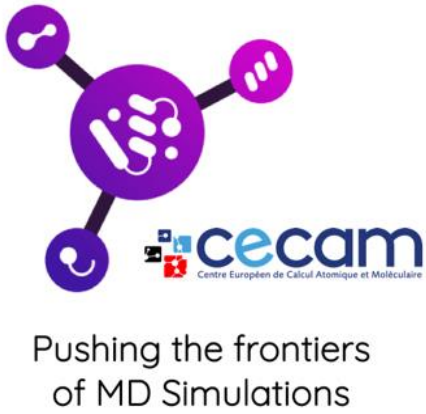
Pushing the frontiers of molecular dynamics simulations



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1. Description

Description

This workshop is part of the MDDB project.

In only a few decades the Molecular Dynamics (MD) world has moved from a field dominated by a few highly specialized groups with a deep knowledge of the technology, who are typically method and software developers, to a situation where MD is present in many more areas of science, including biology. Molecular mechanics is used to relax models e.g. in AlphaFold, a number of experimental techniques like Cryo-EM and NMR now regularly combine their data with simulations, and we are seeing an emergence of data-driven modeling where huge amounts of experimental data e.g. from mutation studies or genome sequencing are combined with simulations (not least during the Covid-19 pandemic). On the one hand, the field has seen tremendous progress with much more accurate force-fields, the development of more efficient MD engines, better understanding of enhanced sampling algorithms – not to mention advances in computers and custom-designed hardware that have transformed MD in a technique with predictive power, which is used extensively to decipher the molecular mechanisms of life.

However, while the field is thriving, we are also faced with numerous challenges: Exascale computers will provide more power than ever before, but it will not be possible to use all that power in simulations without advances in sampling algorithms. Classical force fields are arguably reaching their limits, and with commodity hardware increasingly optimized for AI workloads, it is arguably time to fundamentally revisit our approaches to force fields – but currently those approaches fall orders-of-magnitude short of classical simulations when it comes to simulation length, which brings us back to the sampling efficiency challenge. In parallel, community efforts are coordinating the use of many thousands of private computers whose combined power allows to obtain ensembles in many cases richer than those obtained with large supercomputers. Combination of MD simulations and coarse grained and mesoscopic models open new frontiers on studying small organelles of even eukaryotic chromatin, which is proving to be an exceptionally valuable complement e.g. to cryo-tomography and super-resolution microscopy. However, these models clearly do not reach timescales where thorough sampling is achieved over the entire system; how should this be handled? Can we integrate more experimental data as restraints, or do we need new generations of super-coarse-grained models? Can we find ways to couple model scales without inherently being stuck at the timescale of the innermost/slowest model?

We believe it is time to review recent developments, to critically assess areas where there is potential for major scientific advances, identify bottlenecks and challenges that can be solved, and jointly set out a community roadmap for key issues to work on. We want to interrogate and learn from world leaders in the field on:

- The use of MD simulations to understand the behavior of large supramolecular organisms
- Recent improvements in coarse grained and mesoscopic models
- The most recent advances in ensemble techniques
- The frontier between machine learning and molecular simulations
- The problem of data and how to integrate the MD-field into the data science paradigm

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2. Program

Day 1 - Monday October 7th 2024

- 09:30 to 10:30 - Registration & coffee
- 10:30 to 11:00 - Inaugural: Prof. Modesto Orozco; Prof. Andrea Cavalli

Session I

- 11:00 to 11:45 - **Gerhard Hummer**
  Molecular simulations as windows into cellular dynamics
- 11:45 to 12:30 - **Karissa Sanbonmatsu**
  Large-scale simulations of nucleic acid-based systems
- 12:30 to 13:30 - Lunch
- 13:30 to 14:15 - **Alberto Perez**
  Synergizing simulations and experiments: faster exploration of biologically relevant states
- 14:15 to 15:00 - **Vittorio Limongelli**
  Molecular binding studies in G protein coupled receptors: From ligand binding to receptor dimerization
- 15:00 to 15:30 - Coffee break
- 15:30 to 16:15 - **Gregory Voth**
  Going big: Combining ultra-coarse-graining with high performance computing to access very large length and timescales
- 16:15 to 17:00 - **Adrian Mulholland**
  Dynamical non-equilibrium molecular dynamics to analyze and engineer enzyme activity and inhibition
- 17:00 to 17:30 - **Josep Ll. Gelpi**
  MDDB. Molecular dynamics data bank. The repository for biosimulation data
- 17:30 to 19:00 - Poster session & aperitif

Day 2 - Tuesday October 8th 2024

Session II

- 09:00 to 09:45 - **Tamar Schlick**
  Heterogeneous complex pathways in RNA frameshifting conformational transitions
- 09:45 to 10:30 - **Helmut Grubmueller**
  Flying, freezing and wet proteins
- 10:30 to 11:00 - Coffee break
- 11:00 to 11:45 - **Aleksei Aksimentiev**
  Resolving the structure of viral genomes through multi-resolution simulations
- 11:45 to 12:30 - **Greg Bowman**
  Adaptive sampling and distributed computing
- 12:30 to 13:30 - Lunch

