3DMolNet: A Generative Network for Molecular Structures

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Abstract
With the recent advances in machine learning for quantum chemistry, it is now possible to predict the chemical properties of compounds and to generate novel molecules. Existing generative models mostly use a string- or graph-based representation, but the precise three-dimensional coordinates of the atoms are usually not encoded. First attempts in this direction have been proposed, where autoregressive or GAN-based models generate atom coordinates. Those either lack a latent space in the autoregressive setting, such that a smooth exploration of the compound space is not possible, or cannot generalize to varying chemical compositions. We propose a new approach to efficiently generate molecular structures that are not restricted to a fixed size or composition. Our model is based on the variational autoencoder which learns a translation-, rotation-, and permutation-invariant low-dimensional representation of molecules. Our experiments yield a mean reconstruction error below 0.05 Å, outperforming the current state-of-the-art methods by a factor of four, and which is even lower than the spatial quantization error of most chemical descriptors. The compositional and structural validity of newly generated molecules has been confirmed by quantum chemical methods in a set of experiments.

Introduction
An exploration of the chemical compound space (CCS) is essential in the design process of new materials. Considering that the amount of small organic molecules is in the magnitude of $10^{60}$ (Kenakin 2006), a systematic coverage of molecules in a combinatorial manner is intractable. Furthermore, a precise approximation of quantum chemical properties by solving the Schrödinger’s equation is computationally demanding even for a tiny amount of mid-sized molecules. In recent years, an entirely new research field emerged, aiming a statistical approach by training regression models for quantum chemical property prediction to overcome computational drawbacks (Schütt et al. 2018; Faber et al. 2017; Christensen, Faber, and von Lilienfeld 2019). More recently, deep latent variable models have been introduced to solve the inverse problem and to generate novel molecules. Here, the major focus of the research community is on deep latent variable models that use either string- or

graph-based molecular representations (Gomez-Bombarelli et al. 2018; Kusner, Paige, and Hernández-Lobato 2017; Jin, Barzilay, and Jaakkola 2018; Janz et al. 2018). The precise spatial configuration of the molecules is usually not enclosed. This leads to various drawbacks, for instance, molecules which have the same chemical composition but different geometries, a so called isomers, cannot be distinguished. Furthermore, a targeted exploration of the CCS with respect to quantum chemical property is rather poor and with respect to geometries it is impossible.

To account for this challenges, Gebauer, Gastegger, and Schütt proposed G-SchNet (Gebauer, Gastegger, and Schütt 2019), an autoregressive model for generation of atom types and corresponding 3-d points. The rotation- and translation-
invariances are achieved by using Euclidean distances between atoms. The permutation-invariant features are extracted with continuous-filter convolutions (Schütt et al. 2018). Due to the autoregressive nature of the model, it has no continuous latent space representation for smooth exploration of the CCS. Furthermore, the probability for completion of complex structures decays with the amount of sampling steps. Hoffmann and Noé introduced EDMNet that generates Euclidean distance matrices (EDM) in a one-shot fashion, which can be further transformed into actual coordinates. For generation of the EDMs a GAN architecture (Goodfellow et al. 2014) is used, while the critic network is based on the SchNet architecture (Schütt et al. 2018). This approach, however, is limited to a fixed chemical composition to circumvent the permutation problem. In addition, GANs are frequently difficult to train. A smooth exploration of the nearby areas in the latent space is not possible as well.

In order to overcome the aforementioned limitations, we propose the 3DMolNet, a generative network for 3-d molecular structures. A graphical sketch of our approach is illustrated in Figure 1. The molecule representation consists of two core components, a nuclear charge matrix and an EDM. Since some bond types have high variances in the bond lengths, an exact assignment of bond types often cannot be derived from the distances. For this reason, we additionally include an explicit bond matrix to our representation. To overcome the permutation problem, we use an InChI-based canonical ordering of the atoms.

Due to the absence of canonical identifiers for most of the hydrogen atoms, we involve only heavy atoms in our representation. This is however not problematic, since the backbone of a molecule is the most important part. The hydrogens are explicitly defined if the core structure of a molecule is known. A quantum mechanical approximation of the hydrogen coordinates is computationally an easy optimization task. This is because, given a fixed core structure, a many-body problem has a significantly smaller degree of freedom. Additionally, the positions of the hydrogen atoms are entirely determined only if the stereospecificity is defined.

