Finite Element-Boundary Element Methods for Accurate Modeling of Excluded Volume Effects in Dielectric Relaxation Spectroscopy

Stephan C. Kramer\(^1\),\(^2\) and Gert Lube\(^1\)

\(^1\) Institut für Numerische und Angewandte Mathematik der Universität Göttingen, Lotzestraße 16-18, D-37073 Göttingen, (stkramer|lube)@math.uni-goettingen.de
\(^2\) Max-Planck Institut für biophysikalische Chemie, Am Faßberg 11, D-37077 Göttingen, stephan.kramer@mpibpc.mpg.de

Abstract. We apply the finite element-boundary element method (FEM-BEM) to accurately model a curvilinear interior interface in a finite domain. This avoids unphysical singularities at the interface due to a piece-wise linear approximation. The investigation of this type of FEM-BEM coupling arises from the need to simulate the biophysical problem of dielectric relaxation spectroscopy of solvated proteins. Boundary elements are employed to convert the linear Poisson problem due to the intramolecular charges of the protein into a boundary condition at the protein-solvent interface. The electro-diffusion of ions in the solvent is modeled as a coupled set of convection-diffusion equations. The spatial distribution of the ion species induce an electrostatic potential which solves a Poisson problem. The gradient of the potential constitutes the convective flow field. A numerical solution is obtained from discretizing the system by finite elements. The link to experiments is given by computing the stationary ionic current through the system. This requires Robin-type boundary conditions at the electrodes.

1 Introduction

The coupling of finite and boundary element methods, (FEM) and (BEM), is commonly used for simulating interface problems on unbounded domains. Finite elements are applied to bounded “regions of interest” which contain non-linearities, inhomogeneities and other properties which need a well-resolved volume mesh. The BEM part models unboundedness and is applied where the physics is described by a homogeneous partial differential equation (PDE) with constant coefficients. In this work we discuss the situation in which the BEM part is employed to exclude a subdomain from a finite domain in order to accurately model the geometric shape of an interior, curvilinear and smooth interface and to unify the computational domain for the different components of a PDE model.

The investigation of this subclass of FEM-BEM coupling arises from the need to simulate the biophysical problem of dielectric relaxation spectroscopy (DRS) of solvated proteins, in particular ubiquitin, which plays a fundamental role in cell biology. The discovery of ubiquitin-mediated protein degradation won the nobel prize in chemistry in 2004. The physical basis of DRS is the polarizability of non-conducting materials in the presence of an external electric field. Polarization is the material-specific part of the dielectric displacement which is proportional to the electric field. The proportionality is given by the complex dielectric permittivity. In the frequency domain it quantifies the dynamic response of molecular dipoles (contributing at high frequencies) and mobile charge carriers (predominant influence.
at low frequencies) which depend on the molecular details of the sample under study. The DRS technique allows to measure dielectric properties in the range of $10^{-6}$ to $10^{12}$ Hz. For a detailed review see the monograph [1]. The typical experimental setup is a parallel plate capacitor with the dielectric sample in between the plates [1, Chapter 2]. Application of an alternating voltage yields the dielectric loss spectrum, i.e. the conductivity-corrected imaginary part of the complex dielectric permittivity as function of frequency. In case of ubiquitin in aqueous solution this spectrum is dominated by the “γ” peak at about 10 GHz, which represents the reorientation of the dipoles of water molecules in the bulk, and the “β” peak at roughly 10 MHz which accounts for the tumbling motion of the protein molecule while its molecular dipole aligns with the applied electric field [2]. This is sketched in Fig. 1a. Converting the peak positions back to the time domain gives a direct access to the time scales on which the relaxation processes take place. Recent DRS studies on ubiquitin [3] have suggested that the dynamics of conformational sampling, i.e. a protein’s ability to switch between different molecular conformations (indicated by the different positions of the intramolecular charges in Figs. 1b,1c), influence the direct current component of the dielectric loss spectrum and can be observed as the “sub-β” peak. This important discovery provides a direct experimental access to the rates of the intramolecular dynamics, which are mostly inaccessible to nuclear magnetic resonance (NMR) spectroscopy, the most frequently used experimental technique to characterize protein dynamics. For the detailed explanation of many biomolecular processes, e.g. of protein-protein recognition [4], the exact knowledge of the kinetics of conformational sampling is decisive.