Session III

- 13:30 to 14:15 - **Stefano Piana**
  Ribosome simulations on the millisecond timescale
- 14:15 to 15:00 - **Bert de Groot**
  Molecular dynamics of binding, gating and permeation
- 15:00 to 15:30 - Coffee break
- 15:30 to 16:15 - **Matteo Dal Peraro**
  Integrating simulations and experiments to understand aerolysin pore-forming toxins
- 16:15 to 17:00 - **Paolo Carloni**
  Massively parallel QM/MM MD simulations in the exascale era

  17:00 to 17:30 - **Anna Lappala**
  The X factor: Unveiling the secrets of the X-Chromosome with Data-Driven 3D modelling
- 19:00 to 23:00 - Social dinner

Day 3 - Wednesday October 9th 2024

Session IV

- 09:00 to 09:45 - **Andrea Cavalli**
  Role of molecular dynamics and related methods in drug discovery

- 09:45 to 10:15 - **Jan Stevens**
  The minimal cell under a computational microscope

- 10:15 to 11:00 - Coffee break

- 11:00 to 11:45 - **Giovanni Bussi**
  Towards precise and accurate simulations of RNA dynamics

- 11:45 to 12:15 - **Laura Orellana**
  Conformational transitions of extremely large systems through coarse-grained simulations

- 12:15 to 12:30 - Closing Word

3. Abstracts

Adaptive sampling and distributed computing

Greg Bowman
University of Pennsylvania, United States

Protein dynamics are essential to biological function. Here, I will discuss advances in using adaptive sampling and distributed computing to map out protein's conformational ensembles and connect them to function.

Conformational transitions of extremely large systems through coarse-grained simulations

Laura Orellana
Karolinska Institute, Sweden

Conformational changes in proteins are essential for biological functions, from allosteric regulation to signal propagation, which all involve interconversions between multiple states – bound and unbound, open and close, etc. – triggered by biological signals. These motions are essential to understand the link between structure and function, and of such importance for Life, that are often conserved from bacteria to humans (1). Importantly, the intermediates along connecting transition pathways between conformers are often elusive for both experiments and simulations (2), despite they can hold the key to interpret complex biological mechanisms (3). We have shown that coarse-grained methods like eBDIMS (ENM-driven Brownian Dynamics Importance Sampling) (4,5) are a powerful alternative to computationally heavy Molecular Dynamics (MD) simulations. Modeling the peptide backbone as an elastic network in a Langevin simulation, eBDIMS generates smooth trajectories between end-points that spontaneously visit experimental intermediate states along the transition, overlapping with MD and thus, being also suitable to seed them in order to efficiently sample the conformational landscape (6) or realistically connect cryo-EM structures (7, 8). Nevertheless, despite its high efficiency, even CG-methods struggle to generate pathways for the large protein assemblies (beyond 2-3K residues) routinely solved nowadays by cryo-EM. Here, we present eBDIMS2 (Scaramozzino et al. 2024, in preparation), an improved version of eBDIMS that can predict the transition pathways of sub-mesoscopic proteins (up to ~20k residues) as well as extremely complex transitions in minutes to hours on a standard workstation. We discuss examples of transitions for biomedically relevant and underexplored proteins such as DNA-dependent protein kinase catalytic subunit (~3k residues), neurofibromin (~5k), ITP-receptor 3 (~8k), ryanodine receptor (~15k), fatty acid synthase (~21k), etc, which shed new light on the essential motions and molecular mechanisms of these large systems.

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Dynamical non-equilibrium molecular dynamics to analyze and engineer enzyme activity and inhibition

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The dynamical-nonequilibrium molecular dynamics (D-NEMD) simulation approach, originally proposed by Ciccotti *et al*., is emerging as an attractive approach to identify allosteric effects in proteins [1]. D-NEMD simulations of class A beta-lactamases show coupling between allosteric sites and the active site, and identify networks that contain positions that differ between clinical variants associated with different spectrums of antibiotic resistance [2]. These results indicate that allosteric effects modulate the spectrum of activity of these antibiotic resistance enzymes. D-NEMD simulations identify a distal site which, when mutated experimentally, alters the spectrum of antibiotic breakdown activity [3]. For the SARS-CoV-2 main protease (Mpro/3CLpro), D-NEMD simulations identify positions associated with drug resistance and an allosteric site [4].
Increasingly, simulations are contributing to the design, engineering and directed evolution 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 [5]. Directed evolution of a designed Kemp eliminase unexpectedly introduced curvature into the temperature dependence of reaction, showing the emergence of an activation heat capacity. MD Simulations identify the dynamical networks involved, which may provide useful targets for mutation and directed evolution experiments [6].
Molecular simulations of various types can reveal biomolecular functional mechanisms, and can contribute to protein and inhibitor design. Simulations can be used as computational 'assays' of biological activity, e.g. to predict drug resistance or effects of mutation. Multiscale methods combine different levels of description, facilitating simulation of large, complex systems and e.g., chemical reactions within enzymes. Combined quantum mechanics/molecular mechanics (QM/MM) methods allow modelling of reactions in proteins: they can identify mechanisms of reaction and determinants of catalytic activity e.g. of bacterial enzymes against different antibiotics, e.g. showing that electric fields are an important determinant of the ability to break down carbapenems, so-called 'last resort' antibiotics [7].

