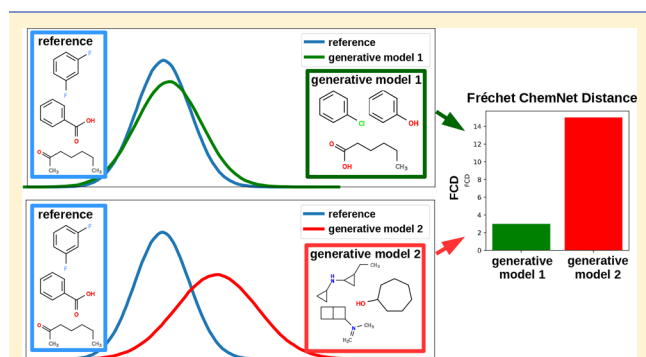


Fréchet ChemNet Distance: A Metric for Generative Models for Molecules in Drug Discovery

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Supporting Information



ABSTRACT: The new wave of successful generative models in machine learning has increased the interest in deep learning driven de novo drug design. However, method comparison is difficult because of various flaws of the currently employed evaluation metrics. We propose an evaluation metric for generative models called Fréchet ChemNet distance (FCD). The advantage of the FCD over previous metrics is that it can detect whether generated molecules are diverse and have similar chemical and biological properties as real molecules.

INTRODUCTION

Deep Learning has recently enabled generative models for molecules.¹ SMILES strings² offer a convenient representation of molecules for generative methods. Therefore, Recurrent Neural Networks (RNNs) are a natural basis for these methods, as they excel at generating text. RNNs have been combined with variational autoencoders (VAE),³ transfer learning,¹ reinforcement learning (RL),^{4,5} and generative adversarial networks (GAN)⁶ to yield generative models for molecules. Recently, also graph generating methods have been suggested,^{7,8} which can be used to generate graph representations of molecules.

Up to now, there is no established evaluation criterion that is consistently used across all publications to assess generative models for molecules. The most basic and commonly reported metric is the fraction of valid SMILES, which is a prerequisite for a generative model. However, this metric can easily be maximized by generating simple molecules, such as “CC” and “CCC”, with a rule-based system. Other metrics focus on numerical or visual comparison of molecular properties like solubility,⁵ number of rotational bonds,⁵ number of aromatic rings,⁵ synthetic accessibility,^{4,6,9} and druglikeness.^{4,6} Additional metrics that are used aim at assessing the diversity of the

generated molecules such as calculating the Tanimoto similarity or distance to the training set^{1,6} or within the generated molecules.¹⁰ The diversity of recently developed methods for molecule generation shows the high interest in this new research field, but the diversity of different evaluation methods inhibits focused and comparative research. Therefore, it is necessary to find a common basis for evaluating generative models for molecules. We will suggest such a metric and show that previously used metrics have their specific flaws and fail to detect certain biases in generative models.

A proficient metric should capture the validity, chemical and biological meaningfulness, and diversity of the generated molecules. We therefore aim at creating a metric that is capable of unifying these requirements into one score. To this end, we adopt a strategy that has been established to compare generative models for images, the Fréchet Inception Distance (FID).¹¹ This distance measure uses a representation obtained from the Inception network¹² to represent the input objects of the network. For these image representations, the Fréchet distance is used as a distance measure. Analogously, we use the hidden representation from a neural network, called ChemNet (see details below), which was trained to predict biological activities, as representation of molecules. This representation contains both chemical and biological information about the molecules, since the input layer can be seen as purely chemical information and the output layer as purely biological information. The layers between input and output contain both chemical and biological information about the molecule, which is a representation that we desire. By taking into account the distribution of these representations within a set of molecules, we also capture the diversity within the set. A purely chemical representation could be also used in combination with the Fréchet distance. This representation could be a set of fingerprints, the principle components calculated on the fingerprints, or the latent space of an autoencoder to name just a few. However, we hypothesize that using just the chemical information is not sufficient to judge generative models for drug design. We will examine our assumption by comparing the Fréchet ChemNet distance (FCD) to a fingerprint based Fréchet distance, which we call Fréchet Fingerprint Distance (FFD).

