An Interpretability-augmented Genetic Expert for Deep Molecular Optimization

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Abstract

The recently proposed Genetic expert guided learning (GEGL) framework has demonstrated impressive performances on several *de novo* molecular design tasks. Despite the displayed state-of-the art results, the proposed system relies on an expert-designed Genetic expert. Although hand-crafted experts allow to navigate the chemical space efficiently, designing such experts requires a significant amount of effort and might contain inherent biases which can potentially slow down convergence or even lead to sub-optimal solutions. In this research, we propose a novel genetic expert named *InFrag* which is free of design rules and can generate new molecules by combining promising molecular fragments. Fragments are obtained by using an additional graph convolutional neural network which computes attributions for each atom for a given molecule. Molecular substructures which contribute positively to the task score are kept and combined to propose novel molecules. We experimentally demonstrate that, within the GEGL framework, our proposed attribution-based genetic expert is either competitive or outperforms the original expert-designed genetic expert on goal-directed optimization tasks. When limiting the number of optimization rounds to one and three rounds, a performance increase of approximately 43% and 20% respectively is observed compared to the baseline genetic expert.

1 Introduction

The ability to discover and design *de novo* molecules with desired properties is of great interest in a wide range of applications ranging from drug discovery [1] to materials engineering [2, 3]. This high-dimensional optimization task can be addressed via the inverse molecular design paradigm [2] which tries to find suitable candidate compounds given some target properties. This task is non-trivial considering the size of the molecular space; the drug-like chemical space alone is estimated to be about 10^{60} [4]. To tackle this challenge, one has to design a model that is computationally tractable and feasible. This optimization challenge can be framed broadly into several classes. Coley et al. [5] divides these classes into physical matters, which encompasses most drug discovery efforts on the output of the compound. These compounds are potentially used as part of a therapeutic. The second class is the process, which is seen as an important step to transition from *in silico* to a real-world experimental phase. The final class is defined as the model itself, which is the core engine driving the design choices behind each generation of *de novo* molecules.

In this paper, we shall focus our effort towards modeling of *de novo* molecules. The key challenges of seeking a *de novo* design is the process of (1) molecule generation, (2) the scoring function of the molecules, and (3) an optimization process for training the model with respect to the scoring function [6]. Each of these components have their own set of challenges. For instance, the process of generating *de novo* molecules requires models that are capable of ensuring structural fidelity

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(i.e., generated molecules should be sensible) and structurally valid (i.e., molecules are stable). The scoring function plays an important role to guide the model during the optimization process. A trivial scoring function might explore undesired or obvious parts of the chemical space. In contrast, an over-complicated scoring function, in terms of imposed constraints, could cause instability during optimization as the model might not be able find suitable solutions. Finally, the optimization process should inherently reduce the training complexity from an enormous search space to circumvent the difficulty of an intractable computation problem.

2 Enhanced Genetic Expert Guided Learning

Recently Ahn et al. [7] introduced *Genetic Expert Guided Learning* (GEGL) framework proposed which combines meta-heuristic optimization with reinforcement learning. GEGL has demonstrated strong capabilities and is at the time of writing the state-of-the-art in deep molecular optimization. The framework is composed of 4 distinct components: a neural apprentice, two reward priority queues and a genetic expert. For more detail, we refer readers to the original framework proposed by Ahn et al. [7].

Inspired by the previous framework, we propose *InFrag*. The framework build upon GEGL and consist of three main parts. The first part consist of fragment extractions from arbitrary molecules based on the computed attribution for each involved atom. Secondly, the obtained fragments are recombined to propose novel candidate molecules. Lastly, we demonstrate the process the expert can be integrated into the GEGL framework to either replace or alternatively be combined with other genetic experts. We denote the complete framework as *eGEGL* for *enhanced GEGL*. The extended framework is depicted in Figure 1.

