Dual Convolutional Neural Network for Graph of Graphs Link Prediction

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Abstract

Graphs are general and powerful data representations which can model complex real-world phenomena, ranging from chemical compounds to social networks; however, effective feature extraction from graphs is not a trivial task, and much work has been done in the field of machine learning and data mining. The recent advances in graph neural networks have made automatic and flexible feature extraction from graphs possible and have improved the predictive performance significantly. In this paper, we go further with this line of research and address a more general problem of learning with a graph of graphs (GoG) consisting of an external graph and internal graphs, where each node in the external graph has an internal graph structure. We propose a dual convolutional neural network that extracts node representations by combining the external and internal graph structures in an end-to-end manner. Experiments on link prediction tasks using several chemical network datasets demonstrate the effectiveness of the proposed method.

1 Introduction

Graphs are general and powerful data representations which can model complex real-world phenomena, ranging from chemical compounds to social networks. However, most of the existing data analysis techniques assume that each data instance is readily represented as a fixed-dimensional feature vector; therefore, graph-structured data analytics has been one of the topics fascinating researchers in the field of machine learning and data mining.

In chemoinformatics, chemical compounds are often represented as molecular graphs whose nodes correspond to their atoms and edges correspond to the chemical bonds among them. Molecular fingerprinting [Morgan, 1965] is a widely used way for molecular graph representation that uses a set of subgraphs responsible for important chemical properties. A molecular fingerprint is a fixed-dimensional binary vector, each of whose elements corresponds to a subgraph (e.g., benzene ring) related to some chemical property (e.g., aromatic). Machine learning methods have been successfully applied to prediction of various molecular properties such as drug efficacy [Gamo et al., 2010].

Aside from the graph structures inside molecules, other types of graphs such as various interaction networks among molecules are sometimes available, where the nodes correspond to the molecules and the links correspond to the chemical interactions between them. This hierarchically structured graph has two types of graph structures: the internal graph structure inside a single molecule and the external graph structure among a set of molecules, which is known as a graph of graphs (GoG) (Fig. 1).

Our focus in this paper is to develop an effective modeling method for the GoG which has a more general and complex graph structure than a single graph, and to consider the link prediction task on a GoG. For example, predicting links in a chemical interaction network provides useful information for drug repositioning (to find new applications of existing drugs) and finding their potential side effects [Lounkine et al., 2012, Medina-Franco et al., 2013].

Recently, deep neural networks (DNNs) have been successfully applied to graph-structured data. Many of the existing approaches employ recursive constructions of graph representations called graph convolution [Duvenaud et al., 2015] and end-to-end learning of the whole networks using backpropagation [Sutskever, Vinyals, and Le, 2014]. Such representation learning has an advantage over existing approaches based on off-the-shelf features such as the molecular fingerprints, since it enables automatic and flexible feature extraction from graph and improves the predictive performance.

In this paper, we extend the graph convolutional neural network to GoG by introducing a new architecture called dual convolution. The dual convolution allows us to (i) seamlessly handle both internal and external graph structures in an end-to-end manner and (ii) efficiently learn low-dimensional representations of the GoG nodes. We conduct experiments of the link prediction task using real GoG datasets such as a drug-drug interaction network, and show that the dual convolution achieves a superior performance to baselines in some datasets. In addition, we analyze the effects of network density and degree distribution for performance; indeed, real-world external graphs (e.g., sparse and heavy-tailed networks) have a variety of structures compared to internal graphs (e.g., small organic molecules). We believe that our performance analysis of dual convolution provides insights into developing practical applications for real-world datasets.
2 Link Prediction Problem in a Graph of Graphs (GoG)

Throughout the paper, we denote vectors by bold lowercase letters (e.g., $v \in \mathbb{R}^d$), matrices by bold uppercase letters (e.g., $M \in \mathbb{R}^{m \times n}$), and scalars and discrete symbols (such as graphs and nodes) by non-bold letters (e.g., $G$ and $n$).

A GoG is a hierarchically structured graph $G = (V, A)$, where $V$ is the set of nodes, $A$ is the adjacency list. Each node in the GoG is also a graph, which we denote by $G = (V, A) \in V$, where $V$ is the set of nodes, and $A$ is the adjacency list. We refer to $G$ as an external graph and $G$ as an internal graph.

For example, an interaction network between chemical compounds is represented as a GoG $G$, whose nodes $V$ are the set of compounds, and whose edges referred to by its adjacency list $A$ are the set of binary relations (e.g., interact or not) among the compounds. For each compound $G = (V, A) \in V$, $V$ is the set of the atoms included in the compound, and $A$ indicates the set of chemical bonds among the atoms.