FRÉCHET CHEMNET DISTANCE

We introduce the Fréchet ChemNet Distance (FCD) to calculate the distance between the distribution $p_w(\cdot)$ of real-

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world molecules and the distribution $p(\cdot)$ of molecules from a generative model. To obtain a numerical representation of each molecule, we use the activations of the penultimate layer of “ChemNet” (see next paragraph). We then calculate the first two moments (mean, covariance) of these activations for each of the two distributions. Since the Gaussian is the maximum entropy distribution for given mean and covariance, we assume the hidden representations to follow a multidimensional Gaussian. The two distributions ($p(\cdot)$, $p_w(\cdot)$) are compared using the Fréchet distance,¹³ which is also known as Wasserstein-2 distance.¹⁴ We call the Fréchet distance $d(\cdot, \cdot)$ between the Gaussian $p_w(\cdot)$ with mean and covariance (m_w, C_w) obtained from the real-world samples and the Gaussian $p(\cdot)$ with mean and covariance (m, C) obtained from a generative model the “Fréchet ChemNet Distance” (FCD), which is given by¹⁵

$$d^2((m, C), (m_w, C_w)) = \|m - m_w\|_2^2 + \text{Tr}(C + C_w - 2(CC_w)^{1/2}) \quad (1)$$

Throughout this paper, the FCD is reported as $d^2(\cdot, \cdot)$ analogously to Heusel et al.¹¹

The FCD is based on the activations of the penultimate layer of ChemNet. The model¹⁶ was trained to predict bioactivities of about 6000 assays available in three major drug discovery databases (ChEMBL,¹⁷ ZINC,¹⁸ PubChem¹⁹). We used long short-term memory (LSTM)²⁰ recurrent neural networks based on the one hot encoded SMILES representation of chemical molecules. The full architecture of this model consists of two 1D-convolutional layers with SELU activations,²¹ followed by a max-pooling layer, two stacked LSTM layers, and a fully connected output layer. Hyperparameter selection and training were done on two-thirds of the available data, and the last third was used for testing. The network was optimized for mean predictive performance. The hidden representation of the second LSTM layer after processing the full input sequence is used for calculating the FCD.

To estimate the mean, m , and covariance, C , of the real and generated samples, sufficiently large data sets should be selected. It can be observed that a sample size of 5000 is already sufficient to get an FCD that is close to 0 meaning that the mean m and covariance C can be accurately estimated (see [Supporting Information](#)).

■ DETECTING FLAWS IN GENERATIVE MODELS

We determine the capability of the FCD to detect if a generative model has produced diverse molecules that possess chemical and biological properties similar to already known molecules. We compare the FCD to four commonly reported metrics: mean logP,²² mean druglikeness,²³ mean Synthetic Accessibility (SA) score,²⁴ and internal diversity score with Tanimoto distance¹⁰ of the generated samples. Additionally, to evaluate if the activations of ChemNet are a suitable representation for molecules we also compare the FCD to the Fréchet Fingerprint Distance (FFD), which is calculated analogously to the FCD. However, in contrast to the FCD, the FFD is based on 2048 bit ECFP₄ fingerprints. A generative model performs well if it produces samples in a similar logP and druglikeness range as the training data and possesses comparable internal diversity.

All compared metrics were calculated in RDKit. The internal diversity score is calculated using Morgan Fingerprints of RDKit with radius 2 (equivalent to ECFP₄²⁵). For the

methods comparison, we have selected a subset of real molecules from the three databases that were used neither for training ChemNet nor to estimate the real sample statistics (m , C) needed for calculating the FCD.

For the real subsample of the combined databases, we calculated each metric, that is, logP, druglikeness, SA score, internal diversity,^a FFD, and FCD, to illustrate the baseline value for real samples. In the next step, to simulate generative models with particular flaws, we created “disturbed data sets” of molecules (a) with low druglikeness (<5th percentile), (b) with high logP values (>95th percentile), (c) with low SA scores (<5th percentile), (d) with high Tanimoto similarity, and (e) stemming from the same target class to simulate generative models producing molecules (a) with a low druglikeness, (b) with a high logP, (c) that are difficult to synthesize, (d) having low diversity, and (e) that are active for a specific target. We aim to show that FCD can detect all four biases, thereby combining the benefits of other metrics into a single one, and is able to identify distribution differences in biologically meaningful subsets.

