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Supported lipid films under a varying electric field: modelling a voltammetry molecular sensor

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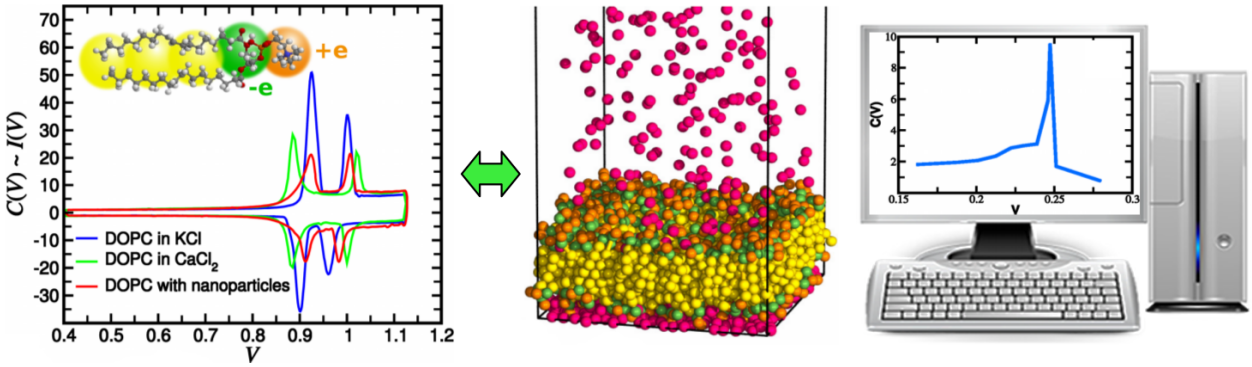
The behaviour of phospholipid layers on mercury (Hg) electrodes in an electric field has excited considerable interest over the past thirty years. Part of the reason for this interest has been the occurrence of very sharp phase transitions as a function of applied potential, which are associated with sudden structural changes in the phospholipid layer. These systems have been studied extensively mainly using electrochemical methods but still the nature of the structural changes underlying the phase transitions has remained elusive. For the first time, a molecular simulation study of lipid layers supported on a flat and smooth electrode is presented, where voltammetry measurements are closely mimicked. In particular, our simulations reproduce a non-trivial capacitance-vs-voltage dependence, $C(V)$, recorded in experiment [1,2]. The Monte Carlo simulations reveal the following rearrangements in hydrophobically adsorbed phospholipid films, being driven by the charge redistribution within the interface: [3]

1. Displacement of the lipid monolayer from the electrode by its counterions (cations), leading to formation of an electric double layer and, consequently, complete monolayer desorption;
2. Transformation of the monolayer into a bilayer upon its desorption;
3. Zwitterionic bilayer readsorption to the electrode through the polar-group interaction with the electric double layer.

The voltammetry peaks reflect a stepwise formation of layers of alternating charge: (a) electric double layer upon transient film desorption, (b) triple or multi-layer upon film readsoption. The simulation evidence suggests that the first peak is due to the cation breakthrough to the electrode resulting in the monolayer desorption, whereas the second peak represents the film rearrangement to form self-organised bilayer structures.



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CCP-SAS 2017 Poster Abstract

