Enzymatic link prediction for biochemical route synthesis via learning graph representations of biochemical networks

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Motivation

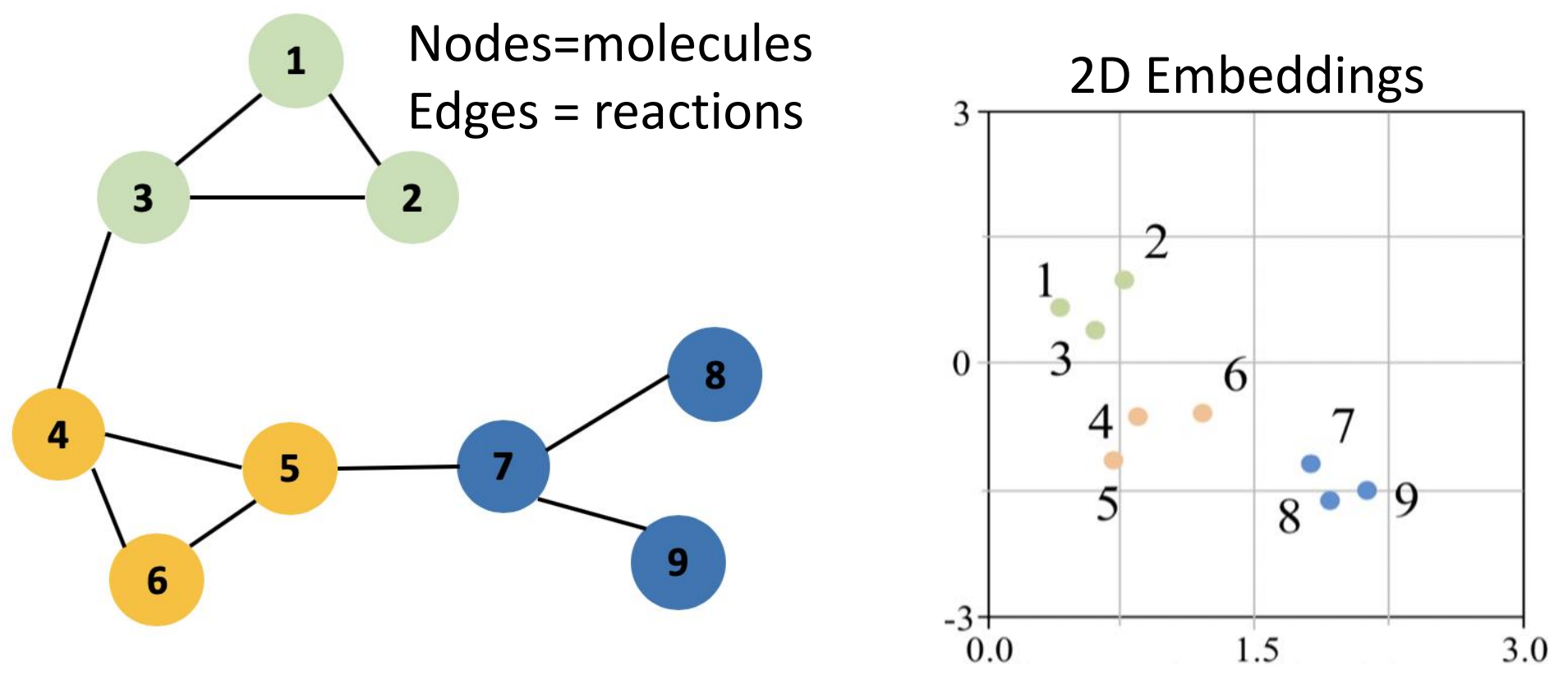
Problem: No complete characterization of enzymatic reactions
The curation of enzyme functions and the reactions they catalyze remains elusive, hindering biological engineering and discovery.

