Predicting Drug-Drug Interactions using Deep Generative Models on Graphs

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Abstract

Latent representations of drugs and their targets produced by contemporary graph autoencoder-based models have proved useful in predicting many types of node-pair interactions on large networks, including drug-drug, drug-target, and target-target interactions. However, most existing approaches model the node's latent spaces in which node distributions are rigid and disjoint; these limitations hinder the methods from generating new links among pairs of nodes. In this paper, we present the effectiveness of variational graph autoencoders (VGAE) in modeling latent node representations on multimodal networks. Our approach can produce flexible latent spaces for each node type of the multimodal graph; the embeddings are used later for predicting links among node pairs under different edge types. To further enhance the models' performance, we suggest a new method that concatenates Morgan fingerprints, which capture the molecular structures of each drug, with their latent embeddings before preceding them to the decoding stage for link prediction. Our proposed model shows competitive results on two multimodal networks: (1) a multi-graph consisting of drug and protein nodes, and (2) a multi-graph consisting of drug and cell line nodes. Our source code is publicly available at `https://github.com/HySonLab/drug-interactions`.

Problem Overview

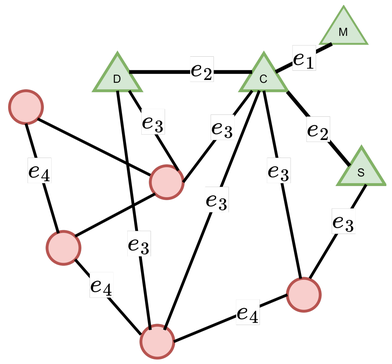


Figure 1: Caption

A biomedical multi-modal graph consists of two node types (e.g., red nodes are protein and the green are drug nodes) and five edge types $\{e_i\}$. The edges can be either polypharmacy side effects, drug responses, or drug-protein interactions, etc.

Formally, let denote $G = (V, E, X)$, where $V = V_d \cup V_p$ is a union of two node sets of different types (i.e. V_d is the set of drug nodes and V_p is the set of protein nodes), E is a set of edges, and $X = X_d \oplus X_p$ is a concatenated matrix denoting the node features of different node types.

Each edge in E is a triplet (v_i, e, v_j) in which node v_i interacts with node v_j under a specific edge type e. The objective is to learn a function $f : E \to T$, where f predicts the value of a particular triplet (v_i, e, v_j); T can be either $\{0, 1\}$ or $\mathbb{R}$.

Graph Variational Autoencoder on Multi-Modal Graphs

We extend graph variational autoencoders proposed in (Kipf and Welling 2016). The VGAE-based model proposed in this paper operates on multi-modal graphs in which different node types have different posterior distributions.

Encoder

$$h_i = \phi\Big(\sum_e \sum_{j \in \mathcal{N}_e^i \cup \{i\}} W_e \frac{1}{\sqrt{c_i c_j}} x_j\Big)$$

where $\mathcal{N}_e^i$ denotes the neighbor set of node x_i under the edge type e. $W_e \in \mathbb{R}^{d_k \times d}$ is a edge-type specific transformation matrices that map $x_i \in \mathbb{R}^{d_i}$ and its neighbors $x_j \in \mathbb{R}^{d_j}$ into d_k-dimensional vector spaces, resulting in $h_i \in \mathbb{R}^{d_k}$.

Graph Variational Autoencoder on Multi-Modal Graphs

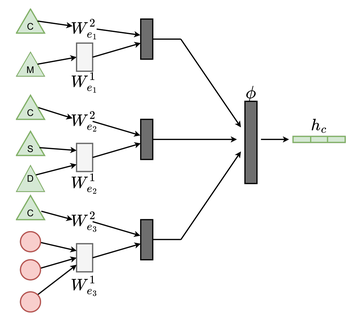


Figure 2: Caption

Latent Encoder

$$q_v(Z_v \mid X, E) = \prod_{i=1}^{|V_v|} q_v(z_v^i \mid X, E)$$

$q_v(z_v^i \mid X, E) = \mathcal{N}(z_v^i \mid \mu_v^i, \mathrm{diag}((\sigma_v^i)^2)$ denotes the posterior distribution of a node of a specific node type. Here, μ_v and $\log \sigma_v$ are computed as follows:

$$\mu_v = W_{\mu_v}^2 \tanh\big(W_{\mu_v}^1 h_v\big)$$

$$\log \sigma_v = W_{\sigma_v}^2 \tanh\big(W_{\sigma_v}^1 h_v\big)$$

where $W_{\mu_v}^i \in \mathbb{R}^{d_k \times d}$, $W_{\sigma_v}^i \in \mathbb{R}^{d_k \times d}$ are the weight matrices, μ_v and $\log \sigma_v$ are the matrices of mean vector μ_v^i and logarithm of standard deviation vector $\log \sigma_v^i$, respectively.

