

# The Conjunctive Disjunctive Graph Node Kernel

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## Abstract

Gene-disease associations are inferred on the basis of similarities between the proteins encoded by genes. Biological relationships used to define similarities range from interacting proteins, proteins that participate in pathways and protein expression profiles. Though graph kernel methods have become a prominent approach for association prediction, most solutions are based on a notion of information diffusion that does not capture the specificity of different network parts. Here we propose a graph kernel method that explicitly models the configuration of each gene's context. An empirical evaluation on several biological databases shows that our proposal achieves state-of-the-art results.

*Keywords:* Graph node kernels, graph decomposition, disease gene prioritization

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## 1. Introduction

Predictive systems for gene-disease associations are often based on a notion of similarity between genes. A common strategy is to encode relations between genes as a network and use graph based techniques to make useful inferences.

5 In the last decades, a number of graph kernel methods have been proposed that directly exploit transitive properties in biological networks. The prototypical method is the Diffusion kernel (DK) [1] inspired by the heat diffusion phenomenon. The key idea is to allow a given amount of *heat* placed on nodes

to *diffuse* through the edges. The similarity between two nodes  $v_i, v_j$  is then  
10 defined as the amount of heat starting from  $v_i$  and reaching  $v_j$  within a given  
time interval. In DK the heat flow is proportional to the number of paths  
connecting two nodes, which introduces an undesired bias that penalize periph-  
eral nodes w.r.t. central ones. This problem is tackled by a modified version  
of DK called Markov exponential diffusion kernel (MED) [2] where a Markov  
15 matrix replaces the Laplacian matrix. Another kernel called Markov diffusion  
kernel (MD) [3], exploits instead the notion of *diffusion distances*, a measure of  
similarity between patterns of heat diffusion. The Regularized Laplacian ker-  
nel (RL) [4] represents instead a normalized version of the random walk with  
restart model and defines the node similarity as the number of paths connecting  
20 two nodes with different lengths. All these approaches can be applied to dense  
networks with high degree nodes. A drawback of these approaches is however  
their relatively low discriminative capacity. This is in part due to the fact that  
information is processed in an additive and independent fashion which prevents  
them from accurately modeling the configuration of each gene’s context. To  
25 address this issue here we propose to employ a *decompositional* graph kernel  
(DGK) [5] technique in which the similarity function between graphs can be  
formed by decomposing each graph into subgraphs and by devising a valid local  
kernel between the subgraphs. To exploit its higher discriminative capacity we  
first decompose the network in a collection of connected sparse graphs and then  
30 we develop a suitable kernel, that we call Conjunctive Disjunctive Node Kernel  
(CDNK).

## 2. Material and methods

We start from the type of similarity notion computed by decomposition ker-  
nels between graph instances and adapt it to express the similarity between  
35 nodes in a single network. In this work we use three key ideas: *i*) genes are  
described using their functional profile encoded as a vector of real values, *ii*)  
the network is marked to distinguish highly connected components from sparsely

connected ones, and *iii*) we transform the neighborhood of each gene in a sparse high dimensional vector that can be easily processed by standard machine learning techniques such as SVMs.

*Definitions.* We represent a problem instance as a graph  $G = (V, E)$  where  $V$  is the set of nodes and  $E$  is the set of links. We define the *distance*  $\mathcal{D}(u, v)$  between two nodes  $u$  and  $v$ , as the number of edges on the shortest path between them. The *neighborhood* of a node  $u$  with radius  $r$ ,  $N_r(u) = \{v \mid \mathcal{D}(u, v) \leq r\}$ , is the set of nodes at distance no greater than  $r$  from  $u$ . The corresponding *neighborhood subgraph*  $\mathcal{N}_r^u$  is the subgraph induced by the neighborhood (i.e. considering all the edges with endpoints in  $N_r(u)$ ). The *degree* of a node  $u$ ,  $\deg(u) = |\mathcal{N}_1^u|$ , is the cardinality of its neighborhood. The maximum node degree in the graph  $G$  is  $\deg(G)$ .

## 2.1. Gene Labeling

Gene-disease associations networks typically represent genes as nodes labeled with a gene identifier. Here we take a different approach and use the node labels to encode abstract information about the genes. In this way downstream machine learning algorithms can generalize from similar examples and allow the identification of overlooked but related genes. We experiment with two types of information: *i*) topological information and *ii*) functional information.

