Geometry Relaxation and Transition State Search throughout Chemical Compound Space with Quantum Machine Learning

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We apply response operator based quantum machine learning (OQML) to the problem of geometry optimization and transition state search throughout chemical compound space. Using legacy optimizers for both applications, the impact of including of OQML based atomic forces on optimization outcome has been explored. Numerical results for randomly sampled small organic query molecules indicate systematic improvement of equilibrium and transition state geometries as training set sizes increase. For geometry optimizations, we have considered 5'989 randomly chosen instances of relaxation paths of 5'500 constitutional isomers (sum formula: C\textsubscript{7}H\textsubscript{10}O\textsubscript{2}) from the QM9-database. Using the resulting OQML models with an LBFGS optimizer reproduces the minimum geometry with an RMSD of 0.15 Å. Training on 3812 instances drawn at random from 200 transition state search trajectories from the QMrnx20 data-set, out-of-sample S\textsubscript{N}2 transition state geometries have been obtained using OQML based forces within the QST2 algorithm with an RMSD of 0.3 Å. For the converged equilibrium and transition state geometries subsequent vibrational normal mode frequency analysis deviates from MP2 reference results on average 39 and 41 cm\textsuperscript{-1}, respectively. The number of steps until convergence is typically larger for OQML than for DFT based forces. However, the success rate for reaching convergence increases systematically with training set size, indicating OQML’s considerable potential applicability.

I. INTRODUCTION

One of the fundamental challenges in quantum chemistry is the understanding of reaction mechanisms in order to predict chemical processes. To this end, numerous neural networks (reaction predictors) have been introduced, proposing the most likely reaction path way\cite{11,12} for a given product. These models were trained on data obtained from experimental studies\cite{13,14} only containing the molecular graph (as SMILES strings\cite{15,16}) and their corresponding yields. However, a crucial property of a chemical reaction is the activation energy (i.e. the difference between reactant and transition state energy), linked to the kinetics of the reaction. To predict activation energies with conventional electronic structure methods, both the reactant complex geometry and the transition state geometry need to be obtained. This is commonly done by iteratively following gradients of the potential energy surface (PES) towards the minimum or the saddle point, respectively. Due to the iterative nature of these schemes, imposing the repeated need to perform self-consistent field calculations to obtain updated forces, the computational burden is as large as it is predictable\cite{17,18}. Furthermore, finding saddle points remain an additional challenge because often enough considerable manual work is required beforehand in order to generate reasonable initial structure guesses. Consequently, it is not surprising that so far only few reaction data-sets which contain transition state geometries as well as corresponding energies have been published in 2020\cite{19,20,21} and 2021\cite{22}.

Only very recently, attempts have been made to use machine learning models to speed up transition state predictions. In 2019, Bligaard and co-workers used the nudged elastic band (NEB)\cite{23,24} method to find transition states relying on neural network based \(\Delta\)-ML model\cite{25} together with a low level of theory as baseline\cite{26}. More recently, Mortensen et al. contributed the ‘atomistic structure learning algorithm’ (ASLA)\cite{27} enabling autonomous structure determination with much reduced need for costly first-principles total energy calculations. Lemm et al.\cite{28} introduced the graph to structure (G2S) machine learning model, predicting reactant complexes and transition state geometries for the QMrxn20\cite{29} data-set without any account for energy considerations, solely using molecular graphs as input. Also, for 30 small organic molecules neural networks predicting energies and forces to accelerate the geometry optimization in between \textit{ab initio} iterations was introduced by Meyer and Hause\cite{30} and by Born and Kästner\cite{31}. Similar to G2S, Makó et al.\cite{32} propose a ‘transition state generative adversarial neural network’ (TS-GAN) which estimates transition state geometries using information from reactants and products only. This procedure allows for better initial geometries for a transition state search reducing the number of steps towards a saddle point. Jackson et al.\cite{33} developed a neural network (TSNet) predicting transition states for a small (~ 50) \(S_N2\) reaction dataset, as well as geometries of the QM9\cite{34} data-set.

