A Review of Biomedical Datasets Relating to Drug Discovery: A Knowledge Graph Perspective

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Abstract

Drug discovery and development is a complex and costly process. Machine learning approaches are being investigated to help improve the effectiveness and speed of multiple stages of the drug discovery pipeline. Of these, those that use Knowledge Graphs (KG) have promise in many tasks, including drug repurposing, drug toxicity prediction and target gene-disease prioritisation. In a drug discovery KG, crucial elements including genes, diseases and drugs are represented as entities, whilst relationships between them indicate an interaction.

However, to construct high-quality KGs, suitable data is required. In this review, we detail publicly available sources suitable for use in constructing drug discovery focused KGs. We aim to help guide machine learning and KG practitioners who are interested in applying new techniques to the drug discovery field, but who may be unfamiliar with the relevant data sources. The datasets are selected via strict criteria, categorised according to the primary type of information contained within and are considered based upon what information could be extracted to build a KG. We then present a comparative analysis of existing public drug discovery KGs and a evaluation of selected motivating case studies from the literature. Additionally, we raise numerous and unique challenges and issues associated with the domain and its datasets, whilst also highlighting key future research directions. We hope this review will motivate KGs use in solving key and emerging questions in the drug discovery domain.

1 Introduction

Discovering new drugs is a complex task, requiring knowledge from numerous biological and chemical domains, as well as understanding in various subtasks. For example, drugs are primarily developed in response to some disease or condition negatively affecting patients. This implicitly requires that the mechanisms in the body by which the disease is caused are sufficiently understood so that a drug can be designed to treat it – a process known as target discovery [68]. However, due to the complexities involved, the process of developing a new drug and bringing it to market is expensive and has a high chance of failure [81].

Preprint. Under review.
Hence, researchers are striving to increase the probability of success for the drug discovery process. Graphs have long been used in the life sciences as they are well suited to the complex interconnected systems often studied in the domain \[7\]. Homogeneous graphs have, for example, been used extensively to study protein-protein interaction networks \[86\], where each vertex represents a protein, and edges capture interactions between them.

Recently Knowledge Graphs (KGs) have begun to be utilised to model various aspects of the drug discovery domain. KGs are heterogeneous data representations and build upon the linked open data and semantic web principles \[55\]. In a KG, both the vertices and edges can be of multiple different types, allowing for more complex and nuanced relationships to be captured \[46\]. In the context of drug discovery, the entities represent key elements such as genes, disease or drugs – with the edge types capturing different categories of interaction between them. As an example of where having distinct edge types could be crucial, an edge between a drug and disease entity could indicate that the drug has been clinically successful in treating the disease. Conversely, an edge between the same two entities could mean the drug was assessed but ultimately proved unsuccessful. This crucial distinction in the precise meaning of the relationship between the two entities would not truly be captured in the simple binary option offered by homogeneous graphs, whereas, a KG representation would preserve this important difference and enable that knowledge to be used to inform better predictions. As a topical concrete application, KGs have been utilised to address various tasks in helping to combat the COVID-19 pandemic \[11, 21, 33, 51, 96, 125\]. Additionally, considering the domain as a KG has the potential to enable recent advances in graph-specific machine learning to be exploited \[38\].

However, constructing a suitable and informative KG requires that the correct primary data is captured in the process. An interesting aspect of the drug discovery domain, and perhaps in contrast to others, is that there is a wealth of well curated, publicly available data sources, many of which can be represented as, or used to construct, KGs \[27\]. Many of these are maintained by government and international level agencies and are regularly updated with new results \[97\]. Indeed, one could argue that there is sometimes too much data available, rather than too little, and researchers working in drug discovery must instead consider other issues when looking to use these data resources with graph analytics. Such issues include assessing how reliable the underlying information is, how best to integrate disparate and heterogeneous resources, how to deal with the uncertainty inherent in the domain, how best to translate key drug discovery objectives into machine learning training objectives, and how to model and express data that is often quantitative and contextual in nature. Despite these complications, an increasing level of interest suggests that KGs could play a crucial role in enabling machine learning approaches for drug discovery \[38, 44, 135\].

We present a review of the publicly available data sources for drug discovery, detailing how they could be utilised in a KG setting and analysing existing pre-constructed graphs. To the best of our knowledge, this is the first time these resources have been compared and evaluated in the literature. The primary contributions of this review are as follows:

- We present an introduction to the drug discovery domain for KG and machine learning practitioners, whilst detailing the numerous unique research challenges it poses.
- We review key data sources within drug discovery, present a taxonomy based on their primary biomedical area and consider how amenable they are for use in KGs by detailing what type of information could be extracted from them (relational versus entity features).
- We perform a comparative analysis of existing public drug discovery KGs based on their underlying data sources and graph composition decisions.
- We detail motivating case studies of KG use within drug discovery.
- We outline the key directions for future research and open problems within the domain.

Our hope is that this review will serve as motivation for researchers and enable greater, easier and more effective use of KGs in drug discovery by signposting key resources in the field and highlighting some of the primary challenges. We aim to help foster a multi-disciplinary and collaborative outlook that we believe will be critical in considering graph composition and construction in concert with analytical approaches and clarity of purpose. We think the review will also be useful for

\[1\] Also commonly known as networks within the biological domain. In this review we use the term graph interchangeably with network and without loss of generality.
researchers in the drug discovery domain who are interested in the potential insights to be gained by applying KG methodologies.

An open-source collection of the resources detailed in this review has also been released.\footnote{https://github.com/AstraZeneca/awesome-drug-discovery-knowledge-graphs}

1.1 Dataset Selection Criteria

For the purpose of this review, we use the following criteria when choosing datasets for inclusion:

- **Publicly Accessible** - The dataset should be available for use within the public domain. Whilst many high quality commercial datasets exist, we choose to focus on only those datasets which are publicly accessible to some degree.
- **High Quality** - The dataset should contain information of the highest quality. This will primarily be assessed through its popularity within the drug discovery literature.
- **Actively Maintained** - The dataset should still be actively maintained and updated.

1.2 Review Organisation

The remainder of the survey is structured as follows: in Section 2 we introduce the required back-ground knowledge, Section 3 details existing work, Section 4 introduces the relevant ontologies, in Section 5 the primary datasets are reviewed, in Section 6 existing drug discovery knowledge graphs are detailed, Section 7 presents some application case studies, Section 8 details future challenges for the field and the final conclusions are presented in Section 9.

2 Background

In this section, we introduce key background concepts including KGs and the field of drug discovery.

2.1 An Introduction To Drug Discovery and Development

Drug discovery and development is a complex and highly multi-disciplinary process \[113\] and is driven by the need to address a disease or other medical condition affecting patients for which no suitable treatment is currently in production, or where current treatments are insufficient \[49\]. Whilst a full review of the area is beyond the scope of our own review (interested readers are referred to relevant reviews \[29\], \[81\], \[120\]) here we present a high-level overview of key concepts. This section will make use of many of the biological terms and concepts defined in Table 1.

Drug discovery involves searching for causally implicated molecular functions, biological and physiological processes underlying disease, and designing drugs that can modify, halt or revert them. There are currently three main routes to drug discovery – selecting a molecular target(s) against which to design a drug (targeted drug discovery), designing a high-throughput experiment to act as a surrogate for a disease process and then screening molecules to find ones that affect the outcome (phenotypic drug discovery), or using an existing drug developed for another disease (drug repositioning). In targeted drug discovery, once a drug target has been identified, the process of finding suitable drug compounds can begin via an iterative drug screening process. Selected possible candidate drugs are then tested through a series of experiments in preclinical models (both in vitro – study in cells or artificial systems outside the body, and in vivo – study in a whole organism), and then clinical trials (drug development) to measure efficacy (beneficial modification of disease process) and toxicity (undesirable biological effects).

The active molecules in drugs have most often been small chemicals (sometimes termed compounds) and antibodies (a type of protein) \[12\], but can also be other types such as peptides, nucleotides, macromolecules, or polymers. Various newer types of drugs, often collectively termed “drug modalities” are also being explored \[12\]. These different types of drugs have particular advantages and disadvantages, but together open up a wider set of potential drug targets compared to historical approaches alone.

\[1\] https://github.com/AstraZeneca/awesome-drug-discovery-knowledge-graphs
Term | Definition
---|---
**Cells** | Important for preclinical research and data generation, e.g. studying drug responses, gene and protein expression, morphological responses via imaging.

**Genes** | Functional units of DNA, encoding RNA, and ultimately proteins. Variants of a gene’s DNA sequence may be associated with disease(s).

**Transcripts** | Gene sequences are transcribed into an intermediate molecule called RNA, which is in turn “read” to produce protein molecules.

**Proteins** | Key functional units of a cell and that can play structural or signalling roles, or catalyse reactions, and interact with other proteins.

**Biological Processes & Pathways** | Molecules and cells function together to perform biological processes which can be conceptualised at different scales, from intracellular (e.g. signalling transmission via “pathways” between molecules) to intercellular processes, and ultimately physiological processes at the tissue and body scale.

**Diseases** | A condition resulting from aberrant biological/physiological processes. Different diseases may share symptoms and underlying aberrant processes, and can often be categorised into subtypes based on clinical and/or molecular features.

**Targets** | A drug target is a molecule(s) whose modulation (by a drug) we hypothesise will alter the course of the disease.

**Compounds** | Small molecules generated and studied as part of drug discovery are sometimes termed “compounds”, with an accompanying chemical structure representation.

**In Vitro** | Studies and experiments taking place outside the body, either in cells or in cell-free, highly defined systems.

**In Vivo** | Studies and experiments taking place in a physiological context (e.g. animal or human study).

Table 1: Definitions of key terms used within the scope of drug discovery.

