The CATALYST

Helping you react with chemical reactions

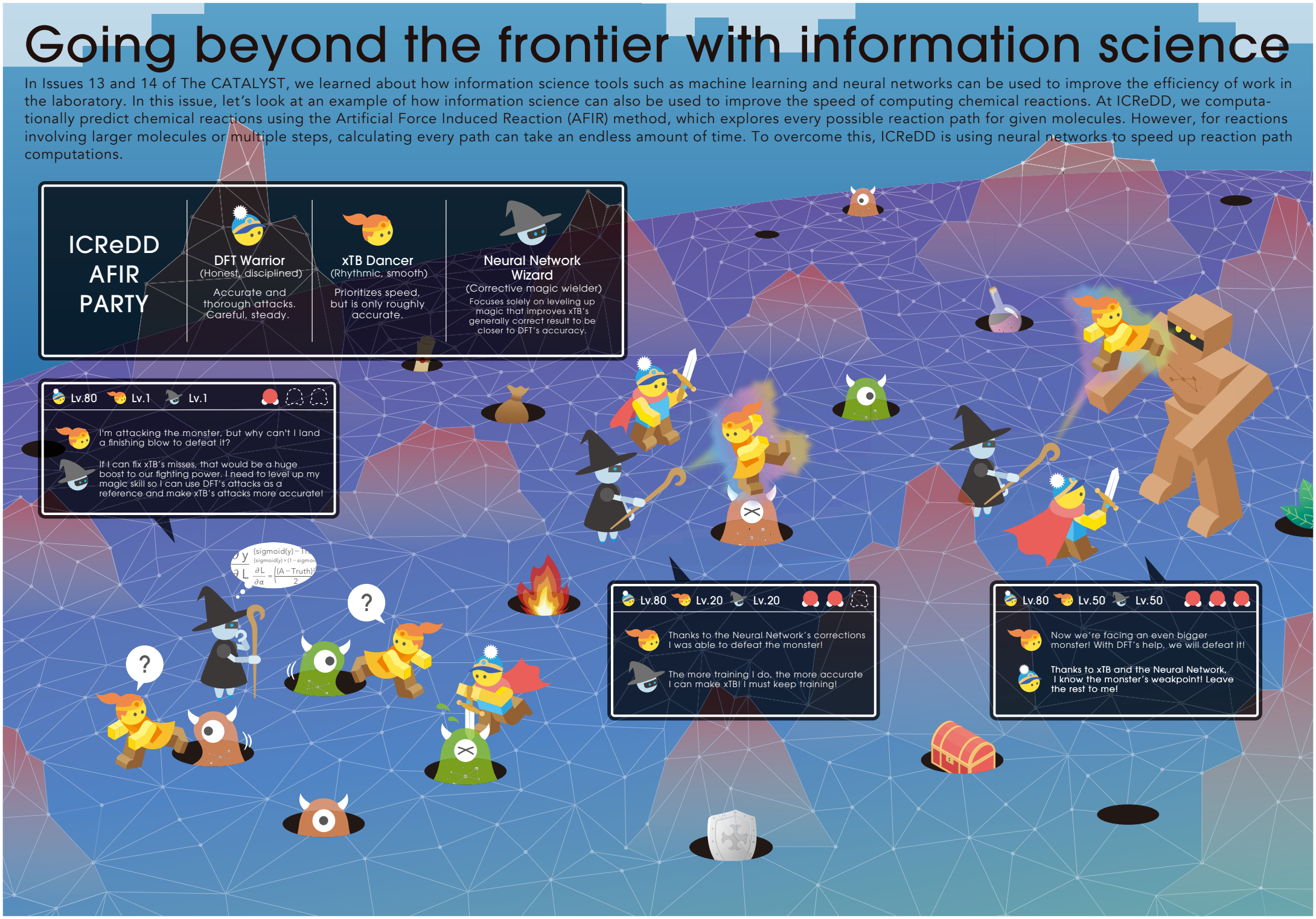
Issue 15
March 2024

Going beyond the frontier with information science

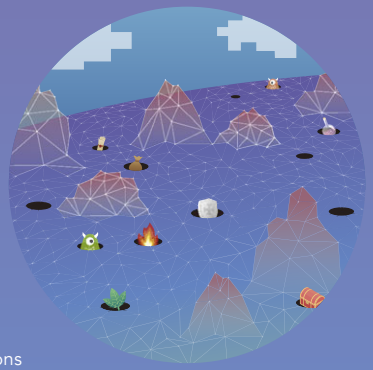
ICReDD
Institute for Chemical Reaction Design and Discovery
HOKKAIDO UNIVERSITY

