Modeling the Electrostatics and Size Effect within a Crowded Bioenvironment

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Summary: Biological fluids typically contain a large number of macromolecules occupying up to 40% of the total volume. Current understanding of the effect of high concentration, or 'macromolecular crowding', on cellular processes is primarily based on the excluded-volume considerations in which all intermolecular interactions beyond the short-ranged repulsion are neglected. In this work, a density functional theory (DFT) accompanied by Monte Carlo simulations is employed to investigate the structural and thermodynamic properties of a crowded cellular environment within the primitive model where biomacromolecules are represented by neutral and charged hard spheres and the solvent by a continuous dielectric medium. The performance of the DFT has been tested with extensive results from Monte Carlo (MC) simulations for the pair correlation functions (PCFs), excess internal energies, and osmotic coefficients under a variety of solution conditions.

Keywords: density functional theory; macromolecular crowding; Monte Carlo simulation; primitive model

Introduction

Dispersions of macroions and neutral species at high volume occupation provide a simple model to represent the crowded cellular environment that contains numerous biomacromolecules and cellular polymers. The so-called 'macromolecular crowding' affects the functions and activities of biomacromolecules and is relevant to most biological processes in every body cell, in the blood, and in all body fluids, especially the intercellular fluids[1,2]. Without exaggeration, essentially all life processes take place in a crowded environment.

The structural and thermodynamic properties of macromolecular crowding are primarily determined by the excluded-volume effects and the long-ranged Coulomb interactions. A number of theoretical and simulation techniques have been applied to investigating the properties of macromolecular crowding in the context of the primitive model where biomacromolecules are treated as charged and neutral hard spheres and the solvent as a continuous dielectric medium[3]. These techniques range from the conventional Poisson-Boltzmann (PB) equation and the

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hypernetted chain (HNC) approximation, to Monte Carlo (MC) simulations. At least within the primitive model, the basic physics is now well understood using conventional approaches. However, quantitative representation of the structural and thermodynamic properties of such systems remains a grand challenge. The difficulty is mainly due to the high asymmetry of the constituents in terms of both size and charge valence. The purpose of present work is to apply a newly developed density functional theory (DFT)[4], along with Monte Carlo simulations, to investigating the structural and thermodynamic properties of macromolecular crowding. Unlike many previous publications for macromolecular crowding, this work accounts for both excluded volume and electrostatic interactions.

Theoretical Background

Within the primitive model for 'macromolecular crowding', the intrinsic Helmholtz free energy functional $F[\{\rho_i(\mathbf{r})\}]$ can be decomposed into four distinctive contributions including an ideal-gas term, the excluded-volume effect, the direct Coulomb interactions, and the intermolecular correlations:

$$F[\{\rho_i(\mathbf{r})\}]=F^{id}[\{\rho_i(\mathbf{r})\}]+F_{hs}^{ex}[\{\rho_i(\mathbf{r})\}]+F_C^{ex}[\{\rho_i(\mathbf{r})\}]+F_{el}^{ex}[\{\rho_i(\mathbf{r})\}]. \quad (1)$$

In Eq.(1), $\{\rho_i(\mathbf{r})\}$ stands for a set of density profiles for all species, i.e., macroions, neutral species and small ions. While the ideal-gas contribution $F^{id}[\{\rho_i(\mathbf{r})\}]$ and the direct Coulomb energy $F_C^{ex}[\{\rho_i(\mathbf{r})\}]$ are known exactly, the other two terms, $F_{hs}^{ex}[\{\rho_i(\mathbf{r})\}]$ and $F_{el}^{ex}[\{\rho_i(\mathbf{r})\}]$, can only be evaluated with some approximations. The excluded-volume term arises from the sizes of small ions and biomacromolecules; it is represented by a modified fundamental measure theory (MFMT). $F_{el}^{ex}[\{\rho_i(\mathbf{r})\}]$ takes into account the intermolecular correlations due to the Coulomb and hard-sphere interactions. This term is calculated by using a quadratic functional Taylor expansion. If $F_{el}^{ex}[\{\rho_i(\mathbf{r})\}]$ vanishes, Eq.(1) leads to the conventional Boltzmann equation for the electrostatic interactions. To evaluate the Helmholtz energy functional due to the intermolecular correlations, we use the direct correlation functions (DCFs) obtained from the mean-spherical approximation (MSA). At equilibrium, the pair correlation functions (PCFs) can be calculated from the Euler-Lagrange equation, and subsequently all thermodynamic properties can be calculated via standard statistical-mechanics relations.

To test the reliability of the analytical results, we have compared the pair distribution functions and internal energies with the corresponding results from the canonical ensemble Monte Carlo simulations. The details of theory and simulations have been given elsewhere[4].

