Abstract

Forming a high-quality molecular candidate set that contains a wide range of dissimilar compounds is crucial to the success of drug discovery. However, compared to the research aiming at optimizing chemical properties, how to measure and improve the variety of drug candidates is relatively understudied. In this paper, we first investigate the problem of properly measuring the molecular variety through both an axiomatic analysis framework and an empirical study. Our analysis suggests that many existing measures are not suitable for evaluating the variety of molecules. We also propose new variety measures based on our analysis. We further explicitly integrate the proposed variety measures into the optimization objective of molecular generation models. Our experiment results demonstrate that this new optimization objective can guide molecular generation models to find compounds that cover a larger chemical space, providing the downstream phases with more distinctive drug candidate choices.

1. Introduction

The goal of drug discovery is to find molecules that can effectively bind to certain targets. This task is often compared to finding needle in the haystack because, for a specific target, only a number of molecules can satisfy the bioactivity requirement while the potential chemical space is tremendous. It is estimated that the small organic chemical space has more than $10^{60}$ molecules (Kirkpatrick & Ellis, 2004; Ruddigkeit et al., 2012). In contrast, the known chemical space is very limited: the current largest authoritative molecular database contains only around $10^8$ compounds (Kim et al., 2020).

Going beyond the existing molecular database, machine-learning-based approaches have demonstrated great potential in helping scientists efficiently navigate through the huge chemical space via de novo molecular generation (Olivecrona et al., 2017; Gómez-Bombarelli et al., 2018; Liu et al., 2018; You et al., 2018; Jin et al., 2018; De Cao & Kipf, 2018; Popova et al., 2019; Shi et al., 2020; Xie et al., 2021). Such molecular generation methods learn to generate candidate drug designs by optimizing various molecular property scores, like the binding affinity scores that are relevant to the drug efficacy. In practice, these scores can be computationally calculated using biological activity prediction models (Olivecrona et al., 2017; Li et al., 2018), which is the key to obtain massive labeled training data for machine learning.

However, there is a huge gap between the in silico property scores of a drug design and its in vivo efficacy and safety, as such computational scores provide limited information about the complex chemical interactions in the real world. Expensive wet experiments and toxicity tests are still required as downstream tasks. In order to increase the chance to identify drug hits with a limited budget, it is therefore crucial to generate a variety of qualified candidate molecules that cover a broad area of the chemical space (Ashenden, 2018), rather than a concentrated cluster of molecules with the highest property scores.

As a first step, we aim to investigate the fundamental question of how to properly measure the variety of a set of candidate molecules in the chemical space. The most reliable way to estimate the variety of molecules is to test their varieties of functionalities through wet experiments. The experiment-tested functionalities provide important reference information for drug design but they are expensive to annotate. Therefore, having an easy-to-calculate variety measure that faithfully reflects the variety of functionalities can be very helpful. While there are a number of existing studies that evaluate the variety of generated compounds with measures such as internal diversity (You et al., 2018; De Cao & Kipf, 2018; Popova et al., 2019; Polykovskiy et al., 2020; Shi et al., 2020; Xie et al., 2021), the validity of these measures is rarely justified. In fact, justifying the measurement of variety appears to be challenging. First, compared with the molecular property scores, the ground
truth of functionality variety is harder to be obtained. Moreover, the chemical space is a complex combinatorial space, which makes the design of measures even more difficult.

In this paper, we address this challenge with a systematic study on measuring the variety of molecules. Specifically, we investigate the validity of measures from two perspectives. First, we propose an axiomatic analysis framework to analyze measures on the variety of molecules. In particular, we define the concept of the variety of molecules as functions that map a set of molecules to a non-negative number, and propose two intuitively natural axioms that a good variety measure should satisfy. Following our framework, we find that some commonly used existing measures do not satisfy the basic axioms. We also propose a few new variety measures based on the axioms. Second, we propose to evaluate the validity of variety measures by their correlation to the ground-truth variety of functionalities of the molecules, such as affinity to different proteins. In our empirical evaluation, we demonstrate that the proposed novel variety measures are better correlated with the variety of functional groups compared to existing ones.

Besides evaluating the validity of variety measures, we also integrate the variety measures into the training objective of molecular generation methods. We demonstrate that by jointly optimizing the molecular property scores and the variety measures selected from our analysis, molecular generation models can discover high-quality molecules that cover a larger chemical space, in comparison to optimizing the molecular property scores alone or other variety measures.

