

# A NEW GENERATION OF DIGITAL LIBRARY TO SUPPORT DRUG DISCOVERY RESEARCH

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**Abstract:** The recent explosion of publicly available biomedical information gave drug discovery researchers unprecedented access to a wide variety of online repositories, but the sheer volume of the available data diminishes its utility. This is compounded by the fact that these repositories suffer from a silo effect: data from one cannot be easily linked to data in another. This is true for both publicly available sources and internal sources such as project reports. The ability to explore all aspects of biological data and to link data across sources is beneficial, as it allows researchers to discover new knowledge and to identify new collaboration opportunities by exploiting links. This paper presents an approach to solving this problem and an application that allows researchers to browse and analyze disparate bio-medical repositories as one semantically integrated knowledge space.

## 1 INTRODUCTION

In the last two years, we have interviewed eighteen drug discovery scientists from several pharmaceutical companies and research institutes in Europe and North America to better understand their research tasks and information needs. These scientists are responsible for identifying new chemical compounds that have therapeutic purposes. They spend between 20 and 90 percent of their time reading scientific articles that might be pertinent to their projects. In some cases, they scan over 900 abstracts and read 200 articles in a month just to keep up. This translates to 45 abstracts and 10 full articles a day – a very time consuming activity.

Until very recently, their primary external source of information was MEDLINE (Katcher, 1999), which contains over twelve million bibliographic citations and abstracts from articles published in over 4,600 bio-medical journals. However, with the recent advancement of computational molecular biology fields such as genomics and proteomics, these scientists find an increasing number of new, more structured information sources indispensable (Elmasri & Navathe, 1999; National Library of Medicine, 2003). Some of these sources include GenBank (gene sequence), KEGG (biological pathways) and OMIM (genetic disorders). Furthermore, as pharmaceutical companies introduce their own corporate intranets, highly valuable

internal information such as project reports, lab notes and screening results become available enterprise-wide and may be relevant to these scientists.

As a result, these scientists have to face dozens of information sources each with its own intricacies, access methods and nomenclature. Even a simple question such as “Is there any internal expert on T4 Polynucleotide Kinase?” can pose significant challenges as no single source may contain the answer. The answer may have to be constructed by examining the authors of various articles, reports and patent documents that are indirectly related to this particular kinase, such as through its proteins and biological pathways. While doing this is certainly possible, it could be very time-consuming as it requires access to multiple heterogeneous internal and external sources.

Existing systems such as GeneLynx (Lambrix & Jakoniene, 2003), DiscoveryLink (Haas et al., 2001) and SRS (Etzold, Ulyanov & Argos, 1996) view this as a distributed database problem and approach it by integrating the underlying schemas of the sources into a global schema and by providing a query language to go against the schema. Few of them deal with the nomenclature issues and the fact that scientists may pose questions at a different level of abstraction than what is available in the underlying sources (Geffner et al., 1999).

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Developing a system that is appealing to the scientists is further complicated by their lack of computer skills making direct exposure to a formal query language, for example, impractical. Form-based user interfaces are not effective as different users with diverse backgrounds fill out the forms differently.

In this paper, we introduce our approach to addressing these issues and the Knowledge Discovery Tool, an application that embodies our answers. Our approach is based on the creation of a semantic index to information contained in the underlying heterogeneous sources. The basis for this index is the *knowledge model* that relates all major concepts in the domain. Domain and application-specific rules utilize this index to infer relationships of potential value to researchers. The tool's visualization framework enables intelligent browsing to support research and investigation tasks by providing the ability to uncover indirect or hidden linkages among pieces of information.

## 2 KNOWLEDGE MODELING

Central to our approach is a technique for modeling the kind of knowledge a scientist needs to perform his or her job (Brody et al., 1999). This model contains a representation of bio-medical concepts: entities and the relationships between them. This model is an ontology designed specifically for scientists performing a predefined set of tasks.

The model shown in Figure 1, contains entities and relationships that depict treatments for a disease, how those treatments are related to a set of drugs, the chemical compounds that comprise those drugs, how the compounds are related to various target proteins, and so on. This knowledge model is a representation of how the scientists think about the information they need in order to perform their tasks.

