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Yukawa-Field Approximation of Electrostatic Free Energy and Dielectric Boundary Force

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Abstract

A Yukawa-field approximation of the electrostatic free energy of a molecular solvation system with an implicit or continuum solvent is constructed. It is argued through the analysis of model molecular systems with spherically symmetric geometries that such an approximation is rational. The construction extends non-trivially that of the Coulomb-field approximation which serves as a basis of the widely used generalized Born model of molecular electrostatics. The electrostatic free energy determines the dielectric boundary force that in turn influences crucially the molecular conformation, stability, and dynamics. An explicit formula of such forces with the Yukawa-field approximation is obtained using local coordinates and shape differentiation.

Keywords

Molecular solvation; electrostatic free energy; Yukawa-field approximation; shape derivative

1 Introduction

Implicit-solvent (or continuum-solvent) modeling is an efficient and widely used approach to the biomolecular solvation [8, 15, 20, 34, 39]. In such a model, the solvent molecules and ions are treated implicitly and their effects are coarse grained. Most of the existing implicit-solvent models are based on various kinds of fixed solute-solvent interfaces, such as the van der Waals surface, solvent-excluded surface, or solvent-accessible surface [13, 14, 27, 32, 33]. Such a predefined interface is used to compute the solvation free energy as the sum of two separate parts. One is the surface energy, proportional to the area of interface. The other is the electrostatic contribution determined by the Poisson–Boltzmann (PB) [1,6,7,16,21–24, 28, 29, 36, 41] or generalized Born (GB) [2, 3, 38] approach in which the solute-solvent interface is used as the dielectric boundary.

In recent years, a new class of implicit-solvent models, termed variational implicit-solvent models (VISM), have emerged [18,19]. Coupled with the robust level-set numerical method, such models allow an efficient and quantitative description of molecular solvation [9,10,12]. Central in the VISM is a free-energy functional of all possible solute-solvent interfaces, or dielectric boundaries, that separate the continuum solvent from all solute atoms. In a simple setting, such a free-energy functional consists of surface energy, solute-solvent van der Waals interaction energy, and continuum electrostatic free energy, all depending solely on a

given solute-solvent interface. Minimizing the functional determines the solvation free energy and stable equilibrium solute-solvent interfaces. Initial applications of the level-set VISM to nonpolar molecular systems have demonstrated its success in capturing the hydrophobic interaction, multiple equilibrium states of hydration, and fluctuation between such states [9, 11, 12, 35, 40], all of which are difficult to be captured by a fixed-surface implicit-solvent model.

The present work concerns the electrostatic free energy, more precisely the electrostatic part of solvation free energy, and the resulting dielectric boundary force in the framework of VISM for charged molecules. Our approach is quite uncommon: instead of solving the PB equation or linearized PB equation—the Debye–Hückel equation [30], we use the Yukawa potential to construct an approximation of the electrostatic free energy. The Yukawa potential is the fundamental solution of the Debye–Hückel equation with a uniform dielectric coefficient [31]. It decays as $e^{-\kappa r}/r$ as the distance r to the solute charges becomes large, where κ is the inverse Debye screening length.

Our approximations are made in two steps. Consider a charged solute molecule that carries atomic charges Q_i at x_i ($i = 1, \dots, N$) in the solute region Ω_- separated by a solute-solvent interface Γ from the solvent region Ω_+ . Our first step is to approximate the electric displacement by that corresponds to the Coulomb-field

$$\sum_{i=1}^N \frac{Q_i (x - x_i)}{4\pi |x - x_i|^3} \quad (1.1)$$

for any spatial point $x \in \Omega_-$ and by

$$\sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i (x - x_i)}{|x - x_i|^3}$$

for any $x \in \Omega_+$. The functions $f_i(\cdot, \kappa, \Gamma)$ ($i = 1, \dots, N$) are constructed to satisfy some basic requirements. They include, for example, the recovery of the known Coulomb-field approximation in the case of $\kappa = 0$, the proper decay at the infinity, and the exactness for model systems with special geometries. Through the analysis of some model systems, we propose a formula of the functions $f_i(x, \kappa, \Gamma)$, cf. (3.5). Our second step is to approximate the electrostatic free energy using the approximated electric displacement. The result is an integral over the solvent region Ω_+ , cf. (3.2). The dielectric coefficient ϵ , which equals one constant ϵ_- in the solute region Ω_- and another ϵ_+ in the solvent region Ω_+ , relates the electric field and electric displacement, and hence appears in our final form of the approximate electrostatic free energy.

The Coulomb-field approximation, i.e., the approximation of electric displacement by (1.1), provides a means of computing generalized Born radii in the GB model that has been widely used for biomolecular systems [3, 38]. In our recent work [40], we use the Coulomb-field approximation to construct the electrostatic free energy

$$\frac{1}{32\pi^2 \epsilon_0} \left(\frac{1}{\epsilon_+} - \frac{1}{\epsilon_-} \right) \int_{\Omega_+} \left| \sum_{i=1}^N \frac{Q_i (x - x_i)}{|x - x_i|^3} \right|^2 dV, \quad (1.2)$$

where ϵ_0 is the vacuum permittivity, and incorporate it into the level-set VISM. Notice that we do not compute generalized Born radii, and hence introduce no additional parameters. Instead we evaluate the integral in (1.2) that is over an arbitrarily shaped domain Ω_+ to

calculate the approximate electrostatic free energy. The Yukawa-field approximation that we construct here is one step forward. It describes the additional effect from the mobile charges with the same kind of efficiency of the Coulomb-field approximation. Both of these approximations are clearly very attractive due to their high efficiency that is largely demanded in biomolecular modeling. In the meantime, these approximations are very accurate in many cases for large molecular systems, since they capture well the long-range behavior that characterizes the electrostatic interaction.

To see the heuristics behind the Yukawa-field approximation, particularly how the functions $f_{\lambda}(x, \kappa, \Gamma)$ are constructed, we consider two simple model systems with spherical symmetry. The first one is a spherical solute molecule with only one charged atom in the center. This system is the same in geometry as that studied by Born in [4] except we include here the ionic charge effect. The second one is a concentric sphere-ring solute with a single charge placed at the center of sphere. For both of these two systems, we solve analytically the boundary-value problem of the Debye–Hückel equation (2.5) to get the corresponding electrostatic potentials. For the second one, we also carry out an asymptotic analysis with respect to the asymptotics $\kappa \ll 1$ and $\epsilon_-/\epsilon_+ \ll 1$.

We study next the normal component of the dielectric boundary force that is defined as the negative variational derivative of the electrostatic free energy with respect to the location change of the dielectric boundary Γ . Such a boundary force is crucial in determining the conformation, stability, and dynamics of the solute molecules. It is exactly the electrostatic part of the “normal velocity” in the level-set method for numerically relaxing the free energy functional in VISM. We define and derive the variational derivative of the free energy using two methods. One is the method of local coordinates. After the boundary variation is defined clearly, the calculations using this method are straight forward. The other is the method of shape differentiation. It begins with a systematic definition of boundary variation. The derivation of the shape derivative formula is a bit more involved. But it is connected to the level-set representation of the boundary. Such a connection will be useful in our future level-set numerical calculations. The final result of our calculations is summarized in Proposition 3.1.

The rest of the paper is organized as follows: In Section 2, we describe the mathematical setting of molecular solvation with an implicit solvent, and the electrostatics part of the solvation free energy. In Section 3, we present our formulas of the Yukawa-field approximation of the electrostatic free energy and the related dielectric boundary force. In Section 4 we study two model systems with spherical symmetry. In Sections 5 and 6, we use the method of local coordinates and shape differentiation, respectively, to derive the formula of dielectric boundary force.

2 Electrostatic Free Energy

We consider the electrostatics of a molecular solvation system in the framework of the continuum-solvent description. We denote by Γ a solute-solvent interface or the dielectric boundary that separates the solute molecular region Ω_- and the implicit or continuum solvent region Ω_+ , cf. Figure 1, where n denotes the unit normal of the interface Γ pointing from Ω_- to Ω_+ . We assume that $\Omega_- \subset \mathbb{R}^3$ is a smooth, bounded, and open set, with possibly multiple connected components, $\Gamma = \partial\Omega_-$ is the boundary of Ω_- , and $\Omega_+ = \mathbb{R}^3 \setminus \overline{\Omega_-}$, where an over-line denotes the closure. We assume that there are N atoms of the solute molecules located at $x_1, \dots, x_N$ in Ω_- and carrying point charges $Q_1, \dots, Q_N$, respectively. We denote by ϵ_- and ϵ_+ the dielectric constants (relative permittivities) of the solute region and the solvent region, respectively.

By the Born cycle [4], the electrostatic component of the solvation free energy ΔG of our underlying solvation system is defined to be $\Delta G = G_2 - G_1$, where G_1 is the electrostatic free energy of a reference state and G_2 that of the solvated state. By definition,

$$G_i = \int_{\mathbb{R}^3} \frac{1}{2} D_i \cdot E_i dV, \quad i=1, 2, \quad (2.1)$$

where E_i and D_i are the electric field and electrostatic displacement of the i th state, respectively, and dV is the volume element of $\mathbb{R}^3$.

