Machine learning based energy-free structure predictions of molecules (closed and open-shell), transition states, and solids

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The computational prediction of atomistic structure is a long-standing problem in physics, chemistry, materials, and biology. Conventionally, force-fields or \textit{ab initio} methods determine structure through energy minimization, which is either approximate or computationally demanding. This accuracy/cost trade-off prohibits the generation of synthetic big data sets accounting for chemical space with atomistic detail. Exploiting implicit correlations among relaxed structures in training data sets, our machine learning model Graph-To-Structure (G2S) generalizes across compound space in order to infer interatomic distances for out-of-sample compounds, effectively enabling the direct reconstruction of coordinates and thereby bypassing the conventional energy optimization task. The numerical evidence collected includes structure predictions for closed and open shell organic molecules, transition states, and crystalline solids. G2S improves systematically with training set size, reaching mean absolute interatomic distance prediction errors of less than 0.2 Å for less than eight thousand training structures — on par or better than conventional structure generators. Applicability tests of G2S include successful predictions for systems which typically require manual intervention, improved initial guesses for subsequent conventional \textit{ab initio} based relaxation, and input generation for structure based quantum machine learning models.

I. INTRODUCTION

The prediction of three dimensional (3D) structures from a molecular graph is a universal challenge relevant to many branches of the natural sciences. Elemental information and 3D coordinates of all atoms define a system’s Hamiltonian, and thereby all observables which can be estimated as expectation values of approximate solutions to Schrödinger’s equation. Energy and force estimates are frequently used to sample the potential energy surface in order to locate structural minima.1,2 The many degrees of freedom and various levels of theory for describing potential energy surfaces make structure predictions challenging. The problem is aggravated by the combinatorially large number of possible conformational isomers (cf. Levinthal’s paradox3) mapping to the same graph. Often, only low energy conformations are desired, e.g. as a practically relevant starting configuration to a chemical reaction4, or to binding poses in computational drug design5, requiring conformational scans to identify promising representative candidate geometries. While feasible for few and smaller systems, conformational scans of large databases remain computationally prohibitive.

State of the art approaches for generating 3D molecular structures e.g. ETKDG6 and Gen3D7 are efficient yet carry significant bias since they are based on mathematically rigid functional forms, empirical parameters, knowledge-based heuristic rules, and do not improve upon increase of training data set sizes. While applicable to known and well behaved regions of chemical compound space, these methods lack generality and are inherently limited when it comes to more challenging systems, such as open-shell molecules or transition states. Recent generative machine learning developments might hold promise since they can produce structural candidates to solve inverse molecular design problems8–12. Unfortunately, however, they have not yet been used to tackle the 3D structure prediction problem, to the best of our knowledge.

To address the 3D structure with modern supervised learning, we introduce the Graph To Structure (G2S) model. While any other regressor, such as deep neural networks and alike might work just as well, we rely on kernel ridge regression (KRR) for G2S in order to predict all elements in the pairwise distance matrix of a single atomic configuration of an out-of-sample molecule or solid. From the pairwise distance matrix, atomic coordinates can easily be recreated. As query input, G2S requires only bond-network and stoichometry based information (see Fig. 1(a)). By exploiting correlations among data-sets of conformer free structural minima (restriction to constitutional and compositional isomers only is necessary to avoid ambiguity), G2S learns the direct mapping from chemical graph to that structural minimum that had been recorded in the training data set, thereby bypassing the computationally demanding process of energy based conformational search and relaxation.

We have evaluated G2S on QM structures of thousands of constitutional isomers, singlet state carbenes, E2/S_N2 transition states (TS) and elpasolite crystals. After training on sufficient examples, we find that G2S generated structures for out-of-sample graphs not only have a lower RMSD than structures from ETKDG6 and Gen3D7 (for those closed shell molecules for which the latter are applicable), but also exhibit high geometric similarity to the reference quantum chemical structure. Further numerical evidence suggests the applicability of G2S to the prediction problem of transition state geometries, carbene structures, and crystalline solids. We also use G2S to generate coordinates for previously uncharacterized

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molecules in the QM9 data-set\textsuperscript{16} that can be used as input for subsequent QM based relaxations, or for QML based property predictions. Not surprisingly, analysis of G2S results indicates that interatomic distances between atoms that share strong covalent bonds are easier to learn than between distant atoms which affect each other only through intramolecular non-covalent interactions.

II. RESULTS

A. G2S performance

We report G2S performance curves for heavy atom coordinates (not hydrogens) of constitutional isomers, carbenes, TS, and elpasolite structure predictions in Fig. 2. For all data sets and representations studied, root mean square deviations of reconstructed geometries of out-of-sample input graphs decrease systematically with training set size. For all QM9 based sets (isomers and carbenes), the Bond Length and Bond Hop representations yield systematic improvements with lowest offset. While Bond Order exhibits a similar slope, its offset however is markedly higher. This difference is likely due to Bond Order encoding substantially less information. Note that graph CM and BoB representation, both yielding better learning curves for atomization energies due to their inverse distance format\textsuperscript{17}, perform both worse than Bond Length. Since geometry is directly proportional to distance (and not inversely such as energy), this trend is therefore consistent with the literature findings. The performance of graph CM and BoB for the transition states is rather disappointing, but it is in line with trends among machine learning models of the activation energy, already discussed in Ref.\textsuperscript{18}. If a user had to select just one representation, the authors would recom-
FIG. 2. Systematic improvement of predictive G2S accuracy with increasing training data for all data sets studied. Performance curves show mean heavy atom root-mean-square deviation (RMSD) of G2S generated structures (with different representations). (a) Performance curves of isomers, carbenes, and transition states (TS). Insets depict exemplary Lewis structures of each dataset. Horizontal lines show mean RMSD of generated structures with ETKDG and Gen3D from SMILES. (b) Performance curves of the elpasolite dataset using the FLLA representation. Top, mid, and bottom panel depict prediction errors for unit cell length, interatomic distances, and coordinates. The inset illustrates the AlNaK$_2$F$_6$ elpasolite crystal.

mend the Bond-length representation which encodes changes in stoichiometry through element-pair specific bond-lengths, and which performs best on average (see Tab 1 and Fig. 2).

For the TS based performance curves, similar trends are observed with the exception of the Bond Order representation now resulting in the most accurate G2S model. This is in line with the findings in Ref.18 where the simple one-hot-encoding representation outperforms more physics based representations when it comes to the prediction of activation energies. It is an open question if and how the physics of transition states can be properly accounted for within a representation.