Our model is based on the Variational autoencoder (Kingma and Welling 2014) and conditional image generation (Sohn, Lee, and Yan 2015). An important line of research are VAEs for disentangled representation learning (Goodfellow et al. 2014) and conditional image generation (Sohn, Lee, and Yan 2015). An important line of research are VAEs for disentangled representation learning (Goodfellow et al. 2014) and conditional image generation (Sohn, Lee, and Yan 2015). An important line of research are VAEs for disentangled representation learning (Goodfellow et al. 2014) and conditional image generation (Sohn, Lee, and Yan 2015).

In summary, the main contributions of this work are:

1. We introduce a translation-, rotation-, and permutation-invariant molecule representation. To overcome the permutation problem a canonical ordering of the atoms is used.
2. We propose a VAE-based model to learn a continuous low-dimensional representation of the molecules and to generate 3-d molecular structures in a one-shot fashion.
3. We demonstrate on the QM9 dataset that the proposed model is able to reconstruct almost all chemical compositions with up to 9 heavy atoms. The reconstruction of coordinates for heavy atoms yields a RMSD below 0.05 Å, outperforming the state-of-the-art method by almost a factor of four.

Related Work

Variational Autoencoder. In recent years, the Variational autoencoder (VAE) (Kingma and Welling 2014) became an important tool for various machine learning tasks such as semi-supervised learning (Kingma et al. 2014) and conditional image generation (Sohn, Lee, and Yan 2015). An important line of research are VAEs for disentangled representation learning (Bouchacourt, Tomioka, and Nowozin 2018; Klys, Snell, and Zemel 2018; Lample et al. 2017; Creswell et al. 2017). More recently, variational autoencoders have shown strong connections to the information bottleneck principle (Tishby, Pereira, and Bialek 1999; Alemi et al. 2017; Achille and Soatto 2018), where multiple model extensions have been proposed in the context of sparsity (Wieser et al. 2020), causality (Parbhoo et al. 2020a), archetypal analysis (Keller et al. 2019, 2020) or invariant subspace learning (Wieser et al. 2020).

Graph-based Deep Generative Models. Deep generative models are heavily used in the context of computational chemistry to generate novel molecular structures based on graph representations. With a text-based graph representation, a SMILES string, (Gomez-Bombarelli et al. 2018) introduced a chemical VAE to generate novel molecules. However, this method has limitations in generating syntactically correct SMILES strings. Several methods have been proposed to overcome this drawback (Kusner, Paige, and Hernández-Lobato 2017; Dai et al. 2018; Janz et al. 2018).

Another line of research deals with explicit graph-based molecular descriptors. Liu et al. introduce a constrained graph VAE to generate valid molecular structures. Subsequently, improved approaches has been introduced by Jin, Barzilay, and Jaakkola (2018; Jin et al. 2019; Li et al. 2018).

Coordinate-based Deep Generative Models. More recently, deep generative models for spatial structures has been proposed to overcome the limitations of graph-based descriptors. Such representations do not take into account precise three-dimensional configurations of the atoms. Manzimov et al. estimated the 3-d configurations of molecules from molecular graphs. Hoffmann and Noé learned the distribution of spatial structures by generating translation- and rotation-invariant Euclidean distance matrices. However, their approach is limited to molecules with the same chemical composition. Current state-of-the-art results are provided by the G-SchNet (Gebauer, Gastegger, and Schütt 2019), which is based on an autoregressive model which, however, is lacking a latent representation of molecules and is inefficient and error-prone when sampling complex and large structures.
Preliminaries

Variational Autoencoder

The Variational autoencoder (VAE) (Kingma and Welling 2014) is a deep latent variable model that combines a generative process (decoder) with a variational inference (encoder) to learn a probabilistic model. The encoder models a posterior distribution $q(z | x)$, where we assume a Gaussian distribution parametrized with $\mu_z$ and $\sigma_z$ and the decoder models the generative distribution $p(x | z)$. In order to learn the probabilistic model, we optimize the following lower bound:

$$
L_{VAE} \geq \mathbb{E}_{z \sim q(z|x)}[\log p(x | z)] - D_{K L}[q(z | x) || p(z)].
$$

Due to the deterministic nature of neural networks, the random variable $Z$ is reparametrized as $z = \mu_z + \sigma_z \epsilon$ where $\epsilon \sim \mathcal{N}(0, 1)$.

