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# On the Synergies Between Quantum Mechanics and Machine Learning in Reaction Prediction

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## Abstract

We demonstrate how machine learning (ML) and quantum mechanical (QM) methods can be used in two-way synergy to build chemical reaction expert systems. The proposed ML approach to reaction prediction identifies electron sources and sinks among the reactants, and then ranks all source-sink pairs. This is used to address a major bottleneck of QM calculations by providing a prioritized list of mechanistic reaction steps. QM modeling can then be used to compute the transition states and activation energies of the top-ranked reactions, providing additional or improved examples of ranked source-sink pairs. Retraining the ML model closes the loop, producing more accurate predictions from a larger training set. The approach is demonstrated in detail using a small set of organic radical reactions.

## Introduction

Predicting the outcome of chemical reactions is a fundamental problem in science and technology with far-reaching applications. No chemical reaction prediction system approaching human-level performance exists today. Broadly speaking, there are three families of approaches to reaction prediction: (1) quantum-mechanics-based approaches; (2) rule-based approaches; and (3)

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3 machine-learning-based approaches. We have previously demonstrated the effectiveness of rule-  
4 based systems,<sup>1</sup> and how these can synergistically help ML-based systems<sup>2</sup> by providing training  
5 examples for the machine learning component. In this letter, we propose a novel strategy focused  
6 on a different, complementary, synergy between QM and ML, where the ML system prioritizes  
7 QM computations on elementary reaction steps, and the QM results are used to provide additional  
8 training examples to refine the ML results. This strategy has the distinct advantage of coupling the  
9 ML and QM approaches within a closed and automated feedback loop.  
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18 The QM and ML approaches are often complementary in chemoinformatics. QM modeling can  
19 directly compute physical properties of small molecules, but is computationally expensive; ML can  
20 only interpolate and generalize from training data, but predictions are fast. The two approaches  
21 can be combined in multiple different ways: QM has been used to compute input features for ML  
22 chemoinformatics systems,<sup>3–5</sup> and ML has been used to approximate or speed up QM computa-  
23 tions.<sup>6</sup> However, few attempts have been made to combine ML and QM within a two-way positive  
24 feedback loop, and only for relatively narrow applications.<sup>7,8</sup> Here we propose a novel specific  
25 strategy for synergistically combining QM and ML for the general problem of reaction prediction.  
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34 In what follows, we summarize the three different approaches to reaction prediction, describe  
35 our proposed ML-QM synergy in detail, and then demonstrate the approach on a set of organic  
36 radical reactions.  
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## 42 QM-based Approaches

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44 QM-based predictions of reactions,<sup>9–14</sup> provide the satisfactory impression that they are derived  
45 from first principles, although any application of the Schrödinger equation to realistic system re-  
46 quires a host of approximations with various degrees of accuracy, ranging from ab-initio Hartree-  
47 Fock approaches or Density Functional Theory (DFT) to semi-empirical methods or mechanical  
48 force fields.<sup>12</sup> These methods require careful setup for individual experiments and are compu-  
49 tationally expensive. For example, many recent physical simulation studies of reaction mecha-  
50 nisms<sup>15–19</sup> involve in-depth exploration of manually-constructed variants of single systems. When  
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successful, these methods can model the effect of reaction conditions (e.g. temperature, phase, concentration, solvent attributes) and they can return important parameters such as transition states and rates. However, QM-based methods are computationally intensive and thus in general cannot be used in high-throughput mode.

## Rule-Based Approaches

Over the years, there have been several attempts at developing rule-based expert systems<sup>20–27</sup> with some success. For instance, the ReactionExplorer system<sup>26,27</sup> has been used to power an interactive educational system that is distributed by Wiley. These approaches however have suffered from several drawbacks. First, a finite set of rules can only provide a limited coverage of chemical space (e.g. ReactionExplorer covers only undergraduate-level chemistry). Second, the rules used often operate at the level of global reactions and do not take into account the elementary mechanisms which, when composed together, produce these global reactions. Drilling down to the level of elementary mechanisms is essential to understand chemical reactivity at a deeper level in order to interpret global reactions in terms of arrow pushing mechanisms and identify side products. Third, and most importantly, rule-based system are hard to maintain and often do not scale well: whenever a new rule is added, it must be tested against all the previous rules as it has a chance to violate or conflict with one of the previous rules.

## ML-based approaches

Finally, there are ML-based approaches<sup>2,28,29</sup> which try to learn from data. Within this broad class, different ML methods can be used. For instance, one could try to learn the “grammar” of chemical reactions, or cast the prediction problem as a language translation problem, from reactants to products. Thus techniques from natural language processing and for inductively learning grammars could be applied to this problem. A different machine learning approach is described in the next section. But in any case, the main obstacle for ML-based approaches is by far the lack of training data. Database of reactions, such as CAS,<sup>30</sup> Beilstein,<sup>31</sup> and SPRESI<sup>32</sup> do exist, but these

are commercial and not readily available for academic research. Furthermore, reactions in these databases are often unbalanced, or non-atom mapped, raising additional processing issues.