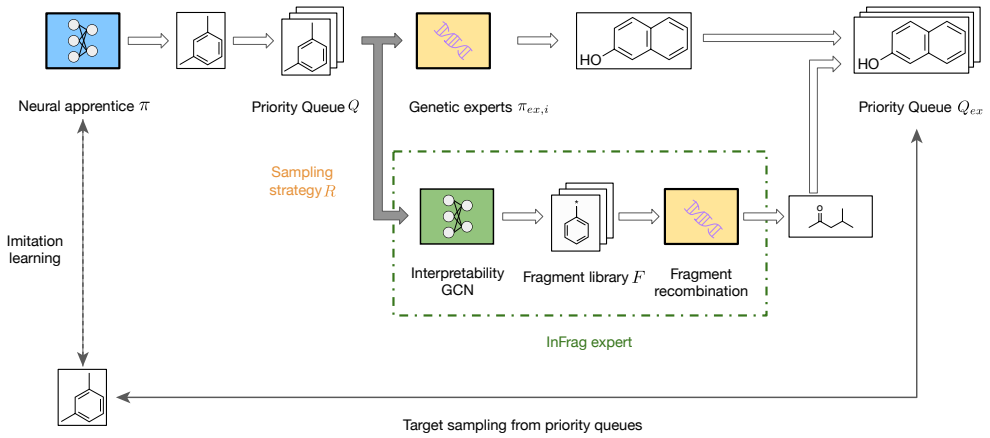

Figure 1: Complete depiction of the *eGEGL* framework. The original framework is enhanced with a fragment-based genetic expert denoted as *InFrag* (depicted in green dotted box). *InFrag* consists of a GCN model which creates attribution for queried molecules from which fragments are extracted. The extracted fragments are then randomly recombined to obtain novel candidate molecules. In addition, we include the possibility to leverage several experts via a chosen sampling strategy *R* which determines how the sampling budget is to be allocated to each expert.

2.1 Molecular Representation

Molecules are represented as undirected graphs $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ with a total number of N nodes $v_i \in \mathcal{V}$ representing the atoms and edges between nodes denoted as $e_{i,j} \in \mathcal{E}$ representing the bonds. Furthermore, we extract the binary Adjacency matrix $\mathcal{A} \in \mathbb{R}^{N \times N}$ from the edges. Each node is represented as a 74-dimensional vector $\boldsymbol{n_i} \in \mathbb{R}^{74}$ containing multiple distinct features.

2.2 Attribution-based Fragment Generation

Understanding the main contributing parts of a molecule towards its property score is an important subject. Motivated by this, we leverage upon an Attribution-based model for its interpretability methods. This allow us to reason between model input features and predicted scores. Such attributions cannot be directly computed from the optimization scoring function which is assumed to be an available. Instead, the scoring function itself is a black-box which is used to evaluate the fitness of candidate molecules. To overcome this issue, we train a pseudo-scoring function that is encouraged to imitate the original black-box scoring function of the optimization task, hence allowing us to obtain the desired attributions through this surrogate model. We implement a Graph Convolutional Network (GCN) [8] that takes the above-mentioned node features and adjacency matrix as inputs and is trained to predict task scores.

To generate attributions, we use the Class Activation Maps (CAM) [9] method due to its implementation simplicity and performance. More precisely , we compute the attribution for each atom via

$$attribution(atom_i) = w_{out}^T \cdot h_i, \tag{1}$$

where w_{out} corresponds to the weights of the final dense layer of the GCN after the average pooling layer and h_i represents the latent node features of the node corresponding to atom i just before the pooling layer. Sanchez-Lengeling et al. [10] demonstrated that CAM is able to perform relatively well, especially when combined with GCN, compared to other interpretability methods in the context of graph neural networks [10]. We note that although we did not experiment with other attribution methods and graph neural networks, other methods and models can be used to generate the necessary attributions.

Fragments of interest are identified by comparing the sign of the attribution for each atom involved in a given bond. In the case where the signs are found to be opposite, we fragment the molecule along that bond. To preserve complex substructures, we only consider and fragment single bonds and bonds which are not aromatic (as determined by RDKIT [11]). We then proceed to sum up the individual attributions of all the atoms in the fragment. If that sum is greater than 0.0, we consider the fragment to contribute positively to the predicted score and keep that fragment. Otherwise, the fragment is discarded.

Our objective is to keep and recombine fragments from high-rewarding molecules only. After processing all of the queried molecules as described above, we end up with fragments contributing positively to the predicted score regardless of its value. In order to sort and only consider high-rewarding fragments, we associate each fragment with the score from the black-box scoring function of the molecule it originated from. All fragments are added to a data-structure we call the fragment library. The fragment library allows to memorize the best scoring fragments and we impose uniqueness of the fragments in the library. When a new fragment is being added, we first check if the fragment is already present in memory. In case the fragment is already present, we set the score associated with the fragment to the maximum score between the original in-memory fragment and the new duplicate fragment. We apply selection pressure on the fragment library by limiting it's memory size to 1,000 fragments. This operation allows to remove low-rewarding fragments and leads the memory to only contain high-rewarding fragments which can be used in future optimization rounds. The complete process of fragment generation is graphically depicted in Figure 2.

