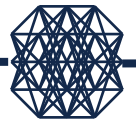

# Graph Neural Networks

*Jimeng Sun*

ILLINOIS

# Outline



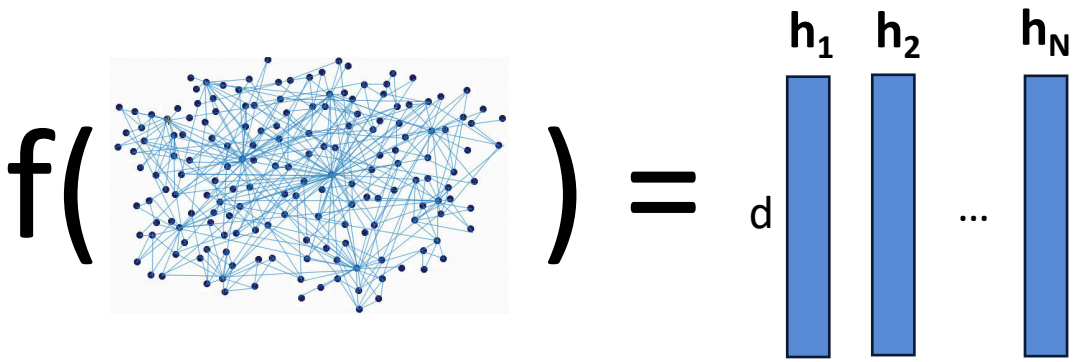
- Fundamentals of deep learning on graphs
- Graph convolutional networks (GCN)
- Message passing neural network (MPNN)
- Graph attention networks (GAT)
- Applications

# GNN fundamental

- Node embedding
- Tasks on graphs
- Challenges with GNN
- Key ideas of GNN

# Node embedding

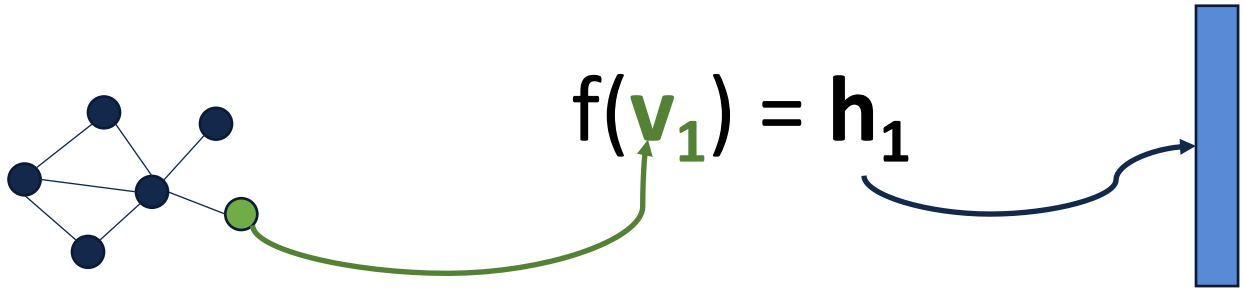
- Goal: Map nodes to d-dimensional vectors such that similar nodes are close to each other




**How to learn embedding function $f$?**

# Key components

- **Embedding function:** map a node to a vector




- **Similarity function:** define relationships of embedding vectors

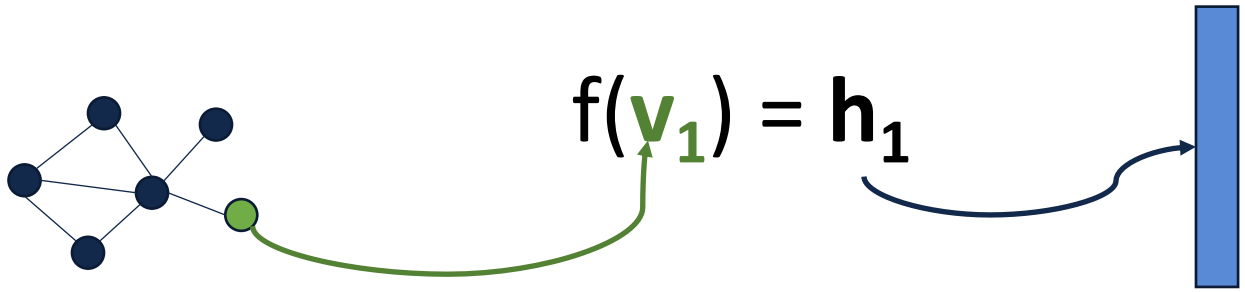
$$S(v_1, v_2) = h_1^T h_2$$

Similarity between nodes

Inner product between embeddings

# Graph neural network

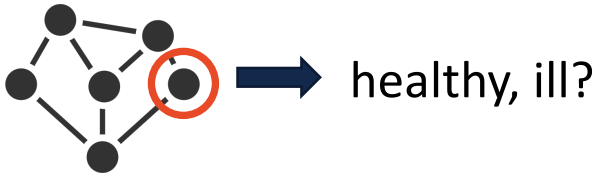
- **Embedding function:** map a node to a vector



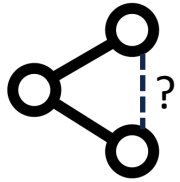

Embedding function is a deep neural network that leverages the graph structure

# Tasks on graphs

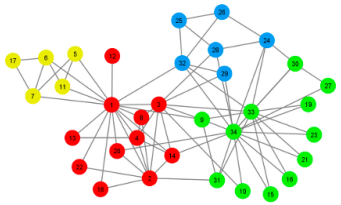
- Node classification




- Link prediction

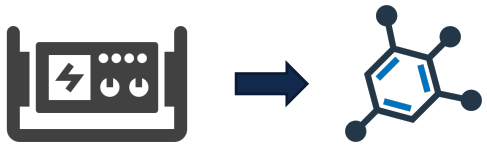



- Community detection



- Graph property prediction


- Graph generation

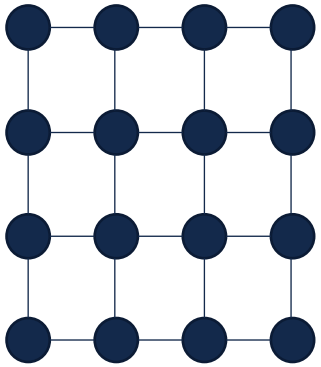


ILLINOIS

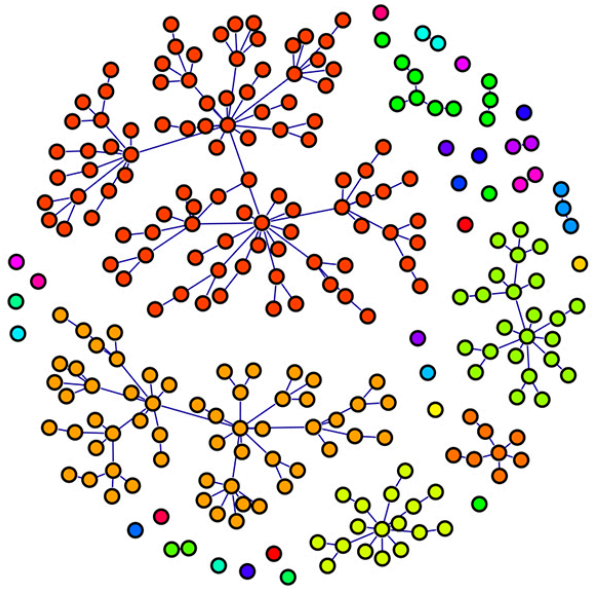
# Challenges of graph neural network

- Arbitrary size and complex structure
- No fixed node ordering
- Dynamic
- Heterogeneous features

Text



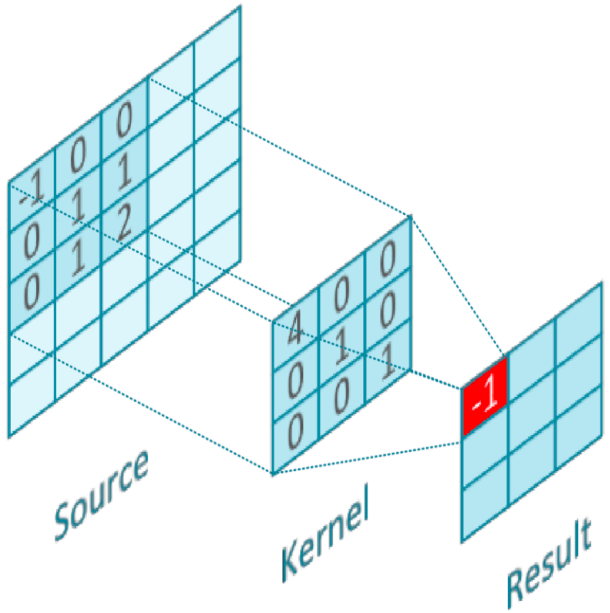
Image

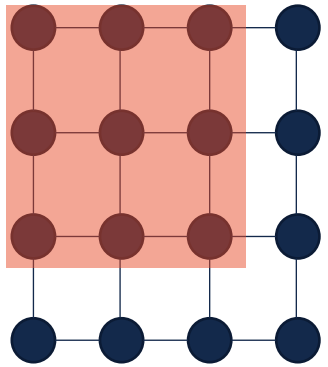


Graph

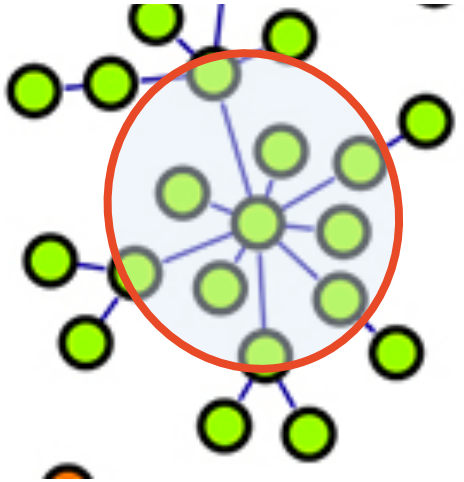
ILLINOIS

# Generalize convolution to graph



Image



Graph convolution

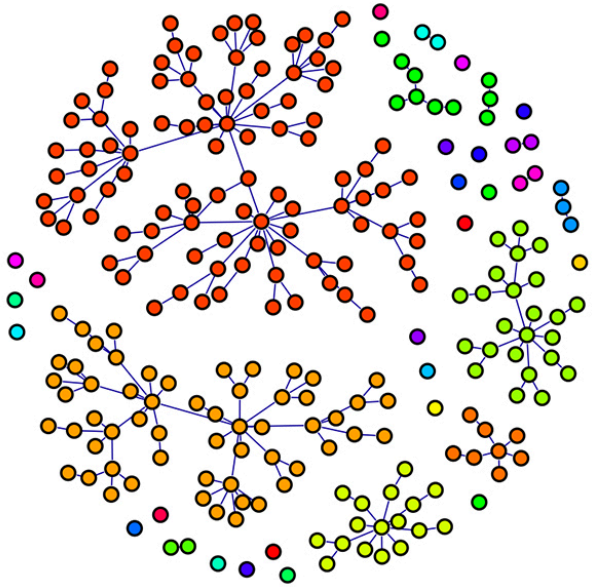
- Aggregate information from neighbors
- Combine them

$\sum W h_i$

ILLINOIS

# Input

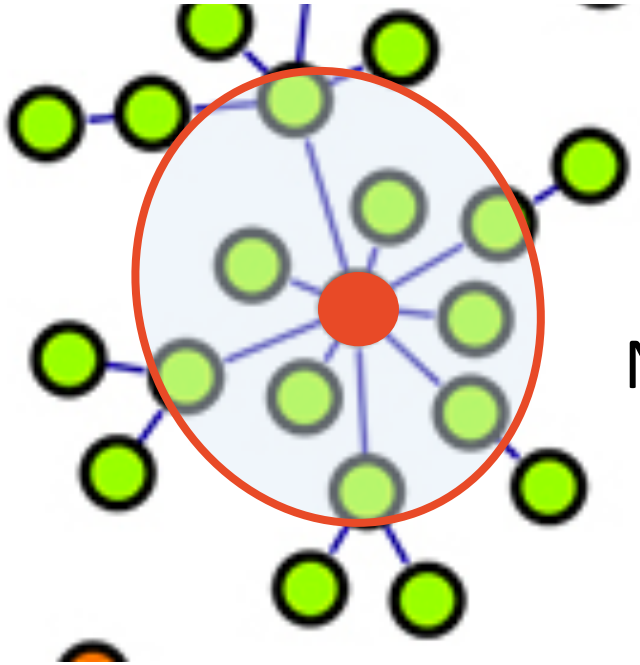
- Graph G = (V, E, X)
- V is the node set
- E is the edge set
- **A** is the adjacency matrix
- **X** is the node features
  - E.g., chemical information in molecule gr
  - No feature:
    - one-hot encoding for a node



