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Learning Chemical Intuition: From Molecular Models to Neural Networks

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Abstract: This article examines how both chemists and neural networks learn to predict chemical reactivity through different yet complementary frameworks, exploring how to effectively combine human chemical intuition with machine learning.

Keywords: Digital chemistry · Machine learning · Predictive chemistry

Chemistry, at its core, is a science of models and abstractions. Chemists have developed sophisticated ways to represent complex molecular phenomena through simplified, yet powerful representations; as noted in a previous CHIMIA column: Chemistry's unique sign language and representations of structural formulas are highly predictive tools.[1] An illustrative example is the curly arrow mechanism notation system – the *lingua franca* of organic chemistry (Fig.1a). When designing reactions, we typically reason through these simplified models while evaluating multiple possible mechanistic pathways. This chemical intuition – the ability to distill, predict and communicate reaction outcomes from structural patterns – becomes second nature through months or years of practice.

This approach interestingly parallels how machine learning (ML) models learn to predict reactions: while chemists use visual models like curly arrows, ML models process reactions through abstract representations such as SMILES strings or graphs, learning from hundreds to thousands of datapoints of reaction examples to replicate the underlying rules that govern reactivity (Fig. 1b). The key difference lies in scale and interpretability: while curly arrows were designed for human understanding, modern ML models work in vast latent spaces we cannot easily interpret.

Building on these parallels between human and machine learning, digital chemistry has emerged as an exciting field at the interface between chemistry and computer science. It integrates computational methods and automation across multiple domains: from molecular modeling and property prediction to laboratory automation and robotics.[2] Recent advances (a non-exhaustive list) showcase its immense potential: self-driving laboratories can autonomously optimize chemical reactions and accelerate materials discovery,[3] while large language model agents integrated with laboratory tools can plan and execute organic syntheses 'from the cloud'.[4] Language models and graph neural networks are increasingly being used for tasks from process simulation to reaction prediction.[5,6] and evolutionary algorithms are efficiently exploring vast chemical spaces for drug design.[7] Perhaps most impressively, deep learning models recently helped discover the first new class of antibiotics in decades by screening over 12 million compounds![8] These tools

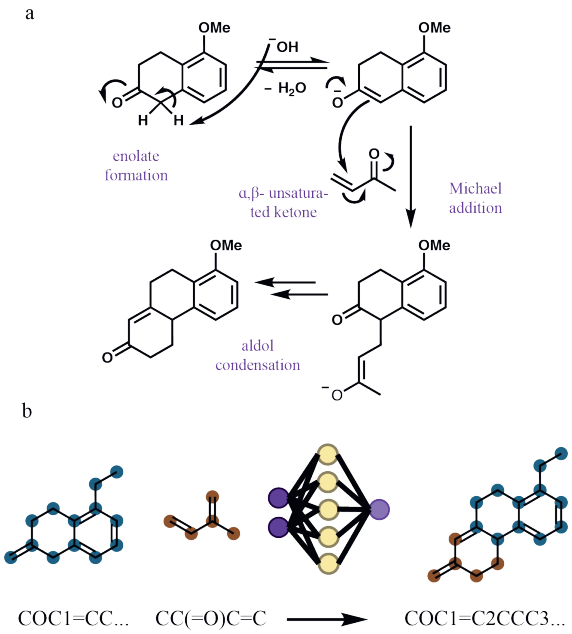

Fig 1. Different approaches to predicting chemical reactivity. (a) Chemists use curly arrows to track a hypothetical electron flow, guided by heuristics that become second nature with practice. The Robinson annulation shown is a succession of known intermediate labels: enolate formation enables a Michael addition, followed by aldol condensation to form the final product. (b) Machine learning approach to the same problem: reactions are encoded as 'machine readable representations' (SMILES strings, graphs), processed through neural networks that learn patterns from data to predict product structures. These models can rapidly analyze millions of reactions, identifying subtle reactivity patterns and generalizing across diverse chemical spaces, though their internal reasoning remains opaque.

highlight new approaches to long-standing challenges in drug discovery, materials science, and chemistry.