However, to the best of our knowledge there is no machine learning model yet using, in strict analogy to the conventional quantum chemistry based protocol, predicted energies and forces only within the conventional optimization algorithms in order to relax geometries or find transition states. To tackle this challenge, we have used for this paper the response operator based quantum machine learning (OQML)\cite{26,27} model with the FCHL representation\cite{35,36} and trained on energies and forces across chemical compound space in order to speed up geometry relaxations as well as transition state searches for new, out-of-sample compounds (see Fig. 1). As for
FIG. 1. Schematic potential energy surfaces in chemical compound space. Arrows show the working principle of OQML based iterative structural optimization: Training on reaction profiles of different chemical systems (purple), the OQML model is able to interpolate forces and energies throughout chemical compound space enabling the relaxation of the reactant and the search of the transition state (orange). Input geometries (squares) are easily obtained, e.g. from universal force field predictions.

any properly trained QML model, prediction errors decay systematically with training set size, and we demonstrate for the chemistries presented that encouraging levels of accuracy can be reached.

First, we have investigated geometry optimizations for all constitutional isomers with $\text{C}_7\text{H}_{10}\text{O}_2$ sum formula drawn from QM9. After training the OQML model on random geometries along the optimization path of 5500 calculations going from a UFF minimum energy geometry to the B3LYP/6-31G(2df) minimum geometry we optimized the remaining 500 constitutional isomers resulting in a total RMSD of only 0.14 Å. To probe transition states, we have trained OQML models on the QMrxn20 data-set with thousands of examples for the S_N2 textbook reaction at MP2/6-311G(d) level of theory, enabling the relaxation of reactant complexes and the search of transition states which both compare well to common density functional theory (DFT) results. As shown in Figure 1, this means training the OQML model on quantum chemistry reference energies and forces along the optimization trajectory obtained for relaxation and transition state search runs of training systems. Starting with universal force field (UFF) geometries, OQML subsequently predicts energies and forces for out-of-sample query systems, thereby enabling the application of legacy relaxation and transition state search algorithms throughout chemical compound space.

II. METHODS

We have relied on operator quantum machine learning (OQML) approach as introduced by Christensen et al. which is a kernel ridge regression (KRR) model which explicitly encodes target functions and their derivatives. A detailed derivation can be found in Christensen et al. section 2 (Operator quantum machine learning). To train a model the regression coefficients $\alpha$ the following cost function is minimized:

$$J(\alpha) = \left\| \begin{bmatrix} y \\ f \end{bmatrix} - \begin{bmatrix} K & \frac{\partial}{\partial r}K \\ \frac{\partial}{\partial r}K^T & K \end{bmatrix} \alpha \right\|^2$$

with $K$ being the training kernel, $y$ the energies, and $f$ the forces. To predict the energies following matrix equation can be used:

$$y_{\text{est}} = K_s \alpha$$

and similarly for the forces:

$$f_{\text{est}} = -\frac{\partial}{\partial r}K_s \alpha$$

where $K_s$ being the test Kernel containing training and test instances.

The representation used throughout this work is the FCHL19 representation. FCHL19 makes use of interatomic distances in its two body terms and includes interatomic angles in the three body term. FCHL19 was selected because of its remarkable performance for QM9 related data-set, and due to being the best structure based representation in direct learning of activation energies in QMrxn20.

To find transition states, the Gaussian09 QST2 algorithm with loose convergence criteria was used, which allows for external energies and forces, in this case from OQML. Note that no explicit Hessian is required by this method nor is one available from our model. For both, reactant complexes and transition states, 300 out of sample reactions were chosen. For these 300 reactions also DFT geometry optimizations as well as transition state searches were performed. The three functionals used were: B3LYP, PBE0, and $\omega$B97X with the def2-TZVP basis set. More details of the training of the models can be found in the SI.

For the RMSD calculations all geometries, including not converged geometries, were used. The python package rmsd with the Kabsch algorithm was used to obtain the RMSD’s. For every training set size, the success rate of the geometry optimization (truncated after 50 iterations) and the transition state search (truncated after 100 iterations which is the gaussian default) was reported.

III. RESULTS AND DISCUSSION

In the context of statistical learning theory, cross-validated learning curves amount to numerical proof of
the robustness and applicability of a machine learning model, and they provide quantitative measures of the data-efficiency obtained. For the three OQML models studied here-within (geometries of constitutional isomers, of reactant complexes, and of transition states), Fig. 2 left) displays the OQML based learning curves for energies (top) and atomic forces (bottom) which indicate the systematic improvement of energy and force predictions as training set size increases.

