Predicting multicellular function through multi-layer tissue networks

Marinka Zitnik and Jure Leskovec

Department of Computer Science, Stanford University, Stanford, 94305, USA

*To whom correspondence should be addressed.

Abstract

Motivation: Understanding functions of proteins in specific human tissues is essential for insights into disease diagnostics and therapeutics, yet prediction of tissue-specific cellular function remains a critical challenge for biomedicine.

Results: Here we present OhmNet, a hierarchy-aware unsupervised node feature learning approach for multi-layer networks. We build a multi-layer network, where each layer represents molecular interactions in a different human tissue. OhmNet then automatically learns a mapping of proteins, represented as nodes, to a neural embedding based low-dimensional space of features. OhmNet encourages sharing of similar features among proteins with similar network neighborhoods and among proteins activated in similar tissues. The algorithm generalizes prior work, which generally ignores relationships between tissues, by modeling tissue organization with a rich multiscale tissue hierarchy. We use OhmNet to study multicellular function in a multi-layer protein interaction network of 107 human tissues. In 48 tissues with known tissue-specific cellular functions, OhmNet provides more accurate predictions of cellular function than alternative approaches, and also generates more accurate hypotheses about tissue-specific protein actions. We show that taking into account the tissue hierarchy leads to improved predictive power. Remarkably, we also demonstrate that it is possible to leverage the tissue hierarchy in order to effectively transfer cellular functions to a functionally uncharacterized tissue. Overall, OhmNet moves from flat networks to multiscale models able to predict a range of phenotypes spanning cellular subsystems.

Availability: Source code and datasets are available at http://snap.stanford.edu/ohmnet.
Contact: jure@cs.stanford.edu

1 Introduction

A unified view of human diseases and cellular functions across a broad range of human tissues is essential, not only for understanding basic biology but also for interpreting genetic variation and developing therapeutic strategies (Yeger-Lotem and Sharan, 2015; Okabe and Medzhitov, 2014; Greene et al., 2015; GTEx et al., 2015). In particular, the precise functions of proteins frequently depend on the tissue, and different proteins can have different cellular functions in different tissues (Lois et al., 2002; Rakyan et al., 2008; Magger et al., 2012; Guan et al., 2012; Fagerberg et al., 2014; Yeger-Lotem and Sharan, 2015; Hu et al., 2016).

While our view of the human protein-protein interaction network as a key source for studying protein function, is constantly expanding, much less is known about networks that form in biologically important environments such as within distinct tissues or in specific diseases (Yeger-Lotem and Sharan, 2015). Although incredibly influential, current computational methods for extracting functional information from protein interaction networks lack tissue specificity as they assume that cellular function is constant across organs and tissues (Barutcuoglu et al., 2006; Mostafavi et al., 2008; Radivojac et al., 2013; Stojanova et al., 2013; Kramer et al., 2014; Zitnik and Zupan, 2015). In other words, cellular functions in heart are assumed to be the same as functions in skin. The methods are, hence, less successful in constructing accurate maps of both where and how proteins act.

In particular, existing network-based methods are probably not the ultimate representation of human tissues for three reasons. (1) First, current methods for cellular function prediction on networks (Mostafavi and Morris, 2009; Radivojac et al., 2013; Zitnik and Zupan, 2015; Vidalin et al., 2016) do not model networks with regards to patterns that span tissues, organs, and cellular systems. This means that a complex tissue involving a multiscale hierarchy of cellular subsystems is not readily captured by current models (Dutkowski et al., 2012; Carvunis and Ideker, 2014). (2) Second, many genome-scale functional maps (Lopes et al., 2011; Rolland et al., 2014; Kotlyar et al., 2014)
et al. (2015; Kitsak et al., 2016; Costanzo et al., 2016; Wang et al., 2016b) are
descriptive maps of physical or functional protein connectivity that do not,
by themselves, predict cellular function. (3) Third, only few computational
approaches (Magger et al., 2012; Guan et al., 2012; Ganegoda et al., 2014;
Antanaviciute et al., 2015) used tissue-specific information to identify
novel genes and relationships between genes. However, their focus was
to leverage tissue specificity to improve prediction of global cellular
functions and global gene-disease associations. As such, these approaches
account for tissue specificity, but they do not resolve the challenge of
predicting gene-function relationships that might be specific to a particular
tissue. To be able to predict a range of tissue-specific functions one needs
to design scalable multiscale models that can relate tissues to each other,
each tissue in a d-dimensional feature space such that proteins with similar
network neighborhoods in similar tissues are embedded closely together.

In OhmNet, we define an objective function that is independent of the
downstream prediction task, meaning that the feature representations are
learned in a purely unsupervised way. This results in task-independent
features, that, as we show, outperform task-specific approaches in
predictive accuracy. Furthermore, since our features are not designed for a
specific downstream prediction task, they generalize across a wide variety
of tasks and tissues. For example, we use the learned features to study
protein functions across different cellular systems (e.g., cell types, tissues,
organs, and organ systems).

OhmNet builds on recent success of unsupervised representation
learning methods based on neural architectures (Mikolov et al., 2013;
Grover and Leskovec, 2016). In particular, we develop a new form of
structured regularization, which makes OhmNet especially suitable
for multi-layer interdependent networks. Our key contribution lies in
modeling the tissue taxonomy constraints by encoding relationships
between the tissues in a tissue hierarchy and then using the structured
regularization with the tissue hierarchy (Figure 1). This way OhmNet
effectively learns multiscale feature representations for proteins that are
consistent with the tissue hierarchy.

Our experiments focus on three tasks defined on a multi-layer tissue
network: (i) a multi-label node classification task, where every protein is
assigned zero, one or more tissue-specific cellular functions; (ii) a
transfer learning task, where we predict cellular functions for a protein in
one tissue based on classifiers trained on features from other tissues; and
(iii) a network embedding visualization task, where we create meaningful
tissue-specific visualizations that lay out proteins on a two-dimensional
space. Since the multiscale protein feature vectors returned by OhmNet
are task-independent, we use OhmNet one time only to learn the features
for proteins in every tissue and at every scale of the tissue hierarchy.
We can then solve the cellular function prediction task for any tissue using
the appropriate tissue-specific protein features.

