Commun. Comput. Phys.

Vol. **13**, No. 1, pp. i-v
January 2013

Preface

Special Issue on Modeling Electrostatics in Molecular Biology (MEMB)

This special issue on Modeling Electrostatics in Molecular Biology (MEMB) is a follow-up of the international meeting which took place in Clemson University in April 4-6, 2011. The meeting attracted 63 participants from 5 countries, USA, UK, Italy, Portugal and Germany, representing prestigious research institutions. The meeting had twenty nine talks, in addition to thirty posters. The goal of the meeting was to gather researchers working in the area of biomolecular electrostatics, both developers and users of computational approaches, and to assess the current state-of-the-art of methods and algorithms for modeling electrostatic potential distribution and the corresponding energies in complex systems made of biological macromolecules.

The importance of electrostatics in biomolecular systems is due to the fact that electrostatic interactions frequently dominate other forces, because practically each atom carries partial charge and distances between atoms in a molecule are very short, of the order of several Angstroms. The corresponding force at such short distance is very strong as it is described by the Coulomb formula. In addition, the electrostatic potential decays as one over the distance, while all other energy terms decay very fast and are practically zero at distances larger than 4 Angstroms. For these reasons, electrostatics plays a vital role in macromolecular interactions, stability and function.

However, modeling and understanding the role of electrostatics in biomolecular systems are not a trivial tasks, since these systems are very complicated, made of macromolecules composed of hundreds of thousands or millions of atoms, and at the same time, surrounded by millions of water molecules, which in turn constantly change their positions and orientations. The number of degrees of freedom in explicit modeling of biomolecular systems is so large that it is frequently computationally very expensive requiring extremely long simulation time, and thus it is prohibited for large systems or cases involving extremely large dimensions. Implicit models offer an alternative approach which dramatically reduces the computational cost, while being accurate enough to predict experimentally measurable quantities.

The outcome of the meeting was that despite of the enormous progress made in computing technology and resources, still many scientific issues remain unsolved. These include the definition of solvent-solute interface, i.e. the boundary between the water phase and macromolecules, the algorithms of solving the corresponding partial differential equations for irregularly shaped objects, the treatment of the ion atmosphere, and implicit modeling of the dynamics and transport of biomolecular systems. Successful

addressing of these challenges would require combined efforts of physicists, mathematicians, computer scientists and biologists. The manuscripts collected in the present special issue reflect part of these efforts. Thereby, we briefly outline the contribution of each paper and group the articles into several distinctive categories.

The main characteristics of any system to be modeled with continuum electrostatics is the function describing the dielectric response, typically evaluated via the properties of the dielectric constant, the definition of the boundary macromolecule-solvent and the polarization effects. With this regard, Zhou and co-worker reviewed the possibility that macromolecules may contain numerous water molecules and thus to have large effective dielectric constant and in terms of the grid algorithm, the distribution of the dielectric constant may have to be calculated using "zero probe radius" [1]. The possibility of having large dielectric response (large dielectric constant) non-homogeneously distributed throughout the macromolecule was also addressed by the team of Alexov and co-workers, who used Delphi capabilities to assign different dielectric constant per amino acid and studied the optimal effective dielectric constant per amino acid type to match the changes of the folding free energy upon mutations involving charged groups [2]. The effect of the polarization was outlined in a mini-review article by Zhan and co-worker, demonstrating the importance of polarization effects in calculating solvation/desolvation energies for protein-ligand interactions [3]. Rocchia and co-workers developed several representations of the molecular surface and studied the effects on the association energy of a pair of amino acids and their results were compared with published data utilizing molecular dynamics simulation with explicit water molecules. It was shown that the smoothest surface definition does not necessary results in the best match, in terms of energies, to the explicit water simulations [4]. In some aspect, the presence of mobile ions in the water phase can be modeled as a part of the dielectric response of the water. Dominy and co-worker demonstrated that the non-polar energy term can play significant role in modeling salt dependent effects associated with protein mutations. It was shown that an optimized surface tension coefficient results in a better match of the folding free energy change induced by protein mutations [5]. Taking all together, it seems that for correct modeling of the electrostatics, one should consider all the abovementioned effects simultaneously in the computational protocol.

