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The van der Waals interaction between protein molecules in an electrolyte solution

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In this report we present a general formulation to calculate the van der Waals interaction between two protein molecules in an electrolyte solution using boundary element method of solving linearized Poisson–Boltzmann equation. Our formulation is based upon an inhomogeneous dielectric model of proteins at the residue level. Our results for bovine pancreatic trypsin inhibitor at various relative orientations indicate that the anisotropy of the interaction can be tens of k_BT.
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I. INTRODUCTION

In this report, we present a general formulation to estimate the van der Waals interactions between two protein molecules in an electrolyte solution. Since one of the main objectives of this work is to assess the extent of anisotropy of such interactions the formulation is given based upon a coarse-grained model of proteins at the residue level. An application of our formulation to the van der Waals interactions between two bovine pancreatic inhibitor (BPTI) molecules in an aqueous solution indicates that the anisotropy can be as large as tens of k_BT as a function of relative orientations between two protein molecules.

Because of the ubiquity of van der Waals interaction in physics, chemistry, and biology, theories of such interactions have a long and rich history. The first elucidation of the quantum mechanical nature of such interactions was given by London,[1] later by Casimir and Polder,[2] taking fully into account the retardation effects. In 1963 McLachlan presented a generalized theory to account for the electronic *and* nuclear polarizabilty of molecules and the solvent effect on the interaction.[3] Along a different line, Lifshitz formulated a general theory for the van der Waals interactions between two macroscopic bodies in a dielectric medium using their dielectric spectra from quantum electrodynamics.[4] After that a semiclassical formulation of Lifshitz theory using a Drude oscillator model of a dielectric body had been developed and our current formulation is greatly influenced by such a formulation.[5] A detailed presentation of these theories and their applications has been given in an authoritative monograph by Mahanty and Ninham.[6]

Up to now, applications of van der Waals theories to proteins have been restricted to simple geometries, essentially between two spherical protein molecules characterized by a frequency-dependent dielectric function.[7] Recently we have shown that anisotropic interactions between proteins molecules play an important role in forming suitable crystals for the diffraction experiments.[8] As a first step toward a realistic model to assess the anisotropy of protein–protein interactions, we have developed a coarse-grained model of a protein at the residue level.[9] Based upon this model the van der Waals interaction between two protein molecules in an electrolyte solution is specified by the intrinsic polarizabilities of twenty amino acids in nature and the dielectric spectra of the electrolyte solution. This report presents a general formulation to estimate such interactions. It should be noted that our formulation is distinctly different from the van der Waals interactions in force field models used in molecular simulations. In that case the van der Waals interaction parameters are obtained from individual atomic electronic polarizabilities. In order to extract the van der Waals contribution to protein–protein interaction in a solution, detailed atomistic simulations are performed to obtain the potential of mean force. In our case the van der Waals interaction is obtained from the polarizabilities of amino acids and the dielectric spectra of solution without atomistic simulations.

The paper is organized in the following manner: In Sec. II we will present a general formulation of the problem and its relations to previous work. In order to apply our general formulation to the van der Waals interaction between two protein molecules with realistic shape frequency-dependent reaction field at various residue positions are needed. Such calculations are presented in Sec. III based upon boundary element method of solving linearized Poisson–Boltzmann equation. An application of our formulation to simple two-sphere system yields results which agree with analytical results from the literature. In Sec. V applications to the BPTI case is given with details of our implementation. The paper is concluded with a discussion on the future applications of our formulation to protein crystallization.

II. GENERAL FORMULATION

In our coarse-grained model of a protein,[9] each residue is represented by a sphere located at the geometric center of the residue determined by the protein's native structure. The diameter of the sphere is determined by the molecular volume of the residue. The molecular surface of our model protein is defined as a Richard–Connolly surface spanned by the union of these residue spheres.[10,11] Each residue carries a permanent dipole moment located at the center of its sphere and the direction of the dipole is given by the amino acid type of

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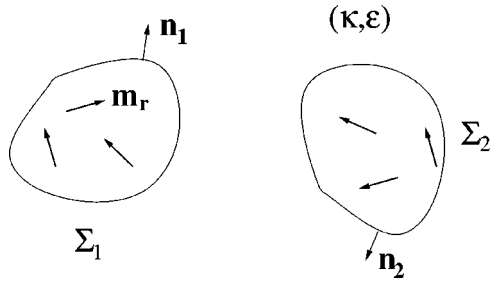

