Transformer Neural Network for Structure Constrained Molecular Optimization

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Abstract

Finding molecules with a desirable balance of multiple properties is a main challenge in drug discovery. Here, we focus on the task of molecular optimization, where a starting molecule with promising properties needs to be further optimized towards the desirable properties. Typically, chemists would apply chemical transformations to the starting molecule based on their intuition. A widely used strategy is the concept of matched molecular pairs where two molecules differ by a single transformation. In particular, a chemist would be interested in keeping one part of the starting molecule (core) constant, while substituting the other part (R-group), to optimize the starting molecule towards desirable properties. Motivated by this, we train a Transformer model, Transformer-R, to generate R-groups given the starting molecule (with its core and R-group specified) and the specified desirable properties. The generated R-groups will be attached to the core to form the final molecules, which are guaranteed to keep the core of interest and are expected to satisfy the desirable properties in the input. Our model could accelerate the process of optimizing antiviral drug candidates in terms of various properties of interest, *e.g.* pharmacokinetics.

1 Introduction

A main challenge in drug discovery is finding molecules with desirable properties. A drug requires a balance of multiple properties, *e.g.* physicochemical properties, ADMET (absorption, distribution, metabolism, elimination and toxicity) properties, safety and potency against its target. To find such a drug in the extremely large chemical space (*i.e.* 10^{23}-10^{60}) (Polishchuk et al., 2013) is challenging. It is often that a promising molecule needs to be improved to achieve a balance of multiple properties. This problem is known as molecular optimization. It plays an important role in the development of antiviral drugs to combat pandemics, where existing drugs can be identified as lead (Huang et al., 2020; Senanayake, 2020; Box & J Thompson, 2020), and chemically modified to improve specific properties, *e.g.* affinity, pharmacology, toxicity and drug resistance profiles (Adamson et al., 2021). For example, ivermectin has been reported to show *in vitro* antiviral activity against SARS-CoV-2 (Caly et al., 2020). However, its application is mainly limited by pharmacokinetic problems such as high cytotoxicity and low solubility (Sharun et al., 2020; Momekov & Momekova, 2020).

Traditionally, chemists would use their knowledge, experience and intuition (Topliss, 1972) to apply some chemical transformations to the promising molecule. In particular, the matched molecular pair (MMP) analysis (Kenny & Sadowski, 2005; Tyrchan & Evertsson, 2017)—which compares the properties of two molecules that differ only by a single chemical transformation—has been widely used as a strategy by medicinal chemists to support molecular optimization (Weber et al., 2013; Griffen et al., 2011; Leach et al., 2006). However, similarity, transferability, and linear analoguing (Hansch et al., 1962; Hansch & Fujita, 1964; Free & Wilson, 1964) are typically assumed, which are not generally true and become more problematic when optimizing multiple properties simultaneously.

Recently, deep learning models have been used to learn the transformations involved in molecular optimization directly from MMPs. The problem of molecular optimization have been framed as a machine translation problem (Bahdanau et al., 2015), where an input starting molecule is translated into a target molecule with optimized properties. While graph representation was used in Jin et al. (2018; 2019; 2020), He et al. (2020) trained a Transformer model based on the simplified molecular-

input line-entry system (SMILES) representation. The starting molecule's SMILES is concatenated with the property constraint tokens as input, and the model outputs the molecule with optimized properties. However, the generated molecule is not guaranteed to keep the core of interest in the given starting molecule being optimized. Here, we train a Transformer model, Transformer-R, where the starting molecule is represented by its core (being kept) and its R-group (being replaced), and the output is the R-group (used to replace the R-group specified in the input) instead of the whole molecule. By doing so, the model is enforced to keep the core of interest. The goal is to generate molecules which (i) have the desirable properties specified in the input (ii) have small and single transformation applied to the starting molecule, and (iii) keep the core specified in the input.

2 METHOD

The SMILES representation of molecules (Weininger, 1988), as a string-based representation, is used in our study to facilitate the use of the Transformer model from natural language processing (NLP). The Transformer is trained on a set of MMPs together with the property changes between source and target molecules. Figure 1 shows an example of a MMP, and the properties of source and target molecules.

