Adaptive Goal-Oriented Solver for the Linearized Poisson-Boltzmann Equation

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Abstract

An adaptive finite element solver for the numerical calculation of the electrostatic coupling between molecules is developed and verified. The development is based on a derivation of a goal-oriented a posteriori error estimates for the electrostatic coupling. These estimates involve the consideration of the primal and adjoint problems for the electrostatic potential of the system. The accuracy of this solver is evaluated by numerical experiments on a series of problems with analytically known solutions. In addition, the solver is used to calculate electrostatic couplings between two chromophores, linked to polyproline helices of different lengths. All the numerical experiments are repeated by using the well known finite difference solvers MEAD and APBS, revealing the advantages of the present finite element solver.

1 INTRODUCTION

Almost all chemical processes in living organisms take place in aqueous solution. The solvation properties of the aqueous environment significantly contribute to the reaction mechanisms and kinetics, and influence the function of biomolecules in general. Dehydrated enzymes are reactivated when they are covered by at least one layer of water molecules and “dynamical” transitions of proteins are triggered by their strong coupling with the hydration water.^{1,2} The presence of water contributes also to protein folding by stabilizing secondary structure elements and their association.³ Mobility and rotational degrees of freedom of the water molecules are responsible for a strong shielding of electrostatic interactions between biomolecules that can influence protein-ligand binding, DNA-protein recognition, etc.

Contemporary models of solvation account for the aqueous environment either explicitly, by inclusion of water molecules, or implicitly, by approximating the mean force exerted by the solvent on a biomolecule. The latter, so called continuum solvation models, represent a solvated molecule at an atomic level of detail inside a molecule-shaped cavity. The electrostatic properties of the molecule are modelled by partial charges placed at the atomic positions, embedded

in a low dielectric region. The degrees of freedom of water molecules in surrounding aqueous solvent may be approximated by that of an isotropic dielectric continuum with high dielectric permittivity.

The dielectric properties of such a model are described by the Poisson-Boltzmann equation (PBE), which also accounts for the presence of mobile ions in the solvent. They are introduced as a continuous Boltzmann-distributed charge density. Apart from the approximations mentioned above, the PBE assumes a linear response of the dielectric medium and neglects correlations between ions. Despite its relative simplicity, the PBE provides an effective way to study electrostatic effects in biomolecular systems and is widely used in different applications:⁴ biomolecular recognition, kinetics of molecular association, enzyme catalysis, etc. However, analytical solutions of the PBE are available only for a limited number of simple systems. For complex biomolecular surfaces and arbitrary distribution of charges numerical methods have to be employed to solve the PBE. From a mathematical point of view the PBE represents a second-order semilinear elliptic partial differential equation with a measure-valued right hand side. The PBE imposes several challenges impacting the accuracy of numerical algorithms. These challenges include discontinuous dielectric coefficients representing interfaces (for example, water-biomolecule), singularities as a result of the representation of the partial charges by delta functions, and the complicated geometry of molecular domains in three spatial dimensions. Overcoming each of these difficulties significantly is the key for an accurate numerical solution.

Most of the common approaches for the numerical solution of the PBE fall in one of the following three categories: finite difference (FD), boundary element (BE) and finite element (FE) methods. The majority of the PBE solvers like DelPhi,⁵ GRASP,⁶ MEAD,⁷ UHBD,⁸ the PBEQ module of CHARMM,⁹ and the PMG solver in the APBS software suite¹⁰ are based on FD methods, utilizing regular 3D lattices, due to the ease of numerical implementation.

Finite difference schemes rely on solving the PBE in a lattice representation. The charges and dielectric permittivity are mapped onto a rectangular grid and a discrete approximation employing difference quotients is applied to

the partial differential equation. As a result a system of linear/nonlinear algebraic equations is build up, which is often solved by iterative methods, e.g., the conjugate gradient method.

To speed up the convergence and reduce the memory requirements, a so-called focusing technique was proposed in Refs. 5 and 11. This procedure involves solving the equation on a coarse grid, covering a large region, followed by a solution on a finer grid on a smaller region, with a boundary condition, interpolated from the values of the coarse grid solution. This approach was further improved in Ref. 12 by implementing it in parallel and then was applied to the electrostatics of microtubules and ribosomes. Due to the noticeably improved performance, focusing schemes are implemented in most of the FD-based solvers for the PBE in which regular cubic lattices are used.

As the underlying grid in regular 3D lattices is not adapted to the molecular surface, accuracy of the approximate solution is lost. The correct assignment of the dielectric constant in points close to the solute-solvent interface is crucial for optimal convergence of FD methods. One way to achieve it is the use of certain averaging procedures. More precisely, for each integer or half-integer grid point the dielectric coefficient ϵ is defined by averaging its values at the neighboring points that depend on which region they belong to.^{11,13} The inverse Debye length $\bar{k}$ is defined in a similar fashion. Due to averaging there is a region around the true interface in which these model parameters vary between their respective values on both sides of the interface. The thickness of this layer depends on the grid spacing h and this is where the discretization error of the FD method is typically much larger than that produced by the FE method, that will be discussed in the end of this section.

Finite difference methods also exhibit difficulties caused by nonsmooth source terms, such as the delta distributions introduced to model fixed point charges. A redistribution of the charges around their closest grid points is necessary in order to minimize the errors occurring in the short-range potential, i.e., the errors close to the charges (see Refs. 11,13 for different approaches to such a redistribution). However, redistribution techniques in general lead to so-called grid artifacts.^{14,15} The latter can be avoided by using Galerkin type FE approximations and combining them with proper splitting techniques for the full potential. By applying such decompositions of the full potential, the delta distributions describing the discrete charge density due to the point charges in the solute are transformed to a more regular distribution, which is interpreted as a certain surface charge density concentrated on the molecular surface. We note that these splitting techniques can also be used in conjunction with FD methods (see, e.g. Refs. 16,17). However, the surface charge density, supported on the interface between the molecular region and the solution region, remains hard to handle with FD methods.

Another disadvantage of the FD method is that the errors, caused by the specific way of handling interfaces and partial charge distribution in the solute, strongly depend on the particular position and orientation of the molecular system relative to the used FD grid. One approach to cope with this problem is to use finer grids, which naturally leads to a larger number of grid points. Another approach is to use a rotational averaging scheme. The idea is to make a number of calculations with a slightly different mutual orientation between the molecular system and the FD grid, and finally take some average (see Refs. 11,17). A third approach that could cope better with curved interfaces and regions where the solution is sharply varying (mainly around the fixed partial charges and across interfaces) is to involve some kind of adaptivity in the FD method in conjunction with splitting techniques for the full potential. Finite difference methods,

based on adaptive Cartesian grids (ACG), have been developed for solving nonlinear equations in domains with curved boundaries.^{18–20} Here, the grid representation is based on quadtrees in two dimensions and octrees in three dimensions. The ACG is recursively adapted by identifying mesh cells, which intersect the molecular surface, and test whether they satisfy one of the following criteria: finest grid-spacing is reached or intersected cell lies more than a prescribed distance from the nearest atomic charge site. The cell, which does not meet either of these criteria is uniformly subdivided into four (in 2D) or eight (in 3D) smaller cells. Using a coarser mesh away from the surface reduces the total number of grid points, which for ACG often is several orders of magnitudes less than that required in a conventional lattice grid. However, the underlying mesh still does not conform to the solute surface and thus the accurate evaluation of the electrostatic potential near the interface remains problematic. This issue is even more pronounced in the presence of non-smooth interfaces which are quite common, e.g. when employing van der Waals’ surfaces. In order to avoid this shortcoming, the technique proposed in Ref. 21 introduces additional mesh points at the Cartesian grid/surface intersection and uses a reconstruction of the electrostatic potential from the solution obtained in the exterior and interior domains. Note that in this approach the continuity of the normal component of the displacement field is not enforced in a strong (pointwise) sense, which is a potential source of error. Moreover, the accuracy typically deteriorates when a charge approaches the surface and the mesh does not adequately resolve the rapid variations of the potential, induced by such a charge. Recently, an FD method based on ACG, was implemented in the finite difference solver CPB, particularly aiming at the approximation of the PBE for complex biomolecular structures.²² This solver also utilizes a splitting technique for the full potential to eliminate the singular behavior at charge sites.

The boundary element method (BEM) is an alternative discretization technique for partial differential equations. It was first adapted to the computation of the electrostatic potential of macromolecules in Ref. 23. Here, the PBE is reformulated into boundary integral equations, living on the boundary of the solute domain, by employing Green’s theorem. Therefore, only the two-dimensional molecular surface needs to be discretized. The resulting boundary integral equations are solved by using collocation, Galerkin, or least squares methods. The first one is the most commonly used by the PBE community since it is the simplest to apply in practice. Further developments of the BEM with the same focus of application can be found in Refs. 24 and 25 and deal mainly with algorithmic improvements. The BE method has some advantages over other numerical methods like the FE and FD methods, which involve volume-domain discretization. Since only the molecular surface is discretized, the number of unknowns is greatly reduced. Moreover, boundary conditions at infinity are exactly treated as opposed to the FE and FD methods. In contrast to the FDM, the jump in the normal component of the electrostatic field across the molecular surface (interface) is explicitly accounted for, which results in a more accurate solution near the solute surface.

At the same time, the BEM also possesses certain disadvantages, mainly related to the requirement of an accurate surface mesh, the efficient evaluation of singular and hyper-singular integrals and numerous other integral operations.²⁶ The conventional BEM requires the evaluation of mutual interactions between all elements. For a problem with N surface elements, the calculation of the potential in all elements then involves $O(N^2)$ interactions to be stored and $O(N^3)$ operations to be performed. Furthermore, the evaluation of each single integral, representing an interaction, is

expensive. Thus, significant efforts have been made in developing fast algorithms for performing this task. Another typical issue with the BE method for the PBE, appearing in the cases when moving ions are present in the solution, is the general practice of leaving out the so called ion exclusion (Stern) layer and thus only using a single surface separating the solute and the solvent.

One of the promising strategies to improve the efficiency of the BE method is to combine it with some versions of the fast multipole method (FMM).^{27,28} Further improvements can be achieved by using an adaptive FMM for accelerating the convolution type matrix-vector multiplications.²⁹ Solvers based on these concepts demonstrate a more efficient use of the memory and improved load-balance between the local- and far-field calculations, resulting in a significant speed up of the computations.

The third approach to the numerical solution of the PBE is the finite-element (FE) method, which approximates the potential by a super-position of a set of basis functions. The FE method is the most successful for elliptic PDE, since it combines geometrical flexibility and satisfactory convergence analysis with the ability to handle nonlinear problems involving interface jump conditions and nonsmooth source terms. Moreover, it enjoys a wide range of efficient iterative solvers for the resulting sparse linear systems. Here the PBE is typically solved on unstructured finite element meshes. The latter in general provide higher geometric flexibility and variable mesh spacing that enables to adapt better the mesh to the shape of the molecule so that no edges or elements intersect its surface. This adaptation allows for inherently more accurate estimates of quantities of interest on the surface, particularly of the electrostatic field. A linear or nonlinear system for the coefficients produced by the weak formulation has to be solved.

One of the first applications of the FE method to continuum electrostatics of biomolecules in solution appeared in Ref. 30. Since then, the popularity of this approach has increased synchronically with the increase of computational power and advancement of FE mesh generation techniques, see, e.g. Refs. 10,31–34. As representatives of the solvers, implementing the FE method for the numerical approximation of the PBE and the linearized PBE (LPBE), we mention APBS¹⁰ (utilizing adaptive mesh refinement based on a residual type error indicator) and mFES,¹⁴ respectively.

However, application of FEM solvers for the PBE and the LPBE to the reliable calculation of the electrostatic interaction between molecules becomes extremely difficult in the absence of appropriate error estimators and adaptive mesh refinement techniques. The two FEM solvers mentioned above face the same issues. More precisely, mFES does not implement error estimation and adaptive mesh refinement techniques, besides the fact that the initial mesh is somehow adapted to the shape and position of the solute¹. On the other hand, APBS utilizes adaptive mesh refinement based on a residual type error indicator. However, in APBS, the error is controlled in the so called energy norm, which is a global (integral) quantity, whereas for the evaluation of the electrostatic coupling between molecules only evaluations of the electrostatic potential at particular points of interest are required. Therefore, adaptive mesh refinement based on energy norm error indicators attempts to enhance the global quality of the solution. This typically yields optimal rates of convergence with respect to this global energy norm, while the improvement in the potential at the points of interest happens at a much slower rate. Thus, an adaptive FE solver which is based on energy norm error indicators is inherently

¹The tetrahedral volume mesh inside the solute has approximately constant edge size related to the mesh size on the solute-solvent interface, whereas the mesh size outside the solute is gradually increasing up to the boundary of the computational domain.

unreliable and ineffective for the computation of electrostatic interaction between molecules.

In the present paper we report an Adaptive Refinement Goal-Oriented Solver³⁵ (ARGOS) for the calculation of the electrostatic interaction between molecules. In order to have a consistent description of the electrostatic interaction, which is symmetric in nature, one needs to consider the linearized PBE with a homogeneous Dirichlet boundary condition as the primal problem governing the electrostatic potential. This is why ARGOS in its present implementation is based on the linearized PBE. The main feature of this solver includes goal oriented a posteriori error control, which allows adaptive refinement of the mesh specifically aiming at the reduction of the error in the electrostatic coupling, herewith significantly improving the accuracy of calculations and computational complexity. We compare the accuracy of computed interaction energies obtained via this new approach with those from FD solvers (MEAD and APBS) both for practically relevant problems and for model problems with known exact solutions.

The structure of the paper is as follows. In METHODS, the theory of a goal oriented error estimator for the electrostatic coupling between molecules and its algorithmic realization are discussed. This is followed by an assessment of the accuracy and efficiency of our new ARGOS for three test cases with analytically known solutions in RESULTS. We proceed with the application of the proposed methods to the computation of the interaction energy between two chromophores, that are attached to a polypeptide.

2 METHODS

2.1 Theoretical background and implementation of the solver

2.1.1 The linearized Poisson-Boltzmann equation

The solution of the Poisson-Boltzmann equation (PBE) gives the electrostatic potential φ in a system of molecules immersed in solvent containing mobile ions. In the special case of only two univalent ion species in the solvent with the same concentration but opposite charges, the PBE is given by

$$-\nabla \cdot (\epsilon \nabla \varphi) + \frac{k_B T}{e_0} \bar{k}^2 \sinh \left(\frac{e_0 \varphi}{k_B T} \right) = 4\pi e_0 \sum_{i=1}^N z_i \delta(x - x_i) \quad (1)$$

where k_B is the Boltzmann constant, T the temperature, e_0 the elementary charge, N the number of charges in the molecule, z_i the valency of the i -th partial charge, and x_i its coordinate in the molecule. The dielectric coefficient ϵ is piecewise constant and defined by

$$\epsilon(x) = \begin{cases} \epsilon_m, & x \in \Omega_m, \\ \epsilon_s, & x \in \Omega_s, \end{cases} \quad (2)$$

where Ω_m is the molecular domain and Ω_s is the solvent domain composed of Ω_{ions} and the ionic exclusion layer (IEL) Ω_{IEL} . The latter is a layer around the molecules which no ions can penetrate and it is defined as the difference between the union of the inflated van der Waals spheres of the atoms by a counterion radius R_{ion} and the molecular region defined by the Connolly surface. For a system of N_{mol} molecules, Ω_m consists of the domains $\Omega_{m_1}, \dots, \Omega_{m_{N_{mol}}}$, where Ω_{m_i} corresponds to the domain of the i -th molecule (see Figure 1).