In this paper we apply the theory of FEM-BEM methods for infinite domains to the case of using the BEM part to exclude a subdomain from a finite domain in order to develop a deeper understanding of the origin of the “sub-β” peak. We use BEM rather than e.g. level-set methods to accurately resolve the geometric shape of the protein-solvent interface. The second issue is a proper incorporation of a stationary current by means of Robin-type boundary conditions (BCs) which provide the link to a comparison with experimental data. The equations are solved by the geometric multigrid (GMG) method [5] from deal.II [6].

2 Poisson-Nernst-Planck Model

Initial theoretical studies have shown that the “sub-β” peak can be explained by a simple 2-state, ratchet-like stochastic model for the conformational dynamics coupled to a Fokker-Planck model for the mobile ions [3, supplementary material]. Depending on its conformation the ubiquitin molecule may bind a varying number of ions in its dielectric double layer thus influencing the density of mobile ions responsible for the direct current component. Although successful in explaining the essential features of the “sub-β” peak, this stochastic model does neither include spatial inhomogeneities nor BCs.

For the effects at the protein-solvent interface $\Gamma$ we need at least a generic anion and cation species with densities $c_-$ and $c_+$, respectively, with charges of equal strength. To incorporate a stationary current through the DRS cell (Fig. 1), we have to take into account the redox reaction $I^+ + e^- \leftrightarrow N$ for converting a cation $I^+$ into a neutral particle $N$ at the cathode $\Gamma_C$ and the anode $\Gamma_A$. Thus, we have to incorporate the density $c_0$ of the neutral particles. The stochastic description of the ion dynamics is replaced by the Poisson-Nernst-Planck equations

$$\partial_t c_a = -\nabla \cdot j_a, \quad \text{(1a)}$$
$$j_a = -(\nabla c_a + ac_a \nabla \Phi) \quad \text{(1b)}$$
$$-\nabla \cdot (\epsilon_r(r) \nabla \Phi) = -(c_+ - c_-) \chi_{\Omega_S} + \rho_f \quad \text{(1c)}$$
Fig. 1: (a) Dielectric loss spectrum of ubiquitin. (b,c) Charge configurations in protein (domain $\Omega_p$) in the DRS cell $\Omega = \Omega_S \cup \Omega_p$. Details see text.

for non-dimensional ion densities $c_a : \Omega_S \to \mathbb{R}$, $a \in \{\pm, 0, -\}$, electro-diffusive fluxes $j_a : \Omega_S \to \mathbb{R}^3$ and the electrostatic potential $\Phi : \Omega \to \mathbb{R}$. The charge density on the right-hand side of Eq. (1c) comprises the mobile ions in the subdomain of the solvent $\Omega_S$, indicated by its characteristic function $\chi_{\Omega_S}$, and the intramolecular charge distribution $\rho_f$ which depends on the conformation, indicated by the index $f$. In our simulations the protein is a dipole with two point charges immersed in a spherical, dielectric domain $\Omega_p = \Omega \setminus \Omega_S$. Hence, instead of striving for an accurate sub-cell resolution of the dielectric interface $\Gamma$ we rather convert the interior constant-coefficient-Poisson equation into a boundary integral equation (BIE) on $\Gamma$. The Johnson-Nédélec coupling [11] needs the normal component of the electric field w.r.t. to the outer normal $\mathbf{n}_p$ on $\Gamma$.
of $\Omega_p$ as independent variable $t^p := -\partial_x \Phi$. From potential theory follows that for $C^1$-smooth, closed surfaces $\Gamma$ the intramolecular contribution $\Phi_p$ to the potential at $x \in \Gamma$ fulfills
\[
\frac{1}{2} \Phi(x) + \int_{\Gamma} \left[ \Phi(x') \frac{\partial G_s}{\partial n_p}(x') - G_s(x') \frac{\partial \Phi}{\partial n_p}(x') \right] d\Gamma(x') = \frac{1}{\varepsilon_p} \int_{\Omega_p} G_s(x') \rho_f(x').
\]
Here, $G_s(y) := 1/(4\pi|x-y|)$ is the Green’s function of the Laplace equation. The right-hand side defines the Newton potential $\Phi^C$. We define the single layer boundary integral operator \textbf{(BIO)} $V : H^{-1/2}(\Gamma) \to H^{1/2}(\Gamma)$ and the double layer BIO $K : H^{1/2}(\Gamma) \to H^{1/2}(\Gamma)$ as usual [12, Secs. 6.2 and 6.4], but instead of $n_p$ we use the outward normal $n = -n_p$ relative to $\Omega_3$
\[
(V\Phi^p)(x) := \int_{\Gamma} G_s(x') \rho_f(x') d\Gamma(x'), \quad (K\Phi^p)(x) := \int_{\Gamma} \frac{\partial G_s}{\partial n(x')}(x') \Phi(x') d\Gamma(x').
\]
From Eq. (4) follows $\varepsilon_5 \partial_x \Phi|_\Gamma = -\varepsilon_p t^p$ and we get
\[
\left( \frac{1}{2} I - K \right) \Phi + \varepsilon_5 V t^p = \Phi^C.
\]
This is the basis for the FEM-BEM method for the potential, such that the computational domain for the potential $\Phi$ is reduced to $\Omega_3 = \Omega \setminus \Omega_p$. The distribution of the other species is governed by convection-diffusion equations with either Neumann or Robin but no Dirichlet BCs. The link to experiments is given by the direct current $I_{dc}$ created by a potential difference $\eta := \Phi_C - \Phi_A$. Due to the redox reaction at the electrodes the current is $I_{dc} = \int_{\Gamma} n \cdot \mathbf{j} d\Gamma_C = K_R \int_{\Gamma} \mathbf{c} \cdot d\Gamma_C$. The conformational sampling introduces a time-dependence on $I_{dc}$. This is modeled by a two-state telegraph process. This simplifies the time-dependence to a switching between two stationary states and removes the explicit time dependence in Eq. (1a).