Quantum-mechanical Background

A molecule as a quantum-mechanical system is fully described by the Schrödinger’s (SE) equation. It is sufficient to consider a non-relativistic and time-independent formulation $H\Psi = E\Psi$. With an additional elimination of the external electromagnetic field, the Hamiltonian $H$ is determined by the external potential $V$ and the nuclear Coulomb repulsion energy:

$$
v(r) = \sum_i Z_i / |r - R_i|,
$$

where $Z \in \mathbb{N}^N$ is a set of nuclear charges, $R \in \mathbb{R}^{N \times 3}$ are the corresponding atomic positions, and $r \in \mathbb{R}^{M \times 3}$ are stationary electronic states. The interatomic energy contributions result from the solution of the full electronic many-body problem and the nuclear Coulomb repulsion energy:

$$
Z_i Z_j / |R_i - R_j|.
$$

Neglecting the former, a physical system depends only on a set of nuclear charge numbers and the corresponding atom coordinates in a three-dimensional space.

Methods

The goal of our learning framework is to capture the distribution of the molecular structures, which are expressed in terms of chemical compositions and geometries. To overcome the permutation problem, we use a canonical ordering of the atoms. In our approach we exclude the hydrogen atoms from the representation, since those can be easily added and the coordinates can be cheaply optimized with quantum-mechanical calculations. Our model involves a VAE-based architecture for smooth exploration of the chemical space. To enforce the quality of the generated EDMs, additional geometry loss terms are added. The molecular core structure is reconstructed from the estimated representation components. The entire molecule is recovered in the post processing steps.

Representation

A physical many-body system depends only on a set of nuclear charge numbers $Z_i \in \mathbb{N}$ and corresponding $R_i \in \mathbb{R}^3$ coordinates. Our molecule representation involves this information with a nuclear charge matrix $C \in \mathbb{R}^{N \times N}$ and an Euclidean distance matrix $D \in \mathbb{R}^{N \times N}$. Additionally, a bond matrix $B \in \mathbb{R}^{M \times 3}$ is included to encode explicit bond types. We define the nuclear charge matrix as follows:

$$
C_{ij} = Z_i Z_j^T.
$$

The distances matrix is defined with

$$
D_{ij} = \| R_i - R_j \|^2.
$$

The bond matrix $B$ includes indices of connected atoms in the first and the second columns. The third column contains bond type values. Although the bond matrix could be extracted from the distances, the variance of the bond lengths relatively high for some bond types, such that an assignment from the distances is often ambiguous. To handle molecules of different sizes, the charge, distance, and bond matrices are padded with zero rows and or columns to a fixed size. The final molecule representation is a set of the three components:

$$
X = \{C, D, B\}.
$$

Canonical Identifier

A major obstacle for a learning algorithm is an arbitrary atom ordering. To overcome this problem we generate a unique atom ordering for molecules. There exist different canonicalization algorithms. We get the canonical identifiers (CIs) with an InChI-based algorithm implemented in the CDK package (Steinbeck et al. 2003). The generation of CIs involves a structure normalization, an InChI-based canonical labelling, and a tree traversal (O’Boyle 2012). With this method, we get CIs for each heavy atom and only for explicit hydrogen atoms. Those are isolated isotops, dihydrogen and hydrogen ions, and hydrogen atoms attached to tetrahedral stereocentres with defined stereochemistry. Due to the absence of canonical labels for most of the hydrogen atoms, our representation involves only heavy atoms.

Model

As previously stated, our aim is to generate novel molecular compositions and corresponding 3-d structures (see Figure 1). Therefore, we want to learn both, a low-dimensional and a rotation-, translation-, and permutation-invariant representation of molecules (see Figure 2). To do so, we reformulate the standard VAE framework (Equation 1) by defining each representation component $C$, $D$, and $B$ in a form of independent random variables. This leads to an extended parametric formulation given with:

