Exploring Chemical Compound Space with Quantum-Based Machine Learning

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Rational design of compounds with specific properties requires conceptual understanding and fast evaluation of molecular properties throughout chemical compound space (CCS) – the huge set of all potentially stable molecules. Recent advances in combining quantum mechanical (QM) calculations with machine learning (ML) provide powerful tools for exploring wide swaths of CCS. We present our perspective on this exciting and quickly developing field by discussing key advances in the development and applications of QM-based ML methods to diverse compounds and properties and outlining the challenges ahead. We argue that significant progress in the exploration and understanding of CCS can be made through a systematic combination of rigorous physical theories, comprehensive synthetic datasets of microscopic and macroscopic properties, and modern ML methods that account for physical and chemical knowledge.

INTRODUCTION

Due to an unfathomably large number of possible molecules and materials [1, 2], and the combinatorially many ways for them to undergo chemical transformations, our understanding of chemistry requires a first-principles approach with proper roots in quantum mechanics (QM) and statistical mechanics (SM). QM gives us the ability to calculate accurate microscopic properties (energies, atomic forces, electronic energy levels, electrostatic multipoles, polarizabilities) for fixed molecular geometries, while SM allows us to sample QM energy surfaces in a given statistical ensemble and calculate macroscopic properties. Accurate QM and SM simulations are computationally demanding, even for a single molecule or material, hence more efficient approaches are urgently needed to address the length- and time-scale dilemma in molecular simulations with sufficient accuracy in order to obtain insights into the evolution of properties throughout CCS. Such efficient methods may eventually enable the long-held dream of in silico chemical and materials design.

In practice, we refer to CCS as the set of all feasible metastable atomic configurations resulting from solving Schrödinger’s equation. Non-equilibrium molecular configurations provide smooth interpolations between points in this high-dimensional chemical space. CCS is large but finite: While accounting for all possible conformations of all stereoisomers of all possible constitutions of all possible compositions, it also encodes repeating patterns, abundant signatures, and low-dimensional building-blocks. Fig. 1 illustrates the pervasiveness of the underpinning constituting patterns when charting CCS by drawing an analogy to stellar constellations. Certain star constellations carry names, and so do certain molecules. More importantly, stellar patterns have been useful for orientation and navigation. Similarly, property patterns throughout chemical space can be combined in “constellations”, from which properties of new molecules of interest can be calculated using linear or nonlinear combination of properties of known molecules or molecular fragments. While relationships for stars and planets are rather well understood, a rigorous understanding of CCS in terms of molecular components and to a similar degree has not yet been achieved but would be of utmost usefulness for rational compound design. In this perspective, we argue that the recently developed machine learning (ML) approaches will significantly aid in achieving a deeper understanding of CCS. We give several examples that illustrate the substantial progress achieved in this field, and outline the many remaining challenges yet to be addressed.

Fundamentally speaking, QM describes the electronic structure of any material compound, thereby determining the behavior of matter at large, and dictating all the mutual relationships between observable microscopic properties [3]. In light of such a large domain of applicability it is not a surprise that fundamental contributions to density-functional theory – one of the more efficient formulations of QM – are among the top cited papers of all times [4]. The unbiased study of chemical space for the purpose of exploration as well as exploitation (computational compound design) imposes a severe need for sampling algorithms with maximal efficiency. While QM based design of materials has already been successfully applied to some specific materials design challenges [5–7], it imposes a prohibitive computational cost in general. Consequently, the improvement in efficiency and robustness of electronic-structure calculations will play an increasingly important role in current and future materials...
design efforts [8–11].

The targeted exploration of CCS aiming to obtain compounds with desired properties is a longstanding endeavor. Many efforts in cheminformatics or materials informatics have relied on statistics and ML to search CCS for relevant pharmaceutical properties such as receptor binding, toxicity [13–14] or materials stability [15–17]. While often useful and computationally efficient, the main drawback of these approaches is that they are not transferable to molecules and properties outside of their domain of applicability, which results from a lack of underlying principles of physics, as also pointed out in Ref. [18].

Here instead we focus on recent fundamental ML developments aimed at a quantum-based understanding of CCS. The key idea is that any observable property for any system can be obtained from solving the relevant quantum-mechanical equations. A more comprehensive QM-based understanding of CCS is now foreseeable because of (i) maturity, efficiency & reproducibility of electronic structure methods and codes, (ii) fast-paced developments in high-performance computing hardware, and (iii) conceptual adaptations of statistical mechanics and statistical learning techniques. Regarding (i), we note the many substantial theory and method developments including density-functional theory (DFT) and post-Hartree-Fock (HF) wavefunction methods, as well as the significant efforts made to ensure reproducibility across different electronic-structure codes [19]. Regarding (ii), the scientific codes in the electronic-structure community have matured to such an extent that a considerable fraction of the world’s top high-performance computing centers busy themselves with QM calculations. Regarding (iii), continuous advances in statistical learning have nowadays enabled performing intelligent data analysis on both small and large data sets, and to extract valuable quantitative insights in a systematic manner. We note in passing that machine learning has already enabled many applications in other fields [20–21], including medical diagnostics [22–24], particle physics [25], bioinformatics [26], brain-computer interfaces [27], social media analysis [28], robotics [29] and team, social, or board games [30–32].