2. Related Work

In the drug discovery literature, most of the related work focuses only on the optimization of molecular properties. To this extent, various methods are designed to find or generate compounds that maximize the property scores. Traditionally, rule-based genetic algorithms (GA) and fragment-based combinatorial methods are widely applied to find drug candidates (Devi et al., 2015). Recently, with the advent of machine learning, more and more deep models are proposed to optimize molecular properties more efficiently. Based on variational autoencoders (VAE), some approaches use Bayesian inference to find optimal molecules in the latent space (Gómez-Bombarelli et al., 2018; Liu et al., 2018; Jin et al., 2018). Another branch of methods employs reinforcement learning (RL) to generate compounds in the explicit chemical space (Olivecrona et al., 2017; You et al., 2018; De Cao & Kipf, 2018; Popova et al., 2019; Polykovskiy et al., 2020; Shi et al., 2020; Xie et al., 2021). In Zhang et al. (2021), the authors propose to use the number of functional groups or ring systems to estimate the chemical space coverage of generated molecules, and they conduct a comparison study for multiple recent generative models. Koutsoukas et al. (2014) study how the choice of molecular fingerprints can affect the internal diversity in the context of compound selection. Despite various existing variety measures, the validity of such measures is rarely justified.

Besides, there is also a small fraction of work that tries to encourage the model to generate molecules that cover a larger chemical space. For example, Nigam et al. (2020) adds an adversarial loss into the fitness function of GA to avoid the trap of local optima; Blaschke et al. (2020) uses a memory unit to score the novelty of generated molecules.

To the best of our knowledge, this is the first work that studies the validity of the molecular variety measures in a principled way. In particular, the axiomatic analysis approach has been commonly used to evaluate the reliability of measure designs, such as utility functions (Herstein & Milnor, 1953) or cohesiveness measurements (Alcalde-Unzu & Vorsatz, 2013). The work closest to this paper is a study that applies axiomatic analysis to the design of diversity measures, with a particular focus in the domain of science of science (Yan, 2021). The application of axiomatic analysis to the measurement of molecular variety is novel.

As far as we know, this is also the first work that explicitly formalizes the molecular generation problem as a joint optimization of both molecular properties and variety measures. Our experiment results demonstrate a great potential of this new optimization objective in drug discovery.

3. An Axiomatic Analysis Framework for Molecular Variety Measures

In this section, we present the proposed axiomatic analysis framework for molecular variety measurements.

3.1. Definition of Variety Measure

To define the variety measure of molecules, we first formalize the notion of chemical space with the following assumption.

**Assumption 1 (Chemical Space.)** The chemical space \( \mathcal{U} \) contains all possible molecules and is a metric space equipped with a distance metric \( d : \mathcal{U} \times \mathcal{U} \rightarrow [0, \infty) \).
whose entries are pairwise similarities or dissimilarities.

As we will see later, this assumption is implicitly implied in many variety evaluation measures defined in previous work. This assumption is also reasonable as we can find plenty of molecular distance metrics in the literature like Tanimoto distance of molecular fingerprints (Tanimoto, 1968) and the root-mean-square deviation (RMSD) of three-dimensional molecular representations (Fukutani et al., 2021).

Then we formally define the variety measure as following.

**Definition 1 (Variety Measure.)** Given the chemical space $\mathcal{U}$, a variety measure $\mu : \mathcal{P}(\mathcal{U}) \to [0, \infty)$ is a function that maps a set of molecules to a non-negative real number, where $\mathcal{P}(\cdot)$ is the notation of power set. In particular, $\mu(\emptyset) = 0$.

### 3.2. Examples of Variety Measures

Many measures estimating the variety of molecules in the literature follow the form of Definition 1 with suitable choices of similarity metric $s$ or distance metric $d$. We are also able to define new variety measures under this definition.

According to how these measures are defined, we summarize them into three categories: dissimilarity-based measures, reference-based measures, and locality-based measures.

