Which Hyperparameters to Optimise? An Investigation of Evolutionary Hyperparameter Optimisation in Graph Neural Network For Molecular Property Prediction

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ABSTRACT
Recently, the study of graph neural network (GNN) has attracted much attention and achieved promising performance in molecular property prediction. Most GNNs for molecular property prediction are proposed based on the idea of learning the representations for the nodes by aggregating the information of their neighbor nodes (e.g. atoms). Then, the representations can be passed to subsequent layers to deal with individual downstream tasks. Therefore, the architectures of GNNs can be considered as being composed of two core parts: graph-related layers and task-specific layers. Facing real-world molecular problems, the hyperparameter optimization for those layers are vital. Hyperparameter optimization (HPO) becomes expensive in this situation because evaluating candidate solutions requires massive computational resources to train and validate models. Furthermore, a larger search space often makes the HPO problems more challenging. In this research, we focus on the impact of selecting two types of GNN hyperparameters, those belonging to graph-related layers and those of task-specific layers, on the performance of GNN for molecular property prediction. In our experiments, we employed a state-of-the-art evolutionary algorithm (i.e., CMA-ES) for HPO. The results reveal that optimizing the two types of hyperparameters separately can gain the improvements on GNNs’ performance, but optimising both types of hyperparameters simultaneously will lead to predominant improvements. Meanwhile, our study also further confirms the importance of HPO for GNNs in molecular property prediction problems.

CCS CONCEPTS
• Computing methodologies → Neural networks; Search methodologies; • Applied computing; • General and reference → Experimentation;

1 INTRODUCTION
Graph neural networks (GNNs) have been applied to solve a wide range of problems, such as social recommendation [10], citation trend prediction [7], and molecular property prediction [9, 11, 19, 41]. One advantage of GNNs is that they can be directly operated on graphs in an end-to-end manner for real-world problems, and task-specific representations can be learned automatically between latent layers. In contrast, traditional machine learning methods require handcrafted features from graph as input. For example, the work presented in [19] mentioned that support vector machine, random forest, and XGBoost took handcrafted descriptors and/or fingerprints from molecular structures as inputs to predict molecular properties. When GNNs are applied to the same problems, given a molecular graph, the vector representations for all atoms are learned at first by aggregating and updating the information of neighbor atoms. Thereafter, the readout operator [33] (i.e., mean, sum) is employed to collapse all atom representations into a molecular (graph-level) representation, which can be passed to subsequent task-specific layers to make predictions. In our experiments, we employed graph convolution [9] because it has been proposed considering molecular domain knowledge.

The study presented in [39–41] indicated that hyperparameter optimization (HPO) by evolutionary computation can improve the GNN’s performance for predicting molecular properties. However, HPO for GNNs is often an expensive task. Evaluating hyperparameter settings on GNNs needs to train models which cost a lot of computational resources. Some methods have been proposed to alleviate this issue such as using surrogate models [5], successive halving [18, 20]. From another angle to consider this issue, the pre-defined hyperparameter search space may directly affect the HPO results. For example, it is very challenging to search for optimal solutions given a very large hyperparameter space and a relatively limited computational budget. The HPO search space is defined by selected hyperparameters (e.g., batch size, learning rate), the ranges
of these hyperparameter values, and the step sizes (i.e., intervals) which determine the resolutions of the hyperparameter values to be searched. From our perspective, the ranges and step sizes depend on individual practical cases to some degree. This research focuses on investigating the impact of selecting different types of hyperparameters to optimize on the GNN’s performance for molecular property predictions. In concrete, we investigated the differences of optimizing hyperparameters related to graph layers and those from task-specific layers. Therefore, we grouped the hyperparameters according to the layer-wise neural architectures of GNNs, which can be considered as being the combination of graph layers and task-specific layers. In this way, we expect to discover that optimizing which types of the hyperparameters may bring more expected gains.