FIG. 1. A schematic illustration of the van der Waals calculation of two protein molecules. The outside solvent is specified by Debye screening length κ and dielectric constant ϵ. The positions of polarizable dipoles $\mathbf{m}_\mathbf{r}$ are determined from protein's native structure. The molecular surfaces of two proteins are Σ_1 and Σ_2. The $\mathbf{n}_1$ and $\mathbf{n}_2$ are the outward unit normal to Σ_1 and Σ_2, respectively.

protein's native structure. If a residue is charged the amount of charge is given by Henderson–Hasselbalch equation using the generic pK values of residues from Table 2-1 of Ref. 12, i.e., the local environmental effects on pK values are neglected. From this information the electrostatic contribution to the protein–protein interaction has been estimated recently.[9] For each residue there is also a polarizable dipole at the center of the sphere (Fig. 1 for a schematic illustration), whose polarizability has been determined from our recent work.[13] As far as the van der Waals interaction between two protein molecules in an electrolyte solution is concerned, the effective action of the system can be written as[14,15]

$$\begin{aligned} S[\mathbf{m}_\mathbf{r}(\tau)] = &-\frac{\beta}{2}\int_0^{\beta\hbar}\frac{d\tau}{\beta\hbar}\int_0^{\beta\hbar}\frac{d\tau'}{\beta\hbar}\sum_\mathbf{r}\ \alpha^{-1}(\mathbf{r},\tau \\ &-\tau')\mathbf{m}_\mathbf{r}(\tau)\cdot\mathbf{m}_\mathbf{r}(\tau') + \frac{\beta}{2}\int_0^{\beta\hbar}\frac{d\tau}{\beta\hbar}\sum_{\mathbf{r},\mathbf{r}'}\ \mathbf{m}_\mathbf{r}(\tau) \\ &\cdot T(\mathbf{r}-\mathbf{r}')\cdot\mathbf{m}_{\mathbf{r}'}(\tau) \\ &+\frac{\beta}{2}\int_0^{\beta\hbar}\frac{d\tau}{\beta\hbar}\sum_\mathbf{r}\ \int d\mathbf{R}\,\mathbf{m}_\mathbf{r}(\tau)\cdot T(\mathbf{r}-\mathbf{R}) \\ &\cdot\mathbf{P}(\mathbf{R},\tau) \\ &-\frac{\beta}{2}\int_0^{\beta\hbar}\frac{d\tau}{\beta\hbar}\int_0^{\beta\hbar}\frac{d\tau'}{\beta\hbar}\int d\mathbf{R}\int d\mathbf{R}'\mathbf{P}(\mathbf{R},\tau) \\ &\cdot\chi^{-1}(\mathbf{R}-\mathbf{R}',\tau-\tau')\cdot\mathbf{P}(\mathbf{R}',\tau'). \end{aligned} \tag{1}$$

In this reduced description the first term represents that each residue is an extended Drude oscillator $\mathbf{m}_\mathbf{r}(\tau)$ with a polarizability $\alpha(\mathbf{r},\tau-\tau')$. Such an action form is adopted to describe the nonlocal nature of the polarizability and to avoid the restriction of the simple Drude oscillator form. The second and third terms account for the dipole–dipole interaction between the residues and with the solvent polarization $\mathbf{P}(\mathbf{R},\tau)$ without retarded effect, and $T(\mathbf{r}-\mathbf{r}')$ is the dipole–dipole interaction tensor. The fourth term indicates that the solvent polarization field follows a Gaussian statistics specified by the susceptibility of the solvent, $\chi(\mathbf{R}-\mathbf{R}',\tau-\tau')$, which has been known to be a good approximation[16–28] for polar solvents. Due to the quadratic nature of the solvent polarization field these degrees of freedom can be integrated out and we arrive at the following effective action in Fourier space;

$$\begin{aligned} S[\mathbf{m}_{\mathbf{r},n}] = &-\frac{\beta}{2}\sum_\mathbf{r}\sum_{n=-\infty}^{n=\infty}\frac{1}{\alpha_{\mathbf{r},n}}\mathbf{m}_{\mathbf{r},n}\cdot\mathbf{m}_{\mathbf{r},-n} \\ &+\frac{\beta}{2}\sum_{\mathbf{r}\neq\mathbf{r}'}\sum_{n=-\infty}^{n=\infty}\mathbf{m}_{\mathbf{r},n}\cdot T(\mathbf{r}-\mathbf{r}')\cdot\mathbf{m}_{\mathbf{r},-n} \\ &+\frac{\beta}{2}\sum_{\mathbf{r},\mathbf{r}'}\sum_{n=-\infty}^{n=\infty}\mathbf{m}_{\mathbf{r},n}\cdot R_n(\mathbf{r}-\mathbf{r}')\cdot\mathbf{m}_{\mathbf{r},-n}, \end{aligned} \tag{2}$$

