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Stabilized finite element methods to simulate the conductances of ion channels

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ABSTRACT

We have previously developed a finite element simulator, ichannel, to simulate ion transport through three-dimensional ion channel systems via solving the Poisson–Nernst–Planck equations (PNP) and Size-modified Poisson–Nernst–Planck equations (SMPNP), and succeeded in simulating some ion channel systems. However, the iterative solution between the coupled Poisson equation and the Nernst–Planck equations has difficulty converging for some large systems. One reason we found is that the NP equations are advection-dominated diffusion equations, which causes troubles in the usual FE solution. The stabilized schemes have been applied to compute fluids flow in various research fields. However, they have not been studied in the simulation of ion transport through three-dimensional models based on experimentally determined ion channel structures. In this paper, two stabilized techniques, the SUPG and the Pseudo Residual-Free Bubble function (PRFB) are introduced to enhance the numerical robustness and convergence performance of the finite element algorithm in ichannel. The conductances of the voltage dependent anion channel (VDAC) and the anthrax toxin protective antigen pore (PA) are simulated to validate the stabilization techniques. Those two stabilized schemes give reasonable results for the two proteins, with decent agreement with both experimental data and Brownian dynamics (BD) simulations. For a variety of numerical tests, it is found that the simulator effectively avoids previous numerical instability after introducing the stabilization methods. Comparison based on our test data set between the two stabilized schemes indicates both SUPG and PRFB have similar performance (the latter is slightly more accurate and stable), while SUPG is relatively more convenient to implement.

1. Introduction

Ion channels are essential for the proper function of cells and organisms [1]. Theoretical treatments of ion transport through channel proteins may be broadly classified as kinetic models, electrodiffusion models, and statistical mechanics based discrete model. The most commonly used theoretical techniques in the field are stochastic models, molecular dynamics (MD) [2] and Brownian dynamics (BD) [3–5]. Classical MD utilizes empirical interaction potentials or force fields calibrated by macroscopic data to describe molecular motions and is able to handle an entire ion channel, including ions, counterions, solvent, lipids and proteins. Unfortunately, there are two issues for commonly used MD methods: one issue is to develop appropriate force fields for the ionic mixtures and concentrated solutions in and near channels; the other issue is that, with MD, it is computationally costly and, in some situations, infeasible to reach the time scale of ion permeation across most channel membranes and to determine ion conductance. Compared to Brownian dynamics (BD) and molecular dynamics (MD), the continuum models, usually using a coarse approximation of continuum dielectric media and a static representation of proteins, have advantages of reducing computational cost and the ease of applying certain boundary conditions. A widely used electrodiffusion model is based on the Poisson–Nernst–Planck equations [6,7], in which ions are not treated as microscopic discrete entities but as continuous charge densities. Therefore, the PNP theory describes both the solvent and ions as continuous distributions. Consequently, there are limitations associated with the PNP model. It is well-known that the PNP theory neglects the finite volume effect of ion particles. Moreover, non-electrostatic interactions between ions are not accounted in the PNP model. PNP theory has previously been applied

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to the study of ion transport in electrochemical liquid junction systems [8] and electron transport in semiconductor devices [9], as well as ion permeation through biological membrane channels [10–12]. A number of numerical algorithms, including finite difference [13–16], finite element [17–19,12,20], spectral element [21] and finite volume methods [22], have been utilized in the past two decades for solving the PNP equations. Although the finite difference (FD) method is straightforward to implement, applying this method to systems that have curved boundaries and complicated geometries is challenging. If the surface and volume mesh of proteins are available, the finite element method has the advantage of naturally handling complex geometries, such as the molecular surfaces of DNA molecules and ion channels. Moreover, the finite element method has a solid mathematical foundation, and there are numerous user-friendly and mature FE software packages available for usage. We recently published one of the first works using FEM to solve the 3D PNP equations for ion channel systems [12]. However, there are still numerical challenges for solving PNP equations for simulating ion transport through large ion channel systems. In [12], we found some existing difficulties to simulate the biggest ion channel listed in the article [23]. Our recent analysis and studies indicate that if there is a strong electrostatic potential (which usually occurs in biomolecular systems), the NP equations have a large drift term (advection-dominated), which may result in numerical divergence with the standard finite element method.

