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Gradient Models in Molecular Biophysics: Progress, Challenges, Opportunities

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Abstract

In the interest of developing a bridge between researchers modeling materials and those modeling biological molecules, we survey recent progress in developing nonlocal-dielectric continuum models for studying the behavior of proteins and nucleic acids. As in other areas of science, continuum models are essential tools when atomistic simulations (e.g. molecular dynamics) are too expensive. Because biological molecules are essentially all nanoscale systems, the standard continuum model, involving local dielectric response, has basically *always* been dubious at best. The advanced continuum theories discussed here aim to remedy these shortcomings by adding features such as nonlocal dielectric response, and nonlinearities resulting from dielectric saturation. We begin by describing the central role of electrostatic interactions in biology at the molecular scale, and motivate the development of computationally tractable continuum models using applications in science and engineering. For context, we highlight some of the most important challenges that remain and survey the diverse theoretical formalisms for their treatment, highlighting the rigorous statistical mechanics that support the use and improvement of continuum models. We then address the development and implementation of nonlocal dielectric models, an approach pioneered by Dogonadze, Kornyshev, and their collaborators almost forty years ago. The simplest of these models is just a scalar form of gradient elasticity, and here we use ideas from gradient-based modeling to extend the electrostatic model to include additional length scales. The paper concludes with a discussion of open questions for model development, highlighting the many opportunities for the materials community to leverage its physical, mathematical, and computational expertise to help solve one of the most challenging questions in molecular biology and biophysics.

1 Introduction

At the molecular scale, much of biology is governed by electrostatic interactions between charges [1–4]. Biological molecules such as proteins and nucleic acids (DNA and RNA) are covered with hundreds or thousands of charges whose interactions govern the stability of molecular conformations (shapes) and their function—for instance, determining the affinity of two molecules to bind each other. These molecular charge distributions interact via Coulomb's law, of course, but there is a crucial and incredibly complicated additional component to the strength of electrostatic interactions within and between molecules: the surrounding water and dissolved ions (e.g. sodium, calcium, and potassium) that make up the intracellular and extra-cellular fluid, or *solvent*. Biology does not happen in a vacuum, but rather in a tightly controlled aqueous electrolyte. In fact, life as we know it depends critically on the difference between the concentrations of salt ions inside the cell and outside the cell; the solution pH (concentration of protons, H^+ ions) is also tightly controlled and

essential to life. The nervous system, and an enormous number of cellular processes, use salt ions and free protons to control cell behavior, e.g. muscle contraction.

Models for biological solvent are therefore a large and central component for predictive theories for understanding the function of biological molecules and the mechanisms of disease progression. Unfortunately, it is not a simple task to describe the collective action of hundreds of thousands of water molecules and ions around a given protein. Computer simulations of atomistic models using classical mechanics (with simple descriptions of interactions between atoms) have become widely known approaches to study biomolecules, with molecular dynamics (MD) simulations [5–8] among the most popular. However, the large numbers of solvent molecules necessitate comparably large investments in computer hardware and in simulation time, and motivate the development of faster models that can account for the solvent influence without explicitly including the solvent molecules' additional degrees of freedom.

Such *implicit-solvent models* represent the focus of this review. Continuum-theory models for the electrostatic effects, based on macroscopic dielectric theory and the Poisson equation, have been described as “unreasonably effective” (echoing Wigner's famous expression “the unreasonable effectiveness of mathematics in the natural sciences”). Indeed, considering the drastic simplifications involved in applying macroscopic concepts at the level of single atoms, it is shocking how successful Poisson-based theories have been [3, 4, 9, 10]. For example, standard Poisson theories provide a simple and intuitive means to consider the contributions of electrostatics to molecular binding [9, 11, 12], and to understand the basis for the fantastic selectivity of ion-channel proteins [13].

Nevertheless, in many investigations and modeling applications, the simplifying approximations lead to inaccurate predictions, and the community has focused substantial resources and efforts to develop more accurate models [10]. In this review we survey theories based on nonlocal dielectric response in the solvent, which Dogonadze and Kornyshev proposed almost forty years ago [14], and which Kornyshev has refined and championed even to the present day, over a broad range of physical and application-driven questions [15]. Evidence for the existence of nonlocal solvent response is overwhelming, ranging from single-molecule computational studies [16, 17] to several forms of experimental studies [18, 19], and in between there have been many “computational experiments” involving atomistic simulations with large numbers of water molecules [20–22]. A recent review by structural biologists highlighted progress in measuring nonlocal effects in molecular biology [23]. Early major demonstrations of the importance of nonlocality came from Warshel and collaborators, whose protein-dipoles-Langevin-dipoles (PDLD) model [2,24] did not use continuum dielectric theory, but did appropriately account for the fact that water molecules have finite size and exhibit nonlinear saturation at high field strengths. The physiological importance of ion-channel proteins has motivated nonlocal studies of selectivity [25,26], and nonlocal models of electrolyte solutions are significantly more accurate than local ones [27]. Because many biological processes involve the approach of cell membranes to one another, nonlocal electrostatics have been widely used [28]. Finally, the intracellular and extracellular fluids themselves are quite densely packed, or

“crowded,” with biological molecules, giving rise to nonlocal effects [29]; accordingly nonlocal colloidal-suspension models have been developed over many years [30–32].

Because other recent articles review important details of the nonlocal solvent theory [15], and their biological applications [33], we focus on the view from a computational modeling perspective, covering an introduction to molecular electrostatics, developments in nonlocal electrostatic theory, and developments in computation and applications. The theoretical side's undisputed leader, A. Kornyshev, has recently published a detailed overview of the field from the perspective of the underlying molecular physics [15]. Readers interested in a primarily biological perspective are referred to the excellent paper by Rubinstein and Sherman [33].

It is worth noting that the range of applications of nonlocal continuum models in biology and biomedical fields is substantial even beyond solvent electrostatics, and many of these areas have grown rapidly since the seminal review of Eringen [34]. First, biological complexity operates on length scales beyond the mesoscale, and nonlocal models have been developed for cellular-scale problems in neuroscience [35], and the contributions of biological degradation to underground contaminants [36]. The former work draws an explicit parallel to materials science, which is a central theme of this paper for the molecular electrostatics problem. At the nanoscale, medical applications of nanotechnology represent an important emerging opportunity for nonlocal models in the life sciences [37]. Early work on nonlocal electrodynamics [38–41] laid the groundwork for modern studies on plasmonics [42–45] and scattering from nanoparticles [46–49], which offer exciting possibilities for important applications in health sciences. On the mechanical side, many biological tissues, including bone, exhibit hierarchical structure relevant to its mechanical properties [50], suggesting applications to tissue engineering; recently gradient elasticity has been applied to bone modeling [51]. Furthermore, nonlocal models have been used by many groups to study carbon nanotubes (the canonical nanotechnology, as it were) [52–56]. Recently, nonlocal elasticity has also been used to model several different kinds of nanoscale biology, including protein microtubules [57], DNA [58], and lipid tubules [59], and connections to molecular dynamics are possible [60]. Nanofluidic devices offer diverse opportunities for biomolecule detection for medicine and security [61], and at this scale nonlocal theories offer more realism [27]. In this area, Aluru et al. have developed quasicontinuum model [62] for the problem of nanoconfined fluids [63].

