ARGOS: An adaptive refinement goal-oriented solver for the linearized Poisson–Boltzmann equation

Svetoslav Nakov1 | Ekaterina Sobakinskaya1 | Thomas Renger1 | Johannes Kraus2

1Institute for Theoretical Physics, Johannes Kepler University, Linz, Austria
2Faculty of Mathematics, University of Duisburg-Essen, Essen, Germany

Correspondence
Svetoslav Nakov and Ekaterina Sobakinskaya,
Institute for Theoretical Physics, Johannes Kepler University, Altenbergerstraße 69, 4040 Linz, Austria.
Email: svetoslav.nakov@jku.at (S. N.);
ekaterina.sobakinskaya@jku.at (E. S.)

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Abstract
An adaptive finite element solver for the numerical calculation of the electrostatic coupling between molecules in a solvent environment is developed and tested. At the heart of the solver is a goal-oriented a posteriori error estimate for the electrostatic coupling, derived and implemented in the present work, that gives rise to an orders of magnitude improved precision and a shorter computational time as compared to standard finite difference solvers. The accuracy of the new solver ARGOS 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 and between the spike protein of SARS-CoV-2 and the ACE2 receptor. All the calculations are repeated by using the well-known finite difference solvers MEAD and APBS, revealing the advantages of the present finite element solver.

KEYWORDS
adaptive finite element method, adaptive solver, biomolecular electrostatics, electrostatic interaction, goal-oriented error estimate, implicit solvent, Poisson–Boltzmann equation

1 | INTRODUCTION

Electrostatics is the key that allows proteins and other biological macromolecules to perform their multiple functions [1–4]. At the heart of many electrostatic theories lies the Poisson–Boltzmann equation (PBE) providing the electrostatic potential (ESP) of a macromolecule in an ionic solution [2, 5–7]. The PBE is widely applied in different areas of research, such as biomolecular recognition, kinetics of molecular association and enzyme catalysis (see [7] and the references therein). It treats the environment of the macromolecule as a polarizable continuum containing a Boltzmann-distributed continuous charge density of the ions. The macromolecule itself is described by atomic partial charges that are embedded in a molecule-shaped cavity with a continuous polarization, characterized by a dielectric coefficient.

Analytical solutions of the PBE are available only for specific 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, including discontinuous dielectric coefficients representing interfaces (e.g., solvent-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. To effectively handle the above challenges, a PBE solver must employ some kind of adaptivity. While the error indicators controlling the mesh refinement steps in the existing adaptive PBE solvers attempt to detect the regions where the error in the electrostatic potential (ESP) is the highest, this is far from the best strategy when it comes to the calculation of the electrostatic interaction between molecules. Since the interaction energy $E$ is a number that depends...
on the ESP, the purpose of the error indicator is to detect the regions for which the error in the ESP contributes the most to the error in the goal quantity \( E \). Those are the regions that should be refined and are not necessarily the regions, where the error in the ESP itself is the highest. The use of standard error indicators results in much denser adaptive meshes with a huge number of nodes and inherently unreliable evaluation of the goal quantity \( E \).

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 [8], GRASP [9], MEAD [10], UHBD [11], the PBEQ module of CHARMM [12], and the PMG solver in the APBS software suite [13] 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, for example, the Conjugate Gradient, multigrid, or the Newton–Raphson method.

To speed up the convergence and reduce the memory requirements, a focusing technique was developed in Refs. [8, 14]. 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. [15] by implementing it in parallel and then was applied to the electrostatics of microtubules and ribosomes. Due to the highly improved performance, focusing schemes are utilized in most of the FD-based solvers for the PBE which use regular cubic lattices.

As the underlying grid in regular 3D lattices is not adapted to the molecular surface, the accuracy of the solution is decreased. The correct assignment of the dielectric coefficient in points close to the solute–solvent interface is crucial for an 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 values of the dielectric coefficient \( \epsilon \) mapped on the grid, are defined by averaging its actual values at the neighboring points, which depend on the modeling assumptions concerning the definition of the solute–solvent interface and the dielectric permittivity in the molecular and solvent regions [14, 16]. The inverse Debye length \( \kappa \) is defined in a similar fashion. Due to the 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 \( \mathcal{h} \) and this is where the discretization error of the FD method is typically much larger than that produced by the FE method, discussed in the end of this section.

Finite difference methods also exhibit difficulties caused by non-smooth source terms, such as the delta distributions introduced as a result of the mathematical modeling of point charges. A redistribution of the charges around their closest grid points is necessary in order to minimize the errors occurring in the electrostatic potential at small distances from the charges (see Refs. [14, 16] for different approaches to such a redistribution). Another problem, even though not unique to the FD method and also present in finite element implementations, that arises in the computation of free energy differences (e.g., the calculation of solvation energies) is the so called grid artifact [17–19]. The reason behind it is the singular charge distribution in the molecular system resulting from the modeling of the atomic charges as discrete point charges instead of using alternative charging models, where the atomic charge is represented by a more regular charge density function (see [20] for an example of such alternative charging model, where each atom is represented as a uniformly charged ball). In the case of such a singular charge distribution, the Coulombic self-interaction energy of the point charges becomes infinite and under certain assumptions (see assumptions 1–3 in section 5 from [18]) it cancels out in analytical expressions for the free energy difference. However, in the discrete FD analog, the Coulombic self-interaction energy participates in the free energy as a finite, but large contribution that is inversely proportional to the grid spacing. Therefore, the discrete approximation of the (infinitesimal) Coulombic self-interaction energy is not guaranteed to cancel out in the difference of the numerically computed electrostatic energies unless one uses exactly the same grids and redistribution of the point charges. Another way to avoid the spurious grid artifact in the calculation of the energy difference is to apply proper splitting techniques for the full potential in the PBE. By applying such decompositions of the full potential, the source term or, equivalently, the right hand side in the PBE, that is the delta distributions describing the discrete charge density due to the point charges in the solute, are transformed to a more regular distribution which becomes the source term in the equation defining the regular part of the potential in all these decompositions. In the so-called weak formulation of the problem defining the regular part of the potential, this better behaved right hand side can be represented as a surface integral over the solute–solvent interface of a (polarization) charge density function, see Equation (21) in [21] and the interpretation after it. Thus, mathematically speaking, this right hand side can be interpreted as a certain charge density concentrated on the molecular surface (see Remarks 3.1 and 3.2 in [22] or Remarks 2.1 and 2.2 in [23]). We note that these splitting techniques can be applied in conjunction with any numerical procedure to solve the PBE, and in particular with the FD method. However, the surface charge density on the interface between the molecular region and the solution region remains hard to handle with the FD method since no explicit molecular surface is constructed (see, e.g., Refs. [21, 24]).

Another disadvantage of FD methods is that the errors, caused by the specific way of handling interfaces and the partial charge distribution in the solute, strongly depend on the particular position and orientation of the molecular system relative to the FD grid. One approach to cope with this problem is to use finer grids, which naturally leads to a computationally more expensive problem. Another approach is to use a rotational averaging scheme. The idea is to make several calculations with slightly different mutual orientation between the molecular system and the FD grid, and finally take an average (see Refs. [14, 21]).
A third approach, which could cope better with curved interfaces and regions where the solution is sharply varying (mainly around the 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 [25–27]. Here, the grid representation is based on quadtree in two dimensions and octree in three dimensions. The ACG is recursively adapted by identifying mesh cells, which intersect the molecular surface, and test whether they satisfy a certain set of conditions. 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 an accurate evaluation of the ESP near the interface remains problematic. In an attempt to avoid this shortcoming, the technique proposed in Ref. [28] introduces additional mesh points at the Cartesian grid-surface intersection and uses a reconstruction of the ESP 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 the exterior and interior domains. The resulting boundary integral equations are solved by using collocation, Galerkin, or least squares methods. The first of these approaches 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. [32, 33] and deal mainly with algorithmic improvements. The BEM 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 treated exactly as opposed to the FE and FD methods. In contrast to the FD method, 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.

The BEM also possesses certain disadvantages, mainly related to the requirement of the efficient evaluation of singular and hypersingular integrals and numerous other integral operations, a dense nonsymmetric coefficient matrix for the linear system of equations [31, 34]. Moreover, in the presence of an ionic charge density of the solvent, BE methods usually neglect the ion exclusion (Stern) layer and thus only take into account a single surface separating the solute and the solvent.

One of the promising strategies to improve the efficiency of the BEM is to combine it with a fast multipole method (FMM) [35, 36]. Further improvements can be achieved by using an adaptive FMM for accelerating the convolution type matrix-vector multiplications [37]. Solvers based on these concepts benefit from 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 superposition of a set of basis functions. The FE method, which is employed in the present work, is the most successful for elliptic PDEs, 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, where the PBE is typically solved on unstructured finite element meshes. The finite element discretization results in a linear or nonlinear algebraic system of equations for the expansion coefficients in the linear combination of basis functions that represents the approximate potential. This system is then solved usually by means of iterative methods such as the Conjugate Gradient or the Newton–Raphson method.

One of the first applications of the FE method to continuum electrostatics of solubilized biomolecules appeared in Ref. [38]. Since then, the popularity of this approach has increased synchronically with the increase of computational power and advancement of FE mesh generation techniques, see, for example, Refs. [13, 39–42]. As representatives of the solvers, implementing the FE method for the numerical approximation of the PBE and the linearized PBE (LPBE), we mention APBS [13] (utilizing adaptive mesh refinement based on a residual type error indicator) and mFES [17], respectively.

However, application of FE solvers for the PBE and the LPBE to a 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 FE 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 solute. The 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. 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 the ESP needs to be evaluated only at particular points of interest. Therefore, adaptive mesh refinement based on energy norm error indicators attempts to enhance the global quality of the solution. This approach typically yields optimal rates of convergence with respect to the 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 unreliable and ineffective for the computation of the electrostatic interaction between molecules.

In the present paper, we report an Adaptive Refinement Goal-Oriented Solver [43] (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 ESP. Besides the smallness of the ESP, this is why ARGOS, in its present implementation, is based on the linearized PBE. The most notable feature of this solver is the 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 the numerical solution and the computational efficiency. 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 analytical solutions.

The structure of the paper is as follows. In Section 2, the theory of a goal-oriented error estimator for the electrostatic coupling between molecules and its algorithmic realization are discussed. In Section 3, we start with an application of our new ARGOS to three test cases with analytically known solutions and evaluate the accuracy of ARGOS in comparison to the FD solvers MEAD and APBS. We proceed with the application of the different solvers to the computation of the interaction energy between two chromophores, that are attached to a polypeptide. Besides reevaluating the coupling between the transition densities of the chromophores [44], we study the interaction between their ground state charge densities for this system as well as the SARS-CoV-2 and the ACE2 cell receptor. The superior performance of ARGOS is used to evaluate the accuracy and numerical efficiency of the FD solvers MEAD and APBS.

