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Transforming Computational Drug Discovery with Machine Learning and AI

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ABSTRACT

In this Viewpoint, we discuss the current progress in applications of machine learning (ML) and Artificial Intelligence (AL) to meet the challenges of computational drug discovery. We identify several areas where existing methods have the potential to accelerate pharmaceutical research and disrupt more traditional approaches.

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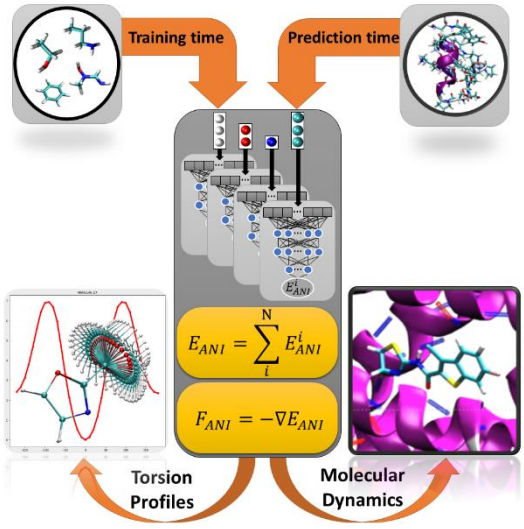

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"Computers are useless. They can only give you answers."
-Attributed to Pablo Picasso

Computational methods play a key role in the design of therapeutically important molecules for modern drug development. These methods can be broadly classified as structure-based or ligand-based. Structure-based methods require knowledge of the structure of both the target and ligand. They include molecular dynamics, protein-ligand docking, and methods for calculating the free energy of binding. Ligand-based methods use only information about the ligand to predict the biological response depending on historical data about known active and inactive ligands. These methods typically include quantitative structure-activity relationships, activity cliffs analysis and similarity search.

In terms of energy evaluation for molecular systems both types of methods still rely on force fields or empirical scoring functions. Parametrizing accurate and transferable force fields is a very difficult task especially if one needs screening millions of different possible ligands. This parametrization requires embedding very high-dimensional quantum physics behavior into a small number of parameters with a very simple analytic functional form. For this reason, a "zoo" of force fields has been developed over the last quarter century for applications in various domains, such as nucleic acids, proteins, carbohydrates, and small drug-like molecules. Understanding exactly where these system-specific force fields work, and where they fail, is an extremely challenging task. This fact boils down to the following two simple statements: force-fields are fast but can perform poorly outside of their fitting set and quantum mechanical methods can be extremely accurate, but at a prohibitive computational cost. This age-old gap between the speed of classical force-fields and the accuracy of quantum mechanical approaches has plagued academic and industrial computational chemists for decades.

We opened this Viewpoint with a quote by Pablo Picasso because it promotes deep thought about how computers have impacted our world. It could be interpreted in many ways. The majority of effort in computational chemistry has focused on methods for producing answers. Traditionally, computers have not been creative, that is, they can only do what humans tell them to do. Perhaps, by saying "they only give answers", Picasso implies that for computers to truly have an impact, then they should be able do *more* than we expect.

Modern artificial intelligence (AI) has the potential to significantly enhance the role of computers and computational methods in science and engineering.[1] The World Economic Forum refers to the combination of big data and AI as both the fourth paradigm of science and the fourth industrial revolution. With machines able to learn and offer solutions to some of the most complex chemistry problems, drug discovery is well positioned to be the next frontier for a potential breakthrough.

Learning Quantum Mechanical Properties

A lot of progress has been made in the development of atomistic potentials using machine learning (ML) with methods such as kernel ridge regression (KRR)[2], neural networks (NN)[3], and gaussian process regression (GPR). The low numerical complexity and high accuracy of machine learning algorithms make them very attractive as a pragmatic substitute for *ab initio* and DFT methods. Thanks to their remarkable ability to find complex relationships among data, in most cases these 'machine learned' models out-perform more physically constrained approximations like force fields. However, these models are critically dependent on the quality and quantity of data used in their training. Neural networks, for example, are highly efficient and effective at modeling

reference training data, due to their flexible functional form. This flexibility comes at a cost: a vast amount of reference data is required to properly train these models in a way that provides good answers over a wide range of inputs.