#### 3.2.1. Dissimilarity-Based Measures

For an arbitrary set with $n$ molecules $\mathcal{S} = \{x_i\}_{i=1}^n$, we can define a similarity matrix $\mathbf{S}$ and a dissimilarity matrix $\mathbf{D}$ whose entries are pairwise similarities or dissimilarities, i.e., $S_{ij} = s(x_i, x_j), D_{ij} = 1 - s(x_i, x_j)$. Then by aggregating the entries of $\mathbf{S}$ or $\mathbf{D}$, we can obtain a series of variety measures:

\[
\text{Diversity}(\mathbf{S}) := \frac{1}{n(n-1)} \sum_{i \neq j} D_{ij} 
\]

\[
\text{SumDiversity}(\mathbf{S}) := \sum_{i=1}^n \frac{1}{n-1} \sum_{j \neq i} D_{ij} = n \cdot \text{Diversity} 
\]

\[
\text{Diameter}(\mathbf{S}) := \max_{i \neq j} D_{ij} 
\]

\[
\text{SumDiameter}(\mathbf{S}) := \sum_{i=1}^n \max_{j \neq i} D_{ij} 
\]

\[
\text{Bottleneck}(\mathbf{S}) := \min_{i \neq j} D_{ij} 
\]

\[
\text{SumBottleneck}(\mathbf{S}) := \sum_{i=1}^n \min_{j \neq i} D_{ij} 
\]

\[
\text{DPP}(\mathbf{S}) := \det(\mathbf{S}) 
\]

Among the above measures, the Diversity (sometimes referred to as the internal diversity) is simply the average dissimilarity and is widely used in the literature. We follow the network theory and define the Diameter and Bottleneck as the maximum and minimum dissimilarity respectively. We also define three Sum... variants for the above three measures. In addition, the determinant of the similarity matrix is also considered as suggested by the studies of determinantal point processes (DPP), which is often employed in diverse subset selection (Kulesza & Taskar, 2011).

#### 3.2.2. Reference-Based Measures

Another broad category of variety measures compare the generated molecules with a reference set. For the generated $n$ molecules $\mathcal{S} = \{x_i\}_{i=1}^n$ and a reference set $\mathcal{R} = \{y_i\}_{j=1}^m$, we can define a reference-based similarity matrix $\mathbf{S}$ or dissimilarity matrix $\mathbf{D}$, i.e., $S_{ij} = s(x_i, x_j), D_{ij} = 1 - s(x_i, x_j)$. Similar to the dissimilarity-based measures, we may aggregate the entries of $\mathbf{S}$ or $\mathbf{D}$ as well to define certain measures.

One way to define a reference-based measure is to consider the coverage of the reference set. In a large body of drug discovery literature, the number of distinct functional groups or ring systems in $\mathcal{S}$ is used to gauge the size of explored chemical space (Zhang et al., 2021). If we denote all possible functional groups or ring systems as the reference set $\mathcal{R}$, then the coverage can be computed as below:

\[
\text{Coverage}(\mathcal{S}, \mathcal{R}) := \sum_{j=1}^m \max_{i} S_{ij} 
\]

where $s(x, y)$ takes the value of one if the molecule $x$ contains the fragment $y$ and otherwise zero.

#### 3.2.3. Locality-Based Measures

Inspired by the sphere exclusion algorithm used in compound selection (Gobbi & Lee, 2003), we introduce a new variety measure that highlights the local information as following:

\[
\#\text{Circles}(\mathcal{S}) := \max_{c \leq \mathcal{S}} |\{x_i \mid x_i \in C, \min_{x_j \in C} s(x_i, x_j) < c\}| 
\]

where $\mathcal{S} = \{x_i\}_{i=1}^n$ are the generated molecules and $c \in (0, 1)$ is a similarity threshold. Intuitively, #Circles can be viewed as the number of mutually exclusive circles in $\mathcal{S}$.

**Richness.** When the threshold is set as $c = 1$, which means two molecules are regarded as similar only if they are exactly the same under a certain representation, #Circles becomes the widely used Richness := $|\{\mathcal{S}\}|$. Sometimes
the richness is normalized by the total number of generated molecules $N$ ($N$ could be greater than $n$ if there are duplicated molecules), i.e., $\text{Uniqueness} := \text{Richness} / N$.

### 3.3. Axiomatic Analysis

While all the aforementioned measures are heuristically sound, these measures do not always agree with each other. It is therefore important to have a principled way to select the most suitable measures when we evaluate the molecular generation methods.