Characterization of the NISTmAb Reference Material Using Small-Angle Scattering

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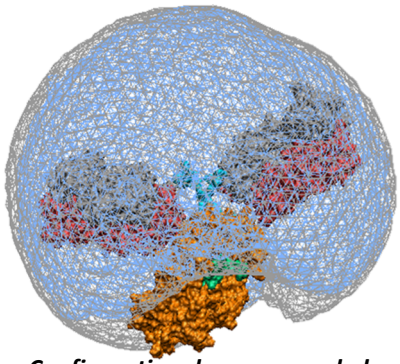
Both conformation and colloidal stability of therapeutic proteins, such as monoclonal antibodies, must be closely monitored and thoroughly investigated to assess the long-term viability of a drug product. Small-angle scattering can provide unique information about structure and interactions of antibodies under a range of experimental conditions. In this poster, I present small-angle X-ray and neutron scattering experiments to characterize the molecular structure and protein-protein interactions on the IgG1 NISTmAb reference material, a biological reference material available to evaluate method performance and serve as a representative test molecule for therapeutic protein characterization. After building a starting structure of the intact NISTmAb from the crystallographic coordinates of the Fc and Fab regions, molecular dynamics and Monte Carlo simulations are performed to explore the configurational space sampled by the Fabs with respect to the Fc. From these simulations, a set of atomistic structures that agree with experimental scattering data are obtained. In addition, small-angle neutron scattering profiles at high concentrations are used to study the colloidal stability of the NISTmAb. The strength of protein-protein interactions upon the addition of sodium chloride is evaluated using the effective structure factor and its consequent effect on the solution viscosity is described. Finally, I describe the conformational stability of the NISTmAb upon freezing samples in-situ while collecting small-angle neutron scattering data. Overall, this study provides new sets of experimental conditions, computational models and instrumentation used to characterize the NISTmAb under dilute and high concentrations, and after freezing/thawing cycles.



Configurational space sampled by the NISTmAb in solution

SASSIE: A Framework for Ensemble Modeling and Analysis

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SASSIE is a set of program modules to prepare structures for simulation, to carry out simulations, calculate experimental SAS and reflectivity data, and compare results to experiment. Simulation modules allow access to modern all-atom and coarse-grain parallelized molecular dynamics (MD) and Monte Carlo (MC) simulation engines. MD programs currently implemented are NAMD and CHARMM. MC programs are provided to sample structures quickly for a variety of protein, nucleic acid and carbohydrate systems. All-atom SAS and reflectivity calculators are provided to generate ensembles of SAXS/SANS and reflectivity data from simulation trajectories. Experimental constraints are easily implemented to sub-sample ensembles based on user supplied distance information between atoms, domains, etc. Heuristic algorithms are available to sub-sample structures that agree with experimental data.

CCP-SAS 2017 Poster Abstract

Non-linearity of the collagen triple helix in solution and implications for collagen function

Presented by Hina Iqbal.

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Collagen adopts a characteristic supercoiled triple helical conformation which requires a repeating $(Xaa\text{-}Yaa\text{-}Gly)_n$ sequence. Despite the abundance of collagen, a combined experimental and atomistic modelling approach has not so far quantitated the degree of flexibility seen experimentally in the solution structures of collagen triple helices. To address this question, we report an experimental study on the flexibility of varying lengths of collagen triple helical peptides, composed of six, eight, ten and twelve repeats of the most stable Pro-Hyp-Gly (POG) units. In addition, one unblocked peptide, $(POG)_{10unblocked}$, was compared with the blocked $(POG)_{10}$ as a control for the significance of end effects. Complementary analytical ultracentrifugation and synchrotron small angle X-ray scattering data showed that the conformations of the longer triple helical peptides were not well explained by a linear structure derived from crystallography. To interpret these data, molecular dynamics simulations were used to generate 50,000 physically realistic collagen structures for each of the helices. These structures were fitted against their respective scattering data to reveal the best fitting structures from this large ensemble of possible helix structures. This curve fitting confirmed a small degree of non-linearity to exist in these best fit triple helices, with the degree of bending approximated as 4-17^o from linearity. Our results open the way for further studies of other collagen triple helices with different sequences and stabilities in order to clarify the role of molecular rigidity and flexibility in collagen extracellular and immune function and disease.

