How Much of the Chemical Space Has Been Explored? Selecting the Right Exploration Measure for Drug Discovery

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Abstract

Forming a molecular candidate set that contains a wide range of potentially effective compounds is crucial to the success of drug discovery. While many aim to optimize particular chemical properties, there is limited literature on how to properly measure and encourage the exploration of the chemical space when generating drug candidates. This problem is challenging due to the lack of formal criteria to select good exploration measures. We propose a novel framework to systematically evaluate exploration measures for drug candidate generation. The framework is built upon three formal analyses: an axiomatic analysis that validates the potential measures analytically, an empirical analysis that compares the correlations of the measures to a proxy gold standard, and a practical analysis that benchmarks the effectiveness of the measures in an optimization framework of molecular generation. We are able to evaluate a wide range of potential exploration measures under this framework and make recommendations on existing and novel exploration measures that are suitable for the task of drug discovery.

1. Introduction

Drug discovery aims to find molecules that can effectively bind to certain targets, which is often compared to finding needles in a haystack. Indeed, it is estimated that the small organic chemical space has more than 10^{60} molecules (Kirkpatrick & Ellis, 2004; Ruddigkeit et al., 2012). In such a tremendous space, only a small number of molecules can satisfy the bioactivity requirement for a specific target. In contrast, the space that has been explored by scientists is very limited: the largest authoritative molecular database contains only around 10^8 compounds (Kim et al., 2020).

Machine learning based approaches have demonstrated great potential in helping scientists go beyond the known molecules and efficiently navigate through the huge chemical space, usually through *de novo* molecular generation (Elton et al., 2019; Schwalbe-Koda & Gómez-Bombarelli, 2020; Bian & Xie, 2021; Deng et al., 2022). 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 obtained using biological activity prediction models (Olivecrona et al., 2017; Li et al., 2018), which is the key to obtaining 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, as such computationally obtained scores provide limited information about the complex chemical interactions in the real world. Expensive wet-lab experiments are still required to verify the true effectiveness of each candidate molecule. To increase the chance of finding drug hits in these experiments, it is crucial to generate a variety of qualified candidates that explore (or cover) a broad area of the chemical space (Huggins et al., 2011; Wawer et al., 2014; Ashenden, 2018), rather than a concentrated cluster of molecules with high property scores.

A fundamental challenge is quantitatively measuring the extent that a set of candidate molecules explores the chemical space, and we call such measures as *exploration measures*. A potential exploration measure for a molecular set is to test their varieties of inhibitory capability, such as half maximal inhibitory concentration (IC_{50}) across a range of biological targets, through wet-lab experiments (Yung-Chi & Prusoff, 1973). These experimental data provide important reference information for drug design but they are expensive to annotate. An easy-to-calculate exploration measure that faithfully reflects the variety of functionalities is extremely valuable. While a number of studies have evaluated more or less related properties of generated compounds such as *internal diversity* (Brown et al., 2019; Polykovskiy et al., 2020), the validity of these measures is rarely justified. In fact, finding a good measure of exploration itself is challenging.

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Table 1. Regarding the three suggested criteria, #Circles is the most recommended exploration measure, and SumBottleneck (noted as SumBot) is also a good alternative choice.

Measures	*(C1) Axiomatic properties (Sec. 3)*		*(C2) Correla -tions (Sec. 4)*		*(C3) Op -timiza -bility (Sec. 5)*
	Subaddi -tivity	*Dissimi -larity*	*Fixed*	*Growing*	
Diversity	✗	✓	Med	Low	1.35x
SumBot	✗	✓	High	Med	1.87x
#FG	✓	✗	Med	Med	
#Circles	✓	✓	High	High	1.86x
Richness	✓	✓	Low	Med	

Compared to molecular property scores, the ground truth about the coverage of biological functionalities is harder to obtain. Moreover, the chemical space is complex and combinatorial, making the design of a good measure even more difficult.

In this paper, we aim to evaluate potential exploration measures for molecular generation and make recommendations accordingly. In particular, we propose a novel evaluation framework that consists of three complementary criteria, based on which we are able to investigate and evaluate a series of existing and new exploration measures: (C1) The first criterion is based on an axiomatic analysis with two intuitive axioms that a good exploration measure should satisfy. Surprisingly, multiple heuristic measures that are commonly used in literature, such as *internal diversity*, fail to satisfy one or both of the axioms. (C2) The second criterion compares the exploration measures with a proxy of gold standard: the number of unique biological functionalities covered by the set of molecules. We find that a novel exploration measure not only satisfies both axioms but also better correlates with the gold standard. (C3) The third criterion further evaluates the selected measures in an optimization setting, *i.e.*, how effectively one can jointly optimize the molecular property scores and each exploration measure. By simply adding novelty terms derived from proper exploration measures to the objective function of a state-of-the-art molecular generation model, the augmented models can discover high-quality molecules that span a larger chemical space, in comparison to optimizing molecular properties alone or with alternative exploration measures.

2. Related Work

2.1. Molecular Generation

Most studies in drug discovery lays their focus on optimizing molecular properties of generated compounds. Traditionally, rule-based genetic algorithms (GA) and fragment-based combinatorial methods are widely applied to find drug candidates (Brown et al., 2004; Devi et al., 2015; Jensen, 2019). Machine learning, especially deep learning models are proposed to optimize molecular property scores with better efficiency. One such example is the variational autoencoder (VAE), which uses 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 to generate compounds in the explicit chemical space (Olivecrona et al., 2017; You et al., 2018; De Cao & Kipf, 2018; Popova et al., 2019; Shi et al., 2020). Recently, Markov chain Monte Carlo (MCMC) methods also present strong performance in optimizing multiple desired properties simultaneously (Xie et al., 2021). Targeting molecular properties usually leads these algorithms into narrow regions of similar compounds and hinders exploration into the broader chemical space.

2.2. Measuring Exploration

Beyond property optimization, some studies evaluate the molecular generation models with measures that are more or less related to the degree of exploration in the chemical space. Commonly used measures include internal diversity, external diversity, and the number or percentage of unique molecules (You et al., 2018; De Cao & Kipf, 2018; Elton et al., 2019; Brown et al., 2019; Popova et al., 2019; Polykovskiy et al., 2020; Shi et al., 2020; Xie et al., 2021). Zhang et al. (2021) propose to use the number of unique functional groups or ring systems to estimate the chemical space coverage and to compare several recent generative models. Similarly in Blaschke et al. (2020), the number of unique Bemis-Murcko scaffolds is used to measure the variety of drug candidates. Koutsoukas et al. (2014) study the effect of molecular fingerprinting schemes on the internal diversity of compound selection. These measures usually mix the concepts of diversity, coverage, or novelty, and their validity as a measure of exploration is not justified.

To the best of our knowledge, this is the first work that formally investigates the validity of the molecular exploration measures. In particular, axiomatic approaches are used to analytically evaluate various designs of a measurement, such as utility functions (Herstein & Milnor, 1953), cohesiveness (Alcalde-Unzu & Vorsatz, 2013), or document relevance (Fang et al., 2004). Using axiomatic analysis to evaluate the exploration measures in the chemical space is novel. With empirical studies in addition to the axiomatic analysis, we make practical recommendations on effective exploration measures, including two novel measures.

2.3. Encouraging Exploration

A handful of work tries to encourage the model to explore broader chemical space. For example, Nigam et al. (2020) add an adversarial loss into the fitness function of GA to avoid the traps of local optima; Blaschke et al. (2020) use a

memory unit to score the novelty of generated molecules; Bengio et al. (2021) suggest to sample a distribution of trajectories instead of generating a single sequence of actions with highest-reward; Fu et al. (2021) incorporate a determinantal point process (DPP) strategy to encourage the diversity of compounds.

One of our analyses explicitly formalizes the molecular generation problem as a joint optimization of both molecular properties and a given exploration measure so we can study the behavior of multiple measures in this optimization setting. This formulation also suggests a strong potential for improving drug discovery by encouraging exploration.

3. Criterion #1: An Axiomatic Analysis of Molecular Exploration Measures

We first present an axiomatic approach to analytically evaluating various exploration measures of the chemical space.

3.1. Definition of Exploration Measures

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

Assumption 3.1 (Chemical space)**.** The chemical space $\mathcal{U}$ contains all possible molecules and is a metric space with a distance metric function $d : \mathcal{U} \times \mathcal{U} \to [0, +\infty)$.

This assumption is widely adopted in cheminformatics, using distance metrics such as the Tanimoto distance (Tanimoto, 1968; Bajusz et al., 2015).

Definition 3.2 (Tanimoto distance)**.** For two molecules $x_1, x_2 \in \mathcal{U}$, whose binary molecular fingerprint vectors are $\boldsymbol{x}_1, \boldsymbol{x}_2 \in \{0, 1\}^n$ where n is the dimensionality of the fingerprint, their Tanimoto distance is defined as

$$d(x_1, x_2) := \frac{\sum_{j=1}^{n} \boldsymbol{x}_{1j} \cdot \boldsymbol{x}_{2j}}{\sum_{j=1}^{n} \max(\boldsymbol{x}_{1j}, \boldsymbol{x}_{2j})}.$$

The Tanimoto distance is also referred to as the Jaccard distance (Jaccard, 1912) in other domains. Its range is $[0, 1]$. For finite sets (*e.g.*, molecular fingerprints), the Jaccard distance is a metric function (Kosub, 2019; Lipkus, 1999).

Besides the Tanimoto distance, one can also use the distance of latent hidden vectors (Preuer et al., 2018; Samanta et al., 2020) or the root-mean-square deviation (RMSD) of three-dimensional molecular conformers (Fukutani et al., 2021).

We then define an exploration measure as the following.

Definition 3.3 (Exploration measure)**.** Given the universal chemical space $\mathcal{U}$, an exploration measure is a function that maps a set of molecules to a non-negative real number that reflects to what extent the set spans the chemical space, *i.e.*, $\mu : \mathcal{P}(\mathcal{U}) \to [0, \infty)$, where $\mathcal{P}(\cdot)$ is the notation of power set. In particular, $\mu(\emptyset) = 0$.

3.2. Examples of Exploration Measures

Definition 3.3 is intentionally left general. Many measures related to the coverage, diversity, or novelty of a molecular set fall into this definition. We summarize these various measures used in literature into three categories: *distance-based* measures, *coverage-based* measures, and *locality-based* measures. We are also able to define new exploration measures under this formulation.