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 ESP \( \phi \) of a discrete charge distribution that is placed in a dielectric continuum containing a continuous ionic charge distribution. 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

\[
- \nabla \cdot (\varepsilon \nabla \phi) + \frac{k_B T}{\varepsilon_0} \sum_{i=1}^{N} z_i \delta(x - x_i)
\]

where \( k_B \) is the Boltzmann constant, \( T \) the temperature, \( \varepsilon_0 \) the elementary charge, \( N \) the number of charges in the molecule, \( z_i \) is the numerical value of the \( i \)-th partial charge (in units of the elementary charge), and \( x_i \) its coordinate in the molecule. The dielectric coefficient \( \varepsilon \) is piecewise constant and defined by

\[
\varepsilon(x) = \begin{cases} 
\varepsilon_m, & x \in \Omega_m, \\
\varepsilon_s, & x \in \Omega_s,
\end{cases}
\]

where \( \Omega_m \) is the molecular domain and \( \Omega_s \) is the solvent domain composed of \( \Omega_{ions} \) and the ionic exclusion layer (IEL) \( \Omega_{IEL} \). The latter is a layer around the molecules which no ions can penetrate. It is defined as the difference between the union of the van der Waals balls of the atoms, where the atomic radii have been increased by a counterion radius \( R_{\text{ion}} \), and the molecular region defined by the solvent excluded surface (SES) formed by the contact points of the van der Waals surface and a (solvent) probe sphere, rolling over it (see Refs. [45–48]). In 1983 Connolly [49] gave an analytical description of the SES, which is, therefore, also known as the Connolly surface. We set the probe radius in the definition of the SES to 1 Å in the calculations on our first test system (Alexa 488 and Alexa 594 dyes in Section 2.4) and to 1.4 Å in our second test system (SARS-CoV-2 and ACE2 cell receptor in Section 2.4), while the counterion radius \( R_{\text{ion}} \) in the definition of the IEL is set to 2 Å in all calculations. It is known that the electrostatic interaction energy depends on the definition of the solute surface (see, e.g., Ref. [50]), but the study of this problem is beyond the scope of this paper. For a system of \( N_{\text{mol}} \) molecules, \( \Omega_s \) consists of the domains \( \Omega_{m_1}, \ldots, \Omega_{m_{N_{\text{mol}}}} \), where \( \Omega_{m_i} \) corresponds to the domain of the \( i \)-th molecule (see Figure 1). The coefficient \( K^2 \) is also piecewise constant and given by

\[
K^2(x) = \begin{cases} 
0, & x \in \Omega_m \cup \Omega_{IEL}, \\
8 \pi N_a \varepsilon_0^2 I_s & x \in \Omega_{ions},
\end{cases}
\]

where the ionic strength \( I_s \) is defined as

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

with the molar concentration of each ion type \( c_1 = c_2 \) and \( N_a \) denoting Avogadro’s number. Assuming the potential \( \phi \) to be small (\( \phi \ll \frac{k_B T}{\varepsilon_0} \)), the PBE (1) can be linearized. The resulting equation

\[
- \nabla \cdot (\varepsilon \nabla \phi) + K^2 \phi = 4 \pi \varepsilon_0 \sum_{i=1}^{N} z_i \delta(x - x_i)
\]
is referred to as the linearized PBE (LPBE) and will be used in this work. For the special case \( l_i = 0 \), Equation (4) becomes the Poisson equation:

\[
-\nabla \cdot (e \nabla \varphi) = 4 \pi e_0 \sum_{i=1}^{N} z_i \delta(x - x_i).
\]

Equations (1), (4), and (5) include a natural interface \( \Gamma \) between the molecular and the solvent domains due to different dielectric coefficients \( \epsilon = \epsilon(x) \) (see (2)). The potential \( \varphi \) and the normal component of the displacement field \( \epsilon \nabla \varphi \) must be continuous across the interface, that is,

\[
[\varphi] = 0,
\]

\[
[\epsilon \nabla \varphi \cdot n] = 0,
\]

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

\[
\varphi = g \text{ on } \partial \Omega,
\]

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 \( \Gamma \), where \( \epsilon \) 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 domain \( \Omega \):

\[
\int_\Omega \nabla \cdot (\epsilon \nabla \varphi) v dx + \int_{\partial \Omega} \epsilon \nabla \varphi \cdot n v ds = 4 \pi e_0 \sum_{i=1}^{N} z_i v(x_i).
\]

On the left-hand side we apply the divergence theorem for integration by parts together with the condition (7) and obtain (for details see Ref. [51])

\[
\int_\Omega \epsilon \nabla \varphi \cdot \nabla v dx + \int_{\partial \Omega} \epsilon \varphi \partial n v ds = 4 \pi e_0 \sum_{i=1}^{N} z_i v(x_i)
\]

for all test functions \( v \).

It can be rigorously shown that under certain conditions on the regularity of the interface \( \Gamma \) there exists a unique potential \( \varphi \) that satisfies the integral formulation (10) for any test function \( v \) in a certain function space [22, 23]. By directly discretizing (10), one obtains an approximation \( \varphi_h \) of the exact potential \( \varphi \).

Another widespread approach, from which both the numerical treatment and analysis of the LPBE (also the PBE) benefits, involves splitting the potential \( \varphi \) into two parts \( G \) and \( u \), that is, \( \varphi = G + u \) (see, e.g., Refs. [21, 24, 52, 53]), where

\[
G = \sum_{i=1}^{N} \frac{z_i e_0}{\epsilon_m |x - x_i|}
\]

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 that takes into account the polarization of the solvent. Thus, one completely avoids the above mentioned grid artifact by computing only the reaction field potential \( u_h \) instead of the potential \( \varphi \) 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, that is, the free energy difference between the solute in vacuum and in a solvent environment

\[
\Delta G^{\text{vac-solv}} = G^{\text{vac}}(\epsilon_{\text{vac}}, \epsilon_m) - G^{\text{solv}}(\epsilon_s, \epsilon_m)
\]

\[
= \frac{1}{2} \sum_{i=1}^{N} q_i \left( u^{\text{vac}}(r_i) - u^{\text{solv}}(r_i) \right).
\]

where \( q_i = z_i e_0 \). \( u^{\text{vac}} \) and \( u^{\text{solv}} \) are the reaction field potentials for the molecule in vacuum and the solvent, respectively.

### 2.1.3 Goal-oriented a posteriori error estimates

The purpose of adaptive finite element methods (AFEM) is to achieve high accuracy at reduced computational costs. The general idea
behind AFEM is the construction of subsequent approximations in appropriately designed finer and finer finite dimensional spaces. Most often, these finer finite dimensional spaces are built by adaptively refining the underlying mesh. For this purpose, a subset of elements (e.g., triangles in 2D and tetrahedrons in 3D) are marked for refinement based on a specifically designed error indicator, the construction of which depends only on the currently available approximation and the problem data.

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 indicators are provided only for the goal quantity. For example, if one is interested in the average value of a solution \( w \), the goal functional acting on \( w \) can be represented by

\[
\mathcal{S}(w) = \int_\Omega j w \, dx
\]

with \( j(x) = 1/|\Omega| \), where \( |\Omega| \) denotes the volume of \( \Omega \). Here \( j \) is the density function associated with the functional \( \mathcal{S} \). The resulting goal oriented error indicator should be able to properly identify the regions contributing the most to the error in the average value, not necessarily the regions where the pointwise error in \( w \) is the highest.

To outline the method, let us consider a general case of a linear differential equation with a solution \( w \) (see, e.g., Ref. [54]):

\[
Aw = f,
\]

where \( A \) is a linear differential operator and \( f \) is a generalized force, exerted by the environment. Problem (14) is called primal. Let \( \mathcal{S}(w) \) be a quantity of interest obtained from the solution \( w \) by applying a goal functional \( \mathcal{S} \) and \( w_h \) an approximation of \( w \) that depends on a discretization mesh parameter \( h \). The strategy involves controlling the error

\[
\mathcal{S}(e) = \mathcal{S}(w) - \mathcal{S}(w_h) \text{ with } e := w - w_h
\]

in terms of the local residuals \( \rho_K(w_h) \) computable on each mesh cell \( K \) (e.g., tetrahedrons or patches of tetrahedrons):

\[
\rho_K(w_h) = (f - Aw_h)_K.
\]

The idea is to consider the adjoint (or dual) problem

\[
A^* z = j,
\]

where \( A^* \) is the adjoint operator defined via \( \langle Au, v \rangle = \langle A^* v, u \rangle \) for all functions \( u \) and \( v \) with the appropriate boundary conditions, where \( \langle \cdot, \cdot \rangle \) is the standard \( L^2 \) integral inner product, and \( j \) is the density function associated with \( \mathcal{S} \). Taking into account the definition of the adjoint operator, (17), and (15), the error in the goal quantity is obtained as

\[
\mathcal{S}(e) = \langle A^* z, w \rangle - \langle A^* z, w_h \rangle = \langle Aw, z \rangle - \langle Aw_h, z \rangle = (f - Aw_h, z),
\]

where \( z \) is unknown and has to be substituted with an approximate solution. In this case, we have

\[
\mathcal{S}(e) \approx \langle \rho(w_h), s_h(z) \rangle = \sum_K \langle \rho(w_h)_K, s_h(z)_K \rangle,
\]

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 local variations of the residual \( \rho(w_h) \) in the primal problem is propagated to the error \( \mathcal{S}(e) \) 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 \( \phi_1 \), produced by \( M_1 \) at the positions \( x_{1,i} \) of the charges \( q_{1,i} \) of molecule \( M_2 \):

\[
E_{1 \rightarrow 2} = \sum_{i=1}^{N_2} \phi_1(x_{1,i})q_{1,i},
\]

where \( q_{1,i} = z_{1i}e_0 \) and \( N_2 \) is the number of charges in \( M_2 \). The energy can also be expressed by the potential \( \phi_2 \) of \( M_2 \) at the position of the charges \( q_{2,i} \) of \( M_1 \), that is,

\[
E_{2 \rightarrow 1} = \sum_{i=1}^{N_1} \phi_2(x_{1,i})q_{2,i},
\]

where \( q_{2,i} = z_{2i}e_0 \) and \( N_1 \) is the number of charges in \( M_1 \). Here, we assume \( \phi_1 \) and \( \phi_2 \) 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, that is, \( E_{2 \rightarrow 1} = E_{1 \rightarrow 2} (= E) \) (see Proposition 5.12 in Ref. [51] for a proof of this fact).

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

\[
-\nabla \cdot (\epsilon \nabla \phi_2) + K^2 \phi_2 = 4\pi \sum_{i=1}^{N_1} q_{1,i} \delta(x - x_{1,i}).
\]

It describes the potential created by the charges of molecule \( M_2 \). For convenience, we denote the right-hand side of (22) as the functional...
Applying (10), we obtain the integral formulation of the primal problem (22), that is,

\[
\int_\Omega \epsilon \nabla \varphi_2 \cdot \nabla v dx + \int_\Omega \mathbf{K}^\prime \varphi_2 v dx = \mathcal{F}(v)
\]

for all test functions \(v\).

(24)

It is easy to see that the goal functional related to our target quantity (21) is given by

\[
\mathcal{L} = \sum_{i=1}^{N_2} q_{i,1} \delta(x - x_{i,1}).
\]

(25)

Therefore, the interaction energy (21) can be written as

\[
\mathcal{E}_{-1} = \mathcal{L}(\varphi_2).
\]

(26)

For further analysis, it is necessary to express the adjoint problem in an integral formulation similar to (24). Recalling the definition (17) and taking into account that in our case \(A^\prime = A\) we obtain

\[
\int_\Omega \epsilon \nabla v \cdot \nabla z dx + \int_\Omega \mathbf{K}^\prime z v dx = \mathcal{F}(v)
\]

for all test functions \(v\).

(27)

where \(z\) is the solution of (27) and is defined to be equal to zero on the boundary \(\partial \Omega\). Here, we would like to emphasize the difference between the primal and adjoint problems: the solution \(\varphi_2\) of the primal problem is generated by the charges of the molecule \(M_2\), whereas the solution \(z\) of the adjoint problem is determined by the charges of \(M_1\) (see (23) and (25)). Now, by taking into account the definitions (23) and (25) of \(\mathcal{F}\) and \(\mathcal{L}\), respectively, and of the potential \(z\), it is clear that the interaction energy \(\mathcal{E}_{1,2} = -\mathcal{E}_{-1,2}\) can also be calculated as

\[
\mathcal{E}_{1,2} = \mathcal{L}(z).
\]

(28)

The optimal adaptive algorithm balances the error distribution of the calculated potential over the domain \(\Omega\) in such a way that for a given number of DOFs the error in the goal quantity

\[
\mathcal{L}(\epsilon) = \mathcal{L}(\varphi_2) - \mathcal{L}(\varphi_{2h}) = \sum_{i=1}^{N_2} q_{i,2} \epsilon_i,
\]

(29)

with \(\epsilon_i = \varphi_2 - \varphi_{2h}\) and \(\epsilon_i = \varphi_2(x_{i,1}) - \varphi_{2h}(x_{i,1})\) is minimal. In general, this minimization problem cannot be solved exactly, but adaptative algorithms aim at approximating its solution well.

A difficulty in the problem under consideration is that the goal functional defining the quantity of interest, that is, the electrostatic interaction, requires point evaluations. Hence, it is not representable in the form (13) through a regular density function \(j\), but defined in terms of the delta functions \(\delta(x - x_{i,1})\), cf. (25). A standard approach in such a situation employs regularization of the goal functional by replacing the point evaluations with averages over small balls \(B(x_{i,1}, r)\), where \(r\) is the radius around the points of interest \(x_{i,1}\). The application of this approach, however, changes the goal functional when the averaged functions are not harmonic 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 these conceptual shortcomings, here, we derive a nontrivial representation of the error in the goal quantity which does not require averaging and directly exploits the original goal functional. The purpose of our goal oriented error indicator is to detect the regions for which the error in the electrostatic potential contributes the most to the error in the goal quantity, that is the interaction energy. Those regions are then being refined and are not necessarily the regions where the pointwise error or the so-called energy norm of the error in the potential are the highest. This is in contrast to the functional type a posteriori error estimates developed in Ref. [23] or the residual-based error indicator used, for example, in the \textit{fe-manual} routine of APBS, which aims at the reduction of the global (integral) energy norm of the error in the potential.

