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A new numerical method for nonlocal electrostatics in biomolecular simulations

S. Weggler [a,*], V. Rutka [b], A. Hildebrandt [a]

[a] Centrum for Bioinformatics, 66123 Saarbrücken, Germany
[b] Department of Mathematics and Physics, Universität Hannover, 30167 Hannover, Germany

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ABSTRACT

The electrostatic behavior of biomolecules solved in water can be described by an elliptic system of partial differential equations for the potential. In previous studies, this system has been solved by the Boundary Element Method (BEM).

In this paper, we apply the Explicit Jump Immersed Interface Method (EJIIM) as an alternative method to the BEM. Such a finite difference approach allows for a completely automatized software for analyzing biomolecules in their natural surrounding.

The new method shows excellent agreement with the BEM results and has good convergence properties and runtimes. In addition, in contrast to the BEM, where the fundamental solutions of operators are necessary, the EJIIM approach can be easily extended to more complex, especially nonlinear models.

1. Introduction

Protein–protein, protein–DNA, and protein–ligand interactions are fundamental to many processes in molecular biology. The latter is the basis for drug development and therefore, it is one of the most important, but also one of the most expensive, fields of research of our time. To reduce the costs as well as the time needed for testing novel drug candidates, effort is made to understand the basic functionalities of molecular interactions. Beside others, the electrostatic interaction energy of molecules is a crucial contribution to the total energy. Moreover, it is important to understand these interactions in the natural solvents of the biomolecules. Here, the basic question is: how does the solvent with its response to the biomolecule's charges influence the electric field and therefore the interaction of the biomolecules between each other?

By molecular dynamic simulations, solvent effects can be studied well, since the solvent molecules can be taken into account explicitly (see [27,48,41]). Another, less time consuming, approach is to develop a macroscopic model, indirectly incorporating the reaction of different media by the so called polarization field, $\boldsymbol{P}$:

$$\nabla \times \boldsymbol{E}(\boldsymbol{r}) = 0, \quad \boldsymbol{r} \in \mathcal{R}, \tag{1a}$$

$$\varepsilon_0 \nabla \boldsymbol{E}(\boldsymbol{r}) = \rho - \nabla \boldsymbol{P}(\boldsymbol{r}), \quad \boldsymbol{r} \in \mathcal{R}, \tag{1b}$$

where ε_0 is the dielectric constant of vacuum, see [16]. To account for the reaction of the medium, the *dielectric operator* ε is introduced. This operator acts on the electric field $\boldsymbol{E}$ as a filter, resulting in a *dielectric field* $\boldsymbol{D}$ caused by the external charges ρ only. Then, (1b) in a region $\mathcal{R}$ with dielectric response ε reads

* Corresponding author.
E-mail addresses: sophie@bioinf.uni-sb.de (S. Weggler), rutka@maphy.uni-hannover.de (V. Rutka), anhi@bioinf.uni-sb.de (A. Hildebrandt).

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$$\nabla \boldsymbol{D}(\boldsymbol{r}) = \rho, \quad \boldsymbol{r} \in \mathcal{R}, \tag{2a}$$

$$\boldsymbol{D}(\boldsymbol{r}) = \varepsilon_0 \boldsymbol{E}(\boldsymbol{r}) + \boldsymbol{P}(\boldsymbol{r}) := \varepsilon_0 \varepsilon(\boldsymbol{E}(\boldsymbol{r})), \quad \boldsymbol{r} \in \mathcal{R}. \tag{2b}$$

Please note that in order to solve the Maxwell equations suitable boundary conditions are required. The simplest linear operator usually taken to measure the dielectric response is a multiplicative factor

$$\boldsymbol{D}(\boldsymbol{r}) = \varepsilon_0 \varepsilon(\boldsymbol{r}) \boldsymbol{E}(\boldsymbol{r}), \quad \boldsymbol{r} \in \mathcal{R}. \tag{3}$$

In the following, this ansatz is called the *local* theory. Eq. (1a) can be directly fulfilled by a gradient ansatz, $\boldsymbol{E} = -\nabla\phi$, where the scalar field ϕ is the so called electrostatic potential.

