# Drug-Target Interaction Prediction by Integrating Chemical, Genomic, Functional and Pharmacological Data

Fan Yang, Jinbo Xu, Jianyang Zeng

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Marten Heidemeyer

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# Outline

# Motivation

Knowledge of Drug-Target interaction is important for:

- drug development
- predicting drug side effects
- identification of new targets for known drugs

Wet lab experiments for Drug-Target interaction are expensive

# Available Resources

- binary/real-value interaction data
  - KEGG, BRENDA, SuperTarget, DrugBank, BindingDB
  - KEGG: 875 Drugs, 249 Proteins, 2596 observations
  - BindingDB: 106527 Ligands, 2133 Proteins, 193603 observations
- KEGG: chemical structure of drugs
- SIDER: drug side effect database
- KEGG: protein sequence of targets
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- GO: functional annotation of targets
- Goal: integrate genomic, chemical, functional and pharmacological data to predict missing interactions

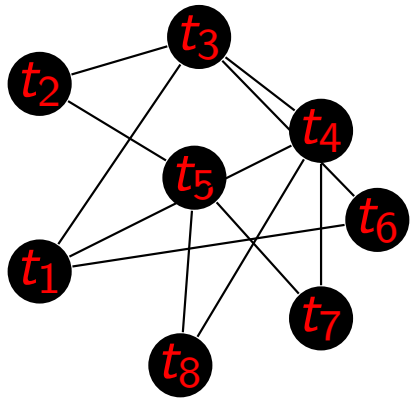
# Conditional Random Field structure

We have given:

$$\text{drugs: } d_i,\ 1 \leq i \leq n_d$$
$$\text{targets: } t_j,\ 1 \leq j \leq n_t$$

For each drug $d_i$, construct CRF over:

$$G = (V_t, E_t), \text{ where } V_t \text{ set of all targets}$$
$$E_t : \text{connect each target to its } k \text{ nearest neighbors}$$



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Do the same for each target $t_i$, where nodes are the drugs.

# formal definition of CRF

Let $Y = (y_1, y_2, \ldots, y_{n_t})$ denote the prediction of target $t_j$.
Let $X$ denote known DTIs and similarity scores.
Define the joint probability density function of $Y$ given $X$:

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Definition of CRF from book:

$$P(Y|X) = \frac{1}{Z(X)} \tilde{P}(Y, X)$$
$$\tilde{P}(Y, X) = \prod_i^m \phi_i(D_i)$$
$$Z(X) = \sum_Y \tilde{P}(Y, X)$$

# formal definition of CRF 2

For joint configuration $Y$ given $X$, define energy:

$$E(Y|X) = \sum_i a_i f(y_i|X) + \sum_{i,j} b_{ij} g(y_i, y_j \ |X)$$

where $f$ and $g$ are penalty functions:

$$f(y_i|X) = -(y_i - H_{x_i}(y_i))^2, \text{ where}$$

$H_{x_i}(y_i)$ average number of observed interactions for $t_i$

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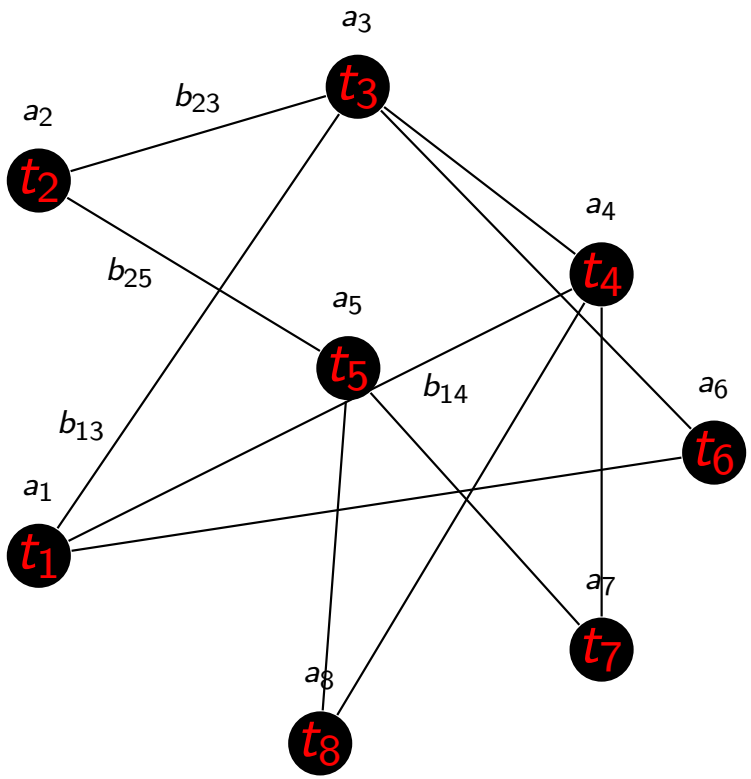
and

$$g(y_i, y_j|X) = -H_{x_i,x_j}(y_i - y_j)^2, \text{ where}$$
$$H_{x_i,x_j}(y_i - y_j) = 0, \text{ if no edge between } t_i \text{ and } t_j$$

we learn $a_i$ and $b_{ij}$.