$$
L_{VAE} \geq \mathbb{E}_{z \sim q(z|c,d,b)}[\log p(c,d,b | z)] - \beta D_{K L}[q(z | c, d, b) || p(z)].
$$
Figure 2: An illustration of the 3DMolNet framework. In the preprocessing step, we apply a canonical ordering and remove all hydrogen atoms. We then get the representation \( X \) as a concatenation of the nuclear charge \( C \), the euclidean distance \( D \), and the bond \( B \) matrices. Subsequently, we map \( X \) into a low-dimensional latent representation \( Z \) using an encoder neural network which is parametrized with \( \phi \). Here, \((x)\) denotes the mean and the surrounding circle the variance of our estimate. To decode a molecule, we use three separate neural networks parametrized with \( \psi, \tau \), and \( \theta \) which decode representation components \( C \), \( D \), and \( B \) separately. In the post processing step, we recover the chemical and structural composition of the heavy atoms with a multidimensional scaling algorithm and add hydrogen atoms with Open Babel (O’Boyle et al. 2011) and fine-tune the coordinates with MOPAC (Stewart 2016) while fixing the positions of heavy atoms.

**Encoder.** The encoder is defined as the KL-divergence between the posterior \( q_{\phi}(z \mid c, d, b) \) and the prior \( p(z) \) and is denoted as:

\[
D_{\text{KL}}[q_{\phi}(z \mid c, d, b) \mid \mid p(z)],
\]

where \( \phi \) are the neural network parameters. We define the posterior as a Gaussian distribution and assume a Gaussian prior \( p(z) = \mathcal{N}(0, I) \).

**Decoder.** The decoder is defined as the the negative log-likelihood of \( p(c, d, b \mid z) \). As we assume conditional independence between \( c, d, \) and \( b \) we can express the joint distribution as follows:

\[
\mathbb{E}_{z \sim q(z \mid c, d, b)}[p(c, d, b \mid z)] = \mathbb{E}_{z \sim q(z \mid c, d, b)}[p_\phi(c \mid z)] \cdot p_\tau(d \mid z) \cdot p_\psi(b \mid z)],
\]

where \( \phi, \tau \) and \( \theta \) denote neural network parameters of each respective decoder. We define each log-likelihood term to be the mean-absolute-error between a particular representation component and the reconstructed counterpart.

**Geometry Loss.** To further improve the quality of the EDM reconstruction, we additionally penalize the negative eigenvalues and the rank of the Gram matrix. To do so, we first define the geometric centering matrix

\[
J = I - \frac{1}{N} 11^T,
\]

where \( I \) is the identity matrix and \( 1 \) is the all-ones vector. The Gram matrix is defined with

\[
G = -\frac{1}{2}JDJJ.
\]

The matrix \( D \) is an EDM, if the Gram matrix \( G \) is positive semi-definite. To enforce this property we penalize negative eigenvalues of the Gram matrix \( G \). Therefore, we first get eigenvalues \( \lambda \) with the eigenvalue decomposition of \( G \). We then apply the ReLU function to the negative of the eigenvalues \( \bar{\lambda} = \text{ReLU}(-\lambda) \). The corresponding loss term is defined as follows:

\[
L_{\text{EV}} = \bar{\lambda}^\top \bar{\lambda}.
\]

Since the atom coordinates exists in a maximally 3-dimensional embedding, we additionally penalize larger than \( k = 3 \) rank of the Gram matrix \( G \). For this, we sort the eigenvalues in descending order \( \lambda = [\lambda_1 \leq \lambda_2 \leq \ldots \lambda_N] \). The rank loss is obtained with

\[
L_{\text{R}} = \sum_{i=k+1}^{N} \lambda_i^2.
\]

**Overall Training Objective.** The total loss function is given with:

\[
L_{\text{total}} = L_{\text{VAE}} + L_{\text{EV}} + L_{\text{R}}.
\]
charge matrix $C$ and the distance matrix $D$. The diagonal of the distance matrix $D$ is set to zero. The reconstructed floating point values of the bond matrix $B$ are rounded to integer values. Subsequently, we recover a set of the nuclear charge numbers and the corresponding coordinates $\{Z_i, R_i\}$. To do so, we use the classical multidimensional scaling algorithm. We then use Open Babel to read-in the molecular structure by setting types and coordinates of the atoms and assign bonds and corresponding bond types. Lastly, we reconstruct a complete molecule by adding hydrogen atoms with Open Babel. To get initial positions of hydrogen atoms we use an efficient force-field method with Open Babel (O’Boyle et al. 2011) and fine-tune by using a semi-empirical ab initio approximation with MOPAC (Stewart 2016).

Since the ordering of the added hydrogen atoms differ from the ordering in the initial molecule, the best matching identity assignment has to be found in order to meaningfully calculate the deviation of the structures. Given the coordinates of the added and the target hydrogen atoms, we use the Hungarian algorithm (Kuhn 1955) to minimize the assignment costs.

