

Constructing Knowledge Graphs and Their Biomedical Applications

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Abstract

Knowledge graphs can support many biomedical applications. These graphs represent biomedical concepts and relationships in the form of nodes and edges. In this review we discuss how these graphs are constructed and applied with a particular focus on the ways machine learning approaches are changing these processes. In many examples in the literature, biomedical knowledge graphs have been constructed from pre-existing databases that are populated by experts via manual curation, but we are now also seeing a more robust use of automatic systems. A number of techniques are used to represent knowledge graphs, but often machine learning methods are used to learn a low-dimensional representation that can support many different applications. This representation is designed to preserve a knowledge graph's local and/or global structure. Additional machine learning methods can be applied to this representation to make predictions within genomic, pharmaceutical, and clinical domains. We frame our discussion first around knowledge graph construction then around unifying techniques and unifying applications separately. Advances in machine learning for biomedicine are creating new opportunities across many domains, and we note potential avenues for future work with knowledge graphs that appear particularly fruitful.

Introduction

Knowledge graphs are a practical resource for many real world applications. They have been used in social media mining to classify nodes [1] or to create a recommendation system [2]. Knowledge graphs have also been used to understand natural language via interpreting simple questions and using relational information to provide answers [3,4]. In a biomedical setting these graphs have been used to prioritize genes relevant to disease [5,6,7,8], perform drug repurposing [9] and identify drug-target interactions [10].

Despite their utility, precisely defining a knowledge graph is a difficult task because there are multiple conflicting definitions [11]. For this review, we define a knowledge graph as the following: a resource that integrates single or multiple sources of information into the form of a graph. This graph allows for the capacity to make semantic interpretation, continuously incorporate new information and uncover novel hidden knowledge through computational techniques and algorithms. Based on this definition resources like Hetionet [9] would be considered a knowledge graph. Hetionet integrates multiple sources of information into the form of a graph (example shown in Figure 1) and was used to derive novel information concerning unique drug treatments [9]. We do not consider databases like DISEASES [12] and DrugBank [13] to be knowledge graphs. These resources contain essential information, but do not represent their data in graph form.

Knowledge graphs are often constructed from manually curated databases [9,14,15,16]. These sources provide previously established information that can be incorporated into a graph. For example, a graph using DISEASES [12] as a resource would have genes and diseases as nodes, while edges would be added between nodes that have an association. This example shows a single type of relationship; however, there are graphs that use databases with multiple relationships. Other approaches have used natural language processing techniques to build knowledge graphs [17,18]. One example used a text mining system to extract sentences that indicated a protein interacting with another protein [19]. Once these sentences have been identified, they are incorporated as evidence for establishing edges in a knowledge graph.

In this review we describe various approaches for constructing and applying knowledge graphs in a biomedical setting. We discuss the pros and cons of constructing a knowledge graph via manually curated databases and via text mining systems. We also compare assorted approaches for applying knowledge graphs to solve biomedical problems. Lastly, we conclude on the practicality of knowledge graphs and point out future applications that have yet to be explored.

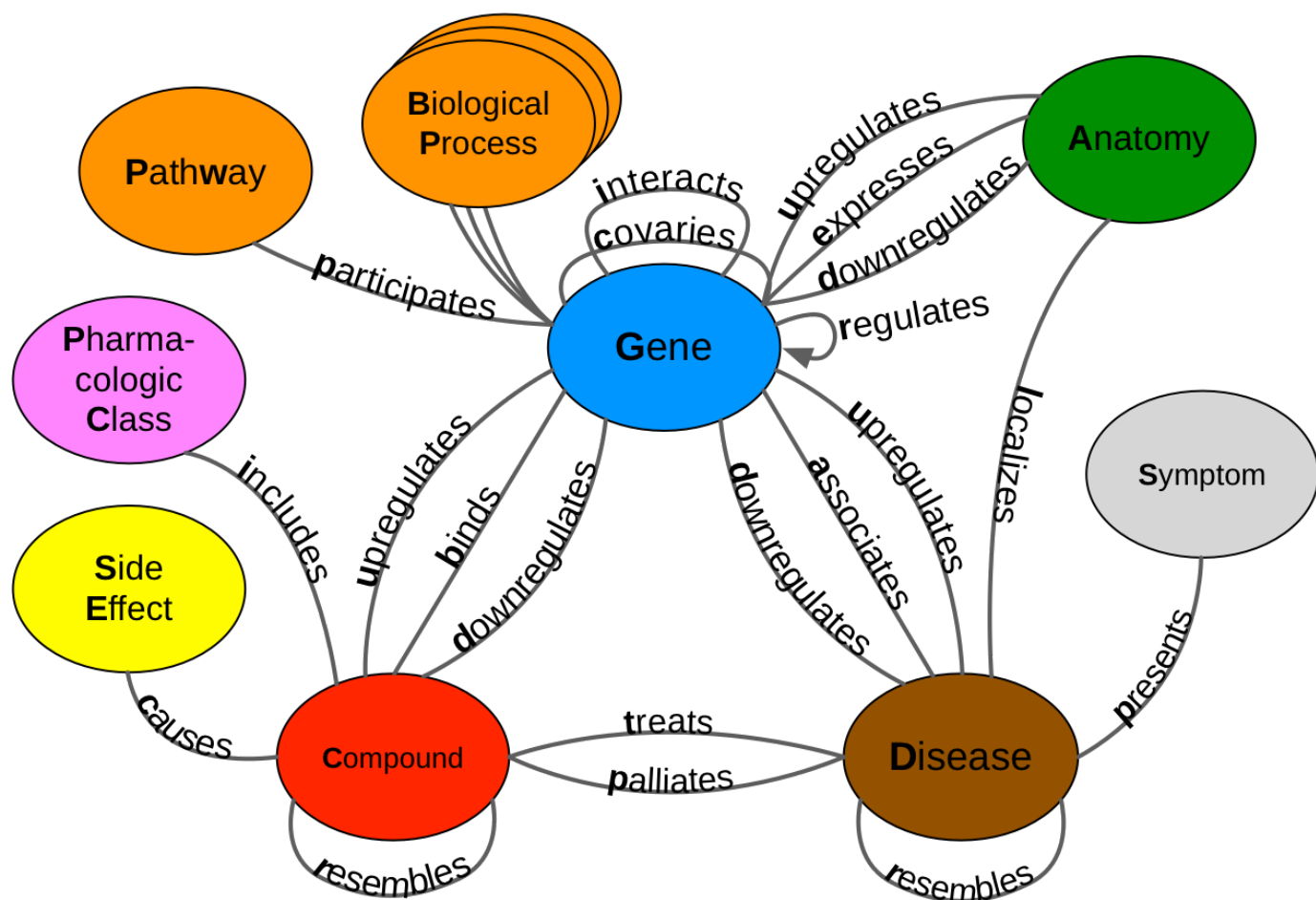


Figure 1: A metagraph (schema) of the heterogeneous network used in the Rephetio project [9]. This undirected network depicts pharmacological and biomedical information. The nodes (circles) represent entities and edges (lines) depict relational information between two entities.

