Deciphering the Contents of Quantum Chemical Neural Networks

April 24, 2017

1 Overview and Objectives

The explosive growth of computing power over the past FiXme: TODO years\{ FiXme: REF} has led to the use of machine learning (ML) models for the accurate calculation of chemical properties. Current ML models are capable predicting energetic properties of small, neutral organic molecules to almost 1 kcal/mol\{ FiXme: REF}. However, it is unclear *what* the quality of a prediction will be when a ML model is given a molecule outside its training set, and *why* the model is giving that prediction. Each ML model is a set of unknown parameters that constitute a black box,[1] where it is not known or understood *how* the model functions, *why* the model gives the predictions it does, and whether or not correct predictions are being made for the right reasons. A critical step for the continued application of ML models to quantum chemistry will be to make predictions beyond the relatively simple example systems that are currently seeing widspread use.[2] Some of the most important, interesting, and unexplored chemistry in terms of reactivity and intrinsic molecular properties involves species that are either charged or have unpaired electrons. If ML models are only coincidentally forming correct predictions for simple species, there can be no guarantee or expectation for accurate predictions on these more realistic species.

The overall objective is to quantify what quantum chemistry-trained machine learning models are actually learning. The central hypothesis is that the application of machine learning to quantum chemistry is physically motivated, *i.e.*, ML models are learning parameters that connect the molecular representation (input features) to predictions in a manner that is qualitatively identical to how a trained chemist would apply their intuition. An implicit connection has already been made[3] between how a molecule is represented as input to ML models and the accuracy of prediction for certain kinds of properties, but this connection has not been explored. The rationale is that by understanding the connection between the molecular representation given to ML models and their predictions, ML models themselves can be used for rationalizing molecular structure-property relationships. The overall objective will be achieved through the following specific aims:

1. **Characterize the parameters learned by existing machine learning models from the literature.** I will use relevance propagation\{ FiXme: REF} to quantify the relative importance of each input feature for each predicted property. Relevance

propagation gives insight into a model's learned coefficients in a fashion that can be used directly in statistical analysis and visualization.

2. **Train multi-stage neural networks on both existing and new properties.** I will train combined unsupervised and supervised neural networks (NNs) to predict vibrational and nonlinear optical properties of the molecules used in aim #1. These properties are the isotropic static polarizability $\bar{\alpha}$, the zero-point vibrational energy E_{ZPVE}, the static parallel first hyperpolarizability $\beta_{\parallel}$, and the set of frequencies $\{\tilde{\nu}\}$ that compose stick vibrational spectra. FiXme: The first two properties are chosen because models have already been trained on them, the second two properties are chosen because they are a natural extension in complexity to the first two. Unsupervised NNs are capable of discovering intrinsic properties of their inputs\{ FiXme: REF}, and adding them to the ML pipeline will increase the likelihood that the models will learn FiXme: "chemical" parameters.

3. **Characterize the parameters learned by the multi-stage neural networks from aim #2.** I will use the relevance propagation techniques from aim #1 to show the underlying causes for the performance of the NNs on both the existing and novel property predictions.

The expected outcomes are

- Clear connections between the input molecular representations and predicted outputs that can be used to build further quantitative structure-function relationships.
- Well-defined and publicly-available protocols for applying more complex ML models to chemical properties, regarding all stages of the prediction pipeline: preparation of the input, training of the model, and analysis of the results.
- ML models capable of predicting complex molecular properties, with the first proof-of-concept predictions of nonlinear optical properties and vibrational spectra.

2 Significance

The expected significance is that this is the first attempt at understanding the parameters of ML models used to predict microscopic and macroscopic molecular properties, rather than treating ML models as black boxes that cannot be understood. If ML models are shown to be learning physically-motivated or chemically-intuitive parameters, ML can become more than just a path for the accurate prediction of molecular properties, but be transformed into a tool itself that can give deep insight into molecular structure-property relationships. Building ML models is expensive in terms of both human and CPU time, FiXme: it would be good to quantify this. If this proposal shows that ML models are not learning properly, then the scientific research community can avoid the wasteful use of resources on model training and shift their focus to developing better model architectures than the current state-of-the-art.

3 Background

3.1 Machine Learning

Machine learning is the ability for computers to "learn" without being given explicit instructions. Rather than providing exact instructions though traditional programming, computers are fed sets of input data and are usually expected to return a certain result. By training itself to reproduce results, a learned ML model would ideally be able to predict outputs for new, unknown inputs. Common applications of ML are in email spam filtering, search engine prediction, image and voice recognition, and self-driving cars.

