# The CATALYST

Helping you react with chemical reactions

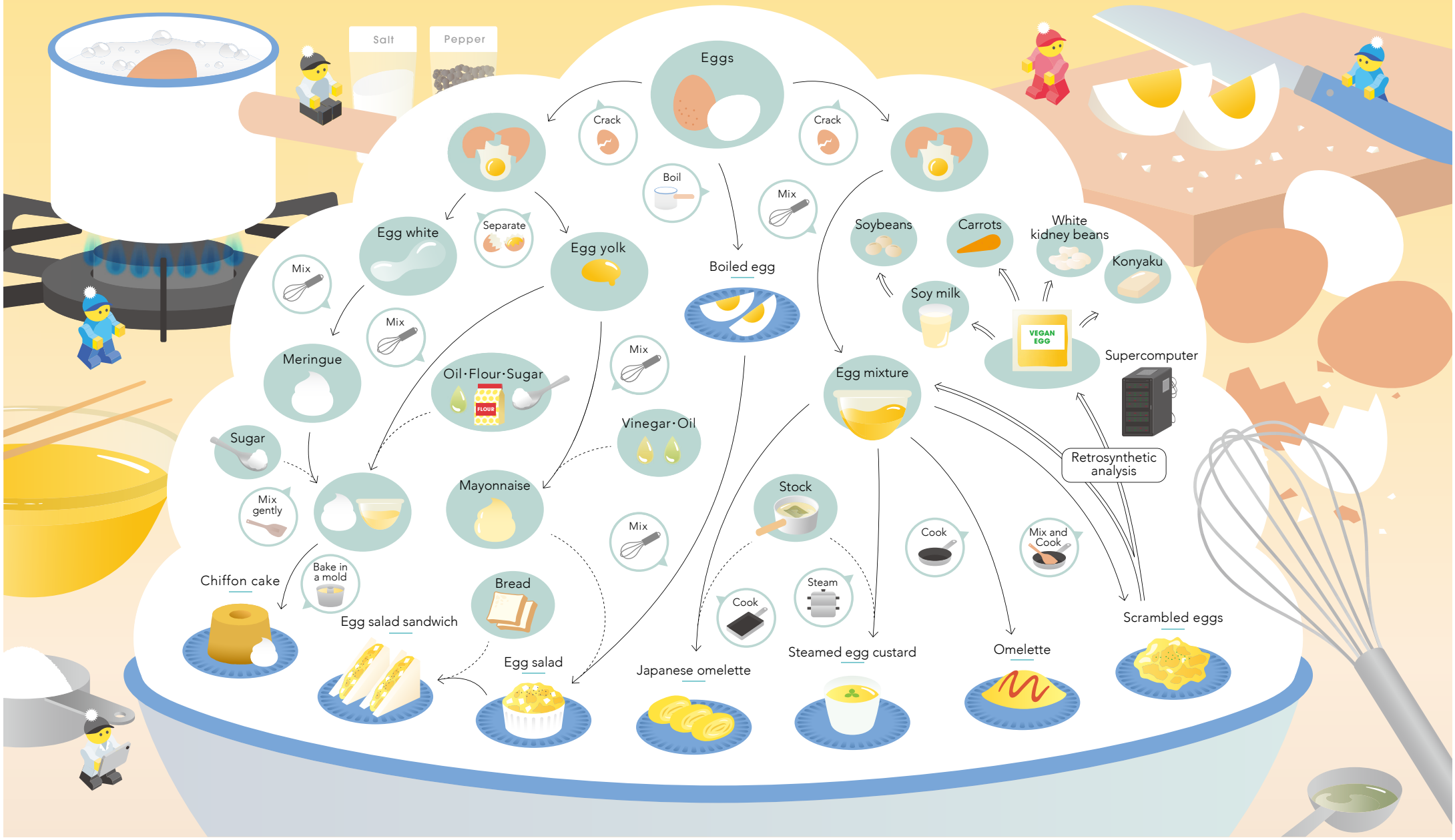
Issue 12
June 2023

## The many combinations of computational chemistry

ICReDD
Institute for Chemical Reaction Design and Discovery
HOKKAIDO UNIVERSITY

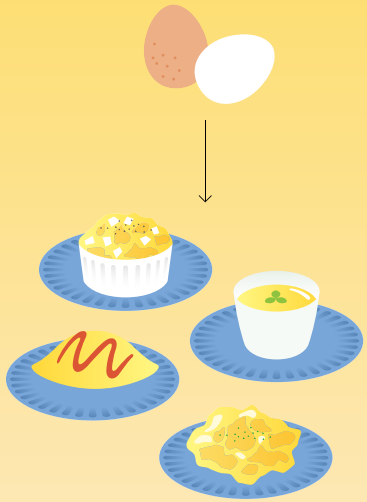
# The many combinations of computational chemistry

Molecules are collections of atoms connected in different arrangements by chemical bonds, and chemical reactions combine different molecules and change how they are connected. The process of combining ingredients and adding energy through heat or light is very similar to the process of cooking. In the laboratory, computers are used to predict chemical reactions through calculations. However, if there are many combinations of ingredients and reaction conditions to explore, the prediction takes an extremely long time. In that case, it is important pick out only the realistic combinations from the massive number of possibilities in order to reduce the calculation time.



# 1. Recipe Variations

So it's about time to make dinner, but when you open your refrigerator, there are only eggs inside. Hmm…what can be made with that? A fried egg? A boiled egg? An omelette? Although there is only one ingredient, there are many cooking methods including frying, boiling, and steaming, and there are many seasonings that can be added, such as salt, pepper, or soy sauce. For example, if you could use four cooking methods and three seasonings, there would be 24 possible combinations. However, if instead you had 15 seasonings in your kitchen, there would be over 100,000 possible combinations! If you tried every recipe, you might discover new dishes that are more delicious (or disgusting!) than anything you've eaten before.