A natural choice of the reference state is the underlying charged solute molecules placed in the entire space with the uniform dielectric constant ε_- . The corresponding electrostatic potential ψ_1 is

$$\psi_1(x) = \sum_{i=1}^N \frac{Q_i}{4\pi\varepsilon_- \varepsilon_0 |x - x_i|} \quad \forall x \in \mathbb{R}^3 \setminus \{x_1, \dots, x_N\}, \quad (2.2)$$

where ε_0 is the vacuum permittivity. It is the unique solution of the boundary-value problem of the Poisson equation

$$\begin{cases} \varepsilon_- \varepsilon_0 \Delta \psi_1 = - \sum_{i=1}^N Q_i \delta_{x_i} & \text{in } \mathbb{R}^3, \\ \psi_1(\infty) = 0, \end{cases}$$

where δ_{x_i} denotes the Dirac delta function concentrated at x_i . The corresponding electric field E_1 and electric displacement D_1 are

$$E_1(x) = -\nabla \psi_1(x) = \sum_{i=1}^N \frac{Q_i(x - x_i)}{4\pi\varepsilon_- \varepsilon_0 |x - x_i|^3}, \quad (2.3)$$

$$D_1(x) = \varepsilon_- \varepsilon_0 E_1(x) = \sum_{i=1}^N \frac{Q_i(x - x_i)}{4\pi |x - x_i|^3}. \quad (2.4)$$

In the solvated state, the solute molecules are immersed in the solvent, creating the solute-solvent interface or the dielectric boundary Γ , resulting a large jump of the dielectric coefficient from the solute molecular region to the solvent region, cf. Figure 1. The corresponding electrostatic potential ψ_2 is the unique solution of a boundary-value problem of the Poisson–Boltzmann equation. In many cases, particularly when ionic concentrations are low, the linearized Poisson–Boltzmann equation, or the Debye–Hückel equation, is a good approximation. Therefore, we assume that the electrostatic potential ψ_2 is the unique solution of the boundary-value problem of the Debye–Hückel equation

$$\begin{cases} \nabla \cdot \varepsilon \varepsilon_0 \nabla \psi_2 - \chi_+ \varepsilon_+ \varepsilon_0 \kappa^2 \psi_2 = - \sum_{i=1}^N Q_i \delta_{x_i} & \text{in } \mathbb{R}^3, \\ \psi_2(\infty) = 0. \end{cases} \quad (2.5)$$

Here ε is the variable dielectric coefficient of the entire solvation region defined by

$$\varepsilon(x) = \begin{cases} \varepsilon_- & \text{if } x \in \Omega_-, \\ \varepsilon_+ & \text{if } x \in \Omega_+, \end{cases}$$

χ_+ is the characteristic function of the solvent region Ω_+ (i.e., $\chi_+(x) = 1$ if $x \in \Omega_+$ and 0 otherwise), and $\kappa > 0$ is the inverse Debye screening length, defined by

$$\kappa^2 = \frac{1}{\varepsilon_+ \varepsilon_0 k_B T} \sum_{j=1}^M c_j^\infty q_j^2,$$

where k_B is the Boltzmann constant, T is the temperature, and c_j^∞ and q_j are the bulk concentration and charge of the j th ionic species of which a total of M is assumed. Since the boundary Γ can be arbitrarily shaped, there is in general no analytical formula of the solution ψ_2 . But the corresponding electric field E_2 and electrostatic displacement D_2 can be still defined as usual by

$$E_2 = -\nabla\psi_2 \quad \text{and} \quad D_2 = \varepsilon\varepsilon_0 E_2, \quad (2.6)$$

respectively.

Notice that both ψ_1 and ψ_2 have singularities at points of charges $x_1, \dots, x_N$. Therefore the integrals in the definition of electrostatic energy (2.1) should be understood as those over the entire space $\mathbb{R}^3$ minus balls centered at $x_1, \dots, x_N$ with a very small cut-off radius.

Alternatively, they should be understood as there are no self-interaction energy terms [25]. For instance, in the reference state, these terms are

$$\int_{\mathbb{R}^3} \frac{Q_i^2}{16\pi^2 |x - x_i|^4} dV, \quad i=1, \dots, N.$$

3 The Yukawa-Field Approximation

Let the solute molecular region Ω_- , the solvent region Ω_+ , the solute-solvent interface or the dielectric boundary Γ , and the positions $x_1, \dots, x_N \in \Omega_-$ and point charges $Q_1, \dots, Q_N$ of the solute atoms be given as above, cf. Figure 1. Let D_1 be the electric displacement of the reference state as given in (2.4). Let D_2 be the electric displacement of the solvated state as given in (2.6), where ψ_2 is the electrostatic potential that solves the boundary-value problem of the Debye-Hückel equation (2.5). We define a Yukawa-field approximation of D_2 to be

$$\tilde{D}_2(x) = \begin{cases} D_1(x) = \sum_{i=1}^N \frac{Q_i(x-x_i)}{4\pi|x-x_i|^3} & \text{if } x \in \Omega_- \setminus \{x_1, \dots, x_N\}, \\ \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x-x_i)}{4\pi|x-x_i|^3} & \text{if } x \in \Omega_+, \end{cases} \quad (3.1)$$

where each $f_i(\cdot, \kappa, \Gamma)$ depends only on x_i , κ , and Γ . We define $\tilde{E}^2$ to be the approximate electric field corresponding to $\tilde{D}_2$, i.e., $\tilde{D}_2 = \varepsilon\varepsilon_0 \tilde{E}_2$ cf. (2.6).

With this approximation, the electrostatic free energy becomes

$$\begin{aligned}
\Delta G &= G_2 - G_1 \\
&\approx \frac{1}{2} \int_{\mathbb{R}^3} \tilde{D}_2 \cdot \tilde{E}_2 dV - \frac{1}{2} \int_{\mathbb{R}^3} D_1 \cdot E_1 dV \\
&= \frac{1}{2} \int_{\mathbb{R}^3} \frac{1}{\varepsilon \varepsilon_0} |\tilde{D}_2|^2 dV - \frac{1}{2} \int_{\mathbb{R}^3} \frac{1}{\varepsilon_- \varepsilon_0} |D_1|^2 dV \\
&= \frac{1}{2} \int_{\Omega_-} \frac{1}{\varepsilon_- \varepsilon_0} |\tilde{D}_2|^2 dV + \frac{1}{2} \int_{\Omega_+} \frac{1}{\varepsilon_+ \varepsilon_0} |\tilde{D}_2|^2 dV \\
&\quad - \frac{1}{2} \int_{\Omega_-} \frac{1}{\varepsilon_- \varepsilon_0} |D_1|^2 dV - \frac{1}{2} \int_{\Omega_+} \frac{1}{\varepsilon_+ \varepsilon_0} |D_1|^2 dV \\
&= \frac{1}{2} \int_{\Omega_+} \frac{1}{\varepsilon_+ \varepsilon_0} \left| \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x-x_i)}{4\pi|x-x_i|^3} \right|^2 dV - \frac{1}{2} \int_{\Omega_+} \frac{1}{\varepsilon_- \varepsilon_0} \left| \sum_{i=1}^N \frac{Q_i(x-x_i)}{4\pi|x-x_i|^3} \right|^2 dV \\
&= \frac{1}{32\pi^2 \varepsilon_0} \int_{\Omega_+} \left[\frac{1}{\varepsilon_+} \left| \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 - \frac{1}{\varepsilon_-} \left| \sum_{i=1}^N \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 \right] dV.
\end{aligned}$$

Therefore we define the Yukawa-field approximation of the electrostatic free energy to be

$$\Delta G[\Gamma] = \frac{1}{32\pi^2 \varepsilon_0} \int_{\Omega_+} \left[\frac{1}{\varepsilon_+} \left| \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 - \frac{1}{\varepsilon_-} \left| \sum_{i=1}^N \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 \right] dV. \quad (3.2)$$

Here we use the same symbol ΔG to denote this approximation. We also indicate its dependence on Γ for the given set of data x_i and Q_i ($i = 1, \dots, N$), ε_- and ε_+ , and κ .

We require that the functions $f_i(\cdot, \kappa, \Gamma) : \Omega_+ \rightarrow \mathbb{R}$ satisfy the following conditions:

1. If $\kappa = 0$ then all $f_i(\cdot, \kappa, \Gamma) = 1$ identically in Ω_+ . This means that the Yukawa-field approximation (3.2) recovers the Coulomb-field approximation (1.2);
2. Each $f_i(x, \kappa, \Gamma) Q_i(x-x_i)/|x-x_i|^3$ decays as $e^{-\kappa r}/r$ as $r = |x| \rightarrow \infty$;
3. The approximation formula (3.2) becomes exact for a spherical solute with a single charge at the center of sphere.