In our recent work, we published the ANI-1 potential[4]. ANI-1 is the first example of a universal NN molecular potential, where we show that training to a large dataset of 22 million small molecule conformations[5] yields a potential capable of predicting energies on much larger systems and on systems wildly different from those in the training set. We show its applicability to systems with up to 70 atoms, including well known drug molecules. ANI-1 shows exceptional predictive power on the external molecular size extensibility test set, with RMSE versus DFT relative energies as low as 0.57 kcal/mol when considering molecular conformations that are within 30 kcal/mol of the energy minimum for each test molecule. More recently, this concept of training an ML model to small fragments of organic molecules to predict on larger systems has been verified independently. Gastegger et. al.[6], showed results for large organic systems that were fragmented into smaller molecules and DFT data was generated on the fly for training. These and many other studies back up the argument that information about the physics of large systems can be learned from data sets of small molecules.

'Smart' Data Sampling and Feedback Loop

In drug discovery, projects operate via feedback loops, the process known as the design, make, test, and analyze (DMTA) cycle. This feedback loop is crucial to adapt, recover and learn from mistakes. Traditional computational methods are static. A particular approximation is predefined; all data is generated up front prior to fitting. They are not concerned with issues of biased or redundant data.

In contrast, ML methods combined with Active Learning (AL) are a natural analogy to the concept of feedback loops. AL is the process of intelligently searching the problem space in an iterative way to generate the minimal data set to achieve the same, or better, results as "random" static learning.[7] Recently, we published improvements to ANI-1 based on AL.[8] We used an ensemble of models (a process known as query by committee) to drive diverse sampling methods and automatically select new molecules and conformations to add to the training set. This process resulted in the ANI-1x potential. ANI-1x was shown to provide a very high-level of potential energy and force accuracy on large drug-like molecules and protein sized systems from the COMP6 benchmark. The level of accuracy provided by an ANI model trained on the ANI-1x dataset is shown to be better than MP2/6-311+G** and the current gold standard small molecule force field (OPLS3) on the Genentech benchmark[9] of small organic molecule torsion profiles (Figure 1a). In some cases, like molecule 36 from the Genentech benchmark (Figure 1b), force fields have a hard time reproducing the shape of the dihedral potential and even produce artificial minima. Both DFT and ANI-1x closely mimic the high level coupled-cluster result. This result might be fortuitous, but it is clear from Figure 1a that ANI-1x performs better over the entire torsion benchmark, yielding credence to the claim that ANI-1x is more accurate that the best force fields, while being several orders of magnitude cheaper than advanced QM methods. Also, it should be considered that the accuracy of the ANI-1x potential is tied to that of the DFT functional used to generate training data. Various claims have been made that neural network type potentials will not be able to do better than DFT because of large data requirements and the low cost of DFT compared to very accurate *ab initio* methods.[10] These claims are likely true if neural network-based potentials cannot reduce data requirement from accurate *ab initio* methods.