where the summation over $\mathbf{r}$ runs over all residues, $\alpha_{\mathbf{r},n}$ is the frequency-dependent polarizability of a residue located at $\mathbf{r}$. $R_n(\mathbf{r}-\mathbf{r}')$ is the reaction field tensor at frequency $\omega_n = 2\pi n/\beta\hbar$ when the surrounding solvent degrees of freedom are integrated out. If the solvent is treated within Debye–Hükel theory, then, this reaction field tensor can be obtained by solving the Poisson–Boltzmann equation (cf. Sec. III), but with dielectric constant $\epsilon(i\omega_n)$. The van der Waals interaction between two molecules can be obtained by calculating the partition function of the effective action.

Due to the quadratic nature of the action the quantum partition function of the system is

$$Q(D,\Omega_1,\Omega_2) = \prod_n\left[\frac{2\pi}{\beta\det A_n(D,\Omega_1,\Omega_2)}\right]^{1/2}, \tag{3}$$

where D is the center to center distance between two protein molecules, Ω_1 and Ω_2 represent the orientations of the two proteins, and $A_n(D,\Omega_1,\Omega_2)$'s matrix element is given by $(1/\alpha_{\mathbf{r},n})\,\delta_{\mathbf{r},\mathbf{r}'} - T(\mathbf{r}-\mathbf{r}') - R_n(\mathbf{r}-\mathbf{r}')$ for residues $\mathbf{r}$ and $\mathbf{r}'$. The symbol "det" represents the determinant of the matrix. Then the van der Waals interaction between these two proteins is

$$\begin{aligned} W(D,\Omega_1,\Omega_2) = &\frac{1}{2}k_BT\sum_{n=-\infty}^{n=\infty}[\ln\{\det A_n(D,\Omega_1,\Omega_2)\} \\ &-\ln\{\det A_n(D=\infty)\}]. \end{aligned} \tag{4}$$

It can be shown that our result will reduce to the expression given by Cao and Berne if there is not solvent present[15] and will reduce to Lifshitz's theory without retarded effect if the protein molecules can be treated as a homogeneous dielectric material.[6]

III. REACTION FIELD CALCULATION OF TWO PROTEIN MOLECULES IN AN ELECTROLYTE SOLUTION

To account for the effect of an electrolyte solution on the van der Waals interaction between two protein molecules in our model, the reaction field matrix $R_n(\mathbf{r},\mathbf{r}')$ has to be evaluated given the properties of the proteins and the electrolyte solution. Recently we have developed a boundary element formulation of solving the linearized Poisson–Boltzmann equation involving two protein molecules.[9] Such formulation can be used to calculate the reaction field.

Consider the two molecular surfaces Σ_1 and Σ_2 spanned by the two protein molecules (Fig. 1). There are N polarizable dipoles $\mathbf{m}_\mathbf{r}$ inside a dielectric cavity enclosed by Σ_1 and there are N polarizable dipoles inside a dielectric cavity en-

closed by Σ_2. Inside the dielectric cavities the dielectric constant is one and the dielectric constant of the solution is ϵ. The ionic strength of the solution yields Debye screening length κ. If we recognize that for the calculation of the potential at the molecular surfaces a dipole $\mathbf{m}$ at $\mathbf{r}_0$ can be described by an effective charge density $\rho_{\text{eff}}(\mathbf{r}) = -\mathbf{m}\nabla\delta(\mathbf{r}-\mathbf{r}_0)$,[29] then, the reaction field matrix involving residues $\mathbf{r}_i$ and $\mathbf{r}_j$ can be written as