The learning curve for the constitutional isomers are in line with the results by Christensen et. al. Surprisingly, although FCHL19 was optimized for small organic closed shell molecules, the learning curves for the reactant complexes and the transition states have a faster learning rate. A possible reason for this trend could be that the reactions in the QMrxn20 data-set share a common scaffold with only the substituents changing which represents a lower effective dimensionality of the problem which typically leads to faster learning. Also, relaxations for only 200 reactions were considered in the training set which implies an overall smaller subset of the chemical universe. By contrast, for the constitutional isomers, geometries from 5500 different compounds were chosen, covering a much broader chemical space.

While accurate OQML based estimates of forces and energies are necessary for subsequent relaxation and transition state search, the actual key figure of merit, the RMSD with respect to query reference coordinates for increasing training set size, amounts to a performance curve as shown in the mid panel of Figure 2. We observe strong systematic improvements with increasing training set size of the RMSD for the constitutional isomers. By contrast, RMSD performance curves for reactant complexes, while also monotonically increasing with training set size, exhibit substantially smaller learning rates. Differences in learning for different data-sets while using the same representations and model architectures implies that the target function is more complicated. One can argue that the constitutional isomers are less pathological since they consist of small organic and closed shell molecules, whereas the reactant complexes as well as the transition states include charged compounds and non-covalent binding to leaving and attacking groups. The relatively flat progress made for the QMrxn20 data-sets might also simply due to the fact that the training set sizes available have been too small to reach the onset of converged learning rates. More specifically, due to the underpinning high dimensionality, the training set grows much more rapidly when adding a new reactive system including optimization steps along the way to the saddle point. This implies that the training will be less efficient. Possible ways to mitigate such a bottleneck could include the use of the Amons approach which decomposes molecules in sub-structures, drastically reducing the effective dimensionality of the problem. Also multi-level grid combination techniques or transfer learning could lead to significant speed-ups and would render the models more transferable.

Regarding the performance curve for the transition states it is encouraging to note that the slope is substantially steeper than for the equilibrium geometry, also indicating that the OQML based energies and gradients also work well for locating saddle-points, which is unprecedented in literature, to the best of our knowledge. 

A direct one-to-one comparison to the equilibrium geometry relaxations, however, is not possible as the differences might also be due to the use of two very different optimizers (LBFGS vs. QST2).

Performance curves for success rates have also been included in Figure 2 right. We note that for all models and data-sets the success rate of the optimization runs systematically increases with training set size. We find that even for OQML models trained on small training set sizes resulting in relatively high RMSDs (∼ 0.3 Å), the success rate increases from 15% to 50% and from 30% to 80% for the reactant complexes and the transition states, respectively, as shown in Figure 2 Surprisingly, even though the RMSD performance curve for the constitutional isomer set is the best, the success performance curve is the worst. This could be due to the higher dimensionality in the QM9 based data-sets, where the optimizer has to locate the minimum for substantially more degrees of freedom. In any case, the systematic increase in success rate represents strong evidence in favor of the proposed model, as one can always improve it through mere addition of training instances, apparently resulting in increasingly smooth potential energy surfaces with few artifacts—an important prerequisite for successful optimization runs using algorithms such as LBFGS.

For further analysis of reactant complexes and transition states we used 300 out-of-sample compounds. Table 4 shows a summary of the predictions of the reactant complex optimization of the ground states (GS) and the transition state (TS) search, as well as the comparison to the three DFT methods (B3LYP, PBE0, ωB97X) with the def2-TZVP basis set. RMSDs for the geometries are around 0.2Å for the DFT methods and 0.3Å for the OQML method considering the transition states. The performance of the ML model reaches the same accuracy for the reactant complexes as the DFT geometry optimization resulting in RMSD’s on the order of 0.1 to 0.2 Å. Using the same model we calculated numerical frequencies and reached a mean absolute error over the 300 test transition states of 41 cm⁻¹ and 39 cm⁻¹ for transition states and reactant complexes, respectively, which is comparable to the DFT errors.