Goal: Predict enzymatic transformations

- Enhance biological discovery of undocumented enzymatic reactions
- Plan synthesis routes using previously undocumented enzymatic transformations

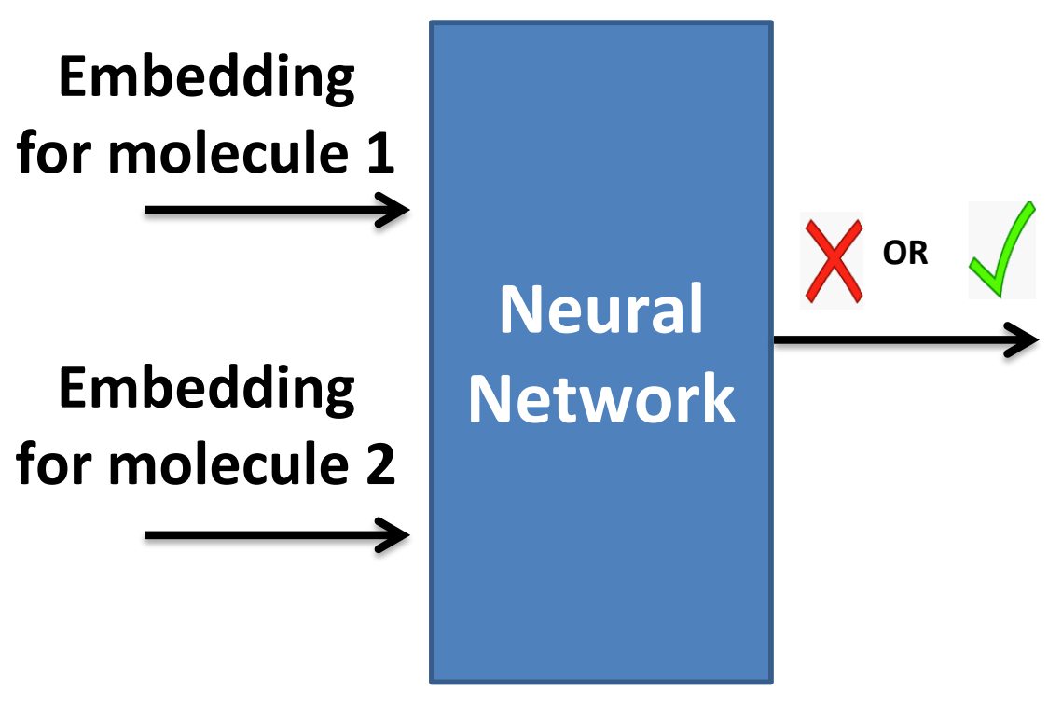
Approach Overview

Graph Embedding



Adapted from [1]

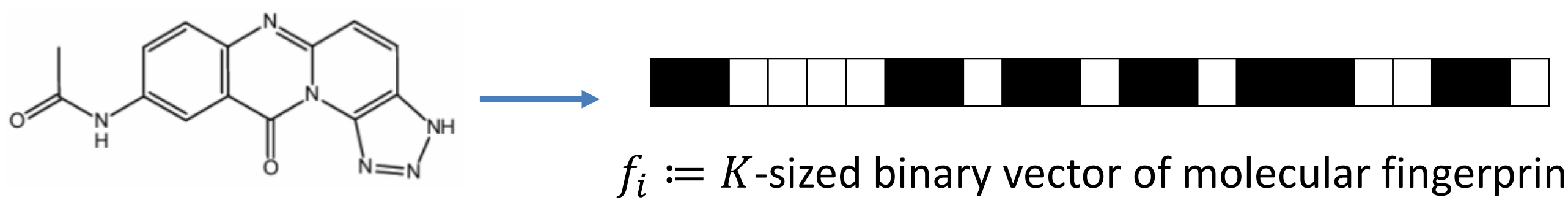
Use learned embeddings to predict likelihood of molecular interactions



Graph Construction

- Use reactions in the KEGG [2] database
  - all reactions are reversible; remove cofactors
- Every molecule is a node
- Each substrate-product pair within a reaction is an undirected edge
- Edge attributes: enzyme commission (EC) number or reaction class (RC)
- Node attributes: fingerprints (MACCS [3] or PubChem [4])

Molecule i

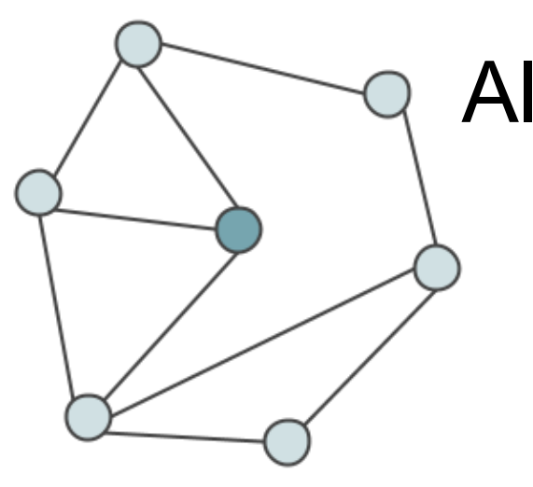


$f_i :=$ K-sized binary vector of molecular fingerprint

Enzymatic Link Prediction (ELP)