Many recent publications, including special journal issues and reviews of quantum-based ML approaches [33–36] have highlighted the fact that combining quantum calculations with ML can lead to considerable leaps in exploring and understanding chemical and materials spaces. In addition to learning quantum-mechanical observables (integrating out electronic degrees of freedom), evidence has been presented that it is equally possible to build ML models of SM ensemble averages (integrating out the atomistic configurational degrees of freedom), such as free energy, entropy, or kinetic pathways [37–38].

To distinguish this emerging field of physics-based machine learning from preceding efforts in chemo-, bio-, and materials-informatics we will refer to combinations of QM and SM approaches with machine learning as QML models in the following. QML refers to the idea of applying modern statistical learning theory to predict electronic and atomistic properties and processes in molecules and materials. We also remark that the goals and reaches of QML models should not be confused with quantum ML algorithms executed on quantum computers. As such, QML models aim to provide a feedback mechanism between QM/SM and (statistical) machine learning. Given sufficient reference data obtained from QM and SM simulations, queries of properly trained ML models can yield accurate properties within milliseconds—as opposed to the many CPU hours or days necessary to solve the corresponding quantum and statistical mechanics problems for representative compounds. Since QML models interpolate rigorously in complex nonlinear spaces with controlled predictive accuracy, the door has now opened for more extensive analysis and study of these interpolated spaces, previously impossible due to the prohibitive computational cost of direct QM and SM simulations.

Given the substantial progress in the QML field dis-
cussed in this perspective article, we argue that significant progress in the exploration and understanding of CCS can be made through systematic combination of rigorous physical theories, comprehensive datasets of QM and SM properties, and sophisticated ML methods that incorporate physical and chemical knowledge. The authors have witnessed the quick development of the QML field from the perspective of electronic structure calculations and hence the focus in this perspective will be on combining QM and ML with the goal of enhanced exploration of CCS. Efforts to use ML to capture SM properties in analogous ways are subject of active current research [39, 40].

BOX1: EXPLANATION OF QML TERMS

Here we give compact explanation for various keywords discussed in this perspective:

- Chemical Compound Space (CCS): The set of all feasible metastable atomic configurations resulting from solving the Schrödinger equation for the corresponding system of interacting electrons and nuclei.

- Machine Learning (ML): Methods based on statistical learning theory for obtaining numerical models from data samples that generalize well on unseen data. Generally, ML models improve with the availability of more data, hence the models are said to “learn from data”. ML models are inductive, i.e. they are typically not based on any underlying physical model, but can, in principle, reconstruct physical models from the provided data. In the context of exploring CCS, data is less abundant than e.g. in typical ML applications like computer vision. It becomes therefore important to most efficiently make use of available data by combining prior knowledge about physics and chemistry with powerful ML models, as we will argue throughout this perspective.

- Representation: The model that encodes the structure of and relations between atoms. It is crucial for quantifying similarities. For molecules, the representation needs to be unique and invariant to atom indexing as well as to molecular translations and rotations in space (see Fig. 3).

- Supervised, unsupervised, and semi-supervised learning: Machine learning with labels is called supervised learning (SL). Examples of SL are classification or regression where for every sample its class label or regression value is given in the training data. Unsupervised learning (USL) on the contrary has no label information; clustering and dimensionality reduction are typical USL problems. Semi-supervised learning assumes that most samples have no label, and only for very few samples labels are provided for training.

- Parametric and nonparametric models: Parametric models assume a finite set of model parameters that need to be estimated (e.g. a mean of a Gaussian), whereas nonparametric models do not make this assumption. Popular nonparametric models such as Gaussian processes can be viewed as having infinitely many parameters.

- Regression: In regression the relationship between an input representation and continuous output variables is estimated. The most common simple regression analysis is linear regression where a linear function (in one dimension a line, in N dimensions a hyperplane) is fitted to the data according to some loss function such as mean squared error. A widely used classical model for non-linear regression is Kernel-Ridge Regression (KRR) that generalizes well to unseen data with limited scalability in larger data sets.

- (Deep) Neural Networks (DNNs): Widely used and flexible non-linear regression models based on neural networks. Deep networks refer to structured architectures that have a large number of hidden layers offering large flexibility and rich multiscale representations. Due to their scalability they are ideally suited to extract complex non-linear relations from large data sets.

- Cross validation: A common ML procedure used for ensuring generalization to unseen data and avoiding overfitting.

- Learning curves: Measure the performance of ML models upon increasing the number of data samples used for training the model.

- Density-Functional Theory (DFT): The workhorse method for electronic-structure calculations on molecules and materials. While DFT is in principle an exact theory, in practice approximations are made for electronic quantum (exchange and correlation) effects. DFT implementations often provide a good compromise between accuracy and efficiency. Most current QML datasets for molecules and materials are based on DFT calculations.

