Biophysics and Physicobiology

Preface

Preface of Special Issue "Protein-Ligand Interactions"

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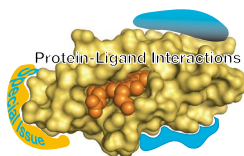[2]*Center for Informational Biology, Ochanomizu University, 2-1-1 Otsuka, Bunkyo, Tokyo 112-8610, Japan*
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When we consider investigating function of macromolecules, it is hardly possible to draw an experiment map without taking interactions of other molecules (ligands) into account, whether they could be metal ion, ATP, hormone, carbohydrate, lipid, nucleic acid, DNA, RNA, peptide and protein. In other words, no biological function can be elucidated without molecular interactions. Therefore, the study of protein-ligand interactions has been one of the long-standing fields in biophysics. Understanding in this field is, for example, a fundamental step for the rational design of a ligand to target a specific protein [1, 2]. The questions to be asked in this topic include mechanisms of selectivity, swift binding, and rapid turnover, if one concentrates on enzyme function, but different emphases can be placed on different aspects. These questions have been addressed both experimentally and computationally for a long time, but they are not fully resolved, hence more than 100 papers around this area is published every year, even when one just counts review literature. Recent progress in the methods for analysing protein-ligand interactions such as proteomics and other omics analyses, X-ray crystallography, NMR, mass spectrometry (MS), computer simulation and so forth, is astonishing and all those methods, with combination, have a potential to completely revolutionise our understanding of this topic. The goal of this special issue is, therefore, to exchange the latest advances amongst the community and to inform researchers in related fields of its potential.

In this special issue, we openly invited submission and finally have the following twelve papers; nine are based on computational study and three are based on wet-lab study. This special issue starts with the literature by Ishii *et al*. [3]

that gave us a good review on the history of MS. Based on the background understanding, they demonstrated the power of MS for detecting conformational changes of protein with ligand, its stoichiometry and its dissociation constant. Then follow several papers focusing on protein structures. Iakovou *et al*. [4] developed a new virtual reality method for protein docking with haptics device. The software enables us to "feel" the docking process of two proteins and gave us a new insight in the mechanisms of protein-protein interactions. Uchikoga *et al*. [5] investigated the protein interfaces of protein-protein interactions, especially the one of hub proteins that has many different partners. Their computational analyses revealed that the composition of interacting amino acid residue pairs was sufficient for determining the properties of protein interaction surfaces. Taguchi *et al*. [6] computationally investigated the allosteric sites in enzymes. They analysed 10 cases of allosteric proteins with and without ligands and found that many of the allostericity were coupled with the dynamics of the proteins by ΔMSF_{bs}, their newly introduced scale for measuring the fluctuation around the ligand. Suzuki *et al*. [7] addressed the role of ATP molecule in GroEL, a well-studied chaperonin. It has been long known that GroEL requires ATP for performing its function, but contrary to other conventional cases, energy extracted by hydrolysis of ATP does not rule the function. Their computer simulation made us speculate that the structure of ATP itself is required for selecting the conformation of GroEL out of a number of different conformations. Oda *et al*. [8] analysed the conformational change in antigen-antibody interactions. A catalytic antibody, an engineered species that specifically recognizes a transition state analogue of chemical substances,

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is one of the greatest advances in engineering chemical reactions. Their kinetics measurement explained the difference in association rate in different antibodies. Nakamura *et al*. [9] extended their previous works on building a new method for comparing the properties of ligand pockets in proteins. The improvement of the comparison method should keep abreast of the increase in the size of the protein structure data, hence enables good prediction of a ligand-binding pocket and a ligand itself. Okuno *et al*. [10] discussed a new virtual screening method for drug discovery, especially in the case that a number of different ligands bind to a protein pocket. Even in the era of high performance computing, they warned that detailed understanding of the mechanisms of protein-ligand interactions is the prerequisite for the improvement of the screening.

The special issue changes gears here to the analysis of genomic data and we have two papers for genome analyses. Yamada *et al*. [11] investigated the variability of ligand-binding sites of protein in human population. Recent advent of sequencing technology for a personal genome uncovered quite a number of variations amongst humans and they mapped all those variations onto protein structures. They found that the variation was rare in the ligand-binding site, which is intuitively acceptable results, but non-negligible number of variations was found slightly apart from enzyme active sites. Imai *et al*. [12] specifically studied the interactions between G protein-coupled receptors (GPCRs) and salicin, a cause of bitter taste. Through a number of mutation experiments, they found that the interaction modes were different on the same proteins in different mammals; hence bitter taste sensitivities have likely evolved independently in different species.

Finally, specific issues on the computational prediction of protein-small molecule interactions are presented. Kim *et al*. [13] performed a specific application of protein-ligand docking method aiming for drug design. They computationally docked saponin, a ligand from Vietnamese ginseng to TNF-α, a potential target receptor. The simulated structure had a reasonable consistency with the experimental fact and may have a sufficient accuracy for playing a role of a decoy for further experimental studies. Sakano *et al*. [14] addressed an importance of dynamics of protein when we consider docking of a ligand to a protein. They used molecular dynamics (MD) simulation and assessed predicted docking poses of ligands. A case study clearly demonstrated that MD simulation helped assessing the prediction, especially in the case that protein is rigid.

It is fortunate that we could gather these nice manuscripts in this special issue, and I hope these papers offer a new insight in the study of protein-ligand interactions to the readers of *Biophysics and Physicobiology*.

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