3.2.1. Distance-based Measures

For a set $\mathcal{S}$ with n molecules, we can define an exploration measure according to the distances among the molecules:

$$\text{Diversity}(\mathcal{S}) := \frac{2}{n(n-1)} \sum_{\substack{x,y \in \mathcal{S} \\ x \neq y}} d(x, y), \tag{1}$$

$$\begin{aligned}\text{SumDiversity}(\mathcal{S}) &:= \sum_{x \in \mathcal{S}} \frac{1}{n-1} \sum_{\substack{y \in \mathcal{S} \\ y \neq x}} d(x, y) \\ &= n \cdot \text{Diversity}(\mathcal{S}),\end{aligned} \tag{2}$$

$$\text{Diameter}(\mathcal{S}) := \max_{\substack{x,y \in \mathcal{S} \\ x \neq y}} d(x, y), \tag{3}$$

$$\text{SumDiameter}(\mathcal{S}) := \sum_{x \in \mathcal{S}} \max_{\substack{y \in \mathcal{S} \\ y \neq x}} d(x, y), \tag{4}$$

$$\text{Bottleneck}(\mathcal{S}) := \min_{\substack{x,y \in \mathcal{S} \\ x \neq y}} d(x, y), \tag{5}$$

$$\text{SumBottleneck}(\mathcal{S}) := \sum_{x \in \mathcal{S}} \min_{\substack{y \in \mathcal{S} \\ y \neq x}} d(x, y), \tag{6}$$

$$\text{DPP}(\mathcal{S}) := \det(\boldsymbol{S}), \tag{7}$$

where x, y are molecules in $\mathcal{S}$, d is a distance metric as defined previously, and $\boldsymbol{S}$ is the similarity matrix of candidate molecules (*e.g.*, $1 - d(x, y)$ for Tanimoto similarity).

Among these measures, Diversity (also referred to as the *internal diversity*), the average distance between the molecules, is widely used in the literature (You et al., 2018; De Cao & Kipf, 2018; Popova et al., 2019; Polykovskiy et al., 2020; Shi et al., 2020; Xie et al., 2021). We follow the topology theory and also introduce Diameter and Bottleneck as the maximum and minimum distance between any pair of molecules respectively (Edelsbrunner & Harer, 2010), since they can also reflect the dissimilarity between molecules in $\mathcal{S}$. We further introduce three Sum- variants for the above measures. The Sum- variants will tend to increase when new molecules are added to the set. In addition, the determinant of the similarity matrix of molecules is also a measure of dissimilarity, which is often employed in diverse subset selection as a key concept of the determinantal point processes (DPP) (Kulesza & Taskar, 2011; 2012).

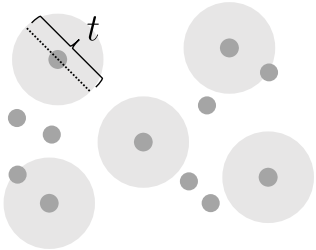


Figure 1. #Circles counts the maximum number of mutually exclusive circles that can fit into the molecular set $\mathcal{S}$, where t is the diameter of circles. In this example, #Circles$(\mathcal{S}) = 5$.

3.2.2. Coverage-based Measures

Another broad category of exploration measures compares the generated molecules $\mathcal{S}$ with a reference set $\mathcal{R}$. In such context, a coverage-based measure can be defined as below:

$$\text{Coverage}(\mathcal{S}, \mathcal{R}) := \sum_{y \in \mathcal{R}} \left(\max_{x \in \mathcal{S}} \text{cover}(x, y) \right), \quad (8)$$

where cover(x, y) indicates how the molecule x can cover the reference y.

When the reference set $\mathcal{R}$ is taken as a collection of molecular fragments, the coverage function can be written as

$$\text{cover}(x, y) := \mathbb{I}[\text{molecule } x \text{ contains fragment } y],$$

where $\mathbb{I}[\cdot]$ is the indication function. A large body of drug discovery literature uses the number of distinct functional groups (FG), ring systems (RS), or Bemis-Murcko scaffolds (BM) in $\mathcal{S}$ to gauge the size of explored chemical space (Zhang et al., 2021; Blaschke et al., 2020), corresponding to the cases where $\mathcal{R}$ is the collection of all possible FG, RS, or BM fragments. We denote these specific coverage-based measures as #FG, #RS, and #BM respectively.

3.2.3. Locality-based Measures

Inspired by the sphere exclusion algorithm used in compound selection (Snarey et al., 1997; Gobbi & Lee, 2003), we introduce a new exploration measure that highlights the local neighborhoods covered by a set of molecules:

$$\begin{aligned} \#\text{Circles}(\mathcal{S}) := \max_{\mathcal{C} \subseteq \mathcal{S}} \ & |\mathcal{C}| \\ \text{s.t. } & d(x, y) > t, \quad \forall x, y \in \mathcal{C}, \end{aligned} \quad (9)$$

where $t \in [0, 1)$ is a distance threshold that corresponds to the diameter of a circle.

Intuitively, as shown in Figure 1, #Circles counts the maximum number of mutually exclusive circles that can fit into $\mathcal{S}$ as neighborhoods, with a subset of its members $\mathcal{C}$ as the circle centers. When the threshold $t = 0$, #Circles becomes the richness measure

$$\text{Richness}(\mathcal{S}) := |\{\mathcal{S}\}|, \quad (10)$$

which is the number of unique molecules (Moore, 2013; Shi & von Itzstein, 2019).

3.3. Axiomatic Analysis

While all the aforementioned measures can heuristically reflect the degree of exploration, they do not always agree with each other. We need a principled way to select the most suitable measures from a variety of possible choices. Ideally, these criteria should not depend on the particular targeted molecular properties or the algorithm used to generate the candidates. We achieve this through an axiomatic approach.

We propose two simple and intuitive principles that a good exploration measure should satisfy: (1) discovering more molecules should not decrease the degree of exploration; (2) molecular sets with more dissimilar molecules have a higher degree of exploration. These two principles are formalized below as two axioms and can be tested analytically.

Axiom 3.4 (Subadditivity)**.** *A good exploration measure μ should be subadditive, i.e., for any two molecular sets $\mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$, it holds that*

$$\max(\mu(\mathcal{S}_1), \mu(\mathcal{S}_2)) \leq \mu(\mathcal{S}_1 \cup \mathcal{S}_2) \leq \mu(\mathcal{S}_1) + \mu(\mathcal{S}_2).$$

A subadditive measure tends to increase when more molecules are included. This tendency is very intuitive in drug discovery as testing more molecules means we can have a higher probability of discovering a potentially effective drug. Some direct corollaries are listed in Appendix A.

A subadditive exploration measure is a special case of *outer measures* in the context of mathematical measure theory. *Outer measures* are relaxations of *measures*, where the latter requires a stricter additivity property, *i.e.*, $\mu(\mathcal{S}_1 \cup \mathcal{S}_2) = \mu(\mathcal{S}_1) + \mu(\mathcal{S}_2)$ for any two disjoint sets $\mathcal{S}_1, \mathcal{S}_2$ (Halmos, 2013). We consider additivity to be too strong and can conflict with intuitions in drug discovery: an additive measure defined on a discrete space must take the form of $\mu(\mathcal{S}) = \sum_{x \in \mathcal{S}} w(x)$, in which $w(\cdot)$ is a weight function that independently assigns a score to each element in the space, meaning that additive measures defined on the discrete chemical space cannot capture the interrelationship between molecules in a candidate set, which counters the reality.

Axiom 3.5 (Dissimilarity)**.** *A good exploration measure should have a preference to dissimilar elements, i.e., for any two molecules $x_1, x_2 \in \mathcal{U}$ and a molecular set $\mathcal{X}(x_1, x_2) =$*

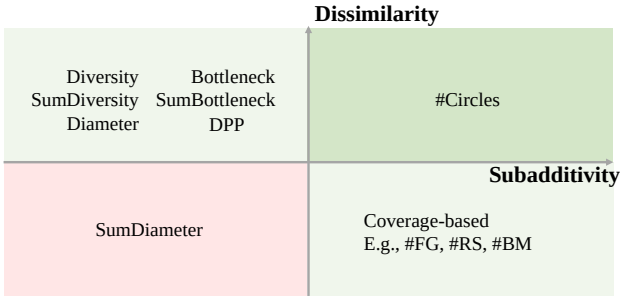


Figure 2. Exploration measures, categorized by whether they satisfy subadditivity and/or dissimilarity. #Circles is the only measure that satisfies both subadditivity and dissimilarity.

$\{x \mid d(x, x_1) + d(x, x_2) = d(x_1, x_2),\ x \neq x_1, x_2\}$, *it holds*

$$\mu(\{x_1, x_2, x^*\}) = \max_{x \in \mathcal{X}} \mu(\{x_1, x_2, x\}),$$

where x^* *satisfies* $d(x^*, x_1) = d(x^*, x_2) = \frac{1}{2} d(x_1, x_2)$ *and* d *is the distance metric on the chemical space* $\mathcal{U}$.

Intuitively, consider two molecules x_1, x_2 that are placed at the two endpoints of a "segment". An exploration measure satisfying the dissimilarity axiom should increase the most when the molecule x^* is added to the middle point of the segment, since x^* is most dissimilar to x_1, x_2 compared to any other points on the segment.

Depending on whether each exploration measure satisfies *subadditivity* and/or *dissimilarity*, we can put it into one of four quadrants as shown in Figure 2. The formal proofs are provided in Appendix B. Despite that the two axioms are simple and intuitive, surprisingly, the proposed #Circles is the only measure that satisfies both axioms.

4. Criterion #2: Correlation with Biological Functionality

While it is encouraging that only one measure stands out in the axiomatic analysis, it does not guarantee its empirical performance. Meanwhile, there are multiple measures that satisfy *one* of the two axioms. We further investigate the validity of the exploration measures by testing their correlation with the variety of the biological functionality of molecules. Such functionalities are expensive to annotate and are biased toward biological functions of human interests, but they still provide valuable information in distinguishing molecules and guiding the exploration of the unknown space.

In this section, we correlate the aforementioned exploration measures to the number of unique biological functionalities covered by a molecular set. A better exploration measure should have a higher correlation to the coverage of biological functionalities.

