Classification in biological networks with hypergraphlet kernels

Jose Lugo-Martinez 1, Daniel Zeiberg 2, Thomas Gaudelet 3, Noël Malod-Dognin 4, Nataša Pržulj 4,5 and Predrag Radivojac 2,*

1Computational Biology Department, Carnegie Mellon University, Pittsburgh, Pennsylvania, U.S.A.; 2Khoury College of Computer Sciences, Northeastern University, Boston, Massachusetts, U.S.A.; 3Department of Computer Science, University College London, London WC1E 6BT, U.K.; 4Department of Life Sciences, Barcelona Supercomputing Center (BSC), Barcelona, Spain; 5ICREA, Pg. Lluís Companys 23, Barcelona, Spain

*To whom correspondence should be addressed.

Abstract

Biological and cellular systems are often modeled as graphs in which vertices represent objects of interest (genes, proteins, drugs) and edges represent relational ties between these objects (binds-to, interacts-with, regulates). This approach has been highly successful owing to the theory, methodology and software that support analysis and learning on graphs. Graphs, however, suffer from information loss when modeling physical systems due to their inability to accurately represent multi-object relationships. Hypergraphs, a generalization of graphs, provide a framework to mitigate information loss and unify disparate graph-based methodologies. We present a hypergraph-based approach for modeling biological systems and formulate vertex classification, edge classification and link prediction problems on (hyper)graphs as instances of vertex classification on (extended, dual) hypergraphs. We then introduce a novel kernel method on vertex- and edge-labeled (colored) hypergraphs for analysis and learning. The method is based on exact and inexact (via hypergraph edit distances) enumeration of hypergraphlets; i.e., small hypergraphs rooted at a vertex of interest. We empirically evaluate this method on fifteen biological networks and show its potential use in a positive-unlabeled setting to estimate the interactome sizes in various species.

Availability: https://github.com/jlugomar/hypergraphlet-kernels/

Contact: predrag@northeastern.edu

Supplementary Information: Supplementary data are available at Bioinformatics online.

1 Introduction

Graphs provide a mathematical structure for describing relationships between objects in a system. Owing to their intuitive representation, well-understood theoretical properties, the wealth of methodology and available code base, graphs have also become a major framework for modeling biological systems. Protein-protein interaction networks, protein 3D structure graphs, drug-target interaction networks, metabolic networks and gene regulatory networks are some of the major representations of biological systems. Unfortunately, molecular and cellular systems are only partially observable and may contain significant amount of noise due to their inherent stochastic nature as well as the limitations of experimental techniques. This highlights the need for the development and application of computational approaches for predictive modeling (e.g., inferring novel interactions) and identifying interesting patterns in such data.

Learning on graphs can be generally seen as supervised or unsupervised. Under a supervised setting, typical tasks involve graph classification, i.e., the assignment of class labels to entire graphs, vertex or edge classification, i.e., the assignment of class labels to vertices or edges, or link prediction, i.e., the prediction of the existence of edges in graphs. Alternatively, frequent subgraph mining, motif finding, and clustering are traditional unsupervised approaches. Regardless of the category, the development of techniques that capture network structure, measure graph similarity and incorporate domain-specific knowledge in a principled manner lie at the core of all these problems.
The focus of this study is on classification problems across various biological networks. A straightforward approach to this problem is the use of topological and other descriptors (e.g., vertex degree, clustering coefficient, betweenness centrality) that summarize graphs and graph neighborhoods. These descriptors, much like embedding techniques (Grover and Leskovec, 2016; Goyal and Ferrara, 2018), readily form vector-space representations, after which standard machine learning algorithms can be applied to learn target functions (Xu and Li, 2006). Another strategy involves the use of kernel functions on graphs (Vishwanathan et al., 2010). Kernels are symmetric positive semi-definite mappings of pairs of objects from an input space $X$ to $\mathbb{R}$, that lead to efficient learning. Finally, classification on graphs can be seen as inference over Markov networks (Deng et al., 2003) and can be approached using related label-propagation (Zhu and Ghahramani, 2002) or flow-based (Nabieva et al., 2005) methods. These inference strategies are often well adjusted to learning smooth functions over neighboring nodes.

Despite the success and wide adoption of these methods in computational biology, it is well-understood that graph representations suffer from information loss since every edge can only encode pairwise relationships (Klamt et al., 2009). A protein complex, for instance, cannot be distinguished from a set of proteins that interact only pairwise. Such disambiguation, however, is important in order to understand the biological activity of these molecules (Gaudel et al., 2018). Hypergraphs, a generalization of graphs, naturally capture these higher-order relationships (Berge, 1973). As we show later, they also provide a representation that can be used to unify several conventional classification problems on (hyper)graphs as an instance of vertex classification on hypergraphs.

