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Consortium for Industry-Academia-Government Collaboration and Fugaku Establish Advanced Platform for *In-Silico* Drug Discovery

The FMO Drug Design Consortium (FMODD) was formed at the end of 2014 by volunteers from industry, academia, and government. Currently, about 140 members are accessing the supercomputer Fugaku from all over the country. There are several ways to utilize Fugaku. In some cases, large-scale calculations are performed using a large number of nodes by a few people; in other cases many small calculations are done by a large number of members, like this consortium. The purpose of the FMODD is to develop the FMO method as a practical means of drug discovery. To that end, the FMODD is accumulating and disclosing basic data and is developing new methods to generate better results. We asked Prof. Fukuzawa, the group's chair, about the achievements and future developments.

Kaori Fukuzawa
Professor, Graduate School of Pharmaceutical Sciences, Osaka University

FMO Method for Rational Drug Design

Many new drugs are currently being developed that target disease-causing proteins. New drug development involves multiple stages. At the earlier stage, we must find a candidate compound that binds to the target protein and inhibits (or enhances) its function. After a candidate compound is found, researchers have to gradually modify its structure to improve its efficacy and safety. At these stages, it is necessary to actually synthesize and test candidate compounds, so the number of compounds synthesized before a single new drug hits the market can reach the tens of thousands, and is one of the factors driving up the time taken and cost of new drug development.

For this reason, “*in silico* drug discovery,” in which researchers calculate on a computer how a compound binds to a target protein and use the results to design a candidate compound, is gaining popularity. “*In silico* drug discovery is efficient because it reduces the number of experiments, and it also has the advantage of being able to investigate the possibility of compounds that have not yet been synthesized,” Prof. Fukuzawa explains.

There are several methods for calculating the binding state of a protein-compound complex. Prof. Fukuzawa and her colleagues use the “fragment molecular orbital” (FMO) method developed by Prof. Kazuo Kitaura of Osaka Prefecture University (currently Guest Professor of Osaka University) in 1999 (Fig.1). “We want to accurately understand the binding state of the protein-compound complex.” To do this, quantum chemical calculations must be performed to reveal the electronic structure. However, the computational cost is too high for macromolecules such as proteins. The FMO method was devised to overcome this problem.