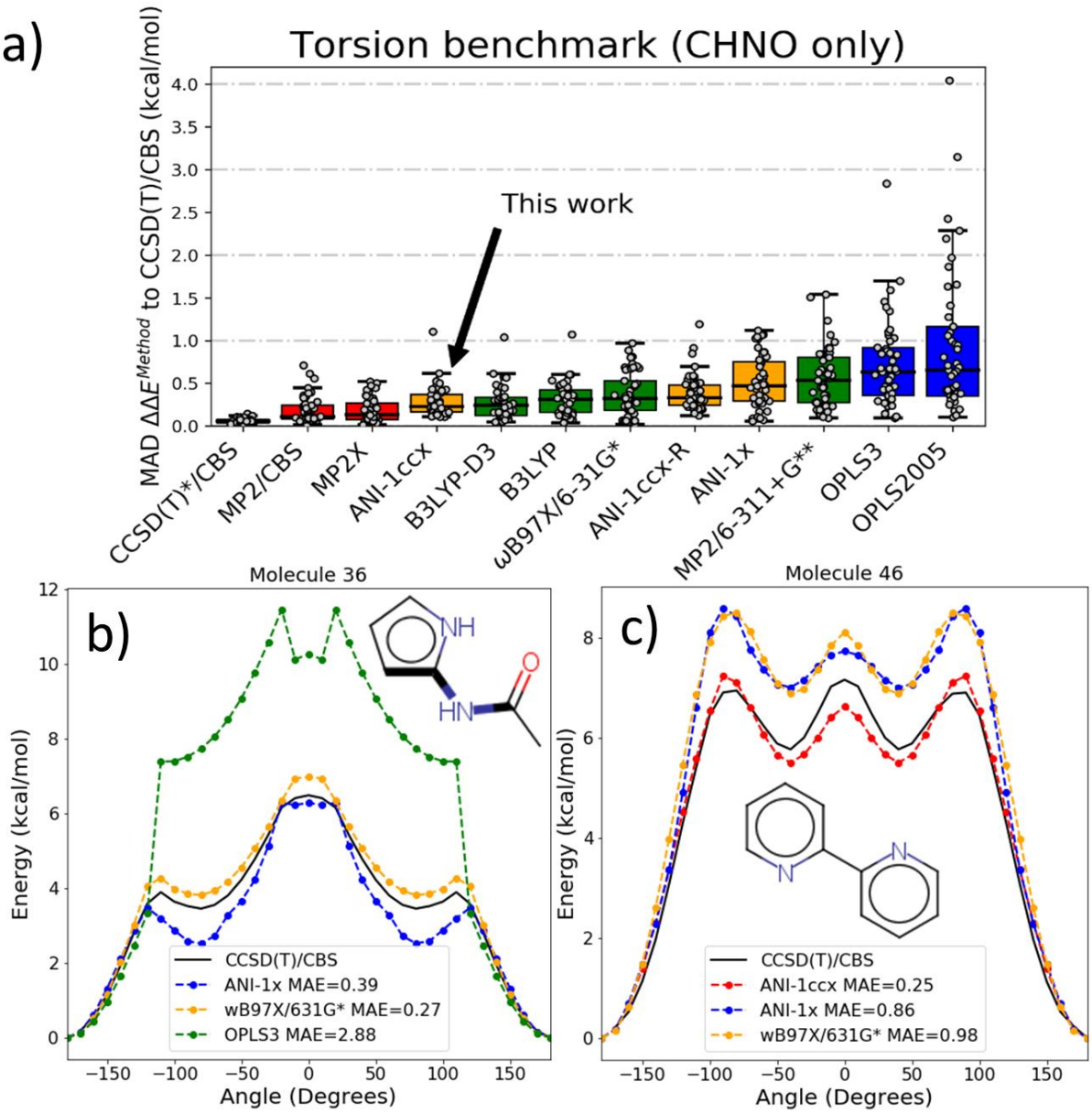

Figure 1: Examples of ANI potential relaxed torsion scans accuracy vs. various levels of theory from Sellers et al. torsion scan benchmark[11]. a) Accuracy of ANI-1x and ANI-1ccx (as presented in the ANI-1ccx[12] work) compared against results from complete torsion benchmark for molecules containing the chemical elements C, H, N, and O. b) Select torsional scan where OPLS3 experiences a large error in the barrier height, but DFT and the DFT trained ANI-1x potential both perform well vs. CCSD(T)/CBS. c) Select torsional scan where DFT and the DFT trained ANI-1x potential perform with similar accuracy, but the transfer learning-based ANI-1ccx potential greatly outperforms the DFT models.

The availability of such high-quality QM reference data allowed us to use these transfer learning techniques to build a chemically accurate universal ANI potential.

There are various techniques from ML for reducing data requirements. Some ML-based methods (more specifically neural networks) can take advantage of information from multiple sources. The key concept is to train a model to some large dataset of medium accuracy, and then retrain the model to less data from a more accurate and difficult to obtain data source. This process is called transfer learning[13], and relies on the assumption that the less accurate data source contains some information that makes it easier to learn correlations in the more accurate data. For ML potentials, we recently employed this process by taking a deep learning model that was pretrained to medium-fidelity DFT, holding some number of parameters in the model constant, and then retraining the remaining parameters to a much smaller, high-fidelity CCSD(T) accurate dataset.[12] The result is