*Topological label.* This information is simply based on the connectivity degree of the gene. The idea is that genes that have the same number of connections are more similar than genes with a different connectivity. The node labeling function  $\ell$  assigns the degree for nodes  $u$  having degree less than or equal a user defined threshold  $T$  ( $T = 5$  in our experimental evaluation). However degree values larger than  $T$  are subsequently discretized into  $k$  levels. Formally, the labeling function is defined as:

$$\ell(u) = \begin{cases} \deg(u), & \text{if } \deg(u) \leq T \\ T + i, & \text{if } \deg(u) > T \end{cases},$$

where  $i = \lceil \frac{\deg(u) - T}{bin} \rceil$ ,  $bin = \frac{\deg(G) - T}{\lambda - T}$  and  $\lambda$  ( $\lambda > T$ ) is the maximum number

of symbols used. The value of  $\lambda$  depends on the degree distribution and can be tuned as a hyperparameter of the approach.

*Functional label.* This type of information is based on the *Gene Ontology* [6] resource. We use the ontology to construct binary vectors representing a bag-  
70 of-words encoding for each gene (i.e. if one of the 26501 GO-terms is associated with the gene). The resulting vectors are then clustered using the k-means algorithm into a user defined number of classes  $K$  (tuned as a hyperparameter of the approach), so that genes with similar description profiles receive the same class identifier as label.

75 *Real valued vector information encoding.* In addition to encoding the functional information as a discrete label we add a richer description by computing the similarity vector w.r.t. to each cluster. In this way we can fully exploit the latent description of the genes in terms of the different functional groups captured by the clustering procedure. Formally, given a vector  $v \in \mathbb{R}^{26501}$  we  
80 compute a similarity vector  $S(v) = \{s_1, s_2, \dots, s_K\}$  with entries  $s_i = \frac{1}{1+d(v, c_i)}$  where  $d(v, c_i)$  is the euclidean distance of  $v$  from the center of the  $i^{th}$  cluster  $c_i = \frac{1}{|C_i|} \sum_{x \in C_i} x$  computed as the geometric mean of the elements in the cluster  $C_i$ .

## 2.2. Network Decomposition

85 In gene-disease associations networks it is not uncommon to find nodes with high degrees. Unfortunately these cases cannot be effectively processed by a neighborhood based decomposition kernel since these are based on the notion of exact matches and the probability of finding identical neighborhoods decreases exponentially as the degree increases. This means that in a finite network it  
90 quickly becomes impossible to find any match and hence learn or generalize at all. As an alternative, we propose a procedure to “sparsify” the network that is observed by the neighborhood kernel. In reality we do not alter the cardinality of the edge set, but rather mark the edges with special attributes that will inform the kernel computation. The result is a procedure that decomposes the network  
95 in a linked collection of sparse sub-networks where each node has a reduced

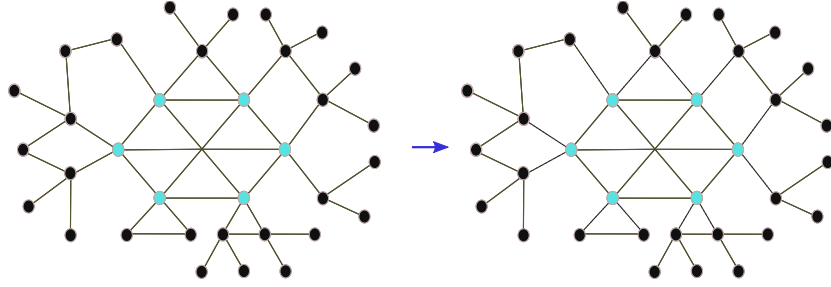


Figure 1: K-core decomposition with degree threshold  $D = 5$

connectivity when considering the edges of a specific type. However the other edges are still available to connect the various sub-networks. We distinguish two types of edges: *conjunctive* and *disjunctive* edges. Nodes linked by conjunctive edges are going to be used jointly to define the notion of context and will be visible to the neighborhood graph kernel. Nodes linked by disjunctive edges are instead used to define features based only on the pairwise co-occurrence of the genes at the endpoints and are processed by our novel kernel.