The present article is intended to introduce the problem of biomolecular electrostatics to the materials modeling community, which has decades of experience developing gradient-based models in mechanics [41, 64–82], and in developing efficient implementations for large scale problems [83–86]. Methods for nonlocal solvent models lag significantly behind those in nonlocal elasticity: consider that Eringen presented a local-PDE formulation for elasticity [87] over twenty years before the first local formulation for solvent electrostatics [88]. We hope that this survey will spark interest in translating the state-of-the-art in gradient-based modeling to biological electrostatics as well as biological problems more generally. As we have indicated, nonlocal models are finding frequent applications across the life sciences and in technologies related to biomedical engineering.

The paper is organized as follows. Section 2 introduces the theoretical framework for modeling molecular electrostatics in solvation, including the rigorous basis underlying Poisson-based models and a brief overview of the formalisms used to go beyond the basic local-dielectric Poisson model. Section 3 covers nonlocal dielectric theories in detail, including (1) major historical developments and a simple version that has become popular recently, (2) models and formulations for solving large, complicated biological systems such as proteins, and (3) criticisms and challenges. In Section 4 we present a systematic approach to develop more realistic nonlocal dielectric models of solvation; whereas current numerical methods are limited to the simplest nonlocal response, we indicate how large-scale problems can be solved efficiently using two or more length scales. Section 5 illustrates the wide range of opportunities for nonlocal/gradient models in biology outside of molecular electrostatics, and the paper concludes in Section 6 with a brief discussion.

2 Theoretical Background

Figure 1 is a schematic of the biomolecule electrostatic problem and a simple local-response continuum model for it; to afford some degree of specificity, we will assume that the solute biomolecule is a protein. The protein is viewed as being surrounded in an infinite solvent bath, and the two volumes are denoted as V_P and V_W (the W denotes water). Note that the use of an pure solvent bath is an approximation known as the “infinite dilution” limit; biological fluids are actually crowded with many types of molecules [89]. The protein model is usually treated atomistically, and the atom coordinates are usually taken from experiments; such structural data is stored in large public databases such as the Protein Data Bank [90].

The two volumes are separated by a surface S that models the protein–solvent interface. A variety of definitions are in common use [91–94], and frequently argued in the literature, but usually one models the protein as a collection of atomic spheres and the protein surface is defined in such a way as to have desirable smoothness properties while containing the union of spheres (the surface normal points out into the solvent). The atom radii are parameters determined such that calculations match either experiments [95] or more accurate theories [96]. The protein charge distribution is usually described as a set of discrete point charges (Dirac delta functions) at the atom locations, but sharply peaked Gaussians are also sometimes used; it is also worth noting that in one of the largest fields of computational chemistry, one couples quantum-mechanical descriptions of the molecular charge density (the Schrodinger equation) to this continuum-model solvent [97–99]. Here we focus on point-charge models directly; their values are usually either fitting parameters [95] or used from existing molecular-dynamics theories [96]. The protein interior is treated as a macroscopic dielectric with permittivity $\epsilon_P \approx 1$ –10 (values larger than 1 capture conformational relaxation in an implicit way) and the solvent exterior as a macroscopic dielectric with permittivity $\epsilon_W \approx 80$. The potential in the protein then obeys a Poisson equation

$$\nabla^2 \varphi_P(\mathbf{r}) = -\rho(\mathbf{r})/\epsilon_P. \quad (1)$$

If the solvent is modeled as pure water, the potential in the solvent obeys the Laplace equation

$$\nabla^2 \varphi_W(\mathbf{r}) = 0; \quad (2)$$

or, if the solvent is modeled as a dilute electrolyte (low salt concentration), one may model the potential using the linearized Poisson–Boltzmann equation:

$$\nabla^2 \varphi_W(\mathbf{r}) = \kappa^2 \varphi_W(\mathbf{r}). \quad (3)$$

In either case, the potential is continuous across the protein–solvent interface

$$\varphi_P(\mathbf{r}_S) = \varphi_W(\mathbf{r}_S), \quad (4)$$

and so is the normal component of the electric displacement field

$$\epsilon_P \frac{\partial \varphi_P}{\partial n}(\mathbf{r}_S^-) = \epsilon_W \frac{\partial \varphi_W}{\partial n}(\mathbf{r}_S^+). \quad (5)$$

The resulting potential is the sum of the direct Coulomb potential φ_{Coul} induced by the protein charge distribution, and the potential that results from the difference in electrostatic response between the protein and solvent, a quantity known as the *reaction potential*:

$$\varphi_{\text{total}}(\mathbf{r}) = \varphi_{\text{Coul}}(\mathbf{r}) + \varphi_{\text{reac}}(\mathbf{r}). \quad (6)$$

For understanding biological processes such as the binding of two molecules, or the relative stability of two protein conformations, one wishes to know, in each state, the interaction energy between the protein charge distribution $\rho(\mathbf{r})$ and the interaction potential $\varphi_{\text{reac}}(\mathbf{r})$, which is called the *reaction energy*

$$\Delta G^{es} = \frac{1}{2} \int_{V_P} \rho(\mathbf{r}) \varphi_{\text{reac}}(\mathbf{r}) d^3\mathbf{r}. \quad (7)$$

Thorough discussions of the limitations of this model may be found elsewhere [10]. Here we highlight a few that suggest the need for more sophisticated and realistic treatments of the solvent. First, these energies show a non-monotonic dependence on the size of the molecule [100]. In addition, calculations of protein electrostatics in solutions of changing pH (i.e. as happens in biological signaling and disease [101]) require very large dielectric constants for the protein, much larger than are measured (see discussion in [10, 102]). It is true that ϵ_P is often a semi-empirical parameter [103], but there exists a rigorous, formal statistical mechanical definition of this model that leads to an unambiguous continuum model in which $\epsilon_P = 1$ by construction.

This elegant approach, known as a potential of mean force (PMF), provides an enormously powerful tool for improving solvent models, by ensuring that arbitrarily challenging tests can be conducted via “computational experiments” such as molecular dynamics simulations—even if there are no experimental equivalents to the test (e.g. an arbitrary charge

distribution in a perfect sphere or ellipsoidal molecule). The most insightful and thorough explanation is Roux and Simonson [104], and here we simply summarize the method.

