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

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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
- GO: functional annotation of Proteins

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- SIDER: drug side effect database
- GO: functional annotation of Proteins
- Goal: integrate genomic, chemical, functional and pharmacological data to predict missing interactions

Conditional Random Field structure

We have given:

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

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:

$$p(Y|X) = \frac{1}{Z(X)} e^{-E(Y|X)}$$

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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:

$$f(y_i|X) = -(y_i - H_{x_i}(y_i))^2, \text{ where}$$
$$H_{x_i}(y_i) \text{ average number of observed interactions}$$

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and

$$g(y_i, y_j|X) = -H_{x_i,x_j}(y_i - y_j)^2$$

we learn a_i and b_{ij}.

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

$\Rightarrow$ log-likelihood:

$$L_\theta = \sum_{i=1}^{n_t} log(p(y_i|X))$$

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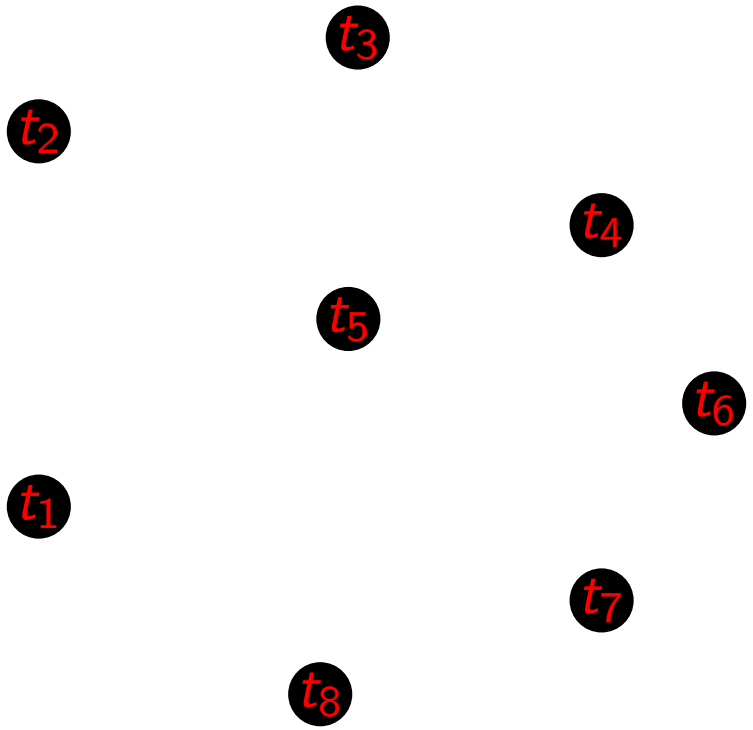
$$L_\theta = \sum_{i=1}^{n_t} log(p(y_i|X)) \Big| \theta = (e^{\theta'_1}, \ldots, e^{\theta'_{n_t}})$$

$\Rightarrow$ 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 θ
- use *contrastive divergence* to deal with $E_\theta(h(Y|X))$

Example: Target-Based CRF



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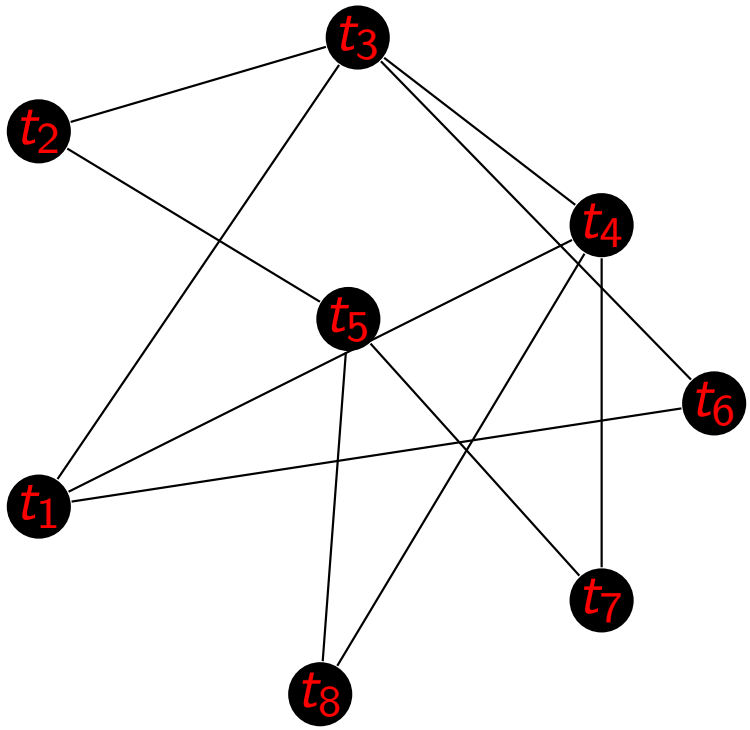