From the curves on display in Fig. 2 (a) it is clear that G2S delivers similar performance no matter if Lewis structures of target systems are well defined or not. For comparison, empirical structure prediction methods ETKDG and Gen3D and have also been applied to the isomer sets (application to carbenes and TS is not possible since these methods are restricted to systems with valid Lewis structure formulas). Their RMSD from QM9 geometries is reached by G2S after training on over 4'000 structures. In addition to their quantitative limitations, ETKDG and Gen3D were respectively in 15% and 1.5% of the cases for C$_7$O$_2$H$_{10}$, and 6.3% and 19% for C$_7$NOH$_{11}$ not able to generate a structure from given SMILES at all. This indicates that structure generation can be a challenge for empirical methods, even when it comes to simple closed shell and small organic molecules. Note how the constant slope of the G2S performance curves suggests that even lower prediction errors should be possible for larger training sets. The kinks in the performance curves of the carbone data set result from noise in the DGSOL prediction when solving the distance geometry problem: Actual learning curves of interatomic distances are smooth for all data-sets (see Supplementary Figures 2-6).

In complete analogy to predicting pairwise atomic distances in molecules, G2S can be trained to predict pairwise distance of atomic sites in a crystal. Due to the dependence on the size of the unit cell, pairwise distances are predicted in fractional coordinate space instead of Cartesian coordinates, and an additional G2S model is trained to predict the lattice
FIG. 3. Exemplary structures generated with G2S (cyan) for all molecular datasets. Reference structures are shown in green with corresponding heavy atom root mean squared deviation. Panels (a)-(b) constitutional isomers C₇O₂H₁₀ and C₇NOH₁₁, respectively. (c)-(d) correspond to E2 and S₅² transition states TS with attacking/leaving groups shown as beads, respectively. Panel (e) Carbenes. (f) Five exemplary structures out of the 90% successful predictions of the 3,054 uncharacterized QM9 molecules.

constant, based on the exact same representation of stoichiometry (FLLA). The performance in Fig. 2(b) indicates, just as for the molecular cases, systematically decaying prediction errors with growing training set size.

To gain an overview, we also report the best mean absolute and root mean square errors for G2S models after training on the largest training set sizes available in Table I. Mean absolute errors of less than 0.2Å are obtained in all cases. Exemplary predicted structures, drawn at random and superimposed with their reference, are on display for all molecular data sets in Fig. 3. Visual inspection confirms qualitative to quantitative agreement, the largest deviations corresponding to conformational isomers which can be expected to exhibit small energy differences.

Based on the promising performance of G2S, we have also assessed its performance for 3,054 uncharacterized molecules which had failed the QM9 generation protocol. To revisit the problem of predicting the geometries for these uncharacterized molecules, G2S has been trained on 5,000 randomly chosen QM9 molecules (varying constitution and composition), and used to predict coordinates for each of them. Subsequent geometry optimization at a B3LYP/6-31G(2df,p) level of theory showed successful convergence of 90% of them (a random selection of unconverged molecules can be seen in Supplementary Figure 7). A similar success rate has been reached with Gen3D® and OpenBabel. Fig. 3 (f) depicts randomly drawn structures together with the respective structural formula. At a B3LYP level of theory, 92% of the uncharacterized molecules are expected to converge to a local minimum, which makes G2S a viable initial guess for ab initio structure relaxation.

| N_{train} | N_{test} | MAE [Å] | RMSD [Å] | Representation |
|-----------|----------|---------|----------|----------------|
| C₇O₂H₁₀   | 4876     | 0.14    | 0.44     | Bond Hop       |
| C₇NOH₁₁   | 4687     | 0.12    | 0.42     | Bond Length    |
| E2 TS     | 1344     | 0.15    | 0.42     | Bond Length    |
| S₅² TS    | 2228     | 0.19    | 0.44     | Bond Order     |
| Carbenes  | 4004     | 0.13    | 0.38     | Bond Length    |
| Elpasolite| 8472     | 0.16    | 0.15     | FLLA           |
Assessing the usefulness of structure prediction models can be challenging. While from a machine learning perspective, naturally the error is calculated w.r.t. to the test dataset (Fig. 4 error type A), energy based optimization methods are typically evaluated by their deviation from the closest minimum of a higher level of theory structure (Fig. 4 error type B). Since G2S is trained on quantum-based structures, it should inherently be able to predict structures close to the minimum of the used reference method, and should therefore be a useful tool for the automatized generation of meaningful initial structure guesses which can subsequently be used as input in energy based convergence of the geometry.

We have relaxed the test sets of the C$_7$NOH$_{11}$ constitutional isomer set and the as E2/S$_N$2 reactant set using G2S output (with Bond Length representation) as an input for subsequent semi-empirical GFN2-xTB$^{20}$ for both, as well as DFT (B3LYP) and post-Hartree-Fock (MP2) based relaxation, respectively. The resulting performance curves are shown in Figure 5 and, again, indicate systematic improvement with training set size, reaching even PM6$^{21}$ (semi-empirical quantum chemistry) level of theory for error type B of the reactants.

The results for error type A in Figure 5 (blue curves), however, show that subsequent QM based structure relaxation does not necessarily lead to further improvement for the reactants. While the constitutional isomers improve by almost 0.1 Å, the E2/S$_N$2 reactants tends to get worse. A possible explanation for this counterintuitive trend is that the conformational space of the E2/S$_N$2 reactants is limited to a single dihedral, and once a structure is predicted by G2S to be in the wrong conformational minimum, further structure relaxation will even increase the error.

Overall, however, G2S predicted input structures result in geometries closer to the minimum of the respective reference method of a semi-empirical method (Figure 5 orange curves). In the case of C$_7$NOH$_{11}$ isomers, the respective error between GFN2-xTB and B3LYP is only 0.13 Å, which could explain an almost equal average distance to both minima. A detailed
FIG. 6. Systematic improvement of energy prediction accuracy with increasing training data using G2S predictions (blue) as well as DFT structures (orange) and ETKDG/UFF structures (red) as an input to QML models. (a) and (b) atomization energy prediction of C$_7$O$_2$H$_{10}$ and C$_7$NOH$_{11}$ constitutional isomers, respectively. (c) Prediction of formation energies of elpasolite crystals. (d) Speedup estimate of a G2S (blue) or ETKDG/UFF (red) based QML model over a DFT dependent QML model. This assumes an average of 16 DFT optimization steps required before a structure can be used in QML.

C. From G2S output to QML predictions

The availability of molecular structures is not only a problem for molecular simulations, but also for structure based machine learning of molecular quantum properties$^{22}$. In order to push the boundary in exploration of chemical space, either a graph-based model is required, or 3D structures have to be generated. In case of the latter, generated structure should be close to the level of theory of the training data in order to avoid large prediction errors. G2S enables us to circumvent this problem by allowing structure based machine learning models to be trained on predicted structures. Thereby, the property predicting machines learn to compensate the noise of G2S structures, which allows for the future query structures to originate from G2S.

