Organic Reaction Mechanism Classification Using Machine Learning

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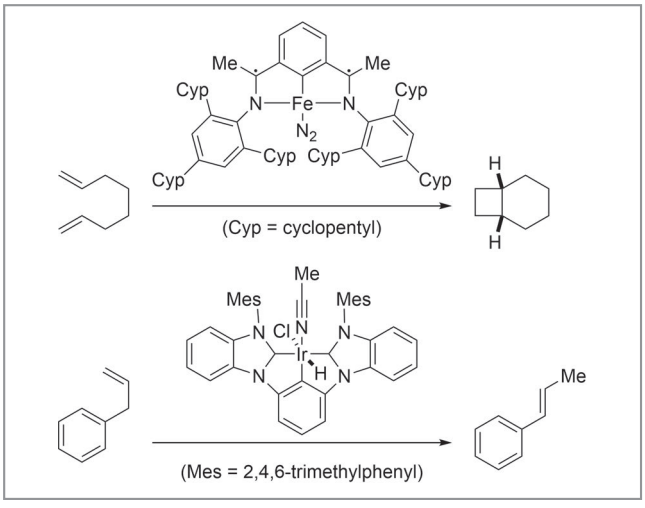
Mechanistic studies are a type of mathematical inverse problem in which chemists analyze a set of observations (kinetic data) to uncover the underlying causes (reaction mechanisms). According to Professor Igor Larrosa, from the University of Manchester (UK), a modern approach to solving these problems involves training deep neural networks with known data. He told SYNFORM: "This can be compared to exposing the human brain to a large quantity of kinetic data generated by each mechanism, allowing it to learn the intrinsic patterns and develop the ability to deduce the reaction mechanism from previously unseen kinetic data." Professor Larrosa and Dr. Jordi Burés, also from the University of Manchester, strongly believe in the potential of using mechanistic insights to enhance the discovery and improvement of catalytic reactions. Dr. Burés said: "Our inspiration dates back to the ground-breaking work of Professor Blackmond and the benefits of open-source modelling programs like COPASI. Since then, we have been driven to explore innovative approaches to extract more comprehensive information from reaction kinetics. With the AI revolution transforming various scientific fields with remarkable outcomes, it was only natural for us to investigate its potential in the area of reaction mechanism elucidation."

During the initial exploratory experiments testing various neural network structures, the researchers achieved promising results early on. "While it took significant effort to ultimately develop a robust model, our initial success confirmed the viability of our idea and motivated us to push hard in developing it, ultimately leading to the publication of the final model," explained Professor Larrosa.



Scheme 1 Two case studies with kinetic data investigated in this work

The researchers found that interpreting the model's performance, however, was sometimes challenging due to the human limitations in understanding large neural networks and predicting the kinetic behaviour of complex chemical reactions. "Midway through the project, we were surprised by the model confusing certain reaction mechanisms, but after further consideration, we realized that it was actually a positive outcome," revealed Dr. Burés. He continued: "The model was revealing that certain mechanisms can produce the same kinetic data in certain conditions. To enhance the model's capabilities, we added the ability for it to provide multiple answers when necessary. This feature greatly improved the model's accuracy in situations where the data were insufficient to differentiate between mechanisms, due to either noise or a limited amount of data."

"We are thrilled with the outcome of this proof-of-concept article as it has opened numerous exciting opportunities in the field of kinetic analysis," said Professor Larrosa. He continued: "Our goal is to create more sophisticated models that address specific mechanistic issues and are tailored to specific experimental data. Additionally, we aim to gain a deeper understanding of how the AI model operates in order to potentially uncover new kinetic features such as reaction orders or induction periods. Furthermore, we are also investigating more ambitious applications, but it may take some time before we are ready to share."

Professor Larrosa concluded by saying: "We are at a unique turning-point in the development of artificial intelligence tools for chemistry. The next years are going to offer lots of exciting opportunities for enthusiastic students seeking to embrace new technologies; we need them!"

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About the authors

Prof. I. Larrosa

Igor Larrosa graduated with a master's in chemistry from the University of Barcelona (Spain) in 2000. He also completed a PhD degree in Barcelona (2004) with Profs. Felix Urpi and Pere Romea, including a research period in Prof. Erick M. Carreira's laboratories at ETH (Zurich). Igor then moved as a postdoctoral researcher to Imperial College London (UK) to work in Prof. Anthony G. M. Barrett's group. In 2007 he started his independent career as a Lecturer at Queen Mary University of London. Since 2014, Igor holds a Chair in Organic Chemistry at the University of Manchester. Igor has held a European Research Council Starting Grant and currently holds an ERC Advanced Grant. Igor's research interests lie in the development of new catalytic processes inspired by mechanistic understanding, with particular emphasis on transition-metal-catalysed C–H and C–C activation.

Dr. J. Burés

Jordi Burés gained his undergraduate degree in chemistry at the University of Barcelona (Spain) in 2003. He then pursued his studies for an MRes and PhD with an FPU studentship in the group of Prof. Jaume Vilarrasa. In 2010, he was awarded a postdoctoral fellowship to join the group of Prof. Donna Blackmond at The Scripps Research Institute, in California (USA). In 2013, he started his independent career at Imperial College London (UK) with an IC Junior Research Fellowship. In 2016, he was appointed Lecturer in Organic Chemistry at The University of Manchester (UK) and promoted to Senior Lecturer in 2020 and to Reader in 2022. Jordi has received the 2018 Thieme Chemistry Journals Award, the 2019 Young Researcher Award from the Spanish Royal Society of Chemistry (RSEQ), and the 2020 Hickinbottom Award from the Royal Society of Chemistry (RSC). The Burés research group develops physical organic chemistry tools to gain a deeper understanding of reaction mechanisms, allowing for the advancement of organic synthesis techniques in a rational, informed manner.

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