Error indicator

The following approach does not involve any splitting of the full potential and is based on a direct discretization of the problem defining \(\varphi_2\). Hence, the primal and adjoint problems are given by the expressions (24) and (27), respectively. The goal quantity is defined in (26), and the approximate interaction energy is simply

\[
\mathcal{E}^{\text{Prim}}_{2,1} = \mathcal{L}(\varphi_{2h}),
\]

(30)

where \(\varphi_{2h}\) is the solution of the discrete primal problem

\[
\int_\Omega \epsilon \nabla \varphi_{2h} \cdot \nabla v dx + \int_\Omega \mathbf{K}^\prime \varphi_{2h} v dx = \mathcal{F}(v)
\]

for all test functions \(v \in V_1^h\).

(31)

Here, \(\varphi_{2h}\) is a continuous piecewise linear function from the finite element space \(V_1^h\) defined on the mesh \(T_h\). By taking into account (26) and (30), and the fact that the goal functional \(\mathcal{L}\) is linear, the error in the interaction energy is obtained as

\[
\mathcal{E}_{2,1} - \mathcal{E}^{\text{Prim}}_{2,1} = \mathcal{L}(\varphi_2 - \varphi_{2h}).
\]

(32)

Furthermore, to obtain an error estimator in terms of the solution to the adjoint problem, we test (27) with the function \(\varphi_2 - \varphi_{2h}\) and (24) with the adjoint solution \(z\) (for a proof that one can do this, see Proposition 5.12 in Ref. [51]), and similarly to the general approach presented by (18) and (19), we obtain

\[
\mathcal{L}(\varphi_2 - \varphi_{2h}) = \langle \rho(\varphi_{2h}), z \rangle = \langle \rho(\varphi_{2h}), s_0(z) \rangle.
\]

(33)
where in our particular case we have

$$\langle \rho(\phi_{2,h},z) = \mathcal{F}(z) - \int_\Omega \varepsilon \nabla \phi_{2,h} \cdot \nabla \phi_{2,h} dx - \int_\Omega K^2 \phi_{2,h} dx $$

$$\approx \langle \rho(\phi_{2,h},s_h(z)) = \sum_{i=1}^{N_v} \eta_{PU}^{h}(\phi_{2,h},z^{(2)_h}) \rangle$$

with

$$\eta_{PU}^{h}(\phi_{2,h},z^{(2)_h}) = \left\langle \mathcal{F}, \left( z^{(2)_h} - I_h z^{(2)_h} \right) \psi_i \right\rangle - \left\langle \varepsilon \nabla \phi_{2,h} \cdot \nabla \left( z^{(2)_h} - h \phi_{2,h} \right), \psi_i \right\rangle - K^2 \phi_{2,h} \left( z^{(2)_h} - h z^{(2)_h} \right) \psi_i \right\rangle$$

In (34), $z^{(2)_h}$ is a FE approximation of the adjoint solution $z^*$ found in a richer space than the one which $\phi_{2,h}$ belongs to. In particular, we find it in the space $V_\Gamma^h$ consisting of continuous piecewise quadratic functions defined on the same mesh $T_h$ (see Eq. (51) in the Supporting Information). Furthermore, $I_h$ is the nodal interpolation operator in $V_\Gamma^h$; $N_v$ is the number of nodes (vertices) in the mesh $T_h$, and $\{\psi_i\}_{i=1}^{N_v}$ are the nodal $P_2$ basis functions in $V_\Gamma^h$ equal to 1 at the $i$-th node and zero elsewhere (see Figure 3). The nodal interpolant $I_h f$ of a continuous function $f$ is a finite element function in the space $V_\Gamma^h$ equal to $f$ at all nodes $V_i$ of the mesh $T_h$ (and thus $I_h x^{(2)_h} \in V_\Gamma^h$ can be taken as a test function in (31)). The functions $\{\psi_i\}_{i=1}^{N_v}$ form the so-called partition of unity (the “PU” in $\eta_{PU}^{h}$), that is, their sum equals one in $\Omega$.

The quantities $\eta_{PU}^{h}(\phi_{2,h},z^{(2)_h})$, $i=1,...,N_v$ are nodewise error indicators that are used to guide the adaptive mesh refinement. Note, that the first term in the definition (34) of the error indicator on the $i$th node patch can be nonzero only if the support of $\psi_i$ contains a partial charge from molecule $M_2$ (recall that the charges of $M_2$ define the primal problem). In this case, the mesh cells $K$ in the notation of (16) and (19) are just nodewise patches of tetrahedrons corresponding to the supports of the $P_2$ basis functions $\{\psi_i\}_{i=1}^{N_v}$.

So far, we have constructed the error indicators $\eta_{PU}^{h}(\phi_{2,h},z^{(2)_h})$ that can guide our adaptive mesh refinement. To obtain an approximation of the goal quantity, that is, the electrostatic interaction between $M_1$ and $M_2$, we could directly use the solution $\phi_{2,h}$ of the primal problem and the expression (30). However, it is better to make use of the approximate solution $z^{(2)_h}$ of the adjoint problem and the expression (28). Indeed, one can show the following equality:

$$E_{1-2}^{Adj} = \mathcal{F}(z^{(2)_h}) = E_{2-1}^{Prim} + \langle \rho(\phi_{2,h}), s_h(z) \rangle. $$

This expression shows that the interaction $E_{1-2}^{Adj}$ computed by means of the more accurate $z^{(2)_h}$ is equal to the interaction $E_{2-1}^{Prim}$ corrected with the approximately evaluated error estimator $\langle \rho(\phi_{2,h}), s_h(z) \rangle$. The quantity $E_{1-2}^{Adj}$ is a more accurate approximation of the electrostatic interaction $E_{1-2}$ (see (28)), which will be used in our applications. It can be shown that, the theoretically optimal convergence rates for the error in the goal quantity using the primal and adjoint solutions are (see eqs. (5.127) and (5.128) in [51])

$$|E_{2-1} - E_{2-1}^{Prim}| = O\left(\#DOFs^{-2/3}\right), $$(36)

$$|E_{2-1} - E_{1-2}^{Adj}| = O\left(\#DOFs^{-1}\right). $$

where $\#DOFs$ denotes the number of degrees of freedom, that is, the number of unknowns for the primal or adjoint problems. From this expression, it is clear that the interaction energy obtained with the adjoint solution $z^{(2)_h}$ converges faster to the exact interaction energy than the one with the primal solution. We will demonstrate these convergence rates in Section 3.

We will refer to the corresponding solver as ARGOS and the solution obtained by ARGOS will be denoted as $E_{1-2}^{ARGOS} = E_{1-2}^{Adj}$. If, for the definition of the primal problem (22), we use the charges of molecule $M_1$ instead, then the definition of the adjoint problem (27) 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 as $E_{1-2}^{Prim}$ 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 obtained from 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 also executed in conjunction with the splitting of the full potential $\phi = G_2 + u_2$, where $G_2$ is the Coulomb potential of the charges of $M_2$ in a uniform dielectric medium with $\varepsilon = \varepsilon_{\infty}$, having the form (11), and $u_2$ is the corresponding reaction field potential. An adaptive algorithm based on a goal oriented error estimation together with a splitting of the potential which eliminates the grid artifact due to the infinite Coulomb self-interaction can be very reliable for the calculation of the solvation energy (12). This feature will be included in future releases of ARGOS.

2.1.4 Adaptive algorithm

In general, adaptive algorithms can be represented by the following flow chart (Figure 2). Instead of the mesh parameter $h$, we will use a subindex $:\ell = 1, 2, \ldots$ to denote the refinement level and we recall that $\sum_{i=1}^{N_v} \eta_{PU}^{h}(\phi_{2,h},z^{(2)_h})$. The adaptive finite element solver based on the error estimator described above can be summarized as follows.

Solve

The solution $\phi_{2,h}$ from the space $V_\ell^1$, defined on the current mesh $T_\ell$, is found by solving (31).

Estimate

Next, we find the solution $z^{(2)_h}$ of the adjoint problem by solving the finite dimensional problem (51). From $z^{(2)_h}$, we compute the nodewise error indicators $\eta_{PU}^{h}(\phi_{2,h},z^{(2)_h})$. 


FIGURE 2  Schematic representation of adaptive refinement as explained in the text

Mark
Based on the values of \( \eta^{NV}_\ell \), a set of node patches \( N_\ell \) is marked for refinement. This set can be chosen through different marking strategies (see the Supporting Information).

Refine
Having performed a refinement based on the marked patches \( N_\ell \), a new mesh \( T_{\ell+1} \) is obtained.

The detailed algorithm of ARGOS reads:

ARGOS

1: \( \ell \leftarrow 0 \), initialize \( T_0, V_0^1, V_0^2 \)

2: repeat

3: \( \phi_{2, \ell} \leftarrow \text{Solve}^{\text{Prim}}(T_\ell, V_\ell^1) \)

4: \( z_{(2)}^{(\ell)} \leftarrow \text{Solve}^{\text{adj}}(T_\ell, V_\ell^2) \)

5: \( \{\eta^{NV}_\ell\}_{\ell=1}^{N_\ell} \leftarrow \text{Estimate}(\phi_{2, \ell}, z_{(2)}^{(\ell)}, T_\ell) \)

6: \( N_\ell \leftarrow \text{Mark}(\{\eta^{NV}_\ell\}_{\ell=1}^{N_\ell}) \)

7: \( T_{\ell+1} \leftarrow \text{Refine}(T_\ell, N_\ell) \)

8: \( \ell \leftarrow \ell + 1 \)

9: until convergence or maximum number of refinement levels reached

2.1.5 | Finite element method

The finite element (FE) method aims at approximating the exact solution of a differential equation by a piecewise polynomial function. For this purpose, 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 the 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, for example, continuity across element interfaces, as used in the adaptive algorithms presented in this paper.

In case of the lowest approximation order, that is, 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, for example, 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 \( V_0^1 \) for the primal problem is based on the Lagrange \( P_1 \) element and consists of continuous piecewise linear functions. The FE space \( V_0^2 \) for the adjoint problem is based on the Lagrange \( P_2 \) element and consists of continuous piecewise quadratic functions. In the case of \( V_0^2 \), there is one basis function \( \psi_i \) for each vertex (node) \( V_i \) of the mesh \( T_\ell \), 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 (31). The system for the adjoint problem can be constructed in a similar way. Recall, that Equation (31) has to be satisfied for all test functions \( v \in V_\ell^1 \).

Equivalently, this means that the equation must hold for all basis functions \( \psi_i, i = 1, \ldots, N_\ell \), that are zero on the boundary \( \partial \Omega \). In this notation, the number of nodes \( N_\ell \) in the mesh \( T_\ell \) equals the number of degrees of freedom \( N_{\text{DOF}}^{\text{Prim}} (=N_\ell) \) plus the number of nodes \( N_{\text{do}} \) on the boundary \( \partial \Omega \). Hence, in the primal problem, we have \( N_{\text{DOF}}^{\text{Prim}} = N_\ell + N_{\text{do}} \) and we obtain \( N_{\text{DOF}}^{\text{Prim}} \) equations for \( \varphi_{2,h} \):

\[
\int_\Omega \epsilon \nabla \varphi_{2,h} \cdot \nabla \psi_i \, dx + \int_\Omega K \varphi_{2,h} \psi_i \, dx = \mathcal{F}(\psi_i), \quad \text{for } i = 1, \ldots, N_{\text{DOF}}^{\text{Prim}}. \tag{38}
\]

Moreover, \( \varphi_{2,h} \) belongs to \( V_\ell^1 \) and \( \varphi_{2,h} = 0 \) on \( \partial \Omega \). Therefore, \( \varphi_{2,h} \) can be represented as a linear combination of the basis functions \( \psi_i \) which are equal to zero on the boundary \( \partial \Omega \) with unknown expansion coefficients \( \varphi_2 \), that is,

\[
\varphi_{2,h}(x) = \sum_{i=1}^{N_{\text{DOF}}^{\text{Prim}}} \psi_i \varphi_2 \psi_i(x). \tag{39}
\]

The goal is to find the vector of unknowns \( \Phi_2 = (\varphi_2, \ldots, \varphi_2^{N_{\text{DOF}}^{\text{Prim}}})^T \) corresponding to the interior vertices. For this purpose, we substitute expression (39) for \( \varphi_{2,h} \) in (38) and use the linearity of the integral, gradient operator, and right-hand side to obtain the following system of linear equations

\[
\sum_{j=1}^{N_{\text{DOF}}^{\text{Prim}}} \left( \int_\Omega \epsilon \nabla \psi_j \cdot \nabla \psi_i \, dx \right) \varphi_2 \psi_j + \sum_{j=1}^{N_{\text{DOF}}^{\text{Prim}}} \left( \int_\Omega K \psi_j \psi_i \, dx \right) \varphi_2 \psi_j = \mathcal{F}(\psi_i), \quad \text{for } i = 1, \ldots, N_{\text{DOF}}^{\text{Prim}}.
\]
In matrix notation, the above equations read

$$A \Phi_2 = F_2,$$

where $A$ is the symmetric positive definite matrix with entries

$$a_{ij} = \int_\Omega \varepsilon \nabla \psi_i \cdot \nabla \psi_j \, dx + \int_\Omega \nabla^2 \psi_i \psi_j \, dx, \quad i,j = 1, \ldots, N_{\text{DOF}}.$$

and

$$F_2 = (\nabla \psi_1, \ldots, \nabla \psi_{N_{\text{DOF}}})^T.$$

The system (40) 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.