In order to quantify the usefulness of G2S for this problem, we have used G2S output coordinates without further geometry optimization as an input to standard QML representations such as FCHL1$^{23}$, FCHL1$^{24}$ or BoB$^{25}$. We have focussed on the prediction of atomization and formation energies of constitutional isomers and elpasolites, respectively. In Fig. 6, we compare the resulting performance curves to standard QML machines that had access to the ‘true’ reference coordinates as input, as well as to QML machines that used topology only (input graphs for G2S) as input (see Supplementary Figure 8 for QML learning curves). Again, we note that all performance curves improve systematically with training set size. For atomization energy prediction of C$_7$O$_2$H$_{10}$ and C$_7$NOH$_{11}$ isomers, G2S and FCHL19 still reaches an accuracy of 5 kcal/mol MAE at 1024 training points, slowly approaching the coveted chemical accuracy of 1 kcal/mol, and almost matching the accuracy of a DFT structure based BoB model. Using ETKDG/UFF based geometries as test structures, the performance curves indicate an increasing discrepancy between ETKDG/UFF geometries and energy. The sensitivity of the FCHL19 representation leads, in that regard, to large prediction errors, whereas for small training sizes the BoB representation seems to be more robust. On average, and as one would expect, performance curves improve as one goes from topology to G2S to QM coordinates as input for QML.

overview of baseline errors of different methods is given in Supplementary Table 1.
D. Analysis and Limitations

The analysis of machine learning predictions is crucial in order to better understand the G2S model. Fig. 7 reports the distribution of predicted (largest training set) and reference distances for the C$_7$NOH$_{11}$ data. We note that, as expected from the integrated results discussed above, the predicted distance distribution overlaps substantially with the respective reference distribution. Small deviations indicate that G2S slightly overestimates covalent bond-lengths, and that it underestimates distances to third neighbours. The density differences for second neighbours can hardly be discerned.

The scatter error heat-map plot of predicted versus reference distances (Fig. 7(b)) indicates absence of major systematic errors (in line with remarkably good averages), but reveals a large variance for distances larger than 2.5 Å. A plausible reason for this could be the natural flexibility of molecular structures for flat and long compounds (as opposed to systems dominated by cage-like connectivities). This explanation is corroborated by the trend observed among individual MAE obtained for each distance pair of the distance matrix of C$_7$NOH$_{11}$ (Fig. 7(c)): The larger the distance the larger the error. As mentioned, the sorting of the representation and distance matrix depends on the norm of the feature values of each row, naturally sorting larger distances to higher indices for the Bond Length representation. Such prediction errors can then lead to the generation of the wrong conformer, or even diastereomer.

A potential solution could be the decomposition of the full distance matrix into only considering close neighbor distances. Conceptually similar to how local atomic representations in QML work, the position of an atom would only depend on the distances of the closest four atoms, making its position uniquely defined. Furthermore, the scalability of G2S would be improved since instead of $n(n-1)/2$ machines for $n$-heavy atoms, only four machines are necessary. Furthermore, since G2S relies on only a single kernel inversion and short representations, the scalability is expected to improve through kernel approximations or efforts in learning efficiency such as the atoms in molecules (AMONS$^{27}$) approach. However, it has to be highlighted that the depicted structures in Fig. 3 have been generated with less than 5,000 training molecules available. To that end, the linear trend of the logarithmic learning curves indicates that more data will still improve the accuracy, meaning that fundamentally the learning capability of G2S has not yet achieved its full potential. An improvement in accuracy would make the solution to the distance geometry problem less ambiguous and, therefore, would lead to fewer cases of conformer/diastereomer misclassifications.

In order to further explore the role of the target format, we have also attempted to build machine learning models of en-
tries in the Z-matrix. However, the Z-matrix based predictions did not improve over the distance matrix based model estimates (see Supplementary Method I.B.). Possible further strategies to improve on G2S could include Δ-machine learning where deviations from tabulated (or universal force-field based) estimates are modeled.

III. DISCUSSION

We have presented Graph To Structure (G2S), a machine learning model capable of reconstructing 3D atomic coordinates from predicted interatomic distances using bond-network and stoichiometry as input. The applicability of G2S has been demonstrated for predicting structures of a variety of system classes including closed shell organic molecules, transition state geometries, carbene geometries, and crystal structures. G2S learning curves indicate robust improvements of predictive power as training set size increases. Training on less than 5’000 structures already affords prediction errors of less than 0.2 Å MAE in interatomic distances for out-of-sample compounds - without any signs of saturation of the learning curve. We find that G2S predicts chemically valid structures with high geometric similarity towards out-of-sample reference geometries. Our error analysis has identified prediction errors of interatomic distances to be the largest for atoms that are the farthest apart, explaining the possibility of substantial deviations in terms of torsional angles or diasteromers. Comparison to empirical structure generators (ETKDG and Gen3D) indicates that G2S predictions, within their domain of applicability, are on par or better—already for modest training set sizes. We have explored the limits of G2S by also considering geometries of unconventional chemistries such as open-shell systems, transition state, or crystalline solids which might be problematic for conventional empirical structure generators. The usefulness of G2S has been illustrated by (a) resolving structures for 90% of the 3’054 characterized molecules mentioned in the QM9 database with subsequent, ab initio based geometry relaxation, and (b) generating coordinate input for subsequent training of structure based machine learning predictions of quantum properties, such as atomization energies, reaching prediction errors with hybrid DFT quality.

We believe that a solely data driven approach is appealing, due to its inherent capability to further improve and generalize across chemical compound space as more training data is being made available. Our extensive numerical evidence suggests that the G2S approach is capable of successfully predicting useful structures throughout chemical compound space and independent of predefined rules or energy considerations. Effectively, G2S accomplishes the reconstruction of atomistic detail from a coarsened representation. Our results for elpasolites, transition states, and carbenes already demonstrate that G2S can be trained and applied across differing stoichiometries and sizes. However, given the size and complexity of chemical space, a one fits all solution will just result in a substantially larger model. In that sense, we believe that it is also of significant advantage of G2S that it adapts already to certain chemical subspaces of interest, and can then be put to good use in that domain. Future work could deal with applications to coarse-grained simulations, Boltzmann averaging or extend above efforts to predict more transition state geometries.