The coefficient $\bar{k}$ is also piecewise constant and given by

$$\bar{k}^2(x) = \begin{cases} 0, & x \in \Omega_m \cup \Omega_{IEL}, \\ \frac{8\pi N_A e_0^2 I_s}{1000 k_B T}, & x \in \Omega_{ions}, \end{cases} \quad (3)$$

where the ionic strength I_s is defined by

$$I_s = \frac{1}{2} \sum_{i=1}^2 c_i (-1)^2$$

with $c_1 = c_2$, the molar concentration of each ion type and N_A denoting Avogadro's number. Assuming the potential φ to be small ($\varphi \ll \frac{k_B T}{e_0}$), the PBE (1) can be linearized. The resulting equation

$$-\nabla \cdot (\epsilon \nabla \varphi) + \bar{k}^2 \varphi = 4\pi e_0 \sum_{i=1}^N z_i \delta(x - x_i) \quad (4)$$

is referred to as the linearized PBE (LPBE) and will be used in this work. For the special case $I_s = 0$ equation (4) becomes the Poisson equation:

$$-\nabla \cdot (\epsilon \nabla \varphi) = 4\pi e_0 \sum_{i=1}^N z_i \delta(x - x_i). \quad (5)$$

The described problems (1), (4), and (5) include a natural interface Γ between the molecular and the solvent domains due to different dielectric constants (see (2)). At the same time the potential φ and the normal component of the displacement field $\epsilon \nabla \varphi$ must be continuous across the interface, i.e.,

$$[\varphi]_\Gamma = 0, \quad (6)$$

$$[\epsilon \nabla \varphi \cdot n]_\Gamma = 0, \quad (7)$$

where $[\cdot]_\Gamma$ denotes the jump of the enclosed quantity across Γ . Moreover, in order to find a unique solution of (1) and (4), a Dirichlet boundary condition for φ must be imposed. The usual approach in physics prescribes a vanishing potential at infinite distance from the boundary of Ω_m . In practical applications, one works in a bounded computational domain Ω and imposes the boundary condition

$$\varphi = g \quad \text{on } \partial\Omega, \quad (8)$$

where g is usually close to zero and calculated accurately enough by solving a simpler problem, possibly with a known analytical solution.

2.1.2 Integral formulation of the problem

The right-hand side of (4) is a functional, consisting of a linear combination of delta functions, while the left hand side defines a proper function everywhere except at the interface Γ , where ϵ is discontinuous and $\nabla \cdot (\epsilon \nabla \varphi)$ is not well defined. A natural way to interpret (4) is to rewrite it in its integral (weak) formulation, where the left-hand side and the right-hand side are comparable objects with well-defined meaning. To obtain the weak formulation, we multiply both sides of (4) by a function v equal to zero on $\partial\Omega$, also called a test function, and then integrate the equation over the

Figure 1: Schematic representation of the different regions in the presence of moving ions in the solvent. Note that, the ions of the solvent are described in continuum approximation.

domain Ω :

$$\int_{\Omega} \nabla \cdot (\epsilon \nabla \varphi) v dx + \int_{\Omega} \bar{k}^2 \varphi v dx = 4\pi e_0 \sum_{i=1}^N z_i v(x_i). \quad (9)$$

On the left-hand side we apply the divergence theorem for integration by parts and obtain (for details see Ref. 36)

$$\int_{\Omega} \epsilon \nabla \varphi \cdot \nabla v dx + \int_{\Omega} \bar{k}^2 \varphi v dx = 4\pi e_0 \sum_{i=1}^N z_i v(x_i) \quad (10)$$

for all test functions v .

It can be rigorously shown that under certain conditions on the regularity of the interface Γ there exists a unique potential φ that satisfies the integral formulation (10) for any test function v in a certain function space.^{36,37} By directly discretizing (10) one obtains an approximation φ_h of the exact potential φ .

Another widespread approach which benefits both the numerical treatment and analysis of the LPBE (also the PBE) involves splitting the potential φ into G and u , i.e., $\varphi = G + u$ (see, e.g. Refs. 13,17,38,39), where

$$G = \sum_{i=1}^N \frac{z_i e_0}{\epsilon_m |x - x_i|} \quad (11)$$

is the singular Coulomb potential of the point charges in a uniform dielectric medium with $\epsilon = \epsilon_m$ without any molecular cavities and u is the reaction field potential. Thus, one has to find only the reaction field potential u_h instead of the potential φ that has singularities at the positions of the charges. This approach is particularly beneficial when one needs the reaction field potential only or when calculating the solvation energy difference

$$\begin{aligned} \Delta G^{\text{vac} \rightarrow \text{solv}} &= G^{\text{vac}}(\epsilon_{\text{vac}}, \epsilon_m) - G^{\text{solv}}(\epsilon_s, \epsilon_m) \\ &= \frac{1}{2} \sum_{i=1}^N q_i (u_{\text{vac}}(\vec{r}_i) - u_{\text{solv}}(\vec{r}_i)), \end{aligned} \quad (12)$$

where $q_i = z_i e_0$, u_{vac} and u_{solv} are the reaction field potentials for the molecule in vacuum and in solvent, respectively. By separating the singular potential G from the full potential φ one avoids the so-called grid artifacts (see Refs 14,15) that appear when computing $\Delta G^{\text{vac} \rightarrow \text{solv}}$ without performing this splitting technique.

2.1.3 Goal oriented a posteriori error estimates

The adaptive finite element method with a posteriori error estimation is designed for achieving high accuracy of a solution at minimum computational costs. Finding the mesh, providing the desired properties, is a nontrivial task, since the solution is unknown. If one is interested in the global quality of the solution over the whole computational domain, the desired mesh is obtained under the condition of error equidistribution, that is, the discretization errors should be approximately equal on each computational element. The errors are estimated by error indicators that are derived based on a particular a posteriori error estimation technique.

In many applications one is interested not in the solution itself, but rather in a specific quantity that depends linearly on the solution. Thus, the target quantity is expressed in terms of a linear functional, called a goal functional. In this case the error estimations are provided only for the goal quantity. The resulting a posteriori estimates are used in the feedback process for mesh refinement in the computational domains, where the error is high, thus, improving the accuracy of the target quantity.

To outline the method let us consider a general case of a linear differential equation with a solution u (see, e.g. Ref. 40):

$$Aw = f, \quad (13)$$

where A is a linear differential operator and f is a generalized force, exerted by the environment. Problem (13) is called primal. Let $\mathcal{L}(w)$ be a quantity of interest obtained from the solution w by applying a goal functional $\mathcal{L}$ and w_h an approximation of w that depends on a discretization parameter h . For the purpose of this introduction we will assume that all involved functions are smooth. The strategy involves controlling the error

$$\mathcal{L}(e) = \mathcal{L}(w) - \mathcal{L}(w_h) \text{ with } e := w - w_h \quad (14)$$

in terms of the local residuals $\rho_K(w_h)$ computable on each mesh cell K :

$$\rho_K(w_h) = (f - Aw_h)_K. \quad (15)$$

The error equation

$$A(w - w_h) = \rho(w_h) \quad (16)$$

demonstrates that the cell residue $\rho_K(w_h)$ influences the error $e_{K'} = (w - w_h)_{K'}$ in another cell K' through the Green's function of the continuous problem (13). In practical applications, usually it is impossible to reveal the error interaction between the local residuals ρ_K and the error $\mathcal{L}(e)$ in the goal quantity, and thus it has to be determined by computation. The idea is to consider the adjoint (or dual) problem

$$A^*z = j, \quad (17)$$

where A^* is the adjoint operator given by $\langle Au, v \rangle = \langle A^*v, u \rangle$ for all functions u and v , where $\langle \cdot, \cdot \rangle$ is the standard integral inner product, and j is the density function associated with $\mathcal{L}$. For example, if one is interested in the average value of a solution w , the goal functional acting on w can be represented by

$$\mathcal{L}(w) = \int_{\Omega} j w dx. \quad (18)$$

Taking into account the definition of the adjoint operator, (17), and (14), for the error in the goal quantity we obtain

$$\begin{aligned} \mathcal{L}(e) &= \langle A^*z, w \rangle - \langle A^*z, w_h \rangle \\ &= \langle Aw, z \rangle - \langle Aw_h, z \rangle = \langle f - Aw_h, z \rangle \\ &= \langle \rho(w_h), z \rangle, \end{aligned} \quad (19)$$

where z is unknown and has to be substituted with an approximate solution. By analogy with the equation (16) for the error $w - w_h$, we see that the error $\mathcal{L}(e)$ in the goal quantity is determined by the local cell values of the residual $\rho_K(w_h)$ through the solution z of the adjoint problem (17). In fact, this kind of goal error representation can be obtained with much less regularity, where f in (13) is exchanged with $\mathcal{F}$ in a space of distributions. Likewise, the approximation w_h and also $\mathcal{L}$ can be less regular. And for this case one obtains

$$\mathcal{L}(e) \approx \langle \rho(w_h), s_h(z) \rangle, \quad (20)$$

where $s_h(z)$ is a sensitivity factor obtained from the approximate solution of the adjoint problem (17). Thus, the adjoint solution demonstrates how the information from the residual $\rho(w_h)$ in the primal problem is propagated to the error $\mathcal{L}(e)$ in the quantity of interest. This approach to a posteriori error estimation with respect to a quantity of interest is called the dual weighted residual (DWR) method since the residual $\rho(w_h)$ is weighted with the quantity $s_h(z)$ obtained by a solution of the adjoint problem (17).

The target quantity in our case is the electrostatic interaction energy E between two molecules, M_1 and M_2 . It can be expressed through the potential φ_1 , produced by M_1 at the positions $x_{i,2}$ of the charges $q_{i,2}$ of molecule M_2 :

$$E_{1-2} = \sum_{i=1}^{N_2} \varphi_1(x_{i,2}) q_{i,2}, \quad (21)$$

where $q_{i,2} = z_{i,2}e_0$ and N_2 is the number of charges in M_2 . At the same time the energy can also be written employing the potential φ_2 of M_2 at the position of the charges $q_{i,1}$ of M_1 , i.e.,

$$E_{2-1} = \sum_{i=1}^{N_1} \varphi_2(x_{i,1}) q_{i,1}, \quad (22)$$

where $q_{i,1} = z_{i,1}e_0$ and N_1 is the number of charges in M_1 . Here we assume φ_1 and φ_2 to be the solutions of the LPBE (4) together with the interface conditions (6) and (7), and a homogeneous Dirichlet boundary condition $g = 0$ in (8). Note that both the linearity of the LPBE and the homogeneous Dirichlet boundary condition on $\partial\Omega$ are necessary in order to reflect the symmetry of the interaction, i.e., $E_{2-1} = E_{1-2}$ ($= E$) (see Proposition 5.12 in Ref. 36 for a proof of this fact).

In what follows, without loss of generality, we define the primal problem to be

$$-\nabla \cdot (\epsilon \nabla \varphi_2) + \bar{k}^2 \varphi_2 = 4\pi \sum_{i=1}^{N_2} q_{i,2} \delta(x - x_{i,2}). \quad (23)$$

Therefore, the primal problem describes the potential, created by the charges of the molecule M_2 . For convenience we

denote the right-hand side of (23) to be the functional

$$\mathcal{F} = 4\pi \sum_{i=1}^{N_2} q_{i,2} \delta(x - x_{i,2}). \quad (24)$$

Applying (10) we obtain the integral formulation of the primal problem (23), i.e.,

$$\int_{\Omega} \epsilon \nabla \varphi_2 \cdot \nabla v dx + \int_{\Omega} \bar{k}^2 \varphi_2 v dx = \mathcal{F}(v) \quad (25)$$

for all test functions v .

It is easy to see that the goal functional related to our target quantity (22) is given by

$$\mathcal{L} = \sum_{i=1}^{N_1} q_{i,1} \delta(x - x_{i,1}). \quad (26)$$

And therefore, the interaction energy (22) can be written as

$$E_{2-1} = \mathcal{L}(\varphi_2). \quad (27)$$

For further analysis it is also necessary to express the adjoint problem in an integral formulation similar to (25). Recalling the definition (17) and taking into account that in our case $A^* = A$ we obtain

$$\int_{\Omega} \epsilon \nabla v \cdot \nabla z dx + \int_{\Omega} \bar{k}^2 v z dx = \mathcal{L}(v) \quad (28)$$

for all test functions v ,

where z is the solution of (28) and is defined to be equal to zero on the boundary $\partial\Omega$. Here we would like to emphasize the difference between primal and adjoint problems: the solution φ_2 of the primal problem is created by the charges of the molecule M_2 , whereas the solution z is determined by the charges of M_1 (see (24) and (26)). Now, by taking into account the definitions (24) and (26) of $\mathcal{F}$ and $\mathcal{L}$, respectively, and of the potential z , it is clear that the interaction energy E_{1-2} ($= E_{2-1}$) can also be calculated as

$$E_{1-2} = \mathcal{F}(z). \quad (29)$$

The optimal adaptive algorithm would balance the error distribution of the calculated potential over the domain Ω in such way that for a given number of degrees of freedom (DOFs) the error in the goal quantity

$$\mathcal{L}(e) = \mathcal{L}(\varphi_2) - \mathcal{L}(\varphi_{2,h}) = \sum_{i=1}^{N_1} q_{i,1} e_i, \quad (30)$$

with $e := \varphi_2 - \varphi_{2,h}$ and $e_i := \varphi_2(x_{i,1}) - \varphi_{2,h}(x_{i,1})$ is minimal. In general this minimization problem cannot be solved but adaptive algorithms aim at approximating its solution well. Hereinafter the index h will indicate that the physical quantity to which it refers is computed approximately by a numerical algorithm on a mesh with mesh parameter h .

A difficulty in the problem under consideration is that the goal functional defining the quantity of interest, i.e., the electrostatic interaction, requires point evaluations. Hence it is not representable in the form (18) through a density function j , but defined in terms of the delta functions $\delta(x - x_{i,1})$, cf. (26). A standard approach in such a situation

employs regularization of the goal functional by replacing point evaluations with averaging over small balls $B(x_{i,1}, \rho)$, where ρ is the radius around the points of interest $x_{i,1}$. The application of this approach, however, changes the goal functional and requires the evaluation of integrals of discontinuous functions over balls. For achieving high enough accuracy, the mesh has to be a priori adapted around the points of interest and special integration rules have to be used. In order to avoid the conceptual shortcomings of this approach, here, we derive representations of the error in the goal quantity which do not require averaging and directly exploit the original goal functional.

Error estimator

This approach does not involve any splitting of the full potential and is based on a direct discretization of the problem defining φ_2 . Hence the primal and adjoint problems are given by the expressions (25) and (28), respectively. The goal quantity is given by (27) and the approximate interaction energy is simply given by

$$E_{2-1}^{Prim} = \mathcal{L}(\varphi_{2,h}), \quad (31)$$

where $\varphi_{2,h}$ is the solution of the discrete primal problem

$$\int_{\Omega} \epsilon \nabla \varphi_{2,h} \cdot \nabla v dx + \int_{\Omega} \bar{k}^2 \varphi_{2,h} v dx = \mathcal{F}(v) \quad (32)$$

for all test functions $v \in V_h^1$.

Here, $\varphi_{2,h}$ is a linear combination of continuous piecewise linear functions from the finite element space V_h^1 defined on the mesh $\mathcal{T}_h$. By taking into account (27), (31), and the fact that the goal functional $\mathcal{L}$ is linear, for the error in the interaction energy we obtain

$$E_{2-1} - E_{2-1}^{Prim} = \mathcal{L}(\varphi_2 - \varphi_{2,h}). \quad (33)$$

Further to obtain an error estimator in terms of the solution to the adjoint problem, we will use the following equalities (for a proof see Proposition 5.12 in Ref. 36):

$$\begin{aligned} \int_{\Omega} \epsilon \nabla(\varphi_2 - \varphi_{2,h}) \cdot \nabla z dx + \int_{\Omega} \bar{k}^2 (\varphi_2 - \varphi_{2,h}) z dx \\ = \mathcal{L}(\varphi_2 - \varphi_{2,h}), \end{aligned} \quad (34)$$

$$\int_{\Omega} \epsilon \nabla \varphi_2 \cdot \nabla z dx + \int_{\Omega} \bar{k}^2 \varphi_2 z dx = \mathcal{F}(z). \quad (35)$$

The equality (34) essentially means that one can test (28) with the function $\varphi_2 - \varphi_{2,h}$ and equality (35) means that (25) can be tested with the adjoint solution z . Successive application of (34) and (35), similarly to the general approach presented by (19), yields

$$\begin{aligned} \mathcal{L}(\varphi_2 - \varphi_{2,h}) &= \mathcal{F}(z) - \int_{\Omega} \epsilon \nabla \varphi_{2,h} \cdot \nabla z dx \\ &= \int_{\Omega} \bar{k}^2 \varphi_{2,h} z dx =: \mathcal{B}(\varphi_{2,h}, z). \end{aligned} \quad (36)$$

Evaluation of the error in (36) requires the solution of the adjoint problem. In practice, one finds a good approxima-

tion of z in a richer space than the one which $\varphi_{2,h}$ belongs to. In particular, we use an approximation $z_h^{(2)}$ from the space V_h^2 consisting of continuous piecewise quadratic functions defined on the same mesh $\mathcal{T}_h$. Thus the solution $z_h^{(2)}$, equal to zero on $\partial\Omega$, is obtained from

$$\int_{\Omega} \epsilon \nabla v \cdot \nabla z_h^{(2)} dx + \int_{\Omega} \bar{k}^2 v z_h^{(2)} dx = \mathcal{L}(v) \quad (37)$$

for all test functions $v \in V_h^2$.