Biomedical science has researched the various processes highlighted in this section at different scales, using technologies that probe the abundance and sequence variation in DNA, RNA and proteins, and for studying specific biological functions via experimentation. For example, studies in genetic variation associated with disease are used to provide support to hypotheses for new drug targets [85, 60]. Databases have been constructed to collate and disseminate such data and information [97] (detailed in Section 5). Ontologies have also been developed to model relevant concepts such as disease and are discussed more in Section 4.

2.1.1 Subtasks Within Drug Discovery

The field is increasingly looking towards computational [113] and machine learning approaches to help in various tasks within the drug discovery process [119]. It can be helpful to consider partitioning the drug discovery process up into smaller subtasks, some of the most common being:

- **Drug Repositioning** - Which drugs previously tested in clinical trials could be ascribed new indications?
- **Disease Target Identification** - Which molecular entities (genes and proteins) are implicated in causing or maintaining a disease? Also known as Target Identification and Gene-Disease Prioritisation.
- **Drug Target Interaction** - Given a drug with unknown interactions, what proteins may it interact with in a cell? Also known as Target Binding and Target Activity.
- **Drug Combinations** - What are the beneficial, or toxicity consequences of more than one drug being present and interacting with the biological system?
- **Drug Toxicity Predictions** – What toxicities may be produced by a drug, and in turn which of those are elicited by modulating the intended target of the drug, and which are from other properties of the drug? Also known as Toxicity Prediction.

2.2 Knowledge Graphs

There is currently not a strict and commonly agreed upon definition of a KG in the literature [46]. Whilst we do not aim to give a definitive definition here, we instead define KGs as they will be used through the remainder of this work. We first start by defining homogeneous graphs, before expanding the definition for heterogeneous graphs.
A homogeneous graph can be defined as $G = (V, E)$ where $V$ is a set of vertices and $E$ is a set of edges. The elements in $E$ are pairs $(u, v)$ of unique vertices $u, v \in V$. An example graph is illustrated in Figure 1a which demonstrates that homogeneous graphs can contain a mix of directed and undirected edges. It is possible for these graphs to have a set of features associated with the vertices, typically represented as a matrix $X \in \mathbb{R}^{|V| \times f}$, where $f$ is the number of features for a certain vertex.

Heterogeneous graphs, or KGs as they are termed, are graphs which contain distinct different types of both vertices and edges, which can be defined as $G = (V, E, R, \Psi)$ [130]. Such graphs now have a set of relations $R$, and each edge is now defined by its relation type $r \in R$ – meaning that edges are now represented as triplet values $(u, r, v) \in E$ [64]. The vertices in knowledge graphs are often known as entities, with the first entity in the triple called the head entity, connected via a relation to the tail entity. In a drug discovery context, multiple relations are crucial as an edge could indicate whether a drug up or down regulates a certain gene for example. Two vertices can also now be linked by more than one edge type, or even multiples of the same type. Again this is important in the drug discovery domain, as multiple edges of the same relation can indicate evidence from multiple sources. Additionally, each vertex in a heterogeneous graph also belongs to a certain type from the set $\Psi$, meaning that our original set of vertices can be divided into subsets $V_i \subset V$, where $i \in \Psi$ and $V_i \cap V_j = \emptyset, \forall i \in \Psi \neq j \in \Psi$ [40]. Given the drug discovery focus, these types could indicate if a vertex represents a gene, protein or drug. Further, these vertex types can limit the type of relations placed between them, $(u, r_1, v) \in E \rightarrow u \in V_i, v \in V_j$ where $i, j \in \Psi$ [40]. An edge relation type of ‘expressed-as’ makes sense between genes and proteins but not genes and drugs for example.

A heterogeneous graph is presented in Figure 1b and contains some key differences with its homogeneous counterpart: there are three types of vertex (v1, v2 and v3) and these are linked through a mix of directed and undirected edges of three relation types (e1, e2 and e3).

2.3 Knowledge Graph Use in Drug Discovery: Research Challenges

The study of KGs in the biomedical sciences and particularly drug discovery brings challenges and opportunities. Opportunities because biomedical information inherently contains many relationships which can be exploited for new knowledge. Unfortunately there are many challenges that arise when constructing a KG suitable for drug discovery tasks, particularly when combined with machine learning. Some of the most interesting research challenges are detailed below:

- **Graph Composition** - Strategies are needed to define how to convert data into information for modelling in a graph (e.g., instantiating a node or edge versus a feature on those entities), and what scale and composition of graph(s) may be optimal for a given task. Is a single large graph best, or should task specific graphs be constructed? In addition, which type of analytical approach to use - reasoning-based, network/graph theoretical, machine learning, or hybrid approaches.

- **Heterogeneous & Uncertain** - In biomedical graphs, the data types are heterogeneous and have differing levels of confidence (e.g. well characterised and curated findings versus
NLP-derived assertions), and much of the data will be dependent on numerous factors both time and the dose of drug used as well as the genetic background in the study. Overall, this means edges are much less certain, and thus less trustworthy, than in other domains.

- **Evolving Data** - The underlying data sources integrated and used in suitable KGs are also often changing over time as the field develops, requiring attention to versioning and other reproducible research practices. As an example of this, the evolution of the frequently used STRING dataset is demonstrated in Figure 2.

- **Bias** - There are various biases evident in different data sources, for example negative data remain under-represented in some sources, including the primary scientific literature, and some areas have been studied more than others, introducing ascertainment bias in the graphs [88].

- **Fair Evaluation** - Several works have shown promise in applying machine learning techniques on a KG of drug discovery data. However, ensuring a fair data split is used for evaluation is perhaps more complicated than other domains, as it is easy for biologically or chemically meaningful data to leak across train/test splits. Thus, care should be taken to construct more meaningful data splits, as well as considering if replicated knowledge has been incorporated in the graph and could potentially leak across from the train/test split. For example, proteochemometrics approaches often employ a clustering-based splitting of chemicals to reduce leakage of similar chemicals between the training and testing sets [71].

- **Meaningful Evaluation** - While most practical applications of link prediction only focus on a single relation type (e.g., chemical modulates protein), metrics are often reported as an aggregate over all relation types. Because bias could be introduced by a large number of relations of other types either scoring much better or worse than the target relation type on average, leading to an inaccurate evaluation, metrics should be reported broken down by relation type.

- **Beware of Metrics** - Because common metrics used in link prediction tasks like mean rank (MR), mean reciprocal rank (MRR), and Hits at K are not comparable on results from KGs of different sizes, alternative metrics like the adjusted mean rank (AMR) should be employed [10]. Different implementations of link prediction evaluation calculate metrics very differently and caution should be observed when comparing results from different packages. Further, link prediction models built on biological KGs often influence real-world experimentation, so discussion on evaluation metrics should be considered with respect to how it can help achieve real-world goals.

Ultimately we feel there is now an interesting opportunity to experiment at the intersection of various research fields spanning graph theoretic and other network analysis approaches for molecule networks [6, 25], machine learning approaches [135], and quantitative systems pharmacology [106].

Figure 2: The evolution of the STRING database over major versions showing the increase in Organisms, Interactions and Proteins.

3 Prior Work

The area of drug repurposing has been addressed in several reviews [111, 72, 133, 75]. Recent worked has detailed over 100 relevant drug repurposing databases, as well as appropriate meth-

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3 This data has been collected from [https://string-db.org/cgi/access.pl?sessionId=dbw44gRU7Xo&footer_active_subpage=archive](https://string-db.org/cgi/access.pl?sessionId=dbw44gRU7Xo&footer_active_subpage=archive)
In [72], a review of repurposing from the view of machine learning is been presented, covering methods and over 20 datasets. KG specific approaches for repurposing have been reviewed, with the authors detailing suitable datasets then choosing 6 to form the KG used in their experimental evaluation [133]. In [75], the authors review and then partition the available drug databases into four categories based upon the type of information contained within: raw data, target-based, area specific and drug design.

The area of drug-target interaction has been reviewed [5, 22], both focusing upon the various methods for predicting interactions, however potential data sources are also presented. Conversely, machine learning based approaches for predicting drug-drug interaction have been detailed, with comparative evaluations conducted [20]. The authors construct a drug-drug interaction KG from a subset of Bio2RDF [8]. A review of 13 drug related databases has been presented [134], covering a broad range of databases detailing drugs and drug-target interactions.

One study reviews both datasets and approaches for biological KG embeddings [79]. Although the review focuses upon the evaluation of different methodologies, 16 relevant databases are also discussed. However, as the work is experimentally driven, only a limited dataset discussion is undertaken. A different survey of the wider biomedical area and KG use within it has been presented [18]. Finally, a recent study presents a detailed overview of the application of graph-based machine learning in drug discovery [38]. The review is wide-ranging but makes no mention of suitable public datasets. We do however feel that it strongly complements our own review and serves as a method-focused counterpart to our dataset overview.

One issue with existing reviews is that they are focused upon a specific subtask, thus they are not giving a clear view of the overall drug discovery landscape. Another trend in the current reviews is for their primary focus to be upon the experimental evaluation of methodologies, with datasets given comparatively less attention. Additionally, most reviews are considering the resources solely as databases, rather than focusing upon how they could form part of a KG. Finally, many of the reviews have been written from a biological point of view, which may make them less accessible for machine learning practitioners who may be new to the domain, but who are interested in experimenting with relevant datasets.

4 Biomedical Ontologies

An ontology is a set of controlled terms that defines and categorises objects in a specific subject area. Modern biomedical ontologies are usually human constructed representations of a domain, capturing key entities and relationships and distilling the knowledge into a concise machine read-
There is a need for consistency when discussing concepts like diseases and gene functions which can be interpreted in multiple ways.