In this paper, we present and evaluate a kernel-based framework for the problems of vertex classification, edge classification and link prediction in graphs and hypergraphs. We first use the concepts of hypergraph duality to demonstrate that all such classification problems can be unified through the use of hypergraphs. We then describe the development of edit-distance hypergraphlet kernels; i.e., similarity functions between local vertex neighborhoods based on flexibly enumerating small labeled hypergraphs rooted at vertices of interest. These similarity functions were subsequently incorporated into a semi-supervised methodology for predicting class labels on vertices. Finally, we use fifteen biological networks to provide evidence that the proposed approaches present an attractive option in this setting.

### 2 Background

#### 2.1 Graphs and hypergraphs

**Graphs.** A graph $G$ is a pair $(V, E)$, where $V$ is a set of vertices (nodes) and $E \subseteq V \times V$ is a set of edges. In a vertex-labeled graph, a labeling function $f$ is defined as $f : V \rightarrow \Sigma$, where $\Sigma$ is a finite alphabet. Similarly, in an edge-labeled graph, another labeling function $g$ is given as $g : E \rightarrow \Xi$, where $\Xi$ is also a finite set. We will focus on undirected graphs ($E$ is symmetric), without self-loops and weights associated with edges. Generalization of our approach to directed and weighted graphs is relatively straightforward.

A rooted graph $G$ is a graph together with one distinguished vertex called the root. We denote such graphs as $G = (V, e)$, where $e \in V$ is the root. A walk $w$ of length $k$ in a graph $G$ is a sequence of nodes $v_0, v_1, \ldots, v_k$ such that $(v_i, v_{i+1}) \in E$, for $0 \leq i < k$. A connected graph is a graph in which there exists a walk between any two nodes.

**Hypergraphs.** A hypergraph $G$ is a pair $(V, E)$, where $V$ again is the vertex set and $E$ is a family of non-empty subsets of $V$, referred to as hyperedges. A hyperedge $e$ is said to be incident with a vertex $v$ if $v \in e$. Two vertices are called adjacent if there is an edge that contains both vertices and two hyperedges are said to be adjacent if their intersection is non-empty. The neighbors of a vertex $v$ in a hypergraph are the vertices adjacent to $v$. Finally, the degree of $v$ in a hypergraph is given by $d(v) = |\{e \in E | v \in e\}|$, whereas the degree of a hyperedge $e$ is defined as $\delta(e) = |e|$. As before, one can define a vertex-labeled, edge-labeled and rooted hypergraphs. When the multiplicity of each hyperedge is one, the hypergraph is said to be simple. A walk $w$ of length $k$ in a hypergraph is a sequence of vertices and hyperedges $v_0, e_0, v_1, \ldots, e_{k-1}, v_k$ such that $(v_i, v_{i+1}) \in e_i$ for each $0 \leq i < k$ and $e_i \in E$. A connected hypergraph is a hypergraph where there exists a walk between any two nodes.

Since we are interested in counting small predefined hypergraphs in large hypergraphs, we define two distinct ways in which these substructures can be counted, as section hypergraphs or sub-hypergraphs. Given a hypergraph $G = (V, E)$, a section hypergraph of $G$ is a hypergraph $G' = (V', E')$ where $V' \subseteq V$ and $E' = \{e \in E | e \subseteq V'\}$. A super-hypergraph of a hypergraph $G$ is a hypergraph $G'' = (V'', E'')$ where $V'' \subseteq V$ and $E'' = \{e \cap V'' | e \in E \land e \cap V'' \neq \emptyset\}$. In other words, when nodes $V \setminus V'$ are removed from $V$, section hypergraphs retain only those edges that were subsets of the remaining nodes $V'$. In sub-hypergraphs, on the other hand, the edges that originally contained nodes from both removed $(V \setminus V')$ and unremoved $(V')$ nodes are retained as subsets of the original edges that now include nodes only from $V'$. Edges from the original graph that only included nodes from $V'$ can now have increased multiplicity.

**Isomorphism.** Consider two graphs, $G = (V, E)$ and $H = (W, F)$. We say that $G$ and $H$ are isomorphic, denoted as $G \cong H$, if there exists a bijection $f : V \rightarrow W$ such that $(u, v) \in E$ if and only if $(f(u), f(v)) \in F$ for all $u, v \in V$. If $G$ and $H$ are hypergraphs, an isomorphism is defined as interrelated bijections $f : V \rightarrow W$ and $g : E \rightarrow F$ such that $e = \{v_1, \ldots, v_k(\in \mathbb{E})\}$ is in $E$ if and only if $g(e) = \{f(v_1), \ldots, f(v_k)(\in \mathbb{E})\}$ is in $F$ for all hyperedges $e \in E$. Isomorphic (hyper)graphs are structurally identical. An automorphism is an isomorphism of a (hyper)graph to itself.