ILLINOIS

# Idea 1: aggregation

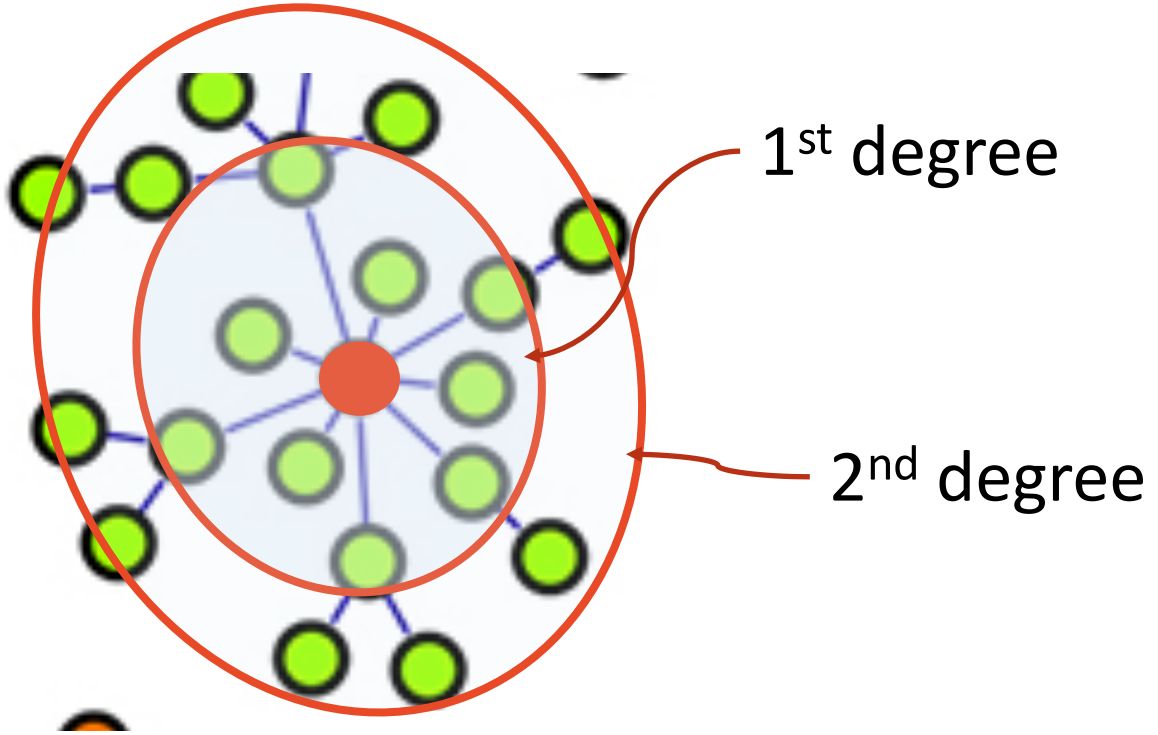
- Neighbors of a node defines the aggregation set



Neighborhood of v

# Idea 2: layering

- Embedding can have multiple layers
- Layer 0: **x**
- Layer 1: $\mathbf{h}^{(1)}$ aggregate one hop neighbors
- Layer K: $\mathbf{h}^{(k)}$ aggregate k-hop neighbors




ILLINOIS

# Aggregation of GNN

- Approach: average neighboring embeddings and apply a neural network

Embedding at layer l  Embedding at layer l-1

$$h_i^{(l+1)} = \sigma(h_i^{(l)} W^l + \sum_{j \in \mathcal{N}_i} h_j^{(l)} W^l)$$

Activation function

Aggregate neighbor's embeddings

ILLINOIS

# Aggregation of GNN

- Approach: average neighboring embeddings and apply a neural network

$$\boldsymbol{h}_i^{(l+1)} = \sigma(\boldsymbol{h}_i^{(l)}\boldsymbol{W}^l + \sum_{j \in \mathcal{N}_i} \boldsymbol{h}_j^{(l)}\boldsymbol{W}^l)$$

Weight parameters

# Loss function for node classification

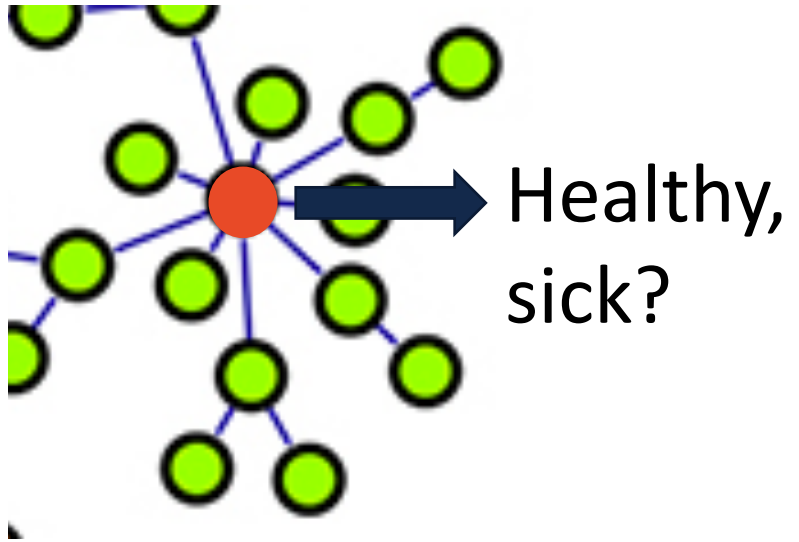
- Train a GNN model for a supervised learning task (such as node classification)

Class label for node $v_i$

$$\mathcal{L} = \sum_i y_i \log(\sigma(\boldsymbol{h}_i^\top \boldsymbol{\theta})) + (1 - y_i) \log(1 - \sigma(\boldsymbol{h}_i^\top \boldsymbol{\theta}))$$

Embedding for node $v_i$

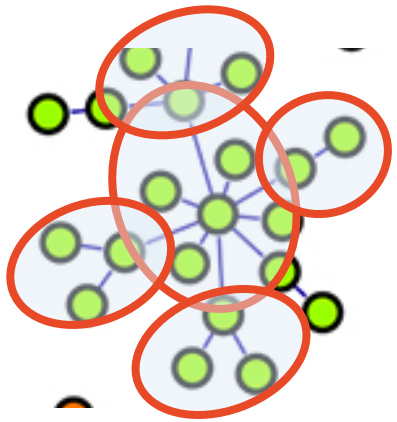
Cross entropy loss




ILLINOIS

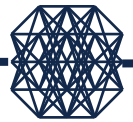
# GNN general design

1. Define a neighborhood aggregation function
2. Define a loss function on the embeddings
3. Train on a set of nodes based on local neighborhoods
4. Generate embeddings for any node based on node features
   - Even the ones that are not trained on – **Inductive learning**



ILLINOIS

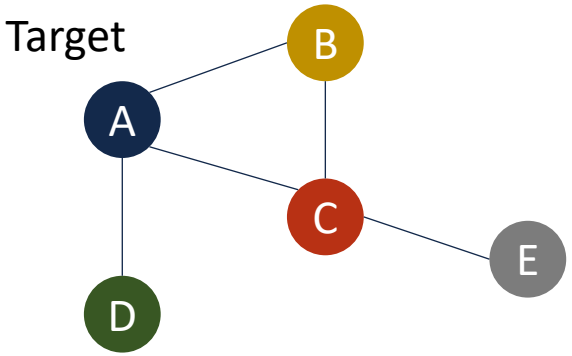
# Outline



- Fundamentals of deep learning on graphs ✓
- Graph convolutional networks (GCN)
- Message passing neural network (MPNN)
- Graph attention networks (GAT)
- Applications

# Graph convolutional networks (GCN)

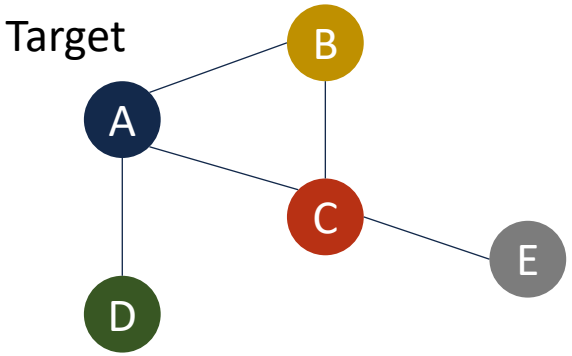
- **Idea**: compute node embedding based on neighboring embeddings




$$h_a = \sigma(h_a W_a + \text{aggregate}(h_u \mid u \in N_a))$$

$$h_a = \sigma(\text{A}\, W_a + \text{aggregate}(\text{B}\ \text{C}\ \text{D}))$$

# Neighbor aggregation function




- Mean
  - Aggregation = average( B C D )
- Pooling
  - E.g., Element-wise max over $\mathbf{h}_u$ for $\mathbf{u} \in \mathbf{N}_a$
- Recurrent neural networks
  - Apply RNN to random shuffled neighbors

# Matrix view of GCN

- Aggregation can be performed in parallel using matrix operations
- Vector view:

$$\boldsymbol{h}_i^{(l+1)} = \sigma(\boldsymbol{h}_i^{(l)}\boldsymbol{W}^l + \sum_{j \in \mathcal{N}_i} \boldsymbol{h}_j^{(l)}\boldsymbol{W}^l)$$

- Matrix view

$$\boldsymbol{H}^{(l+1)} = \sigma\left((\boldsymbol{I} + \boldsymbol{D}^{-1/2}\boldsymbol{A}\boldsymbol{D}^{-1/2}\boldsymbol{H}^{(l)})\boldsymbol{W}^{(l)}\right)$$

Matrix view is much more efficient for training

# Speedup GCN training via sampling

For each node *i*

$$h_i^{(l+1)} = \sigma(h_i^{(l)} W^l + \sum_{j \in \mathcal{N}_i} h_j^{(l)} W^l)$$

Training bottleneck

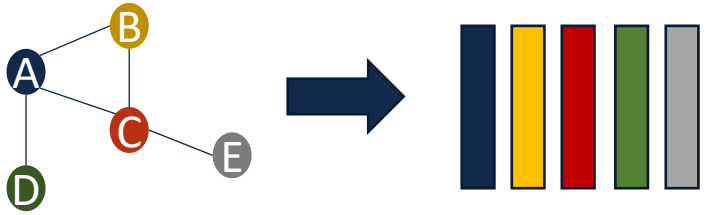
- GraphSage [1] samples a random subset of edges for each node
- FastGCN [2] biased samples a subset of nodes with higher degrees, then sample random edges from the nodes


[1] Hamilton, William L., Rex Ying, and Jure Leskovec. "Inductive Representation Learning on Large Graphs." *NIPS 2017*

[2] Chen, Jie, Tengfei Ma, and Cao Xiao. "FastGCN: Fast Learning with Graph Convolutional Networks via Importance Sampling." *ICLR 2018.*


ILLINOIS

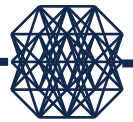
# Summary of GCN




- GCN is an efficient method for generating node embeddings on graphs
- Keys
  - Aggregation function on local neighborhood
  - Loss function
  - Multiple layers are allowed like a standard DNN
  - Sample nodes and edges from a graph or multiple graphs
    - Shared Layer-wise parameters across nodes
- Remarks
  - GCN embeddings are invariant to node orderings
  - Limitation: 1) node features are important to have;  2) Edge features are not supported

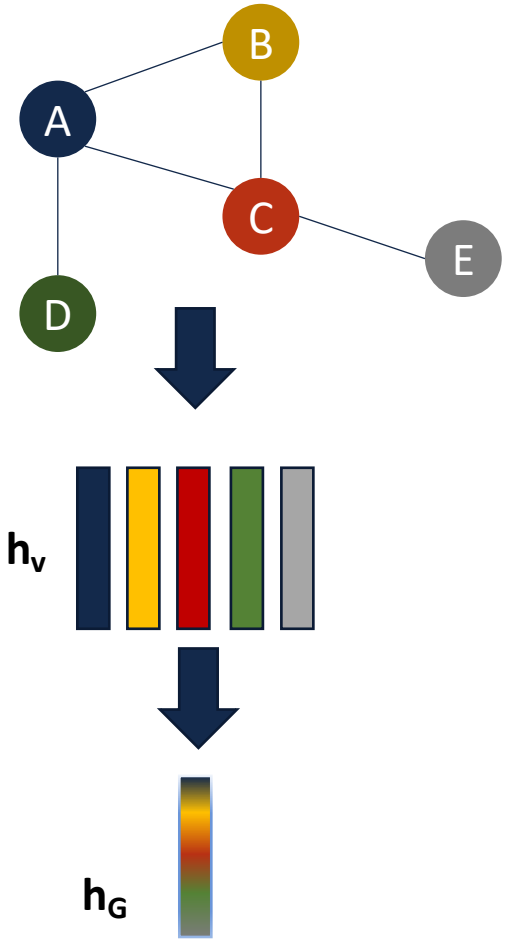
ILLINOIS

# Outline



- Fundamentals of deep learning on graphs ✓
- Graph convolutional networks (GCN) ✓
- Message passing neural network (MPNN)
- Graph attention networks (GAT)
- Applications

# Message passing neural network (MPNN)

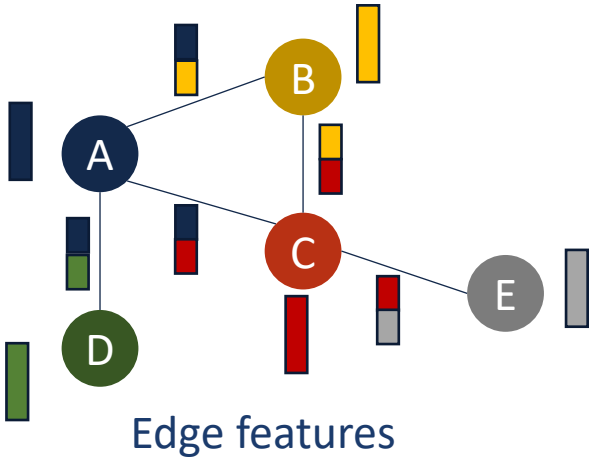



- Goal: Generate both **node embeddings** and **graph embedding**
- MPNN is a GNN framework that handles both node and edge features
- **Message passing stage**:
  - compute the message $\mathbf{m}_v$ for node v
  - update the node embedding $\mathbf{h}_v$
- **Readout stage**
  - Produce an embedding $\mathbf{h}_G$ for the entire graph

