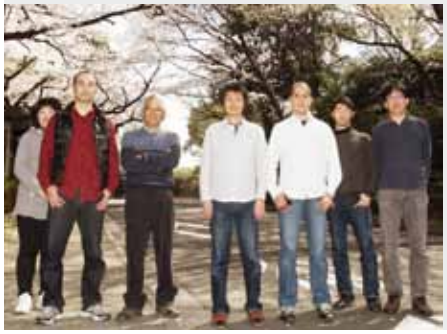
Developing the Statistical Mechanics Theory of Liquids in Chemistry and Biophysics

Department of Theoretical and Computational Molecular Science
Division of Theoretical Molecular Science II



HIRATA, Fumio	Professor
YOSHIDA, Norio	Assistant Professor
MARUYAMA, Yutaka	Post-Doctoral Fellow
PHONGPHANPHANEE, Saree	Post-Doctoral Fellow
SINDHIKARA, Daniel J.	Post-Doctoral Fellow
KIYOTA, Yasuomi	Post-Doctoral Fellow
SUETAKE, Yasumi	Secretary
KONDO, Naoko	Secretary
YAMADA, Mariko	Secretary

"Molecular recognition" is an essential elementary process for protein to function. The process is a thermodynamic process which is characterized with the free energy difference between two states of a host-guest system, namely, associated and dissociated states. It is readily understood that the structural fluctuation of protein gives a big effect on the free energy barrier. In that respect, the "molecular recognition" is a thermodynamic process which is conjugated with the structural fluctuation of protein.

We have been developing a new theory concerning the molecular recognition, based on the 3D-RISM/RISM theory which is a statistical mechanics of liquids. The theory has successfully "probed" small ligands such as water molecules and ions bound in a small cavity of protein.[1–3)]

1. Solvent and Salt Effects on Structural Stability of Human Telomere[4)]

Human telomere DNA is of intense interest because of its role in the biology of both cancer and aging. The single-stranded telomere terminus can adopt the structure of a G-quadruplex, which is of particular importance for anticancer drug discovery, and various G-quadruplex structures have been reported. The solution structure of human telomeric DNA in the presence of Na^+ has been determined by NMR to be anti-parallel basket-type, while the structure in KCl solution is still an open question. So, we have studied telomere structure in the two electrolyte solutions based on the 3D-RISM theory.

In pure water, the chair-type conformation was found to be the most stable one, which is followed by basket-, hybrid-, and propeller-type structures in the order. It is clarified that the order of the stability is determined essentially by the solvation free energy, not by the conformational energy.

The order of the stability changes in 0.1 M NaCl solutions from that in pure water. The basket-type structure becomes the most stable one in the electrolyte solution. The theoretical finding is consistent with the experimental observation due to NMR. The reversed order of the conformational stability was attributed to the salt effect, especially, to that from the Na^+ ions bound at inter-strand spaces of DNA.

Concerning the conformational stability in KCl solutions, our results predict that the order is not changed from that in pure water, that is, the chair-type is the most stable one. The finding suggests that the effect of the potassium ion upon the structure is not so strong as the sodium ion to change the order of the stability determined in pure water.

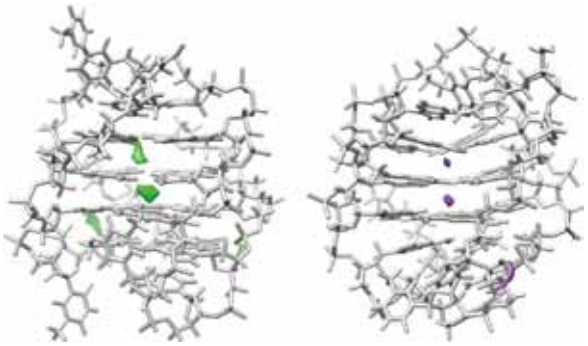


Figure 1. Na^+ and K^+ ions bound, respectively, by the basket- and chair-type structures of human telomere.

2. The Electronic-Structure Theory of a Large Molecular-System in Solution: Application to the Intercalation of Proflavin with Solvated DNA[5)]

A new approach (QM/MM/RISM) to treat the electronic structure of a macromolecule in solutions, which combines the quantum mechanics (QM), molecular mechanics (MM) and the RISM/3D-RISM theory, was presented. In the approach, solute is treated with the QM/MM method, while the solvent effect is handled by the RISM/3D-RISM theory. (Figure 2)

The QM/MM/RISM method was applied to investigate the intercalation of proflavine (PR) to decameric DNA double strands as an illustrative example. The free energy and solvation structure of $[deca(dA\text{-}dT)]_2$ and $[deca(dG\text{-}dC)]_2$ and their

complex with PR were evaluated. The free energy change associated with the intercalation as well as the affinity of PR to two different DNA sequences was considered. The dG-dC base sequence shows greater affinity to proflavine than the dA-dT sequence. The results are consistent with the earlier experimental and computational studies.

