Error-Controlled Exploration of Chemical Reaction Networks with Gaussian Processes

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Abstract

For a theoretical understanding of the reactivity of complex chemical systems, relative energies of stationary points on potential energy hypersurfaces need to be calculated to high accuracy. Due to the large number of intermediates present in all but the simplest chemical processes, approximate quantum chemical methods are required that allow for fast evaluations of the relative energies, but at the expense of accuracy. Despite the plethora of benchmark studies, the accuracy of a quantum chemical method is often difficult to assess. Moreover, a significant improvement of a method’s accuracy (e.g., through reparameterization or systematic model extension) is rarely possible. Here, we present a new approach that allows for the systematic, problem-oriented, and rolling improvement of quantum chemical results through the application of Gaussian processes. Due to its Bayesian nature, reliable error estimates are provided for each prediction. A reference method of high accuracy can be employed, if the uncertainty associated with a particular calculation is above a given threshold. The new data point is then added to a growing data set in order to continuously improve the model, and as a result, all subsequent predictions. Previous predictions are validated by the updated model to ensure that uncertainties remain within the given confidence bound, which we call backtracking. We demonstrate our approach at the example of a complex chemical reaction network.

1 Introduction

The accurate description of chemical processes requires the elucidation of a reaction network comprising all relevant intermediates and elementary reactions. For a

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kinetic analysis, the thermodynamic properties of all intermediates and transition states in this network need to be determined to high accuracy. While state-of-the-art quantum chemical calculations can yield highly accurate results even for large systems, they are computationally expensive and, therefore, restricted to a limited number of elementary steps. For this reason, density functional theory (DFT) remains to be the method of choice, despite its shortcomings with respect to accuracy and systematic improvability. The known existence of the exact exchange-correlation functional and the numerical demonstration of a rung-by-rung accuracy of approximate functionals across Jacob’s ladder have nurtured the hope to eventually arrive at approximate functionals of sufficiently high quality.

The accuracy of approximate exchange–correlation density functionals is often assessed through benchmark studies. While many extensive data sets exist, such as the ones proposed by Pople, Truhlar, and Grimme, studies have shown that the accuracy of density functionals can be strongly system dependent. Even if accurate reference data for given molecular structures were available, one could not assume the error of a DFT result to be transferable to the close vicinity of that particular region of chemical space. Finally, even if one had some upper bound on the error of a calculated property, this bound would be so large that subsequent analyses, such as kinetic studies, would be rendered meaningless. If, however, an error estimate of each result was known, the value of any approximate DFT approach would be dramatically increased as it would flag those results to be considered with caution. An assigned uncertainty would allow one to judge whether conclusions drawn from the data are valid or not.

A few methods have been developed which aim to provide systematic error estimates for individual DFT results. In 2005, Nørskov, Sethna, Jacobsen, and co-workers presented an error-estimation scheme based on Bayesian statistics (see also refs. 34, 35). Instead of focusing on only the best-fit parameters in a density functional, an ensemble of parameters is drawn from a conditional distribution over parameters by which a mean and a variance can be assigned to each computational result. While the developed functionals were parameterized employing a wide range of data sets, the issue of transferability remained. In ad-
dition, the reliability of the error estimates was limited.\textsuperscript{40} Recently, Zabaras and coworkers\textsuperscript{41} developed a new exchange-correlation functional to predict bulk properties of transition metals and monovalent semiconductors. Furthermore, Vlachos and coworkers successfully applied Bayesian statistics to DFT reaction rates on surfaces.\textsuperscript{42}

In 2016, we presented a Bayesian framework for DFT error estimation based on the ideas of Sethna and coworkers\textsuperscript{33} that allows for error estimation of calculated molecular properties. By system-focused reparameterization of a long-range corrected hybrid density functional we obtained an accurate functional that yielded reliable confidence intervals for reaction energies in a specific reaction network. Unfortunately, the accuracy of the functional and the error estimates were limited by the flexibility of the chosen functional and did not improve systematically with the size of the data set. In addition, the process of reparameterizing the functional, which is necessary for this type of uncertainty quantification when new reference data points are incorporated, is cumbersome and slow since quantum chemical calculations must be repeated for the whole data set.

Over the last years, many studies on the application of statistical learning to chemistry have been published, with applications ranging from electronic structure predictions (e.g., refs. \textsuperscript{43–56}) to applications in force-field development (e.g., refs. \textsuperscript{57–64}), and reaction prediction.\textsuperscript{65–70} For recent reviews on the applications of machine learning in chemistry see refs. \textsuperscript{71} and \textsuperscript{72}.