Given a GoG, our goal is to obtain a feature representation of each internal graph $G \in V$ and to predict the probability of the existence of a (hidden) link between arbitrary two internal graphs $G_i, G_j \in V$.

3 Proposed Method: Dual Convolution

We propose the dual convolutional neural network for a GoG that consists of three components (Fig. 2): the internal graph convolution layer (Section 3.1), the external graph convolution layer (Section 3.2), and the link prediction layer (Section 3.3).

3.1 Internal graph convolution

The internal graph convolution layer takes an internal graph $G = (V, A)$ (e.g., a chemical compound) as its input and gives a fixed-dimensional vector representation for the graph. At the bottom of the internal convolution layer, the low-dimensional real-valued
vector representation \( v_k \in \mathbb{R}^d \) for the \( k \)-th node \( v_k \in V \) is randomly initialized, where \( d \) is the dimension of the vector. Each \( v_k \) is initialized differently depending on the types of nodes (e.g., hydrogen or oxygen), and trained using backpropagation as well as the subsequent external convolution and link prediction layers in an end-to-end manner (Section 3.3).

Given the initialized node feature \( v_k \) for each node \( v_k \), starting from \( v_k^{(0)} = v_k \), we update \( v_k^{(t)} \) to \( v_k^{(t+1)} \) by the internal convolution operation:

\[
v_k^{(t+1)} = f_G \left( Wv_k^{(t)} + \sum_{m \in A_k} Mv_m^{(t)} \right),
\]

where \( f_G \) is the non-linear activation function such as ReLU \( \lceil \right \rceil \), \( A_k \) is the adjacency list of \( v_k \), and \( W \in \mathbb{R}^{d \times d} \) and \( M \in \mathbb{R}^{d \times d} \) are the weight matrices to be learned. As with the graph convolution of Duvenaud et al. \cite{Duvenaud2015}, each node gradually incorporate global information on the graph into its representation by iterating the internal convolution step using the representations of its adjacent nodes. We make \( T \) iterations to obtain \( v_k^{(1)}, v_k^{(2)}, \ldots, v_k^{(T)} \).

Finally, summing all of the node features over all of the internal convolution steps to obtain the internal graph representation as

\[
g_i^{(T)} = \sum_{v_k \in V} \sigma_G \left( \sum_{t=0}^{T} v_k^{(t)} \right),
\]

where \( \sigma_G \) is a non-linear function such as the softmax function.

In the following, we denote by \( g_i^{(T)} \) the representation of internal graph \( G_i \in \mathcal{V} \), which will be the initial feature vector in the external graph convolution introduced in the next section.

### 3.2 External graph convolution

The set of representations for all the internal graphs \( \{g_i^{(T)}\}_{G_i \in \mathcal{V}} \) are further updated with the external convolution to incorporate structural information of the external graph. Starting from \( \ell = 0 \), we make \( L \) updates using the external convolution operation given as

\[
g_i^{(T+\ell+1)} = f_G \left( Ug_i^{(T+\ell)} + \sum_{G_m \in A_i} Vg_m^{(T+\ell)} \right),
\]

where \( f_G \) is a non-linear function, \( A_i \) is the adjacency list of internal graph \( G_i \) in the external graph, and \( U \in \mathbb{R}^{d \times d} \) and \( V \in \mathbb{R}^{d \times d} \) are the weight matrices to be learned.

Finally, we obtain the final internal graph representation \( h_i^{(T+L)} \) considering all of the \( L \) external convolution steps as

\[
h_i^{(T+L)} = \sigma_G \left( \sum_{t=0}^{L} g_i^{(T+\ell)} \right),
\]

where \( \sigma_G \) is a non-linear function such as the softmax function. Note that our dual convolution does not aim to obtain a single representation of the external graph, but to obtain the representation of each internal graph considering both the internal and external graphs, which will be used in the following link prediction layer.

### 3.3 End-to-end learning of the link prediction function

The link between two internal graphs \( G_i \) and \( G_j \) is predicted using their final representations \( h_i^{(T+L)} \) and \( h_j^{(T+L)} \). A multi-layer neural network \( p \) outputs a two-dimensional vector \( y \in \mathbb{R}^2 \):

\[
y = p \left( h_i^{(T+L)}, h_j^{(T+L)} \right),
\]

and the softmax function gives the final link probability: \( p_t = \exp(y_t) / \sum_k \exp(y_k) \), where \( t \in \{0, 1\} \) is the binary label (i.e., link or no-link). Note that the symmetry of \( p \) with respect to its two inputs is ensured by its specific implementation described in Section 4.2.