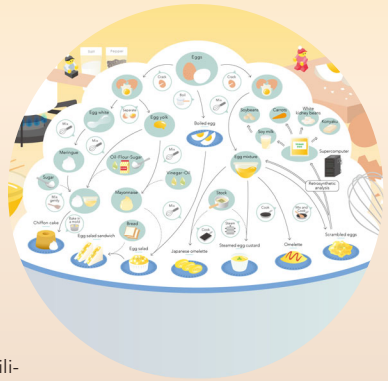


# 2. Too many options…

Similarly, when predicting chemical reactions, as the number of atoms and molecules or the number of steps in the reaction increases, the complexity of the calculation sharply increases. At ICReDD, we use the Artificial Force Induced Reaction (AFIR) method to calculate every possible reaction path. In this method, different strength forces are applied to push or pull atoms and molecules at different locations and in different directions to simulate the next step in a reaction. This process is carried out for each step in the reaction, and if there are many steps, and many atoms and molecules involved, even a supercomputer may not be able to explore every reaction path in a reasonable amount of time.

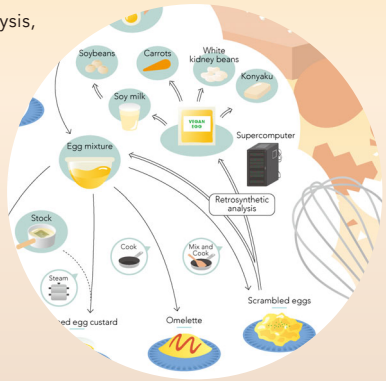
# 3. Narrowing it down

In order to prevent an explosion in the number of combinations that must be simulated, ICReDD developed a method for evaluating reaction paths after calculating each step and discarding paths that are not promising. When performing a calculation, a computer simply tries all possible combinations, without asking whether they are realistic. This leads to unrealistic reaction paths where, for example, the reaction temperature is bizarrely high (i.e., higher than lab equipment capabilities). By not including paths that are unrealistic in the next step of the simulation, unnecessary calculation time can be avoided. Using this method, the number of reaction paths that need to be explored can be reduced by a factor of 1000, which makes it possible for computational chemists to simulate multi-step reactions and other complex systems.



