

The Conjunctive Disjunctive Node Kernel

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Abstract. Gene-disease associations are inferred on the basis of similarities between genes. Biological relationships that are exploited to define similarities range from interacting proteins, proteins that participate in pathways and gene 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 show that our proposal is competitive w.r.t. state-of-the-art kernel approaches.

1 Introduction and Related Work

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. 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) [2] 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 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 vertices, which introduces an undesired bias that penalize peripheral nodes w.r.t. central ones. This problem is tackled by a modified version of DK called Markov exponential diffusion kernel (MED) [3] where a Markov matrix replaces the Laplacian matrix. Another kernel called Markov diffusion kernel (MD) [4], exploits instead the notion of *diffusion distances*, a measure of similarity between patterns of heat diffusion. The Regularized Laplacian kernel (RL) [5] represents instead a normalized version of the random walk with restart model and defines the node similarity as the number of paths connecting 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 address this issue here we propose to employ a *decompositional* graph kernel (DGK) [1] technique. To exploit its higher discriminative capacity we first decompose the network in a

collection of connected sparse graphs and then we develop a suitable kernel, that we call Conjunctive Disjunctive Node Kernel (CDNK).

2 Method

We start from the type of similarity notion computed by decomposition kernels between graph instances and adapt it to express the similarity between nodes in a single network. In this work we use three key ideas: 1) genes are labeled using their functional profile, 2) we transform the network to distinguish highly connected components from sparsely connected ones, and 3) 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.

2.1 Gene Labeling

Gene-disease associations networks typically represent genes as nodes labeled with a gene identifier. Here we take a different approach: since we want to build a predictive system based on the configuration of each gene’s context, we use as labels a discretized functional annotation based on the *gene ontology* [10]. More precisely, we use the gene ontology to construct binary vectors representing the bag-of-words encoding for each gene (i.e. if a GO-term is associated with the gene). The resulting representations are then clustered so that genes with similar description profiles receive the same class identifier as label.

2.2 Network Decomposition

In gene-disease associations networks it is not uncommon to find nodes with high degrees. Unfortunately these cases cannot be effectively processed by decomposition kernels based on exact neighborhood matches¹. Instead we propose to decompose the network in a linked collection of sparse sub-networks where each node has a reduced connectivity. More precisely 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. Nodes linked by disjunctive edges are instead used to define features based only on the pairwise co-occurrence of the genes at the endpoints. The aim of the following decompositions is to link sparse sub-networks (which comprise only conjunctive edges) via disjunctive edges. The final decomposition is obtained by first applying the k-core decomposition and then applying the clique decomposition.

Definitions. A graph $G = (V, E)$ is a structure that consists of a node set $V(G)$ and an edge set $E(G)$. The *distance* between two vertices u and v , notated as $\mathcal{D}(u, v)$, is the length of the shortest path between them. The *neighborhood* with radius r of a vertex v is the set of vertices at a distance no greater than r from v and denoted by $N_r(v)$. The *neighborhood subgraph* with radius r of vertex v , denoted by \mathcal{N}_r^v , is the subgraph formed by the nodes in the neighborhood with radius r of v and the relative edges with endpoints in $N_r(v)$.

¹It is improbable to find multiple cases of nodes with exactly the same, say 73 neighbors.

K-core decomposition [8]: The node set is partitioned in two groups on the basis of the degree of each vertex w.r.t. a threshold degree D . The vertex partition is used to induce the conjunctive vs disjunctive edge partition: edges that have endpoints in the same part are marked as conjunctive, while edges with endpoints in different parts are marked as disjunctive. We apply the K-core decomposition iteratively considering only the graph induced by the conjunctive edges until no node has a degree greater than D^2 .

Clique decomposition [9]: All the cliques (completely connected subgraphs) with a number of nodes greater than a threshold size C are identified. For each clique a new 'representative' node is added to the network. The endpoints of all edges incident on the clique's nodes are transferred to the representative node. Disjunctive edges are introduced to connect each node in the clique to the representative. Finally all edges with both endpoints in the clique are removed.