The model enhances the accessibility of knowledge in three major ways. First, it creates a

layer that is independent of the location of the underlying information. Second, the instantiated model allows the user to search and browse the entire body of knowledge as one homogeneous space of related entities while maintaining links back to the original sources.

Third, when used with classification hierarchies, the model becomes a powerful abstraction mechanism (Geffner et al., 1999). For example, when a scientist inquires about the role of G-protein in Central Nervous System (CNS) diseases, a straight text search might not reveal anything as the underlying sources may not contain the phrase "Central Nervous System" or its synonyms. However, these sources may contain references to the relationship of G-protein and Parkinson's or Alzheimer's diseases. To answer the above question, the system must utilize a disease classification hierarchy such as the one in Medical Subject Headings (Lowe & Barnett, 1994) which classifies Parkinson's and Alzheimer's as sub-diseases of CNS. As a result, the system can exploit these linkages and provide information about the relationship between G-protein and higher level diseases.

In addition to structural relationships, our knowledge model contains dozens of domain-specific functional rules such as "Any person who has authored more than X documents on a protein is an expert in that protein." Such rules constrain and guide the automatic inference process.

## 3 KNOWLEDGE DISCOVERY TOOL

When the model is instantiated with existing data sources as described in section 4, it becomes a giant semantic index into the underlying sources and can support a variety of applications. One can easily build an SQL interface for example, to query the index. However, given that our target users have

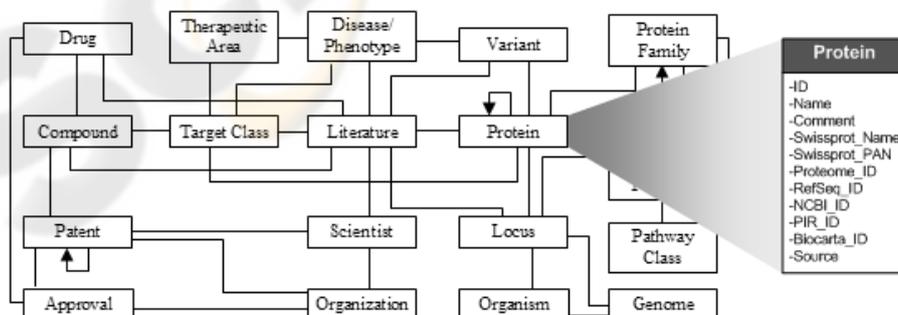


Figure 1: A knowledge model to support drug discovery scientists.

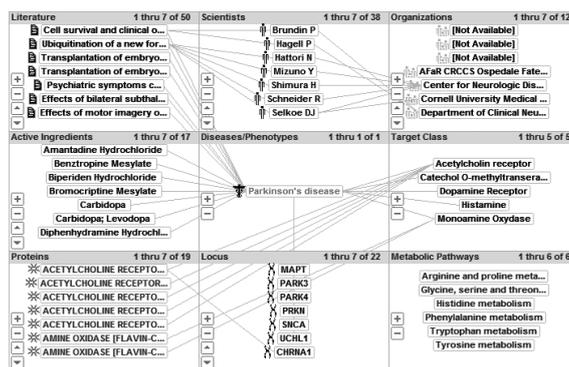


Figure 2: Landscape View of "Parkinson's disease".

little or no SQL or information retrieval skills, we built a web-based intelligent browser called Knowledge Discovery Tool (KDT) that uses our semantic index and the model's inference rules to select and present the most likely relationships among the data of interest to the user.

To demonstrate some of the KDT features, consider the following interaction: A drug discovery scientist who specializes in Oncology is researching a potential link between Parkinson's disease and cancer. She needs to bring herself up-to-speed about Parkinson's disease in a short time. She needs to identify experts in the area and any past work that might be relevant.