3 Weak Formulation and Discretization

We do not solve Eq. (1) in its mixed form, but reduce it to a set of convection-diffusion equations by inserting Eq. (1b) into Eq. (1a), eliminating the currents as independent unknowns.

Let $\langle \cdot, \cdot \rangle_D$ be the $L^2$ inner product on a domain $D$ and $\| \cdot \|_X$ the norm of a function space $X$. For $D \subseteq \Omega_3$ we drop the index. The weak formulation of Eq. (1) is derived as usual by multiplying with test functions, integrating by parts and inserting all flux BCs. The terms in $\partial_x$ are modeled by a two-state telegraph process. This simplifies the time-dependence to a switching between two stationary states and removes the explicit time dependence in Eq. (1a). Hence, to validate the hypothesis about the origin of the ”sub-$\beta$” peak we merely have to compute two different values for $I_{dc}$ from the time-independent version of Eq. (1).
After linearizing $a_l^h(\cdot, \cdot)$ w.r.t. $c_+$ and $c_-$, the associated matrices are $A_D$, $A_U$ and $A_L$, respectively. The left-hand side of the weak form of Eq. (5), with associated matrices $B_K$ and $B_V$, is a sum of the two bilinear forms

\[
B_K(\psi, \Phi) := \left( \psi, \left( \frac{1}{2} I - K \right) \Phi \right)_\Gamma : H^{1/2}(\Gamma) \times H^{1/2}(\Gamma) \to \mathbb{R},
\]

\[
B_V(\psi, \mathbf{P}) := \left( \frac{\partial}{\partial n} \left( \psi, \mathbf{V} \mathbf{P} \right) \right)_\Gamma : H^{-1/2}(\Gamma) \times H^{1/2}(\Gamma) \to \mathbb{R}.
\]

We use conformal discretizations $X_h \subset X$ and $Y_h \subset Y$ by globally continuous Lagrange elements for which we use deal. II’s $\text{FEE}_Q<\text{dim}>$ class. In practice, the trial functions in $Y_h$ are given by the traces of those in $X_h$ because we treat the normal derivative as independent variable. This is due to the way finite elements are implemented in deal. II. The same holds for the test functions $\psi$ in the dual space $Y_h^* \subset H^{1/2}(\Gamma)$. Then, the discretized variational problem is:

\[
\forall \psi_h \in X_h : \quad a(u_h, \psi_h) + \left( w, \varepsilon_p \mathbf{P} \right)_\Gamma = 0,
\]

\[
\forall \psi_h \in Y_h^* : \quad B_K(\psi_h, \Phi_h) + B_V(\psi_h, \mathbf{P}_h) = \left( \psi_h, \Phi_h \right)_\Gamma.
\]