### 2.1.6 | Mesh construction

A very important step in the modeling of the electrostatic potential in biomolecular systems through the PBE is the definition of the solute–solvent interface. Here, two approaches are possible. The first one, and much more commonly used [8, 9, 11–13, 17, 18], is where the transition between the low dielectric region inside the solute cavity and the high dielectric region of the surrounding continuum is sharp and discontinuous. In the second approach, this transition is smooth and depends on the (smoothly varying) electronic charge density of the solute [50, 55–57]. As mentioned in Section 2.1.1, in the present work, we utilize the first approach in combination with a solute charge density described by discrete point charges at atomic positions. In this approach, one needs to define the solute–solvent interface, that is, the molecular surface separating the solute interior from the solvent. There are many possible ways to define this surface. In all our calculations, as a definition of the molecular surface we take the SES with a probe radius of 1 Å for our first test system (Alexa 488 and Alexa 594 dyes, Section 2.4) and 1.4 Å for our second test system (RBD of SARS-CoV-2 and the ACE2 receptor, Section 2.4). On the other hand, when the ionic strength $I_2$ is nonzero, the outer surface of the ion exclusion layer (the inner surface being the SES) is defined as the van der Waals surface where the atomic radii are increased by a counter-ion radius $R_{\text{ion}}$, set to 2 Å. Therefore, the outer surface of the IEL is not smoothed with the rolling ball algorithm used in the definition of the SES. Such a smoothing procedure can be easily performed. Nevertheless, we chose not to do this, since we compare our results with MEAD and APBS which do not smooth the outer surface of the IEL.

To generate a triangulated surface mesh which approximates the SES and/or the van der Waals surface, we use the meshing software NanoShaper [58]. It also has the functionality to detect pockets and cavities in proteins which are defined according to their volumes, compared to the volume of a single water molecule. If the cavity has a volume less than that of a water molecule modeled as a sphere with a radius of 1.4 Å, then it is assigned the dielectric coefficient of the protein. Similarly, the pockets are regions in space that can be accessed by a water molecule, but cannot be accessed by a virtual probe of bigger size, for example, 3 Å. The dielectric constant of water is assigned to these pockets.

The quality of the approximation in NanoShaper is controlled with the parameter GridScale which is used to set the (inverse of the) side of the grid cubes in the marching cubes algorithm used to generate the surface mesh. A GridScale parameter equal to 2 refers to the cubic grid with spacing of $h = 0.5$ Å and GridScale = 4 corresponds to a spacing $h = 0.25$ Å (see Figures S1 and S2). A grid scale of 2 produces an average edge length of the triangulated surface mesh of around 0.45 Å, whereas GridScale = 4 results in an average edge length of around 0.225 Å. The position of the mesh vertices is very accurate since they are analytically sampled by the NanoShaper ray casting routine. However, the quality of the resulting surface triangles is modest as a result of the marching cube triangulation rules [58] (Figures 20A and S1), and thus not appropriate for FE calculations. To improve the quality of the mesh one can instruct NanoShaper to apply a Laplacian smoothing to the output mesh. This results in the same vertex and edge number, and approximately the same average edge length, but more regular triangles, this time suitable for FE simulations. However, after application of the smoothing routine, it is no more guaranteed that all the grid points of the resulting triangulated surface lie on the analytical surface (SES or van der Waals), (Figures 20B and S2). Another issue with the Laplacian smoothing is that it tends to shrink the surface (see Figures S1 and S2). Nevertheless, the shrinkage after the application of the NanoShaper built-in smoothing procedure is practically negligible. This can be seen by comparing the average distance between the center of a model sphere and its mesh vertices before (Figure S1) and after (Figure S2) the smoothing takes place or by computing the Hausdorff distance between the raw and smoothed surface (see the Supporting Information). For this reason, we use this smoothing option in all our calculations.

**External simplification routine**

Instead of using the NanoShaper built-in smoothing routine, one can also use other remeshing and simplification routines, such as mngs_O3 of the software package mng [59, 60]. The two options that we use from mngs_O3 are -hausd and -min. The first option defines the Hausdorff distance in Å between the original and remeshed (simplified) surface, while the second one sets the minimum edge size in Å of the remeshed surface. Unlike the Laplacian smoothing, the simplification procedure implemented in mngs_O3 does not shrink the surface (see Figure S3) while at the same time greatly reduces the number of mesh vertices and maintains the geometric features and quality of the molecular model. We make use of this simplification routine only in the construction of the surface mesh for the
molecular system consisting of the RBD of SARS-CoV-2 and the ACE2 receptor, see Section 3.3.

**Volume mesh generation and mesh refining**

Once the surface meshes are generated, we use TetGen [61] to create the initial tetrahedral meshes, where one can optionally prescribe a uniform mesh size in the molecular domain, related to the average edge length on the molecular surface. Since, our FE algorithm is adaptive, prescribing a uniform mesh size inside the protein is not necessary in order to properly resolve the singularities associated with the fixed point charges. Instead, the mesh will be appropriately refined after a few mesh refinement steps. For the adaptive mesh refinement (AMR) we use mmg3d [59, 60]. The implementation of the prototype version of the adaptive solver is realized in FreeFem [62]. Here, we want to point out that the particular choice of a molecular surface definition and of the IEL, as well as of the utilized meshing software is not essential and other alternatives can also be used.

### 2.2 MEAD solver

Here, we will give a brief overview on the Macroscopic Electrostatics with Atomic Detail (MEAD) software solving the linearized PBE (for more details, see Ref. [18]). Taking into account the finite size of the grid, it prescribes a Dirichlet boundary condition for the ESP given by the analytical expression obtained for molecular point charges in a homogeneous dielectric environment with the dielectric coefficient of the solvent. This condition requires the grid to span a large area, increasing the cost of calculations drastically. To avoid this problem, MEAD adopts a multigrid focusing method. Here, the initial calculations are made with a coarse-grained grid covering a larger domain, followed by calculations on finer grids covering smaller subdomains, centered on the region of interest.

In our calculations, we used MEAD version 2.2.8a and its programs potential and multilex. The former is applied to calculate the ESP at the coordinates specified by the user. We used multilex to calculate the interaction energy. An important issue in the MEAD procedure involves calculating both energies \( E_{1,2} \) and \( E_{2,4} \), expressed through potentials \( \phi_1 \) (see (20)) and \( \phi_2 \) (see (21)). The final result is obtained as the average of the two, that is,

\[
E_{\text{MEAD}}^{\text{APBS}} = \frac{E_{1,2}^{\text{APBS}} + E_{2,1}^{\text{APBS}}}{2}.
\]

To present the best case scenario for APBS, we use the finite difference solver mg-auto with parameters which provide a relatively good computational efficiency and a very high accuracy. Below, we list the keywords, most relevant to our computations, 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 Supporting Information.

- \texttt{mg-auto #} specifies the type of calculations that the finite difference multigrid PMG code performs.
- \texttt{dime nx ny nz #} are the number of grid points in the x-, y-, and z-direction, respectively, for all focused FD grids.
The crystal structure of the receptor binding domain (RBD) of the spike protein of SARS-CoV-2 and the cell receptor ACE2 [66]. (A) Structure of the RBD-ACE2 interfaces reveals a network of hydrophilic interactions, including hydrogen bonds and salt bridges [66]. Hence, ARGOS can be employed to determine the contribution of the electrostatic coupling to the binding between the spike protein and the ACE2 receptor. This information can be useful to understand and predict binding efficiencies of different antibodies to RBD. In our work we apply ARGOS to check the involvement of the two pairs of interacting residues: LYS417 (RBD) and ASP30 (ACE2) (Figure 4B), and ASN501 (RBD) and LYS353 (ACE2) (Figure 4B). The former is especially interesting, because it has a direct contact with aqueous solution, while the latter is almost fully surrounded by the protein. Moreover, this system has 12,647 atoms, a considerably larger number as compared to our first system, and has a complicated surface which includes cavities that may contain water molecules and could be modeled as regions with high dielectric permittivity.

The preparation of the system included the following steps. First, CHARMM GUI was used to add hydrogen atoms to the heavy atoms resolved in the crystal structure 6m0j. In addition, the system was placed in a box of water molecules and explicit ions were added to obtain an overall charge neutral system. The geometry of the system was optimized by using an energy minimization constraining the heavy atom coordinates of the glycans and the protein backbone as in the crystal structure.

The solver will also be applied to compute the interaction energy between the SARS-CoV-2 protein and the human receptor ACE2 placed in aqueous solution with 50 mM NaCl at temperature $T = 300$ K. The system represents a crystal structure (PDB ID: 6m0j) of the receptor binding domain (RBD) of the spike protein of SARS-CoV-2 bound to the cell receptor ACE2 (Figure 4A). The system includes four glycans, linked to ACE2 ASN90, ASN322 and ASN546 and to RBD ASN343. Analysis of the RBD-ACE2 interfaces reveals a network of hydrophilic interactions, including hydrogen bonds and salt bridges [66]. Hence, ARGOS can be employed to determine the contribution of the electrostatic coupling to the binding between the spike protein and the ACE2 receptor. This information can be useful to understand and predict binding efficiencies of different antibodies to RBD. In our work we apply ARGOS to check the involvement of the two pairs of interacting residues: LYS417 (RBD) and ASP30 (ACE2) (Figure 4B), and ASN501 (RBD) and LYS353 (ACE2) (Figure 4B). The former is especially interesting, because it has a direct contact with aqueous solution, while the latter is almost fully surrounded by the protein. Moreover, this system has 12,647 atoms, a considerably larger number as compared to our first system, and has a complicated surface which includes cavities that may contain water molecules and could be modeled as regions with high dielectric permittivity.

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The calculation of the interaction between the Alexa chromophores and the RBD and ACE2 proteins by MEAD, APBS and ARGOS follows the same procedure, starting with computing the ESP from the Poisson or LPBE (see (5) and (4)). This potential is then used to calculate the coupling (see (20) and (21)).

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

\[ \text{Err}^{\text{Adj}} = \frac{|E - E^{\text{Adj}}_1|}{|E|} \times 100, \]
\[ \text{Err}^{\text{Prim}} = \frac{|E - E^{\text{Prim}}_2|}{|E|} \times 100, \]
\[ \text{Err}^{\text{MEAD}} = \frac{|E - E^{\text{MEAD}}|}{|E|} \times 100, \]
\[ \text{Err}^{\text{APBS}} = \frac{|E - E^{\text{APBS}}|}{|E|} \times 100, \]

where \( E \) is the exact (analytical) solution, \( \text{Err}^{\text{Adj}} = \text{Err}^{\text{ARGOS}} \) and \( \text{Err}^{\text{Prim}} \) correspond to the relative errors of the numerical solutions \( E^{\text{Adj}}_1 \) and \( E^{\text{Prim}}_2 \) of the adjoint and the primal problem, respectively, obtained with ARGOS. \( E^{\text{MEAD}}, E^{\text{APBS}} \) are the numerical solutions, obtained with MEAD and APBS, respectively, and \( \text{Err}^{\text{MEAD}} \) and \( \text{Err}^{\text{APBS}} \) are the corresponding relative errors. The different models, studied below, were constructed to focus on particular aspects that limit the accuracy of the numerical solution. The first model includes chromophores without interfaces and examines the effect of discretization of the charges and the imposed boundary conditions on the ESP \( \varphi \). Models 2 and 3 employ a Born ion model, represented by a spherical cavity with a central charge, and are designed to probe the role of the interface and of the ionic charge density of the solvent.

