

## Novel Formulation of Nonlocal Electrostatics

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The accurate modeling of the dielectric properties of water is crucial for many applications in physics, computational chemistry, and molecular biology. This becomes possible in the framework of nonlocal electrostatics, for which we propose a novel formulation allowing for numerical solutions for the nontrivial molecular geometries arising in the applications mentioned before. Our approach is based on the introduction of a secondary field  $\psi$ , which acts as the potential for the rotation free part of the dielectric displacement field  $\mathbf{D}$ . For many relevant models, the dielectric function of the medium can be expressed as the Green's function of a local differential operator. In this case, the resulting coupled Poisson (-Boltzmann) equations for  $\psi$  and the electrostatic potential  $\phi$  reduce to a system of coupled partial differential equations. The approach is illustrated by its application to simple geometries.

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The theory of continuum electrostatics plays a major role in the determination of solvation free energies of atoms, ions, and biomolecules [1]. Recent progress in its applicability to biological systems has been impressive: the electrostatic potentials of large biomolecules such as, e.g., microtubuli and ribosomes, can be determined [2]. Unfortunately, the standard continuum approach ultimately becomes inaccurate when used to determine electrostatic properties on atomic scales [3], as it is featureless; i.e., the correlation between solvent arrangements and the geometrical structure of biomolecular assemblies is not taken into account. On the other hand, continuum electrostatics is still much more efficient from a computational point of view than microscopic simulations based on, e.g., molecular dynamics (MD). Therefore, interest has risen recently in extensions of the theory of continuum electrostatics that allow us to account for spatial variations of the dielectric behavior of the solvent, in particular, near boundaries [1,4]. Part of the motivation for such approaches stems from the field of protein docking, where a realistic and efficient modeling of solvent properties is essential [5].

Within the continuum theory of electrodynamics, spatial dispersion effects can be taken into account in an approach called “nonlocal electrostatics” [6–9]. It assumes a linear relationship between the dielectric displacement field and the electric field mediated by a permittivity kernel depending on two spatial arguments,

$$\mathbf{D}(\mathbf{r}) = \varepsilon_0 \int d\mathbf{r}' \varepsilon(\mathbf{r}, \mathbf{r}') \mathbf{E}(\mathbf{r}'), \quad (1)$$

where  $\varepsilon(\mathbf{r}, \mathbf{r}')$  is the dielectric permittivity tensor. Equivalently to Eq. (1) one can express the nonlocal relationship in terms of the polarization fields [9]. While nonlocal electrostatics remains firmly embedded within the well-understood framework of Maxwell's the-

ory, it introduces a new characteristic length scale absent in local electrostatics: the correlation length  $\lambda$  of the polarization correlations between the solvent molecules. It sets the relevant scale for the deviation of the dielectric properties of the solvent from its bulk value. Thus, nonlocal electrostatics is a serious candidate for a more realistic description of solvent properties, provided it is also computationally tractable. Here, however, difficulties arise. The theory of nonlocal electrostatics, discussed in detail below, is technically considerably more demanding than local electrostatics, as it is usually formulated as a system of coupled integro-differential equations. Consequently, it has so far only been applied to idealized situations, and even then typically after introducing approximations in order to obtain analytical results [10,11]. For complex geometries, the solution of the equations by numerical methods becomes a formidable task.

Thus, a reformulation of the equations of nonlocal electrostatics is needed in order to make the theory ap-

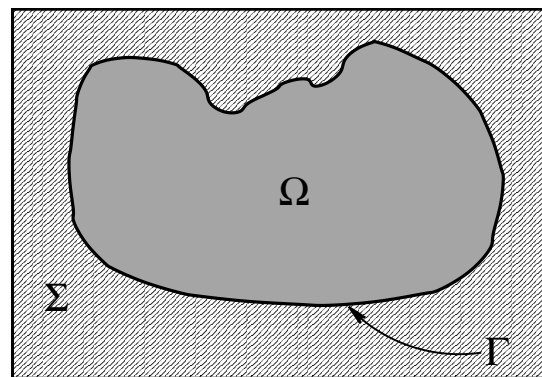


FIG. 1. A cavity with local dielectric constant ( $\Omega$ ) immersed in a medium with spatially varying permittivity ( $\Sigma$ ). The interface between the two spaces is denoted by  $\Gamma$ .

plicable to real-world problems. Here we present a scheme which allows us to rewrite the theory in terms of a system of partial differential equations for local fields which makes it amenable to standard methods of numerical analysis. The derivation relies on two assumptions which are typically valid for, e.g., the discussion of solvation problems for biomolecules: (i) the linearity of the relationship between dielectric response and the electric field, and (ii) the representation of the dielectric function in terms of Green functions of known differential operators. We first derive the set of equations, and then illustrate how to solve them on (simple) examples.