2.3 Node Graph Kernels

We start from the Neighborhood Subgraph Pairwise Distance Kernel (NSPDK) [6] 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: 1) we partition the features according to each node's neighborhood, and 2) the feature creation distinguishes between disjunctive and conjunctive edges.

2.3.1 The Neighborhood Subgraph Pairwise Distance Kernel

The NSPDK is an instance of convolution kernel [1] where the parts are pairs of neighborhood subgraphs whose roots are near. Formally, given a graph $G \in \mathcal{G}$ (\mathcal{G} is the graph domain) and two rooted graphs A_u, B_v , the relation $R_{r,d}(A_u, B_v, G)$ is defined to be true iff A_u and B_v are in $\{\mathcal{N}_r^v : v \in V(G)\}$, where A_u (B_v) needs to be isomorphic with some \mathcal{N}_r and $\mathcal{D}(u, v) = d$. We denote R^{-1} as the inverse relation that returns subgraphs of G , $R_{r,d}^{-1}(G) = \{A_u, B_v | R_{r,d}(A_u, B_v, G)\}$. The kernel $\kappa_{r,d}$ over $\mathcal{G} \times \mathcal{G}$ takes into account the number of identical neighboring graph pairs with radius r at distance d between two graph and is formulated as:

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

where $\mathbf{1}_{A \cong B}$ is the *exact matching function* that returns 1 if A is isomorphic to B and 0 otherwise. In order to solve the graph isomorphism problem, an efficient approximate algorithm is proposed in [6]. 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 r^* and d^* , respectively.

²The degree is defined only considering incident conjunctive edges

2.3.2 The Conjunctive Disjunctive Node Kernel

We extend NSPDK and define a kernel $K(G_u, G_v)$ between two copies of the same network G where we distinguish the nodes u and v respectively. The idea is to define the features of a node u as the NSPDK features limited to have as one of the roots always the vertex u . In addition we distinguish between two types of edges, termed *conjunctive* and *disjunctive* edges. We consider only conjunctive edges when computing distances. When

In our kernel, we consider only conjunctive edges when computing the distance between nodes and extracting neighborhood subgraphs. We define two relations: the *conjunctive relation* $R_{r,d}^\wedge(A_u, B_v, G)$ is true iff (i) A_u and B_v are in $\{\mathcal{N}_r^v : v \in V(G)\}$, where A_u (B_v) needs to be isomorphic with some \mathcal{N}_r , (ii) $\mathcal{D}(u, v) = d$; and the *disjunctive relation* $R_{r,d}^\vee(A_u, B_v, G)$ is true iff (i) A_u and B_v are in $\{\mathcal{N}_r^v : v \in V(G)\}$, where A_u (B_v) needs to be isomorphic with some \mathcal{N}_r , (ii) there exists a vertex w such that $\mathcal{D}(u, w) = d$, and (iii) (w, v) is a disjunctive edge. We define $\kappa_{r,d}$ on the relations $R_{r,d}^\wedge$ and $R_{r,d}^\vee$ as

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

$\kappa_{r,d}$ counts the number of identical pairs of neighboring graphs of radius r at a distance d between two vertices. The CDNK is finally defined as

$$K(G_u, G_v) = \sum_r \sum_d \kappa_{r,d}(G_u, G_v).$$

where once again for efficiency reasons, the values of r and d are upper bounded to a given r^* and d^* .

3 Evaluation

We perform an empirical evaluation of the predictive performance of several kernel based methods on two of the databases used in [3].

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.

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 evaluate the performance of graph node kernels we analyze the *gene prioritization problem*. Given a set of genes known to be associated to a given disease, gene prioritization is the task to rank the candidate genes based on their probabilities to be related to that disease. Similar to the evaluation process used in [3], we choose 12 diseases with at least 30 confirmed genes. 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 that is defining the positive set. In [3] 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.