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

The setup consists of a polyproline helix (POLY6 or POLY20), labeled with charge-neutral Alexa dyes in the electronic ground state. The system is placed in vacuum \((\epsilon_i = 1)\). The dielectric coefficient \( \epsilon_m \) of the chromophores and polyproline are also set 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 pairwise Coulomb interactions between point charges. The couplings were calculated for 19 snapshots (frames), randomly selected from the MD simulations: frames 1 to 10 and 11–19 contain POLY6 and POLY20, respectively. The sizes of the coarse-grained and fine (focused) meshes in the MEAD and APBS calculations are selected taking into account the dimensions of the system. The coarse-grained, the intermediate-focused, 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 Section 2 for more details). The complete specification of configurations M1-1, M1-2 for MEAD and A1 for APBS, used in the computations of Model-1 are given in Tables 1 and 2, respectively.

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 with an average margin (over all frames) of at least 10 Å from all sides. We have chosen the values of the parameters of \( \text{dime} \) and of \( \text{fglen} \) 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 \( \text{fglen} \), however, are chosen much larger, that is, 900 Å, which can improve the accuracy of the APBS computations compared to MEAD. We also note that the \text{mg-auto} solver automatically chooses how many intermediate focusing grids are used between the coarse-grained and the fine mesh. In the case of configuration A1, with \( \text{cglen} 900 \) 900 900 and \( \text{fglen} 80 \) 80 80 or \( \text{fglen} 100 \) 100 100, \text{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, \( \text{Err}^{\text{ARGOS}} \) and \( \text{Err}^{\text{Prim}} \) defined in (43), and average them over all frames (Figure 5). Both \( \text{Err}^{\text{Adj}} \) and \( \text{Err}^{\text{Prim}} \) exhibit the order of convergence, predicted by (36) and (37). The solution of the adjoint problem exhibits a higher convergence order \( O(\#\text{DOFs}^{-1}) \) (see (37)), and thus, much smaller relative errors, ranging from \( 2 \times 10^{-1} \% \) down to \( 2 \times 10^{-4} \% \) for the largest number of DOFs, that is, \( 10^7 \). For a non-homogeneous Dirichlet boundary condition, the relative errors \( \text{Err}^{\text{ARGOS}}, \text{Err}^{\text{Prim}} \) and the respective convergence orders for charged and neutral chromophores are given in Figures S9–S11. This boundary condition is given by the Coulomb potential (see (11)) for the point charges defining the respective problem (primal or adjoint) with a uniform dielectric coefficient \( \epsilon_m = \epsilon_s = 1 \). In this case, it is given by the exact potential on the boundary of the computational domain \( \Omega \) and coincides with the boundary condition used by MEAD and APBS.

The relative errors of MEAD, APBS, and ARGOS are compared in Figure 6. 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%. We conclude that, if the number of iterations in SOR is too small, the iterative error dominates the discretization error. 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 arithmetics used and no further decrease of the overall error is possible.

APBS performs much better than MEAD for almost all frames. The error of the former does not exceed 0.4% and can be lower than the one of ARGOS for mesh refinement level (MRL) = 0. However, further refinements gradually decrease the relative errors of ARGOS, reaching about \(5 \times 10^{-3}\%\) at most for MRL = 4. If one continues with the mesh refinement procedure in ARGOS, the relative errors drop even further, see Figure S8.

### 3.1.2 Model-2: 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), for the potential \(\varphi\) and for the normal component of the displacement field \(\epsilon_{r}\varphi\), are critical for the accuracy, particularly of the FD solvers. The description of sharp interfaces, where the dielectric coefficient 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. Different dielectric coefficients $\epsilon_m = 4$ inside and $\epsilon_s = 80$ outside the cavity are assumed. The spherical cavity with the central charge in a homogeneous dielectric is known from the Born model of ion solvation.

In a first model, a cavity with radius $R = 2$ Å is assumed (Figure 7). The coordinates of the ion center 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 $1 \, \text{Å} < r < 35 \, \text{Å}$. 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 $d_i$, $i = 1, 2, ..., 10$ from the ion’s center, along which the probe charge was placed: $d_1 = (1,0,0)$, $d_2 = (-1,0,0)$, $d_3 = (0,1,0)$, $d_4 = (0,-1,0)$, $d_5 = (0,0,1)$, $d_6 = (0,0,-1)$, $d_7 = (1,1,1)$, $d_8 = (-1,-1,-1)$, $d_9 = (1.05,0,2)$, and $d_{10} = (-1,-0.5,-0.2)$. The relative errors in the interaction energies calculated for the same $r$ along different directions $d_i$ were averaged over all $i \in \{1, 2, ..., 10\}$ to obtain the values $E_{\text{Err}}^{\text{MEAD}}(r)$ and $E_{\text{Err}}^{\text{APBS}}(r)$ for each distance $r$ (for details see Eq. (54)).

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 of Model-2 are given in Tables 3 and 4, respectively. All grids (coarse-grained and focused) for both MEAD and APBS are centered at $(0, 0, 0)$, that is, slightly offset from the center 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 $\text{etol}\ 1e - 06$ and $\text{etol}\ 1e - 09$. Therefore, we present only the latter results.

In the ARGOS calculations, we used $\text{GridScale} = 2$ and 4 with solutions taken at MRL = 5 and MRL = 3, respectively. The computational domain $\Omega$ is a cube with an edge length of approximately $1,350,000$ Å. Here, we only present the ARGOS results for a homogeneous Dirichlet boundary condition (this is possible since the boundary of $\Omega$ is very far from the ion and the probe charge). The results for a nonhomogeneous boundary condition are presented in the Supporting Information, Figure S15. In this case the boundary potential is exactly prescribed, since the Coulomb potential coincides with the exact one given by (44) on the boundary of $\Omega$ and the quality of the potential 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 $\Omega$.

An illustration of the mesh for $\text{GridScale} = 2$ before and after refinement is presented in Figure 7. Comparison of the initial and final mesh topologies 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. The convergence of the relative errors with increasing refinement levels of ARGOS is shown in Figures S12 and S15.

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

$$\phi(r) = \begin{cases} \frac{q_1}{\epsilon_m r}, & r \leq R, \\ \frac{q_1 (\epsilon_m - \epsilon_s)}{\epsilon_s R^2}, & r \geq R. \end{cases}$$

The relative errors of the calculations obtained with MEAD, APBS and ARGOS using different solver configurations are given in Figure 8. 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. Whereas for the default SOR parameters the errors of MEAD increase with increasing $r$, 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 largest relative error occurs at $r = 1$ Å and equals 2 % for $\text{GridScale} = 2$. At the interface, the relative error decreases to 0.4 and 0.2 % for $\text{GridScale} = 2$ 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 S17). This result shows that the presence of charges near sharp interfaces has a strong impact on the accuracy of the FD approximation of the electrostatic interaction. 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 with respect to the mesh refinement levels is shown in Figures S12, S15, and S16.

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 consider interaction between a Born ion with increased radius and a probe charge, placed near the surface of the ion cavity (see Figures S18–S21). The results reveal that the relative error 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 at \( r = 16 \) Å are approximately 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 improve much 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 are approximately 2 % for MEAD and APBS. Although, a relative error of 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 in the interaction energy with FD solvers increases for large molecular systems. This effect will be revealed in Section 3.2, where we investigate the error in the electrostatic interaction between chromophores in a dielectric solvent environment obtained
by MEAD and APBS. Similarly to the results presented in Figures 8 and 9, the relative errors for ARGOS are more than two orders of magnitude smaller around the interface than those of MEAD and APBS (Figure S18).

3.1.3 | Model-3: Presence of interfaces and ions

We supplemented Model-2 with a continuous charge density of ions outside the cavity, described by 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 a radius enlarged by that of a probe ion’s radius $R_{\text{ion}} = 2 \text{ Å}$. For MEAD and APBS we used the configurations, defined in Tables 3 and 4, respectively. The APBS results for $\text{etol} = 1 \times 10^{-06}$ and $\text{etol} = 1 \times 10^{-09}$ again do not differ, and thus we report only the latter results. The computational domain for ARGOS is the same as for Model-2. We compare the solutions of ARGOS obtained at $\text{MRL} = 3$ and 4 for $\text{GridScale} = 2$ 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 Figure S22. The analytical solution for the ESP $\varphi$ in the present model is given as:

$$
\varphi(r) = \begin{cases} 
\frac{q_1}{\epsilon_s r} \left( \frac{1}{\epsilon_{\text{mf}} r} - \frac{1}{\epsilon_s R} \right), & r \leq R, \\
\frac{q_1}{\epsilon_s} \left( \frac{1}{\epsilon_{\text{mf}} R} - \frac{1}{\epsilon_s a} \right), & R \leq r \leq a, \\
\frac{q_1}{\epsilon_s} \left( \frac{1}{\epsilon_{\text{mf}}} \right) \frac{1}{\epsilon_s} \exp \left( \frac{a - R}{\epsilon_s} \right), & r \geq a,
\end{cases}
$$

(45)

where $r$ is the distance of the probe charge from the center of the Born ion and $a = R + R_{\text{ion}}$ and $R = \left( \frac{\lambda_{\text{Debye}} \epsilon_{\text{mf}}}{1000} \right)^{1/2}$.

The results of the calculations, shown in Figure 9, demonstrate a drastic change in the MEAD accuracy for M2-1 in comparison to Model-2 (Figure 8): 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 $r > 20 \text{ Å}$, the error depends more on the mesh spacing than on the SOR parameters, in contrast to Model-2. Obviously, the discretization error dominates the error of the iterative linear solver (for other MEAD configurations see also Figures S13 and S23). It should also be mentioned that for configuration M2-2 the respective maximum iteration number $\text{maxrmdiff}$ is not reached in the iterative process.

Similarly to Model-2, the errors of MEAD and APBS are particularly large around the interface between the ion and the solution, 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 $R = 1 \text{ Å}$, they are as high as 70 % and 50 % for MEAD and APBS, respectively, while ARGOS exhibits even smaller errors than for $R = 2 \text{ Å}$ (Figure S26).

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 coefficient leads to a strong dependence of the accuracy on the mesh spacing and the SOR stopping criterion, especially for long-range interactions. Besides the stopping criterion issue, the use of single precision arithmetics can also lead to significant round-off errors. The results of APBS calculations exhibit much smaller relative errors than MEAD, but still do not reach the accuracy of ARGOS, which exhibits a predicted and uniform convergence. The test calculations also reveal, that $\text{GridScale} = 2$ 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 determine the deviations, $D_{\text{AM}}$ and $D_{\text{AA}}$, of the MEAD and APBS calculations, respectively, relative to the solution $E^{\text{adj}}_{1-2}$ of the adjoint problem of ARGOS as:

$$
D_{\text{AM}} = \frac{|E^{\text{adj}}_{1-2} - E_{\text{MEAD}}|}{|E^{\text{adj}}_{1-2}|} \times 100, 
$$

(46)

$$
D_{\text{AA}} = \frac{|E^{\text{adj}}_{1-2} - E_{\text{APBS}}|}{|E^{\text{adj}}_{1-2}|} \times 100. 
$$

(47)

Refinement level $\ell = 4$ and $\text{GridScale} = 2$ are employed in the ARGOS calculations. The computational domain is a cube with a side length between 160,000 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 (see Tables S3 and S4 for the respective partial charges) in equilibrium with the solvent. The orientational polarization of water molecules dominates the dielectric response of the solvent. The large dielectric coefficient of water results in a sharp interface at the molecular surface, where $\epsilon$ jumps from a low value for the chromophores or the protein ($\epsilon_{\text{mf}} = 4$) 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 investigate different MD frames for POLY6 and POLY20, as in Model-1 studied above, but 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 a dielectric coefficient $\epsilon_s$;
- DYES, dyes-solution interface: chromophores are represented by point charges inside molecule-shaped cavities with a dielectric coefficient $\epsilon_m$ inside, surrounded by a homogeneous dielectric with a coefficient $\epsilon_s$, representing the aqueous solvent (see Figure 10A);
- 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 a dielectric coefficient $\epsilon_m$ inside (see Figure 10B);
- DYES-POLYPRO-IONS, dyes-solution and protein-solution interfaces: the previous model is complemented with ionic charge density in the aqueous solvent, characterized by an ionic strength of 0.3 M (see Figure 10C).