Going beyond the frontier with information science

In Issues 13 and 14 of The CATALYST, we learned about how information science tools such as machine learning and neural networks can be used to improve the efficiency of work in the laboratory. In this issue, let's look at an example of how information science can also be used to improve the speed of computing chemical reactions. At ICReDD, we computationally predict chemical reactions using the Artificial Force Induced Reaction (AFIR) method, which explores every possible reaction path for given molecules. However, for reactions involving larger molecules or multiple steps, calculating every path can take an endless amount of time. To overcome this, ICReDD is using neural networks to speed up reaction path computations.



1. Exploring every possibility



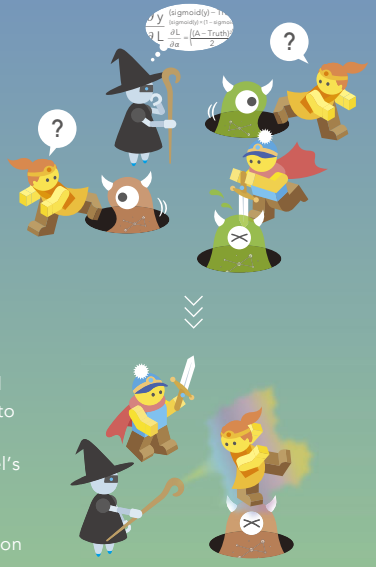
The AFIR method applies a force to a pair of atoms in the starting molecules in order to modify them and then uses a computation method based on a theory called Density Functional Theory (DFT) to calculate the energy needed for that modification. Since AFIR is able to explore reaction paths by automatically and exhaustively calculating each possible modification, it can discover viable reaction pathways that chemists haven't even imagined. DFT calculations are highly accurate, but they take a lot of time. Additionally, it takes hundreds of these calculations to derive a single reaction path. For large molecules with lots of atoms, such as medicines or catalysts, using DFT calculations could take thousands to millions of years depending on their size. The calculation wouldn't finish while we're still alive! At the same time, this endlessness also reflects the massive expanse of reactions that humanity has yet to discover.

2. Speed or Accuracy?

The process of using computations to search unknown possibilities is similar to embarking on a quest in a role-playing game. What will you encounter next? An enemy…a treasure chest… a new chemical reaction? Going up against a large molecule, can you finish the computation and discover a new medicine for humanity? If there were a game like that, how would you play? Would you progress through the game quickly, only spending the time you needed to get a roughly okay result? Or would you take the time to carefully develop an effective plan of attack? In general, it is difficult to have both speed and accuracy. If you prioritize one of them, the other one gets neglected.
In chemistry, computations should first be quick, but also accurate, too…with all computations finishing within a reasonable amount of time. Meeting all of these requirements is very difficult, so in reality chemists are limited to targeting only small molecules that require fewer calculations. Even if they wanted to do a reaction path search for a large molecule, there would be no point in starting.

3. Speed AND Accuracy

To address this dilemma, ICReDD has developed a method that uses a neural network to obtain both speed and accuracy. In this method, instead of using DFT, AFIR first uses a quicker but less accurate method called xTB to calculate all possible reaction paths. Next, one point along each path is also calculated using DFT to check the accuracy of the xTB result and the neural network is trained on the difference between the results of the two methods. Then, AFIR redoes the path search for the same reaction, this time using the trained neural network model to add a correction factor to the xTB result. By further repeating this training process, the neural network model's correction becomes more and more accurate. As a result, it is now possible to use xTB to produce nearly the same reaction paths as DFT.



4. Pedal to the metal

This new method achieves a similarly high level of accuracy as DFT while being hundreds of times faster than a fully DFT-based search. This enables researchers to predict reactions that involve larger molecules or multiple steps in a reasonable time. ICReDD is building on this success, pushing to further improve speeds in order to predict even more complex reactions. Currently, the neural network model starts off completely untrained, but ICReDD researchers are now working to take a model trained on one reaction and apply it to a different reaction. By using what was learned on a previous reaction, the model could potentially be trained to accurately predict the new reaction using fewer DFT calculations to guide it, resulting in even higher speeds.

Activation!

Quiz

When using only DFT calculations for reaction path computations, scientists are limited to targeting only small molecules because for large molecules:

Send us your answer!