- **Bias toward low druglikeness:** A biologically based assessment can be performed in terms of the average druglikeness of the generated compounds. Druglikeness²³ is the geometric mean of several desired molecular properties such as solubility, permeability, and metabolic stability. Therefore, it is often used to determine if generated molecules are close to real samples. Molecules with a low druglikeness are commonly not desired since they possess low bioavailability. We simulated models generating molecules with a druglikeness lower than the 5th percentile of the druglikeness values (i.e., 0.19) of real molecules. We randomly selected 5000 molecules with a low druglikeness for this simulation. This was repeated 5 times to create 5 different generative models producing molecules with a low druglikeness.
- **Bias toward high logP:** Similar chemical properties such as the average logP value of the generated molecules are another way to judge whether created molecules are reasonable or not. Therefore, we simulated a generative model that has a bias toward generating molecules with a high logP. For this purpose, we selected 5000 molecules that have a logP value higher than the 95th percentile of logP values (i.e., >6.15) of real molecules. Although these molecules are valid, they are located on the edge of the logP distribution, which should be detectable by an appropriate metric. This procedure was repeated 5 times to simulate 5 different generative models with a bias toward molecules with a high logP.
- **Low synthetic accessibility:** Furthermore, it is beneficial if a generative model produces molecules that are indeed synthetically feasible. Therefore, we simulated generative models that have a bias toward molecules with a low synthetic accessibility (SA) score. We randomly drew 5000 molecules with a SA score lower than the 5th percentile of the SA scores (i.e., <1.91) of real molecules. This procedure was repeated 5 times to simulate 5 different generative models with a bias toward low SA.
- **Mode collapse:** Another desirable property of generative models is to create a wide variety of different samples. However, generative models might suffer from