$$\begin{aligned} R(\mathbf{r}_i,\mathbf{r}_j) = & \int\int_{\Sigma_p} [\nabla_i F(\mathbf{r}_i,\mathbf{r}_j) \\ & - \nabla_i P(\mathbf{r}_i,\mathbf{r}_j)] \frac{\partial \varphi_p}{\partial n_p}(\mathbf{r}_j,\mathbf{r}_p) d\mathbf{r}_p \\ & + \int\int_{\Sigma_p} \left[-\nabla_i \frac{\partial F}{\partial n_j}(\mathbf{r}_i,\mathbf{r}_j) \right. \\ & \left. + \nabla_i \frac{\partial P}{\partial n_j}(\mathbf{r}_i,\mathbf{r}_j)\epsilon \right] \varphi_p(\mathbf{r}_j,\mathbf{r}_p) d\mathbf{r}_p \\ & + 4\pi \nabla_i \nabla_j F(\mathbf{r}_i,\mathbf{r}_j), \end{aligned} \tag{5}$$

where

$$F(\mathbf{r}_i,\mathbf{r}_j) = \frac{1}{4\pi|\mathbf{r}_i-\mathbf{r}_j|}, \tag{6}$$

$$P(\mathbf{r}_i,\mathbf{r}_j) = \frac{e^{-\kappa|\mathbf{r}_i-\mathbf{r}_j|}}{4\pi|\mathbf{r}_i-\mathbf{r}_j|}, \tag{7}$$

and p can be 1 or 2 depending upon $\mathbf{r}_j$ being in Σ_1 or Σ_2. $\partial\varphi_p/\partial n_p$ and φ_p can be obtained from solving the following integral equations:[9,30]

$$\begin{aligned} & \frac{1}{2}(1+\epsilon)\varphi_1(\mathbf{r}_i,\mathbf{r}_{01}) + \int\int_{\Sigma_1} L_1(\mathbf{r}_1,\mathbf{r}_{01})\varphi_1(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_1} L_2(\mathbf{r}_1,\mathbf{r}_{01}) \frac{\partial \varphi_1}{\partial n_1}(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & - \int\int_{\Sigma_2} L_1(\mathbf{r}_2,\mathbf{r}_{01})\varphi_2(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & + \int\int_{\Sigma_2} L_2(\mathbf{r}_2,\mathbf{r}_{01}) \frac{\partial \varphi_2}{\partial n_2}(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & = \nabla_i F(\mathbf{r}_i,\mathbf{r}_{01}), \end{aligned} \tag{8}$$

$$\begin{aligned} & \frac{1}{2}\left(1+\frac{1}{\epsilon}\right)\frac{\partial \varphi_1}{\partial n_1}(\mathbf{r}_i,\mathbf{r}_{01}) + \int\int_{\Sigma_1} L_3(\mathbf{r}_1,\mathbf{r}_{01})\varphi_1(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_1} L_4(\mathbf{r}_1,\mathbf{r}_{01}) \frac{\partial \varphi_1}{\partial n_1}(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & - \int\int_{\Sigma_2} L_3(\mathbf{r}_2,\mathbf{r}_{01})\varphi_2(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & + \int\int_{\Sigma_2} L_4(\mathbf{r}_2,\mathbf{r}_{01}) \frac{\partial \varphi_2}{\partial n_2}(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & = \nabla_i \frac{\partial F}{\partial n_{01}}(\mathbf{r}_i,\mathbf{r}_{01}), \end{aligned} \tag{9}$$

$$\begin{aligned} & \frac{1}{2}(1+\epsilon)\varphi_2(\mathbf{r}_i,\mathbf{r}_{02}) - \int\int_{\Sigma_1} L_1(\mathbf{r}_1,\mathbf{r}_{02})\varphi_1(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_1} L_2(\mathbf{r}_1,\mathbf{r}_{02}) \frac{\partial \varphi_1}{\partial n_1}(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_2} L_1(\mathbf{r}_2,\mathbf{r}_{02})\varphi_2(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & + \int\int_{\Sigma_2} L_2(\mathbf{r}_2,\mathbf{r}_{02}) \frac{\partial \varphi_2}{\partial n_2}(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & = \nabla_i F(\mathbf{r}_i,\mathbf{r}_{02}), \end{aligned} \tag{10}$$