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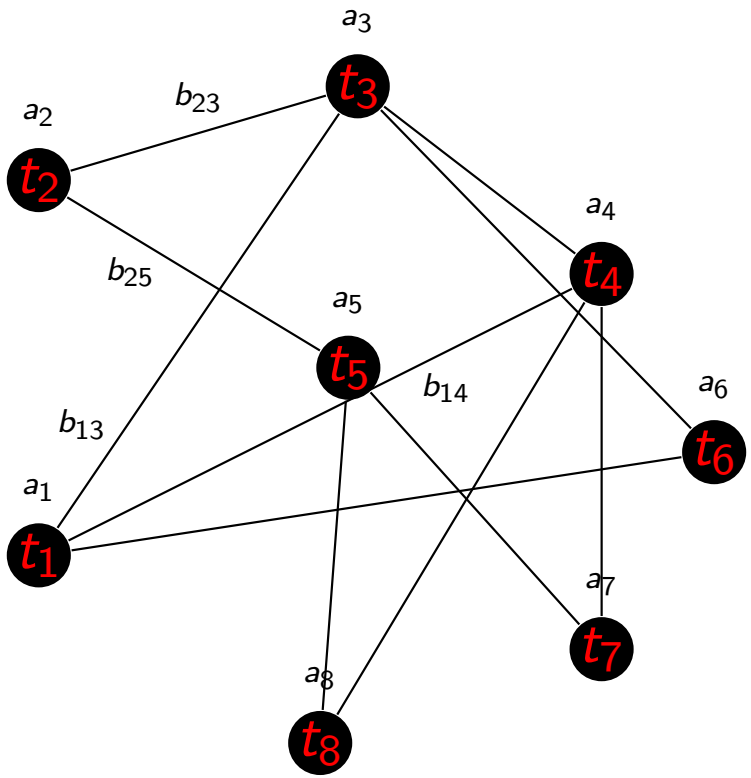

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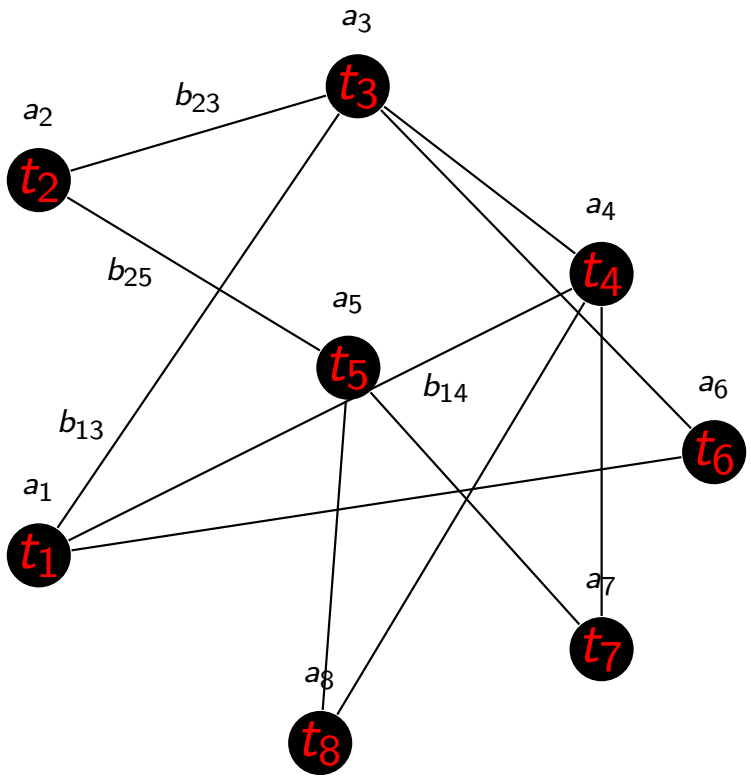

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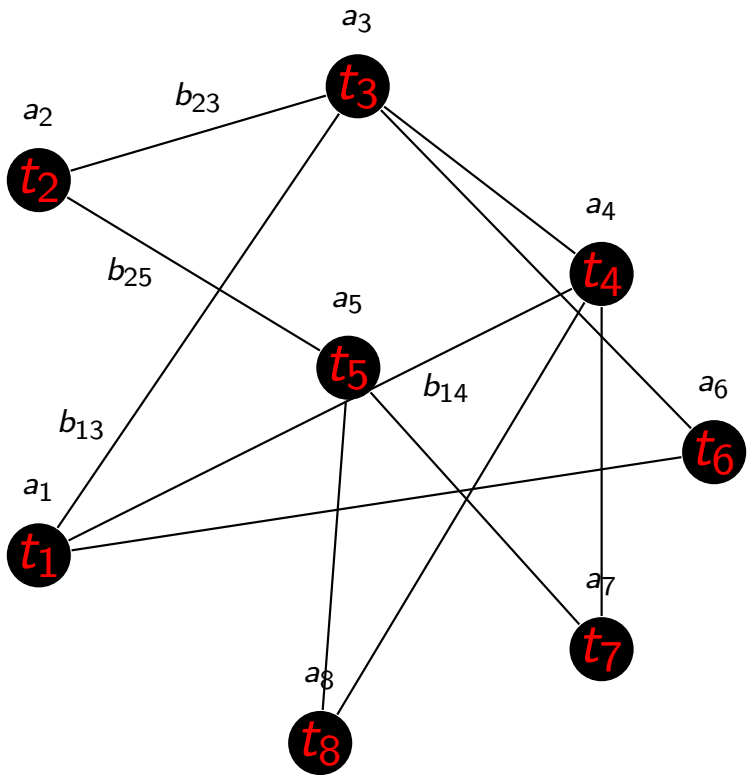

- all Target-Based CRFs share the same a_i and b_{ij}.
- exact same procedure for construction of Drug-Based CRFs.

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
  - $p(y_k|y_{-k}, X) = \frac{p(y_k|X)}{p(y_{-k}|X)}$
- prediction score: conditional expectation of y_k

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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- target-based CRF: sequence similarity measure (Genomic 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!