

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 is competitive w.r.t. state-of-the-art kernel approaches.

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

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 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 peripheral 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 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 kernel (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 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) [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 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 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.

40 2.1. Gene Labeling

Gene-disease associations networks typically represent genes as nodes labeled with a gene identifier. Here we take a different approach: we encode the network as a labeled undirected graph where the node labels are built as a discretized functional annotation based on the *gene ontology* [6]. More precisely, we use the
 45 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. All subsequent graph processing (including graphs isomorphism detection) takes this discretized labeling into
 50 account.

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 matches because of the high
 55 number of neighborhood subgraphs. As an alternative, 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
 60 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.

Definitions. A graph $G = (V, E)$ is a structure that consists of a node set
 65 $V(G)$ and an edge set $E(G)$. The *distance* between two nodes 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 node v is the set of nodes at a distance no greater than r from v and denoted by $N_r(v)$. The *neighborhood subgraph* with radius r of node v , denoted by \mathcal{N}_r^v , is the subgraph formed by the nodes in the neighborhood with
70 radius r of v and the relative edges with endpoints in $N_r(v)$.

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 node 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
75 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 ¹ greater than D .

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.
80 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 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.

85 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) [9] and adapt it to express the similarity between nodes in a single network. The
90 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 the individual node's neighborhood, and 2) feature construction distinguishes between disjunctive and

¹The degree is defined by only considering incident conjunctive edges.

conjunctive edges.

95 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 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
 100 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:

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

where $\mathbf{1}_{A \cong B}$ is the *exact matching function* that returns 1 if A is isomorphic to B
 105 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

We extend NSPDK and define a node kernel $K(G_u, G_{u'})$ between two copies
 110 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 computing distances to induce neighborhood subgraphs, only conjunctive edges
 115 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 . In this way disjunctive edges can still allow an *information flow* even if their endpoints are only considered in a pairwise fashion and not
 120 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 true, (ii) $\exists w$ s.t. $\mathcal{D}(w, v) = d$, and (iii) (u, w) is a disjunctive edge. We define
125 $\kappa_{r,d}$ 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 $K(G_u, G_v) = \sum_r \sum_d \kappa_{r,d}(G_u, G_v)$, where once again for efficiency reasons, the values of r and d are upper bounded to a given maximal r^* and d^* .

130 3. Experimental

We perform an empirical evaluation of the predictive performance of several 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
135 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.

140 To evaluate the performance of graph node kernels we analyze the *gene prioritization*, i.e. 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 [2], we choose 12 diseases [10] with at least 30 confirmed genes. For each
145 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 [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:

150 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. 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.

155 **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 $\{10^{-3}, 10^{-2}, 10^{-1}\}$, time steps in MD in $\{1, 10, 100\}$ and RL parameter in $\{1, 4, 7\}$. For CDNK, we try for the degree threshold values in $\{10, 15, 20\}$, 160 clique size threshold in $\{4, 5\}$, maximum radius in $\{1, 2\}$, maximum distance in $\{2, 3, 4\}$. Finally, the regularization trade off parameter C for the SVM is searched 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 the models trained by using 165 different graph node kernels on 11 gene-disease association problems using the BioGPS and Pathways datasets to materialize the gene relation network. 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 170 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. Low performance cases include networks that have high *average* node degree which 175 is likely to yield very sparse and fragmented network decompositions.

	BioGPS							
Disease	DK	MD	MED	RL	CDNK1	CDNK2	CDNK3	CDNK4
1	51.9/8	57.4/7	59.0/6	59.2/5	65.1/3	65.8/2	67.1/1	64.9/4
2	81.7/5	78.5/6	75.2/7	75.0/8	88.3/1	86.2/3	86.3/2	84.6/4
3	64.3/6	59.6/ 8	71.6/2	71.8/1	65.5/4	66.8/3	64.7/5	61.6/7
4	65.3/7	58.2/8	67.8/5	67.8/6	71.9/3	74.1/1	70.7/4	72.2/2
5	64.0/8	64.1/7	66.5/5	66.2/6	75.9/2	75.7/3	75.5/4	76.1/1
6	74.6/5	70.2/8	71.0/7	71.2/6	79.3/2	83.0/1	75.0/4	77.6/3
7	73.0/4	66.7/7	75.4/2	75.6/1	68.8/6	72.7/5	65.9/8	74.0/3
8	74.4/8	76.8/1	76.2/3	76.4/2	74.7/7	75.5/5	75.4/6	76.0/4
9	71.5/1	65.6/7	67.7/3	69.9/2	66.8/4	65.7/5	63.5/8	65.6/6
10	54.0/6	50.3/8	56.1/5	51.1/7	77.6/4	79.6/1	78.6/3	78.8/2
11	58.2/7	51.3/8	59.3/6	59.3/5	71.8/4	77.0/1	72.1/3	73.4/2
\overline{AUC}	66.6	63.5	67.8	67.6	73.2	74.7	72.2	73.2
\overline{Rank}	5.91	6.82	4.64	4.45	3.64	2.73	4.36	3.45