The Alexa chromophores in their electronic ground state are negatively charged by two elementary units ($-2e_0$) [44]. In order to investigate, how the interchromophore charge density coupling changes, if no monopole moments are present, we artificially neutralize the chromophores by adjusting the charges within the SO$_3$ groups such that the overall charge of the chromophores is zero, as described in Tables S5 and S6. 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. Note also that, these charges have been employed in Model-1 above.

### 3.2.1 Charged dyes

The deviations $D_{AM}$ and $D_{AA}$ of the electrostatic interaction energies between the charged chromophores obtained with MEAD and APBS and the ARGOS reference solutions are presented in Figure 11 for three different models described above.

Examination of the MEAD results shows, that including the polyproline domain can notably change the error (e.g., frames 5, 9 and 10 in Figure 11), 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 investigate the reference interaction energies obtained with ARGOS (see Figure 12, and for logarithmic scale of the y-axis see Figure 13).

As evident from Figure 12, 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 polyproline, increases the interaction energy in comparison to the simple model of a homogeneous dielectric. This effect is due to the lower dielectric coefficient inside the cavities. For larger interchromophore distances this effect gets smaller.
Comparison of the interaction energy between charged chromophores for all models, calculated with ARGOS. The asterisks, circles, squares, triangles correspond to the models NO-INT, DYES, DYES-POLYPRO, and DYES-POLYPRO-IONS, respectively. The different frames correspond to different molecular geometries taken from MD simulations.

The results, shown in Figure 13, 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 13). For the larger distances between the charged 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 13). The large increase in screening for POLY20 with respect to POLY6 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 (45). 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 and 42 Å, respectively. The ratio between the interaction energies, calculated by ARGOS, is about $10^{-6}$ (see Figure 13 for the model DYES-POLYPRO-IONS). The estimation of this ratio, using (45) with $k^2 = 2.529 \text{ Å}^{-2}$, gives $9 \times 10^{-4}$, providing a qualitative explanation of the effect of the exponential screening factor. Without exponential factor we obtain a ratio of 0.5. An examination of the results in Figure 13 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 11).

The significant increase of $D_{IA}$ 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 8 and 9), 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 11 deviate from the reference solution of ARGOS much less, compared to those obtained with MEAD. Only $D_{IA}$ 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 16D. The minimal box that contains the polyproline system has dimensions of $90.7 \times 251 \times 17.1 \text{ Å}^3$ 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 confirm 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 interaction energies, together with their mean values and standard deviations were calculated for a perturbed grid center, given by $(\Delta x_i \Delta y_i \Delta z_i)$ for $i = 1, 2, \ldots, 15$ 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 (S11) from the Supporting Information with $h = 0.15 \text{ Å}$. The interaction energies were averaged over all 15 grid positions, giving average values $E_{APBS}^{12}$ and $E_{APBS}^{21}$, and their respective standard deviations $\sigma_{12}$ and $\sigma_{21}$. The final value for the interaction energy, $E_{APBS}$, was obtained, as usual, by averaging $E_{APBS}^{12}$ and $E_{APBS}^{21}$.

The results for frame 12 with the enlarged fine grid box in configuration A1 are presented in Table 5, demonstrating a pronounced asymmetry in the average values $E_{APBS}^{12}$ and $E_{APBS}^{21}$ for the larger electro value (for details see Table S9 where one can also infer the absolute values of the errors). For comparison, the adjoint solutions $E_{ARGOS}^{12}$ and $E_{ARGOS}^{21}$ of ARGOS are equal to $-5.5959e -10$ and $-5.5967e -10$, respectively, for GridScale = 2 at MRL = 4. The average value of $E_{APBS}^{12}$ and $E_{APBS}^{21}$ comes closer to the above reference value of ARGOS than
the single values (Table 5). Also, the average over different grid positions improves the accuracy, as seen from Table S9 and from the standard deviations in Table 5. Decreasing the value of the parameter etol improves the accuracy as well. All these effects reduce the relative deviation of the APBS result for frame 12 from the reference (ARGOS) value $-5.5959 e^{-10}$ Å in Figures 11 to 3 \% in Table 5.

Reduction of the grid spacing of APBS or equivalently an increase of the number of grid points is expected to further decrease the relative deviation $D_{\text{AA}}$. 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.

### 3.2.2 Neutral dyes

The relative deviations for the interaction energies between ground state charge densities of neutral chromophores, presented in Figure 14, reveal a drastic increase compared to the previous case of charged chromophores in Figure 11. 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 compared to ARGOS (see frames 15 and 10 for M1-1 in Table 6), and even a different sign of $E_{\text{adj}}^{\text{MEAD}}$ and $E_{\text{adj}}^{\text{APBS}}$ (see frames 15 and 16 for M1-1 in Table 6). Obviously, a strong asymmetry ($E_{\text{MEAD}}^{\text{1-2}} \neq E_{\text{MEAD}}^{\text{2-1}}$) is an indicator of a poor accuracy. In contrast to the MEAD calculations, the energies $E_{\text{adj}}^{\text{APBS}}$ computed by ARGOS match the energies $E_{\text{adj}}^{\text{1-2}}$ very well. 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. The ARGOS calculations in Figures 14 and 15 and in Table 6 were performed with $\text{GridScale} = 2$ at $\text{MRL} = 4$. Increasing the GridScale to 4 in the calculations for frames 15 and 10 leads to very similar energies $E_{\text{adj}}^{\text{1-2}}$ and $E_{\text{adj}}^{\text{2-1}}$ of $1.9649 e^{-07}$ and $1.9648 e^{-07}$, and $2.7915 e^{-07}$ and $2.7911 e^{-07}$, respectively.

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

The interaction energies for frames 6 and 10 are analyzed in Tables 7 and 8, respectively (for more details see Tables S10 and S11). Like in the case of charged dyes, the values of $E_{\text{adj}}^{\text{APBS}}$ and $E_{\text{adj}}^{\text{MEAD}}$ for all the tested grid spacings do not exhibit the required symmetry $E_{\text{adj}}^{\text{1-2}} = E_{\text{adj}}^{\text{2-1}}$. The effect is even more pronounced for particular relative positions of the molecular system and the grid, when $E_{\text{adj}}^{\text{1-2}}$ and $E_{\text{adj}}^{\text{2-1}}$ can have different sign (see the Supporting Information, grid centering perturbation $l = 10$ in Table S10 for $h = 0.2$ Å of frame 6). Moreover, the asymmetry of the solutions, as well as the standard deviations $\sigma_{\text{1-2}}$ and $\sigma_{\text{2-1}}$ for some frames, do not scale down as $h \rightarrow 0$. The relative deviations $D_{\text{AA}}$ 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

### Table 5

| $h$ (Å) | $E_{\text{adj}}^{\text{APBS}}$ | $\sigma_{\text{1-2}}$ | $E_{\text{adj}}^{\text{MEAD}}$ | $\sigma_{\text{2-1}}$ | Avg. $E_{\text{adj}}^{\text{APBS}}$ | $D_{\text{AA}}$ (%) |
|--------|------------------|----------------|------------------|----------------|----------------------------|------|
| 0.286 (etol 1e-06) | $-4.82 e - 10$ | 1.80 e - 11 | $-6.94 e - 10$ | 1.23 e - 11 | $-5.88 e - 10$ | 5.08 |
| 0.286 (etol 1e - 09) | $-5.79 e - 10$ | 1.79 e - 11 | $-5.79 e - 10$ | 1.16 e - 11 | $-5.79 e - 10$ | 3.45 |

Note: $\sigma_{\text{1-2}}$ and $\sigma_{\text{2-1}}$ are standard deviations of interaction energies obtained for different grid positions. All energies are in units of $e_0$ Å$^2$.
The table demonstrates an unphysical asymmetry of the MEAD interaction energies: $E_{1-2}^{\text{MEAD}} \neq E_{2-1}^{\text{MEAD}}$. All energies are in units of $\varepsilon_0^2/\text{Å}$.

**Figure 15** Comparison of the interaction energy between the chromophores in the charge-neutral ground states for all models, calculated with ARGOS. The asterisks, circles, squares, triangles correspond to the models NO-INT, DYES, DYES-POLYPRO, and DYES-POLYPRO-IONS, respectively. The different frames correspond to different molecular geometries taken from MD simulations.

**Table 6** Interaction energies between ground state charge densities of neutral dyes, calculated with MEAD and ARGOS (with GridScale = 2 at MRL = 4) for different frames and interface models.

| Frame, Model       | $E_{1-2}^{\text{MEAD}}$ | $E_{2-1}^{\text{MEAD}}$ | $E_{1-2}^{\text{MEAD}}$ | $E_{2-1}^{\text{MEAD}}$ | $E_{1-2}^{\text{MEAD}}$ | $E_{2-1}^{\text{MEAD}}$ |
|--------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Frame 15, DYES     | M1-1 1.20e−07          | −1.87e−07              | −3.36e−08              | 1.9797e−07             | 1.9797e−07             |
|                    | M1-2 1.03e−07          | 9.15e−08               | 9.73e−08               | 2.8530e−07             | 2.8539e−07             |
| Frame 10, DYES     | M1-1 −1.65e−07         | −4.86e−08              | −1.07e−07              | 2.8530e−07             | 2.8539e−07             |
|                    | M1-2 1.36e−07          | 2.00e−07               | 1.68e−07               | 2.9232e−07             | 2.9232e−07             |
| Frame 16, DYES-POLYPRO | M1-1 2.33e−07         | −1.59e−07              | 3.66e−08               | 2.9232e−07             | 2.9232e−07             |
|                    | M1-2 2.75e−07          | 2.68e−07               | 2.71e−07               | 2.9232e−07             | 2.9232e−07             |

Note: The table demonstrates an unphysical asymmetry of the MEAD interaction energies: $E_{1-2}^{\text{MEAD}} \neq E_{2-1}^{\text{MEAD}}$. All energies are in units of $\varepsilon_0^2/\text{Å}$.

Influence of the charge distribution and presence of the interface

Our goal here is to quantify the influence of the charge distribution and the jump in the dielectric coefficient across the solute-solvent interface on the accuracy of the FD solvers MEAD and APBS. While such an investigation was already performed on academic problems with known solutions (Models-1, 2, and 3 in Sections 3.1.1, 3.1.2, and 3.1.3), here we consider the interaction energies in the DYES model with different charge densities and different sharpness of the solute-solvent interface. The latter is characterized by the magnitude of the jump of the dielectric coefficient across the interface, that is, $|\varepsilon_s - \varepsilon_\text{m}|$.

In Table 9, we summarize five setups for the DYES model with different dielectric coefficients $\varepsilon_m$ and $\varepsilon_s$ where the Alexa chromophores are prescribed neutral ground state or transition charges (see Tables S1 and S2 for the transition charges). Setups 1 and 4 were already employed in Sections 3.2.2 and 3.1.1, respectively, while Setups 2, 3, and 5 are new. In Setup 5 we use transition charges and dielectric coefficients $\varepsilon_m = 1$ for the dyes and $\varepsilon_s = 2$ for the solvent. This case is relevant for Förster resonance energy transfer (FRET) between the chromophores [44, 68]. In FRET, only the electronic part of the environmental polarization, described by an optical dielectric coefficient of 2 (typical for organic matter), needs to be taken into account [68]. While Setup 5 is relevant for FRET and Setup 1 is needed for an implicit solvent description, Setups 2–4 just serve as test cases for the numerical solution, without any direct physical application.

Since there are no analytical solutions available for this model except for Setup 4, to assess the accuracy of MEAD and APBS, we use the reference solutions obtained with ARGOS at MRL = 4 and a geometric approximation of the interface GridScale = 4 in NanoShaper.

The relative deviations of the interaction energies obtained with MEAD and APBS from the ARGOS reference solutions for Setups 1–4 are presented in Figure 17. The MEAD results reveal that removing the interface, passing from Setup 1 to Setup 3 and Setup 4, gradually reduces the relative deviations $D_{\text{AM}}$ from ARGOS for almost all
frames, indicating a strong influence of the jump in the dielectric coefficient on the numerical accuracy.

The APBS results exhibit a higher accuracy than the MEAD calculations with \( D_{\text{AA}} \) values not exceeding 22 %, but the same general dependence on the “sharpness” of the interface. The results for frames 14 and 19 depart from this behavior, revealing a noticeable increase of the errors in Setup 3, compared to Setup 1: \( D_{\text{AA}} \) rises from 6 % to 22 % and from 7 % to 9 % for frames 14 and 19, respectively.