Following He et al. (2020), three ADMET properties, *logD*, *solubility* and *clearance* are optimized simultaneously, and the property constraint tokens are included in the input sequence for guidance. Figure 2 shows an example of source and target sequences which are fed into the Transformer model during training. Different from the Transformer model in He et al. (2020) where the source molecule is represented by its SMILES, here it is represented by its core's SMILES and its R-group's SMILES, separated by the separator token. Instead of generating the whole molecule, the R-group is generated, which will be attached to the core in the input to form the final molecule.
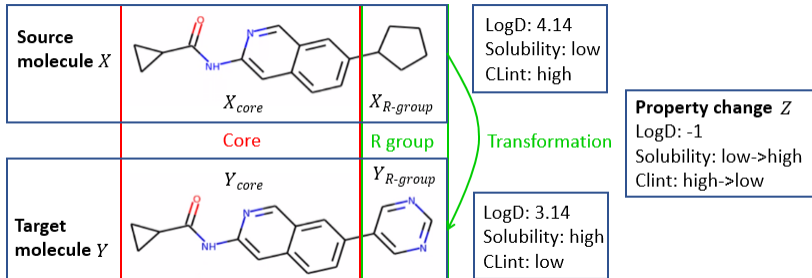

Figure 1: An example of a matched molecular pair and the property changes between the molecules.

Given a set of MMPs $\{(X, Y, Z)\}$ where X represents source molecule, Y represents target molecule, and Z represents the property change between source molecule X and target molecule Y, the Transformer will learn a mapping $(X_{core}, X_{R\text{-}group}, Z) \in \mathcal{X}_{core} \times \mathcal{X}_{R\text{-}group} \times \mathcal{Z} \to Y_{R\text{-}group} \in \mathcal{Y}_{R\text{-}group}$ during training where $\mathcal{X}_{core} \times \mathcal{X}_{R\text{-}group} \times \mathcal{Z}$ represents the input space and $\mathcal{Y}_{R\text{-}group}$ represents the target space. During testing, given a new $(X_{core}, X_{R\text{-}group}, Z) \in \mathcal{X}_{core} \times \mathcal{X}_{R\text{-}group} \times \mathcal{Z}$, the model will generate a set of target R-groups ($Y_{R\text{-}group}$), which will be attached to the core in the input (X_{core}) to form the final molecules. These molecules are expected to have the desirable properties specified in the input (Z).

3 RESULTS

The information of dataset used in this paper can be found in appendix A.1. We compare our model Transformer-R with the following baselines,

Transformer Baseline: The Transformer developed by He et al. (2020) to generate the whole target molecules at once, in contrast to only the R-groups.

Enumeration Baseline: This constitutes of an exhaustive algorithm that for a test starting molecule, consists of (i) attaching each R-group seen in the training data to the molecule's core and (ii) selecting all found R-groups which yielded a molecule with desirable properties.
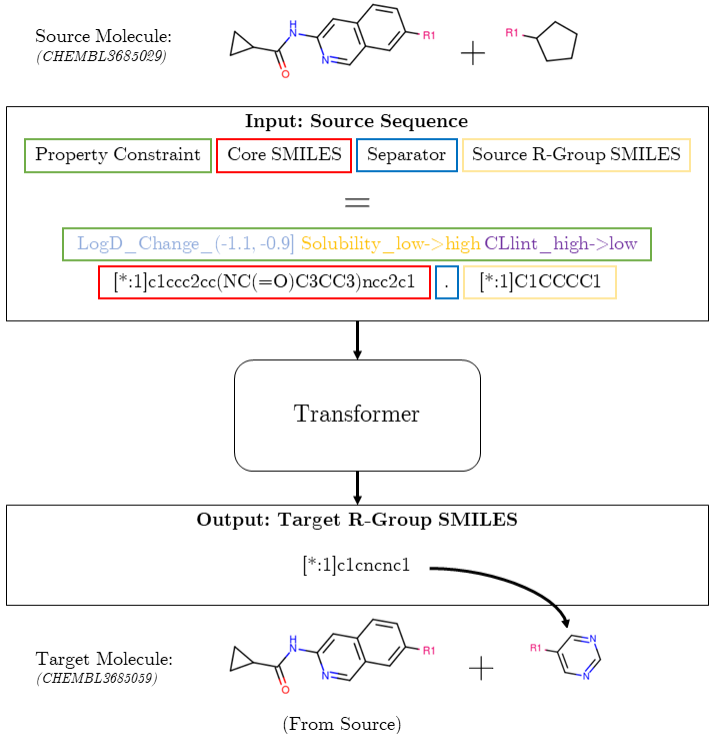
Figure 2: Input and output of the Transformer model. The input consists of property change tokens, the SMILES of the core, the SMILES of the source R-group and the dot (".") -symbol separating the core and R-group representations. The output is a R-group, which, when attached to the core from the source molecule, forms the target molecule which is expected to satisfy the property constraint in the input.

