force-field, TIP3P water model, 0.15 M NaCl, 300K, the hydrogen mass partitioning algorithm and a 4 femtoseconds time step. For each system we ran three replicas of 5 microseconds each. Our results show that cat-delN simulations in both states sample similar energetic landscapes, displaying a scissor-like movement in the helix N interaction pocket; this movement is reduced in the cat-trans and cat-cis simulations, suggesting that it might be involved in complex formation/disassembly. For the cat-cis simulations, helix N formed stable interactions with the active site residues, keeping this segment in the active site pocket. Also, all systems failed to form a complete active site, which suggests that quaternary interactions are necessary for activation. We acknowledge the computer resources provided by the LNS del Sureste de México through grant 202101023N, CONACyT (CVU: 858905, project INF-2014-02-231504), Laboratorio de Supercómputo y Visualización en Paralelo, and LANCAD through grants 99-2021 and 49-2022.

47-POS Board 47

PYBROWN SOFTWARE FOR DIFFUSION AND REACTIONS IN CROWDED ENVIRONMENTS INCLUDING STOKESIAN DYNAMICS

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Devising a predictive computer model of a biological cell poses a grand challenge at the frontier of computer science, biology, and physics. Although cell inner workings are rooted in the microscopic dynamics of its constituents at a molecular scale, the concept of first-principle simulations of whole cells with quantum mechanics/molecular mechanics (QM/MM) methods is currently unfeasible. Roland Netz and William Eaton (PNAS February 9, 2021 118 (6)) estimated that it would take ca. 1 billion years to run a QM/MM simulation of M. genitalium cell for the duration of its doubling time (ca. 2 hours). Because of that, coarse-grained mesoscopic approaches like Brownian dynamics (BD) are of particular interest to computational biophysicists. Here, we report on a versatile software — pyBrown, enabling users to perform coarse-grained simulations in crowded environments. pyBrown allows for BD simulations with and without hydrodynamic interactions (HI). In contrast to similar existing packages, such as BDBOX or BrownMove, which use Rotne-Prager-Yamakawa description for HI, pyBrown also provides short-range HI in the form of lubrication correction, which is of great importance for crowded systems mimicking the intracellular milieu, where various macromolecules are forced to stay close to each other. In addition, pyBrown enables computations of diffusion-limited reaction rates based on the Northrup–Allison–McCammon algorithm and other features. In this contribution, we present the details of pyBrown software and show the results of using it for simple one-component systems. We show the importance of short-range HI by demonstrating that the commonly used Rotne-Prager-Yamakawa description can significantly overestimate the mobility of macromolecules in volume-occupied systems. This work was supported by NCN grant No. 2017/25/B/ST3/02456. We thank PLGrid for providing computational facilities.

50-POS Board 50

MULTIBILLION ATOM MOLECULAR DYNAMICS SIMULATIONS OF COMPLEX CELLULAR MEMBRANES

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Membranes are the basic organizational and defensive unit of the cell, and they thus play a vital role in biological function. Electron microscopy (EM) can provide 3D structures of these membranes, and, with the advent of exascale computing, there is a new opportunity to use molecular dynamics (MD) simulations to elucidate the intricate biophysical connection between the complex composition, structure, and function of these membranes. To take advantage of this opportunity, we have developed xMAS (Experimentally-Derived Membranes of Arbitrary Shape) Builder, software designed to turn EM structures and experimentally-derived lipid and protein compositions of cellular membranes into atomistic models that are suitable for MD. xMAS Builder generates these models using a series of custom-designed modeling steps, including simulating Lennard-Jones particles while attracted to grid-based potentials to optimize the packing of the membrane lipids, fixing ring piercings and other complex lipid clashes using a newly developed energy minimization technique, and utilizing grid-based potentials to equilibrate the models while maintaining their experimentally-derived shapes. Using xMAS Builder, we have built the first cell-scale (~4.5 billion atom, ~1.9μm³) model of a representative cellular membrane (a helicoidal system from the endoplasmic reticulum called a Terasaki ramp), and we have also built several models of a smaller synthetic system with equivalent complexity. Preliminary simulations of these models have demonstrated their potential to reveal fundamental insights into the general behavior of cellular membranes, including the principles that determine the number of lipid molecules that can be accommodated by curved membranes and the natural response of cellular membranes to perturbations to their structures. These preliminary results support the expectation that xMAS Builder will soon enable MD simulations that leverage exascale computing to provide compelling insight into the complex molecular basis of cellular membrane structure and biological function.