### Experiments and Discussion

#### Dataset

For our experiments, we use the QM9 dataset (Ramakrishnan et al. 2014), which includes 133,885 small organic molecules and consist of up to nine heavy atoms (C, O, N, and F). Each molecule has geometric, energetic, electronic, and thermodynamic properties obtained from the Density Functional Theory (DFT) calculations. The chemical space of QM9 is based on the GDB-17 dataset (Ruddigkeit et al. 2012), enumerating more than 166 billion molecules of up to 17 heavy atoms. GDB-17 is systematically generated based on the molecular connectivity graphs and approaches a complete and unbiased enumeration of the chemical compound space of small and stable organic molecules. However, the molecules are generated based on a set of fixed rules, those does not cover all valid molecular structures which could be uncovered with deep generative models.

#### Experimental Setup

We train the 3DMolNet on a set of 50K randomly selected molecules from the QM9 dataset. For validation 5K molecules are randomly selected. The remaining molecules are used for evaluation as a test set. We use Open Babel for validity check of the valences. We also remove molecules from the QM9 dataset which are inconsistent in terms of the provided bonds in the SMILES representation of the molecule and bonds assigned by Open Babel. To compare molecular geometries, we apply Procrustes analysis and calculate the root-mean-square-deviation (RMSD) of pairwise atomic coordinates between generated and ground truth structures. To compare with G-SchNet, we used code and a trained model provided under a published source.

#### Architecture

3DMolNet is based on a classical variational autoencoder architecture. It consists of a single encoder and three decoder networks for generation of the nuclear charge matrix $C$, the distance matrix $D$, and the bond matrix $B$. The encoder and each decoder have a standard fully connected architecture. The latent space is set to 64 dimensions. The compression parameter $\beta$ is reduced after each epoch.

| Model       | Reconstruction Accuracy |
|-------------|-------------------------|
| heavy       | all                     |
| Mansimov    | -                       | 0.37                     |
| G-SchNet    | 0.18                    | 0.21                     |
| 3DMolNet    | **0.05**                | **0.16**                |

#### Reconstruction Accuracy

In order to judge about the quality of the 3DMolNet, we evaluate the reconstruction accuracy of the nuclear charge numbers, the atom coordinates, and the bond matrix. Our experiments show that the chemical compositions are exactly reconstructed in more than 99 % of the cases. The bond matrix is exactly reconstructed in 98 % of the cases. To evaluate the reconstructed geometries, we only accept molecules with exactly reconstructed atoms, bonds, and bond types. The reconstruction of heavy atom coordinates yields a RMSD of 0.048 Å. By using a force-field for optimization of the coordinates of the hydrogen atoms, a RMSD of 0.21 Å is achieved. Applying a further optimization step by using a semi-empirical ab initio method, the RMSD drops to 0.16 Å (see Table 1).

To compare with G-SchNet we first investigate the reconstruction accuracy of the chemical compositions. According to our experiments, the chemical compositions are exactly reconstructed in only 19 % of the cases. Even though this result is obtained with teacher forcing as a one-step-ahead prediction, it still significantly lacks behind our accuracy rates. According to published numbers, G-SchNet yields a RMSD of 0.18 Å for the reconstruction of heavy atom coordinates. This is roughly four times as high compared to our results. By including the hydrogen atoms, G-SchNet achieves a RMSD of 0.23 Å however using a fast force-field solution for optimizing hydrogen coordinates, we achieve comparable results. By using a more precise approximation, our method clearly outperforms G-SchNet.

A comparison with EDMNet in terms of the reconstruction accuracy of the coordinates cannot be directly done, due to the nature of the chosen GAN-based architecture. Beyond that, a fair comparison is not possible anyway, since the EDMNet is trained only on a sub set of molecules of the same chemical composition.
Interpolation between Molecules

An important and useful property of our model is a continuous and smooth latent space, which allows a gradual exploration of the nearby chemical compositions and structures. In a row of experiments, we evaluate and discuss the outcomes of an interpolation between molecular domains. Our start and target molecules are chosen from the test set. To estimate the quality of the sampled structures, we additionally relax the entire geometry of the molecules in each interpolation step.