Building Biomedical Knowledge Graphs

Knowledge graphs can be constructed in many ways using resources such as text or pre-existing databases. Usually, knowledge graphs are constructed using pre-existing databases. These databases are constructed by domain experts using approaches ranging from manual curation to automated techniques, such as text mining systems. Manual curation is a process that involves extensive use of domain experts to read papers and detect sentences that assert a relationship. Automated approaches involve the use of machine learning or natural language processing techniques to rapidly detect sentences of interest. We categorize these automated approaches into the following groups: rule-based extraction, unsupervised machine learning, and supervised machine learning. We discuss examples of each type of approach and synthesize the strengths and weaknesses of each.

Constructing Databases and Manual Curation

Database construction can date back all the way to 1956 where the first database contained a protein sequence of the insulin molecule [20]. This process involves gathering relevant text such as journal articles, abstracts, or web-based text. At this point curators can read gathered text and detect relationship asserting sentences (i.e. relationship extraction). An alternative to use a text mining system to filter out extraneous sentences, then incorporate curators to perfect the system's findings. This semi-automatic approach is way to augment curators throughout the curation process. We discuss the pros and cons of using manual curation for relationship extraction and mention databases that use this method to populate their fields.

Notable databases have been constructed via manual curation (Table {[[??]]}). For example, COSMIC [21] was constructed via a group of domain experts scanning the literature for key cancer related genes. This database has reached close to 35M entries in 2016 [21] and grew to a total of 45M entries in 2019 [22]. Studies have shown that these databases contain relatively precise data, but in low quantities [23,24,25,26,27,28,29]. This happens because the high publication rate is too much for curators to keep up [30]. This findings highlight a critical need for future approaches to be fast enough to compete with an increasing publication rate.

Semi-automatic methods are a way to augment curators during the curation process [27,31,32,33,34,35,36]. First step in this context is to use an automatic system to initially extract sentences from text. This process filters out irrelevant sentences, which means less text for curators to sift through. After the pre-filtering step curators can approve or remove the identified sentences. This semi-automatic process was found to speed up the curation process compared to manual approach [31,37]. Curators in [37] saved an average of 2.8 hours of overall time while curators in [31] saved about the same amount of time (2 hours). Despite the speed up, this process is prone to produce bias results. As automated systems excel in identifying sentences for commonly occurring relationships, they miss out on lessor known relationships [31]. Plus, these systems have a hard time parsing ambiguous sentences that naturally occur in text. This complication results in curators have a difficult time correcting these systems [31]. Given these caveats, a future direction would be using or creating approaches that can mitigate the relationship bias. Furthermore, future approaches should look into using techniques that simplify sentences to solve the ambiguity issue [38,39].

Despite the negatives of manual curation, it is still an essential process for relationship extraction approaches. This process can be used to generate gold standard datasets that automated systems use for validation [40,41]. Furthermore, manual curation can be used during the training process of automated systems (i.e. active learning) [42]. It is important to remember that manual curation alone is precise, but results in low recall rates [29]. Future databases should consider initially relying on automated methods to obtain sentences at an acceptable recall level, then incorporate manual curation as a way to fix or remove irrelevant results.

Database [Reference]	Short Description	Number of Entries	Entity Types	Relationship Types	Method of Population
Entrez-Gene [43]	NCBI's Gene annotation database that contains information pertaining to genes, gene's organism source, phenotypes etc.	7,883,114	Genes, Species and Phenotypes	Gene-Phenotypes and Genes-Species mappings	Semi-automated curation
UniProt [44]	A protein protein interaction database that contains proteomic information.	560,823	Proteins, Protein sequences	Protein-Protein interactions	Manual and Automated Curation
PharmGKB [45]	A database that contains genetic, phenotypic, and clinical information related to pharmacogenomic studies.	43,112	Drugs, Genes, Phenotypes, Variants, Pathways	Gene-Phenotypes, Pathway-Drugs, Gene-Variants, Gene-Pathways	Manual Curation and Automated Methods

Database [Reference]	Short Description	Number of Entries	Entity Types	Relationship Types	Method of Population
COSMIC [21]	A database that contains high resolution human cancer genetic information.	35,946,704	Genes, Variants, Tumor Types	Gene-Variant Mappings	Manual Curation
BioGrid [46]	A database for major model organisms. It contains genetic and proteomic information.	572,084	Genes, Proteins	Protein-Protein interactions	Semi-automatic methods
Comparative Toxicogenomics Database [47]	A database that contains manually curated chemical-gene-disease interactions and relationships.	2,429,689	Chemicals (Drugs), Genes, Diseases	Drug-Genes, Drug-Disease, Disease-Gene mappings	Manual curation and Automated systems
Comprehensive Antibiotic Resistance Database [48]	Manually curated database that contains information about the molecular basis of antimicrobial resistance.	174,443	Drugs, Genes, Variants	Drug-Gene, Drug-Variant mappings	Manual curation
OMIM [49]	A database that contains phenotype and genotype information	25,153	Genes, Phenotypes	Gene-Phenotype mappings	Manual Curation

Table. A table of databases that used a form of manual curation to populate entries. Reported number of entities and relationships are relative to time of publication. {#tbl:manual-curated-databases}

Text Mining for Relationship Extraction

Rule-Based Relationship Extraction

Rule-based extraction consists of identifying sentences that contain important keywords or grammatical patterns that allude to relationships of interest. Keywords are established via expert knowledge or through the use of pre-existing ontologies. Grammatical patterns are constructed via experts curating parse trees, which are tree data structures that depict a sentence's grammatical structure. Parse trees come into two forms: a constituency parse tree and a dependency parse tree. Both trees use part of speech tags, labels that dictate the grammatical role of a word such as noun, verb, adjective, etc, for construction. A constituency parse tree breaks a sentence down into subphrases (Figure 3) while dependency path trees analyze the grammatical structure of a sentence (Figure 2). Many text mining approaches [50,51,52] use such trees to generate features for machine learning algorithms. These approaches are discussed in later sections. For this section we focus on approaches that mainly use rule based extraction to detect sentences that assert a relationship.