53-POS Board 53

OPTIMAL PROTEIN SEQUENCE DESIGN MITIGATES MECHANICAL FAILURE IN SILK BETA-SHEET NANOCRYSTALS

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Spider silk fiber possesses exceptional mechanical strength attributes such as high tensile strength, toughness, and elasticity in tensile loading. Previous experimental and computational studies showed that these extraordinary mechanical properties results mostly from a) hierarchical arrangement of antiparallel β-sheet nanocrystals in disordered matrix, b) corresponding β-strand length and, c) H-bond interactions among them. However, the dependence of mechanical properties of silk nanocrystal on its motifs remains largely unexplored despite these studies. To investigate the significance of β-sheet sequence motifs, we modeled various representative amino acid homopolymers on said β-sheet geometry and analysed their impact and mechanical properties. We chose amino acid sequences having small (Gly/Ala/Ala-Gly) or polar (Thr/Asn) or hydrophobic (Ile/Val) side chains and used Steered Molecular Dynamics (SMD) to pull their central β-strand. Multiple SMD pull-out simulations showed that homopolymers of naturally occurring sequence motifs (Ala/Ala-Gly) have superior mechanical properties than other modeled sequence motifs. Surprisingly, the enhanced side-chain interactions in homo(poly)-polar/hydrophobic amino acid models were unable to augment backbone hydrogen bond cooperativity to increase mechanical strength. Thereafter, we analyzed the hydrogen bond and β-strand pull dynamics of modeled nanocrystals, and this suggested that nanocrystal of pristine silk sequences most likely achieve superior mechanical strength by optimizing side chain interactions, inter-sheet packing, and main-chain H-bond interactions. This advanced our understanding of sequence-dependent mitigating factors and their variations in β-sheet rupture mechanisms. Conclusively, our study suggested that β-sheet nanocrystal's default sequence while being evolutionary optimized is also a key factor in determining nanomechanical properties of silk and this study also provides insight into the silk's molecular design principle with implications in the genetically modified artificial synthesis of silk-like biomaterials.

56-POS Board 56

SYNTHESIS OF LARGE, LIPID MEMBRANES CONTAINING MEMBRANE PROTEINS FROM GAS PHASE

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Objective The aim was to synthesise transportable protein containing membranes of an inherently unlimited size using a nano-electrospray ion source. Methods A nano-electrospray ion source was directed towards the liquid meniscus of a 3 mm wide reservoir holding an aqueous buffer and some SM-2 Biobeads for detergent extraction. In a series of steps bipolar lipids, glycerol and detergent solubilised membrane proteins were sprayed onto the surface and incubated to remove the detergent. Results Finally, the correct conditions were found to allow for the self-assembly of a single lipid bio-membrane containing the proteins. The layer covered the entire surface as verified by transmission electron microscopy. No denatured protein was found. Instead, the images correspond to a protein filled membrane. The protein initially used was the integral membrane protein ompG, a mono-molecular pore. Additionally I used listeriolysin O to investigate whether the procedure is gentle enough to allow non-covalent complex formation. Listeriolysin O assembles on membranes into ring shaped complexes of 30 or more units. These rings insert themselves into membranes and form large pores. Using this method the protein complex assembly process could be directly visualised. Conclusions With the help of nano-electrospray it is possible to synthesise large, transportable lipid bi-layers that contain intact membrane proteins. This is very helpful to speed up cryo-electromicroscopic structure reconstruction. The method has the potential to make the sophisticated enzymatic activity of membrane proteins accessible on a larger scale and in a technical environment, to build bio-similar detectors or enable complex molecular synthesis in large membrane filled bio-reactors. References 1. M. Wilm, bioRxiv, (https://www.biorxiv.org/content/10.1101/661215v1) 2. M. Wilm, bioRxiv, (https://www.biorxiv.org/content/10.1101/661231v1)

59-POS Board 59

MACHINE LEARNING REVEALS THE CRITICAL INTERACTIONS FOR SARS-COV-2 SPIKE PROTEIN BINDING TO ACE2

Zijian Zhang
Georgia Tech

Cancelled

THURSDAY, MAY 19
POSTER SESSION III
15:15 – 17:00
Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Thursday. Presenting authors with odd-numbered poster boards should present from 15:15 – 16:05 and those with even-numbered poster boards should present from 16:05 – 17:00. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Odd-Numbered Boards 15:15 – 16:05 | Even-Numbered Boards 16:05 – 17:00

Amin, Kazi	**3-POS**	**Board 3**
Attou, Aymen	**6-POS**	**Board 6**
Bisht, Konark	**9-POS**	**Board 9**
Buck, Matthias	**12-POS**	**Board 12**
~~**Covino, Roberto**~~	~~**15-POS**~~	~~**Board 15**~~ **CXL**
Depenveiller, Camille	**18-POS**	**Board 18**
Hempel, Tim	**21-POS**	**Board 21**
Jana, Kalyanashis	**24-POS**	**Board 24**
Kohnke, Bartosz	**27-POS**	**Board 27**
Kumar, Vipul	**30-POS**	**Board 30**
Liebl, Korbinian	**33-POS**	**Board 33**
Manivarma, Thiliban	**36-POS**	**Board 36**
Miettinen, Markus	**39-POS**	**Board 39**
Peplowski, Lukasz	**42-POS**	**Board 42**
Sapia, Jennifer	**45-POS**	**Board 45**
Stelzl, Lukas	**48-POS**	**Board 48**
Trollman, Marius	**51-POS**	**Board 51**
Vishwakarma, Krishna	**54-POS**	**Board 54**
Wingbermühle, Sebastian	**57-POS**	**Board 57**
Zülske, Tilo	**60-POS**	**Board 60**

Posters should be set up the morning of May 17 and removed by noon May 20.