When solving the discretized problem we encounter several numerical problems. Only the potential $\Phi$ is unambiguous since it is subject to Dirichlet BCs on some part of the boundary (at the electrodes $\Gamma_A$ and $\Gamma_C$). The equation for the density of the neutral particles $c_0$ effectively is a pure Neumann Laplace problem. Its average merely enters via the boundary terms in Eq. (3) for the cations $c_+$. Due to the stationary state the particle numbers are conserved $\int_{\Omega} c_0 \, d\Omega = \text{const},$ $a \in \{\pm, 0, -\}$. The conservation of the average densities is enforced by introducing a pseudo-time dependence, i.e. adding a scaled identity to the Laplace operator. Since we are looking for stationary states this corresponds to “adding a 0”, i.e. $-\nabla^2 u = f$ becomes $|\delta I - \nabla^2| u^{n+1} = f + \delta u^n$ after time discretization. The small parameter $\delta$ plays the role of an inverse time step and $I$ is the identity operator.

We solve by interleaving successive mesh refinement, pseudo-time stepping and reassembly of the nonlinear terms. This introduces a sequence of finite-dimensional subspaces $X_h \subset X$, parametrized by the cell diameter $h$. Then, on a given mesh, i.e. in FE space $V_h^k \subset V$, $V_h^l \subset V_h^{l+1}$, we run a few steps in pseudo-time (while $\|u^{n+1} - u^n\|_{C_1} \geq \text{Tol}$). In each time step we reassemble the drift terms in $A_U$ after solving the linear algebraic problem by deal. II’s GMRES solver with left-preconditioning.

For the numerical solution of Eq. (6) we have considerably extended the GMG example step 16 of deal. II, v7.2.0. When computing the matrices $B_K$, $B_V$ from the bilinear forms $b_K(\cdot, \cdot)$ and $b_V(\cdot, \cdot)$ the double integration is avoided by using the support points of the test functions for collocation. With $\mathbf{P}_h^l = \sum \mathbf{P}_h^l \phi_i \in Y_h$, e.g. the entries of the matrix representing the single layer BIO are formally given by $B_{V,ij} = (\psi_i, \mathbf{V} \phi_j)$. Let $x_i$ be the support point of DoF $i$, then collocation at $x_i$ can be interpreted as $B_{V,ij} = (\delta(x - x_i), \mathbf{V} \phi_j)$, i.e. $B_{V,ij}$ is computed as

\[
B_{V,ij} = \int_{\partial \Omega_0} G(x, x') \phi_j(x') d\Gamma(x').
\]

To minimize the costs of matrix assembly we recognize that Laplacians, bulk and boundary mass matrices are the recurring themes in the algebraic system. Thus, we compute each of them only once. The definitions of $X^\ast$, $X^\Phi$ require the assembly of two different Laplacians and hence to setup two GMG preconditioners $P^\phi_{MG}$ and $P^\phi_{MG}$. Cell contributions are needed only once and get reused when building the global matrices which differ only in the BCs. In total, the costs of assembling the matrices by numerical quadrature are roughly
equal to two Poisson equations with variable coefficients as the data for the linear Laplacians can be reused to a great extent for the drift terms. The matrix $A$ for the linearized DRS problem, Eq. (6), is stored as dealii::BlockMatrixArray and the preconditioner $P_A$ as dealii::BlockTrianglePecondition which acts like a block Gauss-Seidel method. Its diagonal blocks are $(P_{MG}^c, P_{MG}^r, P_{MG}^p, P_{MG}^V)$, where $P_V$ preconditions $B_V$ and is the identity matrix. The upper off-diagonal blocks of $P_A$ are void. The lower off-diagonal blocks are those already present in $A$, i.e. $A_L$ and $B_X$.

4 Results

In our tests we model the boundary piece-wise by polynomials of order $m = 2$, also explicitly stated in Figs. 2 and 3. This numerical boundary is not $C^1$-smooth. Yet, according to our tests, it approximates the curved surface of a sphere sufficiently well such that we do not have to consider the solid angle subtended by the surface elements at a vertex of the mesh of $\Gamma$. This is dictated by deal.II. Lacking the feature to assign different mappings to different subboundaries. Because of the outer surface of the DRS cell we cannot use the $C^1$-mapping provided by dealII. Throughout we use either linear ($p = 1$) or quadratic ($p = 2$) FEM. We are particularly interested in the convergence behavior of our method for the pure Neumann problem and for the FEM-BEM coupling. We define two simplified test problems with solutions