Like the neural apprentice, the GCN model is trained every epoch such that it can reason over newly discovered and potentially better molecules. We also experimented with the setting where the weights of the GCN model are fixed and not updated during optimization.

2.3 Fragment recombination

To generate novel candidate molecules with our genetic expert, we first collect all fragments of the fragment library which are in SMILES format. New molecules are generated by randomly sampling 2 to 5 fragments and translating the sampled fragments into a SELFIES representation [12]. SELFIES representations posses the convenient property to always be valid, making their use very convenient for the fragment-crossover operation. The sampled fragments are randomly shuffled and combined to obtain a novel candidate SELFIES string from this fragment-crossover procedure. With some predefined probability, we furthermore apply a mutation operation on the obtained string in order to increase exploration and diversity of the generated molecules. Mutations include deletion,

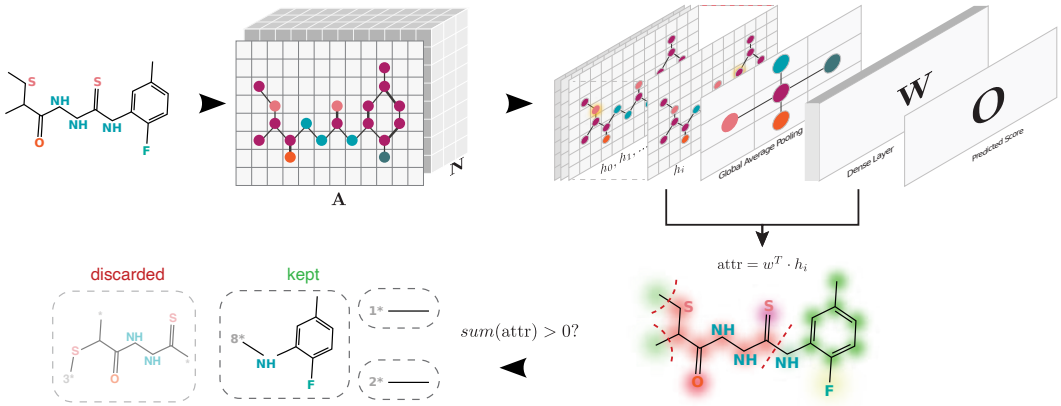

Figure 2: Generation of fragments using interpretability methods. A molecule is first processed to extract the adjacency matrix and node features. A graph convolutional network is used to calculate the last latent node embedding and final dense layer weights to compute the atom-wise class activation maps. The molecule is then fragmented along bonds where the sign of the attributions are opposite to each other. Only fragments contributing positively to the score, as determined by taking the sum over all involved atoms, are kept (depicted by the green arrow) and considered in further steps.

insertion or exchange of one of the SELFIES token on the currently operated string. Each type of mutation has the same probability of occurrence. This generative process is repeated until the number of desired molecules is reached. We note that the SELFIES representation makes use of an internal state when translating from the conventional SMILES representation. This implies that one might require a more complex recombination strategy compared to the one described above to obtain better crossover molecules from the sampled fragments. We empirically found that the simple recombination strategy as described above performs competitively, regardless of the fact that the number of atoms is not necessarily preserved during the crossover operation as illustrated in Figure 3. This representation-blind recombination strategy could be used in other problem settings since no assumptions are made about the task or the underlying representation. In addition, it does not require us to define complicated recombination rules and include expert knowledge on how fragments should relate to each other. This minimizes the potential for biases induced by such expert rules.