**Edit distance.** Let $G$ and $H$ be two vertex- and hyperedge-labeled hypergraphs. The edit distance between these hypergraphs corresponds to the minimum number of edit operations necessary to transform $G$ into $H$, where edit operations are often defined as insertion/deletion of vertices/hyperedges and substitutions of vertex and hyperedge labels. Any sequence of edit operations that transforms $G$ into $H$ is called an edit path; hence, the hypergraph edit distance between $G$ and $H$ is the length of the shortest edit path between them. This concept can be generalized to the case where each edit operation is assigned a cost. Hypergraph edit distance then corresponds to the edit path of minimum cost.

#### 2.2 Hypergraph duality

Let $G = (V, E)$ be a hypergraph, where $V = \{v_1, \ldots, v_n\}$ and $E = \{e_1, \ldots, e_m\}$. The dual hypergraph of $G$, denoted as $G^* = (V^*, E^*)$, is obtained by constructing the set of vertices as $V^* = \{e_1, \ldots, e_m\}$ and the set of hyperedges as $E^* = \{e_1, \ldots, e_n\}$ such that $e_i = \{e_j \mid v_i \in e_j\}$. Thus, the vertices of the dual hypergraph $G^*$ are hyperedges of the original hypergraph $G$, whereas the hyperedges of $G^*$ are constructed using the hyperedges of $G$ that are incident with the respective vertices. Figure 1A-B shows two examples of a hypergraph $G$ and its dual hypergraph $G^*$.

#### 2.3 Classification on hypergraphs

We are interested in binary classification on (possibly disconnected) hypergraphs. The following paragraphs briefly introduce three classification problems on hypergraphs, formulated here so as to naturally lead to the methodology proposed in the next section.

**Vertex classification.** Given a hypergraph $G = (V, E)$ and a training set $\{(v_i, t_i)\}_{i=1}^{m}$, where $t_i \in \{-1, +1\}$ is the class label of vertex $v_i$ and $m < |V|$, the goal is to predict class labels of unlabeled vertices. A number of classical problems in computational biology map straightforwardly
A number of prediction problems in computational biology can be considered within a semi-supervised framework, where a set of labeled and a set of unlabeled examples are used to construct classifiers that discriminate between positive and negative examples. A special category of semi-supervised learning occurs when labeled data contain only positive examples; i.e., where the negative examples are either unavailable or ignored; say, if the set of available negatives is small or biased. Such problems are generally referred to as learning from positive and unlabeled data or positive-unlabeled learning (Denis et al., 2005). Many problems in molecular biology that are often referred to as the open world problems lend themselves naturally to the positive-unlabeled setting.

Research in machine learning has recently established tight connections between traditional supervised learning and (non-traditional) positive-unlabeled learning. Under mild conditions, a classifier that optimizes the ranking performance; e.g., area under the ROC curve (Fawcett, 2006), in the non-traditional setting has been shown to also optimize the performance in the traditional setting (Reid and Williamson, 2010). Similar relationships have been established in approximating posterior distributions (Jain et al., 2016a,b) as well as in recovering the true performance accuracy in the traditional setting for a classifier evaluated in a non-traditional setting (Menon et al., 2015; Jain et al., 2017; Ramola et al., 2019).

3 Methods

3.1 Problem formulation

We consider binary classification problems on graphs and hypergraphs and propose to unify all such learning problems through semi-supervised vertex classification on hypergraphs. First, vertex classification falls trivially into this framework. Second, the problems of edge classification in graphs and hyperedge classification in hypergraphs are equivalent to the problem of vertex classification on dual hypergraphs. As discussed in Section 2.2, both graphs and hypergraphs give rise to dual hypergraph representations and, thus, (hyper)edge classification on a graph G straightforwardly translates into vertex classification on its dual hypergraph $G^\ast$. We note here that vertices with the degree of one in G give rise to self-loops in the dual hypergraph $G^\ast$. To account for them, we add one dummy node per self-loop with the same vertex label as the original vertex and connect them with an appropriately labeled edge. Third, one can similarly see link prediction as vertex classification on hypergraphs, where the set of existing links is treated as positive data, the set of known non-existing links is treated as negative data, and the remaining set of missing links is treated as unlabeled data. This formulation further requires an extension of dual hypergraph representations as follows. Consider a particular negative or missing link $\bar{e} \in \bar{E}$ in the original graph G with its dual hypergraph $G^\ast$ (Fig. 1C). To make a prediction on this edge $\bar{e}$, we first introduce a new vertex $\bar{v}$ in the dual hypergraph as well as modify those hyperedges in $G^\ast$ that correspond to the vertices $v \notin \bar{e}$ in G (Fig. 1C). We denote this extended hypergraph as $G^\ast_{\bar{v}}$. It now easily follows that the sets of negative and unlabeled examples can be created by considering a collection of extended graphs $G^\ast_{\bar{v}}$, one at a time, for select vertices $\bar{v} \in \bar{E}$.

