Artificial intelligence: The future for organic chemistry?

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Abstract

Based on a recent article "*Predicting reaction performance in C-N cross-coupling using machine learning*" appearing in *Science* we had decided to highlight the way forward for artificial intelligence in chemistry. Synthesis of molecules remains one of the most important challenges in organic chemistry and the standard approach involved by a chemist to solve a problem is based on experience and constitutes a repetitive, time-consuming task often resulting in non-optimized solutions. Thus, considering the recent phenomenal progresses that have been made in machine-learning, there is little doubt that these systems, once fully operational in organic chemistry, will dramatically speed up development of new drugs and will constitute the future of chemistry.

Introduction

In 1956, the "Forbidden Planet" movie starred the iconic sci-fi character Robby the robot whose impressive ability to synthesize almost everything was undoubtedly inspirational for generations of young chemists... Did Robby foreshadow the development of artificial intelligence (AI) in chemistry?

Synthesis of organic molecules remains one of the most important tasks in organic chemistry and the standard approach involved by a chemist to solve a problem is based on experience, heuristics and rules of thumb. When chemists design manually a new drug, they not only need

to design a target molecule, but they also need to look at the reaction pathways to synthesize it. Chemists usually work backwards, starting with the molecule they want to create and then analyzing by a process known as retrosynthesis which readily available reagents and sequences ofreactions could be used to produce it. This process is time-consuming and often results in non-optimized solutions or even failure in finding reaction pathways due to human errors.

Results and Discussion

AI is not a new field of research in organic chemistry as chemists have been using computers for years in their daily work and are quite willing to accept the aid of a computer (Figure 1).[1] Preliminary researches started for more than five decades ago with the DENDRAL project[2] even if for many people it is still just a buzz word associated with no real applications. In this context, Corey *et al*. envisioned that both synthesis and retrosynthesis could be designed by a machine using handcrafted rules known as reaction templates.[3] However, a deep chemical expertise was still required and rules writing remained a time-consuming task.

In the early days of AI approach for chemistry, candidate products were generated from the templates and then scored according to their plausibility.[4-5] However, this kind of approach is fundamentally dependent on the rule-based system component and do not lead to accurate predictions outside of the training domain. J. M. Lehn considered: "atoms as letters, molecules as words, supramolecular entities as sentences (...)" and some researchers tried to show that organic chemistry has a structure similar to a natural language and that the concepts of linguistic-based analysis could be used to analyze molecules, their patterns of reactivity and their organic synthesis.[6-8] On the other hand, we can cite the work of Kayala *et al.* who looks at mechanistic steps[9] whereas Liu *et al.* and Nam *et al.* use Sequence-to-Sequence models for retrosynthesis and reaction prediction.[10-11]

The task of finding pathways in chemistry focuses on the best combination of moves leading to a solution and finds the most promising strategy or pathway. It's a bit like a Solitaire game where the game pieces on the board at the beginning of the game would be the precursor molecules, and the only piece that remains at the end of a winning game would be the target molecule. During the game, the movements of the pieces correspond to the reactions applicable to the precursor molecules allowing to progress towards the synthesis of the target molecule; an inadequate combination of moves will prematurely stop the game. In 2016, using fingerprints learned with a neural network algorithm, Wei *et al.* identified with more than 80% accuracy the reaction type in the scope of alkene and alkyl halide reactions (Figure 2A). This algorithm is able to learn the probabilities of a range of reaction types and most importantly, its predictive capabilities can increase with the size of the libraries of training data. This algorithm constituted a step toward the goal of developing a learning machine devoted to the automatic synthesis planning of organic molecules.[12] One year later, a learning machine combining a novel model framework for generating and ranking candidate reaction outcomes and a novel edit-based representation was used by Coley *et al.*to reproduce in silico the qualitative results of actual experimental reactions. This unique framework combining candidate with more direct relevance to chemical reactivity was improved and expanded to achieve high predictive performance (Figure 2B).[13] The same year, using the dataset previously used by Jin *et al.*[14], a team at IBM[15] adopted another innovative approach by creating a tool to solve the forward-reaction prediction problem where the starting materials are known, and the interest is in generating the products. By using such an approach, the team fed chemical components into a neural network trained on a dataset of 395,496 reactions. The neural network then used what it had learned about prior reactions to predict about what would occur under new experimental conditions. The system responded to such requests by offering a list of the most plausible results. Testing showed that the top prediction turned out be correct 80 percent of the time.

