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Localization and visualization of excess chemical potential in statistical mechanical integral equation theory 3D-HNC-RISM

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Abstract

In this study the excess chemical potential of the integral equation theory, 3D-RISM-HNC [Q. Du, Q. Wei, J. Phys. Chem. B 107 (2003) 13463–13470], is visualized in three-dimensional form and localized at interaction sites of solute molecule. Taking the advantage of reference interaction site model (RISM), the calculation equations of chemical excess potential are reformulized according to the solute interaction sites *s* in molecular space. Consequently the solvation free energy is localized at every interaction site of solute molecule. For visualization of the 3D-RISM-HNC calculation results, the excess chemical potentials are described using radial and three-dimensional diagrams. It is found that the radial diagrams of the excess chemical potentials are more sensitive to the bridge functions than the radial diagrams of solvent site density distributions. The diagrams of average excess chemical potential provide useful information of solute–solvent electrostatic and van der Waals interactions. The local description of solvation free energy at active sites of solute in 3D-RISM-HNC may broaden the application scope of statistical mechanical integral equation theory in solution chemistry and life science.

Keywords: Solvation free energy; Integral equation theory; 3D-RISM-HNC; Statistical mechanics; Visual representation

1. Introduction

The solvent effects play an important role in many research fields of chemistry and life science. Quantitative evaluation of solvation free energy is of the main determinant quantities in the study of molecular conformation and association of biomolecules, such as proteins and polynucleotides. Solvation free energy constitutes an important, but difficult-to-find quantity, posing a challenge to computational chemists. The reference interaction site model (RISM) integral equation theory has received a large amount of interest over the past three decades as a means to calculate the solvation free energy surrounding a solute molecule, as described by radial distribution functions of the solvent site densities $\langle \Delta\rho_\alpha(\mathbf{r})\rangle$ [1–9]. Still more importantly, by employing the hypernetted chain (HNC) closure relation, an expression has been derived for the solvation free energy as a function of these solvent distributions [10–15].

The unique merit of three-dimensional RISM is that it describes the solvation structure surrounding a solute molecular space by solvent site density distribution functions $\langle \Delta\rho_\alpha(\mathbf{r})\rangle$. In the 3D-RISM-HNC approach, the site densities $\langle \Delta\rho_\alpha(\mathbf{r})\rangle$ of solvent molecule are the foundational quantities and all other physical properties of solution are described through the solvent site densities. The formulization of excess chemical potentials has been provided by several authors [9,15–18]. In many cases we do not only want to know the total solvation free energy in solution, but also want to know the solvation structure and the solvation free energies at some active sites in solute molecular structure. For example, the local solvation free energy in active pocket of protease is most interesting in protein chemistry for us, and we want to calculate the docking free energy between ligand and its bioreceptor in the active pocket for rational drug design.

Taking the advantage of reference interaction site model (RISM), in this study we reformulize the calculation equations of excess chemical potential according to the solute interaction

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sites s at point $\mathbf{r}$ in molecular space $\langle \Delta\mu_s(\mathbf{r})\rangle$. The goal of this study is to provide a way for the localization and visualization of the excess chemical potential in 3D-RISM-HNC through two examples, *N*-methyl amine (NMA) and ethanol. Although these two molecules are very small comparing with biomolecules, however, the 3D-RISM-HNC approach and the methods provided in this study can be applied in part of macromolecules easily, such as the active pocket of proteins, and to study the excess chemical potential in active sites of proteins.

2. Theory and method

The formulization of 3D-RISM-HNC has been well established in previous works by several authors [9,15–18]. Here we reformulize the equations for localization and visualization of excess chemical potential in 3D-RISM-HNC. The fundamental quantities in RISM for obtaining thermodynamic properties are the reduced average densities $\langle \rho_\alpha(\mathbf{r})\rangle$ of solvent interaction sites. By convention, in this study the Greek letter α is for the solvent interaction sites and the Roman letter s is for the solute interaction sites, respectively. In the 3D-RISM-HNC integral equation theory, average densities $\langle \rho_\alpha(\mathbf{r})\rangle$ are computed from the following HNC iterative closure:

$$h_\alpha(\mathbf{r}) = \mathrm{e}^{[-\beta U_\alpha(\mathbf{r}) + h_\alpha(\mathbf{r}) - c_\alpha(\mathbf{r}) - b_\alpha(\mathbf{r})]} - 1 \tag{1}$$

where $h_\alpha(\mathbf{r}) = \langle \rho_\alpha(\mathbf{r})\rangle/\bar{\rho} - 1$ is the solute–solvent site correlation function and $c_\alpha(\mathbf{r})$ is the solute–solvent direct correlation function defined by

$$\bar{\rho} h_\alpha(\boldsymbol{r}) = \sum_\gamma c_\gamma * \chi_{\gamma\alpha}(\boldsymbol{r}) \tag{2}$$

where $\chi_{\gamma\alpha}(\mathbf{r})$ is the solvent susceptibility response function of pure liquid, and the symbol * represents a special convolution. The function $b_\alpha(\mathbf{r})$ in Eq. (1) is the bridge function of interaction site α in solvent molecule. The interaction potential $U_\alpha(\mathbf{r})$ from the solvent site α is represented by a sum of radially symmetric Lennard–Jones equations (6)–(12), which describes the non-polar van der Waals interactions, and Coulomb electrostatic potential equation centered on the interaction site s of solute,