In the following we consider the situation of Fig. 1. A domain  $\Omega$  (representing a molecule) is embedded in the solvent  $\Sigma$  taking up the whole space except  $\Omega$ . The surface of the embedded domain is denoted by  $\Gamma$ . Within  $\Omega$ , the dielectric properties are assumed to be local, i.e.,  $\varepsilon \equiv \varepsilon_\Omega$ , while in the solvent space  $\Sigma$ , Eq. (1) holds. On large scales, i.e., when  $|\mathbf{r} - \mathbf{r}'| \gg \lambda$ , the dielectric response in the solvent is again local with the bulk dielectric constant  $\varepsilon_\Sigma$ . In this situation the equations of nonlocal electrostatics read as

$$\Delta\phi_\Omega = -\frac{1}{\varepsilon_\Omega\varepsilon_0}\varrho, \quad \mathbf{r} \in \Omega, \quad (2)$$

$$\varepsilon_0 \nabla \int_\Sigma d\mathbf{r}' \varepsilon(\mathbf{r}, \mathbf{r}') \nabla' \phi_\Sigma(\mathbf{r}') = 0, \quad \mathbf{r}, \mathbf{r}' \in \Sigma, \quad (3)$$

where  $\varrho$  is the density of fixed charges assumed to lie confined within  $\Omega \setminus \Gamma$ , which is usually the case for biomolecules in solution. This is no restriction on the validity of our approach: the existence of surface charges on  $\Gamma$  only slightly modifies the boundary conditions. Equations (2) and (3) are the Poisson equations for the geometry of Fig. 1. The primed symbol  $\nabla'$  denotes the differentiation with respect to  $\mathbf{r}'$ . Without surface charges on  $\Gamma$ , the boundary conditions to Eqs. (2) and (3) for the normal ( $n$ ) and tangential ( $t$ ) components of the electric and dielectric displacement field on the boundary  $\Gamma$  are given by

$$\mathbf{D}_{\Omega,n} = \mathbf{D}_{\Sigma,n}, \quad \mathbf{E}_{\Omega,t} = \mathbf{E}_{\Sigma,t}, \quad (4)$$

where, by virtue of Eq. (3), the boundary condition for  $\mathbf{D}$  is also nonlocal.

In order to step over from the integro-differential to a purely differential formulation we introduce, in addition to the potential field  $\phi$ , a potential field  $\psi$  within both compartments  $\Omega$  and  $\Sigma$ . Attempts similar in spirit, but differing in the implementation, have been discussed before in the literature [12], but again lead to systems of integro-differential equations. In  $\Omega$  and  $\Sigma$  we define the relations between the potentials  $\phi$  and  $\psi$  and the physical fields as

$$\mathbf{E}_\Omega \equiv -\nabla\phi_\Omega, \quad \mathbf{D}_\Omega \equiv -\nabla\psi, \quad (5)$$

$$\mathbf{E}_\Sigma \equiv -\nabla\phi_\Sigma, \quad (6)$$

while the dielectric displacement field in  $\Sigma$  can be represented in terms of a scalar and a vector field [13],

$$\mathbf{D}_\Sigma \equiv -\varepsilon_0 \int_\Sigma d\mathbf{r}' \varepsilon(\mathbf{r}, \mathbf{r}') \nabla' \phi_\Sigma \equiv -\nabla\psi_\Sigma + \nabla \times \boldsymbol{\xi}_\Sigma. \quad (7)$$

The scalar field  $\psi$  serves as the potential of the rotation free part  $\tilde{\mathbf{D}} = -\nabla\psi_\Sigma$  of the dielectric displacement field  $\mathbf{D}$ . In our setting  $\phi_\Sigma$  is determined by  $\psi_\Sigma$  alone, and neither  $\psi_\Omega$  nor  $\phi_\Omega$  are affected by  $\boldsymbol{\xi}_\Sigma$ . Note that  $\boldsymbol{\xi}_\Sigma$  can of course be computed from, e.g., Eq. (7) as soon as  $\phi_\Sigma$  is known. Since we here are interested only in the electrostatic potential  $\phi$  and quantities derived from it, we will ignore  $\boldsymbol{\xi}_\Sigma$  in the following.