Essentially, we have a system with both protein degrees of freedom (DOFs) and solvent DOFs, and the energy of interest (the average protein–solvent electrostatic interaction energy) is a function of only the protein degrees of freedom, because the average is taken over all solvent DOFs. Defining the protein degrees of freedom as $\mathbf{X}$ and the solvent degrees of freedom as $\mathbf{Y}$, the probability that the solute and solvent are in a state $(\mathbf{X}, \mathbf{Y})$ is

$$P(\mathbf{X}, \mathbf{Y}) = \frac{\exp(-\beta E(\mathbf{X}, \mathbf{Y}))}{\int \exp(-\beta U(\mathbf{X}, \mathbf{Y})) d\mathbf{X} d\mathbf{Y}} \quad (8)$$

where $\beta = (k_B T)^{-1}$, $E(\mathbf{X}, \mathbf{Y})$ is the potential energy at the given state, and the integration is taken over all degrees of freedom. The PMF $W(\mathbf{X})$ then satisfies

$$\frac{\exp(-\beta W(\mathbf{X}))}{\int \exp(-\beta W(\mathbf{X})) d\mathbf{X}} = \int p(\mathbf{X}, \mathbf{Y}) d\mathbf{Y}, \quad (9)$$

i.e. $W(\mathbf{X})$ plays the role of the energy $E(\mathbf{X}, \mathbf{Y})$ in Eq. (8) after “integrating out” the solvent DOFs. The PMF is frequently modeled as a sum of three components: (1) the intramolecular energy (interactions between bonded atoms), (2) the solute–solvent van der Waals interactions (which are assumed to not depend on the protein charges), and (3) the solute–solvent electrostatic interactions. Our continuum models approximate this last term.

2.1 Approaches for Advanced Continuum Models

The PMF viewpoint represents a formally exact treatment [104, 105], but unfortunately it does not provide a prescriptive route to numerically approximating the PMF to a target level of accuracy. In this section we highlight the variety of approaches taken to increase accuracy, in part to explain our enthusiasm for nonlocal models.

Figure 2 categorizes implicit-solvent models in two simple ways: whether a model is linear or nonlinear, and whether it is local or nonlocal. Theories involving local and linear response—the Poisson equation itself, the linearized form of the Poisson–Boltzmann equation, and the Generalized Born (GB) approximations to both—have been highly successful. Unfortunately, most theoretical frameworks that allow significant improvements lead to models that are not just nonlocal, but highly nonlinear as well, leading to substantial complications. For example, theories based on the reference interaction site model (RISM) [106–109] derive from statistical mechanics and our understanding of the chemical structure of molecular liquids (importantly, RISM models can be shown to exactly reduce to local electrostatics under suitable limits [105]). Physical principles are often a primary source for developing new models based on density functional theories [110–120] and free-energy functionals [121–124]. Quite recently, a number of applied mathematicians have turned their attention to improving solvent models using variational methods [43, 125, 126].

Models that involve local but nonlinear response primarily address ionic solutions using the Poisson–Boltzmann (PB) equation [3, 4, 127] with local-response modifications [128–131]. Local but nonlinear response for water itself is much less common; primarily, such models

incorporate Langevin-type saturation of the polarization density [43,132–135]. Molecular dynamics studies do indicate the presence of nonlinear saturation effects at the level of individual water molecules. However, our own experience with testing solvent models against MD simulations [22], suggests to us that for the purpose of computing biomolecule solvation free energies, nonlinear response is often less relevant than nonlocal response. Recently Pettitt et al. have introduced a fast electrostatic model based on tabulated solvent charge densities around protein chemical groups, achieving exceptional accuracy, while nevertheless employing a superposition principle that essentially imposes linearity [136]. This accuracy supports the notion that nonlocality and linearity will suffice for many applications.

Similarly, but in the study of biological electrolyte solutions, Gillespie et al. showed the importance of nonlocality in electrokinetic nanofluidic channels [27]. In particular, they showed that popular local-response corrections to the nonlinear Poisson–Boltzmann equation, the Bikerman model [128, 137] and the Boublik-Mansoori-Carnahan-Starling-Leland model [129, 138], were qualitatively incorrect for important classes of experimental conditions, whereas a nonlocal density-functional theory provided satisfactory results. Numerous other local corrections to the nonlinear Poisson–Boltzmann equation have been proposed and require testing (see [10] for more discussion on this topic).

3 Nonlocal Dielectric Models

In nonlocal electrostatic models for solvation, the standard description begins with the general expression of anisotropic dielectric behavior with the dielectric tensor $\epsilon_{\alpha\beta}(\mathbf{r}, \mathbf{r}')$, so that

$$\mathbf{D}_{\alpha}(\mathbf{r}) = \sum_{\beta} \int_V \epsilon_{\alpha\beta}(\mathbf{r}, \mathbf{r}') \mathbf{E}_{\beta}(\mathbf{r}') d^3\mathbf{r}'. \quad (10)$$

where V represents the volume occupied by the nonlocal dielectric. Anisotropic response is important at interfaces [139], which are ubiquitous in biology, e.g. cell membranes and the surfaces of proteins; in this work, however, we restrict our scope to isotropic models, which are challenging enough on their own. Then Eq. (10) reduces to

$$\mathbf{D}(\mathbf{r}) = \int_V \epsilon(\mathbf{r}, \mathbf{r}') \mathbf{E}(\mathbf{r}') d^3\mathbf{r}' \quad (11)$$

and the dielectric function ϵ is usually taken to be of convolution form

$$\epsilon(\mathbf{r}, \mathbf{r}') = \epsilon(|\mathbf{r} - \mathbf{r}'|) \quad (12)$$

except in very simple systems, e.g. in one dimension. Eq. (12) is known as the dielectric approximation, and clearly is most sensibly employed for homogeneous systems, i.e. when V is all space; unfortunately, for most biology, it is precisely the *inhomogeneities* that make the system interesting: the proteins, nucleic acids, and other molecules embedded in the solvent. This is a difficult and challenging issue and we will return to it later; for now, we

raise the point to highlight that biological solvent can be viewed as a complex, nanostructured material with heterogeneous defects.

Nonlocal electrostatics of solvation focuses on the development and functional forms of the nonlocal constitutive equation, which differs from the focus in many gradient-type methods, and deserves an explanation. In the linear-response model, statistical mechanics prescribes an exact relationship between the average charge density in the solvent and the dielectric function [15,18]:

$$\tilde{\varepsilon}(k) = \left[1 - \frac{4\pi}{k_B T} \frac{\langle \tilde{\rho}(\mathbf{k}) \tilde{\rho}(-\mathbf{k}) \rangle}{k^2} \right] \quad (13)$$

where k_B is the Boltzmann constant, T the temperature, $\tilde{\rho}(\mathbf{k})$ is the three-dimensional Fourier transform of the charge density $\rho(\mathbf{r})$, and the angle brackets denote an averaging over all $\mathbf{k}$ such that $\|\mathbf{k}\| = k$. The charge density $\tilde{\rho}(\mathbf{k})$ can be estimated from experiments as well as from theory [18,19]. Thus, for physicists and chemists interested in applying nonlocal theories, the natural formulation of nonlocality is expressed in terms of the constitutive relation, i.e. the dielectric function $\varepsilon(\mathbf{r}, \mathbf{r}')$.

3.1 Early Development

Beginning in the late 1960s, condensed-matter physicists began to develop a theory of electrodynamics for “structured media,” that is, for the behavior of electromagnetic waves in materials in which the fields of interest vary significantly over length scales comparable to the characteristic length scales of the media structure [14, 40, 140]. These developments occurred at approximately the same time as the introduction of nonlocal and gradient approaches in nanoscale mechanics [64–67, 141–143], and for essentially the same reason, namely that the scientific and engineering communities were exploring small systems in which the normal continuum-limit assumption (separation in length scales between the system and the “representative” constituents of the material) begins to break down.