Additionally, CMA-ES [14] as a state-of-the-art, derivative-free, and evolutionary black-box optimization method has been employed to optimize hyperparameters. Therefore, we use it as our evolutionary search strategy for HPO. This will allow us to focus on the impact of the two types of hyperparameters with the same search strategy. However, we also point out that more evolutionary HPO approaches could be used in the future to test the impact of hyperparameters, but this is beyond the scope of this research.

The rest of this paper is organized as follows. Section 2 introduces related work. In Section 3, the experiments are reported and the results are analysed. Finally, Section 4 concludes the paper and explores some directions in future work.

2 RELATED WORK

2.1 Graph Neural Networks

Many types of GNNs have been proposed based on the idea of aggregating neighborhood recursively [36] (or message passing [11]). Each node aggregates feature vectors of its neighbors to compute its new feature representation. To generate the representation of the entire graph, many schemes have been proposed such as graph pooling [38], attention sum [23], mean [3], max [13]. When GNNs are applied in molecular property prediction, the representation of the entire graph is then passed to subsequent layers [19]. For example, graph convolution model (GC) [9] makes use of neural networks to imitate circular fingerprint (a representation of molecular structures by encoding the information of atom neighborhoods) [12] to generate molecular representation, the so called neural fingerprint, which can be passed to a simple neural network to predict drug efficiency and photovoltaic efficiency.

Therefore, in general, the architectures of GNNs are classified into graph layers and task-specific layers (Fig. 1). The former denote those layers which take responsibility of processing the structured data by aggregations, and generate vector representations for all the nodes in graph. Task-specific layers are exploited to deal with individual problems (e.g., classification, regression). In Fig. 1, task-specific layers are implemented by fully-connected layers which takes the molecular representation as input to output a value. We also point out that the types of layers such as pooling, readout depend on the individual situations. For example, readout-equivalent operation has been implicitly defined within the graph convolution algorithm [9] because it aims to generate a molecular representations (graph-level), and in this case the readout operation is classified into graph layer. In contrast, graph convolutional networks [21] was originally proposed to learn each node representation for node classification. When it is applied to solve graph-level tasks, the node representations have to be collapsed into a representation by readout, and in this case the readout is classified into task-specific layer.

Furthermore, there is an increasing number of research works about applying GNN into molecular property prediction. The work presented in [31] taxonomies the problems of molecular property prediction into four main types: quantum chemistry, physical chemistry, biophysics, and biological effect. MPNN [11] makes use of the idea of message-passing to update atom hidden states recursively, and the final hidden states of atoms are processed by readout function to predict the multiple properties in quantum chemistry originally. Thereafter, directed MPNN [37], MPNN with SELU activation function [32], MPNN with attention and edge memory mechanisms [32] have been proposed as the variants of MPNN [11] and applied to predict a wider range of molecular properties. Message-passing is a kind of propagating information in spatial manner. Similarly, there are some GNNs which have been proposed based on the idea of performing the spatial-like convolution operation on molecular graphs [6, 9, 29, 35]. In contrast, the number of the applications of spectral GNNs in molecular property prediction is relatively small. LanczosNet [24], GCN [15], AGCN [22], GCN with eigen-pooling [25] which have been proposed based on the spectral decomposition. Furthermore, the work presented in [11] used MPNN framework to unify message-passing-based, spatial, and spectral GNNs.

2.2 CMA-ES

CMA-ES[14] is one of the state-of-the-art evolutionary approaches for HPO. It regularly dominates the black-box optimization benchmarking (BBOB) challenge [17]. The core idea of CMA-ES is maintaining a multivariate normal distribution (Eq. 1) to sample new solutions. The multivariate normal distribution consists of a covariance matrix $C$ and mean $m$, and step size $\sigma$. The update of these parameters is inspired by biological evolution. Specifically, $g$ denotes the generation in Eq. 1. CMA-ES always follows the principle of ‘survival of the fittest’, the number of $\mu$ promising individuals are selected to update $m^{(g)}$ with different weights $w$ by Eq. 2. To update $C^{(g)}$, CMA-ES combines the Rank-$\mu$-Update with Rank-One-Update to keep the balance between exploitation and exploration. Finally, to control the scale of step size and speed up learning process, CMA-ES introduces $\sigma$ which is updated by cumulative path length control.

