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Fast Simulations of Pseudo-time Coupled Nonlinear Biomolecular Solvation Systems

In order to carry out quantitative description and analysis of various important biological processes at the atomic level, including signal transduction, DNA recognition, transcription, translation, protein folding and protein ligand binding, the analysis of the underlying biomolecular solvation is indispensible. This is because these important processes occur naturally in water, which comprises 65-90% of cellular mass. Biologically, the solvation analysis concerns with interactions between solute macromolecules and the surrounding solvent molecules or ions.

Recently, a family of differential geometry based multiscale solvation models have been developed for analysing the equilibrium properties of solvation by Wei and his collaborators. Based on the fundamental laws of physics, a free energy minimization or optimization process is conducted in these models. The total free energy functional for the solvation analysis typically consists of the electrostatic potential, the geometrical effect of the solvent-solute interface, the mechanical work of the system and the dispersive solvent-solute interaction. By using the Euler-Lagrange variation, two coupled nonlinear partial differential equations (PDEs) are derived as governing equations – one nonlinear Poisson-Boltzmann (NPB) equation for electrostatic potential and one generalized Laplace-Beltrami equation defining the solvent-solute interface or the biomolecular surface.

More recently, we have proposed a pseudo-transient continuation model for the theoretical modeling of biomolecular surface and solvation process. The major improvement of this differential geometry based multiscale model in comparison with the previous ones is a more efficient coupling of underlying nonlinear PDEs through the introduction of a pseudo-time in each process. By treating the NPB equation as the steady state solution of a time dependent process, the overall model coupling is accomplished by the explicit Euler time integration and controlled by time increments. This coupling is simpler than the relaxation based iterative procedure used in the literature, with less controlling parameters. Moreover, the NPB equation can be treated in the same manner as the linearized Poisson-Boltzmann (LPB) equation, which is impossible in conventional coupling. However, there are considerable numerical difficulties associated with the temporal discretization of the pseudo-time coupled solvation model. Such difficulties are essentially due to the nonlinear source term of the NPB equation, which involves a hyperbolic sine function of the electrostatic potential in the univalent mobile ions setting. Thus, a very small time increment has to be used in explicit Euler scheme. Moreover, instability issues are encountered for smoothly varied solute-solvent interface so that a filtering process has to be conducted.

Most recently, we have proposed to solve the time-transient NPB equation by using operator splitting based alternating direction implicit (ADI) schemes, while the simple Euler scheme is still used for the generalized Laplace-Beltrami equation. After the time splitting, the nonlinear term can be integrated analytically in the proposed algorithm, so that the overall time stepping scheme for the NPB equation is fully implicit. Thus, the proposed time splitting ADI schemes are found to be unconditionally stable for solving the NPB equation in benchmark examples with analytical solutions. Central finite differences are employed to discretize the inhomogeneous diffusion term of the NPB equation to form tridiagonal matrices in the Douglas and Douglas-Rachford type ADI schemes. The fast Thomas algorithm can thus be employed to solve the tridiagonal systems. Example solvation analysis of various compounds and proteins is carried out to validate the proposed models and algorithms. In solving the coupled system with two nonlinear PDEs, the proposed time splitting based alternating direction implicit (ADI) schemes are no longer unconditionally stable for the NPB equation. Nevertheless, the time stability of the NPB equation can be maintained by using very large time increments, so that the present biomolecular simulation becomes about ten times faster.