We now construct the functions $f_i(x, \kappa, \Gamma)$ ($i = 1, \dots, N$). The ideas behind our constructions can be seen from our analysis of two model systems with spherical symmetry that we present in the next section. Fix an arbitrary index i with $1 \leq i \leq N$. Fix an arbitrary point $x \in \Omega_+$. Denote by $[x_i, x]$ the line segment connecting x_i and x , i.e.,

$$[x_i, x] = \{x_i + s(x - x_i) : 0 \leq s \leq 1\}.$$

See Figure 2. Define

$$l_i^+(x) = |[x_i, x] \cap \Omega_+| \quad \text{and} \quad l_i^-(x) = |[x_i, x] \cap \Omega_-|, \quad (3.3)$$

where $|S|$ denotes the one-dimensional Lebesgue measure along the line $[x_i, x]$. Note that $l_i^+(x)$ and $l_i^-(x)$ are the total lengths of line segments $[x_i, x]$ in Ω_+ and that in Ω_- , respectively. We assume that

$$l_i^+(x) + l_i^-(x) = |x - x_i| \quad \forall x \in \Omega_+, \quad \forall i = 1, \dots, N. \quad (3.4)$$

This way, we have defined for each i two smooth functions $l_i^+ : \Omega_+ \rightarrow \mathbb{R}$ and $l_i^- : \Omega_+ \rightarrow \mathbb{R}$. Notice that our assumption (3.4) can be relaxed. For instance, since our electrostatic free energy (3.2) is an integral over Ω_+ , we need only assume that the three-dimensional

Lebesgue measure of the set $\{x \in \Omega_+ : l_i^+(x) + l_i^-(x) < |x - x_i|\}$ is zero for all $i = 1, \dots, N$. Finally, we define $f_i(\cdot, \kappa, \Gamma) : \Omega_+ \rightarrow \mathbb{R}$ by

$$f_i(x, \kappa, \Gamma) = \frac{1 + \kappa|x - x_i|}{1 + \kappa l_i^-(x)} e^{-\kappa l_i^+(x)}. \quad (3.5)$$

Clearly, these functions satisfy the conditions (1) and (2) above. We shall see in the next section that they also satisfy the condition (3).

We now present our formula of variational derivative $\delta_\Gamma \Delta G[\Gamma]$. Note that the dielectric boundary force is $-\delta_\Gamma \Delta G[\Gamma]$. For each $i \in \{1, \dots, N\}$ and each $x \in \Omega_+$, we denote by $L_i^+(x)$ the intersection of Ω_+ and the half line starting from x in the direction from x_i to x , i.e.,

$$L_i^+(x) = \{x_i + s(x - x_i) : 1 \leq s < \infty\} \cap \Omega_+. \quad (3.6)$$

Proposition 3.1

The variation of ΔG with respect to Γ is a function $\delta_\Gamma \Delta G[\Gamma] : \Gamma \rightarrow \mathbb{R}$, and is given by

$$\begin{aligned} \delta_\Gamma \Delta G[\Gamma](x) = & -\frac{1}{32\pi^2 \varepsilon_0} \left[\frac{1}{\varepsilon_+} \left| \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x - x_i)}{|x - x_i|^3} \right|^2 - \frac{1}{\varepsilon_-} \left| \sum_{i=1}^N \frac{Q_i(x - x_i)}{|x - x_i|^3} \right|^2 \right] \\ & - \frac{1}{32\pi^2 \varepsilon_0 \varepsilon_+} \sum_{i=1}^N \frac{1}{|x - x_i|^2} \int_{L_i^+(x)} |y - x_i|^2 F_i(y) dy \quad \forall x \in \Gamma, \end{aligned} \quad (3.7)$$

where dl denotes the line element and where for each $i \in \{1, \dots, N\}$

$$F_i(y) = -\frac{2\kappa^2 l_i^-(y)}{1 + \kappa l_i^-(y)} f_i(y, \kappa, \Gamma) \frac{Q_i(y - x_i)}{|y - x_i|^3} \cdot \sum_{j=1}^N f_j(y, \kappa, \Gamma) \frac{Q_j(y - x_j)}{|y - x_j|^3} \quad \forall y \in \Omega_+. \quad (3.8)$$

Notice from (3.4) and (3.5) that

$$f_i(x, \kappa, \Gamma) = \frac{1 + \kappa|x - x_i|}{1 + \kappa[|x - x_i| - l_i^+(x)]} e^{-\kappa l_i^+(x)}.$$

Therefore, if we define $F : (\mathbb{R}^3 \setminus \{x_1, \dots, x_N\}) \times \mathbb{R}_+^N \rightarrow \mathbb{R}$, where $\mathbb{R}_+$ is the set of all nonnegative real numbers, by

$$F(u, \alpha_1, \dots, \alpha_N) = \left| \sum_{i=1}^N \frac{(1 + \kappa|u - x_i|) e^{-\kappa \alpha_i}}{1 + \kappa(|u - x_i| - \alpha_i)} \frac{Q_i(u - x_i)}{|u - x_i|^3} \right|^2, \quad (3.9)$$

then the electrostatic free energy $\Delta G[\Gamma]$ is exactly (cf. (3.2))

$$\Delta G[\Gamma] = \frac{1}{32\pi^2 \varepsilon_0} \int_{\Omega_+} \left[\frac{1}{\varepsilon_+} F(x, l_1^+(x), \dots, l_N^+(x)) - \frac{1}{\varepsilon_-} \left| \sum_{i=1}^N \frac{Q_i(x - x_i)}{|x - x_i|^3} \right|^2 \right] dV.$$

Moreover, one verifies that the functions $F_i(x)$ in (3.8) are given by

$$F_i(x) = \partial_{\alpha_i} F(x, I_1^+(x), \dots, I_N^+(x)) \quad \forall x \in \Omega_+ \forall i=1, \dots, N. \quad (3.10)$$

Proposition 3.1 is proved using two different methods in Section 5 and Section 6, respectively. The precise definition of the variation with respect to Γ is also given in the proof.

4 Two Model Systems

4.1 A Spherical Solute

We consider two model systems with spherically symmetric geometry. The first system consists of a single point charge Q at the center of a spherical solute of radius R . Let the center be the origin. Then corresponding to our previous set up, we have now $N=1$, $x_1=0$, $Q_1=Q$, and

$$\Omega_- = \{x \in \mathbb{R}^3 : |x| < R\}, \quad \Omega_+ = \{x \in \mathbb{R}^3 : |x| > R\}, \quad \Gamma = \{x \in \mathbb{R}^3 : |x| = R\}.$$

In this case the solution to the boundary-value problem of Debye–Hückel equation (2.5) is

$$\psi_2(x) = \begin{cases} \frac{Q}{4\pi\epsilon_+\epsilon_0 R(1+\kappa R)} + \frac{Q}{4\pi\epsilon_-\epsilon_0} \left(\frac{1}{|x|} - \frac{1}{R} \right) & \text{if } |x| < R, \\ \frac{Q}{4\pi\epsilon_+\epsilon_0(1+\kappa R)} \frac{e^{-\kappa(|x|-R)}}{|x|} & \text{if } |x| > R. \end{cases}$$

The corresponding electric displacement is

$$D_2(x) = \begin{cases} \frac{Qx}{4\pi|x|^3} & \text{if } |x| < R, \\ \frac{1+\kappa|x|}{1+\kappa R} e^{-\kappa(|x|-R)} \frac{Qx}{4\pi|x|^3} & \text{if } |x| > R. \end{cases}$$

Clearly, in this case, the Yukawa-field approximation (3.1) with $f_1(x, \kappa, \Gamma)$ defined in (3.5) is exact, i.e., the condition (3) stated in the previous section is satisfied.

4.2 A Model Sphere-Ring Solute

The second model system consists of a point charge Q at the origin with solute molecular region Ω_- and solvent region Ω_+ given by

$$\Omega_- = \{x \in \mathbb{R}^3 : |x| < R_1 \text{ or } R_2 < |x| < R_3\}, \quad (4.1)$$

$$\Omega_+ = \{x \in \mathbb{R}^3 : R_1 < |x| < R_2 \text{ or } |x| > R_3\}, \quad (4.2)$$

respectively, for some constants R_1, R_2, R_3 with $0 < R_1 < R_2 < R_3$. See Figure 3.

With this geometry, the electrostatic potential $\psi = \psi_2$ is radially symmetric: $\psi = \psi(r)$ with $r = |x|$. (For convenience we write ψ instead of ψ_2 in the rest of this section.) It is defined to be the solution to the boundary-value problem of the Debye–Hückel equation (2.5). This is equivalent to the elliptic interface problem

$$\begin{cases} \varepsilon_- \varepsilon_0 \Delta \psi = -Q\delta & \text{if } r < R_1 \\ \Delta \psi - \kappa^2 \psi = 0 & \text{if } R_1 < r < R_2, \\ \Delta \psi = 0 & \text{if } R_2 < r < R_3, \\ \Delta \psi - \kappa^2 \psi = 0 & \text{if } r > R_3, \\ [[\psi(r)]] = 0 & \text{at } r = R_1, R_2, R_3, \\ [[\varepsilon \varepsilon_0 \psi'(r)]] = 0 & \text{at } r = R_1, R_2, R_3, \\ \psi(\infty) = 0, \end{cases} \quad (4.3)$$

where δ is the Dirac delta function concentrated at the origin and $[[u(r)]] = u(r^+) - u(r^-)$ for any function u that has both left and right limits at r .