De Vita, Csányi, and coworkers presented a scheme which combines \textit{ab initio} calculation and machine-learning for molecular dynamics simulations.\textsuperscript{73–76} Forces on atoms are either predicted by Bayesian inference or, if necessary, computed by on-the-fly quantum-mechanical calculations and added to a growing machine learning data base.\textsuperscript{74} However, this approach requires a considerable data set size to be accurate. So far, their approach was applied to the simulation of metal solids, but not to molecular systems.

Despite continuous advances, current machine learning approaches are unsuitable for the study of chemical reactivity. First of all, current regression models do not provide the required predictive accuracy of 1 kcal/mol or less. Second, so-called training data sets, which are required for the learning process of the
statistical model, are commonly assembled by drawing from a predefined pool of chemical species. This approach is not applicable to the exploration of a chemical system, since the relevant chemical species are not known \textit{a priori} but are discovered during the exploration. Third, current machine learning studies do not consider the uncertainty associated with each prediction. As a result, predictions on chemical species that lie outside the domain of chemical space covered by the training data set are of unknown reliability.

Here, we present an approach that addresses the aforementioned limitations. A Gaussian processes (GPs) is employed to predict thermodynamic properties for species encountered during the exploration. Due to the Bayesian nature of GPs, confidence intervals are provided for each prediction and the uncertainty attached to each result can be assessed. If the prediction confidence is below a certain threshold, the result will be flagged and accurate quantum chemical methods can be employed to obtain more reliable data for such specific cases singled out by the GP. Subsequently, this data is added to the data set, the GP is retrained to incorporate the new data point, and its predictions improve. In this way, the GP can be systematically improved — a larger data set will result in more accurate predictions. Naturally, the size of this data set depends on the desired accuracy. We demonstrate our approach at the example of a model reaction network consisting of isomers of the C$_{7}$H$_{10}$O$_{2}$ stoichiometry and consider DFT and semi-empirical approaches as approximate models whose reliability is to be assessed in a system-focused way. We emphasize that our approach is applicable to any kind of electronic structure model, ranging from semi-empirical and tight-binding models to multi-configurational approaches with multi-reference perturbation theory, provided that results of higher accuracy are available for several reference points selected by our algorithm.
2 Theory

2.1 Gaussian Process Regression – Overview

GPs have been extensively studied by the machine learning community. They are rooted in a sophisticated and consistent theory combined with computational feasibility. In chemistry, however, GPs are fairly new, and therefore, a short overview is given here. We refer the reader to ref. 77 for a more detailed derivation.

Supervised learning is the problem of learning input to output mappings from a training data set. We define the training data set containing \( N \) observations as \( D = \{(x_i, y_i) | i = 1, \ldots, N\} \), where \( x \) is the input and \( y \) the output. From \( D \) we aim to learn the underlying function \( f \), to make predictions for an unseen input \( x_* \), i.e. input that is not in \( D \). Since not any function which reproduces the training data is equally valid, it is necessary to make assumptions about the characteristics of \( f \).

With a GP, which is a stochastic process describing distributions over functions, one includes all possible functions and assigns weights to these functions depending on how likely they are to model the target function.

By defining a prior distribution we encode our prior belief on the function we are trying to model. The prior distribution over functions includes not only the mean and point-wise variance over the functions at a certain point \( x \), but also how smooth these functions are. The latter is encoded in the covariance function, or kernel. The covariance function also determines how rapidly the functions should change based on a change in the input \( x \). The task of learning is finding the optimal values for the parameters in the model. The posterior distribution is the result of combining the prior and the knowledge we get from \( D \). With a trained GP, one can make predictions on unseen input. Due to its Bayesian nature, an error estimate, indicating the model’s confidence in the prediction, is provided for each prediction. Finally, the GP is systematically improvable, i.e., predictions and their error estimates improve with data set size.
2.2 Gaussian Process Regression – Brief Derivation

Let us consider a simple linear regression model with Gaussian noise

\[ f(x) = \phi(x)^T w, \quad y = f(x) + \varepsilon, \quad (1) \]

where \( x \) is a \( D \)-dimensional input vector, \( w \) is a vector of parameters, and \( y \) is the observed target value. The function \( \phi(x) \) maps a \( D \)-dimensional input vector to a \( D' \)-dimensional feature space. Moreover, we assume that the observed target value \( y \) differs from \( f \) by some noise \( \varepsilon \), which obeys an independent and identically distributed Gaussian distribution \( \mathcal{N} \) with a mean and variance \( \sigma^2_n \)

\[ \varepsilon \sim \mathcal{N}(0, \sigma^2_n). \quad (2) \]