- Hartree-Fock (HF): Fundamental electronic-structure method used as a starting point for essentially all practical calculations of quantum correlation energy in molecular systems. HF provides an exact treatment of electronic exchange effects due to Pauli repulsion.
FIG. 2: Learning curves illustrate last years’ progress of QML models of atomization energies of molecules. This plot shows mean absolute error (MAE) in eV on atomization energies of small molecules in the QM9 dataset [41]. Shown QML models differ solely by representation and model architecture, and correspond to CM (2012) [42], BOB (2015) [43], BAML (2016) [44], HDAD (2017) [45], constant-size-descriptors (2018) [46], DTNN (2017) [47], (a)SLATM [12] (2017), SOAP (2017) [48], FCHL (2018) [49], enn (2017) [50], MTM (2018) [51], MBD (2018) [52], NN (2018) [53], HIP-NN (2018) [54], SchNet (2018) [55], Wavelets (2018) [56]. The black X indicates the so-called “QM9 challenge” (developing a QML model capable of achieving 1 kcal/mol (0.043 eV) accuracy on the QM9 dataset using only information of 100 molecules for training, see https://tinyurl.com/y2e589wj for more details) formulated at the UCLA-IPAM workshop in 2018. To date, this challenge has not been met.

GOALS AND ADVANCES OF QML

The overarching goal of QML is to develop reliable models with accuracy of high-level electronic structure calculations. Depending on the application, the reference data can be obtained from high-level quantum chemistry, i.e. CCSD(T), or from DFT calculations. While much work remains to be done to reach the “dream” of exact QML models, many key advances have been recently achieved that we will review in this section and connect to important remaining challenges where we deem that urgent progress is needed.

The first salient point is that all QML advances hinge on the availability of trustworthy QM data. This data needs to cover a certain important domain, for example the CCS of organic drug-like compounds, as explored by Reymond and co-workers through their GDB list of SMILES strings [62–65]. Subsequent QM calculations on these molecular graphs led to the publication of equilibrium structures and properties of many thousands of small molecules (QM7 and QM9 datasets [41, 66]), their molecular dynamics trajectories with the QM7MD dataset [67], or non-equilibrium molecular structures (ANI-1 dataset [68]). On the side of inorganic materials, one can calculate equilibrium structures of solids (AFLOW, OQMD, and Materials Project datasets [69–71]), or generate equilibrium and non-equilibrium MD data for a single element (for example silicon [72]). The eventual goal of QML is to develop a universal efficient model for all of CCS capable of accurately describing molecular and materials data on equal footing, and possibly leading to new insights on its underlying regularity and chemical relationships. Reorganizing the periodic table represents a first and important stepping stone in that direction [71, 73]. Initially, different models have been developed focusing either on molecular or materials data, while more recent flexible developments can already be applied to both molecules and solids [48, 49, 55].

While CCS is also commonly explored within cheminformatics based approaches, QML differs in the sense that it rigorously adheres to its roots in fundamental physics, i.e. that it is consistent with the laws of QM and SM. Probably the first QML applications employing ML techniques for non-linear interpolation of QM data were aiming to construct reliable system-specific interatomic potentials, or potential-energy surfaces, going beyond conventional force fields [74–79].

Then in 2011, QML was extended to develop a transferable model for describing QM properties, trained and applicable throughout CCS as demonstrated for the QM7 set of organic molecules [12], highlighting the potential of QML for efficient and accurate exploration of CCS. This idea was rapidly demonstrated to be applicable to many electronic properties using neural networks as well as kernel ridge regression [66, 80, 81], or to search for
polymers with useful properties \[82\], explore chemical properties of crystalline solids \[58, 71, 83–85\], and design promising materials for a variety of technological applications \[86, 87\].

A crucial aspect that determines the reliability and applicability of any QML model is its generalization accuracy assessed on the calculated QM properties of a sufficiently large out-of-sample (hold-out) dataset. It is remarkable how quickly the generalization accuracy of QML models has improved during the past few years. As shown in Figure 2 on the example of QM9 dataset, the QML errors have decreased by 40-fold – from 8 kcal/mol in 2012 to 0.2 kcal/mol in 2018, using exactly the same dataset for training and validation. This noticeable increase in accuracy mainly stems from incorporation of physical prior knowledge into the QML models, such as proper description of permutational symmetries of atoms in a molecule \[48, 49, 67, 88\], as well as explicit inclusion of physically-motivated pairwise and many-body terms for interatomic interactions into QML descriptors \[44, 52\].

An illustration of several widely used representations for kernel-based ML of molecules and materials: Atom-centered symmetry functions (Behler et al.) \[57\], Coulomb matrix (Rupp et al.) \[42\], Bag-of-Bonds (Hansen et al.) \[43\], SOAP (Bartók and Csányi et al.) \[48\], PRDF (Schütt et al.) \[49\], FCCHL (Faber et al.) \[60\], MBTR (Huo and Rupp) \[61\], Wavelets (Hirn and Mallat et al.) \[56\], Moment tensor (Shapeev) \[60\], Sine matrix (Faber et al.) \[61\].