Since $\psi = \psi(r)$ is radially symmetric, the equation $\Delta \psi = 0$ is an ordinary differential equation and has two linearly independent solutions 1 and $1/r$. Similarly, the equation $\Delta \psi - \kappa^2 \psi = 0$ is also an ordinary differential equation and has two linearly independent solutions $e^{-\kappa r}/r$ and $e^{\kappa r}/r$. Therefore, from the first four equations and the boundary condition $\psi(\infty) = 0$ in (4.3), we obtain

$$\psi(r) = \begin{cases} C_1 + \frac{Q}{4\pi\varepsilon_- \varepsilon_0 r} & \text{if } r < R_1, \\ \frac{C_2}{r} e^{-\kappa r} + \frac{C_3}{r} e^{\kappa r} & \text{if } R_1 < r < R_2, \\ C_4 + \frac{C_5}{r} & \text{if } R_2 < r < R_3, \\ \frac{C_6}{r} e^{-\kappa r} & \text{if } r > R_3, \end{cases} \quad (4.4)$$

where all C_i ($i = 1, \dots, 6$) are constants. By the fifth and sixth equations in (4.3), we obtain with some calculations that

$$\begin{cases} R_1 C_1 - e^{-\kappa R_1} C_2 - e^{\kappa R_1} C_3 = \frac{Q}{4\pi\varepsilon_- \varepsilon_0}, \\ e^{-\kappa R_1} (1 + \kappa R_1) C_2 + e^{\kappa R_1} (1 - \kappa R_1) C_3 = \frac{Q}{4\pi\varepsilon_+ \varepsilon_0}, \\ e^{-\kappa R_2} C_2 + e^{\kappa R_2} C_3 - R_2 C_4 - C_5 = 0, \\ e^{-\kappa R_2} (1 + \kappa R_2) C_2 + e^{\kappa R_2} (1 - \kappa R_2) C_3 - \frac{\varepsilon_-}{\varepsilon_+} C_5 = 0, \\ R_3 C_4 + C_5 - e^{-\kappa R_3} C_6 = 0, \\ \frac{\varepsilon_-}{\varepsilon_+} C_5 - e^{-\kappa R_3} (1 + \kappa R_3) C_6 = 0. \end{cases}$$

This system of linear equations of $C_1, \dots, C_6$ can be solved. Since we are only interested in the corresponding electric displacement, the values of C_1 and C_4 are not needed. After a series of calculations we obtain the other constants

$$\begin{cases} C_2 = \frac{Q}{4\pi\varepsilon_+ \varepsilon_0} \frac{e^{\kappa R_2} [R_3 - \alpha(1 - \kappa R_2)]}{A}, \\ C_3 = -\frac{Q}{4\pi\varepsilon_+ \varepsilon_0} \frac{e^{-\kappa R_2} [R_3 - \alpha(1 + \kappa R_2)]}{A}, \\ C_5 = \frac{Q \kappa R_2 R_3}{2\pi\varepsilon_- \varepsilon_0 A}, \\ C_6 = \frac{Q}{4\pi\varepsilon_+ \varepsilon_0} \frac{2\kappa R_2 R_3 e^{\kappa R_3}}{(1 + \kappa R_3)A}, \end{cases} \quad (4.5)$$

where

$$\alpha = \frac{R_2}{1 + \kappa R_3} + \frac{\varepsilon_+}{\varepsilon_-} (R_3 - R_2), \quad (4.6)$$

$$A = e^{\kappa(R_2 - R_1)} (1 + \kappa R_1) [R_3 - \alpha(1 - \kappa R_2)] - e^{-\kappa(R_2 - R_1)} (1 - \kappa R_1) [R_3 - \alpha(1 + \kappa R_2)]. \quad (4.7)$$

We now calculate the approximation of the electric displacement $D = -\epsilon\epsilon_0\nabla\psi$. This is the same as D_2 defined in (2.6). Consider first the solute molecular region Ω_- defined by $r < R_1$ and $R_2 < r < R_3$. It is clear from (4.4) that $D(x) = D_1(x)$ if $r = |x| < R_1$, where D_1 is given in (2.4). By Taylor's expansion and a series of calculations, we obtain from (4.7) that

$$A = 2\kappa R_2 R_3 e^{\kappa(R_2 - R_1)} + O(\kappa^2) \quad \text{as } \kappa \rightarrow 0. \quad (4.8)$$

This and (4.5) lead to

$$C_5 = \frac{Q}{4\pi\epsilon_- \epsilon_0} e^{-\kappa(R_2 - R_1)} + O(\kappa^2) = \frac{Q}{4\pi\epsilon_- \epsilon_0} + O(\kappa) \quad \text{as } \kappa \rightarrow 0.$$

Therefore we also get from (4.4) that $D(x) \approx D_1(x)$ if $R_2 < r < R_3$. Hence D_1 is a good approximation of D_2 in the solute molecular region Ω_- in this case. This is the reason to have the Yukawa-field approximation (3.1) in Ω_- .

We now consider the solvent region Ω_+ defined by $R_1 < r < R_2$ and $r > R_3$. Notice that typically $\epsilon_+ \gg \epsilon_-$. Therefore

$$\frac{R_3 - \alpha(1 + \kappa R_2)}{R_3 - \alpha(1 - \kappa R_2)} \approx \frac{1 + \kappa R_2}{1 - \kappa R_2}.$$

Consequently we have by (4.5), (4.4), and a series of calculations that for $R_1 < r < R_2$

$$\psi(r) \approx \frac{Q}{4\pi\epsilon_+\epsilon_0 r} \frac{(1 - \kappa R_2)e^{-\kappa(r - R_1)} - (1 + \kappa R_2)e^{-\kappa(R_2 - r)}e^{-\kappa(R_2 - R_1)}}{(1 + \kappa R_1)(1 - \kappa R_2) - (1 - \kappa R_1)(1 + \kappa R_2)e^{-2\kappa(R_2 - R_1)}}.$$

If we only keep the leading term in the numerator and that in the denominator, and use (4.4), we get for $R_1 < r = |x| < R_2$ that

$$D_2(x) \approx \frac{Q(1 + \kappa|x|)e^{-\kappa(r - R_1)}}{4\pi(1 + \kappa R_1)|x|^3}x.$$

This is the same as the Yukawa-field approximation (3.1) with $f_l(x, \kappa, \Gamma)$ given in (3.5) with $N = 1$, $Q_l = Q$, and $x_l = 0$.

Now from (4.8) and (4.5) we obtain

$$C_6 = \frac{Qe^{\kappa(R_3 - R_2 + R_1)}}{4\pi\epsilon_+\epsilon_0(1 + \kappa R_3)} + O(\kappa^2).$$

This and (4.4) imply that for $r > R_3$

$$D_2(x) \approx \frac{Q(1 + \kappa|x|)e^{-\kappa(r - R_3 + R_2 - R_1)}}{4\pi(1 + \kappa R_1)|x|^3}x.$$

Notice that this is not quite the same as that in (3.1). But for the function $f_k(\cdot, \kappa, \Gamma)$ to be continuous we propose to replace R_1 for the current system by $R_3 - R_2 + R_1$. Therefore the modified electric displacement for $r > R_3$ is

$$D_2(x) \approx \frac{Q(1+\kappa|x|)e^{-\kappa(r-R_3+R_2-R_1)}}{4\pi(1+\kappa(R_3-R_2+R_1))|x|^3}x.$$

This is the same as that in (3.1) with $f_k(\cdot, \kappa, \Gamma)$ given in (3.5) with $N=1$, $Q_1=Q$, and $x_1=0$.

5 Variational Derivative with Local Coordinates

Let all $\Gamma, \Omega_-, \Omega_+, x_i \in \Omega_-$ and $Q_i \in \mathbb{R}$ ($i=1, \dots, N$), $\varepsilon_-, \varepsilon_+, \varepsilon_0$, and κ be all given as in Section 1 and Section 3, cf. Figure 1. We consider the derivative of the electrostatic free energy functional

$$\Delta G[\Gamma] = \int_{\Omega_+} H(x) dV$$

with respect to the variation of the boundary Γ , where $H(x) = H(x, \Gamma)$ is the free energy density—the integrand of the integral in (3.2)—defined on $\mathbb{R}^3 \setminus \{x_1, \dots, x_N\}$.

The variation of the boundary Γ is defined by a family of boundaries Γ_t parameterized by t small, that depend smoothly on the parameter t . These boundaries are small perturbations of the boundary $\Gamma_0 = \Gamma$, and are locally graphs of functions near a point of Γ of interest. The boundaries Γ_t can be viewed as moving surfaces starting from $\Gamma_0 = \Gamma$ and the parameter t is the time variable. Each point $x \in \Gamma$ moves to $x(t)$ at time t . We denote by $v(x)$ the normal velocity of Γ_t at $t=0$ at $x \in \Gamma$:

$$v(x) = \left. \frac{d}{dt} \right|_{t=0} x(t) \cdot n,$$

where n is the unit normal to Γ at x pointing from Ω_- to Ω_+ .