4.1. Experiment Setup

We base the analysis on the BioActivity dataset that is also used to compare different compound selection algorithms (Koutsoukas et al., 2014). This dataset contains 10,000 compound samples extracted from the ChEMBL database (Gaulton et al., 2017) with bio-activity labels, which contain 50 activity classes with 200 samples each. Following Koutsoukas et al. (2014), for a subset of this dataset $\mathcal{S}$, we take the number of unique class labels as a proxy "gold standard" of the variety of the molecules in $\mathcal{S}$, *i.e.*,

$$\text{GS}(\mathcal{S}) := \#\text{unique labels in } \mathcal{S},$$

which represents the number of biological functionality types covered by $\mathcal{S}$. We then compare the behavior of the gold standard and the exploration measures in two settings to determine their correlations.

4.2. Random Subsets with Fixed Sizes

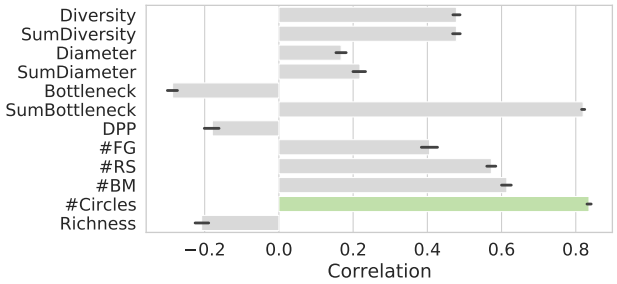
We first consider randomly sampled molecular subsets of the BioActivity dataset with a fixed size n. We randomly sample n molecules $\mathcal{S}$ from the dataset and compute the biological functionality coverage GS($\mathcal{S}$) as well as each exploration measure $\mu(\mathcal{S})$. By repeating the randomization, we can calculate Spearman's correlation between the gold standard GS and each individual measure μ.

From the correlations shown in Figure 3a, #Circles and SumBottleneck have notably higher correlations to the gold standard than other measures. This indicates that the locality information is critical in evaluating exploration, as both of the measures prefer new molecules that are at arm's length from their nearest neighbors.

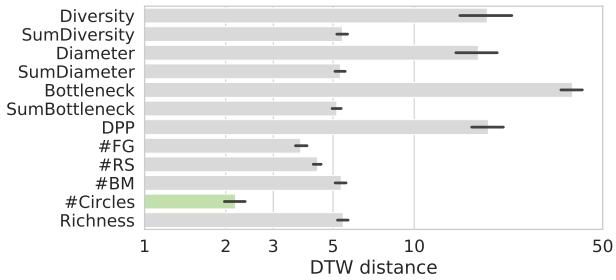
4.3. Random Subsets with Growing Sizes

To mimic the molecular generation process, we also grow the size of the subsets. Specifically, for a maximum size n, we sequentially sample n molecules without replacement to form n subsets $\{\mathcal{S}_i = \{x_1, \ldots, x_i\}\}_{i=1}^n$. For both the gold standard GS and an exploration measure μ, we record their values as $\mathcal{S}$ grows into a time series, *e.g.*, $\{(i, \mu(\mathcal{S}_i))\}_{i=1}^n$. Comparing the trajectory of an exploration measure with the trajectory of the gold standard, we can observe the measure that behaves more similarly to GS. We quantitatively estimate the similarity of their trajectories with the dynamic time warping (DTW) distance of the two time series.

As shown in Figure 3b, #Circles surpasses all other exploration measures. Coverage-based measures such as #FG, #RS, and #BM also perform prominently. Both #Circles and coverage-based measures satisfy the subadditivity property, making them suitable for a "growth" setting. The Sum- variants of distance-based measures outperform their original forms, as they tend to increase when adding new molecules.



(a) Correlations between the gold standard GS and exploration measures in the fixed-size setting. The subset size is set as $n = 200$. A higher correlation is better.



(b) DTW distances between the gold standard GS and exploration measures in the growing-size setting. The maximum size is set as $n = 1000$. A smaller distance is better.

Figure 3. Correlation between each exploration measure and biological functionality coverage. The exploration measure with the highest correlation is highlighted in green. Results are aggregated by running experiments independently for ten times.

4.4. Discussion

The exploration measures behave differently between the *fixed-size* and the *growth* settings; this discrepancy suggests that we might need different measures for different settings. For instance, SumBottleneck performs closely to #Circles in the fixed-size setting but falls behind significantly in the growth setting. This might be attributed to its requirement on subadditivity, which SumBottleneck fails to meet. Notably, #Circles stands out in both settings, suggesting its great potential in practice.

The experiment details are listed in Appendix C, where we also discuss the impact of the distance metric d. As shown in Table 3 and 3, we find the experiment results remain consistent when using a different distance metric (*i.e.*, the latent space dissimilarity). We also study the sensitivity of the subset size n, the strategy of adding new molecules, and the threshold t of #Circles.

The empirical analysis shows that the locality-based #Circles measure is a robust choice for all tested scenarios, which reconfirms the conclusion of the axiomatic analysis. SumBottleneck may be an effective choice when a fixed number of candidates are the target. Coverage-based measures may be a good alternative if carefully-designed and comprehensive reference sets are available. Surprisingly, the widely used Diversity measure is rendered inferior both analytically and empirically, raising doubts on its efficiency in measuring and encouraging exploration in molecular generation.

5. Criterion #3: Optimizability of Exploration Measures

While the previous two criteria validate the quality of exploration measures in theory, their effectiveness also rely on how they are deployed in practice. In particular, a good exploration measure should be optimizable and encourage exploration in the context of real-world molecular generation. In this section, we further investigate the exploration measures in these regards.

5.1. Problem Formulation

In drug discovery, the search for active molecules towards a druggable target is often formulated as the following optimization problem (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):

$$\arg\max_{x \in \mathcal{U}} \quad \text{Property}(x) \tag{11}$$

where x is a molecule in the chemical space $\mathcal{U}$ and Property : $\mathcal{U} \to \mathbb{R}$ is a function that scores particular biological properties of the molecule. This property term can incorporate bio-activity such as binding affinity to protein targets, drug-likeness, synthesizability, *etc*. (Nicolaou et al., 2012; Jin et al., 2020; Xie et al., 2021), and these properties are obtained computationally and often mapped into a single score.

However, the computational models for these properties cannot predict wet-lab results with desired accuracy or lack meaningful impact during the hit identification stage of drug discovery. As pointed out in the chemistry literature, other than optimizing the property scores, it is crucial to generate a variety of compounds that span a wider range of the chemical space (Huggins et al., 2011; Wawer et al., 2014; Ashenden, 2018). We therefore propose the following objective as the goal of molecular generation:

$$\arg\max_{\mathcal{S} \subseteq \mathcal{U}} \quad \mu(\mathcal{S}) \quad \text{s.t.} \quad \text{Property}(x) \geq C, \; x \in \mathcal{S}, \tag{12}$$

where $\mathcal{S} \subseteq \mathcal{U}$ is a molecular candidate set, $\mu(\cdot)$ is an exploration measure, $\text{Property}(x) \geq C$ indicates the property score of a molecule x being at or above threshold C.

This constrained optimization problem is very challenging due to its combinatorial characteristics. To this end, we pro-

Table 2. Exploration measures are optimizable through novelty terms. Adding novelty terms to MARS promotes the chemical space exploration as quantified by the exploration measures on generated molecules (the larger the better). Underline indicates the best performance in each measure. Results are aggregated from 5 independent runs of the experiments. Grey highlights #Circles, which is the best exploration measure in theory (among considered).

Model	#Circles(↑)	SumBottleneck(↑)	#FG(↑)	Richness(↑)	Diversity(↑)
‘ **MARS** (Xie et al., 2021)	380 ± 10	2149 ± 175	346 ± 55	134K ± 14K	0.736 ± 0.007
+ Diversity	514 ± 33	3001 ± 409	441 ± 85	186K ± 29K	0.750 ± 0.006
+ SumBottleneck	709 ± 66	3777 ± 494	868 ± 133	221K ± 30K	0.752 ± 0.003
+ #Circles	706 ± 155	3013 ± 364	601 ± 211	179K ± 31K	0.749 ± 0.006

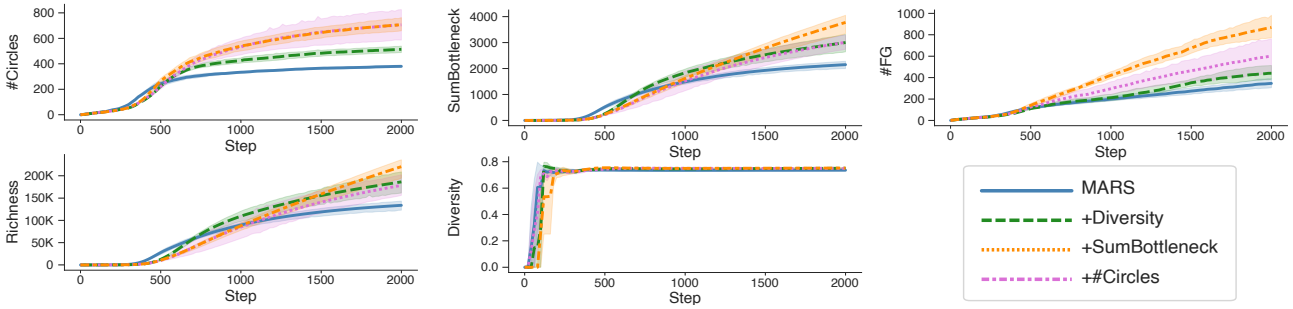


Figure 4. The dynamics of exploration measures over generated molecules. Adding novelty terms increases the exploration in the chemical space. MARS+SumBottleneck achieves the highest degree of exploration over time. All models converge in Diversity quickly.

pose a relaxed alternative to Equation 12. We use a greedy strategy to convert the molecular set generation problem into a single molecule generation problem:

$$\begin{aligned} &\arg\max_{x\in\mathcal{U}} \quad \mu(\mathcal{S}\cup\{x\}) \quad \text{s.t.} \quad \text{Property}(x)\geq C \\ \approx &\arg\max_{x\in\mathcal{U}} \quad \text{Property}(x)+\alpha\cdot\mu(\mathcal{S}\cup\{x\}) \\ = &\arg\max_{x\in\mathcal{U}} \quad \text{Property}(x)+\alpha\cdot[\mu(\mathcal{S}\cup\{x\})-\mu(\mathcal{S})] \\ = &\arg\max_{x\in\mathcal{U}} \quad \text{Property}(x)+\alpha\cdot\text{Novelty}(x,\mathcal{S}), \end{aligned} \tag{13}$$

where x is the molecule to be generated and $\mathcal{S}$ is the generated drug candidates. Then to efficiently find the plausible molecule, we can jointly optimize the molecular property and the exploration measure. In the equations, α is a coefficient related to the property threshold C that controls the balance between the property and the exploration. By introducing a constant term $\mu(\mathcal{S})$ and defining the novelty of a molecule x as how much it expands the exploration, *i.e.*, $\text{Novelty}(x,\mathcal{S}) := \mu(\mathcal{S}\cup\{x\})-\mu(\mathcal{S})$, we obtain a new molecular generation objective as Equation 13.