## A Machine Learning Approach

Here we describe a different deep learning approach used to develop the ReactionPredictor system.<sup>2,29</sup> The fundamental idea is as follows. Composite chemical reactions are made of elementary reactions involving transfers of electrons from electron sources to electron sinks<sup>33,34</sup> (Figure 1). Given, for example, two reactants A and B, one can parse A and B to identify all the possible sources and sinks of electrons in each atom. [A conceptually irrelevant detail, which is however very important in practice, is that the initial list of sources and sinks can be further pruned using machine learning methods]. Assume then that one is left with 10 possible sources and 10 possible sinks. This leads to 100 possible source-sink pairs corresponding to 100 elementary reactions. The reaction prediction problem is then fundamentally reduced to a *ranking* problem, how to rank these 100 elementary possibilities and identify the most productive ones. This ranking problem is very much a machine learning problem similar to, for instance, the ranking problem faced by any search engine. With the availability of training data, deep learning can be applied to solve this ranking problem. In particular, ReactionPredictor uses a Siamese neural network<sup>35,36</sup> to compare source-sink pairs and decide which pair is more favorable. The ranking can be used to compose elementary reactions together into global reactions, explain reactions mechanistically, and identify potential side products. Furthermore, the ranking solution will get better and better as more data becomes available. Thus in short the core idea is to apply machine learning, in particular deep learning, to learn chemical reactions at the level of elementary mechanisms which can then be chained to produce global reactions. Initial training data for ReactionPredictor was constructed using the ReactionExplorer<sup>1</sup> system augmented with manually selected reactions to increase coverage.

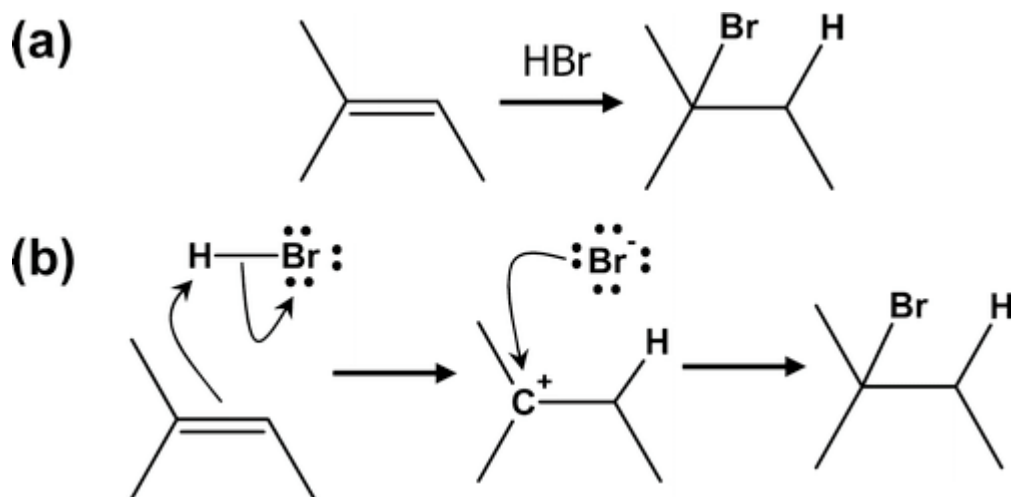


Figure 1: Example overall transformation and corresponding elementary, mechanistic reactions. (a) The overall transformation of an alkene with a hydrobromic acid. This is a single graph rearrangement representation of a multi-step reaction. (b) The details of the two mechanistic reactions which compose the overall transformation. The first involves a proton transfer reaction, and the second involves the addition of the bromide anion. Each detailed mechanism is an example of an “arrow-pushing” diagram<sup>34</sup> involving a single transition state, in which each arrow denotes the movement of a pair of electrons, and multiple arrows on a single diagram denote concerted movement.

## The ML-QM Synergy

We now show how the ML-based approach behind ReactionPredictor can be integrated synergistically with QM-based approaches. The QM simulations are performed using Turbomole,<sup>37</sup> but obviously other systems could be used as well. ReactionPredictor, in combination with a 3D structure prediction system for small molecules such as COSMOS,<sup>38–40</sup> CORINA,<sup>41,42</sup> or open-source packages,<sup>43,44</sup> can provide initial 3D structures for QM calculations. Indeed, one can focus on the top ranked elementary reactions produced by ReactionPredictor, and the 3D coordinates of all the molecules involved, to seed the QM simulation, thus addressing one of the major QM bottlenecks in reaction prediction. The QM simulation in turn can produce relevant parameters, such as transition states, bond dissociation energies, or reaction rates. These parameters are not available in the original version of ReactionPredictor. Assuming that the QM simulation leads to accurate results, these can be used to refine the ranking of elementary reactions produced by ReactionPredictor.

Finally, in principle the QM results could be used over time to curate additional reaction data, at the mechanistic level, which in turn could be used to retrain ReactionPredictor thus creating an automated self-reinforcement loop where ReactionPredictor improves the outcome of QM calculations and vice versa. Validating the latter idea in high-throughput fashion is beyond the scope of this letter, as it would take considerable resources to deploy. Rather we next demonstrate the feasibility of the basic idea on a set of organic radical reactions.