For this purpose, we propose an axiomatic analysis approach. Specifically, we suggest two simple and intuitively justifiable principles that a good variety measure should meet: (1) Adding molecules to a molecular set will not decrease the variety score; (2) Molecular sets with more dissimilar molecules should have larger variety scores. These two principles are formalized below as two axioms.

**Axiom 1 (Subadditivity.)** A variety measure $\mu$ should be subadditive, i.e., for any two molecular sets $S_1, S_2 \subseteq U$,

$$\max(\mu(S_1), \mu(S_2)) \leq \mu(S_1 \cup S_2) \leq \mu(S_1) + \mu(S_2).$$

Subadditive variety measures tend to increase when more molecules are discovered. This tendency is very intuitive in drug discovery, since including more molecules means we can have a higher probability to include a potentially effective drug.

A subadditive variety measure is a special case of *outer measures* in the context of measure theory. Outer measures are relaxations of measures, where the latter requires a stricter additivity axiom, i.e., $\mu(S_1 \cup S_2) = \mu(S_1) + \mu(S_2)$ for any two sets $S_1, S_2$. We consider additivity to be too strong and can conflict with intuitions for drug discovery: an additive and/or dissimilarity, we can put them into four quadrants as shown in Figure 1. Despite the fact that the two axioms are extremely simple and natural, surprisingly, our proposed $\#\text{Circles}$ is the only measure that satisfies both axioms.

**Axiom 2 (Dissimilarity.)** A variety measure should have a preference to dissimilarity, i.e., for any molecular set $S \subseteq U$ and two molecules $x_1, x_2 \in U$, when

$$\text{dissimilarity}(x_1, S) > \text{dissimilarity}(x_2, S),$$

it holds that

$$\mu(S \cup \{x_1\}) > \mu(S \cup \{x_2\}),$$

where $\text{dissimilarity}(x, S)$ is the dissimilarity between a single molecule $x$ and a molecular set $S$.

![Figure 1. variety measures, categorized by whether they will satisfy the subadditivity and dissimilarity axioms. Abbreviations in the brackets are variants of the dissimilarity definition.](image)

The dissimilarity between a molecule $x$ and a molecular set $S$ can be defined in several ways given the similarity metric $s$ between two molecules:

1. **Average dissimilarity (AD):**

$$\text{dissimilarity}(x, S) = \frac{1}{|S|} \sum_{x' \in S} [1 - s(x, x')],$$

2. **Nearest neighbor dissimilarity (NN):**

$$\text{dissimilarity}(x, S) = \min_{x' \in S} [1 - s(x, x')] = 1 - \max_{x' \in S} s(x, x'),$$

3. **Localized nearest neighbor dissimilarity (Local-NN):**

$$\text{dissimilarity}(x, S) = \max_{x' \in S} s(x, x') < c],$$

where $c \in [0, 1]$ is a similarity threshold and $[\cdot]$ indicates the truth value of the inside statement.

In our later empirical studies, we will see different expressions can lead to distinctive behaviors in the measurement of variety.

Depending on whether the variety measures satisfy subadditivity and/or dissimilarity, we can put them into four quadrants as shown in Figure 1. Despite the fact that the two axioms are extremely simple and natural, surprisingly, our proposed $\#\text{Circles}$ is the only measure that satisfies both axioms.

Finally, we point out that, measures falling into the same quadrant are also distinguishable. For example, for the measures that are not subadditive, some (e.g., SumDiversity, SumBottleneck, and SumDiameter) have a larger tendency to increase when adding new molecules than others (e.g., Diversity, Bottleneck, and Diameter).
4. Correlation with Functionality Variety

We further investigate the validity of the variety measures by their correlation with the functionality variety of molecules. The molecule functionalities are expensive to annotate but provide important information distinguishing molecules. A molecular set containing molecules with diverse functionalities also has a better chance of identifying drug hits.

In this section, we empirically compare the correlation between the aforementioned variety measures and the number of unique functionalities on a molecular set.