1 Embedding Propagation on Graph

We use Embedding Propagation [5], a graph embedding method, to learn embedding vectors of nodes



All embeddings are randomly initialized:

- Connectivity-based node embeddings $\{\mathbf{u}_i\}$,
- Fingerprint embeddings $\{\mathbf{v}_k\}$, one for each fingerprint entry
- Enzyme embeddings $\{\boldsymbol{z}_r\}$, one for each enzyme label

- Fingerprint-based node embeddings $\{\mathbf{u}_i^{fp}\}$ are constructed from fingerprint embeddings

$$\mathbf{u}_i^{fp} = \frac{1}{\sum_{k=1}^{K} f_{ik}} \sum_{k=1}^{K} f_{ik}\mathbf{v}_k$$

k^{th} value of node i's fingerprint

Fingerprint embedding of entry k

- Reconstruct node embedding ($\tilde{\mathbf{u}}_i$) from the embeddings of its neighbors

$$\tilde{\mathbf{u}}_i = \frac{1}{|\mathcal{N}(i)|} \sum_{j \in \mathcal{N}(i)} \mathbf{u}_j + \alpha\, \mathbf{z}_{r(i,j)}$$

Neighbors of node i

Node embedding of node j

Enzyme embedding of the edge (i,j)

- Margin-based ranking loss.
- Aim to maximize the similarity between the *reconstruction of node embedding* $\tilde{\mathbf{u}}_i$ with *node embedding* $\mathbf{u}_i$

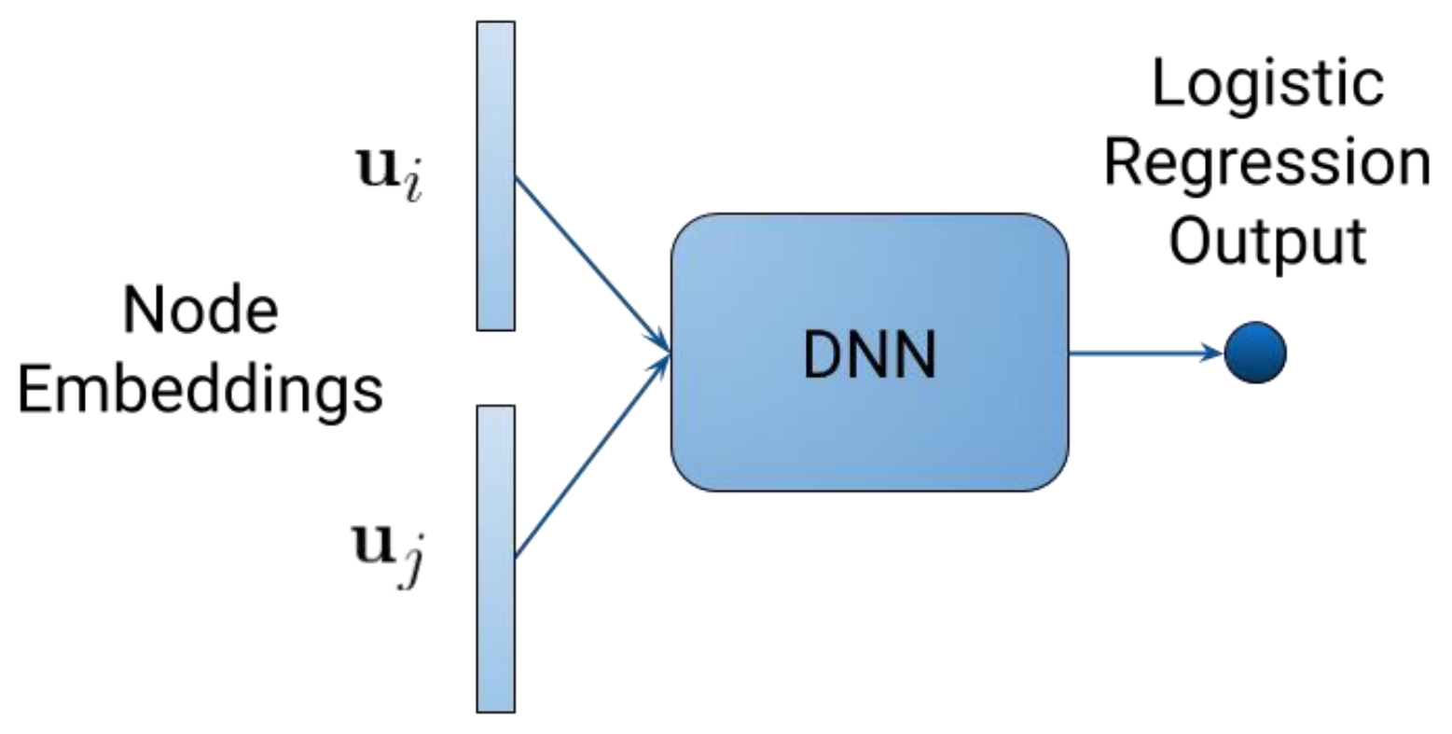
$$\mathcal{L} = \sum_{i \in V} \sum_{j \in V, j \neq i} \max\{\gamma - \tilde{\mathbf{u}}_i^{\top}\mathbf{u}_i + \tilde{\mathbf{u}}_i^{\top}\mathbf{u}_j, 0\}$$