Given a set of all internal graphs and some links among them as the training dataset, we minimize the cross-entropy loss function: \( L(\Theta) = - \sum_{t=1}^{N} \log p_t \), with respect to the model parameters \( \Theta \) including the set of all weight matrices in the dual convolution network and the atom features (that are initialized randomly). \( N \) is the total number of internal graph pairs in the training dataset, \( t_i \) is the \( i \)-th label (link or no-link).

\(^2\)We have freedom of choice in our model such as the non-linear activation function \( f_G \); we give their specifications in Section 4.2.
4 Experiments

We evaluate the idea of the dual convolution that combines the structural information of both internal and external graphs in a GoG. We compare the link prediction accuracy of the proposed method and several baselines using three real chemical networks. Overall, the proposed method works well for moderately dense external networks with heavy-tailed degree distributions. In an extremely sparse and light-tailed external network, external links are almost useless, and the domain specific features (Morgan indices) perform the best. The internal convolution also suffers from the lack of external links as the training data.

4.1 Specific implementation of the proposed model

We have freedom of choice in our dual convolutional network such as the nonlinear activation functions and the depth of each layer. In the experiments, we use the following specific choices. In the internal graph convolution \( (1) \), we use ReLU as function \( f_G \), and use different \( W \) and \( M \) for different degrees \(|A_k| \) and \(|A_m|\) and convolutional steps. The node representation \( v_k \) is randomly initialized depending on their atom types, e.g., \( v_{\text{hydrogen}} = [0.1, 0.5]^T \) and \( v_{\text{oxygen}} = [-0.4, 1.2]^T \) (if \( d = 2 \)) which are generated from a same Gaussian distribution. We set the number of dimension of the internal graph representations as \( d = 64 \). When we obtain the internal graph representations, \( g^{(T)} \) in the internal convolution \( (2) \) and \( h^{(T+L)} \) in the external convolution \( (4) \), we use the softmax function as \( \sigma_G \) and \( \sigma_{\bar{G}} \).

In the external graph convolution \( (5) \), we use the softmax function as \( f_G \), and use different \( U \) and \( V \) for different convolutional steps; we do not distinguish different degrees because the interaction networks have larger numbers of degrees than molecular graphs as shown in Fig. 3.

We use the two-layer neural network as the link prediction network \( (5) \) whose input is given as \( \left( h^{(T+L)}_i + h^{(T+L)}_j \right) \oplus \left( h^{(T+L)}_i \odot h^{(T+L)}_j \right) \), where \( \oplus \) is the concatenation of two vectors and \( \odot \) is the Hadamard product. Note that the input is symmetric with respect to \( h^{(T+L)}_i \) and \( h^{(T+L)}_j \). The layer sizes are \( (128, 64, 2) \), and all the non-linear activation functions are ReLU.

We implement the proposed dual convolution using Chainer [Tokui, Oono, and Hido, 2015] and use ADAM [Kingma and Ba, 2015] as the optimizer. The batch size is set to 256 in the drug-drug dataset and in the drug-function dataset, and set to 128 in the metabolite dataset. The numbers of convolution steps \( T \) and \( L \) are tuned using the grid search; the candidate values are \( \{1, 3, 5\} \) for the drug-drug dataset except \( T \) for the metabolite dataset. We set \( T \in \{1, 3\} \) for the metabolite dataset as due to its large dataset size. We also set the dropout rate 0.2 in Equations \( (1) \) and \( (3) \). We use a validation set to tune those hyperparameters.

4.2 Datasets and performance metric

We prepare three different chemical GoGs with different levels of sparsity and different weights of the tails of the degree distributions.

(a) Drug–drug interaction network

is a network of drug compounds where two compounds have an edge if they are known to interact, interfere, or cause adverse reactions when taken together. From the DrugBank database\(^1\) we used 1,993 approved drugs that have fewer than 64 atoms. Out of all possible \( \binom{1,983}{2} = 1,985,028 \) compound pairs, 186,555 have edges; the link density is 0.0940 which means it is a relatively dense network. Figure 3a shows its degree distribution that shows a very heavy-tailed distribution.

\(^1\)Due to the limitation of the computational resources, we could not help limiting the hyperparameter ranges rather “intuitively” depending on the network sparsity and other data characteristics to perform thorough search over all possible hyperparameter combinations.

https://www.drugbank.ca/releases/latest
Figure 4: Link prediction performance in (a) the drug-drug interaction network, (b) the drug-function network, and (c) the metabolite reaction network. The proposed method performs well for the first two networks ((a) and (b)) with heavy-tailed degree distributions. On the other hand, in the extremely sparse and light-tailed external network (c), the external links are almost useless as features, and therefore the domain specific features (i.e., Morgan indices) perform the best. The internal convolution also suffers from the lack of external links as the training data.