Some definitions and terms that are used throughout this proposal are

- *Architecture*: the formal structure of the network or ML model itself, encompassing the region from equations and diagrams to the implementation (code).
- *Model*: here, an implemented architecture (in code) with learned parameters.
- *Pipeline*: multiple steps and components chained together, such as the preparation of data for input into an architecture, the architecture itself, and any steps required to transform the architecture output into something else useful, such as visualizations or statistics.

There are two categories of learning discussed throughout the proposal:

- *Supervised learning*: Train a machine learning model using data where the correct output prediction is known and given for each input sample, and the goal of the model is to predict similar types of outputs for new inputs\{ FiXme: REF}.
- *Unsupervised learning*: Train a machine learning model using data where the correct output prediction is not given, and the goal of the model is to learn intrinsic properties of the inputs by recreating the input as output\{ FiXme: REF}.

There is a third category of learning called reinforcement learning; since there have not yet been any applications of reinforcement learning to quantum chemical problems, it will not be touched upon in the remainder of the proposal.

3.2 Neural Networks

FiXme: Short background on (artificial) neural networks; goal, general structure (w/ figure) and terminology, how do they learn (backpropagation)

The neural network architectures implied by the two types of learning above leads to the capability of chaining them together in a pipeline, where an unsupervised NN is trained for some amount of time in a "pretraining" step, and the bottom layers (closest to the input) in an unsupervised NN are replaced with the contents of the unsupervised NN, rather than being initialized with random weights.

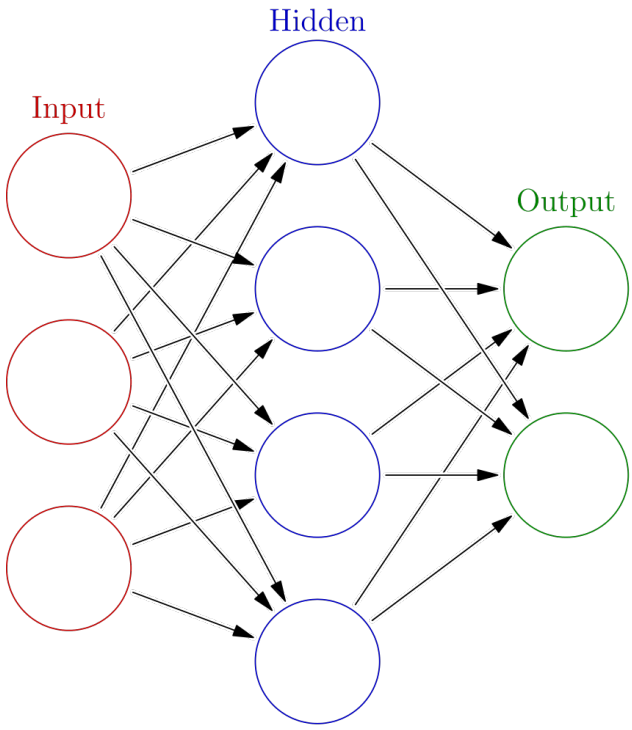

Figure 1: Preliminary representation of a neural net taken from Wikipedia, need one with more info, weight labels, and "bottom up" structure (information density)

3.3 Machine Learning in Chemistry

The use of machine learning to make chemical predictions is not new, with work dating back over 25 years for prediction of NMR spectra using small neural networks trained on experimental data.[4] The largest application of machine learning to chemical problems is within cheminformatics, where it has seen wide use within industrial drug discovery, especially for predicting quantitative structure-activity relationships (QSAR).[5] The goal is to predict the activity of a given drug candidate based on experimental activities of many other molecules, with inputs being information about atom types, bond types, and the number of aromatic rings, among other pieces of structural information, all of which are related to the molecular graph or connectivity\{ FiXme: REF}. FiXme: Maybe say something about extended connectivity fingerprints (ECFPs)

In particular, there is a recent application of deep neural networks (DNNs) to QSAR datasets,[6] which contains a systematic study for determining the best model parameters. The machine learning community calls this "hyperparameter tuning", which is just another term for parameter optimization. However, this is still an empirical black-box approach, where the input is carefully controlled and statistical analysis is performed on the output, but this does not provide enough insight into how or why the quality of a model changes. For example, whether or not a rectified linear unit (ReLU) or sigmoid unit is the best function to represent neuron activation says nothing about why one molecule may be more potent than another in a QSAR study. This brute-force type of parameter optimization *does* provide a

good starting point for understanding the sensitivity of a ML model. Unfortunately, even parameter optimization has not been extensively performed on models trained using quantum chemical data. In that sense, cheminformatics is a step ahead of other sub-disciplines in chemistry regarding the application of machine learning models, but not in the understanding of their models.