Reference:

Walker, K. T., Nan, R., Wright, D. W., Gor, J., Bishop, A. C., Makhatadze, G. I., Brodsky, B. & Perkins, S. J. (2017) Non-linearity of the collagen triple helix in solution and implication for collagen function. *Biochem. J.* In press. **DOI:** https://doi.org/10.1042/BCJ20170217 Pubmed 28533266

CCP-SAS 2017 Poster Abstract

The solution structure of the human complement regulator CFHR5 reveals a compact dimeric structure by X-ray scattering and analytical ultracentrifugation

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Human Complement Factor H Related 5 (CFHR5) belongs to the same complement regulator family as Factor H. The CFHR5 protein comprises a linear sequence of nine short complement regulator (SCR) domains. A mutation of CFHR5 that results in duplication of the N-terminal SCR-1/2 domain pair causes CFHR5 nephropathy, a common cause of kidney failure in Cypriots. To clarify the molecular basis of CFHR5 nephropathy, the domain arrangement of full-length CFHR5 was studied by analytical ultracentrifugation and X-ray scattering. Sedimentation velocity reported a molecular mass of 134 kDa, indicating that CFHR5 is dimeric with 18 SCR domains and not nine. The sedimentation coefficient of 5-6 S for CFHR5 decreased with increase in NaCl concentration, showing that its domain conformation had become more extended in high ionic strength. X-ray scattering also showed that CFHR5 was dimeric to confirm the ultracentrifugation result. The X-ray mean radius of gyration R_G was 5.5 ± 0.2 nm, and its maximum length was 20 nm. This length of 20 nm for a protein with 18 SCR domains is low compared to that of 32 nm for Factor H with 20 SCR domains, indicating that CFHR5 possesses a more compact SCR arrangement than that seen for Factor H. The scattering curve modelling of CFHR5 was performed using a new modelling procedure called SASSIE that involved molecular dynamic simulations to generate physically-realistic atomistic SCR structures for CFHR5. The best-fit modelling structures confirmed that CFHR5 possessed a folded-back compact domain structure. We expressed the single SCR-1 domain and the SCR-1/2 domain pair of CFHR5 to show from analytical ultracentrifugation that SCR-1 was monomeric, while SCR-1/2 was dimeric, thus locating the CFHR5 dimerization site to its N-terminus. We are currently performing functional experiments with the SCR-1 and SCR-1/2 domains to clarify their role in CFHR5 activity. In summary, our results indicate a markedly more compact solution structure of CFHR5 than previously thought, and we have located its dimerization site to SCR-1/2 which may have a major role in causing CFHR5 nephropathy.

CCP-SAS 2017 Poster Abstract

Investigation of the interaction of testosterone-based drugs with dodecyl sulphate surfactants

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A large number of small molecules currently under development as drug candidates are hydrophobic in nature. Indeed it is believed that, depending upon therapeutic area, up to 80% of small drugs do not make it to market because of formulation problems encountered due to their poor-water solubility. Therefore, in order to fully exploit their therapeutic potential it is essential to incorporate such drugs in nontoxic, biocompatible and/or biodegradable formulations that both protect the drug during transportation in the body and release it at the target tissue. In the past few decades, there have been an amazing number of nanoparticle formulations created, many of which have been investigated for biomedical applications. Among these applications, drug delivery has been one of the more prevalent for nanoparticles composed of organic molecules, as such particles can be used to enhance the apparent aqueous solubility of the encapsulated molecules as well as specifically direct the molecules to the site of the diseased tissue.

Here we will present the results of various recent studies that we have performed using classical molecular dynamics simulations of dodecyl sulphate surfactant molecules with different counterions (including Na^+ and NH_3^+ for the most part) and testosterone-based drug molecules to understand how the underlying chemistry of these two compounds effects the ability of the surfactant to solubilize the drug, and the resultant structure of the drug-containing aggregate. We have used these simulations to investigate the interactions of the drugs with the surfactants in both micellar and monolayer structures which have also each been investigated experimentally with neutron scattering.