Water is the main solvent for biomolecules and thus the solvent we will focus on. However, the local ansatz given in (3) does not suffice to describe this complex, dipolar fluid. One aspect neglected in (3) are nonlinearities in the dielectric response, which can easily become substantial, see [2,18,31]. A second effect neglected in (3) is the fact that, apart from the dipole-dipole correlations, the water molecules build up a network formed by their hydrogen bonds, i.e., the solvent molecules are trying to align with the neighbouring molecules as well as with the external charges.

In general, it is often argued that for proteins, the nonlinear effect should be comparatively small in magnitude, since the charge distribution usually consists of partial charges and is smeared out considerably. Thus we assume that a linear response of the medium is valid. In the following, we focus on the correlations of the water molecules by a linear operator ε: in [8], Dogonadze et al. denoted such a linear dielectric operator ε, whose reaction to the medium at position $\boldsymbol{r} \in \mathbb{R}^3$ depends *non-locally* on every other position $\boldsymbol{r}'$:

$$\boldsymbol{D}(\boldsymbol{r}) = \varepsilon_0 \int_{\mathbb{R}^3} \varepsilon(\boldsymbol{r}, \boldsymbol{r}') \boldsymbol{E}(\boldsymbol{r}') d\boldsymbol{r}'. \tag{4}$$

A well-founded model of the nonlocal dielectric operator is motivated in [8]. It reads

$$\varepsilon(\boldsymbol{r}, \boldsymbol{r}') = \varepsilon_\infty \delta(\boldsymbol{r} - \boldsymbol{r}') + \gamma^2 \frac{1}{4\pi} \frac{e^{-|\boldsymbol{r}-\boldsymbol{r}'|\kappa^2}}{|\boldsymbol{r} - \boldsymbol{r}'|}, \tag{5}$$

where $\gamma^2 = (\varepsilon_\Sigma - \varepsilon_\infty)\kappa^2 > 0$ and δ is the Dirac delta function.

In (5), several parameters are introduced to describe the nonlocal effect: the dimensionless parameter ε_∞ defines the dielectric response in the limit of increasing wavenumbers measuring the variations of the electric field, see [38,12]. The second material parameter is κ, where $1/\kappa$ defines the length scale at which solvent molecules interact with each other by their hydrogen bonds. The local dielectric model – a constant response of strength ε_Σ – is recovered in the limiting process $\kappa \to \infty$. More details on the validity can be found in [13].

In previous studies, first steps have been taken to model nonlocal electrostatics of biomolecules in water to get an idea of the relevance of this complex solvent for the functionality of biomolecules [38,40,7]. The resulting integro-differential equations can be solved [9], but they require extremely high computational resources, making an extensive research difficult.

Within certain approximations, Hildebrandt et al. have been able to turn the set of equations into a set of differential equations [14]. These approximations especially include a potential formulation of the dielectric field. We introduce the scalar dielectric potential field ψ and assume in the following

$$\boldsymbol{E} = -\nabla\phi \quad \text{and} \quad \boldsymbol{D} = -\nabla\psi.$$

It has already been demonstrated that the nonlocal model equations investigated in this paper successfully describe the solvation scenario of molecules in water [15,13] and they have been solved numerically using the Boundary Element Method (BEM). However, further model extensions (e.g. to include nonlinearities or to use different models for ε), require the availability of a method which is easily extendable and widely applicable especially for nonlinear equations.

A possibility which additionally acquires highly accurate results is offered by the Explicit Jump Immersed Interface Method (EJIIM) together with suitable conditions along the artificial exterior boundary [45,21,23]. In this work, we present the EJIIM for the nonlocal model equations and compare it with the BEM in terms of accuracy and performance. In addition, we exemplary apply the EJIIM solver to two biomolecules.

2. Equations for nonlocal electrostatics

We consider a molecule $\mathcal{M}$ to be a set of N spheres at fixed positions $\boldsymbol{r}_i$ with radii R_i, and fixed charges q_i, $i = 1, \ldots, N$ at its centers. The sum over all point charges forms the charge density

$$\rho(\boldsymbol{r}) = \sum_{i=1}^{N} q_i \delta(\boldsymbol{r} - \boldsymbol{r}_i), \quad \boldsymbol{r} \in \mathbb{R}^3. \tag{6}$$

With Ω we denote the domain within the so called solvent excluded surface of $\mathcal{M}$, see Section 4 for a description. With $\Sigma = \mathbb{R}^3 \setminus \bar{\Omega}$ we denote the volume occupied by the solvent. The surface Γ separates the solvent region Σ from Ω.