Further to these works dealing with forward prediction, Segler *et al*. focused his attention on retrosynthesis and developed a new deep-learning neural networks that considered around 12.4 million of known single-step chemical reactions and allowed the prediction of the reactions that can be used in any single stepof a multi-step synthesis.[16] This program can deconstruct the considered molecule until it ends up with readily available starting reagents. A first neural network determines the search in promising directions by proposing fewer transformations. A second one predicts whether the selected reactions are feasible whereas a third one samples the transformations during the implementation phase. Simultaneously, by considering the low data regime and calculating theoretical properties of the reactants and reagents, Ahneman *et al.* predicted reaction performance in a palladium Buchwald-Hartwig C-N cross-coupling reactions in the presence of various potentially inhibitory additives with a machine learning in multidimensional space using data obtained via high-throughput experimentation.[17] This methodology is based on scripts that extract various molecular descriptors subsequently used as inputs in the model whereas reaction yields were considered as outputs. Random forest algorithms operate by randomly sampling the data and an overall prediction is generated by constructing aggregated decision trees. It was demonstrated that these algorithms led to significantly improved performance over linear regression analysis. Very recently and after more than 10 years of research, Klucznik *et al.* developed the highly effective Chematica computer program capable of designing novel efficient syntheses of medicinally relevant molecules.[18] This was realized by a subtle analysis of its scoring functions and the comparison with large numbers of logically related criteria such as selectivity or reactivity for example. All this leads Chematica to be able to rapidly propose optimized synthetic pathways for the design of molecules of interest.

All these different intelligent search algorithms have proven their effectiveness in providing chemists with realistic solutions for molecule synthesis. Undoubtedly, the collaboration of all these algorithms would bring an even better predictive relevance to the proposed solutions.

Some chemists may find this provocative, but chemistry considered as an isolated entity without relevant application is not useful and the considerable progresses of AI in this area (summarized above) do not change that.

However, chemistry reaches a whole new dimension when it has applications in other disciplines like in biology or physics of materials. Of course, AI has also infiltrated these disciplines. In biology, for example, the Omics revolution requiring Big Data mining has been the major driving force behind the development of AI. Beyond that application, in 2015, an AI system developed for biology has successfully inferred the first systems-biology comprehensive dynamical model explaining patterning in planarian regeneration.[19] A combination of AI systems developed for chemistry and biology that would be able to synthesize new molecules effective on new therapeutic targets to cure diseases would be a rather optimistic view of a near future. Already some researchers are turning to AI to design and carry out experiments to prospect of fully automated science. However, in the interest of human intelligence and for the social acceptance of AI (in all areas), we believe that an advisable evolution would be for AI to become the investigator's collaborator, bringing him new solutions, but also explains to him how it came to these conclusions. The Google's AI program Alphazero made obsolete the maxim that says that "it takes few minutes to learn to play Chess and a human lifetime to become a master".[20] Indeed, knowing only the rules of the chess game, Alphazero needed just few hours of self-learning to develop an adventurous and unconventional way of playing that allowed it to beat human masters or existing programs. In the same way, and even if the "Chemistry game" is more complex than the Chess game[21], the recent

phenomenal progresses that have been made in machine-learning will undoubtedly dramatically speed up development of new drugs.

Conclusion

Even though today no new drug has been synthesized using AI, experts agree that the commercial issues in this area are enormous.[22] AI will not replace chemists at least in the short term but AI clearly appears as the future of chemistry.[23-25]