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CCP-SAS 2017 Poster Abstract

Large buffer isotope effect on protein phase behaviour and the ELCS

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Understanding protein stability and behavior is of central importance in biology, medicine, and chemistry. While solvent isotope effects have already provided important clues about the structural and thermal stability of disparate proteins, the effects of H/D substitution on protein phase behaviour and interactions remain to be elucidated. Here, we report the large effect of solvent isotope substitution on the phase behaviour and interactions of □B-crystallin, a globular eye lens protein interacting via a short-range attractive interaction potential. Using a combination of scattering techniques (small-angle x-ray scattering and static light scattering), we show that the liquid-liquid phase separation critical temperature T_c increases linearly from 276 K in H2O to 292 K in D2O (Figure 1).[1] Furthermore, we demonstrate that the phase boundaries and the osmotic compressibility of □B-crystallin scale with the reduced second virial coefficient b2, quantifying protein–protein interactions, through the extended law of corresponding states (ELCS). This thermodynamic scaling confirms the applicability of the ELCS to the equilibrium properties of colloids with short-range attractions and provides an extension of its predictive power to systems with varying hydrogen isotope content.

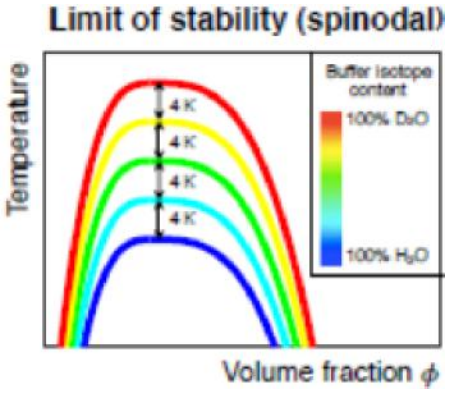

Figure 1. Spinodal of □B-crystallin solutions in buffer with varying hydrogen isotope content. The critical temperature T_c increases by 16 K upon replacing H2O by D2O, while the critical volume fraction □$_c$ remains constant.

References

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CCP-SAS 2017 Poster Abstract

Simulations to understand reflectivity: how coarse can we go?

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As the complexity of the systems studied with neutron and X-ray reflectivity increases, so must the methodology applied to the analysis. The current analytical procedure that is widely used for the interpreting reflectivity measurements involves the use of layer models, which are unsuitable for highly complex systems. For this reason, all-atom and coarse-grained molecular dynamics simulations have been investigated to aid in the calculation of reflectivity profiles [1-3]. These have involved the use of research group-specific code to slice snapshots of the simulation box into layers and apply the Abelès method; generating a reflectivity profile.

In this work, we have produced the open-access software, falass [4] which has been used to determine reflectivity profile from a lipid system at various levels of coarse-graining. This involved the simulation of a DSPC monolayer at a water-air interface, using a series of force fields; including all-atom and Martini coarse grained. Using this we have been able to assess the effectiveness of each force field to reproduce the reflectivity from the DSPC monolayers. This knowledge will inform the level of simulation resolution required to ensure the accurate modelling of systems of higher complexity, such as tethered lipid bilayers, or protein-lipid interactions.

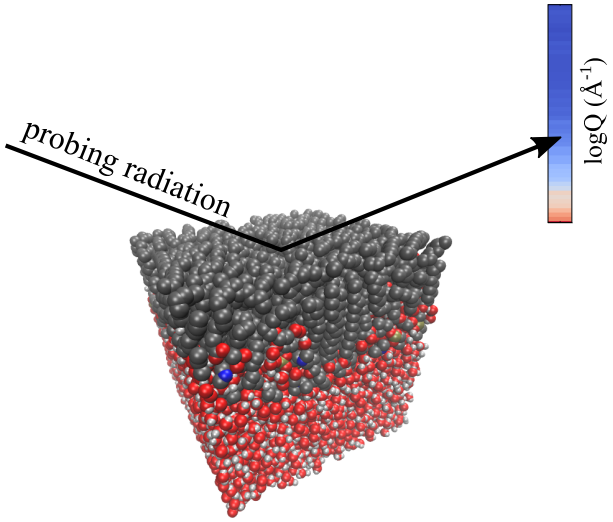

Figure 1. Reflectivity from a MD trajectory.