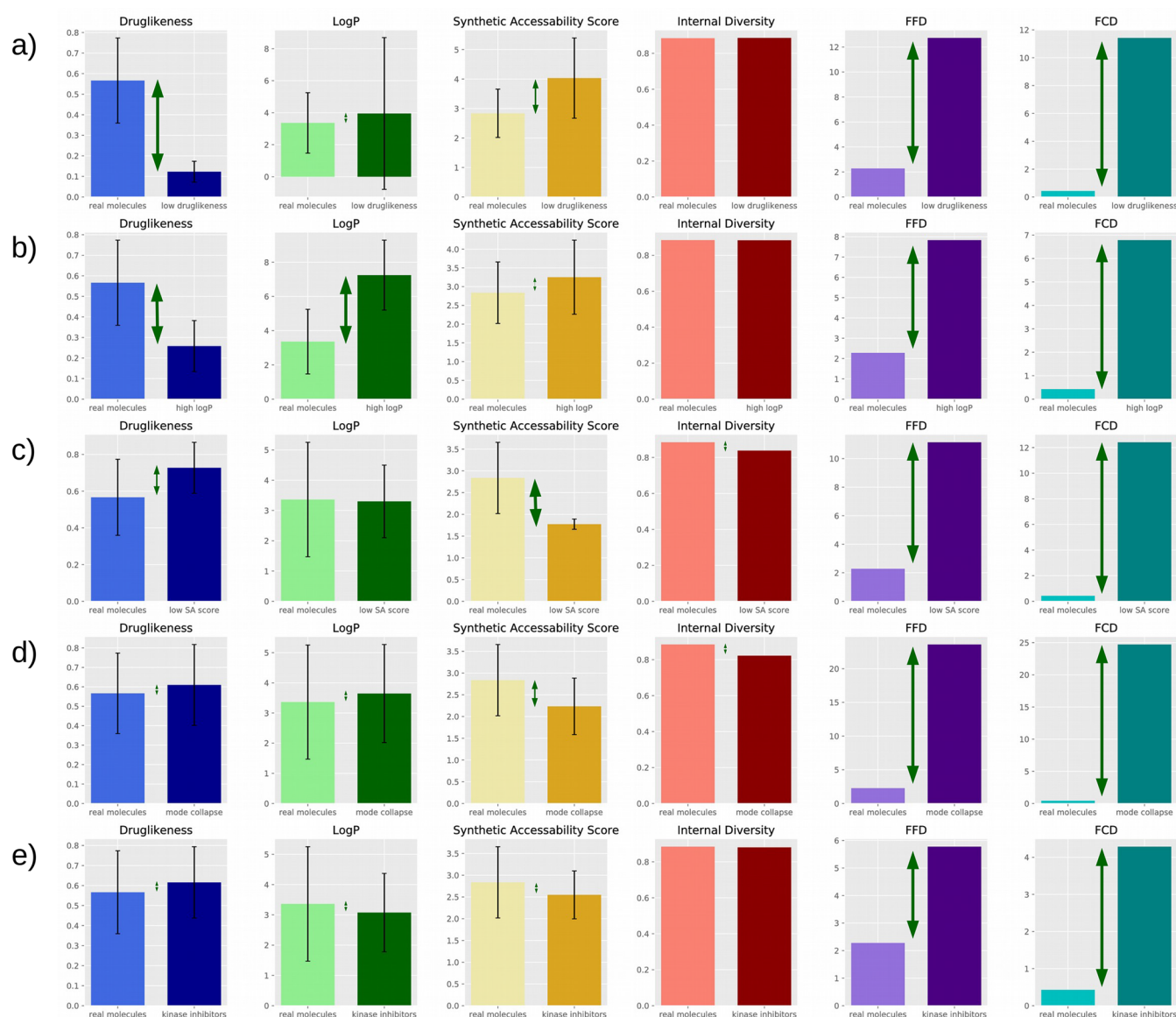


Figure 1. Mean responses of druglikeness (blue), logP (green), synthetic accessibility score (yellow), internal diversity (red), FFD (purple), and FCD (cyan) compared to those of the real sample data set and the disturbed molecule sets (a) with low druglikeness, (b) with high logP, (c) that are difficult to synthesize, (d) that have low diversity, and (e) that stem from one target family. The height of the bars indicates the mean of the metrics over repeated experiments, and the error bars indicate the mean standard deviation across molecules of the repeated experiments. Please note that for the internal diversity, the FFD, and the FCD, the standard deviation cannot be determined because these measures are based on sets and cannot be determined for single molecules. The green arrows indicate the difference between the mean measure of the real set and the disturbed set. In panel a, the low druglike set is clearly detected by druglikeness, the FFD, and the FCD. In panel b, logP, druglikeness, the FFD, and the FCD detect the bias toward high logP molecules. In panel c, the bias toward molecules with a low SA score is clearly revealed by the SA score, the FFD, and the FCD. In panel d, the models suffering from mode collapse are discovered by the internal diversity, the FFD, and the FCD. In panel e, the active molecules for PLK1 are uncovered by the FFD and the FCD.

mode collapse,^{26,27} such that they produce only molecules with a low diversity. Although there also exist models that do not suffer from mode collapse,²⁸ an appropriate metric should be able to assess the internal diversity of the generated molecules. We simulated generative models that suffer from mode collapse. For this purpose, we used single linkage clustering with a Tanimoto similarity cutoff of 0.65. We have chosen a large cluster of which we randomly selected 5000 molecules. This procedure was repeated 5 times to simulate 5 different generative models suffering from mode collapse.

- **Kinase inhibitors:** Conditional generative models are used to produce molecules active for a specific target. We assessed if the metrics can catch the bias toward a certain target family. For this experiment, we have selected a large scale activity assay from PubChem (AID 720504). We have randomly selected 5000 active molecules for polo-like kinase 1–polo-box domain (PLK1-PBD).

We examined the average changes of the metrics when generative models suffer from (a) a bias toward low druglikeness, (b) a bias toward high logP molecules, (c) a bias toward low SA scores, and (d) mode collapse.