### 4.1 Ontology Representations

Most biomedical ontologies are expressed in a knowledge representation language such as the OBO language created by the Open Biological and Biomedical Ontologies Foundry (OBO), Resource Description Framework Schema (RDFS) or the Web Ontology Language (OWL) [3]. OBO is a biologically oriented ontology and is expressive enough to define the required terms, relationships and properties of an ontology, whereas, both OWL and RDFS originate from the semantic web world but are used for creating biomedical ontologies.

### 4.2 Ontology Matching and Merging

There has been a proliferation of ontologies relating to biomedical data, which can cause issues. For example, if database A labels diseases using ontology X and database B labels diseases using ontology Y, it can be hard to know the relation of two different disease entities. Some resources exist to match together ontological terms; e.g. OXO [54] and DODO [37]. However the mappings provided by these resources are different and between any two distinct ontologies, there is no guarantee of a direct mapping or indeed any at all between their ontological terms.

Merging two different ontologies into one is an active area of research. However just mapping terms between ontologies can create logical inconsistencies in the newly created ontology. Therefore merging ontologies often involves manual intervention and is a time consuming and error prone process. The Open Biological and Biomedical Ontologies Foundry was set up to provide rules and advice for ontologies to make them easier to merge and match [114].

### 4.3 Ontology Overviews

This section details the major ontologies which are relevant for use in drug discovery tasks, which are detailed in Table 2. Note that a full review is beyond the scope of this work and interested readers are referred to a dedicated review [100].

| Ontology Name                          | Primary Domain        | Classes | Number of Properties | Max Depth | License       |
|---------------------------------------|-----------------------|---------|----------------------|-----------|---------------|
| Monarch Disease Ontology (MonDO)      | Diseases              | 24K     | 25                   | 16        | Creative Commons |
| Medical Subject Headings (MeSH)       | Medical Terms         | 300K    | 38                   | 15        | Custom        |
| Human Phenotype Ontology (HPO)        | Disease Phenotype     | 19K     | 0                    | 16        | Custom        |
| Disease Ontology (DO)                 | Diseases              | 19K     | 4                    | 33        | Creative Commons |
| Drug Target Ontology (DTO)            | Drug Targets          | 19K     | 43                   | 11        | Creative Commons |
| Gene Ontology (GO)                    | Genes                 | 44K     | 11                   | -         | Creative Commons |
| Experimental Factor Ontology (EFO)    | Integrator            | 28K     | 66                   | 20        | Apache 2.0    |

**Table 2:** An overview of Ontologies suitable for use in drug discovery.

#### 4.3.1 Disease Ontologies

Due to the complexities associated with properly defining, categorising and linking diseases, a large number of ontologies have been developed. Prominent examples include the Medical Subject Headings (MeSH) [69], Human Disease Ontology (DO) [103], Human Phenotype Ontology (HPO) [99] and Monarch Disease Ontology (MonDO) [83]. These typically differ in their intended use-case, for example DO was designed to help in the linking of different datasets, MeSH was created to aid in the indexing of MEDLINE/PubMed articles, HPO describes the phenotypes (the observable traits) of disease, MonDO was designed to harmonise disease definitions between other ontologies.

#### 4.3.2 Gene Related Ontologies

The function of genes and associated products is also frequently captured in ontologies, with common ones used in the construction of biomedical KGs including Gene Ontology (GO) [27] and the
Drug Target Ontology (DTO) \[67\]. GO focuses on defining gene activity on the molecular level, linking genes to locations in the body where its function is performed and establishing links between genes and biological processes. In contrast, DTO focuses on linking gene products in relation to drug discovery considerations such as druggability.

### 4.3.3 Integrator Ontologies

The Experimental Factor Ontology (EFO) was created by the European Bioinformatics Institute to provide a systematic description of experimental variables available in its databases including disease, anatomy, cell type, cell lines, chemical compounds and assay \[74\]. The Open Targets Platform (Section 5.1) uses EFO to provide the description, phenotypes, cross-references, synonyms, ontology and classification for annotating disease entities.

### 5 Primary Domain-Specific Datasets

The drug discovery domain has a wealth of public datasets, many of which have dedicated teams updating them. These include national or international level bodies, for example the US based National Center for Biotechnology Information (NCBI) or the European Bioinformatics Institute (EBI). Additionally the pan-European ELIXIR body, an organisation dedicated to detailing best practices for biomedical data and enabling stable funding, maintains a list of core data resources \[34\].

In this section we introduce some of the key resources providing information on crucial entities which should be included in a drug discovery KG: genes & gene products, disease and drugs, as well as sources capturing the relationships between them via interactions, pathways and processes.

A taxonomy of these datasets is presented in Figure 4. This list is not designed to be exhaustive, instead here we signpost some of the most popular and trusted ones and suggest what relations could be captured from them for a KG.

**Note on tables:** Tables 3, 4, 6, 8, 10 and 12 compare datasets on when they were first released, how regularly they are updated, ELIXIR core resource status and if free commercial use is allowed.

### 5.1 Integrated Drug Discovery Resources

Table 3 outlines resources which are tailored specifically for the drug discovery field. Typically these resources combine entity specific data sources and add additional information useful for the domain. These resources can also be useful as a reference point for some best practices with regards to data handling and integration.

**Open Targets Platform.** The Open Targets Platform is a resource which collects various disparate data sources together, covering the key entities for target discovery including genes, drugs and diseases \[62, 19\]. As of version 21.09, it contains data on 14K diseases and 27K targets. Each release
contains detailed version information for the constituent datasets. Recently, Open Targets has been expanded with the addition of a Genetics portal [39], for studying genetic variants and their relation to disease.

As Open Targets is specifically designed to link potential target genes/proteins to diseases, each link is provided with annotated associative evidence scores for a variety of evidence classes including genetic, drug and text mining. This information is aggregated into a final association score, indicating how associated a certain target-disease pair is overall. Thus far, Open Targets has not been integrated into any of the existing drug discovery KGs. However it is a prime resource, with clear scope to enrich a KG with pertinent target discovery information. Further, the various associative scores could be used to weight relations and provide some notion of confidence.

Pharos. The Pharos resource provides data integrations with a particular focus on the druggable genome [87]. Pharos is the front-end access point, with the underlying data resource being the Target Central Resource Database (TCRD), part of a National Institutes of Health (NIH) program.

The information contained within Pharos could be used to provide links between proteins and diseases. However, it also contains detailed weighted protein-protein interactions. Additionally, Pharos contains various information types which could be used as entity features. For example, for a given protein entity, Pharos contains structural and expression information which could be transformed into a generic and task agnostic set of features.

5.2 Gene and Gene Products

Genes and gene products (i.e., transcripts, proteins) are the key entities related to drug discovery and as such there are numerous rich public resources related to them. The gene and gene product datasets are summarised in Table 4.

| Dataset | First Released | Update Frequency | ELIXIR Core | Data Access | Commercial Use | Summary |
|---------|----------------|-----------------|-------------|-------------|----------------|---------|
| UniProtKB | 2003 | 8 Weeks | ✓ | REST, Python, Java, SPARQL | ✓ | Primary protein resource. Can be mined for protein-protein interactions and protein features. |
| Ensembl | 1999 | 3 Months | ✓ | REST, MySQL dump | ✓ | Primary source for gene and transcripts. Gene-gene and gene-disease relationships can be extracted, as well as many gene-based features. |
| RNAcentral | 2014 | 3–6 Months | ✓ | REST, Flat file | ✓ | One of the primary sources of non-coding transcript data. |
| Entrez Gene | 2003 | Daily | ✓ | Flat file | ✓ | Another primary gene data resource. Used in existing KGs for gene entity annotations. |

Table 4: Primary data sources relating to Genes and Proteins.

UniProt. UniProt is a collection of protein sequence and functional information started in its current form in 2003 and provides three core databases: UniProtKB, UniParc, UniRef [4]. The UniProtKB database is the main protein resource and comprises two different resources: Swiss-Prot and TrEMBL [4]. Swiss-Prot contains the expert annotated and curated protein information, whilst TrEMBL stores the automatically extracted information. Thus, as of UniProt version 2020.6, TrEMBL contains a greater volume of entities at 195M versus the 563K entities in Swiss-Prot.

Ensembl. Ensembl is primarily a data resource for genetics from the EBI, covering many different species [129]. It provides detailed information on gene variants, transcripts and position in the overall genome. This data is extracted via an automated annotation process which considers only experimental evidence.

RNAcentral. RNAcentral is an integrative resource of non-coding RNA transcripts from 28 expert databases covering 296 organisms [108]. It provides the sequence information, Gene Ontology
annotations, RNA family definitions, and identifier mappings between the many RNA transcript and gene controlled vocabularies that are necessary to semantically harmonize the nomenclature used across RNA interaction databases such as miRTarBase [26].

**Entrez Gene.** Entrez Gene is the database of the NCBI which provides gene-specific information [73]. Gene can be viewed as an integrated resource of gene information, incorporating information from numerous relevant resources. As such, it contains a mix of curated and automatically extracted information [15]. Owing to its status as an integrator of relevant resources, it provides the GeneID system, a unique integer associated to each catalogued gene. The GeneID can be useful as a translation service between other resources and is used by many of the existing KGs (see Section 5) as the primary ID for its gene entities.