Nonlocal electrostatic models of polar *solvents* (fluids) were pioneered in 1974 by Dogonadze and Kornyshev, whose interests in electrochemistry led them to address the electrostatic interactions between an ionic solute (e.g., the positively charged sodium ion Na^+) and a surrounding solvent composed of polar molecules such as water [14]. Dogonadze and Kornyshev expressed the challenge of molecular solvation electrostatics clearly and succinctly: “In the electrostatics of a medium with spatial dispersion the medium may be characterized by [a local dielectric constant] only when the fields being considered vary slowly over characteristic structure distances. In most cases, the fields of ions decrease considerably over the distances of the structure of the medium (e.g., at the average length of a hydrogen bonding chain). Therefore the electrostatics with [a local dielectric constant] is inapplicable here . . . the structure of the solvent is taken into account by considering the spatial dispersion.” In later work, Hildebrandt et al. have popularized the description of nonlocal models as “structured continuum” theories [144].

In the original Dogonadze–Kornyshev (DK) model, the polarization field $\mathbf{P}(\mathbf{r})$ is considered as a sum of three modes of response,

$$\mathbf{P} = \mathbf{P}_{el} + \mathbf{P}_{lib} + \mathbf{P}_D \quad (14)$$

where $\mathbf{P}_{el}$ is the electronic response (within a solvent molecule), $\mathbf{P}_{lib}$ is the libration response (corresponding to orientational vibrations of a single solvent molecule), and $\mathbf{P}_D$ is the response associated with correlations between solvent molecules [14,145]. Each mode has a characteristic length scale λ ; for water, the DK model used $\lambda_{el} = 0.53 \text{ \AA}$, $\lambda_{lib} = 1 \text{ \AA}$, and $\lambda_D = 11.7 \text{ \AA}$. Such parameterizations can be obtained from experiments, e.g. dielectric absorption spectra [14], and DK note that the three-mode model is a first approximation. For further discussions of the relevant length scales, see [146–148].

In later work, Kornyshev and collaborators addressed a wide range of problems involving interfaces between an electrolyte and a solid medium, often a metal electrode for the purposes of understanding the structure of the electric double layer [149] or electron transfer [150, 151]. To enable broad conclusions about nonlocal models despite the mathematical complexities introduced by nonlocal response, most of these works addressed one-dimensional geometries for which analytical methods could be applied to very general functional forms of the nonlocal constitutive equation (e.g., the dielectric function does not need to be of convolution form [152]).

Biological systems provide important motivation for nonlocal models in 1D cases, because cell membranes (phospholipid bilayers) can be modeled as planar or nearly planar, and theory has not yet adequately explained the existence of “hydration forces,” the experimentally observed phenomena associated with the repulsive forces experienced by two parallel phospholipid bilayers as they are brought together. Parsegian and Zemb, leading figures in the area, introduced a recent special issue of review articles on hydration forces by describing them as “still basically empirical, lacking satisfactory theory and sufficient measurement” [153]. Nonlocal models have made much progress since they were first applied to the problem by Gruen and Marcelja [154], and later by Kornyshev [152]. Kornyshev and Leikin et al. found that with nonlocal models, stochastic boundary conditions were required to improve agreement with experiment [155,156], as did accounting for the lateral (in-plane) distribution of membrane charges [157].

With regard to PMF-based developments of nonlocal models, Kornyshev found that the dielectric response function computed from atomistic simulations depends sensitively on the actual charge distribution in the molecular model, which may help parameterization of MD models [158]. Other primary developments by Kornyshev include approaches to estimating the onset of nonlinear response [159, 160], the influence of nonlocal response on polar solvation dynamics [161] and on interactions between ions [162], and, notably, the development of more sophisticated models for the dielectric function [147, 163]. Here we draw another parallel to nonlocal mechanics, where the form of the nonlocal response has also been the subject of much analysis (see discussion in Picu [164]). For more details on these topics, see Fedorov and Kornyshev [15].

3.2 The Lorentz model

The Lorentz nonlocal dielectric is a particularly simple model in which

$$\varepsilon(\mathbf{r}, \mathbf{r}') = \varepsilon(\mathbf{r} - \mathbf{r}') \quad (15)$$

$$\varepsilon(\mathbf{r} - \mathbf{r}') = \varepsilon_* \delta(\mathbf{r} - \mathbf{r}') + (\varepsilon_{bulk} - \varepsilon_*) \sqrt{\frac{\varepsilon_*}{\varepsilon_{bulk}}} \frac{1}{2\Lambda} \exp\left(-\frac{1}{\Lambda} \sqrt{\frac{\varepsilon_*}{\varepsilon_{bulk}}} |\mathbf{r} - \mathbf{r}'|\right), \quad (16)$$

where Λ corresponds to a characteristic length scale for polarization fluctuations, and ε_* is the short-range dielectric constant. As discussed previously, the translation-invariant ε significantly simplifies the problem, because then the operator relating $\mathbf{D}(\mathbf{r})$ and $\mathbf{E}(\mathbf{r})$ in Eq. (11) is a convolution. In the Fourier domain, Eq. (16) is written

$$\tilde{\varepsilon}(k) = \varepsilon_* + \frac{\varepsilon_{bulk} - \varepsilon_*}{1 + \frac{\varepsilon_{bulk}}{\varepsilon_*} \Lambda^2 k^2}. \quad (17)$$

Rubinstein et al. have used this model to study numerous biomolecular processes, using geometries with high symmetry to simplify calculations [33, 165, 166]. Similarly, Paillusson et al. solved one-dimensional problems with a nonlocal Poisson–Boltzmann equation, and extended their model to higher-order theories [167]. Fernandez and Scott have also used the notion of nonlocality extensively [168–170], and employed the Lorentz model to study ions in a carbon nanotube [169].

Hildebrandt's publication of the local formulation for the Lorentz model [88, 88] was an important advance for the field because it opened the possibility of simulating large molecules very efficiently. To our knowledge, no calculations of proteins using the Lorentz model had been reported prior to Hildebrandt's work, but then the approach became a popular subject for the development of efficient implementations. Weggler and Hildebrandt, for example, developed a volumetric solver based on the Explicit Jump Immersed Interface Method (EJIM) [171, 172]. Xie, Scott et al. developed a finite-element method [173]. Hildebrandt, in his thesis, developed a boundary-integral equation (BIE) formulation [144], and Hildebrandt and Bardhan have developed a linear-scaling BEM solver [174], using a local-theory fast BEM solver as a starting point [175, 176]. Fasel et al. have presented an elegant, purely second-kind BIE formulation [177] and we hope that fast implementations will follow soon.

