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UNCONDITIONALLY STABLE TIME SPLITTING METHODS FOR THE ELECTROSTATIC ANALYSIS OF SOLVATED BIOMOLECULES

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Abstract. This work introduces novel unconditionally stable operator splitting methods for solving the time dependent nonlinear Poisson-Boltzmann (NPB) equation for the electrostatic analysis of solvated biomolecules. In a pseudo-transient continuation solution of the NPB equation, the nonlinear term is analytically integrated, so that the difficulties in direct treatment of the strong nonlinearity can be bypassed. However, in a pseudo-time NPB computation, the use of large time increments is necessary to reach the steady state efficiently. The existing alternating direction implicit (ADI) methods for the transient NPB equation are known to be conditionally stable, although being fully implicit. To overcome this difficulty, we propose several new operator splitting schemes, in both multiplicative and additive styles, including locally one-dimensional (LOD) schemes and additive operator splitting (AOS) schemes. The proposed schemes become much more stable than the ADI methods, and some of them are indeed unconditionally stable in dealing with solvated proteins with source singularities and non-smooth solutions. By using finite differences in space and implicit integrations in time, the numerical orders of the proposed schemes are found to be one in both space and time. Nevertheless, the precision in calculating the electrostatic free energy is low, unless a small time increment is used. Further accuracy improvements are thus considered, through constructing a Richardson extrapolation procedure and a tailored recovery scheme in treating the vacuum case. After acceleration, the optimized LOD method can produce a reliable energy estimate by integrating for a small and fixed number of time steps. Since one only needs to solve a tridiagonal matrix in each one dimensional subsystem, the overall computation is very efficient. The unconditionally stable LOD method scales linearly with respect to the number of atoms in the protein studies, and is over 20 times faster than the conditionally stable ADI methods.

Key words. Nonlinear Poisson-Boltzmann equation, pseudo-transient continuation approach, time splitting, alternating direction implicit (ADI), locally one dimensional (LOD), additive operator splitting (AOS), electrostatic free energy.

1. Introduction

Analysis of the underlying biomolecular solvation is critical when carrying out quantitative descriptions of various important biological processes at the atomic level, such as protein folding and protein ligand bonding, DNA recognition, transcription, and translation. From a biological perspective, solvation analysis is concerned with interactions between a solute macromolecule and surrounding solvent ions. From a mathematical perspective, these solute-solvent interactions may be represented via solvation energies with contributions from polar and nonpolar sources. The polar portion arises from electrostatic interactions, which may be represented with the Poisson-Boltzmann (PB) model [6, 14]. The PB model provides a framework by which to model the distribution of electrostatic potential along the surface of a solute macromolecule within a surrounding solvent with a particular ionic concentration.

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TABLE 1. Acronyms used in this paper.

ADI	alternating direction implicit	LOD	locally one-dimensional
AOS	additive operator splitting	IE	implicit Euler
CFL	Courant-Friedrich-Lewy	NPB	nonlinear Poisson Boltzmann
CN	Crank-Nicolson	PB	Poisson Boltzmann
FFT	fast Fourier transform	RE	Richardson extrapolation
MAOS	multiplicative-additive operator splitting		

In the PB model, the PB equation governing electrostatic potentials takes the form of a nonlinear elliptic equation on multiple domains with discontinuous dielectric coefficients across the molecular surface or solute-solvent interface [3, 4]. The PB equation cannot be solved analytically for molecules with complex geometries, only admitting analytical solutions for shapes such as spheres or rods [12, 16]. However, solving the PB equation numerically also presents significant difficulties because of the discontinuous dielectric coefficients, singularities in the source-term, non-smoothness of the solution, and significant nonlinearity when strong ionic effects are present.

Recently, a pseudo-transient continuation approach has been proposed for solving the nonlinear PB (NPB) equation [27, 28, 34], which creates a different way to tackle the nonlinear term of the NPB equation. In classical finite difference and finite element solutions of the NPB equation, a nonlinear algebraic system is typically formed through the discretization of the boundary value problem. A nonlinear relaxation method [15, 24] or inexact Newton method [13] can be employed to solve such a nonlinear system. In the pseudo-transient continuation approach [27, 28, 34], a pseudo-time derivative is added to the NPB equation so that one solves an initial-boundary value problem now. The steady state solution of this problem gives rise to the solution to the original boundary value problem. Numerically, it is desired that a large time step can be used so that the steady state can be computed quickly. Thus, the efficiency of a pseudo-time NPB solver is directly related to its stability, which critically depends on the nonlinear term of the NPB equation – a hyperbolic sine function that could be exponentially large.

Several time stepping schemes have been considered for solving the time dependent NPB equation. The explicit Euler solution is straightforward, but invokes a severe stability constraint [34]. Implicit time integrations have also been studied [27, 28], for which care has to be exercised in handling the nonlinear term. In [27], a linearization technique based on the first order Taylor expansion is proposed so that a linear system is formed at each step of the implicit Euler integration. This linearization essentially evaluates the nonlinear term at the previous time instant. Similarly, by treating the nonlinear term explicitly, a modified alternating direction implicit (ADI) method has been introduced in [28]. Since the Thomas algorithm [21] can be employed to solve the tridiagonal finite difference systems in this time splitting method, the efficiency is greatly improved. However, a very large time increment is still prohibited in these methods, because these implicit schemes are of semi-implicit nature.

More recently, we have successfully developed two fully-implicit ADI schemes [11, 35] for solving the time dependent NPB equation. The success lies in an analytical integration of the nonlinear term, and the use of a time splitting framework. This completely suppresses the nonlinear instability, so that these fully-implicit ADI