Population-based de novo molecule generation, using grammatical evolution

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Abstract

Automatic design with machine learning and molecular simulations has shown a remarkable ability to generate new and promising drug candidates. Current models, however, still have problems in simulation concurrency and molecular diversity. Most methods generate one molecule at a time and do not allow multiple simulators to run simultaneously. Additionally, better molecular diversity could boost the success rate in the subsequent drug discovery process. We propose a new population-based approach using grammatical evolution named ChemGE. In our method, a large population of molecules are updated concurrently and evaluated by multiple simulators in parallel. In docking experiments with thymidine kinase, ChemGE succeeded in generating hundreds of high-affinity molecules whose diversity is better than that of known binding molecules in DUD-E.

1. Introduction

Designing new molecules with desirable properties is an important task for pharmaceutical science and materials science, with the improvement of binding affinity and ADMET profile, a priority for hit-to-lead and subsequent optimization stages of drug discovery. Fragment-based methods, such as RECAP \cite{1}, generate molecules by linking known fragments, but these methods have problems in structural diversity and patentability. Recently, several de novo molecule generation methods that do not require fragments have been proposed. They formulate the molecule generation problem as a black-box optimization of SMILES strings \cite{2} and solve it with deep neural networks and molecular simulations. Recent approaches include (1) Bayesian optimization,
over a continuous space, of variational autoencoders [3, 4], (2) optimization of recurrent neural network through fine-tuning or reinforcement learning [5, 6, 7], (3) sequential Monte Carlo search over a language model of SMILES [8], and (4) Monte Carlo tree search guided by recurrent neural network [9].

Although these methods achieved great results in finding drug candidates, most still have problems in simulation concurrency and molecular diversity. Few, often no more than one, molecules are generated at a time, making it difficult to parallelize their subsequent evaluation through molecular simulation. The lack of diversity in generated molecules is also a problem [10], due mainly to the way most methods are designed to find an optimal molecule based on an a priori defined score: drug discovery is a stage-wise process and it is impossible to design a perfect score reflecting all aspects. Improving molecular diversity is necessary to increase the chance of survival, down the drug discovery pipeline.

In this paper, we propose a new population-based approach named ChemGE, which uses grammatical evolution [11] to optimize a population of molecules (Figure 1). Grammatical evolution is a population-based optimization technique to optimize a population of strings that follow a context-free grammar. Such population-based evolutionary methods have been regaining popularity for solving black-box optimization problems, such as hyperparameter optimization and neural network design (e.g., [12]). Their main advantage is inherent concurrency: ChemGE allows many simulations to run simultaneously and can easily be adapted for parallel computation. In addition, mutation operations in evolution ensure large diversity throughout the optimization process. In benchmarking experiments using a druglikeness score, we confirmed that ChemGE is able to find many more molecules than deep learning-based methods using identical computational resources. ChemGE was also used to find novel molecules docking to thymidine kinase using rDock [13]. Employing 32 cores in parallel, ChemGE generated 349 molecules whose docking scores are better than the best molecule in DUD-E [14] in 26 hours. The generated molecules were highly diverse, and dissimilar to known active ones in DUD-E.

2. Method

2.1. Context-free grammar of SMILES

This section reviews SMILES and its context-free grammar. A context-free grammar $G$ is defined as a 4-tuple: $G = (V, \Sigma, R, S)$, where $V$ is a finite set of non-terminal symbols, $\Sigma$ is a finite set of terminal symbols, $R$ is a finite set of production rules, and $S$ is a special non-terminal symbol called the start symbol. A production rule defines a transformation from a non-terminal symbol $V$ to $(V \cup \Sigma)^*$, where the asterisk denotes a Kleene star. To generate a string, a sequence of production rules is applied to non-terminal symbols until no non-terminal symbol remains.

SMILES (Simplified Molecular Input Line Entry System) [2] is a notation of chemical structure using ASCII strings. OpenSMILES [15] specifies the context-free grammar of SMILES. In this paper, we used a subset of the grammar.
2.2. ChemGE

ChemGE maintains a population of $\mu$ molecules, each of which is doubly encoded. A molecule is represented as a SMILES string, which is then encoded as a sequence of $N$ integers called a chromosome $C$. A chromosome is translated to a SMILES string by a mapping process (Figure 3): the initial string contains

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Figure 1: Population-based molecular design with ChemGE. A population of molecules are updated to achieve better fitness. When we aim to generate molecules docking to a target protein, the fitness is set to the affinity score of a docking simulator. A new generation of molecules is made by choosing some molecules and modifying them (i.e., mutation).

shown in Figure 2. Note that following the grammar alone is not sufficient for generating valid molecules. For example, C#O indicates a molecule where a carbon and oxygen atoms are connected by a triple bond, but such a molecule does not exist. A string is called a valid SMILES, if the string represents a molecule. One can use, e.g., RDKit \[16\] to check the validity of a generated string.