Like Equation 11, Equation 13 can be optimized with methods like deep generative models, reinforcement learning, Markov chain Monte Carlo (MCMC), or genetic algorithms (GA). However, one should notice that the new objective is always shifting as the set of generated molecules $\mathcal{S}$ grows. Besides, there is still a gap between the original objective (Equation 12) and the relaxed objective (Equation 13).

5.2. Experiments

In the experiments, we study which exploration measures are more compatible with the optimization objective Equation 13 and encourage better chemical space exploration. The implementation details are listed in Appendix D.

5.2.1. Experiment Setup

Properties. Following previous studies (Li et al., 2018; Jin et al., 2020), we consider the inhibition against an Alzheimer-related target protein c-Jun N-terminal kinase-3 (JNK3) as the biological objective. JNK3 is the neuron-specific isoform of JNK that expresses primarily in the brain and heart. Designing the inhibitor of JNK3 signaling has raised interest in the science community as it could become a potential drug for neural-degenerative diseases such as Alzheimer (Antoniou et al., 2011; Nakano et al., 2020). The JNK3 binding affinity score is predicted by a random forest model[1] based on Morgan fingerprint of a molecule (Rogers & Hahn, 2010). A higher score indicates that the small molecule design is likely to bind to the JNK3 target. Besides, to obtain drug-like and synthesizable molecules, we also consider the quantitative estimate

[1]The JNK3 prediction model we adopt in the experiments is provided at https://github.com/wengong-jin/multiobj-rationale.

of drug-likeness (QED) (Bickerton et al., 2012) and the synthetic accessibility (SA) (Ertl & Schuffenhauer, 2009) as suggested in Jin et al. (2020) and Xie et al. (2021). In summary, the overall property scoring function can be written as $\text{Property}(x) = \text{JNK3}(x) + \text{QED}(x) + \text{SA}(x)$, where $\text{JNK3}(\cdot)$, $\text{QED}(\cdot)$, and $\text{SA}(\cdot)$ are all re-scaled to $[0, 1]$ (the larger the better).

Models. We use the recently proposed molecular generation model MARS (Xie et al., 2021) as our baseline. MARS is based on MCMC sampling and aims at optimizing multiple drug discovery objectives simultaneously. We choose MARS mainly because of its state-of-the-art performance on multi-objective molecular generation. The model is suitable in dealing with the additional novelty objective in Equation 13.

Novelty terms. Based on the axiomatic and empirical analyses in previous sections, we choose the better-performing exploration measures #Circles and SumBottleneck to derive the novelty terms. The Coverage-based measures are not included due to the consideration of computational efficiency. In addition, we include the most commonly-used Diversity measure for the purpose of comparison. Specifically, we consider the following three novelty terms[2]:

$$\text{Novelty}_{\text{Diversity}}(x, \mathcal{S}) := \frac{1}{|\mathcal{S}|} \sum_{y \in \mathcal{S}} d(x, y) \tag{14}$$

$$\text{Novelty}_{\text{SumBottleneck}}(x, \mathcal{S}) := \min_{y \in \mathcal{S}} d(x, y) \tag{15}$$

$$\text{Novelty}_{\text{\#Circles}}(x, \mathcal{S}) := \left[\min_{y \in \mathcal{S}} d(x, y) > t\right] \tag{16}$$

We use MARS to optimize both Equation 11 and Equation 13 with different novelty terms as in Equation 14-16.

Evaluation. We compare the molecules generated with and without the novelty term, using multiple exploration measures to validate whether adding the novelty terms indeed increases exploration. We examine the difference in three high-quality exploration measures, #Circles, SumBottleneck, and #FG, since they all have a relatively high correlation with the biological functionality coverage. Note we cannot directly measure the biological functionality coverage as in Section 4, as many of the generated molecules are not in the BioActivity database. We also include Richness and Diversity as they are widely used in the literature, even though they perform weakly in the previous analyses (denoted as weak measures). For each model variant, 10M molecules are generated. Duplicated molecules are removed, and the candidates that satisfy JNK3 ≥ 0.5, QED ≥ 0.6, and SA ≥ 0.67 are selected for computing the exploration measures as suggested in Jin et al. (2018); Xie et al. (2021).

[2]Equations 14-16 are approximations of $[\mu(\mathcal{S} \cup \{x\}) - \mu(\mathcal{S})]$ defined to avoid numerical issues and for computational efficiency.

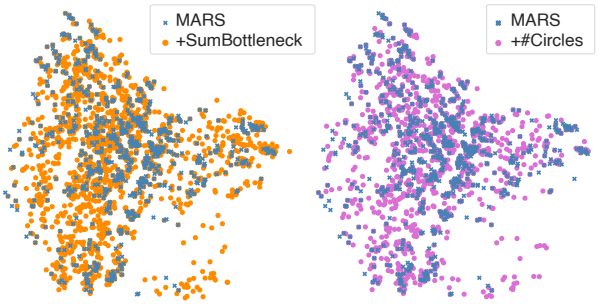


Figure 5. Optimizing exploration measures encourages the molecular generation model to explore a larger span of the chemical space. This figure shows principal component analysis (PCA) of functional groups discovered by different models.

5.2.2. Results and Discussion

Table 2 lists the values of exploration measures with and without the novelty terms, estimated for the molecules generated in 2000 sampling steps.

By introducing novelty terms, all exploration measures are significantly improved during molecular generation, showing a strong optimizability of these measures. Comparing model variants implemented with different novelty terms, both MARS+SumBottleneck and MARS+#Circles obtain a higher degree of exploration (in all three high-quality measures) than MARS+Diversity does. In particular, MARS+SumBottleneck leads in all measures and even outperforms the MARS+#Circles variant. We note a larger variance of MARS+#Circle, which indicates it might be less efficient to optimize. In summary, while all novelty terms encourage the model to explore chemical space to a greater extent, SumBottleneck and #Circles are much better performing than Diversity.

We plot the dynamics of each exploration measure over the generated molecules from the four models in Figure 4. The MARS+SumBottleneck model converges to a higher degree of exploration in multiple measures, suggesting that it gradually spans a larger portion of the chemical space. MARS+#Circles behaves similarly but with a larger variance. Interestingly, all four models converge in Diversity very quickly, disregarding the large number of new molecules discovered, again suggesting the widely used Diversity might not be suitable for measuring exploration.

In Figure 5, the chemical space explored by the baseline (MARS) and MARS+SumBottleneck as well as MARS+#Circles is visualized by principal component analysis (PCA). The data points are calculated from Morgan fingerprints (Rogers & Hahn, 2010) of the unique functional groups in the generated molecules. The larger number and

the spread from the models with exploration-based novelty term suggest a more diverse set of structures being explored.

In summary, SumBottlenck and #Circles are both well optimizable when they are incorporated into the objective as novelty terms, and they truly encourage molecular generation models to explore expansively in the chemical space.

A few limitations of optimization with novelty terms should be noted. First, the computation of novelty terms on large molecular generation campaigns is significantly more costly. This limitation is to be addressed by more efficient algorithms of the measures. Second, the performance of the MARS+#Circles model can be influenced by the selection of the distant threshold t (circle diameter); more sensitivity tests and hyper-parameter tuning strategies are needed to determine the optimal threshold.

6. Conclusion

We present a systematic study on the measurement of chemical space exploration in drug discovery. We formally define the concept of exploration measures and propose a novel framework of validation in three aspects: analytical validation with two axioms, examination of the correlations between exploration measures and biological functionality coverage, and benchmark of the optimizability in the real-world molecular generation task. Overall, we find that the #Circles measure is an outstanding choice both theoretically and empirically. A new distance-based measure, SumBottleneck, also demonstrates excellent empirical and practical performance. Diversity, although widely reported to be used in literature, is sub-optimal as a measure of exploration.

For future work, it would be interesting to design and evaluate more exploration measures under this framework and apply them to practical drug discovery scenarios. The optimization of Equation 13 inspires further investigation, since the objective will be consistently shifting. The proposed exploration measures can be applied to other domains.

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A. Subadditivity Corollaries

Corollary A.1. ***(Subtraction)****. If an exploration measure μ is subadditive, then for any two molecular sets $\forall \mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$, we have*

$$\mu(\mathcal{S}_1) \geq \mu(\mathcal{S}_1 \setminus \mathcal{S}_2) \geq \mu(\mathcal{S}_1) - \mu(\mathcal{S}_2).$$

Corollary A.2. ***(Monotonicity)****. If an exploration measure μ is subadditive, then for any molecular set $\forall \mathcal{S} \subseteq \mathcal{U}$ and a single molecule $x \in \mathcal{U}$, we have $\mu(\mathcal{S} \cup \{x\}) \geq \mu(\mathcal{S})$ and $\mu(\mathcal{S} \setminus \{x\}) \leq \mu(\mathcal{S})$.*

Corollary A.3. ***(Dominance)****. If an exploration measure μ is subadditive, then for any two molecular sets $\forall \mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$, if $\mathcal{S}_1 \subseteq \mathcal{S}_2$, then $\mu(\mathcal{S}_1) \leq \mu(\mathcal{S}_2)$.*

B. Proofs for Subadditivity and Dissimilarity

In Figure 2 we show the exploration measures according to whether they will satisfy subadditivity and/or dissimilarity. In this section, we provide proofs to verify each measure's subadditivity and dissimilarity.

Note that for distance-based measures, when $|\mathcal{S}| = 1$, $\mu(\mathcal{S})$ is not defined through Equation 1-7. So without loss of generality, we assume $\mu(\{x\}) = w(x),\ x \in \mathcal{U}$ in such cases, where $w : \mathcal{U} \to \mathbb{R}$ is an importance function. However in the following proofs, we can see that the choice of $w(\cdot)$ will not influence our conclusion.