FIG. 3: Illustration of several widely used representations for kernel-based ML of molecules and materials: Atom-centered symmetry functions (Behler et al.) \[57\], Coulomb matrix (Rupp et al.) \[42\], Bag-of-Bonds (Hansen et al.) \[43\], SOAP (Bartók and Csányi et al.) \[48\], PRDF (Schütt et al.) \[49\], FCCHL (Faber et al.) \[60\], MBTR (Huo and Rupp) \[61\], Wavelets (Hirn and Mallat et al.) \[56\], Moment tensor (Shapeev) \[60\], Sine matrix (Faber et al.) \[61\].

combination of (known) properties of only few other molecules, which are not necessarily chemically similar. In order to further the search for improved QML models, the authors are among a group of professors who each agreed to award US$100 to the scientist(s) who devise(s) a QML model which meets the IPAM “QM9 challenge” [https://tinyurl.com/y2e589wj] (See Fig. 3).
representation \cite{12, 80, 92} using one scale per kernel, deep neural networks such as SchNet or DTNN \cite{17, 53, 55} are able to construct an implicit multiscale representation as an outcome of a scalable learning process.

In QM calculations using quantum chemistry or DFT, different properties of an atomistic system (electronic energy, atomic forces, multipole moments, polarizability, electronic energy levels) can be evaluated as QM operators acting on the electronic wavefunction. The situation is more intricate in the case of QML models. Initially, separate QML models were used to describe different properties, i.e. one model for total energy, and another one for the polarizability. A first success of neural networks applied to QM7 dataset was to demonstrate the transferability of a single NN to predict multiple electronic properties at the same time \cite{60}. In other words, the NN had learned an invariant representation, universal enough to capture several properties simultaneously. Since then, kernel methods and deep neural networks have also been extended to reflect multi-property prediction \cite{81, 93}. However, beyond that it would be very advantageous to view QML models as a coarse-grained surrogate for electronic interactions in an atomistic system, akin to a downfolded version of the wavefunction. In such a model, electronic properties in QML could be calculated similarly to explicit QM calculations, namely as operators on manifolds. This idea of using response operators for ML in chemical space has been recently introduced by Christensen \textit{et al.} \cite{91}. Various QML models of electron densities and wavefunctions have by now also been introduced \cite{94–100}.

In general, the chemical space of molecules and materials can be expanded into compositional (chemical elements forming bonds) and configurational (same bonds, but different structures) degrees of freedom. Up to now, we have mainly discussed models that explore compositional degrees of freedom in CCS. On the other hand, configurational degrees of freedom are crucial to understand dynamics of molecules under given external conditions. QML models have also been successfully employed for the construction of interatomic potentials for MD applications that aim beyond the realm of classical, system-dependent force fields \cite{18, 55, 57, 60, 67, 92}. As indicated earlier, the construction of reliable ML force fields from QM data was the first examples of successful applications of QML \cite{74, 77, 78}. Recently, the focus has been shifting towards emphasizing data efficiency of QML force fields. For example, the symmetrized gradient-domain machine learning (sGDML) model \cite{88} is able to reconstruct global force fields of small molecules at the “gold standard” coupled cluster level of quantum chemistry (demonstrated so far for molecules with up to 25 atoms). The sGDML model achieves a typical accuracy of 0.2 kcal/mol in energies and 1 kcal/mol/Å in atomic forces when using only a few hundreds of molecular conformations obtained from an MD trajectory. Such an accuracy turns out to be crucial when modeling conformational transitions and vibrational spectroscopy of even rather small molecules such as ethanol and aspirin \cite{101}. Hence, in the domain of dynamics of small molecules, QML has already enabled essentially exact MD simulations corresponding to a full QM treatment of both electrons and nuclei. Likewise, MD simulations of materials have largely benefited from the application of QML approaches. A recent highlight is the QML-enabled simulation of the growth mechanism of tetrahedral amorphous carbon \cite{102, 103}, which demonstrates the potential to develop a transferable DFT-level force field for studying complex processes in elemental solids.

In light of such substantial theoretical advances it is reasonable to wonder whether QML based predictions compare favorably to experimental observables, and if they could even assist with the analysis and possibly even help in the decision making process of the design of new experiments. In this context it is encouraging to note that QML based MD is already beginning to reach the accuracy and efficiency necessary to predict experimental outcomes. For example, Ref. \cite{104} uses path-integral molecular dynamics using the sGDML QML force field fitted with CCSD(T) atomic forces to demonstrate that low-frequency excitations of ethanol arise from highly anharmonic combination of vibrational normal modes, thus resolving a long-standing experimental controversy (See Fig. 4 and Ref. \cite{104} for a detailed analysis).

Scalability of QML models has also been demonstrated. Atom-by-atom based training on small fragments represented by aforementioned AMONS was shown to yield promising results for energies, forces, NMR shifts, and other QM properties for systems of increasing size \cite{12}. Extensible QML models have also been proposed in Refs. \cite{40, 17, 53, 105, 106}. Another way to reduce complexity and increase accuracy of QML models consists of combining various levels of theory for training and testing \cite{37, 107, 109}. For example, it is possible use a lower level efficient electronic-structure method as a baseline to learn QM properties of a much higher and more expensive level of theory \cite{37}.