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Flying, freezing and wet proteins

Helmut Grubmueller, Daniel Szöllözi, Lars Bock, Leonard Heinz
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Three examples demonstrate how atomistic simulations, experiments, and statistical mechanics nicely complement each other. First, we will show how atomistic simulations of ion mobility spectrometry provide an improved structural interpretation [1]. In particular, our simulations explain a frequently observed bimodal ion mobility distribution in terms of quenched peptide conformations. Second, non-equilibrium shock-freeze simulations of solvated ribosomes reveal how much of the room temperature structural ensemble of these RNA/protein complexes is preserved during plunge-freezing in single particle cryo-electron microscopy experiments [2,3]. Third, we will turn our attention towards biomolecular solvation shells, which contribute to protein stability. A new method, permutation reduction, provides a spatially resolved picture of how the interplay between entropies and interaction enthalpies of both protein and solvent contributes to solvation and protein folding free energies [4-6]. We show that solvent-correlations do contribute to the free energy of solvation and resolve a seeming contradiction to Ben Naim's Theorem [7].

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Going big: Combining ultra-coarse-graining with high performance computing to access very large length and timescales

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Advances in theoretical and computational methodology will be presented that are designed to simulate complex (biomolecular and other soft matter) systems across multiple length and time scales. At the heart of this “bottom-up” approach are methods for deriving CG models from molecular structures and their underlying atomic-scale interactions. An important component of this work in the past few years has been the concept of the “ultra-coarse-grained” (UCG) model and its associated computational implementation. In the UCG approach, the CG sites or “beads” can have internal states, much like quantum mechanical states, so the UCG model involves a conceptual abstraction beyond simply Newtonian or Langevin dynamics for the CG beads. These internal states help to self-consistently quantify a more complicated set of possible interactions within and between the CG sites, while still maintaining a high degree of coarse-graining in the modeling. Recent breakthroughs include the implementation of these methods on high performance computers (scalable CPU and GPU) to access the behavior of very large systems. As time allows, one “pay-off” application from our multi-year effort will focus on processes in virus replication, and especially on the assembly of the HIV-1 virus capsid from over one thousand proteins – a phenomenon involving a billion atoms or more over long timescales that cannot be approached through AA MD simulation. The efficient and accurate “back mapping” of CG models to the all-atom model scale will also be discussed as an important validation component for any form of CG model.

Heterogeneous complex pathways in RNA frameshifting conformational transitions

Tamar Schlick, Shuting Yan
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Frameshifting is an essential viral replication mechanism for compact RNA genomes. For SARS-CoV-2, a specific 3-stem RNA pseudoknot has been identified to stimulate frameshifting, but other folds have been suggested. By using transition path sampling with BOLAS free energy computations, Markov State Modeling, and Cluster Analysis we capture atomic-level transition pathways between two key pseudoknots and demonstrate how they critically direct the placement of the viral RNA in the narrow ribosomal channel. Our work explains the role of the alternative pseudoknot in ribosomal pausing, clarifies why the experimentally captured pseudoknot is preferred for frameshifting, and provides new insights to target key transitions for therapeutic applications.
The capturing of an unprecedented large-scale RNA structure transition highlights complex biomolecular pathways and enhances our understanding of viral frameshifting. Our methods are generally applicable to other large-scale biomolecular transitions.

Integrating simulations and experiments to understand aerolysin pore-forming toxins

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Evolution has found countless ways to transport material across cells and cellular compartments separated by membranes. Protein assemblies are the cornerstone for the formation of channels and pores that enable this regulated passage of molecules in and out of cells, contributing to maintaining most of the fundamental processes that sustain living organisms.
Using integrative structural biology, i.e. combining molecular modeling and simulations along with biochemical and cryo-EM analysis, we have revealed the structure and assembly mechanism of one of the most studied bacterial pore-forming toxins, namely aerolysin from A. hydrophila, recently obtaining its highest resolution structure at 2.2 Å by cryo-EM in nanodiscs.
Leveraging this structural and functional understanding, we have been able to characterize its properties as a molecular sensing device that can accurately discriminate nucleic acids and peptides, as well as detect post-translational modifications associated with validated biomarkers of neurodegenerative diseases. The sensitivity of aerolysin pores makes the ideal for developing the next generation of sensor devices for single-molecule proteomics and analytical chemistry.

Massively parallel QM/MM MD simulations in the exascale era

Paolo Carloni
Forschungszentrum Jülich and RWTH Aachen University, Germany

Exascale supercomputers have opened the door to MD simulations (from quantum to coarse grain), facilitated by ML techniques, that model biomolecular motions over unprecedented length and time scales. This new capability holds the potential to revolutionize our understanding of fundamental biological processes.
Here we report examples of large-scale QM/MM MD simulations and the future possibilities enabled by crossing the exascale threshold. We close the talk by discussing some of the challenges to be overcome in optimizing the usage of these powerful resources.