Furthermore, as our prior, we place a zero-mean Gaussian with covariance matrix \( \Sigma_p \) on the weights

\[ w \sim \mathcal{N}(0, \Sigma_p). \quad (3) \]

Following Bayes’ rule, the posterior distribution reads

\[ p(w|X, y) = \frac{p(y|X, w) p(w|X)}{p(y|X)}, \quad (4) \]

where \( X = \{x_i| i = 1, \ldots, N\} \) and \( y = [y_0, \ldots, y_N]^T \). In eq. (4), the marginal likelihood, \( p(y|X) \), is independent of the weights and can be calculated according to

\[ p(y|X) = \int p(y|X, w) p(w) \, dw. \quad (5) \]

For some unseen \( x_* \), the distribution \( f(x_*) \) is given by the following expression:

\[ p(f_*|x_*, X, y) = \int p(f_*|x_*, w) p(w|X, y) \, dw, \quad (6) \]

where \( p(f_*|x_*, w) = \mathcal{N}(\phi(x_*)w, \sigma^2_n I) \) and \( I \) is the identity matrix. This can be
shown to be\cite{77}

\[ p(f_\ast | x_\ast, X, y) = \mathcal{N} \left( \phi_\ast \Sigma_p \Phi (\Phi^\top \Sigma_p \Phi + \sigma_n^2 I)^{-1} y, \phi_\ast \Sigma_p \Phi_\ast - \phi_\ast \Sigma_p \Phi (\Phi^\top \Sigma_p \Phi + \sigma_n^2 I)^{-1} \Phi^\top \Sigma_p \Phi_\ast \right), \]  

(7)

where \( \phi_\ast = \phi(x_\ast) \) and \( \Phi = \Phi(X) \) is the column-wise aggregation of \( \phi(x) \) for all inputs in \( \mathcal{D} \). In eq. (7), the feature space always enters in the form of \( \phi(x) \Sigma_p \phi(x') \), where \( x \) and \( x' \) are in either the training or test set. It is useful to define the covariance function or kernel \( k(x, x') = \phi(x) \Sigma_p \phi(x') \) and the corresponding kernel matrix \( K(X, X') = \Phi(X) \Sigma_p \Phi(X') \). Since the covariance matrix \( \Sigma_p \) is positive semidefinite, we can define \( \Sigma^{1/2} \) so that \( \left( \Sigma_p^{1/2} \right)^2 = \Sigma_p \). Therefore, we can write \( \phi(x) \Sigma_p \phi(x') \) as an inner product \( \langle \psi(x), \psi(x') \rangle \), where \( \psi(x) = \Sigma_p^{1/2} \phi(x) \). This is also known as the kernel trick. It allows one to circumvent the explicit representation of the function \( \phi \) in eq. (1) that is needed to learn nonlinear functions using a linear learning algorithm. Conveniently, based on Mercer’s theorem\cite{78} it suffices to verify that \( k(x, x') \) satisfies Mercer’s condition. For a more elaborate explanation see section 4.3 in ref. \cite{77}. Finally, the key predictive equations for a GP regression are\cite{77}

\[ f_\ast | X, y, X_\ast \sim \mathcal{N} \left( \bar{f}_\ast, \text{cov}(f_\ast) \right), \]  

(8)

where

\[ \bar{f}_\ast \triangleq E[f_\ast | X, y, X_\ast] = K(X_\ast, X) [K(X, X) + \sigma_n^2 I]^{-1} y \]  

(9)

and

\[ \text{cov}(f_\ast) = K(X_\ast, X_\ast) - K(X_\ast, X) [K(X, X) + \sigma_n^2 I]^{-1} K(X, X_\ast). \]  

(10)

A GP trained on \( \mathcal{D} \) to make predictions on \( f \) can be employed to model functions such as:

\[ g(x, x') = f(x) - f(x') \]  

(11)

The prediction mean can be readily obtained from the individual prediction means

\[ \bar{g}(x, x') = \bar{f}(x) - \bar{f}(x') \]  

(12)

and the prediction uncertainty can be estimated employing the individual vari-
ances and covariance $\text{cov}(f(x), f(x'))$, which can be computed with eq. (10):

$$\text{cov}(g(x, x')) = \text{cov}(f(x)) + \text{cov}(f(x')) - 2 \text{cov}(f(x), f(x'))$$  \hspace{1cm} (13)

2.3 Molecular Kernels

From eqs. (9) and (10) it can be seen that, in order to be able to apply GPs to learn a molecular target $T(x)$ (e.g., an enthalpy of atomization), the kernel $k(x, x')$ needs to be evaluated. Here, $x$ may be some point in chemical space, i.e., the atomic configuration, charge, and spin multiplicity. The kernel should measure similarity between two points in chemical space and satisfy physical invariances such as translations, rotations, and permutation of atoms of the same element. The search for new kernels to encode physical invariances is subject of active research.