Each Γ_t divides the entire solvation region into the open sets Ω_-^t and Ω_+^t that are small perturbations of Ω_- and Ω_+ , respectively. In particular, all the points $x_1, \dots, x_N$ remain in Ω_-^t for all t . If we denote $H_t(x) = H(x, \Gamma_t)$ with $H_0(x) = H(x)$ then

$$\Delta G[\Gamma_t] = \int_{\Omega_+^t} H_t(x) dV.$$

The derivative, $\delta_\Gamma \Delta G[\Gamma]$, of the functional $\Delta G[\Gamma]$ with respect to the variation of Γ in the normal direction at Γ from Ω_- to Ω_+ is a function defined on Γ such that

$$\left. \frac{d}{dt} \right|_{t=0} \Delta G[\Gamma_t] = \left. \frac{d}{dt} \right|_{t=0} \int_{\Omega_+^t} H_t(x) dV = \int_\Gamma (\delta_\Gamma \Delta G[\Gamma])(x) v(x) dS,$$

where dS is the surface element of Γ .

In the rest of this section, we first derive a general expression of the derivative $\delta_\Gamma \Delta G[\Gamma]$. We then handle our free energy functional $\Delta G[\Gamma]$, proving the main formula (3.7) first for a

single solute atom ($N = 1$) and then for multiple solute atoms ($N > 1$). We remark that our results can be generalized to those for an ambient space $\mathbb{R}^d$ of any dimension $d \geq 3$.

5.1 A General Result

With the above setting, we claim that

$$\left. \frac{d}{dt} \right|_{t=0} \int_{\Omega_+^t} H_t(x) dV = - \int_{\Gamma} H(x) v(x) dS + \int_{\Omega_+} \left[\left. \frac{d}{dt} \right|_{t=0} H_t(x) \right] dV. \quad (5.1)$$

To prove this formula, we let $\{(U_i, \eta_i)_{i=0}^p\}$ for some $p \geq 1$ be a partition of unity of $\overline{\Omega_+}$. We assume the open sets $U_1, \dots, U_p$ are bounded and smooth (e.g., balls) whose union covers a neighborhood of Γ . The open set U_0 is also smooth but is unbounded, covering the complement of a neighborhood of Γ in Ω_+ . For each i ($0 \leq i \leq p$), $\eta_i \in C_c^\infty(\mathbb{R}^3)$ and $\text{supp}(\eta_i) \subset U_i$. We also assume that for each i with $1 \leq i \leq p$ all the surfaces $\Gamma \cap U_i$ are locally graphs. Now using the property of the partition of unity that $\sum_{i=0}^p \eta_i = 1$ we obtain

$$\left. \frac{d}{dt} \right|_{t=0} \int_{\Omega_+^t} H_t(x) dV = \sum_{i=0}^p \left. \frac{d}{dt} \right|_{t=0} \int_{U_i \cap \Omega_+^t} \eta_i(x) H_t(x) dV. \quad (5.2)$$

Since $U_0 \cap \Omega_+^t = U_0$ is independent of $t > 0$ and that $\text{supp}(\eta_0) \subset U_0$, we have

$$\left. \frac{d}{dt} \right|_{t=0} \int_{U_0 \cap \Omega_+^t} \eta_0(x) H_t(x) dV = \int_{U_0} \eta_0(x) \left[\left. \frac{d}{dt} \right|_{t=0} H_t(x) \right] dV. \quad (5.3)$$

Fix an index $i \in \{1, \dots, p\}$. Assume $\Gamma \cap U_i$ and $\Gamma_t \cap U_i$ are graphs of functions $z = u(y)$ and $z = u_t(y)$, respectively, in a local Cartesian coordinate system with $z \in \mathbb{R}$ and $y \in \mathbb{R}^2$. Assume also that

$$U_i \cap \Omega_+^t = \{x = (y, z) \in U_i : z \geq u_t(y)\}.$$

Extend the functions $u(y)$ and $u_t(y)$ continuously onto the entire $\mathbb{R}^2$. Since $\text{supp}(\eta_i) \subset U_i$, the integral of the function $\eta_i H_t$ over $U_i \cap \Omega_+^t$ is then the same as that over

$$\{x = (y, z) \in \mathbb{R} \times \mathbb{R}^2 : z \geq u_t(y)\}.$$

The normal velocity $v = v(x)$ at a point $x = (y, z) \in \Gamma \cap U_i$ is given by

$$v(x) = \frac{1}{\sqrt{1 + |\nabla u(y)|^2}} \left. \frac{d}{dt} \right|_{t=0} u_t(y).$$

The surface element dS of Γ and the surface element dA of $\mathbb{R}^2$ are related by

$$dS_y = \sqrt{1 + |\nabla u(y)|^2} dA_y.$$

Since $\text{supp}(\eta_i) \subset U_{\bar{b}}$ we have

$$\begin{aligned} \frac{d}{dt} \Big|_{t=0} \int_{U_i \cap \Omega_+^t} \eta_i(x) H_t(x) dV &= \frac{d}{dt} \Big|_{t=0} \int_{\mathbb{R}^2} \int_{u_t(y)}^{\infty} \eta_i(y, z) H_t(y, z) dz dA \\ &= - \int_{\mathbb{R}^2} \eta_i(y, u(y)) H_0(y, u(y)) \left[\frac{d}{dt} \Big|_{t=0} u_t(y) \right] dA \\ &\quad + \int_{\mathbb{R}^2} \int_{u_t(y)}^{\infty} \eta_i(y, z) \left[\frac{d}{dt} \Big|_{t=0} H_t(y, z) \right] dz dA \\ &= - \int_{\Gamma} \eta_i(x) H(x) v(x) dS + \int_{\Omega_+} \eta_i(x) \left[\frac{d}{dt} \Big|_{t=0} H_t(x) \right] dV. \end{aligned}$$

This, together with (5.2) and (5.3), implies (5.1).

5.2 Single Solute Atom

We now consider $H(x) = F(x, l_1^+(x), \dots, l_N^+(x))$, where F is defined in (3.9). The functions $l_i^+(x)$ ($i=1, \dots, N$) are defined in (3.3). In this subsection, we consider the case of a single solute atom, i.e., $N=1$. For convenience, we denote $x_0 = x_1 \in \Omega_-$ and $l^+(x) = l_1^+(x)$. We define $l^{+t}(x)$ similar to that of $l^+(x)$ but using Γ_t instead of Γ . By (5.1),

$$\frac{d}{dt} \Big|_{t=0} \int_{\Omega_+^t} F(x, l^{+t}(x)) dV = - \int_{\Gamma} F(x, l^+(x)) v(x) dS + \int_{\Omega_+} \left[\frac{d}{dt} \Big|_{t=0} F(x, l^{+t}(x)) \right] dV. \quad (5.4)$$

Consider the spherical coordinates (ρ, θ) based around x_0 with $\theta = (\theta_1, \theta_2) \in \mathcal{S}^2$. Assume the set of points x of Γ with normal vector orthogonal to the line through x_0 and x has measure zero. Then given $x \in \Gamma$ there exists a neighborhood of x in Γ such that for compactly supported normal velocities v in this neighborhood, Γ and Γ_t for small enough t can be parameterized in terms of spherical coordinates. This means that Γ and Γ_t are graphs of functions $\rho = u(\theta)$ and $\rho = u_t(\theta)$, respectively, for $\theta = (\theta_1, \theta_2) \in U$ for some open set $U \subset \mathcal{S}^2$. A consequence of this is that if $x = (\rho, \theta) \in \Omega_+$ with $\theta \notin U$ then

$$\frac{d}{dt} \Big|_{t=0} F(x, l^{+t}(x)) = 0.$$

Otherwise if $\theta \in U$ then

$$\frac{d}{dt} \Big|_{t=0} F((r, \theta), l^{+t}(r, \theta)) = \begin{cases} 0 & \text{for } r < u(\theta), \\ -F_1((r, \theta), l^+(r, \theta)) \frac{d}{dt} \Big|_{t=0} u_t(\theta) & \text{for } r \geq u(\theta), \end{cases} \quad (5.5)$$

where F_1 is the partial derivative of F with respect to the variable $\alpha_1 = l^+(x)$, cf. (3.10), and where we used the fact that

$$\frac{d}{dt} \Big|_{t=0} l^{+t}(r, \theta) = - \frac{d}{dt} \Big|_{t=0} u_t(\theta) \quad \text{for } r \geq u(\theta).$$

Further simplification can be made by noticing that the normal velocity of Γ_t at $t=0$ at $x = (r, \theta) \in \Gamma$ is

$$v(x) = \frac{1}{\sqrt{1 + \frac{|\nabla_\theta u(\theta)|^2}{(u(\theta))^2}}} \frac{d}{dt} \Big|_{t=0} u_t(\theta)$$

and that the surface measure dS on $\text{graph}(u) \subseteq \Gamma$ is

$$dS_x = (u(\theta))^2 \sqrt{1 + \frac{|\nabla_\theta u(\theta)|^2}{(u(\theta))^2}} d\theta,$$

where $|\nabla_\theta u(\theta)|^2 = |\partial_{\theta_1} u(\theta)|^2 + |\partial_{\theta_2} u(\theta)|^2$. Thus

$$v(x) dS_x = (u(\theta))^2 \left[\frac{d}{dt} \Big|_{t=0} u_t(\theta) \right] d\theta. \quad (5.6)$$