Grammatical patterns can simplify sentences for easy extraction [39,53]. Jonnalagadda et al. used a set of grammar rules inspired by constituency trees to reshape complex sentences with simpler versions [39]. These simplified versions were manually curated to determine the presence of a relationship. By simplifying sentences this approach achieved high recall, but had low precision [39]. Other approach used simplification techniques to make extraction easier [54,55,56,57]. Tudor et al., simplified sentences to detect protein phosphorylation events [56]. The sentence simplifier broke complex sentences that contain multiple protein events into smaller sentences that contain only one distinct event. By breaking these sentences down the authors were able to increase their recall. However, sentences that contained ambiguous directionality or multiple phosphorylation events were too complex for the simplifier. As a consequence the simplifier produced errors in recall [56]. These errors highlight a crucial need for future algorithms to be generalizable enough to handle various forms of complex sentences.

Pattern matching is a fundamental approach used to detect relationship asserting sentences. In this context patterns can consist of phrases from constituency trees, a set of keywords or some combination of both to detect sentences [27,58,59,60,61,62]. Xu et al. designed a pattern matcher system to detect sentences in PubMed abstracts that indicate drug-disease treatments [61]. This system matched drug-disease pairs from clinicaltrials.gov to drug-disease pairs mentioned in abstracts. This matching process aided the authors in identifying sentences that were used to create simple patterns, such as “Drug in the treatment of Disease” [61], to match sentences in a wide variety of abstracts. The authors hand curated two datasets for evaluation and achieved a high precision score of 0.904 and a low recall score of 0.131 [61]. This low recall score was based on constructed patterns being very specific to top occurring drug pairs. This flaw resulted in rarely occurring pairs having a high likelihood of being missed. Following approaches using constituency trees, some approaches used dependency trees to construct patterns [50,63]. Depending upon the nature of the algorithm, dependency trees could be more appropriate than constituency trees and vice versa. The performance difference between the two approaches still remains as an open question for future exploration.

Rules based methods provide a basis for many relationship extraction systems. Approaches in this category range from simplifying sentences for easy extraction to identifying sentences based on matched key phrases or grammatical patterns. Both require a significant amount of manual effort and expert knowledge to perform well. A future direction is to develop ways to automatically construct these hand-crafted patterns, which would accelerate the process of creating new rule-based systems.

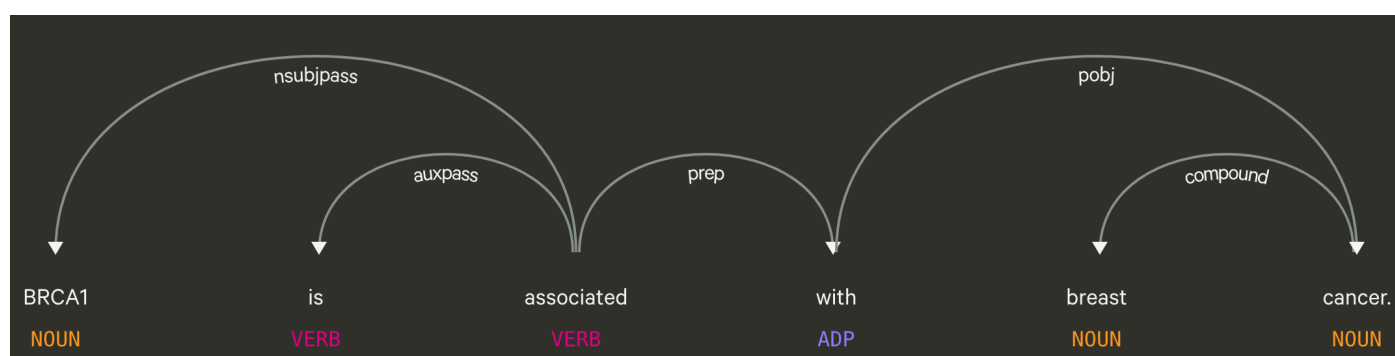


Figure 2: A visualization of a dependency parse tree using the following sentence as in example: “BRCA1 is associated with breast cancer” [64]. For these type of trees the root begins at the main verb of a sentence. Each arrows depicts the dependency shared between two words. For example, the dependency between BRCA1 and associated is nsubjpass, which stands for passive nominal subject. This means that BRCA1 is the subject of the sentences and it is being referred to by the word associated.

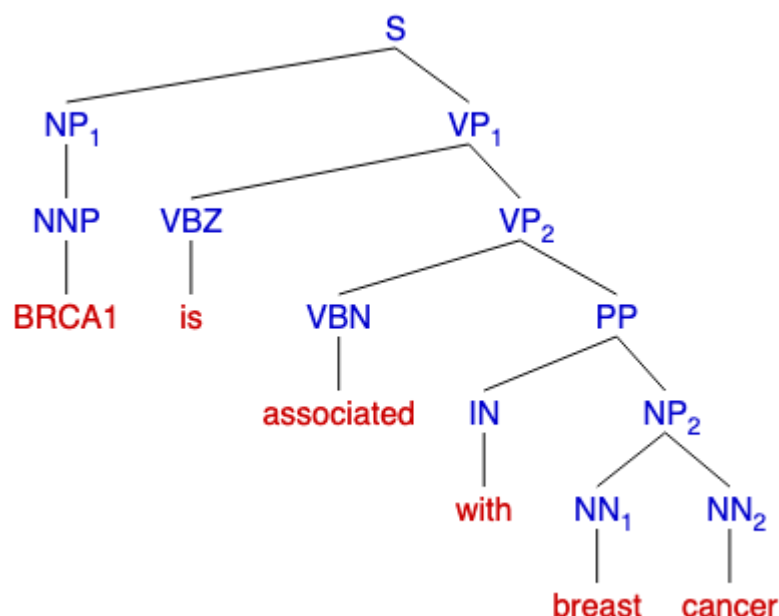


Figure 3: A visualization of a constituency parse tree using the following sentence: “BRCA1 is associated with breast cancer” [65]. This type of tree has the root beginning at the start of the sentence. Each word is grouped into subphrases depending on the part of speech tags of a word. For example, the word “associated” is a past participle verb (VBN) that belongs to the verb phrase (VP) subgroup.