If the target $T(x)$ can be approximately decomposed as a sum of local contributions the formulation of the kernel can be simplified:

$$T(x) = \sum_{\ell=1}^{n} t(\tilde{x}_\ell),$$  \hspace{1cm} (14)

where $\ell$ is an atomic index and $n$ is the total number of atoms. This approximation can be appropriate for properties such as the energy or molecular polarizability.

Then, we can model $t(\tilde{x}_\ell)$ as a linear combination of abstract descriptors $\hat{\phi}(\tilde{x}_\ell)$ (see eq. (1)):

$$\hat{t}(\tilde{x}_\ell) = \hat{\phi}(\tilde{x}_\ell)^\top w.$$  \hspace{1cm} (15)

In analogy to equation (14), we obtain

$$\hat{T}(x) = \sum_{\ell=1}^{n} \hat{\phi}(\tilde{x}_\ell)^\top w = \phi(x)^\top w$$  \hspace{1cm} (16)

where $\phi(x) = \sum_{\ell=1}^{n} \hat{\phi}(\tilde{x}_\ell)$ so that we recover eq. (1). One can see that the kernel
$k(x, x')$ can be written as a sum of kernels acting on local atomic environments

$$k(x, x') = \phi(x)^\top \Sigma_p \phi(x') = \sum_{\ell=1}^n \sum_{\ell'=1}^{n'} \tilde{k}(\tilde{x}_\ell, \tilde{x}'_{\ell'}), \quad (17)$$

where $\tilde{k}(\tilde{x}_\ell, \tilde{x}'_{\ell'}) = \tilde{\phi}(\tilde{x}_\ell) \sum_p \tilde{\phi}(\tilde{x}'_{\ell'})$. There are many kernels developed to act on atomic environments $\tilde{k}(\tilde{x}_\ell, \tilde{x}'_{\ell'})$, such as the kernel developed by Behler and Parrinello,\textsuperscript{43} the Smooth Overlap of Atomic Potentials (SOAP),\textsuperscript{80} or the Graph Approximated Energy (GRAPE).\textsuperscript{81}

### 2.4 Error-Controlled Exploration Protocol

In the exploration of a chemical reaction network, the data set $\mathcal{D}$ is not known beforehand and must be generated during the exploration for a system-focused uncertainty quantification. Naturally, the size of this data set should be related to the desired level of confidence with which the target $\mathcal{T}$ needs to be determined. Our protocol starts with an initial training data set $\mathcal{D}$ of size $m > 0$ and the desired level of confidence given by the variance $\sigma^2_{\text{thresh}}$. The initial data set consists of the first $m$ structures $s_{1:m} = \{x_1, \ldots, x_m\}$ encountered during the exploration and the corresponding targets. This is necessary to allow for reliable predictions by the learning algorithm. Subsequently, new structures $s_{m+1:N}$ (given by a list of structures here (see Supporting Information), but constructed in a rolling fashion in practice) are encountered. Each structure $x_i$ is fed to the GP and a prediction mean $\overline{T}(x_i)$ and a variance $\sigma_i^2$ are obtained. If $\sigma_i^2$ is less than $\sigma^2_{\text{thresh}}$, the prediction confidence will be sufficiently high and the next structure will be attained. If $\sigma_i^2$ is larger than $\sigma^2_{\text{thresh}}$, the prediction will be discarded and the target will be explicitly calculated (e.g., with an electronic structure reference method) for that structure. The newly obtained data point is added to $\mathcal{D}$ and the GP is retrained on the extended data set. Naturally, there is a trade-off between confidence and computational effort. If $\sigma^2_{\text{thresh}}$ is decreased, the prediction confidence will be required to be higher throughout the exploration. This requires a larger data set, and hence, more reference calculations. If, however, $\sigma^2_{\text{thresh}}$ is increased, fewer reference calculations are needed, but the overall prediction accuracy is lower. Next,
all predictions made before are repeated with the updated GP. Through this process, which we refer to as backtracking, we ensure that predictions on previously encountered structures are still within the given confidence interval after the GP was updated. Our error-controlled exploration protocol with backtracking can be summarized as:

\[
\text{Input: } \mathcal{D} = \{(x_i, T(x_i))\}_{i=1}^m, \alpha_{\text{thresh}}^2
\]

\[
\text{for } i \leftarrow m + 1, N \text{ do }
\]

\[
\bar{T}(x_i) \leftarrow \mathbb{E}_{GP}[T(x_i)|\mathcal{D}, x_i]
\]

\[
\sigma_i^2 \leftarrow \mathbb{V}_{GP}[T(x_i)|\mathcal{D}, x_i]
\]

\[
\text{if } \sigma_i^2 > \sigma_{\text{thresh}}^2 \text{ then }
\]

\[
\text{add } (x_i, T(x_i)) \text{ to } \mathcal{D}
\]

\[
\text{update GP and backtrack (i.e., check } x_j < i)\]

\[
\text{return } \mathcal{D}
\]