The recent development of the Lorentz-model local formulation is a central piece of our belief that the materials modeling community has much expertise and wisdom to share with the field of implicit-solvent modelers. Eringen published a local formulation of the nonlocal elasticity theory more than 20 years earlier [87]. It seems likely that the solvent-modeling community must have some open questions today that the materials community can address quickly and confidently—and if not, the unanswered questions might spark shared development between the communities.

3.3 Challenges for nonlocal theory

3.3.1 Increased mathematical and computational complexity—An immediate challenge that arises in the introduction of nonlocal dielectric response is the fact that one moves from a purely partial differential equation

$$\nabla \cdot \mathbf{D}(\mathbf{r}) = \rho(\mathbf{r}) / \epsilon_0 \quad (18)$$

$$\nabla \cdot (\epsilon(\mathbf{r}) (-\nabla \varphi(\mathbf{r}))) = \rho(\mathbf{r}) / \epsilon_0, \quad (19)$$

where again $\rho(\mathbf{r})$ is the charge distribution and ϵ_0 is the permittivity of free space, to an integrodifferential equation

$$\nabla \cdot \left(\int_V \epsilon(\mathbf{r} - \mathbf{r}') (-\nabla \varphi(\mathbf{r}')) d^3\mathbf{r}' \right) = \rho(\mathbf{r}) / \epsilon_0. \quad (21)$$

Kornyshev et al. resolved this difficulty for model geometries by formulating a Fredholm integral equation to invert the dielectric function [178, 179]. This elegant approach offers significant flexibility in the class of dielectric functions that can be modeled, but unfortunately it does not seem well suited for large scale computation of highly complicated geometries such as proteins.

3.3.2 Parameterization of Length Scales—In their original nonlocal work, Dogonadze and Kornyshev addressed model parameterization from dielectric absorption experiments [14]. The simple Lorentz model, which cannot address the individual physical mechanisms associated with nonlocal response, should be viewed as a phenomenological theory of the same functional form as the physically motivated DK model. Consequently, there are multiple approaches to parameterization one may take. In [180], Kornyshev and Ulstrup fit the two key parameters of the Lorentz model, the short-range dielectric constant and the solvent length scale, to experimental measurements of the energetics of interactions between chemical groups, finding that $\epsilon_* \approx 3.5 - 4$ and that $\Lambda \approx 4\text{\AA}$; however, the authors noted the significant challenges associated with modeling realistic analogues of the experiments. On the other hand, Kanth et al. have studied orientational correlations in water using large molecular dynamics (MD) simulations, using the popular TIP3P and TIP5P models of water [181, 182]. They found two correlation lengths, one at about $5\text{\AA}$ and one at $24\text{\AA}$ fitting to a single mode gave an optimal correlation length of approximately $10.5\text{\AA}$. Hildebrandt et al., in their reformulation of the problem using a gradient-type method [88], used the solvation free energies of monatomic ions and found an optimal length scale between 15 and $24\text{\AA}$ (see also the discussion in Hildebrandt [183]); however, ion solvation free energies are very sensitive to the radii used, and must therefore be carefully calibrated for a given application.

3.4 Weaknesses of the form of the dielectric function

Attard et al. have detailed serious weaknesses with the single-mode Lorentz model [184], and numerous that compare it to more complicated models support these criticisms (e.g., [147, 185]). More sophisticated dielectric functions have been proposed [147, 148, 163, 185], which account at least qualitatively for water's complicated dielectric response as a function of wavenumber k (see Figure 3. In particular, the dielectric function actually changes sign

from positive to negative, and then back to positive, as a function of distance, which can be understood simply by considering a positive charge that is centered in a small sphere. The water oxygens will tend to surround it, but then further away one must have a high density of the hydrogens, and around them will cluster the next “solvation shell” of water oxygens. This oscillation, known as “dielectric overscreening,” is associated with a range of length scales in which the dielectric function is actually negative [147, 148, 186]. Basilevsky and Parsons have suggested that such oscillating functions are inconsistent with the standard definition of a fixed solute cavity that is specified *a priori* [187]. However, their evidence for this conclusion relied on a numerical iteration scheme whose stability properties have not yet been established, and it is possible that their convergence problems were associated with the formulation of the model, rather than with the model itself (similar considerations complicate modeling of electromagnetic scattering).

4 Improving Nonlocal Continuum Models By Adding Modes

In this section we present new gradient-type extensions of Hildebrandt's local formulation [88, 183] to include more than the single length scale of the Lorentz nonlocal model. After illustrating the basic strategy using only two modes, we propose a local formulation for the four-mode model that captures the essential features of dielectric overscreening [147]. Future work will calibrate these models against MD simulations and develop efficient numerical solvers.

4.1 Two-Mode Model

Consider

$$\mathbf{D}(\mathbf{r}) = \int_V \varepsilon(\mathbf{r} - \mathbf{r}') \mathbf{E}(\mathbf{r}') d\mathbf{r}' \quad (22)$$

with

$$\varepsilon(\mathbf{r} - \mathbf{r}') = \varepsilon_0 \delta(\mathbf{r} - \mathbf{r}') + \varepsilon_1 \frac{\exp(-k_1 |\mathbf{r} - \mathbf{r}'|)}{|\mathbf{r} - \mathbf{r}'|} + \varepsilon_2 \frac{\exp(-k_2 |\mathbf{r} - \mathbf{r}'|)}{|\mathbf{r} - \mathbf{r}'|}, \quad (23)$$

We know that

$$\mathbf{E}(\mathbf{r}) = \nabla \varphi(\mathbf{r}) \quad (24)$$

and that

$$\nabla \cdot \mathbf{D}(\mathbf{r}) = 0, \quad (25)$$

so using the Helmholtz decomposition, we have

$$\mathbf{D}(\mathbf{r}) = \nabla \psi(\mathbf{r}) + \nabla \times \xi(\mathbf{r}) \quad (26)$$

and after again dropping the second term on physical grounds [88,183], we have

$$\nabla^2 \psi(\mathbf{r}) = 0. \quad (27)$$

Substituting the constitutive equation, Eq. (23), into Eq. (22), we obtain

$$\nabla \psi(\mathbf{r}) = \varepsilon_0 \nabla \varphi(\mathbf{r}) + \varepsilon_1 \int_V G_1(\mathbf{r}; \mathbf{r}') \nabla \varphi(\mathbf{r}') d\mathbf{r}' + \varepsilon_2 \int_V G_2(\mathbf{r}; \mathbf{r}') \nabla \varphi(\mathbf{r}') d\mathbf{r}', \quad (28)$$

where we have defined

$$G_i(\mathbf{r}; \mathbf{r}') = \frac{\exp(-k_i |\mathbf{r} - \mathbf{r}'|)}{|\mathbf{r} - \mathbf{r}'|} \quad (29)$$

for $i = 1, 2$. By taking the Fourier transform of both sides, we obtain

$$i\mathbf{k}\tilde{\psi}(\mathbf{k}) = \varepsilon_0 (i\mathbf{k}\tilde{\varphi}(\mathbf{k})) + \varepsilon_1 \left(\frac{1}{k^2 + k_1^2} \right) (i\mathbf{k}\tilde{\varphi}(\mathbf{k})) + \varepsilon_2 \left(\frac{1}{k^2 + k_2^2} \right) (i\mathbf{k}\tilde{\varphi}(\mathbf{k})), \quad (30)$$

so simplifying,

$$i\mathbf{k}\tilde{\psi}(\mathbf{k}) = \left[\varepsilon_0 + \varepsilon_1 \left(\frac{1}{k^2 + k_1^2} \right) + \varepsilon_2 \left(\frac{1}{k^2 + k_2^2} \right) \right] i\mathbf{k}\tilde{\varphi}(\mathbf{k}). \quad (31)$$