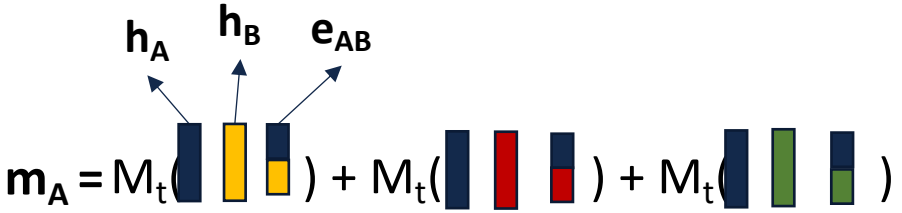
Gilmer et al. 2017. "Neural Message Passing for Quantum Chemistry." *ICML 2017*

ILLINOIS

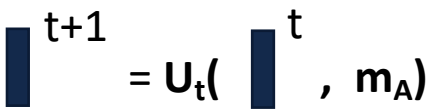
# Message passing phase




Message passing $\boldsymbol{m}_v^{t+1} = \sum_{w \in \mathcal{N}_v} M_t(\boldsymbol{h}_v^t, \boldsymbol{h}_w^t, \boldsymbol{e}_{vw})$




Node embedding $\boldsymbol{h}_v^{t+1} = U_t(\boldsymbol{h}_v^t, \boldsymbol{m}_v^{t+1})$



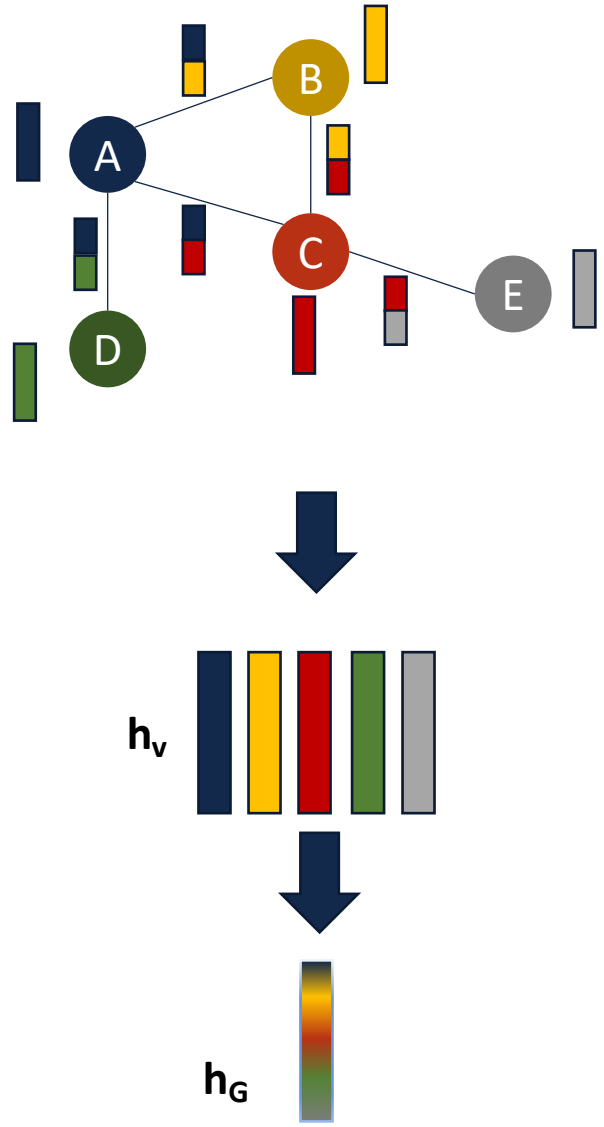

ILLINOIS

# Readout phase


- Input: node embedding $\mathbf{h}_1, \mathbf{h}_2, \ldots, \mathbf{h}_N$
- Output: an embedding vector for the entire graph $\mathbf{h}_G$
- Algorithm options
  - Average($\mathbf{h}_1, \mathbf{h}_2, \ldots, \mathbf{h}_N$)
  - Max-pool($\mathbf{h}_1, \mathbf{h}_2, \ldots, \mathbf{h}_N$)
  - RNN over random-shuffle($\mathbf{h}_1, \mathbf{h}_2, \ldots, \mathbf{h}_N$)

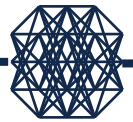
# Summary of MPNN

- MPNN is a GNN that handles both node features and edge features.
- Two phases
  - Message passing phase
  - Readout phase
- Limitation:
  - computationally more expensive to train and only can handle smaller graphs such as molecule graphs.



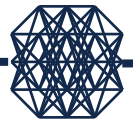

ILLINOIS

# Outline



- Fundamentals of deep learning on graphs ✓
- Graph convolutional networks (GCN) ✓
- Message passing neural network (MPNN) ✓
- Graph attention networks (GAT)
- Applications

# Graph attention networks (GAT)



- **Recall** GCN aggregates neighborhoods uniformly with equal weight

$$\boldsymbol{h}_i^{(l+1)} = \sigma\left(\boldsymbol{h}_i^{(l)}\boldsymbol{W}^l + \sum_{j\in\mathcal{N}_i} \boldsymbol{h}_j^{(l)}\boldsymbol{W}^l\right)$$

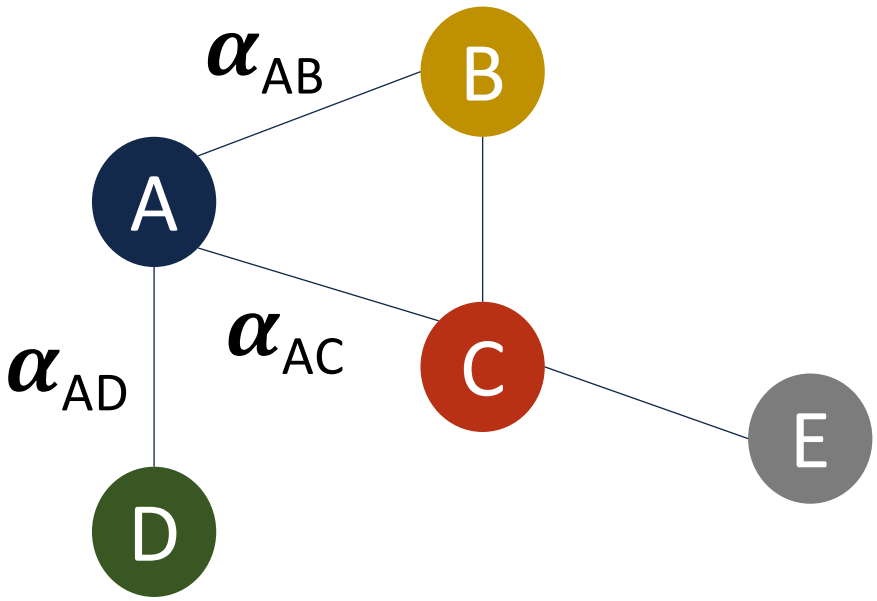
Equal importance for each neighbor

- **Idea**: assign different weights for different neighbors based on their importance

Veličković et al. "Graph Attention Networks." *ICLR 2018*

ILLINOIS

# Graph attention networks (GAT)




- Attention mechanism on graph: compute attention weight $\alpha_{ij}$ from embeddings of neighboring nodes

Alignment : $e_{ij} = \texttt{LeakyReLU}(\boldsymbol{a}^\top [\boldsymbol{W}\boldsymbol{h}_i || \boldsymbol{W}\boldsymbol{h}_j])$

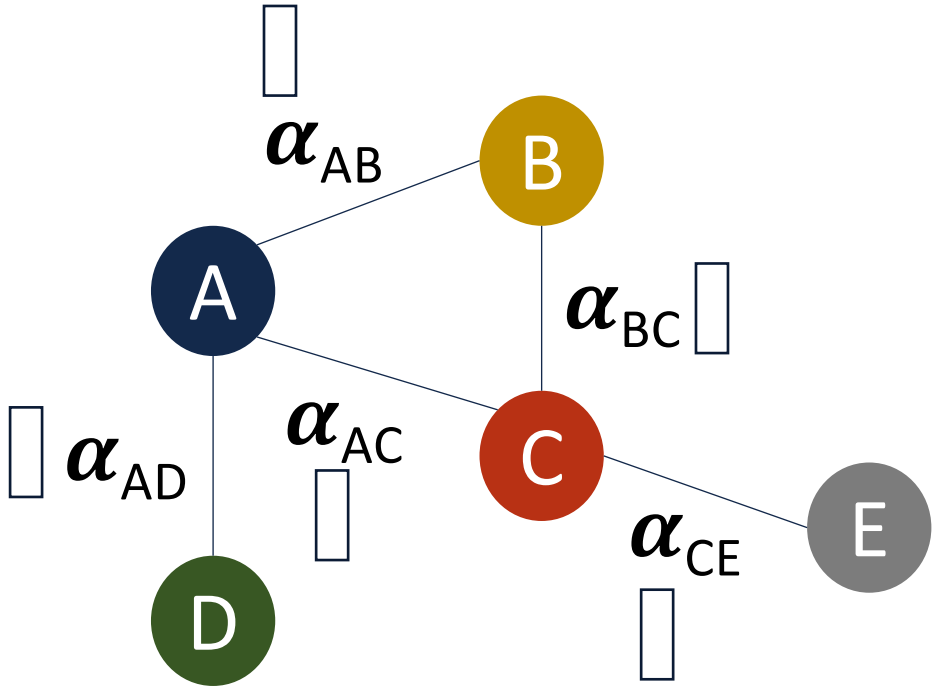
concatenation

Attention weight $\alpha_{ij} = \text{Softmax}(e_{ij}) = \dfrac{\exp(e_{ij})}{\sum_{v_j \in \mathcal{N}_i} \exp(e_{ij})}$

Attention $\alpha_{ij}$ is only computed for neighbors
(the rest has 0 attention)

ILLINOIS

# Multihead attention




- Repeat the attention process R times

$$e_{ij} = \texttt{LeakyReLU}(\boldsymbol{a}^\top [\boldsymbol{W}\boldsymbol{h}_i || \boldsymbol{W}\boldsymbol{h}_j])$$

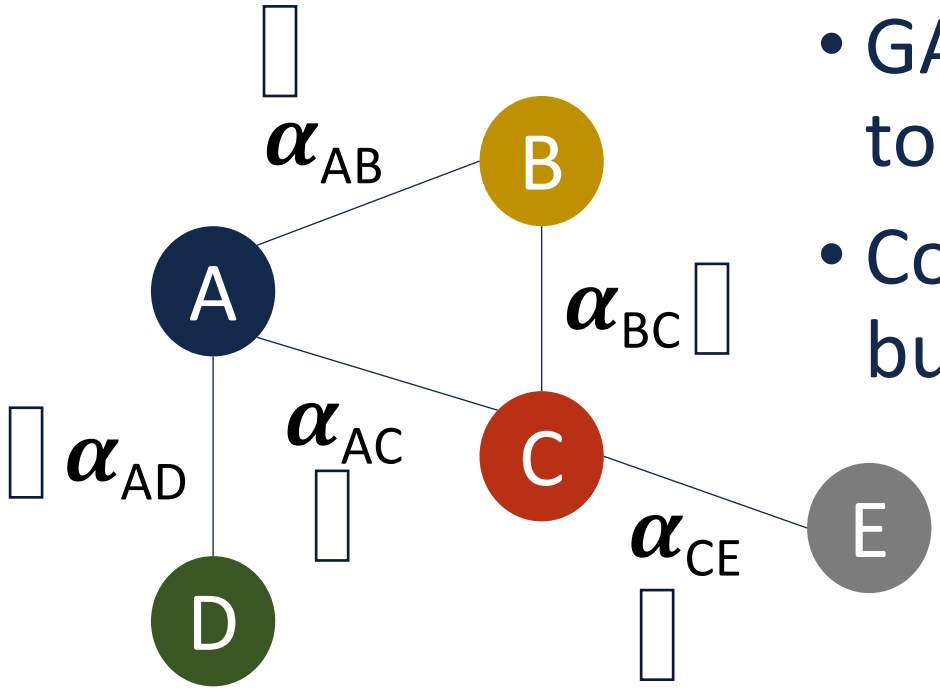
Repeat R times with different W

$$\alpha_{ij} = \text{Softmax}(e_{ij}) = \frac{\exp(e_{ij})}{\sum_{v_j \in \mathcal{N}_i} \exp(e_{ij})}$$

- Benefit: Stabilize the learning process of attention mechanism
- Attention weight $\boldsymbol{\alpha}_{ij}$ becomes a vector of size R

ILLINOIS

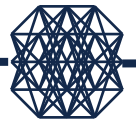
# Summary of Graph attention network




- GAT is a combination of attention mechanism and graph convolutional network
- GAT allows assigning different importance $\alpha_{ij}$ to different neighbors
- Computationally: more efficient than MPNN but slower than GCN

