Using Simulations to Search Existing Drugs for Possible COVID-19 Treatments

The COVID-19 pandemic has upended our way of life. Pharmaceutical companies and research institutes around the world are laboring away to develop drugs to fight it. Running precision simulations with innovative High Performance Computing Infrastructure centered on supercomputer Fugaku, researcher Yasushi Okuno was able to find promising candidate drugs that are potential treatments for COVID-19 from among 2,128 existing drugs already being used against other diseases.

Yasushi Okuno
Deputy Program Director, Medical Sciences Innovation Hub Program, RCSTI, RIKEN
Professor, Department of Biomedical Data Intelligence, Graduate School of Medicine, Kyoto University

“Surprising Results” from Precision Simulations

Vaccines and pharmaceutical treatments for COVID-19 are being developed at a breakneck pace in order to limit the disease's impact and hasten social and economic recovery. A lot of this activity is focused on identifying drugs that are potentially effective against this new coronavirus from among existing drugs, including antivirals. Since they've already been proven safe in clinical trials, the time required to develop treatments based on existing drugs should be significantly shorter. Yet, despite all the research underway worldwide, from experiments at the cellular level to clinical trials, effective therapeutics remain elusive.

Given this state of affairs, a lot of hope is riding on supercomputer-based simulations.

“That's because we can examine the efficacies of many medications in much less time than it takes for experimental evaluations, and we can also understand how these medications work,” explains Yasushi Okuno. In April 2020, Okuno began his search for therapeutic drug candidates among existing drugs. Under the “Fugaku Preliminary Use Projects” program, he used the supercomputer Fugaku, developed and maintained by RIKEN and other institutes, and under the “High-Performance Computing Infrastructure COVID-19 Research Access Projects” program, he used the supercomputer Cygnus at the University of Tsukuba.

The Fugaku research project searched for drug candidates among 2,128 existing drugs. It targeted the “Non-Structural Protein 5” (NSP5) main protease of the coronavirus, which is critical to coronavirus replication in infected cells. Okuno's research team constructed models of the main protease and existing drug molecules in Fugaku, and ran molecular dynamics simulations to investigate their behaviors. “These computations allowed us to faithfully reproduce the molecular behaviors, showing the conformational transition of the protein’s active site pocket*1 between the closed and open states, and the transition of the drug from an unbound state to a bound state at the active site pocket or other sites on the molecular surface (Fig.1).”

Then, sorting by how long the drug molecules being evaluated remain in the main protease active pocket and other factors, they were able to find dozens of promising candidates from the existing drugs studied (Fig.2). “These drugs are expected to have a strong binding affinity to the main protease, and may be effective in fighting the new coronavirus. Before we ran the simulations, I was concerned that we might not find enough promising drugs like these, or might even find too many. But we found a suitable number of candidates. And 12 of these are being used in clinical studies and clinical trials as new coronavirus treatments in other countries. I was surprised how good the results were,” said Okuno. The fact that 12 of the drug candidates discovered through these simulations are already at the clinical study or clinical trial stages for COVID-19 speaks well to the reliability of the simulations.

*1 Active site pocket: Some proteins have pocket-like indentations on their surface where certain molecules bind to them to start working. These indentations are called “active site pockets” or “active pockets”. A molecule that occupies the active pocket instead of the usual molecule can prevent that protein from functioning. Thus, discovering such a molecule is the first step in drug development.

Fig. 1 **Molecular Dynamics Simulated on Fugaku**

This is a still from a movie based on the Fugaku simulations investigating the molecular interactions between the main protease critical to the coronavirus replication (gray) and the existing drug Niclosamide (pink). One of the drug molecules has settled into an active site pocket (yellow), others have bound elsewhere, and still others have not bound to the protein. These simulations were performed on 2,128 existing drugs.

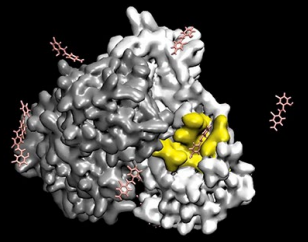
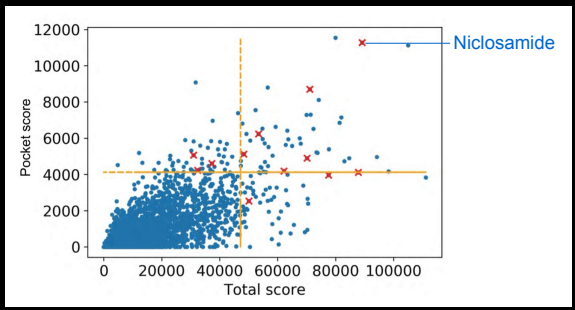


Fig. 2 **Identifying Therapeutic Drug Candidates**

The simulations shown in Fig. 1 examined how long a drug molecule stays in the active pocket of the protein (vertical axis) and how long it stays anywhere along the surface of the protein (horizontal axis). Each dot in Fig. 2 represents one of the 2,128 existing drugs evaluated in this research. Drugs undergoing clinical studies or clinical trials in other countries are marked with a red “X”. The closer to the upper right a drug is located, the better its expected ability to bind with the protein. Those in the upper right quadrant were considered suitable candidates for COVID-19 therapeutic drugs.