<smiles> ::= <chain>
<atom> ::= <bracket_atom> | <aliphatic_organic> | <aromatic_organic>
<aliphatic_organic> ::= "B" | "C" | "N" | "O" | "S" | "P" | "F" | "I" | "Cl" | "Br"
<aromatic_organic> ::= "c" | "n" | "o" | "a"
<bracket_atom> ::= "[" <BAI> "]"
<BAI> ::= <isotope> <symbol> <BAC> | <symbol> <BAC> | <isotope> | <symbol>
<BAC> ::= <chiral> | <BB> | <BAH> | <chiral>
<BAH> ::= <hcount> <BACH> | <BACH> | <hcount>
<BACH> ::= <charge> <class> | <class> <charge> | <class>
<symbol> ::= <aliphatic_organic> | <aromatic_organic>
<isotope> ::= <DIGIT> | <DIGIT> <DIGIT> | <DIGIT> <DIGIT> <DIGIT> | <DIGIT> <DIGIT> <DIGIT> | <DIGIT> <DIGIT> <DIGIT> | <DIGIT> <DIGIT> <DIGIT> | <DIGIT> <DIGIT> <DIGIT>
<charge> ::= "+" | "+" <DIGIT> | "=" | "+" <DIGIT> <DIGIT> | "=" <DIGIT> | "+" | "+" <DIGIT> <DIGIT> | = ""
<hcount> ::= "H" | "H" <DIGIT>
<branch> ::= "+" | "+" <DIGIT> | "+" <DIGIT> <DIGIT> | "+" <DIGIT> <DIGIT> | "=" | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT>
<bond> ::= "+" | "=" | "=" <DIGIT> | "=" <DIGIT> <DIGIT> | "+" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT> | "=" <DIGIT> <DIGIT>
<ringbond> ::= <DIGIT> | <chord> <DIST> <branch> ::= <bracket_atom> ::= <atom> | <atom> <BB> | <atom> <BB> | <atom> <BB> | <atom> <BB>
<BB> ::= <BB> <ringbond> | <ringbond>
<chain> ::= "(" <chain> ")" | "+" <chord> <chain>
<branch> ::= "(" <chain> ")" | "+" <chord> <chain> <branch>

Figure 2: Context-free grammar used by ChemGE in BackusNaur form.
the start symbol only, and is successively turned into the final string by picking up the leftmost non-terminal symbol and applying a production rule to it. At the $k$-th step of the mapping process, the $k$-th integer in the chromosome $c = C[k]$ is looked up. Denote by $r$ the number of rules applicable to the leftmost non-terminal symbol. Among them, the $((c \mod r) + 1)$-th rule is chosen and applied. The process iterates until the string has no non-terminal symbol or the final integer of the chromosome is used.

Figure 3: Mapping process. This figure shows how the mapping process translates a chromosome into SMILES. A chromosome is a sequence of integers. At the $k$-th step, the $k$-th integer is looked up and it specifies the production rule applied to the leftmost non-terminal symbol.

Evolution is conducted according to the $(\mu + \lambda)$ evolution strategy [17] as follows: (1) create $\lambda$ new chromosomes by repeatedly drawing a random chromosome from the population, and changing one integer at a random position to a random value (i.e., mutation). (2) Each of the $\lambda$ chromosomes is translated
to a SMILES string and then to a molecule and its fitness is evaluated (e.g. by docking simulation). If translation fails, the fitness is set to $-\infty$. (3) A new generation is made by selecting the $\mu$ top-fit molecules from the merged pool of existing and new molecules. We did not use a crossover operation here, as it did not improve the performance (data not shown).

3. Results and Discussion

To validate the usefulness of our method, we conducted two types of experiments to generate 1) drug-like molecules, and 2) high scoring ligands for a protein.

3.1. Benchmark on druglikeness score

We optimized the $J^{\log P}$ score \[3\], which is an indicator of druglikeness. It is the octanol-water partition coefficient ($\log P$) penalized by synthetic accessibility \[18\] and number of carbon rings of size larger than 6. The score $J^{\log P}$ of a given molecule $m$ is defined as

$$J^{\log P}(m) = \log P(m) - SA(m) - \text{ring-penalty}(m),$$

where $\log P(m)$, $SA(m)$ and $\text{ring-penalty}(m)$ are normalized so that their mean is zero and standard deviation is one. Roughly speaking, molecules with larger $J^{\log P}$ scores have more suitable structural profiles as pharmaceutical drugs. Since very large logP values ($\log P > 5$) cause low metabolic stability and other pharmacokinetic defects, $J^{\log P}$ values of launched drugs and clinical tested compounds collected from Clarivate Analytics Cortellis database are ranging from -10 to 5.