Since most biological networks lack large sets of representative negative examples, we approach vertex classification, (hyper)edge classification and link prediction as instances of vertex classification on (extended, dual) hypergraphs in a positive-unlabeled setting. We believe this is a novel and useful attempt at generalizing three distinct graph classification problems in a common semi-supervised setting. The following sections introduce hypergraphlet kernels that are the next step of our classification approach.

3.2 Hypergraphlets

Inspired by graphlets (Pruzulj et al., 2004; Przulj, 2007), we define a hypergraphlet as a small, simple, connected, rooted hypergraph, without self-loops, where the root of the hypergraph is its automorphism orbit (Gaudel et al., 2018). A hypergraphlet with $n$ vertices is called an $n$-hypergraphlet; and the $i$-th hypergraphlet of order $n$ is denoted as $n_i$. We consider hypergraphlets up to isomorphism and will refer to these isomorphisms as root- and label-preserving isomorphisms when hypergraphs are rooted and labeled. Figure 2 displays all non-isomorphic unlabeled $n$-hypergraphlets with up to three vertices. There is only one hypergraphlet of order 1 ($1_1$; Fig. 2A), one hypergraphlet of order 2 ($2_1$; Fig. 2B), nine hypergraphlets of order 3 ($3_1, \ldots, 3_9$; Fig. 2C) and 461 hypergraphlets of order 4 (Supplementary Materials). We refer to all these hypergraphlets as base hypergraphlets since they correspond to the case when $|\Sigma| = |\Xi| = 1$. 

![Fig. 1. Examples of hypergraph duality. Panel(A) shows a hypergraph $G = (V, E)$, where $V = \{v_1, v_2, v_3, v_4\}$ and $E = \{e_1, e_2, e_3, e_4, e_5\}$ with its dual hypergraph $G^\ast = (V^\ast, E^\ast)$, where $V^\ast = \{e_1, e_2, e_3, e_4, e_5\}$, $E^\ast = \{e_1, e_2, e_3, e_4\}$ such that $e_1 = \{e_1, e_2, e_3\}, e_2 = \{e_1, e_2\}, e_3 = \{e_2, e_3, e_4\}$ and $e_4 = \{e_4, e_5\}$. Panel (B) shows an example of graph G with two degree-one vertices that lead to the dual hypergraph $G^\ast$ with self-loops; $e_2$ and $e_4$. Panel (C) shows an extended dual hypergraph that is proposed to formulate link prediction as an instance of vertex classification in hypergraphs. To make a prediction regarding the existence of edge $\bar{e}$, shown as a dashed line on the left side, an extended dual hypergraph is created in which $\bar{e}$ is added to the set of vertices $V^\ast$. Updates are made to hyperedges $\bar{e}_1$ and $\bar{e}_4$ (dashed) that correspond to those vertices in $G$ that are incident with the edge $\bar{e}$.](https://academic.oup.com/bioinformatics/advance-article/doi/10.1093/bioinformatics/btaa768/5901538)
Consider now a vertex- and hyperedge-labeled (or fully labeled for short) hypergraphlet with $n$ vertices and $m$ hyperedges, where $\Sigma$ and $\Xi$ denote the vertex-label and hyperedge-label alphabets, respectively. If $|\Sigma| > 1$ and/or $|\Xi| > 1$, automorphic structures corresponding to the same base hypergraphlet may exist; hence, the number of fully labeled hypergraphlets per base structure is generally smaller than $|\Sigma|^n |\Xi|^m$. For example, if one only considers vertex-labeled 3-hypergraphlets, then there are $|\Sigma|^3$ vertex-labeled hypergraphlets corresponding to the asymmetric base hypergraphlets $3_2$, $3_4$, and $3_5$ but only $\frac{1}{2}(|\Sigma|^3 + |\Sigma|^2)$ corresponding to the base hypergraphlets $3_1$, $3_3$, $3_5$, $3_6$, $3_8$, $3_9$. This is a result of symmetries in the base hypergraphlets that give rise to automorphisms among vertex-labeled structures. Similarly, if $|\Xi| > 1$, new symmetries may form with respect to the base hypergraphlets that give rise to different automorphisms among hyperedge-labeled structures.