*Iterative k-core decomposition* [7]: The node set is partitioned in two groups on the basis of the degree of each node w.r.t. a threshold degree  $D$ , the first part contains all nodes with degree smaller or equal than  $D$  and the second part the remaining ones. The node partition is used to induce the “conjunctive” vs “disjunctive” notion for the edge partition: edges that have both endpoints in the same part are marked as conjunctive, otherwise they are marked as disjunctive. We apply the k-core decomposition iteratively, where at each iteration we consider only the graph induced by the conjunctive edges. We stop iterating the decomposition after a user defined number of steps. Note that this decomposition does not alter the cardinality of the edge set, it is simply a procedure to mark each edge with the attribute conjunctive or disjunctive.

*Clique decomposition* [8]: To model the notion that nodes in a clique are tightly related, we summarize the whole clique with a new “representative” node. All the cliques (completely connected subgraphs) with a number of nodes greater than a threshold size  $C$  are identified. The endpoints of all edges incident

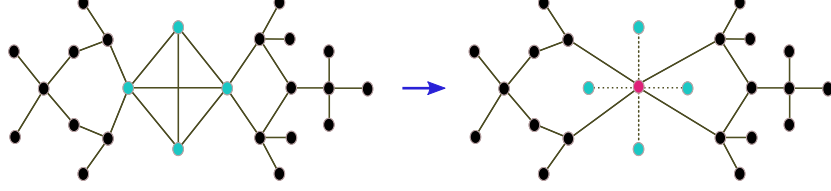


Figure 2: Pairwise neighborhood subgraphs with  $r = 1$ ,  $d = 3$  using “conjunction” and “disjunctive” edges

on the clique’s nodes are moved to the representative node. Disjunctive edges are introduced to connect each node in the clique to the representative. Finally  
120 all edges with both endpoints in the clique are removed.

In our work a network is transformed by applying first the iterative k-core decomposition and then the clique decomposition.

### 2.3. Node Graph Kernels

We start from the Neighborhood Subgraph Pairwise Distance Kernel (NSPDK)  
125 [9] and adapt it to express the similarity between nodes in a single network. The key idea in NSPDK is to decompose graphs in small fragments and count how many pairs of fragments are shared between two instances. We introduce two improvements: *i*) we partition the features according to the individual node’s neighborhood, and *ii*) we introduce a distinction between “disjunctive” and  
130 “conjunctive” edges.

#### 2.3.1. The Neighborhood Subgraph Pairwise Distance Kernel

The NSPDK is an instance of convolution kernel [5] where given a graph  $G \in \mathcal{G}$  and two rooted graphs  $A_u, B_v$ , the relation  $R_{r,d}(A_u, B_v, G)$  is true *iff*  
 $A_u \cong \mathcal{N}_r^u$  is (up to isomorphism  $\cong$ ) a neighborhood subgraph of radius  $r$  of  $G$   
135 and so is  $B_v \cong \mathcal{N}_r^v$ , with roots at distance  $\mathcal{D}(u, v) = d$ . We denote  $R^{-1}$  as the inverse relation that returns all pairs of neighborhoods of radius  $r$  at distance  $d$  in  $G$ ,  $R_{r,d}^{-1}(G) = \{A_u, B_v | R_{r,d}(A_u, B_v, G) = \text{true}\}$ . The kernel  $\kappa_{r,d}$  over  $\mathcal{G} \times \mathcal{G}$ , counts the number of such fragments in common in two input graphs:

$$\kappa_{r,d}(G, G') = \sum_{\substack{A_u, B_v \in R_{r,d}^{-1}(G) \\ A'_{u'}, B'_{v'} \in R_{r,d}^{-1}(G')}} \mathbf{1}_{A_u \cong A'_{u'}} \cdot \mathbf{1}_{B_v \cong B'_{v'}},$$

140 where  $\mathbf{1}_{A \cong B}$  is the *exact matching function* that returns 1 if  $A$  is isomorphic to  $B$  and 0 otherwise. Finally, the NSPDK is defined as  $K(G, G') = \sum_r \sum_d \kappa_{r,d}(G, G')$ , where for efficiency reasons, the values of  $r$  and  $d$  are upper bounded to a given maximal  $r^*$  and  $d^*$ , respectively.

### 2.3.2. The Conjunctive Disjunctive Node Kernel

145 We extend NSPDK and define a node kernel  $K(G_u, G_{u'})$  between two copies of the same network  $G$  where we distinguish the nodes  $u$  and  $u'$  respectively. The idea is to define the features of a node  $u$  as the subset of NSPDK features that always have the node  $u$  as one of the roots. In addition we distinguish between two types of edges, called *conjunctive* and *disjunctive* edges. When  
150 computing distances to induce neighborhood subgraphs, only conjunctive edges are considered. When choosing the pair of neighborhoods to form a single feature, we additionally consider roots  $u$  and  $v$  that are not at distance  $d$  but such that  $u$  is connected to  $w$  via a disjunctive edge and such that  $w$  is at distance  $d$  from  $v$  (Figure 3 is an illustration). In this way disjunctive edges can  
155 still allow an *information flow* even if their endpoints are only considered in a pairwise fashion and not jointly.