With this definition, the differential equations and boundary conditions, Eqs. (2)–(7) can be brought into the form

$$\Delta\psi_\Omega = -\varrho, \quad \mathbf{r} \in \Omega, \quad \Delta\psi_\Sigma = 0, \quad \mathbf{r} \in \Sigma, \quad (8)$$

$$\nabla\psi_\Sigma|_n = \nabla\psi_\Omega|_n, \quad \mathbf{r} \in \Gamma, \quad \nabla\phi_\Sigma|_t = \nabla\phi_\Omega|_t, \quad \mathbf{r} \in \Gamma. \quad (9)$$

In addition, there are now two equations relating the potential fields  $\phi$  and  $\psi$ ,

$$\varepsilon_0\varepsilon_\Omega\phi_\Omega = \psi_\Omega, \quad \mathbf{r} \in \Omega, \quad (10)$$

and Eq. (7), to be fulfilled in  $\Sigma$ . So far, the introduction of  $\psi$  has made it possible to rewrite the boundary conditions in a completely local way. The nonlocal problem now only is with Eq. (7) in which the nonlocal integral kernel still remains. The latter expression can be simplified under an additional assumption on the form of  $\varepsilon(\mathbf{r}, \mathbf{r}')$ . We assume it can be written as

$$\varepsilon(\mathbf{r}, \mathbf{r}') = \varepsilon_\ell \delta(\mathbf{r} - \mathbf{r}') + \tilde{\varepsilon} \mathcal{G}(\mathbf{r}, \mathbf{r}'), \quad (11)$$

where  $\tilde{\varepsilon} = (\varepsilon_\Sigma - \varepsilon_\ell)/\lambda^2 > 0$ , and the Green function  $\mathcal{G}$  solves  $\mathcal{L}\mathcal{G}(\mathbf{r}, \mathbf{r}') = -\delta(\mathbf{r} - \mathbf{r}')$  for a differential operator  $\mathcal{L}$  with constant coefficients. Note that  $\varepsilon_\ell$  is the dielectric function on smallest scales (i.e.,  $\mathbf{r} \rightarrow \mathbf{r}'$ ) which is related to the frequency spectrum of the dielectric function [9]. While our construction clearly restricts the theory of nonlocal electrostatics to a certain class of dielectric functions, this restriction is not problematic as it applies to most situations of physical interest.

The application of  $\mathcal{L}$  to Eq. (7) yields

$$\varepsilon_0[\varepsilon_\ell \mathcal{L} - \tilde{\varepsilon}] \nabla \phi_\Sigma = -\mathcal{L} \nabla \psi_\Sigma. \quad (12)$$

As  $\phi$  and  $\psi$  are determined only up to an arbitrary constant, we drop the gradients on both sides of Eq. (12) and are left with

$$\varepsilon_0[\varepsilon_\ell \mathcal{L} - \tilde{\varepsilon}] \phi_\Sigma = -\mathcal{L} \psi_\Sigma. \quad (13)$$

Equations (8)–(10) and (13) constitute the novel formulation of nonlocal electrostatics based entirely on partial differential equations.

In order to apply the equations to specific physical situations, the nonlocal dielectric function and the

Green function of the differential operator  $\mathcal{L}$  need to be determined. To keep the computations simple and focus on the conceptual features of our approach we further assume that the dielectric function is isotropic, i.e.,  $\mathcal{G}(\mathbf{r}, \mathbf{r}') \approx \mathcal{G}(\mathbf{r} - \mathbf{r}')$ , which is exact far from any boundary. The use of more general expressions is clearly permitted and is in fact needed for the treatment of realistic situations [14–16], and will be discussed in a detailed study later.