These symmetries are important for counting vertex- and hyperedge-labeled hypergraphlets within larger graphs. The enumeration steps described above also determine the dimensionality of the Hilbert space in which the prediction is carried out. Detailed results on hypergraph enumeration are given in Supplemental Materials.

### 3.3 Hypergraphlet kernels

Motivated by the case for graphs (Shervashidze et al., 2009; Vagic et al., 2010; Lugo-Martinez and Radijovic, 2014), we introduce hypergraphlet kernels. Let $G = (V, E, f, g, \Sigma, \Xi)$ be a fully labeled hypergraph where $f$ is a vertex-labeling function $f : V \rightarrow \Sigma$, $g$ is a hyperedge-labeling function $g : E \rightarrow \Xi$, and $|\Sigma|, |\Xi| \geq 1$. The vertex- and hyperedge-labeled $n$-hypergraphlet count vector for any $v \in V$ is defined as

$$\phi_n(v) = (\phi_{n_1}(v), \phi_{n_2}(v), \ldots, \phi_{n_\kappa(n, \Sigma, \Xi)}(v)), \tag{1}$$

where $\phi_{n_i}(v)$ is the count of the $i$-th fully labeled $n$-hypergraphlet rooted at $v$ and $\kappa(n, \Sigma, \Xi)$ is the total number of vertex- and hyperedge-labeled $n$-hypergraphlets. Observe that, $\phi_{n_i}(v)$ must be defined over a section hypergraph or sub-hypergraph of $G$ which will lead to distinct vectors of counts $\phi_n(v)$. A kernel between the $n$-hypergraphlet counts for vertices $u$ and $v$ is defined as an inner product between $\phi_n(u)$ and $\phi_n(v)$; i.e.,

$$k_n(u, v) = \langle \phi_n(u), \phi_n(v) \rangle. \tag{2}$$

The hypergraphlet kernel function incorporating all hypergraphlets up to the size $N$ is given by

$$k(u, v) = \sum_{n=1}^{N} k_n(u, v), \tag{3}$$

where $N$ is a small integer. In this work we use $N = 4$ due to the exponential growth of the number of base hypergraphlets.

### 3.4 Edit-distance hypergraphlet kernels

Consider a fully labeled hypergraph $G = (V, E, f, g, \Sigma, \Xi)$. Given a vertex $v \in V$, we define the vector of counts for a $\tau$-generalized edit-distance hypergraphlet representation as

$$\phi_{(n, \tau)}(v) = (\psi_{(n_1, \tau)}(v), \psi_{(n_2, \tau)}(v), \ldots, \psi_{(n_\kappa(n, \Sigma, \Xi), \tau)}(v)), \tag{4}$$

where

$$\psi_{(n, \tau)}(v) = \sum_{n_j \in E(n, \tau)} c(n_i, n_j) \cdot \varphi_{n_j}(v). \tag{5}$$

Here, $E(n, \tau)$ is the set of all $n$-hypergraphlets such that for each $n_j \in E(n, \tau)$ there exists an edit path of total cost at most $\tau$ that transforms $n_i$ into $n_j$ and $c(n_i, n_j) \geq 0$ is a user-defined parameter. In other words, the counts for each hypergraphlet $n_j$ are updated by also counting all other hypergraphlets $n_i$ that are in the $\tau$ vicinity of $n_j$. The parameter $c$ can be used to adjust the weights of these pseudocounts or learned from data to add sophistication. We set $c(n_i, n_j) = 1$ for all $i$ and $j$ and the cost of all edit operations was also set to 1. This restricts $\tau$ to nonnegative integers.

The length-$\tau$ edit-distance $n$-hypergraphlet kernel $k_{(n, \tau)}(u, v)$ between vertices $u$ and $v$ can be computed as an inner product between the respective count vectors $\phi_{(n, \tau)}(u)$ and $\phi_{(n, \tau)}(v)$; i.e.,

$$k_{(n, \tau)}(u, v) = \langle \phi_{(n, \tau)}(u), \phi_{(n, \tau)}(v) \rangle. \tag{6}$$

The length-$\tau$ edit-distance hypergraphlet kernel function is given as

$$k_{\tau}(u, v) = \sum_{n=1}^{N} k_{(n, \tau)}(u, v). \tag{7}$$

The edit operations considered here incorporate substitutions of vertex labels, substitutions of hyperedge labels, and insertions/deletions (indels) of hyperedges (see example in Figure S1). Given these edit operations, we also define three subclasses of edit-distance hypergraphlet kernels referred to as vertex label-substitution $k_{\tau}^v(u, v)$, hyperedge label-substitution $k_{\tau}^e(u, v)$ and hyperedge-indel kernels $k_{\tau}^i(u, v)$. Although the functions from Equations (2) and (6) are defined as inner products, other formulations such as radial basis functions can be similarly considered (Shawe-Taylor and Cristianini, 2001). We also note that the combined kernels from Equations (3) and (7) can be generalized beyond linear combinations. For the simplicity of this work, however, we only explore equal-weight linear combinations and normalize the functions from Equations (3) and (7) using the cosine transformation. Computational complexity and implementation details are described in Supplemental Materials.