4.1. Experiment Setup

Our empirical studies are based on a BioActivity dataset that is also used to compare different compound selection algorithms (Koutsoukas et al., 2014). This dataset contains 10,000 compound samples excerpted from the ChEMBL database (Gaulton et al., 2017) with bio-activity labels. There are 50 activity labels in total and each has 200 samples. Following Koutsoukas et al. (2014), for a subset of this dataset \( S \), we take the number of unique labels as a proxy “golden standard” of variety on \( S \), i.e.,

\[
\text{GS}(S) := \#\text{unique labels in } S,
\]

which can represent the number of functionality types covered by \( S \). We then compare the behavior of the functionality golden standard and the above-listed variety measures in two settings to find out which measures perform best empirically.

4.2. Random Subsets with Fixed Sizes

In this setting, we consider random molecular subsets of the BioActivity dataset with fixed sizes. Particularly, for a fixed size \( n \), we randomly sample \( n \) molecules \( S \) from the dataset and compute the value of the golden standard \( \text{GS}(S) \) as well as each variety measure \( \mu(S) \). By repeating the random experiment multiple times, we can calculate Spearman’s correlation between the golden standard and any specific measure. We run the experiment for three different fixed sizes \( n = 50, n = 200, \) and \( n = 1000 \) to represent different molecular distribution density. The correlations are shown in Figure 2. The pair-wise correlations between measures are displayed in Figure 3. The experiment implementation details are listed in Appendix A.

As the plots display, #Circles and SumBottleneck perform constantly better than the rest. We assume this is because the local information is critical in evaluating coverage, as these two measures both prefer new molecules with a more distant nearest neighbor.

Furthermore, when \( n = 50 \) and the molecules are distributed sparsely, all variety measures are positively correlated with the golden standard. However, when the subset size increases to \( n = 200 \) and \( n = 1000 \), Bottleneck and DPP becomes negatively correlated, while other measures tend to perform better. This is because these two measures will be bounded by the most similar molecular pair, thus severely conflicting with the subadditivity axiom.

4.3. Random Subsets with Growing Sizes

To mimic the molecular generation process, we also include a growing random subset setting. More specifically, for a maximum subset size \( n \), we sequentially sample \( n \) molecules from the dataset to form \( n \) subsets \( \{S_i = \{x_1, \ldots, x_i\}\}_{i=1}^n \). So for the golden standard and each variety measure, we can plot measure value curves as Figure 4 displays. The experiment details are listed in Appendix A. The similarity between the two curves can reflect the similarity of measuring behaviors. We quantitatively estimate such curve similarity with the dynamic time warping (DTW) distance of corresponding incremental curves, which is conventionally used to tell the similarity of two time series. The random experiment is conducted several times and the results are visualized in Figure 5.

As shown in the figure, the commonly employed Diversity is significantly inferior to others. Among all
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Figure 3. Similarity heatmaps of the golden standard GS and variety measures for \( n = 200 \).

Figure 4. Variety measure curves for a growing random subset (the trend more similar to GS the better). The x axis is the growing subset size and the y axis is the normalized value for variety measures.

Figure 5. DTW distances between the golden standard GS and variety measures (the lower the better). The results are obtained by running the random experiment for five times, and the error bar lines are shown in black. The y axis is log-scaled.

4.4. Discussion

In the experiments, \#FG performs the best, leading a slight advantage over other good measures like \#Circles and \#RS. \#FG's outstanding performance regardless of the failure in satisfying the dissimilarity axiom highlights the importance of carefully choosing a reference set. In contrast, \#RS is also a reference-based measure, but its performance is relatively worse because its reference set is not so appropriate in this experimental setting.

Comparing the two empirical settings, a discrepancy can be found in the variety measure performance rankings, which suggests the fixed-size subsets and the growing-size subsets might need different designs of measures. For instance, in the fixed-size setting, SumBottleneck performs closely to \#Circles, but in the growing setting, SumBottleneck falls behind \#Circles remarkably. This might be attributed to the higher requirement for subadditivity in the growing setting, which SumBottleneck fails. Notably, the \#Circles measure works very well in both settings, suggesting its great potential to be widely used in practice.

Overall, the locality-based \#Circles measure is an excellent choice for all the tested practical scenarios and is also theoretically sound. Reference-based measures can be good alternatives as well if the reference sets are designed wisely given enough domain knowledge. Surprisingly, the widely used Diversity measure is actually inferior to others theoretically and empirically, which means it may not be appropriate to evaluate molecular generation models with Diversity in the molecular generation setting.

