Modeling Polypharmacy with Graph Convolutional Networks

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Why polypharmacy?

Many patients take multiple drugs to treat complex or co-existing diseases:

- 25% of people ages 65-69 take more than 5 drugs
- 46% of people ages 70-79 take more than 5 drugs
- Many patients take more than 20 drugs to treat heart disease, depression, insomnia, etc.

[Charlesworth et al., 2015]
Unwanted Side Effects

Prescribed drugs

Drug side effect

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\{ \}

\{ \}

30% prob.

65% prob.
Unwanted Side Effects

- Side effects due to drug-drug interactions
- Extremely difficult to identify:
  - Impossible to test all combinations of drugs
  - Side effects not observed in controlled trials
- 15% of the U.S. population affected
- Annual costs exceed $177 billion

[Kantor et al., 2015]
Existing Research

- **Experimental screening of drug combs:**
  - Expensive, combinatorial explosion

- **Computational methods:**
  - **Supervised methods:** Predict probability of a drug-drug interaction [Chen et al., 2016; Shi et al., 2017]
  - **Similarity-based methods:** Similar drugs have similar interactions [Gottlieb et al., 2012; Ferdousi et al., 2017; Zhang et al., 2017]

These methods do not predict side effects of drug combinations
How likely with a pair of drugs $c, d$ lead to side effect $r$?

Our study: Model and predict side effects of drug pairs

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Challenges

- Large number of types of side effects:
  - Each occurs in a small subset of patients
  - Side effects are interdependent
- No information about drug pairs that are not yet used in patients
- Molecular, drug, and patient data:
  - Heterogeneous and multi-relational
Our Approach

*In silico* screening of drug combinations

- Use molecular, drug, and patient data
- **Task:** Given a drug pair $c, d$, predict side effects of that drug pair

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Problem Formulation: Graphs

Drug pair $c, d$ leads to side effect $r_2$

$\{r_2, r_3, r_4\}$

$\{r_1, r_2\}$

$r_1$ Gastrointestinal bleed side effect
$r_2$ Bradycardia side effect
$r_3$ Nausea side effect
$r_4$ Mumps side effect

Drug-protein interaction
Protein-protein interaction
Goal: Given a partially observed graph, predict labeled edges between drug nodes.

Query: Given a drug pair $c, d$, how likely does an edge $(c, r_2, d)$ exist?

Co-prescribed drugs $c$ and $d$ lead to side effect $r_2$. 
Graph Neural Network

**Input**

Graph convolutions

Regularization, e.g., dropout

Graph convolutions

**Output:** Drug pair $c, d$ leads to side effect $r_2$
Why Is It Hard?

- Modern deep learning toolbox is designed for grids or simple sequences
  - Images have 2D grid structure
  - Can define convolutions (CNN)
Why Is It Hard?

- Modern deep learning toolbox is designed for grids or **simple sequences**
  - Sequences have linear 1D structure
  - Can define sliding window, RNNs, word2vec, etc.
Why Is It Hard?

- But networks are far more complex!
  - Arbitrary size and complex topological structure (i.e., no spatial locality like grids)

Goal: Generalize convolutions beyond simple lattices

- No fixed node ordering or reference point
- Often dynamic and have multimodal features
**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

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Embedding Nodes

\[ f(\cdot) = \text{Embedding Nodes} \]

Intuition: Map nodes to \(d\)-dimensional embeddings such that similar nodes in the graph are embedded close together.

Heterogeneous graph

2-dimensional node embeddings

How to learn \(f\)?

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**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
Encoder: Embeddings

One-layer computation graph for drug $\Delta$

$r_1$ Gastrointestinal bleed effect

$r_2$ Bradycardia effect

Drug target relation
Encoder: Embeddings

A batch of computation graphs

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Decoder: Link Prediction

Query drug pair

Predictions

$p(\text{C}, r_1, \text{S})$

$p(\text{C}, r_2, \text{S})$

$p(\text{C}, r_3, \text{S})$

$p(\text{C}, r_4, \text{S})$

\[ \vdots \]

$p(\text{C}, r_n, \text{S})$

$p \rightarrow \text{probability}$
Graph Neural Network

Output: Drug pair $c, d$ leads to side effect $r_2$
Deep Learning for Network Biology

snap.stanford.edu/deepnetbio-ismb

Tutorial at ISMB 2018:
- From basics to state-of-the-art in graph neural nets
- Deep learning code bases:
  - End-to-end examples in Tensorflow/PyTorch
  - Popular code bases for graph neural nets
  - Easy to adapt and extend for your application
- Network analytics tools and biological network data
Data: Molecular, Drug & Patient

- Protein-protein interactions: Physical interactions in humans [720 k edges]
- Drug-target relationships [19 k edges]
- **Side effects of drug pairs:** National adverse event reporting system [4.6 M edges]
- Additional side information

Final graph has **966 different edge types**
Experimental Setup

Construct a heterogeneous graph of all the data

Side-effect centric evaluation:

- **Train:** Fit a model on known side effects of drug pairs
- **Test:** Given a query drug pair, predict all types of side effects

Drug pair $c, d$ leads to side effect $r_2$
Results: Side Effect Prediction

36% average in AP@50 improvement over baselines
## De novo Predictions

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug $c$</th>
<th>Drug $d$</th>
<th>Side effect $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyrimethamine</td>
<td>Aliskiren</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>2</td>
<td>Tigecycline</td>
<td>Bimatoprost</td>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole</td>
<td>Dacarbazine</td>
<td>Telangiectases</td>
</tr>
<tr>
<td>4</td>
<td>Tolcapone</td>
<td>Pyrimethamine</td>
<td>Breast disorder</td>
</tr>
<tr>
<td>5</td>
<td>Minoxidil</td>
<td>Paricalcitol</td>
<td>Cluster headache</td>
</tr>
<tr>
<td>6</td>
<td>Omeprazole</td>
<td>Amoxicillin</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>7</td>
<td>Anagrelide</td>
<td>Azelaic acid</td>
<td>Cerebral thrombosis</td>
</tr>
<tr>
<td>8</td>
<td>Atorvastatin</td>
<td>Amlodipine</td>
<td>Muscle inflammation</td>
</tr>
<tr>
<td>9</td>
<td>Aliskiren</td>
<td>Tioconazole</td>
<td>Breast inflammation</td>
</tr>
<tr>
<td>10</td>
<td>Estradiol</td>
<td>Nadolol</td>
<td>Endometriosis</td>
</tr>
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</tr>
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<td>Bicker et al. 2017</td>
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### Case Report

**Severe Rhabdomyolysis due to Presumed Drug Interactions between Atorvastatin with Amlodipine and Ticagrelor**
Decagon predicts side effects of any drug pair:

- The first method to do that
- Even for drug combinations not yet used in patients

Project website with data & code: 

snap.stanford.edu/decagon

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