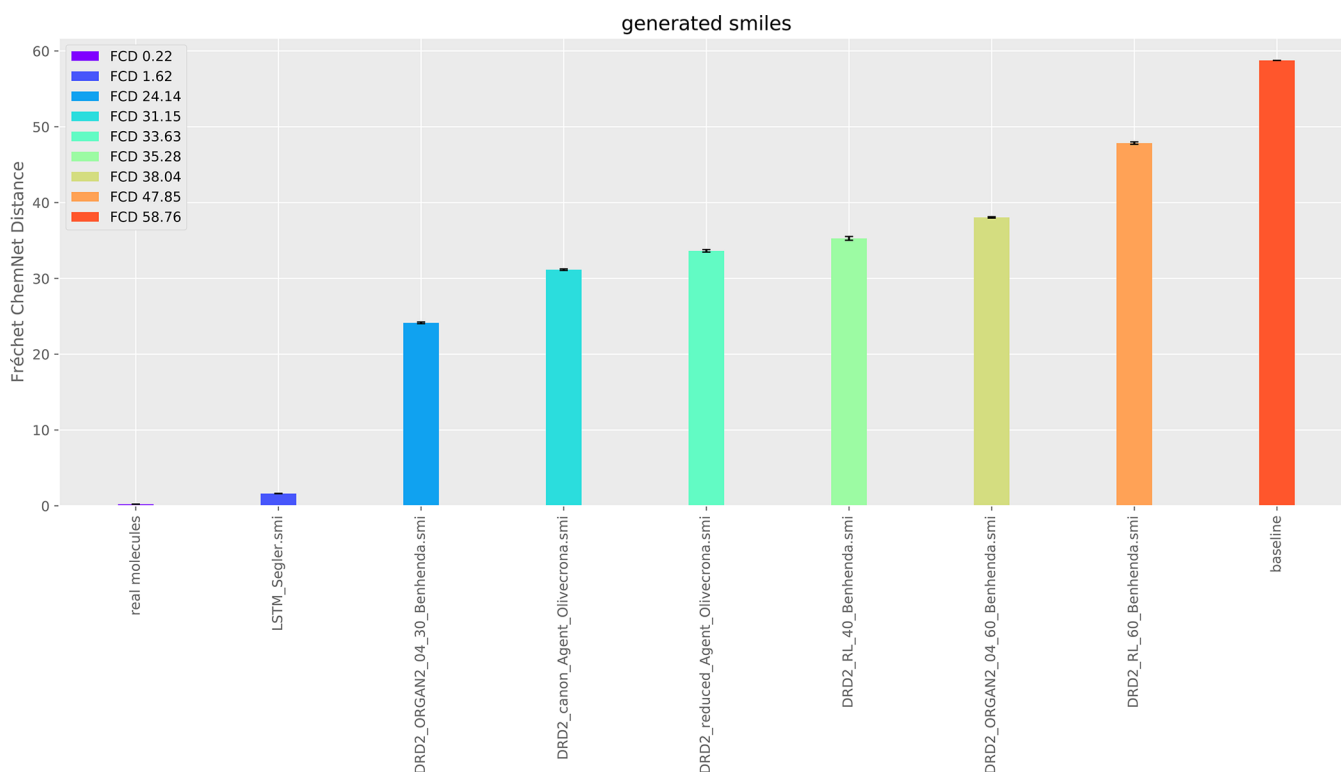


Figure 2. FCD of generated molecules based on different methods. A low value indicates that the distribution of the real molecules was approximated well by the generated molecules. The method “Segler” was optimized to produce molecules similar to the molecules present in the ChEMBL database. Six further models were optimized to produce molecules with activity on a certain protein target. This optimization process leads to a higher FCD value indicating a larger difference from the distribution of real molecules.

Furthermore, we assess the changes of the metrics for (e) molecules stemming from the same target class (see Figure 1). In part a, druglikeness, the FFD and the FCD are able clearly to detect the disturbed data set. In part b, the bias toward high logP values is reflected in the druglikeness, logP, FFD, and FCD. In part c, the disturbed set is recognized by the SA score, the FFD, and the FCD and to a minor extend by druglikeness and internal diversity. The mode collapse of part d is clearly revealed by internal diversity, the FFD, and the FCD. The active compounds for PLK1 are only uncovered by the FFD and the FCD. Both FFD and FCD show in all four cases a clear difference in the mean of the disturbed and undisturbed data sets. The difference is especially high for both metrics in the case in which we simulated a generative model that suffers from mode collapse. Although, FFD is able to detect all the biased sets, FCD is able to make more distinct differentiations. Especially in experiment e, where more biological relevant information is necessary, the FCD shows superior behavior.

FCD OF RECENT GENERATIVE MODELS

We calculated the FCD for publicly available SMILES strings of recently developed generative models.^{1,5,10} Segler et al.¹ generated more than 450 000 SMILES strings with an LSTM network used for next character prediction. Benhenda¹⁰ aimed at producing SMILES strings with ORGAN⁶ and RL that are active against the dopamine receptor D2 (DRD2); 32 000 molecules were generated after 40 and 60 training iterations for RL and after 30 and 60 training iterations for ORGAN. Olivecrona et al.⁵ trained two RL agents to produce molecules active for the DRD2 receptor. The canonical and the reduced agent were trained on the complete ChEMBL and a subset

from which molecules similar to celecoxib were removed, respectively. Each agent produced 128 001 molecules. Furthermore, we examined a simple rule-based approach, which randomly draws C, N, and O atoms and concatenates them to obtain SMILES with random lengths between 1 and 50. The sample statistic was calculated with 200 000 randomly selected real molecules that were not used for training ChemNet. For each model, we have randomly drawn 10 000 samples of the generated SMILES 10 times and determined the FCD score.