We contrast OhmNet’s performance with that of state-of-the-art
approaches for feature learning (Nickel et al., 2011; Tang et al., 2015;
Cannistraci et al., 2013; Grover and Leskovec, 2016), approaches for
tissue-independent cellular function prediction (Mostafavi et al., 2008;
Zuberi et al., 2013), and approaches for prioritization of disease-causing
genes in tissue-specific protein interaction networks (Magger et al., 2012;
Guan et al., 2012), which we adapted for the cellular function prediction
task. We experiment with a multi-layer network having 107 genome-
wide tissue-specific protein interaction layers, and we consider a tissue
hierarchy describing 219 cellular systems in the human body. Experiments
demonstrate that tissue-specific protein interaction layers provide the
necessary protein and tissue context for predicting cellular function.
OhmNet outperforms alternative approaches by up to 14.9% on multi-label
classification and up to 20.3% on transfer learning. Another notable finding
is that OhmNet outperforms alternative approaches, which are based on
non-hierarchical versions of the same dataset, alluding to the benefits of
modeling hierarchical tissue organization. We observe that neglecting the
existence of tissues or aggregating tissue-specific interaction networks into
a single network discards important biological information and affects
performance on multi-label classification and transfer learning tasks.
Finally, we exemplify the utility of OhmNet for exploring the multiscale
structure of tissues. In a case study on nine brain tissue networks, we show
that OhmNet’s features inherently encode a multiscale brain organization.

The rest of the paper is organized as follows. In Section 2, we briefly
survey related work in feature learning for networks. We present the
technical details of OhmNet in Section 3. In Section 4, we describe
the multi-layer tissue network and the tissue hierarchy. We empirically
evaluate OhmNet in Section 5 and conclude with directions for future
work in Section 6.

2 Related work

We have seen in Section 1 that despite the abundance of methods
for cellular function prediction, only a few, if any, take into account
biologically important contexts given by human tissues. We now turn our focus to the problem of feature learning in networks.

Most approaches for automatic (i.e., non-hand-engineered) feature learning in networks can be categorized into matrix factorization and neural network embedding based approaches. In matrix factorization, a network is expressed as a data matrix where the entries represent relationships. The data matrix is projected to a low dimensional space using linear techniques based on SVD (Tang et al., 2012), or non-linear techniques based on multi-dimensional scaling (Tenenbaum et al., 2000; Belkin and Niyogi, 2001; Hou et al., 2014). These methods have two important drawbacks. First, they do not account for important structures typically exhibited in networks such as high sparsity and skewed degree distribution. Second, matrix factorization methods perform a global factorization of the data matrix while a local-centric method might often yield more useful feature representations (Kram et al., 2014).

Limitations of matrix factorization are overcome by neural network embeddings. Recent studies focused on embedding nodes into low-dimensional vector spaces by first using random walks to construct the network neighborhood of every node in the graph, and then optimizing an objective function with network neighborhoods as input (Perozzi et al., 2014; Tang et al., 2015; Grover and Leskovec, 2016). The objective function is carefully designed to preserve both the local and global network structures. A state-of-the-art neural network embedding algorithm is the Node2vec algorithm (Grover and Leskovec, 2016), which learns feature representations as follows: it scans over the nodes in a network, and for every node it aims to embed it such that the node’s features can predict nearby nodes, that is, node’s feature predict which other nodes are part of its network neighborhood. Node2vec can explore different network neighborhoods to embed nodes based on the principles of homophily (i.e., network communities) as well as structural equivalence (i.e., structural roles of nodes).

However, a challenging problem for neural network embedding-based methods is to learn features in multi-layer networks. Existing methods can learn features in multi-layer networks either by treating each layer independently of other layers, or by aggregating the layers into a single (weighted) network. However, neglecting the existence of multiple layers or aggregating the layers into a single network, alters topological properties of the system as well as the importance of individual nodes with respect to the entire network structure (De Domenico et al., 2016). This is a major shortcoming of prior work that can lead to a wrong identification of the most versatile nodes (De Domenico et al., 2015) and overestimation of the importance of more marginal nodes (De Domenico et al., 2014). As we shall show, this shortcoming also affects predictive accuracy of the learned features. Our approach OhmNet overcomes this limitation since it learns features in a multi-layer network in the context of the entire system structure, bridging together different layers and generalizing methods developed for learning features in single-layer networks.

In biological domains, measures based on similarities of nodes’ extended network neighborhoods are well established for predicting protein functions. Several approaches use graphlets (Pržulj, 2007) to systematically describe network structure around each node. This is done by counting how many instances of small subgraph patterns occur in the network neighborhood of a given node. Graphlet-based methods, such as graphlet degree vectors (Hayes et al., 2013), can thus be seen as an alternative approach for extracting feature representations for nodes. In contrast to neural embedding-based methods, such as OhmNet, which learn continuous feature representations, graphlet-based methods return discrete counts of motif occurrences. Further, graphlet-based methods in their current form cannot be applied to multi-layer networks without collapsing the network layers into one network.

Finally, there exists recent work for task-dependent feature learning based on graph-specific deep network architectures (Zhai and Zhang, 2015; Li et al., 2015; Xiaoyi et al., 2014; Wang et al., 2016a). Our approach differs from those approaches in two important ways. First, those architectures are task-dependent, meaning they directly optimize the objective function for a downstream prediction task, such as cellular function prediction in a particular tissue, using several layers of non-linear transformations. Second, those architectures do not model rich graph structures, such as multi-layer networks with hierarchies.

3 Feature learning in multi-layer networks

We formulate feature learning in multi-layer networks as a maximum likelihood optimization problem. Let $V$ be a given set of $N$ nodes (e.g., proteins) $\{u_1, u_2, \ldots, u_N\}$, and let there be $K$ types of edges (e.g., protein interactions in different tissues) between pairs of nodes $u_1, u_2, \ldots, u_N$. A multi-layer network is a general system in which each biological context is represented by a distinct layer $i$ (where $i = 1, 2, \ldots, K$) of a system (Figure 1). We use the term single-layer network (layer) for the network $G_i = (V_i, E_i)$ that indicates the edges $E_i$ between nodes $V_i \subseteq V$ within the same layer $i$. Our analysis is general and applies to any (un)directed, (un)weighted multi-layer network.

We take into account the possibility that a node $u_i$ from layer $i$ can be related to any other node $u_j$ in any other layer $j$. We encode information about the dependencies between layers in a hierarchical manner that we use in the learning process. Let the hierarchy be a directed tree $M$ defined over a set $M$ of elements by the parent-child relationships given by $\pi: M \rightarrow M$, where $\pi(i)$ is the parent of element $i$ in the hierarchy (Figure 1). Let $T \subseteq M$ be the set of all leaves in the hierarchy. Let $T_i$ be the set of all leaves in the sub-hierarchy rooted at $i$. We assume that each layer $G_i$ is attached to one leaf in the hierarchy. As a result, the hierarchy $M$ has exactly $K$ leaves. For convenience, let $C_i$ denote the set of all children of element $i$ in the hierarchy.