The electrostatic potential at infinity is zero, so we need not worry about the $\mathbf{k} = 0$ case; thus we may write

$$\tilde{\psi} = \left[\varepsilon_0 + \varepsilon_1 \left(\frac{1}{k^2 + k_1^2} \right) + \varepsilon_2 \left(\frac{1}{k^2 + k_2^2} \right) \right] \tilde{\varphi}, \quad (32)$$

where we have left off the $\mathbf{k}$ arguments for simplicity. Further simplification gives

$$(k^2 + k_1^2)(k^2 + k_2^2) \tilde{\psi} = \left[\varepsilon_0 (k^2 + k_1^2)(k^2 + k_2^2) + \varepsilon_1 (k^2 + k_2^2) + \varepsilon_2 (k^2 + k_1^2) \right] \tilde{\varphi}. \quad (33)$$

Eq. (27) indicates that

$$k^2 \tilde{\psi} = 0, \quad (34)$$

so the left-hand side of Eq. (33) simplifies further, to

$$(k^2 + k_1^2)(k^2 + k_2^2) \tilde{\psi} = k_1^2 k_2^2 \tilde{\psi}. \quad (35)$$

Defining

$$\alpha = \varepsilon_0 \quad (36)$$

$$\beta = \varepsilon_0 (k_1^2 + k_2^2) + \varepsilon_1 + \varepsilon_2 \quad (37)$$

$$\gamma = \varepsilon_0 (k_1^2 + k_2^2) + \varepsilon_1 k_2^2 + \varepsilon_2 k_1^2 \quad (38)$$

we have

$$[\alpha k^4 + \beta k^2 + \gamma] \tilde{\varphi} = k_1^2 k_2^2 \tilde{\psi}. \quad (39)$$

Then defining

$$\tilde{u} = k^2 \tilde{\varphi} \quad (40)$$

gives

$$(\alpha k^2 + \beta) \tilde{u} = k_1^2 k_2^2 \tilde{\psi} - \gamma \tilde{\varphi} \quad (41)$$

$$k^2 \tilde{\psi} = 0 \quad (42)$$

$$k^2 \tilde{\varphi} = \tilde{u}. \quad (43)$$

Inverse Fourier transforms finally give

$$\nabla^2 \psi(\mathbf{r}) = 0 \quad (44)$$

$$\nabla^2 \varphi(\mathbf{r}) = u(\mathbf{r}) \quad (45)$$

$$\left(\nabla^2 + \frac{\beta}{\alpha} \right) u(\mathbf{r}) = \frac{k_1^2 k_2^2}{\alpha} \psi(\mathbf{r}) - \frac{\gamma}{\alpha} \varphi(\mathbf{r}). \quad (46)$$

For problems with dielectric interfaces, i.e. with biological molecules embedded in the solvent, the boundary conditions relating u and ϕ are simple; those relating ϕ and ψ have been addressed by multiple authors including Kornyshev (e.g., [15]) Hildebrandt et al. [183], and Basilevsky and Parsons [185], and more detailed analysis is required [188].

4.2 Four-Mode Model: Capturing Overscreening

To address the problem of dielectric overscreening, and the regions in which the dielectric function is negative, Kornyshev and Sutmann proposed the functional form [147,163]

$$\varepsilon(k) = \varepsilon_* - \frac{\varepsilon_* - \varepsilon_{bulk}}{1 + \left(\frac{\varepsilon_{bulk}}{\varepsilon_*} \right) \left(\frac{1 + \lambda^2 k^2}{F(k)} - 1 \right)} \quad (47)$$

with

$$F(k) = 1 + \frac{Ak^2 + Bk^4}{(\alpha^2 + (\kappa - k)^2)(\alpha + (\kappa + k)^2)} + \frac{Ck^2}{1 + \gamma^2 k^2}, \quad (48)$$

where λ is a characteristic correlation length, ϵ_* is the short-range dielectric constant, and A , B , C , α , γ , and κ , are fitting constants [147]. Medvedev has developed these equations further [148], but in the section we focus on the combinations of parameters described by Kornyshev and Sutmann. Also, it should be noted that we term this a “four-mode” model due to the number of terms required to express the dielectric function $\epsilon(k)$; the physical model proposed by Kornyshev and Sutmann, however, includes only one direct length scale, λ ; other length scales arise from the functional form and empirically fit parameters [147].

Expanding Eqs. (47) and (48) leads to an expression of the form

$$\tilde{\psi} = \frac{N(k)}{D(k)} \tilde{\psi} \quad (49)$$

where $N(k)$ and $D(k)$ are eighth-order polynomials; $N(k)$ is the same degree as $D(k)$, due to the first term in Eq. (47). We denote

$$D(k) = (k - p_1)(k - p_2) \dots (k - p_8) \quad (50)$$

where p_i is the i th root and $N(k)$ similarly, with z_i denoting its i th root. Note that the functional forms given by Eqs. (47) and (48) mean that $D(k)$ can be written in the form

$$D(k) = (k^2 + |p_1|^2)(k^2 + |p_2|^2)(k^2 - |p_3|^2)(k^2 - |p_4|^2). \quad (51)$$

Because $k^2 \tilde{\psi} = 0$, multiplying both sides of Eq. (49) by $D(k)$ gives

$$|p_1|^2 |p_2|^2 |p_3|^2 |p_4|^2 \tilde{\psi} = N(k) \tilde{\varphi} \quad (52)$$

and defining $\xi = |p_1|^2 |p_2|^2 |p_3|^2 |p_4|^2$,

$$\xi \tilde{\psi} = N(k) \tilde{\varphi}. \quad (53)$$

To illustrate the characteristics of the four-mode model, we turn to the model BKLS(1 Å) in Kornyshev and Sutmann [147], which gives an $N(k)$ with roots $\pm i$, $\pm 20i/3$, $-3 \pm 0.8i$, and $+3 \pm 0.8i$. Then

$$\xi \tilde{\psi} = (k^2 + 1) \left(k^2 + \frac{400}{9} \right) (k^4 - 16k^2 + 100) \tilde{\varphi}, \quad (54)$$

and we define auxiliary potentials $\hat{u}$ and $\hat{v}$ such that

$$(k^2 + 1) \hat{u} = \xi \tilde{\psi} \quad (55)$$

$$\left(k^2 + \frac{400}{9}\right) \tilde{v} = \tilde{u} \quad (56)$$

$$\left(k^4 - 16k^2 + 100\right) \tilde{\varphi} = \tilde{v}. \quad (57)$$

The two pairs of complex conjugate roots could be treated separately using complex wavenumbers, or we can define

$$\tilde{w} = k^2 \tilde{\varphi} \quad (58)$$

so that

$$\left(k^2 - 16\right) \tilde{w} = \tilde{v} - 100 \tilde{\varphi}. \quad (59)$$