3-POS Board 3

IMPROVED MONOVALENT CATION-PROTEIN INTERACTIONS IN THE CHARMM DRUDE POLARIZABLE FORCE-FIELD

Kazi S Amin[1]; Justin A Lemkul[3]; Alexander D MacKerell Jr.[2]; Dennis Salahub[4]; Sergei Noskov[1];
[1]University of Calgary, Biological Sciences, Calgary, AB, Canada
[2]University of Maryland, School of Pharmacy, Baltimore, MD, USA
[3]Virginia Tech, Department of Biochemistry, Blacksburg, VA, USA
[4]University of Calgary, Department of Chemistry, Calgary, AB, Canada

Explicit atomic polarizability is crucial to the accurate description of interactions between ions and biomolecules. The CHARMM Drude polarizable force-field models atomic polarizability by including charged particles with a small mass linked to non-hydrogen atoms through a harmonic bond. This complicates the parametrization process, and while partial charges and polarizabilities have been mostly parametrized, Lennard Jones (LJ) parameters for monoatomic ions still need to be revised. Here we present a new set of pair-specific LJ Rmin and Thole Coulomb screening parameters for each of Li^+, Na^+, and K^+ ions paired with several important biomolecular oxygen atom types, which include carbonyl, carboxylate, and phosphate oxygens. To obtain target data for parameter optimization, we computed single point quantum mechanical (QM) interaction energies of representative ion-molecule complexes, varying the ion position with respect to the molecule. We then used a novel scoring criterion to fit the Drude interaction energies to the target data. The scoring criterion prioritizes fitting the local shape of the minima of both QM and Drude energy surfaces, rather than the absolute energies, as is usually done. The parameter optimization was performed using a global search over a range of LJ Rmin and Thole screening factors. The parameters obtained for ion-carboxylate interactions agree very well with osmotic pressures in condensed phase MD simulations. Thus, we were able to select parameters which fitted both gas-phase QM data and condensed phase osmotic pressure data reasonably well. However, for other oxygen atom types belonging to uncharged functional groups, the same criterion was not as effective and we had to compare the energy surfaces more holistically to obtain reasonable parameters. This implies that careful criteria selection during force field parametrization is crucial, especially when exact reproduction of QM energy is impossible and when considering transferability of gas-phase derived parameters to condensed phase systems.

6-POS Board 6

EFFECTS OF CTCF AND COHESIN COMPLEXES ON CHROMATIN ARCHITECTURE AND GENOME TOPOLOGY

Aymen Attou[1]; Gero Wedemann[1]; Tilo Zülske[1];
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The sophisticated spatial organization of DNA in eucaryotes starts from nucleosome chains forming chromatin loops that can cluster together establishing fundamental units called topologically associating domains (TADs). TADs are an important factor for gene regulation by facilitation or repressing long range contacts in the genome. Those loops are formed and held together by a ring-shaped protein complex called cohesin together with the effect of CTCF, an 11-zinc finger DNA-binding protein. This cohesin complex causes a bi-directionally extruding process and forms a loop anchor when encountering the right directed CTCF. A loop has a residence time of several minutes. For the purpose of clarifying the spatial structure of a loop we investigated these processes at a super nucleosomal level, where we modeled the 3D-nuclear organization by computer simulations in the presence and depletion of cohesin and CTCF. The simulations are based on our established coarse grained model utilizing a Metropolis-Monte Carlo procedure combined with replica exchange to generate a statistical representative ensemble of configurations in thermal equilibrium. We studied differences in the spatial structure and of contacts probabilities of different domains, These results of systems with present and depleted cohesin and CTCF were compared with experimental data. It allowed us to understand the role of cohesin and CTCF and their impact on the 3D structure of chromatin.

9-POS Board 9

TRANSMEMBRANE PEPTIDES WITH DIPOLE MOMENT AS VOLTAGE SENSING ELEMENTS

Konark Bisht[1]; Himanshu Khandelia[1];
[1]University of Southern Denmark, Department of Physics, Chemistry and Pharmacy, Odense, Denmark

Transmembrane (TM) voltage plays a vital role in the behaviour and functions of the lipid bilayer membrane. It regulates the exchange of particles across the membrane through TM proteins such as voltage-gated ion channels. This work studies a novel mechanism for sensing membrane voltage, which involves the reorientation of alpha-helices present in the TM proteins with the change in the membrane electric field. We consider model peptides having electrical dipole moments in a lipid bilayer and perform coarse-grained molecular dynamics simulations to study the effect of variation of TM voltage on their tilt angles and ascertain the optimal parameters for designing a sensitive membrane voltage sensor.

12-POS Board 12

STRUCTURAL BASIS OF EPHA1 AND EPHA2 HOMO-DIMERIZATION AND WHOLE RECEPTOR INTERACTIONS USING COARSE GRAINED MARTINI 3 SIMULATIONS

Matthias Buck; Amita Sahoo[1];
[1]Case Western Reserve University, Physiology and Biophysics, Cleveland, OH, USA

EphA1 and EphA2 are receptor tyrosine kinases which play a critical role in cellular growth, differentiation and cell motility. Transmembrane dimerization is a key regulatory step in the activity and signaling process of these receptors. However, the involvement of the transmembrane (TM), the immediate two extracellular Fibronectin III domains (FN1&2) and the juxtamembrane (JM) region in the dimerization process is not clearly defined [1]. Therefore, studying the structural mechanisms of EphA1 and EphA2 dimerization and membrane interactions will help us better understand the signaling of these receptors. Molecular dynamics simulations have become a powerful tool to study membrane proteins and their interactions. Here, we modeled the domains of the EphA1 and EphA2 receptors and studied their structural mechanism of activation by using the coarse-grain (CG) molecular dynamics simulations using the recently published Martini3 potential function [2]. We show that the FN, TM and JM domains all differ in their interactions and in their interactions with the membrane between EphA1 and A2. In case of EphA2 most structures are non-dimeric, whereas FN domain dimerization is more compatible with TM helix dimers in EphA1. The underlying differences in the primary sequence which are likely responsible for these observations are discussed. Finally, we have started simulations on the whole length EphA2 receptor of around 600,000 particles (compared to the 6,500,000 atoms required for all atom simulations) and we have been able to run simulations of dimers-tetramers to 4 μs. References: [1] Sahoo AR, Buck M. Structural and Functional Insights into the Transmembrane Domain Association of Eph Receptors. Int J Mol Sci. 2021;22(16):8593. [2] Sahoo, AR, et al. Predicting Transmembrane (TM) Domain Dimer Structures using Martini 3. BioRxiv doi: https://doi.org/10.1101/2021.09.10.459840