### 5.2.1 Gene and Gene Products Resource Comparison

Table 5 summarises the potential types of relations and features which could be extracted from the gene and gene product resources. The table highlights that many of these resources contain rich information which could be mined for gene level features, be that from the gene or protein sequence (the sequence of nucleic or amino acids represented as base pair letters which can be mined to form a representation [98]), structure (the structure the protein forms once folded) or expression level (to what level is the gene expressed in different tissue types). The table also shows these resources to be good for extracting gene or protein interactions, as well as links to functional annotations via links to Gene Ontology (GO).

| Potential Relations | Potential Features |
|---------------------|-------------------|
| Dataset             | G/GP              | Gene-Protein | G/GP- GO |
|                     | Sequence | Structure | Expression |

Table 5: Comparing gene (G) & gene product (GP) resources on what relational information and entity-level features they provide.

### 5.3 Interactions, Pathways and Biological Processes

In this section, we detail the resources specialising in the linking of the entities through interaction, processes and pathways. The interaction resources are presented in Table 6, whilst the processes and pathways resources are detailed in Table 8.

| Dataset     | First Released | Update Frequency | ELIXIR Core | Data Access | Commercial Use | Summary |
|-------------|----------------|------------------|-------------|-------------|----------------|---------|
| STRING      | 2003           | Monthly          |            | REST, Flat file, edgelist | ✔             | One of the most commonly used sources for physical and functional protein-protein interactions in existing KGs. |
| BioGRID     | 2003           | Monthly          | ✔           | REST, Flat file, edgelist, Cytoscape | ✔             | Contains interactions between gene, protein and chemical entities with could be included directly in a KG. |
| IntAct      | 2003           | Monthly          | ✔           | Flat file   | ✔             | Contains molecular reactions between gene, protein and chemical entities. Uses UniProt for identifiers. |
| OmniPath    | 2016           | > Annually       | ✔           | REST, Flat file, Cytoscape, Python, R | ✔             | An integrator of interaction resources that could be included in a KG via its RDF version. |

Table 6: Primary data sources relating to interactions.

### 5.3.1 Interaction Resources

**STRING.** The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) captures protein-protein interactions from over 5K different organisms [109]. The interactions in STRING are taken from a range of sources, including curated ones taken directly from experimental data and those which are mined from the literature using NLP techniques.
BioGRID. The Biological General Repository for Interaction Datasets (BioGRID) is a resource maintained by a range of international universities which specialises in collecting information regarding the interactions between biological entities including proteins, genes and chemicals [107].

IntAct & MINT. IntAct is a database of molecular interactions maintained by the EBI [43]. Protein entities in IntAct are represented using UniProt IDs allowing for cross-resource linking. IntAct is closely linked with Molecular Interaction database (MINT), another core resource providing various interaction types between proteins [66].

OmniPath. OmniPath is a comparatively new resource for biological signalling pathway information with a focus on humans and rodents [117]. It integrates over 100 literature curated data resources containing information on signalling pathways, this including many datasets covered in this present review such as IntAct, Reactome and ChEMBL.

5.3.2 Interactions Resource Comparison

Table 7 summarises the potential relations types and features which could be extracted from the interaction resources. The table shows these data sources to be a rich potential for mining gene-gene or protein-protein interactions, with resources like IntAct and BioGrid also being suitable for extracting relations between gene products and compounds. All of the resources are also suitable for extracting features from the including weightings between the interactions or by providing different types or levels of interaction.

| Dataset       | Potential Relations | Potential Features |
|---------------|---------------------|--------------------|
|               | Gene-Gene | Protein-Protein | Gene-Protein | Gene-Drug | Protein-Drug | Types | Weightings |
| STRING       | ✓         | ✓             | ✓            | ✓         | ✓            | ✓     | ✓          |
| BioGRID      | ✓         | ✓             | ✓            | ✓         | ✓            | ✓     | ✓          |
| IntAct       | ✓         | ✓             | ✓            | ✓         | ✓            | ✓     | ✓          |
| OmniPath     | ✓         | ✓             | ✓            | ✓         | ✓            | ✓     | ✓          |

Table 7: Comparing interaction resources on what relational information and features they provide.

5.3.3 Pathway Resources

Pathway resources comprise expert-curated subsets of interactions that are relevant for a given biological processes (e.g., apoptosis) or pathogenic mechanisms that lead to disease. There are implicit biases in the definitions which have been shown to be mitigated by harmonizing and combining their definitions when possible [82].

| Dataset       | First Released | Update Frequency | ELIXIR Core | Data Access | Commercial Use | Summary                                           |
|---------------|----------------|------------------|-------------|-------------|----------------|---------------------------------------------------|
| Reactome      | 2003           | > Annually        | ✓           | Neo4J, Flat files | ✓             | A core resource for pathways and reactions. Amiable for graph representation and already included in several KGs. |
| WikiPathways  | 2008           | Monthly          | ✓           | REST, SPARQL, RDE, Python, R, Java | ✓             | A crowdsourced collection of pathway resources. Also provided in graph amiable formats. |
| KEGG Pathways | 1995           | Bi-Annually      | ✓           | REST, R, Python | ✓             | A highly influential resource for pathways. Free use is limited to academic work only. |

Table 8: Primary data sources relating to pathways and processes.

Reactome. Reactome is a large and detailed resource comprising biological reactions and pathways collected across multiple species including those from several model organisms and humans [53]. Resources from Reactome have also already been included in existing KG resources like Hetionet.

WikiPathways. The WikiPathways project explores the use of crowdsourcing for community curation of pathway and interaction resources [105]. Owing to its crowdsourced nature, domain scientists can add new and edit existing information to ensure better overall quality and it has been designed to complement existing resources such as Reactome.

KEGG Pathways. The Kyoto Encyclopedia of Genes and Genomes (KEGG) provides a database of manually curated pathways covering metabolism, cellular processes, diseases, drug pathways, ge-
nomic information processing, environmental information processing, and organismal systems [57]. However, the data licensing prevents redistribution or bulk access. Despite this, it remains a highly influential bioinformatics resource.

5.3.4 Pathway Resource Comparison

Table 9 summarises the potential types of relations and features which could be extracted from the pathway resources. The table shows all resources can be mined for gene-pathway links, with Reactome and KEGG Pathway also providing links from drugs to affected pathways. The table also highlights how all of the resources contain text descriptions of the pathways, as well as a graph-based representation which could further be mined for features.

| Dataset          | Potential Relations | Potential Features |
|------------------|---------------------|--------------------|
|                  | Protein-Protein     | Gene-Pathway       | Drug-Pathway       | Graph Representation | Text Description |
| Reactome         | ✓                   | ✓                  | ✓                  | ✓                    | ✓                |
| WikiPathways     | -                   | ✓                  | -                  | ✓                    | ✓                |
| KEGG Pathways    | -                   | ✓                  | ✓                  | ✓                    | ✓                |

Table 9: Comparing pathway resources on what relational information and features they provide.

5.4 Diseases

We now detail the resources whose primary focus is providing information about diseases. These resources are detailed in Table 10.

KEGG DISEASE. The KEGG DISEASE database is part of the larger KEGG resource, in which diseases are modelled as perturbed states of the molecular network system [56]. Each disease entry contains information of the perturbants to this system including genetic and environmental factors of diseases, as well as drugs. Different types of diseases, including single-gene (monogenic) diseases, multifactorial diseases, and infectious diseases, are all treated in a unified manner by accumulating such perturbants and their interactions. Users must register to gain access and industry users are charged for use.

DISEASES. DISEASES is a dataset designed to integrate evidence on disease-gene associations from automatic text mining, manually curated literature, cancer mutation data, and genome-wide association studies [94], with clear indication given as to whether the data is curated or exacted from text.

DisGeNET. The DisGeNET resource integrates a variety of data sources from expert curated repositories, GWAS catalogues, animal models and the scientific literature [92]. The data is integrated from four primary source types including expert curated databases and inferred associations.

Online Mendelian Inheritance in Man. Online Mendelian Inheritance in Man (OMIM) is a comprehensive, authoritative compendium of human genes and genetic phenotypes, with particular focus on the molecular relationship between genetic variation and phenotypic expression [41]. However access is controlled and users must register with OMIM in order to be able to download it.
GWAS Catalog. The Genome-Wide Association Studies (GWAS) performed in the literature provide an unprecedented opportunity to investigate the impact of common variants on complex diseases. The GWAS Catalog provides a consistent, searchable and freely available database of Single Nucleotide Polymorphism (SNP) to trait associations which are extracted from both published and unpublished GWA studies [16]. The data inside the GWAS Catalog is taken from studies found in the literature which are curated by experts before being added.

5.4.1 Disease Resource Comparison

Table [11] summarises the potential relations and features which could be extracted from the disease resources. The table shows that, unsurprisingly establishing gene to disease links is the primary focus of these resources. However, KEGG DISEASE could also be used to extract links from disease to both drugs and pathways, whilst DisGeNET also provides disease-disease similarity links. All of the resources provide some level of evidence for the links, whilst KEGG DISEASE and OMIM contain text descriptions which could be mined for features.

| Dataset          | Potential Relations | Potential Features |
|------------------|---------------------|--------------------|
|                  | Disease-Disease     |                     |
|                  | Disease-Gene        |                     |
|                  | Disease-Drug        |                     |
|                  | Disease-Pathway     |                     |
| KEGG DISEASE     | -                   | ✓                  |
| DISEASES         | -                   | ✓                  |
| DisGeNET         | ✓                   | -                  |
| OMIM             | ✓                   | -                  |
| GWAS Catalog     | -                   | ✓                  |

Table 11: Comparing disease resources on what relational information and entity-level features they provide.

