New Materials/Devices that Revolutionize the Existing Paradigm

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New materials, so far, have generally been developed through repetition of numerous experiments based on researchers' experience and knowledge. Recently, materials informatics (MI), which allows for the identification of guidelines for material design on computers, is attracting attention along with improvements in computer processing capacity and advances in information science and technology. Fujitsu Laboratories has been conducting research on this MI technology with the aim of creating new materials and devices and new drugs. MI is based in data, and the challenge is how to exhaustively gather and utilize good quality data. Fujitsu Laboratories is taking the approach of making the enormous amounts of accumulated material and device data into databases for analysis with AI technology. Meanwhile, we are also studying informatics-based design using data and AI by applying simulation technology, at which we excel, to generate the data on computers with a degree of accuracy equivalent to that of experiments. This paper presents the realization of an IT-based drug discovery that makes use of molecular simulations based on physics and chemistry, as well as the optimum design of magnetic devices that combines magnetic simulations and AI technology. It then presents informatics-based design technology aimed at new material development. It also describes the MI approach utilizing experiments, analyses, and simulations as an MI technique that includes the process as well as material search and presents future prospects.

1. Introduction

Development of new materials is a source of innovation that dramatically improves performance of products and brings new products into existence. However, development of new materials requires enormous time and costs and has so far depended on repetition of extensive experiments based on researchers' experience and knowledge. Generally, development of innovative materials and devices is said to require 10 to 30 years.

For example, consider an inorganic compound $A_xB_yC_z$ made of three elements A, B, and C selected out of about 80 elements used in material science. In this case, the number of possible combinations that use an integer ratio satisfying $x + y + z = 10$ alone amounts to 8 million, and identifying a substance that realizes the desired characteristics is far from easy. Even if a new substance is discovered, development and commercialization of a device or equipment that uses the substance involves a massive trial and error process through prototypes. Furthermore, to take development of a new drug as an example, the number of possible combinations of a protein that cause a disease and a drug candidate compound, at about 10^{65}, is enormous,[1] and generating an unprecedented substance that may provide a new drug is extremely difficult.

Fujitsu Laboratories has been conducting research on materials informatics (MI) technology with the aim of creating new materials and devices and new drugs. MI is a new material development methodology that makes use of big data analysis technology, AI technology, and high-performance computing (HPC) technology.

MI is now a global trend; following the announcement in 2011 of the "Materials Genome Initiative,"[2] a national project by the US, similar projects were launched in Europe, China, and South Korea, and more than one national project was initiated in Japan as well. MI is based in data and the challenge is how to exhaustively gather and utilize good quality data.

Fujitsu Laboratories is taking the approach of making the enormous amounts of accumulated material and device data into databases for analysis using AI. Meanwhile, we are making use of simulation technology, at which we excel, to generate data on computers with a degree of accuracy equivalent to that of experiments and working on analysis by combining the data and AI.

This paper first presents our IT-based drug discovery technology that utilizes the molecular simulation technology based on physics and chemistry aimed at the discovery of original drug candidate compounds. Next, it describes the informatics-based design technology for magnetic devices that combines the magnetic simulation technology with the AI technology by using EXAMAG, a large-scale multi-scale magnetic-field simulator (a Fujitsu proprietary technology). Lastly, it presents Fujitsu Laboratories' future approaches to MI and prospects.

2. IT-based drug discovery technology

A general drug discovery process involves searching a library of existing compounds for a hit compound with activity against the target protein that causes a disease and developing it into a lead compound, which has greater suitability as a drug, based on the hit compound. Meanwhile, with the IT-based drug discovery that Fujitsu aims for, first a new compound is designed on a computer, and a large-scale computer simulation is used to quantitatively predict the binding affinity of the compound to the target protein.

Unlike an experimental method that uses existing compounds, IT-based drug discovery allows compounds to be freely designed on computers. Therefore, original compounds with high patentability can be designed. In this way, the aim with IT-based drug discovery is the replacement of conventional experiments involving the synthesis of compounds and measurement of the binding affinity with molecular simulations that use IT and the acquisition of unique drug candidate compounds. Meanwhile, replacement of the conventional drug discovery methodology with IT-based drug discovery essentially requires the achievement of prediction accuracy comparable to that of experiments by using realistic computational resources.

