Boosting quantum machine learning models with multi-level combination technique: Pople diagrams revisited

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Inspired by Pople diagrams popular in quantum chemistry, we introduce a hierarchical scheme, based on the multi-level combination (C) technique, to combine various levels of approximations made when calculating molecular energies within quantum chemistry. When combined with quantum machine learning (QML) models, the resulting CQML model is a generalized unified recursive kernel ridge regression which exploits correlations implicitly encoded in training data comprised of multiple levels in multiple dimensions. Here, we have investigated up to three dimensions: Chemical space, basis set, and electron correlation treatment. Numerical results have been obtained for atomization energies of a set of ~7'000 organic molecules with up to 7 atoms (not counting hydrogens) containing CHONFClS, as well as for ~6'000 constitutional isomers of $\text{C}_2\text{H}_{10}\text{O}_2$. CQML learning curves for atomization energies suggest a dramatic reduction in necessary training samples calculated with the most accurate and costly method. In order to generate milli-second estimates of CCSD(T)/cc-pvdz atomization energies with prediction errors reaching chemical accuracy (∼1 kcal/mol), the CQML model requires only ~100 training instances at CCSD(T)/cc-pvdz level, rather than thousands within conventional QML, while more training molecules are required at lower levels. Our results suggest a possibly favorable trade-off between various hierarchical approximations whose computational cost scales differently with electron number.

I. INTRODUCTION

Chemical compound space, the property space spanned by all possible chemical compounds, is unfathomably large due to its combinatorial nature. Exploring chemical space from first principles is desirable in the context of computational materials design as well as to fundamentally deepen our understanding of chemistry. Over the last couple of years overwhelming evidence has been collected indicating that quantum machine learning (QML) models, trained throughout chemical space, hold great promise to dramatically reduce the cost for predicting quantum properties, such as atomization energies of molecules, for arbitrary out-of-sample molecules. The core idea of QML is to learn the implicit mapping from geometrical and compositional information encoded in nuclear charges and positions to corresponding electronic properties from a set of training molecules with precomputed properties at a specific level of theory. The knowledge thus obtained from training is then applied to molecules out-of-sample, i.e., molecules not in the training set. Nowadays, QML is a well-established technique and has several supervised learning variants, including mainly neural networks and kernel ridge regression. Currently, most of the efforts towards QML in literature are devoted to developing more efficient molecular representations and adapting machine learning models to a growing number of applications. Recent overviews on the field were published in Refs. and an entire issue in J. Chem. Phys. was recently devoted to the theme of "Data-enabled theoretical chemistry." This progress was made possible due to the advent of modern computers which enabled routine calculations of electronic properties such as ground state energies for large training sets of medium-sized organic molecules using common density functional approximations. While QML prediction errors have been converged to values smaller than DFT accuracy, the predictive power of any QML model inherently hinges on the accuracy of the employed reference data used for training. However, while the latest machine learning models are now able to make rather accurate and yet efficient predictions, the time required to compute training samples for large datasets with chemical accuracy is still prohibitive. More specifically, in order to routinely match the experimental uncertainty of thermochemistry, the highly coveted “chemical accuracy” of ∼1 kcal/mol, typical approximations made within density functional theory do not suffice, and computationally expensive theories, e.g., CCSD(T) in a large basis, have to be used even when dealing just with closed-shell molecules in relaxed geometries. Unfortunately, due to its substantially larger computational complexity, the routine generation of CCSD(T) numbers in large basis sets for thousands of training molecules remains prohibitive.

The hierarchies encoded in model chemistries, well established in quantum chemistry, can be used to exploit
systematic trends in cancellation of errors among differ-
ent levels of theory, as proposed and demonstrated
by Pople and co-workers.\textsuperscript{36,37} Composite methods are
based on these ideas\textsuperscript{38} and include, among many others,
Gaussian-n theories,\textsuperscript{39} the Weizmann-n method,\textsuperscript{40}
and complete basis set (CBS) methods.\textsuperscript{41,42} They can
reach chemical accuracy at the computational cost of
combinations of more efficient models. When it comes to
chemical space, the Pople diagram is a two-dimensional
display of the relationship of the size of any molecule
and level of theory.\textsuperscript{43} Pople diagrams can easily be ex-
tended to accommodate additional or other dimensions
such as relativistic effects\textsuperscript{44} or accuracy.\textsuperscript{45} In this study,
we apply the idea of a Pople diagram to combine vary-
ing levels of theory in the training set of QML models
(See Fig. 1 for the general idea). More specifically, we
apply the sparse-grid combination (C) technique to esti-
mate the optimal balance among (i) electron correlation
(HF, MP2, CCSD(T)), (ii) basis set size (sto-3g, 6-31g,
cc-pvdz), and (iii) number of organic molecules. We find
that the resulting CQML models require substantially
less training instances at the computationally most de-
manding target level of theory.

To showcase our new developments, we will discuss
a series of multi-level and multi-space machine learning
models, as well as results for molecules from the QM7b
data set.\textsuperscript{50} Using several levels in the space of electron
correlation approximations already leads to a very strong
improvement in the learning results, with respect to the
amount of necessary training data at target accuracy.
Further improvement is found by adding different levels
of basis sets.

This paper is structured as follows: Section II briefly
introduces the CQML model, as well as the data sets used
for training and testing. In Section IV results of the
CQML model are presented and discussed for 2D and
3d CQML models. Finally, Section V summarizes the
main-findings, draws general conclusions and presents an
outlook. Section VI provides detailed methodological in-
formation to facilitate reproducibility of our findings.

II. COMPUTATIONAL DETAILS

A. Datasets

Two datasets were used for proof of principle: QM7b\textsuperscript{51}
and 6k constitutional isomers\textsuperscript{52} (dubbed ‘CI9’), both are
subsets of GDB-17 universe.\textsuperscript{53} QM7b is composed of
molecules with up to 7 heavy atoms, including C, N,
O, S and Cl (H not counted), totaling 7211 molecules.
Molecules in CI9 correspond to 6095 constitutional iso-
mers of C7H10O2.