5.5 Drugs and Compounds

We will now detail datasets containing information relating to drugs and compounds. This includes information on the relationships between the drugs and the targets or diseases as well other information such as potential adverse side effects or drug-drug interactions. These resources are detailed in Table [12].

| Dataset     | First Released | Update Frequency | ELIXIR Core | Data Access | Commercial Use | Summary |
|-------------|----------------|------------------|-------------|-------------|----------------|---------|
| ChEMBL      | 2009           | Annually         | ✓           | REST, SQL dump, SPARQL | ✓ | One of the primary resources for drug-like molecules. Could provide relational information between gene and drugs. |
| PubChem     | 2004           | As Sources Are  | ✓           | REST, Flat file, SPARQL | ✓ | A comprehensive integrator of other chemical resources provided in RDF format, enabling easy incorporation into a KG. |
| DrugBank    | 2006           | Annually         | ✓           | REST, Flat file | ✓ | A rich source of drug, disease and gene information. Free use is limited to academic work only. |
| DrugCentral | 2016           | Annually         | ✓           | SQL, Flat file | ✓ | A collection of drug information extracted from literature and other sources. A potential source of drug features. |
| BindingDB   | 1995           | Weekly           | ✓           | REST, Flat file | ✓ | A data resource of target protein and compound information. Already incorporated in existing KGs. |
| RepoDB      | 2017           | No Set Schedule  | ✓           | Flat file | ✓ | A resources of drug to disease links containing both successful and failed examples. A rare source of negative information. |

Table 12: Primary data sources relating to drugs.

ChEMBL. The ChEMBL dataset is one of the primary resources containing information on drug-like molecules and compounds [76]. The records captured in the database are taken from the literature and curated before being added. ChEMBL has been included in many other integrated resources such as OpenTargets and Pharos.

PubChem. The PubChem is a resource collecting information on chemical molecules maintained by the NCBI [59]. PubChem can be considered an integrator resource, aggregating over 700 disparate resources including UniProt, ChEMBL and Reactome.

DrugBank. The DrugBank database can be considered both a bioinformatics and a cheminformatics resource, thus containing information on drugs and potential targets [127].
**DrugCentral.** DrugCentral is a resource containing information on drugs and other pharmaceuticals [118]. The database focuses upon collecting information on FDA and EMA approved drugs, with the information being collected and curated from the literature and drug-labels, as well as from external sources.

**BindingDB.** BindingDB is a resource containing information primarily on the interactions between potential drug-target proteins and drug-like molecules [23]. BindingDB contains information taken from a range of sources including information curated from the literature, as well as from ChEMBL. BindingDB contains information which could be used to add relations between compound, protein and pathway entities, as well as potentially some compound-based feature information.

**RepoDB.** RepoDB is a smaller and more focused resource containing information more suitable for drug repositioning than many of the ones highlighted thus far. It focuses upon providing drug to disease links, however it not only provides information about approved drugs, but also on drugs which failed at various stages of clinical trials or that have been withdrawn [14]. This is interesting when considering knowledge graphs, as the data could be used to provide negative edges between drugs or diseases.

### 5.5.1 Drug Resource Comparison

Table 13 summarises potential relations and features which could be extracted from the drug resources. The table shows all the resources focus on providing links between drugs and genes, with PubChem and DrugBank being sources of drug-drug interactions and DrugCentral providing potential drug-disease linkages. Almost all of the resources provide compand structure information (Usually in a string-based format called SMILES which can be used to learn a representation [45]) and numerical attributes (molecular weight for example). KEGG DISEASE and OMIM also provides text based descriptions of the drugs which could be mined.

| Dataset     | Drug-Drug | Drug-Gene | Drug-Disease | Drug-Pathway | Text Description | Structure | Attributes |
|-------------|-----------|-----------|--------------|--------------|-----------------|-----------|-----------|
| ChEMBL      | ✔         | ✔         |              |              |                 |           |           |
| PubChem     | ✔         | ✔         |              |              |                 |           |           |
| DrugBank    | ✔         | ✔         | ✔            |              |                 |           |           |
| DrugCentral | ✔         | ✔         |              | ✔            |                 |           |           |
| BindingDB   | ✔         | ✔         |              |              |                 |           |           |
| RepoDB      | ✔         | ✔         |              |              |                 |           |           |

Table 13: Comparing drug resources on what relational information and entity-level features they provide.

### 5.6 Dataset Evaluation

This section summarises the key comparison points we have identified in our consideration of primary domain-specific datasets.

#### 5.6.1 Data Trust

Table 14 highlights the different types of information in the resources, in addition to information pertaining to the the level of annotation available. Resources are compared as to whether they are curated by human experts, if information is taken from some form of experimental evidence or predicted and automated pipelines, and if the dataset contains information extracted from other primary resources. Resources are also compared if the province of the information is available (linking to the original manuscript or source), if any form of confidence weight is provided on the information and the directionality of potential edges that could be mined. The table shows that many of the covered resources have some level of human curation but it should be noted that this does not guarantee the accuracy of the information, as human bias and error can still be a factor. The table also highlights that predicted and automatically derived data is contained within many key resources such as STRING and DisGeNET, something to be cognisant of when including these in a KG. There are also various integrator resources available, like Omnipath and PubChem, which aggregate other primary datasets. Whilst caution is needed around potential replicated knowledge, they offer a way for KGs to incorporate diverse information from a single resource.
Table 14: Comparing sources and annotations for the primary resources.

| Dataset          | Data Sources | Annotations |
|------------------|--------------|-------------|
|                  | Expert Curated | Experimental Evidence | Predicted & Automated | Integrator Resource | Provenance | Confidence | Directionality |
| UniProtKB        | ✓            | ✓            | ✓            | -            | ✓            | ✓            | Undirected |
| Ensembl         | -            | -            | -            | -            | -            | -            | Undirected |
| RNACentral       | -            | -            | -            | ✓            | ✓            | -            | Mix        |
| EntrezGene       | ✓            | -            | -            | -            | -            | -            | Undirected |
| STRING           | ✓            | ✓            | ✓            | -            | ✓            | ✓            | Undirected |
| BioGRID          | ✓            | ✓            | -            | -            | ✓            | ✓            | Mix        |
| IntAct           | ✓            | -            | -            | -            | ✓            | -            | Undirected |
| OmniPath         | -            | -            | -            | -            | ✓            | -            | Mix        |
| Reactome         | ✓            | ✓            | ✓            | -            | ✓            | ✓            | Mix        |
| WikiPathways     | ✓            | -            | -            | -            | ✓            | -            | Mix        |
| KEGG Pathways    | ✓            | -            | -            | -            | ✓            | -            | Mix        |
| KEGG DISEASE     | ✓            | ✓            | -            | -            | ✓            | -            | Mix        |
| DISEASES         | ✓            | ✓            | ✓            | -            | ✓            | ✓            | Undirected |
| diseaseNET       | ✓            | ✓            | -            | -            | ✓            | ✓            | Undirected |
| OMIM             | ✓            | ✓            | -            | -            | ✓            | -            | Undirected |
| GWAS Catalog     | ✓            | ✓            | -            | -            | ✓            | -            | Undirected |
| ChEMBL           | ✓            | ✓            | ✓            | -            | ✓            | ✓            | Undirected |
| PubChem          | ✓            | ✓            | ✓            | -            | -            | ✓            | Mix        |
| DrugBank         | ✓            | ✓            | ✓            | -            | -            | -            | Undirected |
| DrugCentral      | ✓            | ✓            | ✓            | -            | -            | -            | Undirected |
| BindingDB        | ✓            | -            | -            | -            | ✓            | -            | Undirected |
| RepoDB           | -            | -            | -            | -            | -            | -            | Undirected |

5.6.2 Relation Mining

Figure 5 shows how the different resources covered in this review could be used to link key entities within a KG. The figure highlights how certain relation types are over-represented by the datasets, with Gene-Gene and Gene-Drug having many potential sources. Care should be taken to avoid duplicated edges if many of these resources are used in graph composition. The figure also highlights where information is lacking, with Disease-Pathway links only being present in one source. It also is interesting to note that many of the resources detailed here are already provided in some form that is amenable for ingestion into a knowledge graph – either as edgelists or by providing RDF versions. This reduces the complexity of incorporating the resources as any issues arising from parsing and formatting process are avoided.

5.6.3 Graph Enrichment

There are many primary data sources which capture more information about key entities within drug discovery than just relational interactions. UniProtKB, for example, details numerous sequence and functional properties of proteins which may not be captured by relations alone. However, thus far, this wealth of information is under-explored and could be used to greatly enrich a KG with more domain knowledge. Of course this would come at the potential cost of some level of manual feature engineering being required – an often complicated, domain specific and iterative process by itself, and one that much of the research into representation learning is attempting to avoid [9, 78].

5.6.4 Untapped Resources

Finally there are resources specific to drug discovery, such as OpenTargets and Pharos, which have thus far not been incorporated into any public KG. However, they are not currently provided in a format enabling easy incorporation into a KG, meaning that some manual conversion process is required. Yet they still hold great potential as a way to create a more drug discovery focused resource.

6 Existing Biomedical Knowledge Graphs

This section highlights the few existing knowledge graph datasets covering various aspects of the drug discovery process. These datasets often comprise graphs extracted from resources covering more primary information on the various relevant entities and relations. These datasets are interesting as they could form a good initial starting point for ML practitioners looking to test algorithms on suitable KGs. A selection of the most relevant resources is summarised in Table 15.
Figure 5: Dataset usage for relations to link entity types in a simplified drug discovery knowledge graph schema.

| KG Dataset     | Design Usecase | Entities | Triples | Entity Types | Relation Types | Contains Features | Constituent Datasets | Version Info | Last Update |
|----------------|----------------|----------|---------|--------------|----------------|------------------|--------------------|--------------|-------------|
| Hetionet [44]  | Repurposing    | 47K      | 2.2M    | 11           | 24             | x                | 29                 | x            | 2017        |
| DRKG [51]      | Repurposing    | 97K      | 5.7M    | 13           | 107            | molecular embeddings | categorical | 34          | 2020        |
| BioKG [121]    | General        | 105K     | 2M      | 10           | 17             | x                | molecularembeddings | 13          | 2020        |
| PharmKG [132]  | Repurposing/Target Prediction | 7.6K | 500K  | 3 | 29 | continuous | 7 | 2020 |
| OpenBioLink [13] | Benchmark  | 184K    | 4.7M    | 7            | 30             | x                | 17                 | x            | 2020        |
| Clinical Knowledge Graph [101] | Personalised Medicine | 16M | 220M | 35 | 57 | x | 35 | 2020 |

Table 15: Pre-existing knowledge graphs suitable for use in various drug discovery applications.