5. Joint Optimization of Molecular Property Scores and Variety Measures

In this section, we further integrate the variety measures into the training objective of molecular generation models to improve the variety of generated candidate molecules.

5.1. Problem Formulation

In drug discovery, the search for potentially effective drugs is often explicitly or implicitly formulated as the following optimization problem (Olivecrona et al., 2017; Gómez-
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Table 1. Variety measure values estimated for generated molecules. Each model variant samples 8.5M molecules in total, and we compute the variety measure based on unique drug candidates, i.e., generated compounds that are predicted to be bioactive, drug-like, and synthesizable. Green represents an improvement to the baseline while red indicates a decrease.

![Figure 6. Variety measure curves. The x axes are sampling steps and y axes are values of variety measures. The blue line corresponds to the baseline model, the orange line stands for the AD variant, and the green line stands for the NN variant.](image)

\[ \max_{x \in \mathcal{U}} \text{Property}(x) \quad \text{(10)} \]

where \( x \) is a molecule in the chemical space \( \mathcal{U} \) and \( \text{Property} : \mathcal{U} \rightarrow \mathbb{R} \) is a property score prediction function. This property term can incorporate bioactivity like affinity to certain proteins, drug-likeness, synthesizability, etc. (Nicolaou et al., 2012; Xie et al., 2021).

However, as pointed out in the chemistry literature, rather than focus on optimizing the predicted property scores, it is more crucial to generate a variety of compounds that span a wider range of the chemical space (Ashenden, 2018). To this extent, we propose the following optimization objective as the ultimate goal of molecular generation:

\[ \max_{\mathcal{S} \subseteq \mathcal{U}} \mu(\mathcal{S}) \quad \text{(11)} \]

s.t. \( \text{Property}(x) \geq C, x \in \mathcal{S} \)

where \( \mathcal{S} \subseteq \mathcal{U} \) is the molecular candidate set, \( \mu() \) is a variety measure, \( \text{Property}(x) \geq C \) means the molecule \( x \) satisfies the given property constraint with a threshold \( C \).

This constrained optimization problem is very hard to solve due to its combinatorial characteristics. To address this problem, we propose a relaxation alternative to Equation 11. First, we can use a greedy strategy to convert the molecular set generation problem into a single molecule generation problem:

\[ \max_{x \in \mathcal{U}} \mu(\mathcal{S} \cup \{x\}) \quad \text{(12)} \]

s.t. \( \text{Property}(x) \geq C \)

where \( x \) is a new molecule to generate and \( \mathcal{S} \) is the already-generated drug candidates. Then to efficiently find the plausible molecule, we can jointly optimize the molecular property and the variety measure as below:

\[
\begin{align*}
\max_{x \in \mathcal{U}} & \quad \text{Property}(x) + \alpha \cdot \mu(\mathcal{S} \cup \{x\}) \\
= & \max_{x \in \mathcal{U}} \quad \text{Property}(x) + \alpha \cdot [\mu(\mathcal{S} \cup \{x\}) - \mu(\mathcal{S})] \\
= & \max_{x \in \mathcal{U}} \quad \text{Property}(x) + \alpha \cdot \text{Novelty}(x, \mathcal{S}) \\
\end{align*}
\]

where \( \alpha \) is a coefficient related to the property threshold \( C \) that controls the balance between the property and the variety. By introducing a constant term \( \mu(\mathcal{S}) \) and defining the novelty of a molecule \( x \) as \( \text{Novelty}(x, \mathcal{S}) := \mu(\mathcal{S} \cup \{x\}) - \mu(\mathcal{S}) \), we can obtain a new molecular generation objective as Equation 13.

Similar to solving Equation 10, we can also optimize Equation 13 with models or methods like deep generative models, reinforcement learning, Markov chain Monte Carlo (MCMC) sampling, and genetic algorithms (GA). However, one should also notice that the new objective is always shifting as the set of generated molecules \( \mathcal{S} \) grows, making the optimization a much more interesting problem. Besides, there is still a huge gap between the original objective as Equation 11 and the relaxed objective as Equation 13.
5.2. Experiments

To empirically demonstrate the effectiveness of our proposed new optimization objective, we try to generate molecules with an emphasis on chemical space coverage and compare the generated results with methods that only focus on molecular property optimization. The implementation details are listed in Appendix B.