Formally, we define two relations: the *conjunctive relation*  $R_{r,d}^\wedge(A_u, B_v, G_u)$  identical to the NSPDK relation  $R_{r,d}(A_u, B_v, G)$ , and (ii)  $\mathcal{D}(u, v) = d$ ; the *disjunctive relation*  $R_{r,d}^\vee(A_u, B_v, G_u)$  is true iff (i)  $A_u \cong \mathcal{N}_r^u$  and  $B_v \cong \mathcal{N}_r^u$  are  
160 true, (ii)  $\exists w$  s.t.  $\mathcal{D}(w, v) = d$ , and (iii)  $(u, w)$  is a disjunctive edge. We define  $\kappa_{r,d}$  on the inverse relations  $R_{r,d}^{\wedge^{-1}}$  and  $R_{r,d}^{\vee^{-1}}$ :

$$\kappa_{r,d}(G_u, G_{u'}) = \sum_{\substack{A_u, B_v \in R_{r,d}^{\wedge^{-1}}(G_u) \\ A'_{u'}, B'_{v'} \in R_{r,d}^{\wedge^{-1}}(G_{u'})}} \mathbf{1}_{A_u \cong A'_{u'}} \cdot \mathbf{1}_{B_v \cong B'_{v'}} + \sum_{\substack{A_u, B_v \in R_{r,d}^{\vee^{-1}}(G_u) \\ A'_{u'}, B'_{v'} \in R_{r,d}^{\vee^{-1}}(G_{u'})}} \mathbf{1}_{A_u \cong A'_{u'}} \cdot \mathbf{1}_{B_v \cong B'_{v'}}.$$

The CDNK is finally defined as  $K(G_u, G_{u'}) = \sum_r \sum_d \kappa_{r,d}(G_u, G_{u'})$ , where once again for efficiency reasons, the values of  $r$  and  $d$  are upper bounded to a given  
165 maximal  $r^*$  and  $d^*$ .

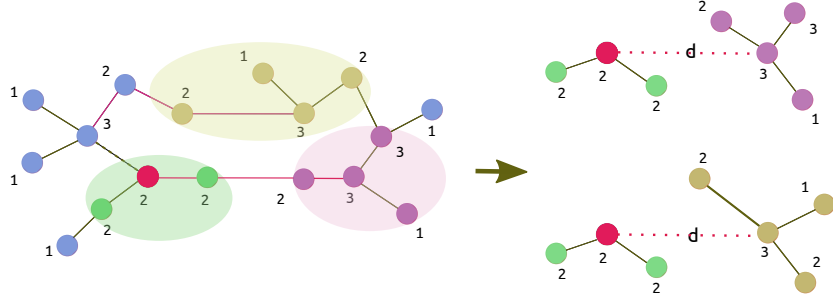


Figure 3: Pairwise neighborhood subgraphs for the “red” node with  $r = 1$  and  $d = 3$  using “conjunction” and “disjunctive” edges

#### 2.4. Real valued node information

In order to integrate the information of real vectors we proceed as follows. We compute a sparse vector representation for the neighborhood graph rooted in node  $v$  following [9]: for each neighborhood subgraph we calculate the quasi-isomorphism certificate hash code; we then combine the hashes for the pair  
170 of neighborhoods and use the resulting integer as a feature indicator. This yields a direct sparse vector representation (associated to node  $u$  in graph  $G$ )  $f : G_u \mapsto \mathbb{R}^L$  where  $L \approx 10K - 1M$ . Given the real valued vector information (associated to node  $u$  in graph  $G$ )  $g : G_u \mapsto \mathbb{R}^K$  computed as the multi-class  
175 similarity to the  $K$  clusters (c.f.r. Section 2.1), we update the computation of CDNK considering the discrete convolution of the discrete information with the real valued information:

$$K(G_u, G_{u'}) = \left\langle f(G_u) \otimes g(G_u), f(G_{u'}) \otimes g(G_{u'}) \right\rangle$$

where the discrete convolution is defined as:

$$(f \otimes g)[n] = \sum_{m=0}^{K-1} f[n-m]g[m].$$

In words, we are starting a scaled copy of the real valued vector at the position indicated by each feature computed on the basis of the discrete information.  
180 Intuitively, when both the real valued and the discrete information match, the



kernel computes a large similarity, but if there is a discrepancy in either one of the sources of information, the similarity will be penalized.