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Exploring protein association pathways with time-resolved SAXS and SANS

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Protein performs its biological functions by interacting with other proteins. Protein complexes, which are formed as a result of these interactions, consist of two or more components that associate along specific pathways - protein association pathways. The association pathway from monomer to oligomer is critical in a range of biological processes and thus it is of a vital importance to elucidate both atomic-resolution structures of intermediates along the pathway as well as the structure of the final state. Although considerable progress has been made in using experimental and computational techniques to determine start and final structural states, we have a limited understanding of what happens in between.

By enabling both time resolution and structural detail Time-Resolved Small Angle X-ray/Neutron Scattering (TR-SAXS/TR-SANS) is uniquely suited to interrogate complex self-assembly reactions and to provide a molecular understanding of self-assembly pathways. However, the analysis of such data is complicated because scattering arises from a mixture of many components, the information content in each spectrum is limited and there is no framework for simultaneous analysis of data from different data sources. The similar problem is faced when resolving conformational ensembles from small angle scattering data.

To overcome this problem we develop a method that combines a computational structural modeling (which delivers atomic-resolution structures) with experimental data (which provides information about the population of different states). The method applies Bayesian probabilistic model to analyze scattering data from mixtures of oligomeric species. The method allows for modeling large structural ensembles, it can be used to assess uncertainty of all modeling parameters and enables minimization of over-fitting.

We will demonstrate that ensembles determined with our approach explain experimental data to a higher degree and are less prone to over-fitting than the current state-of-art methods used to analyze data. We will also discuss how the method will become available to ESS users at the early stage of operation.

Application of Information Theory to SAS Modeling

Robert P. Rambo

Diamond Light Source

Small angle X-ray scattering measurements of dilute, homogenous particles in solution are resolution limited measurements of the thermodynamic ensemble. Similar to X-ray crystallography and electron microscopy, SAXS observations made at higher resolutions imply a greater detail in the structural measurement. Here, I present a new approach to understanding bioSAXS data using two fundamental properties of Information Theory (namely, the Shannon Sampling and Noisy-Coding Channel theorems). These theorems allow for the error-free recovery of the SAXS signal, in the form of a real-space, cross-validated pair-distance, P(r), distribution function. The P(r)- distribution contains the structural assessment of the thermodynamic ensemble. An Information Theory framework has been developed and applied to the structural modeling problems of shape determination and docking. The modeling algorithm targets the P(r)-distribution using the Kullback-Liebler divergence, an Information Theory difference metric. The algorithm scales with resolution. Using a SAXS dataset of a 25 base-pair, double-stranded DNA, the volumetric model illustrates features of the major and minor groove as the resolution of the SAXS dataset increases. Further tests on SAXS of the P4-P6 group I intron RNA domain reveal the large solvent channels observed in the X-ray crystal structure. Furthermore, the Information Theory approach can be used in antibody-antigen studies to uniquely determine the structure of the complex in the solution state. Our approach shows that modeling can be made more reliable by exploiting theorems from Information Theory.

Wide angle scattering to probe the solvent layer in lysozyme

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Proteins exist in Nature in aqueous solutions, but there are remarkably few direct measurements of the interaction of the protein with the surrounding solvent. Numerous theoretical, physical chemical measurements and crystallographic studies have supported a model whereby there is a tightly bound first layer of solvent followed by successive layers of water extending out to some tens of Angstroms from the surface. Using total neutron diffraction data as a constraint in Empirical Potential Simulation Refinement we measured directly the scattering associated with this layer for the well characterised protein lysozyme. From this we are able to deduce a layer extending some 7-8 angstroms away from the surface of the protein, consistent with a depth of 2-3 water molecules.