Proposition B.1 (Subadditivity of exploration measures.)**.** *Coverage-based exploration measures and #Circles are subadditive. Distance-based exploration measures including Diversity, SumDiversity, Diameter, SumDiameter, Bottleneck, SumBottleneck, and DPP are not subadditive.*

Proof. For the **coverage-based** exploration measures, we denote the cover$(\cdot, \cdot)$ function as cov$(\cdot, \cdot)$ for short. We prove the subadditivity of coverage-based measures by first proving the subadditivity of the maximum of cover$(\cdot, \cdot)$.

To prove the subadditivity of the maximum of cov$(\cdot, \cdot)$, we consider combining any two molecular sets $\mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$. For any reference $y \in \mathcal{R}$, we have

$$\begin{aligned}
&\max\left(\max_{x \in \mathcal{S}_1} \text{cov}(x, y), \max_{x \in \mathcal{S}_2} \text{cov}(x, y)\right) \\
\leq &\max_{x \in \mathcal{S}_1 \cup \mathcal{S}_2} \text{cov}(x, y) \\
\leq &\max_{x \in \mathcal{S}_1} \text{cov}(x, y) + \max_{x \in \mathcal{S}_2} \text{cov}(x, y).
\end{aligned}$$

Therefore,

$$\begin{aligned}
&\max\left(\text{Coverage}(\mathcal{S}_1), \text{Coverage}(\mathcal{S}_2)\right) \\
\leq &\text{Coverage}(\mathcal{S}_1 \cup \mathcal{S}_2) \\
\leq &\text{Coverage}(\mathcal{S}_1) + \text{Coverage}(\mathcal{S}_1),
\end{aligned}$$

thus proving the Coverage measure is subadditive.

For the **#Circles** exploration measure, we denote #Circles$(\cdot)$ as #C$(\cdot)$ for short and define $\mathcal{C}^*(\mathcal{S}) \subseteq \mathcal{S}$ as an arbitrary set that satisfies $|\mathcal{C}^*(\mathcal{S})| = \#\text{C}(\mathcal{S})$. We prove the subadditivity of #C in two parts.

In the first part, we prove the left-hand side of the subadditivity inequation, *i.e.*, $\max(\#\text{C}(\mathcal{S}_1), \#\text{C}(\mathcal{S}_2)) \leq \#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2)$. For any two molecular sets $\mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$, since $\mathcal{C}^*(\mathcal{S}_1) \subseteq \mathcal{S}_1 \cup \mathcal{S}_2$, according to the definition of #C, we have

$$\#\text{C}(\mathcal{S}_1) \leq \#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2).$$

Similarly, we also have

$$\#\text{C}(\mathcal{S}_2) \leq \#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2),$$

proving the left-hand side of subadditivity.

In the second part, we prove the right-hand side of the subadditivity inequation, *i.e.*, $\#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2) \leq \#\text{C}(\mathcal{S}_1) + \#\text{C}(\mathcal{S}_1)$. We prove this by contradiction. For any two molecular sets $\mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$, we assume $\#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2) > \#\text{C}(\mathcal{S}_1) + \#\text{C}(\mathcal{S}_1)$. Use the notations $\mathcal{C}_1 := \mathcal{C}^*(\mathcal{S}_1 \cup \mathcal{S}_2) \cap \mathcal{S}_1$ and $\mathcal{C}_2 := \mathcal{C}^*(\mathcal{S}_1 \cup \mathcal{S}_2) \cap \mathcal{S}_2$. We have

$$|\mathcal{C}_1| + |\mathcal{C}_2| \geq \#\text{C}(\mathcal{S}_1 \cup \mathcal{S}_2) > \#\text{C}(\mathcal{S}_1) + \#\text{C}(\mathcal{S}_1).$$

Since all values are non-negative, we must have $|\mathcal{C}_1| > \#\text{C}(\mathcal{S}_1)$ or $|\mathcal{C}_2| > \#\text{C}(\mathcal{S}_2)$, contradicting with the definition of $\#\text{C}(\mathcal{S}_1)$ or $\#\text{C}(\mathcal{S}_1)$, thus proving the right-hand side of subadditivity.

For the **Diversity** exploration measure, we denote it as Div$(\cdot)$ for short. We disprove its subadditivity by proving it violates the monotonicity corollary. For a molecule $x \in \mathcal{U}$ and a molecular set $\mathcal{S} \subseteq \mathcal{U}$ with size $n > 1$. If $x \notin \mathcal{S}$, we have

$$
\begin{aligned}
&\text{Div}(\mathcal{S} \cup \{x\}) \\
&= \frac{2}{(n+1)n} \left[\sum_{\substack{y,y' \in \mathcal{S} \\ y \neq y'}} d(y,y') + \sum_{y \in \mathcal{S}} d(x,y) \right] \\
&= \frac{n-1}{n+1} \cdot \text{Div}(\mathcal{S}) + \frac{2}{(n+1)n} \sum_{y \in \mathcal{S}} d(x,y).
\end{aligned}
$$

And the change in Div is

$$
\begin{aligned}
&\text{Div}(\mathcal{S} \cup \{x\}) - \text{Div}(\mathcal{S}) \\
&= \left(\frac{n-1}{n+1} - \frac{n+1}{n+1} \right) \text{Div}(\mathcal{S}) + \frac{2}{(n+1)n} \sum_{y} d(x,y) \\
&= \frac{2}{n+1} \left[-\text{Div}(\mathcal{S}) + \frac{1}{n} \sum_{y} d(x,y) \right].
\end{aligned}
$$

When the average distance of x and $\mathcal{S}$, *i.e.*, $\frac{1}{n}\sum_y d(x,y)$, is less than $\text{Div}(\mathcal{S})$ (*e.g.*, adding an molecule on the "segment" between two existing molecules), Diversity would decrease, thus violating the monotonicity corollary and proving Diversity is not subadditive.

For the **SumDiversity** exploration measure, we denote it as $\text{SD}(\cdot)$ for short. We disprove its subadditivity by proving it violates the right-hand side of the subadditivity, *i.e.*, $\text{SD}(\mathcal{S}_1 \cup \mathcal{S}_2) \leq \text{SD}(\mathcal{S}_1) + \text{SD}(\mathcal{S}_2)$. For two disjoint molecular sets with two molecules in each, *i.e.*, $\{x_1, x_2\}$ and $\{x_3, x_4\}$, we denote $d_{ij} = d(x_i, x_j)$. Then we have

$$
\begin{aligned}
&\text{SD}(\{x_1, x_2, x_3, x_4\}) \\
&= 4 \cdot \text{Div}(\{x_1, x_2, x_3, x_4\}) \\
&= 4 \cdot \frac{2}{4 \cdot 3} (d_{12} + d_{13} + d_{14} + d_{23} + d_{24} + d_{34}),
\end{aligned}
$$

and

$$
\text{SD}(\{x_1, x_2\}) + \text{SD}(\{x_3, x_4\}) = 2 \cdot d_{12} + 2 \cdot d_{34}.
$$

When the inter-set distances are larger than the inner-set distances, *i.e.*, $d_{13}, d_{14}, d_{23}, d_{24} > d_{12}, d_{34}$, we will have $\text{SD}(\{x_1, x_2, x_3, x_4\}) > \text{SD}\{x_1, x_2\} + \text{SD}\{x_3, x_4\}$, violating the right-hand side of the subadditivity, thus proving the SumDiversity measure is not subadditive.

For the **Diameter** exploration measure, we denote it as $\text{Dia}(\cdot)$ for short. We disprove its subadditivity by proving it violates the right-hand side of the subadditivity, *i.e.*, $\text{Dia}(\mathcal{S}_1 \cup \mathcal{S}_2) \leq \text{Dia}(\mathcal{S}_1) + \text{Dia}(\mathcal{S}_2)$. For two disjoint molecular sets $\mathcal{S}_1, \mathcal{S}_2 \subseteq \mathcal{U}$ whose sizes are larger than one, we have

$$
\text{Dia}(\mathcal{S}_1 \cup \mathcal{S}_2) = \max_{\substack{x,y \in \mathcal{S}_1 \cup \mathcal{S}_2 \\ x \neq y}} d(x,y),
$$

and

$$
\text{Dia}(\mathcal{S}_1) + \text{Dia}(\mathcal{S}_2) = \max_{\substack{x,x' \in \mathcal{S}_1 \\ x \neq x'}} d(x,x') + \max_{\substack{y,y' \in \mathcal{S}_2 \\ y \neq y'}} d(y,y').
$$

When the maximum inter-set distance is larger than the maximum inner-set distance, *i.e.*, $\max_{x,y,\in \mathcal{S}_1 \cup \mathcal{S}_2} d(x,y) > \max_{x,x',\in \mathcal{S}_1} d(x,x') + \max_{y,y',\in \mathcal{S}_2} d(y,y')$, we will have $\text{Dia}(\mathcal{S}_1 \cup \mathcal{S}_2) > \text{Dia}(\mathcal{S}_1) + \text{Dia}(\mathcal{S}_2)$, violating the right-hand side of the subadditivity inequation, thus proving the Diameter measure is not subadditive.

For the **SumDiameter** exploration measure, we denote it as $\text{SD}(\cdot)$ for short. We disprove its subadditivity by proving it violates the right-hand side of the subadditivity, *i.e.*, $\text{SD}(\mathcal{S}_1 \cup \mathcal{S}_2) \leq \text{SD}(\mathcal{S}_1) + \text{SD}(\mathcal{S}_2)$. For two disjoint molecular sets with two molecules in each, *i.e.*, $\{x_1, x_2\}$ and $\{x_3, x_4\}$, we denote $d_{ij} = d(x_i, x_j)$. Then we have

$$
\text{SD}(\{x_1, x_2, x_3, x_4\}) = \sum_{i \in [4]} \max_{\substack{j \in [4] \\ j \neq i}} d(x_i, x_j),
$$

and

$$
\text{SD}(\{x_1, x_2\}) + \text{SD}(\{x_3, x_4\}) = 2 \cdot d_{12} + 2 \cdot d_{34}.
$$

When the inter-set distances are larger than the inner-set distances, *i.e.*, $d_{13}, d_{14}, d_{23}, d_{24} > d_{12}, d_{34}$, we will have $\text{SD}(\{x_1, x_2, x_3, x_4\}) > \text{SD}\{x_1, x_2\} + \text{SD}\{x_3, x_4\}$, violating the right-hand side of the subadditivity, thus proving the SumDiameter measure is not subadditive.