We compared ChemGE with CVAE \[3\], GVAE \[4\], and ChemTS \[9\] using this score. CVAE uses variational autoencoder (VAE) \[19\] to obtain continuous representation of SMILES strings, conduct Bayesian optimization over the continuous space, and obtain strings from the optimized representation. GVAE is an updated version of CVAE, where grammar information on SMILES is taken into account. ChemTS uses Monte Carlo tree search and recurrent neural networks to design SMILES strings.

In this experiment, ChemGE is applied with different initial population sizes: $(\mu, \lambda) = (10, 20), (100, 200), (1000, 2000), (10000, 20000)$, randomly chosen from the ZINC database, which contains 35 million commercially available compounds \[20\]. $J^{\log P}(m)$ was used as fitness score, but set to $-\infty$, if the molecular weight was bigger than 500 or an identical molecule had already been generated before. In order to compare with other methods, no parallel computation was conducted here. We used a computing core of Intel Xeon CPU E5-2630 v3.

Table 1 shows the maximum score of each method after running for 2, 4, 6, and 8 hours. The importance of choosing a suitable population size is well-documented in evolutionary algorithm literature \[11\], as an overly small population cannot have sufficient diversity, while an overly large population cannot
optimize each molecule sufficently due to the small number of generations. We found that, at \((\mu, \lambda) = (1000, 2000)\), the final ChemGE score was largest and outperformed other methods in score and speed of generating molecules. The efficiency of ChemGE enables to evaluate a much larger number of molecules than computationally-demanding deep learning models, such as RNN or VAE, or than Bayesian optimization, which is used in CVAE and GVAE, and gets slower as search progresses.

Table 1: Maximum score \(J \) at time points 2, 4, 6, and 8 hours achieved by different molecular generation methods. The average values and standard deviations over 10 trials are shown. The two numbers after ChemGE specifies \((\mu, \lambda)\). The rightmost column shows the number of generated molecules per minute (duplication is eliminated).

| Method          | 2h          | 4h          | 6h          | 8h          | Molecules/Min | Generation |
|-----------------|-------------|-------------|-------------|-------------|---------------|------------|
| ChemGE (100, 20) | 4.46 ± 0.34 | 4.46 ± 0.34 | 4.46 ± 0.34 | 4.46 ± 0.34 | 14 ± 4.9      | 10000      |
| ChemGE (1000, 2000) | 5.17 ± 0.26 | 5.17 ± 0.26 | 5.17 ± 0.26 | 5.17 ± 0.26 | 135 ± 22      | 8360 ± 1340|
| ChemGE (10000, 20000) | 4.45 ± 0.24 | 5.32 ± 0.43 | 5.73 ± 0.33 | 5.88 ± 0.34 | 527 ± 62      | 704 ± 59   |
| ChemGE (100000, 200000) | 4.20 ± 0.33 | 4.28 ± 0.28 | 4.40 ± 0.27 | 4.53 ± 0.26 | 555 ± 68      | 72.5 ± 9.5 |
| CVAE [3]        | −30.18 ± 26.91 | −1.39 ± 2.24 | −0.61 ± 1.08 | −0.096 ± 0.92 | 0.14 ± 0.08  | -          |
| GVAE [4]        | −4.34 ± 3.14 | −1.29 ± 1.67 | −0.17 ± 0.96 | 0.25 ± 1.31 | 1.38 ± 0.91   | -          |
| ChemTS [2]     | 4.91 ± 0.38 | 5.41 ± 0.51 | 5.49 ± 0.44 | 5.56 ± 0.50 | 40.89 ± 1.57  | -          |

3.2. Design of high-scoring molecules for thymidine kinase

ChemGE was applied to the design of high-scoring molecules that are predicted to have strong binding affinity for a specific target protein using rDock [13], one of the fastest and most accurate docking simulation program, commonly used in high throughput virtual screening. We used thymidine kinase (KITH), a well-known target of antiviral drugs, as the target protein for this study. After taking the structure data from a KITH-ligand complex (PDB ID: 2B8T), we generated a cavity using the default reference ligand method (radius: 6 Å). To calculate ChemGE’s fitness, we took the best intermolecular score \(S_{\text{inter}}\) among three rDock runs from different initial conformations under default parameter settings. The fitness was defined as \(-S_{\text{inter}}\), because a small intermolecular score implies high affinity. If the molecular weight was bigger than 500 or the molecule was already generated, the fitness was set to \(-\infty\).

In order to first test its performance, we generated up to 10,000 molecules with ChemGE that were then evaluated with rDock, starting from an initial populations randomly chosen from ZINC. As can be seen in Figure 4, which shows the progress of the best intermolecular score over number of evaluations, ChemGE optimizes molecules faster than random sampling, by a large margin.