In this case, by using (32) (for similar techniques of error estimator localization see, e.g. Refs. 40,41) we obtain

$$\begin{aligned} \mathcal{B}(\varphi_{2,h}, z_h^{(2)}) &= \mathcal{F}(z_h^{(2)} - I_h z_h^{(2)}) - \int_{\Omega} \epsilon \nabla \varphi_{2,h} \cdot \nabla (z_h^{(2)} - I_h z_h^{(2)}) dx \\ &\quad - \int_{\Omega} \bar{k}^2 \varphi_{2,h} (z_h^{(2)} - I_h z_h^{(2)}) dx \\ &= \sum_{i=1}^{N_V} \eta_i^{PU}(\varphi_{2,h}, z_h^{(2)}) =: \eta^{PU}(\varphi_{2,h}, z_h^{(2)}), \end{aligned} \quad (38)$$

where I_h is the nodal interpolation operator in V_h^1 (and thus $I_h z_h^{(2)} \in V_h^1$ and can be taken as a test function in (32)), N_V is the number of nodes (vertices) in the mesh $\mathcal{T}_h$, and

$$\begin{aligned} \eta_i^{PU}(\varphi_{2,h}, z_h^{(2)}) &= \langle \mathcal{F}, (z_h^{(2)} - I_h z_h^{(2)}) \psi_i \rangle \\ &\quad - \left(\epsilon \nabla \varphi_{2,h}, \nabla (z_h^{(2)} - I_h z_h^{(2)}) \psi_i \right) \\ &\quad - \left(\bar{k}^2 \varphi_{2,h}, (z_h^{(2)} - I_h z_h^{(2)}) \psi_i \right). \end{aligned} \quad (39)$$

In (39), $\{\psi_i\}_{i=1}^{N_V}$ are the nodal P_1 basis functions equal to 1 at the i -th node and zero elsewhere (for details, see Section 2.1.6). The functions $\{\psi_i\}_{i=1}^{N_V}$ form the so-called partition of unity, i.e., their sum $\sum_{i=1}^{N_V} \psi_i(x) = 1$ for each $x \in \Omega$, which justifies the second equality in (38). The nodal interpolant $I_h f$ of a continuous function f is a finite element function in the space V_h^1 , equal to f at all nodes V_i of the mesh $\mathcal{T}_h$.

The quantities $\eta_i^{PU}(\varphi_{2,h}, z_h^{(2)})$, $i = 1, \dots, N_V$ are nodewise error indicators that are used to drive the adaptive mesh refinement. Note that the term $\langle \mathcal{F}, (z_h^{(2)} - I_h z_h^{(2)}) \psi_i \rangle$ in the definition of η_i^{PU} can be nonzero only if the support of ψ_i contains a partial charge from molecule M_2 in it (recall that the charges of M_2 define the primal problem). Finally, for the error estimate we have

$$\mathcal{L}(\varphi_2 - \varphi_{2,h}) = \mathcal{B}(\varphi_{2,h}, z_h^{(2)}) + \mathcal{E}(\varphi_2, \varphi_{2,h}, z, z_h^{(2)}), \quad (40)$$

where $\mathcal{E}(\varphi_2, \varphi_{2,h}, z, z_h^{(2)})$ is a higher order term that can be neglected². For this reason, in practical applications we

²The exact expression for $\mathcal{E}(\varphi_2, \varphi_{2,h}, z, z_h^{(2)})$ can be deduced from (40) by using the expressions (36) and (38) for $\mathcal{L}(\varphi_2 - \varphi_{2,h})$ and $\mathcal{B}(\varphi_{2,h}, z_h^{(2)})$, respectively. To see why $\mathcal{E}(\varphi_2, \varphi_{2,h}, z, z_h^{(2)})$ is a higher-order term with respect to the mesh parameter h we refer to 36.

will employ the approximate equality

$$E_{2-1} - E_{2-1}^{Prim} \approx \mathcal{B}(\varphi_{2,h}, z_h^{(2)}) \quad (41)$$

and use the elementwise localization (38) of $\mathcal{B}(\varphi_{2,h}, z_h^{(2)})$ as an error indicator for our adaptive algorithm.

In our calculation of interaction energies we will use the approximate solution $z_h^{(2)}$ of the adjoint problem since it is more accurate than $\varphi_{2,h}$. By first taking into account (32) together with the fact that $I_h z_h^{(2)} \in V_h^1$, and then noting that $\varphi_{2,h} \in V_h^1 \subset V_h^2$, from (38) we find that

$$\mathcal{B}(\varphi_{2,h}, z_h^{(2)}) = \mathcal{F}(z_h^{(2)}) - \mathcal{L}(\varphi_{2,h}). \quad (42)$$

Therefore, from (41) the interaction energy can be expressed as follows:

$$E_{2-1} \approx E_{2-1}^{Prim} + \left(\mathcal{F}(z_h^{(2)}) - \mathcal{L}(\varphi_{2,h}) \right) = \mathcal{F}(z_h^{(2)}). \quad (43)$$

Now, from (42) and (43), we obtain

$$E_{1-2}^{Adj} := \mathcal{F}(z_h^{(2)}) = E_{2-1}^{Prim} + \mathcal{B}(\varphi_{2,h}, z_h^{(2)}). \quad (44)$$

The expression (44) demonstrates that the interaction E_{1-2}^{Adj} computed by means of the more accurate $z_h^{(2)}$ is equal to the interaction E_{2-1}^{Prim} corrected with the approximately evaluated error estimator $\mathcal{B}(\varphi_{2,h}, z_h^{(2)})$. The quantity E_{1-2}^{Adj} is a more accurate approximation of the electrostatic interaction E_{1-2} (see (29)), which will be used in our applications. We will refer to the corresponding solver as ARGOS and the solution obtained by ARGOS will be denoted $E^{ARGOS} := E_{1-2}^{Adj}$. If for the definition of the primal problem (23) we use the charges of molecule M_1 instead, then the definition of the adjoint problem (28) will involve the charges of molecule M_2 . In this case, the numerical approximations of the interaction energies E_{1-2} and E_{2-1} obtained by ARGOS are denoted E_{1-2}^{Prim} and E_{2-1}^{Adj} , respectively. The reasoning here is that this time the energy E_{1-2} is computed by using the solution of the primal problem, whereas E_{2-1} is computed by using the more accurate solution of the adjoint problem.

We note that a similar approach to the estimation of the error in the goal quantity E can be undertaken in conjunction with the splitting of the full potential $\varphi_2 = G_2 + u_2$, where G_2 is the Coulomb potential of the charges of M_2 in a uniform dielectric medium with $\epsilon = \epsilon_m$ and u_2 is the corresponding reaction field potential. An adaptive algorithm based on goal oriented error estimation together with a splitting of the potential can be very reliable for the calculation of the solvation energy difference (12) and will be included in ARGOS in the future.

2.1.4 Convergence order

It can be shown (see Ref. 36), that provided φ_2 and z are regular solutions, and under uniform mesh refinement in 3D,

the error estimates satisfy

$$\left| E_{2-1} - E_{2-1}^{Prim} \right| = |\mathcal{B}(\varphi_{2,h}, z)| \leq C_1 h^2 \approx \frac{C_1}{(\#DOFs)^{2/3}}, \quad (45)$$

$$\left| E_{2-1} - E_{1-2}^{Adj} \right| = |\mathcal{E}(\varphi_2, \varphi_{2,h}, z, z_h^{(2)})| \leq C_2 h^3 \approx \frac{C_2}{\#DOFs}, \quad (46)$$

where $C_1, C_2 > 0$ are constants independent of the maximum mesh size h . Here we introduced $\#DOFs$ as the number of degrees of freedom since it is more appropriate to measure the approximation error in terms of $\#DOFs$ than in h under adaptive mesh refinement. From this expression it is clear that the interaction energy obtained with the adjoint solution z converges faster to the exact interaction energy than the one with the primal solution. We will demonstrate these convergence rates in the RESULTS section.

2.1.5 Adaptive algorithm

In general, adaptive algorithms can be represented by the following flowchart (Figure 2): Instead of the mesh param-

Figure 2: Schematic representation of adaptive refinement as explained in the text.

eter h , we will use a subindex $\ell = 1, 2, \dots$ to denote the refinement level and we recall that $\sum_{K \in \mathcal{T}_\ell} \eta_K = \mathcal{B}(\varphi_{2,h}, z_\ell^{(2)})$.

By N_E we will denote the number of elements in the mesh $\mathcal{T}_\ell$ at mesh refinement level (MRL) ℓ . The adaptive finite element solver based on the two error estimators above can be summarized as follows.

Solve

The solution $\varphi_{2,\ell}$ from the space V_ℓ^1 , defined on the current mesh $\mathcal{T}_\ell$, is found by solving (32).

Estimate

Next, we find the solution of the adjoint problem by solving the finite dimensional problem (37). Once we obtain $z_\ell^{(2)}$, we compute the error indicators $\eta_K(\varphi_{2,\ell}, z_\ell^{(2)})$.

Mark

Based on the values of η_K , a set of elements $\mathcal{M}_\ell \subset \mathcal{T}_\ell$ is marked for refinement. This set can be chosen through different marking strategies (see the SI).

Refine

Having performed a refinement based on the marked elements $\mathcal{M}_\ell$, a new mesh $\mathcal{T}_{\ell+1}$ is obtained.

The detailed algorithm of ARGOS reads:

ARGOS

```

1:  $\ell \leftarrow 0$ , initialize  $\mathcal{T}_0, V_0^1, V_0^2$ 
2: do
3:    $\varphi_{2,\ell} \leftarrow \text{Solve}^{\text{prim}}(\mathcal{T}_\ell, V_\ell^1)$ 
4:    $z_\ell^{(2)} \leftarrow \text{Solve}^{\text{adj}}(\mathcal{T}_\ell, V_\ell^2)$ 
5:    $\{\eta_K\}_{K \in \mathcal{T}_\ell} \leftarrow \text{Estimate}(\varphi_{2,\ell}, z_\ell^{(2)}, \mathcal{T}_\ell)$ 
6:    $\mathcal{M}_\ell \leftarrow \text{Mark}(\{\eta_K\}_{K \in \mathcal{T}_\ell})$ 
7:    $\mathcal{T}_{\ell+1} \leftarrow \text{Refine}(\mathcal{T}_\ell, \mathcal{M}_\ell)$ 
8:    $\ell \leftarrow \ell + 1$ 
9: while convergence or maximum number of refinement
    levels reached
  
```

2.1.6 Finite element method

The finite element (FE) method aims at approximating the exact solution of a differential equation by a piecewise polynomial function. In order to achieve this, the computational domain is split into individual small (finite) elements, such as triangles in 2D or tetrahedrons in 3D. The construction is such that the FE space used for approximation is finite dimensional with a basis consisting of locally (on patches of elements) supported piecewise polynomials. The latter have to satisfy certain interpolation conditions, e.g. continuity across element interfaces, as used in the adaptive algorithms presented in this paper.

In case of the lowest approximation order, i.e., piecewise linear polynomials, each basis function is associated with a node in the mesh, that is, a vertex of an element. The approximate solution is represented in the chosen basis with unknown expansion coefficients, e.g. the nodal values of the approximate solution. Based on a variational formulation of the differential equation, taking into account boundary conditions, a system of algebraic equations is derived for these expansion coefficients.

In our case the FE space for the primal problem, V_h^1 , consists of continuous piecewise linear functions P_1 . The FE space for the adjoint problem consists of continuous piecewise quadratic functions P_2 . In the case of P_1 elements, there is one basis function ψ_i for each vertex (node) V_i of the mesh $\mathcal{T}_h$, which is equal to 1 at V_i and 0 at all other vertices, see Figure 3. Here we will outline the construction of the system of linear algebraic equations arising from (32). The system for the adjoint problem can be constructed in a similar way. Recall, that equation (32) has to be satisfied for all test functions $v \in V_h^1$. Equivalently, this means that the equation must hold for all basis functions ψ_i , $i = 1, \dots, N_\Omega$ that are zero on the boundary $\partial\Omega$. In this notation, the number of nodes N_V in the mesh $\mathcal{T}_h$ equals the number of degrees of freedom N_{DOFs}^{Prim} plus the number of nodes on the boundary $\partial\Omega$. This means that in the primal problem, $N_{DOFs}^{Prim} = N_\Omega$ and we obtain N_{DOFs}^{Prim} equations for $\varphi_{2,h}$:

$$\int_{\Omega} \epsilon \nabla \varphi_{2,h} \cdot \nabla \psi_i dx + \int_{\Omega} \bar{k}^2 \varphi_{2,h} \psi_i dx = \mathcal{F}(\psi_i), \quad (47)$$

for $i = 1, \dots, N_{DOFs}^{Prim}$.

Moreover, $\varphi_{2,h}$ belongs to V_h^1 and $\varphi_{2,h} = 0$ on $\partial\Omega$. Hence $\varphi_{2,h}$ can be represented as a linear combination of the basis functions ψ_i with unknown expansion coefficients φ_2^j , i.e.,

$$\varphi_{2,h}(x) = \sum_{j=1}^{N_{DOFs}^{Prim}} \varphi_2^j \psi_j(x). \quad (48)$$

The goal is to find the vector of unknowns $\Phi_2 =$

$(\varphi_1^1, \dots, \varphi_2^{N_{DOFs}^{Prim}})^T$ corresponding to the interior vertices.

For this purpose, we substitute the expression (48) for $\varphi_{2,h}$ in (47) and use the linearity of the integral, gradient operator, and right-hand side to obtain the following system of linear equations

$$\sum_{j=1}^{N_{DOFs}^{Prim}} \left(\int_{\Omega} \epsilon \nabla \psi_j \cdot \nabla \psi_i dx \right) \varphi_2^j + \sum_{j=1}^{N_{DOFs}^{Prim}} \left(\int_{\Omega} \bar{k}^2 \psi_j \psi_i dx \right) \varphi_2^j = \mathcal{F}(\psi_i), \text{ for } i = 1, \dots, N_{DOFs}^{Prim}.$$

In matrix notation the above equations read

$$\mathbf{A} \Phi_2 = \mathbf{F}_2, \quad (49)$$

where $\mathbf{A}$ is the symmetric positive definite matrix with entries

$$a_{i,j} = \int_{\Omega} \epsilon \nabla \psi_j \cdot \nabla \psi_i dx + \int_{\Omega} \bar{k}^2 \psi_j \psi_i dx, \quad i, j = 1, \dots, N_{DOFs}^{Prim}$$

and

$$\mathbf{F}_2 = \left(\mathcal{F}(\psi_1), \dots, \mathcal{F}(\psi_{N_{DOFs}^{Prim}}) \right)^T.$$

The system (49) is then solved either by a direct or by an iterative method. In our numerical tests we have used the conjugate gradient method with a sufficiently high accuracy in order to make the error due to the iterative solution of the linear system subordinate to the overall error. In this way it is possible to study the effect of the adaptive mesh refinement in a reliable way.

Figure 3: Interior P_1 basis function in 2D.

Our computations are performed with two levels of geometric approximation of the solvent excluded surface (SES). The triangulated surface meshes are generated with NanoShaper,⁴² where the quality of the approximation is controlled with the parameter *GridScale*. A *GridScale* parameter equal to 2 refers to the cubic grid with spacing of $h = 0.5 \text{ \AA}$ used in the construction of the surface mesh. *GridScale* = 4 corresponds to the spacing $h = 0.25 \text{ \AA}$, see Figure 4. A grid scale of 2 produces an average edge length of the triangulated surface mesh of around $0.45 \text{ \AA}$, whereas *GridScale* = 4 results in an average edge length on the molecular surface of around $0.225 \text{ \AA}$.