For the **Bottleneck** exploration measure, we denote it as $\text{Bot}(\cdot)$ for short. We disprove its subadditivity by proving it violates the monotonicity corollary. Consider adding a molecule x into a molecular set $\mathcal{S}$ with size $n > 1$. If $x \notin \mathcal{S}$, we have

$$
\text{Bot}(\mathcal{S} \cup \{x\}) = \min \left(\text{Bot}(\mathcal{S}), \min_{y \in \mathcal{S}} d(x,y) \right).
$$

When x introduces a more restricting bottleneck, *i.e.*, $\min_y\ d(x,y) < \text{Bot}(\mathcal{S})$, we will have $\text{Bot}(\mathcal{S}\cup\{x\}) < \text{Bot}(\mathcal{S})$, violating the monotonicity corollary, thus proving Bottleneck is not subadditive.

For the **SumBottleneck** exploration measure, we denote it as $\text{SB}(\cdot)$ for short. We disprove its subadditivity by proving it violates the monotonicity corollary. Consider adding a molecule x into a molecular set $\mathcal{S}$ with size $n > 1$. If $x \notin \mathcal{S}$, we have

$$\begin{aligned}&\text{SB}(\mathcal{S}\cup\{x\})\\ &= \sum_{y\in\mathcal{S}} \min\left(\min_{\substack{y'\in\mathcal{S}\\ y'\neq y}} d(y,y'),\ d(x,y)\right) + \min_{y\in\mathcal{S}} d(x,y),\end{aligned}$$

and

$$\text{SB}(\mathcal{S}) = \sum_{y\in\mathcal{S}} \min_{\substack{y'\in\mathcal{S}\\ y'\neq y}} d(y,y').$$

When x introduces some more restricting bottlenecks, *i.e.*, for many $y\in\mathcal{S}$, $d(x,y)$ is small (*e.g.*, adding a molecule into a set whose size is two, and the new molecule is added near one of the two molecules), we will have $\text{SB}(\mathcal{S}\cup\{x\}) < \text{SB}(\mathcal{S})$, violating the monotonicity corollary, thus proving SumBottleneck is not subadditive.

Fot the **DPP** exploration measure, we disprove its subadditivity by proving it violates the monotonicity corollary. Consider adding x into $\{x_0\}$ where $x \neq x_0$ $1 - d(x,x_0)$ is denoted as b. We have

$$\text{DPP}(\{x_0,x\}) = \begin{vmatrix} 1 & b \\ b & 1 \end{vmatrix} = 1 - b^2.$$

When $b > 0$ we will have $\text{DPP}(\{x_0,x\}) < \text{DPP}(\{x_0\}) = 1$, violating the monotonicity corollary, thus proving DPP is not subadditive.

□

Proposition B.2 (Dissimilarity property of exploration measures.)**.** *Diversity, SumDiversity, Diameter, Bottleneck, SumBottleneck, DPP, and #Circles have preferences to dissimilarity. The SumDiameter measure does not has the dissimilarity property.*

Proof. In the proof, for adding a molecule x into the molecular set $\{x_1,x_2\}$, we denote $d(x_1,x_2)$ as a, $d(x,x_1)$ as δ, and $d(x,x_2)$ as $a-\delta$ for short.

For the **Diversity** exploration measure, we denote it as $\text{Div}(\cdot)$ for short. For the molecular set $\{x_1,x_2\}$, when adding a new molecule x from $\mathcal{X}(x_1,x_2)$ as defined in the dissimilarity axiom, we have

$$\begin{aligned}&\text{Diversity}(\{x_1,x_2,x\}) = \frac{2}{3\cdot 2}(a+\delta+(a-\delta)) = \frac{2a}{3}\\ &= \text{Diversity}(\{x_1,x_2,x^*\}) = \frac{2}{3\cdot 2}(a+\frac{a}{2}+\frac{a}{2}) = \frac{2a}{3},\end{aligned}$$

which means it can take the optimal value at $x = x^*$, thus proving the dissimilarity property of Diversity.

For the **SumDiversity** exploration measure, we denote it as $\text{SD}(\cdot)$ for short. For the molecular set $\{x_1,x_2\}$, when adding a new molecule $x\in\mathcal{X}(x_1,x_2)$, we have

$$\begin{aligned}&\text{SD}(\{x_1,x_2,x\}) = a+\delta+(a-\delta) = 2a\\ &= \text{SD}(\{x_1,x_2,x^*\}) = a+\frac{a}{2}+\frac{a}{2} = 2a,\end{aligned}$$

which means it can take the optimal value at $x = x^*$, thus proving the dissimilarity property of SumDiversity.

For the **Diameter** exploration measure, we denote it as $\text{Dia}(\cdot)$ for short. For the molecular set $\{x_1,x_2\}$, when adding a new molecule $x\in\mathcal{X}(x_1,x_2)$, we have

$$\begin{aligned}&\text{Dia}(\{x_1,x_2,x\}) = \max\{a,\delta,a-\delta\} = a\\ &= \text{Dia}(\{x_1,x_2,x^*\}) = \max\{a,\frac{a}{2},\frac{a}{2}\} = a,\end{aligned}$$

which means it can take the optimal value at $x = x^*$, thus proving the dissimilarity property of Diameter.

For the **Bottleneck** exploration measure, we denote it as $\text{Bot}(\cdot)$ for short. For the molecular set $\{x_1,x_2\}$, when adding a new molecule $x\in\mathcal{X}(x_1,x_2)$, we have

$$\begin{aligned}&\text{Bot}(\{x_1,x_2,x\}) = \min\{a,\delta,a-\delta\} = \min(\delta,a-\delta)\\ &\leq \text{Bot}(\{x_1,x_2,x^*\}) = \min\{a,\frac{a}{2},a\frac{a}{2}\} = \frac{a}{2},\end{aligned}$$

which means it can take the optimal value at $x = x^*$, thus proving the dissimilarity property of Bottleneck.

For the **SumBottleneck** exploration measure, we denote it as $\text{SB}(\cdot)$ for short. For the molecular set $\{x_1,x_2\}$, when adding a new molecule $x\in\mathcal{X}(x_1,x_2)$, we have

$$\begin{aligned}&\text{SB}(\{x_1,x_2,x\}) = \delta+(a-\delta)+\min(\delta,a-\delta)\\ &\leq \text{SB}(\{x_1,x_2,x^*\}) = \frac{a}{2}+\frac{a}{2}+\frac{a}{2} = \frac{3a}{2},\end{aligned}$$

which means it can take the optimal value at $x = x^*$, thus proving the dissimilarity property of SumBottleneck.

For the **DPP** exploration measure, for the molecular set $\{x_1, x_2\}$, when adding a new molecule $x \in \mathcal{X}(x_1, x_2)$, we have

$$\begin{aligned}
&\text{DPP}(\{x_1, x_2, x\}) \\
&= \begin{vmatrix} 1 & 1-a & 1-\delta \\ 1-a & 1 & 1-(a-\delta) \\ 1-\delta & 1-(a-\delta) & 1 \end{vmatrix} \\
&= (2a-4)(\delta^2 - a\delta).
\end{aligned}$$

This term will take its largest value when $\delta = \frac{a}{2}$, *i.e.*, when $x = x^*$, thus proving the dissimilarity property of DPP.

For the **#Circles** exploration measure, we denote it as #C$(\cdot)$ for short. we denote #Circles$(\cdot)$ as #C$(\cdot)$ for short and define $\mathcal{C}^*(\mathcal{S}) \subseteq \mathcal{S}$ as an arbitrary set that satisfies $|\mathcal{C}^*(\mathcal{S})| = \#\text{C}(\mathcal{S})$. We prove the dissimilarity property of #C by contradiction.

For the molecular set $\{x_1, x_2\}$, consider adding an arbitrary new molecule $x \in \mathcal{X}(x_1, x_2)$ or the molecule x^*. We assume $\#\text{C}(\{x_1, x_2, x\}) > \#\text{C}(\{x_1, x_2, x^*\})$. This means that we must have $\#\text{C}(\{x_1, x_2, x\}) = 3$ and $\mathcal{C}^*(\{x_1, x_2, x\}) = \{x_1, x_2, x\}$, otherwise according to the monotonicity corollary of #C's subadditivity, $\#\text{C}(\{x_1, x_2, x\}) = \#\text{C}(\{x_1, x_2\}) \leq \#\text{C}(\{x_1, x_2, x^*\})$.

Therefore, according to the definition of #C, we have $\delta > t$ as well as $a - \delta > t$ where t is the distance threshold, indicating that

$$\frac{a}{2} > \min(\delta, a - \delta) > t.$$

This means $\mathcal{C}^*(\{x_1, x_2, x^*\})$ can also simultaneously include x_1, x_2, and x^*, contradicting with our assumption, thus proving the dissimilarity property of #Circles.

For the **SumDiameter** exploration measure, we denote it as SD$(\cdot)$ for short. For the molecular set $\{x_1, x_2\}$, when adding a new molecule $x \in \mathcal{X}(x_1, x_2)$, we have

$$\begin{aligned}
&\text{SD}(\{x_1, x_2, x\}) = a + \max(\delta, a - \delta) \\
&\geq \text{SD}(\{x_1, x_2, x^*\}) = a + \max(\frac{a}{2}, \frac{a}{2}) = \frac{3a}{2},
\end{aligned}$$

which means x can be better than x^* when one of δ and $a - \delta$ is larger than $\frac{a}{2}$, thus disproving the dissimilarity property of SumDiameter.

□

Discussing the dissimilarity property of coverage-based measures. We denote the cover$(\cdot, \cdot)$ function as cov$(\cdot, \cdot)$ for short. Then for the molecular set $\{x_1, x_2\}$, when adding a new molecule $x \in \mathcal{X}(x_1, x_2)$, we have

$$\begin{aligned}
&\text{Coverage}(\{x_1, x_2, x\}) \\
&= \sum_{y \in \mathcal{R}} \max\left(\text{cov}(x_1, y), \text{cov}(x_2, y), \text{cov}(x, y)\right).
\end{aligned}$$

The value of Coverage$(\{x_1, x_2, x\})$ will depend on the particular definition of cov$(\cdot, \cdot)$. Generally, an arbitrary coverage function does not necessarily meet the dissimilarity requirement. In our study, we define this function as $\text{cov}(x, y) := \mathbb{I}[\text{molecule } x \text{ contains fragment } y]$, where $\mathbb{I}[\cdot]$ is the indication function, which is loosely correlated with the distance metric d. So the dissimilarity property does not hold for exploration measures #FG, #RS, and #BM.