# 4. Going in reverse

One such complex system is retrosynthetic analysis, in which the reaction is predicted in the reverse direction using only information about the final product molecule. Instead of going from starting materials to the product, the computer begins with the product molecule and searches for paths backwards to starting materials. For example, rather than thinking "what can I make with an egg?" , it's like thinking, "what are these scrambled eggs made from?" Of course, "eggs" is the only answer, right? Actually, if we search backward from the finished dish to find all possible ingredients, we realize there are also vegan egg substitutes, which we hadn't predicted. For reaction path exploration, there are near limitless starting material possibilities, so it is important to discard unrealistic paths along the way. ICReDD is working to improve retrosynthetic analysis, so that in the future chemists can think of a new molecule they want to make, and then simply press the "rewind button" in a computer program to find out how to make that molecule!




## Activation!

### Quiz

The number of combinations to compute

_____

as molecules become larger and reactions have more steps.

Send us your answer!

- **A** decreases sharply
- **B** stays the same
- **C** increases slightly
- **D** increases sharply

Check our Instagram highlights for the answer to the quiz!
#ReactWithUs
@ICReDDconnect

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# ICReDD News

June 2023

## New Researchers

Suvankar Debbarma
Organocatalysis, photocatalysis

Zannatul Ferdous
Cancer stem cell characterization

Milena Lama
Materials science, hydrogels

Dmitry Zankov
Chemoinformatics, retrosynthetic analysis

## Selected Publications (from March 2023 to May 2023)

Healing the brain: hydrogels enable neuronal tissue growth
(M. Imajo, M. Tsuda, J.P. Gong, S. Tanaka)
https://www.icredd.hokudai.ac.jp/research/8753

Customizing catalysts for solid-state reactions
(K. Kubota, H. Ito)
https://www.icredd.hokudai.ac.jp/research/8776

Synthesis of bicyclo[1.1.1]pentane-based, straight-shaped diphosphine ligands
(H. Hayashi, T. Mita, S. Maeda, Y. Hasegawa)
https://www.icredd.hokudai.ac.jp/research/8935

Birch reduction simplified to a one-minute mechanochemical process
(K. Kubota, H.Ito)
https://www.icredd.hokudai.ac.jp/research/8947

Real-time, macro-scale visualization of molecular-scale mechanochemical damage in double-network hydrogels
(Y. Zheng, M. Jin, K. Kubota, T. Nakajima, S. Maeda, H. Ito, J.P. Gong)
https://www.icredd.hokudai.ac.jp/research/9194

## Outreach

- Promotional video featuring ICReDD's new building
- Monthly Research Postcard
- The CATALYST 11th Issue

Promotional video
Watch here!

Monthly Research Postcard


The CATALYST 11th Issue

## Symposia

- Joint Symposium of WPI-ICReDD and the Research Faculty of Agriculture in Hokkaido University

## Awards

- American Physical Society Polymer Physics Prize (J.P. Gong)
- The Japanese Society of Pathology Japan Pathology Award (S. Tanaka)