We have only positive links in this dataset; this situation is sometimes dealt with positive-and-unlabeled learning [Cerulo, Elkan, and Ceccarelli, 2010]; however, we just regard sampled no-links as the negative links for simplicity [Mordelet and Vert, 2008]. We randomly choose \( n \) positive links and \( n \) no-links (i.e., negative links) as the training dataset. We vary \( n \) from 1k to 10k to investigate the importance of incorporating the information of the external graph by the external convolution. As the test dataset, we randomly extract positive and negative links from the same data distribution as the original network to preserve the data imbalance, which results in 9,398 positive links and 90,601 negative links.

(b) Drug–function network

is a network of drug compounds where two compounds have an edge if they share the same target protein. From the original dataset [Takigawa, Tsuda, and Mamitsuka, 2011], we used 3,918 compounds that have fewer than 64 atoms. Out of all possible \( \binom{3918}{2} = 7,673,403 \) compound pairs, 35,562 have edges; the link density is 0.0046 which means it is a sparse network. Figure 3b shows its degree distribution that shows a relatively heavy-tailed distribution.

As well as the drug-drug interaction dataset, this network also has only positive links; therefore, we sample no-links as the negative links. We have 1,390 positive links and 298,609 negative links in the test set.

(c) Metabolite reaction network

is a network of metabolite compounds where two compounds have an edge if they are the substrate-product pair in an enzymatic reaction on metabolic pathways [Kotera et al., 2014]. In this study we collected 5,920 compounds that have fewer than 64 atoms. Out of all possible \( \binom{5920}{2} = 17,520,240 \) compound pairs, only 5,041 have edges; the link density is 0.0003 which means it is an extremely sparse network. Figure 3c shows its degree distribution that shows a light-tailed distribution.

Different from the other two datasets, this network has both 5,041 positive links and 220,096 negative links; the test set consists of 223 positive links 9,777 negative links.

In all of the three chemical networks, each external node is a relatively small compound (i.e. with up to 64 atoms), while they have different levels of sparsity and degree distributions as shown in Fig. 3 which is a typical variation in chemical networks.
Our main interest is to obtain insights about the conditions of chemical networks in which the dual convolution is effective.

### 4.3 Compared methods

We compare the proposed dual convolutional network with several baselines, namely, (i) a model using only internal graph convolution, (ii) models based only on external graph structures, and (iii) a model based on hashed Morgan fingerprints instead of the internal graph convolution,

(i) **Internal graph convolution**

obtains 64-dimensional representations of molecular graphs. We do not use the external graph convolution, but we create a feature vector for each molecule by the internal convolution and directly use it as an input to the link prediction network. We use the same convolution formula as that by Duvenaud et al. (2015).

(ii) **External graph embedding**

is a standard approach to link prediction using only the external graph. We test DeepWalk [Perozzi, Al-Rfou, and Skiena, 2014] that is one of the well-known embedding methods, and also test the general relational embedding model proposed by Yan et al. [Yang et al., 2015] where the latent representation for each molecule is initialized to a 64-dimensional random vector. The link prediction network (5) is applied to a pair of molecules.

(iii) **Hashed Morgan fingerprints**

define molecular graph features using chemical substructures. We use 2048-dimensional Morgan fingerprints as a feature vector of a molecule. The link prediction network (5) is applied to a pair of molecules.

### 4.4 Results

As we mentioned in Section 4.2, all the datasets have imbalance nature in terms of the number of positive and negative labels; therefore we measure the predictive performance of each method using (i) ROC-AUC which is not affected by the label imbalance and (ii) PR-AUC which can suitably evaluate the performance on imbalanced datasets.

Figure 4 shows the comparison of the proposed method and four baselines with different training set sizes in terms of ROC-AUC and PR-AUC. In Figure 4b, our dual convolution achieves consistently better ROC-AUC and PR-AUC scores over the baselines in the drug-drug interaction dataset. This is probably due to the heavy-tailed degree distribution of its external graph. In such networks, external links are likely to form a longer path, and therefore, the dual convolution successfully extracts structural features in the external graph.