3 Results

3.1 Model System

We demonstrate our error-controlled exploration strategy at the example of a subset of the GDB-9 database\(^{82}\) consisting of three-dimensional molecular structures of 6095 constitutional isomers of the C\(_7\)H\(_{10}\)O\(_2\) stoichiometry. We chose this data base in order to adhere to a publicly available data set that promotes reproducibility and comparability of new algorithms such as the one proposed in section 2.4 above.

We constructed a graph in which nodes represent items in this data set. Edges are placed between two nodes if their molecular graphs can be interconverted by at least one of a set of transformation rules. These rules describe reactions commonly found in organic chemistry including nucleophilic addition and substitution, isomerization, and cycloaddition reactions (see the Supporting Informa-
The application of these rules divided this graph into multiple strongly connected subgraphs, the largest of which contained 1494 nodes. This subgraph will serve as an artificial exploration network for the rest of this article and is provided in the Supporting Information. The exploration network is shown in Fig. 1. The color of each node represents the graph distance to some randomly chosen node in the network, i.e., the number of edges in a shortest path connecting them.

In this work, our data set contains stable intermediates and no transition-state structures. The charge and spin multiplicity of structures did not enter the predictive model, as all structures lie on the same potential energy hypersurface. However, it should be obvious that our approach can be easily extended to transition states and charged species. In this case, one may keep intermediates and transition states and species of different charge or spin multiplicity in separate
data sets in order to best account for these different types of electronic structures (i.e., ground-state minimum, ground-state bond-activated with a tendency to multi- configurational nature, neutral vs. excess charge, and so forth). If intermediates of different stoichiometry are encountered during the exploration, the smallest collection of atoms from which every molecule in the set can be constructed, needs to be considered. Then, when comparing structures, the atoms that are not needed to form either of the two molecules in question would still be part of the comparison, in the form of idealized “isolated” species.

3.2 Learning and Predictions

To calculate thermodynamic properties \( P^{\text{ref}}(x) \) (e.g., the standard enthalpy of atomization) with accurate methods, such as G4MP2, is computationally demanding. Statistical learning can be employed to improve a result of computationally (comparatively) inexpensive quantum chemical methods, \( P^{\text{base}}(x) \), by predicting the error of a method with respect to some accurate reference result:

\[
\Delta P^{\text{ref}}_{\text{base}}(x) = P^{\text{ref}}(x) - P^{\text{base}}(x). \tag{18}
\]

This strategy is often referred to as \( \Delta \)-machine learning. It is based on the idea that inexpensive quantum chemical methods are able to describe a significant portion of the underlying physics (e.g., nuclear repulsion) but fail to capture more complex phenomena such as electron correlation. It is these effects which are then learned in a \( \Delta \)-machine learning approach. By design, \( \Delta \)-machine learning approaches require the evaluation of the inexpensive \( P^{\text{base}} \) to arrive at the desired property.

In this work, we apply the \( \Delta \)-machine learning approach by learning the difference in the calculated standard enthalpy of atomization between G4MP2 and the density-functional approach with PBE \( (\Delta H_{\text{PBE}}^{\text{G4MP2}}) \) as well as G4MP2 and the semi-empirical model PM7 \( (\Delta H_{\text{PM7}}^{\text{G4MP2}}) \). We emphasize that the choice of the inexpensive (here, PBE and PM7) and reference (here, G4MP2) method are to a certain degree arbitrary and other choices work as well for our protocol (provided that the reference method has been demonstrated to be more accurate than the
Figure 2: Distributions of $\Delta H_{\text{G4MP2}}^{\text{PBE}}$ and $\Delta H_{\text{G4MP2}}^{\text{PM7}}$ for the data set.

inexpensive models for the data set under consideration). The distributions of $\Delta H_{\text{G4MP2}}^{\text{PBE}}$ and $\Delta H_{\text{G4MP2}}^{\text{PM7}}$ in the data set are shown in Fig. 2 (see the appendix for details on the computational methodology). Due to the more approximate nature of the semi-empirical PM7 method compared to the PBE density functional, the distribution of $\Delta H_{\text{G4MP2}}^{\text{PM7}}$ is much wider than the one of $\Delta H_{\text{G4MP2}}^{\text{PBE}}$.