C. Random Subset Experiment Details

C.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, hydrolases, and kinases) and membrane receptors (*e.g.*, GPCRs and non-GPCRs). The label distribution is shown in Figure 6.

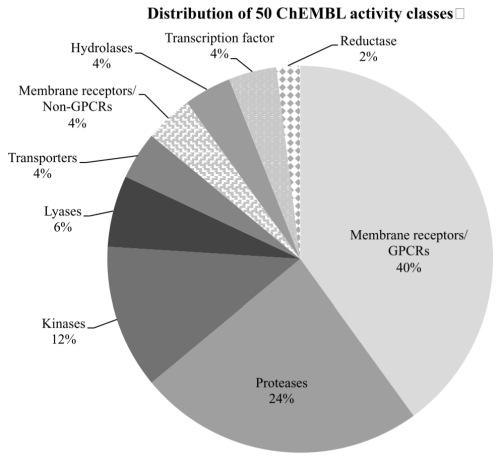


Figure 6. Label distribution of the BioActivity dataset (Koutsoukas et al., 2014). 50 bio-activity functionality classes are included.

We use UMAP (McInnes et al., 2018) to visualize the molecules in this dataset based on their Morgan fingerprints (Rogers & Hahn, 2010) as displayed Figure 7. From the visualization, we can see that the fingerprint similarity is indeed correlated with the bio-activity similarity.

Figure 7. UMAP visualization of compounds in the BioActivity dataset. Different colors stand for different bio-activity labels.

C.2. Random Subsets with Fixed Sizes

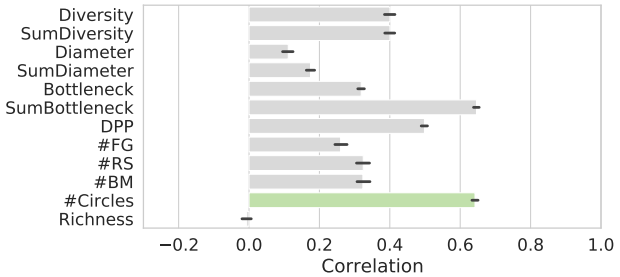
In this experiment, we repeat Algorithm 1 for ten times to obtain reliable correlations.

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

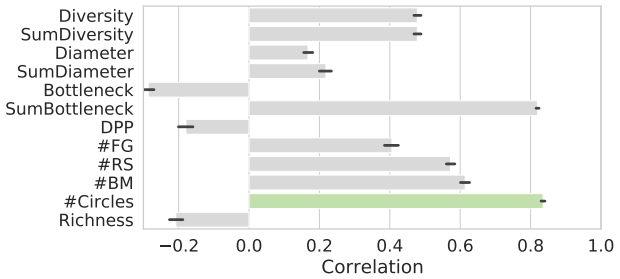
Input: The fixed subset size n; The bio-activity dataset $\{(x_i, y_i)\}_{i=1}^{10\text{K}}$ where $y_i \in \mathcal{Y}$ are bio-activity labels and $|\mathcal{Y}| = 50$; K exploration measures $\{\mu_k\}_{k=1}^{K}$.
repeat
  Sample a number m uniformly from $\{1, \ldots, 50\}$.
  Sample m labels $\mathcal{Y}'$ uniformly from $\mathcal{Y}$.
  Sample n molecules $\mathcal{S}$ with labels in $\mathcal{Y}'$ uniformly.
  Compute $\text{GS}(\mathcal{S})$ and $\mu_k(\mathcal{S})$ for $k \in [K]$.
until repeated for 1000 times
Calculate the correlations between GS and $\{\mu_k\}_{k=1}^{K}$ based on the 1000-times experiment results.

Experiment results. We show the experiment results for different fixed random set size n in Figure 8. We find the #Circles and SumBottleneck measures perform constantly better than all other measures.

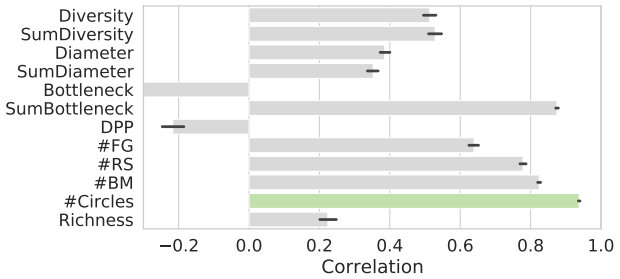
When the fixed size n increases, most exploration measures' performances also increase, except for Bottleneck and DPP, meaning they are not suitable for measuring the variety when the molecules are distributed crowdedly.



(a) Random subsets with a fixed size $n = 50$.



(b) Random subsets with a fixed size $n = 200$.



(c) Random subsets with a fixed size $n = 1000$.

Figure 8. Correlations between the gold standard GS and exploration measures in the fixed-size random subset setting. The fixed size is set as different values. A larger correlation indicates the better. The average results are obtained by running experiments independently for ten times.

Correlation between exploration measures. We also visualize the pairwise correlation between exploration measures in Figure 9. From the figure we can see that, the gold standard GS, #Circles, and SumBottleneck are most similar with each other in the fixed-size setting.

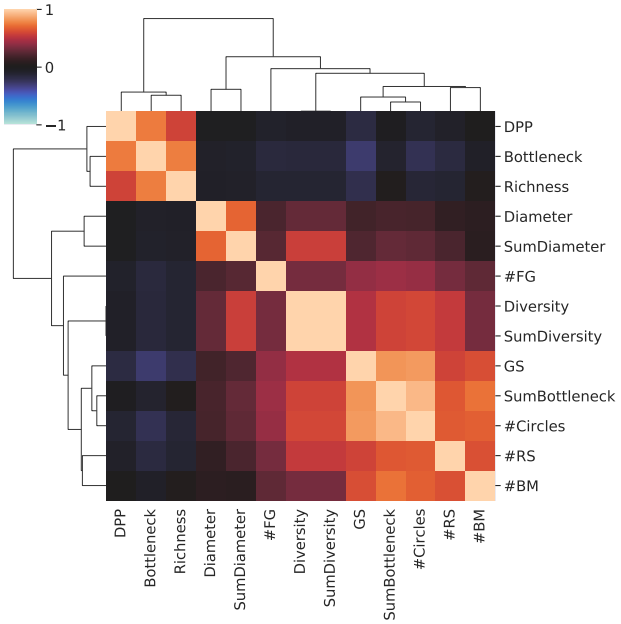


Figure 9. Correlations between exploration measures in the fixed-size random subset setting. The fixed size is set as $n = 200$. A larger correlation indicates the better. The average results are obtained by running experiments independently for ten times.

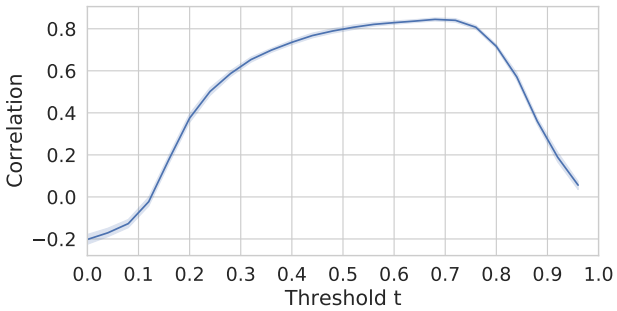


Figure 10. Correlations between the gold standard GS and the #Circles measure in the fixed-size random subset setting with different threshold t. The fixed size is set as $n = 200$. A larger correlation indicates the better. The average results are obtained by running experiments independently for ten times.

Threshold t for #Circles. The #Circles threshold t is selected to maximize the correlation to the gold standard GS. Taking $n = 200$ as an example, we test different t values as Figure 10 displays and select $t = 0.70$ as the threshold. We can see #Circles works well for a wide range of thresholds

like $[0.40, 0.70]$. In Olivecrona et al. (2017), the authors suggest to use a threshold $t = 0.60$ to decide whether two molecules are dissimilar with each other[3], which aligns our results. For $n = 50$ and $n = 1000$, the threshold is set as $t = 0.70$ and $t = 0.65$ respectively.

Distance metric d. We also study the impact of distance metric d. In Table 3, we listed the experiment results for both fingerprint-based Tanimoto distance and VAE-based latent space dissimilarity (Samanta et al., 2020). We find the experiment results obtained with the VAE dissimilarity remain consistent with the results obtained with the Tanimoto distance.

Table 3. Correlations between the gold standard and exploration measures in the fixed-size random subset setting. The fixed size is set as $n = 200$. A larger correlation indicates the better. Results are obtained by averaging ten independent experiments. *Italic* texts indicate molecular representation and the distance metric. Top three measures are highlighted in green, and the best measure is printed in **bold**.

	Distance-based	
	Tanimoto distance	*VAE dissimilarity*
Diversity	0.478 ± 0.011	0.388 ± 0.040
SumDiversity	0.478 ± 0.011	0.388 ± 0.040
Diameter	0.179 ± 0.031	0.112 ± 0.022
SumDiameter	0.228 ± 0.028	0.201 ± 0.029
Bottleneck	-0.293 ± 0.015	-0.298 ± 0.027
SumBottleneck	0.821 ± 0.010	0.527 ± 0.013
DPP	-0.183 ± 0.021	-0.244 ± 0.030
	Coverage-based	
	Fgragment	
#FG	0.421 ± 0.033	
#RS	0.574 ± 0.025	
#BM	0.610 ± 0.028	
	Locality-based	
	Tanimoto distance	*VAE dissimilarity*
#Circles	**0.831 ± 0.008**	0.745 ± 0.014
	SMILES	
Richness	-0.207 ± 0.025	

[3]In the original text, the authors suggest a similarity threshold of 0.40 that is equivalent to a distance threshold of 0.60.