In general, we could observe smooth transitions between molecular structures and chemical compositions, meaning that structure- and composition-related molecules are mapped close to each other in the latent space, i.e. the latent space is structured with respect to compositional features. Figure 3a depicts an example of a smooth transition between structurally related molecules, yet consisting of different atom types. Here, the first and the last molecule are recovered from the mean of data points picked out of the test set. By moving towards the target molecule, we plot each intermediate molecule when ever the decoded chemical composition changes. Additional gray plots depict corresponding relaxed geometries of the molecules.

In the second example (see Figure 3b), the chemical composition, as well as the molecular geometry changes, as the interpolation takes place between less related molecules. During the interpolation process we discovered molecular geometries which closely correspond with the relaxed counterparts. However, we also found molecules which deviate from the relaxed geometries. The most common differences occur within the reconstructs of the hydrogen coordinates. Further deviations are caused by core sub-structures of the molecule, naturally leading to significantly different outcomes for the hydrogen coordinates. This phenomenon is more closely discussed in the next paragraph.

A direct comparison of our results with the G-SchNet and EDMNet is at this point not possible, since those models do not allow a continuous exploration of the latent space. Hence, an interpolation between molecular domains cannot be performed. In case of the EDMNet, even a transition between different chemical compositions and molecule sizes is not possible.

Molecule Discovery

For discovery of novel molecules within the QM9 dataset, we randomly sample from the latent space around the mean regions of the molecules from the training set. To identify a novel chemical composition, first, we generate a set of canonical SMILES strings for the entire QM9 dataset. We then compare the canonical SMILES string of the generate molecule with the QM9 references. A molecule is accepted and is considered as novel if no identical canonical SMILES string is found within the QM9 dataset. Molecules with invalid bond and bond types are rejected. We were able to identify more than 20K novel molecules with new chemical compositions (see Figure 4). To investigate the quality of the generated molecular structures we relaxed the structures with MOPAC and computed the pair-wise atom distances yielding in a RMSD of 0.32 Å.

![Figure 3](image-url) Figure 3: An illustration of the interpolation steps between related molecules. The colored atoms and bonds represent generated molecules, while gray structures represent relaxed counterparts. The hydrogen atoms are removed. (a) depicts an interpolation between different chemical compositions within a fixed structural domain, while (b) shows an interpolation between different geometries as well.

In Figure 4, we illustrate a selection of the discovered molecules with increasing RMSD values between the generated structures and corresponding equilibrium states. One sees that the heavy atoms deviate the least from the ground-truth. The hydrogen atoms contribute most to the deviation. However, from the chemical perspective the exact reconstruction of the hydrogen atoms is least important, since most of them are not restricted to a fixed configuration. In terms of qualitative exploration of the chemical space, heavy atoms contribute most to the structural features of the molecules.

To put our results into relation, for G-SchNet a me-
Figure 4: An illustration of novel molecules discovered with 3DMolNet. The colored atoms and bonds represent generated structures and the translucent plot is the relaxed counterpart. The molecules are labeled with the RMSD for the relaxation.

dian of around 0.3 Å is reported, being a comparable result achieved in our experiments. However, a direct comparison between G-SchNet and our model is not appropriate, since our molecules are sampled from a continuous latent space which can produce distorted and unstable molecular structures as well. In fact, it turned out to be problematic to fairly reason about the structural closeness to the equilibrium conformations of the relaxed counterparts. Due to a high-dimensional latent space it is computationally demanding to find mean coordinates within a latent space domain of discovered molecules. This is, however, important in order to decode the least distorted version of the molecule. Furthermore, some novel molecules could be within a domain of isomers, i.e. being in a family of different molecular structures with the same chemical composition, which are mapped closely in the latent space. Hence, sampling in the nearby regions can generate considerably different relaxations and worsen the results. Additionally, generated molecules require a further criterion to filter out potential chemically unstable structures or even to penalize those reconstructions during the training.

1. We introduced a translation-, rotation-, and permutation-invariant molecule representation involving a canonical ordering of the atom and coordinate pairs.

2. We proposed an extended version of the Variational autoencoder, which allow to efficiently generate 3-d molecular structures and explore molecular domains within a continuous low-dimensional representation of the molecules.

3. We achieved a high reconstruction precision of the atom coordinates, which is below 0.05 Å and is in the range of a typical spatial quantization error of common chemical descriptors. Furthermore, our model almost perfectly reconstructs exact chemical compositions and bond types on a QM9 test set.