15-POS Board 15

EARLY EVENTS OF THE ACTIVATION OF THE MET RECEPTOR IN BACTERIAL INVASION

Roberto Covino
Frankfurt Institute for Advanced Studies

Cancelled

18-POS Board 18

MODELLING OF ELASTIN POLYPEPTIDES BY ASSEMBLY OF RIGID BODIES AND SIMULATIONS IN AN EXTRACELLULAR MATRIX VIRTUAL MODEL

Camille Depenveiller[1]; Hua Wong[1]; Jean-Marc Crowet[1]; Stéphanie Baud[1]; Manuel Dauchez[1]; Nicolas Belloy[1];
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Extracellular matrix (ECM) is a tridimensional network composed of large macromolecules and plays a key role in supporting tissues and organs. Dysfunction of ECM components, due to structure changes or generation of fragments with physiopathological effects, may lead to some diseases. The precise organization of the ECM remains poorly known, since experimental data is rare or difficult to obtain. Classical molecular dynamics simulations are of interest to study domains of ECM proteins, but inappropriate for large multi-domain macromolecules. However, to handle such huge molecules at the mesoscopic scale, a dedicated numerical environment allowing to model and simulate large biological systems as dynamic chains of rigid bodies has been developed. Rigid bodies are modules representing the domains composing each molecule and allow to describe representative conformations of molecules by simple shapes called primitives. The project aims to extend this approach to elastin and its monomer tropoelastin. Thus, classical molecular dynamics are first performed on characteristic peptide motifs of tropoelastin. Then, using different clustering methods allows to sample the conformational space along molecular dynamics trajectories, in order to get the main characteristic conformations of the peptides. Properties such as hydrophobicity and electrostatics are also analyzed. Simulations are then adapted at the mesoscopic scale to rigid bodies. Each polypeptide is built by an assembly of rigid bodies, linked together with molecular joints, on which constraints determined by characteristic angles between motifs are defined. Elastin polypeptides conformations and properties will be integrated in the ECM virtual model. These results will enable to understand the behavior of the proteins and the structure-function-dynamics relationships. These new insights will allow for a better understanding of the elasticity, the structural properties and thus the complexity of the ECM.

21-POS Board 21

A SPATIAL DECOMPOSITION APPROACH TO MARKOV MODELING

Tim Hempel[1,2]; Frank Noé[1,2,3];
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[2]Freie Universität Berlin, Department of Physics, Berlin, Germany
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Modeling the dynamics of ever-larger biological systems is becoming increasingly relevant to our understanding of molecular cell biology. The combination of molecular dynamics (MD) simulations with classical Markov state models (MSMs) or related deep learning techniques such as VAMPnets have proven important tools in that regard, providing access to simplified models of molecular kinetics. Despite their successes, these approaches are inherently limited by the size of modeled systems. As larger macromolecular complexes come with an increased number of weakly coupled subsystems, the number of combinatorial global states grows exponentially, hampering our efforts to sample all distinct global state transitions. Here, we leverage weak couplings between subsystems to estimate a global kinetic model without requiring the sampling of all combinatorial global states. First, this approach is implemented with classical MSMs, yielding a method we term independent Markov decomposition (IMD). Using the example of empirical few-state MSMs of ion channel models, we show that IMD can reproduce experimental conductance measurements with a major reduction in sampling when compared with standard MSMs. Second, IMD is combined with VAMPnets, forming an end-to-end deep learning framework that automatically decomposes a system into subdomains, while simultaneously learning individual subsystem Markov models (iVAMPnets). We show that iVAMPnets can successfully model high-dimensional MD data for the synaptotagmin C2A domain, even when the sampling is insufficient for standard VAMPnets. Both methods, IMD and iVAMPnets, strive to provide data-efficient and easily interpretable models of molecular kinetics that are applicable to highly complex biological systems.

24-POS Board 24

DEMONSTRATING THE FUNCTION OF THE SURFACE-EXPOSED LIPOPROTEIN BTUG IN EFFICIENT B_{12} TRANSPORT IN ASSOCIATION WITH THE OUTER-MEMBRANE BTUB PROTEIN

Kalyanashis Jana[1]; Javier Abellón-Ruiz[2]; Bert van den Berg[2]; Ulrich Kleinekathöfer[1];
[1]Jacobs University Bremen, 1Department of Physics & Earth Sciences, Bremen, Germany
[2]Newcastle University, 2Biosciences Institute, Faculty of Medical Sciences, Newcastle upon Tyne, United Kingdom