Now denote by $L_0^+(x)$ by (3.6) with x_0 replacing x_f . Denote also by $d\ell$ the line element on $L_0^+(x)$. We have by (5.5) and (5.6) that

$$\begin{aligned} & \int_{\Omega_+} \left[\frac{d}{dt} \Big|_{t=0} F(x, l^{+t}(x)) \right] dV \\ &= \int_{\{(r,\theta): \theta \in U, r \geq u(\theta)\} \cap \Omega_+} \left[\frac{d}{dt} \Big|_{t=0} F((r,\theta), l^{+t}(r,\theta)) \right] dV \\ &= - \int_U \int_{\{(r,\theta) \in \Omega_+, r \geq u(\theta)\}} F_1((r,\theta), l^+(r,\theta)) \left[\frac{d}{dt} \Big|_{t=0} u_t(\theta) \right] r^2 dr d\theta \\ &= - \int_U \left\{ \int_{\{(r,\theta) \in \Omega_+, r \geq u(\theta)\}} F_1((r,\theta), l^+(r,\theta)) r^2 dr \right\} \left[\frac{d}{dt} \Big|_{t=0} u_t(\theta) \right] d\theta \\ &= - \int_\Gamma \left(\int_{L_0^+(x)} F_1(y, l^+(y)) |y - x_0|^2 d\ell_y \right) \frac{1}{|x - x_0|^2} v(x) dS_x. \end{aligned}$$

Combining this and (5.4), we have

$$\begin{aligned} & \frac{d}{dt} \Big|_{t=0} \int_{\Omega_+} F(x, l^{+t}(x)) dV \\ &= - \int_\Gamma \left[F(x, l^+(x)) + \frac{1}{|x - x_0|^2} \left(\int_{L_0^+(x)} F_1(y, l^+(y)) |y - x_0|^2 d\ell_y \right) \right] v(x) dS_x. \end{aligned} \quad (5.7)$$

5.3 Multiple Solute Atoms

We now consider the general case of $N - 1$ solute atoms and derive our main formula (3.7). For boundaries Γ_t that perturb Γ , we denote as before by Ω_+^t the corresponding perturbations of Ω_+ . We also define $l_1^{+t}(x), \dots, l_N^{+t}(x)$ similar to $l_1^+(x), \dots, l_N^+(x)$ but using Γ_t instead of Γ , cf. (3.3). By the general result (5.1), the chain rule, and a similar argument used in deriving (5.7), we obtain

$$\begin{aligned}
& \left. \frac{d}{dt} \right|_{t=0} \int_{\Omega_+} F(x, l_1^{+t}(x), \dots, l_N^{+t}(x)) dV \\
&= - \int_{\Gamma} F(x, l_1^+(x), \dots, l_N^+(x)) + \sum_{i=1}^N \int_{\Omega_+} F_i(x, l_1^+(x), \dots, l_N^+(x)) \left[\left. \frac{d}{dt} \right|_{t=0} l_i^{+t}(x) \right] dV \\
&= - \int_{\Gamma} \left[F(x, l_1^+(x), \dots, l_N^+(x)) \right. \\
&\quad \left. - \sum_{i=1}^N \frac{1}{|x-x_i|^2} \left(\int_{L_i^+(x)} F_1(y, l_1^+(y), \dots, l_N^+(y)) |y-x_i|^2 dy \right) \right] v(x) dS_x,
\end{aligned} \quad (5.8)$$

where all $L_i^+(x)$ are defined in (3.6) and F_i is the partial derivative of $F = F(u, a_1, \dots, a_N)$ with respect to a_i .

We finally prove our main formula (3.7). It follows from (3.2) that

$$\Delta G[\Gamma] = \frac{1}{32\pi^2 \varepsilon_0 \varepsilon_+} \Delta G_1[\Gamma] + \frac{1}{32\pi^2 \varepsilon_0 \varepsilon_-} \Delta G_2[\Gamma], \quad (5.9)$$

where

$$\Delta G_1[\Gamma] = \int_{\Omega_+} \left| \sum_{i=1}^N f_i(x, \kappa, \Gamma) \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 dV \quad \text{and} \quad \Delta G_2[\Gamma] = \int_{\Omega_+} \left| \sum_{i=1}^N \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 dV.$$

It is clear from (5.1) that

$$\delta_{\Gamma} \Delta G_2[\Gamma](x) = - \left| \sum_{i=1}^N \frac{Q_i(x-x_i)}{|x-x_i|^3} \right|^2 \quad \forall x \in \Gamma. \quad (5.10)$$

We can express $\Delta G_1[\Gamma]$ as

$$\Delta G_1[\Gamma] = \int_{\Omega_+} F(x, l_1^+(x), \dots, l_N^+(x)) dV \quad (5.11)$$

with $F(u, a_1, \dots, a_N)$ given in (3.9). By (5.8) we obtain that

$$- \sum_{i=1}^N \frac{1}{|x-x_i|^2} \left(\int_{L_i^+(x)} F_1(y, l_1^+(y), \dots, l_N^+(y)) |y-x_i|^2 dy \right). \quad (5.12)$$

For our function $F = F(u, a_1, \dots, a_N)$ in (3.9), we can compute directly its partial derivative $F_i = \frac{\partial F}{\partial a_i}$ to get (3.8). The main formula (3.7) now follows from (3.8), (3.9), and (5.9), (5.10), and (5.12).

6 Shape Derivative

We first define the shape derivative of the electrostatic free energy with respect to the local perturbation of the dielectric boundary. We then calculate the shape derivative of a functional defined on the boundary Γ in a form more general than our electrostatic free energy functional. Finally, we use our general result to derive the main formula (3.7).

6.1 Shape Derivative via Local Perturbation

Let $z \in \Gamma$ and $d > 0$. Denote by $B(z, d)$ the open ball in $\mathbb{R}^3$ centered at z with radius d . Let $V \in C^\infty(\mathbb{R}^3, \mathbb{R}^3)$ be such that $V = 0$ outside the ball $B(z, d)$. See Figure 4. The vector field V defines the solution map $x: [0, \infty) \times \mathbb{R}^3 \rightarrow \mathbb{R}^3$ of the dynamical system

$$\begin{cases} \dot{x} = V(x(t, X)) & \forall t > 0, \\ x(0, X) = X, \end{cases}$$

for any $X \in \mathbb{R}^3$, where a dot denotes the derivative with respect to t . We shall denote $T_t(X) = x(t, X)$ for all t and X . For each $t \geq 0$, $T_t: \mathbb{R}^3 \rightarrow \mathbb{R}^3$ is a diffeomorphism. It maps Ω_- , Ω_+ and Γ to $T_t(\Omega_-)$, $T_t(\Omega_+)$ and $T_t(\Gamma)$, respectively. We denote $\Gamma_t = T_t(\Gamma)$ for all $t \geq 0$. The dependence on V is suppressed. Clearly $\Gamma_0 = \Gamma$.

Let $t_0 > 0$ and consider the boundaries Γ_t for $t \in [0, t_0]$. We assume both d and t_0 are small so that the following hold true:

1. All the points $x_1, \dots, x_N$ lie outside the closed ball $\overline{B(z, d)}$. This implies particularly that $x_i = T_t(x_i) \in T_t(\Omega_-)$ for $i = 1, \dots, N$ and for all $t \geq 0$;
2. If $t \in [0, t_0]$ then $B(z, d) \cap \Gamma_t = \emptyset$ and $(\Gamma_t \setminus \Gamma) \cup (\Gamma \setminus \Gamma_t) \subseteq B(z, d/2)$ (the ball centered at z with radius $d/2$);
3. If $X \in \Omega_+$ and $1 \leq i \leq N$, then either $[x_i, X] \cap \Gamma_t \cap B(z, d) = \emptyset$ for all $t \in [0, t_0]$ or $[x_i, X] \cap \Gamma_t \cap B(z, d)$ contains exactly one point for all $t \in [0, t_0]$. This point can depend on t .

For each $t > 0$ we define the electrostatic free energy $\Delta G[\Gamma_t]$ by (3.2) with Γ_t replacing Γ . We define the derivative of the electrostatic free energy $\Delta G[\Gamma]$ with respect to the vector field V to be [5,17,26,37]

$$\delta_{r,V} \Delta G[\Gamma] = \left. \frac{d}{dt} \right|_{t=0} \Delta G[\Gamma_t].$$

This is a surface integral over Γ , or more precisely over $\Gamma \cap B(z, d)$, of the product of $V \cdot n$ and some function that is independent of V , where n is the unit normal along Γ pointing from Ω_- to Ω_+ . We identify this function on $\Gamma \cap B(z, d)$ as the shape derivative of $\Delta G[\Gamma]$ over $\Gamma \cap B(z, d)$ and denote it by $\delta_\Gamma \Delta G[\Gamma]$. In particular, this defines the shape derivative at the arbitrarily chosen point $z \in \Gamma$.