MDDB: Molecular dynamics data bank. The repository for biosimulation data

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After decades of development and a Nobel prize, Molecular Dynamics (MD) has reached maturity. It is no longer an exotic technique used by a small group of theoreticians but rather a method extensively used by a very large community of users. Millions of supercomputer hours are devoted to collecting trajectories, thus producing a deluge of simulation data that the community is unable to handle. A poor tradition of data sharing and the lack of appropriate infrastructures to do so lead to the loss of data after limited analysis that most likely revealed only a small fraction of the information contained. Sparse initiatives to build trajectory repositories have encountered difficulties related to: i) the lack of trust of the community in the reliability of the data deposited; ii) the lack of interoperable standards and simulation ontologies; iii) uncertainties regarding the database technology required; v) difficulties of the users to interact in an open manner with the data; and vi) disconnection of the MD-field with neighboring communities. The MDDB project intends to design a European-scale repository of MD simulation (and associated analysis tools), which will: i) optimize computational resources; ii) favor the analysis (and meta-analysis) of trajectories for many different perspectives and fields; iii) guarantee a fast and efficient interchange of information between groups; and iv) facilitate the integration of the MD simulation field into biological data infrastructures. The overall result will be a more efficient use of MD and the integration of the MD field into mainstream biology and chemistry research. MDDB Consortium includes main MD codes (GROMACS, Sweden), supercomputing centers (BSC, Spain), structural repositories (PDBe, EMBL-EBI), power MD providers (IRB Spain, Univ. Oxford, UK), and a specialist on dissemination and training on molecular simulations (CECAM Switzerland).

Molecular binding studies in g protein coupled receptors: From ligand binding to receptor dimerization

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Elucidating the structural and energetic properties of G Protein Coupled Receptors (GPCRs) is of paramount relevance to guide rational drug discovery studies. However, the complexity and the long timescale of receptor activation process make many aspects of GPCRs functioning elusive to both experimental and computational techniques.
Here, I demonstrate that such limitations can be overcome by employing advance calculations like funnel-metadynamics [1,2] and coarse-grained molecular dynamics calculations [3,4], which allow disclosing the thermodynamic and kinetic properties of drug binding to GPCR, and investigating important processes such as receptor activation and dimerization. In particular, I show the case of adenosine A2A receptor in which ligand binding occurs by hopping in multiple binding modes and the transition between the vestibular and the orthosteric binding site determines the ligand (un)binding rate. The agonist and antagonist binding allosterically perturbs the receptor state that passes from a pseudo-active state - here described for the first time - to the full active and inactive state, respectively [5]. In addition, the minute timescale formation of receptor dimers can affect the access to the binding sites of the ligand (*extracellular*) and the effector G protein (*intracellular*), indicating that dimerization *de facto* is a fine allosteric regulatory mechanism of GPCR activity [4]. The advancement in molecular binding simulation techniques [6] is expected to impact on future drug discovery studies where structural, energetic and dynamic properties of the receptor could be taken into account to achieve ligands with tailored bias signaling properties and great therapeutic potential for a broad spectrum of diseases.

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Molecular dynamics of binding, gating and permeation

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How does fast, selective ion permeation take place? What are the determinants of ion channel gating? How accurately can simulations predict the binding free energy of drug-like molecules to receptors? These are some of the questions that will be addressed. Based on atomistic equilibrium molecular dynamics simulations, non-equilibrium alchemical transformations, as well as machine learning based predictions, potassium channel permeation and modulation will be presented, as well as ligand-protein binding affinity and pKa predictions.

Molecular simulations as windows into cellular dynamics

Gerhard Hummer
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Molecular dynamics simulations perfectly complement electron and light microscopy to capture the dynamics and function of living cells at the molecular scale. By adding dynamics in atomic detail and on a sound physical basis, simulations link structure to function, and in turn help us to identify new sites targetable by therapeutics. An explosion in raw computational power, the development of powerful simulation algorithms, and sophisticated artificial intelligence methods now make it possible to tackle biological systems and processes of significant size and complexity. In my presentation, I will highlight our work on autophagy and nuclear transport, and conclude with efforts for AI-guide simulation. As programs critical to cell function and the defense of pathogens, both are subject to rich regulatory control. Molecular simulations combined with experiments by our collaborators have allowed us to

identify some of the molecular interactions ensuring precise targeting and tight control over the initiation of autophagy [1,2], a process to remove dysfunctional cellular components and intruding pathogens. With simulations and our collaborators' experiments, we have also started to characterize the nuclear pore complex as the permeability barrier controlling the molecular traffic in and out of the nucleus [3], up to the passage of entire viral capsids of the HIV-1 retrovirus [4]. We overcome time-scale limitations by combining traditional enhanced sampling with machine-learning in a closed cycle mechanism learning and simulations [5]. By revealing the molecular interactions regulating the complex cellular programs, molecular simulations also point to new avenues for possible therapeutic interventions

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Resolving the structure of viral genomes through multi-resolution simulations

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A string of nucleotide letters confined within a protein capsid contains all the instructions necessary to make a functional virus particle, a virion. While the structure of protein capsid is known for many species of viruses, the structure of their genomes has mostly evaded experimental probes. Here, we report complete all-atom structures of a mature HK97 bacteriophage virion, including its entire 39,732 base-pair DNA genome, obtained through multi-resolution simulations. Mimicking the action of a DNA packaging motor, the genome was gradually packed into a protein capsid with or without an additional torque that twisted the DNA. The structure of the assembled particles was then iteratively refined through a series of simulations of increasing resolution, ultimately producing a 27 million-atom model of the complete virion, including water and ions confined within the capsid. Strikingly, we find DNA packaging within the capsid to occur via a loop extrusion mechanism that, starting from nearly identical configurations, can produce wildly different global configurations of the final packaged genome, giving each viral particle individual traits. Multiple microsecond-long simulations of the packaged phages found the packaged genome to diminish structural fluctuations of the capsid while reducing water and ion passage through the capsid's pores. The isocohedral confinement of the capsid was found to imprint reproducible features on the structure of the genome at the capsid-genome interface whereas the internal pressure of a packaged virus was largely independent of the presence of the twist during the packaging process. We show how our computational approach to reconstructing the structure of viral genomes can be generalized to other viral species.