In this paper, stabilized finite element methods are introduced to enhance the robustness of the solver. Stabilized finite element methods are formed by adding variational terms into the standard Galerkin method, which are mesh-dependent, consistent and numerically stabilizing. The Streamline-Upwind/Petrov–Galerkin (SUPG) method, introduced by Brooks and Hughes for advection–diffusion equations and incompressible Navier–Stokes equations [24], can be considered as the first successful stabilization technique to prevent oscillations in advection-dominated problems in the FEM. The main steps are as follows: (1) introduce artificial diffusion in streamline direction only, (2) interpret this as a modification of the test function of the advection terms, (3) enforce consistency so that this modified test function is applied to all terms of the weak form. The SUPG method has been applied to various other problems, e.g., coupled multidimensional advective–diffusive systems [25], first-order linear hyperbolic systems [26] or first-order hyperbolic systems of conservation laws [27]. Because of its structural simplicity, generality and the quality of numerical solutions, the SUPG method has attracted considerable attention over the past two decades and many theoretical and computational results have been published. The major part of the theoretical analysis of the SUPG has been done by Johnson [26]. Motivated from mathematical analysis, another type of stabilization scheme, the Galerkin/Least-Squares (GLS) method, has been established. The GLS method is similar to the SUPG method in certain aspects. For linear interpolation functions, the two become identical. In the GLS method, least-squares forms of the residuals are added to the Galerkin method, enhancing stability of the Galerkin method without giving up consistency or degrading accuracy [28].

Another approach, the Residual-Free Bubbles (RFB) method [29–32], which is based on enriching the finite element space, has been recently introduced to solve the advection-dominated elliptic problems. The bubble functions are defined to be as rich as possible within an element. In other words, these functions are assumed to satisfy strongly the PDE in the interior of the element, up to the contribution of the piecewise polynomial functions. In practice, unless in very special situations (one-dimensional problems, limit cases, etc.), they require the actual solution of PDE problems (the bubble problems) in each element. An intuitive description of the RFB method is to find a cheap way to compute approximately the solution of the bubble problem in each element. This provides, as a consequence, an effective way to calculate good approximations for the optimal values of the stabilization parameters. The Pseudo Residual-Free Bubble (PRFB) method aims to get sub-grid nodes to approximate bubble functions cheaply using piecewise linear functions. The PRFB method also fits into the general stabilization method framework as the SUPG method, but differs in the stabilizing parameters and the operators on unknown variables and testing functions. For the stabilizing parameters of the PRFB method we refer to recent studies [32–36] which are restricted in one-dimensional and two-dimensional cases. Since our numerical experiments are based on a 3D ion channel, we have done derivations on the stabilizing parameters under specific choices of subgrid.

The SUPG, GLS and PRFB stabilizations are most frequently applied to fluid problems, such as Stokes and incompressible Navier–Stokes equations [37–40,32]. The SUPG scheme was used to simulate ion flow through a nanopore [41], in which, a "Fast SUPG" scheme was presented for SMPNP equations because the standard SUPG is expensive to evaluate for the SMPNP equations. In this work, we will try to study and implement two stabilized finite element algorithms for solving the 3D PNP/SMPNP equations for models based on experimentally determined ion channel structures, which, to our knowledge, have not been applied in computational biology.

In this paper, we describe a robust parallel FEM solver for both PNP and SMPNP equations for the simulation of ion transport through large ion channel systems, which can handle irregular geometries and complex boundary conditions. We found that the SUPG and PRFB schemes have good performance for solving PNP and SMPNP equations, even if there exists strong electrostatic potential around the molecule.

This paper is organized as follows. The PNP model and the stabilized FE schemes are introduced in the section Numerical Methods. First, we briefly review the 3D ion channel model and the PNP equations. Then, we present the robust stabilized finite element algorithms for solving the coupled nonlinear discretized equations. In the section Numerical experiments, we present some numerical results and assess the performance of our ion channel simulator in ion transport simulations. The solver is applied to VDAC and PA ion channel, and the simulation results are compared with our previous results [12]. The paper ends with the section Summary.

2. Numerical methods

2.1. The PNP and SMPNP equations

The PNP model combines the Nernst–Planck theory describing electrodiffusion of ions in the transmembrane channel with the Poisson theory describing the electrostatic potential whose gradient serves as a driving force of the ion motion. Consider an open domain $\Omega \in \mathbb{R}^3$, $\overline{\Omega} = \overline{\Omega}_m \cup \overline{\Omega}_s$, where Ω_m represents the protein and membrane region and Ω_s represents the solvent reservoirs and the channel region. The PNP equations couple the Nernst–Planck equations

$$\frac{\partial c_i}{\partial t} = \nabla \cdot D_i(\nabla c_i + \beta q_i c_i \nabla \phi), \quad x \in \Omega_s,\ 1 \le i \le N, \tag{1}$$

and the electrostatic Poisson equation:

$$-\nabla \cdot (\epsilon \nabla \phi) = \lambda \sum_i q_i c_i + \rho^f, \quad x \in \Omega, \tag{2}$$

where $c_i(x, t)$ is the concentration of the ith ion species carrying charge q_i. D_i is the spatial-dependent diffusion coefficient, and ϕ is the electrostatic potential. N is the number of diffusive ion species in the solution that are considered in the system. The constant $\beta =$