Extracting Relationships Without Labels

Unsupervised methods of extraction involve drawing inferences from data without the use of labels. These methods involve some form of clustering or statistical calculations. In this section we discuss methods that use unsupervised learning to detect relationship asserting sentences from text.

An unsupervised method to extract relationships exploits the fact that two entities can appear together in text. This kind of event is called co-occurrence and studies that use this phenomenon can be found in table 1. Two databases DISEASES [12] and STRING [66] were populated using a co-occurrence scoring method on PubMed abstracts. Both databases used the same scoring method that measured the frequency of co-mention pairs within individual sentences as well as the abstracts themselves. This method assumes independence between each individual occurrence. Under this assumption mention pairs that occur more than expected were presumed to indicate the presence of an association or interaction. This approach was able to identify 543,405 disease gene associations [12] and 792,730 high confidence protein protein interactions [66], but is limited to only using PubMed abstracts.

Full text articles are able to drastically amplify text mining power to detect relationships [67,68]. Westergaard et al. used a co-occurrence approach, similar to DISEASES [12] and STRING [66], to mine full articles for protein-protein interactions and other protein related information [67]. The authors discovered that full text provided better prediction power than using abstracts alone. This improvement suggests that future text mining approaches should consider using full text to increase detection power.

Unsupervised methods have been focused on treating multiple biomedical relationships as multiple isolated problems. These methods repeatedly use the same model for each biomedical relationship type. An alternative to this perspective is to capture all different relationship types at once. Clustering is an approach that accomplish this concept of simultaneous extraction. Percha et al. used a biclustering algorithm on generated dependency parse trees to group PubMed abstract sentences [69]. Each cluster was manually curated to determine which relationship they represented. This approach captured 4,451,661 dependency paths for 36 different groups [69]. Despite the success, this approach suffered from technical issues such as dependency tree parsing errors. This type of error

resulted in sentences not being grouped by the clustering algorithm [69]. Future clustering approaches should consider simplifying sentences to prevent this type of issue.

Overall unsupervised methods provide a means to rapidly find relationship asserting sentences without the need of annotated text. Approaches in this category range from using co-occurrence scores to clustering sentences. These methods provide a generalizable framework that can be used on large repositories of text. Future methods can improve detection power by considering the use of methods that simplify sentences and use datasets that include full text articles.

Table 1: Table of approaches that mainly use a form of co-occurrence.

Study	Relationship of Interest
CoCoScore [70]	Protein-Protein Interactions, Disease-Gene and Tissue-Gene Associations
Rastegar-Mojarad et al. [71]	Drug Disease Treatments
CoPub Discovery [72]	Drug, Gene and Disease interactions
Westergaard et al. [67]	Protein-Protein Interactions
DISEASES [12]	Disease-Gene associations
STRING [73]	Protein-Protein Interactions
Singhal et al. [74]	Genotype-Phenotype Relationships

Supervised Relationship Extraction

Supervised extraction uses labeled relationships to learn text patterns that correspond to positively labeled relationships instead of negative ones. Most of these approaches have flourished due to pre-labelled publicly available datasets (Table 2). These datasets were constructed by curators for shared open tasks [75,76] or as a means to provide the scientific community with a gold standard [76,77,78]. Approaches that use these available datasets range from using support vector machines (SVMs) with custom kernels to deep learning with algorithms that can construct their own features. In the rest of this section we discuss approaches that use supervised methods to detect relationship-asserting sentences.

Extracting relationships in a supervised setting can involve mapping textual input onto a high dimensional space. Support vector machines are a type of classifier that can accomplish this task with a mapping function called a kernel [52,79]. These kernels take information such as a sentence's dependency tree [50,51], part of speech tags [52] or even word counts [79] and map them onto a dense feature space. Within this space, the methods learn a hyperplane that separates sentences in the positive class (mentions a relationship) from the negative class (does not mention a relationship). Kernels can be manually constructed or selected to cater to the relationship being extracted [51,52,79,79]. Determining the correct kernel requires expert knowledge to be successful and is a nontrivial task depending on the relationship. In addition to single kernel methods, a recent study used an ensemble of SVMs to extract disease-gene associations [80]. The ensemble outperformed notable disease-gene association extractors [63,81] in terms of precision, recall and F1 score. Overall, SVMs have been shown to be beneficial in terms of relationship mining; however, major focus have shifted to utilizing deep learning techniques to extract relationships as these approaches can perform non-linear mappings of high dimensional data.

Deep learning is an increasingly popular class of techniques that can construct their own features within a high dimensional space [82,83]. These methods use different forms of neural networks, such as recurrent or convolutional neural networks, to perform classification.

Recurrent neural networks (RNN) are designed for sequential analysis that consist of using a repeatedly updating hidden state to make predictions. An example of a recurrent neural network is a long short term memory (LSTM) network [84]. Cocos et al [85] used a LSTM to extract drug side effects from de-identified twitter posts, while Yadav et al. [86] used an LSTM to extract protein-protein interactions. Other works have used LSTMs to perform relationship extraction [85,87,88,89,90]. Despite the success of these networks, training can be difficult as these networks are highly susceptible to vanishing and exploding gradients [91,92]. One solution to this problem is to clip the gradients while the neural network trains [93]. Besides the gradient problem, these approaches peak in performance when the dataset reaches at least a tens of thousand of data points [94].

Convolutional neural networks (CNNs), which are widely applied for image analysis, use multiple kernel filters to capture small subsets of an overall image [83]. In the context of text mining an image is replaced with words within a sentence mapped to dense vectors (i.e., word embeddings) [95,96]. Peng et al. [97] used a CNN to extract sentences that mentioned protein-protein interactions and Zhou et al. [98] used a CNN to extract chemical-disease relations. Other approaches have used CNNs and variants of CNNs to extract relationship-asserting sentences [100,101,99]. Just like RNNs, these networks perform well when millions of labeled examples are present [94]. Future approaches that use CNNs or RNNs should consider solutions to obtaining these large quantities of data through means such as weak supervision [102], semi-supervised learning [103] or using pre-trained networks via transfer learning [104,105].