IV. METHODS

A. Kernel Ridge Regression (KRR)

We rely on kernel based methods which have shown promise in predicting quantum properties throughout chemical compound space after training on sufficient data. Developed in the 1990s, kernel methods learn a mapping function from a representation vector x to a target property y. G2S attempts to predict interatomic distances in a sorted distance matrix. The focus on the prediction of internal degrees of freedom facilitates the learning process because of rotational, translational, and index invariance. Note that the subsequent reconstruction of the Cartesian coordinates from a complete set of noisy interatomic distances is straightforward (see below). Within G2S, the interatomic distance target label y between any pair of atoms I and J is defined as

$$y_{IJ}^{G2S}(x) = \sum_{i}^{N} \alpha_{i}^{(IJ)} k(x_i, x)$$

with α being the i-th regression coefficient, x_i being the i-th molecule in the training set and k being a kernel function to quantify the similarity of two molecules. The regression coefficients α are obtained from reference interatomic distances y^ref according to standard KRR training procedure.

$$\alpha^{IJ} = (K + \lambda \lambda) \cdot y_{IJ}^{	ext{ref}}$$

with a regularization coefficient λ and the identity matrix I. The regularization strength λ is dependent on the anticipated noise in the data and has been determined by hyperparameter optimization. Note that while each interatomic distance matrix element IJ is predicted by a separate G2S model (Eq. 1), formally the training for all models requires only one matrix inversion (Eq. 2). In this sense, G2S represents a single kernel/multi-property KRR model.

Due to numerical efficiency, however, in practice we have simply relied on repeated Cholesky decomposition as implemented in QMLcode.

To relate the molecular representations via a similarity measure, a kernel function k has to be chosen, as for example,

$$k(x_i, x_j) = \exp \left(-\frac{||x_i - x_j||^2}{\sigma} \right)$$

Equations 3 and 4 represent Laplacian and Gaussian kernel functions, respectively, a standard choice in KRR based
While index-dependent representations can benefit from Wasserstein norms, we enforce index invariance by sorting (see below), and have therefore only used either L1 or L2 norm.

We optimize the hyperparameters $\sigma$, $\lambda$ with different choices of kernel function (Gaussian or Laplacian) and representation by using a grid-search and nested five-fold cross-validation. The performance of all models has been tracked in terms of mean-absolute-error (MAE) of all distances, as well as root-mean-square-deviation RMSD.

To assess the generalizing capability of G2S for various representations, kernels, and data-sets the test error has been recorded in terms of training set size $N$, a.k.a. learning curve, is known to be linearly decaying on a logarithmic scale, which facilitates assessment of learning efficiency and predictive power.

### B. Graph-based Representations

We use bond order matrices to define molecular graphs, with elements being a 0, 1, 2, 3 for bond types none, single, double, and triple, respectively (Bond Order). For disconnected molecular graphs, e.g. transition states, a fully connected graph between attacking/leaving groups and reaction centers is assumed. We have also used a denser way to describe the connectivity of a molecule by counting the number of bonds between atoms following the shortest connecting path (Bond Hop). These representations capture the connectivity of a molecule but neglect information about atom types. To incorporate atomic information as well as a form of spatial activity of a molecule but neglect information about atom types.

For hydrogens, only the distances to the four closest heavy atoms (matrices for smaller molecules are padded with zeros). This limits the size of any query molecule to at most $n$ distance-pair, resulting in $n(n - 1)/2$ machines to be trained. For hydrogens, only the distances to the four closest heavy atom neighbors (not forming a plane) are being considered, requiring four machine learning models. This working hypothesis is consistent with the observation that the deprotonation of small molecules typically only involves local electron density changes, making only local geometries predominantly important.

In order to predict interatomic distances for out-of-sample molecules (Fig. 1 (a)), only information about the bonding pattern and nuclear charges is required, e.g. by providing a simplified molecular-input line-entry system (SMILES) or SELFIE string. RDKit is used to generate the corresponding adjacency matrix from which we construct the representation.

To convert the predicted interatomic distances to 3D coordinates, the distance geometry problem has to be solved. For heavy atoms, we use DGSOL, a robust distance geometry solver that works with noisy and sparse distance sets.

After reconstructing the heavy atom coordinates, all valencies are saturated by placing hydrogens on a spherical surface provided by a Lebedev sphere. Note that solving the distance geometry problem is independent from G2S, any other approach could have been used just as well.

Regarding the Elpasolite crystal structure predictions and in order to allow the conversion from fractional to Cartesian coordinates, an additional machine has been trained to also predict the unit cell length of each stoichiometry. By learning the length of the unit cell with an additional machine, fractional coordinates can then be converted back to Cartesian coordinates.

The training of G2S starts with the separation of heavy atoms and hydrogens from the target molecules (Fig. 1 (a)). We generate the heavy atom scaffold first, followed by saturating all valencies with hydrogens. This leads to the scaffold and hydrogen training being independent problems.

After the separation, the input’s molecular bonding patterns have to be featureized into a fixed size graph representation. To learn the pairwise distance matrix, we use one model per distance-pair, resulting in $n(n - 1)/2$ machines to be trained.

### C. Work flow

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D. Data

To assess G2S, several quantum-based datasets containing structures of closed shell, open shell, transition states as well as crystal structures have been considered. The QM9 database\textsuperscript{16} has already served as an established benchmark and recently has been used to test generative machine learning models.\textsuperscript{8–12} All QM9 molecules were optimized at the B3LYP/6-31G(2df,p)\textsuperscript{50–55} level of theory. From QM9, the largest subsets of constitutional isomers, i.e. 6’095 and 5’859 molecules with C\textsubscript{2}H\textsubscript{6},C\textsubscript{2}H\textsubscript{4}H\textsubscript{3}O and C\textsubscript{2}H\textsubscript{5}NOH\textsubscript{1} sum formula, respectively, have been selected for this work. Note that already pure constitutional isomers (fixed composition) constitute a difficult target since similar molecular graphs can lead to vastly different 3D geometries. Fig. 1 illustrates three exemplary molecules, as well as distance, energy, and moments of inertia distributions for both constitutional isomer sets. As evident from inspection of the latter, the molecular shapes tend to be long and flat with few spherical structures.

In order to push G2S to its limits, systems without well-defined Lewis structures have been considered as represented by two distinct and recent data sets: Carbenes and transition state (TS) geometries. The QMSpin\textsuperscript{56} database reports over 5 thousand singlet and triplet carbone structures (derived through hydrogen abstraction of random molecules drawn from QM9), for which common structure generation methods would require manual intervention. These structures were optimized using CASSCF\textsuperscript{57–59} in a cc-pVDZ-F12\textsuperscript{60} orbital basis, and aug-cc-pVTZ\textsuperscript{60} density fitting basis. We have used all singlet state carbone structures for training and testing of G2S.