For QM7b molecules, geometries were first optimized
at the level of B3LYP/6-31g(d) using Gaussian 09\textsuperscript{54}, then
single point calculations were calculated using three lev-
els of theory (HF, MP2, CCSD(T)) and three basis sets
(sto-3g, 6-31g and cc-pvdz) using Molpro\textsuperscript{55}, resulting in
9 single point energies per molecule.

For the CI9 molecules, three different methods were
used: PM7, B3LYP/6-31g(2df,p) and G4MP2. Relaxed
geometries and energies were retrieved directly from
reference\textsuperscript{56} for the latter two methods, while PM7
relaxed geometries and energies were obtained using
MOPAC2016.\textsuperscript{57}

B. QML details

We used both, the sorted Coulomb matrix\textsuperscript{58,59} and
SLATM\textsuperscript{10} for modeling the CI9 data set, while SLATM\textsuperscript{10}
only was used for QM7b. Though slightly better perform-
ing representations have been published previously, such
as SOAT\textsuperscript{60,61}, aSLATM\textsuperscript{10} or FCHL\textsuperscript{20}, comparison be-
tween CM and SLATM results indicates that trends are
stable and that the conclusions drawn are independent of
choice of representation. As kernel-functions, we have al-
ways chosen the Laplace kernel $e^{-\frac{1}{2}\|R_q-R_i\|^2}$ with $\sigma$ being a
hyper-parameter. The hyper-parameter $\sigma$ was optimized
manually and converged to $\sigma=400$. Furthermore we use a
Lavrentiev regularization of size $10^{-10}$. All presented
errors are mean absolute error (MAE) comparing the pre-
diction by the CQML method with the true solution of
the target theory level. The MAE is computed as out-
of-sample error over 200 randomly chosen molecules that
are not part of the training data set. These results are
averaged over 20 training runs. Note that we randomly
choose the $N_{\text{val}}=20$ training molecules on the lowest level,
while randomly selecting subsets of them on higher lev-
els. This sequence of drawing ensures the nestedness of
all the training samples.

III. THEORY

In this section, we start by reviewing systematic error
cancellation, composite methods, the CQML approach,
kernel ridge regression based QML and $\Delta$-ML\textsuperscript{62}, as well as
two-, and n-dimensional CQML.

A. From Pople diagrams to CQML

Telescoping series, as a means to systematic conver-
gence of error cancellation, are a well established mathe-
atical tool. In short, if $a_n$ is a sequence of numbers, then

$$\sum_{\ell=1}^{N} (a_\ell - a_{\ell-1}) = a_N - a_0, \quad \text{(1)}$$

and if we define $\Delta_{\ell-1} = a_\ell - a_{\ell-1}$ and $a_0 = 0$, one has

$$a_N = a_0 + \sum_{\ell=1}^{N} \Delta_{\ell-1} \quad \text{(2)}$$
Error cancellation is also at the root of many common practices in theoretical chemistry. Most notable are composite methods, recently reviewed in Ref. 65, which correspond to computational protocols which combine various quantum chemical approximations such that high accuracy (frequently chemical accuracy, i.e. $\sim 1$ kcal/mol) is achieved for thermodynamic quantities (e.g., atomization enthalpies). Typically, they combine the results of a high level of theory with a small basis set with methods that employ lower levels of theory with larger basis sets. Importantly, they impose a computationally much reduced burden when compared to brute-force convergence in basis set size and electron excitations. For example, an extensively used composite method called Gaussian-2 (G2), approximates the energy as (starting from a geometry optimized at MP2/6-31g(d) level)

$$E_{\text{true}} \approx E^{\text{G2}} := E_{\text{QCISD(T)}/6-311g(d)} + \Delta_1 + \Delta_2 + \Delta_3,$$

where further correction terms have been neglected. Note that here and throughout, we denote approximations and reference results by upper and lower indices, respectively. The individual terms read,

$$\Delta_1 = E_{\text{MP4/6-311g(2df,p)}} - E_{\text{MP4/6-311g(d)}};$$
$$\Delta_2 = E_{\text{MP4/6-311+g(d,p)}} - E_{\text{MP4/6-311g(d)}};$$
$$\Delta_3 = E_{\text{MP2/6-311g(3df,2p)}} + E_{\text{MP2/6-311g(d)}} - E_{\text{MP2/6-311g(2df,p)}} - E_{\text{MP2/6-311g+(d,p)}}$$

with $\Delta_1$ accounting for the effect of adding the polarization functions, $\Delta_2$ correcting for the diffuse functions and
In this work, we generalize the core ideas of ∆-ML to arrive at a multi-level combination technique QML (CQML) approach. CQML is a unified kernel ridge regression machine learning model incorporating training data from several spaces and levels of information. As proposed by e.g. John Pople, we distinguish between

1. the space of electron correlation (e.g. MP2) and
2. the space of basis set (e.g. 6-31g), and we also add
3. the space of training molecules (e.g. some training set drawn from QM9) as third degree of freedom which can easily be exploited through machine learning models.

We call a specific choice of training information, e.g. Hartree-Fock calculations on a 6-31g basis set done for 256 molecules, a subspace. Within each space, we assume a multi-level hierarchy of growing accuracy and computational complexity. E.g. in electron correlation and basis set space, one commonly expects that the degree of approximative nature decays systematically as one goes from HF to MP2 to CCSD(T), from sto-3g to 6-31g to cc-pvdz, respectively. In chemical space, it is less obvious how to establish a hierarchy of accuracy. For the purpose of our approach, we rely on the well established tenet in statistical learning that the predictive accuracy for out-of-sample increases systematically with training set size, which is applicable to chemical space and quantum chemistry as demonstrated first in 2012.

This finding has by now been confirmed and reproduced within multiple studies for various quantum properties and system classes. As such, and when drawing training molecules at random, we can consider their number made available to training (e.g. N = 16, 32, 64 ... ) as the chemical space equivalent to the space of theory (e.g. HF/MP2/CCSD(T)) or basis set (e.g. sto-3g/6-31g/cc-pvdz). Generally speaking, a CQML model built on low levels of theories / basis sets / small number of training molecules, will result in a model with low accuracy and easily accessible training data. Conversely, including more levels in each dimension, the resulting CQML model will become increasingly more accurate, requiring, however, also access to ever more valuable training data. Figure 1 exemplifies these ideas for various levels of electron correlation, basis sets, and molecular training set sizes.