$$\begin{aligned} & \frac{1}{2}\left(1+\frac{1}{\epsilon}\right)\frac{\partial \varphi_2}{\partial n_2}(\mathbf{r}_i,\mathbf{r}_{02}) - \int\int_{\Sigma_1} L_3(\mathbf{r}_1,\mathbf{r}_{02})\varphi_1(\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_1} L_4(\mathbf{r}_1,\mathbf{r}_{02}) \frac{\partial \varphi_1}{\partial n_1}(\mathbf{r}_i,\mathbf{r}_1) d\mathbf{r}_1 \\ & + \int\int_{\Sigma_2} L_3(\mathbf{r}_2,\mathbf{r}_{02})\varphi_2(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & + \int\int_{\Sigma_2} L_4(\mathbf{r}_2,\mathbf{r}_{02}) \frac{\partial \varphi_2}{\partial n_2}(\mathbf{r}_i,\mathbf{r}_2) d\mathbf{r}_2 \\ & = \nabla_i \frac{\partial F}{\partial n_{02}}(\mathbf{r}_i,\mathbf{r}_{02}), \end{aligned} \tag{11}$$

where

$$L_1(\mathbf{r},\mathbf{r}_1) = \frac{\partial F}{\partial n}(\mathbf{r},\mathbf{r}_1) - \frac{\partial P}{\partial n}(\mathbf{r},\mathbf{r}_1)\epsilon, \tag{12}$$

$$L_2(\mathbf{r},\mathbf{r}_1) = P(\mathbf{r},\mathbf{r}_1) - F(\mathbf{r},\mathbf{r}_1), \tag{13}$$

$$L_3(\mathbf{r},\mathbf{r}_1) = \frac{\partial^2 F}{\partial n \partial n_1}(\mathbf{r},\mathbf{r}_1) - \frac{\partial^2 P}{\partial n \partial n_1}(\mathbf{r},\mathbf{r}_1), \tag{14}$$

$$L_4(\mathbf{r},\mathbf{r}_1) = -\frac{\partial F}{\partial n}(\mathbf{r},\mathbf{r}_1) + \frac{\partial P}{\partial n}(\mathbf{r},\mathbf{r}_1) 1/\epsilon. \tag{15}$$

Using the collocation method by Atkinson and co-workers[9,31,32] the above-mentioned integral equations can be solved and the reaction field matrix elements can be obtained from Eq. (5). It should be noted that for each frequency ω_n there is a reaction field matrix corresponding to dielectric constant $\epsilon(i\omega_n)$.

At room temperature ω_n is the order of 10^{14} rad/s.[6,33] For the electrolyte solution of interests, say 0.1 molar, the ion plasma frequency is of the order of 10^{12} rad/s. At frequencies higher than the plasma frequency, the ionic motions can be neglected. Thus, the $n=0$ term in Eq. (4) should be calculated from Poisson–Boltzmann equation, whereas the $n>0$ terms can be calculated from Poisson equation.

IV. VAN DER WAALS INTERACTION BETWEEN TWO POLARIZABLE DIPOLES LOCATED AT THE CENTERS OF TWO SPHERES IN AN ELECTROLYTE SOLUTION

In order to illustrate the application of the above-noted general formation we will calculate the van der Waals inter-

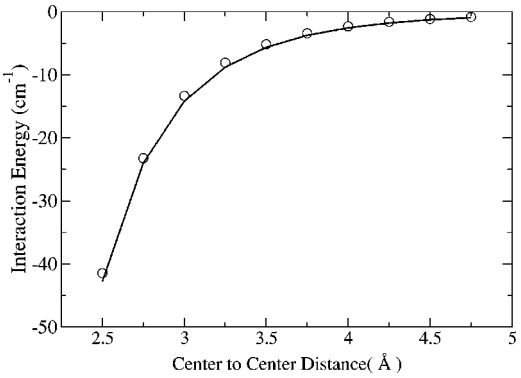

FIG. 2. The van der Waals interaction between two polarizable dipoles located at the centers of two spheres. Our calculation is given by the circles and the analytical solution is given by the solid line. The radius of both spheres is 1.0 Å and there is a polarizable dipole with polarizability $\alpha(0)=2.0$ Å^3 and $\omega_c=4000$ cm^{-1} at each center of the sphere. The dielectric constant of the solution is 80.0 and the Debye screening length is 0.1 Å^{-1}.