Future Work

In future work we want to improve the quality of the geometries by including molecular stability constraints to generate energetically more reasonable configurations. Furthermore, we want to extend the model with a decoder for hydrogen atoms. Lastly, to improve the process of the latent space exploration, we would like to investigate alternative forms of latent representations.

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References

Achille, A.; and Soatto, S. 2018. Information Dropout: Learning Optimal Representations Through Noisy Computation. *IEEE Transactions on Pattern Analysis and Machine Intelligence*.

Alemi, A. A.; Fischer, I.; Dillon, J. V.; and Murphy, K. 2017. Deep Variational Information Bottleneck. In *International Conference on Learning Representations*.

Bouchacourt, D.; Tomioka, R.; and Nowozin, S. 2018. Multi-Level Variational Autoencoder: Learning Disentangled Representations From Grouped Observations. In *AAAI Conference on Artificial Intelligence*.

Christensen, A. S.; Faber, F. A.; and von Lilienfeld, O. A. 2019. Operators in quantum machine learning: Response properties in chemical space. *The Journal of chemical physics*.

Creswell, A.; Mohamed, Y.; Sengupta, B.; and Bharath, A. A. 2017. Adversarial Information Factorization. In *arXiv:1711.05175*.

Dai, H.; Tian, Y.; Dai, B.; Skiena, S.; and Song, L. 2018. Syntax-Directed Variational Autoencoder for Structured Data. *International Conference on Learning Representations*.

Faber, F. A.; Hutchison, L.; Huang, B.; Gilmer, J.; Schoenholz, S. S.; Dahl, G. E.; Vinyals, O.; Kearnes, S.; Riley, P. F.; and Von Lilienfeld, O. A. 2017. Prediction errors of molecular machine learning models lower than hybrid DFT error. *Journal of chemical theory and computation*.

Gebauer, N.; Gastegger, M.; and Schütt, K. 2019. Symmetry-adapted generation of 3d point sets for the targeted discovery of molecules. In *Advances in Neural Information Processing Systems*.

Gebauer, N.; Gastegger, M.; and Schütt, K. 2019. Symmetry-adapted generation of 3d point sets for the targeted discovery of molecules. In *Advances in Neural Information Processing Systems*.

Gomez-Bombarelli, R.; Wei, J. N.; Duvenaud, D.; Hernández-Lobato, J. M.; Sanchez-Lengeling, B.; Sheberla, D.; Aguilera-Iparraguirre, J.; Hirzel, T. D.; Adams, R. P.; and Aspuru-Guzik, A. 2018. Automatic Chemical Design Using a Data-Driven Continuous Representation of Molecules. In *ACS Central Science*.

Goodfellow, I.; Pouget-Abadie, J.; Mirza, M.; Xu, B.; Warde-Farley, D.; Ozair, S.; Courville, A.; and Bengio, Y. 2014. Generative adversarial nets. In *Advances in neural information processing systems*.

Hoffmann, M.; and Noé, F. 2019. Generating valid Euclidean distance matrices. *arXiv:1910.03131*.

Janz, D.; van der Westhuizen, J.; Paige, B.; Kusner, M. J.; and Hernández-Lobato, J. M. 2018. Learning a generative model for validity in complex discrete structures. *International Conference on Learning Representations*.

Jin, W.; Barzilay, R.; and Jaakkola, T. 2018. Junction Tree Variational Autoencoder for Molecular Graph Generation. In *International Conference on Machine Learning*.

Jin, W.; Yang, K.; Barzilay, R.; and Jaakkola, T. S. 2019. Learning Multimodal Graph-to-Graph Translation for Molecular Optimization. *International Conference on Learning Representations*.

Keller, S. M.; Samarin, M.; Torres, F. A.; Wieser, M.; and Roth, V. 2020. Learning Extremal Representations with Deep Archetypal Analysis. In *arXiv:2002.00815*.

Keller, S. M.; Samarin, M.; Wieser, M.; and Roth, V. 2019. Deep Archetypal Analysis. In *German Conference on Pattern Recognition*.

Kenakin, T. 2006. *A Pharmacology Primer: Theory, Applications, and Methods*. Elsevier.

Kingma, D. P.; Mohamed, S.; Jimenez Rezende, D.; and Welling, M. 2014. Semi-supervised Learning with Deep Generative Models. In *Advances in Neural Information Processing Systems*.