$$x^{(g+1)}_k \sim m^{(g)} + \sigma^{(g)} \mathcal{N}(0, C^{(g)}) \quad \text{for } k = 1, \ldots, \lambda \quad (1)$$

$$m^{(g+1)} = \sum_{i=1}^{\mu} w_i x^{(g+1)}_{i, \lambda} \quad (2)$$

The most surprising discovery about CMA-ES is that the learning of the distribution parameters is similar to the descent in direction of a sampled natural gradient of the expected objective function value [2]. Additionally, the using of covariance matrix in the method
provides promising future for dealing with multi-dimensions HPO problems [27]. In concrete, there are some hyperparameters are not independent for all deep learning models, for example, the learning rate and batch size. Covariance matrix helps to automatically build the relation between them and coordinate them smoothly.

### 3 EXPERIMENTS

ESOL [8], FreeSolv [26], and Lipophilicity [16] are three representative molecular benchmark datasets used in our experiments, and they respectively correspond the tasks of predicting solubility, hydration free energy, and octanol/water distribution coefficient. The sizes of them are 1,128, 642, 4,200 respectively. Each dataset is split into training, validation, and test sets with the ratio 80%/10%/10%. The training set is used to train GNNs, the validation set is used for guiding HPO, and test set is used to do final evaluations. Compared with the common designs of HPO experiments, we made the modification that the evaluation of a solution (hyperparameter setting) is repeated three times, and the mean of the root mean squared errors (RMSE) is used to score the solutions.

Meanwhile, we employed the graph convolution model (GC) [9] to predict these properties in the above mentioned three datasets. GC was proposed with the molecular domain knowledge which fits our research problem (molecular property prediction) compared with other GNNs. For ease of implementation, we leveraged the DeepChem (Python toolkit for deep learning in drug discovery, materials science, quantum chemistry, and biology) [28] to preprocess molecular data and implement GC. In addition, we make use of Optuna [1] to conduct the HPO experiments with CMA-ES.

To assess the impact of optimizing different types of hyperparameters on the performance of GNNs, we first look at the graph-related hyperparameters, and for GC, they include the number of graph convolution layer $n_g$, the sizes of the graph convolution layer $s_g$, and the size of dense layer $s_d$ which is defined in GC to generate molecular representations. The range of $n_g$ is $1 \sim 6$ with the step size 1. $s_g$ and $s_d$ are in the ranges of $32 \sim 512$ (step size 32) and $64 \sim 1024$ (step size 64), respectively. These ranges are set according to the default value provided in [34], while the step sizes are selected following [39]. As for the task-specific hyperparameters (i.e., the hyperparameters in task-specific layers), in order to predict molecular properties $R$, we employed a simple feedforward neural network which consists of a few fully-connected layers. So the task-specific hyperparameters include the number of fully-connected layers $n_f$ (excluding the output layer), and the sizes of those layers $s_f$, and the activation function $a$. The options of $a$ are $\text{Sigmoid}$, $\text{Tanh}$, and $\text{ReLU}$. Meanwhile, the ranges of $s_f$ referring to $s_d$ are from $64 \sim 1024$ with the step size 64. The arrangement of $n_f$ is the same as $n_g$ for facilitating analysis. The above hyperparameters are summarized in Table 1. Furthermore, $n_g$ and $n_f$ will determine the number of $s_g$ and $s_f$, so our search space is dynamic. The dynamic feature of the search space will change the dimensions of the problem during the search, which makes HPO more challenging.