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Ribosome simulations on the millisecond timescale

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The precise machinery of large ribosomal complexes underlies the fundamental biological process of translation from RNA to protein. In order for an amino acid to be incorporated into a growing polypeptide chain in both an accurate and efficient manner, the various components of the ribosome must coordinate in a dynamic interplay that moves the ribosome through the states of the elongation cycle. A deeper understanding of these processes at atomic resolution can potentially be achieved through the use of long-timescale molecular dynamics simulations. With the increased availability of high-resolution structural data due to advancements in cryo-EM, simulations can be performed with a number of starting structures representing ribosomes at different states. We present simulations that complement the low-temperature static structures obtained using cryo-EM by providing dynamical information for the system at room temperature, and in particular give insight into key aspects of the tRNA selection mechanism.

Role of molecular dynamics and related methods in drug discovery

Andrea Cavalli
CECAM - HQ, Switzerland

TBA

Synergizing simulations and experiments: Faster exploration of biologically relevant states

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BET proteins are involved in immune response, they have an Extraterminal Domain that acts as an interaction hub capable of interacting with regulatory as well as viral proteins. While a few peptide epitopes have been identified to bind ET, many more remain to be discovered. Here we combine NMR information, integrative structural biology tools (MELD simulations) and AI in order to characterize novel peptide epitopes interacting with ET, as well as ranking them according to binding affinities.

The minimal cell under a computational microscope

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Molecular dynamics (MD) is a well-established simulation method that has successfully been applied to study a wide range of biomolecular processes. As a result of continuous improvements in both modeling methods and computational infrastructures, the study of mesoscopic, multi-component systems has become more attainable. However, the intricacies involved in setting up MD simulations for these systems remain daunting, requiring the integration of diverse data from both experimental and in silico sources.
Here we present how the coarse-grained Martini force field and its associated tools [1,2], form an ideal ecosystem for facilitating a mesoscale modeling pipeline. Employing a CG resolution, typically representing four heavy atoms by one CG bead, significantly reduces the computational cost inherent in simulating mesoscale models. Furthermore, a key feature of the force field is its universality, which allows us to create CG models of all major biological components and construct complete cellular environments.
The Martini force field's capabilities are showcased in an ongoing effort to simulate a genetically minimal cell: JCVI-syn3A [3]. We constructed the first near-atomistic MD model of a cell based on data from kinetic models [4], Cryo-Electron Tomograms [5] , and omics experiments [4,6]. Studying entire cells under the computational microscope will allow us to look into a wide range of problems, ranging from drug design to understanding the internal organization of cellular environments.

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Towards precise and accurate simulations of RNA dynamics

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RNA molecules play a fundamental role in cellular processes, and their conformational dynamics are key to understanding their interactions with ions, ligands, and proteins [1]. Molecular dynamics simulations serve as a virtual microscope to visualize these dynamics, but are subject to both statistical and systematic errors. Statistical errors can be mitigated through extensive simulations and enhanced sampling methods [2], while systematic errors can be reduced by incorporating experimental data [3]. In fact, experiments can be used to derive transferable force field corrections or directly refine conformational ensembles.

In this talk, I will present recent work from our group in all these directions. First, I will discuss how force field corrections can be derived from a variety of experimental data sources, aiding in the parametrization of modified nucleobases [4,5]. Next, I will show how we used ensemble refinement methods to model the dynamics of a ribozyme using cryo-electron microscopy data [6]. Finally, I will demonstrate how enhanced sampling methods can accelerate the binding of divalent cations to RNAs (manuscript in preparation).

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4. Posters

A generalizable framework to augment machine learning with molecular dynamics trajectories

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Despite the rapid growth of machine learning in biomolecular applications, information about protein dynamics is rarely utilized. Here, we introduce Nearl, an automated Python pipeline designed to extract dynamic features from large ensembles of molecular dynamics (MD) trajectories. Nearl aims to identify intrinsic patterns of molecular motion and to provide informative features for predictive modelling tasks. We implement two classes of dynamic features, termed marching observers and property-density flow, to capture local atomic motions while maintaining a view of the global configuration. Complemented by standard voxelization techniques, Nearl transforms substructures of proteins into 3D grids, suitable for contemporary 3D convolutional neural networks (3D-CNNs). The pipeline leverages modern GPU acceleration, and prioritizes flexibility and user-friendliness, allowing customization of input formats and feature extraction.

All atom simulations elucidate the molecular basis of RNA-membrane interactions

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RNA-membrane interactions are starting to emerge as an important organizing force in both natural and synthetic biological systems. Recently, RNA molecules were revealed to be present on the extracellular surface of living cells, where they mediate intercellular signaling. Furthermore, RNA-membrane interactions importantly influence the efficacy of lipid-based RNA delivery systems. However, molecular terms which drive RNA to localize at the membrane surface remain poorly understood. In this work, we investigate how RNA-phospholipid membrane interactions occur by means of molecular dynamics simulations and well-tempered metadynamics. We find that among the four nucleobases, guanine exhibits the strongest interaction with the membrane due to extensive hydrogen bond formation. Additionally, by analyzing a 19-mer in the unfolded and folded quadruplex state, we show that base-pairing significantly hinders RNA binding to the membrane. Elucidating the molecular details of RNA-membrane association will importantly contribute to improving the design of lipid-based RNA delivery systems and parsing out RNA transport and localization mechanisms.