# Example: Target-Based CRF



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$$\Rightarrow p_\theta(Y|X) = \frac{1}{Z_\theta(X)} e^{\theta h}$$

$\Rightarrow$ log-likelihood:

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$$L_\theta = \sum_{i=1}^{n_t} log(p(y_i|X)) \Big| \theta = (e^{\theta'_1}, \ldots, e^{\theta'_{n_t}})$$

$\Rightarrow$ derivative of log-likelihood:

$$\frac{\delta L_\theta}{\delta \theta'} = \theta \sum_{i=1}^{n_t} h(y_i|X) - E_\theta(h(Y|X))$$

- use *stochastic gradient ascent* to find maximizing $\theta$
- use *contrastive divergence* to deal with $E_\theta(h(Y|X))$

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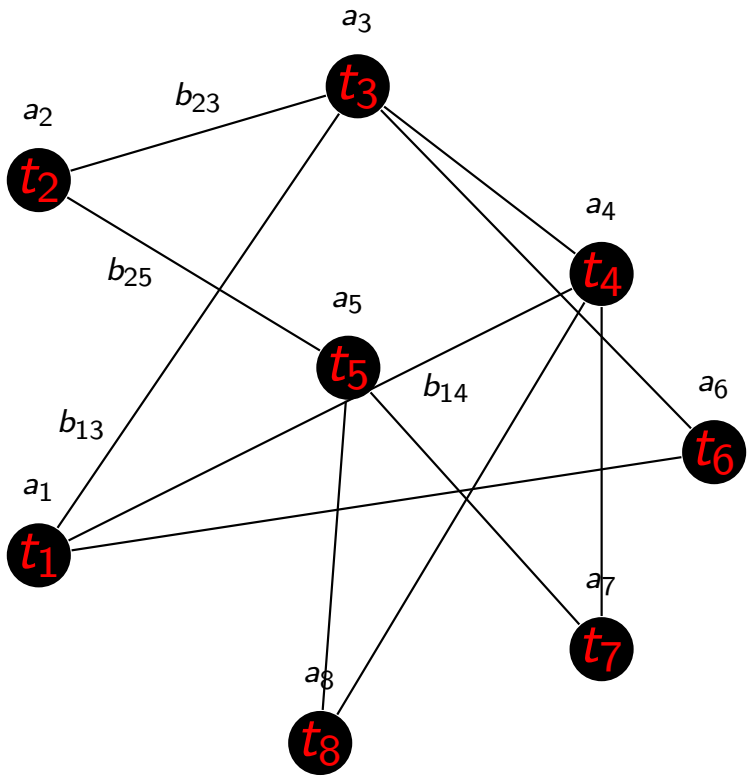

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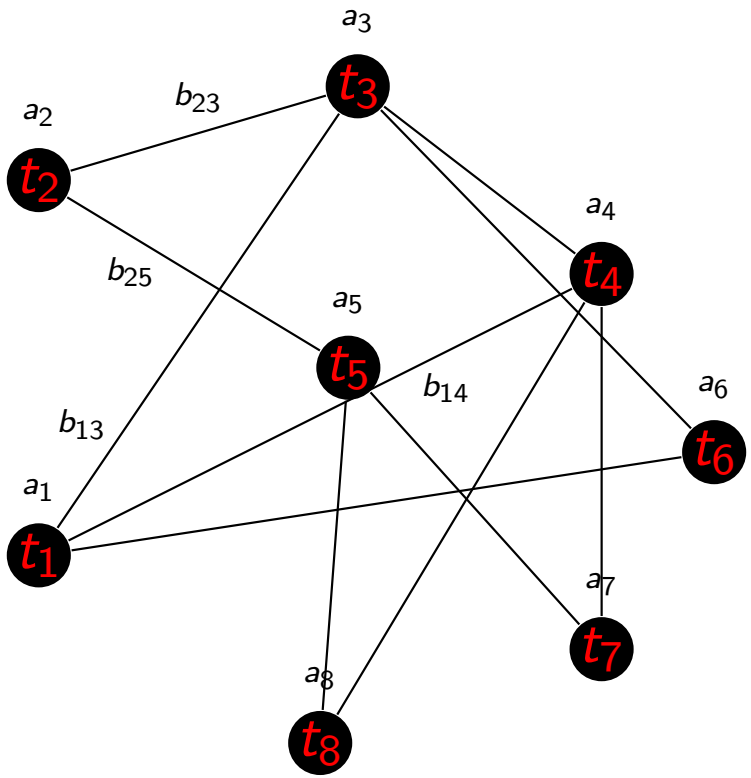