Once the surface meshes are generated, we use TetGen⁴³ to create the initial tetrahedral meshes. For the adaptive mesh refinement (AMR) we use mmg3d⁴⁴ and the implementation of the prototype version of the adaptive solver is realized in FreeFem++,⁴⁵ developed and maintained by Frederich Hecht.

(a) *GridScale*=2.

(b) *GridScale*=4.

Figure 4: Triangulated surfaces of a sphere with radius $R = 1$, using NanoShaper .

2.2 MEAD package

Here we will give a brief overview on the MEAD software (for more details, see Ref. 15). The package solves the linearized PBE. Taking into account the finite size of the grid, it prescribes a Dirichlet boundary condition given by a simple Coulomb formula for the molecular point charges with the dielectric constant set to that of the exterior region, i.e., the solvent. This condition requires the grid to span a large domain, increasing the cost of calculations drastically. To avoid this problem, MEAD adopts a multigrid configuration, called focusing method. Here the initial calculations are made with a coarse-grained grid of large extent, followed by calculations on finer grids of smaller extents, centered on the region of interest.

In the presented tests we used MEAD version 2.2.8 a and its programs *potential* and *multiflex*. The former is applied to calculate the potential, which is displayed for the coordinates, specified by the user. We used *multiflex* to calculate the interaction energy. An important issue in the MEAD procedure involves calculating both energies E_{1-2} and E_{2-1} , expressed through potentials φ_1 (see (21)) and φ_2 (see (22)). The final result is obtained by the average of the two, i.e.,

$$\bar{E}^{MEAD} = \frac{E_{1-2}^{MEAD} + E_{2-1}^{MEAD}}{2}. \quad (50)$$

The implementation of MEAD allows the user to set model parameters including dielectric constants, ionic strength, grids dimensions and spacing, as well as to revert to the old way of testing for convergence of the iterative solver Successive Over Relaxation (SOR). The latter is a variant of the Gauss-Seidel method for solving a linear system of equations. The algorithm is controlled by the following, hidden from the user, parameters: **minits**, **maxrmsdiff** and **maxiter**. The parameter **minits** specifies the minimum number of iterations and is defined as $30(N_d - 1)/2$, where N_d is the number of grid points in each coordinate direction for both the coarse-grain mesh and the fine one. The parameter **maxrmsdiff** is the tolerance for the maximum root mean square of the difference (**rmsdiff**) between two consecutive solutions φ_k and φ_{k+1} in the SOR method. By default, **maxrmsdiff** is set to $2 \cdot 10^{-5}/(N_d - 1)$. The parameter **maxiter** denotes the maximum number of iterations and is set to 10·**minits**. The SOR iterative method is terminated when either the maximum number of iterations is reached, or the current iteration number is greater than or equal to **minits**, while **rmsdiff** is less than or equal to **maxrmsdiff**. It turns out that the default values of these parameters are inappropriate in the majority of our tests. Therefore, in this paper, we also present the results of MEAD for a set of manually improved values of the SOR parameters, which is achieved by recompiling the source code. The selected values of these and other method parameters will be given for every problem separately. It is important to note that MEAD

performs the calculations in single-precision arithmetic.

2.3 APBS package

Similar to MEAD, Adaptive Poisson-Boltzmann Solver (APBS) solves the linearized PBE³, applying a FD method.¹⁰ However, unlike MEAD, it employs double precision arithmetics in combination with a multigrid iterative solver and a better stopping criterion.

In analogy with the MEAD calculations, for each frame we make two computations with APBS: one to find the potential φ_1^{APBS} generated by the charges of molecule M_1 and one to find the potential φ_2^{APBS} generated by the charges of molecule M_2 . Then, by calling two times its subprogram (application) *multivalue*, we find the two lists of values $\{\varphi_1^{APBS}(x_{i,2})\}_{i=1}^{N_2}$ and $\{\varphi_2^{APBS}(x_{i,1})\}_{i=1}^{N_1}$ with which we compute the electrostatic interactions, using (21) and (22). The final result is obtained by the average of the two, in analogy with (50):

$$\bar{E}^{APBS} = \frac{E_{1-2}^{APBS} + E_{2-1}^{APBS}}{2}. \quad (51)$$

To present the best case scenario for APBS, we use the finite difference solver **mg-auto** with parameters which provide a relatively good efficiency of the computations and a very high accuracy.

Below, we list the keywords, most relevant to our considerations from the input ".in" file of APBS, where "#" denotes the beginning of a comment in the input file. The full list of keywords together with particular values of the parameters they define is given in the SI.

mg-auto # Specifies the type of calculations that the finite difference multigrid PMG code performs.

dime nx ny nz # Here, *nx*, *ny*, *nz* are the number of grid points in the x-, y-, and z-direction for all focused FD grids in a computation.

cgcent mol 1 # The coarse grid is centred at the centre of the minimal box, with sides parallel to the coordinate axes, such that it contains all the atoms' centers of the system under study (mol 1 is its internal number).

cglen xlen ylen zlen # The computational domain is a rectangular parallelepiped with side lengths *xlen*, *ylen*, and *zlen* in Å, in the x-, y-, and z-directions, respectively.

fgcent mol 1 # All focused grids, including the finest one, are centred at the centre of the minimal box, with sides parallel to the coordinate axes, such that it contains all the atoms' centres of the system under study (mol 1 is its internal number).

fglen xlen ylen zlen # Specifies the fine mesh domain, a rectangular parallelepiped with side lengths *xlen*, *ylen*, and *zlen* in Å, in the x-, y-, and z-directions, respectively.

etol tol # Specifies the tolerance for iterations of the partial differential equation solvers. This keyword is optional for the finite difference solvers and in particular for **mg-auto**. Its default value is *tol* = 1e-06 according to the APBS manual.

Note that the values of the arguments *nx*, *ny*, *nz* of the keyword **dime** are dependent on the depth of the multilevel hierarchy used in the multigrid solver **mg-auto** by the formula $n = c2^{l+1} + 1$, where *n* is any of the **dime** arguments *nx*, *ny*, *nz*, *c* is a nonzero positive integer, *l* is the depth of the multilevel hierarchy. The choice $n = 321$ is compatible with $l = 5$, whereas $n = 385$ is compatible with $l = 4$.

³APBS can solve both the PBE and the linearized PBE with the FD method. The application of the finite element method however is still at a very experimental stage and in our calculations we could not make any use of it.

2.4 System under study

In this work we consider electrostatic interactions between the chromophores Alexa 488 and Alexa 594, attached to all-trans polyproline helices with 6 and 20 residues (POLY6 and POLY20), placed in aqueous solution with 300 mM NaCl at constant temperature $T = 300$ K (see Figure 5), investigated in our earlier work with molecular dynamics (MD) simulations and electrostatic calculations, using MEAD.⁴⁶ While in our earlier work only the electrostatic interaction between transition charges of the dyes was investigated, here we include also the interaction between ground-state charge densities in order to compare the performance of different solvers for systems with different properties. The coupling between

Figure 5: System under study, composed of polyproline, labeled with Alexa 594 and Alexa 488.

the dyes was computed for certain time frames taken from all-atom molecular dynamics (MD) simulations, performed with the NAMD software package.⁴⁷ For both polyproline lengths (6 and 20 residues), we generated 10 trajectories, each with a time window of 200 ns. The standard CHARMM force field (*version v35b3*)⁴⁸ was used for polyproline. The force field parameters of the Alexa chromophores were created by an analogy approach from that of similar chemical groups in the CHARMM force field (for details on the MD simulations including force field parameters see Ref. 46). The water molecules in the MD simulations were parameterized, using the TIP3P model.⁴⁹

The calculation of the interaction between Alexa chromophores by MEAD, APBS and ARGOS follows the same procedure, starting with computing the electrostatic potential (ESP) from the Poisson or LPBE (see (5) and (4)). This potential is then used to calculate the coupling (see (21) and (22)).

3 RESULTS

3.1 Evaluation of the accuracy of the numerical methods

We start with three models, for which analytical solutions for the ESP exist. By comparing the numerical with the analytical solutions, the sources of numerical errors and their magnitude will be determined. The numerical accuracy of the solvers (MEAD, APBS and ARGOS) is evaluated by the relative errors (in %) defined as

$$\begin{aligned} Err^{Adj} = Err^{ARGOS} &= \frac{|E - E_{1-2}^{Adj}|}{|E|} \cdot 100, \\ Err^{Prim} &= \frac{|E - E_{2-1}^{Prim}|}{|E|} \cdot 100, \\ Err^{MEAD} &= \frac{|E - \bar{E}^{MEAD}|}{|E|} \cdot 100, \\ Err^{APBS} &= \frac{|E - \bar{E}^{APBS}|}{|E|} \cdot 100, \end{aligned} \quad (52)$$

where E is the exact (analytical) solution of the problem, $Err^{Adj} = Err^{ARGOS}$ and Err^{Prim} correspond to the relative errors of the numerical solutions $E_{1-2}^{Adj} (= E^{ARGOS})$ and E_{2-1}^{Prim} of the adjoint and the primal problem, respectively, obtained with ARGOS. Err^{MEAD} and Err^{APBS} are the relative errors of MEAD and APBS, E_{MEAD} and E_{APBS} are the numerical solutions, obtained with MEAD and APBS, respectively. The accuracy was evaluated separately for each critical aspect of the problem solving discussed in the INTRODUCTION. The first model includes chromophores without interfaces and examines the effect of discretization of the charges and the imposed boundary conditions. Models 2 and 3 employ a Born model, represented by a spherical ion, and are designed to probe the role of the interfaces and other (implicit) ions.

3.1.1 Model-1: Boundary conditions and discretization of the charges

The setup consists of a polyproline helix (POLY6 and POLY20), labelled with charge-neutral Alexa dyes in the electronic ground state. The system is placed in vacuum ($\epsilon_s = 1$). The dielectric constants of the chromophores and polyproline are equal to 1. Therefore, the model does not include any interfaces and the analytical solution of the electrostatic coupling between the dyes is just a sum over Coulomb interactions between point charges. The couplings were calculated for 19 time frames, randomly selected from the MD simulations: frames 1 to 10 correspond to POLY6, frames 11 - 19 are taken from MD simulations of POLY20. To check the accuracy of MEAD and APBS, the sizes of the coarse-grained and fine (focused) meshes were selected taking into account the dimensions of the system: about 60 Å in diameter for POLY6 and 85 Å in diameter for POLY20 across all the frames we used. The coarse-grained, the intermediate-focused meshes, and the fine-focused meshes for MEAD are centered at the geometric center of the system, whereas the meshes in the APBS calculations are centered at the center of the minimal box (with sides parallel to the coordinate planes) that contains all the atoms of the molecule. Since the default stopping criterion for the iterative solver SOR in MEAD is not adequate in most of our tests, we used 2 different sets of SOR parameters (see Table 1 and METHODS for more details). The complete specification of the configurations M1-1, M1-2 for MEAD and A1 for APBS, used in the computations related to Model-1 are given in Table 1 and Table 2, respectively.

Table 1: Computational configurations for MEAD for Model-1

Configuration	Coarse-grained mesh number of nodes/spacing (Å)	Intermediate mesh number of nodes/spacing (Å)	Fine mesh number of nodes/spacing (Å)	SOR maxiter	SOR maxrsdiff
M1-1	101/3	201/1	POLY6: 321/0.25 POLY20: 401/0.25	default (POLY6: 1500 and 4800 POLY20: 1500 and 6000)	default $2 \cdot 10^{-5}/(N_d - 1)$
M1-2	101/3	201/1	POLY6: 321/0.25 POLY20: 401/0.25	for all cases 12000	$2 \cdot 10^{-5}/(N_d - 1)$

Table 2: The configuration A1 of APBS for Model-1.

	dime	cglen grid spacing (Å)	fglen grid spacing (Å)	Automatically placed intermediate focused mesh: size / grid spacing (Å)
POLY6	321 321 321	900 900 900 / 2.813	80 80 80 / 0.25	268.33 268.33 268.33 / 0.839
POLY20	385 385 385	900 900 900 / 2.344	100 100 100 / 0.26	300 300 300 / 0.781

The fine mesh domain for both MEAD and APBS is a box with a side length of 80 Å for POLY6 and 100 Å for POLY20,

and encompasses the polyproline and the chromophores altogether. We have chosen the values of the parameters of **dime** and of **fglen** in APBS so that they are as close as possible to the parameters in the grid configurations M1-1 and M1-2 for MEAD. The values of **cglen**, however, are chosen much larger, i.e., 900 Å, which can enhance the accuracy of the APBS computations compared to MEAD. We also note that the **mg-auto** solver automatically chooses how many intermediate focusing grids to use between the coarse one and the fine one. In the case of configuration A1, with **cglen** 900 900 900 and **fglen** 80 80 80 or **fglen** 100 100 100, **mg-auto** places one intermediate focusing grid with dimensions given in Table 2.

The computational domain for ARGOS is a cube with a side length of around 160 000 Å for all frames with POLY6 and around 400 000 Å for all frames with POLY20. To demonstrate the convergence of the ARGOS results with respect to the number of degrees of freedom (DOFs), we compute the relative errors for the interaction energies obtained from the solutions of the adjoint and primal problems, Err^{ARGOS} and Err^{Prim} defined in (52), and average them over all frames (Figure 6). Both Err^{Adj} and Err^{Prim} exhibit the order of convergence, predicted by (45) and (46). The solution of the adjoint problem exhibits a higher convergence order $O(\#DOFs^{-1})$ (see (46)), and thus, much smaller relative errors, ranging from 2×10^{-1} % down to 2×10^{-4} % for the largest number of DOFs (10^7). The relative errors Err^{ARGOS} , Err^{Prim} and the respective convergence orders when using a nonhomogeneous Dirichlet boundary condition for the charged and neutral chromophores are given in Figures S5, S6, and S7. The nonhomogeneous Dirichlet boundary condition that is used there is given by the Coulomb potential (see (11)) for the point charges defining the respective problem (primal or adjoint) with a uniform dielectric coefficient $\epsilon = \epsilon_m = 1$. In this case, the boundary condition prescribes the exact potential on the boundary of the computational domain Ω and coincides with the boundary condition used by MEAD and APBS.

Figure 6: Model-1. Convergence of the averaged (over 19 frames) interaction energies E_{1-2}^{Adj} and E_{2-1}^{Prim} computed by ARGOS against the average number of DOFs (over the same 19 frames). The dashed lines represent the optimal convergence rates for the used finite element spaces, i.e. P_1 for the primal and P_2 for the adjoint problem (see (45) and (46)).

The relative errors of MEAD, APBS, and ARGOS are compared in Figure 7. As evident from Figures 6 and 7 the FE-solver ARGOS is orders of magnitude more accurate than the FD-solvers MEAD and APBS. In the case of MEAD, adjusting the SOR parameters in M1-2 helps to decrease the relative errors for many frames, except frame 12. The maximum error for configuration M1-2 is limited to 2%. From this example, we see, first of all, that if the number of

iterations in SOR is too small, the iterative error dominates the one resulting from the discretization. Next, a significant increase of the number of SOR iterations helps to improve the accuracy up to a certain point. Further increase results in an accumulation of round off errors, due to the single precision arithmetic used and no further decrease of the overall error is possible.

APBS performs much better than MEAD for almost all frames. Its error does not exceed 0.4% and can be lower than the one of ARGOS for MRL=0. However, further refinements gradually decrease the relative errors, reaching about 5×10^{-3} % at most for MRL=4. If one continues with the mesh refinement procedure in ARGOS, the relative errors drop even further, see Figure S4.

Figure 7: Model-1. Relative accuracy in % of the MEAD and ARGOS solvers with respect to the analytical solution for coupling between chromophores in charge-neutral ground state in a uniform dielectric for different configurations of MEAD and MRL of ARGOS.

3.1.2 Model-2: accuracy of the interface description

As discussed in the introduction, the approximation of the geometric features of the interfaces between different dielectric media, as well as the approximation of the continuity conditions, (6) and (7), on the potential ϕ and on the normal component of the displacement field $\epsilon \nabla \phi$, are critical for the numerical methods, particularly for the FD ones. The description of the sharp interfaces, where the dielectric constant undergoes a considerable jump, is especially important for the computation of the electrostatic interaction. Furthermore, the presence of charges close to the interface can also have a strong impact on the accuracy.

