

Predicting Drug-Drug Interactions Through Similarity-Based Link Prediction Over Web Data

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ABSTRACT

Drug-Drug Interactions (DDIs) are a major cause of preventable adverse drug reactions and a huge burden on public health and the healthcare system. On the other hand, there is a large amount of drug-related (open) data published on the Web, describing various properties of drugs and their relationships to other drugs, genes, diseases, and related concepts and entities. In this demonstration, we describe an end-to-end system we have designed to take in various Web data sources as input and provide as output a prediction of DDIs along with an explanation of why two drugs may interact. The system first creates a knowledge graph out of input data sources through large-scale semantic integration, and then performs link prediction among drug entities in the graph through large-scale similarity analysis and machine learning. The link prediction is performed using a logistic regression model over several similarity matrices built using different drug similarity measures. We present both the efficient link prediction framework implemented in Apache Spark, and our APIs and Web interface for predicting DDIs and exploring their potential causes and nature.

Keywords

Drug-Drug Interactions, Link Prediction, Semantic Web, Big Data on the Web

1. INTRODUCTION

Adverse drug reactions (ADRs) are a major cause of serious health complications and a major burden on the healthcare system. Drug-Drug Interactions (DDIs) are among the leading causes of “preventable” ADRs, in part due to the extreme difficulty of identifying potential DDIs early in the drug design process and through clinical studies. On the other hand, there is a wealth of information on the Web related to drugs, with several sources publishing structured and semi-structured data on the Web. A recent study has shown that none of the existing public sources that contain DDI information provide a reasonable coverage of all the

known interactions [2], and most sources are either incomplete or too conservative by listing a large number of insignificant DDIs. Furthermore, existing sources rarely provide an evidence or an explanation for a DDI. As a result, a simple integration of all the public sources would be far from usable in real clinical and pharmaceutical settings.

In this paper, we present *Tiresias*, a system that takes in as input a variety of drug-related data sources from the Web, including a (small) set of known DDIs, and provides as output a list of potential (unknown) DDIs along with an explanation for each DDI. The system first performs a semantic integration of the input data, building a knowledge graph describing drugs and connecting them to various related entities such as enzymes, chemical structures, and pathways. Similar to content-based recommender systems, the prediction an interaction between a candidate pair of drugs is performed by comparing it against known interacting pairs of drugs. A large number of robust similarity measures taking into account the properties of various sources are calculated and then used to build a linear regression learning model, all in a highly scalable way implemented in Apache Spark.

In what follows, we describe the overall architecture of the system along with a brief summary of various novel solutions implemented in the system to perform semantic integration, feature engineering, and large-scale learning suitable for sparse features gathered from various information sources on the Web. We then present a summary of our demonstration plan.

2. SYSTEM OVERVIEW

The overall architecture of our similarity-based DDI prediction approach is illustrated in Figure 1. In what follows, we briefly describe each of the components

2.1 Knowledge Curation

We construct a knowledge graph by ingesting data from variety of sources (including XML, relational, and CSV formats) from the Web. As partially shown in Figure 2, our data comes from variety of sources such as *DrugBank* [11] that offers data about known drugs and diseases, *Comparative Toxicogenomics Database* [7] that provides information about gene interaction, *Uniprot* [1] that provides details about the functions and structure of genes, *BioGRID* database that collects genetic and protein interactions [6], *Unified Medical Language System* that one is the largest repository of biomedical vocabularies including *NCBI* taxonomy, *Gene Ontology (GO)*, the *Medical Subject Headings (MeSH)* [3], and the *National Drug File - Reference Termi-*

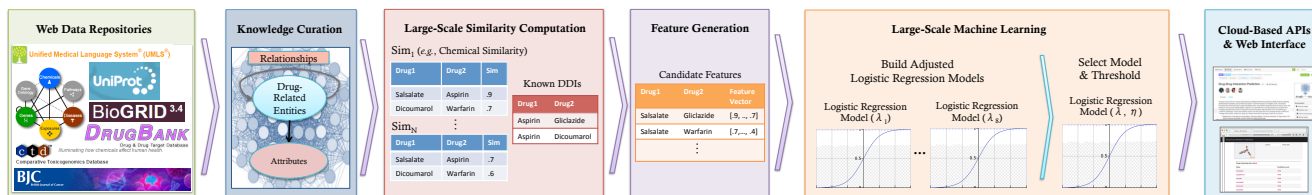


Figure 1: Tiresias System Architecture.

nology (*NDF-RT*) that classifies drug with a multi-category reference models such as cellular or molecular interactions and therapeutic categories [4].

As part of our knowledge graph curation task, we identify which attributes or columns refer to which real world entities (i.e., data instances). Therefore, our constructed knowledge graph possess a clear notion of what the entities are, and what relations exist for each instance in order to capture the data interconnectedness. These may be relations to other entities, or the relations of the attributes of the entity to data values. As an example, in our ingested and curated data, we have a table for *Drug*, and have the columns *Name*, *Targets*, *Symptomatic Treatment*. Our knowledge graph has an identifier for a real world drug *Methotrexate*, and captures its attributes such as *Molecular Structure* or *Mechanism of Actions*, as well as relations to other entities including *Genes* that *Methotrexate* targets (e.g., *DHFR*), and subsequently, *Conditions* that it treats such as *Osteosarcoma (bone cancer)* that are reachable through its target genes, as demonstrated in Figure 2. Constructing a rich knowledge graph is a necessary step before building our predication model as discussed next.