The problem of feature learning in a multi-layer network is to learn functions $f_1, f_2, \ldots, f_K$, such that each function $f_i : V_i \rightarrow \mathbb{R}^d$ maps nodes in $V_i$ to feature representations in $\mathbb{R}^d$. Here, $d$ is a parameter specifying the number of dimensions in the feature representation of one node. Equivalently, $f_i$ is a matrix of $|V_i| \times d$ parameters.

We proceed by describing OhmNet, our approach for feature learning in multi-layer networks. OhmNet has two components:

- **single-layer network objectives**, in which nodes with similar network neighborhoods in each layer are embedded close together,
- **hierarchical dependency objectives**, in which nodes in nearby layers in the hierarchy are encouraged to share similar features.

We start by describing the model that considers the layers independently of each other. We then extend the model to encourage nodes which are nearby in the hierarchy to have similar features.

3.1 Single-layer network objectives

We start by formalizing the intuition that nodes with similar network neighborhoods in each layer should share similar features. For that, we specify one objective for each layer in a given multi-layer network. We shall later discuss how OhmNet incorporates the dependencies between different layers.

Our goal is to take layer $G_i$ and learn $f_i$ which embeds nodes from similar network regions, or nodes with similar structural roles, closely together. In OhmNet, we aim to achieve this goal by specifying the following objective function for each layer $G_i$. Given a node $u \in V_i,$
the objective function $\omega_i$ seeks to predict, which nodes are members of $u$’s network neighborhood $N_i(u)$ based on the learned node features $f_i$:
\[
\omega_i(u) = \log Pr(N_i(u)|f_i(u)),
\]  
where the conditional likelihood of every node-neighborhood node pair is modeled independently as:
\[
Pr(N_i(u)|f_i(u)) = \prod_{v \in N_i(u)} Pr(v|f_i(u)).
\]  
The conditional likelihood is a softmax unit parameterized by a dot product of nodes’ features, which corresponds to a single-layer feed-forward neural network:
\[
Pr(v|f_i(u)) = \frac{\exp(f_i(v)f_i(u))}{\sum_{z \in V_i} \exp(f_i(z)f_i(u))}.
\]  
Given a node $u$, maximization of $\omega_i(u)$ tries to maximize classification of nodes in $u$’s network neighborhood based on $u$’s learned representation.

The objective $\Omega_i$ is defined for each layer $i$:
\[
\Omega_i = \sum_{u \in V_i} \omega_i(u), \text{ for } i = 1, 2, \ldots, K.
\]  
The objective is inspired by the intuition that nodes with similar network neighborhoods tend to have similar meanings, or roles, in a network. It formalizes this intuition by encouraging nodes in similar network neighborhoods to share similar features.

We found that a flexible notion of a network neighborhood $N_i$ is crucial to achieve excellent predictive accuracy on a downstream cellular function prediction task (Grover and Leskovec, 2016). For that reason, we use a randomized procedure to sample many different neighborhoods of a given node $u$. Technically, the network neighborhood $N_i(u)$ is a set of nodes that appear in an appropriately biased random walk defined on layer $G_i$ and start at node $u$ (Grover and Leskovec, 2016). The neighborhoods $N_i(u)$ are not restricted to just immediate neighbors but can have vastly different structures depending on the sampling strategy.

Next, we expand OhmNet’s single-layer network objectives to leverage information provided by the tissue taxonomy and this way inform embeddings across different layers.

### 3.2 Hierarchical dependency objectives

So far, we specified $K$ layer-by-layer objectives each of which estimates node features in its layer independently of node features in other layers. This means that nodes in different layers representing the same entity have features that are learned independently of each other.

To harness the dependencies between the layers, we expand OhmNet with terms that encourage sharing of protein features between the layers. Our approach is based on the assumption that nearby layers in the hierarchy are semantically close to each other and hence proteins/nodes in them should share similar features. For example, in the tissue multilayer network, we model the fact that the “medulla” layer is part of the “brainstem” layer, which is, in turn, part of the “brain” layer. We use the dependencies among the layers to define a joint objective for regularization of the learned features of proteins.

We propose to use the hierarchy in the learning process by incorporating a recursive structure into the regularization term for every element in the hierarchy $\mathcal{M}$. Specifically, we propose the following form of regularization for node $u$ that resides in element $\pi(i)$ of the hierarchy $\mathcal{M}$:
\[
c_i(u) = \frac{1}{2} \| f_i(u) - f_{\pi(i)}(u) \|^2_2.
\]  
This recursive form of regularization enforces the features of node $u$ in the hierarchy to be similar to the features of node $u$ in $\pi(i)$’s parent $\pi(i)$ under the Euclidean norm. When regularizing features of all nodes across all elements of the hierarchy, we obtain:
\[
C_i = \sum_{u \in L_i} c_i(u), \text{ where } L_i = \bigcup_{j \in T_i} V_j
\]  
In words, we specify the features for both leaf as well as internal, i.e., non-leaf, elements in the hierarchy, and we regularize the features of sibling (i.e., sharing the same parent) hierarchy elements towards features in the common parent element in the hierarchy.

**Node features at multiple scales.** It is important to notice that OhmNet’s structured regularization allows us to learn feature representations at multiple scales. For example, consider a multi-layer network in Figure 2, consisting of four layers that are interrelated by a two-level hierarchy. OhmNet learns the mappings $f_1$, $f_2$, $f_k$, and $f_l$ that map nodes in each layer into a d-dimensional feature space. Additionally, OhmNet also learns the mapping $f_1$ representing features for nodes appearing in the hierarchy leaves $T_2$, i.e., $V_i \cup V_j$, at an intermediate scale, and the mapping $f_1$ representing features for nodes appearing in the hierarchy leaves $T_1$, i.e., $V_i \cup V_j \cup V_k \cup V_l$, at the highest scale.

The modeling of relationships between layers in a multi-layer network has several implications:

- First, the model encourages nodes which are in nearby layers in the hierarchy to share similar features.
- Second, the model shares statistical strength across the hierarchy as nodes in different layers representing the same protein share features through ancestors in the hierarchy.
- Third, this model is more efficient than the fully pairwise model. In the fully pairwise model, the dependencies between layers are modeled by pairwise comparisons of nodes across all pairs of layers, which takes $O(K^2 N)$ time, where $K$ is the number of layers and $N$ is the number of nodes. In contrast, OhmNet models inter-layer dependencies according to the parent-child relationships specified by the hierarchy, which takes only $O(|\mathcal{M}| N)$ time. Since OhmNet’s hierarchy is a tree, it holds that $|\mathcal{M}| \ll K^2$, meaning that the proposed model scales more easily to large multi-layer networks than the fully pairwise model.