ILLINOIS

# Summary



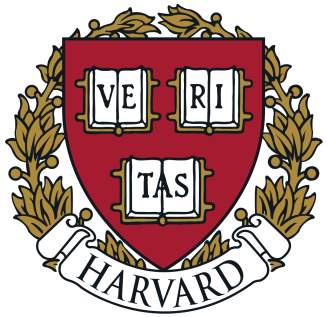
- Fundamentals of deep learning on graphs ✓
- Graph convolutional networks (GCN) ✓
- Message passing neural network (MPNN) ✓
- Graph attention networks (GAT) ✓
- Applications ✓
  - Side-effect prediction
  - Antibiotic discovery

ILLINOIS

# Learning actionable representations of biomedical data

Marinka Zitnik

Assistant Professor, Department of Biomedical Informatics
Associate Member, Broad Institute of Harvard and MIT




zitniklab.hms.harvard.edu

Slides credit to Marinka Zitnik

ILLINOIS

# Polypharmacy

## Patients take multiple drugs to treat complex or co-existing diseases

**46%** of people over 65 years take more than 5 drugs

Many take more than **20** drugs to treat heart diseases, depression or cancer

**15%** of the U.S. population affected by unwanted side effects

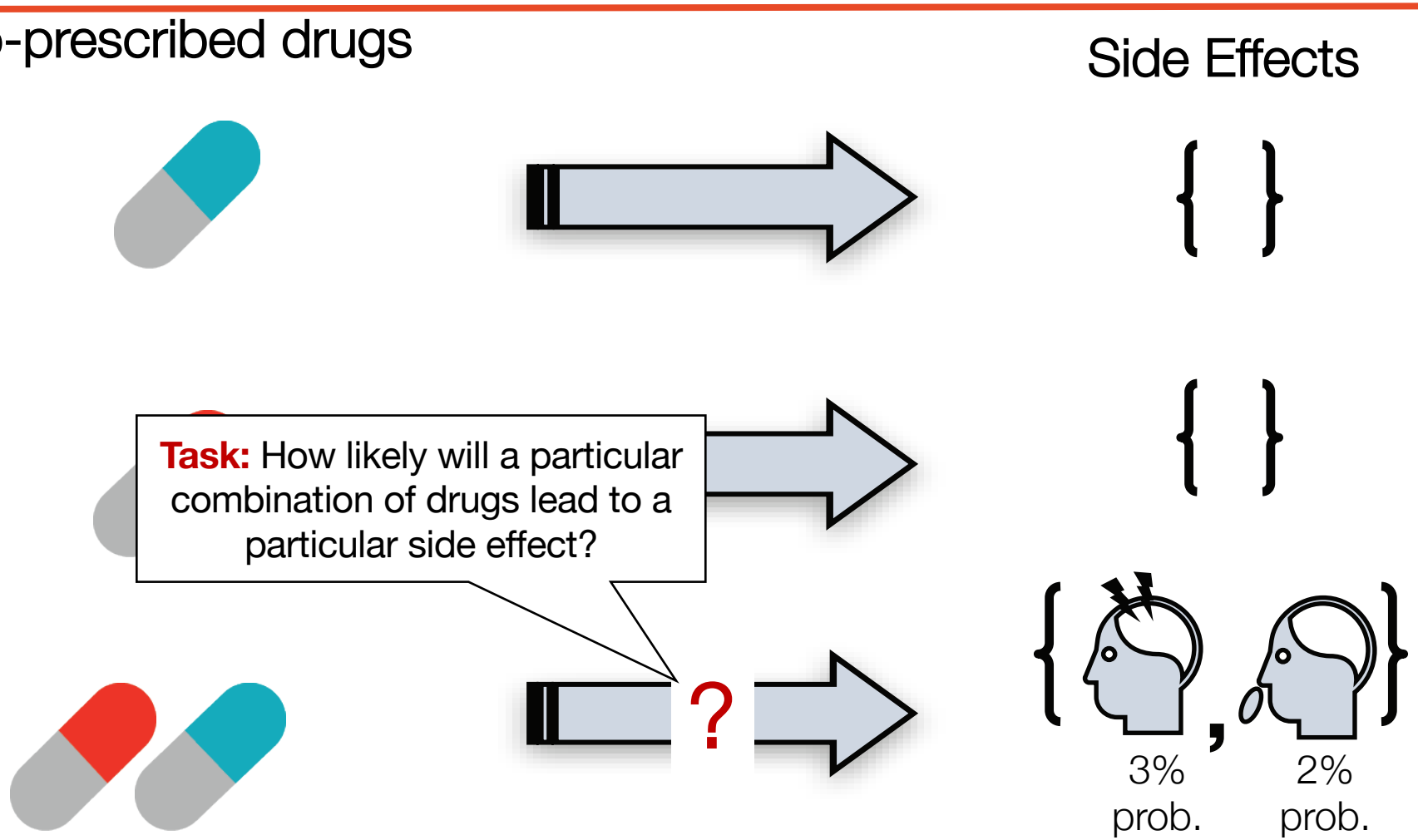
Annual costs in treating side effects exceed **$177** billion in the U.S. alone

[Ernst and Grizzle, JAPA'01; Kantor et al., JAMA'15]

Slides credit to Marinka Zitnik

ILLINOIS

# Unexpected Drug Interactions

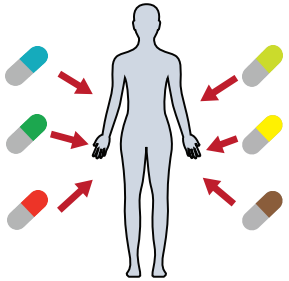



Slides credit to Marinka Zitnik

# Why is modeling polypharmacy hard?

## Combinatorial explosion

- >13 million possible combinations of 2 drugs
- >20 billion possible combinations of 3 drugs

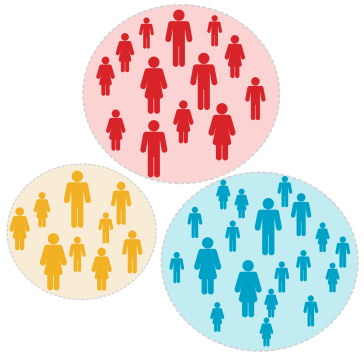


## Non-linear & non-additive interactions

- Different effect than the additive effect of individual drugs

## Small subsets of patients

- Side effects are interdependent
- No info on drug combinations not yet used in patients



Slides credit to Marinka Zitnik

Modeling Polypharmacy Side Effects with Graph Convolutional Networks, *Bioinformatics* 2018

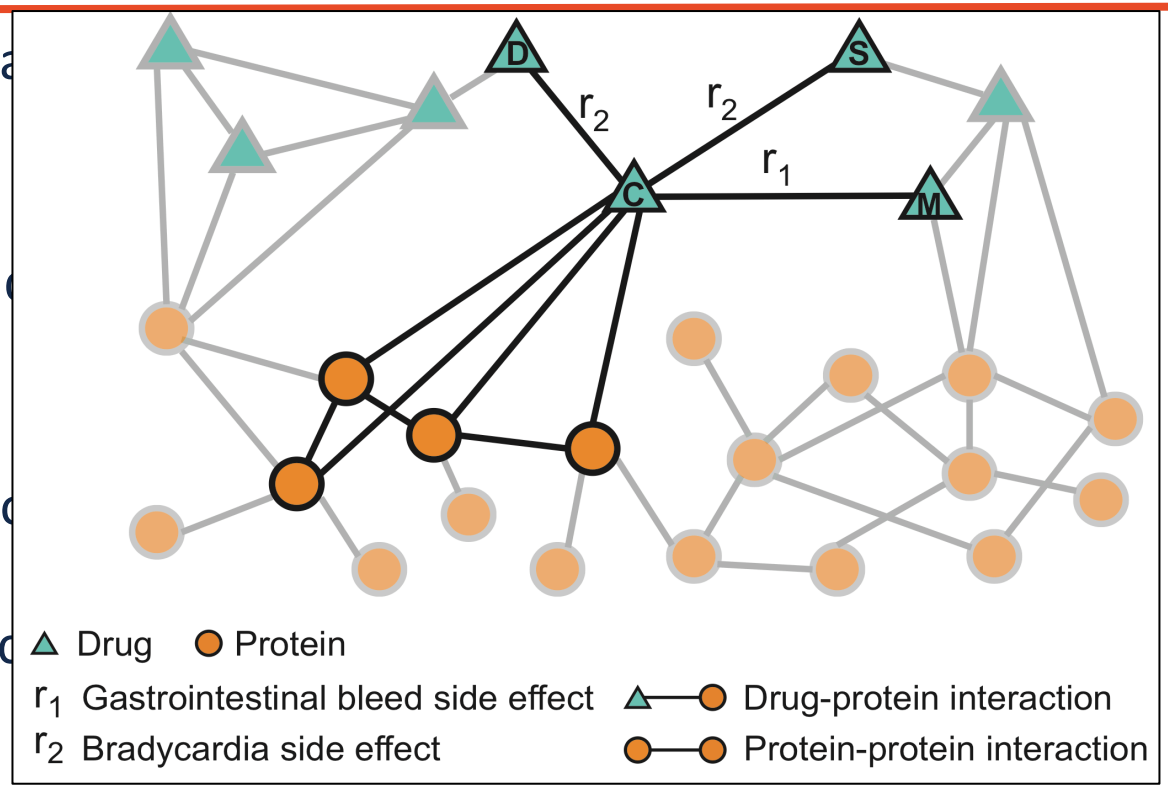
ILLINOIS

# We need polypharmacy dataset

Objective: Capture molecular, drug, and patient da
prescribed in the U.S.

The authors build a unique dataset:

- 4,651,131 drug-drug edges: Patient data from a
tested for confounders [FDA]
- 18,596 drug-protein edges
- 719,402 protein-protein edges: Physical, metab
and signaling interactions
- Drug and protein features: drugs' chemical struc
membership in pathways



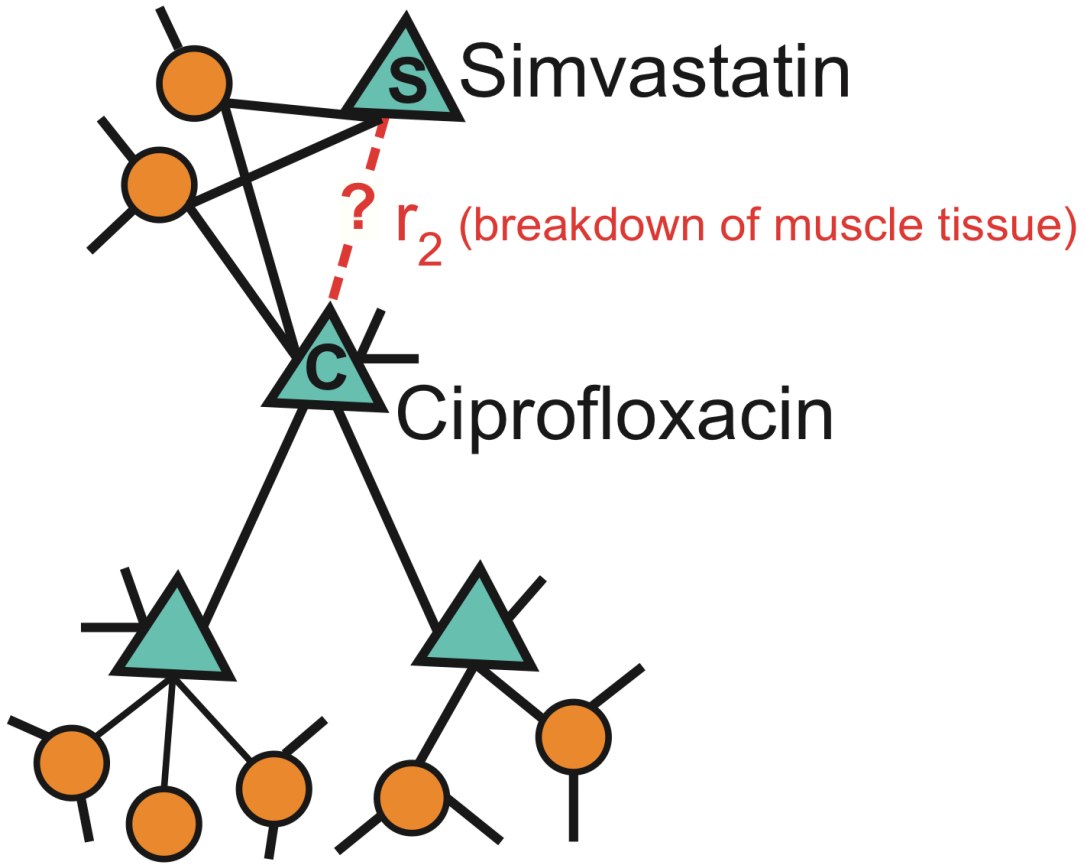

A polypharmacy network with over 5 million edges and over 1,000 different edge types

Slides credit to Marinka Zitnik

ILLINOIS

# We apply our deep methods to the polypharmacy network

E.g.: How likely will Simvastatin and Ciprofloxacin, when taken together, break down muscle tissue?