The relation $k^2 \tilde{\psi} = 0$, combined with Eqs. (55), (56), (58), and (59) represent the local formulation for this functional form of the dielectric function. In real space, the equations are

$$\nabla^2 \psi(\mathbf{r}) = 0 \quad (60)$$

$$\left(\nabla^2 - 1\right) u(\mathbf{r}) = \xi \psi(\mathbf{r}) \quad (61)$$

$$\left(\nabla^2 - \frac{400}{9}\right) v(\mathbf{r}) = u(\mathbf{r}) \quad (62)$$

$$\nabla^2 \varphi(\mathbf{r}) = w(\mathbf{r}) \quad (63)$$

$$\left(\nabla^2 + 16\right) w(\mathbf{r}) = v(\mathbf{r}) - 100 \varphi(\mathbf{r}) \quad (64)$$

Figure 3 contains plots of $\varepsilon(k)$ from experiment [18], from the BKLS model discussed here, and from the single-mode Lorentz model. As Kornyshev and Sutmann discuss, the BKLS model exhibits the correct behavior qualitatively but not quantitatively, whereas the Lorentz model is qualitatively incorrect except in the $k \rightarrow 0$ and $k \rightarrow \infty$ limits. Also indicated in the figure is the standard local-response model.

5 Opportunities

In this section, we list challenges that seem likely to have been addressed in the mechanics of materials community, as well as emerging application areas for nonlocal electrostatics,

where the mechanics community's expertise with implementation may translate to high-impact research.

5.1 Boundary conditions

Numerous researchers in nonlocal electrostatics are interested in developing a more thorough analysis of boundary conditions, particularly at an interface between a local-response dielectric and a nonlocal dielectric. In mechanics, the importance of interfaces for composites has been demonstrated by Aifantis and Willis et al. [80,81], so we hope that crossover between these communities will be fruitful.

At interfaces between two different dielectric media in which both obey local, linear response, the boundary conditions are merely the continuity of the potential, and the normal component of the electric displacement, which can be written

$$\mathbf{n} \cdot (\mathbf{D}_P(\mathbf{r}^-) - \mathbf{D}_W(\mathbf{r}^+)) = 0 \quad (65)$$

$$\mathbf{n} \cdot (\varepsilon_P \mathbf{E}_P(\mathbf{r}^-) - \varepsilon_W \mathbf{E}_W(\mathbf{r}^+)) = 0, \quad (66)$$

where we have assumed that there is no fixed (permanent) charge at the interface itself. For interfaces where one medium is a local dielectric and the other is a nonlocal dielectric, the question is more complicated. The potential itself is continuous across the interface, but the normal-field boundary condition requires evaluating the volume integral from the constitutive equation for the material, e.g.

$$\mathbf{n} \cdot (\varepsilon_P \mathbf{E}_P(\mathbf{r}^-) - \int_{V_W} \varepsilon(\mathbf{r}^+, \mathbf{r}') \mathbf{E}_W(\mathbf{r}') d^3 \mathbf{r}') = 0. \quad (67)$$

and the integral is over the volume of the solvent, rather than the entire volume of the system. The thesis of Weggler provides a framework to treat inhomogeneous problems consistently [172].

Hildebrandt argued on physical grounds that for problems in which the dielectric function has a short-range component modeled with a delta function (e.g. the models discussed here, Eqs. (16), (23), and (47)), the $\varepsilon(\mathbf{r}, \mathbf{r}')$ in the volume integral may be usefully approximated by just the delta function term [88, 183]. Basilevsky and Parsons suggested that the normal displacement field is continuous in their early work [185]. Numerical investigations by Weggler [172] suggest that in many cases, the effect of the particular boundary condition chosen is small compared to the overall effect of moving from a local-response model to a nonlocal one. These results support the notion that nonlocal models robustly improve prediction (i.e. are not extremely sensitive), but nevertheless a satisfactory understanding of boundary conditions is essential.

5.2 Inhomogeneous systems

The dielectric approximation, in which the dielectric function $\varepsilon(\mathbf{r}, \mathbf{r}')$ is assumed to be translation invariant, is clearly justifiable for homogeneous systems. However, one naturally

expects that the presence of an interface leads to non-translational invariance in the response function, and analysis of the deviations is ongoing [15]. In early work, Birman et al. [189, 190] studied this problem for nonlocal electrodynamics. For solvation electrostatics, Dzhavakhidze, Kornyshev and Levadny highlighted the problem of the interface [191], as have Basilevsky and Parsons [188]. Encouragingly, Leikin and Kornyshev found in a study on hydration forces between planar bilayers that the dielectric approximation (using $\epsilon(\mathbf{r} - \mathbf{r}')$ rather than $\epsilon(\mathbf{r}, \mathbf{r}')$) causes only minor quantitative changes while leaving the qualitative results intact [157]. However, a thorough physical and mathematical understanding remains elusive.

5.3 Anisotropic response

As mentioned elsewhere, continuum electrostatic models are valuable in other areas of molecular science and engineering, outside of biological systems. The importance of anisotropic models may be seen, for example, in the fact anisotropy has been a key development in polarizable-continuum models (PCM) for computational chemistry [97, 99, 192], wherein a quantum-mechanical treatment of a molecular solute is solved self-consistently with a Poisson-type model for the surrounding solvent using boundary-integral equations [98]. It is also worth noting that these anisotropic PCM approaches are motivated by investigations involving liquid crystals, which are a useful model for biology [193, 194] and which have been treated using nonlocal models [195].

In the case of water and aqueous electrolytes, Attard et al. have criticized the use of isotropic nonlocal models, pointing out that such approaches essentially treat the longitudinal and transverse responses equally [184]; this criticism is supported by experimental and computational studies, e.g. [139]. However, Basilevsky and Parsons have indicated that the transverse response can be neglected [187], and Hildebrandt has justified this approach in his thesis [183]. The discrepancy may lie in the perspective taken on whether one requires a solvent electrostatic model to reproduce the polarization charge density in the solvent [196], or merely reproduce the reaction potential in the solute and its deviations from standard continuum models [197]; the latter remains an active area of research in its own right, and the former is still a challenging modeling problem. If anisotropic response near interfaces is biologically relevant, one major challenge for nonlocal models will be the fact that “longitudinal” and “transverse” are more difficult to define in the vicinity of a protein (with a complicated shape) than it is in the context of a planar interface. On the other hand, we should be able to obtain some insights by modeling DNA as a cylinder, as has been done in the past [198].