We have also trained and tested G2S on thousands of TS geometries from the QMrxn20\textsuperscript{4} dataset. QMrxn20 consists of C\textsubscript{2}H\textsubscript{6} based reactant scaffolds, substituted with -NO\textsubscript{2}, -CN, -CH\textsubscript{3}, -NH\textsubscript{2}, -F, -Cl and -Br functional groups, for which E2/S\textsubscript{N}2 reaction profiles were obtained using MP2/6-311G(d)\textsuperscript{61–65} level of theory.

Regarding solids, we have relied on the Elpasolite dataset corresponding to 10,000 training systems made up from main-group elements.\textsuperscript{45} All crystal structures had been relaxed using DFT (PBE) with projector augmented wave pseudopotentials.\textsuperscript{45,66,67}

Finally, we have also extracted the list of 3,054 SMILES of ‘uncharacterized’ molecules from the QM9 database, for which the structure generation and B3LYP geometry optimization procedure had led to a mismatch with initial Lewis structures.

E. Structure Generation and Optimization

The ETKDG\textsuperscript{7} method in RDKit version 2019.09.3 and the Gen3D\textsuperscript{6} method in Open Babel version 3.0.0 have been used to generate 3D structures from SMILES. As a baseline, B3LYP/6-31G(2df,p) structures of the constitutional isomers and MP2/6-311G(d) E2/S\textsubscript{N}2 reactants have been optimized with UFF\textsuperscript{68}, MMFF\textsuperscript{69–75}, GFN2-xtB\textsuperscript{20} and PMG\textsuperscript{21}, respectively (see Supplementary Table 1). Structure relaxations at the B3LYP/6-31G(2df,p) or MP2/6-311G(d) level of theory have been performed using ORCA version 4.0.\textsuperscript{76,77} PM3 and PM6 calculations have been performed using MOPAC2016\textsuperscript{78}. If not stated otherwise, no further geometry relaxation with any of the methods has been performed after structures have been generated.

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AUTHOR CONTRIBUTIONS

DL acquired data and wrote new software used in the work. DL, GvR and AvL conceived and planned the project, analyzed and interpreted the results and wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY

The QM9 constitutional isomer data used in this study is available in the QM9 database at https://dx.doi.org/10.6084/m9.figshare.c.978904.v5. The QMSpin and QMrxn databases used in this study are available in the materialscloud database at https://dx.doi.org/10.24435/materialscloud:2020.0051/v1 and https://dx.doi.org/10.24435/materialscloud:sf-tz, respectively. The elpasolite dataset used in this study is available as part of the supplemental information at https://dx.doi.org/10.1103/PhysRevLett.117.135502.

CODE AVAILABILITY

A static implementation of Graph-To-Structure is available at https://dx.doi.org/10.5281/zenodo.4792292. The distance geometry solver DGSOl is available at https://www.mcs.anl.gov/~more/dgsol/.
Neural Information Processing Systems 6 (J. D. Cowan, G. Tesauro, and J. Alspector, eds.), pp. 327–334, Morgan-Kaufmann, 1994.

P. Pyykkö and M. Atsumi, “Molecular Single-Bond Covalent Radii for Elements 1–118,” Chemistry – A European Journal, vol. 15, pp. 186–197, Jan. 2009. Publisher: John Wiley & Sons, Ltd.

P. Pyykkö and M. Atsumi, “Molecular Double-Bond Covalent Radii for Elements Li–E112,” Chemistry – A European Journal, vol. 15, pp. 12770–12779, Nov. 2009. Publisher: John Wiley & Sons, Ltd.

P. Pyykkö, S. Riedel, and M. Patzschke, “Triple-Bond Covalent Radii,” Chemistry – A European Journal, vol. 11, pp. 3511–3520, June 2005. Publisher: John Wiley & Sons, Ltd.

F. A. Faber, A. Lindmaa, O. A. von Lilienfeld, and R. Armiento, “Machine Learning Energies of 2 Million Elpasolite S(AB(C))_2[DB]_6[S-crys-
tals,” Physical Review Letters, vol. 117, p. 135502, Sept. 2016. Publisher: American Physical Society.

J. Schmidt, J. Shi, P. Borlido, L. Chen, S. Botti, and M. A. Marques, “Predicting the thermodynamic stability of solids combining density functional theory and machine learning,” Chemistry of Materials, vol. 29, no. 12, pp. 5090–5103, 2017.

G. F. v. Rudorff and O. A. v. Lilienfeld, “Rapid and accurate de-
protonation energies from quantum alchemy,” Physical Chemistry Chemical Physics, vol. 22, no. 19, pp. 10519–10525, 2020. Publisher: Royal Society of Chemistry.

L. Li, V. G. Levy, and M. A. Marques, “Coulomb distance geometry and applications,” arXiv:1205.0349 [q-bio], May 2012. arXiv: 1205.0349.

V. I. Lebedev, “Quadratures on a sphere,” USSR Computational Mathematics and Mathematical Physics, vol. 16, pp. 10–24, Jan. 1976.

A. D. Becke, “Density-functional thermochemistry. III. The role of exact exchange,” The Journal of Chemical Physics, vol. 98, pp. 5648–5652, Apr. 1993. Publisher: American Institute of Physics.

C. Lee, W. Yang, and R. G. Parr, “Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density,” Physical Review B, vol. 37, pp. 785–789, Jan. 1988. Publisher: American Physical Society.

P. J. Stephens, F. J. Devlin, C. F. Chabalowski, and M. J. Frisch, “Ab Initio Calculation of Vibration Absorption and Circular Dichroism Spectra Using Density Functional Force Fields,” The Journal of Chemical Physics, vol. 98, pp. 11623–11627, Nov. 1994. Publisher: American Chemical Society.

R. Ditchfield, W. J. Hehre, and J. A. Pople, “Self-Consistent Molecular-Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules,” The Journal of Chemical Physics, vol. 54, pp. 724–728, Jan. 1971. Publisher: American Institute of Physics.

W. J. Hehre, R. Ditchfield, and J. A. Pople, “Self—Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian—Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules,” The Journal of Chemical Physics, vol. 56, pp. 2257–2261, Mar. 1972. Publisher: American Institute of Physics.

P. C. Hariharan and J. A. Pople, “The influence of polarization functions on molecular hydrogenation energies,” Theoretica chimica acta, vol. 28, pp. 213–222, Sept. 1973.

M. Schwilk, D. N. Tahchivea, and O. A. von Lilienfeld, “Large yet bounded: Spin gap ranges in carbenes,” arXiv:2004.10600 [physics], Apr. 2020. arXiv: 2004.10600.