We recall some properties of the transformation $T_t(X)$ that will be used later [17]. First, by the definition of $T_t(X) = x(t, X)$, we have

$$T_0(X) = X \quad \text{and} \quad \left. \frac{d}{dt} \right|_{t=0} T_t(X) = V(X) \quad \forall X \in \mathbb{R}^3. \quad (6.1)$$

Denote by $\nabla T_t(X)$ the Jacobian matrix of T_t at X defined by $(\nabla T_t(X))_{ij} = \partial_j T_t^i(X)$, where T_t^i is the i th component of T_t ($i = 1, 2, 3$). Denote $J_t(X) = \det \nabla T_t(X)$. Then

$$J_0 = 1 \quad \text{and} \quad \left. \frac{dJ_t}{dt} \right|_{t=0} = \nabla \cdot V \quad \text{in } \mathbb{R}^3. \quad (6.2)$$

For any smooth function $u: \mathbb{R}^3 \rightarrow \mathbb{R}$ and any $t \geq 0$, we also have

$$\left. \frac{d}{dt} \right|_{t=0} (u \circ T_t) = \nabla u \cdot V \quad \text{in } \mathbb{R}^3. \quad (6.3)$$

6.2 Shape Derivative of a General Functional

We consider the following functional of Γ which is more general than our free-energy functional $\Delta G[\Gamma]$ defined in (3.2):

$$I[\Gamma] = \int_{\Omega_+} F(x, l_1^+(x), \dots, l_N^+(x)) dV.$$

Here F is a smooth and integrable function defined on $\mathbb{R}^3 \setminus \{x_1, \dots, x_N\} \times \mathbb{R}_+^N$, where $\mathbb{R}_+$ denotes the set of all nonnegative real numbers, and $l_1^+, \dots, l_N^+$ are the same as before, cf. Section 3. Here and below dV denotes the volume element and the letter V in dV is not the vector field V . We derive in this section the following formula of the shape derivative:

$$\begin{aligned} \delta_\Gamma I[\Gamma](x) = & -F(x, l_1^+(x), \dots, l_N^+(x)) \\ & - \sum_{i=1}^N \frac{1}{|x - x_i|^2} \int_{L_i^+(x)} |y - x_i|^2 F_i(y, l_1^+(y), \dots, l_N^+(y)) dy \quad \forall x \in \Gamma, \end{aligned} \quad (6.4)$$

where F_i is the partial derivative of $F = F(u, a_1, \dots, a_N)$ with respect to a_i and $L_i^+(x)$ is defined in (3.6).

Notice that with the same argument as in Subsection 5.3 and this formula, we can obtain our main formula (3.7).

Let $z \in \Gamma$, $B(z, d)$, $V \in C^\infty(\mathbb{R}^3, \mathbb{R}^3)$, and $t_0 > 0$ be given as in the previous subsection. For each $i \in \{1, \dots, N\}$ and each $t \in (0, t_0]$, we define $l_i^{+t}: T_t(\Omega_+) \rightarrow \mathbb{R}$ in the same way as for $l_i^{+t}: (\Omega_+) \rightarrow \mathbb{R}$ but using the boundary $\Gamma_t = T_t(\Gamma)$ instead of Γ . We then have by the change of variable $x = T_t(X)$ that

$$\begin{aligned} I[\Gamma_t] &= \int_{T_t(\Omega_+)} F(x, l_1^{+t}(x), \dots, l_N^{+t}(x)) dV_x \\ &= \int_{\Omega_+} F(T_t(X), l_1^{+t}(T_t(X)), \dots, l_N^{+t}(T_t(X))) J_t(X) dV_X. \end{aligned}$$

Consequently, it follows from the chain rule, our notation $F = F(u, a_1, \dots, a_N)$, (6.1) and (6.2), and integration by parts that

$$\begin{aligned}
\frac{d}{dt}\bigg|_{t=0} I[\Gamma_t] &= \int_{\Omega_+} \nabla_u F(X, l_1^+(X), \dots, l_N^+(X)) \cdot V(X) dV \\
&\quad + \sum_{i=1}^N \int_{\Omega_+} F_i(X, l_1^+(X), \dots, l_N^+(X)) \left[\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(T_t(X)) \right] dV \\
&\quad + \int_{\Omega_+} F(X, l_1^+(X), \dots, l_N^+(X)) \nabla \cdot V(X) dV \\
&= \int_{\Omega_+} \nabla_u F(X, l_1^+(X), \dots, l_N^+(X)) \cdot V(X) dV \\
&\quad + \sum_{i=1}^N \int_{\Omega_+} F_i(X, l_1^+(X), \dots, l_N^+(X)) \left[\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(T_t(X)) \right] dV \\
&\quad - \int_{\Gamma} F(X, l_1^+(X), \dots, l_N^+(X)) V(V(X) \cdot n(X)) dV \\
&\quad - \int_{\Omega_+} \nabla_u F(X, l_1^+(X), \dots, l_N^+(X)) \cdot V(X) dV \\
&\quad - \sum_{i=1}^N \int_{\Omega_+} F_i(X, l_1^+(X), \dots, l_N^+(X)) \nabla l_i^+(X) \cdot V(X) dV \\
&= \sum_{i=1}^N \int_{\Omega_+} \left[\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(T_t(X)) - \nabla l_i^+(X) \cdot V(X) \right] F_i(X, l_1^+(X), \dots, l_N^+(X)) dV \\
&\quad - \int_{\Gamma} F(X, l_1^+(X), \dots, l_N^+(X)) (V(X) \cdot n(X)) dS.
\end{aligned}$$

Note that the minus sign in front of the boundary integral term follows from our convention that the unit normal n along Γ points from Ω_- to Ω_+ .

By the chain rule, (6.3), and (6.1), we have for each $i(1 \leq i \leq N)$ that

$$\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(T_t(X)) = \frac{d}{dt}\bigg|_{t=0} l_i^{+t}(X) + \nabla l_i^+(X) \cdot V(X).$$

Therefore,

$$\begin{aligned}
\frac{d}{dt}\bigg|_{t=0} I[\Gamma_t] &= \sum_{i=1}^N \int_{\Omega_+} \left[\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(X) \right] F_i(X, l_1^+(X), \dots, l_N^+(X)) dV \\
&\quad - \int_{\Gamma} F(X, l_1^+(X), \dots, l_N^+(X)) (V(X) \cdot n(X)) dS.
\end{aligned} \tag{6.5}$$

It will be shown later in this section that for each $i(1 \leq i \leq N)$

$$\begin{aligned}
&\int_{\Omega_+} \left[\frac{d}{dt}\bigg|_{t=0} l_i^{+t}(X) \right] F_i(X, l_1^+(X), \dots, l_N^+(X)) dV \\
&= - \int_{\Gamma} \frac{1}{|X - x_i|^2} \left[\int_{L_i^+(X)} F_i(Y, l_1^+(Y), \dots, l_N^+(Y)) |Y - x_i|^2 d\ell_Y \right] V(X) \cdot n(X) dS.
\end{aligned} \tag{6.6}$$

This and (6.5) then imply (6.4).

We now fix $i(1 \leq i \leq N)$ and prove (6.6). For convenience, we denote

$X_0 = x_i, l^+(X) = l_i^+(X), l_i^+ = l_i^{+t}(x)$, and $g(X) = F_i(X, l_1^+(X), \dots, l_N^+(X))$. Denote by Λ the open set of points $X \in \mathbb{R}^3$ such that $[X_0, X] \cap \Gamma \cap B(z, d) = \emptyset$. Clearly,

$$\frac{d}{dt}\bigg|_{t=0} l_i^+(X) = 0 \quad \text{if } X \in \Omega_+ \setminus \overline{\Lambda}.$$

Hence

$$A := \int_{\Omega_+} \left[\frac{d}{dt} \Big|_{t=0} l_t^+(X) \right] g(X) dX = \int_{\Lambda \cap \Omega_+} \left[\frac{d}{dt} \Big|_{t=0} l_t^+(X) \right] g(X) dX, \quad (6.7)$$

where $A := B$ means A is defined to be B .

We proceed in four steps.

Step 1—Let $X \in \Lambda \cap \Omega_+$. By our assumption on the locality of perturbation (cf. the previous subsection), the line segment $[X_0, X]$ and the boundary Γ_t intersect at exactly $2k - 1$ points with some $k = k(X)$ for all $t \in [0, t_0]$:

$$P_j(X, t) = X_0 + s_j(X, t)(X - X_0), \quad j = 1, \dots, 2k - 1,$$

where all $s_j(X, t) \in [0, 1]$ are smooth functions such that

$$0 < s_1(X, t) < \dots < s_{2k-1}(X, t) < 1.$$

See Figure 4 where these intersection points are marked by dots. Set $s_0(X, t) = 0$, $s_{2k}(X, t) = 1$, $P_0(X, t) = X_0$, and $P_{2k}(X, t) = X$ for all $t \in [0, t_0]$. It then follows from the definition of l_t^+ that

$$\begin{aligned} l_t^+(X) &= \sum_{j=1}^k |P_{2j}(X, t) - P_{2j-1}(X, t)| \\ &= |X - X_0| \sum_{j=1}^k [s_{2j}(X, t) - s_{2j-1}(X, t)] \\ &= |X - X_0| \sum_{j=1}^{2k} (-1)^j s_j(X, t). \end{aligned}$$

Notice that there exists exactly one index $j_0 = j_0(X) \in \{1, \dots, 2k - 1\}$ such that $[X_0, X] \cap \Gamma_t \cap B(z, d) = \{P_{j_0}(X, t)\}$ for all $t \in [0, t_0]$. For all other indices $j \neq j_0$, the intersection points $P_j(X, t)$, and hence the functions $s_j(X, t)$ as well, are independent of $t \in [0, t_0]$. Therefore $s_j(X, 0) = 0$ if $j \neq j_0$. Consequently,

$$\frac{d}{dt} \Big|_{t=0} l_t^+(X) = (-1)^{j_0} |X - X_0| \partial_t s_{j_0}(X, 0). \quad (6.8)$$