BtuB, a TonB-dependent transporter, is an outer membrane protein in Gram-negative bacteria that enables the active transport of cyanocobalamin (vitamin B_{12}) and essential nutrients (1). The protein consists of a channel with 22 β-strands combined with a large N-terminal domain, the luminal domain, folded back into and blocking the interior of the barrel. Substrate binding changes the conformational equilibrium in the Ton box as well as the luminal domain to favor an unfolded state that facilitates substrate translocation through BtuB (1–3). A newly determined BtuBG crystal structure purified from Bacteroides the taiotaomicron has been considered for the present computational study. The BtuG, a surface-exposed lipoprotein, adopts a seven-bladed β-propeller fold. The BtuG is strongly connected to the BtuB protein through a hinge loop and can move away from BtuB in a hinge-like fashion (4, 5). We explore how the BtuG protein moves away from BtuB protein and the role of BtuG in the transport of the large B_{12} molecule. To explore the B_{12} acquisition mechanism, unbiased molecular dynamics (MD) along with multiple walker well-tempered metadynamics (WTMtD) simulations have been carried out. The MD simulation results demonstrate that the BtuBG protein transports cyanocobalamin through a pedal-bin mechanism: the substrate first binds to the open BtuG lid before moving to the BtuB binding site. To this end, multiple walker WTMtD simulations have been employed to determine free energy for the anticipated B_{12} transport from the BtuG to BtuB active site cavity.

27-POS Board 27

FAST MULTIPOLE METHOD FOR A CONSTANT PH ALGORITHM IN GROMACS

Bartosz Kohnke[1]; Eliane Briand[1]; Carsten Kutzner[1]; Helmut Grubmüller[1];
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Molecular dynamics (MD) simulations of biomolecules with dynamic protonation changes have lately become increasingly important. Constant pH molecular dynamics (CPHMD) allows to dynamically alter the protonation during simulations to correctly model protonation probabilities at a fixed pH level. Typically, CPHMD utilizes a λ-dynamics method with Hamiltonian scaling, where a fictitious λ-particle continuously interpolates between protonated and deprotonated Hamiltonian. The dynamics of the λ-particle depends on the local electrostatic environment of a protonatable site; however, the long-range nature of coulombic forces requires reevaluation of the complete Hamiltonian at each protonation state. This step becomes a prohibitive factor for efficient usage of CPHMD systems with many sites since pairwise interactions evaluation is the most performance-limiting factor in MD simulations. To obtain atomistic trajectories of proteins on biologically relevant timescales, MD utilizes efficient approximation algorithms. The most prominent one in the field is particle mesh Ewald (PME), which is extremely fast but lacks the flexibility to perform Hamiltonian recalculations efficiently. A slightly different approach to CPHMD is a charge scaling method, which allows a more efficient interpolation scheme and a proper PME utilization. However, to enable efficient λ-dynamics with Hamiltonian scaling, we implemented a fast multipole method (FMM). In contrast to PME, FMM utilizes a flexible tree structure that preserves local charge differences, and therefore it allows for very fast Hamiltonian recalculations. Here, we present our NVIDIA CUDA FMM for CPHMD. The FMM GPU implementation has been tailored for MD calculations. Its performance is about a third of that of highly optimized PME on a single GPU node. However, the FMM allows simulation systems with many protonatable sites with negligible computational overhead. Additionally, on larger exascale GPU clusters, where PME scaling breaks down, the efficiency of FMM for CPHMD should become even more apparent.

30-POS Board 30

EQUILIBRIUM AND DYNAMIC PROPERTIES OF UNFOLDED POLYPEPTIDE CHAINS: A MARKOV CHAIN ANALYSIS OF INTERNAL POLYMER DYNAMICS

Vipul Kumar[1]; Thomas Kiefhaber[1];
[1]Martin Luther University, Institute of Biochemistry and Biotechnology, Halle, Germany

Contact formation between different segments of a polypeptide chain is the most elementary step of protein folding. However, carrying out experiments to study such rapid event has remained a challenge. We have been able to gain information on the dynamic and structural properties of unfolded polypeptide chains by using intrinsically disordered polypeptide sequences labeled with chromophore dyes at the two ends, to probe for the intrachain distance measurement and the intrachain diffusion coefficient by FRET[1] as well as to measure the rate constant of loop formation by triplet-triplet energy transfer[2]. These studies indicate a higher mobility of the residues close to the ends of the disordered chain as compared to the ones in the interior. To gain information on the origin of the experimentally observed higher mobility at the chain ends we explore the dynamics of unfolded polypeptide chains by Monte-Carlo simulations, where randomly selected sigma bonds are rotated arbitrarily within sterically allowed regime, followed by a Markov Chain analysis of the end-to-end distance transitions. The simulations, although not exact replica of physiological conditions, mimic the properties of a good solvent. This method, in combination with our previous experimental studies, provides the frequency of chain fluctuations, the flux of the ends to approach or recede from each other and the distance distributions. Finally, we discuss the unique properties of the ends of a chain and why loop formation between internal residues is slower than loop formation between the chain ends. References:1. Möglich A., Joder K., Kiefhaber T., (2006), PNAS 103, 12394-123992. Fierz B., Kiefhaber T., (2006), JACS 129, 672-679

33-POS Board 33

DEVELOPMENT OF DNA FORCE FIELDS AND THE IMPACT OF TOPOLOGICAL STRESS ON REGULATORY SITES AND DNA DAMAGES

Korbinian Liebl[1,2]; Martin Zacharias[2];
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The quality of force fields is central to the accuracy of Molecular Dynamics (MD) simulations. However, many of the modern DNA force fields still rely on non-bonded parameters derived more than 20 years ago. In this talk, I explain how this motivated me to develop an entirely new DNA force field ('Tumuc1') based on quantum-mechanical calculations. I discuss the development of Tumuc1, show problems and strategies in force field parameterization and analyze the performance of Tumuc1. Advanced sampling techniques allowed me to compute base-pair stacking energies. Here, the comparison to experimental data reveals systematic overstabilization of the current force fields. Thus, I also present recent attempts to fix this deficiency and outline the route to a force field which captures DNA's stability accurately. In a next step, I share unpublished data of MD simulations of ~200 base-pair long, circularly closed DNA molecules exposed to explicit solvent. These simulations were performed on the NHR supercomputer in Erlangen, hence facilitating sufficient sampling, and give valuable insight into how topological stress exposes regulatory DNA sequences and UV damages. This topic is of outmost biological relevance, as DNA is constantly under topological stress in vivo, and I point out how this affects base-pair flipping and local melting, for instance.