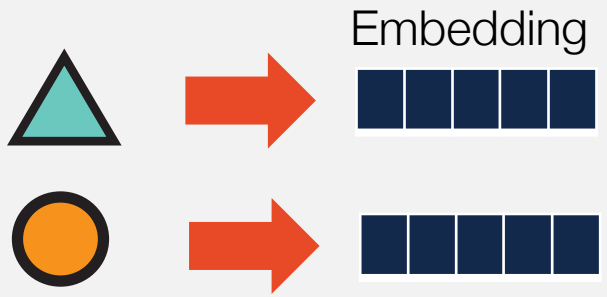



Slides credit to Marinka Zitnik

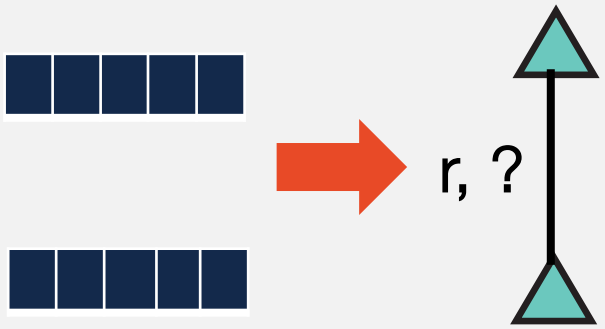
ILLINOIS

# *Decagon:* Graph Neural Net

1. **Encoder:** Take the graph and learn an *embedding* for every node



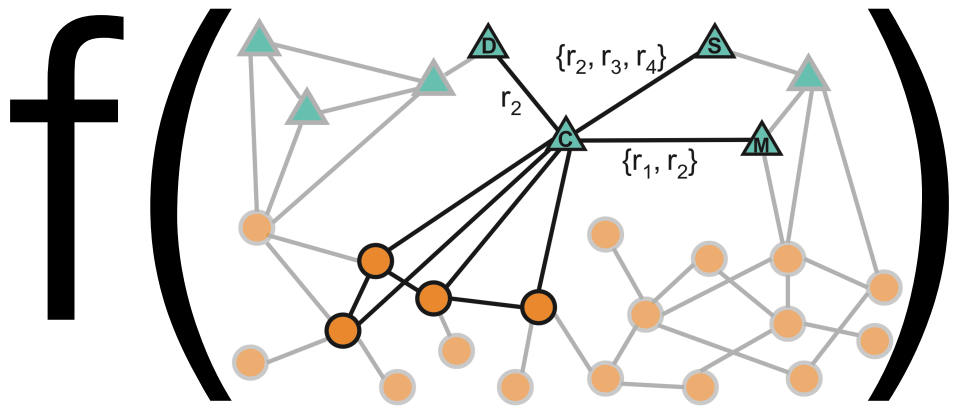

2. **Decoder:** Use the learned embeddings to predict side effects



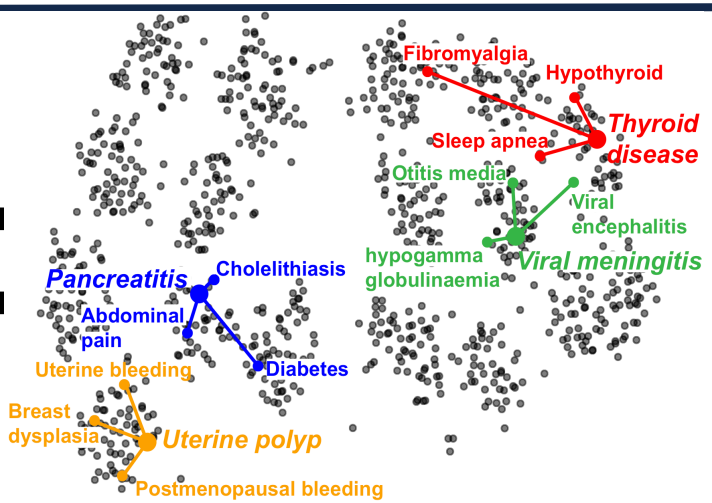

ILLINOIS

Slides credit to Marinka Zitnik

# Embedding Nodes




Heterogeneous graph




2-dimensional node embeddings

## How to learn f?

**Intuition:** Map nodes to d-dimensional embeddings such that similar nodes in the graph are embedded close together

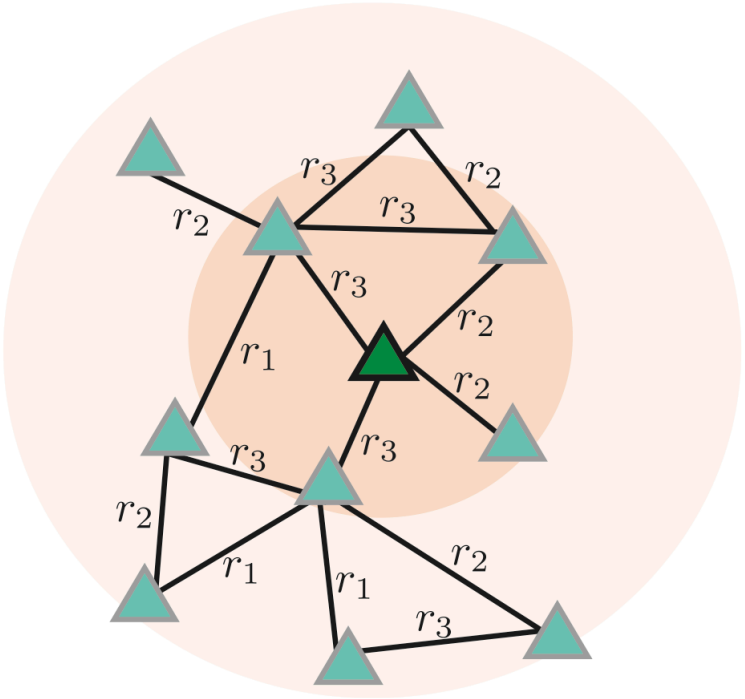
Slides credit to Marinka Zitnik

ILLINOIS

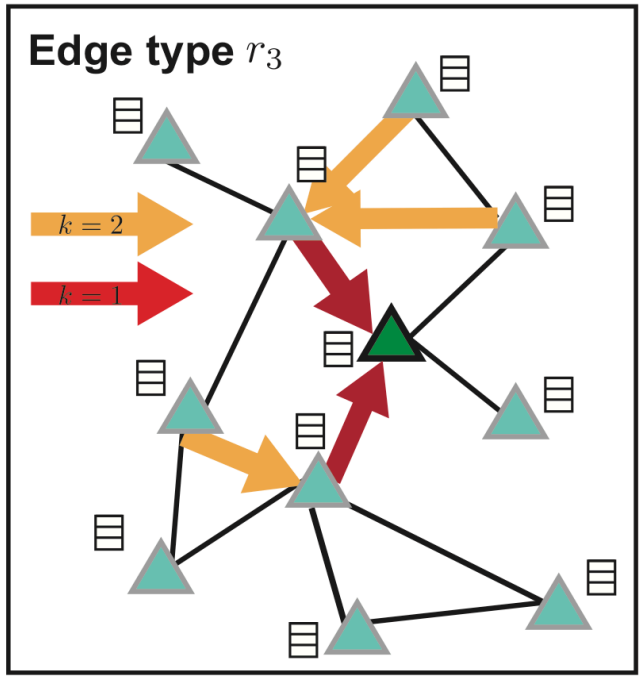
# Encoder: Principle

**Key idea:** Generate node embeddings based on local network neighborhoods

Each edge type is modeled separately




**Determine a node's computation graph**

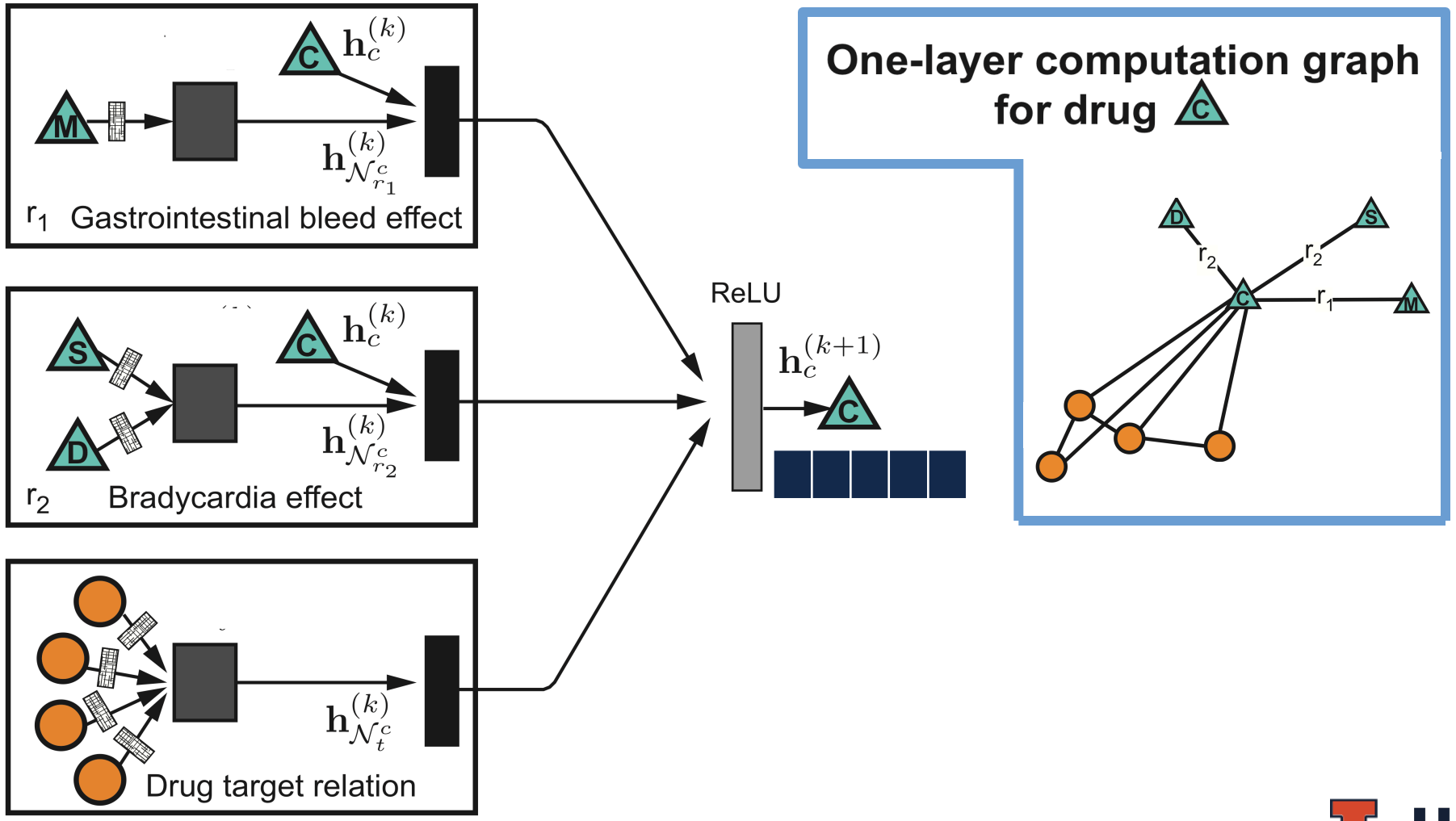



**Learn how to transform and propagate information across the graph**

Slides credit to Marinka Zitnik

ILLINOIS

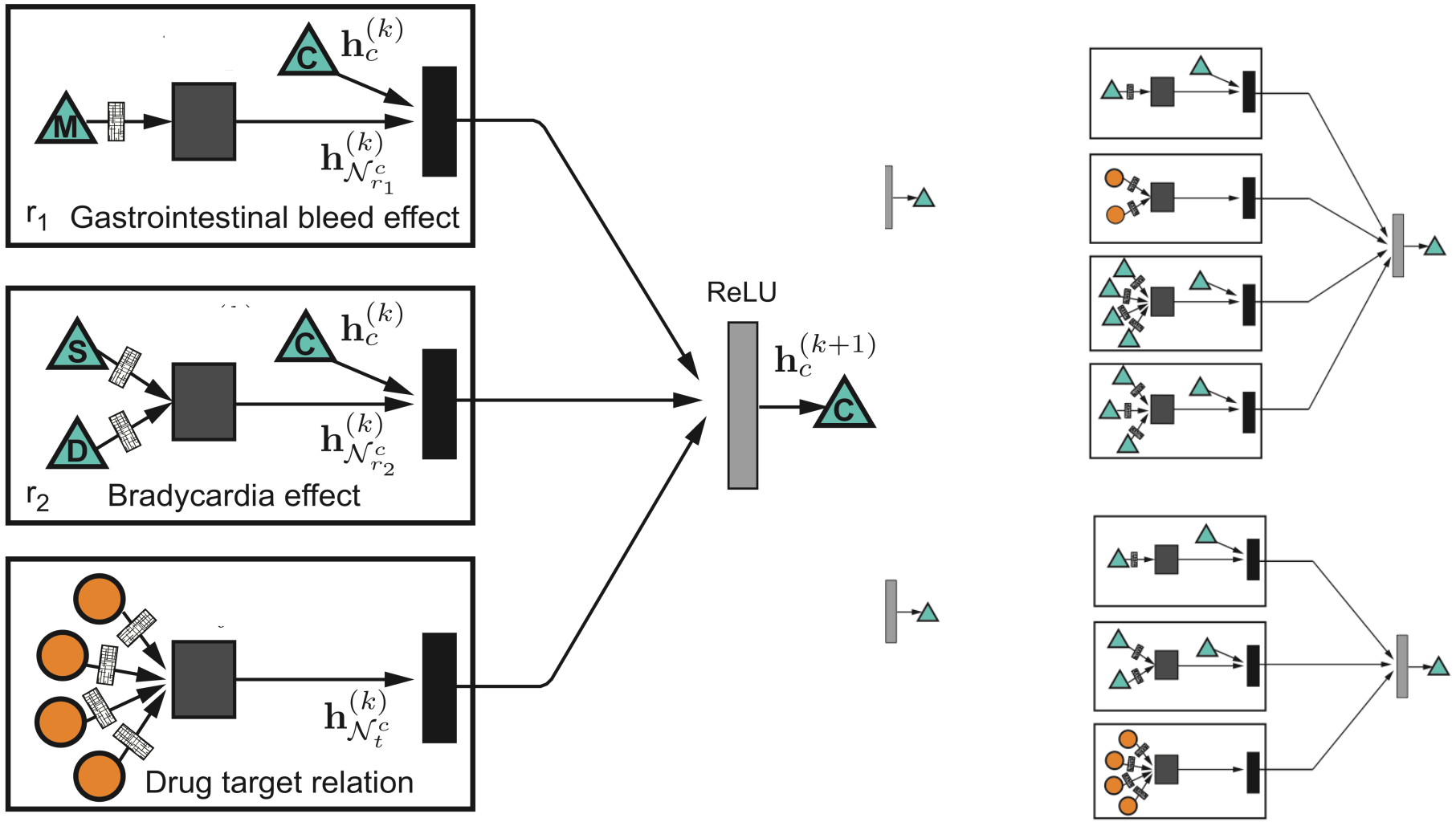
# Encoder: Embeddings




Slides credit to Marinka Zitnik

ILLINOIS

# Encoder: Embeddings

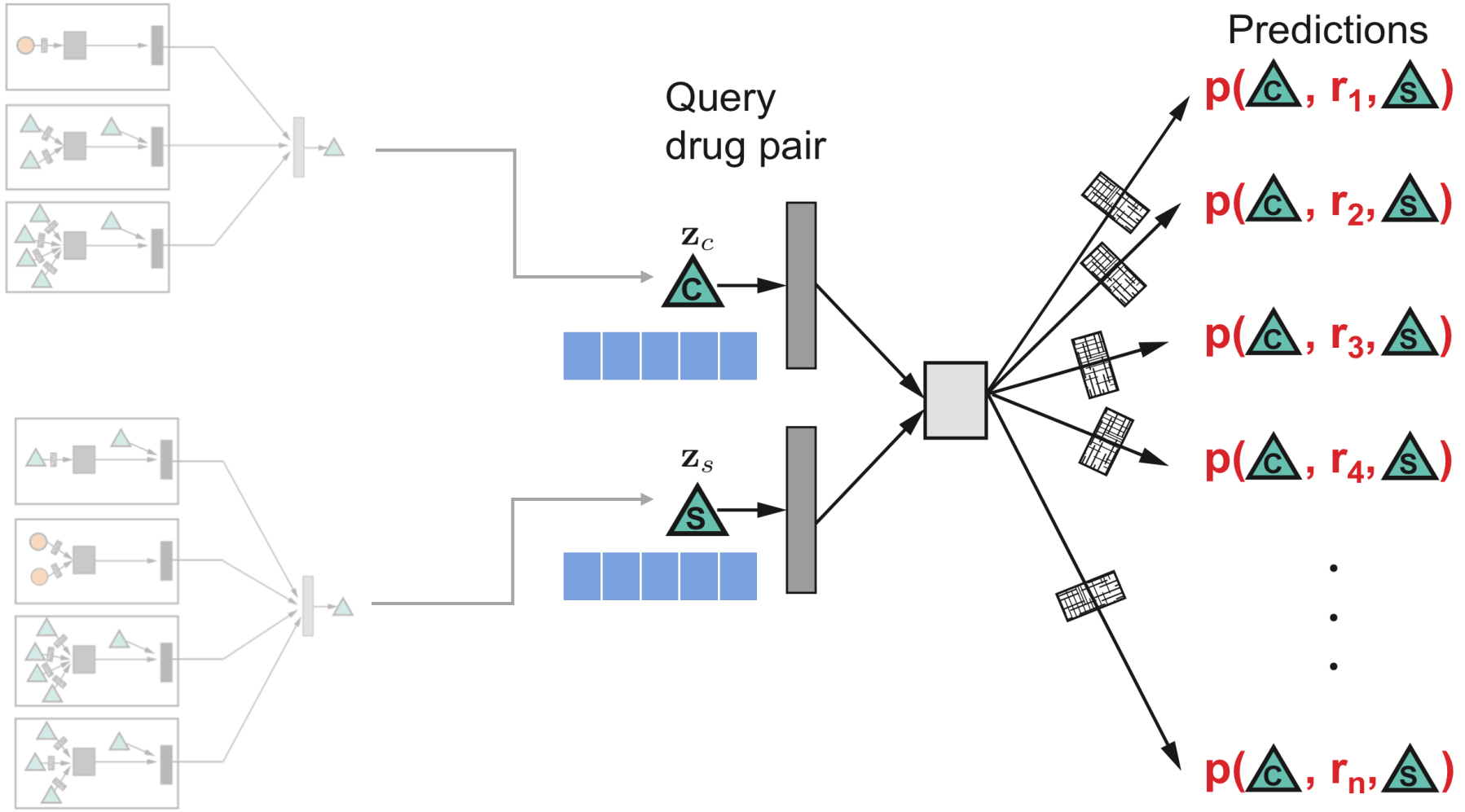



A batch of computation graphs

Slides credit to Marinka Zitnik

LINOIS

# Decoder: Link Prediction

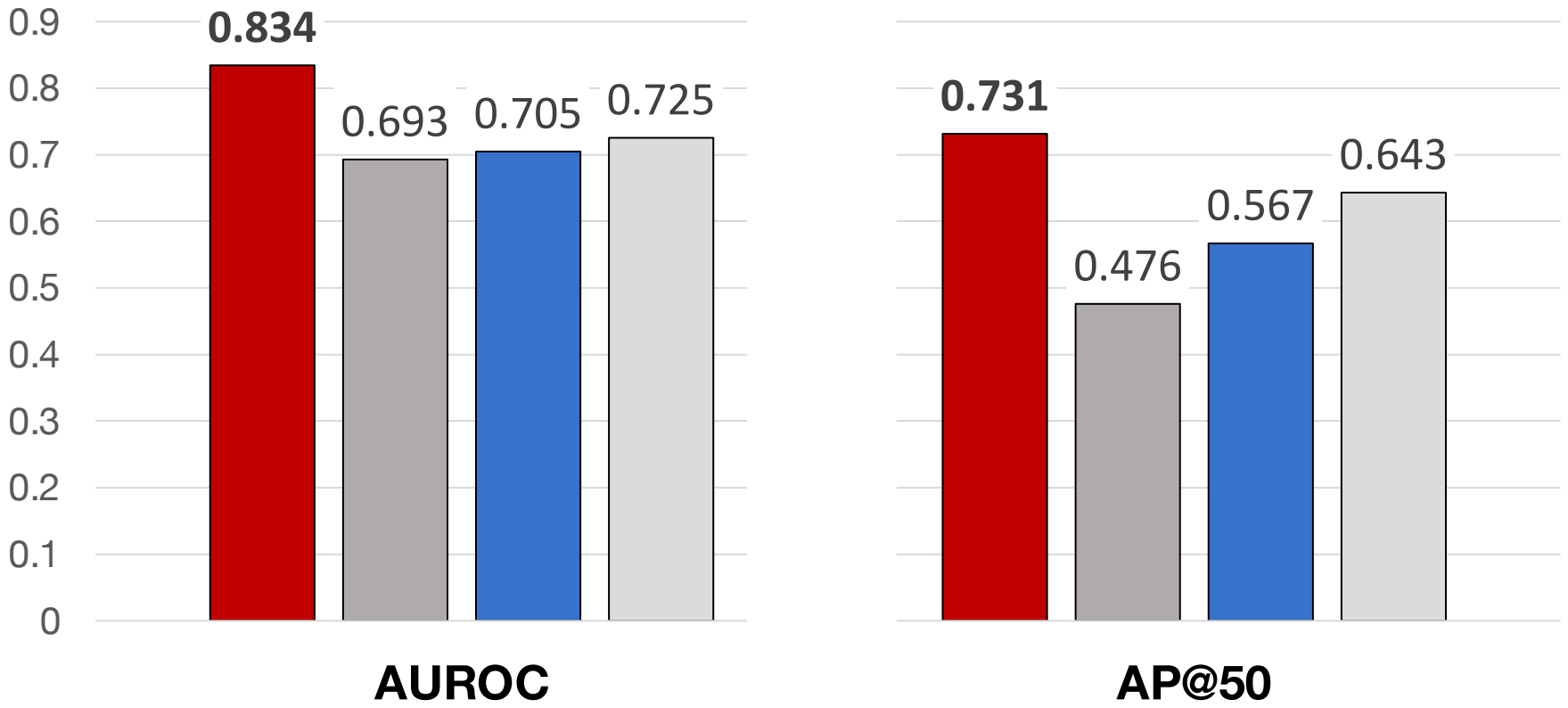



p – probability

Slides credit to Marinka Zitnik

ILLINOIS

# Results: Polypharmacy Side Effect Prediction




Slides credit to Marinka Zitnik

ILLINOIS

# New Predictions

**Next:** Can the method generate hypotheses and give:

- **Doctors** guidance on whether it is a good idea to prescribe a particular combination of drugs to a particular patient
- **Researchers** guidance on effective wet lab experiments and new drug therapies with fewer side effects