### 3.1 Pseudo-dynamic Search Space

However, it is noted that CMA-ES does not support dynamic search space [1]. Therefore we turn to implement the pseudo-dynamic process, and the process of HPO is shown in Algorithm 1. In Algorithm 1, $\Lambda_{HPO}$ denotes the entire hyperparameter space, and $|\Lambda| = N$ means the number of hyperparameters. Furthermore, $\Lambda^0_{HPO}$ is used
to define a dynamic hyperparameter. For example, in our experiments, $s_g$ is a list in which each element represents the size of the corresponding graph convolution layer. Meanwhile, the number of elements in $s_g$ is dynamic as it is determined by $n_g$. It is not possible to decrease/increase the dimensions of the multivariate normal distribution after initialization, so that we keep the CMA-ES to sample the maximum number of elements. Regarding this, we make use of $n_g$ to decide how many elements will be used to instantiate the model. In this way, the search space maintained by CMA-ES is not changed, but in practical it affects the generation of models.

**Algorithm 1: HPO on Pseudo-dynamic Search Space**

```plaintext
input: the hyperparameter space $A = \Lambda_1 \times \Lambda_2 \times \ldots \Lambda_N$,
where $\Lambda_n$ denotes the $n$-th hyperparameter; if $\Lambda_n$ is a dynamic hyperparameter, $\Lambda_n = \{\Lambda_n^1, \Lambda_n^2, \ldots \Lambda_n^N\}$,
where $i \in \Lambda_n$, $(\Lambda_m, \Lambda_n)$ are paired, $\Lambda_m$ will determine the number of elements in $\Lambda_n$; a GNN $M$; the total number of trials $T$
1 initializing CMA-ES; $\lambda_{best}$ current best hyperparameter setting;
2 sort($\Lambda$); // move all dynamic hyperparameters backward
3 $t=1$;
4 while $t < T$ do
5     $\lambda = []$; // null list for collecting sampled hyperparameters
6     for $n = 1$ to $N$ do
7         if $\Lambda_n$ is a dynamic hyperparameter then
8             lookup (($\Lambda_m, \Lambda_n$));
9                 for $z = 1$ to $I$ do
10                     $v = $ CMA-ES.suggest($\Lambda_n^z$);
11                     if $z <= i$ then
12                         $\lambda$.append($v$);
13                 end
14             else
15                 $v = $ CMA-ES.suggest($\Lambda_n$);
16                 $\lambda$.append($v$);
17             end
18     $M$ is instantiated with $\lambda$;
19     evaluate($M$);
20     update($\lambda_{best}$);
21     $t++ = 1$;
22 end
```

Overall, we designed four sets of experiments. The first set of experiments take the default values of hyperparameters from DeepChem [28] to train a GC model for thirty times on ESOL, FreeSolv, and Lipophilicity datasets, respectively. The average of root mean squared errors (Mean RMSE) and standard deviations (Mean Std) are shown in Table 2. Batch size $s_b$, the number of training epochs $n_e$, and learning rate $l_r$ which are not considered to optimize because this study focuses on discovering the impact of optimizing the two different types of GNNs’ hyperparameters.

Meanwhile, $s_g = 128$, $n_e = 100$, and $l_r = 0.0005$ are set for all our experiments. In Table 2, $n_f$, $s_f$ and $a$ are 0 or none because the task-specific layer only has a single output layer (i.e., no hidden layers) according to the original settings in DeepChem [28]. The purpose of this group of experiments is to set a baseline for our following experiments.

| Datasets          | ESOL     | FreeSolv | Lipophilicity |
|-------------------|----------|----------|---------------|
| Hyperparameters   |          |          |               |
| Train             | Mean RMSE| 0.3202   | 0.7782        | 0.2146        |
|                   | Mean Std | 0.0487   | 0.0785        | 0.0259        |
| Valid             | Mean RMSE| 1.1145   | 2.1353        | 0.7245        |
|                   | Mean Std | 0.0479   | 0.2326        | 0.0247        |
| Test              | Mean RMSE| 1.1570   | 1.8482        | 0.7424        |
|                   | Mean Std | 0.0700   | 0.1679        | 0.0203        |

Table 2: The Results by Using the Hyperparameters Provided by MoleculeNet

The other three sets of experiments are conducted the HPO for GC on ESOL, FreeSolv, and Lipophilicity, respectively. In Section 3.2, we will discuss the process of HPO on the three datasets (Figs. 2–4). Thereafter, we will start to analyse the results in details for each dataset (Tables 3–5).