Figure 1 gives an overview of Fujitsu's IT-based drug discovery technology. Its basis is in two Fujitsu proprietary technologies: the combination of Optimum Packing of Molecular Fragments (OPMF), a technology for designing compounds with activity against a target protein; and MAssively ParalLEl Computation of Absolute binding Free Energy with well-Equilibrated system (MAPLECAFEE), a technology for quantitatively predicting the binding affinity to the target protein.[3] Furthermore, various elemental technologies exist for realizing these technologies. Here, we will present technologies that provide the key to improving prediction accuracy, with a focus on MAPLECAFEE.

MAPLECAFEE uses massively parallel molecular dynamics simulation to predict the binding affinity between the target protein and the compound. For further improvement of MAPLECAFEE, Fujitsu Laboratories

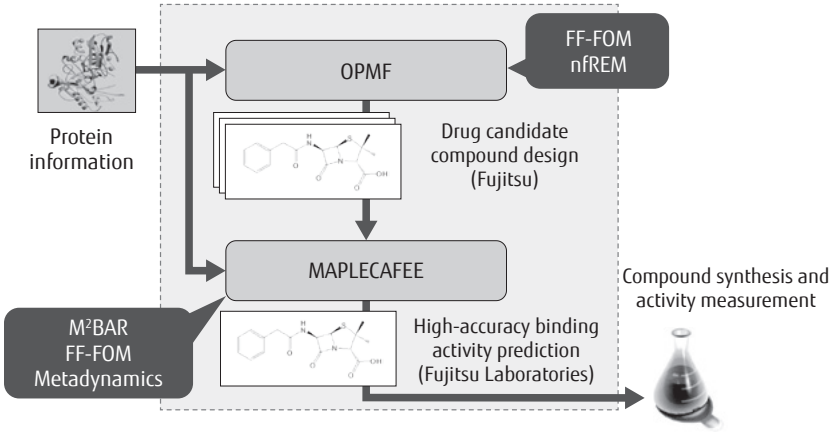


Figure 1
Fujitsu's IT-based drug discovery technology.

has developed the Multiple trajectories Multistate Bennett Acceptance Ratio (M^2BAR) method.[4] In this method, a harmonic potential with spring constant k is applied to restrain the compound to the binding site. This has led to successful effective sampling only of the bound space and realized high-speed and high-accuracy binding affinity prediction. We have confirmed that this technology achieves a level of accuracy for binding affinity prediction as high as ±1 kcal/mol, which is considered sufficient to allow the replacement of experiments.[4]

Meanwhile, MAPLECAFEE uses molecular dynamics simulation to calculate how the bond between the designed compound and the target protein changes moment by moment. In this process, the force that acts between the atoms is calculated with the potential function between the atoms called a force field. The accuracy of this potential function depends on that of the value of the parameter used for the function system (force field parameter value).

Dihedral angle parameter, a parameter that represents the degree of torsion in the bonding site, is directly linked to the predicted binding affinity value. Fujitsu Laboratories has developed a technology for generating this parameter taking into account not only the bonding site where the torsion will occur but also the impact on neighboring atoms.[5] We have implemented this technology in Force Field Formulator for Organic Molecules (FF-FOM), a software capable of generating sophisticated force field parameters that we have spent over 10 years developing.[3] Having evaluated its performance, the estimation error for the degree of torsion has been confirmed to be less than 1/10 on average of that of conventional technologies.

This technology has realized high-accuracy reproduction of dynamic structures of compounds. This technology also allows for the prediction of the dynamic shape of a compound bonded to a protein. It therefore improves the prediction accuracy of the binding affinity of compounds with large dynamic structural changes and raises expectations for discovery of unprecedented drug candidate compounds.

In addition, we are also working on the development of the following two technologies capable of integrated evaluation of compounds, from design to the prediction of binding affinity.

1) Non-bonding potential functions replica-exchange method (nfREM), which predicts the bonding site of the target protein by preparing multiple replicas with different force field parameters and randomly exchanging them.[6]
2) A method of predicting the bonding structure between the target protein and the compound by using an enhanced sampling method called metadynamics.

We intend to continue working on the discovery of original drug candidate compounds that cannot be obtained through the conventional drug discovery process while increasing examples of applications.

3. Magnetic simulation technology

Accurate estimation of energy loss (magnetic loss) in a magnetic material is required in the design and development of devices that use magnetic materials in major parts, such as power supplies and motors. This is gaining importance more than ever with the recent increase in IoT devices and demand for improved performance of electric vehicle (EV) motors. However, high-accuracy simulations of loss arising from magnetic hysteresis or magnetic domain structure are not easy. Consequently, trial and error using simulations and prototyping is a must at present.