We calculate the SOAP kernel $k(x, x')$ for every pair of structures in the data set. This kernel also provides a definition of the distance between two structures.

$$d(x, x') = \sqrt{2 - 2 d(x, x')}.$$  \hspace{1cm} (19)

To illustrate the notion of distance in a reaction network, a subnetwork of the whole reaction network is arranged according to $d(x, x')$ in Fig. 3, where $x$ is some reactant and $x'$ a possible product.

For both targets separately, we trained a GP on randomly selected subsets of different size and employed the remaining structures as an out-of-sample validation set. For predictions on the validation set we calculated the mean absolute error (MAE),

$$\text{MAE} = \frac{1}{N} \sum_{i=1}^{N} |\mathcal{T}(x_i) - \mathcal{T}(x_i)|,$$  \hspace{1cm} (20)
Figure 3: Illustration of the distance metric in eq. (19) introduced by the kernel at the example of a reaction subnetwork. The contour lines represent the distance $d(x, x')$ between the reactant in the center ($x$) and possible reaction products present in the data set ($x'$). Double arrows are drawn between structures if there is a transformation rule interconverting their molecular graphs.

and root-mean-square error (RMSE),

$$RMSE = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\bar{T}(x_i) - T(x_i))^2}, \quad (21)$$

where $N$ is the size of the out-of-sample validation set, $\bar{T}(x_i)$ the prediction mean and $T(x_i)$ the target value. To better assess the behavior of the GP, we also calculated the MAE (MAE_{ref}) and the RMSE (RMSE_{ref}) of a trivial statistical model that simply predicts the mean of the training data set for every test input. In addition, to guarantee the accuracy of the error estimates we calculate the percentage of predictions $r_{cb}$ for which the target lies outside the 95% confidence band given by $\bar{T}(x_i) \pm 2\sigma(x_i)$. We repeated this process 25 times to ensure that the average of the above metrics converged. The average properties are summarized in Table 1. It can be seen that the prediction accuracy improves significantly with the size of the training data set. When comparing the MAE and the RMSE to the MAE_{ref} and the RMSE_{ref}, respectively, the benefit of employing a GP over simply predicting the mean of the training data set is evident for training data set sizes of 200 and larger. It can also be seen that the prediction error $\Delta H_{\text{PBE}}^{\text{G4MP2}}$ is far greater than that of $\Delta H_{\text{PM7}}^{\text{G4MP2}}$. Finally, the results suggest that the prediction error estimates are reliable as $r_{cb}$ is close to 5% for all data set sizes and targets.

For the study of chemical reactivity, not enthalpies of formation but (free)
Table 1: Mean absolute error (MAE), reference MAE (MAE$_{ref}$), root-mean-square error (RMSE), reference RMSE (RMSE$_{ref}$) (in kJ/mol), and $r_{cb}$ of GP predictions on $\Delta H_{G4MP2}^{PBE}$ and $\Delta H_{G4MP2}^{PM7}$ for different training data set sizes.

| Size | Target         | MAE  | MAE$_{ref}$ | RMSE | RMSE$_{ref}$ | $r_{cb}$ |
|------|----------------|------|-------------|------|--------------|----------|
| 50   | $\Delta H_{G4MP2}^{PBE}$ | 7.82 | 8.42        | 9.71 | 10.53        | 5.24     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 21.61 | 26.24       | 27.86 | 33.13        | 6.40     |
| 100  | $\Delta H_{G4MP2}^{PBE}$ | 7.30 | 8.42        | 9.03 | 10.53        | 4.53     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 19.15 | 26.16       | 25.01 | 32.99        | 6.03     |
| 200  | $\Delta H_{G4MP2}^{PBE}$ | 6.37 | 8.40        | 7.84 | 10.50        | 3.52     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 15.71 | 26.12       | 21.06 | 32.97        | 6.48     |
| 500  | $\Delta H_{G4MP2}^{PBE}$ | 4.42 | 8.39        | 5.45 | 10.48        | 3.83     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 8.31 | 26.16       | 11.25 | 32.99        | 6.21     |
| 1000 | $\Delta H_{G4MP2}^{PBE}$ | 2.90 | 8.37        | 3.64 | 10.45        | 4.26     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 4.64 | 26.15       | 6.21 | 32.91        | 4.74     |