Finally, we note that creating universal QML based force-fields trained and applicable across CCS still remains an open challenge due the substantially more diverse range of chemistries and non-local quantum interactions encountered when navigating configurational and compositional space at once \cite{17, 55, 91, 105, 110, 112}.
into QM properties of molecules and materials, and ultimately enable expedient exploration of CCS and rational design of molecules and materials with tailored properties. Most commonly ML methods are employed in the sciences and industry for creating highly predictive models. It has been only very recently that ML models were used as a source of inspiration to learn and obtain insights about the unknown underlying inner regularities hidden in data (e.g. [17]). Given that the ML models achieve this task based on rigorous statistical theory [113], they have become helpful to generate novel research insights (e.g. [27]) or actionable hypotheses (e.g. [114]) that can be exploited in subsequent steps of (experimental) validation and testing. In other words ML modeling has become a powerful and indispensable part of the scientific discovery process itself.

Fig. 2 illustrates six select chemical examples of how such insights were gained through the help of QML, coming partially from the authors’ work, as well as from other literature. First, the development of an accurate and data efficient sGDML force field model [67, 104] (see Fig. 4a) has allowed to carry out quantum molecular dynamics simulations with essentially exact atomic forces computed with CCSD(T) level of theory. For the first time, this enabled the computation of very accurate thermodynamic and spectroscopic observables for molecules as large as aspirin without compromising between accuracy of atomic forces and accessible time scale of MD simulations. Future work on scaling the molecular size with frameworks such as sGDML will enable fully predictive MD simulations where both electrons and nuclei are treated rigorously via exact quantum-mechanical equations without introducing unnecessary compromises between accuracy and efficiency of molecular simulations.

Beyond energies and forces, a general QML model needs to be able to predict accurate electronic response properties (akin to evaluating properties as expectation values of the quantum-mechanical wavefunctions). For example, the application of response operator theory to QML models is illustrated in Fig. 4b: The QML model of the binding curve of hydrogen fluoride improves qualitatively through the explicit inclusion of its derivative with respect to interatomic distance. The same formalism also improves dramatically the prediction of the electrostatic dipole moment, the electric field derivative of the energy, upon inclusion of the corresponding derivatives [114]. The ultimate goal of QML should be creating a unified surrogate quantum model that can simultaneously learn many quantum-mechanical properties in a data-efficient and accurate manner.

In other work by Gómez-Bombarelli et al. [115], the generation of optimal new compounds was optimized through use of generative models in latent space (Fig. 4c). This approach has resulted in promising light-harvesting materials candidates. Conceptually, this way of tackling the “inverse problem” (property → compound) [117] through an intermediate step of effectively coarse-graining chemical space is intriguing. It constitutes an alternative to the more conventional approaches which iteratively solve the “forward problem” (compound → property) using gradient-based [118, 120], Monte Carlo [5], or genetic algorithms [9, 117] or combinations thereof [121]. Furthermore, the problem of generating meaningful compounds is solved elegantly in an implicit fashion by directly training on valid SMILES strings, automatically ensuring that the grammar of newly generated SMILES is not being violated.

Another way to obtain new insights is by analyzing what the QML models have learned from the data, in the spirit of explainable artificial intelligence (AI) where machine learning models are dissected to analyze their inner mechanisms that lead to their respective predictions (see e.g. [113, 122–124] and references therein). A suitable example of this concept is the analysis of the molecular representation learned by deep tensor neural networks (DTNN) [47]. DTNN models (and other flexible nonparametric ML models) are trained on QM molecular energies and, in the limit of infinite data, would be able to learn the exact mapping between molecular structures and the solution of the Schrödinger equation. Since the exact solution can only be formally achieved in the limit by exactly representing the wavefunction, there is mathematically no other choice for DTNN than forming an exact representation of the wavefunction. In practice, the representation is trained on a finite number of molecules, hence DTNN learns the “Schrödinger mapping” on a finite set of molecules which does not necessarily need to be a one-to-one representation of the wavefunction. One can query the learned representation by adding a probe atom to a given molecule [47]. By visualizing the energy isosurface of the probe atom, one can immediately see that the obtained representation exhibits features that closely resemble electron densities or electrostatic potentials, indicating that the model is able to infer QM features in the representation directly from a restricted set of QM energies (see Figure 4d). Hence, the DTNN approach is attempting to solve an inverse problem [125] of constructing a coarse-grained QM representation from a finite set of molecular energies or other QM properties (see Fig. 4d). Despite being trained only on total energies of molecules, the DTNN approach clearly grasps fundamental chemical concepts such as bond saturation and different degrees of aromaticity. For example, the DTNN model predicts the C₆O₂H₆ molecule to be “more aromatic” than benzene or toluene [47]. It turns out that C₆O₂H₆ does have higher ring stability than both benzene and toluene and DTNN predicts it to be the molecule with the most stable aromatic carbon ring among all molecules in the QM9 database [47]. Interestingly, the mathematical construction of the DTNN model (and other flexible nonparametric models based on atomic contributions) provide statistically rigorous par-
We note that while DTNN is in principle able to construct a “Schrödinger map” between molecular Hamiltonians and molecular quantum properties, detailed analysis of the underlying representation learned by DTNN amounts to a complex inverse problem. To address this problem, some of us have recently developed a generalized SchNOrb architecture that learns the DFT wavefunction directly [97]. As an outlook into future work, it would be desirable to unify both ML architectures (DTNN/SchNet and SchNOrb) to gain enhanced understanding into quantum mechanics of molecules by combining the direct “Schrödinger map” (SchNOrb) with the inverse “Schrödinger map” (DTNN/SchNet).