Fujitsu and Fujitsu Laboratories are developing EXAMAG, a large-scale multi-scale magnetic field simulator, for application in wide-ranging areas from magnetic material development to motor efficiency calculation.[7] Furthermore, we aim for the realization of an informatics-based design service that combines analysis technology and AI technology and for innovation in research and development for material design through its use.

EXAMAG is a simulator based on micro-magnetics techniques, which analyze magnetic states in a magnetic material on a highly detailed level, as a core technology. Implementation of coupled analysis with finite-element method and massively parallel functionality in EXAMAG is Fujitsu's proprietary technology, and a simulator that implements some of the features was released in 2013. At present, we are developing a next-generation simulator that incorporates hysteresis models for magnetic materials to allow macro-scale analysis.[8]

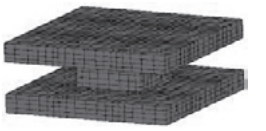
An example of the calculation of magnetic flux density distribution using EXAMAG is shown in **Figure 2**. One area of application of this simulator is

the high-accuracy analysis of dimensional resonance in a ferrite toroidal core.[9] For example, it is capable of highly accurate reproductions of how behavior near the resonant frequency may greatly vary depending on the sample size. Because verification of this level of accuracy requires accurate high-frequency loss measurement technology, we are also working on the development of high-accuracy measurement technology.

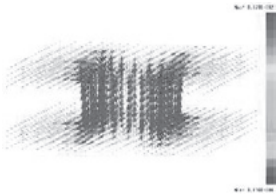
Because magnetic simulation involves a large amount of computation, utilizing AI is effective in performing efficient area searches to realize design optimization. To realize automated design technology utilizing AI, Fujitsu Laboratories is working on building a multi-objective optimization system that makes use of a genetic algorithms.[10] Coupled analysis of a hysteresis model and finite-element method involves a large amount of computation and generally takes a long time. Accordingly, to reduce the time required for global search, we are also developing a high-speed method that uses a neural network.

An example of multi-objective optimization of an inductor core called an EI core is shown in **Figure 3**.[10] The core has a structure composed of cores called an E-core and an I-core as shown in Figure 3 (a), with coils wound around the center leg of the E-core. We carried out multi-objective optimization of the volume and loss of the inductor core. For the volume, with the external dimensions (A, E, H, and I in the figure) fixed, we specified other dimensional parameters (B, C, D, F, G, and J) as variables. However, we set a lower limit to the opening through which the coils run (spool) to secure space for the coils.

The graph in Figure 3 (b) shows Pareto optimal fronts obtained with the inductance value L_{LC} used as the constraint condition. In this case, the volume is shown to have a trade-off relationship with the loss. The possible

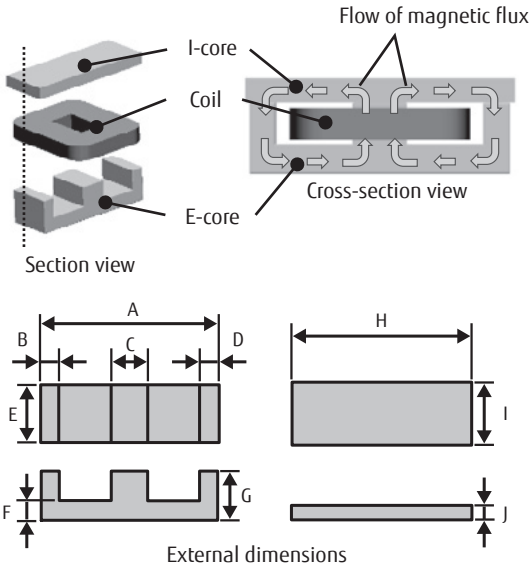


Analysis model

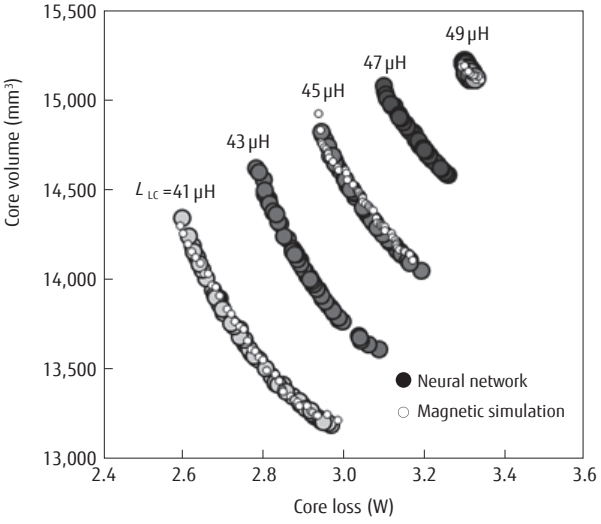


Magnetic flux density distribution

Figure 2
Magnetic simulation.