Results and Discussion

We first examine the performance of the DFT for predicting the microscopic structures (as represented by various PCFs) of crowded systems containing macroions, neutral particles and small ions. Throughout this work, the symbols g_{++}, g_{--}, g_{+-}, g_{0+}, g_{0-} and g_{00} designate, respectively, the macroion-macroion, counterion-counterion, macroion-counterion, neutral-macroion, neutral-counterion and neutral-neutral pair correlation functions (PCFs). For all the systems considered in this work, the size ratio of the macroions, counterions and neutral particles is fixed at 4.0nm/0.4nm/1.6nm, and the concentration of electrolyte C_e and the valence of macroions Z_+ are retained at 0.002M and +15, respectively.

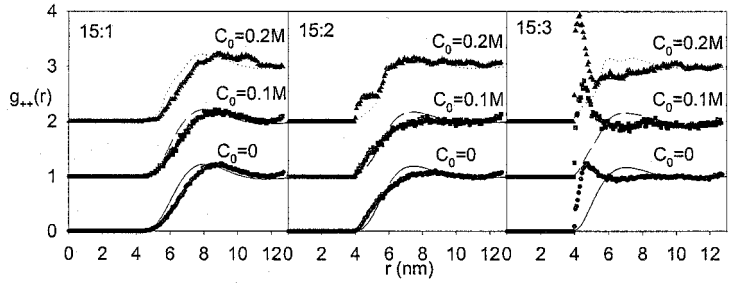

Figure 1. Macroion-macroion PCFs. Symbols and lines represent MC data and DFT results respectively. The curves for C_0=0.1M and 0.2M have been consecutively shifted upward by one unit.

Figures 1 to 6 display the calculated results from DFT and Monte Carlo simulations for the PCFs under a number of solution conditions. In these calculations, the concentration of neutral component C_0 varies from 0 to 0.2M, the valence of counterions Z_- varies from -1 to -3, and the total volume occupation of neutral particles varies from 4.03% to 29.86%. In Figures 1 and 2, one may observe that the repulsion between macroions is reduced while that between counterions is increased with the increase of the counterion valence. The potential of mean force between similarly charged macroions becomes strongly attractive in trivalent solutions, in particular at high concentration of

neutral species, while they are purely repulsive in the corresponding monovalent solution. In general, the correlation between like-charged ions decreases when more neutral particles are added. Figure 3 shows that the accumulation between unlike-charged ions is more evident with the increase of counterion valence or the content of neutral component. Figures 4 to 6 indicate that the change of counterion valence has only minor influence on the distributions of macroions, counterions and neutral particles near the surface of a fixed neutral particle but their accumulation in the vicinity of the fixed neutral particle will be enhanced when the concentration of neutral species rises.

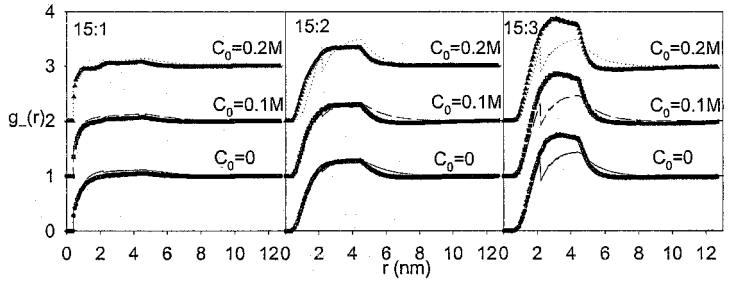

Figure 2. Counterion-counterion PCFs. Notation is the same as that in Figure 1.

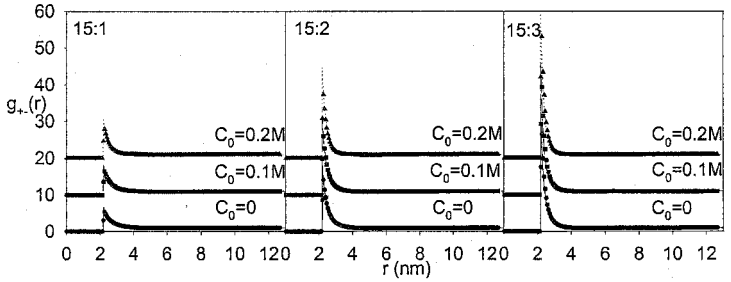

Figure 3. Macroion-counterion PCFs. The curves for C_0=0.1M and 0.2M have been consecutively shifted upward by ten units.

Under most circumstances, the DFT agrees fairly well with MC for predicting the macroion-counterion, neutral-macroion, neutral-counterion and neutral-neutral distributions. However, for systems with strong electrostatic interactions, i.e., in 15:2 and 15:3 solutions, the DFT fails to faithfully reproduce the macroion-macroion and counterion-counterion correlation functions. Besides a serious deviation on the macroion-macroion distributions, the DFT mistakenly predicts a

discontinuity of the counterion-counterion pair correlation function. This deficiency is probably caused by the inaccuracy of the DCFs from MSA and the quadratic Talyor expansion for the intermolecular correlations.