The accuracy for those two frames in Setup 3 can be improved by reducing the grid spacing and averaging the interaction energy over different relative positions of the grid and the molecular system, like above. This procedure reduces the deviation \( D_{\text{AA}} \) to 3 % for frame 14 and to 1 % for frame 19 (see details in Tables S13 and S15), restoring the correct trend and demonstrating again the strong sensitivity of the APBS results on the relative position of the grid (see also Tables S12 and S14 for the inspection of frames 14 and 19 with Setup 1).

Application of the transition charges in Setup 2 leads to smaller relative deviations \( D'_{\text{AM}} \) and \( D'_{\text{AA}} \) in the interaction energies for all frames. However, the deviations can still exceed 10 % for both MEAD and APBS calculations with \( D'_{\text{AA}} \) values not exceeding 22 %.
and APBS. The one noteworthy exception here is frame 1 which shows the opposite trend: for Setup 2 with transition charges $\Delta \rho_{\text{t}}$ increases almost 10 times, compared to Setup 1 with ground-state charges. Calculations of averaged $E_{\text{APBS}}^4$ on grids with smaller spacing $h$ (see Table S16) cut down the relative deviation $\Delta \rho_{\text{t}}$ between APBS and ARGOS to 0.5 %, which is again an evidence that the ARGOS reference solutions are indeed accurate.

The smaller relative deviations obtained for the coupling between transition charges can be explained in the following way: in the case of transition charges the potential is created by a smaller number of nonzero charges (see Tables S3 and S4, and S1 and S2 for the ground-state and transition charges, respectively, for the two dyes) compared to the case of ground-state charges, and then multiplied again by a smaller number of nonzero charges$^4$ to obtain the interaction energy.

In order to describe a situation relevant for FRET, the dielectric coefficients $\epsilon_m$ and $\epsilon_s$ of the dyes with transition charges and the solvent, respectively, have to be decreased from $\epsilon_m = 4$ and $\epsilon_s = 80$ in Setup 2, considered so far, to $\epsilon_m = 1$ and $\epsilon_s = 2$ (Setup 5 in Table 9). The electrostatic interaction energies in this case have been assessed with MEAD in our previous publication [44]. Here, we reinvestigate these results for a large number of frames of POLY6 (Figure S27). For most frames of POLY6, the relative deviation of MEAD from ARGOS stays below 3 %, while for some the error can reach up to 20 %. The large deviations, however, occur only for small couplings and, therefore, do not affect the FRET efficiencies calculated previously [44].

Hence, it is not the calculation of the coupling between transition densities but that between the ground state charge densities of the chromophores that can be critically improved by ARGOS. The latter aspect will be crucial in an implicit description of the solvent in MD simulations that will allow one to simulate much larger time scales than by using an explicit description. In this way the sampling of chromophore conformations can be improved which is critical for the interpretation of FRET experiments. An important aspect of an implicit solvent description concerns the screening of the inter-chromophore coupling by the ions, which is investigated in the following.

**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:

- **DYES-IONS** includes ionic charge density in the aqueous solvent, characterized by the same ionic strength of 0.3 M as before and the IEL around the chromophores (as in Figure 1);
- **DYES-POLYPRO-IONS-2** includes ionic charge density in the solvent with ionic strength of 0.3 M and the IEL around the chromophores and polyproline helix.

Please note that, the ions are not allowed to penetrate into the region surrounded by the IEL.

![Figure 18](image-url)  
**Figure 18** Interaction energies of the chromophores in a charge-neutral ground state, calculated by ARGOS with GridScale $= 2$ at MRL $= 4$ for different interface models. The blue and red colors of the symbols correspond to positive and negative interaction energies, respectively. The different frames correspond to different molecular geometries taken from MD simulations.

The model NO-INT (no interface, $\epsilon_m = \epsilon_s = 80$, see Section 3.2) differs from the model DYES-IONS only by the absence of ions. In DYES-IONS, ions penetrate in the area between the dyes and this ionic screening decreases the electrostatic inter-chromophore coupling (as seen in Figure 18 by comparing the stars with the rombs). The screening is particularly effective for POLY20 (frames 11 to 19) because of the large inter-chromophore distances. For POLY6, in three cases (frames 1, 3 and 8) the dyes are so close that the ionic screening is practically zero. The molecular configuration of frame 1 in Figure 16A shows that the molecular cavities of the two dyes start to overlap and, hence, there is no space for the ions.

Exclusion of the ions from the polyproline domain, while passing from the model DYES-IONS to DYES-POLYPRO-IONS, can substantially change the interaction energy for both POLY6 and POLY20. The interaction energy is enhanced for frames 4, 5, 7–9, 12, 14, 17, 19, decreased for frames 2, 11, 13, 16, 18 and left practically unchanged for the remaining frames (as seen by comparing the crosses with the rombs in Figure 18). The effect depends mostly on the orientation of the dyes with respect to the polyproline helix. In the closed conformation, when the chromophore with a long linker (Alexa 488) is close to the helix (as in frames 2 and 11 shown in Figure 16B,C, respectively), the dipole of the chromophore is not completely surrounded by the ions. This configuration results in partial ionic screening of the charges that changes the magnitude and orientation of the effective dipole of the chromophores, modifying the interaction between the dyes. The rotation of the effective dipoles (frames 11, 13, 18) can even change the sign of the interaction. On the other hand, the open configuration (see Figure 16D) experiences a complete screening by the ions. In this case, the effective dipole is not rotated but just decreased in magnitude, and excluding the ions, therefore, leads to an increase of the interaction.

Similar effects are observed while passing from the model DYES-POLYPRO to DYES-POLYPRO-IONS. Here, the presence of the ionic
charge density in the solvent leads to a change of the sign of the interaction energy for some frames in comparison to the model DYES-POLYPYRO (compare triangles with squares for frames 6, 12, 14, 16, 19 in Figure 18). As before, the presence of the ionic charge density in the solvent does not always lower the magnitude of the interaction energies. For example, the interaction energy is not changed for frames 1, 3, 8, 9 of POLY6, while frame 2 shows an enhanced interaction between the chromophores.

Interestingly, analysis of Figures 14 and 18 shows that the highest $D_{AM}$ and $D_{AA}$ (for the model DYES-POLYPYRO-IONS) correspond to frame 6, in spite of the fact that 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 MEAD and APBS. As it was shown above, the APBS relative deviation $D_{AA}$ in the calculated energy for frame 6 can be reduced down to 15% by decreasing the grid spacing $h$ and taking averages over different relative positions of the grid and the molecular system. However, this percentage is still much larger than the relative deviation $D_{AA}$ between the APBS calculations and the reference solutions of ARGOS for frames 4 and 5. The difference in the relative deviations between frames 6 and 4 (or 5) is most probably due to the particular geometry of the solute–solvent interface and the distribution of the charges near them, resulting in the poor performance of both FD solvers in the case of frame 6.

The above screening effects will 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) mentioned above. In the common approaches the charges are screened using either the Debye–Hückel theory or generalized Born models. The first method [69] describes ionic screening of electrostatic interactions, essentially using Equation (45), though this expression is accurate only for a spherical charged particle, completely surrounded by the solvent. The authors of Ref. [70] propose to model partial screening in the generalized Born model with modified atomic radii. The latter are parameterized to characterize the extent of the screening. However, the parameterization in this approach was performed so far only for the dielectric screening without including the ionic charge density in the solvent. The present results demonstrate that both conditions—partial screening due to the particular geometry of the solute and the nonzero ionic strength of the solvent—are important for the interaction energy. With calculations as shown above a reliable parameterization of ionic screening is within reach.

3.3 Interaction between SARS-CoV-2 protein and cell receptor ACE2

Now, we present the electrostatic interaction between the RBD of the spike protein of SARS-CoV-2 and the cell receptor ACE2 (see Section 2.4) calculated with APBS and ARGOS. In order to investigate how the electrostatic coupling between RBD and ACE2 changes if LYS417–ASP30 or ASN501–LYS353 interactions are absent (see Figure 4B), we artificially set to zero the charges of the corresponding residues. Thus, in our work we have used three different setups for the charge distribution:

- SARS2-WT corresponding to the crystal structure;
- SARS2-NK with neutralized charges on ASN501 and LYS353;
- SARS2-KD with neutralized charges on LYS417 and ASP30.

Without loss of generality, let $M_1$ denote the ACE2 receptor and $M_2$ denote the RBD of SARS-CoV-2. The total charge in $M_1$ and $M_2$ for the three setups SARS2-WT, SARS2-NK, and SARS2-KD is $-27 \varepsilon_0$ and $2 \varepsilon_0$, $-28 \varepsilon_0$ and $2 \varepsilon_0$, and $-26 \varepsilon_0$ and $1 \varepsilon_0$, respectively. We have calculated the electrostatic couplings $E_{1,-2}$ and $E_{2,-1}$ (Eqs. (20) and (21)) between $M_1$ and $M_2$ for, both, vanishing ionic strength $I_s$ and for $I_s = 0.05$ M. The dielectric coefficients in the molecular and solvent regions are set, as before, to $\varepsilon_m = 4$ and $\varepsilon_s = 80$. This time, the probe radius in the definition of the SES is set to 1.4 Å, while the counterion radius $R_{ion}$ in the definition of the IEL is again 2 Å for both, APBS and ARGOS. The size of the minimal box with sides parallel to the coordinate axes that contains the molecular system is $119.94 \times 75.46 \times 66.67 \, \text{Å}^3$. For the calculations with APBS we use configuration A4 given in Table S17.

Surface and volume meshes in ARGOS

Concerning the surface mesh in ARGOS, now we make use of the external routine $\text{mmgs/O3}$ to simplify the molecular model, unlike in the case of the Alexa dyes where we directly used the meshes generated by NanoShaper using its built in Laplacian smoothing. It would be best to apply $\text{mmgs/O3}$ to the nonsmoothed by NanoShaper raw surface mesh (Figure 20A) since this raw mesh has its vertices analytically sampled from the SES. However, with the current version 5.5.2 of $\text{mmgs/O3}$ this was not possible due to some really bad quality, needle-like triangles (Figure S28) that prevented the completion of the procedure. Therefore, we simplify the surface already smoothed by NanoShaper. Nevertheless, the final mesh (Figure 20C) after the application of $\text{mmgs/O3}$ is still very close to the raw surface mesh on Figure 20A. This is seen by computing the (symmetric) Hausdorff (H-)distance (0.16 Å) and the mean H-distance (0.018 Å) between these two meshes (see Eqs. (S12) and (S13)). For the case of the Alexa dyes where we directly used the meshes generated by NanoShaper using its built-in Laplacian smoothing. It would be best to apply $\text{mmgs/O3}$ to the nonsmoothed by NanoShaper raw surface mesh (Figure 20A) since this raw mesh has its vertices analytically sampled from the SES. However, with the current version 5.5.2 of $\text{mmgs/O3}$ this was not possible due to some really bad quality, needle-like triangles (Figure S28) that prevented the completion of the procedure. Therefore, we simplify the surface already smoothed by NanoShaper. Nevertheless, the final mesh (Figure 20C) after the application of $\text{mmgs/O3}$ is still very close to the raw surface mesh on Figure 20A. This is seen by computing the (symmetric) Hausdorff (H-)distance (0.16 Å) and the mean H-distance (0.018 Å) between these two meshes (see Eqs. (S12) and (S13)). For the case of nonzero ionic strength $I_s$, the outer surface of the IEL is constructed following a similar procedure as for the SES, that is, we first construct the raw van der Waals surface with $R_{ion} = 2$ Å in NanoShaper to which we apply its built-in Laplacian smoothing and then we simplify the result with $\text{mmgs/O3}$ (Figure S31).

In this example, the molecular system contains a total of 7 cavities, detected by NanoShaper in the surface mesh construction phase (see Figure S29). Since the formed cavities are relatively small, the computed by ARGOS interaction energies are practically the same for an assignment of their dielectric coefficient as the dielectric coefficient $\varepsilon_s$ of the solvent or $\varepsilon_m$ of the protein (see Tables S19 and S20).

The tetrahedralization of the inside and outside of the molecular surface mesh is performed using TetGen without an edge size
constraint inside or outside the molecular model. This means that our volume mesh only conforms to the surface mesh on Figure 19A, but is irregular inside and outside, becoming coarser and coarser away from the molecular surface (Figure 19B). The boundary of the computational domain is a cube with a side length of around 1,000,000 Å and the edge length of the tetrahedrons at the boundary is approximately 200,000 Å. The total number of grid points and tetrahedrons in the volume mesh for the case \( I_s = 0 \) without cavities \(^5\) is 274,758 and 1,501,864, respectively, while for positive ionic strength where an IEL is present, the respective values are larger by a factor of 1.6.