The QML approach is evidently also applicable to solids. In Ref. [71], formation energies of ~2 million Elpasolite crystals (of $ABC_2D_6$ sum formula) made up of main group elements were estimated (see Fig. 4e). Ranking by estimated thermodynamic stability on the convex hull resulted in the identification of nearly one hundred novel crystals, all expected to be stable, and subsequently added to the Materials Project data base [69]. Furthermore, detailed analysis of oxidation states resulted in the discovery of an exotic crystal, NFAI$_2$Ca$_6$, in which Al carries an unusual negative oxidation state – this surprising find was made possible only through the systematic combination of quantum-mechanical calculations and machine learning.

The fundamental nature of QML is not restricted to pre-calculated datasets. Within seminal work, Lee and others have applied ML to experimental data in order to understand and enhance ligand-protein binding [116], shown in Fig. 4f. In particular, random matrix theory was used to identify those chemical groups and features which do and do not strongly affect binding. Such analysis can provide invaluable information on how to exploit local chemistries in order to steer a complex chemical property such as drug-target binding.

All of these examples demonstrate the great potential of QML for extracting statistical insights and new knowledge about quantum property relationships throughout CCS, which are not directly available through conventional quantum calculations.

The data-driven nature of QML approach based on exploring increasingly larger swaths of CCS also enables new insights into the possibility of rational design of molecules with multiple desired properties. For example, in a hypothetic drug design scenario, one could be interested in finding a particularly stable molecule with a large polarizability $\alpha$ (hence stabilizing drug-protein
van der Waals interaction) and a large electronic HOMO-LUMO gap $E_{\text{gap}}$ (exhibiting stability to external electrostatic fields). These three requirements would normally be considered contradictory to each other. Firstly, stability is typically inversely correlated with polarizability – stable molecules are normally thought to have small polarizability [126-128]. Secondly, HOMO-LUMO gap is the leading-order contribution that appears in the denominator of the polarizability formula, hence it is often assumed that polarizable molecules should have small HOMO-LUMO gaps. One is then faced with a difficult question of whether the formulated design problem of low $E$, high $\alpha$, and high $E_{\text{gap}}$ is hopeless? This question can be partially answered by analyzing the pairwise correlation between different molecular properties for a large but finite set of drug-like molecules. These correlations are shown in Figure 5 for roughly 7k molecules in the QM7 dataset. The first observation is that the correlation between most electronic properties is rather weak, if at all present. Most strikingly, above the lower bound of polarizability and atomization energy (both must be bounded from below) we observe no visible correlation. The same observation is made for polarizability vs. HOMO-LUMO gap. This pairwise comparison of three different properties leads us to the suggestion that one can find many drug-like molecules that satisfy the seemingly contrasting requirements of high stability, high polarizability, and a large HOMO-LUMO gap. Similar “freedom of design” is observed for HOMO vs. LUMO eigenvalues, as well as for HOMO-LUMO gap vs. heat capacity. This data-driven analysis, spurred by the QML approach, illustrates a novel way to look at rational design in CCS, breaking conventional descriptor-property rules as well as notions of restricted chemical diversity.

These developments result in a paradigm shift in atomistic simulations, due to (a) usage of rigorous QM/SM priors and data, instead of heuristic cheminformatics, (b) a holistic explorative and comprehensive view on CCS, rather than the traditionally assumed encyclopedic view where each process is studied one compound at a time, and (c) insights provided by novel tools relevant for several scientific communities, i.e. electronic structure prediction, material science, organic chemistry, molecular dynamics and drug discovery. Figure 6 illustrates how this new view could be leveraged for boosting more conventional computational compound design applications, and contribute substantially to on-going experimental efforts, as also recently reviewed in the context of catalyst design [36]. As such, QML is clearly already taking the first steps in the direction of generally tackling the inverse design question in CCS [87, 117, 125].

Furthermore, we are confident that QML is not just limited to direct and inverse design, but it amounts to a fresh view on molecules and materials, and it opens many possibilities to be explored. For example, QML represents a unique opportunity to rigorously test and assess known rules in chemistry, derived from human intuition and empiricism, up to an unprecedented degree of statistical confidence if sufficient data is made available. Furthermore, QML models could also help us discover and extract new concepts, which have hitherto escaped the notion of chemists. These developments may provide a further boost to attempts to gain a holistic understanding of CCS, its structure, and what it holds in store for us in terms of interesting materials, properties, or processes.