Random node j as the negative example for each node in every iteration

- Concatenate $\mathbf{u}_i$ and $\mathbf{u}_i^{fp}$ to form final node embedding vectors

2 Link Prediction Using Embedding Vectors

Train a logistic regression model using deep neural nets to predict the likelihood of an edge between two nodes



Experiments & Results

Transductive Learning

- Model is trained on all nodes and evaluated for edge recovery on a held out set of test edges.
- Training graph must be connected

Baseline: other embedding methods

Baseline: no connectivity embedding

Method	Connectivity Embedding	Node Attribute	Edge Attribute	AUC Test Ratios 0.1	0.3	0.5
A. Connectivity-based embeddings only						
ELP	Yes	–	–	0.801	**0.789**	0.761
node2vec	Yes	–	–	0.824	0.736	**0.776**
DeepWalk	Yes	–	–	**0.847**	0.763	0.749
B. Connectivity and one additional attribute						
ELP	Yes	MACCS	–	**0.953***	**0.935***	**0.900**
ELP	Yes	PubChem	–	0.891	0.882	0.864
ELP	Yes	–	EC	0.795	0.808	0.810
ELP	Yes	–	RC	0.810	0.798	0.810
C. Connectivity with one node and one edge attribute						
ELP	Yes	MACCS	EC	0.941	**0.933**	**0.922***
ELP	Yes	MACCS	RC	**0.942**	0.929	0.895
ELP	Yes	PubChem	EC	0.892	0.879	0.867
ELP	Yes	PubChem	RC	0.892	0.876	0.859
D. Embedding based on MACCS fingerprints						
ELP	No	MACCS	–	0.931	0.916	0.898
ELP	No	MACCS	EC	**0.940**	**0.925**	**0.913**
ELP	No	MACCS	RC	0.939	0.904	0.896
E. Embeddings based on PubChem fingerprints						
ELP	No	PubChem	–	0.665	**0.709**	0.682
ELP	No	PubChem	EC	**0.745**	0.707	**0.728**
ELP	No	PubChem	RC	0.728	0.706	0.720
F. Jaccard index similarity scoring; no embeddings						
Jaccard	No	MACCS	–	**0.808**	**0.778**	**0.767**
Jaccard	No	PubChem	–	0.542	0.526	0.535