![Fig. 2: A multi-layer network with four layers. Relationships between the layers are encoded by a two-level hierarchy $\mathcal{M}$. Leaves of the hierarchy correspond to the network layers. Given networks $G_i$ and hierarchy $\mathcal{M}$, OhmNet learns node embeddings captured by functions $f_i$.](image)
Finally, the hierarchy is a natural way to represent and model biological systems spanning many different biological scales (Carvunis and Ideker, 2014; Greene et al., 2015; Yu et al., 2016).

3.3 Full OhmNet model

Given a multi-layer network consisting of layers \( G_1, G_2, \ldots, G_K \), and a hierarchy encoding relationships between the layers, the OhmNet’s goal is to learn the functions \( f_1, f_2, \ldots, f_K \) that map from nodes in each layer to feature representations. OhmNet achieves this goal by fitting its feature learning model to a given multi-layer network and a given hierarchy, i.e., by finding the mapping functions \( f_1, f_2, \ldots, f_K \) that maximize the data likelihood.

Given the data, OhmNet aims to solve the following maximum likelihood optimization problem:

\[
\begin{align*}
\max_{f_1, f_2, \ldots, f_M} & \sum_{i \in T} \sum_{j \in M} C_{ij} - \lambda \sum_{j \in M} C_{jj},
\end{align*}
\]

which includes the single-layer network objectives for all network layers, and the hierarchical dependency objectives for all hierarchy elements. In Eq. (7), parameter \( \lambda \) is a user-specified parameter representing the regularization strength. While the optimization problem in Eq. (7) is non-convex due to the non-convexity of the single-layer objective (Grover and Leskovec, 2016), stochastic gradient with negative sampling can be used to efficiently solve the problem.

One appealing property of OhmNet is that by solving the problem in Eq. (7) we obtain estimates for functions \( f_1, f_2, \ldots, f_K \) located in the leaf elements of the hierarchy (i.e., layers of a given multi-layer network), as well as estimates for functions \( f_{K+1}, f_{K+2}, \ldots, f_M \) located in the internal elements of the hierarchy.

3.4 The OhmNet algorithm

The pseudocode for OhmNet is given in Algorithm 1.

In the first phase, OhmNet applies the Node2vec’s algorithm (Grover and Leskovec, 2016) to construct network neighborhoods for each node in every layer. Given a layer \( G_i \) and a node \( u \in V_i \), the algorithm simulates a user-defined number of fixed length random walks started at node \( u \) (step 4 in Algorithm 1).

In the second phase, OhmNet uses an iterative approach in which features associated with each object in the hierarchy are iteratively updated by fixing the rest of the features. The iterative approach has the advantage that it can easily incorporate the closed-form updates developed for the internal objects of the hierarchy (step 11 in Algorithm 1), thereby accelerating the convergence of OhmNet algorithm. For each leaf object \( i \), OhmNet isolates the terms in the optimization problem in Eq. (7) that depend on the model parameters defining function \( f_i \). OhmNet then optimizes Eq. (7) by performing one epoch of stochastic gradient descent (SGD1) over \( f_i \)’s model parameters (step 15 in Algorithm 1).

The two phases of OhmNet are executed sequentially. The OhmNet algorithm scales to large multi-layer networks because each phase is parallelizable and executed asynchronously. The choice to model the dependencies between network layers using the hierarchical model requires \( O(|M|N) \) time instead of the fully pairwise model, which requires \( O(K^2N) \) time.

4 Tissue-specific interactome data

To construct the human protein-protein interaction (PPI) network, tissue-specific network layers, tissue hierarchy, and tissue-specific gene-function relationships, we downloaded and used standard protein, tissue, and function information from various reputable data sources.

Algorithm 1: The OhmNet algorithm.

**Input:** Multi-layer network, \((G_1, G_2, \ldots, G_K)\) with \( G_i = (V_i, E_i) \), hierarchy, \( H \), Feature representation size, \( d \), Network neighborhood strategy, \( S \), Regularization strength, \( \lambda \)

```
1: \textbf{for} i \in T \textbf{do}
2: \quad \textbf{for} u \in V_i \textbf{do}
3: \quad \quad \text{Node2vecWalk}(G_i, u, S)
4: \quad \textbf{end for}
5: \textbf{end for}
6: \textbf{while} f_1, f_2, \ldots, f_M \textbf{ not converged do}
7: \quad i \in M \textbf{do}
8: \quad \quad \text{SGD1}(N_i(u), d, \lambda) \textbf{ by Eq. (7)}
9: \quad \textbf{end for}
10: \quad \textbf{else}
11: \quad \quad \text{for} u \in \bigcup_{j \in T} V_j \textbf{ do}
12: \quad \quad \quad f_i(u) = \frac{1}{|\mathcal{C}_i| + 1} (f_{\pi(i)}(u) + \sum_{c \in \mathcal{C}_i} f_c(u))
13: \quad \quad \textbf{end for}
14: \quad \textbf{end if}
15: \textbf{end while}
16: \textbf{return} f_1, f_2, \ldots, f_M
```

Fig. 3: The tissue hierarchy considered in this work. The tissue hierarchy is a directed tree defined over \(|M| = 219\) tissue terms from the BRENDA Tissue Ontology. Edges in the tree point from children to parents based on ontological relationships: “develops_from”, “is_a”, “part_of”, and “related_to”. The \( K = 107 \) tissues with tissue-specific protein interaction networks are the blue leaves in the tree.

4.1 Tissue hierarchy

We retrieved the mapping of tissues in the Human Protein Reference Database (HPRD) (Prasad et al., 2009) to tissues in the BRENDA Tissue Ontology (Chang et al., 2014) from Greene et al. (2015). The data is provided as a supplementary dataset in Greene et al. (2015). The hierarchical relationships between tissues were then determined by the directed acyclic graph structure of the BRENDA Tissue Ontology. Examples of tissues included: muscle, adrenal cortex, bone marrow, and spleen (Figure 3).
4.2 Tissue-specific interaction networks

We took the gene-to-tissue mapping compiled by Greene et al. (2015). Greene et al. mapped genes to HPRD tissues based on low-throughput tissue-specific gene expression data. The gene-to-tissue mapping was then combined with the human PPI network. The resulting multi-layer tissue network had 107 layers, each layer corresponded to a PPI network specific to a particular tissue. Details are provided next.