36-POS Board 36

DIVERSE ROLES OF MEMBRANE IN FERROPTOTIC CELL DEATH. INSIGHTS FROM MOLECULAR DYNAMICS STUDY OF 15LOX1-PEBP1 COMPLEX

Thiliban Manivarma[1,2]; Karolina Mikulska-Ruminska[1,2]; Wieslaw Nowak[1,2];
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Ferroptosis is recently discovered mechanism of cells death induced by unbalanced regulation one out of three major metabolic pathways involving iron, thiols or lipids, Ferroptosis is connected with such diseases as Alzheimer's disease, Parkinson's disease, sepsis, kidney injury, cancer etc. The process involves enzymatic and non-enzymatic means where the specific mechanisms are still unclear. The enzymatic form of ferroptosis involves iron dependent peroxidation of lipids performed by lipoxygenase (LOX). Presence of products (lipid peroxides) leads to the cell death. LOX is membrane-associated enzyme which imports lipids from the membrane. For the activity, a promiscuous Phosphatidylethanolamine Binding Protein 1 (PEBP1) is recruited. In a recent paper, 15LOX1-PEBP1 complex was modelled using coarse-grained approach in a simplified water environment (1). Here, we present extensive all-atoms molecular dynamics data on 15LOX1-PEBP1 system embedded in a realistic membrane environment. We repeat simulations for membrane-free complex and in that way we pinpoint structural differences in this system induced by interactions with membrane composed out of 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) and 1-stearoyl-2-arachidonyl-phosphoethanolamine (SAPE). Moreover, we will discuss timescales involved in ferroptotic cell death and indicate metabolic steps requiring exa-scales computing power. Acknowledgment: Support of National Science Centre, Poland, No 2019/35/D/ST4/02203 (KMR, TM), is acknowledged. IDUB NCU #MEMOBIT grant (WN) and ICNT UMK computer facilities are acknowledged as well.1. Wenzel, S. E., et al. 2017. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Cell. 171(3):628-641. e626.

39-POS Board 39

GPU-AIDED OPTIMIZATION OF HIGH-FIDELITY LIPID FORCE FIELDS

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The NMRlipids community (nmrlipids.blogspot.fi)—an open science project devoted to benchmarking current lipid force field against nuclear magnetic resonance (NMR) data—has showed that none of the current lipid molecular dynamics (MD) models (force fields) captures the correct conformational ensemble of lipids in bilayers [1,2]. More recently, we used the open databank of bilayer simulations predominantly originating from the NMRlipids project, to show that the conformational dynamics of the models are not fully correct either [3], although the best models capture the experimental data well. The correct representation of both the conformations and the dynamics is a crucial prerequisites when drawing conclusions from the simulations. Unfortunately, further development of the MD models is hindered by the overwhelming workload, lack of comprehensive comparison to experiments, and outdated approaches (such as hand-tuning parameters). We address these issues by combining atomistic resolution data (NMR C-H order parameters) with an evolutionary optimization algorithm to create a semi-automated force field building tool. As each optimization round requires running MD simulations to test the force field candidates against the experimental target, the approach is solely made feasible by the usage of GPU-accelerated MD engine. Using the algorithm, we have created the first POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) models that reproduce the conformational ensemble as described by the C–H order parameters and have dynamics comparable to the best existing force fields (CHARMM36 and Slipids). Additionally, we have validated the models against other types of experimental data and assessed their response to changing conditions.[1] Botan et al., J. Phys. Chem. B, 199(49), 2015.[2] Antila et al., J. Phys. Chem. B, 123(43), 2019.[3] Antila et al., J. Chem. Inf. Model, 61(2), 2021.

42-POS Board 42

SIGNALS TRANSDUCTION INSIDE PROTEINS AFTER LIGAND PHOTOEXCITATION. INSIGHTS FROM APOMYOGLOBIN MOLECULAR DYNAMICS SIMULATIONS

Lukasz Peplowski[1]; Przemyslaw Miszta[2]; Wieslaw Nowak[1];
[1]Nicolaus Copernicus University, Faculty of Physics, Astronomy and Informatics, Torun, Poland
[2]University of Warsaw, Faculty of Chemistry, Warsaw, Poland