Semi-supervised learning [103] and weak supervision [102] are techniques that can construct large datasets for machine learning classifiers. Semi-supervised learning consists of combining labeled data with unlabeled data to extract relationships. For example, one study used a variational auto encoder with a LSTM network to extract protein-protein interactions from pubmed abstracts and full text [106]. This is an elegant solution to handle the small dataset problem, but requires labeled data to start. The dependency on labeled data makes finding under-studied relationships difficult as one would need to find or construct examples of the missing relationships in the beginning.

Weak or distant supervision takes a different approach that uses noisy or even erroneous labels to train classifiers [102,107,108,109]. Under this paradigm sentences are labeled based on their mention pair being present (positive) or absent (negative) in a database. Once these labels are obtained a machine learning classifier can now be trained to predict sentences [102]. For example, Thomas et al. [110] used distant supervision to train a support vector machine to extract sentences mentioning protein-protein interactions (ppi). Their SVM model achieved comparable performance against a baseline model; however, the noise generated via distant supervision was difficult to eradicate [110]. A number of efforts have focused on combining distant supervision with other types of labeling strategies to reduce the negative impacts of noisy knowledge bases [111,112,113]. Nicholson et al. [101] found that, in some circumstances, these strategies and rules can be reused across different types of biomedical edges to learn a heterogeneous knowledge graph if those edges describe similar physical concepts. This remains an active area of investigation with numerous associated challenges and opportunities. Overall, semi-supervised learning and weak supervision provide promising results in terms of relation extraction and future approaches should consider using those paradigms to train machine learning classifiers.

Table 2: A set of publicly available datasets for supervised text mining.

Dataset	Type of Sentences
AIMed [41]	PPI
BioInfer [114]	PPI
LLL [115]	PPI
IEPA [116]	PPI

Dataset	Type of Sentences
HPRD5 [77]	PPI
EU-ADR [40]	DaG
BeFree [81]	DaG
CoMAGC [78]	DaG
CRAFT [117]	DaG
Biocreative V CDR [76]	Compound induces Disease
Biocreative IV ChemProt [75]	CbG

Applying Knowledge Graphs to Biomedical Challenges

Knowledge graphs can help researchers tackle many biomedical tasks such as finding new treatments for existing drugs [9], aiding efforts to diagnose patients [118] and predicting associations between diseases and biomolecules [119]. In many cases, solutions rely on representing knowledges graphs in a low dimensional space, which is a process called representation learning. This space preserves a knowledge graph's local and/or global structure and can support efforts to apply machine learning methods to make predictions. We discuss the unifying techniques to construct this low dimensional space and unifying applications that use this space to solve biomedical problems.

Unifying Techniques

Mapping high dimensional data into a low dimensional space has greatly improved modeling performance in fields such as natural language processing [95,96] and image analysis [120]. The success of these approaches provides rationale for projecting knowledge graphs into a low dimensional space as well [121]. Techniques that perform this projection often require information on how nodes are connected with one another [122,123,124,125], while other approaches can work directly with the edges themselves [126]. We group methods for producing low-dimensional representations of knowledge graphs into the following three categories: matrix factorization, translational methods, and deep learning (Figure 4).

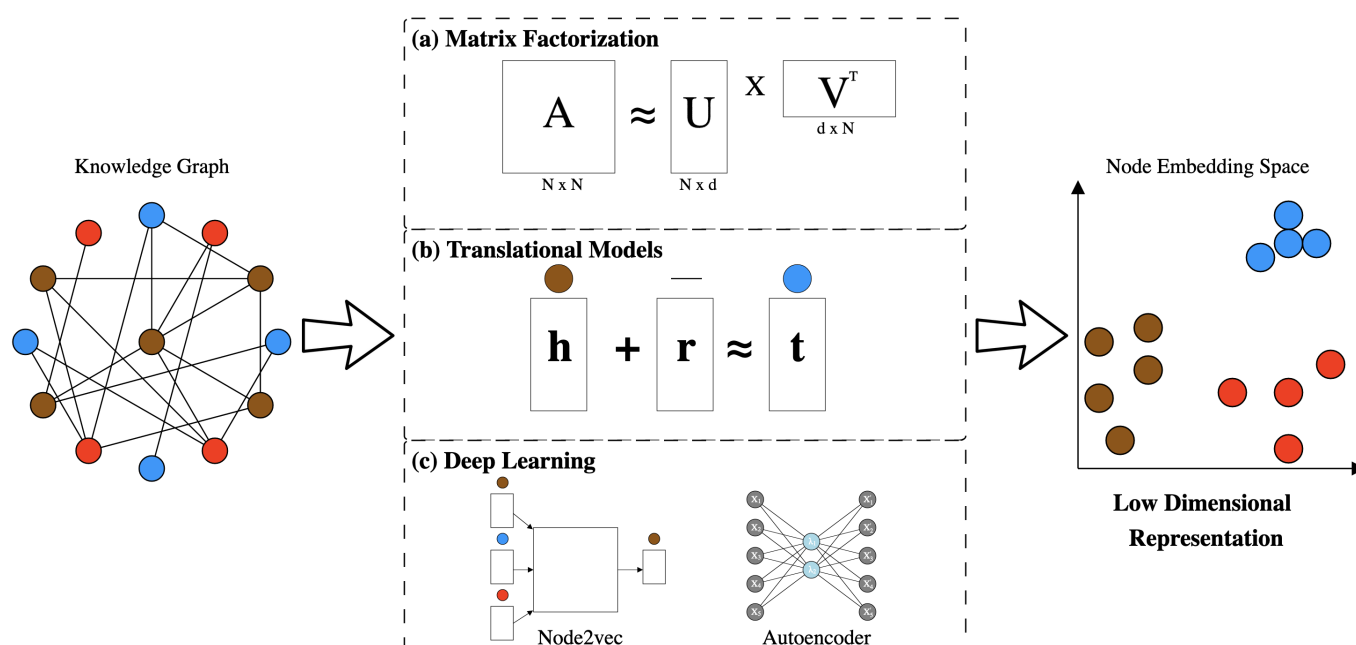


Figure 4: Pipeline for embedding knowledge graphs into a low dimensional space. Starting with a knowledge graph, embeddings can be generated using one of the following options: Matrix Factorization (a), Translational Models (b) or

Deep Learning (c). The output of this pipeline is an embedding space that clusters similar node types together.