For the activation energy $E_a$, the ML model outperforms the DFT methods which are in general 50 kcal/mol off. Although, the error of 10 kcal/mol is still high, other ML models could be used to learn the activation energies e.g. the R2B model which was applied on this data-set and solely uses the molecular graph as input for the ML model.

Finally, we showcase the OQML predicted results for the transition state of one randomly drawn exemplary reaction, involving 3-amino-3-chloro-
FIG. 2. Learning curves for energies (top left) and atomic forces (bottom left). RMSD performance curves of geometry vs. training set size $N$ (middle). Success rates of the optimization and transition state searches (right). Colours correspond to results based on three distinct data-sets: constitutional isomers (QM9), reactant complexes (QMrxn20), and transition states (QMrxn20). Dashed green horizontal line corresponds to the success rate of the MP2 reference TS searches.

2-methylpropanenitrile $[\text{H(NH}_2\text{C-C(CH}_3\text{)(CN)}]$ with Cl and F as leaving group and nucleophile respectively. In Figure 3 the calculated transition state normal modes are shown, energies once predicted by OQML and once as obtained from MP2 for comparison. Even though, the RMSD of the predicted geometries are off by 0.3 Å, the curvature is described reasonably well by the OQML model, which is supported by the relatively small errors in frequencies, as well as by the high success rate of the transition state search.

CONCLUSION

Our findings indicate that OQML can be used to optimize geometries and search for saddle points (transition states) across chemical compound space. OQML is a surrogate model of conventional quantum based energies and forces, and can be successfully employed within legacy optimizers. Based on the OQML approach accuracies for RMSDs, frequencies, and activation energies improve as training set sizes increase. Similarly, the convergence success rates also improve for larger training set sizes.

Learning curves exhibit linear decay as a function of the training set size on logarithmized scales, indicating that even further improvements of the model could be reached by adding more training data. Performance curves of RMSDs suggest that the optimization process (RMSD as well as success rate) based on these models could also be further improved by increasing the training set size. Especially for the constitutional isomers (small, organic, and closed shell molecules) the description of the potential energy surfaces improves steadily by adding more training data, which improves the success rate from 27% to 52% for the lowest and the largest training set size, respectively. Vibrational frequencies obtained by OQML for our maximal training set size deviate from the reference MP2 frequencies no more than DFT.

To explore out of equilibrium geometries farther away from a local minima the QM7x data-set could be investigated in the future. To make OQML more transferable and applicable also to larger reactants, an Amon based extension could be implemented. OQML could also be helpful for the generation of large and consistent data-sets in quantum chemistry, especially for the study of reactions.

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| Method       | RMSD [Å] | Δν [cm⁻¹] | Eₐ [kcal-mol⁻¹] |
|--------------|----------|-----------|-----------------|
| OQML (FCHL19) | 0.186    | 0.329     | 4.39            | 10.01 |
| B3LYP/def2-TZVP | 0.195    | 0.234     | 5.00            | 51.97 |
| PBE0/def2-TZVP | 0.180    | 0.205     | 4.50            | 53.41 |
| ωB97XD/def2-TZVP | 0.098    | 0.207     | 3.20            | 54.46 |

TABLE I. Summary of results for 300 out of sample test cases for geometry optimizations (left) and transition state searches (right) for OQML models and three DFT methods for comparison with MP2/6-311G(d) as reference. The table shows the difference in geometry (RMSD), in frequency (Δν), and in activation energy (Eₐ) for each method. Geometry optimizations using the LBFGS algorithm from the ASE package were truncated after 50 iterations and the default threshold (fmax = 0.05 eV/Å) was used. The limit for the transition state search was the default iteration limit of 100 steps.

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FIG. 3. Example normal mode scan showing energy changes as a function of distortion along TS modes for the transition state of the $S_N2$ reaction of 3-amino-3-chloro-2-methylpropanenitrile with F$^-$. Geometry of an MP2/6-311G(d) converged and validated TS was used and distorted along its normal modes. Subsequently, single point calculation (MP2), as well as ML predictions were plotted for the first 23 normal modes and their displacements. The x-axis describes the index of the distorted geometry and the y-axis describes the energy relative to the MP2 equilibrium geometry. Both energies, MP2 (blue) and ML (orange) are scaled by the equilibrium geometry (index 10).

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