Once dielectric properties of the system under consideration are known, the next question is how to obtain the corresponding potential distribution and how to calculate the energies. McCammon and co-workers summarized the mathematical and numerical advances in the development of the adaptive fast multipole Poisson-Boltzmann (AFMPB) solver. This approach utilizes boundary integral equation and fast multipole formulations. Technical aspects in surface meshing, node-patch discretization and Krylov subspace iteration were discussed and preliminary numerical results were presented [6]. Jacobs and co-workers extended their recently developed image-charge solvation model (ICSM) to the investigation of the impact of the reaction field on the force and torque of water molecules. It was shown that the ICSM reproduces key physical properties, including density, radial distribution function, diffusion constants and dielectric proper-

ties. Their work revealed that the reaction field plays a crucial role on water torques and is an essential component in the ICSM [7]. Gibou and co-workers applied their adaptive grid finite difference method for the solution of the Poisson-Boltzmann equation in the biomolecular context. This approach utilizes a level set to represent biomolecular surface and non-graded, adaptive octree grids to reduce memory usage. Interface jump conditions are enforced to gain better accuracy as described in [8]. Xie and Volkmer presented a modified nonlocal continuum electrostatic model to reduce the computational cost of conventional nonlocal integro-differential equations. Their approach transforms the integral-differential equation into an equivalent system of partial differential equations and make use of analytical solutions. The authors showed that the solution to the modified nonlocal continuum electrostatic model satisfies the original integro-differential equation [9]. Fenley and co-workers discussed their new Monte-Carlo based linear Poisson-Boltzmann solver that offers several attractive features. Their approach allows an easy-evaluation of Gaussian errors and a fast calculation of multiple solvent environments. Implemented algorithm optimizations make their solver competitive with existing deterministic Poisson-Boltzmann solvers [10].

Once these powerful algorithms were developed, the next step is to use and make them available to the biophysical community and to create methods and software packages to utilize their capabilities. Thus, using the continuum electrostatics approaches, Alexov and co-workers investigated the role of pH on the binding free energy of two protein complexes with specific pharmaceutical applications. It was demonstrated that His residues are the crucial factor for the pH dependence of binding in physiological pH [11]. The role of electrostatics was further demonstrated in the work of Dominy and co-worker, indicating the importance of electrostatic interactions in the formation of a stable B DNA structure. The continuum electrostatics was applied to characterizing the base flipping free energy profile for undamaged and damaged DNA bases [12]. The work of Moreira and co-workers emphasized on the impact of interface and solvation for the structure and function of protein complexes. Hot spots are identified as key residues that are responsible for the protein-protein binding. It was shown that such a binding leads to the shielding of warm- and hot-spots from water [13]. In terms of developing tools for the biophysical community, Amaro and co-workers developed VMD-plugin (elEnsembleElec) utilizing DelPhi to calculate the electrostatic potential of an ensemble of structures. The "elEnsembleElec" is downloadable and easy to install GUI, allowing users to select various parameters for the DelPhi and to visualize the results in the VMD [14]. Another tool was developed by Alexov and co-workers, the DelPhi webserver. The webserver is aimed to help non-experienced users or users not having computer infrastructure to use DelPhi to calculate electrostatic properties of biological macromolecules and nano objects. The web server is interfaced with the JMol, allowing the users to see the system being investigated and to map the electrostatic potential onto its surface [15].

Another aspect in electrostatic modeling is the development of new implicit models for the dynamics and transport of biomolecular systems. Chen and Wei introduced a variational multiscale model for proton transport in transmembrane proteins. In their

model, the solvent, except for protons, is treated implicitly and the electrostatics of the system is described by the Poisson-Boltzmann equation. Protons are described quantum mechanically via a non-equilibrium density functional theory approach. By using a number of mathematical techniques, the authors showed that their multiscale formalism is able to provide a good prediction of experimental current-voltage data [16].

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