**CHALLENGES AND OUTLOOK**

While the QML field has seen a tremendous progress over the past few years, many more challenges remain to be addressed. In the following, we proceed by charting some of the challenges we consider as most interesting and pressing.

**Towards Big Data in CCS**

An important limitation that the QML field is slowly encountering is the lack of large comprehensive datasets. While datasets like QM7 [42, 66], QM9 [41], materials project [69], OQMD [70], Elpasolites [71], MD17 [67], ANI-1 dataset [68], Silicon structures [72], have served well for the development and testing of novel ML techniques, there is an inherent danger to overfit to bench-
FIG. 6: Application concept of QML: Multiple properties can be iteratively optimized in chemical space, spanned by structural and compositional degrees of freedom. After selection of some initial representative target compound(s), quantum mechanics is invoked to calculate relevant \textit{ab initio} properties and to subsequently generate (update) a QML model. Multi-objective property optimization algorithms can subsequently create a new list of candidate structures until convergence.

marks – a fact that has driven e.g. the field of computer vision to exploring larger and ever more complex scenarios (e.g. [129, 130]). It will be therefore important to establish high quality large scale data resources that can enable a new model generation that increasingly explores both compositional and configurational aspects of CCS [47, 105].

However, while having comprehensive big data in CCS would be helpful, due to the combinatorially scaling CCS it remains crucial to develop efficient models that only rely on small amounts of data. Clearly, learning with abundant data is straightforward, but it becomes more challenging to reliably learn from small datasets. Here it becomes crucial to include prior physics-based knowledge and invariance information to become more data efficient without compromising the robustness and accuracy of the QML model [67, 88, 104].

In addition, this new generation of models should ideally quantify the uncertainty of its own prediction [24, 131, 132] possibly in combination with active learning strategies that may lead to improved sampling of CCS and effectively lead to lower model uncertainties [51, 133]. It is important to note that active learning actually induces non-stationarity in learning [134]. In addition, models will need to be able to explain their prediction (e.g. [113, 122]) such that a model will not only serve as predictor but in addition as a source of generating insight [47, 55]. In other words, novel developments need to consider data generation, model building, explanation, insight extraction and sampling in a single comprehensive framework. The recently introduced AMON approach (see Fig. 1), which selects molecular fragments and trains QML models on the fly, represents a first step in this direction [12].

Learning Complex Electronic Properties

Furthermore, current limitations and shortcomings of QML models include predicting intensive properties such as the eigenvalues of molecular orbitals [45], or excited state properties such as excitation energies [135, 136]. Transferable yet accurate QML models of electron densities [137] and molecular orbitals in molecules and band structures in solids also remain a challenge. Another issue, lurking behind rigorous and robust statistical learning procedures, such as \textit{k}-fold cross-validation and converged learning curves, is the selection bias encoded in many of the training sets employed in the field: Stability or property distributions are typically unknown in CCS, and therefore hamper the rigorous assessment of the degree to which any given data set is truly representative of broader chemical spaces. Similar problems of representability were also encountered when trying to measure how accessible website content is reflected in search results when using different search engines [138, 139].

Other challenges include (i) the determination of the irreducible set of variables (formal scaling is only an upper bound but what is effective dimensionality? (see e.g. [89]), (ii) the question of how to render prediction errors constant throughout CCS, and (iii) a quantitative understanding of the relation between the QML models’ learning efficiency, as manifested in learning curves, and the dimensionalities of CCS as encoded in the training data.

Multiscale QML models

A very promising research direction is the integration of QML models across different levels of theory. Exploiting decades of research on the validity and applicability of the various approximations made when solving the Schrödinger’s equation, ample data obtained with computationally less demanding approximations can be combined with fewer but more accurate data points. As a result, the QML models must only learn the differences between the various levels of theory, which is substantially less demanding in terms of data needs. As such, these \textDelta-learning approaches allow to invest the model complexity on the truly difficult aspects [37, 107, 108, 130, 142].

Many studies so far have successfully explored structure-property relationships in restricted chemical spaces. However, the final goal is to enable global and universal exploration of CCS exploiting the appropriate framework offered by the combination of QM, SM, and ML. Here, we have connected some of the ongoing efforts
Towards molecular design with QML

In the following, we would like to outline three concrete open challenges where QML tools still have to be developed in order to find broad application.

(i) More observables The use of QML in order to estimate statistical mechanics observables, e.g. leading to the prediction free energy profiles of rare events, remains an outstanding challenge. This will enable direct validation by comparison to experimental gas-phase rate constants from the literature, as well as to vibrational or linear free energy perturbation based free energy estimates. In order to compare to liquid chemistry results, one has to also include solvent effects (calculated through continuum solvent models, through addition of shells of solvent, or through periodic boundary conditions). If necessary, one should also include nuclear quantum effects through use of path-integral simulations. These developments will serve the goal of establishing once and for all the validity of the QML based approach by direct comparison to experiment, rather than to pre-calculated quantum results.