In order to have an analytical solution to compare with, we investigate the interaction between a charge $q_1 = 1e_0$ in the center of a spherical cavity and a probe charge $q_2 = -1e_0$ outside the cavity. The different dielectric constants are assumed $\epsilon_m = 4$ inside and $\epsilon_s = 80$ outside the cavity. The spherical cavity with the charge represents the Born model of ion solvation.

In a first model a cavity with radius $R = 2 \text{ \AA}$ is assumed (Figure 8). The coordinates of the ion are $(0.05, -0.03, -0.25)$. The electrostatic interaction energy was calculated for different distances r of the probe charge from the center of the ion for $1 \text{ \AA} < r < 35 \text{ \AA}$. To track the dependence of the MEAD and APBS results on the relative orientation of the FD-solver's grid and the probe charge position, we computed the electrostatic interaction for 10 different directions $\vec{d}_i$ from the ion's centre, along which the probe charge was placed: $\vec{d}_1 = (1, 0, 0)$, $\vec{d}_2 = (-1, 0, 0)$, $\vec{d}_3 = (0, 1, 0)$, $\vec{d}_4 = (0, -1, 0)$, $\vec{d}_5 = (0, 0, 1)$, $\vec{d}_6 = (0, 0, -1)$, $\vec{d}_7 = (1, 1, 1)$, $\vec{d}_8 = (-1, -1, -1)$, $\vec{d}_9 = (1, 0.5, 0.2)$, $\vec{d}_{10} = (-1, -0.5, -0.2)$. The relative errors in

the interaction energies calculated for the same r along different directions $\vec{d}_i$ were averaged over all i to obtain the values $\overline{Err}^{MEAD}(r)$ and $\overline{Err}^{APBS}(r)$ for each distance r from the ion's center (for details see the SI).

To obtain the interaction energy with MEAD and APBS, we computed the ESP at the position of the probe charge, and multiplied it by q_2 . The configurations M2-1 and M2-2 for MEAD, and A2 for APBS used in the computations related to Model-2 are given in Tables 3 and 4. All grids for both MEAD and APBS, initial coarse and all focused grids, are centered at $(0, 0, 0)$, i.e., slightly offset from the centre of the ion. In the case of MEAD the calculations were performed for two different sets of SOR parameters (Table 3). APBS yields very similar results for calculations with `etol` $1e-06$ and `etol` $1e-09$. Therefore we present only the ones for the latter.

Table 3: Computational configurations, used in MEAD calculations for Model-2.

Configuration	Coarse-grained mesh number of nodes/spacing (Å)	Intermediate mesh number of nodes/spacing (Å)	Fine mesh number of nodes/spacing (Å)	SOR maxiter	SOR maxrmediff
M2-1	101/3	161/1	161/0.25	default (1440 and 2400)	default $2 \cdot 10^{-8}/(N_d - 1)$
M2-2	101/3	161/1	161/0.25	for all meshes 12000	$2 \cdot 10^{-8}/(N_d - 1)$

Table 4: The configuration A2 of APBS for Model-2. The `etol` is set to $1e-09$.

dime	cglen grid spacing (Å)	fglen grid spacing (Å)	Automatically placed intermediate focused mesh: size / grid spacing (Å)
385 385 385	900 900 900 / 2.344	96 96 96 / 0.25	293.94 293.94 293.94 / 0.765

In the ARGOS calculations we used *GridScale*=2 and 4 with solutions taken at MRL=5 and MRL=3, respectively. The computational domain Ω was a cube with an edge length of approximately $1350000 \text{ \AA}$. Here, we only present the results of ARGOS for a homogeneous Dirichlet boundary condition (this is possible since the boundary of Ω is very far from the ion and the probe charge). The results for a nonhomogeneous boundary condition, given by a simple Coulomb formula for the charges with $\epsilon = \epsilon_s$ are presented in the SI, Figure S11. In this case the boundary potential is exactly prescribed, since the Coulomb potential coincides with the exact one given by (53) on the boundary of Ω and the quality of the potential (the limit error after many refinement levels, Figures S8 and S11 in the SI) depends only on the geometric approximation of the surface of the spherical cavity. This boundary condition, being exact, also ensures the validity of the natural symmetry $E_{1-2} = E_{2-1}$ for the large, but still bounded computational domain Ω .

An illustration of the mesh for *GridScale*=2 before and after refinement is presented in Figure 8. Comparison of the initial and final mesh structures shows significant refinement in the critical areas: around the ion surface, the points, where the ion charge and probe charge are located, and in between the two charges (see Figure 8). The convergence of the relative errors with increasing refinement levels of ARGOS is shown in Figures S8 and S11 in the SI.

The analytical solution for the interaction energy between the ion and the probe charge follows from the well-known expression for the electrostatic potential φ :

$$\varphi(r) = \begin{cases} \frac{q_1}{\epsilon_m r} + \frac{q_1 (\epsilon_m - \epsilon_s)}{\epsilon_m \epsilon_s R}, & r \leq R, \\ \frac{q_1}{\epsilon_s r}, & r \geq R. \end{cases} \quad (53)$$

Figure 8: ARGOS (*GridScale*=2) mesh refinement for the solution of the primal and adjoint problems for Model-2. Here, the ion sphere radius is 2 Å and the probe charge is at a distance $r = 15$ Å from the center of the spherical ion. The color code corresponds to the solution of the adjoint problem (28) in units of $10^{-3}e_0/\text{Å}$.

Figure 9: Model-2. Relative errors with respect to the analytical solution: averaged (over 10 directions $\vec{d}_i$) relative errors $\overline{Err}^{MEAD}$ and $\overline{Err}^{APBS}$ for MEAD and APBS together with the relative errors for ARGOS at MRL=5 and MRL=3 for *GridScale*=2 and 4, respectively.

The relative errors of the calculations obtained with MEAD, APBS and ARGOS using different solver configurations are given in Figure 9. It is readily seen, that all configurations of MEAD and APBS produce a significant error at the interface ($r = 2$ Å) between the ion and the solvent. With increasing r , the errors of MEAD increase and the accuracy gets worse for the default SOR parameters. For the adjusted SOR parameters, the relative errors drop for distances $r > 2$ Å and do not exceed 0.3 % for distances larger than 6 Å. The errors of ARGOS are substantially smaller for short distances. The highest relative error occurs at $r = 1$ Å and reaches 2% for *GridScale*=2. At the interface the relative error decreases to 0.4 and 0.2 for *GridScale*=2 and 4, respectively.

For an ion radius $R = 1$ Å, the relative errors of MEAD and APBS are approximately 60 % at the interface between the two dielectrics (See Figure S13 in the SI). This result shows that the presence of charges near sharp interfaces has a very strong impact on the accuracy of the FD approximation of the electrostatic interaction. On the other hand, the relative error for ARGOS is also maximal at the interface, but it does not exceed 1 % for both *GridScale*=2 and 4. The error for $r > 1$ Å is around 10^{-2} % for both *GridScale*=2 and 4. The convergence of the relative error for ARGOS for both *GridScale*=2 and 4 with respect to the mesh refinement levels is shown in the SI, Figures S8, S11, and S12.

We also recall that the results obtained by MEAD and APBS for a grid spacing $h = 0.25$ Å in the final focused mesh should be compared to the ARGOS results with *GridScale*=4, since the resolution of the triangulated molecular surface mesh in this case is determined from the intersection of a cubic grid with the same grid spacing $h = 0.25$ Å and the analytical representation of the SES.

To further investigate the influence of the interface on the accuracy of MEAD, APBS, and ARGOS we considered

interaction between a Born ion with increased radius and a probe charge, placed near the Born sphere (see Figures S14, S15, S16, and S17 in the SI). The results revealed that the relative error of the interaction for the probe charge on the interface decreases, when the interface is further away from the charge of the ion (located in the center of the spherical cavity). The relative errors at the interface $r = 16$ Å reaches more than 3 % on average for both MEAD and APBS with a grid spacing $h = 0.25$ Å in the last focused grids. The accuracy does not much improve when the grid spacing h of the last focused grids is reduced to 0.15 Å. In this case, the relative errors at the interface reach more than 2 % for both MEAD and APBS. Although relative error 2-3 % is not large, one should keep in mind that this case corresponds to only one ion and one probe charge. Since the error is additive, the chance of getting large errors with FD solvers in the interaction energy increases for large molecular systems. This will be revealed in Section 3.2 where we investigate the error in the electrostatic interaction between chromophores obtained by MEAD and APBS. On the other hand, similarly to the results presented in Figures 9 and 10, the relative errors for ARGOS are more than two orders of magnitude smaller around the interface (for details see the SI).

3.1.3 Model-3: accuracy in the presence of interfaces and ions

Here, we supplemented Model-2 with ions, introducing an ionic strength of 0.3 M and taking into account the ion exclusion layer (IEL). Here, the IEL is enclosed between the ion sphere and another concentric sphere with an enlarged radius by that of a probe ion's radius $R_{\text{ion}} = 2$ Å. For MEAD and APBS we used the configurations, defined in Table 3 and Table 4, respectively. The APBS results for `etol` $1e-06$ and `etol` $1e-09$ do not differ again, and thus we report them only for the latter case. The computational domain for ARGOS is the same as for Model-2. We compare the solutions of ARGOS obtained at MRL=3 and 4 for *GridScale*=2 and 4, respectively, with those obtained by MEAD and APBS. The convergence of the ARGOS relative errors with increasing mesh refinement levels is shown in the SI, Figure S18. The analytical solution for the electrostatic potential φ in this

case is given as:

$$\varphi(r) = \begin{cases} \frac{q_1}{\epsilon_m r} + \frac{q_1 (\epsilon_m - \epsilon_s)}{\epsilon_m \epsilon_s R} - \frac{q_1 \frac{\bar{k}}{\sqrt{\epsilon_s}}}{\left(1 + a \frac{\bar{k}}{\sqrt{\epsilon_s}}\right) \epsilon_s}, & r \leq R, \\ \frac{q_1}{\epsilon_s r} - \frac{q_1 \frac{\bar{k}}{\sqrt{\epsilon_s}}}{\left(1 + a \frac{\bar{k}}{\sqrt{\epsilon_s}}\right) \epsilon_s}, & R \leq r \leq a, \\ \frac{q_1 \exp\left(a \frac{\bar{k}}{\sqrt{\epsilon_s}}\right) \exp\left(-r \frac{\bar{k}}{\sqrt{\epsilon_s}}\right)}{\left(1 + a \frac{\bar{k}}{\sqrt{\epsilon_s}}\right) \epsilon_s}, & r \geq a, \end{cases} \quad (54)$$

where r is the distance of the probe charge from the center of the Born ion and $a = R + R_{ion}$.

Figure 10: Model-3. Relative errors with respect to the analytical solution: averaged (over 10 directions $\vec{d}_i$) relative errors $\overline{Err}^{MEAD}$ and $\overline{Err}^{APBS}$ for MEAD and APBS together with the relative errors for ARGOS at MRL=3 and MRL=4 for $GridScale=2$ and 4, respectively.

The results of the calculations, shown in Figure 10, demonstrate a drastic change in the MEAD accuracy for M2-1 in comparison to Model-2 (Figure 9): the errors do not exceed 2% for all distances r , while for Model-2 the errors go beyond 10%, when r is increasing. Moreover, for $r > 20$ Å, the computational error for MEAD depends more on the mesh spacing than on the SOR parameters, in contrast to Model-2. This means that the discretization error dominates the error of the iterative linear solver (for other MEAD configurations see also Figures S9 and S19 in the SI). It should also be mentioned that for configuration M2-2 the respective maximum iteration number `maxrmsdiff` is not reached in the numerical solution.

Similarly to Model-2, the errors of MEAD and APBS around the interface between the ion and the solution are particularly large, reaching more than 30 %. Decreasing the distance between the singular charge density and the interface results in a further increase of those errors. For an ion with a radius $R = 1$ Å, they are as high as 70 % and 50 % for MEAD and APBS, respectively, while ARGOS displays even lower errors than in the case $R = 2$ Å (Figure S22 in the SI).

The results for all test models, studied above, reveal that the accuracy of MEAD is greatly compromised even for the simplest case of point charges in vacuum. The presence of interfaces with a high jump in the dielectric constant leads to a strong dependence of the accuracy on the mesh spacing and SOR stopping criteria, especially for long-range interactions. Besides the stopping criteria issue, the use of single precision arithmetics can also lead to significant round-off errors. ARGOS, on the other hand, exhibits a predicted and uniform convergence. The results of APBS calculations demonstrate much smaller relative error, than MEAD, but

still do not reach the accuracy of ARGOS. The test calculations also reveal, that $GridScale=2$ and refinement levels between 3 and 5 for ARGOS result in a high enough accuracy and should be sufficient for most cases.

In the next sections we will use ARGOS as a reference to explore the accuracy of the MEAD and APBS solvers in computations of interaction energies in real systems.

3.2 Interactions between chromophores in a dielectric environment

The interaction energy between two chromophores, described by molecule-shaped cavities with atomic partial charges, in a dielectric environment cannot be computed analytically. Therefore, we exploit the high accuracy of the ARGOS results and determined the deviations, D_{AM} and D_{AA} , of the MEAD and APBS results, correspondingly, with respect to the former, defined analogously to (52) by:

$$D_{AM} = \frac{|E_{1-2}^{Adj} - \overline{E}^{MEAD}|}{|E_{1-2}^{Adj}|} \cdot 100. \quad (55)$$

$$D_{AA} = \frac{|E_{1-2}^{Adj} - \overline{E}^{APBS}|}{|E_{1-2}^{Adj}|} \cdot 100. \quad (56)$$

Refinement level $\ell = 4$ and $GridScale=2$ are employed for calculations with ARGOS. The computational domain is a cube with a side length between 160 000 Å and 400 000 Å depending on the size of the smallest box containing the molecular system. For MEAD and APBS we used configurations M1-2 and A1 given in Tables 1 and 2, respectively.

We start with the coupling between the charge densities of the electronic ground states of the two chromophores in equilibrium with the solvent. The orientational polarization of water molecules dominates the dielectric response of the solvent. The large dielectric constant of water results in a sharp interface at the molecular surface, where ϵ jumps from a low value for the chromophores or the protein ($\epsilon_m = 4$) to the large value $\epsilon_s = 80$ for the aqueous solvent. In this case the accuracy of the numerical solution of the electrostatic problem critically depends on the approximation of the interfaces.

To study the impact of the description of interfaces, we calculated the charge density coupling between electronic ground states of the chromophores for different MD frames for POLY6 and POLY20. For every frame we computed the coupling between the dyes, using the following models with different types of interfaces:

- NO-INT, no interfaces: chromophores are represented by point charges placed at the positions of atoms, immersed in a homogeneous environment with dielectric constant ϵ_s ;
- DYES, dyes-solution interface: chromophores are represented by point charges inside molecule-shaped cavities with dielectric constant ϵ_m inside, surrounded by a homogeneous dielectric with ϵ_s , representing the aqueous solvent (see Figure 11a);
- DYES-POLYPRO, dyes-solution and protein-solution interfaces: chromophores are represented like in the previous model; polyproline is included as a molecule-shaped cavity with dielectric constant ϵ_m inside (see Figure 11b);

- DYES-POLYPRO-IONS, dyes-solution and protein-solution interfaces: the previous model is complemented with ions in the aqueous solvent, characterized by an ionic strength of 0.3 M (see Figure 11c).

The Alexa chromophores in their electronic ground state are negatively charged by two elementary units ($-2e_0$).⁴⁶ In order to investigate, how the interchromophore charge density coupling changes, if no monopole moments are present, we artificially neutralized the chromophores by redistribution of the charges within the SO_3 groups such that the overall charge of the chromophores is zero, as described in the SI. Please note that this neutralization is not realistic for the present chromophores but represents a common situation for other chromophores, which would, of course, differ in the details of the charge density.

It is known, that the interaction energy also depends on the definition of the solute surface (see, for example, Ref. 51), but the study of this problem is beyond the scope of this paper. Here, for all cases we define the molecular surface of the chromophores as a Connolly surface, formed by the contact points of the van der Waals surface and a (solvent) probe sphere, rolling over it (see Refs. 52–56). The probe radius was set to 1 Å in all calculations.

3.2.1 Charged dyes

The relative deviations between solutions of MEAD, APBS and ARGOS for charged chromophores are presented in Figure 12 for the three different models described above.