Bidirectional path-based nonequilibrium simulations for binding free energy estimation and dissipation analysis

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Estimating free energy is a relevant and complex computational task, especially in complex biological systems characterized by numerous degrees of freedom. In this study, we investigate the possibility of leveraging non-equilibrium free energy estimators coupled with path-based approaches; this offers an appealing opportunity of trivial parallelism. Building upon our prior work on protein-ligand binding free energy calculations, we develop its non-equilibrium counterpart here. We begin by validating our computational strategy on a simple toy model, and then extend our analysis to more intricate, relevant pharmaceutical system to evaluate the performance of our computational pipeline. A key aspect in this kind of computations is the minimization of the dissipated work to speed-up the convergence of the estimation. It not only inherently depends on the transformation route but also on the physico-chemical parameters of the system of interest. Hence, these are key factors to be taken into account when devising such non-equilibrium protocols. To this aim we investigate some key aspects which affect the

amount of dissipation, namely the proper definition of the path collective variable and the water models employed during the performed irreversible transformations. Our results not only demonstrate the feasibility of this approach but also shed light on potential limitations. Furthermore, we showcase the capabilities of the Jarzynski and Crooks estimators employed in our study.

Computer simulations of the effect of surfactants on the SARS-CoV-2 virus

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Surfactants are commonly used as disinfection agents against bacteria and viruses, including SARS-CoV-2. However, there is a lack of understanding of the molecular mechanisms of the inactivation of viruses by surfactants. Here, we employ coarse grain (CG) molecular dynamics simulations to investigate the interaction between general families of surfactants and the SARS-CoV-2 virus. To this end, we considered a CG model of a full virion.

Overall, we found that surfactants have only a small impact over the virus envelope, being inserted into the envelope without dissolving it or generating pores, at the conditions considered here. However, we found that surfactants may induce a deep impact on the spike protein of the virus (responsible for its infectivity), easily covering it and inducing its collapse over the envelope surface of the virus.
Our results suggest that the best strategy for the design of surfactants as virucidal agents will be to focus on those strongly interacting with the spike protein. In addition, we have also done molecular dynamics simulations using atomistic models of different parts of the SARS-CoV-2 virus. We have observed that the surfactants are able to insert themselves into the virus envelope and also to strongly interact with the spike protein [1].

In addition to these simulations, a recent study has experimentally analyzed the mechanisms of inactivation of a type of coronavirus using surfactants [2]. It has been proven that non-ionic surfactants inactivate the virus by destroying its envelope, while ionic surfactants (positive and negative) mainly affect the spike protein in the envelope.

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Constrained adiabatic dynamics for free energy reconstruction

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The calculation of the free energy landscape associated to activated events in complex systems remains an interesting challenge in molecular dynamics. In this poster, we present a novel approach to tackle this problem. The method considers the values assumed by the reaction coordinates as dynamical variables in an extended Lagrangian scheme. These new variables guide the physical degrees of freedom through the free energy landscape via the imposition of constraints, sampling a probability density closely related to the free energy. Similarly to Temperature Accelerated Molecular Dynamics [1] and Adiabatic Dynamics [2], we show that increasing the temperature of these auxiliary degrees of freedom enables the system to overcome barriers and, in the limit of infinite mass for the auxiliary degrees of freedom, sample the physical free energy. This method might present an interesting alternative to current approaches for applications to soft and biological matter.

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DynaRepo: A repository of macromolecular conformational dynamics

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Biomolecules such as proteins, RNA, and DNA are at the heart of virtually all fundamental cellular processes. They often interact together and form macromolecular complexes to execute their functions. These complexes can undergo conformational changes in response to different environmental conditions, such as mutations or binding of other molecules. Such conditions can happen at one site and their effects could even be propagated across the structure to a distant site through allostery. Therefore, understanding the structure and dynamics of macromolecular complexes is highly important to elucidate their mechanisms. The recent advances of deep learning for the prediction of protein structures and the outbreak of AlphaFold2, specifically have shown the potential of data-driven approaches when high-quality data are available. While these approaches provided a molecular landscape of the structure of many macromolecules, they often fail to address macromolecular complex prediction when some extent of flexibility or dynamic heterogeneity is involved such as antibody-antigen interactions, intrinsically disordered protein interactions, or protein-nucleic acid interactions. To this end, a community-wide effort to build dynamic repositories of macromolecular structures and complexes is crucial. Here, we built a repository of macromolecular conformational dynamics, DynaRepo, for a large set of macromolecular complexes and used this data to answer two important questions: 1) elucidating communication networks and allosteric signaling and 2) predicting binding sites across macromolecular complexes. Currently, DynaRepo includes a set of 540 macromolecular complexes selected from the PDBbind and ASBench datasets. They were subjected to all-atom molecular dynamics simulations. For each complex we performed 3 replicates of 500 ns MD simulations leading to a total of 810 µs simulation time. In this poster we will present the pipeline used to select and generate the trajectories. Taking advantage of DynaRepo, we developed a method based on graph theory to elucidate the network of pathways mediating allosteric signaling across large complexes. Moreover, by learning conformational heterogeneity of macromolecular complexes, we proposed a novel dynamic-aware deep learning architecture for the prediction of binding interfaces with other macromolecules including proteins and ligands. The preliminary results highlight that having access to high quality data of conformational heterogeneity could significantly improve our fundamental understanding of advantages of using dynamics. This project opens new avenues to utilize and incorporate dynamic features into deep learning frameworks to enhance the performance on the downstream tasks.