Decoder

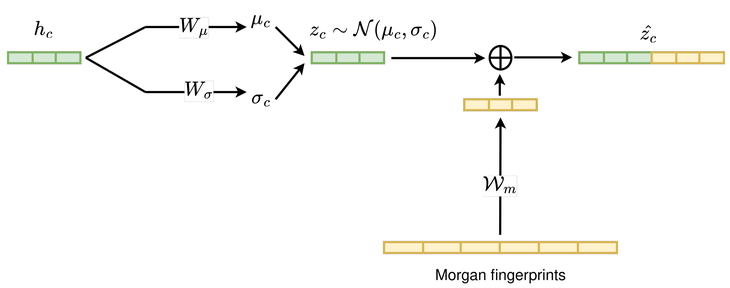
$$g(v_i, e, v_j) = \begin{cases} z_i^T D_e R D_e z_j & \text{if } v_i \text{ and } v_j \text{ are drugs} \\ z_i^T M_e z_j & \text{if } v_i \text{ and } v_j \text{ are a protein and a drug, or vice versa.} \end{cases}$$

where $D_e, R, M_e \in \mathbb{R}^{d \times d}$ are learnable parameters. R denotes the global matrix representing all drug-drug interactions among all polypharmacy side effects; M_e is a edge-type-specific matrix modeling drug-protein and protein-protein relations. Also, D_e is a diagonal matrix, and its on-diagonal entries model the significance factors of z_i and z_j in multiple dimensions under the side effect type e.

Finally, the probability of edge (v_i, e, v_j) is calculated via a sigmoid function σ.

$$p_e(v_i, v_j) = \sigma(g(v_i, e, v_j))$$

Augment latent variables by Morgan fingerprints



We concat the molecular structure information of drugs, which are resepresented as Morgan fingerprints, with the latent variables computed by the previous graph varia

Polypharmacy Side Effects Prediction

Drug combinations consisting of many drugs affecting distinct targeted proteins can effectively modulate the process of severe diseases (Sun et al. 2015). Albeit commonly applied, polypharmacy is one of the major underlying issues that cause adverse medical outcomes, also known as side effects caused by drug combinations (Zitnik et al. 2018) .

Method	AUROC	AUPRC	AP@50
RESCAL tensor factorization	0.693	0.613	0.476
DEDICOM tensor factorization	0.705	0.637	0.567
DeepWalk neural embeddings	0.761	0.737	0.658
Concatenated drug features	0.793	0.764	0.712
Decagon	0.872	0.832	0.803
GAE	0.893 ± 0.002	0.862 ± 0.003	0.819 ± 0.006
VGAE (ours)	0.905 ± 0.001	0.880 ± 0.001	0.853 ± 0.005
VGAE + Morgan fingerprints (ours)	**0.944 ± 0.005**	**0.926 ± 0.005**	**0.920 ± 0.004**

The proposed methods are evaluated in 6 different random seeds for random link split on the network and weight initialization. We compare the performance of VGAE to alternative approaches. In addition to VGAE, we also implement a graph autoencoder. The baseline results are taken from (Zitnik et al. 2018). Our approach outperforms the competitors across three metrics.

Anticancer Drug Response Prediction

Integrated information between drugs and cell lines are an effective approach to calculate anticancer drug responses using computational methods.

Method	RMSE ↓	R^2 ↑	PCC ↑	fitness ↑
ADRML	0.49	**0.68**	**0.85**	1.04
CDRscan	0.76	0.67	0.83	0.74
CDCN	0.48	0.67	0.83	1.02
SRMF	**0.25**	0.40	0.80	0.95
CaDRRes	0.53	0.31	0.52	0.3
KNN	0.56	0.57	0.78	0.79
VGAE (ours)	0.46 ± 0.02	0.67 ± 0.03	**0.85 ± 0.01**	**1.05 ± 0.06**

This table demonstrates the comparisons between VGAE and other baselines which are taken from (Ahmadi Moughari and Eslahch 2020). The results reveal that VGAE can achieve comparable results with other baselines.

Software

Our PyTorch implementation is publicly available at:

`https://github.com/HySonLab/drug-interactions`

Reference

Kipf, Thomas N., and Max Welling. "Variational graph auto-encoders." arXiv preprint arXiv:1611.07308 (2016).

Marinka Zitnik, Monica Agrawal, and Jure Leskovec. Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics, 34(13):i457–i466, 06 2018.

Sun, Yi, et al. "Combining genomic and network characteristics for extended capability in predicting synergistic drugs for cancer." Nature communications 6.1 (2015): 1-10.

Fatemeh Ahmadi Moughari and Changiz Eslahchi. Adrml: anticancer drug response prediction using manifold learning. Scientific reports, 10(1):1–18, 2020