### 4 Experiment design

#### 4.1 Data sets

**Protein-protein interaction data.** The protein-protein interaction (PPI) data was used for both edge classification and link prediction. In the context of edge classification, we are given a PPI network where each interaction is annotated as either direct physical interaction or a co-membership in a complex. The objective is to predict the type of each interacting protein pair as physical vs. complex (PC). For this task, we used the budding yeast *S. cerevisiae* PPI network assembled by Ben-Hur and Noble (2005).

Another important task in PPI networks is discovering whether two proteins interact. Despite the existence of high-throughput experimental methods for determining interactions between proteins, the PPI network data of all organisms is incomplete (Lewis et al., 2012). Furthermore, high-throughput PPI data contains a potentially large fraction of false positive interactions (von Mering et al., 2002). Therefore, there is a
Table 1. Summary of binary classification tasks and data sets. For each learning problem, we show the number of vertices (\(V\)) and edges (\(E\)) in the full hypergraph, as well as the largest connected component (\(V^{\text{lc}}\), \(E^{\text{lc}}\)). We also show the number of positive (\(n_+\)), negative (\(n_-\)), or unlabeled (\(n_u\)) data points.

| Type          | Dataset | \(|V|\) | \(|E|\) | \(|V^{\text{lc}}|\) | \(|E^{\text{lc}}|\) | \(n_+\) | \(n_-\) | \(n_u\) |
|---------------|---------|--------|--------|----------------|----------------|-------|-------|-------|
| Edge classification | PPI PC  | 4,761  | 22,988 | 10,517 | 12,471 |       |       |       |
|                | ID      | 544 drugs | 10,436 | 4,284   | 6,152     |       |       |       |
|                | AI      | 378 drugs | 2,261 targets | 1,039 | 249   | 790 |       |       |
| Hyperedge classification | PPI BC  | 3,436  | 2,357 | 145 | 161 |       |       |       |
|                | MP      | 3,436  | 2,357 | 175 | 200 |       |       |       |
| Link prediction | EC      | 393    | 391   | 100 | 153 |       |       |       |
|                | CE      | 3,026  | 5,163 | 2,779 | 5,014 |       |       |       |
|                | AT      | 5,391  | 12,825 | 5,063 | 12,631 |       |       |       |
|                | SP      | 853    | 1,197 | 685   | 1,092     |       |       |       |
|                | RN      | 526    | 532   | 301   | 388        |       |       |       |
|                | MM      | 2,065  | 2,833 | 1,590 | 2,522     |       |       |       |
|                | EZ      | 445 drugs | 664 targets | 2,926 | 809 | 2,556 |       |       |
|                | IC      | 210 drugs | 204 targets | 1,476 | 400 | 1,473 |       |       |
|                | DTI     | 223 drugs | 95 targets | 635 | 240 | 570 |       |       |
|                | GR      | 54 drugs | 26 targets | 90 | 42 | 50 |       |       |
|                | NR      | 100     | 100   | 100   | 100        |       |       |       |

\(a\) The size of \(n_+\) and \(n_-\) is given by \(|E^{\text{lc}}|\).

Link prediction setting, the learning task is to predict drug-target protein interactions. We focused on four drug-target classes: (1) enzymes (EZ), (2) ion channels (IC), (3) G protein-coupled receptors (GR), and (4) nuclear receptors (NR); originally assembled by Yamashita et al. (2008).

Hyperedge classification data. Hypergraphs provide a natural way to encode protein complexes. Here, we used CoupN 3.0 (Giurgiu et al., 2019) which provides manually annotated protein complexes from mammalian organisms. Under this setting, the learning objective is to predict the functional annotation of each protein complex. For this task, we defined two data sets: (1) protein binding vs. cell cycle (BC), and (2) protein modification vs. DNA processing (MP). Table 1 summarizes all data sets used in this work.