Achieving light control of matter is a promising goal. Chromophores undergoing conformational changes upon photon absorption trigger useful biological signals: vision, phototropism, etc. In recent years a boom in the optogenetics is observed. Prompted by these developments we ask: to what extent a change in a local dipole moment or a change of a ligand shape in a protein interior may affect the protein dynamics? The answer may help designing new molecular switches or light-controlled drugs. As model systems we used apomyoglobin H93G (ApoMb) with popular fluorescent charge transfer probes (PRODAN, ALADAN) or photoactive azobenzene derivative JB253 (possible antidiabetic drug) inserted in the heme cavity. PRODAN exhibits fluorescence very sensitive to the environment's polarity. We exploited a concept that its dual emission originates from two states: one weakly polar - planar and the other one strongly polar, twisted [1,2]. We consider this fluorophore as a simple "limiting case" model for computational studies of electronic excitation induced conformational changes in proteins. Our docking studies show that both PRODAN and JB353 molecules can bind in the ApoMb pocket. Using a simplified sudden excitation approach [3] for the docked structures we monitored a protein structure evolution on hundreds of nanoseconds time scale using classical and excited state MD. Results show, that there are noticeable changes in the local protein dynamics but even a very large charge transfer does not affect globular protein model dynamics dramatically. This study delineates a possible range of conformational changes accessible for a small globular protein triggered by a photon absorption in an endogenous chromophore. Complete studies of light-controlled channels may require exascale computing. Acknowledgement: NCN Grant no. 2016/23/B/ST4/01770 [1] Cohen BE. et al., Science 2002, 296:1700 [2] Balter A, et al., Chem Phys Lett 1988, 143:565 [3] Rydzewski J, et al. Handbook of Computational Chemistry, Springer, 2016

45-POS Board 45

DISSECTING PERILIPIN 1 MEMBRANE TARGETING AND FUNCTION USING MOLECULAR DYNAMICS SIMULATIONS

Jennifer Sapia[1];
[1]University of Fribourg, Biology, Fribourg, Switzerland

Perilipins are lipid droplets (LDs) associated proteins that play a vital role in fat storage. Particularly, Perilipin 1 (or PLIN1) is essential for maintaining adipocytes' homeostasis, as it is involved in the regulation of triglyceride storage and mobilization. PLIN1 is synthesized on free ribosomes, and, under basal conditions, it constitutes a protective coating of the LD surface from lipases. PLIN1 sequence contains amphipatic helices that can reversibly bind lipid monolayers. However, a molecular mechanism describing its preferential localization to LDs is not yet known. Even if the protein structure of PLIN1 has not been solved using experimental methods, a high-confidence model of some regions of PLIN1 structure has been recently proposed thanks to AlphaFold. To investigate the mechanism through which PLIN1 localizes on the surfaces of LDs, and to gain insight into its molecular function in LD formation, we performed atomistic and coarse-grain molecular dynamics simulations of high-confidence model protein regions embedded in membrane systems mimicking LDs and the endoplasmatic reticulum membrane. Our results shed light into the dynamical behavior of PLIN1 and on its mechanism of action, providing testable molecular clues on its LD-related activity.

48-POS Board 48

UNDERSTANDING THE EFFECTS OF POST-TRANSLATIONAL MODIFICATIONS ON THE PHASE BEHAVIOUR OF TDP-43 AND ITS ROLES IN DISEASE

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[1]Johannes Gutenberg University, Mainz, Germany
[2]Institute of Molecular Biology (IMB), Mainz, Germany
[3]Max Planck Institute of Biophysics, Theoretical Biophysics, Frankfurt am Main, Germany
[4]Goethe University, Institute of Biophysics, Frankfurt am Main, Germany

The discovery of liquid-liquid phase separation is revolutionizing our understanding of cellular biophysics. Dysregulation of phase separation is implicated in neurodegenerative diseases. According to the "stickers and spacers" model from polymer science, some residues - the "stickers" - engage in favorable interactions with other chains but most residues form few stabilizing interactions - the "spacers". However, these interactions are not understood at the molecular scale and thus we lack a predictive understanding of how mutations and post-translational modifications affect phase behavior and how phase-separated condensates recognize other molecules. With multi-scale simulations, we can simulate the phase behavior of proteins and zoom in on biomolecular condensates with atomic resolution to understand protein-sequence specific interactions and molecular recognition. Investigating TDP-43, which is involved in neurodegenerative disease, we find that aromatic residues act as "stickers". Phosphorylation of TDP-43 is a hallmark of neurodegenerative disease. TDP-43 phosphorylation is thought to drive condensation and subsequent pathological aggregation, but recent experiments have suggested the opposite: Phosphorylation protects rather than harms cells. Indeed, we find that in coarse-grained simulations of TDP-43 phase behaviour that hyper-phosphorylation can prevent TDP-43 condensation. To better understand how TDP-43 condensates are shaped by sequence-specific interactions we use atomistic molecular dynamics simulations. We find that phosphomicking mutations increase interactions with solvent, which suggests a mechanistic basis for the protective effect of phosphorylation. Chain-growth Monte Carlo enables us to generate meaningful and independent start configurations and we envisage that this could provide a way forward for large-scale atomistic molecular dynamics simulations on the emerging next generation of high-performance computing resources.