H. Werner and P. J. Knowles, “A second order multiconfiguration SCF procedure with optimum convergence,” The Journal of Chemical Physics, vol. 82, pp. 5053–5063, June 1985. Publisher: American Institute of Physics.

D. A. Kreplin, P. J. Knowles, and H.-J. Werner, “Second-order MCSCF optimization revisited. I. Improved algorithms for fast and robust second-order CASSCF convergence,” The Journal of Chemical Physics, vol. 150, p. 194106, May 2019. Publisher: American Institute of Physics.

T. Busch, A. D. Esposti, and H. Werner, “Analytical energy gradients for multiconfiguration self-consistent field wave functions with frozen core or-
bitals,” The Journal of Chemical Physics, vol. 94, pp. 6708–6715, May 1991. Publisher: American Institute of Physics.

K. A. Peterson, T. B. Adler, and H.-J. Werner, “Systematically convergent basis sets for explicitly correlated wavefunctions: The atoms H, He, B–Ne, and Al–Ar,” The Journal of Chemical Physics, vol. 128, p. 084102, Feb. 2008. Publisher: American Institute of Physics.

M. J. Frisch, J. A. Pople, and J. S. Binkley, “Self-consistent molecular or-
bitals methods 25. Supplementary functions for Gaussian basis sets,” The Journal of Chemical Physics, vol. 80, pp. 3265–3269, Apr. 1984. Publisher: American Institute of Physics.

L. A. Curtis, M. P. McGrath, J. Blaudeau, N. E. Davis, R. C. Binning, and L. Radom, “Extension of Gaussian-2 theory to molecules containing third-
row atoms Ga–Kr,” The Journal of Chemical Physics, vol. 103, pp. 6104–6113, Oct. 1995. Publisher: American Institute of Physics.

A. D. McLean and G. S. Chandler, “Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, Z=11–18,” The Journal of Chemical Physics, vol. 72, pp. 5639–5648, May 1980. Publisher: American Institute of Physics.

R. Krishnan, J. S. Binkley, R. Seeger, and J. A. Pople, “Self-consistent molecular orbital methods. XX. A basis set for correlated wavefunctions,” The Journal of Chemical Physics, vol. 72, pp. 650–654, Jan. 1980. Publisher: American Institute of Physics.

T. Clark, J. Chandrasekhar, G. W. Spitznagel, and P. V. R. Schleyer, “Effi-
cient diffuse function-augmented basis sets for anion calculations. II. The 3-21+G basis set for first-row elements, Li–F,” Journal of Computational Chemistry, vol. 4, pp. 294–301, Sept. 1983. Publisher: John Wiley & Sons, Ltd.

F. E. Blöchl, “Projector augmented-wave method,” Physical Review B, vol. 50, pp. 17953–17979, Dec. 1994. Publisher: American Physical Society.

G. Kresse and D. Joubert, “From ultrasoft pseudopotentials to the projector augmented-wave method,” Physical Review B, vol. 59, pp. 1758–1775, Jan. 1999. Publisher: American Physical Society.

A. K. Rappe, C. J. Casewit, K. S. Colwell, W. A. Goddard, and W. M. Skiff, “UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations,” Journal of the American Chemical Society, vol. 114, pp. 10024–10035, Dec. 1992. Publisher: American Chemical Society.

T. A. Halgren and R. B. Nachbar, “Merck molecular force field. IV. Confor-
national energies and geometries for MMFF94,” Journal of Computational Chemistry, vol. 17, no. 5-6, pp. 587–615, 1996.

T. A. Halgren, “Merck molecular force field. III. Molecular geometries and vibrational frequencies for MMFF94,” Journal of Computational Chemistry, vol. 17, no. 5-6, pp. 553–586, 1996.

T. A. Halgren, “Merck molecular force field. II. MMFF94 van der Waals and electrostatic parameters for intermolecular interactions,” Journal of Computational Chemistry, vol. 17, no. 5-6, pp. 520–552, 1996.

T. A. Halgren, “Merck molecular force field. I. Basis, form, scope, pa-
rameterization, and performance of MMFF94,” Journal of Computational Chemistry, vol. 17, no. 5-6, pp. 490–519, 1996.

T. A. Halgren, “Merck molecular force field. V. Extension of MMFF94 us-
ing experimental data, additional computational data, and empirical rules,” Journal of Computational Chemistry, vol. 17, no. 5-6, pp. 616–641, 1996.

T. A. Halgren, “MMFF VI. MMFF94s option for energy minimization stud-
ies,” Journal of Computational Chemistry, vol. 20, no. 7, pp. 720–729, 1999.

T. A. Halgren, “MMFF VII. Characterization of MMFF94, MMFF94s, and other widely available force fields for conformational energies and for intermolecular-interaction energies and geometries,” Journal of Compu-
tational Chemistry, vol. 20, no. 7, pp. 730–748, 1999.

F. Neese, “The ORCA program system,” WIREs Computational Mol-
ecular Science, vol. 2, no. 1, pp. 73–78, 2012. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/wcms.81.

F. Neese, “Software update: the ORCA program system, version 4.0,” WIREs Computational Molecular Science, vol. 8, no. 1, p. e1327, 2018. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/wcms.1327.

J. P. Stewart, “Mopac2016, stewart computational chemistry, colorado springs, co, usa,” 2016.
Supplementary Material

I. SUPPLEMENTARY METHODS

A. Bond Length based Representations

To construct representations from a molecular graph that rely on bond lengths, covalent atomic radii are required for each type of bond (single, double, triple). Using the atomic radii as weights, the bond length distance or shortest path $l_{ij}$ between two atoms $i$ and $j$ in a graph is calculated using Dijkstra’s algorithm as implemented in igraph. Calculating the bond length distances for all atom pairs in a molecule results in a representation of the following form:

$$\text{Bond Length}_{ij} = \begin{cases} 0, & i = j, \\ l_{ij}, & i \neq j. \end{cases}$$ (1)

with $l_{ij}$ being the bond length distance/shortest path between the atoms $i$ and $j$. To include more physics, the bond length distance can be used to approximate 2-body interactions that are commonly used in QML representations such as the Coulomb Matrix (CM) or Bag-of-Bonds (BoB). The CM representation contains the coulomb interaction scaled by the interatomic distance as off-diagonal elements, while the diagonal represents an approximation to the atomic energy of the nuclear charge $Z_i$. This leads to a representation with the following form:

$$\text{CM}_{ij} = \begin{cases} 0.5Z_i^2, & i = j, \\ \frac{Z_iZ_j}{|\mathbf{R}_i - \mathbf{R}_j|}, & i \neq j. \end{cases}$$ (2)