The human PPI network was collected from Orchard et al. (2013); Rolland et al. (2014); Chatr-Aryamontri et al. (2015); Prasad et al. (2009); Ruepp et al. (2010); Menche et al. (2015). Considered were physical protein-protein interactions with supported by experimental evidence. It should be noted that interactions based on gene expression and evolutionary data were not considered. The global (unweighted) human PPI network has 21,557 proteins interconnected by 342,353 interactions. The reader is referred to Menche et al. (2015) for a detailed description of the data.

For each of 107 tissues, a tissue-specific human PPI network was constructed based on the global PPI network. For a given tissue, every edge in the global PPI network was labeled as specifically co-expressed in that tissue using the criterion developed by Greene et al. (2015). Greene et al. labeled each edge as specifically co-expressed if either both proteins are specific to that tissue or one protein is tissue-specific and the other is ubiquitous. Lists of specifically co-expressed proteins were retrieved from Greene et al. (2015). Finally, the PPI network specific to a particular tissue is a subnetwork of the global PPI network, induced by the set of specifically co-expressed edges in that tissue.

4.3 Tissue-specific cellular functions and gene annotations

Associations between tissues and cellular functions were retrieved from Greene et al. (2015). Greene et al. manually curated biological processes in the Gene Ontology (Ashburner et al., 2000) (GO) and mapped them to tissues in the BRENDA Tissue Ontology (Chang et al., 2014) based on whether a given biological process is specifically active in a given tissue. The data is provided as a supplement dataset in Greene et al. (2015). An example of a cellular function-tissue pair is “low-density lipoprotein particle remodeling” in the blood plasma tissue.

All gene annotations were propagated along the ontology hierarchy. Considered are functions with at least 15 annotated proteins (Guan et al., 2012). In total, there are 584 tissue-specific cellular functions covering 48 distinct tissues. Each tissue-specific function is assigned to one or more leaves in the tissue hierarchy (Section 4.1).

5 Results

The OhmNet’s objective in Eq. (7) is independent of any downstream task. This flexibility offered by OhmNet makes the learned feature representations suitable for a variety of analytics tasks discussed below.

5.1 Prediction of tissue-specific cellular functions

Experimental setup. We view the problem of predicting cellular functions as solving a multi-label node classification task. Here, every node (i.e., protein) is assigned one or more labels (i.e., cellular functions from the GO) from a finite set of labels (i.e., all cellular functions in the GO, see Section 4.3).

We apply OhmNet, which for every node in every layer learns a separate feature vector in an unsupervised way. Thus, for every layer and every function we then train a separate one-vs-all linear classifier using the modified Huber loss with elastic net regularization. Using cross validation, we observe 90% of proteins and all their cellular functions across the layers during the training phase. The task is then to predict the tissue-specific functions for the remaining 10% of proteins.

We evaluate the performance of OhmNet against the following feature learning approaches:

- RESCAL tensor decomposition (Nickel et al., 2011): This is a tensor factorization approach that takes the multi-layer network structure into account. Given $X_i$, a normalized Laplacian matrix of layer $G_i$, matrix $X_i$ is factorized as: $X_i = A R_i A^T$, for $i = 1, 2, \ldots, K$. Here, matrix $A$ contains $d$-dimensional feature representation for nodes.
- Minimum curvilinear embedding (Cannistraci et al., 2013): This is a non-linear unsupervised framework that embeds nodes in a low-dimensional space. The approach was originally developed for protein interaction prediction, aiming to embed protein pairs representing good candidate interactions closer to each other. It utilizes a network denoising method as well as structural information provided by the PPI network topology.
- LINE (Tang et al., 2015): This approach first learns $d/2$ dimensions based on immediate network neighbors of nodes, and then the next $d/2$ dimensions based on network neighbors at a 2-hop distance.
- Node2vec (Grover and Leskovec, 2016): This approach learns $d$-dimensional features for nodes based on a biased random walk procedure that flexibly explores network neighborhoods of nodes.

In addition, we evaluate the performance of OhmNet against the following tissue-specific/agnostic function prediction approaches:

- GeneMania (Zuberi et al., 2013): This is a supervised approach that takes a multi-layer network as input and directly predicts cellular functions in two separate phases. In the first phase, it aggregates the layers into one weighted network by weighting the layers according to their utility for predicting a given function. It then uses a label propagation algorithm on the weighted network to predict the function.
- Tissue-specific network propagation (Magger et al., 2012): This approach assigns a prior score to proteins associated with known functions that are phenotypically similar to the query function. This score is then propagated through a network in an iterative process. The approach was developed for tissue-specific disease gene prioritization.
- Network-based tissue-specific SVM (Guan et al., 2012): This approach adopts the network-based candidate gene prediction scheme. Essentially, the connection weights in a network to all positive examples (i.e., genes already known to be related to a phenotype) are utilized as features for linear support vector machine (SVM) classification. The approach was developed for tissue-specific phenotype and disease gene prioritization.

The parameter settings for every approach are determined using internal cross validation procedure with a grid search over candidate parameter values. Specifically, $d = 128$ is used in all experiments.

Last, we aim to evaluate the benefit of our proposed multi-layer representation of the tissue networks. To this end we also consider two additional network representations:

- Independent layers: This approach learns features for nodes in each layer by running LINE or Node2vec algorithm on one layer at a time and independently of other layers in the network.
- Collapsed layers: This approach first aggregates the layers into a single network by connecting nodes representing the same entity in different layers to each other. It then learns feature for nodes in the aggregated network.
Experimental results. Table 1 and Figure 4 give the area under the curve (AUC) scores of tissue-specific protein function prediction.

From the results, we see how modeling the tissues and their hierarchy spanning multiple biological scales allows OhmNet to outperform other benchmark approaches. OhmNet outperforms GeneMania (Mostafavi et al., 2008; Zuberi et al., 2013) by 10.7%, which can be explained by GeneMania’s inability to weight layers in the tissue network according to a multiscale tissue organization that is consistent with the tissue taxonomy constraints. We also compared OhmNet to two other methods (Guan et al., 2012; Magger et al., 2012) that were so far demonstrated as useful for mining tissue-specific protein relationships. OhmNet has produced more accurate predictions, surpassing other methods by up to 12.0% (AUROC) and up to 26.8% (AUPRC).

Independent modeling of the layers showed worse performance than collapsing the layers into one network. We observed that Collapsed LINE achieved a gain of 3.3% over Independent LINE, and Collapsed Node2vec achieved a gain of 7.4% over Independent Node2vec. However, approaches that neglect the existence of tissues or collapse tissue-specific protein interaction networks into a single network discard important information about the rich hierarchy of biological systems, giving OhmNet a 14.0% gain over Collapsed LINE, and a 8.5% gain over Collapsed Node2vec in AUC scores. This result is a good illustration of how tissue specificity is related to specialization of protein function (Greene et al., 2015), and approaches able to directly profile proteins’ distinct interaction neighborhoods in different tissues can leverage this specificity to generate more accurate hypotheses about tissue-specific protein actions.