6.1 Biomedical Knowledge Graphs Overviews

This section details graphs which we feel meet the criteria to be considered full knowledge graphs.

**Hetionet v1.0.** One of the first attempts to create a holistic KG suitable for various tasks within drug discovery was Hetionet [44]. Hetionet was developed as part of project Rephetio, a study looking at drug purposing through the use of KG-based approaches. The graph is publicly available[^4] and is provided as a Neo4j[^42] dump, as well as in JSON and edge list. The underlying data is mined from sources including Entrez Gene[^73], DrugBank[^126], DisGeNET[^93], Reactome[^53] and Gene Ontology[^28]. The thresholds for the edges are not included in the graph, instead the preselected values are detailed in the accompanying paper [44].

From the time of writing, Hetionet has not been updated since 2017, although a project called the Scalable Precision Medicine Oriented Knowledge Engine (SPOKE)[^84] looks to update Hetionet with extra data sources. However, to date, this updated resource has not been made publicly available, thus it has been excluded from our review.

**Drug Repurposing Knowledge Graph.** The Drug Repurposing Knowledge Graph (DRKG) [51] is a resource which builds upon Hetionet by integrating several additional data resources and was originally developed as part of a project for drug repurposing to target COVID-19 [52]. The dataset is closely aligned with the Deep Graph Library (DGL) package for graph-based machine learning [122], with pre-trained embeddings being provided from the package with the dataset. The data is publicly available[^5] and provided in edgelist format.

DRKG has enriched Hetionet with recent COVID-19 related data from STRING [109], DrugBank [126] and GNBR [91]. DRKG also includes pre-computed GNN-based embeddings for molecules, however no other entities have associated features.

[^4]: https://het.io/
[^42]: https://github.com/gnn4dr/DRKG
BioKG. BioKG is a project for integrating various biomedical resources and creating a KG from them [121]. As part of the project, various tools are provided to enable a simplified KG construction process. A public pre-made version of the graph is available, as well as the code for building it.

The data which makes up BioKG is taken from 13 different data sources, including UniProt [4], Reactome [53], OMIM [41] and Gene Ontology [28]. One interesting aspect of BioKG is that a small number of categorical features are provided with some of the entities. For example, drug entities are enriched with information pertaining to any associated negative side effects.

PharmKG. The PharmKG project had the goal of designing a high quality general purpose KG and associated GNN-based model for use within the drug discovery domain [132]. Table 15 shows that compared to others highlighted in this section, PharmKG is compact, containing entities of just three types: chemical, gene and disease.

The data is initially integrated from 7 sources including OMIM [41], DrugBank [127], PharmGKB [124], Therapeutic Target Database (TTD) [24], SIDER [63], HumanNet [50] and GNBR [91]. A filtering process is then applied to ensure that only high quality knowledge is kept, for example by only including well studied genes. One unique aspect is that numerical features are provided with all the entities. Such features include chemical connectivity and other physiochemical features for the chemical entities, the use of BioBERT [65] to create features for the disease entities and a reduced expression matrix to create a feature vector for gene entities. The unfiltered PharmKG graph, as well as model code, is available to download, however at the time of writing, neither the filtered graph nor the entity features vectors have been released.

OpenBioLink. OpenBioLink (OBL) is a project to allow for easier and fairer comparison of KG completion approaches for the biomedical domain [13]. As part of the project, a benchmark KG has been created covering aspects of the drug discovery landscape. The dataset is publicly available and is provided in edgelist and RDF formats.

Data is taken from 17 datasets including STRING [109], DisGeNET [93], Gene Ontology [28], CTD [31], Human Phenotype Ontology [61], SIDER [63] and KEGG [58], among other resources. Of interest is that OpenBioLink contains additional true negatives for a selection of relation types, meaning that this relation was explicitly detailed not to exist. This can be used to avoid the issues inherent with the choice of negative sampling strategy when training KG embedding models [131].

Clinical Knowledge Graph. The Clinical Knowledge Graph (CKG) builds upon previous benchmark KGs but with additional focus on -omics data. Its relations come from 25 databases and 10 ontologies, many of which overlap with previous examples but notably include protein state information such as post-translational modifications from PhosphoSite [47]. The CKG GitHub repository not only provides code for rebuilding the graph, but also tools for uploading it into Neo4J as well as visualization and exploration in Jupyter Notebooks. However, CKG cannot redistribute many of its constituent datasets because of licensing restrictions, so the distributed version of the CKG is much smaller than stated in the manuscript.

6.2 Comparative Analysis of KG Resources

We now present a comparative analysis of the KGs by considering graph composition choices, dataset usage and documentation levels. This analysis is undertaken to better understand the types of drug discovery problems each graph is suitable for addressing, as well as allowing interpretation of the level of trust that can be placed in each graph through exploration of dataset province. We believe this is the first time these resources have been compared and contrasted in the literature.

6.2.1 Graph Composition: Entities

Table 16 highlights which entity types are included in the KGs as well as offering a fine grained view of how larger concepts like gene-products are modelled, whilst Figure 6a shows the amount of these different entities present across the KGs. These show that the KGs take differing approaches

[https://github.com/dsi-bdi/biokg](https://github.com/dsi-bdi/biokg)
[https://github.com/MindRank-Biotech/PharmKG](https://github.com/MindRank-Biotech/PharmKG)
[https://zenodo.org/record/3834052](https://zenodo.org/record/3834052)
[https://github.com/MannLabs/CKG/](https://github.com/MannLabs/CKG/)

[10] Note that we exclude CKG from much of this analysis due to licensing limitations.
Table 16: Comparison of a subset of entity types named across the knowledge graphs.

| KG Dataset     | Gene Products | Compounds | Disease |
|----------------|---------------|-----------|---------|
|                | Gene          | Proteins  | Transcripts | Drugs | Chemicals | Disease | Genetic Disorder | Anatomy | Pathways | Side Effect | Symptoms |
| Hetionet       | ✓             | -         | -          | ✓     | -         | ✓       | ✓               | -         | ✓         | -          | -        |
| DRKG           | -             | ✓         | -          | -     | ✓         | ✓       | ✓               | -         | ✓         | -          | -        |
| BioKG          | -             | ✓         | -          | -     | -         | -       | -               | -         | -         | -          | -        |
| PharmKG        | ✓             | -         | -          | -     | -         | -       | -               | -         | -         | -          | -        |
| OpenBioLink    | ✓             | ✓         | -          | -     | -         | -       | -               | -         | -         | -          | -        |
| CKG            | ✓             | ✓         | -          | -     | -         | -       | -               | -         | -         | -          | -        |

Table 17: Entity identifiers used in the different knowledge graphs. Multiple IDs being present means all are used as entity identifiers within the graph.

| KG Dataset     | Gene/Products | Compound | Disease | Pathways |
|----------------|---------------|----------|---------|----------|
| Hetionet       | Entrez GeneID | DrugBank AN | DOID    | Custom   |
| DRKG           | Entrez GeneID | DrugBank AN | MeSH    | Custom   |
| BioKG          | UniProt       | DrugBank AN | MeSH    | Reactome/KEGG |
| PharmKG        | Entrez GeneID | PubChem ID | MeSH    | ✓        |
| OpenBioLink    | Entrez GeneID | PubChem ID | DOID    | Reactome/KEGG |

Figure 6: Sankey diagrams showing relationship between entity and relations in the KGs. Line thickness equates to entity volume. Note that for the relations, the value is the sum of all relation types between the two entities.

6.2.2 Graph Composition - Relations

Table 18 shows the number of different relationship types in the KGs between key entity pairs. The table highlights the different nuance with which the relationships are modelled. It is clear there is a large variation in what an edge between entity pairs is actually representing. However, note that the
values for DRKG are inflated as the data source is captured in the relationship name. Considering
the relation granularity can further help guide on KG task suitability. For example Hetionet and
OpenBioLink both have multiple relationship types between gene entities, whilst other KGs have
only one, perhaps indicating these to be good choices if a complex understanding of gene interaction
is required. Whereas, OpenBioLink would not be the graph to use if interaction between drugs
was crucial to the task as it has no drug-drug edges. Overall, some general trends are observable
regarding relation modelling choices. For example, BioKG tends to use only a single relation type,
whilst PharmKG, despite its smaller overall size, often choses to have multiple types. Additionally,
it can be seen in Table 18 that drug entity pairs are consistently modelled as only a single relation
type across the graphs.

Figure 6b displays the volume of each relation category contained within the graphs and shows there
to be a marked difference between the KGs. For example, DRKG has a large number of both Gene-
Gene and Drug-Drug edges in comparison to other types, whilst OpenBioLink choses to include
more gene interactions and BioKG has a large number of drug interactions. Overall Gene-Gene
and/or Drug-Drug relations form the majority in many of the KGs. This has the potential to cause
issues for tasks like target discovery, which relies on gene to disease connections, as there tend to
be fewer examples in the graph. Thus, any model training on top of these graphs will have fewer to
learn from, potentially leading to suboptimal predictive performance.

| KG Dataset   | Gene-Gene | Gene-Disease | Gene-Drug | Drug-Drug | Drug-Disease |
|--------------|-----------|--------------|-----------|-----------|--------------|
| Hetionet     | 3         | 3            | 3         | 1         | 2            |
| DRKG         | 32        | 15           | 34        | 2         | 10           |
| BioKG        | 1         | 1            | 5         | 1         | 1            |
| PharmKG      | 1         | 6            | 7         | 1         | 6            |
| OpenBioLink  | 10        | 1            | 10        | ×         | 1            |

Table 18: The number of relation types between entities across the KGs.