4.2 Integrating domain knowledge via a vertex alphabet

To incorporate domain knowledge into the PPI networks, we exploited the fact that each vertex (protein) in the graph is associated with its amino acid sequence. In particular, we used protein sequences to predict their Gene Ontology (GO) terms using the FANN-GO algorithm (Clark and Radivojac, 2011). Hierarchical clustering was subsequently used on the predicted term scores to group proteins into \(|\Sigma_{\text{GO}}|\) broad functional categories. In the case of DTI data, target proteins were annotated in a similar manner. For labeling drug compounds, we used the chemical structure similarity matrix computed from SIMCOMP (Hattori et al., 2003), transformed it into a dissimilarity matrix and then applied hierarchical clustering to group compounds into \(|\Sigma_{\text{SS}}|\) structural categories.

4.3 Evaluation methodology

We evaluated all hypergraphlet kernels by comparing them to two in-house implementations of random-walk-with-restarts kernels. Given a hypergraph \(G\) and two vertices \(u\) and \(v\), simultaneous random walks \(u_{\text{walk}}\) and \(v_{\text{walk}}\) were generated from \(u\) and \(v\) for a fixed number of times \(N_{\text{walks}}\). In each step during a walk, one must pick hyperedges \(e_{u,r}\) and \(e_{v,r}\) incident with current vertices \(u'\) and \(v'\), respectively, and then pick next vertices \(u''\) \(\in e_{u,r}\) and \(v''\) \(\in e_{v,r}\). After a transition is made to the next pair of nodes \(u''\) and \(v''\), the walk is terminated with some probability \(0 < p < 1\), or continued. In the conventional random walk implementation, a walk is scored as 1 if the sequences of all vertex and hyperedge labels between \(u_{\text{walk}}\) and \(v_{\text{walk}}\) are identical; otherwise, a walk is scored as 0. After \(N_{\text{walks}} = 10,000\) walks are completed, the scores over all walks are summed to produce a kernel value between the starting vertices \(u\) and \(v\). In order to construct a random walk similar to the hypergraphlet edit-distance approach, a cumulative random walk kernel was also implemented. Here, any match between the labels of vertices \(u'\) and \(v'\), or hyperedges \(e_{u,r}\) and \(e_{v,r}\) of each walk is scored as 1, while a mismatch is scored as 0. Thus, a walk of length \(l\) can contribute between 0 and \(2l - 1\) to the total count. In each of the random walks, the probability of restart \(p\) was selected from a set \([0.1, 0.2, \ldots, 0.5]\). On the link prediction data sets we also evaluated the performance of the preferential attachment method (Barabási et al., 2002) and the L3 framework (Kovács et al., 2019). Furthermore, we evaluated pairwise spectrum kernels (Ben-Hur and Noble, 2005) on the PPI data sets (excluding the protein complex data). The \(k\)-mer size for pairwise spectrum kernels was varied from \(k \in \{3, 4, 5\}\). Finally, in the case of the edit-distance kernels, we computed the set of normalized hypergraphlet kernel matrices \(K\) using \(k_{u,r}^{(k)}(x_i, x_j)\), \(k_{v,r}^{(k)}(x_i, x_j)\), \(k_{u,v}^{(k)}(x_i, x_j)\), and \(k_{u,v}^{(k)}(x_i, x_j)\) for all pairs \((x_i, x_j)\) obtained from a grid search over \(\tau = \{0, 1\}, |\Sigma| = \{2, 4, 8, 16\}\) and \(N = \{3, 4\}\).

The performance of each method was evaluated through a 10-fold cross-validation. In each iteration, 10% of nodes in the dual network were selected for the test set, whereas the remaining 90% were used for training. When evaluating link prediction methods, the negative examples were
5.2 Performance on link prediction

The performance of hypergraphlet kernels was further evaluated on the problem of link prediction on multiple PPI and DTI network data sets. Table 2 and Supplementary Table S2 show the performance accuracies for each hypergraph-based method across all link prediction data sets. These results demonstrate good performance of our methods, with edit-distance kernels generally having the best performance. Interestingly, the *bona fide* hypergraphlet approaches displayed the highest accuracy on most PPI data sets (excluding CE), with a minor variation regarding the best method between section hypergraphlet and sub-hypergraphlet approaches. Both approaches have outperformed the state-of-the-art L3 link prediction framework as well as preferential attachment method and pairwise spectrum kernels. On the other hand, dual graphlet kernels (Supplementary Materials) showed the best performance on drug-target data sets suggesting that at this time, the increased resolution of modeling does not lead to increased performance on these networks (Supplementary Table S3). Note that pairwise spectrum kernels could not be applied to DTI data sets because they expect two pairs of objects of the same type as input, which further strengthens the appeal of our approach. Further breakdown of results based on the categories of difficulty identified by Park and Marcotte (2012) is shown in Supplementary Tables S2 and S3.