Among the 12 candidates, the drug Niclosamide is expected to have a particularly strong tendency to bind to the active site pocket. Not yet approved in Japan, it is inexpensive and has been confirmed safe overseas, where it is used to treat parasitic infections. Given these results, clinical research is expected to gain momentum.

Taking Full Advantage of Fugaku's Processing Capabilities

Okuno and his team began running simulations on Fugaku at the end of April 2020. Despite having less than a month to prepare, everything went smoothly and they had treatment candidates in hand by the end of June. He says they pulled this off thanks to “previous experience on the K computer, and because Fugaku was very easy to use.”

Okuno and his team had previously run drug discovery simulations on the K computer. But for simulations at this level of detail, the K computer was only able to examine a few dozen existing drug types. “In the early stages of drug discovery, it's important to ‘choose from many’. Although a huge number of candidates is evaluated at this stage in the experimental approach, the K

computer hadn't quite reached the point where it's realistic to fully simulate those processes. But, Fugaku could run calculations for more than 2,000 kinds of drugs, which is much more practicable.” Identifying viable drug candidates from over 2,000 types of existing drugs through these precise molecular dynamics simulations was a ‘world's first’ achievement. It was of great significance both as a computational technique and from an academic perspective. What's more, these simulations were done using only 5,500 nodes, which are a fraction of Fugaku's total processing power.

In addition to Fugaku's raw calculating power, this achievement was also the result of several endeavors and innovations in the computational approach. One of those is running each simulation with hundreds more drug molecules present, so interactions with the proteins become a more common occurrence. This can reduce the run time needed for the simulations. Too many drug molecules, on the other hand, could prevent the simulations from executing properly. Thus, the number of drug molecules present had to be carefully controlled. The team also confirmed that the length of time the virtual drug molecules remained in the active pockets was consistent with actual laboratory test results. Because the Fugaku simulations can produce such massive amounts of data, they also needed to devise ways to analyze all that data.

Using the Power of Cygnus to Simulate Another Protein

Using the University of Tsukuba's Cygnus supercomputer, the team investigated whether the therapeutic drug candidates selected from the Fugaku simulations would also bind to NSP16, another protein produced by the new coronavirus. NSP16 inhibitors, which bind to NSP16 to suppress its function, haven't been studied as much as the main protease inhibitors. Running simulations to explore the therapeutic potential of existing drugs against NSP16 is an ambitious experiment.

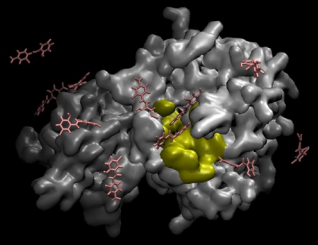
The Cygnus computer is outfitted with an abundance of modern GPUs[*2], which are often used for artificial intelligence research, and can quickly execute molecular dynamics simulations. “Since Cygnus was already fully up and running, it didn't take as long to pre-process the data for these simulations, and they ran reliably.”

Cygnus ran simulations with higher concentrations of the drug molecules to efficiently capture the molecular interactions (Fig.3), like those run on the Fugaku, evaluating each drug molecule's ability to bind to the NSP16 active site pockets. The results are still being analyzed, but different drugs are expected to bind more easily to different proteins. It will be interesting to see if the findings bear that out.

*2 GPU: Short for “Graphics Processing Unit”, a special type of computer chip optimized in design for image processing. For certain types of calculations, GPUs can be much faster than the CPUs (Central Processing Unit) commonly used for doing math.

Fig. 3 **Molecular Dynamics Simulated on Cygnus**

The interactions between the main protease-targeting candidate drug Niclosamide and NSP16 were computed on Cygnus the same way Niclosamide and main protease interactions were computed on Fugaku.



About the

Researcher

The approach that Yasushi Okuno took in this battle against COVID-19 can be applied in the search for drugs for other diseases. In fact, with Fugaku operating at full capacity, Okuno intends to search for drug candidates for cancer and other challenging diseases. His research work places the priority on the patients. “I hope to use the power of Fugaku to quickly identify a suitable drug for each patient’s particular cancer, and to search existing drugs for those effective against diseases that currently lack medications.” In addition to his supercomputing work, he is also involved in a consortium that brings together pharmaceutical companies and researchers from different fields to accelerate drug discovery. Driven to provide the patients he encounters with suitable medications as soon as possible, Okuno continues to lead in the field of computational drug discovery.

Associated Research Projects

- “Promotion of Innovative Drug Discovery Infrastructure for Acceleration of Precision Medicine” (hp200129)
- “MD-based Screening of Drugs with Novel Action Mechanism Against COVID-19” (hp200155)

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**Research Organization
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1-5-2, Minatojimaminami-machi, Chuo-ku, Kobe, Hyogo, 650-0047 JAPAN
Tel: +81-78-599-9511

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