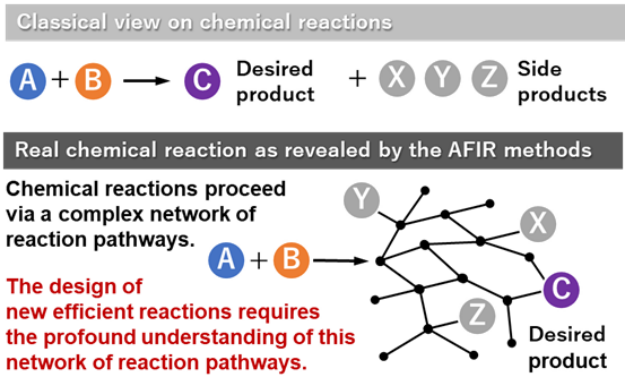
Center Director's Vision

Hokkaido University Prof. Satoshi Maeda

The development of new chemical reactions is intrinsically entangled with the prosperity of humanity and the preservation of the environment. One of the most notable chemical reactions discovered in the last century was the Haber-Bosch process, which catalytically synthesizes ammonia (NH_3) from nitrogen (N_2) and hydrogen (H_2). Also known as "the reaction that turns air into bread," the Haber-Bosch process enables the mass production of fertilizer, which helped overcoming the global food shortages at the beginning of the 20th century. A more recent example of such transformative chemical reactions with profound impact are 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.** However, the currently used methods for the design and development of bespoke chemical reactions is highly inefficient. Usually, these methods are based on trial and error, which is not only very laborious and time-consuming, but the discovery of truly innovative reactions is relatively rare. **As the development and implementation of new chemical reactions often takes decades in reality, fundamentally new scientific approaches are required.**

The goal of this initiative is to establish the scientific field of "Chemical Reaction Design and Discovery (CReDD)", which should allow the efficient development of chemical reactions through a combination of computational, information, and experimental sciences. CReDD will elevate the state-of-the-art methods for the development of chemical reactions to the next level by (1) establishing design guidelines for chemical reactions based on quantum-chemical calculations, (2) understanding the complexity of chemical reactions and designing new reactions via informatics methods, and (3) experimentally validating the theoretically proposed reactions. Quantum-chemical calculations that will be implemented at the proposed Institute for Chemical Reaction Design and Discovery (ICReDD) are different from previous approaches that have been employed to verify *known* reaction mechanisms. Quantum-chemical calculations that are capable of unveiling *unknown* pathways should represent a scientific advancement of substantial magnitude. A key technology that enables such calculations is the "automated reaction path search (AFIR) method" developed by Prof. Maeda, the designated director of the institute, who is an internationally renowned pioneer in this area. Merely 10 years ago, automatic searches for chemical reaction paths based on quantum-chemical calculations were considered impossible. However, Prof. Maeda proposed the idea of applying a virtual mechanical force to reaction systems in order to unveil potential pathways. Based on this idea, he developed the world's first general method to systematically predict *unknown* reaction paths. This method is not only of academic interest, and several companies are currently conducting collaborative research with Prof. Maeda.

It is highly remarkable that when the AFIR method is used for the analysis of chemical reactions, the results often show that these reactions proceed via paths that are very different from those initially anticipated. Simple chemical formulae reveal a large volume of uncharted **reaction path networks**, which show all possible pathways from the reactants to the major product and minor byproducts. Understanding reaction path networks will ultimately allow discovering unknown pathways to targeted product and blocking those to undesired byproducts. For the bespoke design of chemical reactions, **it is thus inevitable to study reaction path networks and identify controllable reaction pathways.**



In addition, the AFIR method also addresses the considerable challenge of 'complexity'. Even simple reactions that include only few atoms may exhibit very complicated reaction-path networks, rendering the differentiation between significant and insignificant reaction paths highly difficult. Thus, the aid of information science is essential in order to identify promising reaction paths. The faculty at Hokkaido University hosts numerous internationally renowned researchers in e.g. path enumeration, data mining, and machine learning, who could help analyzing such complex networks. By including the knowledge of information scientists, this initiative aims to understand intricate reaction-path networks and extract important factors that should be considered prior to the experimental stage. Simultaneously, large volumes of previously obtained experimental data will be examined and meaningful data will be forwarded to computational scientists in order to simplify the calculations required to obtain the reaction-path networks.