### 3.2 The Process of Hyperparameter Optimization

In Figs. 2–4, the x-axis denotes the index of each trial. One trial represents a process of sampling and evaluating a new hyperparameter setting. CMA-ES was assigned with 200 trials for each dataset. The y-axis denotes the metric of RMSE for evaluating each trial; the values are drawn in these figures. The reason for using the mean value of multiple evaluations is that we observed the results for multiple evaluations are not stable, which may mislead the HPO. In Fig. 2–4, the blue points represent the RMSEs for optimizing graph-related hyperparameters, the green points represent the RMSEs of optimizing task-specific hyperparameters, and the orange points denote the results of optimizing both graph-related and task-specific hyperparameters simultaneously. The nine lines are used to represent the trends of performing HPO on different types of hyperparameters, and these lines are drawn by connecting all current best points in time sequence. It is easy to observe that most of the lines hold obviously decreasing trends, which indicates that CMA-ES works for optimizing hyperparameters. Furthermore, in Figs. 2 and 4, the decreasing trends of RMSEs for red and purple lines are less significant, compared with those for the blue lines. From these observations, we can see that, Fig. 2 implies that appropriate settings for both graph and task-specific layers are needed together, and they may complement with each other to achieve better performance in molecular prediction tasks.
get more gains given the same number of trials, even the search space becomes larger because the number of possible combinations of different hyperparameters increases.

3.3 The Results

The best hyperparameter values obtained from Section 3.2 are used to instantiate GCs, and these GCs are trained respectively on ESOL, FreeSolv, and Lipophilicity datasets. The detailed results are shown in Tables 3 ~5.

In general, the models configured with the CMA-ES optimized hyperparameters on the three datasets achieved better performances than the original ones (Tab 2). For example, in ESOL, the RMSE of the GC with default hyperparameters (Table 2) is 1.1570 on the test set. The models with HPO on graph layers, task-specific layers, and both of them have the Mean RMSE of 1.0854, 0.9505, and 0.8824, respectively (Table 3). To statistically analyse the improvements, we conducted the $t$-test for the RMSEs on the test dataset between Table 2 and Table 3 with the $t$ values of 4.0000, 12.7625, and 18.1311. When the significance level $\alpha = 0.001$, their performance are all significantly better than original ones??
In Tables 3−5, we can see that HPO on graph and fully connected (task-specific) layers outperforms HPO on either graph or fully connected layers. With the same number of trials in HPO, optimizing graph or fully connected layers face a large search space, but it achieved promising performance. Meanwhile, in Tables 4 and 5, we observed that only optimizing fully-connected layers has relatively more serious over-fitting problem compared with the optimizing both types of hyperparameters, since it always obtained less RMSE values on the training datasets, and inversely had larger RMSE values on validation and test sets. In this case, it indicates optimizing fully-connected layers only would help to fit the problems, but without optimizing graph layers, the molecular representations may not be better learnt, which leads to reduced performance of GNNs in test set. Conducting HPO on graph layers only achieved lower performance than performing HPO on task-specific layers and the both in the three datasets. We believe the reason is that the default setting of GC only provides a output layer without hidden layers; this means molecular representations are only passed to a linear layer (without non-linear transformation) which dramatically restricts the learning capability. Interestingly, after HPO, the hyperparameter $a$ was assigned to ReLU in all experiments which is the same choice as described in [9], where the ReLU activation function was manually selected.

In summary, although graph layers and task-specific layers play different roles in GNNs, they need to be optimized together when solving practical problems. The reason is as follows: a better graph representation learned from graph layers needs to be supported by tailored task-specific layers to accomplish tasks. Similarly, task-specific layers also need appropriate graph representations to achieved good performances.

From the above analysis, we can conclude that when only limited computational budget is available, we should still optimize the hyperparameters of both types of layers, rather than focusing on one of them.