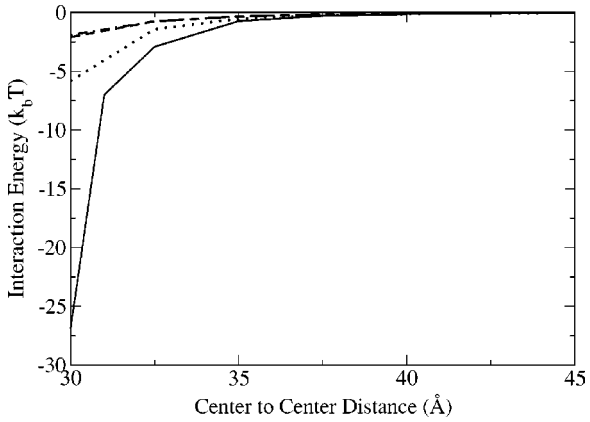

FIG. 3. The van der Waals interaction between two BPTI molecules at four different relative orientations. The molecular surface is generated by SANNER program (Ref. 35). The frequency-dependent dielectric constant of water is from Parsegian's parametrization of experimental data (Ref. 34). The Debye screening length is 0.1 Å^{-1} and the temperature is 298 K. The error of the interaction is within 1 kcal/mol when there are about 2000 triangulations on each protein surface.

action between two polarizable dipoles at the centers of two spheres. For simplicity we assume the polarizability takes the Drude oscillator form with static polarizability $\alpha(0)$ and the characteristic frequency ω_c, an approximation solution for the $n=0$ term has been obtained

$$W_0(D)=-\frac{\alpha(0)^2 k_B T}{2\epsilon^2(0)D^6}[6+12\kappa D+10\kappa^2 D^2+4\kappa^3 R^3 + \kappa^4 D^4]\exp^{-2\kappa D}, \tag{16}$$

where $\epsilon(0)$ is the zero-frequency dielectric constant of the electrolyte solution.[6] The above-mentioned result was obtained by solving the linearized Poisson–Boltzmann equation for two spheres with a superposition approximation.[6] If there is no electrolyte solution, the summation in Eq. (4) yields the well-known results, $-3/4\hbar\omega_c\alpha(0)^2/D^6$.[1] Using the integral equation form of the linearized Poisson–Boltzmann equation[9] the reaction field of two spheres system can be solved numerically and, hence, the $n=0$ term contribution of the van der Waals interaction. A comparison between our numerical calculation and the analytical expression is shown in Fig. 2. Except for some small minor deviations when the two spheres are really close, where the superposition approximation is not accurate anymore, the comparison demonstrates the utility of our approach.

V. THE VAN DER WAALS INTERACTIONS BETWEEN TWO BPTI MOLECULES IN AN ELECTROLYTE SOLUTION

Using the above-mentioned formulation the effective interactions between two BPTI molecules can be calculated at various distances and orientations. The static nuclear and electronic polarizabilities of each amino acid are given in Table 1 of Ref. 13. But accurate frequency-dependent polarizabilities are not available either from theoretical or experimental studies. In the work, we adopt a simple model to account for the frequency-dependent polarizability.[33] Namely, the total polarizability of a residue can be written as

$$\alpha(i\omega_n)=\frac{\alpha_{\rm nu}}{1+\omega_n/\omega_{\rm rot}}+\frac{\alpha_{\rm el}}{1+(\omega_n/\omega_I)^2}, \tag{17}$$

where $\alpha_{\rm nu}$ is the static nuclear polarizability of a residue and $\omega_{\rm rot}$ is a characteristic frequency of its nuclear collective motion, hence, our frequency-dependent nuclear polarizability is a generalization of the Debye model. $\alpha_{\rm el}$ is the static electronic polarizability of a residue and ω_I is the ionization frequency of a residue as in the traditional Drude oscillator model of electronic polarizabilities. For all residues we choose $\omega_{\rm rot}=20$ cm^{-1} and $\omega_I=10\,000$ cm^{-1}, which are the typical rotational frequency and electronic absorption frequency of molecules.[33] For water, an accurate parametrization of $\epsilon(i\omega)$ based on experimental data is available from Parsegian,[34] which is used in this work.

Figure 3 shows the results at four different relative orientations and it clearly indicates that the effective interaction can vary tens of k_BT among different relative orientations. Combined with our previous work[9] on the electrostatic contribution to the effective interaction between two protein molecules we now have a reliable way to evaluate protein–protein interactions in an aqueous solution within the framework of DLVO theory. Our method can be applied to any realistic shape of protein molecules, thus, an accurate orientationally dependent potential between two protein molecules can be obtained. Such a potential will be the first step toward the study of phase behaviors of protein solutions. It should be noted that the estimated anisotropy may change as two protein molecules become really close since the continuum model is adopted in our formulation. Thus, it is worthwhile to explore the effect due to the molecular nature of the solvent on the anisotropy.

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