In the FMO method, a macromolecule is divided into small fragments. Quan-

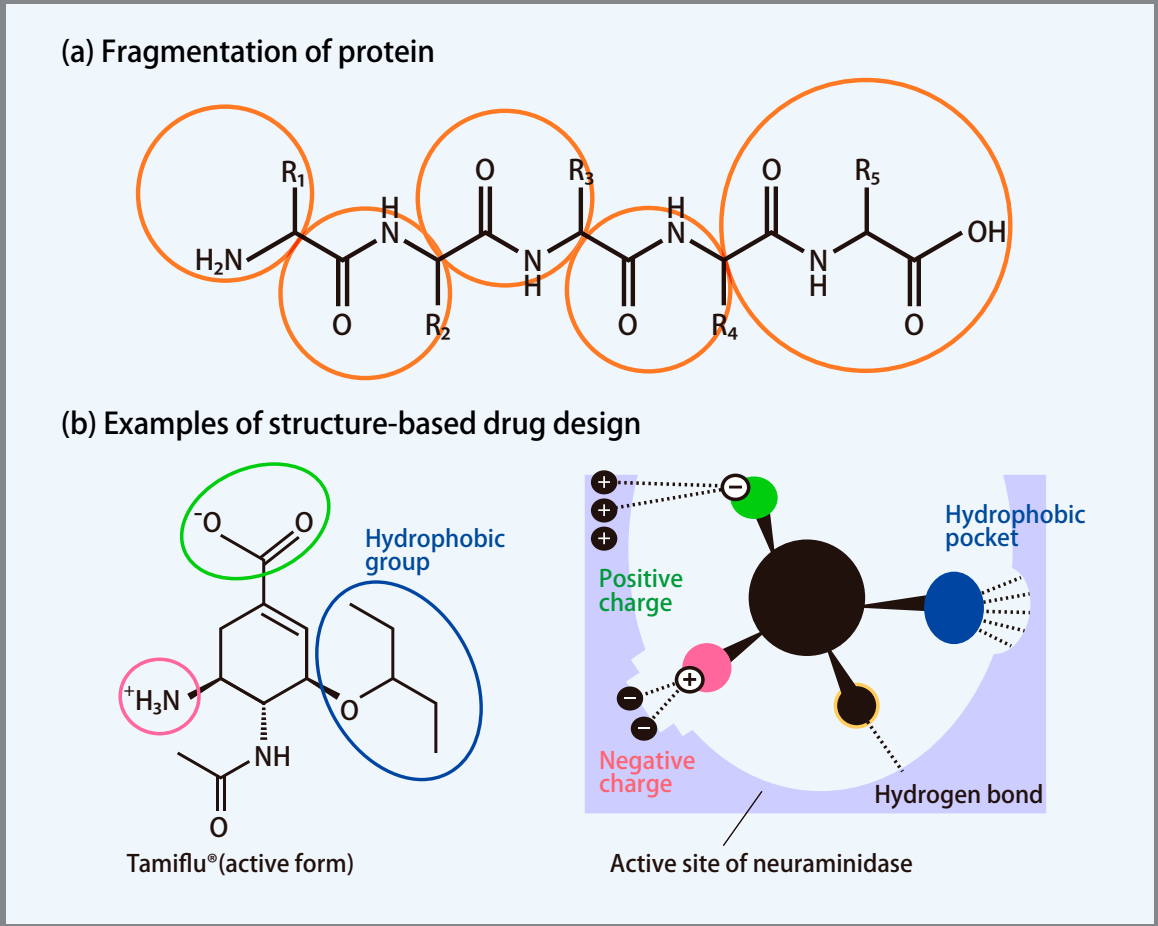

Fig. 1

Fragment molecular orbital (FMO) method and structure-based drug design

(a) In the FMO method, a macromolecule is divided into small fragments. A protein is divided into amino acid units, as circled. A compound that binds to a protein is often treated as a single fragment, but can also be divided into functional moieties.
(b) Tamiflu® (generic name: oseltamivir), which is used to treat influenza, binds to the active site of neuraminidase, an enzyme necessary for the replication of influenza viruses, and suppresses its action. Tamiflu® is designed to bind to the active site through various interactions, such as electrostatic interactions where positive and negative charges attract and hydrogen bonding. This strategy is called “structure-based drug design.” When the FMO method is applied to structure-based drug design, it is possible to precisely know which fragments of the protein the drug candidate compound interacts with and how strong the interactions are. That allows researchers to construct a candidate compound that interacts more strongly with the target protein at the appropriate parts.

tum chemical calculation is done for each fragment or fragment pair, and the calculation results are used to reconstruct the electronic structure of the whole protein. By taking the influence of surrounding fragments into account when calculating each one, the electronic structure can be calculated efficiently and precisely.

More importantly, the FMO method provides a quantitative understanding of various interactions between a protein and a compound. “When interactions are well understood, candidate compounds can be designed rationally. For this reason, the FMO method is increasingly being used in drug discovery by pharmaceutical companies, although it is rarely clearly disclosed,” says Prof. Fukuzawa, explaining the significance of using the FMO method.

Steadily Accumulating Data Using Large-Scale Computational Resources

“However, no matter how good the FMO method is, it will not develop into a practical drug discovery method if researchers in academia and pharmaceutical companies are working on their calculations independently,” Prof. Fukuzawa says. “We thought it necessary to use large-scale computational resources through industry - academia - government collaboration, and to develop and disseminate databases and methodologies.”

At the end of 2014, she and her colleagues called on industry, academia, and government researchers to launch a consortium to apply the FMO method project to the K computer. “Just around that time, the HPCI network began to be used, so members from all over Japan could access the K computer and perform calculations with the same quality in the same environment. I think it helped us establish the consortium's foundation,” Prof. Fukuzawa recalls.

The consortium focused on proteins such as enzymes and receptors, which are likely targets for drug discovery, and calculated the binding states of protein-compound complexes one after another. Then, the “FMO database (FMODB)” was constructed, and in February 2019, the data calculated up to that point was made publicly available for anyone to use. Since then, more and more data has been added, and as of Oct. 14, 2022, there are 15,653 public data points -- 17,625, including private data points.