## 4 CONCLUSIONS AND FUTURE WORK
With the rapid development of GNNs, applying them in molecular machine learning problems becomes increasingly compelling and meaningful. For example, accurate molecular property prediction can significantly facilitate the entire process of drug discovery in a faster and cheaper way. However, the performance of GNNs are largely affected by hyperparameter selection, so the research of HPO on GNNs is of extremely important.

In this paper, we elaborated the problem of HPO on GNNs for molecular property prediction, and investigated in depth that which types of hyperparameters should be selected to optimize when computational resources are limited. Based on our experiments, we conclude that both graph-related hyperparameters and task-specific hyperparameters should be optimised simultaneously, and leaving any one out will result in reduced performance. Even doing this means a larger search space, which seems to be more challenging given the same number of trials (limited computational resources), such a strategy can surprisingly achieve better performance.

Finally, we acknowledge that our experiments are based on one type of GNN model and one evolutionary strategy. However, we believe that our conclusion can be further generalised, because we have selected the representative GNN model, used state-of-the-art evolutionary HPO approach, and the benchmark datasets used for experiments are also representative in molecular property prediction problems.

Still, we propose two future directions to carry out our research in the next step. First, there exist various GNNs, and most of them comply with the rule of aggregating the neighbor information to learn the node representations. However, they can be classified into spectral and spatial GNNs [4]. In this research, we have extensively investigated the impact of HPO on GC, which is a representative of spatial GNNs. Therefore, it would be interesting and worthwhile to investigate whether the same conclusion holds for HPO of spectral GNNs. Second, we employed CMA-ES as the HPO strategy because
Table 3: HPO on the ESOL Dataset

| Hyperparameters | Graph Layers | Fully Connected Layers | Graph and Fully Connected Layers |
|------------------|--------------|------------------------|----------------------------------|
| $n_g = 3$ $s_g = 320, 384, 128$, $s_d = 448$ | $n_f = 5$, $s_f = [512, 768, 832, 320, 192]$, $a = \text{relu}$ | $n_g = 1$, $s_g = 512$, $s_d = 640$, $n_f = 5$, $s_f = [1024, 832, 640, 192, 832]$, $a = \text{relu}$ |
| Mean RMSE | 0.1917 | 0.2328 |
| Mean Std | 0.0368 | 0.0651 |

Table 4: HPO on the FreeSolv Dataset

| Hyperparameters | Graph Layers | Fully Connected Layers | Graph and Fully Connected Layers |
|------------------|--------------|------------------------|----------------------------------|
| $n_g = 1$, $s_g = [256]$, $s_d = 192$ | $n_f = 2$, $s_f = [1024, 448]$, $a = \text{relu}$ | $n_g = 2$, $s_g = [512, 352]$, $s_d = 128$, $n_f = 5$, $s_f = [192, 640, 320, 320, 768]$, $a = \text{relu}$ |
| Mean RMSE | 0.4565 | 0.4926 |
| Mean Std | 0.1361 | 0.1510 |

Table 5: HPO on the Lipophilicity Dataset

| Hyperparameters | Graph Layers | Fully Connected Layers | Graph and Fully Connected Layers |
|------------------|--------------|------------------------|----------------------------------|
| $n_g = 6$, $s_g = [416, 256, 512, 320, 384, 128]$, $s_d = 768$ | $n_f = 4$, $s_f = [1024, 896, 832, 64]$, $a = \text{relu}$ | $n_g = 5$, $s_g = [480, 512, 256, 192, 224]$, $s_d = 960$, $n_f = 4$, $s_f = [704, 320, 128, 768]$, $a = \text{relu}$ |
| Mean RMSE | 0.1369 | 0.1701 |
| Mean Std | 0.0206 | 0.0361 |

it is a state-of-the-art evolutionary HPO method. However, it does not support the dynamic search space, which constrains its scalability. In our future work, other evolutionary HPO approaches can be applied to explore their effectiveness on optimizing hyperparameters with dynamic search space for GNNs.

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