Starting from the output scores, we compute a decision score q_i for the test gene g_i as the top percentage value of score s_i among all scores. $q_i = \frac{|\{j|s_i \geq s_j\}|}{N}$, $i = 1, 2, \dots, N$, where s_i, s_j are scores, N is the length of gene list. We collect all decision scores for every gene in the training set of a disease to form a global decision score list. The performance of the algorithm is finally measured as the AUC ROC on that list.

3.1 Model Selection

The hyper parameters of the various methods are set using a k-fold on a dataset set that is then never used in the predictive performance estimate. We try the values for diffusion parameter in DK and MED in $\{10^{-3}, 10^{-2}, 10^{-1}\}$, for time steps in MD in $\{1, 10, 100\}$ and for RL parameter in $\{1, 4, 7\}$. For CDNK, we try for the degree threshold values in $\{10, 15, 20\}$, clique size threshold in $\{4, 5\}$, maximum radius in $\{1, 2\}$, maximum distance in $\{2, 3, 4\}$. Finally, the C of SVM is searched in $\{10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10, 10^2\}$.

4 Results and Discussion

Table 1 shows the AUC performance of the models trained by using different graph node kernels on 11 gene-disease association problems using the BioGPS and Pathways datasets to materialize the gene relation network. In the table, the best result on each disease is marked in bold. We note that CDNK ranks first in 7 out of 11 cases using both networks. CDNK is the top performant kernel also when considering the average AUC ROC and the average rank with 73.3/2.0, 76.5/1.8, with a difference w.r.t. the second best of 5.5% and 1% on BioGPS and Pathways, respectively. MED and RL show similar and moderate results with small gap between them. DK and MD exhibit modest performance on average and are ranked last in many cases: 7 times out of 11 for MD in BioGPS and 10 out of 11 for DK in Pathways. Finally note that although CDNK has state of the art performance, there are cases that would lead to a significant decrease in the quality of the results, namely when networks have high *average* node degree as this would lead to very sparse and fragmented decompositions.

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. In future work we will investigate how to extend the CDNK approach to network problems when multiple heterogeneous information sources are available.

	BioGPS					Pathways				
Disease	K1	K2	K3	K4	K5	K1	K2	K3	K4	K5
1	52/5	57/4	59/3	59/2	65/1	75/5	76/4	79/3	79/2	80/1
2	82/2	79/3	75/4	75/5	88/1	55/5	65/4	77/3	77/2	81/1
3	64/4	60/5	72/2	72/1	66/3	55/5	63/4	64/3	66/2	67/1
4	65/4	58/5	68/3	68/2	72/1	54/5	65/4	74/1	74/2	66/3
5	64/5	64/4	67/2	66/3	76/1	53/5	56/4	63/2	63/3	68/1
6	75/2	70/5	71/4	71/3	79/1	83/5	93/4	97/2	97/1	93/3
7	73/3	67/5	75/2	76/1	69/4	85/5	88/4	89/2	90/1	89/3
8	74/5	77/1	76/3	76/2	75/4	54/5	66/4	72/3	72/2	73/1
9	72/1	66/5	68/3	70/2	67/4	53/5	65/2	64/4	64/3	81/1
10	54/3	50/5	56/2	51/4	78/1	69/3	65/5	74/2	74/1	67/4
11	58/4	51/5	59/3	59/2	72/1	54/5	69/4	75/2	74/3	77/1
\overline{AUC}	66.6	63.5	67.8	67.5	73.3	62.7	70.1	75.3	75.5	76.5
\overline{Rank}	3.5	4.3	2.8	2.5	2.0	4.8	3.9	2.5	2.0	1.8

Table 1: *Predictive performance on 11 gene-disease associations using networks induced by the BioGPS and the Pathway database. We report the AUC ROC and the rank for each kernel method: K1 = DK, K2 = MD, K3 = MED, K4 = RL, K5 = CDNK.*

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