Their parameter optimization study is especially relevant to this proposal because it examines the effect of placing an unsupervised NN before other NNs for unsupervised pretraining. Surprisingly, the authors found that an unsupervised pretraining step decreased the accuracy of their predictions, which is counter to the expected outcome of this proposal. However, the paper implies that their results are not even valid due to algorithmic restrictions in their software. Therefore it seems incorrect to draw any conclusions from this, such as "no unsupervised pretraining is needed". It would be interesting to see if the same conclusion is drawn for models trained on quantum chemical data using the proper algorithms, as will be done in this proposal.

Additionally, it is unclear why a DNN trained on the combination of all QSAR data sets (called a "joint DNN") performs better than separate DNNs for each data set when considering the lack of overlap in the training sets. The methods developed in this proposal, while being applied to models trained on quantum chemical data, should be applicable to any DNN (consider that relevance propagation is mostly developed in computer vision/image recognition). One goal of this proposal is to transfer the idea of relevance propagation from its original intended application field to other fields. If it is indeed transferable, then it may shed some light on why 1. unsupervised learning resulted in decreased prediction performance, and 2. the improvement of join DNNs over separate DNNs.

3.4 Machine Learning in Quantum Chemistry

FiXme: Here is where I cite Aspuru-Guzik, Parkhill, von Lilienfeld (others?), with focus on the Arxiv paper from 2017-02,[3] need to keep digesting paper from 2017-04-04.[7] The former is the paper I base most of my proposal argument on.

3.5 Relevance Propagation

Relevance propagation (sometimes abbreviated as "relprop") is one method for identifying what a ML model has learned.[8] Others methods are FiXme: TODO, there aren't many. See figure 2 for a concrete example of what the output from relevance propagation looks like when applied to image classification by a neural network. Here, we assume that the network correctly identified the subject of the image as a cat (rather than a dog or a potted plant), but relevance propagation shows which image pixels were most important for the network to determine the photo is of a cat. The pixel-wise importance is a single number for each pixel that can be interpreted as a contribution for that pixel to the final classification of the image. More generally, is it the relative importance of each input feature to the predicted output; here and in other image recognition examples, pixels are input features. Applications to image classification resulting in pixel importance naturally lends itself to visualizing the output as a heatmap on top of the original input.

- FiXme: What are the advantages of using relprop over other methods/algorithms?

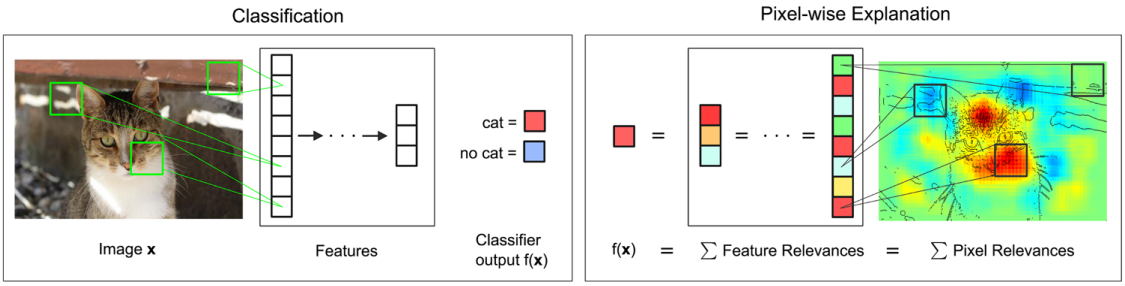

Figure 2: Example of output from relevance propagation showing which sections of an image the neural network considered important during classification. Taken from.[8]

Although no improvements will be made to the basic relevance propagation algorithm itself, there is novelty in two areas. To the best of the author's knowledge, this is the first time relevance propagation will be applied to a regression task rather than a classification task, and the first time relevance propagation will be applied outside of image classification or computer vision. A potential connection between the heatmap representation and generative adversarial networks (GANs), which have been applied to quantum chemistry[\{ FiXme: TODO, John Parkhill's paper\}] is an interesting future research area.