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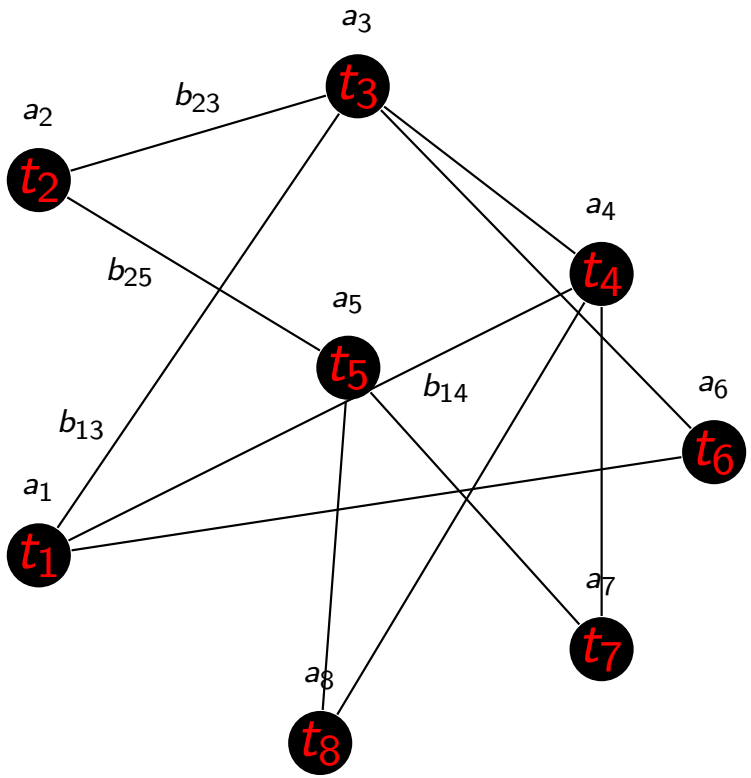


- all Target-Based CRFs share the same $a_i$ and $b_{ij}$.
- exact same procedure for construction of Drug-Based CRFs.

# Predicting New Drug-Target Interactions

prediction for target $t_k$:

- previously we learned $P(Y|X)$
- compute conditional probability distribution $p(y_k|y_{-k}, X)$
  - $y_{-k}$: all other targets except $t_k$, set this value to 1 if target is known to interact with query drug, and 0 otherwise
  - $p(y_k|y_{-k}, X) = \frac{p(Y|X)}{p(y_{-k}|X)}$
- prediction score: conditional expectation of $y_k$
- reminder:

$$E(Y|X) = \sum_i a_i f(y_i|X) + \sum_{i,j} b_{ij} g(y_i, y_j \ |X)$$

# Construction of CRF

Different approaches to define edges:

- target-based CRF: sequence similarity measure (Genomic approach)
- target-based CRF: functional similarity measure (Functional approach)
- target-based CRF: OR of Genomic and Functional measure (Integrated Genomic-Functional approach)

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- drug-based CRF: chemical similarity measure (Chemical approach)
- drug-based CRF: side effect similarity measure (Pharmacological approach)
- drug-based CRF: OR of Chemical and Pharmacological measure (Integrated Chemical-Pharmacological approach)

# Full Integration approach

For a given drug-target pair:

- let $S_d$ denote prediction score using the drug-based CRF
- let $S_t$ denote prediction score using the target-based CRF

Compute score for this query drug-target pair as

$$S = \alpha S_d + (1 - \alpha) S_t$$

# Testdata and similarity metrics

- experimentally-verified drug-target interactions from *KEGG* database.
- 875 drugs, 249 proteins, 2596 tested interactions $\Rightarrow$ 0.4%
- graph kernel approach to compute chemical similarities between drugs.
- local alignment kernel approach to compute sequence similarities between targets.
- *FunSimMat* to compute functional similarities between targets.
- pharmacological information from *SIDER* database.

# Performance Evaluation

| Approach | | Evaluation Criterion | |
|---|---|---|---|
| | | AUC | AUPR |
| Target-based CRF | GEN | 97.3 | 80.7 |
| | FUN | 97.7 | 80.9 |
| | IGF | 98.0 | 83.9 |
| Drug-based CRF | CHEM | 96.0 | 81.5 |
| | PHAR | 96.6 | 79.9 |
| | ICP | 98.1 | 85.9 |
| Full Integration Approach (FI) | | **99.2** | **94.9** |

Table 1: Prediction results using 10-fold cross validation

# Comparison with existing approaches

- *KEGG* dataset, where all drugs have records in drug side-effects databases *SIDER*, *JAPIC* and *AERS*
- 359 drugs, 226 targets, 1188 drug-target interactions $\Rightarrow$ 1.4%

| **Approach** | **AUPR** | |
|---|---|---|
| | CRF | PKR |
| AERS-freq | 85.7 | 80.6 |
| AERS-bit | 85.4 | 81.3 |
| SIDER | 87.3 | 76.8 |
| JAPIC | 91.2 | 87.7 |
| CHEM | 87.7 | 79.7 |
| INTEG-P | 90.7 | 87.4 |
| INTEG-PC | 90.4 | 88.5 |
| INTEG-ALL | **91.5** | \ |

Table 2: comparison with existing Pairwise Kernel Regression model

# Future work

- incorporate other data such as drug-drug interaction and protein-protein interaction

Thank You!