First AI method to **predict side effects of drug combinations,** even for combinations not yet used in patients

Slides credit to Marinka Zitnik

ILLINOIS

# New Predictions

**Approach:**

1) Train deep model on data generated **prior to 2012**
2) How many **predictions** have been **confirmed after 2012**?

| Rank | Drug | Drug | Side effect | Evidence found |
|---|---|---|---|---|
| **1** | Pyrimethamine | Aliskiren | Sarcoma | |
| **2** | Tigecycline | Bimatoprost | Autonomic neuropathy | |
| **3** | Telangiectases | Omeprazole | Dacarbazine | |
| **4** | Tolcapone | Pyrimethamine | Blood brain barrier | |
| | | | eadache | |
| | | | ular acidosis | |
| **7** | Anag[illegible] | Azelaic acid | Cerebral thrombosis | |
| **8** | Atorvastatin | Amlodipine | Muscle inflammation | |
| **9** | Aliskiren | Tioconazole | Breast inflammation | |
| **10** | Estradiol | Nadolol | Endometriosis | |

*Case Report*

**Severe Rhabdomyolysis due to Presumed Drug Interactions between Atorvastatin with Amlodipine and Ticagrelor**

Slides credit to Marinka Zitnik

# A Deep Learning Approach to Antibiotic Discovery

Jonathan M. Stokes, Kevin Yang, Kyle Swanson, ..., Tommi S. Jaakkola, Regina Barzilay, James J. Collins

Stokes et al. 2020. “A Deep Learning Approach to Antibiotic Discovery.” *Cell* 180 (4): 688–702.e13.

ILLINOIS

# Antibiotic Discovery

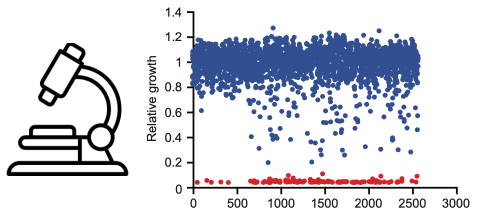

- Antibiotic drug is essential for modern medicine
- Continued efficacy of existing antibiotics is uncertain due to antibiotic-resistance determinants
- Lack of economic incentive for new antibiotic development
- The discovery of new antibiotics is becoming increasingly difficult

**New approaches to antibiotic discovery are needed**

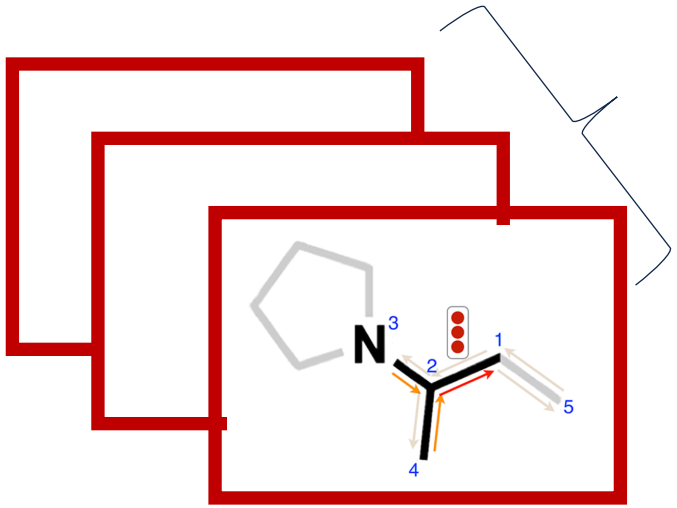
Franco et al. 2009. "The Determinants of the Antibiotic Resistance Process." *Infection and Drug Resistance* 2 (April): 1–11.