5.2 Transfer of cellular functions to a new tissue

Experimental setup. In the transfer learning setting, we attempt to transfer knowledge learned in one or more source layers and use it for prediction in a target layer.

As before, we apply OhmNet to obtain a separate feature vector for every node and every layer in an unsupervised way. We then consider, in turn, every tissue as a target layer and all other tissues as source layers. For every function and every source layer, we train a separate classifier using the same classification model as in Section 5.1. We then predict functions for the target layer using only classifiers trained on the source layers. That is, we aim to predict cellular functions taking place in the target tissue without having access to any cellular function gene annotation in that tissue, i.e., we pretend the target tissue has no annotations. Prediction for one node in the target layer is the weighted average of predictions of the classifiers trained on source layers. Weights reflect hierarchy-based distances of source tissues from the target tissue. They are determined by the closed-form expressions mathematically equivalent to OhmNet’s regularization (details omitted due to space constraints).

Experimental results. Table 2 shows the classification accuracy results for transfer learning. Shown are the scores for ten tissues with best performance on cellular function prediction task. “Non-transfer”: a classifier is trained on a target tissue and then used to predict functions, surpassing other methods by up to 12.0% (AUROC) and area under precision-recall curve (AUPRC) scores for tissue-specific cellular function prediction. Values in the brackets are halves of the interquartile distance. OhmNet’s results are statistically significant with a p-value of less than 0.05.

Table 1. Area under ROC curve (AUROC) and area under precision-recall curve (AUPRC) scores for tissue-specific cellular function prediction. Values in the brackets are halves of the interquartile distance. OhmNet’s results are statistically significant with a p-value of less than 0.05.

| Approach                              | AUROC (Non-transfer) | AUROC (Transfer) |
|---------------------------------------|-----------------------|------------------|
| Tensor decomposition                  | 0.674 (± 0.124)       | 0.235 (± 0.052)  |
| Minimum curvilinear embedding         | 0.674 (± 0.064)       | 0.248 (± 0.071)  |
| Independent LINE                      | 0.642 (± 0.053)       | 0.261 (± 0.068)  |
| Collapsed LINE                        | 0.663 (± 0.047)       | 0.271 (± 0.053)  |
| Independent Node2vec                  | 0.649 (± 0.063)       | 0.283 (± 0.052)  |
| Collapsed Node2vec                    | 0.697 (± 0.085)       | 0.298 (± 0.061)  |
| GeneMania                             | 0.683 (± 0.077)       | 0.274 (± 0.094)  |
| Network-based tissue-specific SVM     | 0.701 (± 0.091)       | 0.281 (± 0.059)  |
| Tissue-specific network propagation   | 0.675 (± 0.051)       | 0.265 (± 0.083)  |
| OhmNet                                | 0.756 (± 0.067)       | 0.336 (± 0.045)  |

Table 2. Area under ROC curve (AUROC) scores for transfer learning. Shown are the scores for ten tissues with best performance on cellular function prediction task. “Non-transfer”: a classifier is trained on a target tissue and then used to predict cellular functions in the same tissue (Section 5.1). “Transfer”: classifiers are trained on all non-target tissues and then used to predict cellular functions in the target tissue (Section 5.2).

| Target tissue              | AUROC (Non-transfer) | AUROC (Transfer) |
|---------------------------|----------------------|------------------|
| Natural killer cell       | 0.834 (± 0.076)      | 0.776 (± 0.063)  |
| Placenta                  | 0.830 (± 0.082)      | 0.758 (± 0.068)  |
| Spleen                    | 0.803 (± 0.030)      | 0.799 (± 0.043)  |
| Liver                     | 0.803 (± 0.047)      | 0.741 (± 0.025)  |
| Forebrain                 | 0.796 (± 0.036)      | 0.755 (± 0.037)  |
| Macrophage                | 0.789 (± 0.037)      | 0.724 (± 0.024)  |
| Epidermis                 | 0.785 (± 0.030)      | 0.749 (± 0.032)  |
| Hematopoietic stem cell   | 0.784 (± 0.035)      | 0.744 (± 0.036)  |
| Blood plasma              | 0.784 (± 0.027)      | 0.703 (± 0.039)  |
| Smooth muscle             | 0.778 (± 0.031)      | 0.729 (± 0.041)  |
| Average                   | 0.799                | 0.746            |
to an only 7% average decrease in the AUC scores. We get the smallest performance differences for target tissues with many biologically similar source tissues (i.e., source layers) in the tissue network. For example, performance difference for the forebrain is only 5.2%, which is due to the fact that there are nine other layers in the tissue network closely related to the forebrain, such as the cerebellum and the midbrain. Considering all 48 tissues with tissue-specific cellular functions, OhmNet outperforms all comparison methods on most transfer tasks, achieving a gain of up to 20.3% over the closest benchmark in AUC scores (scores not shown). Notice that we exclude GeneMania in the comparison because it is not amenable to transfer learning. This result suggests that considering the relationships between tissues when learning features for proteins has a significant impact on transfer performance.

Generally speaking, we observed that the transferability of classifiers decreased when the tree-based distance between the source and the target tissue in the tissue hierarchy increased, which is consistent with the empirical evidence in transfer learning (Yosinski et al., 2014). This also matches our intuition that a source tissue should be most informative for predicting cellular functions in an anatomically close target tissue (e.g., source and target tissues are both part of the same organ).

5.3 The multiscale model of brain tissues

We have seen in Section 4.1 that human tissues have a multi-level hierarchical organization. The tissue hierarchy categorizes tissues into: cell types, groups of cells with similar structure and function; organs, groups of tissues that work together to perform a specific activity; and organ systems, groups of two or more tissues that work together for the good of the entire body. We now aim to empirically demonstrate this fact and show that OhmNet in fact can discover embeddings that obey this organization.

We first construct a multi-layer brain network by integrating nine brain-specific protein interaction networks (e.g., the cerebellum, frontal lobe, brainstem, and other brain tissues). Each of nine brain-specific networks is one layer in the multi-layer network. The layers are organized according to a two-level hierarchy (Figure 5a). We run OhmNet on this multi-layer network to find node features in a purely unsupervised way. We then map the nodes to the 2-D space based on the learned features. This way we assign every node in every layer to a point in the two-dimensional space based solely on the node’s learned features. We then visualize the points and color them based on the layer they belong to.