5.2.1. Experiment Setup

Properties. Following the previous paper (Li et al., 2018), we consider the inhibition against an Alzheimer-related target protein c-Jun N-terminal kinase-3 (JNK3) as the biological objective. The score is given by a random forest model \(^1\) that predicts based on Morgan fingerprint features of a molecule (Rogers & Hahn, 2010). Besides, to obtain drug-like and synthesizable molecules, we also consider the drug-likeness QED score (Bickerton et al., 2012) and the synthetic accessibility (SA) (Ertl & Schuffenhauer, 2009) as suggested in Jin et al. (2020); Xie et al. (2021). In summary, the overall property scoring function can be written as 

\[
\text{Property}(x) = JNK3(x) + \text{QED}(x) + \text{SA}(x),
\]

where \(JNK3(\cdot), \text{QED}(\cdot)\), and \(\text{SA}(\cdot)\) are all re-scaled to \([0, 1]\) (the larger the better).

Novelty terms. According to the results of theoretical analysis and empirical studies in Section 3, we choose the outstanding variety Measure \#Circles to derive the novelty term. In addition, we include the Diversity Measure as well since it is widely used to evaluate molecular generation models in the literature. Specifically, we consider the following two novelty terms:

\[
\text{Novelty}_{\text{NN}}(x, S) := \min_{y \in S} [1 - s(x, y)] \quad (14)
\]

\[
\text{Novelty}_{\text{AD}}(x, S) := \frac{1}{|S|} \sum_{y \in S} [1 - s(x, y)] \quad (15)
\]

Models. We use a recently proposed molecular generation model MARS (Xie et al., 2021) as our baseline model. This approach is based on MCMC sampling and is one of the state-of-the-art methods that aim for multi-objective optimization. We run the baseline model by optimizing both Equation 10 and Equation 13 for different novelty terms discussed above, and then compare the generated molecules.

5.2.2. Results and Analysis

Table 1 lists variety Measure values estimated for generated molecules. The model variants NN and AD stand for adding properties.py.

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\(^1\)The JNK3 prediction model: https://github.com/wengong-jin/multiobj-rationale/blob/master/
the novelty terms as Equation 14-15 correspondingly. Each variant equally generates 8.5M molecules in total. We select all unique drug candidates from the 8.5M compounds. These candidates satisfy JNK3 $\geq 0.5$, QED $\geq 0.6$, and SA $\geq 0.67$ (Xie et al., 2021). Then we compute the variety measure values for the selected candidates.

From the table, we can see that both the NN and AD variants improve almost all the variety measures significantly. Remarkably, compared with the baseline model, NN improves $\#FG$ for 4.2 times and $\#Circles$ for 2.4 times. The astounding improvements powerfully illustrate the effectiveness of our proposed coverage formulation. Interestingly, we find the AD variant, derived from Diversity, actually lowers the value of Diversity, which might indicate a conflict between the property term and the novelty term in the optimization.

We also display the variety measure curves in Figure 6 to show how the coverage goes over time. From these figures we can find that the NN variant will converge to much higher variety measure values, meaning it can explore a wider span of chemical space. In Figure 7 we show the pairwise similarity heatmaps of sampled compounds. The molecules generated by the NN variant are much more dissimilar with each other than the rest two models. Again, we observe the AD variant performs worst in terms of fingerprint-based pairwise dissimilarity.

The functional groups discovered by models are visualized in Figure 8. The visualization is obtained by conduct principal component analysis (PCA) on Morgan fingerprints of discovered functional groups. We can intuitively see that the compounds generated by the NN model cover a much larger functional-group space.

6. Conclusion

With an emphasis on the variety of molecular candidates in drug discovery, this paper presents a systematic study on the measurement of such variety. In particular, we formally define the concept of variety measures as functions that map molecular sets to non-negative real numbers and provide an axiomatic analysis as well as empirical studies to investigate the validity of potential variety measures. Overall, we find our suggested $\#Circles$ measure to be an excellent choice both theoretically and practically.

In addition to the study on measuring variety, we also propose a new molecular generation objective that jointly optimize molecular properties and variety measures. Through experiments, we demonstrate that by incorporating the variety measure $\#Circles$, which performs extraordinarily in our systematic measurement analysis, the molecular generating model can discover high-quality compounds that span a wider range of the chemical space.