6.2.3 Underlying Dataset Use

Figure 7 represents dataset use in the KGs for a series of key relationship types, where the typed
edges indicate relations are taken from that dataset. PharmKG and CKG are missing as it was not
possible to determine the data sources used for the relations. The figure shows that the KGs utilise
many of the same underlying datasets, with DrugBank for example being used in the majority of the
graphs, with often multiple relationship types being extracted from it.

Considering the difference in dataset usage, we can see some of the choices made during the com-
position pertaining to the KGs intended use cases. For example DRKG, extracts four different
relationship types from the text mining-based GNBR [91] dataset, whilst no other KG uses any. The
creators of DRKG must have deemed these lower-confidence edges useful for discovering potential
repurposing candidates for COVID-19. It can also be seen that Hetionet tends to use multiple smaller
datasets to build a single relation type, the gene-disease edges use three for example. Hetionet also
differs in that its drug-disease edges don’t come from larger aggregator resources DrugBank or
DrugCentral used by the other KGs. In contrast, OpenBioLink has a one-to-one mapping between
dataset and relation type and makes use of larger resources like STRING and STITCH, perhaps
showing its intended benchmark use.

Figure 7 also highlights some of the pitfalls of mining multiple resources for relations of the same
type. DRKG extracts gene-gene interaction edges from both IntAct and STRING, which could result
in duplicated edges being present as both datasets contain many of the same interactions. Without
care during the composition and evaluation process, this could lead to situations where training
edges used in a model could also potentially be used for evaluation.

6.2.4 Evaluation of Documentation Quality and Reproducibility

Table 19 presents our evaluation of the documentation quality (be that from the original paper, sup-
plementary material, code repository or website) and overall reproducibility of the KGs. The graphs
are evaluated using the following criteria, where the documentation quality categories are scored
from one to three - Schema Overview: Is the graph schema design well explained and justified? A
score of three means all entity and relation types detailed in full, two means the schema is outlined
but not fully justified and one means only basic details are provided. Dataset Filtering: Is there a
Figure 7: The relationship between drug discovery knowledge graphs and underlying data sources. Relationships are presented for five major relation categories: Gene-Gene ($\sigma$), Gene-Disease ($\mu$), Gene-Drug ($\lambda$), Drug-Drug ($\theta$) and Drug-Disease ($\gamma$).

clear description of how the underlying datasets were filtered? A score of three indicates filtering thresholds detailed enough for reproducibility, two means that some description is provided but not enough to reproduce the work and one that only a limited amount of information is provided. Relation Explanation: Is the meaning behind relations well explained? A score of three indicates each relation type is fully explained and linked to the source dataset, two that either a full relation explanation or source dataset mapping was missing and one that no mappings were provided. Updates: Are any future planned updates detailed? Data-Relation Mappings: Is it possible to map edges directly back to the underlying data sources? Construction Code: Is code available to construct the graph? Licence Info: Are underlying dataset licences detailed?

Table 19 highlights that, despite being the oldest resource, Hetionet remains the KG with the highest overall level of documentation quality. Regarding reproducibility, two of the KGs did not provide code to recreate the graphs from the source datasets. It was also interesting to note that none of the resources provided any details on whether they would be updated going forward. Overall it clear that further work needs to be undertaken to improve documentation and reproducibility which will aid in both increasing trust and also ease of use of future KG resources.

| KG Dataset | Schema Overview | Dataset Filtering | Relation Explanation | Updates | Reproducibility Overview | Data-Relation Mappings | Construction Code | Licence Info |
|------------|----------------|-------------------|----------------------|---------|--------------------------|------------------------|-------------------|-------------|
| Hetionet   | /*/*          | /*/*              | /*/*                 | ✗       | ✗                        | ✗                      | ✗                 | ✗           |
| DRKG       | /*/*          | /*/*              | /*/*                 | ✗       | ✗                        | ✗                      | ✗                 | ✗           |
| BioKG      | /*/*          | /*/*              | /*/*                 | ✗       | ✗                        | ✗                      | ✗                 | ✗           |
| PharmKG    | /*/*          | /*/*              | /*/*                 | ✗       | ✗                        | ✗                      | ✗                 | ✗           |
| OpenBioLink | /*/*        | /*/*              | /*/*                 | ✗       | ✗                        | ✗                      | ✗                 | ✗           |

Table 19: Comparing documentation levels and reproducibility across the KGs. Documentation quality is scored on scale of 1 to 3.

6.3 Shortcomings of Existing KG Resources

When looking at these existing KG as a whole, we can identify the following shortcomings:

- **Lack of Updates** - None of the detailed KGs have any form of maintenance or update schedule in place. This means they will become increasingly out of date as the underlying data resources continue to evolve.
- **Lack of Detailed Documentation** - Some of the resources are not properly documented, missing clear justifications for some of the design choices, not including crucial information for reproducibility such as threshold information and lacking clear mappings back to
the source datasets. This makes the graphs more challenging to use in tackling real-world problems.

- **Lack of Features** - Almost all of these graphs do not provide any additional features for the entities or relations. Features that are provided are usually limited to only a small number of entities.

- **No Dataset Version Information** - Many of the resources do not detail from which version or year of a certain dataset the information has been collected.

### 6.4 Other Associated Graphs & Projects

#### 6.4.1 Other Graph Datasets

Despite not being full KGs, there are a number of other graphs of note in the domain. For example, the Stanford Biomedical Network Dataset Collection (BioSNAP)\(^{11}\) is collection of homogeneous graphs, where each graph captures the interactions between two (from a total of ten) entity types such as gene-gene or gene-disease \(^{136}\). BioSNAP also includes a small number of features for a selection of disease, side-effect and gene entities. This includes disease class information, pre-extracted network motifs, text-based synopses and structural pathway measures. Bio2RDF was an earlier project based on integrating disparate biological datastores \(^8\), using technologies from the Semantic Web stack. It incorporates data from 35 resources and the total Bio2RDF graph is over 10B triples. It is not explicitly focused towards the drug discovery domain and does not curate the resources in any way. In a similar vein, the Network Data Exchange (NDEX) is a repository for storing user submitted biological graphs, many of which are pertinent for drug discovery \(^95\). BioGraakn is a biomedical knowledge project released as part of the GRAKN.AI graph analytics platform \(^77\), including a collection of graphs, with the two most relevant being the precision medicine and disease focused graphs.

#### 6.4.2 Graph Construction Resources

There are a growing number of resources designed to enable simpler construction of biomedical KGs, which include parsers for common resources, various filtering options and support for outputting into common formats. One such resource is Phenotype Knowledge Translator (PheKnowLator) which aims to build a framework for easier biomedical knowledge graph construction \(^{17}\) and is available for public download \(^{12}\). Additionally, the Biological Expression Language (BEL), a domain-specific language for representing causal, correlative, and associative relationships between biological entities, is one way to help integrate disparate data sources \(^{104}\). The Bio2BEL framework uses the PyBEL software ecosystem \(^{48}\) to programmatically convert biological data sources into BEL then to semantically align and merge them at scale. Each converter is loaded as a plugin such that the 70+ pre-defined converters can be used or new ones implemented, for example, to leverage data that is internal to the user’s organization. Bio2BEL allows for *ad hoc* KG assembly and is an alternative to static KG sources \(^2\).

### 7 Case Studies

In this section we highlight case studies from the literature, detailed in Table 20, where KGs have been successfully exploited in the drug discovery domain. We choose one approach from each of the areas of Polypharmacy, Drug-Target Interaction and Gene-Disease Prioritisation to highlight how KGs are being used across a range of tasks. We detail the successes, as well as analysing areas for further improvement.

#### 7.1 Polypharmacy Prediction

The problem of adverse side effects that arises through the use of Polypharmacy (the use of more than one drug simultaneously to treat one or multiple conditions) has been modelled through the use of a KG and a novel GNN-based model entitled Decagon \(^{135}\).

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11. https://snap.stanford.edu/biodata/
12. https://github.com/callahantiff/PheKnowLator
Table 20: An overview of drug discovery related approaches in the literature employing the use of KGs.

**Graph Composition.** The KG constructed was actually bipartite, containing only drug (over 900 unique entities) and protein (over 19K unique entities) entities [135]. These are linked through 964 unique edge types between drug-drug pairs, representing the various types of adverse side effects and a single edge type used to represent drug-protein and protein-protein interactions. Compared to the existing public KGs (Section 6), this graph places a lot of its complexity in the relation types, which has the potential drawback of limiting the amount of each seen during model training. Also unlike the existing public KGs, the graph is limited to just two entity types, suggesting disease or pathway information was deemed unimportant.

**Underlying Datasets.** Data was extracted from protein centric databases like BioGRID [89], STRING [109], STITCH [110], as well as drug centric resources like SIDER [63], OFFSIDES, and TWOSIDES [112]—with much of the processed data being available in the BioSNAP project. Additionally, the graph is enriched with features on only the drug vertices containing descriptive single drug side-effect information.