with nuclear charge $Z$ and atomic coordinates $\mathbf{R}$. Since the atomic coordinates are not available for a structure prediction task, the representation has to be adapted for molecular graphs. The bond length distance approach described above suits as an approximation to the intermolecular distance and can therefore be used to adapt the off-diagonal term of the CM to work in a graph setting. The adapted representation, dubbed graph CM, has the following form:

$$\text{graph CM}_{ij} = \begin{cases} 0.5Z_i^2, & i = j, \\ \frac{Z_iZ_j}{l_{ij}}, & i \neq j. \end{cases}$$ (3)

with nuclear charge $Z$ and bond length distance $l_{ij}$. To convert the CM into a BoB representation, the CM has to be vectorized by grouping all matrix terms into specific bins. The thereby created canonical order (bag of bonds) ensures that during the kernel calculation only similar bins are compared. Each bin describes a particular bond type (H-H, C-C, C-H etc.). In this regard, the BoB and graph BoB representation use the same components as their respective matrix counterpart (CM and graph CM), but only differ through transforming the matrix into a canonical vector. Since the distance matrix is sorted based on the sorting of the representation, the distance matrix undergoes the same vectorization and binning procedure as the graph BoB representation.

B. Z-Matrix Learning

An alternative internal coordinate representation of atomistic structures is the so called Z-matrix. Instead of using pairwise distances, a Z-matrix contains information about bond distances, bond angles as well as dihedral angles. Conversion between a Z-matrix and Cartesian coordinates is possible. G2s has been used to predict bond distances, bond angles and dihedral angles,
respectively. Contrary to the distance matrix approach, the sorting of the representation was only dependent on the atom indices of the respective Z-matrix entry, making the machines independent of how the Z-matrix has been constructed. While bond distances and angles appear easier to learn, achieving remarkable accuracies of 0.01 Å MAE on distances and 2 degree MAE on bond angles, the learning of dihedral angles only achieved a MAE of 36 degree. The conversion from Z-matrix to a reasonable 3D geometry was not possible given these errors. It is worth to mention that the Z-matrix conversion suffers from error propagation, amplifying errors from atom to atom during the reconstruction. The distance geometry problem is superior in this regard since the compatibility of all distances is being optimized, leading to error cancellation instead of propagation.

C. Software

The Graph To Structure software is build upon Numpy\(^1\), Scipy\(^2\), Quadpy\(^3\), RDKit\(^4\) and igraph\(^5\). To extract adjacency matrices from xyz-files, the xyz2mol\(^6\)\(^,7\) package has been used. For high performance kernel ridge regression, the QML\(^8\) package was used. Visualizations have been created using Matplotlib\(^9\), Seaborn\(^10\) and VMD\(^11\).

II. SUPPLEMENTARY TABLES

Supplementary Table I. Baseline and test errors of structure generation methods. Errors are reported in terms of mean MAE of pairwise distances and RMSD for structures with (w) and without (w/o) hydrogen atoms, respectively. For the machine learning methods, the results of the largest training set size have been reported. 1) Errors towards a reference geometry, when the reference geometry has been optimized with one of the listed methods (UFF, MMFF, GFN2-xTB, PM6). 2) Structure generation with ETKDG from RDKit. Rows with UFF/MMFF have subsequently been optimized with either force field. 3) Structure generation with Gen3D from Open Babel with and without force field optimization. 4) Structure generation with G2S using the listed representations. 5) Hydrogen prediction with G2S.

|                      | C$_7$O$_2$H$_{10}$ |           | C$_7$NOH$_{11}$ | E2/S$_N$2 Reactants |
|----------------------|-------------------|-----------|-----------------|-------------------|
|                      | MAE [Å] | RMSD [Å] | MAE [Å] | RMSD [Å] | MAE [Å] | RMSD [Å] |
|                      | w   | w/o   | w   | w/o   | w   | w/o   | w | w/o   | w | w/o   | w | w/o   |
| UFF                  | 0.10 | 0.06  | 0.26 | 0.16  | 0.11 | 0.07  | 0.29 | 0.17  | 0.09 | 0.08  | 0.23 | 0.21  |
| 1) MMFF              | 0.07 | 0.05  | 0.19 | 0.13  | 0.08 | 0.05  | 0.21 | 0.14  | 0.09 | 0.08  | 0.26 | 0.22  |
| xTB                  | 0.04 | 0.02  | 0.09 | 0.06  | 0.19 | 0.15  | 0.22 | 0.13  | 0.09 | 0.08  | 0.28 | 0.22  |
| PM6                  | 0.06 | 0.04  | 0.15 | 0.09  | 0.06 | 0.05  | 0.14 | 0.09  | 0.12 | 0.13  | 0.38 | 0.29  |
| ETKDG                | 0.35 | 0.17  | 0.92 | 0.54  | 0.35 | 0.15  | 0.93 | 0.44  | 0.37 | 0.24  | 0.94 | 0.70  |
| 2) ETKDG UFF         | 0.32 | 0.14  | 0.90 | 0.50  | 0.33 | 0.12  | 0.87 | 0.40  | 0.36 | 0.23  | 0.90 | 0.69  |
| ETKDG MMFF           | 0.31 | 0.13  | 0.90 | 0.49  | 0.32 | 0.11  | 0.84 | 0.39  | 0.37 | 0.24  | 0.93 | 0.69  |
| 3) Gen3D              | 0.32 | 0.14  | 0.85 | 0.50  | 0.34 | 0.13  | 0.79 | 0.42  | 0.35 | 0.22  | 0.88 | 0.66  |
| Gen3D MMFF           | 0.32 | 0.14  | 0.85 | 0.50  | 0.34 | 0.13  | 0.79 | 0.42  | 0.35 | 0.22  | 0.88 | 0.66  |
| 4) Null              | 0.84 | 0.88  | 0.84 | 0.88  | 0.84 | 0.88  | 0.84 | 0.88  | 0.84 | 0.88  | 0.84 | 0.88  |
| Bond Order           | 0.41 | 0.17  | 0.98 | 0.48  | 0.51 | 0.24  | 1.02 | 0.60  | 0.31 | 0.22  | 0.76 | 0.51  |
| 4) Bond Hop          | 0.38 | 0.13  | 0.85 | 0.44  | 0.41 | 0.14  | 0.90 | 0.43  | 0.32 | 0.23  | 0.77 | 0.54  |
| Bond Length          | 0.38 | 0.13  | 0.87 | 0.46  | 0.41 | 0.12  | 0.91 | 0.42  | 0.26 | 0.21  | 0.69 | 0.41  |
| CM                   | 0.42 | 0.16  | 0.91 | 0.50  | 0.46 | 0.17  | 0.98 | 0.53  | 0.28 | 0.24  | 0.70 | 0.42  |
| BoB                  | 0.40 | 0.16  | 0.94 | 0.48  | 0.45 | 0.15  | 0.96 | 0.52  | 0.27 | 0.23  | 0.70 | 0.42  |
| 5) Null              | 0.17 | 0.17  | 0.17 | 0.17  | 0.17 | 0.17  | 0.17 | 0.17  | 0.17 | 0.17  | 0.17 | 0.17  |
| Bond Length          | 0.06 | 0.06  | 0.06 | 0.06  | 0.06 | 0.06  | 0.06 | 0.06  | 0.06 | 0.06  | 0.06 | 0.06  |
III. SUPPLEMENTARY FIGURES