Figure 5b shows the example for the brainstem tissues: substantia nigra, pons, midbrain, and medulla oblongata. Laying out these tissue-specific networks is very challenging as the four brainstem tissues are very closely related to each other in the human body. However, the visualization using OhmNet performs quite well. Notice how points of the same color are closely distributed, and how well regions of the same color are separated from each other. In the brainstem example, this means that OhmNet generates a meaningful layout of the brainstem tissue-specific networks, in which proteins belonging to the same tissues are clustered together.

Figure 5c shows the example for the brain, which is located one level up from the brainstem in the tissue hierarchy. Again, OhmNet produces a meaningful layout of the nine brain tissue-specific networks.

Additionally, we repeated this analysis by visualizing protein features learned by running principal component analysis (PCA) or non-negative matrix factorization (NMF) algorithm on the brain-specific PPI networks. Acknowledging the subjective nature of this analysis, we observed that visualizations using PCA or NMF were not very meaningful, as proteins belonging to the same tissue were not clustered together (data not shown).

OhmNet’s result in Figure 5 is especially appealing because of two reasons. First, it shows that OhmNet can learn node features that adhere to a given hierarchy of layers. In the brain example, OhmNet learns the protein features that expose the multiscale tissue hierarchy. Second, it shows that OhmNet can generate meaningful visualizations of network embeddings despite the fact that OhmNet’s objective is independent of the visualization task.

6 Conclusion

We presented OhmNet, an approach for unsupervised feature learning in multi-layer networks. We use OhmNet to learn state-of-the-art task-independent protein features on a multi-layer network with 107 tissues. OhmNet models tissue interdependence up and down a tissue hierarchy spanning dozens of biological scales. The learned features achieve excellent accuracy on the cellular function prediction task, allow us to transfer functions to unannotated tissues, and provide insights into tissues.

There are several directions for future work. Our approach assumes the dependencies between layers are given in the form of a hierarchy. In several biological scenarios, the dependencies are given in the form of a graph, and we hope to extend the approach to handle graph-based dependencies. As the learned protein features are independent of any downstream task, it would be interesting to see whether our approach performs equally well for gene-disease association prediction and disease pathway detection.

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References

Antanaviciute, A. et al. (2015). GeneTIER: prioritization of candidate disease genes using tissue-specific gene expression profiles. Bioinformatics, 31(16), 2728–2735.

Ashburner, M. et al. (2000). Gene Ontology: tool for the unification of biology. Nature Genetics, 25(1), 25–29.

Baracaldo, G., Schapire, R. E., and Troyanskaya, O. G. (2006). Hierarchical multi-label prediction of gene function. Bioinformatics, 22(7), 830–836.

Belkin, M. and Niyogi, P. (2003). Laplacian eigenmaps and spectral techniques for embedding and clustering. In NIPS, volume 14, pages 585–591.

Cannistraci, C. V., Alainis-Lobato, G., and Ravasi, T. (2013). Minimum curvature line to enhance topological prediction of protein interactions by network embedding. Bioinformatics, 29(13), 1199–1209.

Carvunis, A.-R. and Ideker, T. (2014). Siri of the cell: what biology could learn from the iPhone. Cell, 157(3), 534–538.

Chang, A., Schomburg, I., Placek, S., Jeske, L., Ulbrich, M., Xiao, M., Sensen, C. W., and Schomburg, D. (2014). BRENDA in 2015: exciting developments in its 25th year of existence. NAR, page gku1068.

Chatzi-Aryamonti, A. et al. (2015). The BioGRID interaction database: 2015 update. NAR, 43(D1), D470–D478.

Costanzo, M. et al. (2016). A global genetic interaction network maps a wiring diagram of cellular function. Science, 355(6306), aaf1420.

De Domenico, M. et al. (2014). Navigability of interconnected networks under random failures. PNAS, 111(23), 8351–8356.

De Domenico, M., Solé-Ribalta, A., Omodei, E., Gómez, S., and Arenas, A. (2015). Ranking in interconnected multilayer networks reveals versatile nodes. Nature Communications, 6.

De Domenico, M., Granell, C., Porter, M. A., and Arenas, A. (2016). The physics of spreading processes in multilayer networks. Nature Physics, 12, 901–906.
Fig. 5: **Visualization of the brain tissue-specific protein interaction networks.** A. The two-level brain tissue hierarchy as specified by the BRENDA Tissue Ontology (Chang et al., 2014) and used in the case study in Section 5.3. Leaves of the hierarchy (in blue) represent nine brain tissues each of which is associated with a tissue-specific protein interaction network. B. Visualization of the brainstem-specific networks. The proteins are mapped to the 2-D space using the t-SNE package with learned features as input. Color of a node indicates the tissue of the protein. C. Visualization of the brain-specific networks. The proteins are mapped and colored using the same procedure as in B.

Dutkowski, J., Kramer, M., Surma, M. a., Balakrishnan, R., Cherry, J. M., Krogan, N. J., and Ideker, T. (2012). A gene ontology inferred from molecular networks. *Nature Biotechnology*, 31(1), 38–45.

Fagerberg, L. et al. (2014). Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Molecular & Cellular Proteomics*, 13(2), 397–406.

Gangoda, G. U., Wang, J., Wu, F.-X., and Li, M. (2014). Prediction of disease genes using tissue-specific gene-gene network. *BMC Systems Biology*, 8(3), S3.

Greene, C. S. et al. (2015). Understanding multicellular function and disease with human tissue-specific networks. *Nature Genetics*, 47(6), 569–576.

Grover, A. and Leskovec, J. (2016). Node2vec: Scalable feature learning for networks. In *KDD*, pages 855–864.

GTEx, C. et al. (2015). The genotype-tissue expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science*, 348(6235), 648–660.

Guo, Y. et al. (2012). Tissue-specific functional networks for prioritizing phenotype and disease genes. *PLoS Computational Biology*, 8(9), e1002694.

Hayes, W., Sun, K., and Pržulj, N. (2013). Graphlet-based measures are suitable for biological network comparison. *Bioinformatics*, 29(4), 483–491.

Hou, C., Nie, F., Li, X., Yi, D., and Wu, Y. (2014). Joint embedding learning and sparse regression: A framework for unsupervised feature selection. *IEEE Transactions on Cybernetics*, 44(6), 793–804.

Hu, J. X., Thomas, C. E., and Brunak, S. (2016). Network biology concepts in complex disease comorbidities. *Nature Reviews Genetics*, 17, 615L–629.

Kitsak, M. et al. (2016). Tissue specificity of human disease module. *Scientific Reports*, 6.

