



# Hidden peak of radial distribution function and effective attraction between like-charged proteins caused by translational motion of solvent molecules



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## ABSTRACT

To discuss the effective interactions between macroanions, such as acidic proteins, the radial distribution function between macroanions,  $g_{MM}(r)$ , was calculated using an integral equation theory with a charged hard spheres model under weak coupling conditions. Explicit and implicit solvent models were examined. The  $g_{MM}(r)$  for the explicit solvent model indicated a significant peak at the contact distance, which was caused by the translational motion of solvent molecules. In contrast, the  $g_{MM}(r)$  for the implicit solvent model did not indicate any significant peak at the distance because of no explicit solvent particles. Although there was a significant difference in the  $g_{MM}(r)$  for the explicit and implicit models, the structure factor  $S_{MM}(k)$  was nearly the same and the shapes and peak shifts caused by macroanion concentration changes were also similar to the experimental results. To reproduce the first sharp peak in  $g_{MM}(r)$ , the structure factor  $S_{MM}(k)$  provided by scattering experiments was not sufficiently long for standard analyses. This showed that the results provided by conventional small-angle scattering experiments cannot deny the existence of a first sharp peak in  $g_{MM}(r)$ .

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## 1. Introduction

Effective interactions between proteins are important for understanding information flow, work, biomolecule production, etc., in biological systems [1]. These interactions can be divided into two parts: direct and indirect interactions. Kinoshita et al. theoretically established the importance of indirect interactions, particularly the effective attractive interactions driven by the translational motion of solvent molecules [2–14]. The aggregation of proteins and colloidal particles has also been discussed on the basis of effective attractions [2–7]. These theoretical results suggest that attraction between macromolecules also occurs and that the radial distribution functions (or reduced density profiles) indicate a remarkable peak at the contact configuration. These inter-macromolecular interactions are important for information flow in bio-systems and should be related to equilibrium protein-cluster formation.

However, the experimental interpretations of equilibrium clusters are controversial [15,16]. These remarkable peaks have not been clarified in individual systems based on scattering experiments. Basically, assignments for the structure factor for macromolecules,  $S_{MM}(k)$ , have been based on models that do not incorporate explicit solvent particles [17–24]. These models often provide reasonable  $S_{MM}(k)$ , and effective

interactions have been discussed. These agreements with experimental results have given validity to implicit solvent models.

However, these agreements do not necessarily mean that these implicit solvent models are valid when discussing the association behaviors between macromolecules, such as the formation of equilibrium clusters of proteins. If reasonable results are also provided using other models, such as an explicit solvent model, then we cannot decide which model is most suitable. At least, we need other reasons to decide which model is better.

In the present study, explicit solvent models were also examined to discuss the effective attractions driven by the translational motion of solvent molecules. Both the radial distribution function,  $g_{MM}(r)$ , and the structure factor  $S_{MM}(k)$  were calculated to show the differences between these two models in  $k$ -space.

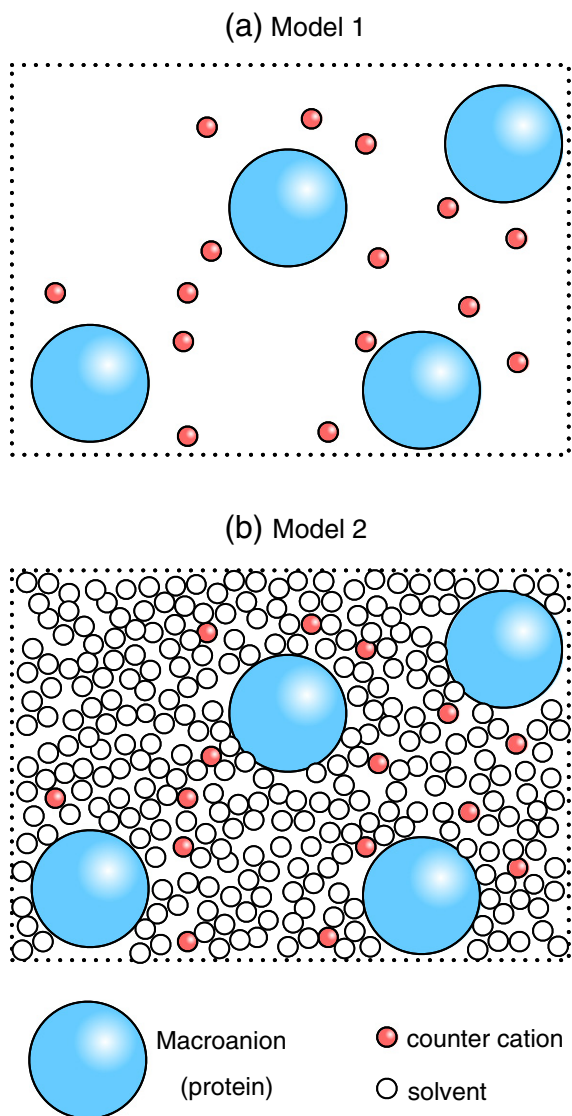
## 2. Theory and model

We calculated  $g_{MM}(r)$  by using an integral equation theory: the Ornstein–Zernike (OZ) equation with hypernetted-chain (HNC) theory [25]. We compared the results for two types of model systems: an implicit solvent model system (Model 1) and an explicit solvent model system (Model 2). Schematic diagrams for these models are shown in Fig. 1.