5.4 Extensions: electrolytes, solvation dynamics, and other solvents

We have noted that biological solvents are in fact electrolytes, and the mobile ions play critical roles in physiology. Such solutions are substantially more complex than pure water, and efforts to develop theories more accurate than Debye-Huckel and the Poisson–Boltzmann equation go back decades. Classical density-functional theories of electrolytes [27, 117, 199], which are nonlocal and also nonlinear, are fully consistent thermodynamically but highly complicated to solve in complicated geometries such as proteins [118]. Recently a number of promising nonlocal or nonlocal-like theories have been

proposed. For instance, Buyukdagli and Ala-Nissila have developed a nonlocal Poisson-Boltzmann model for polarizable ions in aqueous solution [200]. In addition, Bazant, Storey, and Kornyshev have developed a fourth-order modified Poisson model for ionic liquids [201], which Storey and Bazant have applied to electrokinetics [202, 203]. As an indication of the field's interest in these models, numerical methods for the Bazant–Storey–Kornyshev model have already been developed [204] and others have begun to use the theory [205].

The problem of solvation dynamics addresses the time-dependent response of the solvent to a change in the solute charge distribution (for instance, during photoexcitation), which may be modeled using a time-dispersive continuum model [206]. Zhang et al. have shown that this dispersion can be modeled successfully as a sum of Debye modes [207], a practice common in electromagnetics and especially in modeling biological tissues [208, 209]. Emerging applications involving ionic liquids (green chemistry, clean energy, etc. [98, 210]) have driven recent work in solvation dynamics [207, 211, 212]. Accordingly, Parsons, Basilevsky, and Vener have developed a nonlocal theory for solvation dynamics [213].

5.5 Incorporating nonlocal models into protein simulations

Implicit-solvent models are often valuable tools for dynamical simulations as well [214–216], if they have continuous gradients. The speed with which a model can be calculated then offers a major constraint, and it is desirable to have approximations. The Generalized-Born (GB) model [214,217,218] approximates the local-response Poisson or Poisson–Boltzmann models quickly, and is widely used in MD simulations. However, semi-empirical approximation schemes do not necessarily illustrate how more advanced underlying theories can be approximated. We have therefore been developing a systematic approximation using boundary-integral equation theory [219–221], which provides a rigorous framework for GB models. Extensions to nonlocal models developed using boundary-integral formulations [144,174,177] are underway.

6 Discussion

In this review, we have described how biology depends centrally on the electrostatic interactions between biological molecules and their surrounding solution environment. As a result, truly predictive engineering of biological systems, whether novel therapeutic drugs for improved public health or engineered proteins for clean energy, requires accurate mechanistic models for water's influence on molecular solutes. Nonlocal electrostatic models have a long history in electrochemistry [14,178], and studies with simplified model geometries have raised the possibility of their importance in biology [33,139]. Historically, the main challenge in applying nonlocal models to specific biological systems, e.g. the binding between two given molecules, has been a lack of available computational software to solve these more complicated models in a reasonable amount of time and memory. Happily, recent developments [88, 144, 171, 174] now allow successful applications of at least the simple Lorentz model to atomistically detailed structures of large biomolecules [174]. We may now turn to asking what model extensions are most important to improve agreement with biological experiment; to this end, in this paper we propose a local formulation for a model capable of treating dielectric overscreening [147].

In biology the traditional view of course has been that the biomolecule itself is the main attraction, and that models for water should be built to serve it. Practical limitations of computer memory and speed have reinforced this view: due to the enormously increased computational cost to include water and ions, almost all of the early computer simulation methods for proteins treated the surrounding solvent in incredibly simplistic ways. Although we have much more powerful computers today, our models for water still have much room for improvement. In this review, we propose that the proper approach to improving electrostatic models in biology is to change our viewpoint to the following: *at the molecular scale, solvent is a material*. The parallels between nonlocal mechanics and nonlocal electrostatics, which span the physical motivations, the mathematical tools, the computational approaches, and even the historical developments, could hardly be clearer. Perhaps just as important, the fields share an important application in supporting the development of new energy storage and conversion technologies (e.g. [222]).

This viewpoint does not diminish the importance of biological molecules, but instead focuses the modeler on the question of *exploring the space of models*. The potential-of-mean-force (PMF) interpretation of continuum models provides the critical bridge allowing modelers to focus exclusively on the solvent response; extensive molecular dynamics simulations can then employ reasonably simple models of solutes in order to investigate deviations from expected continuum behavior [22]. Experiments are reality, of course, and simulations are only theory; to first order, however, today we are in a situation in which the major weaknesses in our continuum theories can be identified using higher-level theory (e.g. atomistic simulation). Finding functional forms to correct our continuum models becomes the main challenge, and finding sufficient data to constrain the search. To this end, MD experts can easily share the data files that illustrate average electrostatic potentials and charge densities, allowing model developers to test hypotheses against common reference results.

The remarkable success of linear, local electrostatic models in molecular modeling suggests that nonlocal models can dramatically improve the accuracy of predictions for many biological studies and design problems. In contrast to gradient-based methods in mechanics, nonlocal electrostatics remain a largely unexplored area in biological modeling, in part because the field is dominated by researchers trained in chemistry, biology, and physics. These scientists naturally develop improved continuum models using the formalisms native to their disciplines, such as statistical mechanical integral equations or free-energy functionals. Which of these approaches may yet prevail is not certain, of course, and any number of details might render nonlocal models less appealing for applications that demand high accuracy or formal exactness. Nevertheless, nonlocal approaches remain a uniquely promising approach because *from the outset* they offer (1) a unified mathematical and computational foundation that spans both local Poisson and the advanced models; (2) the ability to be solved efficiently and accurately on massively parallel computers without complication; and (3) strong mathematical frameworks from which to obtain fast approximations for multiscale modeling and molecular engineering.

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Figure 1.

The basic molecular electrostatics problem: the solute molecule (e.g. a protein) is modeled as a homogeneous macroscopic dielectric medium whose volume V_P is defined in terms of a collection of atomic spheres; the permittivity is ϵ_P and the protein charge distribution is frequently modeled as discrete point charges at the atom centers. Consequently, the potential in V_P obeys a Poisson equation. The solute is embedded in an infinite solvent bath, V_W , that is modeled as a homogeneous dielectric with permittivity ϵ_W ; here, the potential obeys either a Laplace equation (in pure water) or the linearized Poisson-Boltzmann equation (in a dilute electrolyte).

	Linear	Nonlinear
Local	Poisson Linearized Poisson-Boltzmann Generalized Born	Nonlinear Poisson-Boltzmann Langevin-Debye
Nonlocal	Dogonadze-Kornyshev Lorentz model Kornyshev-Sutmann	Reference interaction site models Density/free energy functionals Dipolar Poisson-Langevin

Figure 2.

Simple models for protein–solvent electrostatics can be categorized roughly into four categories, depending on whether they are linear or nonlinear, and local or nonlocal.

Figure 3.

The dielectric function $\varepsilon(k)$ estimated from experiment and from multiple models [147]. The data points associated with the experimental curve were obtained from Fig. 2 of [147] using the image processing software PlotDigitizer. The multi-mode BKLS model captures the experimental results qualitatively though not quantitatively, and the simple Lorentz model is accurate only in the $k \rightarrow 0$ and $k \rightarrow \infty$ limits.