(ii) Experimental design QML forms the natural basis for software capable to run assisted (automatized/robot) experiments or helping scientists with experimental design decisions. Some work along those lines, suggesting new materials, has already been published [71,115,143,144]. Latent space applications and computational alchemy can be combined with state-of-the-art optimizers, in essence paving the way towards the experimental realization of aforementioned multi-property design tasks relevant to the identification of promising drug, photovoltaic, battery or catalyst candidates.

(iii) Reaction design using QML. Computer based reaction planning and discovery has a longstanding history in chemistry dating back to the sixties, and including contributions by Corey et al in 1972 [145], or Herges and Hoock in 1992 [146]. A comprehensive review of the field has recently been published [147], also discussing the Chematica software which proposes new synthetic routes based on new combinations of already established reactions reported in the literature. Laino and co-workers [148] and Segler et al [149] also introduced literature based ML models for chemical reactions. Such approaches can be problematic, however, when it comes to combinations or reaction conditions for which previously published reactions are not representative. Moreover, the approach is inherently biased to historically known chemistries and combinations thereof, excluding the possibility to discover entirely new reaction mechanisms and synthesis pathways. The latter point, however, is critical for example in the context of developing new catalysts, and more fundamentally to fill any existing "gaps" of our understanding of potentially useful reactions. In order to computationally predict novel reaction profiles we must rely on universal first principles based numerical simulation of the relevant quantum and statistical mechanics which accounts for the electronic and atomic movements resulting in the relevant reaction energies and barriers [150–152]. QM and SM represent the appropriate physics framework necessary to describe the electronic rearrangements occurring during a reaction and for the freedom to dial in atomic configurations and chemical composition at will. When optimizing reactions through screens of prospective combinations of reactants, products, and external conditions, the role of solvents and catalysts is crucial as they can alter the ranking and even render reactions realistic which otherwise would have been impossible. One therefore has to expand training sets to include libraries of solvents and simple catalysts, and apply extended QML models not only of energies and forces but also of statistical mechanical averages. Once trained, these QML models could be used to optimize reaction conditions (solvents, ions, temperature, pressure) in chemical space using gradient-free optimizers such as Monte Carlo/Genetic/or simplex algorithms. First steps in this direction were already taken in 2012 by Rupp et al. [153].

CONCLUSIONS

Over recent years, overwhelming evidence has been gathered by the community suggesting that QML models can truly generalize throughout CCS. As such, a paradigm shift has occurred when moving from globally fitting parameters in fixed functional forms, inspired by physics informed models (such as UFF [154] or semi-empirical methods (such as PM6 [155,156] or DFTB [157]), to locally optimizing regression weights in generic basis set expansions which can be converged in size. Resulting QML models enable (a) rapid predictions of relevant quantum properties for new out-of-sample systems (after training) and (b) converged predictive power through sufficiently large training sets (as
evinced by convergence properties of learning curves). Thanks to the tremendous reduction in computational cost of query tasks, QML models enable to shift the focus away from studying individual instances in CCS towards entire ensembles of compounds. Recovery (or rejection) of known, and discovery and elucidation of unknown structure-property relationships has therefore become a feasible, realistic, and valuable goal which was previously not accessible.

Conceptual challenges include the definition of locality in CCS, i.e. when the QML models are interpolating or rather when their validity fades. While ensemble methods and Gaussian Processes provide a first direction of uncertainty quantification in a limited domain of applicability, mathematically and physically more well founded methods are still waiting to be discovered. Rigorous definitions of diversity (e.g. [158]), properly rooted in QM and SM, might also be necessary to tackle selection bias problem and to maximize data efficiency. First principles based diversity measures would have to properly account for all sorts of systems including metal organic frameworks (MOFs), nano-materials, organic materials, functional materials, inorganic crystals, metastable solids, liquid mixtures, or bio-systems.

An educational challenge corresponds to the establishment of the academic curriculum for this interdisciplinary young field, where chemistry, physics, and computer science have to develop tightly interwoven research programs. Conventional curriculae in traditional departments of chemistry, materials science, physics, computer science, or biology departments do not cover the coursework necessary for students to appropriately reach a level where they can meaningfully contribute to this line of research.

Finally, we would like to stress that the progress made and described herein is dwarfed by the scope of the problem: Gaining virtual control of CCS through physics based understanding has remained elusive for all of humanity’s past scientific efforts. One of the many rewards of reaching this goal would be the routine discovery and design of interesting molecules and materials with desired properties. As such, the community has so far just been scratching the surface of what is to come. To further push the frontier of this field of science, sustained and increasing investments are necessary in terms of computer power, interdisciplinary education and training, funding agencies and most importantly: human interdisciplinary creativity.

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Appendix: Software

Here some pointers are provided to software packages of the discussed machine learning methods for quantum chemistry. General code for running QML is found in [159]. Deep learning methods such as DTNN and SchNet can be readily implemented using the SchNetpack [160]. The technical intricacies of sGDM where prior information has been included in the learning system (i.e. symmetries, sampling and energy conservation) is readily and easily usable in [88]. The iNNvestigate toolbox that allows to explain nonlinear learning methods such as deep learning is described in [161].

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