Exploring thermal adaptation through molecular dynamics and metadynamics simulations

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Malate dehydrogenases (MalDH), which catalyze the conversion of oxaloacetate into pyruvate in the tricarboxylic acid cycle, serve as a model for studying enzyme evolution and adaptation. Ancestral sequence reconstruction and paleoenzymology revealed that the hyperthermostable ancestor of MalDH evolved into two distinct lineages: one retained its hyperthermophilic properties, and the other underwent multiple independent adaptations to colder environments.
It is possible to mimic the adaptation trajectory toward mesophily by introducing key mutations into the hyperthermophilic *M. jannaschii* MalDH (WT), which has an optimal temperature around 90°C. These mutants shifted the optimal temperature to 60°C and 65°C; despite this, they did not affect the enzyme's thermostability. Here, we employed molecular dynamics (MD) simulations combined with metadynamics to explore the molecular mechanisms that reduced the optimal activity temperature.
The 1 µs MD simulations revealed that the apo WT exhibits an open-closed motion of the loop, which contains catalytic residues and must close over the catalytic site for the reaction. This motion depended on the conformation of two helices at higher temperature. We obtained free energy profiles along a pathsmd collective variable that describes this open-closed motion for WT and the mutants. These profiles indicated that the WT remains in a closed conformation at lower temperatures, thereby blocks the catalytic site from substrate binding, and the temperature increase led to stabilization of opened conformations. In contrast, the free energy profiles of the mutants have a global minimum in open states

at lower temperatures and the range of open-closed motion broadens as the temperature rises up to the optimal temperature.

Modeling the A40s aptamer to enhance glioblastoma treatment

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Glioblastoma (GBM), the most prevalent and lethal primary brain tumor in adults, remains difficult to treat despite advances in radiotherapy and chemotherapy. GBM stem cells (GSCs) contribute to both chemoresistance and tumor recurrence, complicating treatment outcomes. The A40s aptamer, a 30-nucleotide 2-fluoropyrimidine RNA discovered through SELEX, is the first aptamer reported to directly target GSCs in human GBM tissue. It selectively binds to GSCs by ephrin type-A receptor 2 (EphA2) recognition, inhibiting GSC growth, stemness, and migration. Optimizing the A40s aptamer could significantly enhance its therapeutic efficacy in targeting GSCs and preventing GBM recurrence. In this study, we model the A40s aptamer and investigate its binding interactions with EphA2 using a combination of computational and experimental techniques. We first predict the aptamer's secondary structure using bioinformatic tools and experimental data, then predict and simulate its 3D conformation through microsecond-long all-atom Molecular Dynamics (MD) simulations. Finally, we analyze its interaction with EphA2 to identify key binding sites. These findings aim to improve the A40s aptamer's binding affinity and stability, potentially advancing its use in GBM treatment.

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ModTox: A database of toxicity-related proteins

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The digital revolution is transforming the pharmaceutical industry and healthcare systems, with machine learning, large-scale simulations, and big data analytics playing pivotal roles in drug design and development [1]. The **ModTox** database will leverage these technologies to address the critical challenge of predicting drug-induced toxicity, and maximum recommended therapeutic doses [2]. By compiling extensive simulation data on proteins associated with adverse drug reactions and including common sequence variants, ModTox will provide an invaluable resource for early toxicity prediction. This platform aims to significantly lower investment risks and reduce time to market by identifying potential toxic effects before clinical trials. As part of its mission, ModTox simulation data will be computed using BioExcel Building Blocks [3] and integrated into MDDB advanced analytical workflows, tested for interoperability with related disease and medicinal chemistry databases, and used as a pilot for flexible implementations on high-performance computing platforms. This initiative will enhance predictive toxicology and support European competitiveness in pharmaceutical innovation and safety assessment.

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Simulation-guided conformational space exploration to assess reactive conformations of a ribozyme

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The discovery of ribozymes, nucleotide sequences with catalytic properties, reinforced the hypothesis of a prebiotic world based on RNA [1]. Self-replicating complexes were designed from viral ribozymes, enabling the first Darwinian evolution in the laboratory [2]. However, these systems are too large to have emerged spontaneously in prebiotic conditions. In fact, small ribozymes promote cleavage of the phosphodiester bond while large ribozymes catalyze its ligation. Here, we propose to **investigate the link between sequence, length and RNA catalytic properties** by studying a model system, the hairpin ribozyme.

The Hairpin Ribozyme raises interest as it has been shown experimentally to accelerate its reaction in its longest version compared to its short [3]. However, being **self-reactive**, it cannot be directly investigated in the lab, and so far no experimental study has been reported to describe the molecular details of the reaction mechanism. Computationally, the chemical self-cleavage reaction mechanism has been extensively studied, but all come up against a major problem: the **absence of** pre-catalytic **structural data**. Instead, simulations are initiated from a chemically altered version of the precatalytic state catalytic site, where O2' is methylated to block the nucleophilic attack.