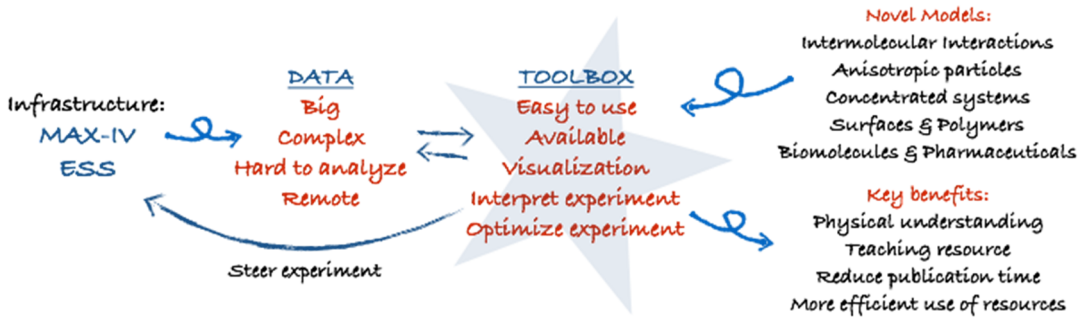
CCP-SAS 2017 Poster Abstract

Computational Toolbox for Scattering Infrastructure

A Proposal from Lund, Sweden: Department of Chemistry, MAX IV, ESS

Contact Person: Marie Skepö

Division of Theoretical Chemistry, Lund University, Sweden



Our overall goal is to develop a computational toolbox for scattering infrastructure, aiming for interpretations at the molecular level, of structures and interactions in colloidal and macromolecular systems. In summary, we aim to:

- Reduce the time from measurement to publication, which currently is around 2 years.
- Facilitate knowledge transfer via master and PhD projects, which include peer-reviewed publications and conference presentations.
- Improve the quality of used beamtime by predictions of expected results as well as interpretations of scattering data.
- Develop a lasting scattering course with a theoretical emphasis, aiming at improving skills of master and PhD students.

We will develop state-of-the-art modelling tools and algorithms to interpret scattering data from x-rays or neutrons, primarily on systems within the areas of Soft Matter and Life Science. We will devote extensive efforts to include the role of intermolecular interactions. Specific examples of macromolecular systems for which our tools will be well suited include:

- Polymers
- Proteins
- Surfactants
- Inorganic nanoparticles (clays, fibers etc.)
- Mixtures of polymers and colloidal particles
- Interfacial processes
- Decorated colloidal particles, for instance carrying grafted polymers

Unravelling the solution structures of therapeutic antibodies with and without glycans

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Immunoglobulin G (IgG) is the most abundant glycoprotein in serum and encompasses four subclasses IgG1, IgG2, IgG3, and IgG4. IgG is a Y-shaped structure composed of two Fab regions which interacts with antigen, and the Fc region that interacts with FcγR receptors. The Fc region contains two conserved glycan chains at Asn297 near the hinge that connects the Fab and Fc regions. In order to understand the molecular role of the two glycans, a multidisciplinary approach for monoclonal IgG1 and IgG4 was implemented using mass spectrometry (MS), analytical ultracentrifugation (AUC) and small angle neutron scattering (SANS). A non-denaturing enzymatic deglycosylation protocol using PNGase F was optimized using native MS, which confirmed the occurrence of non-denaturing deglycosylation with the retention of the native charged state distribution and a decrease in overall mass. In AUC studies so far, a small overall compaction of the Fab and Fc regions in IgG1 structure was indicated from a slight increase in the sedimentation coefficient (native ~6.5S; deglycosylated ~6.7S). This analysis is yet to be done for IgG4. SANS data analyses did not show any change in IgG1 after deglycosylation. By SANS, IgG4 showed a slight reduction in the radius of gyration Rg accompanied by an increase in the cross-sectional Rg value (Rxs-1), and small changes in the distance distribution function. These first studies indicate that removal of the N-linked glycans have probably perturbed the overall antibody structure of IgG1 and IgG4. SASSIE analyses will clarify the extent, if any, of any conformational changes that take place after glycan removal.