- **A** the calculation time would be endless
- **B** the molecular energy is too high
- **C** there are too many possible reaction paths
- **D** A and C

Check our Instagram highlights for the answer to the quiz!
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ICReDD News

March 2024

New Researchers

Joyce Antonia Anna Grimm
Asymmetric catalysis, organocatalysis

Saswati Adhikary
Subcellular biofluorophores

Selected Publications (from December 2023 to February 2024)

Elusive "phantom state" of photoisomerization reactions verified after decades of mystery
(T. Taketsugu)
https://www.icredd.hokudai.ac.jp/research/10416

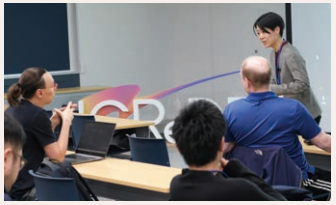
Cancer GPS method evaluates model tumor malignancy
(M. Wang, Y. Kitagawa, M. Tsuda, S. Tanaka, Y. Hasegawa)
https://www.icredd.hokudai.ac.jp/research/10383

Clutch-stack-driven molecular gears in crystals could propel material innovation
(M. Jin, A. Mikherdov, M. Tsitsvero, A. Lyalin, T. Taketsugu, H. Ito)
https://www.icredd.hokudai.ac.jp/research/10367

Turning plastic trash into chemistry treasure
(K. Kubota, S. Maeda, H. Ito)
https://www.icredd.hokudai.ac.jp/research/10191

Symposia

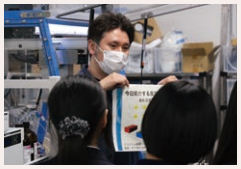
- The 7th ICReDD International Symposium —The Rising Star Program



Question and answer session at The 7th ICReDD International Symposium

Outreach

- Academic Fantasista 2023 (Lecture and tour for high school students)
- Monthly Research Postcard
- The CATALYST Issue 14



Academic Fantasista 2023

Monthly Research Postcard

The CATALYST 14th Issue

Award

- The 41st Chemical Society of Japan Award for Creative Work (Inokuma)
- Asian Core Program Lecture-ship Award (Korea) (Hayashi)

Researcher Profile

vol.15

Ruben Staub

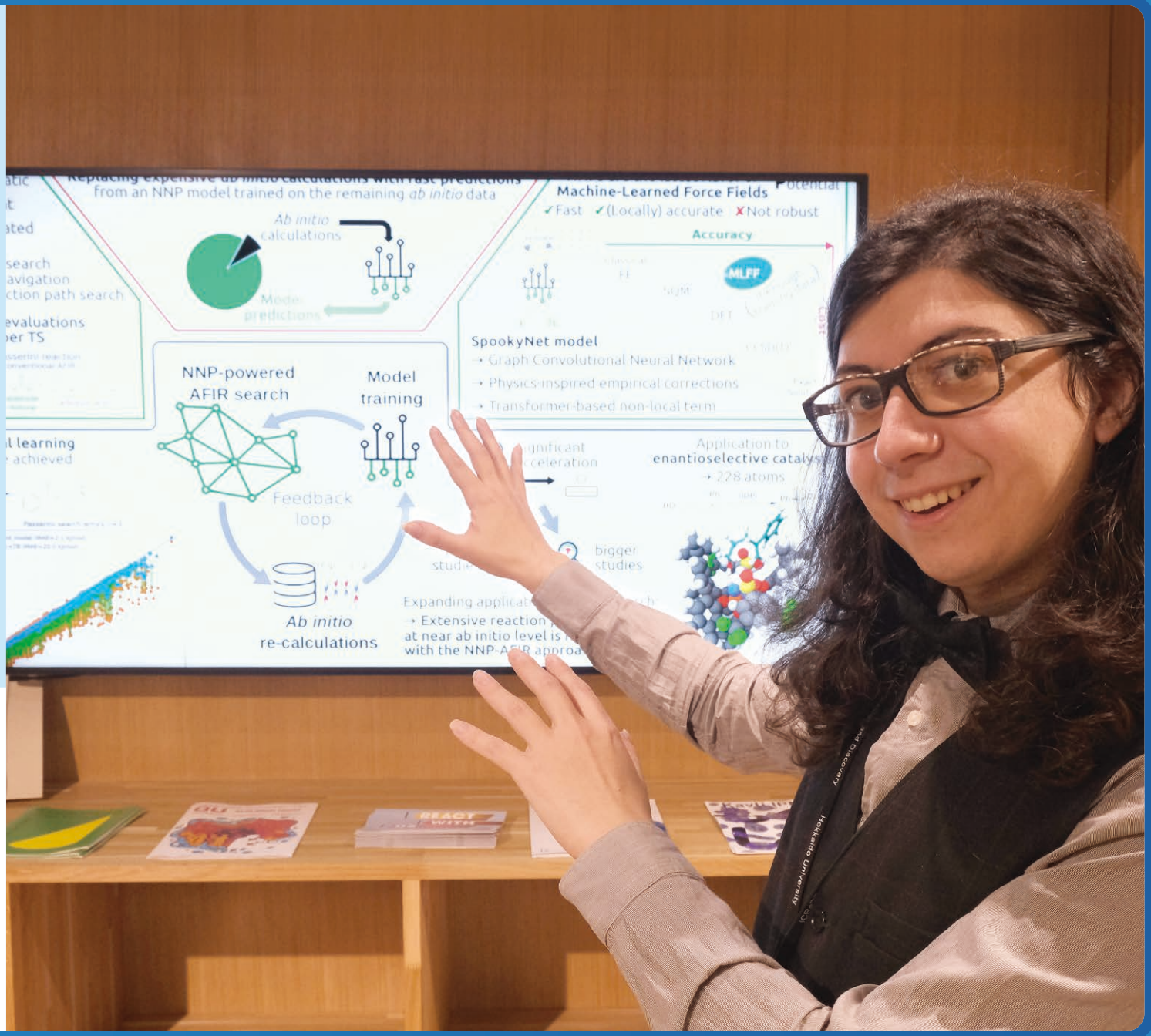
Specially Appointed Assistant Professor Ruben Staub is working at the frontier between computer science and theoretical chemistry. He aims to improve computer simulations of molecular systems to tackle chemical challenges more efficiently. In particular, he is recently using the latest advances in artificial intelligence to accelerate the discovery and understanding of chemical reactions.