Considering Fluctuations to Obtain More Realistic Data

FMODD not only accumulated data but also developed new methods for drug discovery. The background is, "*in vivo*, the structures of proteins and compounds are always fluctuating, but the FMO calculation consider only a single 'static' structure, so dynamic interactions that should be occurring *in vivo* are not known." To incorporate protein fluctuations, Prof. Fukuzawa and her colleagues came up with the idea of combining the FMO method with the molecular dynamics (MD) method, which simulates the movement of molecules (Fig. 2). First, the team generates a "movie" of the fluctuating protein-compound complex by the MD method, and obtains "snapshots" at a regular time interval. Then the FMO calculations are performed for each structure, and the results are averaged. By this method, the team is trying to examine the interactions taking into account molecular fluctuation.

"We started this calculation on the K computer around 2017," Prof. Fukuzawa said. "Regarding the MD method, we received the cooperation of the consortium (KBDD) headed by Prof. Yasushi Okuno of Kyoto University. The calculations didn't go very

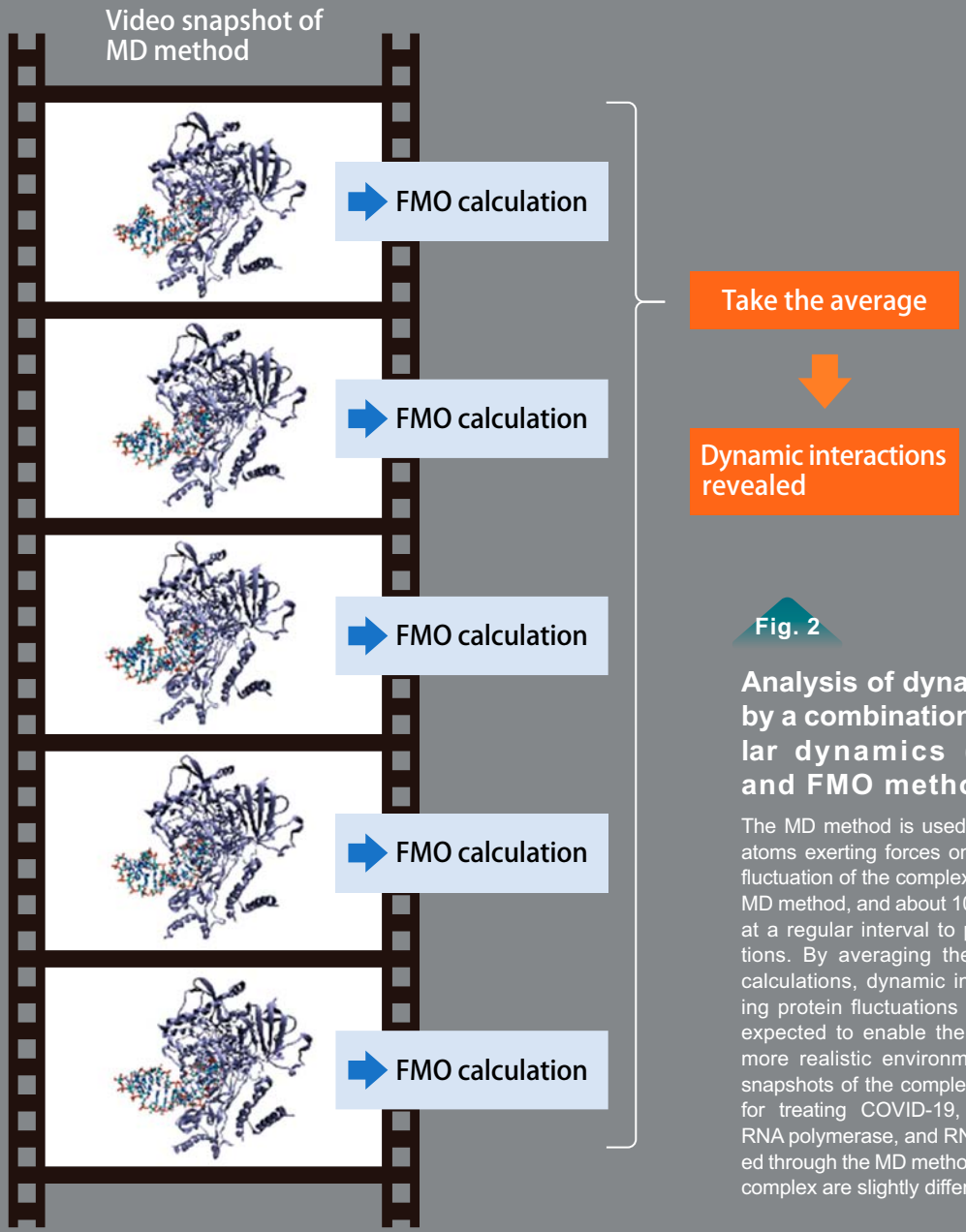

Fig. 2

Analysis of dynamic interaction by a combination of the molecular dynamics (MD) method and FMO method