In our recent work [4], we investigated the relevant conformational basins of the minimal hairpin ribozyme, an effort that is frequently overlooked in mixed quantum/classical studies that predominantly concentrate on the chemical reaction itself. Our findings highlight **the crucial importance of using specific enhanced sampling techniques** to provide reliable conformational sampling, which is typically not achieved even with microsecond brute force simulations.

Extensive conformational exploration of hairpin ribozymes of different sizes and sequences has led us to consider the **accessibility to reactive conformations** as a key determinant of RNA reactivity. Specifically, our findings indicate that the longest hairpin ribozyme arranges more frequently in its ready-to-react arrangement, thanks to long-range tertiary contacts, and independently of its sequence.

A complete understanding of the hairpin ribozyme's catalytic properties requires a comprehensive approach beyond the chemical reaction itself. Indeed, the self-ligation/cleavage process encompasses multiple stages, including prior structural folding. Here, the sampling time-efficiency challenge reaches another dimension, leading us to consider coarse-grained models and/or the integration of the many available experimental data [5][6]. We believe that data-driven modeling could provide valuable insights into the understanding of the catalytic properties of ribozymes.

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The molecular dynamics data bank: bridging gaps in biomolecular simulation interoperability

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The Molecular Dynamics Data Bank (MDDB), the global repository for biosimulation data aims to build a research infrastructure tailored for communities engaged from various life science fields and unify these under a common platform using F.A.I.R (findability, accessibility, interoperability, and reusability) data principles. MDDB is a collaborative initiative that unites some of Europe's leading institutions to revolutionize the handling of molecular dynamics simulation data. By creating this platform, we aim to facilitate data sharing within the scientific community, recognizing the necessity of a joint effort to achieve this goal.

Interoperability ensures the seamless collaboration and consistent exchange of information between various systems, devices, applications, and products. By adhering to common data formats, standards, and data exchange protocols, MDDB aims to drive significant advancements in the interoperability of MD data and sharing it effectively, facilitating their integration and interpretation. In this poster, MDDB's approach to achieving interoperability is presented across various dimensions of interoperability:

- Technical: providing programmatic access to MD data via a REST API with data interchange primarily using JSON formats.
- Syntactic: MDDB supports standardized formats for different data types, such as HDF5/H5MD for trajectories and topologies, JSON/YAML for metadata or other formats like PDBx/mmCIF, which we are exploring to ensure compatibility with the structural domain.
- Semantic: by leveraging scalable and extensible formats like PDBx/mmCIF and PDBe-KB data exchange MDDB ensures meaningful and automated interpretation of data or metadata.
- Cross-domain and cross-organizational interoperability: MDDB aims to join research infrastructures such as ELIXIR, INSTRUCT-ERIC and BioExcel to build a community driven project.
- MD data integration: with major biological databases such as PDBe, PDBe-KB, 3D-beacons, and UniProt, showing the utility of such data in life sciences.

Unlocking stability: Exploring the role of disulfide bonds in the structural dynamics of human TFF1

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Trefoil factor (TFF) peptides are characteristic secretory peptides of mucous epithelia, playing significant roles in maintaining gastrointestinal mucosal homeostasis. These peptides harbor a well-defined TFF domain stabilized by six conserved cysteine residues forming three intramolecular disulfide bonds.[1] The distinctive conformation of the TFF domain is associated with enabling the TFF peptides to adapt to different conditions in the gastrointestinal tract and making them resistant to degradation.[1,2] Despite their known resilience, the stability of disulfide bonds in the TFF peptides under reductive conditions and their relevance to the structural stability and integrity of the TFF domain remain elusive.
In this study, we scrutinized the stability of the disulfide bonds in human TFF1 through reductive stability experiments and elucidated the effect of disulfide bond reduction on the domain structure and dynamics by employing microsecond-long molecular dynamics (MD) simulations. Our experiments unveiled that the TFF1 domain was highly resistant to reduction, with complete disulfide bond reduction occurring only under the condition of an excess reducing agent. For further investigations, all-atom MD simulations were performed for all possible redox states of the disulfide bonds in TFF1 (i.e., all-intact, mono-, di-, and fully-reduced states). Our results revealed that, despite minor structural and conformational changes upon reduction, the overall compactness and integrity of the domain were retained in the all-intact and mono- and di-reduced states. Most disulfide bonds remained buried within the domain, which may explain the high resistance of disulfide bonds to reduction as observed in our experiments. Only in the fully-reduced state did structural changes become obvious, including a shift towards a less ordered protein fold. Our study sheds light on the notable stability of the TFF1 domain under reductive conditions, supporting its ability to maintain functionality in the harsh environment of the gastrointestinal tract.

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VTX: High-performance molecular structure and dynamics visualization software

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VTX is a high-performance molecular visualization software capable to handle most molecular structures and dynamics trajectories file formats. It features a real-time high-performance molecular graphics engine that uses only analytical representations which allows pixel perfect quality rendering of massive molecular scenes with reduced memory usage [1]. Thanks to this engine, VTX handles massive molecular systems (several hundred million atoms) and massive molecular dynamics trajectories (microseconds of several million atoms). VTX integrates an interactive camera system that includes free-fly navigation and a fully modular graphical user interface designed for maximal usability. VTX design is focused on performance and usability for research, teaching and educative purposes. It is open source, free for non-commercial use, and available on Linux and Windows at http://vtx.drugdesign.fr and https://github.com/VTX-Molecular-Visualization

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