**Model.** The model encoder, similar to a Relational Graph Convolutional Network (R-GCN) [102], uses a separate parameter matrix for each edge type to learn relational aware vertex level embeddings. These embeddings are then input into a tensor factorisation-based decoder to directly predict potential negative drug-drug interactions via link prediction. The presented results show that compared with non-graph specific and homogeneous models, Decagon is better able to predict existing, and even propose novel, drug-drug interactions.

### 7.2 Drug-Target Interaction Prediction

Work has explored the task of Drug-Target Interaction prediction using a KG, containing existing protein and drug compound interactions, and a model entitled TriModel [80].

**Graph Composition.** The graph is composed of 11 different entity types including genes and drugs, linked via 26 different relationship types. However, a precise discussion of why the chosen relation and entity types included in the graph is missing in the paper. Although the approach is focused on finding links between genes and drugs, only a single relation types is used to capture all possible interactions between these two entities.

**Underlying Datasets.** The graph was constructed from KEGG, UniProt and DrugBank, with other known drug-target interaction resources such as Yamanishi08 [128] being used for evaluation. As such, the graph draws on fewer datasets than is typically seen in the existing public resources.

**Model.** The authors propose that DTI can be formulated as a link-prediction task and introduce a model entitled TriModel in order to accomplish this. Similar to other Knowledge Graph Embedding (KGE) approaches [123], TriModel learns an embedding for all entities and relations in the graph by optimising the parameters such that true triplets are more accurately predicted over randomly sampled negatives. Over various traditional and non-relational graph methods, TriModel demonstrates superior performance, perhaps highlighting the importance of complex multi-relational information in generating accurate predictions.

### 7.3 Gene-Disease Prioritisation

The task of gene prioritisation (detailed in Section 2.1) has been addressed via the use of a KG [90]. The overall approach, entitled Rosalind, details the construction of a knowledge graph and the choosing of a suitable model with which to make predictions. The work proposes that the disease target identification problem can be modelled as a link prediction task where the prediction of an edge between a disease and a gene entity would indicate possible association between the two.
Graph Composition. The Rosalind KG comprises five entity type (genes, compounds, diseases, biological processes and pathways) linked via eleven relation types. As such, Rosalind most closely resembles existing KGs like Hetionet and BioKG in structure. Of note is that it captures some of the subtlety around disease-gene prioritisation, as ideally the model would predict which genes have some causal effect on the disease, not just an association. In Rosalind, they use two different types of edge between disease and gene entities – one indicating association and the other therapeutic links (a drug exists targeting the gene to help alleviate disease). However, to date, the authors have not released the KG, making reproducibility challenging.

Underlying Datasets. The Rosalind KG is constructed from many of the datasets detailed in this review. For example, the graph incorporates disease information from resources like DisGeNET, OMIM, and GWAS Catalog, interaction information from BioGRID, pathway information from Reactome and compound information from ChEMBL.

Model. The model chosen for the work is the ComplEx tensor factorisation approach. The evaluation of the approach demonstrates that it outperforms competing methods, including OpenTarget, by as much as an extra 20% of recall when predicting potential gene-disease relationships over 198 diseases. Model performance is evaluated only on this therapeutic edge type. Additionally, results are presented on a time-slices graph, where the model is trained on historical data and predictions are made on future edges. This is attempting to replicate the task we would ideally want performed - using the currently available knowledge to predict currently unknown information, in this case, unknown relationships between genes and diseases.

7.4 Evaluative Summary

These case studies have highlighted the considerable potential and successes of KGs aiding in a diverse set of drug discovery tasks. However, there are still areas for improvement regarding aspects of underlying data use and graph composition. Thus, we make the following observations:

- **Composition.** The composition of the KGs in these studies varies dramatically regarding entity and relation type quantities. This suggests there is not yet a consensus on the optimal way to compose drug discovery KGs for use in ML pipelines.

- **Dataset Usage.** These studies use many of the datasets covered in this review to build their KGs. However there is still variety in where common relationship types are extracted from and usually no justification as to why a certain source was chosen.

- **One graph to rule them all?** It is striking that none of the approaches utilise an existing KG. Instead, custom task-specific graphs are still typically created, perhaps highlighting the challenge in creating a single KG to address all possible tasks within drug discovery.

8 Future Challenges & Key Issues

Whilst there has been significant progress made in the field, there are still numerous open challenges and issues to be addressed. In this section, we detail major areas still needing improvement, which could help produce better drug discovery KGs. Here, we build upon many of the challenges of working with drug discovery data we established in Section 2.3 and the issues with pre-existing KGs in Section 6.3.

Graph Composition. Constructing a useful KG for use in the drug discovery domain is still a challenging problem, especially when performed by non-domain experts. Many choices must be made when transforming a data source into a graph, especially if it is not relational by nature. Here, there is however great scope for interdisciplinary collaborations between domain scientists and KG and machine learning researchers. Additionally, we would like to see more high quality pre-constructed KGs, designed and validated by domain scientists, be made available for use by researchers. Further, creating graph construction toolkits, in which source datasets can be parsed in a unified and reproducible manner, would enable simpler creation of bespoke KGs.

Data Value. The availability of massive datasets has been partially credited with enabling the success of recent neural network models in areas such as computer vision. It might be tempting then to incorporate as much data as possible into drug discovery KG. However, much work still
needs to be done in assessing the benefit of incorporating different data modalities. The consideration of value can also be extended to a financial viewpoint: data collection, storage and processing can be expensive, especially if larger datasets do not improve performance in the task of interest. Another question is whether a single super graph should be created, which attempts to capture all knowledge around drug discovery, or whether smaller, more task specific, projections enable better predictions overall.

**Better Metadata.** As highlighted throughout the review, many of the core data resources are typically updated and refined at frequent intervals. However, many of the pre-existing KGs do not capture exactly which version of a certain resource was used during its construction. Storing this information might allow for better reproducibility, as well as measuring any change in predictive performance as the underlying knowledge is updated over time. Improved metadata could also capture if the relationship was taken from an expert curated, or automated pipeline. Additionally, graphs could provide common alternative identifiers (for example including both Entrez Gene and Ensembl identifiers for gene entities) as properties to enable easier incorporation of additional resources into the graph.

**Incorporation of Features.** Typically many existing KGs are provided as little more than edge lists, with models trying to make predictions using this relational information alone. Throughout this review, we have attempted to highlight where data resources may be used to add additional features for entities and relations. However, it is easier to imagine suitable features for certain entities (proteins and chemicals for example, where structural information could be incorporated) than others. Additionally, any potential benefits of incorporating these extra features would need to be assessed fairly. Nevertheless, we feel that there is scope for the incorporation of features to enable graph-specific neural models to be better exploited in the domain, with some recent promising work being demonstrated in the literature [132].

**Addressing Bias.** Many biases will be present in a drug discovery KG and any model being trained upon it, may have its predictive performance skewed away from under-represented, but potentially crucial relationships. Even manually curated resources may suffer incur bias from the person performing the curation. Practitioners should be aware of these issues and steps could be taken to mitigate them by, for example, reweighing the model training process. Additionally, users could consider removing over represented entities if they are confident that they are not required in the area of study. The lack of true negative samples in many graphs also means that the negative sampling strategy employed can bias the results. Recent inclusion of true negative samples in a benchmark graph [13] is encouraging, however where they are not possible to collect, more domain-aware sampling strategies should be investigated.

**Fair Evaluation.** Due to the combinatorial ingestion process used to construct KGs, it is common for edges to be duplicated if the relationship is captured in more than one underlying source. This can cause obvious issues when it comes to creating train/test splits for evaluation if the issues are not considered. Further, the presence of trivial inverse relationships, many of which may be present, can also skew performance metrics [115]. It may also be more useful to assess model performance on more biologically meaningful data splits, for example by splitting on disease or protein family. It could help move the field forward if meaningful splits for key tasks within drug discovery could be created by experts and made available for public use.

**Uncertainty.** So much of the data represented in a biological KG is uncertain, either due to the nature of the experiment that generated it, or because it has been automatically mined from the literature. Yet this uncertainty is rarely represented in the graph itself, perhaps leading to a false sense of trust being created by the presence of certain relationships. We feel that more should be done to incorporate any uncertainty directly inside the KG. This could allow methods to directly learn from this information, thus creating better and more robust predictions.

**Reproducibility.** As in many areas of machine learning [30, 36, 70], reproducibility of results is still a major issue in the KG field [1]. It is common for many papers to publish results without also providing the exact graph constructed to generate them. We believe further improvements in this area are essential for continued development in the field.
9 Conclusion

The use of KGs, combined with machine learning techniques, has the potential to help address key challenges in the field of drug discovery, with promising early applications already being demonstrated in the tasks of drug repositioning, drug-drug interactions and gene prioritisation. In this review we have presented an overview of the various key related datasets which could provide some of the fundamental building blocks for a hypothetical drug discovery KG. The review has also detailed and evaluated the range of pre-existing public KGs in the drug discovery domain. Additionally, we have highlighted the many pitfalls and challenges of working with drug discovery-based data and signposted key issues practitioners should consider when choosing suitable sources.

Our hope is that this review of suitable data sources, combined with recent works evaluating graph-specific machine learning models in the context of drug discovery [38], can help guide researchers from across the KG mining and machine learning fields in applying state-of-the-art techniques in the field. Overall, we hope this review can serve as a catalyst in making the drug discovery domain more accessible, sparking new thought and innovation, whilst allowing researchers to more easily address key tasks within the domain, ultimately helping to improve and extend human life through new medicines.

Acknowledgement

We would like to thank Manasa Ramakrishna, Ufuk Kirik, Benedek Rozemberczki, Natalie Kurbatova, Elizaveta Semenova and Claus Bendtsen for help and feedback throughout the preparation of this manuscript. Stephen Bonner is a fellow of the AstraZeneca postdoctoral program.

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