4 Research Plan

4.1 Specific Aim #1: Characterization of Existing Literature Neural Networks

4.1.1 Introduction

- The objective is to quantify what already-published neural network-based ML models have learned.
- The hypothesis is that when predicting an output, the most important (relevant) parts of the input for that output align with our trained intuition. Specifically, for strongly geometry-dependent properties, such as the ZPVE, more relevance will be placed on geometric input features such as bond lengths, angles, and dihedrals. For strongly wavefunction- or density-dependent properties, such as the isotropic polarizability or the HOMO-LUMO gap, more relevance will be placed on electronic input features such as atomic charges compared to other features.
- To test this hypothesis, I will develop the necessary ML pipeline for adding relevance propagation and analysis steps to the already-published ML models. This will involve reproducing the pipeline and results from the literature,[3] followed by connecting existing relevance propagation tools[\{ FiXme: TODO\}] to the end of this pipeline.

4.1.2 Research Design

Unfortunately, the learned models for the results presented in[3] are not available, only descriptions of the architectures. The inputs are available as modified XYZ files from the Quantum Machine (`http://quantum-machine.org/`) website under the QM9 Dataset section.[2,9]

There are two neural network-based architectures described in:[3] Graph Convolutions[10] (GC) and Gated Graph Neural Networks[11] (GG). These NN architectures are used again as baselines in.[7] FiXme: It is unclear to this author why the performance of one over the other switches between the two publications. Since the original GC implementation referenced in[3] is openly available, I will use the GC-based architecture with modifications described in section E5 of.[3] FiXme: Is it safe to just reference this paper, or are more details necessary? Details for the GC architecture input, called the Molecular Graph representation, are shown in tables 1 and 2 of.[3]

Achieving the goal of aim #1 requires the following steps:

- Transform the input data into the Molecular Graph representation.
- Modify the original Graph Convolutions architecture to the one described in Section E5 of.[3]
- Using the model parameters described in that section, train two separate models, one for the isotropic static polarizability $\bar{\alpha}$, and another for the zero-point vibrational energy E_{ZPVE}.
- The trained models will be used to reproduce the original literature results (,[3] table 3, very last line) as verification of the pipeline's correctness.

FiXme: {I now see that α and E_{ZPVE} are not mentioned in the first specific aims section, since I am not training/analyzing all possible observables; that will have to be rewritten later.}

FiXme: Still need to collect my thoughts on the relevance propagation section.

- Relevance propagation (`http://heatmapping.org/`)
  - available as a "toolbox" on top of TensorFlow, which is convenient considering that the original GC model is also on top of TensorFlow
  - which relprop model is appropriate? need to be one that conserves relevance
  - are there any other (free) parameters that I will need to control/adjust?
  - perform relevance propagation
  - derive form for analyzing contributions of input features to results, such as coefficients $\{c\}$ where $\sum_i^{\text{input features}} c_i^2 = 1$
  - analyze results from relevance propagation: graphs, histograms, etc.
    - how are the results represented straight out of the relprop algorithms? may need to do some transformations

FiXme: I am also now thinking that this aim should be broken up into two, where the first is the recreation of the literature model and training, and the second is the relevance propagation part.

4.1.3 Expected Outcomes

- FiXme: Evidence for or against published ML models having learned chemically-intuitive parameters
- FiXme: A model ML pipeline for applying relevance propagation to quantum chemistry models

4.2 Specific Aim #2: Construction and Training of Novel Neural Networks

4.2.1 Introduction

- The objective is to construct and train neural networks that can be analyzed for what they have learned.
- The already-trained properties will be the isotropic static polarizability $\bar{\alpha}$ and the ZPVE, and the not-before trained properties will be the static parallel first hyperpolarizability, $\beta_{\|}$, and full vibrational (stick) spectra, the set of frequencies $\{\tilde{\nu}\}$.
- The hypothesis is that because the multi-stage NN will be at least as sophisticated as the single-stage NN used previously in the literature, both E_{ZPVE} and $\bar{\alpha}$ should be predicted using the multi-stage NN with equal or less error than the single-stage NN. The more complex properties $\beta_{\|}$ and $\{\tilde{\nu}\}$ are expected to have larger relative errors, in particular the set of vibrational frequencies, as predictions of the highest fundamental frequency ω_1 alone already have large errors.[3]
- Applying new ML architectures to already well-studied properties is a safety check for the architeture's use; if it performs worse than current models for existing property predictions than it cannot be expected that it will perform well for new/more complex property predictions.