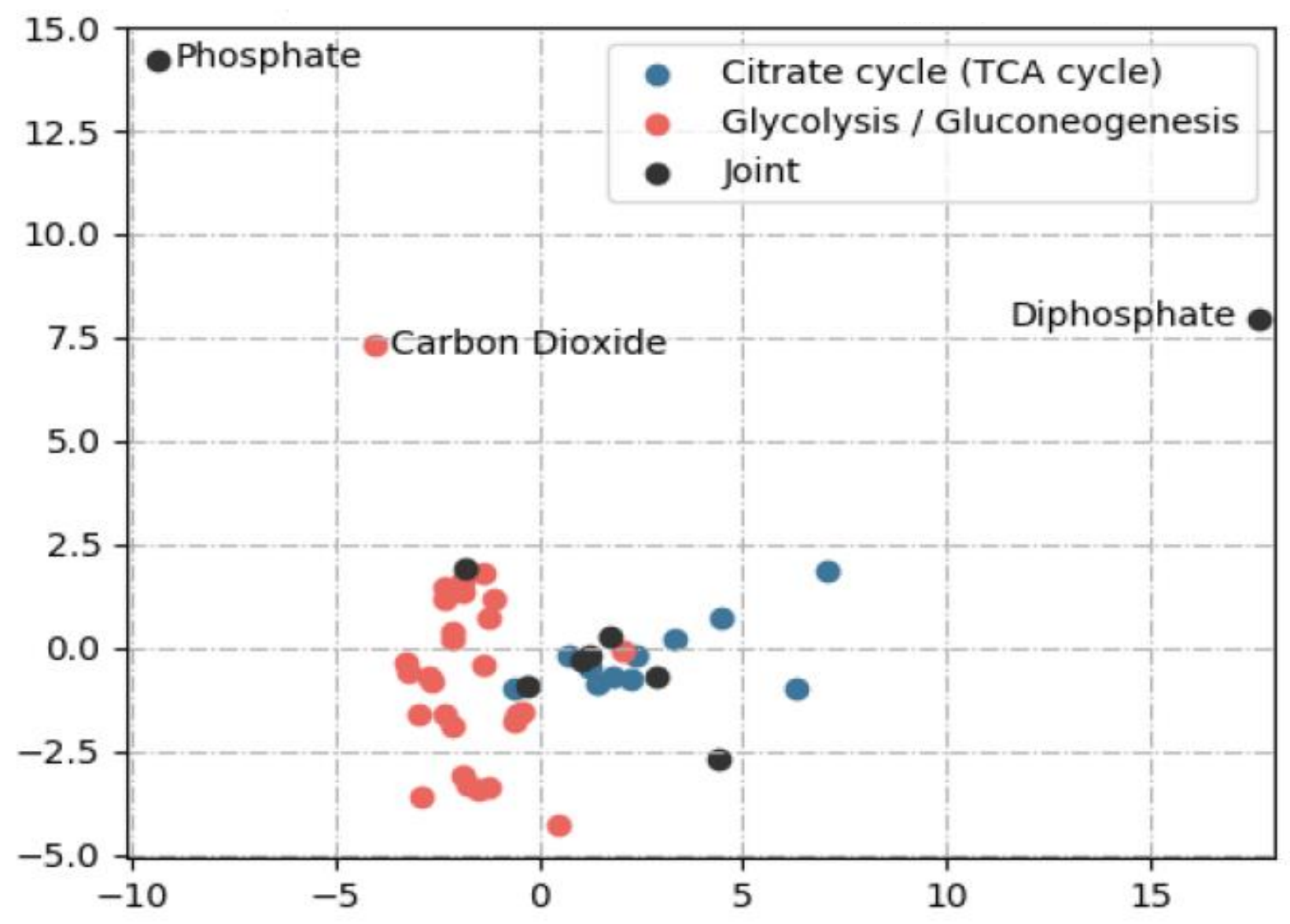
Bold value indicates best result.
* Indicates best overall results

Inductive Learning

- Model is trained to predict possible interactions for *out-of-sample* nodes excluded from training
- This type of prediction is made possible by only using fingerprint-based node embeddings

Method	Connectivity Embedding	Node Attribute	AUC
A. Embeddings based on node attributes			
ELP	Yes	MACCS	**0.921**
ELP	Yes	PubChem	0.605
B. Jaccard index similarity scoring			
Jaccard	No	MACCS	0.744
Jaccard	No	PubChem	0.553

Other applications of embeddings: Visualization of Metabolites within Pathways using t-SNE



Conclusion

ELP learns molecular representations that capture graph connectivity, enzymatic properties, and structural molecular properties

- ELP shows high accuracy in link prediction when using both graph connectivity and molecular attributes
- ELP can be used as a guide to identifying catalyzing enzymes when constructing novel synthesis pathways or predicting interaction between microbes and human hosts
- ELP can enhance link prediction in chemical networks, where previously rule-based and path-based link prediction respectively yielded 52.7% and 67.5% prediction accuracy [6]

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