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

	Pathways							
Disease	DK	MD	MED	RL	CDNK1	CDNK2	CDNK3	CDNK4
1	74.7/8	76.4/7	78.7/5	78.8/4	80.2/2	81.2/1	78.2/6	78.8/3
2	55.1/8	64.9/7	76.6/5	76.6/4	81.1/1	76.4/6	78.2/3	79.8/2
3	55.0/8	62.7/6	64.1/4	65.6/3	67.1/1	63.6/5	62.5/7	67.0/2
4	54.3/8	65.2/7	73.7/1	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	69.1/1	64.2/4	65.0/3
6	83.4/8	92.7/7	96.5/2	96.5/1	93.0/6	94.1/4	93.9/5	94.4/3
7	84.5/8	88.3/5	89.4/2	89.5/1	88.5/7	87.5/6	88.7/3	88.3/4
8	53.7/8	65.6/7	72.0/5	72.3/2	72.5/4	72.5/3	72.3/1	71.9/6
9	52.5/8	64.9/5	64.2/6	64.2/7	81.3/1	81.0/2	77.4/4	77.7/3
10	68.8/6	65.4/8	74.4/4	74.4/3	66.9/7	76.8/1	69.8/5	75.5/2
11	53.7/8	69.2/7	74.6/5	74.1/6	77.0/2	78.7/1	75.4/3	75.1/4
\overline{AUC}	62.6	70.1	75.2	75.3	76.5	77.2	75.3	76.3
\overline{Rank}	7.82	6.64	4.00	3.55	3.45	3.00	4.09	3.45

Table 2: *Predictive performance on 11 gene-disease associations using network induced by the Pathways. Best results are in bold. We report the AUC ROC and the rank for each kernel method in which CDNK1 uses ontology for discrete labels, CDNK2 uses ontology for both discrete and continuous labels, CDNK3 uses node degree for discrete labels and CDNK4 uses degree and ontology for discrete and continuous labels, respectively.*

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 1) decompose networks in a data driven way and 2) extend the CDNK approach to gene-disease association problems exploiting multiple heterogeneous information sources.

References

- [1] R. I. Kondor, J. Lafferty, Diffusion kernels on graphs and other discrete input spaces, in: ICML, Vol. 2, 2002, pp. 315–322.
- [2] B. Chen, M. Li, J. Wang, F.-X. Wu, Disease gene identification by using graph kernels and markov random fields, *Science China. Life Sciences* 57 (11) (2014) 1054.
- [3] F. Fouss, L. Yen, A. Pirotte, M. Saerens, An experimental investigation of graph kernels on a collaborative recommendation task, in: *Data Mining, 2006. ICDM'06. Sixth International Conference on*, IEEE, 2006, pp. 863–868.
- [4] P. Chebotarev, E. Shamis, The matrix-forest theorem and measuring relations in small social groups, *arXiv preprint math/0602070*.
- [5] D. Haussler, Convolution kernels on discrete structures, Tech. rep., Technical report, Department of Computer Science, University of California at Santa Cruz (1999).
- [6] G. O. Consortium, et al., The gene ontology (go) database and informatics resource, *Nucleic acids research* 32 (suppl 1) (2004) D258–D261.
- [7] J. I. Alvarez-Hamelin, L. Dall'Asta, A. Barrat, A. Vespignani, k-core decomposition: A tool for the visualization of large scale networks, *arXiv preprint cs/0504107*.

- [8] R. E. Tarjan, Decomposition by clique separators, *Discrete mathematics* 55 (2) (1985) 221–232.
- 205 [9] F. Costa, K. De Grave, Fast neighborhood subgraph pairwise distance kernel, in: *Proceedings of the 26th International Conference on Machine Learning*, Omnipress, 2010, pp. 255–262.
- [10] K.-I. Goh, M. E. Cusick, D. Valle, B. Childs, M. Vidal, A.-L. Barabási, The human disease network, *Proceedings of the National Academy of Sciences* 104 (21) (2007) 8685–8690.
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