Theoretical predictions become meaningful only after they have been experimentally proven, however. In this initiative, we aim to merge experimental science with computational and information sciences on a globally leading level. The hitherto insufficient conceptual understanding that chemical reactions proceed via an extensive network of chemical reaction paths has left experimental scientists with no other alternative but to continue the laborious, expensive, and inefficient processes of trial and error. In contrast, CReDD (1) uses the AFIR method to calculate chemical reaction-path networks, and (2) applies concepts of information science in order to extract meaningful information for experiments, thus narrowing down optimal experimental conditions. This approach enables "pinpointing" promising experiments, which should considerably shorten the time required to develop chemical reactions. As the majority of the experimental scientists who will join this initiative have already collaborated with computational or information scientists, synergy among scientists from different backgrounds will be easily attained. In addition, information science provides a feedback loop, in which data obtained by the experimental scientists is circulated back to the computational scientists; the synergetic effects from the combination of three fields should lead to the improvement and refinement of CReDD.

The development of CReDD will enable the discovery of reactions that afford (1) high-value-added chemicals (small to medium size molecules), (2) new materials (macromolecules), and (3) state-of-the-art medical technology (complex systems). Reactions of the type (1) create useful chemical agents from low-value materials, e.g. via the synthesis of biologically relevant molecules from CO_2. Reactions of the type (2) produce materials with advanced functionality, e.g. highly luminescent or stimuli-responsive materials. Finally, reactions of the type (3) afford advanced materials for applications in a clinical context, e.g. improved biomedical materials leading to reagents for regenerative medicine and diagnosis. These reactions vary widely in complexity and environments for the reacting molecule(s). To cover this broad scope, we will strategically assemble a team of researchers from different disciplines. As a practical example, let us explain one of reactions predicted by automated reaction path searches. A path of amino acid synthesis from CO_2, which is a high-value-added chemical synthesis, has been predicted by Prof. Maeda in 2004. However, due to the lack of CReDD, the amino acid synthesis could not be realized experimentally until 2016. In similar situations, **CReDD will be able to provide experimental scientists with the most promising prospective reactions from the reaction path network by applying information-science-based approaches. The target reaction will be carefully selected based on social demand.**

Another goal of this initiative is to generate, nurture, and train a new generation of researchers who master all three subjects, i.e. computational, information, and experimental sciences, so that CReDD can be developed further in the future. **The continued relevance of CReDD will be ensured by sharing the results of this initiative with the world via the foundation of the MANABIYA (Japanese for 'school') system, where researchers from outside the proposed WPI will have the opportunity to collaborate and benefit from the innovative technology and knowledge developed there.** Specifically, foreign experimental researchers will have the opportunity to join MANABIYA and learn about e.g. the AFIR method and machine learning by collaborating with WPI researchers. These researchers will use the knowledge and techniques acquired at the proposed WPI upon returning to their home institutes. Through MANABIYA, our WPI will become a global research hub that continuously welcomes researchers from all over the world. This will allow our institute to not only thrive, but also to contribute to the research of other universities, research institutes, and companies that develop chemical reactions. **In the future, the MANABIYA system will evolve into the new "Graduate School of Chemical Reaction Design and Discovery". Furthermore, sharing the management system of excellence acquired through the WPI, the ICReDD will reform Hokkaido University.**

Reaction development that relies solely on the trial-and-error approach is too time-consuming to solve current global problems that include pollution as well as the scarcity of energy and resources. CReDD will revolutionize the traditional approach to developing reactions by fusing computational, information, and experimental sciences. We strive to spread the benefits of this approach by establishing a global WPI and integrating other disciplines. Our sincere hope is that our WPI may contribute to a brighter and more prosperous future for all of humanity.