We evaluated the three-dimensional distribution function (3D-DF) of solvent around solutes, DNA, PR, and DNA-PR complexes. We also calculated the radial distribution functions (RDFs) of solvent atoms around a designated atom of solutes. The intercalation induces a drastic change in the solvation structure of PR represented by the distribution functions. The exclusion of water molecules upon the intercalation contributes to increasing in Δμ of DNA-PR complexes. The solvent distribution also indicates that the polar solvent is distributed around negatively charged phosphates, and the amine of proflavine mitigates the electronic interaction between those atoms. Our results clearly support the hypothesis proposed by Ruiz *et al*.

It was demonstrated in this article that the method is applicable to a variety of nano- and biochemical problems involving the electronic structure of a large molecules in solvent. Such studies with the QM/MM/RISM method are in progress.

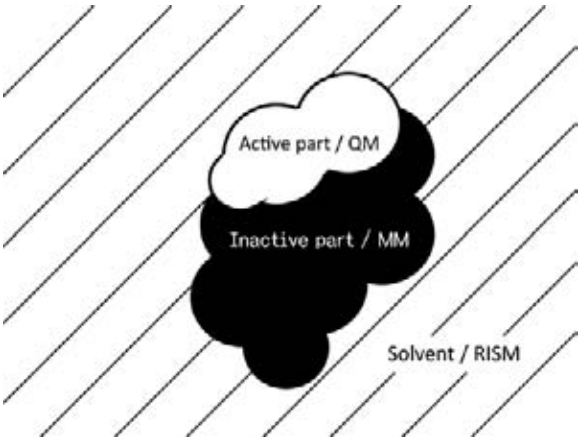


Figure 2. Schematic descripttion of partitioning of the system in QM/MM/RISM method.

3. A New Approach for Investigating the Molecular Recognition of Protein: Toward Structure-Based Drug-Design Based on the 3D-RISM Theory[6)]

Recently, we started our effort on drug design based on the 3D-RISM theory. Our strategy to realize “drug binding” or molecular recognition (MR) has been to consider a drug molecule as a component of solvent or solution, and to find the distribution of drug molecules around the binding site of protein by solving the 3D-RISM equation. The method was so successful as far as the size of drug molecules is reasonably small, such as water and ethanol. However, we have realized that the method becomes increasingly difficult as molecular size of drug gets bigger and bigger. It is because numerical solutions of the 1D-RISM equation for solvent, which should be done prior to the 3D-RISM calculation, becomes unstable due to inherent non-linearity of the equation.

However, many ligands of biological interests, including ordinary drug molecules, are not so small. Therefore, we proposed a new approach to tackle the MR of large ligand molecules by protein based on the 3D-RISM and RISM theories. The strategy of the method is to regard both a ligand molecule and a receptor protein as solutes, which are immersed in solvent in the infinite dilution. The distribution of ligand molecules around a receptor protein is described by the sol**u**te–sol**u**te 3D-RISM (or uu-3D-RISM) instead of conventional sol**u**te–sol**v**ent 3D-RISM (or uv-3D-RISM).

The new method is applied to Phospholipase A2 (PLA2) which is known as a receptor of acetylsalicylic acid (aspirin). Since the size of aspirin is much larger and more complex than those we have examined previously, to analyze the density distribution function (DDF) from uu-3D-RISM is not a trivial problem. So, we developed a new method to analyze DDF, defining a new function which locates the center of the most probable distribution of ligand. The orientation of aspirin inside the binding-site of PLA2 was determined by defining a score function which ranks the fitting level of trial orientations with DDF. The binding mode of the ligand inside the pocket was in fair agreement with that determined from the X-ray crystallography. (Figure 3)

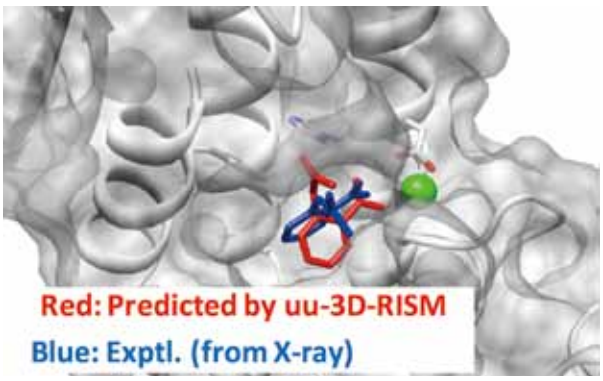


Figure 3. Predicted binding-mode of aspirin, which is obtained from uu-3D-RISM. The binding-mode determined by X-ray structure is depicted with blue sticks.

References

1) F. Hirata, *Molecular Theory of Solvation*, Kluwer; Dordrecht, Netherlands (2003).
2) A. Kovalenko and F. Hirata, *J. Chem. Phys.* **110**, 10095–10112 (1999).
3) T. Imai, R. Hiraoka, A. Kovalenko and F. Hirata, *J. Am. Chem. Soc. (Communication)* **127**, 15334–15335 (2005).
4) Y. Maruyama, T. Matsushita, R. Ueoka and F. Hirata, *J. Phys. Chem.* **115**, 2408 (2011).
5) N. Yoshida, Y. Kiyota and F. Hirata, *J. Mol. Liq.* **159**, 83 (2011).
6) Y. Kiyota, N. Yoshida and F. Hirata, *J. Chem. Theory Comput.* **7**, 3803–3815 (2011).