The sparse grid combination technique known for high-dimensional approximation and quadrature / uncertainty quantification in numerical analysis corresponds to a rigorous means to generate QML models constructed on a combination of sets of different subspaces. The general idea is to combine the subspaces such that only very few very expensive training samples are needed at target accuracy (e.g. CCSD(T) for cc-pvdz at high sample count), some less expensive subspaces with higher training sample count are needed, and so on. Figure 2 outlines a choice of subspaces by a modified sparse grid combination technique.
grid combination technique. Here, each subspace is represented by a colored cube.

In this work, we will first generalize the aforementioned \( \Delta \)-ML approach to a multi-level approach that incorporates the space of theories, basis sets, and training molecules. The CQML approach differs from existing multi-fidelity machine learning models\(^{[22]}\) in that it is (a) generalized to multiple dimensions, and (b) does not unite the various spaces within one kernel matrix, but rather through a series of independently trained kernels. While the CQML approach accounts for an arbitrary number of information spaces, for the sake of brevity and without any loss of generality, we restrict ourselves only to the three spaces discussed above.

### C. Kernel ridge regression and the \( \Delta \)-ML approach

In order to properly discuss CQML, we first need to briefly recall the principal idea of the established kernel ridge regression based QML models. With \( \mathbf{R} \) (some) representation of a molecule, we denote by \( E_\ell(\mathbf{R}) \) the ML based approximation of the electronic ground state property of that molecule at a certain level of theory \( \ell \). We train the ML model using \( N \) training molecules \( \mathbf{R}_i \) with \( i = 1, \ldots, N \) with corresponding reference energies at the corresponding specified level, \( E_\ell^{\text{ref}}(\mathbf{R}) \). The objective is to predict energy \( E_\ell^{\text{ref}} \) for an out-of-sample query molecule \( \mathbf{R}_q \), neither part of training nor validation sets.

The ML model \( E_\ell \) within kernel ridge regression is then given by \( E_\ell^{\text{ref}}(\mathbf{R}_q) \approx E_\ell(\mathbf{R}_q) := \sum_{i=1}^{N} \alpha_i k(\mathbf{R}_q, \mathbf{R}_i) \), where \( k \) is an appropriate unit-less kernel function. For this study, we always choose the radial basis kernel function, \( \exp[-\|\mathbf{R}_q - \mathbf{R}_i\|_1/\sigma] \) (Laplace) with length-scale \( \sigma \). Optimization of kernel function space could represent yet another potentially interesting dimension for future investigations. As described in detail elsewhere\(^{[22]}\), the coefficients \( \alpha_i \) are obtained by solving the kernel matrix inversion problem \( \mathbf{K} + \lambda \mathbf{I} \approx \mathbf{e}_\ell \) for given regularizer \( \lambda \) and reference energy vector \( \mathbf{e}_\ell \). Here, we use matrix-notation with capital and small case letters for matrices and vectors, respectively.

The \( \Delta \)-ML approach\(^{[21]}\) models the difference between a baseline and target level of theory, e.g. HF and MP2, respectively. Note, that we here have decided to adapt a slightly different notation in contrast to Ref\(^{[21]}\) in order to facilitate the generalization of the \( \Delta \)-ML to the CQML approach. Here, \( P_{(b)}(\mathbf{R}) \) and \( P_{(t)}(\mathbf{R}) \) represent the properties of interest computed at baseline and target level of theory, respectively. Note that within \( \Delta \)-ML, \( P_{(b)} \) and \( P_{(t)} \) it is not mandatory to estimate the same property, e.g. it could be the ground state energy in the baseline theory and the enthalpy in the target theory. Hence, the \( \Delta \)-ML model prediction is given by

\[
P_{(t)}(\mathbf{R}_q) := P_{(b)}(\mathbf{R}_q) + \Delta_{(t)}^\ell(\mathbf{R}_q) \quad \text{(6)}
\]

where \( \Delta_{(t)}^\ell(\mathbf{R}_q) = \sum_{i=1}^{N} \alpha_i k(\mathbf{R}_q, \mathbf{R}_i) \). We emphasize that within the \( \Delta \)-ML model a potentially costly baseline evaluation of the query compound is still necessary when making a prediction. This differs from the CQML approach which recovers the original speed of QML by modeling even the baseline through a machine.

### D. Two-dimensional multi-level learning

The CQML approach generalizes the \( \Delta \)-ML model to several spaces \( \text{and} \) levels. This is illustrated in Figure\(^{[2]}\) for three dimensions and levels which we have also considered in this study (\textit{vide infra}). To facilitate the discussion, we first discuss the adaptation of the Pople diagram in order to exemplify the general idea of the CQML approach for the simple case of only two dimensions. More specifically, we now consider the space of theory and training molecules. Thereafter, we will also discuss the generalization to three, as well as n-dimensional cases in Section III B

Assuming \( L \) levels of theory with running index \( \ell = 0, 1, \ldots, L - 1 \), for which the calculated energy increases in accuracy \( a \) (with respect to an experimentally yet unknown truth) and computational cost with growing theoretical complexity, \( a^{\ell+1} > a^\ell \), \( \forall \ell < L - 1 \). Multi-level learning in two dimensions is performed as follows

1. on level \( \ell = 0 \) compute reference energies \( E_{\ell=0}^{\text{ref}} \) for \( N_{\ell=0} \) molecules and train standard QML kernel ridge regression model to predict \( E_{\ell=0} \).

2. on level \( \ell = 1 \) compute reference energies \( E_{\ell=1}^{\text{ref}} \) for \( N_{\ell=1} < N_{\ell=0} \) training molecules.

3. Still on level \( \ell = 1 \), train a model of the difference between \( E_0 \) and \( E_{\ell=1}^{\text{ref}} \) for the \( N_1 \) molecules.

4. repeat recursively until target level \( \ell = L - 1 \) is reached.

Note that while \( N_\ell \) and \( N_{\ell+1} \) molecules do not have to be identical, in this study all \( N_{\ell+1} \) molecules are also part of the \( N_\ell \) molecules out of convenience.