Matrix Factorization

Matrix factorization is a technique that uses linear algebra to map high dimensional data into a low dimensional space. This projection is accomplished by decomposing a matrix into a set of small rectangular matrices (Figure 4 (a)). Notable methods for matrix decomposition include Isomap [127], Laplacian eigenmaps [128] and Principal Component Analysis (PCA) [129]/Singular Vector Decomposition (SVD) [130]. These methods were designed to be used on many different types of data; however, we discuss their use in the context of projecting knowledge graphs into a low dimensional space.

SVD [130] is an algorithm that uses matrix factorization to represent knowledge graphs in a low dimensional space. The input for this algorithm is an adjacency matrix (A), which is a square matrix where rows and columns represent nodes and each entry represents the presence of an edge between two nodes. This adjacency matrix (A) gets decomposed into three parts: a square matrix Σ and a set of two small rectangular matrices U and V^T . The values within Σ are called singular values, which akin to eigenvalues [130]. Each row in U and each column in V^T represents nodes projected onto a low dimensional space [129,130]. In practice U is usually used to represent nodes in a knowledge graph, but V^T can also be used [130,131]. Typically, SVD appears in recommendation systems via collaborative filtering [132]; however, this technique can also be used as a standalone baseline to compare to other approaches [133].

Laplacian eigenmaps assume there is low dimensional structure in a high dimensional space [128]. This algorithm preserves this structure while projecting data into a low dimensional space. Typically, the first step of this algorithm is to construct a figurative knowledge graph where nodes represent datapoints and edges are constructed based on similarity of two datapoints; however, in this context, the knowledge graph has already been constructed. The next step in this algorithm is to obtain both an adjacency matrix (A) and a degree matrix (D) from the knowledge graph. A degree matrix is a diagonal matrix where each entry represents the number of edges connected to a node. The adjacency and degree matrices are converted into a laplacian matrix (L), which is a matrix that shares the same properties as the adjacency matrix. The laplacian matrix is generated by subtracting the adjacency matrix from the degree matrix ($L = D - A$) and, once constructed, the algorithm uses linear algebra to calculate eigenvalues and eigenvectors from the matrix ($Lx = \lambda Dx$). The generated eigenvectors represent the knowledge graph's nodes projected onto a low dimensional space [128]. A number of approaches have used variants of this algorithm to perform their own node projection [122,123,134]. Typically, eigenmaps work well when knowledge graphs have a sparse number of edges between nodes but struggle when presented with denser networks [133,134,135]. A future direction is to adapt these methods to scale to knowledge graphs that have a large number of edges.

Matrix factorization is a powerful technique that uses a matrices such as an adjacency matrix as input. Common approaches involve using SVD, Laplacian eigenmaps or variants of the two to perform embeddings. Despite reported success, the dependence on matrices like an adjacency matrix creates an issue of scalability as matrices of large networks would take too much memory for a regular computer to handle. Furthermore, these methods treat all edge types the same, but a possible extension for future approaches that use matrix factorization would be to incorporate node and edge types as sources of input.

Translational Distance Models

Translational distance models treat edges in a knowledge graph as linear transformations. As an example, one such algorithm, TransE [136], treats every node-edge pair as a triplet with head nodes represented as \mathbf{h} , edges represented as \mathbf{r} , and tail nodes represented as \mathbf{t} . These representations are

combined into an equation that mimics the iconic word vectors translations (**king** – **man** + **woman** \approx **queen**) from the Word2vec model [96]. The equation is shown as follows: $\mathbf{h} + \mathbf{r} \approx \mathbf{t}$. Starting at the head node (**h**), add the edge vector (**r**) and the result should be the tail node (**t**). TransE optimizes embeddings for **h**, **r**, **t**, while guaranteeing the global equation ($\mathbf{h} + \mathbf{r} \approx \mathbf{t}$) is satisfied [136]. A caveat to the TransE approach is that it the training steps force relationships to have a one to one mapping, which may not be appropriate for all types of relationships.

Wang et al. [137] attempted to resolve the one to one mapping issue by developing the TransH model. TransH treats relations as hyperplanes rather than a regular vector and projects the head (**h**) and tail (**t**) nodes onto the hyperplane. Following this projection, a distance vector (\mathbf{d}_r) is calculated between the projected head and tail nodes. Finally, each vector is optimized while preserving the global equation ($\mathbf{h} + \mathbf{d}_r \approx \mathbf{t}$) [137]. Other approaches [138,139] have built off of the TransE and TransH models. In the future, it may be beneficial for these models is to incorporate other types of information such as edge confidence scores, textual information, or edge type information when optimizing these embeddings.

Deep Learning

Deep learning is a paradigm that uses multiple non-linear transformations to map high dimensional data into a low dimensional space. Many techniques that use deep learning for knowledge graphs are based on word2vec [95,96], a set of approaches that are widely used for natural language processing. The goal of word2vec is to project words into a low dimensional space that preserves their semantic meaning. Strategies for training word2vec models use one of two neural network architectures: skip-gram and continuous bag of words (CBOW). Both models are feed-forward neural networks, but CBOW models are trained to predict a word given it's context while skip-gram models are trained to predict the context given a word [95,96]. Once training has finished, words are now associated with dense vectors that downstream models, such as feed forward networks or recurrent networks, can use for input.

Deepwalk [140] is an early method designed to project a knowledge graph into a low dimensional space. The first step of this method is to perform a random walk along a knowledge graph. During the random walk, every generated sequence of nodes is recorded and treated like a sentence in word2vec [95,96]. After every node has been processed, a skip-gram model is trained to predict the context of each node thereby projecting a knowledge graph into a low dimensional space [140]. A limitation of this method is that the random walk cannot be controlled, so every node has an equal chance to be reached. Grover and Leskovec [141] demonstrated that this limitation can hurt performance when classifying edges between nodes and developed node2vec as a result. Node2vec [141] operates the in the same fashion as deepwalk; however, this algorithm specifies a parameter that lets the random walk be biased when traversing nodes. A caveat to both deepwalk and node2vec is that both algorithms ignore information such as edge type and node type. Various approaches have evolved to fix this limitation by incorporating node, edge and even path types when projecting nodes into a low dimensional space [142,143,144,145]. These approaches primarily capture a network's local structure. An emerging area of work is to develop approaches that capture both the local and global structure of a network when projecting knowledge graphs into a low dimensional space.