The examination of the relative deviations for MEAD demonstrates, first of all, that including the polypyrrolone domain can notably change the error (for example, frames 5, 9 and 10 in Figure 12), but it still stays small: the maximum value of D_{AM} does not exceed 3%. Furthermore, for all frames, except frame 16, including the ionic strength of the solvent results in an increase of D_{AM} . For example, the relative deviations for frames 5 and 9 have increased 100 times. To understand these effects we calculated the interaction energy for all models with ARGOS (see Figure 13 and Figure 14 for logarithmic scale of the y -axis).

As evident from Figure 13, the difference between interaction energies, computed for different models, is more pronounced for POLY6 (frames 1 to 10). Introducing molecular cavities for the dyes and polypyrrolone, increases the interaction energy in comparison to the simple model of a homogeneous dielectric. This effect is due to the lower dielectric constant inside the cavities. For larger interchromophore distances this effect gets smaller.

The results, shown in Figure 14, demonstrate a significant screening of the interaction by the ions, resulting in a decrease of the interaction energy for all frames. The magnitude of the screening effect for POLY6 can vary significantly, reducing the interaction energy by factors between 1.5 and 100, depending on the conformation of the system (see Figure 14). For larger distances between the chromophores in POLY20, the magnitude of the screening effect varies stronger: between 10^2 to 10^6 times (see the results for frames 11 and 12 in Figure 14). The large increase in screening for POLY20 with respect to POLY6 and its large variation can be explained in the following way. When the charged chromophores are far apart, they can be approximated by Born ions, immersed in the dielectric continuum with ionic strength. In this case, the interaction energy can be obtained analytically from the potential in (54). It includes an exponential factor, which imposes a highly nonlinear decline with increasing distance. To estimate its influence we compare the screening effect for frames 12 and 14, which correspond to interchromophore distances of 78 Å and

42 Å respectively. The ratio between the interaction energies, calculated by ARGOS, is about 10^{-4} (see Figure 14 for the model DYES-POLYPRO-IONS). The estimation of this ratio, using (54) with $\bar{k}^2 = 2.529 \text{ Å}^{-2}$, gives $9 \cdot 10^{-4}$, thereby, providing a qualitative explanation of the effect of the exponential screening factor. Without exponential factor we obtain only a ratio of 0.5.

Furthermore, an examination of the results in Figure 14 shows a significant drop in the interaction energies due to ion screening for frames 12, 18 and 19. At the same time these frames exhibit the largest relative deviations for MEAD (Figure 12).

The significant increase of D_{AM} for the model DYES-POLYPRO-IONS has several reasons. First of all, the accuracy of MEAD for M1-2 is worse for systems with ions and long distances between interacting chromophores. This effect can be readily seen from comparison of the results for Model-2 and Model-3 in setup M2-2 (see Figures 9 and 10), which has the same parameters (grid spacing and SOR) as M1-2. The errors for Model-3 increase with distance. The accuracy for the model DYES-POLYPRO-IONS can probably be improved by applying a finer mesh, but this would increase the computational costs substantially.

The APBS results in Figure 12 deviate from the reference solution of ARGOS much less, compared to those obtained with MEAD. Only D_{AA} for frame 12 (in the model DYES-POLYPRO-IONS) approaches 20%. Similar to the MEAD case, the deteriorated accuracy can originate from the extremely small interaction energy. On the other hand, in this frame the system is in a maximally stretched conformation, see Figure 17d. The minimal box that contains the polypyrrolone system has dimensions of $90.7 \times 25.1 \times 17.1 \text{ Å}^3$ and it is only slightly smaller, than the box of the finest focused grid (`fglen` 100 100 100) in configuration A1 of APBS. Hence, it probably does not provide enough margins between the sides of the fine grid box and the atoms of the system together with the IEL. To check this hypothesis, we computed the electrostatic energy with enlarged fine grid box (`fglen` 110 110 110), keeping all other parameters of configuration A1. Moreover, this configuration of APBS was employed to analyze the sensitivity of the results (for frame 12) with respect to the relative position of the molecular system and the grid. For this setup, electrostatic energies, together with their mean values and standard deviations were calculated for a perturbed grid center, given by $(x_0 + \Delta x_i, y_0 + \Delta y_i, z_0 + \Delta z_i)$ for $i = 1, 2, \dots, 15$ where (x_0, y_0, z_0) is the center of the minimal box, containing all atoms' centers, with sides parallel to the coordinate axes, and $(\Delta x_i, \Delta y_i, \Delta z_i)$ takes the values in (10) from the SI with $\Delta h = 0.15 \text{ Å}$. The obtained results were averaged over all 15 grid positions, giving interaction energies $\bar{E}_{1-2}^{APBS}$ and $\bar{E}_{2-1}^{APBS}$, and their respective standard deviations σ_{1-2} and σ_{2-1} . The final value for the interaction energy, $\bar{E}^{APBS}$, was obtained as usual by averaging of $\bar{E}_{1-2}^{APBS}$ and $\bar{E}_{2-1}^{APBS}$.

The results, presented in Table 5, demonstrate a high standard deviation for lower `etol` values, indicating significant sensitivity of the calculations with respect to the relative position of the grid center. Moreover, one can readily see a pronounced asymmetry in the values of the averaged interaction energies $\bar{E}_{1-2}^{APBS}$ and $\bar{E}_{2-1}^{APBS}$ (for details see Table S9 in the SI where one can also infer the absolute values of the errors). For comparison, the adjoint solutions E_{1-2}^{ARGOS} and E_{2-1}^{ARGOS} of ARGOS are equal to $-5.5959e - 10$ and $-5.5967e - 10$, respectively, for `GridScale`=2 at `MRL`=4. It is readily seen from Table 5 that the average value $\bar{E}^{APBS}$ provides a much better accuracy than single values, calculated for certain grid positions. Decreasing the value of the parameter `etol` improves the accuracy as well. Reduction

Figure 11: Models with different types of interfaces. Figures generated using VisIt.⁵⁰

Figure 12: Relative deviations from ARGOS solutions in the interaction energies of charged chromophores, obtained with MEAD (green symbols) and APBS (blue symbols). The electrostatic energies are calculated for MEAD configuration M1-2 from Table 1 and APBS configuration A1 from Table 2. The circles, squares, triangles correspond to the models DYES, DYES-POLYPRO, DYES-POLYPRO-IONS, respectively, that are explained in the text

of the grid spacing of APBS or equivalently an increase of the number of grid points is expected to further decrease the relative deviation D_{AA} . However, a limiting factor for this strategy would be primarily the memory capacity, required to store the coefficients and the potential values at all grid points.

Table 5: Sensitivity of the APBS results to the `etol` parameter and relative position of the grid and the system for **frame 12** for model **DYES-POLYPRO-IONS** with **charged chromophores**.

h (Å)	$\bar{E}_{1-2}^{APBS}$	σ_{1-2}	$\bar{E}_{2-1}^{APBS}$	σ_{2-1}	Avg. $\bar{E}^{APBS}$	$D_{AA}(\%)$
0.286 etol 1e-06	-4.82e-10	1.80e-11	-6.94e-10	1.23e-11	-5.88e-10	5.08
0.286 etol 1e-09	-5.79e-10	1.79e-11	-5.79e-10	1.16e-11	-5.79e-10	3.45

Figure 13: Comparison of the interaction energy between the charged chromophores for all models, calculated with ARGOS. The circles, squares, triangles correspond to the models DYES, DYES-POLYPRO, and DYES-POLYPRO-IONS, respectively.

Figure 14: Same as in Figure 13, but with logarithmic scale.

3.2.2 Neutral dyes

The relative deviations for the interaction energies between neutral chromophores, presented in Figure 15, reveal a drastic increase in relative deviations, compared to the previous case of charged chromophores in Figure 12. For MEAD computations, the relative deviations exceed 10% for most of the models and frames. Moreover, for some frames MEAD produces a different sign of the interaction energies than ARGOS (see frames 15 and 16 for M1-1 in Table 6) and hence a qualitatively different interaction. Obviously, a strong asymmetry ($E_{1-2}^{MEAD} \neq E_{2-1}^{MEAD}$) is an indicator of poor accuracy. At the same time, the energies E_{1-2}^{Adj} , computed by ARGOS from the adjoint problem defined by the charges of molecule M_1 , match the energies E_{2-1}^{Adj} com-

Figure 15: Relative deviations from ARGOS solutions in the interaction energies of chromophores in the charge-neutral ground states, obtained with MEAD (green) and APBS (blue). The electrostatic energies are calculated for MEAD configuration M1-2 from Table 1 and APBS configuration A1 from Table 2. The circles, squares, triangles correspond to the models DYES, DYES-POLYPRO, DYES-POLYPRO-IONS, respectively.

Figure 16: Comparison of the interaction energy between the chromophores in the charge-neutral ground states for all models, calculated with ARGOS. The circles, squares, triangles correspond to the models DYES, DYES-POLYPRO, and DYES-POLYPRO-IONS, respectively.

puted from the adjoint problem with the charges of molecule M_2 . The respective values are even computed on two different sequences of adapted meshes, both starting from one and the same initial mesh, demonstrating again a very good symmetry, and thus the superior performance of the FE-solver. In addition, frames 10 and 15 were also computed with $GridScale=4$ for ARGOS. The corresponding energies E_{1-2}^{Adj} and E_{2-1}^{Adj} at $MRL=4$ (again computed on two different sequences of adaptively refined meshes) are $2.7915e-07$ and $2.7911e-07$, and $1.9649e-07$ and $1.9648e-07$, respectively.

Similarly to the previous case, the APBS results deviate much less from the ARGOS solutions, compared to the MEAD calculations: D_{AA} values do not exceed 10% except frames 6 (model DYES-POLYPRO-IONS) and frame 10 (model DYES). However, unlike the case with frame 12 in the system of charged dyes, the minimal boxes for frames 6 and 10 ($31.2 \times 20.7 \times 15.3 \text{ \AA}^3$ and $48.2 \times 24.6 \times 19.9 \text{ \AA}^3$, respectively) are well covered by the final focused grid box. To examine if the results can be improved by decreasing the spacing of the finest focusing grid, h , and decreasing the `etol` parameter, we compare the interaction energies, calculated for h equal to $0.25 \text{ \AA}$, $0.2 \text{ \AA}$, $0.15 \text{ \AA}$ and `etol` $1e-6$ and $1e-9$. For every case, the sensitivity of the results to the grid centre position was also analysed in the same way as in the previous case of charged dyes. For both frames the results, computed with `etol` values $1e-6$ and $1e-9$, do not

Table 6: Interaction energies, calculated with MEAD and ARGOS with $GridScale=2$ at $MRL=4$ for different frames and interfaces models with neutral dyes. The table demonstrates the “asymmetry” of the interaction energies, calculated by MEAD: $E_{1-2}^{MEAD} \neq E_{2-1}^{MEAD}$.

		E_{1-2}^{MEAD}	E_{2-1}^{MEAD}	$\bar{E}^{MEAD}$	E_{1-2}^{Adj}	E_{2-1}^{Adj}
Frame 15,	M1-1	1.20e-07	-1.87e-07	-3.36e-08	1.9797e-07	1.9796e-07
	DYES	M1-2	1.03e-07	9.15e-08		
Frame 10,	M1-1	-1.65e-07	-4.86e-08	-1.07e-07	2.8530e-07	2.8539e-07
	DYES	M1-2	1.36e-07	2.00e-07		
Frame 16,	M1-1	2.33e-07	-1.59e-07	3.66e-08	2.9233e-07	2.9232e-07
	DYES-POLYPRO	M1-2	2.75e-07	2.68e-07		

differ significantly and so in what follows we will present the results only for the latter case.

The interaction energies for frames 6 and 10 are presented in Tables 7 and 8, respectively (for more details see Tables S10 and S11 in the SI). Like in the case of charged dyes, the values of E_{1-2}^{APBS} and E_{2-1}^{APBS} for all the tested grid spacings do not exhibit the natural symmetry $E_{1-2}=E_{2-1}$. The effect is even more pronounced for particular relative positions of the molecular system and the grid, when E_{1-2}^{APBS} and E_{2-1}^{APBS} can have different sign (see the SI, grid centering perturbation $i = 10$ in Table S10 for $h = 0.2 \text{ \AA}$ of frame 6). Moreover the asymmetry of the solutions, as well as the standard deviations σ_{1-2} and σ_{2-1} for some frames, do not scale down as $h \rightarrow 0$. The relative deviations D_{AA} show a slow convergence to the ARGOS solution: even at the smallest grid spacing the variation of computed energies with respect to small perturbation of the grid position remains substantial. On the other hand, the convergence also indicates that the ARGOS solution is indeed accurate. Similar to the case of charged dyes, our analysis demonstrates that one calculation per frame is in general not sufficient to obtain a reliable result. Instead, an averaged value, obtained from a series of calculations with variations in the grid centering and of the grid spacing h is required. This example also shows that if one wishes to use a finer final focused grid, it is required to considerably increase the values of the `dime` parameter of APBS (see Table S10 in the SI) which, on the other hand, increases the computational costs.

Table 7: Sensitivity of the APBS results to the grid spacing and relative position between grid and the system for **frame 6** in model **DYES-POLYPRO-IONS** with **neutral chromophores**.

$h \text{ (\AA)}$	$\bar{E}_{1-2}^{APBS}$	σ_{1-2}	$\bar{E}_{2-1}^{APBS}$	σ_{2-1}	Avg. $\bar{E}^{APBS}$	$D_{AA}(\%)$
0.25	1.74e-06	6.55e-07	1.79e-06	6.76e-07	1.77e-06	83.47
0.2	1.17e-06	5.73e-07	1.27e-06	4.98e-07	1.22e-06	26.69
0.15	7.88e-07	2.32e-07	8.48e-07	2.21e-07	8.18e-07	15.00

Both FD solvers do not ensure the natural symmetry condition. Reducing the grid spacing helps to improve the accuracy, but not to the level obtained for the charged chromophores. In contrast to the latter, in the present case, the leading term in the interactions is due to dipoles. The results strongly depend on their mutual orientation of dipoles. The magnitude and orientation of molecular dipole are determined by the distribution of the charges. Therefore, the discretization of the charges near the sharp interface can significantly contribute to the accuracy of the computations. Furthermore, in contrast to the case of charged dyes, where

Table 8: Sensitivity of the APBS results to the grid spacing and relative position between grid and the system for **frame 10** in model **DYES** with **neutral chromophores**.

h (Å)	$\bar{E}_{1-2}^{APBS}$	σ_{1-2}	$\bar{E}_{2-1}^{APBS}$	σ_{2-1}	Avg. $\bar{E}^{APBS}$	$D_{AA}(\%)$
0.25	2.23e-07	3.40e-08	2.71e-07	3.66e-08	2.47e-07	11.50
0.2	2.62e-07	2.43e-08	2.65e-07	6.28e-08	2.63e-07	5.74

the DYES-POLYPRO-IONS model exhibits the largest errors for almost all frames, here the highest D_{AA} and D_{AM} are obtained for other models for half of the frames.

Influence of the charge distribution and presence of the interface

Here we introduce a new setup for the DYES model, using transition charges and dielectric constants $\epsilon_m = 1$ for the dyes and $\epsilon_s = 2$ for the solvent. This case represents Förster resonance energy transfer (FRET) between the chromophores. In FRET only the electronic part of the environmental polarization, described by an optical dielectric constant of 2 (typical for organic matter), needs to be taken into account.⁵⁷ The relative errors for the dyes with transition charges are compared with different other setups, where the chromophores have neutral ground-state charges and different values of the dielectric constants, see Table 9.

Table 9: Setups for calculations of interactions between neutral dyes in charge-neutral state.

Setup	ϵ_m	ϵ_s	charge type
1	4	80	ground state
2	4	80	transition
3	1	2	ground state
4	1	1	ground state
5	1	2	transition state

The results of ARGOS for the setups featuring interfaces, i.e., a jump in the dielectric constant ϵ , were obtained using MRL=4 with a geometric approximation of the interface given by *GridScale*=4 in NanoShaper. The MEAD results (Figure 18) reveal that removing the interface, passing from Setup 1 to Setup-3 and Setup-4, gradually reduces the relative deviations for almost all frames, indicating a strong influence of the jump in dielectric constant on the numerical accuracy. The only exception is the frame 14. Here we have an increase of D_{AM} for Setup-3 compared to Setup-1, but then the deviation drops for Setup-4.