### 3. Experimental

We perform an empirical evaluation of the predictive performance of several  
185 kernel based methods on two of the databases used in [2].

**BioGPS:** A gene co-expression network is constructed from BioGPS dataset, which contains 79 tissues, measured with the Affymetrix U133A array. Edges are inserted when the pairwise Pearson correlation coefficient (PCC) between genes is larger than 0.5.

190 **Pathways:** Pathway information is retrieved from KEGG, Reactome, PharmGKB and the Pathway Interaction Database. If a couple of proteins co-participate in any pathway, the two corresponding genes are linked.

To compare the performance of graph node kernels we focus on the *gene prioritization* problem, which is the task to rank genes based on their probabilities  
195 to be related to a specific disease given a set of genes known to be associated to the disease. We follow [2] and analyze 12 diseases [10] for which it is known that at least 30 genes are involved. For each disease, we construct a positive set  $\mathcal{P}$  with all confirmed disease genes, and a negative set  $\mathcal{N}$  which contains random genes associated at least to one disease class which is not related to the class  
200 that is defining the positive set. In [2] the ratio between the dataset sizes is chosen as  $|\mathcal{N}| = \frac{1}{2}|\mathcal{P}|$ . The predictive performance of each method is evaluated via a leave-one-out cross validation: one gene is kept out in turn and the rest are used to train an SVM model. We compute a decision score  $q_i$  for the test gene  $g_i$  as the top percentage value of score  $s_i$  among all candidate gene scores.  
205 We collect all decision scores for every gene in the training set to form a global decision score list on which we compute the AUC-ROC.

**Model Selection:** The hyper parameters of the various methods are tuned using a k-fold strategy. However due to the non i.i.d. nature of the problem, we employ a stronger setup to ensure no information leakage. The dataset on

210 which we are validating the performance is never subsequently used in the predictive performance estimate. The values for diffusion parameter in DK and MED are sampled in  $\{10^{-3}, 10^{-3}, 10^{-2}, 10^{-1}\}$ , time steps in MD in  $\{1, 10, 100\}$  and RL parameter in  $\{1, 4, 7\}$ . For CDNK, the degree threshold values are sampled in  $\{10, 15, 20\}$ , clique size threshold in  $\{4, 5\}$ , maximum radius  
215 in  $\{1, 2\}$ , maximum distance in  $\{2, 3, 4\}$ , number of clusters  $K$  in  $\{5, 7\}$ . Finally, the regularization trade off parameter  $C$  for the SVM is sampled in  $\{10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10, 10^2\}$ .

#### 4. Results and discussion

Table 1 and 2 show the AUC performance of different graph node kernel  
220 models. Predictive models based on CDNK variations are ranked in top positions in all cases on BioGPS dataset and 9 out of 11 cases on Pathways when compared to diffusion based kernels. CDNK is ranking first when considering both the average AUC-ROC and the average rank with a difference, w.r.t. the best diffusion kernel, ranging from 5.4% to 10% and from 1.2% to 3.2% on  
225 BioGPS and Pathways, respectively. Regarding the variations of CDNK, the integration of real valued vector information improves the performance in most cases on using discrete labels only. The improvement in average ranges from 1.3% to 4.6%. Note that also in the case where only topological information is used to induce the discrete label (CDNK3 in the Table 1 and 2), the proposed  
230 approach improves on state-of-the-art.

#### 5. Conclusions

We have shown how decomposing a network in a set of connected sparse graphs allows us to take advantage of the discriminative power of CDNK, a novel decomposition kernel, to achieve state-of-the-art results. Moreover, we  
235 have also introduced the way to integrate “side” information in form of real valued vectors when it is available on graph to get even better performance of CDNK. In future work we will investigate how to *i*) decompose networks in a

Table 1: *Predictive performance on 11 gene-disease associations in percentage using network induced by the BioGPS. Best results in bold. We report the AUC ROC and the rank for each kernel method. CDNK1 = ontology for discrete labels, CDNK2 = ontology for both discrete and vector labels, CDNK3 = node degree for discrete labels and CDNK4 = node degree for discrete labels and ontology for vector label.*