5.3 Estimating interactome sizes

A positive-unlabeled formulation for link prediction presents an opportunity to estimate interactome sizes in biological networks. As a proof of concept, here we used the AlphaMax algorithm (Jain et al., 2016a) for estimating class priors in positive-unlabeled learning to estimate both the number of missing links and false positive interactions in different PPI networks. To do this, we used BIND, BioGRID, DIP, HPRD, and IntAct to construct *Homo sapiens* and *Saccharomyces cerevisiae* PPI networks. The human network contained 10,841 nodes and 45,386 edges (10,729 and 45,327 in the largest connected component), whereas the yeast network contained 4,690 nodes and 26,165 edges (4,674 and 26,156 in the largest connected component). The negative examples were sampled uniformly randomly from the set of all possible edges, which was necessary in order to correctly estimate class priors and posteriors (Jain et al., 2016a).

Assuming a tissue and cellular component agnostic model (i.e., any two proteins can interact), we obtained that the number of missing interactions on the largest component of the human PPI network is about 5% (i.e., approximately 2.5 million interactions), while the number of misannotated interactions is close to 11% which translates to about 4,985 false interactions. In the case of yeast, we computed that less than 1% of the potential protein interactions are missing which is close to 95,000. At the same time, the number of misannotated interactions is close to 13%, which is about 3,400 misannotated protein pairs. Some of these numbers fall within previous studies that suggest that the size of the yeast interactome is between 13,500 (Stumpf et al., 2009) and 650,000 (Stumpf et al., 2008) interactions. A more recent paper by Lewis et al. (2012) presents a scenario where yeast and human interactome size could reach 400,000 and over two million interactions, respectively. Although these results serve as a validation of our problem formulation and approach, additional tests and experiments, potentially involving exhaustive classifier and parameter optimization, will be necessary for more accurate and reliable estimates, especially for understanding the influence of potential biases within the PPI network data.

6 Related work

The literature on the similarity-based measures for learning on hypergraphs is relatively scarce. Most studies revolve around the use of random walks for clustering that were first used in the field of circuit design (Cong et al., 1991). Historically, typical hypergraph-based learning approaches can be divided into (1) tensor-based approaches, which extend traditional matrix (spectral) methods on graphs to higher-order relations for hypergraph clustering (Cong et al., 1991; Leordeanu and Sminchisescu, 2012), and (2) approximation-based approaches that convert hypergraphs into
standard weighted graphs and then exploit conventional graph clustering and semi-supervised learning (Agarwal et al., 2005; Zhou et al., 2006). The methods from the first category provide a direct and mathematically rigorous treatment of hypergraph learning, although most tensor problems are NP-hard. As a consequence, this line of research remains largely unexplored despite a renewed interest in tensor decomposition approaches (Hein et al., 2013; Purskaitis et al., 2014). Regarding the second category, there are two commonly used transformations for graph-based hypergraph approximation, reviewed and compared in Agarwal et al. (2006).

Under a supervised learning framework, Wachman and Khardon (2007) proposed walk-based hypergraph kernels on ordered hypergraphs, while Sun et al. (2008) presented a hypergraph spectral learning formulation for multi-label classification. More recently, Bai et al. (2014) introduced a hypergraph kernel that transforms a hypergraph into a directed line graph and computes a Weisfeiler-Lehman isomorphism test between directed graphs. A major drawback of most such approaches is that no graph representation fully captures the hypergraph structure.

## 7 Conclusions

This paper presents a learning framework for the problems of vertex classification, hyperedge classification, and link prediction in graphs and hypergraphs. The key ideas in our approach were (i) the use of hypergraph duality in order to cast each classification problem as an instance of vertex classification, and (ii) the use of a new family of kernels defined directly on labeled hypergraphs. Using the terminology of Bleakley et al. (2007), our method belongs to the category of “local” learners. This is, it captures the structure of local neighborhoods, rooted at the vertex of interest, and should be distinguished from “global” models such as Markov Random Fields or diffusion kernels (Kondor and Lafferty, 2002). The body of literature on graph learning is vast; see Supplementary Materials for more details. We therefore selected to perform extensive comparisons against a limited set of methods that are most relevant to ours.

The development of hypergraphlet kernels derives from the graph reconstruction conjecture, an idea of using small graphs to probe large graphs (Bondy and Hemminger, 1977; Borgs et al., 2006). Hypergraphlet kernels prioritize accuracy over run time and are not an optimal choice for huge dense graphs where real-time performance is critical. However, biological networks (for now) are sparse and moderate in size, making accurate prediction to prioritize biological experiments an appealing choice. We additionally believe that unification of disparate prediction tasks on biological networks via hypergraph duality reduces the need for custom method development. Overall, our work provides evidence that hypergraph-based inference and hypergraphlet kernels are competitive with other approaches and readily deployable in practice.

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