APBS demonstrates a better accuracy with D_{AM} values not exceeding 10%, but the same dependence on the "sharpness" of the interface. Although the results for frames 14 and 19 depart from this behaviour, revealing an increase of errors in Setup-3, compared to Setup-1: D_{AA} rises from 5.6% to 21.7% and from 6.8% to 9.1% for frames 14 and 19 respectively. The accuracy for Setup-3 can be improved by reducing the grid spacing and averaging the interaction energy over relative positions of the grid and the system, like it was done in the previous cases. This procedure reduces the deviation D_{AA} to 3.35% for frame 14 and to 0.88% for frame 19 (see details in the SI, Tables S13 and S15), restoring the correct trend and demonstrating again the strong sensitivity of the APBS results on the relative position between the grid and the molecular system.

Application of the transition charges leads to smaller deviations D_{AM} and D_{AA} for all frames, where the error in

Setup-1 is still larger than 10%. Frame 1 shows the opposite trend: for Setup-2 with transition charges D_{AA} increases almost 10 times, compared to Setup-1 with ground-state charges. Calculations of averaged $\bar{E}^{APBS}$ on grids with smaller spacing (see Table S16 in the SI) cut down the error to 0.51% which confirms the general behaviour of the numerical errors where D_{AM} and D_{AA} decrease significantly upon reducing the magnitude and the number of nonzero charges.

The above effect can be explained in the following way: in the case of transition charges the potential is created by a smaller number of nonzero charges (as a result it is more accurately approximated by the FD solvers) compared to the case of ground-state charges, and then multiplied by, again, a smaller number of nonzero charges⁴ (see Tables S3 and S4, and S1 and S2 for the ground-state and transition-state charges, respectively, for the two dyes). However, MEAD demonstrates much worse accuracy for Setup-2, than APBS (Figure 18). To investigate, if it can be improved by "smoothing" the interface, like it was in the case of ground-state charges, we performed extensive calculations for POLY6 with Setup-5 from Table 9 (see Figure S23 in the SI). This case is of particular interest, since it corresponds to the FRET effect, mentioned above. It has been investigated in our previous publications.^{46,57} The results demonstrate that for the most frames of POLY6, MEAD relative deviations stay below 3%, while for several ones the error can reach up to 20%, similar to the case of the chromophores with transition-state charges in Setup-2. Therefore, in the case of transition charges, reduction of the dielectric constants jump does not improve much the accuracy of MEAD.

Analysis of the above examples show, first of all, how important the correct treatment of the interfaces is to obtain accurate results, especially in the case of the ground-state charges. In addition, in order to improve the accuracy of the APBS results it is required to take an average over a series of calculations per frame with respect to many relative positions of the grid and the system. Calculations for decreasing grid spacings h are also necessary for APBS. Application of the smaller grid spacings h and better SOR parameters together with averaging over different relative positions of the grid and the system could also help to decrease the relative deviations between MEAD and ARGOS.

Influence of the screening by ions

In order to investigate the ionic screening effects in more detail, we applied ARGOS to calculate the reference interaction energies for all interface models. Two additional models without dielectric boundaries ($\epsilon_m = \epsilon_s = 80$), but including the ion exclusion layer (IEL) around different parts of the molecular system, were introduced as well (the rombs and the crosses in Figure 19):

- DYES-IONS includes the IEL around the chromophores;
- DYES-POLYPRO-IONS-2 includes the IEL around the chromophores and polyproline helix.

Please note that the ions are not allowed to penetrate into the region, defined by the IEL around the chromophores (in model DYES-IONS) and around the dyes and the polyproline (in model DYES-POLYPRO-IONS-2).

Results, presented in Figure 19 reveal, first of all, that the magnitude and even the sign of the interaction energy for a given configuration of chromophores can be drastically different in the different models. For example, excluding

⁴Here by a smaller number of nonzero charges we also refer to the fact that almost all charges in both dyes are either zero or negligible in magnitude relative to a few nonzero ones.

the ions from the polyproline domain for POLY6 can decrease the interaction energy (see frame 6 of POLY6, Figure 19). Moreover, for a few frames, the presence of the ions in the polyproline domain leads to a change of the sign of the interaction energy (see frames 6, 12, 14, 16, 19 in Figure 19). Furthermore, this presence does not always lower the interaction energies. For frames 1, 3, 8, 9 of POLY6 the energy is not changed and frame 2 shows an enhanced interaction between the dyes (compare the triangles with the squares), which is not observed for the large interchromophore distances present in POLY20 (frames 11-19). Analysis of Figures 15 and 19 shows that the highest D_{AM} and D_{AA} (for the model DYES-POLYPRO-IONS) are obtained for frame 6, despite the interaction energy is not the smallest in the set. Moreover, this coupling is of the same order of magnitude as the interaction energies obtained for frames 4 and 5. The latter, however, exhibit much lower relative deviations for both solvers. As it was shown above, the APBS error for frame 6 can be reduced up to 15 % by averaging over different relative orientations of the grid, but this magnitude is still much higher than D_{AA} for frames 4 and 5. Further, Figure 15 shows that introducing a new interface, while passing from model DYES to DYES-POLYPRO increases the relative deviations for both solvers. On the other hand, the smallest interaction energies (frames 12, 18, 19) do not possess the largest errors in contrast to the results for the charged chromophores.

Comparing the results for both peptides, we find that the decrease in electrostatic interaction, caused by the ionic screening, is less for POLY 6 than for POLY20. The reason for this difference can be attributed to the much shorter distances between the chromophores for POLY6. In this case the ions can penetrate much less into the area between the dyes. For frames 1, 3 and 8, which correspond to the strongest coupling and shortest interchromophore distances, the interaction energies, calculated for models without ions (NO-INT, stars) and with ions (DYES-IONS, rombs) are practically the same. While for all frames of POLY20 (frames 11-19) the two differ by several orders of magnitude. An example of a strong interaction is given by the chromophore conformation in frame 1 (Figure 17a). Here one can readily see that the dyes are very close to each other, forming, probably, a joint cavity. And the results for this frame demonstrate that the interaction energies mostly depend on the dielectric constant inside the chromophore cavities and not on the presence of the peptide domain and ions in the solution.

In general, excluding the ions from the polyproline domain (in the model DYES-POLYPRO-IONS-2) can substantially increase (frames 7 and 12) or decrease (frames 11 and 13) the interchromophore coupling for both POLY6 and POLY20. The effect depends mostly on the orientation of the dyes with respect to the polyproline. In the closed conformation, when the chromophore with a long linker (Alexa 488) is close to the peptide (see Figure 17b and Figure 17c), the dipole of the chromophore is not surrounded by the ions completely. This configuration results in partial ionic screening of the charges that changes the magnitude and orientation of the effective dipole and, thus, modifies the interaction between the dyes. On the other hand, the open configuration (see Figure 17d) experiences a complete screening by the ions. Obviously, excluding the ions from the the polyproline domain leads to an increase of the interaction.

The demonstrated screening effects can be of particular interest for the development and applications of coarse-grained models of biomolecules, which use an implicit representation of the solvent (water and ions). In the common approaches the charges are screened using either the Debye-Hückel theory or generalized Born models. The first method describes ionic screening of electrostatic interactions, practically, using

(54),⁵⁸ though this expression is accurate only for a spherical charged particle, completely surrounded by the solvent. The authors of Ref. 59 propose to model partial screening in the generalized Born model with modified atomic radii. The latter are parametrized to characterize the extent of the screening of a solute atom due to shielding it from the solvent by other solute atoms. However, the parametrization in this approach is performed for the solvents without ions. At the same time, our results demonstrate that both conditions - partial screening due to the specific geometry of the solute and presence of the ions - are important for the interaction energy.

It is interesting to compare the results, obtained for neutral and charged chromophores. In contrast to the latter, the interaction energies for the neutral dyes in models DYES and DYES-POLYPRO are subject to a high variation, spanning a range of about 2 orders of magnitude.

Moreover, the overall screening effect in the present case is drastically diminished, compared to the case of charged chromophores. The maximum screening for the present case corresponds to a factor 10^{-3} (Figure 19, frame 12), while the maximum screening factor for the charged chromophores is about 10^{-6} (Figure 14, frame 12).

Analysis of the relative deviations of the FD-solvers revealed that while in the case of charged dyes the errors for smaller absolute interactions are usually larger, for neutral dyes it is their mutual orientation, that significantly affects the numerical accuracy. Furthermore, application of ARGOS for calculation of the interaction energies for different distances and relative orientations of chromophores demonstrated that the presence of ions in the solution can both decrease and increase the coupling and even change its sign, emphasizing the importance of the correct model and accurate calculations.

3.3 CPU times

Although ARGOS³⁵ is currently in a prototype version (implemented in FreeFem⁴⁵) and could be vastly improved, here we give some preliminary idea of the CPU times for ARGOS in comparison to APBS obtained on a machine with Intel(R) Core(TM) i5-7500 CPU @ 3.40GHz and 16 GB of RAM. Since the primal problem is discretized using the P_1 Lagrange finite element and the adjoint problem is discretized using the P_2 one, the number of DOFs, N_{DOFs}^{Adj} , in 3D for the adjoint problem is approximately 8 times larger than that for the primal⁵. Consequently, the major part of the CPU time per MRL for ARGOS is spent for the solution of the discrete adjoint problem and the refinement of the mesh for the next MRL. In all the presented examples, we use a basic Jacoby-preconditioned conjugate gradient (CG) method (with a stopping criterion ensuring a very high precision⁶) as an iterative solver for the resulting linear systems for both the primal and adjoint problem. As it was mentioned above, the mesh refining is done using mmg3d v4.0,⁴⁴ but a newer version of it can also be used. Any other remeshing software can be utilized as well, which could drastically reduce the CPU time for the mesh refining steps. In Tables 10 and 11 we present the CPU times for some examples with an increasing number of vertices in the initial mesh. We note that the reference solutions

⁵With a homogeneous Dirichlet BC the number of DOFs for the P_1 FE space, N_{DOFs}^{Prim} , is exactly equal to $N_V - N_{\partial\Omega}$, where $N_{\partial\Omega}$ is the number of mesh vertices on the boundary. In the case of nonhomogeneous BC, $N_{DOFs}^{Prim} = N_V$.

⁶The reference solutions of ARGOS presented in the paper are obtained with an error tolerance between $1e - 14$ and $1e - 12$ for the residual in the linear system, measured in the norm generated by the inverse of the matrix C , where C is the diagonal matrix with a diagonal equal to that of the system's matrix.

Figure 17: Conformations of the chromophores for different frames of MD simulations.

Figure 18: Relative deviations between interaction energies of the chromophores in a charge-neutral ground state, obtained with APBS (blue symbols) and MEAD (green symbols). Calculations are done for the model SURF-DYES and different setups (Table 9), using APBS configuration A1 from Table 2 and MEAD configuration M1-2 from Table 1.

Figure 19: Interaction energies of the chromophores in a charge-neutral ground state, calculated by ARGOS for different interface models. The blue and red colours of the symbols correspond to positive and negative interaction energies, respectively.

of ARGOS given previously are computed on meshes with uniform mesh size in the molecular regions, whereas the results below are obtained with coarser initial meshes of lower quality (the molecular surfaces are still the same). Nevertheless, the computed values for the interaction energy are practically the same. Below, t_{MRL} , t_{mat}^{Adj} , t_{CG}^{Adj} , t_{ref} denote the total CPU time per MRL, the CPU time to assemble the matrix for the adjoint problem, the CPU time to solve the adjoint problem, and the CPU time to refine the mesh, respectively.

As a first example, in Table 10, we consider Model-2 where the test charge is placed at a distance $r = 10$ Å from the Born ion. The total execution time for ARGOS with $GridScale=2$ and a CG tolerance of $1e-09$ is 46.9 sec (the corresponding time for a CG tolerance of $1e-12$ is 51.14 sec., see foot-

note 6). In comparison, APBS with configuration A2 (see Table 4) for **eto1** $1e-06$ takes 658 sec on average. Note that from this one computation with APBS one can extract the interaction energies for all distances $r \leq 48$ Å. However, the size of the final focused grid does not allow to place the test charge at a larger distance, whereas with ARGOS the size of the molecular system is not an issue. A further comparison of the CPU times for $GridScale=2$ and 4 in ARGOS is given in Tables S17 and S18 in the SI.

In Table 11 we give the CPU times of ARGOS for frame 10 of model DYES with neutral ground-state charges (see Figure 18). The total execution time for $GridScale=2$ and with a CG tolerance of $1e-09$ is 99 sec. compared to 109 and 143 sec. of APBS for configuration A1 (see Table 2) with **eto1** $1e-06$ and **eto1** $1e-09$, respectively. However, those CPU times of APBS are only for the computation of E_{1-2}^{APBS} , which alone is not enough to obtain a somehow reliable interaction energy and do not include the time of 17 sec. needed by the plugin *multivalue* to read each of the potential “dx” files and return the potential at the atom’s centres. Taking only one of E_{1-2}^{APBS} and E_{2-1}^{APBS} can result in a very high error (see Table S11 in the SI, together with the other tables concerning the inspection of problematic APBS frames).

Therefore, to compute $\bar{E}^{APBS}$ (see (51)), it takes in total 218 and 286 sec. for **eto1** $1e-06$ and **eto1** $1e-09$, respectively.

Finally, we report the CPU times for frame 12 of model DYES-POLYPRO-IONS in the case of charged dyes (see Table 5 and Table S9 in the SI). ARGOS with a CG tolerance of $1e-09$ and three MRLs takes 616 sec. compared to 837 sec. necessary to compute E_{1-2}^{APBS} with configuration A1 for **eto1** $1e-09$ (recall that $1e-06$ is not enough for this frame), and 747 sec. for **eto1** $1e-06$. Again, those times do not include the time of around 32 sec. spent by *multivalue* to read the “dx” file for each run and return the potential at the specified atom’s centres. If the CG tolerance in ARGOS is decreased to $1e-12$, then the time needed increases to 1114 sec., even though the resulting interaction energy is practically the same. However, we note that exchanging the Jacoby-preconditioned CG algorithm for an advanced iterative method, for example a CG with an appropriate preconditioner or a multigrid method, will dramatically improve the performance of ARGOS, which is already higher than that of APBS.

4 Conclusions

A new finite element method, termed ARGOS, for the solution of the linearized Poisson-Boltzmann equation is formulated, implemented and tested. The advantages of the method include a correct handling of the interfaces and an appropriate error estimation techniques for the target quantity, which leads to an efficient mesh adaptation and an efficient numerical solution.

Applications of ARGOS to model systems, for which analytical solutions exist, demonstrate the high accuracy of this solver. This high accuracy was used to evaluate the performance of FD solvers in an application to chromophore-labelled polyproline helices. A critical source of errors con-

Table 10: CPU times (including the generation of the initial mesh with NanoShaper and TetGen) in seconds for Model-2 with ARGOS for $GridScale=2$, a CG tolerance of $1e-09$, and a homogeneous Dirichlet boundary condition. The test charge is placed at a distance $r = 10 \text{ \AA}$ from the Born ion’s charge.

MRL	N_V	N_{DOFs}^{Adj}	Err^{ARGOS} (%)	$t_{MRL}; \{t_{mat}^{Adj}/t_{CG}^{Adj}/t_{ref}\}$
0	2437	18201	2.5353	3.79; {0.19/0.24/3.27}
1	2900	21811	0.4458	4.10; {0.22/0.26/3.37}
2	4447	34038	0.1274	4.97; {0.38/0.46/3.75}
3	7879	61117	0.0424	7.32; {0.74/1.09/4.80}
4	15306	120060	0.0148	13.28; {1.63/2.99/7.21}
5	28711	226208	0.0067	13.44; {3.35/8.22/0.00}

Table 11: ARGOS CPU times (including the generation of the initial mesh with NanoShaper and TetGen) in the CPU time for MRL=0) in seconds for frame 10 of model DYES with neutral ground-state charges, $GridScale=2$ and a CG tolerance of $1e-09$. The values of E_{1-2}^{Adj} for MRL=4 and 5 are $2.78e-07$ and $2.79e-07$, respectively. The latter value coincides with the value reported in Table S11, obtained from a better quality initial mesh.