$$
\Phi_{SP} := 0.1(2x+y+z) + 0.01xyz,
$$

$$
\Phi_D := \frac{1}{4\pi|x-x_+|} - \frac{1}{4\pi|x-x_-|},
$$

with $x_\pm = (0.0, \pm 0.5)$ in a sphere of radius 1. As $\Phi_{ref}$ is either $\Phi_{SP}$ or $\Phi_{DSP}$, we use $\Phi = \Phi_D + \Phi_{SP}$. Note that $\Phi_{SP}$ is harmonic. The FEM-BEM convergence is assessed on the simplified problem: find $(\Phi, t^p) \in X^\Phi \times Y$ s.t. $\forall (\nu, \psi) \in X^\Phi \times Y$:

$$
(\nabla \nu, \nabla \Phi) + (\nu, \varepsilon \psi t^p)_{\Gamma} = 0,
$$

$$
b_K(\psi_h, \Phi_h) + b_V(\psi_h, t_h^p) = (\nu, \psi^C)_{\Gamma},
$$

with $\Phi_{|\Gamma \cup \Omega_b \cup \Omega_c} = \Phi_{ref}$. The test for pure Neumann BCs is: find $\Phi \in H^1(\Omega_b)$ s.t.

$$
(\nabla \nu, \nabla \Phi) = (\nu, \partial_n \Phi_{ref}) \quad \forall \nu \in H^1(\Omega_b).
$$

To measure the error we use the standard $L^2(\Omega_b)$- and $H^1(\Omega_b)$-norm for the FEM part. For the BEM part we measure the $L^2$ error of the trace of $\Phi$ on $\Gamma$ by $\|\Phi_{ref} - \Phi_h\|_{L^2(\Gamma)}$, and the $L^2$ error in the trace of $\partial_n \Phi \equiv -t^p$ on $\Gamma$ which we sloppily denote as $H^1(\Gamma)$ semi-norm $\|\Phi_{ref} - \Phi_h\|_{H^1(\Gamma)} := \|\Phi_{ref}-\Phi_h\|_{L^2(\Gamma)}^2 + \|t^p\|_{L^2(\Gamma)}^2$. In case of Eq. (11) and $\Phi_{ref} = \Phi_{DSP}$ convergence is as expected. For FEM of order $p$ we get $\|u-u_h\|_{L^2(\Omega_b)} = O(h^{p+1})$ and $\|u-u_h\|_{H^1(\Omega_b)} = O(h^p)$ independent of the order of the boundary approximation $m$, cf. Fig. 2a. Figure 2b shows that for $\Phi_{ref} = \Phi_{DSP}$ we roughly lose half an order which we attribute to the right-hand side of the BEM part containing the $\delta$-distributions for the point charges. Figure 3a shows the convergence of the FEM part of Eq. (10). Surprisingly, for Lagrange finite elements of order $p = 2$ the $L^2(\Omega_b)$ and $H^1(\Omega_b)$ error have the same asymptotic behavior. The error in the BEM part, Fig. 3b, is as expected for linear elements ($p = 1$). Due to the collocation the decay of the error in $t^p$ does not improve. However, the error of $\Phi_{|\Gamma}$ partly profits from higher order elements. Figure 4 shows that our simulations are able to resolve local inhomogeneities of the cation density in the vicinity of the protein surface. It also shows that the current-carrying species (cations and neutral particles) are distributed opposite to each other.
FEM-BEM for Modeling of Excluded Volume Effects in DRS

5 Conclusion

We have derived a mathematical model for the detailed simulation of the electro-diffusive processes in dielectric relaxation spectroscopy of proteins in solution including boundary effects inaccessible in previously derived stochastic models. The key feature is the modeling of the protein-solvent interface as excluded volume with a smooth surface by taking into account its electrostatic properties by means of a boundary integral equation. For the efficient solution of the resulting FEM-BEM model we have extended the geometric multigrid example of the deal.II library (step-16) to vector-valued problems and higher order elements. Unlike the strategy proposed in deal.II's step-34 for boundary elements we have to use the traces of the finite elements as boundary elements. Most of the equations in the DRS model are pure Neumann problems and subject to a conservation of particle numbers. To assure their unique solvability we implemented an interleaved pseudo-time stepping / mesh refinement strategy which avoids the saddle-point problems arising from Lagrange multipliers. The convergence is as expected. The convergence of the FEM-BEM method depends on the particular test case.
Fig. 4: Distribution of cations and neutral particles in the DRS cell.

but is consistent with the literature. Applied to the full DRS problem our numerical results indicate the validity of the proposed explanation of the origin of the “sub-β” peak.

References