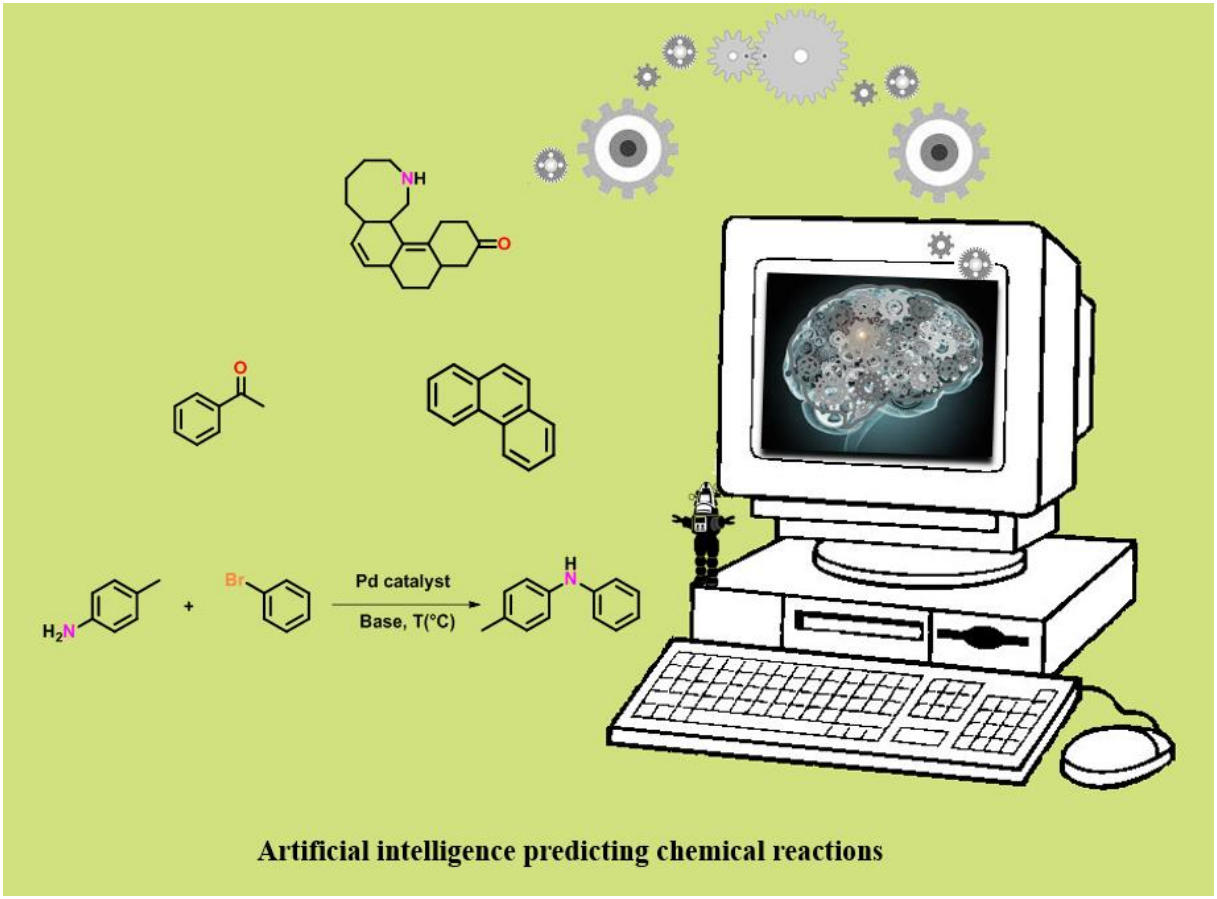

Figure 1. Oversimplified vision of artificial intelligence in the collective unconscious