Formally, one can recursively define the intermediate multi-level 2D model \( E_\ell \) for \( \ell = 0, 1, \ldots, L - 1 \), and built on the lowest level baseline \( (\ell = 0) \), as

\[
E_\ell(\mathbf{R}_q) := E_{\ell-1}(\mathbf{R}_q) + \sum_{i}^{N_\ell} \alpha_i^{(\ell-1,\ell)} k(\mathbf{R}_q, \mathbf{R}_i), \quad \text{(7)}
\]

where we set \( E_0^0 \equiv 0 \). For example, the CQML model which combines PM7 \( (\ell = 0) \), DFT \( (\ell = 1) \), and G4MP2
\( (\ell = 2) \) reads
\[
E_2(R_q) = E_1(R_q) + \sum_{i}^{N_2} \alpha_k^{(1,2)} k(R_q, R_i)
\]
where
\[
E_1(R_q) = E_0(R_q) + \sum_{j}^{N_1} \alpha_j^{(0,1)} k(R_q, R_j)
\]
where
\[
E_0(R_q) = \sum_{k}^{N_0} \alpha_k^{(0)} k(R_q, R_k),
\]
where the last term corresponds to the conventional direct QML model of the PM7 energy. For numerical results obtained from this model, and their discussion vide infra. To compute the coefficients \( \alpha_k^{(\ell)} \), we solve the previously mentioned kernel ridge regression problem.

Let us briefly compare this approach to the conventional \( \Delta \)-ML models discussed before in Section III C. In the single-level case, the resulting model \( E_1 \) is the direct conventional QML kernel ridge regression model. In the two-level case, the resulting model \( E_2 \) bears similarity with the \( \Delta \)-ML model, the major difference being that also the baseline is a machine. Thereby, it becomes possible to use different amounts of training information \( (N_1, N_2) \) on both levels. Nevertheless, if we chose the training molecules on the first and the second level identical and skipped regularization in the regression problem, \( E_2 \) and conventional direct QML would be identical. And if we chose the training molecules on the first and the second level identical and built only one ML model (namely of the difference), \( E_2^{\text{ref}} \) and \( \Delta \)-ML would be identical. \( E_3 \) and higher order approximations have, to the best of our knowledge, not yet been discussed in the literature.

Using above definition, we did not fix yet how to choose the amount of training samples on each level. This choice is based on the sparse grid combination technique [23,24]. Qualitatively, the combination technique implies to use many training samples on the lower levels of theory and to reduce the number of samples to very few samples on higher levels and the target level of theory. As we will see, the balance between the amount of training samples per level can be a point of optimization within our method. In Section IV we discuss our choices of level balancing based on the sparse grid combination technique. These choices have been evaluated for different training data, and with respect to two possible optimality measures. Future work will deal with a more systematic assessment of how to tailor and optimize the relative ratios of training molecules at each level and in each dimension.

### E. Three-dimensional multi-level learning

Extending Eq. (7) to more than two dimensions results in dimension-dependent levels. Table I provides an exemplifying overview of levels in three dimensional multi-level learning for basis sets (B), electron correlation (C), and molecular training set (M).

| Level | 0 | 1 | 2 |
|-------|---|---|---|
| \( \ell_B \) | HF | MP2 | CCSD(T) |
| \( \ell_M \) | N\(_0\) | N\(_1\) | N\(_2\) |

Thus, any given combination of levels can be specified as the ordered triplet \( \ell \) of respective level indices, \( \ell = (\ell_C, \ell_B, \ell_M) \). For example, the combination CCSD(T)/cc-pvdz, \( N_2 \) is encoded by the triplet \( \ell = (\ell_C = 2, \ell_B = 0, \ell_M = 1) = (2, 0, 1) \). The corresponding CQML model is given by \( E_{(2,2,2)}(R_q) \) and reads
\[
E_{(2,2,2)}(R_q) = E_{0(0,2,0)}(R_q) - 2E_{0(1,0,0)}(R_q)
+ E_{1(1,0,0)}(R_q) + E_{0(1,1,0)}(R_q)
- 2E_{1(0,0,0)}(R_q) + E_{0(0,0,0)}(R_q)
- 2E_{0(0,1,0)}(R_q) + E_{2(0,0,0)}(R_q)
+ E_{1(0,1,0)}(R_q) + E_{0(0,0,2)}(R_q)
\]
with \( \ell_C, \ell_B, \ell_M = 0, \ldots, 2 \). The reader is referred to Appendix A for the details of the derivation.

### F. \( n \)-dimensional multi-level learning

Above, we discussed the low-dimensional multi-level method which profits from space of electron correlation, basis set, and molecular training set size. In order to extend this principle to even more spaces, we now generalize this approach following the lines of the sparse grid combination technique. We introduce for \( d \) spaces levels \( \ell_1, \ldots, \ell_d \), which we collect together in the \( d \)-dimensional multi-index \( \ell = (\ell_1, \ldots, \ell_d) \). In the example of the previous section, \( d = 3 \) and \( \ell_1 \) corresponds to \( \ell_C \), \( \ell_2 \) corresponds to \( \ell_B \), and \( \ell_3 \) corresponds to \( \ell_M \). Following the notation that the last level index refers to molecular training set size, i.e. \( \ell_d = \ell_M \), we define the energy \( E_{(\ell)}^{\text{ref}} \) given on a subspace \( \ell \), and the QML model \( E_{\ell} \) for each subspace,
\[
E_{\ell}(R_q) := \sum_{i=1}^{N_{\ell_d}} \alpha_i^{(\ell)} k(R_q, R_i).
\]
Computing the coefficients \( \alpha_i^{(\ell)} \) for a fixed subspace \( \ell \) is done by solving the regression problem
\[
E_{(\ell)}^{\text{ref}}(R_i) \approx \sum_{i=1}^{N_{\ell_d}} \alpha_i^{(\ell)} k(R_j, R_i)
\]
for all \( j = 1, \ldots, N_{\ell_d} \).