The MD method is used to track the motion of atoms exerting forces on each other. First, the fluctuation of the complex is simulated using the MD method, and about 100 snapshots are taken at a regular interval to perform FMO calculations. By averaging the results of the FMO calculations, dynamic interactions incorporating protein fluctuations become clear. This is expected to enable the design of drugs in a more realistic environment. Shown here are snapshots of the complex of remdesivir, a drug for treating COVID-19, viral RNA-dependent RNA polymerase, and RNA, which was generated through the MD method. The structures of the complex are slightly different from one other.

smoothly, partly because we were unfamiliar with MD," she added.

"After the K computer ended its operation, we were able to use the HPCI computational resources TSUBAME3.0 and Oakforest-PACS, and finally completed the calculation." The method they established with a struggle at that time is now demonstrating its power in Fugaku. They have elucidated in detail the action of therapeutic drugs for COVID-19 (see Fig. 2). They are also studying membrane proteins, which are important drug discovery targets, and nucleic acid drugs*1, which are expected to become new types of drugs, using this method.

"Now, members from all over the country are accessing Fugaku and performing calculations just as they were in the project with the K computer. Fugaku's computational power is huge, and I feel that it's about 100 times more powerful than the K computer. FMO calculations of 100 structures obtained by an MD simulation can be done in about 30 hours using one rack of Fugaku, and then, we can immediately start scientific discussions to further improve the quality of the calculations," Prof. Fukuzawa says. As the next step, she plans to spread the MD-FMO combination method to young researchers and apply it to various complexes.

I Want to Elucidate Life Phenomena with Quantum Chemical Calculations

Meanwhile, Prof. Fukuzawa and her colleagues are also working on utilizing the huge amount of data they have accumulated. One example is prediction of interaction strength by machine learning. "There are several types of interactions between fragments, such as electrostatic interactions where positive and negative charges attract each other, and hydrogen bonds (see Fig. 1b). By learning the data for each interaction type, we can get information on the strengths of the interactions depending on the distance between fragments. By accumulating such information, we want to eventually predict the strength of the interaction without performing FMO calculations," she explains.

In this way, the FMODD has accumulated FMO calculation data that forms the interaction information basis of *in silico* drug

discovery, and has developed new methods and achieved excellent results. However, this is not Prof. Fukuzawa's goal. She has a dream as an expert in quantum chemical calculations. "Quantum chemical calculations are first-principles calculations that do not use assumptions or empirical parameters. So as long as the calculations are performed correctly, correct results can be obtained. I want to use those quantum chemical calculations to understand all life phenomena."

To realize this dream, Prof. Fukuzawa advances her research step by step, by setting goals to be achieved using the next supercomputer after Fugaku and the one after that, such as more accurate calculation of thermal fluctuations, FMO calculation of enzyme reactions and metalloproteins, and RNA kinetics.

*1: Artificially produced DNA and RNA used as pharmaceuticals. Practical application is progressing, particularly for drugs for the treatment of genetic diseases.

About the

Researcher

Prof. Fukuzawa believes it is important to lead a fulfilling life as a person, not to sacrifice everything other than research. In fact, she loves cooking and has taken lessons from a Michelin-starred Japanese chef, and she also interacts with artists. Through communication with people other than scientists, she learned "it is not necessary to cook exactly following a recipe, but enough to grasp the flow between the lines with my five senses." She also became aware that when doing research as well as playing music we begin with the interpretation of what our predecessors left behind, and then deepen it. "As a result of seeking a post that would allow me to do the research I wanted, I am currently working in Osaka without my family. I'm worried about my two children, a second-grade junior high and a sixth-grade elementary school student whom I left behind in Tokyo, so I return home on weekends as much as possible," says Prof. Fukuzawa, showing her mother's face. Her multifaceted nature seems to attract people and has helped bring together the people in the consortium.

Associated Research Projects

Construction of platform of FMO-based drug design using HPCI system
(hp190133/hp200101/hp210130/hp220143)
Principal Investigator: Kaori Fukuzawa, Graduate School of Pharmaceutical Sciences, Osaka University
(Current affiliation from April 2022, Hoshi University until March 2022)

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