## Demonstration

We examined three sets of organic reactants to demonstrate the ML-QM synergy. The initial ML rankings were produced using ReactionPredictor's deep Siamese neural network ranking model consisting of 226 inputs, three hidden layers of 50 hidden tanh units, and a sigmoid output. The model weights were initialized according to Glorot, et al.,<sup>45</sup> then updated with stochastic gradient descent on mini-batches of size ten, an exponentially-decaying learning rate, and 50% dropout in the final hidden layer. The training set consisted of 6000 pairs of reactions that were either derived from ReactionExplorer or manually-selected to increase coverage, with 10% of these used for validation and early stopping.

Given a set of reactants, ReactionPredictor produces a ranking of the most likely reaction pathways, specified by SMIRKS codes.<sup>46</sup> Each of the top reactions is then modeled using DFT to compute the activation energy. This modeling proceeds in stages: First, 3D geometries of the individual reactants and products are produced and optimized using QM. Second, a rough 3D geometry of the transition state is produced, either by 1) algorithmically aligning the reactant/product models along the bonds that are formed/broken and performing a grid search to find a good initialization of the atoms directly involved in the reaction, or 2) using Newtonian mechanics models to search for a reasonable transition state configuration. Third, the atoms directly involved in the reaction are frozen while the geometry of the rest of the system is optimized using QM. Fourth, the Turbomole transition state search algorithm is run. If this converges to a geometry with more

than one imaginary mode, the *screw* algorithm is used (scanning over the distortion parameter) to attempt to fix the result, or else the search is restarted from another initialization. For transition state searches on more complex reactions, we are investigating more sophisticated algorithms such as Elastic Band methods.

Table 1 lists the automatically-calculated activation energies for the top-ranked reactions from ReactionPredictor, while Figure 2 displays the transition state geometry of the single most-favorable reaction in each set. For the most part, these quantitative calculations validated the results from ReactionPredictor. However, there was a discrepancy in the ranking of Reactant 3, where the third reaction was correctly calculated to be slightly more favorable than the second reaction. This pair of reactions was fed back into the training data set and the entire ReactionPredictor system was retrained; as a result, the new predictions agree with the QM calculations.

Table 1: Computed activation energies of the top-ranked reaction pathways for each of three example reactant sets.

Reactant(s)	RP Rank	Product(s)	Activation Energy (Hartree)
CCCCC(C)CCCC.O[O]	1	CCCC[C](C)CCCC.OO	0.0251
	2	CCC[CH]C(C)CCCC.OO	0.0279
	3	CC[CH]CC(C)CCCC.OO	0.0282
CCCCCCC([O])CCC	1	CCCCCCC=O.[CH2]CC	0.0251
	2	CCCCC[CH2].O=CCCC	0.0257
	3	CCCCCCC(=O)CCCC.[H]	0.0390
CCCCC(C)([O])CCCC	1	CCC[CH2].CCCCC(=O)C	0.0207
	2	[CH3].CCCCC(=O)CCCC	0.0267
	3	OC(C)(CCCC)C[CH]CC	0.0259

## Conclusion

Machine learning has the potential to push chemical reaction expert systems to human-level performance and beyond, but the paucity of training data is a major limitation, preventing systems like ReactionPredictor from taking full advantage of recent advances in deep learning. We have described a synergy between ML and QM approaches in which ML can prioritize reaction pathways for investigation with QM, while QM provides the requisite “ground truth” to improve ML



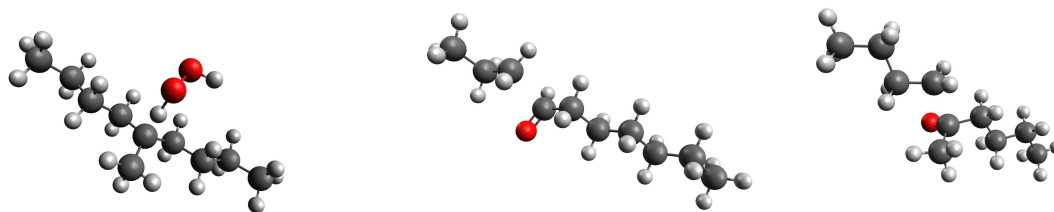


Figure 2: Transition states found for the top reactions from each example set of reactants: (i) Hydrogen abstraction by peroxy radical,  $\text{CCCCC(C)CCCC} + \text{O[O]} \rightarrow \text{CCCC[CH](C)CCCC} + \text{OO}$ ; (ii) Alkoxy beta scission of secondary alkoxy radical,  $\text{CCCCCCC([O])CCC} \rightarrow \text{CCCCCCC=O} + [\text{CH}_2]\text{CC}$ ; (iii) Alkoxy beta scission of tertiary alkoxy radical,  $\text{CCCCC(C)([O])CCCC} \rightarrow \text{CCCCC(C)(=O)} + \text{HC(H)CCC}$ .

predictions. The resulting positive-feedback loop could propel chemical reaction expert systems to higher levels of accuracy and into new areas of chemistry.

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## Graphical TOC Entry