The generalized CQML machine learning model is then given as

\[
E_\mathcal{I}(R_q) := \sum_{\ell \in \mathcal{I}} \beta_\ell \sum_{i=1}^{N_{\ell_d}} a_i^{(\ell)} k(R_q, R_i) .
\] (11)

In fact, it is the combination of the machine learning models from \( \mathcal{I} \) for different subspaces \( \ell \) that are collected in the index set \( \mathcal{I} \). The classical sparse grid combination technique proposes to use the index set

\[
\mathcal{I} := \{ \ell \in \mathbb{N}^d \mid \| \ell \|_1 = (L - 1) - i, i \in \{0, \ldots, d - 1\} \}
\] (12)

with \( \| \ell \|_1 := \sum_{s=1}^d \ell_s \). In the following, the coefficients \( \beta_\ell \) can always be evaluated as

\[
\beta_\ell := \sum_{z \in \{0,1\}^d} (-1)^{\|z\|_1} \chi_{\mathcal{I}}(\ell + z) .
\] (13)

Here, the sum is to be understood in the sense that vector \( z \) of size \( d \) takes all possible combinations of zeros and ones. Moreover we define the characteristic function \( \chi_{\mathcal{I}} \) of index set \( \mathcal{I} \) by

\[
\chi_{\mathcal{I}}(\ell + z) := \begin{cases} 
1 & \text{if } (\ell + z) \in \mathcal{I} , \\
0 & \text{else}.
\end{cases}
\] (14)

It is well-known that the above choice of the index set \( \mathcal{I} \) and coefficients \( \beta_\ell \) in \( d = 2 \) is equivalent to the multi-level learning approach from Section IID.

For \( d = 3 \) the above choice of index set \( \mathcal{I} \) leads to the subspace choice in Eq. (5), exemplified with the spaces discussed in Section I. Note, however, that this choice does not use any training data from the target subspace, here CCSD(T) calculations with a cc-pvdz basis set. In practice, it is preferable to include the corresponding subspaces with this accuracy to the training set, at least with a small training set size, in order to include the physics of the corresponding target accuracy. To this end, in \( d = 3 \), we shift the index set \( \mathcal{I} \) such that the subspace choice from Figure 2 is achieved.

IV. RESULTS AND DISCUSSION

Before entering the detailed discussion of our results, we now briefly discuss the use of learning curves as a measure of machine learning model quality. Clearly, reporting a single out-of-sample error for any machine learning model is hardly meaningful: It is the very point of machine learning that models should improve with training set size. Vapnik and co-workers discussed already in the nineties that prediction errors, i.e. out-of-sample estimates of statistically estimated functions, decay inversely with training set size \( N \). More specifically, for kernel ridge regression models (used throughout this study), the leading prediction error term was shown to be proportional to \( a/N^b \), where \( a \) and \( b \) are proportionality constant and power law exponent, respectively. In order to facilitate comparison among models, it is therefore recommended practice\( ^{25} \) to discuss the performance in terms of learning curves on log-log scales, i.e. for prediction errors decaying linearly with training set size, i.e. \( \log(\text{Error}) = \log(a) - b \log(N) \). Saturation of errors indicates failure to learn; and small off-sets and steep slopes indicate preferable models.

A. Data

For all the \( \sim 7`000 \) QM7b molecules\( ^{26} \), we have calculated total energies for all combinations among the various levels of correlation energies (HF, MP2, CCSD(T)) and basis set sizes (sto-3g, 6-31g, cc-pvdz). Resulting effective atomization energies (see SI for the entire data set), are shown within scatter-plots in Fig. 3. Depending on stoichiometry and size, the molecules spread out over the various levels and dimensions.

More specifically, molecules can be divided into two clusters: the one dominating the distribution is almost sulfur-free; while the other cluster of molecules, clearly separated from the majority, contains sulfur atoms (see bottom row in Fig. 3). This pattern indicates that sto-3g and 6-31g are too small basis sets, and should not be used to describe S containing molecules. By comparing the three figures in each column of the first three rows in Figure 3, one can see that the shape of distribution changes significantly upon introduction of electron correlation (going from HF treatment to the MP2). When going from MP2 to CCSD(T), however, the change in the distribution is barely noticeable.

Considering the right hand panel in the third row in Fig. 3, the color code corresponds exactly to the correlation energy contribution to the atomization energy, as estimated by CCSD(T) - HF within cc-pvdz basis. As one would expect, the larger the molecule, the more electron correlation energy is being contributed. The two hundred molecules with the largest and smallest correlation energy contribution to the atomization energy are on display in Fig. 3. We note that molecules with high degree of saturation exhibit the largest amount of electron correlation in their atomization energy, while atomization energies of molecules with multiple double bonds, triple bonds, and aromatic moieties contain the least electron correlation energy. This trend is to be expected because the electrons in unsaturated bonding patterns can contribute less to binding than in saturated species, thereby also decreasing their electron correlation energy contribution to binding.

The reason for developing the CQML model is based on the hypothesis that it will systematically exploit all these underlying implicit correlations which are on display in these figures.
Figure 3. Scatter plots for QM7b. Size in chemical space as measured by 1-norm of Coulomb matrix [a.u.] (i.e., \(|\text{CM}|_1\)) vs. energy differences [kcal/mol] due to various basis set size differences for HF (first row), MP2 (second row), and CCSD(T) (third row). The colour code corresponds to the atomization energy difference \(\Delta\) [kcal/mol] between electron correlation models at cc-pvdz for MP2 vs. CCSD(T) (left), HF vs. MP2 (mid), and HF vs. CCSD(T). In the upper leftmost panel, the brackets enclosing N indicate that nitrogen atoms may or may not be present. The bottom row corresponds to the 2D projection of the third row.

B. 2D results for QM7b

As a first test, we have investigated our QM7b derived data set for the two dimensional \((d = 2)\) case of atomization energies at a fixed basis set (6-31g) for three levels of electron correlation, i.e. HF \((\ell_C = 0)\), MP2 \((\ell_C = 1)\) and CCSD(T) \((\ell_C = 2)\). The second dimension corresponds to three variable molecular training data set sizes \((\ell_M = 0, 1, 2)\). Their relative extent is fixed at ratios which are independent of absolute training set size. In this study, we considered two such sets of ratios \((s = 1\) and \(s = 2\)) which reflect different sample size increases for higher levels. These ratios are summarized in Table II. The number of training molecules \(N_{\ell_M}\) on each level of the CQML with \(d = 2\) as a function of training set size at the highest level \(N_{\ell_M=2}\) is thus given by \(N_{\ell_M} = r_{\ell_M} \times N_{\ell_M=2}\), where \(r_{\ell_M}\) is the ratio as displayed in Table II. Recall that all ML model results presented in this section have been obtained using kernel ridge regression, a Laplacian kernel, and the SLATM representation.