Model 1 (Fig. 1(a)) contains negatively charged hard spheres as macroanions (diameter  $\sigma_M = 16.8 \text{ \AA}$ , and charge  $Q_M = -4e, -5e, \text{ or } -6e$ ) and positively charged hard spheres as the counter ions (diameter  $\sigma_C = 2.8 \text{ \AA}$ , and charge  $Q_C = +1e$ ); however, there is no explicit

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**Fig. 1.** Schematic of (a) Model 1, our implicit solvent model, and (b) Model 2, our explicit solvent model.

solvent particle in this system. Here, the macroanion concentration is finite and the system does not contain additional salt. The concentration dependence for macroanions was examined, and charge neutrality ( $Q_M \rho_M + Q_C \rho_C = 0$ ) was maintained for all concentrations. The system temperature was 298 K. The Coulomb interaction was divided by a factor of 78.5, which is the dielectric constant of water at this temperature.

For comparisons, neutral hard spheres (diameter,  $\sigma_V = 2.8 \text{ \AA}$ ) were also added as solvent molecules for Model 2 (Fig. 1(b)). The total packing fraction (0.383), which is the packing fraction of water, was maintained for all macroanion concentrations.

The function  $g_{MM}(r)$  was calculated to discuss the potential of mean force (effective interaction) between macroanions,  $W_{MM}(r)$ , which is defined as

$$W_{MM}(r) = -k_B T \ln g_{MM}(r)$$

where  $k_B$  and  $T$  are the Boltzmann factor and temperature, respectively [25,26]. In this paper, the values of the effective potential are shown, but the plot of  $W_{MM}(r)$  is not shown.  $S_{MM}(k)$  is defined by

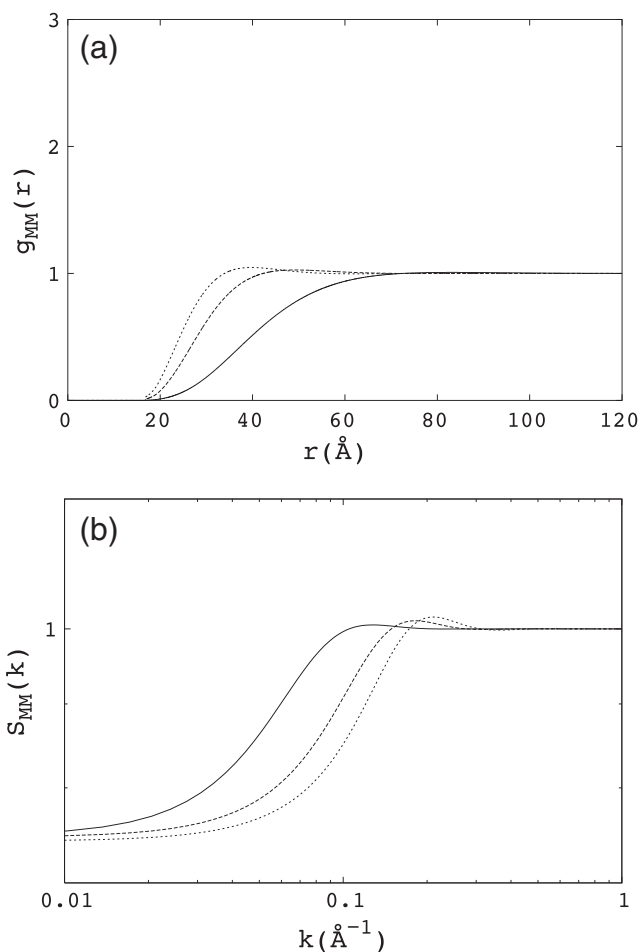
$$S_{MM}(k) = 1 + \frac{4\pi\rho_M}{k} \int_0^\infty [g_{MM}(r) - 1] r \sin(kr) dr$$

where  $\rho_M$  is the number density of macroanions and  $k$  is the wave number [25,26]. Then,  $S_{MM}(k)$  is obtained from the Fourier transformation of  $g_{MM}(r)r$ .

Computer simulations cannot readily obtain  $g_{MM}(r)$  for these systems, which include charged particles. In the present study, the concentration dependence was examined from a dilute to a semi-dense system. The calculations for these systems and studying their dependencies are difficult. Thus, the HNC–OZ theory was adopted in the present study, as it is known to provide reasonable results for the systems described above, at least qualitatively [27–32]. The details of these calculations are nearly similar to those of the methods used in previous reports [7,27,28,33–38]. The equations for the dilute limit of macroanions were used to obtain  $g_{MM}(r)$  in previous reports [7,27,28]. However,  $g_{MM}(r)$  and  $W_{MM}(r)$  can be directly obtained using the HNC–OZ equation for a multicomponent fluid because the macroanion concentration is considered to be finite in the present study.

### 3. Results and discussion

We calculated the correlation functions for a system that contains macroanions with  $Q_M = -4e, -5e, \text{ or } -6e$ . Here, we show the results for macroanions with charges of  $-6e$  because the features of these results are nearly similar to each other. The plots of  $g_{MM}(r)$  and  $S_{MM}(k)$  for Model 1 are shown in Fig. 2(a) and (b), respectively. When the protein concentration is low (packing fraction  $\phi_p = 0.0060$ ), there is a broad peak around  $83 \text{ \AA}$  in  $g_{MM}(r)$ . The broad peak position is shifted to a smaller  $r$  value as the concentration increases. These peaks are



**Fig. 2.** (a) Radial distribution function between two macroanions,  $g_{MM}(r)$ , and (b) the effective structure factor of macroanions,  $S_{MM}(k)$ , for Model 1. Dotted line:  $\phi_p = 0.0060$ ; dashed line:  $\phi_p = 0.0210$ ; solid line:  $\phi_p = 0.0360$ .

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