Table 2: Mean absolute error (MAE), root-mean-square error (RMSE) (in kJ/mol), and $r_{cb}$ of predictions on differences in the standard enthalpy between molecular structures from GPs trained on targets $\Delta H_{G4MP2}^{PBE}$ and $\Delta H_{G4MP2}^{PM7}$.

| Size | Target         | MAE  | RMSE | $r_{cb}$ |
|------|----------------|------|------|----------|
| 50   | $\Delta H_{G4MP2}^{PBE}$ | 10.96 | 13.67 | 5.35     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 30.69 | 39.11 | 6.34     |
| 100  | $\Delta H_{G4MP2}^{PBE}$ | 10.22 | 12.74 | 4.91     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 27.54 | 35.26 | 5.56     |
| 200  | $\Delta H_{G4MP2}^{PBE}$ | 8.88  | 11.07 | 4.22     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 22.95 | 29.75 | 5.81     |
| 500  | $\Delta H_{G4MP2}^{PBE}$ | 6.17  | 7.70  | 4.37     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 12.13 | 15.88 | 5.96     |
| 1000 | $\Delta H_{G4MP2}^{PBE}$ | 4.09  | 5.15  | 4.53     |
|      | $\Delta H_{G4MP2}^{PM7}$ | 6.72  | 8.78  | 5.36     |

enthalpy differences between intermediates are usually of interest. From a GP trained on a molecular target, predictions on differences with respect to that target between molecular structures are readily available through eqs. (12) and (13). For both targets separately, we trained a GP on randomly selected subsets of different size and then predicted relative energies between the remaining structures. This process was repeated 25 times to obtain converged means of the MAE, RMSE, and $r_{cb}$. From the results shown in Table 2 it can be seen that the MAE and the RMSE decrease rapidly with data set size, however, the accuracy is lower than that of predictions on the standard enthalpy of atomization. Nonetheless, $r_{cb}$ indicates, that the error estimates remain reliable.

Hence, we demonstrated that GPs are capable of learning molecular properties.
of molecular structures with reliable error estimates. Furthermore, relative molecular properties can be predicted with sufficient accuracy employing a statistical model trained on individual molecular properties.

### 3.3 Error-Controlled Exploration

For the consecutive discovery of intermediates in the exploration of a chemical system, we generated sequences of nodes from our reaction network. Whereas all nodes are already known in our example network, an actual exploration procedure would expand the network in a continuous fashion (see refs. 87 and 88). Starting from a random initial node in the reaction network, the remaining nodes are visited in the order of their graph distance to the initial node (see Fig. 1). Nodes with the same graph distance are discovered in a random order.

Next, the error-controlled exploration strategy outlined in section 2.4 was applied. Here, the initial data set $\mathcal{D}$ consisted of $m = 25$ nodes. The explorations were separately performed for the targets $\Delta H_{\text{G4MP2}}^{\text{PBE}}$ and $\Delta H_{\text{G4MP2}}^{\text{PM7}}$. For each target, three different runs with different variance thresholds were carried out. Results for the exploration with targets $\Delta H_{\text{G4MP2}}^{\text{PBE}}$ and $\Delta H_{\text{G4MP2}}^{\text{PM7}}$ (on the same sequence) are shown in Figs. 4 and 5, respectively.
From Fig. 4 it can be seen that initially the size of the training data set constantly increases. This is due to the low prediction confidence at the beginning of the exploration. The data set increases until the prediction uncertainty is below $\sigma^2_{\text{thresh}}$ (shown as a horizontal line in Fig. 4 right). This is the point at which the predictions made by the GP are trusted for the first time. If, however, the exploration reaches regions of chemical space that are distant to the previously explored ones, the confidence will drop and new reference calculations will be required. This can be observed in Fig. 4 right, where the variance exceeds $\sigma^2_{\text{thresh}}$. Naturally, the total number of reference calculations for the entire exploration depends on $\sigma^2_{\text{thresh}}$. For example, in this particular exploration, the required data set sizes are 344 and 233 for $\sigma^2_{\text{thresh}} = 36$ and 64 kJ$^2$/mol$^2$, respectively. Finally, it can be seen that the backtracking mechanism described in Section 2.4 is indeed necessary. In Fig. 4 for $\sigma_{\text{thresh}} = 8$ kJ/mol at $i = 145$, the GP is updated and predictions which previously were inside the confidence bound now lie outside of it. As a result, data points are added to the data set until all predictions are within the confidence bound.