Researcher Profile

vol.12

# Yu Harabuchi

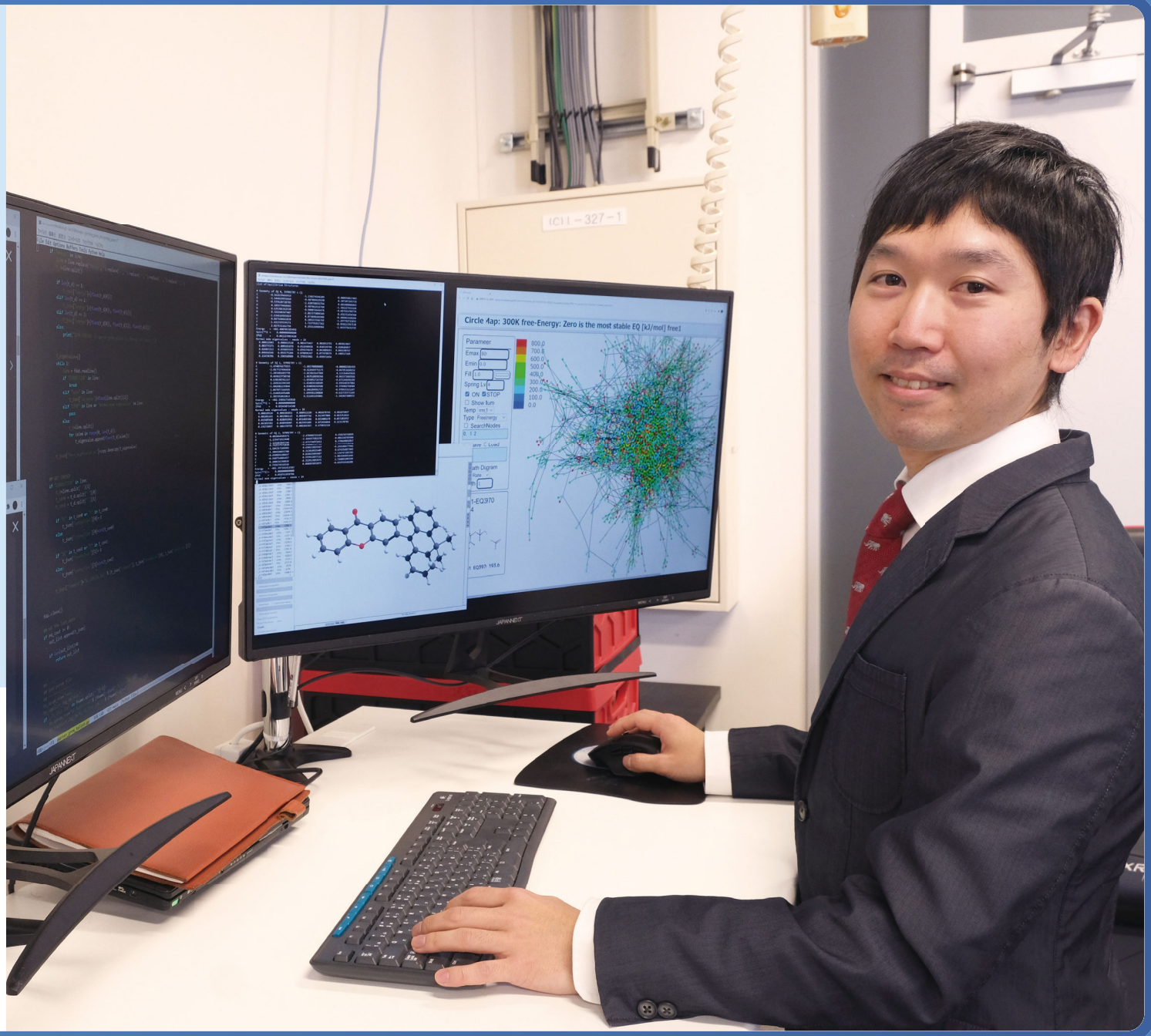
Specially Appointed Associate Professor Harabuchi uses quantum chemistry to develop computational tools in order to fully understand how molecules respond to light. He uses computers to analyze phosphorescence, photoswitching and the mechanism of photosensitization. Recently, he has been using these methods combined with reaction path networks to understand radical-based reactions that use photoelectron transfer catalysts.

Representative Papers:

Phys. Chem. Chem. Phys., 17, 22561 (2015)
Nat. Comm., 11, 3909 (2020).
Angew. Chem. Int. Ed., 62, e202211936 (2023).

## Short Biography

Assistant to the Center Director, Fusion Research Coordinator and Specially Appointed Associate Professor. In 2013, Prof. Harabuchi received his PhD from the Hokkaido University Graduate School of Chemical Sciences and Engineering. After this he worked as postdoctoral researcher at Hokkaido University and Iowa State University and as a JST-PRESTO researcher. He then became an Assistant Professor in the Department of Chemistry, Faculty of Science at Hokkaido University before starting his current position in April 2023.



# 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**

ICReDD moved into its newly constructed building in March 2023. The spacious Fusion Research Office (top) spans two floors and accommodates 100 researchers and our new server room (bottom) is equipped with supercomputers used for predicting chemical reactions.

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