Next we proceeded to construct the molecular library. We reserved 32 cores for calculation and set \((\mu, \lambda) = (32, 64)\). Evaluation of molecules in a population was conducted in parallel. The computation for 1000 generations was finished in about 26 hours, resulting in a large library of 9466 generated molecules. Figure 5 shows the distribution of intermolecular scores of ChemGE-generated molecules. We compared it with the score distribution of 57 known inhibitors derived from DUD-E [14], and the baseline score distribution of ZINC. Knowing that a small intermolecular score implies high affinity, we can see that the distribution of ChemGE is biased towards high affinity in comparison to ZINC,
showing the success of evolutionary optimization. More remarkably, it is also
more biased than that of known inhibitors. We found 349 molecules whose
intermolecular score was better than the best score of 57 known inhibitors.
Figures S1-S3 show all of these molecules. Although synthetic routes and ADMET
properties are unknown for these molecules, this large-scale library can offer
great opportunities and inspiration for medical chemists.

We investigated the diversity of molecules found by ChemGE. Larger diver-
sity generally increases the chance of survival at multiple ADMET endpoints.
Using Morgan fingerprints [21], the internal diversity of a set of molecules $A$ is
defined as

$$I(A) = \frac{1}{|A|^2} \sum_{(x,y) \in A \times A} T_d(x, y),$$

where $T_d$ is the Tanimoto distance $T_d(x, y) = 1 - \frac{|x \cap y|}{|x \cup y|}$. We evaluated a
"ChemGE-active" molecule set consisting of 349 molecules whose scores were
better then the best known inhibitor. The internal diversity was 0.55, larger
than that of known inhibitors, 0.46. The difference is substantial, considering
that the diversity of the whole ZINC database is 0.65. Deep reinforcement learn-
ing methods often generate very similar molecules [10] and special countermea-
sures are necessary to maintain diversity. In grammatical evolution, diversity
is inherently built-in, because a large fraction of molecules are mutated in each
generation.

Figure 6 shows a visualization of how the chemical space is explored by
ChemGE. A mapping from fingerprints to a two dimensional space is constructed
by applying the ISOMAP algorithm [22] to ZINC. Then, the following molecule
sets are mapped to the two dimensional space: (a) known inhibitors, (b) ini-
tial population of ChemGE, (c) 100-th generation, (d) 1000-th generation. The
initial population is distributed in various places and a large fraction lies close
to known inhibitors. As evolution goes on, the distribution moves away from
the known inhibitors and the final generation occupies a completely different
place. This observation suggests that ChemGE detected a new class of bind-
ing molecules, although they need to be confirmed by biological assays, and
synthesizability and ADMET issues would have to be solved.
Figure 4: **Progress of molecule optimization by ChemGE and random sampling.** The best intermolecular score computed by rDock and random sampling is shown. For random sampling, we also showed standard deviation over four trials.

Figure 5: **Score distributions.** The distribution of rDock’s intermolecular score of the molecules generated by ChemGE (red) is biased more favorably in comparison to that of ZINC (green) and that of known thymidine kinase inhibitors in DUD-E (blue).
4. Conclusions

To summarize, we developed ChemGE, a new method to generate functional molecules using grammatical evolution. In benchmark experiments, ChemGE efficiently generated far more molecules than deep learning methods, at similar resource levels. In computational docking experiments with thymidine kinase, a large library of activity-biased molecules were successfully obtained. Among them, hundreds of molecules had better scores than known active molecules. Our library was shown to retain high diversity, which may contribute to increasing the survival rate in the following steps of the drug discovery process. Our method is suitable for parallel computation and our implementation can be applied to even larger computational environments including cloud platforms such as Amazon Web Services (AWS). This work demonstrated that molecule generation is possible without costly deep learning and showed a new direction for research. Nevertheless, to increase performance further, exploitation of a probabilistic or neural model in the evolutionary process might be beneficial [23].
Availability of data and material. Our implementation is available at https://github.com/tsudalab/ChemGE.

Competing interests. The authors declare that they have no competing interests.

Author’s contributions. N. Y., K. O., and K. Tsuda proposed the idea of the molecular design algorithm. N. Y. and K. Terayama implemented the algorithm and performed the experiments. N. Y., K. Tsuda, T. H. and K. Terayama analyzed the experiments. All authors discussed the results and wrote the manuscript.

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Supplementary report

This supplementary report shows the generated molecules whose intermolecular scores are better than known inhibitors.
Figure 7: All molecules whose scores are better than the best known molecule. Part 1.
Figure 8: All molecules whose scores are better than the best known molecule. Part 2.
Figure 9: All molecules whose scores are better than the best known molecule. Part 3.