C.3. Random Subsets with Growing Sizes

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

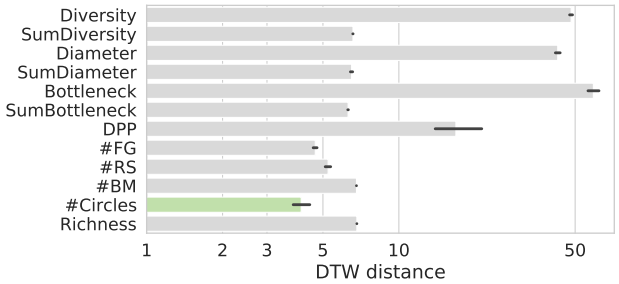
Algorithm 2 Calculating exploration measures for random subsets with growing sizes.

Input: The maximum subset size n; The bio-activity dataset $\{(x_i, y_i)\}_{i=1}^{10\text{K}}$ where $y_i \in \mathcal{Y}$ are bio-activity labels and $|\mathcal{Y}| = 50$; K exploration measures $\{\mu_k\}_{k=1}^{K}$.
Sample a number m uniformly from $\{1, \ldots, 50\}$.
Sample m labels $\mathcal{Y}'$ from $\mathcal{Y}$.
for i **in** $\{1, \ldots, n\}$ **do**
  Sample an unseen molecule x_i whose label is in $\mathcal{Y}'$.
  Set $\mathcal{S}_i := \{x_1, \ldots, x_i\}$
  Compute GS$(\mathcal{S}_i)$ and $\mu_k(\mathcal{S}_i)$ for $k \in [K]$.
end for
Plot exploration measure curves for GS and $\{\mu_k\}_{k=1}^{K}$ where the x axes are $i \in \{1, \ldots, n\}$ and the y axes are exploration measure values GS$(\mathcal{S}_i)$ and $\mu_k(\mathcal{S}_i)$.
Transform the cumulative curves into incremental ones.
Calculate DTW distances between incremental curves.

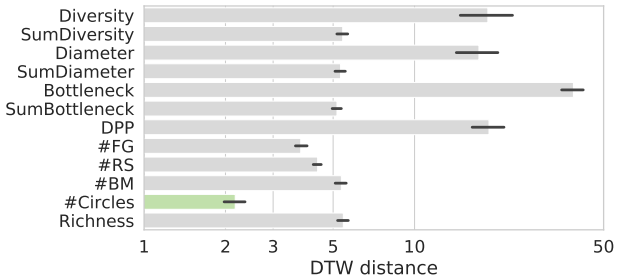
Experiment results. To mimic the way in which generation models propose new molecules, in Algorithm 2, we require the newly sampled molecule x_i to be similar to the already sampled molecules $\{x_1, \ldots, x_{i-1}\}$. The specific implementation can be found in our code[4]. Moreover, we also test the following two cases: (1) All molecules are sampled uniformly; (2) The newly 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 11.

From Figure 11 we can see that, #Circles performs the best. Also, as the new molecules to add become more similar to the existing ones, the advantage of #Circles over other measures becomes larger. This makes #Circles especially suitable for measuring molecular generation models.

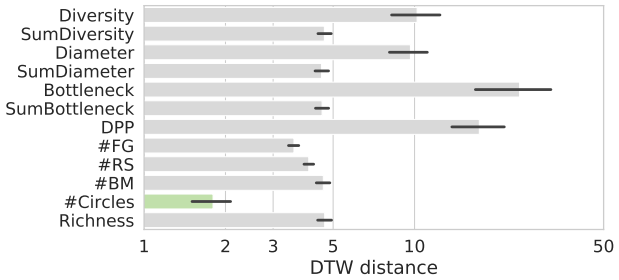
[4]The code will be released after publication.



(a) The new molecule x_i is uniformly sampled from all unseen molecules.



(b) The new molecule x_i needs to be similar to the already sampled ones $x_1, \ldots, x_{i=1}$.



(c) The new molecule x_i needs to be most similar to the already sampled ones $x_1, \ldots, x_{i=1}$.

Figure 11. DTW distances between the gold standard GS and exploration measures in the growing-size random subset setting. The maximum size is set as $n = 1000$. A smaller distance indicates the better. The average results are obtained by running experiments independently for ten times.

DTW distances between exploration measures. We visualize the pairwise DTW distances between exploration measures in Figure 12. From the figure, we can see that the gold standard GS and the #Circles measure are almost similar to each other in the growing-size setting.

In addition, we find the Richness, SumDiversity, SumDiameter, SumBottleneck, and #BM are forming a large cluster, while #FG and #RS tend to be similar with each other.

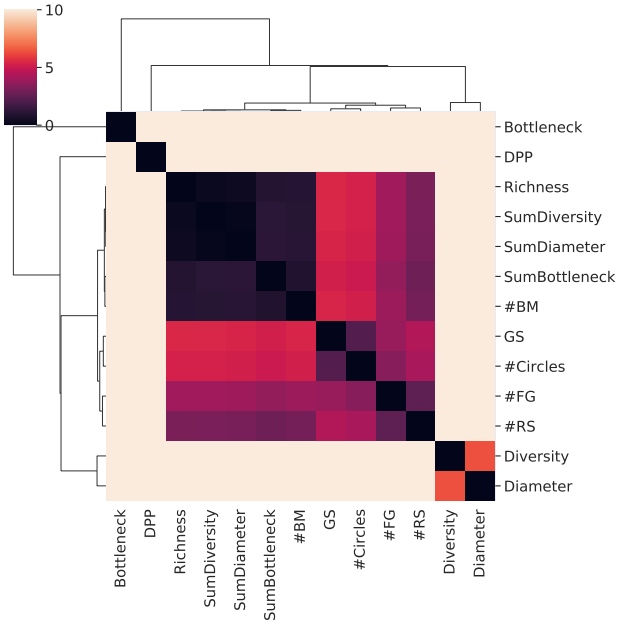


Figure 12. DTW distances between exploration measures in the growing-size random subset setting. The maximum size is set as $n = 1000$, and the new molecule needs to be similar to the already samples ones. A smaller distance indicates the better. The average results are obtained by running experiments independently for ten times.

Threshold t for #Circles. The #Circles threshold t is selected to minimize the DTW distance to the gold standard GS. Taking the second scenario as an example, we test different t values as Figure 13 displays and select $t = 0.76$ as the threshold. For the first and the third scenarios, the threshold is set as $t = 0.84$ and $t = 0.78$ respectively.

Distance metric d. We also study the impact of distance metric d. In Table 4, we listed the experiment results for both fingerprint-based Tanimoto distance and VAE-based latent space dissimilarity (Samanta et al., 2020). We find the experiment results obtained with the VAE dissimilarity remain consistent with the results obtained with the Tanimoto distance.

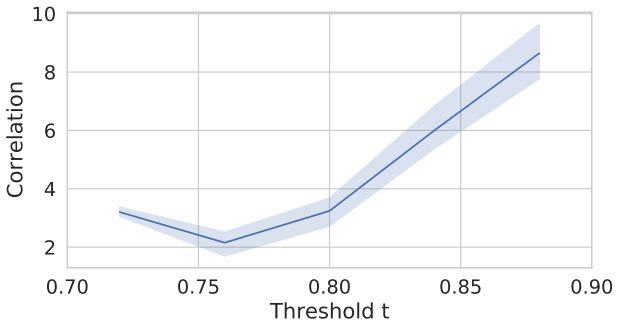


Figure 13. DTW distances between the gold standard GS and the #Circles measure in the growing-size random subset setting with different threshold t. The maximum size is set as $n = 1000$, and the new molecule needs to be similar to the already samples ones. A smaller distance indicates the better. The average results are obtained by running experiments independently for ten times.

Table 4. DTW distances between the gold standard and exploration measures in the growing-size random subset setting. The maximum size is set as $n = 1000$, and the new molecule needs to be similar to the already samples ones. A smaller distance indicates the better.

	Distance-based	
	Tanimoto distance	*VAE dissimilarity*
Diversity	18.668 ± 6.973	30.063 ± 4.284
SumDiversity	5.425 ± 0.404	5.484 ± 0.296
Diameter	17.299 ± 4.801	28.071 ± 3.917
SumDiameter	5.328 ± 0.396	5.472 ± 0.297
Bottleneck	38.668 ± 5.769	37.168 ± 5.422
SumBottleneck	5.167 ± 0.353	5.432 ± 0.293
DPP	18.845 ± 3.962	12.052 ± 2.176
	Coverage-based	
	Fgragment	
#FG	3.797 ± 0.295	
#RS	4.382 ± 0.247	
#BM	5.365 ± 0.396	
	Locality-based	
	Tanimoto distance	*VAE dissimilarity*
#Circles	$\mathbf{2.173 \pm 0.910}$	2.470 ± 0.629
	SMILES	
Richness	5.454 ± 0.347	

D. 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[5].

For the model variants, we test different α values from $\{0.1, 0.3, 1.0, 3.0\}$ and report the best performance. Specifically, we use $\alpha = 1.0$ for MARS+Diversity, $\alpha = 0.3$ for MARS+SumBottlenck, and $\alpha = 0.1$ for MARS+#Circles. The threshold we use for the #Circles measure is $t = 0.60$.

The computing server has two 2.4 GHz Intel Xeon Gold 6148 CPUs, 192GB memory (about 50G used), and one NVIDIA Tesla V100 GPU with 16G memory. It takes approximately 40 hours for the MARS model to sample in total 10M molecules within 2000 steps.

We show the molecular clustering results in Figure 14. Clusters are calculated based on Morgan fingerprints of the generated molecules and their Tanimoto similarity. Compared to the baseline model, a larger number of clusters can be obtained from MARS+SumBottleneck.

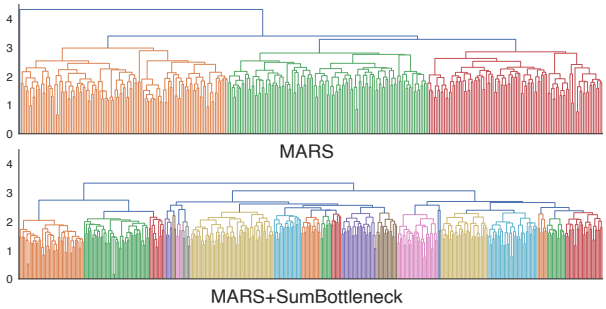


Figure 14. Hierarchical clustering results of generated molecules. Different colors stand for different clusters. The clustering threshold is set as $0.7\times$ the height of the highest linkage in accordance with SciPy's default value.

[5]MARS code: https://github.com/yutxie/mars.