Some deep learning approaches use an adjacency matrix as input [95,96] instead of using the word2vec framing. Algorithms such as auto-encoders can also generate network embeddings [146,147,148]. Autoencoders [149,150] are neural networks that map input such as an adjacency matrices into a low dimensional space and then learns how to construct this space by reconstructing the same input. The generated low dimensional space captures the node connectivity structure of the knowledge graph and every node is mapped onto this space [146,147,148]. Despite the high potential of this approach, this method relies on an adjacency matrix for input. If a knowledge graph

asymptotically increases in size, these approaches could run into scalability issues as discovered by Khosla et al. [151]. Plus, Khosla et al. [151] discovered that approaches akin to node2vec outperformed algorithms using autoencoders when undergoing link prediction and node classification. Overall, the performance of these models largely depends upon the structure of nodes and edges within a knowledge graph [151]. Future approaches should consider creating hybrid models that use both node2vec and autoencoders to construct complementary low dimensional representations of knowledge graphs.

Unifying Applications

Knowledge graphs have been used in many biomedical applications ranging from identifying protein functions [152] to prioritizing cancer genes [153] to recommending safer drugs to patients [154,155] (Figure 5). In this section we discuss how knowledge graphs are being applied in biomedical settings and put particular emphasis on an emerging set of techniques: those that project knowledge graphs into a low dimensional space.

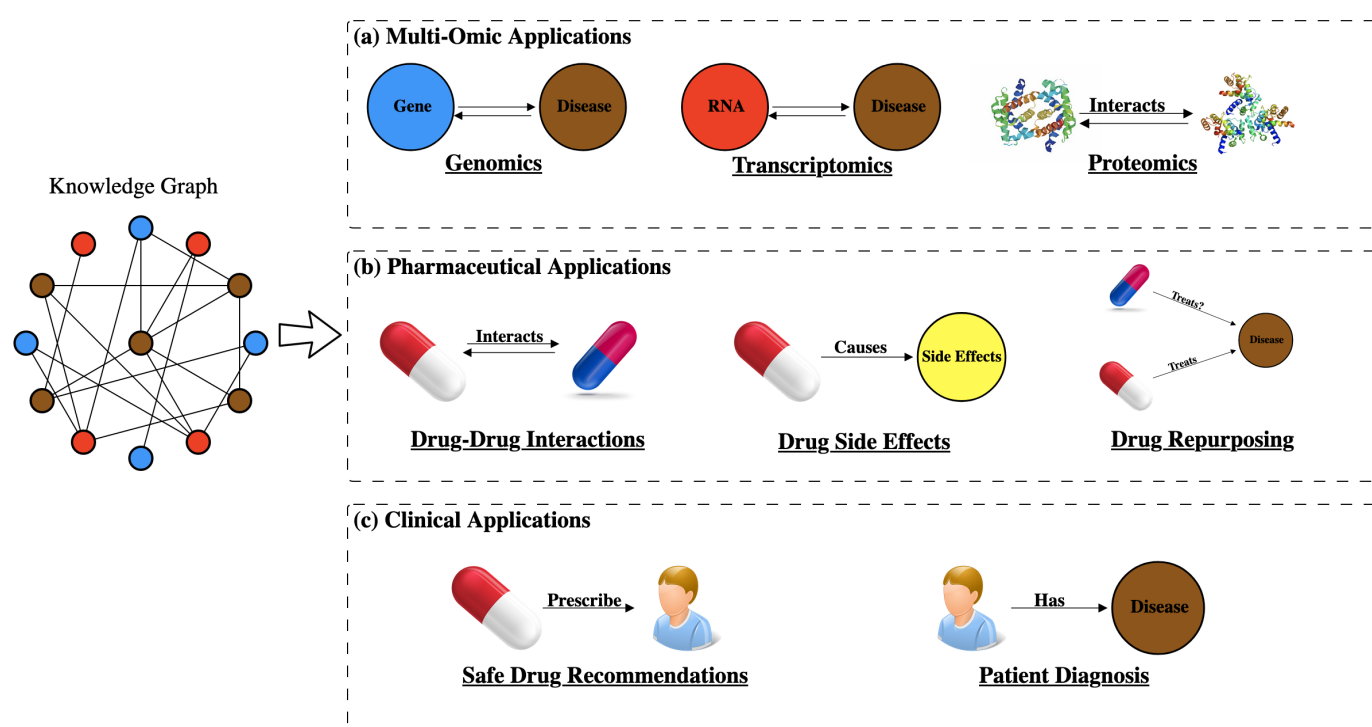


Figure 5: Overview of biomedical applications that make use of knowledge graphs. Categories consist of: (a) Multi-Omic applications, (b) Pharmaceutical Applications and (c) Clinical Applications.

Multi-Omic Applications

Multi-omic applications for knowledge graphs include efforts to study the genome, how genes are expressed in the transcriptome, and how the products of those transcripts interact in the proteome. Approaches in this category use knowledge graphs to establish connections between -omic entities as well as diseases. Such tasks include gene-symptom prioritization [156], protein-protein interaction prediction [157,158], and detecting miRNA-disease associations [119]. We focus specifically on multi-omic applications of algorithms that project knowledge graphs into a low dimensional space to make connections.