Step 2—To calculate $\partial_t s_{j_0}(X, 0)$, we set

$$a_{j_0}(X, t) = T_t^{-1}(P_{j_0}(X, t)) = T_t^{-1}(X_0 + s_{j_0}(X, t)(X - X_0)) \in \Gamma,$$

Clearly, $a_{j_0}(X, 0) = P_{j_0}(X, 0)$ and

$$T_t(a_{j_0}(X, t)) = X_0 + s_{j_0}(X, t)(X - X_0).$$

Take the derivative with respect to t and then set $t = 0$ to get by (6.1) that

$$V(P_{j_0}(X, 0)) + \partial_t a_{j_0}(X, 0) = \partial_t s_{j_0}(X, 0)(X - X_0),$$

leading to

$$\partial_t a_{j_0}(X, 0) = \partial_t s_{j_0}(X, 0)(X - X_0) - V(P_{j_0}(X, 0)). \quad (6.9)$$

Let Λ_0 denote the cone generated by X_0 and $\Gamma \cap B(z, d)$, cf. Figure 4. Precisely, Λ_0 is the set of points $Y \in \mathbb{R}^3$ such that the intersection of the half line $\{X_0 + s(Y - X_0) : s \geq 0\}$ and the set $\Gamma \cap B(z, d)$ contains exactly one point, denoted $P(Y)$. Clearly $\Lambda \subset \Lambda_0$. For $X \in \Lambda \cap \Omega_+$ as above, we have $P(X) = P_{j_0}(X, 0)$. Define

$$\phi(Y) = \frac{Y - P(Y)}{|Y - X_0|} \cdot \frac{P(Y) - X_0}{|P(Y) - X_0|} \quad \forall Y \in \Lambda_0.$$

For any $Y \in \Lambda_0$, $\phi(Y) = 0$ if and only if $Y = P(Y) \in \Gamma$, i.e., $\Gamma \cap B(z, d)$ is the (zero) level-set of $\phi: \Lambda_0 \rightarrow \mathbb{R}$.

Clearly $\phi(a_{j_0}(X, t)) = 0$. Thus, taking the derivative against t and setting $t = 0$, we obtain by the chain rule that $\nabla \phi(a_{j_0}(X, 0)) \cdot \partial_t a_{j_0}(X, 0) = 0$. This and (6.9), with the notation $P(X) = P_{j_0}(X)$, then imply

$$\partial_t s_{j_0}(X, 0) = \frac{V(P(X)) \cdot \nabla \phi(P(X))}{(X - X_0) \cdot \nabla \phi(P(X))}.$$

Plugging this into (6.8), we obtain that

$$\left. \frac{d}{dt} \right|_{t=0} l_t^+(X) = (-1)^{j_0(X)} |X - X_0| \frac{V(P(X)) \cdot \nabla \phi(P(X))}{(X - X_0) \cdot \nabla \phi(P(X))}. \quad (6.10)$$

Notice that $\phi(P(X))/|\phi(P(X))|$ is a unit normal at $P(X)$ along Γ . It differs from $n(P(X))$ by a sign. Observe that $j_0 = j_0(X)$ is odd if and only if $X_0 + s(P(X) - X_0) \in \Omega_-$ for $s \in (0, 1)$ sufficiently close to 1, cf. Figure 4. Since the unit normal n points from Ω_- to Ω_+ , that j_0 is odd then implies ϕ increases at $P(X)$ in the direction $n(P(X))$, i.e., $n(P(X)) \cdot \nabla \phi(P(X)) > 0$. Therefore

$$(-1)^{j_0(X)} \frac{\nabla \phi(P(X))}{|\nabla \phi(P(X))|} = -n(P(X)). \quad (6.11)$$

Step 3—Since $X \in \Lambda \cap \Omega_+$, we have $\phi(X) = |X - P(X)|/|X - X_0|$. Moreover

$$P(X) = X_0 + (1 - \phi(X))(X - X_0). \quad (6.12)$$

Thus

$$\phi(P(X)) = \phi(X_0 + (1 - \phi(X))(X - X_0)) = 0.$$

By taking the partial derivative with respect to X_I for $I \in \{1, 2, 3\}$, we obtain by the chain rule that

$$-\nabla\phi(P(X)) \cdot (X - X_0) \partial_I \phi(X) + (1 - \phi(X)) \partial_I \phi(P(X)) = 0,$$

leading to

$$\frac{\nabla\phi(P(X))}{(X - X_0) \cdot \nabla\phi(P(X))} = \frac{\nabla\phi(X)}{1 - \phi(X)}. \quad (6.13)$$

Since ϕ increases in the direction from X_0 to X , this particularly implies that $(X - X_0) \cdot \nabla\phi(P(X)) > 0$. Also, $|\phi(X)| < 1$. Hence

$$\frac{\nabla\phi(X)}{|\nabla\phi(X)|} = \frac{\nabla\phi(P(X))}{|\nabla\phi(P(X))|}. \quad (6.14)$$

Now combining (6.13) with (6.10) and then using (6.14) and (6.11), we obtain that

$$\begin{aligned} \frac{d}{dt} \Big|_{t=0} I_t^+(X) &= (-1)^{j_0(X)} |X - X_0| \frac{V(P(X)) \cdot \nabla\phi(X)}{1 - \phi(X)} \\ &= -|X - X_0| \frac{V(P(X)) \cdot n(P(X))}{1 - \phi(X)} |\nabla\phi(X)|. \end{aligned} \quad (6.15)$$

Step 4—Denote by $\chi_+ : \mathbb{R}^3 \rightarrow \mathbb{R}$ the characteristic function of Ω_+ , i.e., $\chi_+(Y) = 1$ if $Y \in \Omega_+$ and $\chi_+(Y) = 0$ if $Y \notin \Omega_+$. Notice that $|\nabla\phi(Y)| = |\nabla(1 - \phi(Y))|$ and that $1 - \phi(Y) \in (0, 1)$ if $Y \in \Lambda$. We then have by (6.7) and (6.15), and by an application of the co-area formula that

$$\begin{aligned} A &= - \int_{\Lambda} \chi_+(X) g(X) |X - X_0| \frac{V(P(X)) \cdot n(P(X))}{1 - \phi(X)} |\nabla(1 - \phi(X))| dX \\ &= - \int_0^1 \frac{1}{\sigma} \left[\int_{\{X \in \Lambda : 1 - \phi(X) = \sigma\}} \chi_+(X) g(X) |X - X_0| V(P(X)) \cdot n(P(X)) dS \right] d\sigma. \end{aligned} \quad (6.16)$$

Fix $\sigma \in (0, 1)$. Under the change of variable $Y = P(X)$, the surface $\{X \in \Lambda : 1 - \phi(X) = \sigma\}$ is mapped to that defined by $\phi(X) = 0$ which is $\Gamma \cap B(z, d)$. Moreover, by (6.12), this change of variable is $Y = P(X) = X_0 + \sigma(X - X_0)$. The change of surface element is

$$dS_Y = |(\text{Cof } \nabla Y(X)) n(X)| dS_X = \sigma^2 dS_X,$$

where $\text{Cof } B$ denotes the cofactor matrix of a matrix B and $n(X)$ is the unit normal along Γ . Therefore, it follows from (6.16) and using X instead of Y that

$$A = - \int_{\Gamma} |X - X_0| \left[\int_0^1 \frac{1}{\sigma^4} \chi_+ \left(X_0 + \frac{X - X_0}{\sigma} \right) g \left(X_0 + \frac{X - X_0}{\sigma} \right) d\sigma \right] V(X) \cdot n(X) dS.$$

For any $X \in \Gamma \cap B(z, d)$, by parameterizing $L_0^T(X)$ using $Y = X_0 + (1/\sigma)(X - X_0)$ with $\sigma \in (0, 1)$, we get

$$\int_{L_0^T(X)} g(Y) |Y - X_0|^2 dl_Y = |X - X_0|^3 \int_0^1 \frac{1}{\sigma^4} \chi_+ \left(X_0 + \frac{X - X_0}{\sigma} \right) g \left(X_0 + \frac{X - X_0}{\sigma} \right) d\sigma.$$

These two equations together with (6.7) implies the desired (6.6) with our notations.

6.3 Derivation of the Main Formula

By defining $\Delta G_1[\Gamma]$ as in (5.11) with $F(u, \alpha_1, \dots, \alpha_N)$ given in (3.9), we obtain (5.12) by (6.4). The rest of the derivation is the same as that presented in Subsection 5.3.

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Figure 1.
The geometry of a solvation system with an implicit solvent.

Figure 2.
Definition of the function $f_k(\cdot, \kappa, \Gamma)$.

Figure 3.

A spherically symmetric model system. The grey region is the solute molecular region Ω_- defined by (4.1). The white region is the solvent region Ω_+ defined by (4.2).

Figure 4.
Local perturbation of the boundary Γ near $z \in \Gamma$.