Table II. Level-dependent ratios between training set sizes for the two sample size increases \(s\) considered. \(L\) is the total number of levels.

| \(s\) | \(r_{\ell_M=L-1}\) | \(r_{\ell_M=L-2}\) | \(r_{\ell_M=L-3}\) |
|------|--------------------|--------------------|--------------------|
| 1    | 1                  | 2                  | 4                  |
| 2    | 1                  | 4                  | 16                 |

In Figure 5, various learning curves for atomization en-
ergies, estimated according to Eq. [1], are shown. First of all, we note the rapid and systematic lowering for all CQML models as training set size increases. The models exhibit differing off-sets, and similar slopes, in line with previous results for training-set optimization experiments using ensembles of training sets within genetic optimization protocols[29]. The learning curves of conventional QML pass the chemical accuracy threshold (∼1 kcal/mol) at ∼4'000 training molecules calculated at target level, CCSD(T)/6-31G. This learning curve has a slightly larger off-set with respect to the original SLATM benchmark results (see supplementary materi-
als in Ref. [59] due to the use of (i) the Laplacian instead of a Gaussian kernel function, (ii) B3LYP rather than PBE0 geometries, and (iii) CCSD(T) rather than PBE0 energies.

Addition of MP2 reference energies of further molecules affords a systematic decrease in the learning off-set resulting in ∼2'000 and ∼1'000 CCSD(T) training molecules necessary to reach chemical accuracy for \( s = 1 \) and \( s = 2 \), respectively. The corresponding necessary MP2 training set sizes (not shown in the figure) amount to 4'000 molecules for both \( s \)-values (see Table II). Slightly worse results are obtained by replacing MP2 reference energies with HF energies. This result may seem puzzling, but is in full agreement with what we have found in Figure 3, i.e., the values of \( \Delta_{\text{MP2}} \) and \( \Delta_{\text{HF}} \) are of the same magnitude. This result also implies the possibility to optimize the levels of theory by minimizing the computational cost, meanwhile retaining the accuracy.

Adding Hartree-Fock treatment for additional training molecules, we observe even further improvement, reaching chemical accuracy already at ∼1'000 and ∼300 CCSD(T) training molecules for \( s = 1 \) and \( s = 2 \), respectively. According to the ratios in Table II the corresponding necessary MP2 and HF training set sizes (not shown in the figure) amount respectively to 2'000 and 4'000 for \( s = 1 \), and to 1'200 and 2'400 for \( s = 2 \).

These results are very encouraging; they suggest that reductions by an order of magnitude are possible with respect to high-level reference numbers (from expensive computation or experiment) necessary to reach chemical accuracy. Effectively, the CQML model appears to exploit correlations inherent among the various approximation levels that live within hierarchical spaces of theories.

C. 3D results for QM7b

We have also studied the extension of the 2D-CQML model by a third dimension \((d = 3)\) which explicitly introduces the effect of basis set size on atomization energies. More specifically, we have considered sto-3g \((\ell_B = 0)\) as our lowest level, 6-31g \((\ell_B = 1)\) as an intermediate size, and cc-pvdz \((\ell_B = 2)\) as the largest set. Obviously, larger basis set choices as well as additional levels with more subtle differences could have been included just as well. Here, we assume that the general trend and the conclusions drawn are not affected by the relatively modest size of the basis sets employed.

In Fig. 5 we show corresponding learning curves of 2D-CQML models which connect the different basis sets according to Eq. (7) with just one correlation energy model, CCSD(T). In line with the behavior encountered above for the fixed basis set CQML models, a systematic improvement is found. The error approaches chemical accuracy already with ∼1'000 training examples with the largest basis set used (cc-pvdz). Again, increasing the ratios between levels by going from \( s = 1 \) to \( s = 2 \) (see Table II) leads to systematic lowering of the learning curve.

Finally, when combining multiple basis set and electron correlation levels into a single 3D-CQML model, obtained according to Eq. (8), the most favorable learning curves are obtained (See Fig. 5). For \( s = 1 \) and \( s = 2 \), extrapolation indicates that chemical accuracy can be reached with just 500 and 100 training instances at CCSD(T)/cc-pvdz level, respectively. Note that the learning curves end already for relatively small training set sizes because the necessary number of molecules required at lower levels of theory rapidly reaches the maximal number of available molecules in QM7b. For example, for the \( s = 2 \) case, 100 training molecules at the highest level combination would have required 100 × 4\(^4\) = 25,600 training molecules at the lowest level combination. However, QM7b is comprised of only 7'211 molecules. As such, this is an artefact of the finite size of QM7b, and we expect these learning curves to further decay linearly when using larger data sets in the future.

Overall, these results amount to numerical evidence that it is beneficial to include not only multiple levels but also multiple dimensions. The obvious consequence is that an additional substantial reduction in need for high-level reference numbers (from expensive computation or experiment) is possible through the use of CQML based exploitation of training data obtained for smaller basis sets and more approximate electron correlation models. We believe that this is possible because of inherent error-cancellation between various levels and dimensions.
D. 2D results for CI9

For the stoichiometrical isomers C_7H_{10}O_2, data set CI9, we have also investigated the 2D-CQML model corresponding to Eq. (7). The resulting models differ from the previous 2D-CQML models in that they unite energy approximation effects and basis sets into a single dimension (PM7, B3LYP/6-31g(D), G4MP2). Furthermore, and in analogy to the original Δ-ML model [21–24], all small changes in geometry due to use of different level of theory, are also being accounted for through the ML model. As such, only PM7-quality input geometries are required for the 2D-CQML models discussed in this section. Resulting learning curves are shown in Fig. 9 for two different representations, the Coulomb matrix and SLATM, as well as for two different number of levels (L = 2 and L = 3).