(a) E-core and I-core



(b) Pareto optimal front

Figure 3
Ferrite EI core and multi-objective optimization.

range of the Pareto optimal front may vary according to the value of the corresponding constraint condition L_{LC}. For this optimization calculation, a neural network-based surrogate model is used to increase speed.

As a reference, we also present Pareto optimal fronts directly calculated with magnetic simulation. The results of the calculations of the two methods are in good agreement. We picked out one of the Pareto optimal solutions with the value of the inductance as the constraint condition of 49 μH to prototype an actual core for evaluation. As a result, the error from the actual measurement has been confirmed to be less than 10% for both the inductance and the loss, which is in agreement at a level that causes no practical problem.

In the future, application of topology optimization technology that allows for the search of arbitrary shapes will make it possible to search for various shapes that were unexpected in past design development. We intend to use this technology to achieve the realization of optimal designs that go beyond human thinking and feedback for new material development.

4. Future approaches to MI and prospects

Up to now, we described technologies based on simulations, at which Fujitsu Laboratories excels: IT-based drug discovery technology aimed at the discovery of original drug candidate compounds that cannot be obtained through the conventional drug discovery process, and magnetic simulation technology intended to realize optimal device designs that go beyond human thinking.

In addition to advanced simulation technology, Fujitsu Laboratories has strengths in its capability to produce actual materials and devices and evaluate their characteristics, and conduct analyses in-house that use electron microscopy and synchrotron radiation. One example of the successful development of a material with desired characteristics out of an enormous number of combinations of elements is a cathode material for lithium rechargeable batteries.[11)]

This cathode material can substitute an inexpensive ferrous material for what could conventionally only be realized with materials such as lithium cobalt oxide ($LiCoO_2$), which uses cobalt, an expensive rare metal. The composition of the material successfully developed is complicated: $Li_{5.33}Fe_{5.33}(P_2O_7)_4$. This development was successfully achieved through trial and error based on the conventional knowledge and experience of researchers. At present, we are moving ahead with material development that makes use of MI for further voltage increases and characteristic improvements of the developed cathode material.

In particular, existing databases lack data complete with the crystal structures and the corresponding characteristics, which are required for advanced material development. In addition, exhaustive experimental data rarely exist in large quantities. To deal with the insufficiency of experimental data, at Fujitsu Laboratories we calculate the electronic states based on the fundamental rules of quantum mechanics to supplement the data with first-principle calculations to find the physical properties of materials. In addition, we actually synthesize the material candidates deduced by MI and verify their efficacy using characteristic evaluations and analyses. When the desired characteristics were found to not have been obtained as a result of the verification, the results are used as new data to repeat the MI cycle, thereby improving the accuracy of material design.

At the same time, even if a candidate material is deduced by MI, its synthesis does not necessarily succeed. This is because synthesis of a material first requires the selection of raw materials as well as the development of the synthesis process, including mixing conditions, synthesis temperature, and pressure. At material development sites, these process conditions are recorded by hand in developers' laboratory notebooks, which are often not even shared within the development group.

To solve these problems, Fujitsu Laboratories has introduced electronic notebooks to digitize process data. Process data provides the basis for material development because research papers and other open data seldom have detailed descriptions while containing considerable know-how. Therefore, Fujitsu Laboratories aims to establish the MI methodology, including the optimization of the process conditions for actually synthesizing desired materials, in addition to MI for material searches.

5. Conclusion

This paper described an IT-based drug discovery technology aimed at the discovery of original compounds providing new drug candidates by utilizing

molecular simulation technology based on physics and chemistry. It has also described an informatics-based design technology that combines magnetic simulation and AI technology aimed at realizing optimal designs that go beyond human thinking and new material development. In addition to MI for material searches, it has also presented an approach to establish MI methodology, including the optimization of process conditions, as well as future prospects.

In the future, we intend to work on the establishment of Fujitsu's unique MI methodology utilizing Fujitsu's proprietary AI technologies, such as Digital Annealer[12] and Deep Tensor.[13]

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