$$U_\alpha(\mathbf{r}) = \sum_s U_{\alpha s}^{(\mathrm{LJ})}(\mathbf{r}) + \sum_s U_{\alpha s}^{(\mathrm{elec})}(\mathbf{r}) \tag{3}$$

with

$$U_{\alpha s}^{(\mathrm{LJ})}(\mathbf{r}) = 4\varepsilon_{\alpha s}\left[\left(\frac{\sigma_{\alpha s}}{|\mathbf{r}-\mathbf{r}_s|}\right)^{12} - \left(\frac{\sigma_{\alpha s}}{|\mathbf{r}-\mathbf{r}_s|}\right)^{6}\right] \tag{4}$$

and

$$U_{\alpha s}^{(\mathrm{elec})}(\mathbf{r}) = \frac{q_\alpha q_s}{|\mathbf{r}-\mathbf{r}_s|} \tag{5}$$

where $\varepsilon_{\alpha s}$, $\sigma_{\alpha s}$, q_α, and q_s are the L–J parameters and atomic charges, respectively. The parameters used in 3D-RISM-HNC are commonly taken from the molecular mechanical force fields, such as AMBER [19], CHARMM [20] and OPLS [2].

The excess chemical potential on site s of solute is the sum of non-polar and electrostatic free energy contributions. For numerical convenience, the two parts of excess chemical potential are evaluated by integration over scaling factor λ [9,11,17] of L–J radius, $\lambda\sigma_{\alpha s}$, and of the solute atomic charges, λq_s, from 0 to 1, respectively,

$$\langle \Delta\mu_s^{(\mathrm{np})}(\mathbf{r})\rangle = \int_0^1 \mathrm{d}\lambda \sum_\alpha \frac{\partial U_{\alpha s}^{(\mathrm{LJ})}(\mathbf{r};\lambda)}{\partial\lambda} \langle \rho_\alpha(\mathbf{r})\rangle \tag{6}$$

and

$$\langle \Delta\mu_s^{(\mathrm{elec})}(\mathbf{r})\rangle = \int_0^1 \mathrm{d}\lambda \sum_\alpha \frac{\partial U_{\alpha s}^{(\mathrm{elec})}(\mathbf{r};\lambda)}{\partial\lambda} \langle \rho_\alpha(\mathbf{r})\rangle \tag{7}$$

The total average excess chemical potential $\langle \Delta\mu(\mathbf{r})\rangle$ is obtained by adding these two parts,

$$\langle \Delta\mu_s(\mathbf{r})\rangle = \langle \Delta\mu_s^{(\mathrm{np})}(\mathbf{r})\rangle + \langle \Delta\mu_s^{(\mathrm{elec})}(\mathbf{r})\rangle \tag{8}$$

In Eqs. (6)–(8), the average excess chemical potential $\langle \Delta\mu_s(\mathbf{r})\rangle$ is formulized according to the solute interaction sites s and at point $\mathbf{r}$ in space, which describe the local solvation free energies at interaction sites of solute. In this way we can plot the radial and three-dimensional diagrams of average excess chemical potentials for solute interaction sites, and also provide local description for solvation free energy in the vicinity where we are interested.

In Eq. (1), the potential energy function $U_\alpha(\mathbf{r})$ plays an important role for the accuracy of calculation results. However, using accurate and sophisticated potential function (e.g. quantum mechanical potential functions) is very difficult and it may lose the merit of simplicity and efficiency in 3D-RISM-HNC approach. One method to improve the accuracy of 3D-RISM-HNC is the bridge functions $b_\alpha(\mathbf{r})$ for each interaction site of solvent molecule [9,17,18], which are the remediation terms for potential function $U_\alpha(\mathbf{r})$. The bridge function $b_\alpha(\mathbf{r})$ has well-defined formal diagrammatic structure in the theory of liquids [4]. The bridge functions play the role of effective potentials, which are adjusted empirically in this study to improve the accuracy of the calculation results. Water molecule has three interaction sites, one oxygen atom and two hydrogen atoms. The hydrogen bridge function $b_\mathrm{H}(\mathbf{r})$ is simply a remedial term for the L–J interaction function,

$$b_\mathrm{H}(\mathbf{r};\lambda) = -\ln[\omega_\mathrm{OH} * \mathrm{e}^{[-\beta U_\mathrm{O}^{(\mathrm{LJs})}(\mathbf{r};\lambda)]}] \tag{9}$$

and ω_OH is the site–site intramolecular correlation function,

$$\omega_\mathrm{OH} = \frac{\delta(|\mathbf{r}| - l_\mathrm{OH})}{4\pi l_\mathrm{OH}^2} \tag{10}$$

where the symbol * represents a three-dimensional convolution. The hydrogen bridge function describes the repulsive interaction of solute–water in short distance. Because there is no repulsive branch in potential equation at short distance for hydrogen, if the water TIP3 model [21] is used.