Theory and simulation
Editorial overview

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This year's reviews for the theory and simulation section have been chosen in order to show the increasing sophistication of computational approaches and the wide range of applications to which such methods can be successfully applied. Perhaps even more importantly, they show an increasing awareness of the need to be critical, to compare different computational approaches and to validate each against experimental data. An area in which computer simulations have contributed greatly to our understanding is that of the solvation of biopolymers. The most realistic and accurate simulations involve explicit inclusion of solvent using full atomistic representations.

In practice, however, there have been many conceptual and computational hurdles to overcome. These include the more limited sampling of the biopolymer conformations that is possible when carrying out simulations with detailed atomistic models for the solvent, the need to develop more accurate ways of treating the long range electrostatic interactions in simulations of this kind, and the need for improvements in the force fields for biomolecular simulations. Of course, the promise of obtaining a molecular-level understanding of the role of water in the folding and stabilization of biopolymers in their native state, and not least in their function, has stimulated continued improvements in modelling based on this fully atomistic viewpoint. Several different perspectives on the current state of the computer simulations that include solvent in molecular detail are presented in this volume of *Current Opinion in Structural Biology*.

Warshel and Papazyan (pp 211–217) provide a review of the current state of modelling the electrostatic effects in macromolecules and the crucial role of solvent in their thermodynamics. This group has long advocated the use of dipolar solvent models as a bridge between all-atom models and continuum electrostatic models. The authors emphasise the limitations of these different approaches and point out the problem of protein reorganisation, which is not handled well by the continuum approaches. They also focus on the nature of the protein dielectric constant, which can be addressed using their dipolar models. The correspondence between these different viewpoints is clarified in the review and recent applications to modelling the thermodynamics of redox proteins, ligand binding, and catalysis are discussed.

Three of the reviews in this issue summarise recent results concerning the hydration of proteins, nucleic acids, and ion channels, with emphasis on structural aspects. Pettitt and co-workers (pp 218–221) explain why it may be more useful to consider hydration patterns around biomolecules using the concepts of probability distributions that are familiar in liquid state theory, rather than focusing on a search for discrete sites for water molecules. They note the excellent agreement that can now be obtained in comparisons between theoretical and experimental solvent electron density radial distributions. The statistical viewpoint is also stressed in Brooks' review of protein folding and unfolding (pp 222–226). In this field, theory seems to be driving experiment as the general features of the free energy landscape for protein folding have been described using highly reduced protein models. Molecular dynamics simulations of protein folding using more detailed atomic models are beginning to bridge the gap between the more abstract protein folding models and experiment. Auffinger and Westhof (pp 227–236) review the recent progress in detailed atomic-level molecular dynamics simulations of DNA and RNA. The development of improved models for treating the electrostatics of these highly charged systems, particularly the use of Ewald summation methods, has led to increased accuracy. Still, they note that several of the papers discussed point to a force field and protocol dependence of the structural results. This remains a barrier to using the full power of molecular dynamics simulations to study recognition phenomena and folding of nucleic acids. As the authors point out, the use of multiple molecular dynamics trajectories may provide the first step towards a more statistical evaluation of the results from simulations and can lead to a clearer assessment of the validation of simulation protocols. Improvements in methodology should allow us to better assess the relationship between the induced-fit mechanisms of nucleic acid–ligand complexes and the structural heterogeneity found in simulations.

Continuing the theme of solvation of biopolymers, Sansom (pp 237–244) focuses both on ion channels and on related membrane proteins. Gramicidin has been studied by many groups and continues to be the ideal model channel for testing computational approaches. Interesting studies focus on the area of proton hopping along channels of hydrogen-bonded water molecules and the need for water

reorientation to help this process. As well as the simpler models of ion channels, more complex channels such as the pore domains of the nicotinic acetylcholine receptor, Shaker K^+ channels and channels consisting of helical bundles have been modelled. These more elaborate models depend on experimentally derived constraints, especially when high resolution structures are not available. Finally, we see the progress that has been made in the modelling of peptides and proteins on or in a lipid bilayer, with bacteriorhodopsin being one of the key proteins studied in simulations of this type. Validation of these models awaits more detailed experimental data, especially from cryo-electron microscopy and X-ray crystallography.

The papers by McCammon (pp 245–249) and Sternberg *et al.* (pp 250–256) provide an overview as to how computer simulations are currently being used to model complex interactions between biomolecules that form the basis of biomolecular recognition. For a limited set of problems, free energy perturbation methods, based on detailed atomic-level molecular dynamics or Monte-Carlo simulations, are being used to study the association of small molecule ligands with their protein receptors. Many people believe that the conformational sampling problems and force-field inaccuracies are such that it is more productive at present to continue to develop and refine reduced representations for simulations of the association between biomolecules. Sternberg *et al.* describe the recent developments in algorithms for predicting the docking of two proteins, considering both the initial rigid-body global search and subsequent screening and refinement. McCammon reviews the new computational techniques that have been developed based upon both atomistic and continuum models for studying thermodynamic and kinetic aspects of recognition.

The computer simulations of biomolecular hydration, protein folding, and macromolecular association that are the focus of this section are all based upon molecular mechanics models for the potential surfaces that govern these processes. The review by Friesner and Beachy (pp 257–262) concerns recent developments in quantum mechanical methods for the parametrisation of improved classical force fields as well as for studying biological processes by direct quantum mechanical calculations. The rapid increase in computer power, coupled with the development of new electronic structure algorithms for large molecules, has made such calculations possible. Recent applications to the modelling of transition metal-containing enzyme active sites and mixed quantum mechanical and molecular mechanical studies of a variety of enzyme mechanisms are described.

In conclusion, it is now possible to see the interplay between computational and experimental approaches to functions of biopolymers in a number of areas. This has been brought about both by conceptual advances in algorithms for biomolecular simulations, and by the increase in computer power — allowing better sampling of complex systems and a more critical approach to validation. We are seeing clear insights into the behaviour of biomolecules from computer simulations and with the increased accuracy of such methods we are hopeful of many more in the future.