Supplementary Figure 1. Systematic improvement of prediction accuracy of the Z-Matrix components atom distances, bond angles and dihedral angles for QM9 C\textsubscript{7}O\textsubscript{2}H\textsubscript{11} constitutional isomer set using the bond length representation.
Supplementary Figure 2. Learning curves showing the MAE of pairwise distances of hydrogens to the closest four heavy atom neighbors. The null model represents the baseline accuracy calculated using the average pairwise distances in a dataset as a predictor.
Supplementary Figure 3. Learning curves of the QM9 constitutional isomers showing the MAE of pairwise distances of heavy atoms with increasing training set sizes $N$. The null model represents the baseline accuracy calculated using the average pairwise distances in a dataset as a predictor. (a) MAE before 3D reconstruction. (b) MAE after 3D reconstruction. (c) MAE between the distances before and after reconstruction.
Supplementary Figure 4. Learning curves of the QMSpin carbene dataset showing the MAE of pairwise distances of heavy atoms with increasing training set sizes $N$. The null model represents the baseline accuracy calculated using the average pairwise distances in a dataset as a predictor. (a) MAE before 3D reconstruction. (b) MAE after 3D reconstruction. (c) MAE between the distances before and after reconstruction.
Supplementary Figure 5. Learning curves of QMrxn20 E2/SN2 transition states showing the MAE of pairwise distances of heavy atoms with increasing training set sizes $N$. The null model represents the baseline accuracy calculated using the average pairwise distances in a dataset as a predictor. (a) MAE before 3D reconstruction. (b) MAE after 3D reconstruction. (c) MAE between the distances before and after reconstruction.
Supplementary Figure 6. Learning curves of elpasolite crystals showing the MAE of pairwise fractional distances of atoms with increasing training set sizes $N$. The null model represents the baseline accuracy calculated using the average pairwise distances in a dataset as a predictor. (a) MAE before 3D reconstruction. (b) MAE after 3D reconstruction. (c) MAE between the distances before and after reconstruction.
Supplementary Figure 7. 30 exemplary 2D structures of uncharacterized QM9 molecules which after structure generation with G2S that dissociated during geometry optimization at B3LYP/6-31G(2df,p) level of theory.
Supplementary Figure 8. Systematic improvement of energy prediction accuracy with increasing training data using G2S predictions (blue) as well as DFT structures (orange) and ETKDG/UFF structures (red) as an input to QML models. (a) and (b) atomization energy prediction of C$_7$O$_2$H$_{10}$ and C$_7$NOH$_{11}$ constitutional isomers, respectively. (c) Prediction of formation energies of elpasolite crystals. (d) Speedup estimate of a G2S (blue) or ETKDG/UFF (red) based QML model over a DFT dependent QML model. This assumes an average of 16 DFT optimization steps required before a structure can be used in QML.
IV. SUPPLEMENTARY REFERENCES

1. C. R. Harris, K. J. Millman, S. J. van der Walt, R. Gommers, P. Virtanen, D. Cournapeau, E. Wieser, J. Taylor, S. Berg, N. J. Smith, R. Kern, M. Picus, S. Hoyer, M. H. van Kerkwijk, M. Brett, A. Haldane, J. F. del Rio, M. Wiebe, P. Peterson, P. Gérard-Marchant, K. Sheppard, T. Reddy, W. Weckesser, H. Abbasi, C. Gohlke, and T. E. Oliphant, “Array programming with NumPy,” Nature, vol. 585, pp. 357–362, Sept. 2020. Number: 7825 Publisher: Nature Publishing Group.

2. P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, S. J. van der Walt, M. Brett, J. Wilson, K. J. Millman, N. Mayorov, A. R. J. Nelson, E. Jones, R. Kern, E. Larson, C. J. Carey, I. Polat, Y. Feng, E. W. Moore, J. VanderPlas, D. Laxalde, J. Perktold, R. Cimrman, I. Henriksen, E. A. Quintero, C. R. Harris, A. M. Archibald, A. H. Ribeiro, F. Pedregosa, P. van Mulbregt, and SciPy 1.0 Contributors, “SciPy 1.0: Fundamental Algorithms for Scientific Computing in Python,” Nature Methods, vol. 17, pp. 261–272, 2020.

3. N. Schlömer, N. Papior, D. Arnold, M. Ancellin, and R. Zetter, “nschloe/quadpy v0.16.5,” Dec. 2020.

4. RDKit: Open-source cheminformatics http://www.rdkit.org/.

5. G. Csardi and T. Nepusz, “The igraph software package for complex network research,” InterJournal, vol. Complex Systems, p. 1695, 2006.

6. J. C. Kromann and J. H. Jensen, “Convert cartesian coordinates to one or more molecular graphs,” Github, 2021. https://github.com/jensengroup/xyz2mol.

7. Y. Kim and W. Y. Kim, “Universal structure conversion method for organic molecules: From atomic connectivity to three-dimensional geometry,” Bulletin of the Korean Chemical Society, vol. 36, pp. 1769–1777, June 2015.

8. A. S. Christensen, F. A. Faber, B. Huang, L. A. Bratholm, A. Tkatchenko, K.-R. Müller, and O. A. v. Lilienfeld, “QML: A Python Toolkit for Quantum Machine Learning” https://github.com/qmllcode/qml,” 2017.

9. J. D. Hunter, “Matplotlib: A 2D Graphics Environment,” Computing in Science Engineering, vol. 9, pp. 90–95, May 2007. Conference Name: Computing in Science Engineering.

10. M. Waskom and t. s. d. team, “mwaskom/seaborn,” Sept. 2020.

11. W. Humphrey, A. Dalke, and K. Schulten, “VMD: Visual molecular dynamics,” Journal of Molecular Graphics, vol. 14, pp. 33–38, Feb. 1996.