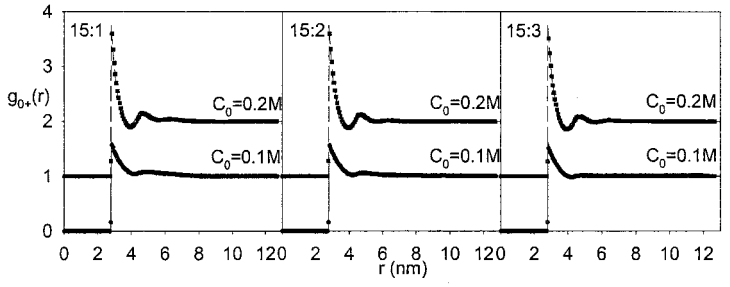

Figure 4. Neutral-macroion PCFs. The curves for C_0=0.2M have been consecutively shifted upward by one unit.

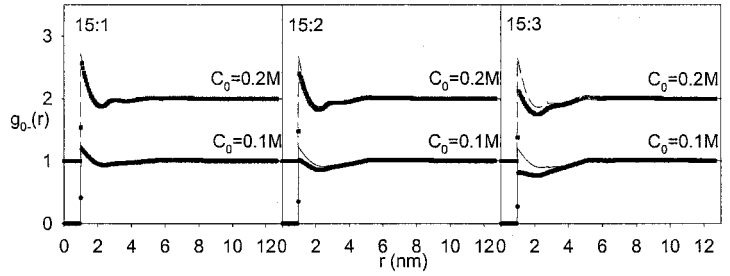

Figure 5. Neutral-counterion PCFs. Notation is the same as that in Figure 4.

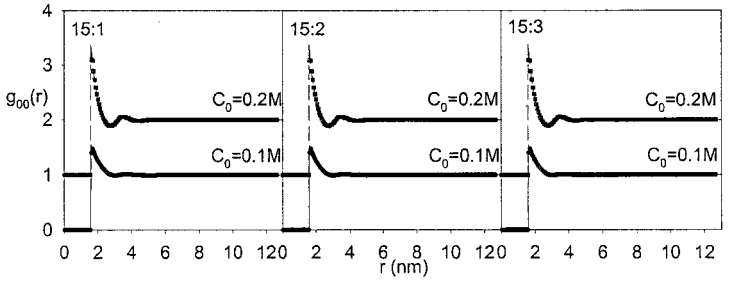

Figure 6. Neutral-neutral PCFs. Notation is the same as that in Figure 4.

Next we compare the thermodynamic properties of above systems calculated from DFT and MC. Table 1 gives the reduced excess internal energy per particle and the osmotic coefficients from MC and DFT. The agreement between theory and simulation is excellent for all cases studied in this work, even for systems in which DFT predicts inaccurate microscopic structures. This is because the thermodynamic properties are mainly determined by the macroion-counterion PCFs, which the DCF provides an accurate representation.

Table 1. The excess internal energies and osmotic coefficients obtained by MC and DFT.

		-Excess Internal Energy		Osmotic Coefficient	
C_0 (M)	Z_-	MC	DFT	MC	DFT
0	-1	1.70	1.78	0.741	0.747
	-2	4.13	4.31	0.429	0.421
	-3	7.12	7.11	0.0860	0.0857
0.1	-1	0.422	0.444	1.77	1.77
	-2	0.611	0.642	1.81	1.80
	-3	0.776	0.777	1.81	1.81
0.2	-1	0.245	0.261	3.50	3.49
	-2	0.497	0.355	3.53	3.59
	-3	0.416	0.420	3.61	3.62

Conclusion

We have shown that the DFT is able to describe the nonideality of highly asymmetric electrolyte and neutral component mixtures that simulate 'macromolecular crowding'. The PCFs, excess internal energies and osmotic coefficients predicted by DFT are in good agreement with results from MC simulations except when there is a very strong electrostatic interaction. Although the DFT fails to reproduce the macroion-macroion and counterion-counterion PCFs for systems with strong electrostatic interactions owing to the limitations of MSA and quadratic expansion, it successfully reproduces other PCFs and the thermodynamic properties.

Certainly the primitive model is oversimplified for representing 'macromolecular crowding', but it provides at least a step forward beyond merely excluded-volume considerations. Other interactions such as chain connectivity and van der Waals attractions also affect the behaviors of biological crowded environments. In our previous work, we have demonstrated the versatility of DFT to account for the influences of other non-bonded interactions such as chain connectivity, van der Waals attraction and association. [5-10] Therefore, the extention of the current DFT for crowding under more realistic situations will be a natural direction for our future work.

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