Kotlyar, M., Pastrello, C., Sheahan, N., and Jurisica, I. (2015). Integrated interactions database: tissue-specific view of the human and model organism interactomes. *Nucleic Acids Research*, page gkv1115.

Kramer, M. et al. (2014). Inferring gene ontologies from pairwise similarity data. *Bioinformatics*, 30(12), i34–i42.

Li, Y., Tarlow, D., Brockschmidt, M., and Zemel, R. (2015). Gated graph sequence neural networks.

Lois, C., Hong, E. J., Pease, S., Brown, E. J., and Baltimore, D. (2002). Germline transmission and tissue-specific expression of transgenes delivered by lentiviral vectors. *Science*, 295(5556), 868–872.

Lopes, T. J. et al. (2011). Tissue-specific subnetworks and characteristics of publicly available human protein interaction databases. *Bioinformatics*, 27(17), 2414–2421.

Magger, O., Waldman, Y. R., Ruppin, E., and Sharan, R. (2012). Enhancing the prioritization of disease-causing genes through tissue-specific protein interaction networks. *PLoS Computational Biology*, 8(9), e1002600.

Menche, J., Sharma, A., Kitsak, M., Ghiaasian, S. D., Vidal, M., Loscalzo, J., and Barabási, A.-L. (2015). Uncovering disease-disease relationships through the incomplete interactome. *Science*, 347(6224), 1257601.

Mikolov, T., Chen, K., Corrado, G., and Dean, J. (2013). Efficient estimation of word representations in vector space. In *ICLR*.

Mostafavi, S. and Morris, Q. (2009). Using the gene ontology hierarchy when predicting gene function. In *IJCAI*, pages 419–427.

Mostafavi, S., Ray, D., Warde-Farley, D., Grouios, C., and Morris, Q. (2008). GeneMANIA: a real-time multiple association network integration algorithm for predicting gene function. *Genome Biology*, 9(1), 1.

Nickel, M., Tresp, V., and Kriegel, H.-P. (2011). A three-way model for collective learning on multi-relational data. In *ICML*, pages 809–816.

Okabe, Y. and Medzhitov, R. (2014). Tissue-specific signals control reversible program of localization and functional polarization of macrophages. *Cell*, 157(4), 832–844.

Orchard, S. et al. (2013). The MIntAct project: L*’*intact as a common curation platform for 11 molecular interaction databases. *NAR*, page gkt1115.

Perozzetti, B., Al-Rifai, R., and Skiena, S. (2014). Deepwalk: Online learning of social representations. In *KDD*, pages 701–710.

Prasad, T. K., Goel, R., Kandasamy, K., Keerthikumar, S., Kumar, S., Mathivanan, S., Telikicherla, D., Raju, R., Shafran, B., Venugopal, A., et al. (2009). Human protein reference database 2009 update. *NAR*, 37(suppl 1), D767–D772.

Pržulj, N. (2007). Biological network comparison using graphlet degree distribution. *Bioinformatics*, 23(2), e177–e183.

Radvanac, P., Clark, W. T., Oron, T. R., Schnoes, A. M., Wittkop, T., Sokolov, A., Graim, F., Funk, C., Verspoor, K., Ben-Hur, A., et al. (2013). A large-scale evaluation of computational protein function prediction. *Nature Methods*, 10(3), 221–227.

Rakyan, V. K. et al. (2008). An integrated resource for genome-wide identification and analysis of human tissue-specific differentially methylated regions (tdhms). *Genome Research*, 18(9), 1518–1529.

Rolland, T., Taşan, M., Charlotteaux, B., Pevzner, S. J., Zhong, Q., Sahni, N., Yi, S., Lennm, I., Fontanillo, C., Mosca, R., et al. (2014). A proteome-scale map of the human interactome network. *Cell*, 159(5), 1212–1226.

Ruepp, A., Waegele, B., Lechner, M., Brauner, B., Denger-Kaltenbach, I., Fobo, G., Frishman, G., Montrone, C., and Mewes, H.-W. (2010). CORUM: the comprehensive resource of mammalian protein complexes-2009. *NAR*, 38(suppl 1), D497–D501.

Stojanova, D., Ceci, M., Malerba, D., and Dzeroski, S. (2013). Using PPI network evaluation of computational protein function prediction. *Nature Methods*, 10(3), 221–227.

Tang, J., Qu, M., Wang, M., Zhang, M., Yan, J., and Mei, Q. (2015). Line: Large-scale information network embedding. In *WWW*, pages 1067–1077.

Tang, L., Wang, X., and Liu, H. (2012). Scalable learning of collective behavior. *IEEE Transactions on Knowledge and Data Engineering*, 24(6), 1080–1091.

Tenenbaum, J. B., De Silva, V., and Langford, J. C. (2000). A global geometric framework for nonlinear dimensionality reduction. *Science*, 290(5500), 2319–2323.
Vidulin, V., Šmuc, T., and Supek, F. (2016). Extensive complementarity between gene function prediction methods. *Bioinformatics*, page btw532.

Wang, D., Cui, P., and Zhu, W. (2016a). Structural deep network embedding. In *KDD*, pages 1225–1234. ACM.

Wang, W., Hao, J., Zheng, S., Fan, Q., He, A., Wen, Y., Guo, X., Wu, C., Wang, S., Yang, T., *et al.* (2016b). Tissue-specific pathway association analysis using genome-wide association study summaries. *Bioinformatics*, page btw595.

Xiaoyi, L., Du Nan, L. H., *et al.* (2014). A deep learning approach to link prediction in dynamic networks. In *SDM*.

Yeger-Lotem, E. and Sharan, R. (2015). Human protein interaction networks across tissues and diseases. *Frontiers in Genetics*, 6, 257.

Yosinski, J., Clune, J., Bengio, Y., and Lipson, H. (2014). How transferable are features in deep neural networks? In *NIPS*, pages 3320–3328.

Yu, M., Kramer, M., Dutkowski, J., Srivas, R., Licon, K., Keesberg, J., Ng, C., Sharan, R., and Ideker, T. (2016). Translation of genotype to phenotype by a hierarchy of cell systems. *Cell Systems*, 2(2), 77–88.

Zhai, S. and Zhang, Z. (2015). Dropout training of matrix factorization and autoencoder for link prediction in sparse graphs. SIAM.

Zitnik, M. and Zupan, B. (2015). Data fusion by matrix factorization. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 37(1), 41–53.

Zuberi, K., Franz, M., Rodriguez, H., Montojo, J., Lopes, C. T., Bader, G. D., and Morris, Q. (2013). GeneMANIA prediction server 2013 update. *NAR*, 41(W1), W115–W122.