For future work, it would be interesting to investigate and design more variety measures and apply them to practical scenarios. The optimization of Equation 13 is worth studying as well since the objective will be consistently shifting. We would also be glad to see how our general formulations can be applied to other domains.

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A. Random Subset Experiment Details

A.1. Bio-Activity Dataset

The 10K BioActivity dataset (Koutsoukas et al., 2014) contains 10,000 compound samples excerpted from the ChEMBL database (Gaulton et al., 2017) with bio-activity labels. These labels are the 50 largest ChEMBL activity classes, including enzymes (e.g., proteases, lyases, reductases, hydrolyases, and kinases) and membrane receptors (e.g., GPCRs and non-GPCRs). The label distribution is shown in Figure 9.

![Figure 9. Label distribution of the BioActivity dataset (Koutsoukas et al., 2014). There are 50 classes in total.](image)

We visualize the molecules in the dataset based on their Morgan fingerprints (Rogers & Hahn, 2010) as Figure 10. From the visualization, we can see that the fingerprint similarity is indeed correlated with the bio-activity similarity.

![Figure 10. UMAP visualization of compounds in the BioActivity dataset. Different colors stand for different bio-activity labels.](image)

A.2. Random Subsets with Fixed Sizes

In this experiment, we repeat Algorithm 1 for five times to obtain reliable correlations.

Algorithm 1 Calculating variety measures for random subsets with fixed sizes.

**Input:** The fixed subset size $n$; The bio-activity dataset $\{(x_i, y_i)\}_{i=1}^{10K}$ where $y_i \in \mathcal{Y}$ are bio-activity labels and $|\mathcal{Y}| = 50$; $K$ variety measures $\{\mu_k\}_{k=1}^K$.

**repeat**

Sample a number $m$ uniformly from $\{1, \ldots, 50\}$.
Sample $m$ labels $\mathcal{Y}'$ uniformly from $\mathcal{Y}$.
Sample $n$ molecules $S$ with labels in $\mathcal{Y}'$ uniformly.
Compute $GS(S)$ and $\mu_k(S)$ for $k \in [K]$.
**until** repeated for 100 times

Calculate the correlations between $GS$ and $\{\mu_k\}_{k=1}^K$ based on the 100-times experiment results.

The results we present in Figure 2 for $\#Circles$ is using the threshold $c = 0.35$ (the same to all later experiments). We also study how different choices for the threshold can affect the results. The study is shown in Figure 11, from which we can see $\#Circles$ works well for a wide range of thresholds like $[0.30, 0.45]$. In Olivecrona et al. (2017), the authors suggest to use a threshold $c = 0.40$ to decide whether two molecules are dissimilar with each other, which aligns our results.

A.3. Random Subsets with Growing Sizes

In this experiment, we repeat Algorithm 2 for five times to obtain reliable DTW distances.

To mimic the way in which generation models propose new molecules, in Algorithm 2, we require the newly sampled molecule $x_i$ to be similar to the already sampled molecules $\{x_1, \ldots, x_{i-1}\}$. The specific implementation can be found in our code. Moreover, we also test the following two cases:

1. All molecules are sampled uniformly;
2. The newly
measuring the variety of candidate set in molecular generation

figure 11. umap visualization of compounds in the bioactivity dataset. different colors stand for different bio-activity labels.

sampled molecule $x_i$ have to be most similar to the already sampled molecules $\{x_1, \ldots, x_{i-1}\}$. the results of dtw distances for these two cases are shown in figure 12.

(a) the new molecule $x_i$ is sampled uniformly from unseen molecules.

(b) the new molecule $x_i$ need to be similar to the already samples ones $x_1, \ldots, x_{i-1}$.

(c) the new molecule $x_i$ need to be most similar to the already samples ones $x_1, \ldots, x_{i-1}$.

figure 12. correlations between the golden standard gs and variety measures (the higher the better). three different sampling strategies are shown.

b. molecular generation experiment details

we implement the mars baseline (xie et al., 2021) by following the official code provided by the author and set the hyperparameters as default. for the nn and ad variants, we test different $\alpha$ values in $\{0.3, 1.0, 3.0\}$ and report the best performance ($\alpha = 3.0$ for ad, $\alpha = 1.0$ for nn).