Figure 4b shows the result for the drug-function network. It shows that the highest ROC-AUC score by the dual convolution. The advantage of the dual convolution still remains when the external network is relatively sparse. The external graph is moderately heavy-tailed and external links are still likely to form a path; the dual convolution benefits from both the internal and external graphs. In addition, the ROC-AUC score of DeepWalk improves as the size of the training set increases; this implies that DeepWalk successfully extracts structural features from the relatively dense external graph. Surprisingly, DeepWalk significantly outperforms the others in terms of PR-AUC, while our dual convolution achieves the best ROC-AUC score. Given that DeepWalk does not consider the internal graph structure at all, information of the external graph is more crucial than the internal graphs in the drug-function network.

In contrast to the other two networks, the metabolite network is an extremely sparse that has very few links and a light-tailed degree distribution. The external links are almost useless in this network, and therefore the relational embedding method and DeepWalk that solely depend on external links perform poorly (Figure 4c). Especially, DeepWalk performs the worst in terms of both ROC-AUC and PR-AUC because it cannot “walk” over the external links. Similarly, the proposed method cannot even benefit from the external convolution, and it suffers from the sparse external links. The lack of the external links as the training dataset is also a severe limitation for extracting features from the internal graphs. In such a sparse data domain, traditional off-the-shelf features such as Morgan indices are still reliable choices.

In summary, our experimental results suggest that the dual convolution is effective for relatively dense networks, especially when both the internal and external structures must be considered in an integrated manner. Among the three networks, the links of the drug-drug interaction network represent direct chemical interactions between two compounds. In such networks, nontrivial combination of different internal substructures of both ends of a link contributes to the interaction. On the other hand, the links represent rather indirect chemical relations in the other two networks, where the benefit of the dual convolution remains limited.

### 5 Related work

We briefly review the two-decade history of learning with graphs, especially from the viewpoints of internal graphs and external graphs. Our present work attempts to unify these two lines of research that have been separately studied in different contexts.

The first generation of internally graph-structured data analysis appeared in the data-mining community. The underlying idea is that local substructures of graphs are responsible for the properties of graphs. Frequent pattern mining methods are extended to find such local substructures from a set of internally-structured graphs [Inokuchi, Washio, and Motoda, 2000; Yan and Han, 2002], and later are combined with boosting to find local patterns correlated with the target labels [Kudo, Maeda, and Matsumoto, 2005].
In contrast with the graph-mining approaches that explicitly find subgraph features, kernel methods perform implicit feature extraction. The first graph kernels use paths as features [Kashima, Tsuda, and Inokuchi, 2003; Gärtner, Flach, and Wrobel, 2003, and the recent state-of-the-art graph kernels use more complex subgraph patterns [Shervashidze et al., 2011].

Neural networks are also successfully applied to graphs, especially due to their capability of extracting flexible features from graphs. Following the seminal work by Scarselli et al. (2009), various graph convolutional neural-network models have been proposed (e.g., [Duvenaud et al., 2015] [Niepert, Ahmed, and Kutzkov, 2016]). Recent studies give a generalization of various existing models in terms of message passing [Gilmer et al., 2017] and connections to the kernel methods [Lei et al., 2017].

Analysis of external graph structured data is often called link mining [Getoor and Diehl, 2005]. Its typical tasks include ranking, clustering, and classification of nodes, as well as link prediction. Recently, node-embedding approaches that preserve node proximity in a graph have been extensively studied [Perozzi, Al-Rfou, and Skiena, 2014; Grover and Leskovec, 2016]. External graphs are also considered as object relations to which neural network approaches have also been applied successfully [Socher et al., 2013; Yang et al., 2015].

Because studies on graph-structured data analysis are wide-ranging and rapidly growing, it is quite difficult to cover all of them here; however, more to the point, internal and external graph analyses have been studied rather independently. GoG is the very intersection where these two lines of studies meet, and our dual convolution approach makes it possible to extract features from both internal and external graph structures in an end-to-end manner.

6 Conclusion

We addressed a problem of learning feature representations for a graph of graphs (GoG) and presented a dual convolution approach that combines both the external and internal graphs in an end-to-end manner. The proposed method was particularly designed for link prediction on an external graph and we demonstrated the effectiveness of the proposed method for predicting interactions among molecules by using three chemical network datasets. Our dual convolution approach achieved high prediction performance even though the features were lower-dimensional compared to the off-the-shelf features in networks with heavy-tailed degree distributions. We found that the performance of the dual convolution approach becomes inferior on an extremely-sparse external network with a light-tailed degree distribution because of the difficulty of exploiting the information about the external network.

Although we focused only on link prediction in this paper and the applications in other prediction tasks, such as node classification or clustering, will be addressed in future work.

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