Coarse graining biological systems: Towards large-scale interactions and assembly

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Report

This workshop brought together 40 participants including chemists, physicists and mathematicians from Europe and the United States to discuss one of the most rapidly developing areas in computational biology today, namely, the use of coarse-grain models. While all-atom representations of biological macromolecules and assemblies (proteins, nucleic acids, polysaccharides and lipid membranes) are now well established and progress continues to be made both in force fields and in conformational search strategies, these methods have clear limitations. Biological systems often involve very large numbers of atoms (tens of thousands to millions) and processes which can stretch into the millisecond to second range. Despite dramatic increases in computer power, this puts many systems and processes out of reach for all-atom models.

The ability to simplify our representations and replace groups of atoms, or even whole macromolecules, with pseudoparticles opens the door to modeling in this otherwise inaccessible area. However, coarse-graining must be carried out with two things in mind. First, how to best choose the coarse-grain representation and its degrees of freedom and, second, how to calculate interactions between the resulting pseduoparticles. It is also necessary to consider how to move (in both directions) between all-atom and various degrees of coarse-graining, without losing more information than is necessary. These fundamental questions constituted the basis for our workshop. The 24 lectures included presentations of the various routes being pursued for coarse-graining: the extraction of data from all-atom dynamic simulations or the use of physical intuition to define models of varying degrees of sophistication, parameterized term by term from experimental data or fitted from ensembles of experimental structures using the so-called Boltzmann inversion approach.

At present, many coarse-grain models and interaction potentials coexist, each being adapted to a given area of application. The applications presented during the workshop were representative of the field today: lipid membrane behavior including large scale deformations and fusion; membrane interactions with peptides and proteins; slow motions within proteins and protein folding; protein-protein and protein-nucleic acid interactions; using low resolution experimental data in conjunction with coarse-grain models to predict large molecular structures. A number of presentations dealt with very large molecular assemblies (at or beyond the million atom boundary) and also with complex macromolecular mixtures, mimicking the crowded environment within the cell.

Interaction potentials for coarse-grain systems and appropriate conformational sampling methods were both discussed extensively. While there is no unique solution to these problems, given the range of systems and processes studied, it is clear that electrostatics, including interactions with the solvent and counterion environment, and the effects of solvent viscosity on dynamics, represent significant challenges.

The workshop included a poster session and a lively open discussion period which was centered on two important questions relevant to the present state of affairs with coarse-grain models: (1) Can we correctly assemble a macromolecular complex from its components *in silico*, notably when the component macromolecules are flexible and when the components are mixed with "bystanders" (molecules or macromolecules) not involved in the complex? (2) Can we predict *in silico* how a macromolecule or macromolecular complex functions in the absence of multiple experimental structures? That is, what are its functional motions and how do these achieve its biological activity (for example, the

rotation of a molecular motor or the selective catalytic action of an enzyme)? The answer to both these questions today is probably no, although the degree of optimism varied amongst the participants. They however represent exciting challenges for our field. There is no doubt that coarse-grain models are indispensable for modeling many aspects of biological systems. We are still at an early stage of their development and progress will certainly be made in all areas, including cross-pollenization with other fields (for example, materials science) where coarse-grain methods are equally important. Given this potential and the positive feedback from the participants of the workshop, it would be well-worth organizing another meeting in this field in roughly two years.