Fig. 5 shows that a larger data set is required for the target $\Delta H_{\text{PM7}}^{\text{G4MP2}}$ to reach a confidence band of ±30 kJ/mol (415), than for the target $\Delta H_{\text{PM7}}^{\text{G4MP2}}$ to reach
a confidence band of ±12 kJ/mol (344). This finding is in accordance with the results presented in Table[1]. While the calculation of the enthalpy of atomization is faster with PM7 than with PBE, the GP requires far more computationally expensive reference calculations to learn $\Delta H_{\text{PM7}}^{\text{G4MP2}}$ than to learn $\Delta H_{\text{PBE}}^{\text{G4MP2}}$, which illustrates the philosophy of the $\Delta$-machine learning approach that should work more efficiently for the physically more reliable model (in our case this is PBE). As a result, given a required confidence level, a trade-off needs to be found between the required number of reference calculations and the computational effort of the base method.

4 Conclusions

In this work, a novel approach for the rolling improvement of quantum chemical results through the application of GPs is presented. By learning the error of an efficient quantum chemical method with respect to some reference method of higher accuracy, we obtained accurate standard enthalpies of formation for configurational isomers of the C$_7$H$_{10}$O$_2$ stoichiometry. Accurate differences in standard enthalpy between isomers are accessible as well. Furthermore, we showed that the uncertainty estimates provided by our predictive model for both the standard enthalpies of formation for molecules and differences in this standard enthalpy of different molecules are reliable. If the uncertainty associated with a particular calculation is above a given threshold, the chosen reference method will be employed to produce additional reference data. In this way, reference calculations are performed only if truly necessary, i.e., if regions of chemical space unknown to our model are approached and explored. We emphasize that our approach is independent of the chosen electronic structure models, ranging from semi-empirical and tight-binding models to multi-configurational approaches with multi-reference perturbation theory. Through backtracking, previous predictions are validated by the updated model to ensure that uncertainties remain within the given confidence bound.

Our approach will be beneficial for mechanism-exploration algorithms, of which our Chemoton algorithm is one example designed to be applicable to
molecules from the whole periodic table of the elements. In combination with our KiNetX\textsuperscript{95} algorithm for kinetic modeling under uncertainty propagation, reliable first-principles explorations of those portions of chemical reaction space that are relevant for a specific chemical problem become accessible. Obviously, this requires the accessibility to accurate reference calculations on demand. Exploiting, for instance, our multi-configurational diagnostic\textsuperscript{96} allows one to decide on the single-reference vs. multi-reference nature of the molecular structure subjected to a reference calculation. For single-reference cases, explicitly correlated, local coupled-cluster calculations\textsuperscript{97} are the method of choice as they can be easily launched in an automated manner and are known to be highly accurate. For multi-configurational cases, automated complete-active-space type calculations can be launched with our fully automated procedure\textsuperscript{98} for the selection of active orbital spaces.\textsuperscript{99–101}

5 Computational Methodology

The data set employed in this study is a subset of the GDB-17 data set.\textsuperscript{102} All G4 geometries were taken from ref. 82. G4MP2 enthalpies of atomization were also taken from ref. 82. DFT enthalpies of atomization were based on electronic energies obtained with the PBE exchange-correlation functional\textsuperscript{85} and a double-\(\zeta\) basis.\textsuperscript{103} DFT calculations were performed with the program packages Q-Chem (version 4.3).\textsuperscript{104} Vibrational frequencies and rotational constants were taken from ref. 82. Accordingly, \(\Delta H_{\text{G4MP2}}^{\text{PBE}}\) is given by the difference in G4MP2 and PBE electronic energies of atomization as the nuclear contributions cancel in this setup. By contrast, PM7 enthalpies of atomization were calculated from enthalpies of formation obtained with the MOPAC program (version 2016).\textsuperscript{105}

The SOAP average kernel was evaluated with the \texttt{glosim} package.\textsuperscript{52} Following previous work\textsuperscript{80,81} we chose an exponent of \(\zeta = 4.0\). In addition, we set the Gaussian width parameter to be \(\sigma = 0.3\ \text{Å}\) and the cutoff radius to be \(R_{\text{cut}} = 4.0\ \text{Å}\). Furthermore, we chose the number of radial and angular functions to be 12 and 10, respectively. Our model would likely benefit from an exhaustive search over hyperparameters, however, consistent with previous findings,\textsuperscript{52} the performance
of the kernel is not highly sensitive to the chosen set of parameters.

GP predictions were carried out with the library GPy. Data analysis and visualization were performed with the Python libraries pandas and matplotlib respectively. The graphical representation of the reaction network were created by the Graphviz program.

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Supporting Information

In the supporting information the data set and the reaction network employed in this work can be found. In addition, it contains a figure on the GPs’ prediction accuracy.

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