2.2 Similarity Computation

In this phase, data originating from multiple sources that are integrated in our knowledge graph are used to create various drug similarity measures (represented as blue tables in Figure 1) and a known DDIs table. Similarity measures are not necessarily complete in the sense that some drug pairs may be missing from the similarity tables. The known DDIs table, denoted *KDDI*, contains the set of 12,104 drug pairs already known to interact in DrugBank. In the 10-fold cross validation of our approach, *KDDI* is randomly split into 3 disjoint subsets: $KDDI_{train}$, $KDDI_{val}$, and $KDDI_{test}$ representing the set of positive examples respectively used in the training, validation and testing (or prediction) phases. Contrary to most prior work, which partition *KDDI* on the DDI associations instead of on drugs, our partitioning simulates the scenario of the introduction of newly developed drugs for which no interacting drugs are known. In particular, each pair (d_1, d_2) in $KDDI_{test}$ is such that either d_1 or d_2 does not appear in $KDDI_{train}$ or $KDDI_{val}$.

Due to space limitation, we describe here only 4 of the 13 similarity metrics are presented in detail in [8], including

DrugBank: Bioinformatics & Cheminformatics Resource

Drug Name	Drug Targets (Genes)	Symptomatic Treatment
Ibuprofen	PTGS2	Rheumatoid Arthritis
Acetaminophen	PTGS2	Relief Fever
Methotrexate	DHFR	Antineoplastic Anti-metabolite
Warfarin	TP53	Embolism (Blood Clot)

CTD: Comparative Toxicogenomics Database

Gene	Interaction	Gene	Disease
PTGS2	TP53 (Gene)	TP53	Osteosarcoma

Uniprot: Universal Protein Resource

Chemical	Pathways	Linked Data Source	Gene	Function
Ibuprofen	Metabolic Pathways	KEGG	TP53	Tumor Suppressor
Acetaminophen	Signal Transduction	Reactome	DHFR	Limits Cell Growth
Methotrexate	Immune System	Reactome		

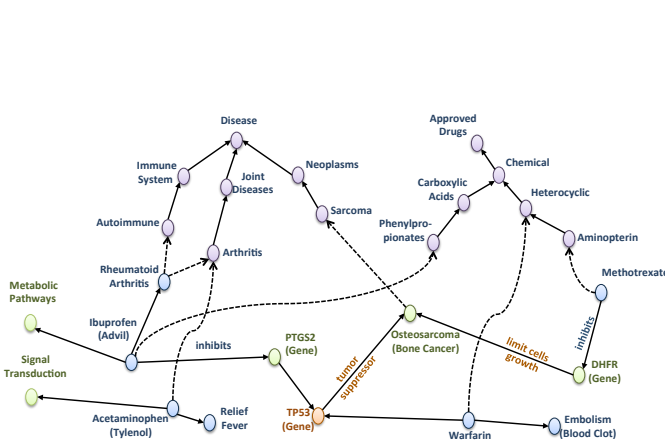


Figure 2: Semantic Curation and Linkage of Data from Variety of Sources on the Web.

all the ancestor codes are included). The ATC similarity of two drugs is defined as the cosine similarity between the IDF-weighted ATC code vectors of the two drugs, which are computed in a similar way as IDF-weighted mechanism of action vectors.

2.3 Feature Generation

Given a pair of drugs (d_1, d_2) , we construct its machine

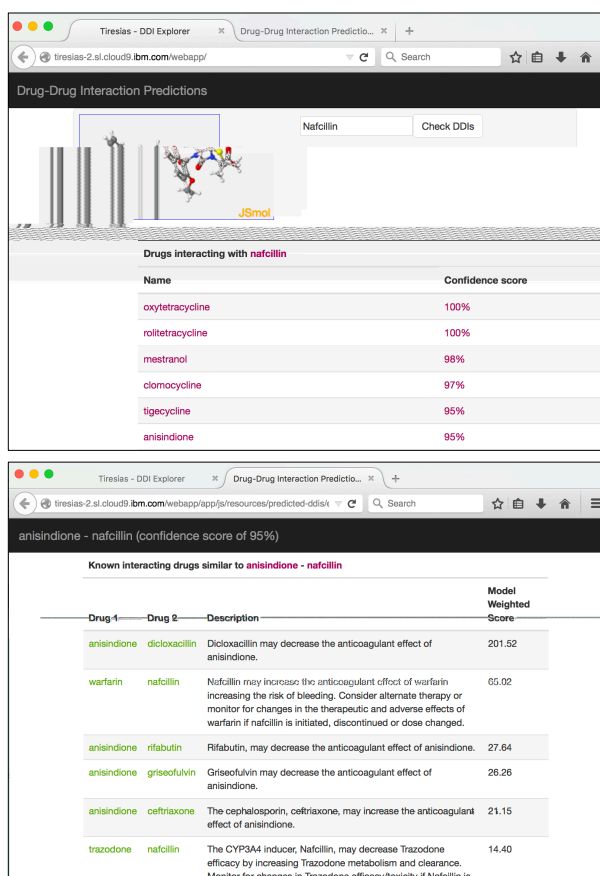


Figure 3: DDI Exploration Web Interface

across drugs that are useful for DDI prediction. We also show how the results could be incomplete for certain DDIs due to the different coverage of the input sources.

- **DDI Predictions & Explanations** The main part of our demonstration will be showcasing the end result of DDI predictions. First, we present a Web interface to look up known and predicted interactions for a given drug, and provide evidence and explanation for each DDI as shown in Figure 3. The explanation is based on the existing evidence for interaction between similar drugs. We then present the results of retrospective analysis which relies on DDI information from an older version of DrugBank to predict interactions that were unknown at the time, verify some new interactions that have been discovered since then, and compare the explanation our system provides with the new evidence supporting the existence of the DDI.

Our demonstration will be using a prototype cloud service that is currently at Alpha stage. In addition to the above, we will share the current technical documentation, API design, business use cases, and our plan for commercial offering of the solution.

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