51-POS Board 51

STRUCTURE AND PHASE TRANSITION OF MRNA LIPID NANOPARTICLES

Marius Trollmann[1,2]; Rainer A Böckmann[1,2];
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mRNA-based vaccines have recently gained attention for their promising therapeutic potential in the prevention of a severe SARS-CoV-2 infection. An important part in their mode of action are lipid nanoparticles (LNPs) which act as a carrier system to deliver the bioactive mRNA into the target cells. The nanoparticles protect the nucleotides against a premature degradation leading to an increased expression of the encoded protein. In addition, the nanoparticles increase the transfection rate of the vaccine through an enhanced interaction with the membrane of the target cells. Unfortunately, less is known about the molecular organization of the nanoparticles. Here, we characterize the molecular organization and the physico-chemical properties of the lipid composition used in the BioNTech & Pfizer vaccine employing molecular dynamics (MD) simulations of both lipid bilayer systems and full LNPs at atomistic resolution. At physiological pH, the LNP is characterized by an oil-like core that is surrounded by a lipid monolayer formed by both DSPC lipids and cholesterol and PEGylated lipids creating an external PEG layer around the LNP. Self-assembly simulations with nucleoside-modified mRNA strands further show that the negatively charged poly-nucleotides reside within the core of the LNPs and are enveloped by protonated cationic aminolipids. Such inverted micellar structures within the LNPs provide a shielding and likely protection from environmental factors. At low pH, in contrast, the lipid composition used in the Comirnaty vaccine spontaneously forms lipid bilayers that display a high degree of elasticity. Thus, a change in pH of the environment as occurring upon LNP transfer to the endosome, likely acts as a trigger for membrane remodeling followed by mRNA cargo release from the LNP core.

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MOLECULAR DYNAMICS SIMULATIONS STUDY OF ATP BINDING IN ACETYLATED CDK1

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The cyclin-dependent kinase 1 (CDK1) is an essential enzyme that controls cell cycle progression from the G2 to M phase. The molecular function of CDK1 is to transfer a gamma phosphate from ATP to the target protein substrate. While several factors regulate the activity of CDK1, the role of acetylation, a post-translational modification (PTM), at catalytic lysine (K33) located in the active site pocket is less understood. Acetylation removes the positive charge of K33 which serves as an anchor to negatively charged ATP molecules and is thus intuitively expected to lower ATP binding affinity. However, previous studies on kinases by others as well as on CDK1 by our group have suggested that acetylation may not impact ATP binding. Here using multiple long all atom molecular dynamics (MD) simulations (a total time of 20 μs) combined with structural, dynamic, and binding free energy analysis, we examine the underlying molecular mechanisms by which CDK1 preserves ATP binding despite the loss of the positive charge at the K33 site. Our results show that the loss in the enthalpic contribution to free energy of ATP binding upon acetylation or acetyl-mimic mutation (K33Q) is compensated by a gain of entropic contributions. Rather surprisingly, the entropic stabilization does not appear to be only localized at the active site but also at distant loop regions away from the active site. We will discuss the implications of these long-range effects on the functional activation of CDK1.

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CALCULATING RELATIVE PROTEIN-LIGAND BINDING AFFINITIES WITH THE ACCELERATED WEIGHT HISTOGRAM METHOD - A BENCHMARK STUDY

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To identify a lead compound, hundreds of thousands of drug candidates are synthesized and tested in high-throughput screening assays. The corresponding time and resources could be saved if a computational workflow combining docking and atomistic molecular dynamics (MD) simulations scanned the initial compound library and recommended a set of tens of potential lead compounds to be actually synthesized. To this end, the drug candidates scoring best in the docking step are ranked according to their relative binding free energies estimated in MD simulations. In the context of the EU project LIGATE, the following approach to calculate relative binding free energies is applied here: For each pair of ligands, an alchemical path converting them into each other is defined and parameterized in λ. The Accelerated Weight Histogram method (AWH) frequently updates the value of λ during the MD simulation and adapts a bias potential on the fly such that each value of λ is sampled according to a target distribution. With the uniform sampling of λ targeted here, the bias potential converges to the free energy profile along λ. This approach is tested on a benchmark set including in total 13 proteins and approximately 500 ligand pairs for which experimental relative binding free energies and previous simulation results (equilibrium free energy perturbation and non-equilibrium thermodynamic integration) are available. As soon as the relative protein-ligand binding affinities obtained with AWH can be proven to be precise and reliable estimates with this benchmark, the AWH simulations run with GROMACS will be combined with docking simulations performed with LiGen to provide a workflow that scales well on modern HPC machines and can handle several thousands of drug candidates.

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ENABLING COMPUTER SIMULATIONS OF CHROMATIN AT PHYSIOLOGICAL DENSITY WITH A RESOLUTION OF INDIVIDUAL NUCLEOSOMES

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In chromatin DNA is wrapped around histone proteins forming nucleosomes. The nucleosome chain folds into higher order structures as topological domains, chromosomes and the whole nucleus. Despite experimental advancements in electron microscopy, single molecule techniques and mapping of nucleosomes and their modifications, many fundamental features of chromatin remain undiscovered. Due to the poor experimental accessibility of chromatin, computer simulations are valuable tools for research. Computer simulation models of chromatin are usually coarse-grained models describing the main characteristics of the chromatin-fiber. During the last decade simulation approaches mainly focus on small chains, with less than 1000 nucleosomes, because of the high computing resources and time they consume. With the advent of new high-performance computers this barrier can be overcome, and larger systems can be researched. That way the in vivo density situation in the nucleus can be represented better than before. But that is only half the truth: For better computing performance the software needs to be improved e.g., applying technique like parallelization. The application of a technique lies in the responsibility of the developers and can be a complex process. Therefore, we analysed our simulation software with different profiling tools in order to identify the computing bottlenecks. In addition, we enhanced our parallelization strategy and proved the suitability of the used data structures for better computing resource allocation. Finally, we developed a novel Monte Carlo step that enables sampling in high density regimes. We could significantly increase the computing performance of our software. On the supercomputer system HLRN, now we can simulate chains with up to 6000 nucleosomes mimicking conditions of physiological nucleosome concentrations as the interphase nucleus.