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Estimation of binding free energy based on the MM/3D-RISM method for the Pim1-ligand system

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To seek the drug candidate molecules, it is necessary to assess the binding affinity of a protein with its inhibitors. A large number of computational methods for estimation the binding free energy have been proposed. MD simulation is a powerful method for computationally estimating the physical quantity including the binding free energy. Although the estimation of the physical quantity of the system which has a huge amount of the degree of the freedom requires enormous computational cost, we sometimes cannot explore the enough structural space to evaluate an accurate value. On the other hand, 3D-RISM theory, a statistical theory for the molecular liquid, can estimate the solvation free energy in a reasonable computational cost by analytically calculating configuration integral of the solvent. In this regards, the combination of the 3D-RISM theory and MD simulation can escape the insufficient sampling. However, the quantitative capability of the MM/3D-RISM method has been ambiguous so far since this is a somehow novel method and has been applied to few systems. We apply this method to estimate binding free energy between Pim1 kinase and its inhibitors. Pim1 kinase is a famous target protein for treating hematopoietic malignancies, such as leukemia, lymphoma and prostate cancer. As a result, we get an approximately R=0.7 of the correlation coefficient between experimental and calculated values. Furthermore, we suggest a way of possible a lead optimization procedure by means of the 3D-RISM theory and MM/3D-RISM method.

Biography

Takeshi Hasegawa is currently a graduate student of Ritsumeikan University at Department of Bioinformatics of College of Life Sciences.

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