4.2.2 Research Design

- Results for $\bar{\alpha}$, E_{ZPVE}, and $\{\tilde{\nu}\}$ are already present in the labeled data that was used is inputs in aim #1 (that is, the GDB-9 data set[2]).
- I will use the DALTON quantum chemistry program package[12] for the hyperpolarizability calculations, as it is free for academic use and designed especially for the calculation of molecular response properties such as hyperpolarizabilities. These calculations will employ the B3LYP density functional in combination with the 6-31G(2df,p) basis set to maintain comparability with past calculations from the GDB-9 data set.[2]
- Start with the resulting (supervised) NN architectures/models from the literature that were used in aim #1.
- Build a "small" unsupervised NN architecture that can be connected to the front of the existing GC NN architecture (the "combined" architecture).

4.2.3 Expected Outcomes

- Models with unsupervised learning steps have improved prediction accuracy of chemical properties compared to those without. FiXme: That is, the models developed and trained in this aim should show better prediction performance than the literature models from aim #1. This implies the models from this aim are of higher-quality and are more likely to have "learned correctly" in the sense that they learned "chemical intutition".

4.3 Specific Aim #3: Characterization of Novel Neural Networks

4.3.1 Introduction

- The objective is to determine the relative importance of each component in the molecular representation to predictions of complex molecular properties. This will be done by applying the analysis techniques developed in aim #1 to the neural networks trained in aim #2.

- The hypothesis is that the most important input features for $\beta_{\parallel}$ and $\{\tilde{\nu}\}$ are similar to those for $\bar{\alpha}$ and E_{ZPVE}, respectively.

4.3.2 Research Design

FiXme: This specific aim, as currently planned, is just the application of the analysis from aim #1 to the models developed and trained in aim #2. Although the goal of each specific aim sounds logical, the actual division of work between each of the specific aims seems very uneven.

4.3.3 Expected Outcomes

- The parameters learned by ML models, and therefore their predictions, will show a strong dependence on the input features in chemically-intuitive manner.

- Neural network-based ML architectures are a valid path forward for predicting novel and more complex chemical properties.

5 Broader Impacts

Three crucial components of scientific method development are validation, reproducibility, and replicability.[13] As the application of machine learning within quantum chemistry is relatively new and fast-moving, still being in the "discovery" phase, there have not been attempts at replicating machine learning pipelines, peer-reviewed or otherwise. Additionally, in traditional quantum chemistry there are a plethora of well-known program packages for performing electronic structure calculations[12,14–16] that are self-contained, *e.g.* a single program can calculate optimized geometries, vibrational spectra, NMR chemical shifts, reaction energies, etc. Any potential application of machine learning will require the construction

of a *pipeline*, where multiple components such as programs or analysis steps are chained together so the output from one step is used as input for another step. This infrastructure exists to some degree for machine learning, with base packages such as scikit-learn\{ FiXme: REF} and TensorFlow\{ FiXme: REF} themselves being self-contained with excellent tutorials and examples. This infrastructure does not exist for quantum chemistry-derived machine learning models. Introductions to machine learning are numerous and extensive using the standard "fruit fly" of NNs, the MNIST database of handwritten digits\{ FiXme: REF}, and similar fully-worked examples should exist for chemistry as well.

A crucial reason for the growth in cross-disciplinary applications of machine learning is the openness and extensiveness of introductory tools, specifically tutorials and examples. Historically, chemistry lags behind other sciences in terms of openness of procedures and results. The current infrastructure surrounding the combination of machine learning and quantum chemistry is very poor: disorganized work, disorganized results, and not all components are available for reuse. The development of these machine learning pipelines will constitute the development of open-source, freely available infrastructure that will be easily extendable. I will provide openly **all** components of the machine learning pipeline developed in this proposed work, including the fully-trained models, meaning the implementations using open-source software and the learned parameters for each model. All components will be placed on GitHub, the premier location for the open hosting of machine learning tools. Making these tools available will enable the verification of future, more advanced machine learning models that has not been possible to date. The tools will also serve as a pedagogical example for how machine learning can be applied to quantum chemical problems. This pipeline can then serve as the "fruit fly" for quantum chemistry in machine learning.

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