Again, when compared to conventional QML, we note systematic and improved (through lower off-sets) learning as the number of different levels increases from two to three. The relative performance for Coulomb matrix and SLATM meets the expected trend [20], SLATM systematically leading to a substantially lower off-set. These results suggest a certain independence of the CQML methodology from other salient features of QML models, such as training set selection [25,49] or choice of representation [20,24]. In this case, the best 2D-CQML SLATM based model reaches chemical accuracy with respect to G4MP2 based on a training set consisting of ~1’000, 2’000, and 4’000 at G4MP2, B3LYP/6-31g(D), and PM7 level reference results, respectively.

V. CONCLUSIONS

We have extended the ideas manifested in Pople-diagrams within the systematic framework of the multi-level sparse grid combination technique and machine learning. A generalized CQML model has been presented, and we have demonstrated its performance for various 2D variants and for one 3D application using atomization energies of organic molecules as property of interest. Using learning curves to compare models, we have found for all cases investigated that the addition of levels and spaces enables a systematic and substantial reduction in necessary training data at the highest level of theory. As such, we have shown how to construct QML models for which an expensive training molecule can be replaced by multiple cheaper training molecules. Due to the unfavourable polynomial scaling and large prefactors of the more expensive quantum approximations, such trade-offs can deliver significantly more accurate QML models at constant training data compute budget. In conclusion, our numerical findings support the idea that there is an additional “knob” one can use to improve QML models: In addition to improved representations [25,49] or training set selection [20,24], one can also exploit the intrinsic correlations among the various hierarchies which exist among different levels of approximations.

For future work, we will consider the inclusion of more intermediate levels, e.g., the various rungs on Jacob’s ladder, or MP4, CCSD, CCSDT(Q), etc., or continuous changes in basis set size through plane-waves. Other dimensions, such as relativistic effects, spin-orbit coupling, or nuclear quantum effects can be envisioned. While we have focussed on atomization energies only for this study, we will consider CQML models of other quantum properties within subsequent studies. Technical settings can also be investigated, e.g. the relative amount of training data obtained at different levels (currently set globally through parameter s), could still be adapted in a locally optimal manner. Finally, we plan to include this implementation in qmcode [101].

Appendix A: Derivation of the combination technique for quantum machine learning

In applied mathematics, the sparse grid combination technique is a means to approximate, e.g., high-dimensional functions. Let's assume that such a function \( f \) is in some (function) space \( V := V^{(1)} \otimes V^{(2)} \otimes \cdots \otimes V^{(d)} \). That is, it is in the tensor product of \( d \) spaces. Then, we introduce for each of the \( L_m \)-dimensional function spaces \( V^{(m)} \) a series of subspaces of lower dimension

\[
V_0^{(m)} \subset V_1^{(m)} \subset V_j^{(m)} \subset \ldots \subset V_{k_{m}}^{(m)} \quad (A1)
\]

(indicated by the lower index). Classic (full tensor-product) approximation would now approximate this function \( f \) on a level \( j \) in the space \( V_j := V_j^{(1)} \otimes V_j^{(2)} \otimes \cdots \otimes V_j^{(d)} \). However, this leads to the so-called curse of dimensionality, i.e. the exponential growth in computational work with growing dimension \( d \).

In many cases, the sparse grid combination technique allows to approximate \( f \) in a much cheaper way. This is done by recursively introducing the sparse approximation space \( \tilde{V}_j \) with

\[
\tilde{V}_j^{(d)} := \sum_{k=0}^{j} \left( V_{j-k}^{(d)} \otimes \hat{V}_{k}^{(d-1)} \right) , \quad (A2)
\]

where \( \hat{V}_{k}^{(d-1)} \) is the sparse approximation space

\[
\hat{V}_j^{(d-1)} := \sum_{k=0}^{j} \left( V_{j-k}^{(d-1)} \otimes \hat{V}_{k}^{(d-2)} \right) . \quad (A3)
\]

That is, it is recursively built from the first \( d-1 \) spaces in the same way.

In this work, we transfer this approach to the field of quantum machine learning. To this end, we provide a derivation for the combination technique for quantum machine learning in two and three dimensions / spaces.
Let us first briefly introduce a general machine learning model for a given subspace \((e_C, \ell_B, \ell_M)\). Note that we assume here that \(e_C, \ell_B, \ell_M \in \{0, \ldots, L\}\). The general ML model for a given subspace \((e_C, \ell_B, \ell_M)\) reads as

\[
E_{(e_C, \ell_B, \ell_M)}(R_q) := \sum_{i=1}^{N_{e_M}} \alpha_i^{(e_C, \ell_B, \ell_M)} k(R_q, R_i) \quad (A4)
\]

We identify this model with some subspace \(V_{e_C}^{(1)} \otimes V_{\ell_B}^{(2)} \otimes V_{\ell_M}^{(3)}\). Following equation \([A2]\), the two-dimensional combination technique for QML on level \(j_2\) for the spaces of theory and training set size and a fixed basis set level \(\ell_B\) can be introduced as

\[
E_{(j_2, \ell_B, j_2)}(R_q) := \sum_{k_2=0}^{j_2} E_{(j_2-k_2, \ell_B, k_2)}(R_q) \quad (A5)
\]

Note that, whenever a level index becomes negative, we assume the machine learning model to be exactly zero, i.e.

\[
E_{(-1, \cdot, \cdot)} = E_{(-1, -1)} = E_{(-1, \cdot, -1)} = 0 \quad (A6)
\]

For the choice of \(j_2 = 2\) and \(\ell_B = 2\), we can explicitly derive

\[
E_{(2,2,2)}(R_q) = (E_{(2,0,2)}(R_q) - E_{(2,1,2,0)}(R_q))
+ (E_{(2,1,2)}(R_q) - E_{(2,1,2,1)}(R_q))
+ (E_{(2,2,2)}(R_q) - E_{(2,1,2,2)}(R_q))
= (E_{(2,2,0)}(R_q) - E_{(1,2,0)}(R_q))
+ (E_{(1,2,1)}(R_q) - E_{(0,2,1)}(R_q))
+ (E_{(0,2,2)}(R_q) - E_{(-1,2,2)}(R_q))
= E_{(2,2,0)}(R_q) - E_{(1,2,0)}(R_q)
+ E_{(1,2,1)}(R_q) - E_{(0,2,1)}(R_q)
+ E_{(0,2,2)}(R_q) \quad (A7)
\]

Note that we have the equalities

\[
E_{(2,2,0)}(R_q) - E_{(1,2,0)}(R_q) = \sum_{i=1}^{N_{e_C}} \alpha_i^{(1,2)} k(R_q, R_i),
E_{(1,2,1)}(R_q) - E_{(0,2,1)}(R_q) = \sum_{i=1}^{N_{e_M}} \alpha_i^{(0,1)} k(R_q, R_i),
E_{(0,2,2)}(R_q) = \sum_{i=1}^{N_{e_M}} \alpha_i^{(0,0)} k(R_q, R_i),
\]

with the notation from Section \(\text{[III]}\). That is, model \(E_{(2,2,2)}\), as derived here, is exactly the model discussed in Section \(\text{[III]}\).