ILLINOIS

# Approach




Training data collection




Directed MPNN model

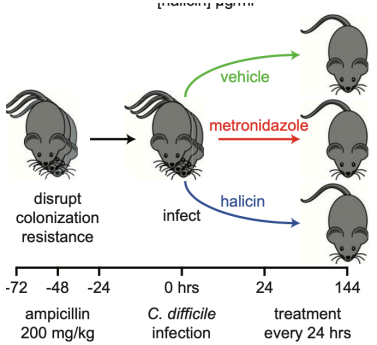
Model ensembles


Score potential antibiotic compounds

99 candidates

Toxicity prediction

halicin




Animal study

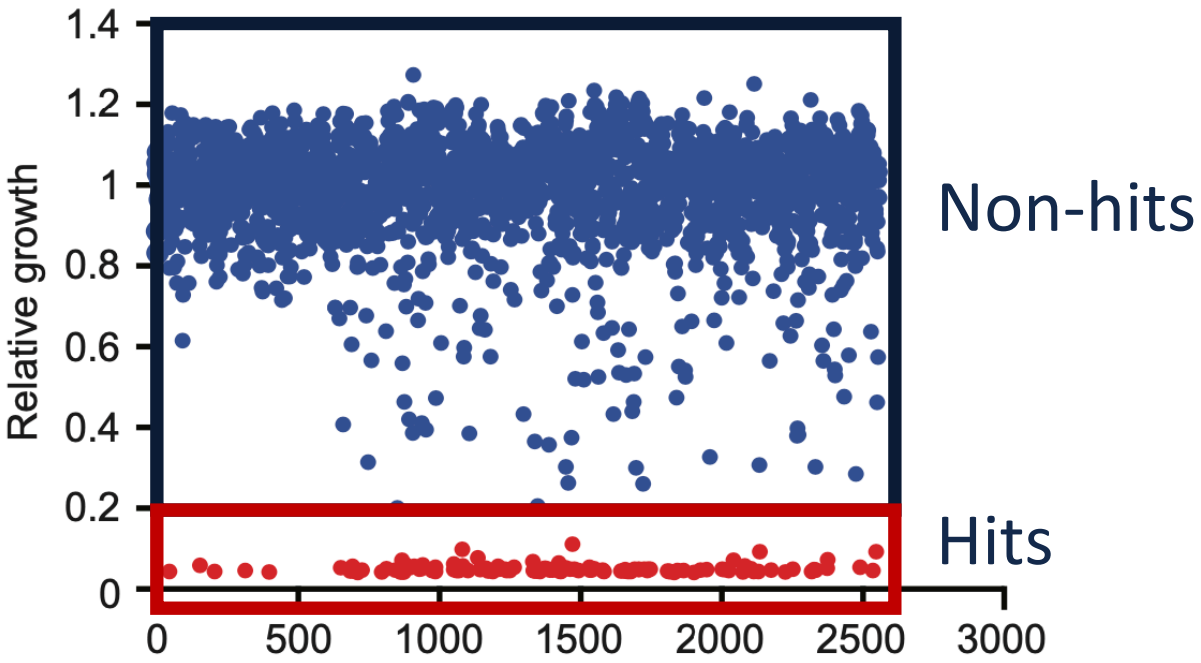
ILLINOIS

# Data collection

1760 molecules


800 molecules


Screen *E. coli*

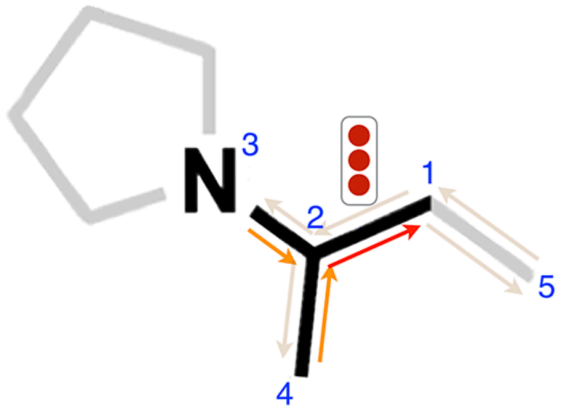



- 2,335 compounds from the primary training dataset were binarized as hit or non-hit.

ILLINOIS

# Directed MPNN model

- Consider edge directions
- Update edge representation with neighboring edges
- Ignore the impact of reversal edges
  - Update $\mathbf{h}_{vw}$ from neighboring edges  except the reversal $\mathbf{h}_{wv}$




Yang, et al. 2019. “Analyzing Learned Molecular Representations for Property Prediction.” *Journal of Chemical Information and Modeling* 59 (8): 3370–88.

ILLINOIS

# Node and Edge features

Node features

| feature | description | size |
|---|---|---|
| atom type | type of atom (ex. C, N, O), by atomic number | 100 |
| # bonds | number of bonds the atom is involved in | 6 |
| formal charge | integer electronic charge assigned to atom | 5 |
| chirality | unspecified, tetrahedral CW/CCW, or other | 4 |
| # Hs | number of bonded hydrogen atoms | 5 |
| hybridization | sp, sp2, sp3, sp3d, or sp3d2 | 5 |
| aromaticity | whether this atom is part of an aromatic system | 1 |
| atomic mass | mass of the atom, divided by 100 | 1 |

Edge features

| feature | description | size |
|---|---|---|
| bond type | single, double, triple, or aromatic | 4 |
| conjugated | whether the bond is conjugated | 1 |
| in ring | whether the bond is part of a ring | 1 |
| stereo | none, any, E/Z or cis/trans | 6 |

ILLINOIS

# Edge embedding update

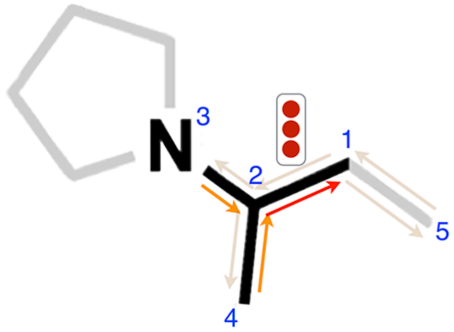
Directed message passing

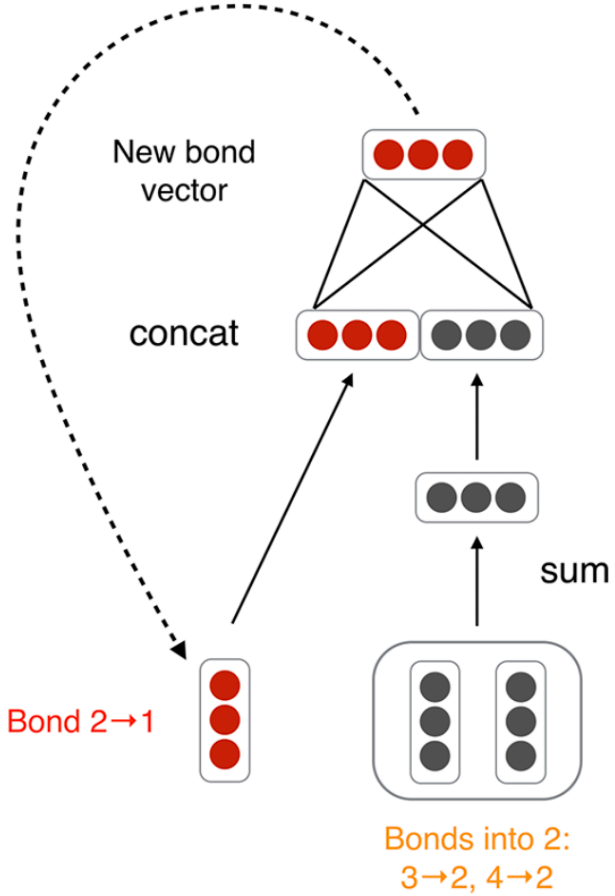
$$m_{vw}^{t+1} = \sum_{k \in \{N(v) \setminus w\}} M_t(x_v, x_k, h_{kv}^t) = h_{vw}^t$$

$$h_{vw}^{t+1} = U_t(h_{vw}^t, m_{vw}^{t+1}) = \text{ReLU}\left(h_{vw}^0 + W_m m_{vw}^{t+1}\right)$$