We point out that the coarse initial mesh inside and outside the molecular region does not affect the accuracy of ARGOS, because it is being refined by the adaptive algorithm precisely where it is needed to resolve the problematic regions contributing the most to the error in the electrostatic coupling (Figure 21). The CPU times to construct and simplify the surface and volume meshes are given in Table 13 in Section 3.4.

**Results of APBS and ARGOS**

The results of APBS and ARGOS for the three setups SARS2-WT, SARS2-NK, SARS2-KD with \( I_s = 0 \) \( \text{M} \) and \( I_s = 0.05 \) \( \text{M} \) are given only for ARGOS in Table 10 (for the detailed results, see Tables S18, S20–S22). The comparison of the data demonstrates a high accuracy of the averaged APBS values that is likely due to the fact, that both

![FIGURE 19](image-url)  
(A) Surface mesh \( S_3 \) of the molecular system RBD of SARS-CoV-2 and the ACE2 receptor. The red rectangle represents the zoomed-in part of the system shown on Figure 20. (B) Cross section of initial volume mesh (MRL = 0) based on the surface in (A) and with removed cavities. Molecular region is marked in red, while the solvent region is in green.

![FIGURE 20](image-url)  
(A) \( S_1 \) with \( N_{S_1} = 752 \) 110, \( h_{A,1} = 0.24 \) Å  
(B) \( S_2 \) with \( N_{S_2} = 752 \) 110, \( h_{A,2} = 0.23 \) Å  
(C) \( S_3 \) with \( N_{S_3} = 194 \) 579, \( h_{A,3} = 0.43 \) Å

![FIGURE 21](image-url)  
Adjoint (A) and (C) and primal (B) and (D) solutions for the molecular system RBD of SARS-CoV-2 and the ACE2 receptor with the SARS2-KD setup for \( I_s = 0 \) \( \text{M} \) and with \( \epsilon = \epsilon_m \) inside the cavities. Solutions computed on the initial mesh (MRL = 0) with 274,758 grid points and on MRL = 5 with 1,208,750 grid points. The adjoint solution \( z^{(2)} \) is defined with the charges of \( M_1 \) (the ACE2 cell receptor). The primal solution \( \phi^{(2)} \) is defined with the charges in \( M_2 \) (the RBD of SARS-CoV-2). Potential in units of \( e_0/\text{Å} \). Red color denotes values of the potential lower than \( -0.1 \) and blue color values higher than \( 0.1 \). The electrostatic interaction computed on MRL = 2 and 344,887 grid points is already accurate enough and within 0.1% of the one computed on MRL = 5 (for comparison, the relative distance between the interaction computed on MRL = 0 and the one on MRL = 5 is 22.4%). However, here we show the mesh and the solutions for MRL = 5 to better demonstrate how the adaptive algorithm in ARGOS works. There are regions where the mesh is very fine and other regions where it is orders of magnitude coarser. Regions which are left coarse contribute much less to the overall error in the electrostatic coupling than those that are heavily refined. A similar comparison between the meshes for the case \( I_s = 0.05 \) \( \text{M} \) is shown in Figure S32.
proteins are highly charged (one can expect less accuracy for neutral molecules). Analysis of the interaction energies in Table 10 reveals that the contribution of the LYS417-ASP30 coupling is one order of magnitude larger, than that of the ASN501-LYS353 pair. The former alone contributes 29% and 25% to the overall electrostatic coupling between the proteins for $l_i = 0$ M and 0.05 M, respectively. This example demonstrates a successful application of ARGOS to larger and more complicated systems. Considering that it is a good practice to run at least two computations with APBS with charges in each of $M_1$ and $M_2$ in order to rule out possible discrepancies in the results (see e.g., Tables 7 and 8), ARGOS is also more efficient than APBS, see Section 3.4.

### 3.4 CPU times

Although ARGOS [43] is currently in a prototype version (implemented in FreeFem [62]) and is currently undergoing a substantial performance improvement, we present first CPU times in comparison to APBS obtained on a machine with Intel(R) Core(TM) i5-7500 CPU @ 3.40 GHz and 16 GB of RAM. Since the primal and adjoint problems are discretized using the linear and quadratic Lagrange finite elements, respectively, the number of DOFs, $N_{DOFs}$, in 3D for the adjoint problem is approximately 8 times larger than that for the primal. Here, we note that for a Dirichlet BC the number of DOFs for the FE space $V_{h, r}$, $N_{DOFs}^{min}$, is exactly equal to $N_V - N_{bd}$, where $N_{bd}$ is the number of mesh vertices on the boundary. 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 related to the Alexa 488 and Alexa 594 chromophores, we use a basic Jacobi-preconditioned conjugate gradient (CG) method (with a stopping criterion ensuring a very high precision) as an iterative solver for the resulting linear systems for both, the primal and adjoint problem. For the system consisting of the RBD of the spike protein of SARS-CoV-2 and the ACE2 receptor, we also use the CG method, but this time with a block-Jacobi preconditioner for both, the primal and adjoint problem (see Footnote 6). As it was mentioned above, the mesh refining is done using mmg3d v4.0 [60], 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 11 and 12 we present the CPU times for some examples with an increasing number of vertices in the initial mesh. We note that the reference solutions of ARGOS given in Sections 3.1 and 3.2 are computed with initial meshes of uniform mesh size in the molecular regions, whereas the results below are obtained with coarser initial meshes of lower quality inside the molecules, similar to the one on Figure 19B (the molecular surfaces are still the same). Nevertheless, the computed values for the interaction energy are practically the same.

As a first example, in Table 11, we consider Model-2 where the probe charge is placed at a distance $r = 10$ Å from the center of 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 Footnote 6). In comparison, APBS with configuration A2 (see Table 4) for $etol = 1e-06$ 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 S23 and S24.

In Table 12 we give the CPU times of ARGOS for frame 10 of model DYES (Figure 10A) with neutral ground-state charges (see Figure 17). 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 $etol = 1e-06$ and etol 1e-09, respectively. However, those CPU times of APBS are only for the computation of $E^{APBS}$, 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 centers. Taking only $E^{APBS}$ or $E^{APBS}$ can result in a very large error (see Table S11, together with the other tables concerning the inspection of problematic APBS frames). Therefore, to compute $E^{APRO}$ (see [42]), it takes in total 218 and 286 sec for etol 1e-06 and etol 1e-09, respectively.

For comparison, we report the CPU times for a calculation with non-zero ionic strength of 0.3 M involving frame 12 of model DYES-POLY-PRO-IONS in the case of charged dyes (see Tables 5 and S9). ARGOS with a CG tolerance of 1e-09 and three MRLs takes 616 sec compared

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**Table 10** Electrostatic coupling, obtained with ARGOS for MRL = 2, error tolerance in the CG of 1e-14, and $\epsilon = \epsilon_n$ inside the cavities, between the RBD of the spike protein of SARS-CoV-2 and the cell receptor ACE2 for the wild type (WT) and two modified systems (NK, KD) whose charges of certain amino acids were set to zero, as explained in the text.

|        | WT            | NK            | KD            |
|--------|---------------|---------------|---------------|
|        | $E^\text{Adj}_{1-2}$ | $E^\text{Adj}_{2-1}$ | $E^\text{Adj}_{1-2}$ | $E^\text{Adj}_{2-1}$ |
| $l_i = 0$ M | $-0.09025$ | $-0.09033$ | $-0.08775$ | $-0.08757$ | $-0.06409$ | $-0.06408$ |
| $l_i = 0.05$ M | $-0.07728$ | $-0.07733$ | $-0.07361$ | $-0.07365$ | $-0.05808$ | $-0.05805$ |

Note: The results obtained for $\epsilon = \epsilon_n$ inside the cavities are practically the same and are given in Table S19. All energies are calculated in units of $e_0^2 / \AA$. The values of $E^\text{Adj}_{1-2}$ and $E^\text{Adj}_{2-1}$ are obtained on two different sequences of refined meshes, both starting from the same initial mesh in Figure 19B.
to 837 sec necessary to compute $E_{adj}^{t_{Adj}}$ with configuration A1 for etol 1e – 09 (recall that 1e – 06 is not enough for this frame), and 747 sec for etol 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 centers. 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.

Finally, in Table 13, we report the CPU times for the calculation of the electrostatic coupling for the setup SARS2-KD with vanishing ionic strength. The corresponding times for $l_s = 0.05$ M are given in Table S25. From our experience with the calculations presented in this work, an error tolerance of 1e – 9 in the CG method and 2 refinement steps are always enough to achieve an accuracy7 within 0.5 %. The solution of the adjoint problem (using a block-Jacobi preconditioned CG with a very low error tolerance of 1e – 14) takes the largest part of the CPU time per MRL, followed by the refinement of the mesh and the assembling of the corresponding stiffness matrix. It is important to note that the mesh quality can be crucial for the convergence and stability of the direct or iterative method used to solve the primal and adjoint linear systems. Therefore, the mesh refining routine should be chosen with care. We also note that using a more reasonable error tolerance of 1e – 9 in the CG, exploiting parallelism and exchanging the Jacobi-preconditioned CG algorithm for a direct solver such as MUMPS [72, 73] or 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 comparable or higher now than that of APBS. The CPU time for APBS with the configuration A4 in Table S17 for this same problem amounts to two times (770 + 32) = 1604 sec which is the time for the computation with the charges placed in each of $M_1$ and $M_2$ plus the time for two calls of the subroutine multivalue. For comparison, the CPU time for ARGOS with a CG tolerance of 1e – 9 and for MRL = 0, 1, and 2 drops down to 1448 sec.
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 technique for the target quantity (the electrostatic interaction energy), 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-labeled polyproline helices and between the SARS-CoV-2 protein and a cell receptor. Critical sources of errors are complex geometries of interfaces with interacting charges in a close vicinity, 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. We note that in the jump in the dielectric coefficient between solute and solvent is less than considered in the present models. Nevertheless, a quantitative evaluation of these effects requires an accurate solver as the present one.

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 the MEAD results is much worse in the presence of interfaces with large changes in the dielectric coefficient, 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 arithmetics can significantly influence the accuracy of MEAD calculations.

Most of the time, APBS performs much better than MEAD. However, it still exhibits the common fundamental issues typical for FD based solvers: a trade-off between grid spacing and the dimensions of the final focused grid, a strong dependence of the results on the relative position of the focused grids and the molecular system, as well as of the grid spacing $h$, which in some cases 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 $E_{1,2}^{\text{APBS}}$ and $E_{1,2}^{\text{APBS}}$ (or $E_{1,2}^{\text{MEAD}}$ and $E_{1,2}^{\text{MEAD}}$ 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 inexperienced in numerical methods.

Due to the use of an appropriate (goal-oriented) error estimation in combination with an adaptive mesh refinement 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. First benchmark studies show that ARGOS already in its present nonoptimized version is faster and more accurate than the standard FD solvers MEAD and APBS at least for medium sized systems of around 10,000 atoms.

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ENDNOTES

1 The finite element method can be thought of as a discretization of the weak formulation of a problem.

2 APBS 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 use it.

3 In the case of exactly prescribed Dirichlet boundary data, the numerical solution converges to the exact solution of the LPBE for the particular triangulation of the spherical cavity. This exact solution is different from the exact solution given by (44) for a cavity which is a perfect sphere, see Figures S12 and S15 for the convergence of the relative error with respect to the MRLs in the case of non-homogeneous Dirichlet BC.

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

5 For the case with cavities, the mesh inside the molecular region is slightly denser in order for the volume mesh to conform to the surface of those cavities, and the total number of grid points and elements in the mesh becomes 278,128 and 1,520,738, respectively.

6 The reference solutions of ARGOS presented in the paper are obtained with an error tolerance between $1 \times 10^{-14}$ and $1 \times 10^{-12}$ for the examples related to the Alexa chromophores and an error tolerance of $1 \times 10^{-14}$ for the system consisting of the RBD of the spike protein of SARS-CoV-2 and the ACE2 receptor. This means that on the last CG iteration the residual in the linear system, measured in the norm generated by the inverse of the preconditioner matrix $C$, is smaller than that error tolerance. In particular, $C$ is a diagonal matrix whose diagonal is equal to the diagonal of the system’s matrix in the case of the Alexa chromophores and a block-diagonal matrix in the case of the SARS-CoV-2 example.

7 Here, by 0.5% we mean the relative distance from the reference solution after 5 or 6 refinement steps when no exact solution is available.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Svetoslav Nakov https://orcid.org/0000-0002-2784-8699

Thomas Renger https://orcid.org/0000-0001-9245-3805