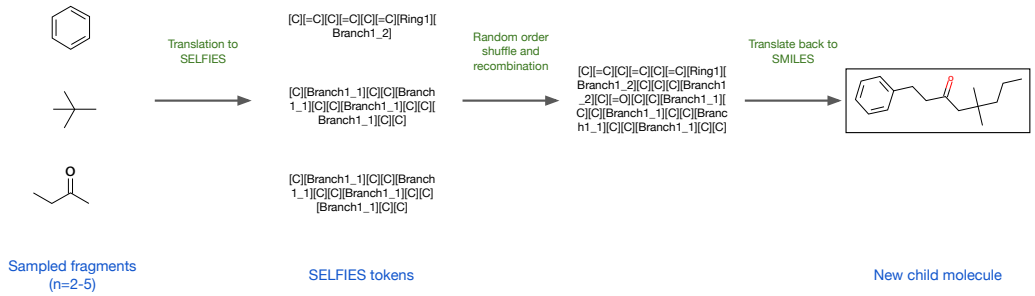

Figure 3: Recombination method for high-rewarding fragments. Fragments are sampled from the fragment library which contains high-rewarding fragments only. The fragments are first translated into their respective SELFIES representation, randomly shuffled and recombined. The final SELFIES token string is translated back to a SMILES representation and the resulting string is the new candidate child molecule resulting from the fragments. Please note that the proposed crossover rule is highly general and unbiased as it makes no assumptions about the used molecular representation.

3 Results and Discussion

3.1 Baselines and benchmarks

We benchmark and report performances of the enhanced framework against the original framework. In addition, we also add a baseline consisting of a simplified version of the STONED genetic operators proposed by Nigam et al. [13] which we will denote as *simplified-STONED* henceforth. More precisely, we limit the number of sampled chemical paths between any two parent molecules to a single one for this genetic expert. For other tasks, we include and compare against results obtained for selected baselines as reported in the original GEGL paper unless noted otherwise.

As for benchmarks, we follow the original GEGL work and compared the trained models on the penalized logp task and a subset goal-directed Guacamol benchmarks which we will describe in more details below. Furthermore, we used the same pretrained neural apprentice LSTM model as described in the original work.

Penalized LogP is a standard benchmark to evaluate *de novo* generative methods. The objective is to maximize the penalized octanol-water partition coefficient score defined as:

$$PenalizedLogP(x) = LogP(x) - SyntheticAccessibility(x) - RingPenalty(x) \quad (2)$$

where *LogP* is the unpenalized octanol-water partition coefficient[14], *SyntheticAccessibility* is a penalty term accounting for synthesizability [15] and *RingPenalty* is a penalty for rings with a size larger than 6. We impose a constraint onto the generative model by limiting the number of SMILES characters to 81 following previous work.

Goal-directed Guacamol benchmarks are a set of 20 benchmarks proposed by Brown et al. [16] which were specifically designed for comparing generative models. The benchmarks evaluate a set of molecules to account for molecular diversity. More specifically and following the notation in Ahn et al.[7], the final benchmark score for a given molecule set X is computed as

$$Guacamol(X) \coloneqq \sum_{S \in Q} \sum_{s=1}^{S} \frac{r(x_{\Pi(s)})}{S|Q|} \text{ for } s = 1, ..., |X| - 1 \quad (3)$$

where Q is a list of integers and Π is a permutation function which ensures that the molecules $x \in X$ are sorted in descending order with respect to their respective scores. The goal-directed benchmarks contain a variety of tasks such as *rediscovery*, *similarity* or *multi property optimization*. We refer readers to either the original Guacamol and GEGL papers for a more detailed description of each task type [16, 7]. For the tested tasks, we limit the number of characters to 100 for all generated SMILES strings.

3.2 Penalized logP task

Table 1 summarizes the mean and standard deviation comparison between several reported baselines and the enhanced GEGL framework we propose. We ran 5 independent experimental runs for each of our models where each round consists of 200 optimization rounds following previous work. The results demonstrate that there is no gain or decrease in performance by swapping out the genetic expert. This is remarkable because it indicates that expert-designed genetic experts can potentially be replaced with simpler and bias-free genetic-experts without loss in performance.

We furthermore note that the *InFrag* genetic expert is able to extract useful information from the pretraining phase of the GCN which can be leveraged from the start of the optimization process. To demonstrate this, we additionally compared the different genetic experts in the setting where obtaining and evaluating candidate molecules is assumed to be undesirable. Concretely, we limit the optimization process to a single and three optimization rounds respectively and evaluate the generated molecules. As can be seen in Table 2, our *InFrag* genetic expert is able to generate higher-rewarding molecules in this setting, even surpassing the *JT-VAE* and *ChemTS* baselines as can be seen from Table 1 and achieving similar results to the reinforcement learning based *GCPN* method. These results indicate that our genetic expert is appropriate in settings where obtaining *additional* labels for novel candidate molecules is expensive or difficult, as is usually the case in real-world applications. This is to be expected as the GCN is able to leverage the learned representations from the pretraining phase and therefore can reason and propose high-rewarding novel molecular candidates from the beginning of the optimization process.