Initialization

$$h_{vw}^0 = \tau(W_i \, \text{cat}(x_v, e_{vw}))$$




ILLINOIS

# Node and Graph embedding

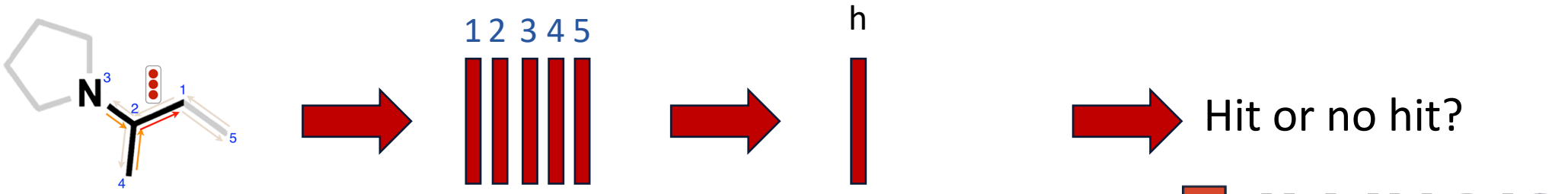
Node embedding updates

$$m_v = \sum_{k \in N(v)} h_{kv}^T$$

$$h_v = \tau(W_a \, \mathrm{cat}(x_v, m_v))$$

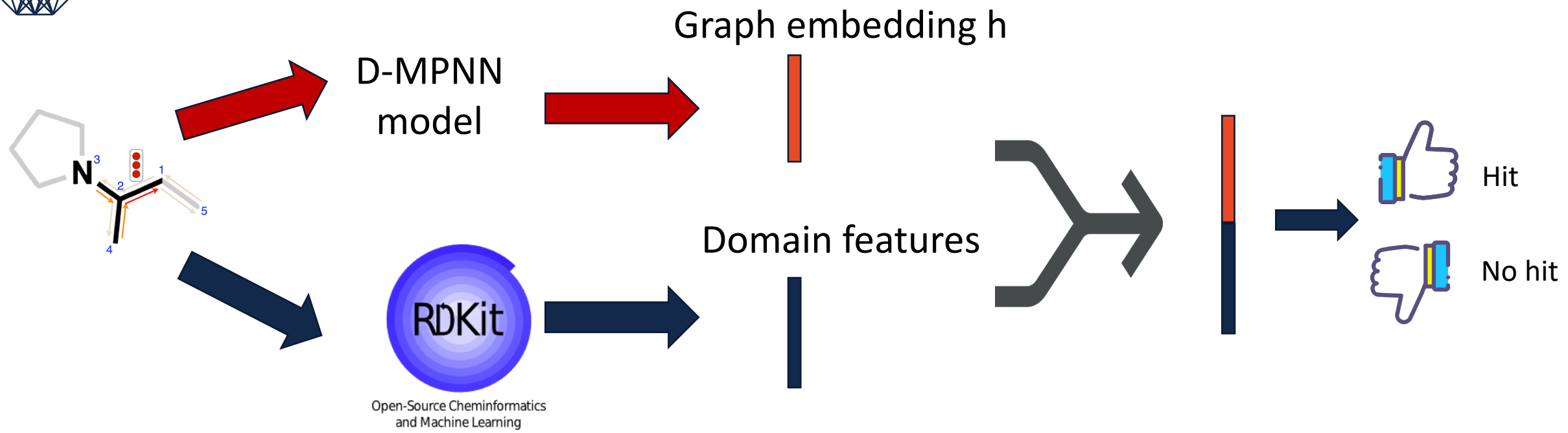
Readout operation: graph embedding

$$h = \sum_{v \in G} h_v$$




ILLINOIS

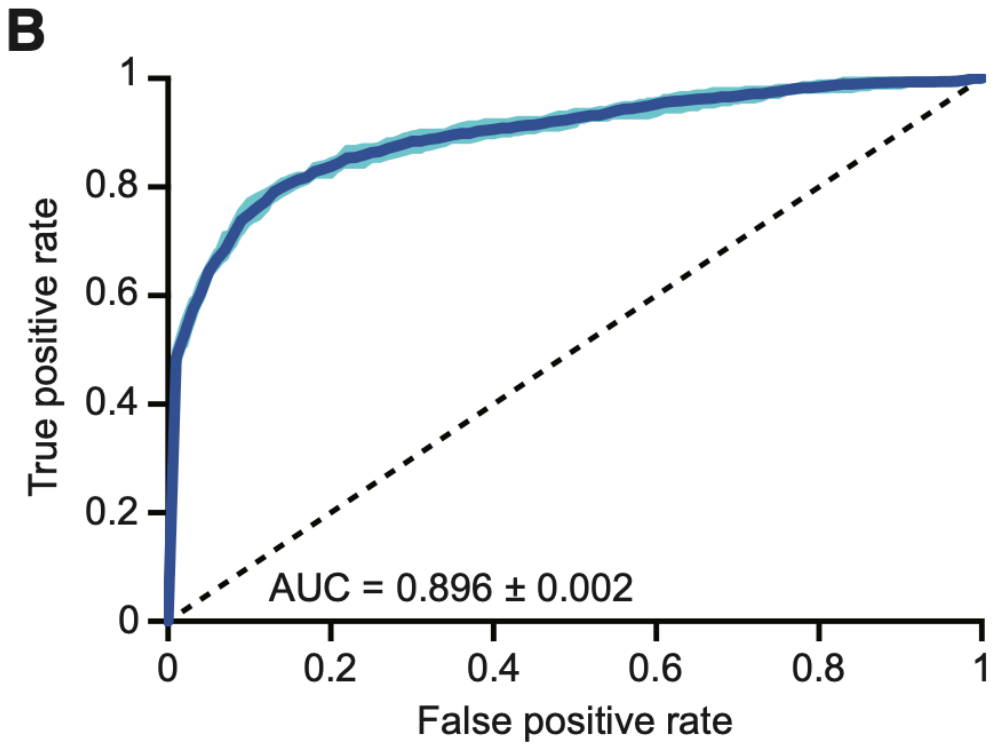
# Hit prediction

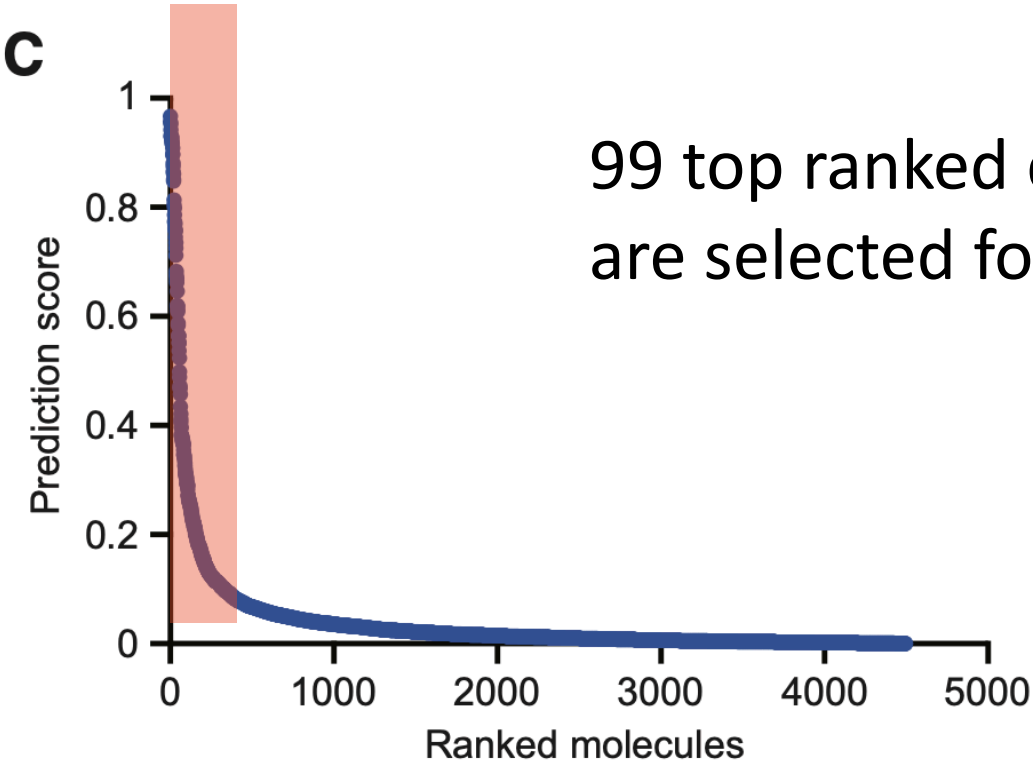



- 20-fold cross validation are used to select the best parameters
  - 80-10-10 split on train, validation and test
- An ensemble of 20 models are used for the final prediction

ILLINOIS

# Result: Initial DL model performance

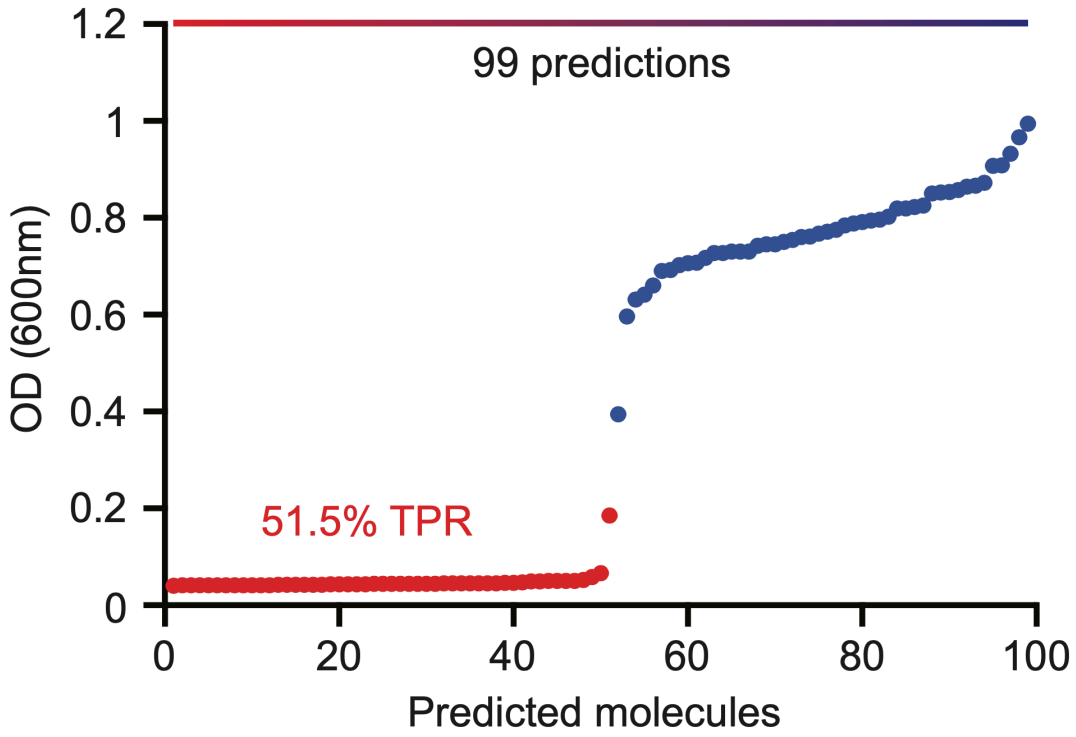



99 top ranked candidates are selected for lab validation

ILLINOIS

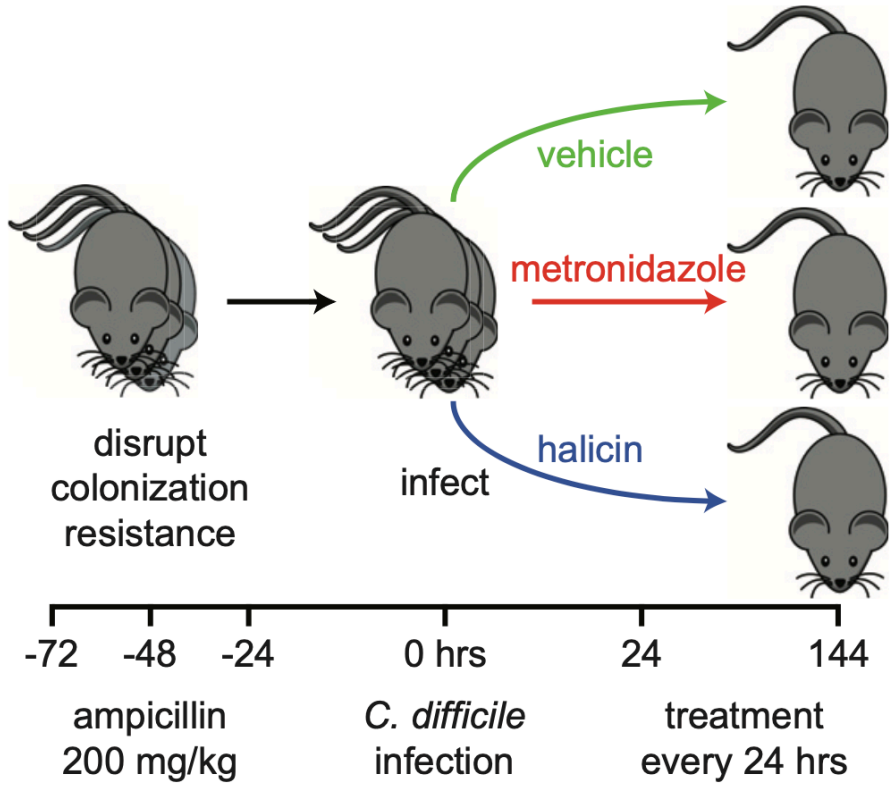
# Result: Growth inhibition of *E. coli*

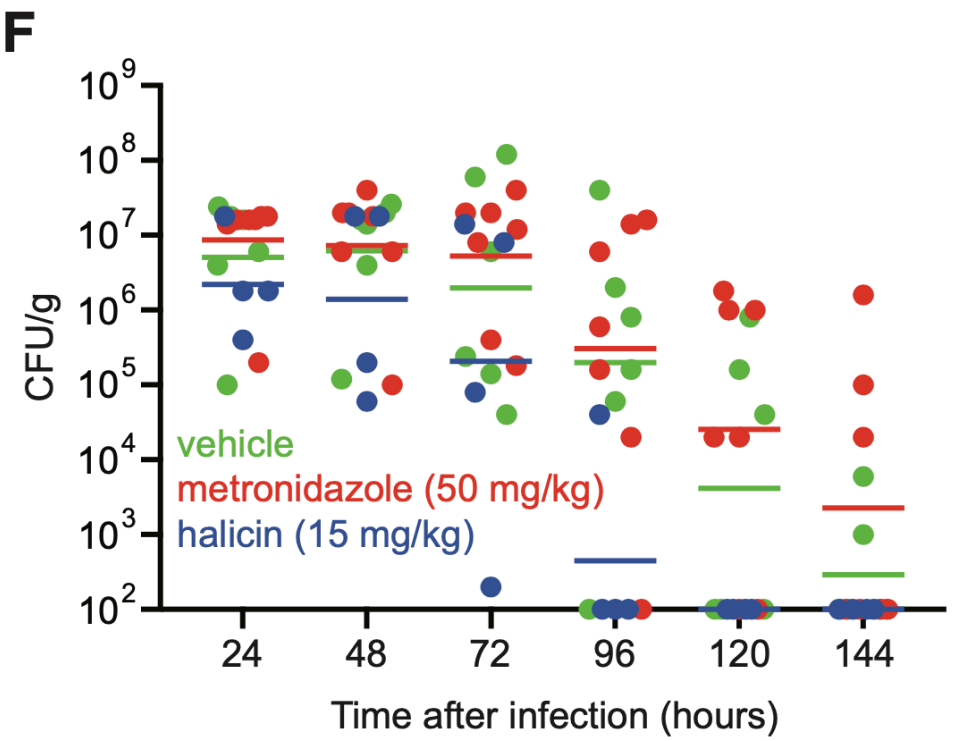



51.5% True Positive Rate

ILLINOIS

# Result: Effectiveness of treating bacteria

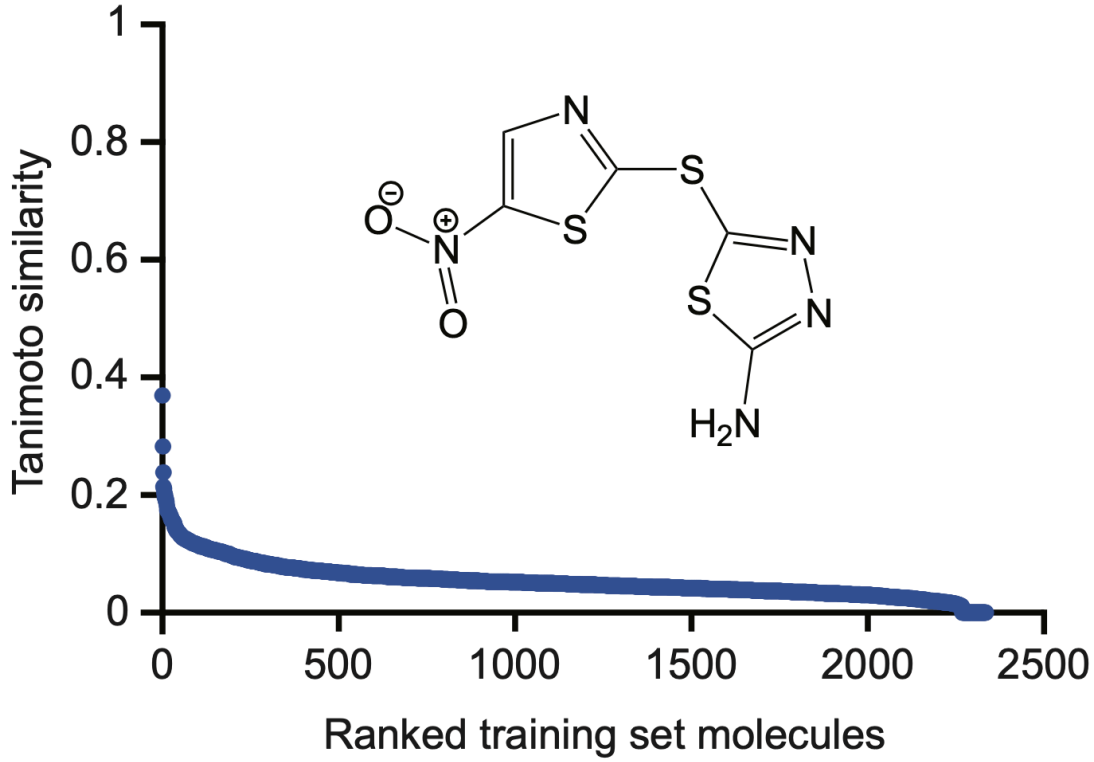



- **Halicin** (the new antibiotic) works much better than existing antibiotic Metronidazole

ILLINOIS

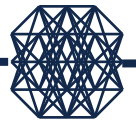
# Result: Structural diversity to known antibiotics




- The identified target Halicin is structurally different from existing antibiotics

ILLINOIS

# Summary



- Fundamentals of deep learning on graphs ✓
- Graph convolutional networks (GCN) ✓
- Message passing neural network (MPNN) ✓
- Graph attention networks (GAT) ✓
- Applications ✓
  - Side-effect prediction
  - Antibiotic discovery

ILLINOIS