	BioGPS							
Disease	DK	MD	MED	RL	CDNK1	CDNK2	CDNK3	CDNK4
1	51.9/8	57.4/7	59.0/6	59.2/5	65.1/4	69.5/2	69.3/3	<b>70.3/1</b>
2	81.7/5	78.5/6	75.2/7	75.0/8	88.3/2	<b>88.8/1</b>	85.1/4	86.8/3
3	64.3/7	59.6/8	71.6/3	71.8/2	65.5/5	<b>72.5/1</b>	64.7/6	66.4/4
4	65.3/7	58.2/8	67.8/6	67.8/5	71.9/4	<b>78.7/1</b>	73.9/3	77.0/2
5	64.0/8	64.1/7	66.5/5	66.2/6	75.9/4	76.2/3	76.9/2	<b>77.4/1</b>
6	74.6/5	70.2/8	71.0/7	71.2/6	79.3/2	<b>83.7/1</b>	76.7/4	79.0/3
7	73.0/5	66.7/8	75.4/3	75.6/2	68.8/6	73.9/4	67.3/7	<b>76.9/1</b>
8	74.4/8	76.8/3	76.2/5	76.4/4	74.7/7	<b>77.7/1</b>	76.0/6	76.8/2
9	71.5/2	65.6/8	67.7/5	69.9/3	66.8/7	<b>71.7/1</b>	67.1/6	68.1/4
10	54.0/6	50.3/8	56.1/5	51.1/7	77.6/4	<b>82.7/1</b>	80.5/2	80.0/3
11	58.2/7	51.3/8	59.3/6	59.3/5	71.8/4	<b>80.2/1</b>	75.3/3	77.1/2
$\overline{AUC}$	66.6	63.5	67.8	67.6	73.2	<b>77.8</b>	73.9	76.0
$\overline{Rank}$	6.18	7.18	5.27	4.82	4.45	<b>1.55</b>	4.18	2.36

Table 2: Predictive performance on 11 gene-disease associations in percentage using network induced by the Pathways. Best results in bold. We report the AUC ROC and the rank for each kernel method.  $CDNK1$  = ontology for discrete labels,  $CDNK2$  = ontology for both discrete and vector labels,  $CDNK3$  = node degree for discrete labels and  $CDNK4$  = node degree for discrete labels and ontology for vector label.

	Pathways							
Disease	DK	MD	MED	RL	CDNK1	CDNK2	CDNK3	CDNK4
1	74.7/8	76.4/7	78.7/6	78.8/5	80.2/3	<b>82.4/1</b>	80.6/2	79.4/4
2	55.1/8	64.9/7	76.6/6	76.6/5	81.1/2	80.3/3	79.8/4	<b>82.2/1</b>
3	55.0/8	62.7/7	64.1/5	65.6/4	67.1/3	63.6/6	68.5/2	<b>71.5/1</b>
4	54.3/8	65.2/7	<b>73.7/1</b>	73.7/2	66.1/5	68.1/3	67.5/4	65.6/6
5	52.9/8	55.7/7	62.7/5	62.7/6	68.3/2	<b>69.6/1</b>	66.3/4	66.8/3
6	83.4/8	92.7/7	96.5/2	<b>96.5/1</b>	93.0/6	94.1/5	94.4/4	95.5/3
7	84.5/8	88.3/7	89.4/3	89.5/2	88.5/6	88.5/5	88.7/4	<b>90.5/1</b>
8	53.7/8	65.6/7	72.0/6	72.3/5	72.5/3	72.5/2	72.3/4	<b>76.5/1</b>
9	52.5/8	64.9/5	64.2/7	64.2/6	<b>81.3/1</b>	81.0/2	79.6/3	78.8/4
10	68.8/6	65.4/8	74.4/5	74.4/4	66.9/7	76.8/2	76.1/3	<b>79.5/1</b>
11	53.7/8	69.2/7	74.6/5	74.1/6	77.0/2	<b>78.7/1</b>	75.4/4	77.0/3
$\overline{AUC}$	62.6	70.1	75.2	75.3	76.5	77.8	77.2	<b>78.5</b>
$\overline{Rank}$	7.82	6.91	4.64	4.18	3.64	2.82	3.45	<b>2.55</b>

data driven way and *ii*) extend the CDNK approach to gene-disease association problems exploiting multiple heterogeneous information sources in a joint way.

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