Based on the two-dimensional combination technique model, we can now recursively build a three-dimensional combination technique further integrating the space of basis set size and with the global three-dimensional level \(j_3\) as follows

\[
E_{(j_3, j_3, j_3)}(R_q) := \sum_{k_3=0}^{j_3} E_{(k_3, j_3-k_3, j_3)}(R_q) - E_{(k_3, j_3-j_3, k_3)}(R_q) \quad (A8)
\]

This construction uses the definition of the two-dimensional combination technique in a recursive fashion.

We finally exemplify the tree-dimensional combination technique for \(j_3 = 2\). That is, we first expand the recursive model for the three-dimensional combination technique by

\[
E_{(2,2,2)}(R_q) = (E_{(0,2,0)}(R_q) - E_{(0,2,1,0)}(R_q))
+ (E_{(1,2,1)}(R_q) - E_{(1,2,1,1)}(R_q))
+ (E_{(2,2,2)}(R_q) - E_{(2,2,1,2)}(R_q))
= (E_{(0,2,0)}(R_q) - E_{(0,1,0)}(R_q))
+ (E_{(1,2,1)}(R_q) - E_{(1,0,1)}(R_q))
+ (E_{(2,2,2)}(R_q) - E_{(2,1,2)}(R_q))
= (E_{(0,2,0)}(R_q) - E_{(0,1,0)}(R_q))
+ (E_{(1,2,1)}(R_q) - E_{(1,0,1)}(R_q))
+ (E_{(2,0,2)}(R_q)).
\]

Then, we expand each of the term by means of the two-dimensional combination technique. Thus we compute

\[
E_{(0,2,0)}(R_q) = E_{(0,0,2)}(R_q) - E_{(0,1,0,2)}(R_q)
= E_{(0,2,0)}(R_q),
\]

\[
E_{(0,1,0)}(R_q) = E_{(0,0,1,0)}(R_q) - E_{(0,1,0,1,0)}(R_q)
= E_{(0,1,0)}(R_q),
\]

\[
E_{(1,1,1)}(R_q) = E_{(1,0,1,0)}(R_q) - E_{(1,1,0,1,0)}(R_q)
+ E_{(1,1,1,1)}(R_q) - E_{(1,1,1,1,1)}(R_q)
= E_{(1,1,0)}(R_q) - E_{(0,1,0)}(R_q)
+ E_{(0,1,1)}(R_q),
\]

\[
E_{(1,0,1)}(R_q) = E_{(1,0,0,0)}(R_q) - E_{(1,1,0,0,0)}(R_q)
+ E_{(1,0,1,1)}(R_q) - E_{(1,1,0,1,1)}(R_q)
= E_{(1,0,0)}(R_q) - E_{(0,0,0)}(R_q)
+ E_{(0,0,1)}(R_q),
\]

\[
E_{(2,0,2)}(R_q) = (E_{(2,0,0)}(R_q) - E_{(2,1,0,0)}(R_q))
+ (E_{(2,1,1)}(R_q) - E_{(2,1,1,1)}(R_q))
+ (E_{(2,2,2)}(R_q) - E_{(2,2,1,2)}(R_q))
= (E_{(2,0,0)}(R_q) - E_{(0,0,0)}(R_q))
+ (E_{(2,1,1)}(R_q) - E_{(0,0,1)}(R_q))
+ (E_{(2,2,2)}(R_q) - E_{(-1,0,2)}(R_q))
= (E_{(2,0,0)}(R_q) - E_{(0,0,0)}(R_q))
+ (E_{(2,1,1)}(R_q) - E_{(0,0,1)}(R_q))
+ (E_{(2,0,2)}(R_q)).
\]
Finally, we combine these results with the previous calculations for $E_{(2,2,2)}$ and obtain

$$E_{(2,2,2)}(R_q) = E_{(0,2,0)}(R_q) - E_{(0,1,0)}(R_q) + E_{(1,1,0)}(R_q) - E_{(1,0,1)}(R_q) + E_{(2,0,2)}(R_q)$$

$$= E_{(0,2,0)}(R_q) - E_{(0,1,0)}(R_q) + [E_{(1,1,0)}(R_q) - E_{(0,1,0)}(R_q)] + [E_{(2,0,0)}(R_q) - E_{(1,0,0)}(R_q)] - [E_{(2,0,0)}(R_q) - E_{(1,0,0)}(R_q)]$$

$$= E_{(0,2,0)}(R_q) - 2E_{(0,1,0)}(R_q) + E_{(1,1,0)}(R_q) - E_{(0,1,1)}(R_q) + E_{(2,0,0)}(R_q) + E_{(0,0,1)}(R_q) + E_{(1,0,0)}(R_q) + E_{(0,0,2)}(R_q) + E_{(1,0,1)}(R_q) + E_{(0,0,2)}(R_q)$$

This is exactly the spelled out version of equation 8 for $E_{222}$.

SUPPLEMENTARY MATERIAL

Geometries are provided as xyz files. Two types of energy data are available for each of the three basis sets (sto-3g, 6-31g and cc-pvdz), i.e., the total energy ($E$) and effective averaged atomization energies ($E^*$). The latter is defined as $E - \sum I n_I * e_I$, where $n_I$ is the number of atom $I$ in the molecule and $e_I$ is the effective atomic energy of atom $I$ obtained through a linear least square fit of $E = \sum I n_I * e_I$ for all molecules in the dataset. Free atom energies for all basis sets and electron methods are also included. Every type of energy data for any basis set used is given as a text file, consisting of three columns representing HF, MP2 and CCSD(T) energies, respectively.

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