Table 1: PenalizedLogP results. Results are displayed as mean and standard deviation.

Algorithm	Objective
JT-VAE[17]	4.90 ± 0.33
ChemTS[18]	5.60 ± 0.50
GCPN[19]	7.86 ± 0.07
GB-GA[20]	15.76 ± 5.76
DA-GA[21]	20.72 ± 3.14
GEGL (GB-GA expert)[7]	$\mathbf{31.40 \pm 0.00}$
GEGL (simplified-STONED expert)	$\mathbf{31.40 \pm 0.00}$
GEGL (InFrag expert)	$\mathbf{31.40 \pm 0.00}$

Table 2: One- and Three-round PenalizedLogP results. Entries are displayed as mean and standard deviation.

Algorithm	1-round optimization	3-round optimization
GEGL (GB-GA expert)[7]	5.44 ± 0.17	7.92 ± 0.42
GEGL (simplified-STONED expert)	4.29 ± 0.14	6.82 ± 0.25
GEGL (InFrag expert)	$\mathbf{7.81 \pm 0.61}$	$\mathbf{9.50 \pm 0.24}$
Improvement over baseline	$\mathbf{43.6\%}$	$\mathbf{19.9\%}$

3.3 Goal-directed guacamol benchmarks

Finally, we evaluated the proposed enhancements and genetic expert on a subset of the goal-directed benchmark tasks proposed in the Guacamol benchmark. More precisely, we excluded all *Rediscovery* and all *Similarity* tasks for which multiple baselines are able to obtain a perfect score of 1.0. Table 3 summarizes the obtained experimental results.

Table 3: Results for the goal-directed Guacamol benchmarks for different genetic experts leveraging the GEGL framework. We show selected baselines for comparison as reported by the original GEGL work[7].

	Baselines			GEGL-based models		
Task	GB-GA[20]	MSO[22]	CReM[23]	GB-GA[7]	simplified-STONED	InFrag
C11H24	0.971	0.997	0.966	**1.000**	**1.000**	**1.000**
C9H10N2O2PF2Cl	0.982	**1.000**	0.940	**1.000**	**1.000**	**1.000**
Median molecules 1	0.406	0.437	0.371	**0.455**	**0.455**	**0.455**
Median molecules 2	0.432	0.395	0.434	**0.437**	0.419	0.427
Osimertinib MPO	0.953	0.966	0.995	**1.000**	**1.000**	**1.000**
Fexofenadine MPO	0.998	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**
Ranolazine MPO	0.920	0.931	0.969	0.958	**0.981**	0.959
Perindopril MPO	0.792	0.834	0.815	0.882	**0.886**	0.882
Amlodipine MPO	0.894	0.900	0.902	**0.924**	0.905	0.905
Sitagliptin MPO	0.891	0.868	0.763	0.922	**0.958**	0.952
Zaleplon MPO	0.754	0.764	0.770	0.834	**0.840**	**0.840**
Valsartan SMARTS	0.990	0.994	0.994	**1.000**	**1.000**	**1.000**
Deco Hop	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**
Scaffold Hop	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**

We observe that the genetic experts can be exchanged with each other without significant loss or increase in performance. Furthermore, the empirical results show that no expert dominates across all of the tested tasks. This indicates that combining and sampling several experts simultaneously to leverage the best of all experts can potentially lead to better overall results.

4 Conclusions

We have shown in this work that it is possible to pretrain and utilize an attribution-based genetic expert to propose novel molecules. The expert we called *InFrag* is able to leverage a pretraining phase to reason over the potential score of candidate molecules and produces atom-wise attributions to generate high-rewarding fragments. Our genetic expert which is capable of expert- and bias-free fragment-level crossover operations is able to produce high-rewarding molecules and performs comparable to other genetic experts when embedded into the GEGL framework. Furthermore, we demonstrated that *InFrag* significantly outperforms other genetic experts when the number of optimization rounds is limited. This implies that *InFrag* is a good choice for real-world optimization cases were evaluation of novel generated molecules might be difficult or expensive. We have not yet experimented with different genetic experts, attribution methods, graph neural network architectures or sampling strategies, leaving a potentially large room for improvement. We leave this area of research for future work.

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