A standard model for an isotropic nonlocal dielectric function is given by the so-called Fourier-Lorentzian model with a Yukawa-type kernel in real space. The corresponding Green function reads

$$\mathcal{G}(\mathbf{r} - \mathbf{r}') = \frac{1}{4\pi} \frac{e^{-|\mathbf{r} - \mathbf{r}'|/\lambda}}{|\mathbf{r} - \mathbf{r}'|}, \quad (14)$$

with the differential operator  $\mathcal{L}$  being given by  $\mathcal{L} \equiv \Delta - 1/\lambda^2$ . With this choice Eq. (13) reads

$$\varepsilon_0[\varepsilon_\ell \lambda^2 \Delta - \varepsilon_\Sigma] \phi_\Sigma = \psi_\Sigma. \quad (15)$$

Note that due to  $\Delta\psi_\Sigma = 0$ , no differential operator appears on the right-hand side (rhs) of Eq. (15).

This result is interesting for two reasons. First, it illustrates that in the limit  $\lambda \rightarrow 0$ , i.e., on length scales large compared to the scale of the orientational correlations, the local limit is recovered. Second, for the differential operator chosen, the form of the equation is apparently that of a Debye-Hückel equation in which the role of the Debye-Hückel screening length is played by the combination  $\lambda(\varepsilon_\ell/\varepsilon_\Sigma)^{1/2}$ , while the potential  $\psi$  plays the role of the density of mobile charges. We can thus interpret  $\psi$  as a density of polarization charges in the bulk whose gradient gives rise to the rotation free part of the displacement field  $\mathbf{D}$ .

To illustrate how our formulation of nonlocal electrostatics can be put to use we first consider the case of a charge  $q$  placed at the center of a spherical shell of radius  $a$ , which is a model for ion solvation [9]. Inside the shell,  $\varepsilon_\Omega = 1$ . In the nonlocal case the role of the Poisson equation for  $\phi$  is taken over by the equation for  $\psi$  according to Eqs. (8) and (9). The  $\psi$  potential inside the shell is given by  $\psi_\Omega = (q/4\pi r)$ , and similarly outside,  $\psi_\Sigma = (q'/4\pi r)$ . The tangential boundary condition is trivially fulfilled, while the normal boundary condition at  $r = a$  leads to  $q = q'$ . Because of radial symmetry, Eq. (15) reads

$$\varepsilon_0 \left\{ \varepsilon_\ell \lambda^2 \left[ \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial}{\partial r} \right) \right] - \varepsilon_\Sigma \right\} \phi_\Sigma = \frac{q}{4\pi r}, \quad (16)$$

which is solved by

$$\phi_\Sigma(r) = \frac{1}{4\pi\varepsilon_\Sigma\varepsilon_0} \frac{q}{r} [1 + A \exp(-\gamma r)], \quad (17)$$

where  $A$  and  $\gamma$  follow from coefficient matching and the continuity of  $\phi$  at the boundary,  $\phi_\Sigma(a) = \phi_\Omega(a)$ , yielding  $A \equiv (\varepsilon_\Sigma - \varepsilon_\ell/\varepsilon_\ell)(\sinh\nu/\nu)$ ,  $\nu \equiv \sqrt{\varepsilon_\Sigma/\varepsilon_\ell}(a/\lambda)$ ,  $\gamma \equiv$

$\nu/a = \sqrt{\varepsilon_\Sigma/\varepsilon_\ell}(1/\lambda)$ . The electrostatic potential allows to estimate the solvation energy of monovalent and divalent ions. From  $\phi_\alpha(r)$  and  $\psi_\alpha(r)$ , with  $\alpha \in \{\Omega, \Sigma\}$ , we obtain the free energy of solvation as the difference of the electrostatic energies in water and vacuum (where the local computation is valid) from  $\Delta G = \frac{1}{2} \int \{\rho\phi - \rho\phi_{\text{vac}}\} dr$ , where the integrals are split into integrals over  $\Omega$  and  $\Sigma$ . The result is shown Fig. 2, comparing our results to local computation (the Born-model). The correlation length  $\lambda$  is the only adjustment parameter in the theory. Like the ion radii, it can also be obtained from microscopic simulations. Our result compares favorably to the experimental data taken from [17]. The value for  $\lambda$  we took is 24.13 Å; for the ion radii we chose values according to the Åqvist [18]. Shannon radii [19,20] were also tested, without significant differences on our results. A detailed discussion of the choice of ion radii within nonlocal electrostatics is found in [21].