For each starting molecule in the test set, 10 unique valid molecules, which are not the same as the starting molecule, were generated using multinomial sampling. Table 1 shows the performance of our model Transformer-R and the baselines (Transformer and Enumeration) in terms of various evaluation metrics. Aligning with our goal, we firstly examine the following three aspects,

Desirable: This metric gives the proportion of generated molecules that fulfill the desirable properties specified by model input. A slight improvement was observed from Transformer-R over the Transformer baseline.

MMP33: This refers to the proportion of generated molecules for which (i) a single transformation (*i.e.* MMP) has been applied compared to the starting molecule and (ii) the ratio between the number of heavy atoms in the R-group and the number of heavy atoms in the entire molecule is less than 0.33. This evaluates how well the model captures the chemist's intuition that small and single transformations are applied to the starting molecules. From Table 1, Transformer-R generates much more molecules with small and single transformations to the starting molecules, which mimics the chemist's strategy when optimizing a starting molecule.

Unchanged Core: This refers to the proportion of generated molecules that keep the core specified by model input. Clearly, the generated molecules from Transformer-R always keeps the core (100%), while the number for the Transformer baseline dropped significantly to around 44%-70%. The reason is that Transformer-R only generates the R-groups which are attached to the core to form the final molecules, while the Transformer baseline generates the whole molecule directly which is not guaranteed to keep the core of interest.

In addition to the above three metrics, we are interested in how well the models can generate transformations and R-groups not seen in the training set. Note that many unseen transformations and novel R-groups are not preferable if the model performs bad in the above three metrics.

Table 1: Comparison of our model Transformer-R and the baselines (Transformer and Enumeration) in terms of various evaluation metrics on three test sets.

Test set	Method	Metric				
		Desirable	MMP33	Unchanged Core	Unseen Trans.	Novel R-groups
Test-Original	Transformer-R	**58.97%**	**97.67%**	**100.00%**	53.92%	**4.30%**
	Transformer	56.14%	90.45%	69.10%	51.31%	3.99%
	Enumeration	16.93%	77.85%	**100.00%**	**96.62%**	0.00%
Test-Core	Transformer-R	**56.76%**	**97.42%**	**100.00%**	32.37%	2.14%
	Transformer	55.61%	86.82%	44.60%	34.76%	**2.27%**
	Enumeration	18.64%	77.93%	**100.00%**	**98.36%**	0.00%
Test-Property	Transformer-R	**42.90%**	**97.57%**	**100.00%**	57.84%	**4.66%**
	Transformer	41.75%	90.69%	62.25%	57.98%	4.25%
	Enumeration	15.91%	81.19%	**100.00%**	**96.65%**	0.00%

Unseen Transformations: This refers to the proportion of generated molecules yielding a transformation (*i.e.* specific R-group change) which has not been seen in the training set. Transformer-R and the Transformer baseline obtain similar performance: both have learned to use not only the existing transformations in the training set, but also unseen transformations (32%-58%) to optimize unseen combinations of starting molecule and property constraint. The Enumeration baseline resulted in above 96% unseen transformations since it enumerated all the combinations of R-groups in the training set. However, more unseen transformations do not necessarily result in better score on Desirable and MMP33 without learning involved.

Novel R-groups: This metric gives the proportion of generated molecules that contain R-groups which have not been seen among the R-groups in the training set. Both Transformer-R and the Transformer baseline have generated novel R-groups (2%-5%). For the Enumeration baseline, no novel R-groups are generated since it only enumerates the existing R-groups in the training set. Figure 3 in appendix shows the top 20 most frequent novel R-groups generated by Transformer-R.