Knowledge graphs have been used as recommendation systems to establish links between RNA with disease and proteins with other proteins. Shen et al. [119] used an algorithm called collaborative filtering to establish an association between miRNA and diseases. The authors constructed an miRNA-Disease network using the HMDDD database [159] and generated an adjacency matrix with the rows

representing miRNA and the columns representing diseases. This adjacency matrix was decomposed into small rectangular matrices using SVD, then these matrices were used to calculate similarity scores between the miRNA and diseases. High scores implied a high likelihood that a given miRNA had an association with a given disease [119]. Other approaches have built off of Shen et al.'s [119] work by incorporating novel ways to perform matrix factorization [160,161,162] or by integrating machine learning models in conjunction with matrix factorization [163]. These methods provided high AUROCs, but new discoveries have been hard to validate as experiments in this space are costly and time consuming at best [119]. Apart from miRNA, collaborative filtering has been used to predict protein-protein interactions [157,158,164]. Though extensive validation of newly generated candidates may be impractical, it would be helpful to see future efforts in this space include a blinded literature search for prioritized and randomly selected candidates as part of the standard evaluation of such approaches.

Approaches that use deep learning have mainly used the node2vec model [141] or variants of that model. Yang et al. [156] used node2vec to create a recommendation system to infer associations between genes and disease symptoms. The authors constructed a gene-disease symptom knowledge graph by combining two bipartite graphs: genes-diseases and diseases-disease symptoms. The generated knowledge graph was embedded via node2vec and similarity scores were calculated for every gene-symptom pair in the graph. High scores implicated high chance for an association [156]. This approach outperformed methods that didn't use a knowledge graph; however, validation was difficult as it involved manual curation of the literature [156]. Similar approaches used variants of the node2vec algorithm to predict gene-disease associations [8,165,166] analyze RNA-seq data [167] and infer novel protein information [152,168,169,170]. Future extensions of these applications should consider incorporating more sources of data such as compounds, anatomic locations or even gene pathways to improve prediction performance.

Knowledge graphs have aided the multi-omics field by generating novel discoveries. Most approaches to date use matrix factorization and node2vec to project knowledge graph into a low dimensional space, and translational models may be an untapped resource that could aid future efforts. Another area of exploration could be the incorporation of multiple sources of information such as anatomic locations or genetic pathways to improve the specificity of findings (i.e., to predict that a protein-protein interaction happens in a specific cell type or tissue).

Pharmaceutical Applications

There are many examples of how knowledge graphs are applied to identify new properties of drugs. Tasks in this context involve prediction drugs interacting with other drugs [171], identifying molecular targets a drug might interact with [172] and identifying new disease treatments for previously established drugs [173]. As with other applications, we focus on those that use low-dimensional representations.

Similar to multi-omic applications knowledge graphs have been used in recommendation systems to infer novel links between drugs and diseases. Dai et al. [172] used collaborative filtering to infer drug-disease associations. The authors constructed a drug-disease network by integrating two bipartite networks: a drug-gene interaction network and a disease-gene interaction network. They integrated both networks under the assumption that drugs associated with a disease interact with the same gene of interest. Then the authors generated an adjacency matrix where rows represent drugs and columns represent diseases and decomposed this matrix into two small rectangular matrices. These matrices were used to calculate similarity scores between all drugs and all diseases where high values implicate an association [172]. Related approaches have been used to infer drug-target interactions [174,175,176] and drug-disease treatments [177,178,179,180,181]. In spite of reported success, these approaches are limited to the drugs and diseases contained in the network. Combining these

approaches with representations of chemical structures might make it possible to one day make predictions about novel compounds.

Deep learning applications have used node2vec [182,183] and auto-encoder [184,185] approaches to project knowledge graphs into a low dimensional space. Zong et al. [182] used a node2vec-like model to predict drug-target associations. The authors constructed a disease-target-disease network using drug centered databases: Drugbank [186] and Disesome [187]. Next, the authors applied a random walk to the network and trained a skip-gram model to generate node embeddings. Lastly, the authors constructed a similarity metric to rank how similar drugs are to their targets [182]. A limitation to this method is that their network is missing information such as pharmacological class or drug chemical structure that may help in prediction performance. Overall, deep learning provides a robust set of techniques that has been shown to outperform most linear approaches in this context [188,189].

Knowledge graphs can support drug discovery efforts by predicting drug information such as drug side effects and new disease treatments. Most methods to date use matrix factorization and deep learning techniques to produce a low-dimensional representation. Due to the success of deep learning [188,189] the focus of the field has shifted to these techniques; however, a possible extension is to use an ensemble of deep learning techniques and linear methods to improve performance. Plus, another area of exploration is to incorporate information such as pharmaceutical classes for drugs or chemical structure to improve knowledge graph detection power.

Clinical applications

Using knowledge graphs for clinical applications is in early stages of development, but the long-term goal is to use analyses of knowledge graphs to aid patient care. Typically, graphs for these applications are constructed from electronic health records (EHR) and nodes represent patients, drugs and diseases and edges represent relationships such as a patient being prescribed a treatment or a patient being diagnosed with a disease [17,190,191,192]. Tasks range from improving patient diagnoses [193,194] to recommending safer drugs for patients [154,194].

Early work in this field applied translational models (Figure 4 (b)) to knowledge graphs to recommend safe drugs. Wang et al. [154] used a variant of the TransH [137] model to create such a system for patients. They constructed a disease-patient-drug network by integrating a patient-disease bipartite network with a patient-drug bipartite network. Every node in the graph was embedded while satisfying the following equation: $\mathbf{h} - \mathbf{r} \approx \mathbf{t}$. Following the embedding step, the authors formulated their own similarity metric that selected drug combinations with a low number of interactions [154]. Researchers in [139] applied a similar variant of the TransH model to a medical knowledge graph and evaluated their model for link prediction rather than patient recommendation.

In contrast with other applications where node2vec and auto-encoder models have become established, deep learning methods in this area often use graph attention models [195]. These models mimic machine translation models [196] and aim to simultaneously embed knowledge graphs into a low dimensional space and perform the task at hand. Choi et al. [118] used a graph attention model to predict patient diagnoses. The authors constructed a directed graph using medical concepts from patient EHR data. This directed graph was fed into a graph attention network and then used to predict a patient's likelihood of heart failure [118]. Other approaches have used graph attention models to perform clinical tasks such as drug safety recommendations [155] and patient diagnoses [197].

Knowledge graphs have shown promising results when used for clinical applications; however, there is still room for improvement. Most approaches have run into the common problem with missing data from EHR [118,154,155]. Future directions consist of designing algorithms that can fill in this missing data gap or construct models that can take missing data into account.

Conclusion

1. Summarize discussed positives and pitfalls
2. Leave some open ended questions yet to be explored
3. Will come into play as I write this review paper

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