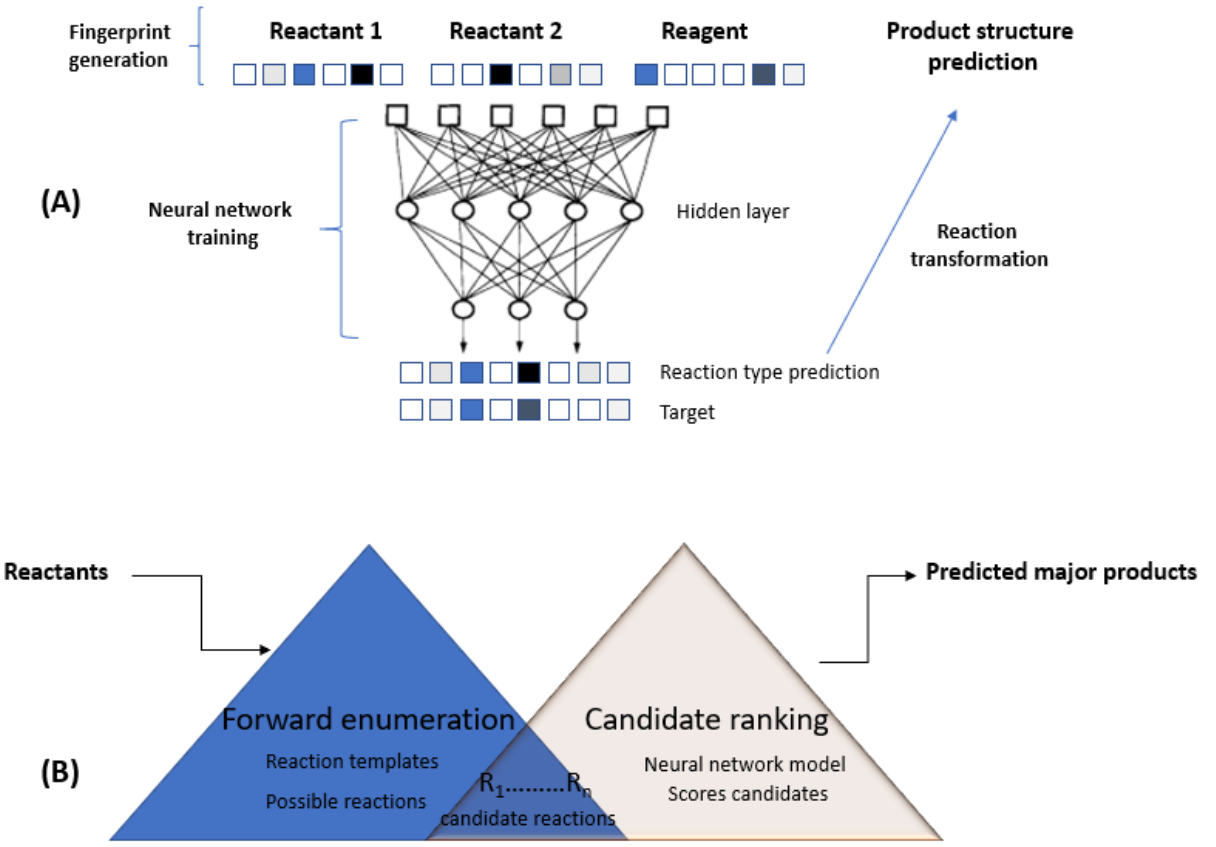

Figure 2. (A) A reaction fingerprint is the input for a neural network predicting the probability of numerous different reaction types as well as a potent product formation by applying to the reactants a transformation that corresponds to the most probable reaction type (Ref. 8). (B) Model framework combining forward enumeration and candidate ranking (Ref. 9).

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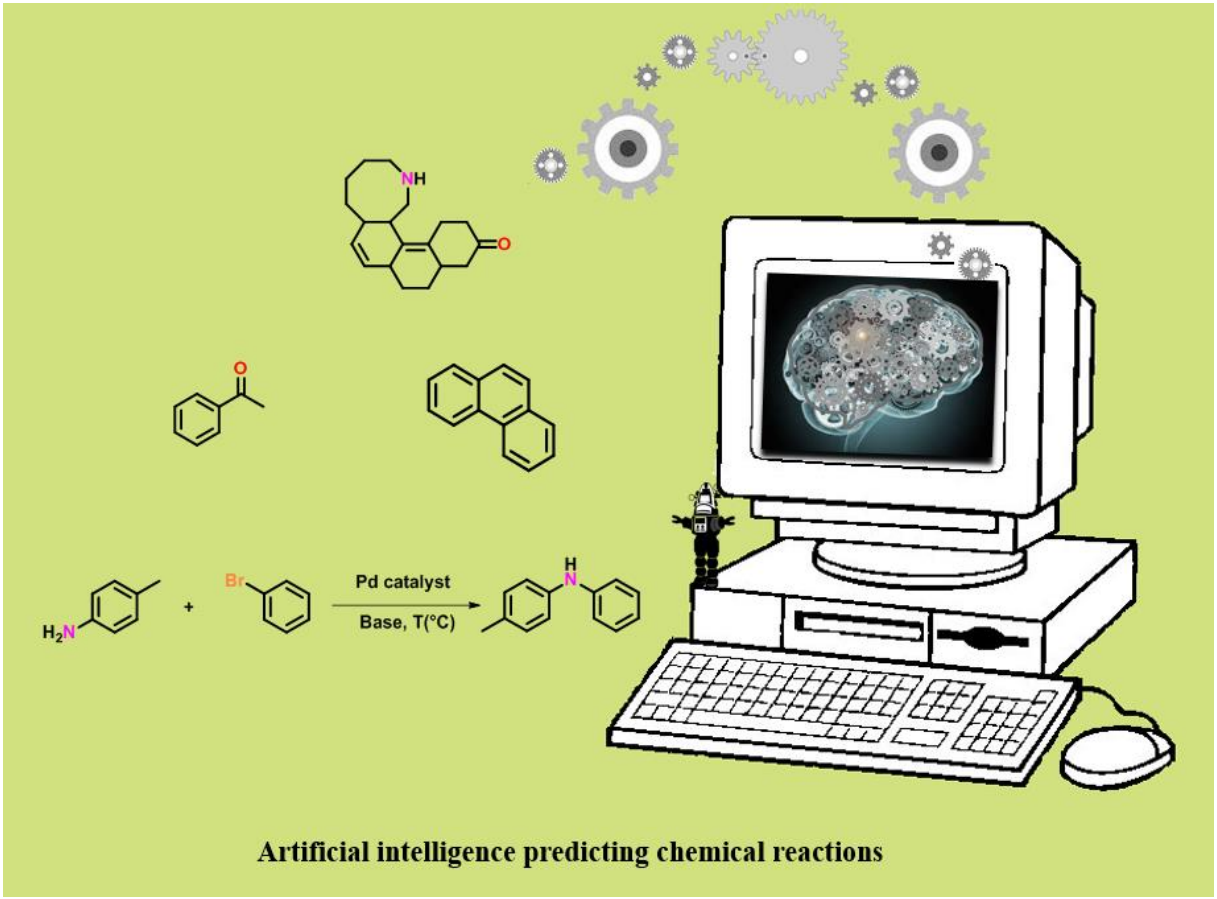

Artificial intelligence predicting chemical reactions