In the radially symmetric problem the tangential boundary condition is trivially fulfilled. We thus next consider the potential generated by a charge  $q$  placed at a distance  $d$  from a planar dielectric phase boundary, as sketched in Fig. 3. Within local electrostatics, this problem can be solved by the method of image charges. The symmetry of the situation allows the use of cylindrical coordinates. At a point  $P$  inside  $\Omega$ , the local dielectric medium, the electrostatic potential  $\phi$  is given by  $\phi_\Omega(\rho, z) = -(1/4\pi\varepsilon_0\varepsilon_\Omega)(\frac{q}{R_1} + \frac{q'}{R_2})$  where  $R_1 = \sqrt{\rho^2 + (d-z)^2}$  and  $R_2 = \sqrt{\rho^2 + (d+z)^2}$  are the lengths of the vectors pointing from the charge  $q$  located at  $z = d$ , and the image charge  $q'$  at  $z = -d$  to the point  $P$ . Inside the charge-free half-space  $\Sigma$  the potential is given by  $\phi_\Sigma = (1/4\pi\varepsilon_0\varepsilon_\Sigma)\frac{q''}{R_1}$  with the image charge  $q''$ . The application of the boundary conditions for the normal and tangential components then yields the relations between the image charges  $q + q' = \frac{\varepsilon_\Omega}{\varepsilon_\Sigma} q''$ ,  $q - q' = q''$  so that the potential is determined explicitly in both half-spaces. Inside  $\Omega$ , e.g., one has

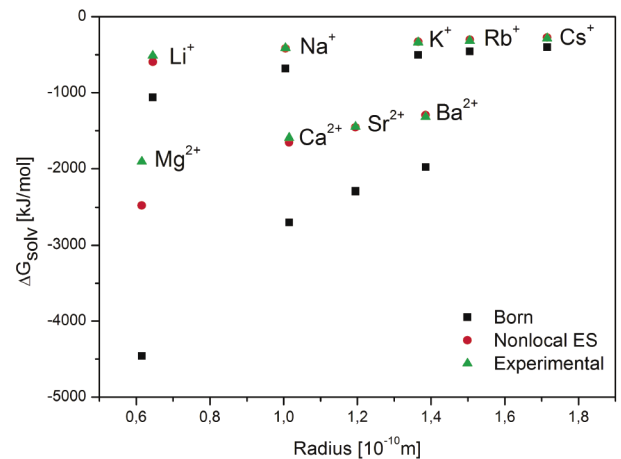


FIG. 2 (color online). Solvation free energy of ions.

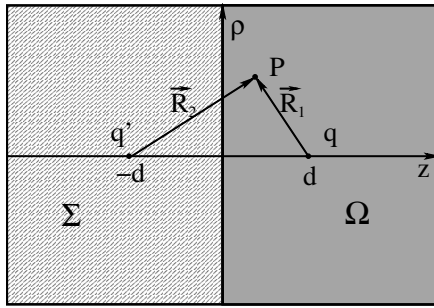


FIG. 3. Geometry of the problem of a charge  $q$  placed at a distance  $d$  from a dielectric boundary. For a discussion, see the text.

$$\phi_{\Omega}(\varrho, z) = \frac{q}{4\pi\epsilon_0\epsilon_{\Omega}} \left( \frac{1}{R_1} + \frac{\epsilon_{\Omega} - \epsilon_{\Sigma}}{\epsilon_{\Omega} + \epsilon_{\Sigma}} \frac{1}{R_2} \right). \quad (18)$$

In the nonlocal case, the equations for  $\psi$  have the same form as those for  $\phi$  in the local case, so we assume the solutions to be similar. The normal boundary condition then remains unchanged while the tangential boundary condition leads to

$$\partial_{\varrho}\phi_{\Sigma} = \frac{1}{4\pi\epsilon_0\epsilon_{\Omega}} \frac{(q + q')}{[\varrho^2 + d^2]^{3/2}} \varrho \quad (19)$$

at  $z = 0$ . This equation can be readily integrated along  $\varrho$  and determines the potential at the dielectric boundary. For  $\varrho, z \rightarrow \infty$ , on the other hand,  $\phi_{\Sigma}$  must vanish. These two conditions then allow to compute the potential  $\phi_{\Sigma}$  from Eq. (15) within  $\Sigma$ , which needs to be done numerically. Here, we only give the lowest order effect nonlocality within  $\Sigma$  has on  $\Omega$ . For  $\varrho \ll \sqrt{2}d$ , the electrostatic potential inside  $\Omega$  has the same form as in the local theory, but with a “renormalized” bulk value of the dielectric function  $\epsilon_{\Sigma} = \epsilon_{\Sigma, \text{loc}} - 2\epsilon_{\ell}(\lambda^2/d^2)$ . Transverse variations of the permittivity in the nonlocal medium thus induce a change of the local permittivity proportional to  $(\lambda/d)^2$  in the vicinity of the boundary, an effect which vanishes for  $\lambda \rightarrow 0$ , and for deeply buried charges,  $d \rightarrow \infty$ .