Representative Papers:

Molecules, 2023, 28, 4477;
Appl. Math. Comput., 2021, 399, 125996;
J. Chem. Phys., 2020, 152, 024124;

Short Biography

ICReDD Specially Appointed Assistant Professor and Co-PI of the Varnek Group at ICReDD. During his undergraduate and master's studies, Professor Staub focused on computer science, physics, and chemistry. In 2020, he received his PhD in theoretical chemistry from the École Normale Supérieure de Lyon (France). He then joined ICReDD as a postdoctoral researcher in August 2021, and started his current position in July 2022.



About ICReDD

The development of new chemical reactions is intrinsically entangled with the prosperity of humanity and the preservation of the environment. A recent example of such transformative chemical reactions with profound impact is cross-coupling reactions, the discovery of which was awarded with the 2010 Nobel Prize in Chemistry. These reactions are used to produce approximately 20% of all medicinal reagents, and almost all liquid crystalline and organic electroluminescent materials. The industrial use of these chemical reactions contributes ~60 trillion yen per annum to the global economy. The development of new chemical reactions thus significantly affects the evolution of society.

ICReDD is the Institute for Chemical Reaction Design and Discovery, a WPI center at Hokkaido University where researchers from different disciplines combine their strengths to take full control over chemical reactions. The institute was born out of the realization that the purposeful design of chemical reactions requires cross-sectional collaborations at every step. Working on such a fundamental natural process, quantum-chemical computations, information technology, modern experimental techniques, and the development of advanced materials can no longer be separate fields if we want to achieve significant breakthroughs. Rather, they have to become part of a diverse toolbox for truly integrated research.

The Catalyst is inspired by catalysts used in chemistry to bring molecules together, to reduce reaction barriers, and to activate molecules—to make reactions happen faster. In this spirit, this poster series should enable its readers to make the connection between chemical reactions and the wellbeing of our society, and to look at the world in a new way, seeing how chemical reactions and chemistry shape the world around them. And if we can take this opportunity to introduce ourselves, too, this may also catalyze new friendships and opportunities. #ReactWithUs

React With Us!

To stay up to date
with what's happening at ICReDD,
follow us on our social media channels:

@ICReDDconnect

(Top) Specially Appointed Associate Professor Yu Harabuchi explained computation-guided chemical reaction design and discovery to high school students visiting ICReDD as part of the "Academic Fantasista 2023" event. Students got hands-on experience with analyzing chemical reactions using quantum chemical computations while solving practice problems. (Bottom) Researchers actively exchanged opinions during the lectures and poster session of The 7th ICReDD International Symposium-The Rising Star Program.

Published in March 2024

Published by the Institute for Chemical Reaction Design and Discovery (WPI-ICReDD)

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