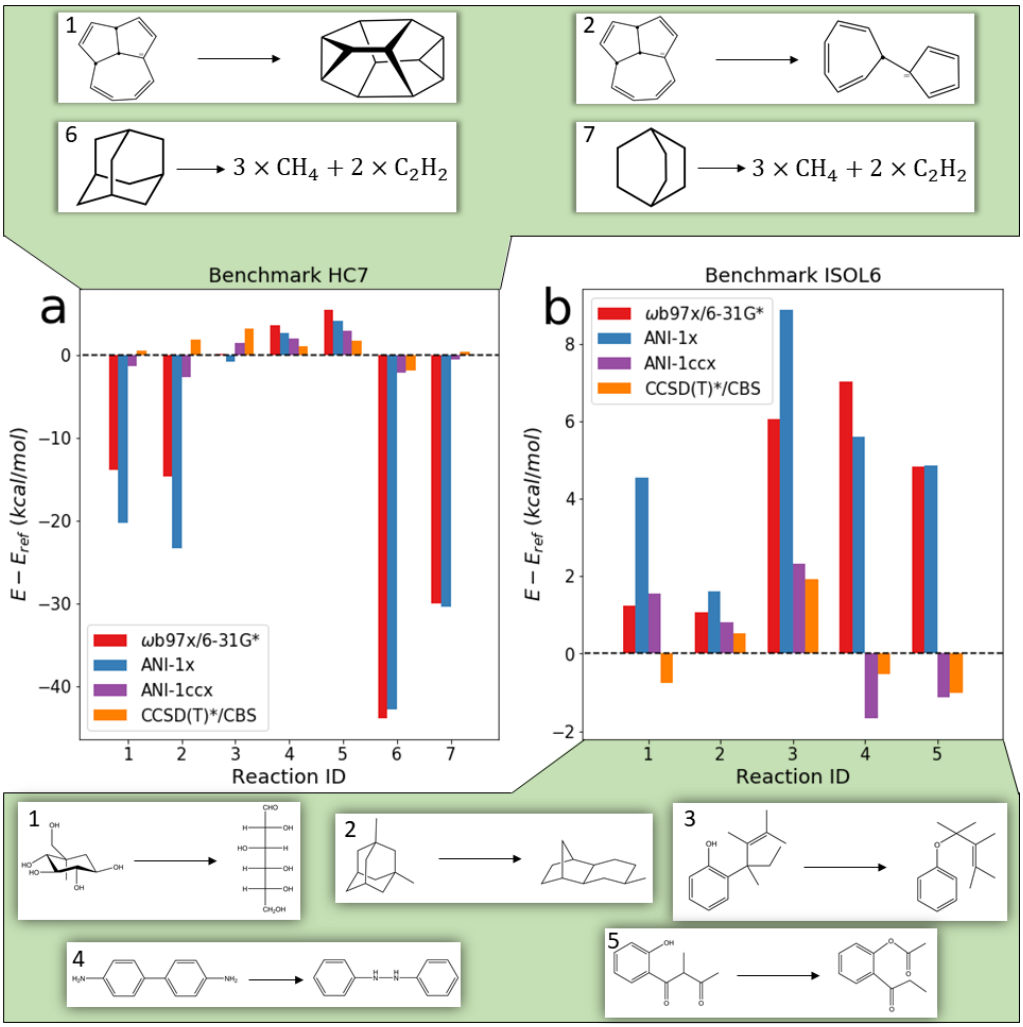

Figure 2: Comparison of the original ANI-1x reference DFT (ωB97X-D3/6-31g*), ANI-1x, ANI-1ccx and our high-level reference CCSD(T)*/CBS on the HC7/11 and ISOL6 benchmarks. a) depicts the individual HC7/11 reaction and isomerization energy differences from reference calculations while b) shows the ISOL6 (C, H, N, and O atoms only) isomerization energy differences from reference. The top panel provides the HC7 reactions numbered 1, 2, 6, and 7 and bottom panel shows the ISOL6 reactions numbered 1-5. This figure appeared in Smith et al. (2018).[12]

the ANI-1ccx potential. The ANI-1ccx potential is shown to be an attractive alternative to density functional theory approaches and standard force fields for conformational searches, molecular dynamics, and the calculation of reaction energies. The reaction energy results show that the transfer learning-based ANI-1ccx outperforms (Figure 2) DFT on test cases, including cases where DFT fails to capture reaction thermochemistry. In the ANI-1ccx work, we utilize a new extrapolation scheme to CCSD(T)/CBS for high-throughput and very accurate QM data generation.