We calculated our new FCD performance metric for the following methods:

- **Segler:** The next-character LSTM approach by Segler et al.¹
- **Olivecrona canon agent:** An RNN-based RL approach to generate active molecules for DRD2.⁵
- **Olivecrona reduced agent:** An RNN-based RL approach to generate active molecules for DRD2 using a reduced training set.⁵
- **RL 40/60 iterations:** An LSTM-based RL approach to generate active molecules for DRD2 trained for 40/60 iterations.¹⁰
- **ORGAN 30/60 iterations:** A GAN using an LSTM-based generator and a CNN-based discriminator trained for 30/60 iterations.¹⁰
- **baseline:** A generative model producing just methane.

Figure 2 shows the results for the different methods. Please note that this is not a methods comparison but should demonstrate that the ranking by the FCD matches our intuition. The lowest FCD value of 0.22 is obtained for randomly drawn real molecules. Since this value is close to zero

the randomly drawn subsamples sufficiently represent the underlying distribution of real molecules. The method “Segler”¹ achieved the second lowest FCD of 1.62, indicating that the distribution of these generated molecules is closer to the real molecule distribution than distributions produced by other methods. This matches our intuition, because the other methods (“Olivecrona”, “RL”, and “ORGAN”) were optimized to generate molecules that are active for DRD2 and are therefore not designed to approximate the distribution of the complete set of real molecules. This optimization procedure is clearly captured by the FCD metric: for all these methods, the FCD is notably higher, ranging from 24.14 to 47.85. Furthermore, ORGAN after 60 iterations and RL after 60 iterations produce molecules that are more distant from real molecules than ORGAN after 30 iterations and RL after 40, respectively. Intuitively, more training iterations lead to more DRD2 specific molecules and therefore to molecules more distant to the complete real molecule distribution and lower diversity.¹⁰ Additionally, the FCD captures that the canonical and the reduced agents both learn a similar chemical space as concluded by Olivecrona et al.⁵ The rule-based system has the highest FCD of 58.76, which can be considered an easily achievable baseline. Overall, the ranking of the methods by their FCD matches our intuition and previous findings. In this comparison, randomly drawn molecules from the combined data set were used to determine the sample statistic underlying FCD; therefore methods that are optimized to capture the distribution of active molecules for DRD2 have a higher FCD. By using a different distribution to calculate the sample statistic, the FCD could also be used to evaluate targeted molecule generation.

CONCLUSIONS

In previous studies, the assessment of generative molecules was based on specific properties such as logP, druglikeness, or SA score. However, looking at all these properties individually makes the comparison of generative models difficult. We introduce the FCD, a novel metric for generative models for drug design. FCD is based on a multitask network and therefore incorporates a wide variety of important chemical and biological features into a single metric. FCD was able to detect four potential flaws of generative models, as we have demonstrated in our experiments. Furthermore, we also show that the FCD can catch a biological bias (active PLK1 kinase inhibitors). Our proposed approach is not restricted to generative models that produce SMILES strings but can readily be used for graph generating methods by converting the produced molecules into a SMILES format. Within our experiments, we compare the FCD also to a fingerprint based Fréchet distance. This comparison clearly illustrates that by incorporating biological information the metric further improves and the differences between the real and biased sets are more distinct. It has not escaped our notice that the representations of ChemNet could also be used as a new type of molecular descriptors. Overall, we show that FCD is a comprehensive, simple, and powerful metric for the evaluation of generative models in drug discovery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jcim.8b00234.

Mean and covariance estimation of FCD, FCD comparison for different reference and real molecule sets, additional information on used generated molecule sets, and ChemNet architecture (PDF)

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Notes

The authors declare no competing financial interest.

Code to calculate the FCD measure is provided at: <https://github.com/bioinf-jku/FCD>.

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ADDITIONAL NOTE

^aThe calculation of the full distance matrix required for this metric is too time and memory intense; therefore, we have averaged the results from 5 subsets of randomly drawn 5000 samples.

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