Kingma, D. P.; and Welling, M. 2014. Auto-encoding variational bayes. *International Conference on Learning Representations*.

Klys, J.; Snell, J.; and Zemel, R. 2018. Learning Latent Subspaces in Variational Autoencoders. In *Advances in Neural Information Processing Systems*.

Kuhn, H. W. 1955. The Hungarian method for the assignment problem. *Naval research logistics quarterly* 2(1-2): 83–97.

Kusner, M. J.; Paige, B.; and Hernández-Lobato, J. M. 2017. Grammatical Variational Autoencoder. In *International Conference on Machine Learning*.

Lample, G.; Zghidiour, N.; Usunier, N.; Bordes, A.; Denoyer, L.; and Ranzato, M. 2017. Fader Networks: Manipulating Images by Sliding Attributes. In *Advances in Neural Information Processing Systems*.

Li, Y.; Vinyals, O.; Dyer, C.; Pascanu, R.; and Battaglia, P. W. 2018. Learning Deep Generative Models of Graphs. *CoRR* abs/1803.03324.

Liu, Q.; Allamanis, M.; Brockschmidt, M.; and Gaunt, A. 2018. Constrained Graph Variational Autoencoders for Molecule Design. In *Advances in Neural Information Processing Systems*.

Mansimov, E.; Mahmood, O.; Kang, S.; and Cho, K. 2019. Molecular Geometry Prediction using a Deep Generative Graph Neural Network. *Scientific Reports*.

O’Boyle, N.; Banck, M.; James, C.; Morley, C.; Vandermeersch, T.; and Hutchison, G. 2011. Open Babel: An open chemical toolbox. *Journal of chemical information and modeling* 51(1): 97–114.

O’Boyle, N. M. 2012. Towards a Universal SMILES representation-A standard method to generate canonical SMILES based on the InChI. *Journal of cheminformatics* 4(1): 22.

Parbhoo, S.; Wieser, M.; Roth, V.; and Doshi-Velez, F. 2020a. Transfer Learning from Well-Curated to Less-Resourced Populations with HIV. In *Machine Learning for Healthcare (MLHC)*.

Parbhoo, S.; Wieser, M.; Wiezorek, A.; and Roth, V. 2020b. Information Bottleneck for Estimating Treatment Effects with Systematically Missing Covariates. *Entropy*.

Ramakrishnan, R.; Dral, P. O.; Rupp, M.; and von Lilienfeld, O. A. 2014. Quantum chemistry structures and properties of 134 kilo molecules. In *Scientific Data*.

Rezende, D. J.; Mohamed, S.; and Wierstra, D. 2014. Stochastic Backpropagation and Approximate Inference in Deep Generative Models. In *International Conference on Machine Learning*.

Ruddigkeit, L.; van Deursen, R.; Blum, L. C.; and Reymond, J.-L. 2012. Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17. *Journal of Chemical Information and Modeling*.

Schütt, K. T.; Sauceda, H. E.; Kindermans, P.-J.; Tkatchenko, A.; and Müller, K.-R. 2018. SchNet – A deep learning architecture for molecules and materials. *The Journal of Chemical Physics*.

Sohn, K.; Lee, H.; and Yan, X. 2015. Learning Structured Output Representation using Deep Conditional Generative Models. In *Advances in Neural Information Processing Systems*.
Steinbeck, C.; Han, Y.; Kuhn, S.; Horlacher, O.; Luttmann, E.; and Willighagen, E. 2003. The Chemistry Development Kit (CDK): An Open-Source Java Library for Chemo- and Bioinformatics. *Journal of Chemical Information and Computer Sciences*.

Stewart, J. J. P. 2016. MOPAC2016. *Stewart Computational Chemistry* URL OpenMOPAC.net.

Tishby, N.; Pereira, F. C.; and Bialek, W. 1999. The information bottleneck method. In *Allerton Conference on Communication, Control and Computing*.

Wieczorek, A.; Wieser, M.; Murezzan, D.; and Roth, V. 2018. Learning Sparse Latent Representations with the Deep Copula Information Bottleneck. In *International Conference on Learning Representations*.

Wieser, M.; Parbhoo, S.; Wieczorek, A.; and Roth, V. 2020. Inverse Learning of Symmetry Transformations. *arXiv e-prints* arXiv:2002.02782.