Generative Methods and De Novo Design

The field of "*de novo*" or inverse molecular design has benefited tremendously from recent advances in ML. Within a very short time, numerous approaches have been suggested. Notably, methods like recurrent neural networks (RNN)[14], generative adversarial networks (GANs)[15] and autoencoders[16] were adapted to problems of rational design of organic and inorganic materials, synthesis planning and device optimization.[17]

Popova et al. proposed a method called ReLeaSE for generating chemical compounds and focused chemical libraries with desired physical, chemical, and/or bioactivity properties that is based on deep reinforcement learning (RL).[18] The general workflow for the ReLeaSE method includes generative (G) and predictive (P) neural networks. In this system, the generative model G is used to produce novel chemically feasible molecules, that is, it plays the role of an agent, whereas the predictive model P plays the role of a critic. P estimates the agent's behavior by assigning a numerical reward (or penalty) to every generated molecule. The reward is a flexible function of the numerical property/activity of a generated molecule, and the generative model is trained to maximize the expected reward.

Synthesis Planning

Recently, ML-based methods have been employed in breakthroughs involving synthesis planning. Chematica, a computer program, was used to plan complete syntheses of medicinally important molecules without human help.[19] Chematica by Grzybowski et al. implements about 50,000 rules of synthesis into decision trees. The reaction rules are combined into graphs connecting millions of possible molecules and different synthetic routes from which the viable synthetic pathways are extracted.

Segler et al. demonstrated that retrosynthetic routes can be discovered using Monte Carlo tree search and symbolic AI without using human expert rules.[20] This neural network was trained on essentially all reactions published in organic chemistry. In a double-blind test, synthetic chemists considered computer-generated routes to be on par with methods reported in literature.

Conclusions

The continued improvement of ML methods in chemistry, that compete with standard approaches or expert skill, are poised to become a force for change in modern computational medicinal chemistry. Machine learning potentials capable of carrying out high-throughput calculations in milli-second time scales with DFT accuracy or better will accelerate ligand conformational searching and help to avoid false positives and false negatives. Further, continued progress toward bulk phase protein/ligand simulation will allow QM accurate free energy of binding calculations that can be performed with minimal human intervention for parametrization.

De novo molecular design can potentially supply accurate predictions of lead compounds to target for simulation, effectively shrinking the search space for high-throughput screening applications. Automated synthesis planning promises to provide better, higher yield, and more cost-effective synthetic routes. The combination of the methods discussed in this opinion, and other methods not discussed, such as robotic synthesis[21], could eventually provide a fully automated drug discovery pipeline driven by AI.

There are various routes researchers could take to bring these game-changing tools into reality. Researches in the development of ML-based potentials should move from a benchmark/model centric culture to a culture of improved application. This can be done in similar way that modern force-field developers have done for decades, by aiming to reproduce experimental observables. For maximum impact, researchers should also aim to make their codes more accessible to the scientific community, while not sacrificing the speed and accuracy gained through these ground-breaking methods. Further, humanity vast knowledge of physics should be utilized to improve the performance and further constrain possible models, while also not sacrificing speed and accuracy.

In Pablo Picasso's quote, he could be saying that it isn't the answers which are important. He might be saying that answers are easy to supply, once you *know* the question. It is just a matter of looking for the right answer. However, coming up with new and meaningful questions is hard. Then, asking those questions pushes the frontiers of our creativity and understanding of the world to the limit. Humans have always enjoyed reasoning and creative capabilities that far exceed those of machines. Human intuition currently drives methods and the experiment design. However our experience, performance and the pressure to publish tend to favor inclusion of "successful" points and often to forget "failed" ones. As AI erodes the barrier of human capabilities, chemical sciences must not only adopt these new and powerful AI methods but also push the frontier of AI to mimic and then surpass the chemical intuition and decision making of expert scientists. Therefore, the immediate frontiers lie in (i) elevate ML from generating data models to generating human-understandable explanations and conclusions (ii) enable autonomous reasoning about these outcomes and developing an actionable research plan. These accomplishments are critical for conducting basic science where knowledge and understanding take precedence over quantitative results. So perhaps one day, machines can not only give you answers, *but also ask the right questions.*

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