Symposium: Combining Simulation and Experiment in Molecular Imaging

16:00 Jon Essex, Ivo Tews – Welcome
16:10 Corey Hecksel - eBIC @ Diamond - New horizons in electron microscopic imaging
16:45 Albert Solernou, Leeds - Bridging the scales in modeling
17:20 Kresten Lindorff-Larsen, Copenhagen - The dynamic nature of biomolecules
17:55 - 18:20 break (cofee & cake, refreshments)
18:20 Tom Burnley, CCPEM - More than one - crystal structures ensemble refinement
18:55 Robert Rambo, Diamond B21 - Small angle scattering and conformational space
19:30 - 20:00 reception (wine and nibbles)

eBIC @ Diamond – New horizons in electron microscopic imaging

Alistair Siebert, Dan Clare, Corey Hecksel
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The latest generation of electron microscopes and direct electron detectors have revolutionised the role of cryoEM in structural biology and it is now possible to routinely and rapidly determine protein structures at near atomic resolution. Unfortunately the cost of purchasing and operating this cutting-edge equipment is prohibitive for most academic institutions. To enable free at the point of access by all scientific groups and institutions, the Electron BioImaging Centre (eBIC) was established at Diamond Light Source with funding from the Wellcome Trust, MRC and BBSRC. Titan Krios I at eBIC has now been operational for approximately 10 months and has hosted >70 peer-reviewed external user visits. The data collected has generated two recent high-impact publications and multiple high-resolution single-particle reconstructions. eBIC's ability to provide access to cutting-edge equipment will be significantly increased with the addition this summer of Titan Krios II.

Modelling Biomolecules at the Mesoscale with Fluctuating Finite Element Analysis

Albert Solernou[1], Ben Hanson[1], Robin Richardson[1], Daniel Read[2], Oliver Harlen[2]and Sarah Harris[1,3]
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A wide range of fundamental biological processes occur at the mesoscale, with length scales ranging from hundreds of nanometers to some micrometers and time scales from tens of nanoseconds to microseconds. Biophysical techniques that provide structural information at this scale, such as cryo-electron microscopy and 3D tomography, have experienced great advances during the last years and continuously report maps at their own online repository called the EMDataBank (EMDB). Aiming to model computationally these same length and time scales, we have developed a continuum mechanics description of proteins which uses this new experimental data as input to the simulations. The continuum equation of motion, which we have generalised to correctly include the thermal fluctuations, is iteratively solved using Finite Element Analysis, and therefore the model is known as Fluctuating Finite Element Analysis (FFEA) [1].

We will explain the physical principles underlying FFEA, which we are developing into a software tool for use by the biomolecular science community. We will then demonstrate how FFEA can be used to model flexible biomolecular complexes from EM and other structural data using our simulations of the molecular motor dynein and fibrinogen aggregation as illustrative examples.Finally, we will talk about the current limitations of this approach, together with some of our latest research to overcome them.

FFEA is a new algorithm for biomolecular simulation, therefore, we welcome suggestions for improving the accuracy and efficiency of the method, for validating its results and for new applications of our model.

1. Oliver R., Read D. J., Harlen O. G. & Harris S. A. "A Stochastic finite element model for the dynamics of globular macromolecules", (2013)*J. Comp. Phys*. 239, 147-165.

Molecular dynamics and NMR: A perfect match?

Kresten Lindorff-Larsen
Structural Biology and NMR Laboratory & Linderstrøm-Lang Centre for Protein Science,
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Recent years have seen dramatic advances in both the accuracy and precision of molecular dynamics simulations. Thus, with all-atom resolution we are now in favourable cases able to simulate processes that occur on millisecond timescales and with accuracies that, in some cases, are approaching experimental uncertainties.

Despite these advances, molecular force fields remain approximate and imperfect, and sampling complex or large systems for long timescales is difficult. In cases where standard simulation methods fail, one useful strategy is to use experimental data directly as restraints in molecular simulations in a way similar to what is done in traditional structure determination. By combining good force fields and enhanced sampling methods with experimental restraints, one may be able to obtain relatively accurate structural models with limited data. For dynamic systems, where the experimental data represents a convoluted average over space and time, special care needs to be taken when using data as restraints. One possibility is to use so-called replica-averaging through the principle of maximum entropy.

Following a brief introduction to the current state of the art of molecular dynamics simulations, I will present two examples of how NMR data can be used as restraints in simulations. One example represents a situation where untraditional sources of experimental restraints may be used to determine a high-resolution structure. The second case highlights how replica-averaged simulations may be needed to determine the structure of a dynamic protein.

Ensemble refinement of protein crystal structures in PHENIX

Tom Burnley, CCPEM, Diamond Light Source Ltd, Harwell Science & Innovation Campus, Didcot, Oxfordshire

Despite recent advances in data collection and processing in protein crystallography, there remains a significant discrepancy between measurement and model error for macromolecular crystal structures. This has been attributed, at least in part, to the incomplete modelling of atomic disorder. Here we present an alternative refinement method which simultaneously includes anisotropic and anharmonic disorder. This ensemble refinement uses a molecular dynamics approach augmented with time-averaged x-ray restraints to produce a population of Boltzmann-weighted structures that represents the conformational space sampled during a simulation. The resulting ensemble model typically contains 100-250 structures and is shown to significantly improve the model error (as judged by Rfree), in comparison with traditional methods.

Ensemble refinement was developed, and is available, within the PHENIX software suite. It utilises a maximum-likelihood target function in conjunction with a dual explicit- and bulk-solvent model and can be used with any heterogeneous atom or group. In addition to the improved global statistics, ensemble refinement reveals highly-resolved local disorder features which are demonstrated to reflect important functional details for a number of test cases The development of phenix.ensemble_refinement will be presented alongside a practical test case.

Diamond B21 - Small angle scattering and conformational space

Robert Rambo, B21: Solution State SAXS, Diamond Light Source Ltd, Harwell Science & Innovation Campus, Didcot,

Small angle X-ray scattering (SAXS) of dilute, biological particles in solution is a resolution-limited, structural measurement of the particle's thermodynamic state. This measurement provides a complete picture of the entire structural ensemble suggesting experimental SAXS information can be used as a target to drive structural modeling of the solution state. I will discuss contemporary methods that use SAXS information directly and indirectly during modeling and highlight data quality issues that effect the false positive rate. In addition, I will present a structural modeling approach to bioSAXS using concepts from Information Theory and Computational Geometry.

Experimental data from various sources can be used to steer simulations of biomolecules and molecular assemblies. With this Micro-Symposium, we explore the interface between simulation and experiment, covering techniques such as Small Angle X-ray Scattering (SAXS), Nuclear Magnetic Resonance (NMR) and X-ray Crystallography.