CCP-SAS 2017 Poster Abstract

Building Atomistic Models from SAXS Experiments Using Bayesian Refinements of Accelerated Molecular Dynamics Trajectories

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Small angle X-ray scattering (SAXS) experiments capture the full solution ensemble of flexible biomolecules, but SAXS data is typically low-dimensional and difficult to interpret without additional structural knowledge from complementary techniques. In principle, this information may be provided by molecular dynamics (MD) simulations, but conventional MD (cMD) trajectories are often restricted to local minima. One method for enhancing MD sampling is accelerated MD (aMD), which reduces the height of potential energy barriers by introducing a bias to the underlying energy landscape, and unlike many similar techniques does not require the definition of a reaction coordinate. However, the bias potential disturbs the Boltzmann distribution, and determining the appropriate populations of states directly from an aMD simulation can be difficult, especially for large complexes. Therefore, it is beneficial to use these two techniques together, SAXS and aMD, to produce atomistic-level models of biomolecular solution ensembles. Here, we present a method for fitting aMD simulations of poly ubiquitin trimers with SAXS data using an iterative Bayesian procedure. Candidate scattering states are first identified from MD trajectories, and then their populations are re-weighted against empirical data using a Bayesian Monte Carlo approach. Resistance to ensemble over-fitting is achieved by iteratively considering increasing subsets of scattering states and by reducing experimental data to the Shannon sampling limit. Using this protocol, we find that aMD simulation can be used to produce higher quality models in shorter timescales than standard cMD simulations. We analyze several different trimer linkages and find that the location of each linkage is strongly coupled to the populations of the resulting models. This site-specific alteration of solution flexibility may play a key role in the disparate roles of each linkage in cellular signaling and processes.

References

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DL_FIELD – A force field and model development tool for DL_POLY

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DL_FIELD is a computer program that primarily serves as a support application software tool for DL_POLY molecular dynamics (MD) simulation package. The program is intended to serve as an important application tool to enhance the usability of DL_POLY MD simulation package and to facilitate the use of a wide range of advance features included in the MD program suite.

DL_FIELD program has three main functions:
(i) Force field model convertor. Conversion of a user's atomic configuration into force field (FF) files that are readily run in DL_POLY. The available popular FF schemes are: CHARMM, AMBER (including Glycam), OPLS, CVFF, PCFF, DREIDING and Gromos G54A7. It also includes inorganic force fields for ionic solids, minerals, glass and clay minerals.
(ii) Force field editor: Allows users to edit or modify a particular FF scheme to produce a customised scheme that is specific to a particular molecular model.
(iii) Force field model repertoire: DL_FIELD has a consistent file structure format for all FF schemes and molecular structure definitions.

DL_FIELD is designed to handle a wide range of molecular system of varying complexity: from simple ionic compounds, small covalent molecules to systems with complex topologies such as biomolecules, carbohydrates, drug molecules and organic cages. It is also capable to construct force field models for random structures such as hydrogels, networked systems and random polymers. In addition, the unification of file formats and data structures based on the DL_FIELD framework facilitates migration of one class of FF system model to another, with minimum learning curve. In this way, DL_FIELD not only speeds up research efforts and scientific output for DL_POLY users but also encourages researchers to carry out new classes of molecular systems spanning across multidisciplinary fields, from material sciences to biological and pharmaceutical areas.

DL_FIELD also implements the universal DL_F notation [1], a human-readable notation format which unifies the ambiguity of atom type assignments for a range of FF schemes in a single universal format that are easily interpreted by both the modellers and experimentalists. This allows the analysis of molecular simulation models and, from such, relates to the real chemical systems and to facilitate functional and relational queries in data analysis.

[1] C. W. Yong, J. Chem. Inf. Model. vol.56, pp 1405-1409 (2016)