Grand Challenges

The Collaborative Computational Project for Biomolecular Simulation (CCPBioSim)

Over the next five to ten years, a key challenge for biomolecular simulation is to couple our different computational tools together into multi-scale models that propagate information from the regime of quantum chemistry up towards the cellular level

The Community

CCPBioSim

ww.ccpbiosim.ac.uk

CCPBioSim promotes the use of computer simulations for understanding biological molecules and their function. Many of these simulations provide information that is inaccessible or difficult to obtain experimentally, such as biomolecular dynamics. Running training, conferences and supporting software development, CCPBioSim cares about building an inclusive and creative community where everyone interested in biomolecular simulations is welcome and encouraged to learn and share knowledge to produce the best science possible, including experimental teams who need simulation to gain further insight from their data. As well as basic science, CCPBioSim develop the next generation of methods for computational drug-discovery, which is becoming increasingly complex as drugs move away from being simple small molecules towards biologics such as antibodies, affimers, nucleic acid therapeutics, proteolysis targeting chimeras (PROTACs) and molecular glues that form bioactive ternary protein complexes. The use of GPUs has massively Increased the use of biomolecular simulations by industry, because they have improved the efficiency of methods that were previously too slow. Showcasing the most exciting simulations and tools and interfacing with experiments and industry, CCPBioSim continuously works on sharing expertise within their highly multidisciplinary community.

The Challenge

Expanding the length and time-scales accessible to biomolecular simulations

Dynamics plays a role in biology right down to the atomic level. Dynamics and flexibility are important in the catalytic function of enzymes, and in the free energy changes driving molecular recognition, which is the key process in rational drug design. Molecular machines, which burn chemical energy to perform work, necessarily require dynamics to perform their functions, and perform many vital jobs such as processing DNA and carrying cargos around the cell.

Grand Challenges

Physics based models such as molecular dynamics (MD) are well established as tools for calculating biomolecular dynamics from structures obtained experimentally (or from AlphaFold). These methods compute the ensemble of conformations of a biological molecule at room temperature using a molecular mechanics energy function and an empirical forcefield. Fully atomistic simulations of single proteins or small protein complexes in explicit solvent can typically explore microsecond timescales. Coarse-grained simulations using Brownian Dynamics and ridged protein models can represent sections of the eukaryotic cytoplasm, and sections of protein-bound eukaryotic and bacterial membranes. Even larger length-scales right up to whole cell models require continuum mechanics simulations, and/or reaction diffusion models. Our first Grand Challenge is to improve the efficiency and accuracy of our existing methods, for example by using the machine learning/artificial intelligence (ML/AI) methods currently under development to provide better forcefields. A second key Grand Challenge for biomolecular simulation is to couple our different computational tools together into a multi-scale dynamic model that propagates information from the atomistic through to the cellular level, and vice versa.

The Solution

Integrated workflows for modelling biomolecular dynamics at multiple scales

To understand dynamic systems such as molecular machines, metabolic networks or the formation (and disassembly) of cellular architectures such as the cytoskeleton we need multi-scale computational models. We also need to include omics data sets into our models, as these provide information about the chemical composition of cellular structures. This requires the coupling of different software methods together into organised workflows, and will need to be computationally efficient on HPC/HTC platforms to achieve the necessary throughput. We will also need to be able to make our tools usable and understandable across multiple domain boundaries, which requires, for example, complex physics based workflows to be accessible to experimental biologists.

The Outcome

Improved design tools for drug discovery and biotechnology

A better understanding of biomolecular dynamics across multiple scales is essential if we are to fully understand the relationship between biomolecular structure and function. The biggest biological questions, such as how drugs which operate at the molecular level affect the whole organism, or how genome instability leads to cancer will remain unanswered unless we apply a combination of different biophysical tools, including simulations. The benefits will be improved design tools for the pharmaceutical industry, and a better understanding of pathogens and how we might prevent, diagnose and cure disease. There is also the

potential for entirely new biotechnologies, such as designed proteins or molecular motors that are novel active materials, that perform bespoke mechanical activities at the nanoscale.

More Information

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