The nonlocal theory of electrostatics can also be applied when mobile charges are present in  $\Sigma$ , described by Poisson-Boltzmann theory within local electrostatics. Within the nonlocal theory, the Boltzmann distribution of the charges simply modifies the rhs of Eq. (8), and allows one to explain experimental results of atomic-force microscopy measurements on force-deflection curves at charged mica substrates in water and solutions of monovalent ions, with  $\lambda$  values on the order of 10 nm [22].

To conclude, we have presented a novel formulation of nonlocal electrostatics including the effects of spatial dispersion in the dielectric permittivity on surfaces em-

bedded in a solvent, by reformulating it in terms of a two-potential model. While the resulting equations still need to be solved numerically even for simple geometries, this can now be done by standard methods for partial differential equations. Because of the generality of Eq. (13), dielectric functions of greater complexity than the radially symmetric choice made here for illustration can be used, provided they can be related to known Green functions.

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- [1] B. Honig and A. Nicholls, *Science* **268**, 1144 (1995).
- [2] N. A. Baker, D. Sept, S. Joseph, M. J. Holst, and J. A. McCammon, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 10037 (2001).
- [3] T. Simonson, *Curr. Opin. Struct. Biol.* **11**, 243 (2001).
- [4] V. Ballenegger and J.-P. Hansen, *Europhys. Lett.* **63**, 381 (2003).
- [5] G. R. Smith and M. J. E. Sternberg, *Curr. Opin. Struct. Biol.* **12**, 1 (2002).
- [6] A. A. Kornyshev, A. I. Rubinstein, and M. A. Vorotyntsev, *J. Phys. C* **11**, 3307 (1978).
- [7] M. A. Vorotyntsev, *J. Phys. C* **11**, 3323 (1978).
- [8] A. A. Kornyshev and M. A. Vorotyntsev, *J. Phys. C* **12**, 4939 (1979).
- [9] A. A. Kornyshev, in *The Chemical Physics of Solvation* (Elsevier, Amsterdam, 1985), pp. 77ff.
- [10] V. G. Levadny, M. L. Belaya, D. A. Pink, and M. H. Jericho, *Biophys. J.* **70**, 1745 (1996).
- [11] D. A. Cherepanov, B. A. Feniouk, W. Junge, and A. Mulikidjanian, *Biophys. J.* **85**, 1307 (2003).
- [12] M. V. Basilevsky and D. F. Parsons, *J. Chem. Phys.* **105**, 3734 (1996).
- [13] G. Arfken, in *Mathematical Methods for Physicists* (Academic Press, Orlando, FL, 1985), 3rd ed., pp. 78–84.
- [14] U. Ritschel, L. Wilets, J. J. Rehr, and M. Grabiak, *J. Phys. G* **18**, 1889 (1992).
- [15] P. Attard, D. Wei, and G. N. Patey, *Chem. Phys. Lett.* **172**, 69 (1990).
- [16] P. A. Bopp, A. A. Kornyshev, and G. Sutmann, *Phys. Rev. Lett.* **76**, 1280 (1996).
- [17] Y. Marcus, *Ion Solvation* (Wiley, New York, 1985).
- [18] J. Åqvist, *J. Phys. Chem.* **94**, 8021 (1990).
- [19] R. D. Shannon and C. T. Prewitt, *Acta Crystallogr. Sect. B* **25**, 925 (1969).
- [20] R. D. Shannon, *Acta Crystallogr.* **32**, 751 (1976).
- [21] A. Hildebrandt *et al.*, <http://www.arxiv.org/pdf/physics/0212074> (2002).
- [22] O. Teschke, G. Ceotto, and E. F. de Souza, *Phys. Rev. E* **64**, 011605 (2001); R. Blossy (unpublished).