Artificial Intelligence (AI) has transformed countless aspects of society, including chemical education in ways that seemed like science fiction just years ago. A landmark study at EPFL demonstrated that ChatGPT-4 could achieve passing grades in 83.3% of first-year chemistry courses, spanning both multiple-choice and open-ended questions. In other words, ChatGPT 'could' get an engineering degree.[9] At ETH Zurich, since fall 2024, a *virtual teaching assistant* named Ethel has supported assignment grading and course management across three chemistry courses.[10] Tools like NotebookLM generate podcasts from research papers within minutes.[11] Yet these impressive results fail to account for fundamental limitations: chemistry combines complex molecular phenomena, mathematical models, experimental techniques, and visual representations - a multifaceted nature that cannot be reduced to simple text- or multiple-choice-based evaluations. While these tools demonstrate promising capabilities in supporting chemical education, they fundamentally lack the ability to integrate and assess the multidimensional aspects of chemical intuition.

This creates what researchers call a jagged frontier in the capabilities of AI.[12] Take image recognition as an example: while telling apart a mop from a dog is trivial for humans (try it for yourself in Fig. 2a), it is surprisingly challenging for ML models. The opposite occurs in drug discovery, where AI, when trained on high-quality experimental data, may excel at spotting subtle structural changes that dramatically affect drug potency (Fig. 2b).[15]

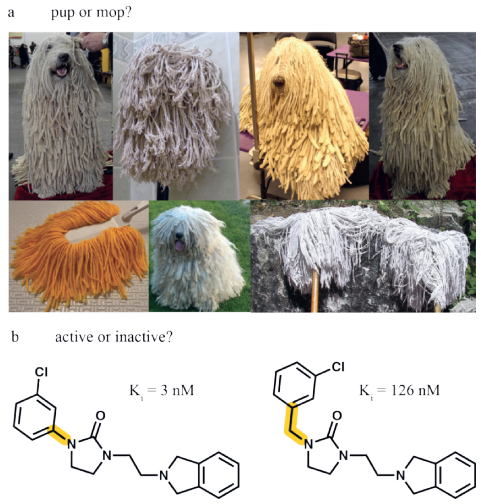

Fig. 2. Recognizing (not so) subtle differences. (a) Pup or mop? While humans easily distinguish between images of household items and dogs, ML models find this task challenging.[13,14] (b) Activity cliffs in drug discovery: Minor structural changes lead to 42-fold differences in potency - patterns humans might overlook, but ML models can detect and predict.[15]

While machine learning is increasingly enabling data-driven discovery in the chemical sciences, it requires careful consideration of chemical constraints. ML models may generate unrealistic predictions or fail when applied outside their training domain. Fig. 3 demonstrates one of these failure modes: when tasked with generating molecules for protein binding without synthesizability constraints, an algorithm generated structures that, while theoretically not impossible to exist, are rather infeasible to synthesize in the lab.[16] This illustrates how ML models, without being aware of proper chemical constraints and intuition, produce impractical results.

Rather than viewing AI as a replacement for chemical intuition, we should focus on it as an enhancement for research and education. Following FAIR data principles,[17] careful documentation and sharing of chemical data can help ground ML models in meaningful chemical data, advancing both human and machine understanding of chemistry – and ultimately accelerating the development of sustainable technologies and life-saving drugs.

The path into digital chemistry is more accessible than ever: one can begin with basic programming, building simple models relevant to specific research areas or coursework, while leveraging existing resources – from tutorials to open-source guides for digital chemistry.[18,19] A practical approach starts with selecting a focused research problem or model system, exploring available computational tools, and gradually building a digital chemistry toolkit. The entry barrier may seem high at first, but a chatbot (without an engineering degree, yet) might lower that activation energy just enough.

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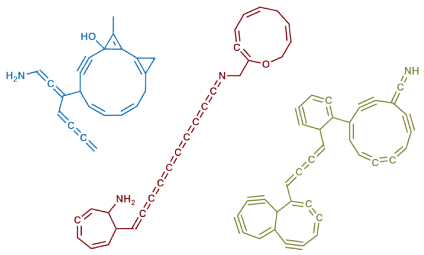

Fig. 3. Predictions of drug candidates by a generative ML model without synthesizability constraints.[16] Structures achieving highest docking scores in benchmark experiments reveal how unconstrained ML models generate molecules that, while not violating chemical valency rules *per se*, are unfeasible to synthesize.

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