4 CONCLUSION

We have introduced Transformer-R to generate only R-groups instead of the whole molecule when optimizing a starting molecule towards its desirable properties as specified in the input. The generated R-groups are attached to the core in the input starting molecule to form the final molecules. Our results show that Transformer-R generates (i) slightly more molecules with desirable properties specified in the input; (ii) many more molecules which have small and single transformations applied to the starting molecule, which mimics the chemist's strategy; and (iii) molecules which always keep the core specified in the input constant. This is particularly useful to chemists who want to keep certain part of the starting molecule unchanged. Additionally, in contrast to the Enumeration baseline, our model can generate novel R-groups not present in the training set.

We have focused on optimizing three ADMET properties following He et al. (2020). In principle, Transformer-R can be trained to optimize other properties as well, *e.g.* synthetic accessibility and bioactivity. This could help to optimize small molecule antiviral drug candidates against *e.g.* COVID-19 in a more efficient way.

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A APPENDIX

A.1 DATASET

The same dataset in He et al. (2020) is used in this paper. In particular, a set of MMPs are extracted from ChEMBL (Gaulton et al., 2012) using the open-source matched molecular pair tool (Dalke et al., 2018). The three properties (*logD*, *solubility* and *clearance*) of the source and target molecules are predicted from models built using the in-house experimental data. The property prediction models are used for constructing data during training and also for evaluating the generated molecules during testing. For the test sets, in addition to Test-Original and Test-Property in He et al. (2020), we create Test-Core, which is a subset of the molecular pairs in Test-Original where we have excluded molecular pairs for which the core is present in the training set.
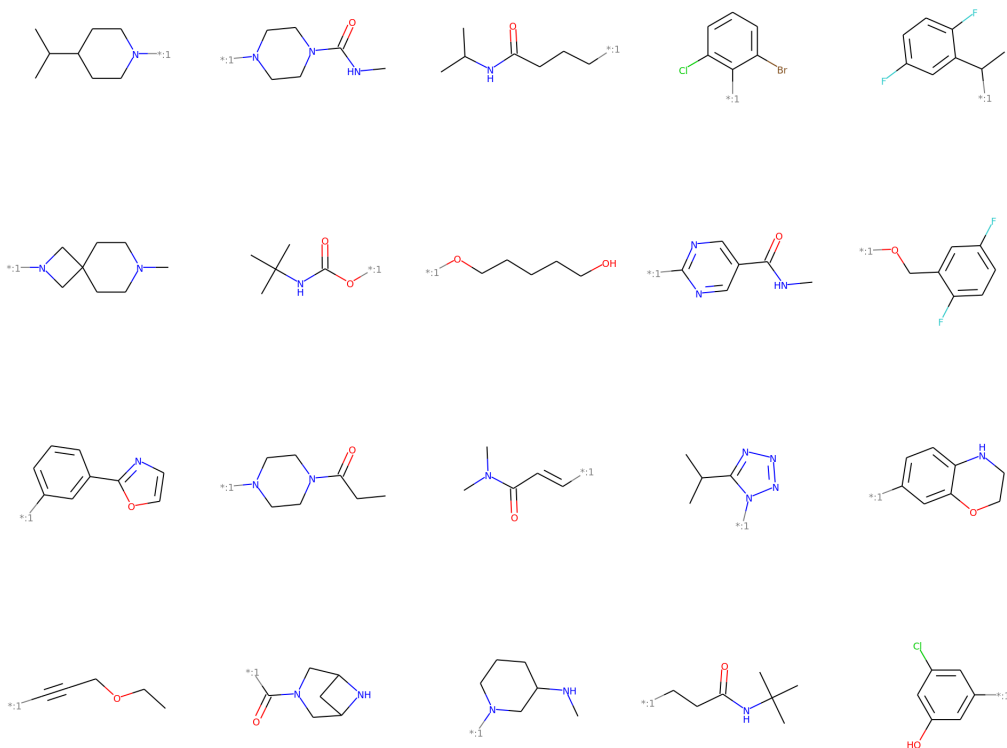
A.2 ADDITIONAL FIGURES

Figure 3: Top 20 most frequent novel R-groups generated by Transformer-R on Test-Original.