MRL	N_V	N_{DOFs}^{Adj}	E_{1-2}^{Adj} ($e_0^2/\text{\AA}$)	$t_{MRL}; \{t_{mat}^{Adj}/t_{CG}^{Adj}/t_{ref}\}$
0	14684	111448	$2.75e-07$	17.42; {1.64/3.29/5.89}
1	19829	152680	$2.73e-07$	16.49; {2.24/4.33/7.73}
2	31378	244342	$2.78e-07$	29.94; {3.74/8.37/14.14}
3	55058	431526	$2.77e-07$	35.17; {6.89/23.93/0.00}

cerns complex geometries of interfaces, especially in the presence of ionic screening. An accurate description of such scenarios will be important for the development of implicit-solvent models. Moreover, if the motion of solvent molecules is restrained, a spatially varying dielectric coefficient would result in the solvent domain. The present solver is ready to take this dependence into account.

The new method exhibits a uniform and fast convergence of the solution with respect to the number of degrees of freedom. Comparison with the well-known finite difference solvers MEAD and APBS demonstrates the superior performance of ARGOS and reveals critical inaccuracies of MEAD and APBS, originating from both numerical implementation and general problems of the FD methods. In particular, the accuracy of MEAD results is much worse in the presence of interfaces with large changes in the dielectric constant, a common problem of FD approaches. In addition, we find that inappropriate stopping criteria in the iterative solver (successive over relaxation (SOR)) in combination with single precision arithmetic can significantly influence the accuracy of MEAD calculations.

In the most of the examples, APBS performed much better than MEAD. However, it still exhibits the common fundamental issues typical for FD based solvers: a trade off between grid spacing h and the dimensions of the final focused grid, a strong dependence of the results on the relative position of the focused grids and the molecule system, as well as of the grid spacing h , which in some cases (see, e.g., frames 6, 10, 12 in Sections 3.2.2 and 3.2.1) requires a thorough inspection of the calculated values to detect inaccurate results. A typical inspection includes the recalculation with perturbation in the focused grids’ centering and/or with slight changes in the grid spacing h , comparison of the two values E_{1-2}^{APBS} and E_{2-1}^{APBS} (or E_{1-2}^{MEAD} and E_{2-1}^{MEAD} for MEAD) and looking for more pronounced violation of

the symmetry condition $E_{1-2} = E_{2-1}$. All this extra work required to ensure reliable results takes a lot of computational and post processing time (see, e.g., the inspection of frames 6, 10, and 12 in Sections 3.2.2 and 3.2.1), which also provokes uncertainty in users who are unexperienced in numerical methods.

Due to the use of appropriate (goal-oriented) error estimation in combination with an adaptive mesh generation the present FE solver requires much less degrees of freedom than MEAD or APBS to obtain a comparable or better accuracy. This advantage, if complemented with parallelization techniques, will make ARGOS a very fast and reliable PBE solver.

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References

- (1) Brovchenko, I.; Oleinikova, A. Which Properties of a Spanning Network of Hydration Water Enable Biological Functions? *Chem. Phys. Chem* **2008**, *9*, 2695–2702.
- (2) Chen, S.-H.; Liu, L.; Fratini, E.; Baglioni, P.; Faraone, A.; Mamontov, E. Observation of fragile-to-strong dynamic crossover in protein hydration water. *Proc. Nat. Acad. Sci. USA* **2006**, *103*, 9012–9016.
- (3) De Simone, A.; Dodson, G.; Verma, C.; Zagari, A.; Fraternali, F. Prion and water: tight and dynamical hydration sites have a key role in structural stability. *Proc. Nat. Acad. Sci. USA* **2005**, *102*, 7535–7540.
- (4) Fogolari, F.; Brigo, A.; Molinari, H. The Poisson-Boltzmann Equation for biomolecular electrostatics: a tool for structural biology. *J. Mol. Recognit.* **2002**, *15*, 377–392.
- (5) Klapper, I.; Hagstrom, R.; Fine, R.; Sharp, K.; Honig, B. Focusing of electric fields in the active site of Cu-Zn superoxide dismutase: Effects of ionic strength and amino-acid modification. *Proteins* **1986**, *1*, 47–59.
- (6) Nicholls, A.; Sharp, K.; Honig, B. Protein folding and association: insights from the interfacial and thermodynamic properties of hydrocarbons. *Proteins* **1991**, *11*, 281–296.
- (7) Bashford, D. An Object-Oriented Programming Suite for Electrostatic Effects in Biological Molecules. Proceedings of the Scientific Computing in Object-Oriented Parallel Environments. London, UK, 1997; pp 233–240.
- (8) Madura, J.; Briggs, J.; Wade, R.; Davis, M.; Luty, B.; Ilin, A.; Antosiewicz, J.; Gilson, M.; Bagheri, B.; Scott, L.; McCammon, J. Electrostatics and diffusion of molecules in solution: simulations with the University of Houston Brownian Dynamics program. *Comp. Phys. Comm.* **1995**, *91*, 57 – 95.
- (9) Jo, S.; Vargyas, M.; Vasko-Szedlar, J.; Roux, B.; Im, W. PBEQ-Solver for online visualization of electrostatic potential of biomolecules. *Nucleic Acids Res.* **2008**, *36*, W270–W275.

- (10) Holst, M.; Baker, N.; Wang, F. Adaptive multilevel finite element solution of the Poisson-Boltzmann equation I. Algorithms and examples. *J. Comput. Chem.* **2000**, *21*, 1319–1342.
- (11) Gilson, M. K.; Sharp, K. A.; Honig, B. H. Calculating the Electrostatic Potential of Molecules in Solution: Method and Error Assessment. *J. Comput. Chem.* **1988**, *9*, 327–335.
- (12) Baker, N.; Sept, D.; Joseph, S.; Holst, M.; McCammon, J. Electrostatics of nanosystems: Application to microtubules and the ribosome. *Proc. Nat. Acad. Sci USA* **2001**, *98*, 10037–10041.
- (13) Rogers, N.; Sternberg, M. Electrostatic interactions in globular proteins: Different dielectric models applied to the packing of α -helices. *Mol. Biol.* **1984**, *174*, 527–542.
- (14) Sakalli, I.; Schöberl, J.; Knapp, E. W. mFES: A Robust Molecular Finite Element Solver for Electrostatic Energy Computations. *J. Chem. Theory and Comput.* **2014**, *10*, 5095–5112.
- (15) Bashford, D. Macroscopic electrostatic models for protonation states in proteins. *Frontiers in Bioscience* **2004**, *9*, 1082–1099.
- (16) Zhou, Z.; Payne, P.; Vasquez, M.; Kuhn, N.; Levitt, M. Finite-difference solution of the Poisson-Boltzmann equation: Complete elimination of self-energy. *J. Comput. Chem.* **1996**, *17*, 1344–1351.
- (17) Niedermeier, C.; Schulten, K. Molecular dynamics simulations in heterogeneous dielectrics and Debye-Huckel media-application to the protein bovine pancreatic trypsin inhibitor. *Mol. Simul.* **1992**, *8*, 361–387.
- (18) Froese, B.; Salvador, T. Higher-order adaptive finite difference methods for fully nonlinear elliptic equations. *J. Sci. Comput.* **2018**, *75*, 1282–1306.
- (19) Oberman, A.; Zwiers, I. Adaptive finite difference methods for nonlinear elliptic and parabolic partial differential equations with free boundaries. *J. Sci. Comput.* **2016**, *68*, 231–251.
- (20) Mirzadeh, M.; Theillard, M.; Gibou, F. A second-order discretization of the nonlinear Poisson-Boltzmann equation over irregular geometries using non-graded adaptive Cartesian grids. *J. Comput. Phys.* **2011**, *230*, 2125–2140.
- (21) Harris, R.; Boschitsch, A.; Fenley, M. Numerical Difficulties Computing Electrostatic Potentials Near Interfaces with the Poisson-Boltzmann Equation. *J. Chem. Theory and Comput.* **2017**, *13*, 3945–3951, PMID: 28640608.
- (22) Boschitsch, A.; Fenley, M. A Fast and Robust Poisson-Boltzmann Solver Based on Adaptive Cartesian Grids. *J. Chem. Theory and Comput.* **2011**, *7*, 1524–1540, PMID: 21984876.
- (23) Zauhar, R.; Morgan, R. A new method for computing the macromolecular electric potential. *Mol. Biol.* **1985**, *186*, 815–820.
- (24) Rashin, A.; Namboodiri, K. A simple method for the calculation of hydration enthalpies of polar molecules with arbitrary shapes. *J. Phys. Chem.* **1987**, *91*, 6003–6012.
- (25) Zauhar, R.; Morgan, R. The rigorous computation of the molecular electric potential. *J. Comput. Chem.* **1988**, *9*, 171–187.
- (26) Lu, B.; McCammon, J. Improved Boundary Element Methods for Poisson-Boltzmann Electrostatic Potential and Force Calculations. *J. Chem. Theory and Comput.* **2007**, *3*, 1134–1142, PMID: 26627432.
- (27) Fenley, M.; Boschitsch, A.; Zhou, H.-X. Fast Boundary Element Method for the Linear Poisson-Boltzmann Equation. *J. Phys. Chem. B* **2002**, *106*, 2741–2754.
- (28) Lu, B.; Cheng, X.; Huang, J.; McCammon, J. Order N algorithm for computation of electrostatic interactions in biomolecular systems. *Proc. Nat. Acad. Sci USA* **2006**, *103*, 19314–19319.
- (29) Lu, B.; Cheng, X.; Huang, J.; McCammon, J. An Adaptive Fast Multipole Boundary Element Method for Poisson-Boltzmann Electrostatics. *J. Chem. Theory and Comput.* **2009**, *5*, 1692–1699.
- (30) Orttung, W. Direct solution of the Poisson equation for biomolecules of arbitrary shape, polarizability density, and charge distribution. *Ann. N.Y. Acad. Sci.* **1977**, *303*, 22–37.
- (31) Cortis, C.; Friesner, R. Numerical solution of the Poisson-Boltzmann equation using tetrahedral finite-element meshes. *J. Comput. Chem.* **1997**, *18*, 1591–1608.
- (32) Holst, M. *The Poisson-Boltzmann Equation: Analysis and Multilevel Numerical Solution*; Applied Mathematics and CRPC, California Institute of Technology; 1994.
- (33) Ji, N.; Liu, T.; Xu, J.; Shen, L. Q.; Lu, B. A Finite Element Solution of Lateral Periodic Poisson-Boltzmann Model for Membrane Channel Proteins. *Int. J. Mol. Sci.* **2018**, *19*.
- (34) Bank, R.; Holst, M. A New Paradigm for Parallel Adaptive Meshing Algorithms. *SIAM J. Sci. Comp.* **2000**, *22*, 1411–1443.
- (35) Nakov, S. ARGOS (Adaptive Refinement Goal-Oriented Solver). <https://doi.org/10.5281/zenodo.4269441>, 2020.
- (36) Nakov, S. The Poisson-Boltzmann Equation: Analysis, A Posteriori Error Estimates and Applications. Ph.D. thesis, Johannes Kepler University, 2019; Available at <https://www.numa.uni-linz.ac.at/Teaching/PhD/Finished/nakov>.
- (37) Kraus, J.; Nakov, S.; Repin, S. Reliable Computer Simulation Methods for electrostatic Biomolecular Models Based on the Poisson-Boltzmann Equation. *Comput. Methods Appl. Math.* **2020**, *20*, 643–676.
- (38) Chen, L.; Holst, M. J.; Xu, J. Adaptive Finite Element Modeling Techniques for the Poisson-Boltzmann Equation. *Siam J. Numer. Anal.* **2007**, *45*, 2298–2320.

- (39) Holst, M.; McCammon, J.; Yu, Z.; Zhou, Y. C.; Zhu, Y. Adaptive Finite Element Modeling Techniques for the Poisson-Boltzmann Equation. *Commun. Comput. Phys.* **2012**, *11*, 179–214.
- (40) Becker, R.; Rannacher, R. An optimal control approach to a posteriori error estimation in finite element methods. *Acta Numer.* **2001**, *10*, 1–102.
- (41) Richter, T.; Wick, T. Variational localizations of the dual weighted residual estimator. *J. Comput. Appl. Math.* **2015**, *279*, 192–208.
- (42) Decherchi, S.; Rocchia, W. A general and Robust Ray-Casting-Based Algorithm for Triangulating Surfaces at the Nanoscale. *PLOS ONE* **2013**, *8*, 1–15.
- (43) Si, H. TetGen, a Delaunay-Based Quality Tetrahedral Mesh Generator. *ACM Transactions on Mathematical Software (TOMS)* **2015**, *41*.
- (44) Dobrzynski, C. *MMG3D: User Guide*; Technical Report RT-0422, 2012.
- (45) Hecht, F. New development in FreeFem++. *J. Numer. Math.* **2012**, *20*, 251–265.
- (46) Sobakinskaya, E.; Schmidt am Busch, M.; Renger, T. Theory of FRET "Spectroscopic Ruler" for Short Distances: Application to Polyproline. *J. Phys. Chem. B* **2018**, *112*, 54–67.
- (47) Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kale, L.; Schulten, K. Scalable Molecular Dynamics with NAMD. *J. Comput. Chem.* **2005**, *26*, 1781–1802.
- (48) Brooks, B. R.; Brooks III, C. L.; Mackerell Jr., A. D.; Nilsson, L.; Petrella, R. J.; Roux, B.; Won, Y.; Archontis, G.; Bartels, C.; Boresch, S.; Caffisch, A.; Caves, L.; Cui, Q.; Dinner, A. R.; Feig, M.; Fischer, S.; Gao, J.; Hodoscek, M.; Im, W.; Kucsera, K.; Lazaridis, T.; Ma, J.; Ovchinnikov, V.; Paci, E.; Pastor, R. W.; Post, C. B.; Pu, J. Z.; Schaefer, M.; Tidor, B.; Venable, R. M.; Woodcock, H. L.; Wu, X.; Yang, W.; York, D. M.; Karplus, M. CHARMM: The biomolecular simulation program. *J. Comput. Chem.* **2009**, *30*, 1545–1614.
- (49) Jorgensen, W. L.; Madura, J. D. Quantum and statistical mechanical studies of liquids. 25. Solvation and conformation of methanol in water. *J. Am. Chem. Soc.* **1983**, *105*, 1407–1413.
- (50) Childs, H.; Brugger, E.; Whitlock, B.; Meredith, J.; Ahern, S.; Pugmire, D.; Biagas, K.; Miller, M.; Harrison, C.; Weber, G. H.; Krishnan, H.; Fogal, T.; Sanderson, A.; Garth, C.; Bethel, E. W.; Camp, D.; Rübel, O.; Durant, M.; Favre, J. M.; Navrátil, P. *High Performance Visualization—Enabling Extreme-Scale Scientific Insight*; 2012; pp 357–372.
- (51) Andreussi, O.; Hörmann, N. G.; Nattino, F.; Fisi-caro, G.; Goedecker, S.; Marzari, N. Solvent-Aware Interfaces in Continuum Solvation. *J. Chem. Theory and Comput.* **2019**, *15*, 1996–2009.
- (52) Connolly, M. L. Analytical molecular surface calculation. *J. Appl. Crystallog.* **1983**, *16*, 548–558.
- (53) Richards, F. M. Areas, volumes, packing, and protein structure. *Ann. Rev. Biophys. Bioeng.* **1977**, *6*, 151–176.
- (54) Greer, J.; Bush, B. L. Macromolecular shape and surface maps by solvent exclusion. *Proc. Nat. Acad. Sci. USA* **1978**, *75*, 303–307.
- (55) Sanner, M. F.; Olson, A. J.; Spehner, J.-C. Reduced surface: An efficient way to compute molecular surfaces. *Biopolymers* **1996**, *38*, 305–320.
- (56) Engel, T. In *Chemoinformatics. Basic Concepts and Methods*; Engel, T., Gasteiger, J., Eds.; Wiley-VCH, 2018; Chapter 3, pp 103–106.
- (57) Renger, T.; Müh, F. Theory of excitonic couplings in dielectric media. *Photosynth. Res.* **2012**, *111*, 47–52.
- (58) Knotts, T.; Rathore, N.; Schwartz, D.; de Pablo, J. A coarse grain model for DNA. *J. Chem. Phys.* **2007**, *126*, 084901.
- (59) Marenich, A.; Cramer, C.; Truhlar, D. Universal Solvation Model Based on the Generalized Born Approximation with Asymmetric Descreening. *J. Chem. Theory and Comput.* **2009**, *5*, 2447–2464.