She starts up KDT, selects the search type "Disease" and types "Parkinson's" into the search box. KDT then displays all diseases whose names include "Parkinson's". She clicks on "Parkinson's disease" and is brought to the Landscape View for that disease (Figure 2). The view divides the screen into 9 (3x3) panes. The center pane shows her current focus (Parkinson's Disease). Each outer pane displays information related to the current focus as filtered by the knowledge model. She sees recent literature related to the disease in the top left pane, a list of experts on the disease in the top center pane,

and a list of organizations that have published articles or own patents related to the disease in the top right pane. The center row contains a list of related chemical compounds; the disease itself; and a list of biological target classes used for treatments of the disease.

The researcher can see linkages among the items in the panes indicated by light grey lines that are visible without cluttering the screen. The lines let users visually maintain the connectivity among entities, which seems to be intuitive to many users. Studies have shown that exposing a large number of relationships stimulates fresh thoughts and breaks through creative blocks (Schneiderman, 2000).

The view facilitates fast browsing by minimizing the need for mouse clicking. For example, if the user hovers the mouse over an item, a tool-tip will pop up displaying the item's full title and attributes and it will also highlight its links. Since each item represents an index to the underlying source, the user can view the source by double clicking on the item.

Single clicking on an item will re-orient the knowledge model, move the item to the center pane, and refresh the contents of the outer panes accordingly. Figure 3a shows how the view looks

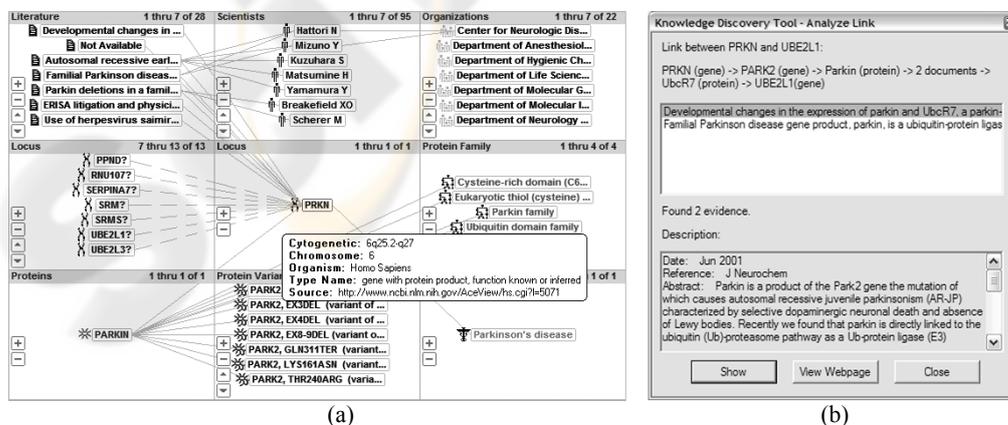


Figure 3: (a) Landscape view of gene "PRKN", (b) A window showing a path that substantiates the link between PRKN and UBE2L1

after the user has clicked on PRKN - the third gene (locus) in the bottom middle pane of Figure 2.

Each outer pane of the browser presents the results of a query run against the underlying semantic index, filtered and prioritized according to the rules in the knowledge model. The user can easily customize the view in each pane by picking from a large library of predefined views. For example, the user can change the list of disease expert shown in top center pane of Figure 3a to show those people that have been published about PRKN in the past 3 years and sort the list based on their most recent publication date. A user who is an oncologist can tailor a pane to display only genes that relate to PRKN and cancer-related diseases.

KDT provides utilities to explore potential linkages among entities that are depicted as grey lines. For example, one of the items in the left center pane in figure 3a, UBE2L1, is a gene that has been associated with several forms of cancer including Leukemia and Breast Cancer (Ardley et al., 2000). The link between PRKN and UBE2L1 is drawn as a dashed line indicating there are multiple degrees of separation between them. By clicking on the right menu over the line, the user can query the tool to show how this link is derived. The tool found two paths that substantiate the link. Figure 3b shows one of them: a path with six items as follows. Gene PRKN has been renamed to PARK2 and this gene produces the Parkin protein. Parkin is linked to another protein UbcR7 through two articles. The bottom half of figure 3b shows one of the articles that describes an interaction between Parkin and UbcR7 in rat brain (Wang et al., 2001). UbcR7 in turn is produced by UBE2L1. Deriving links in this manner to expose hidden or indirect links that the users might not have thought of is a powerful capability (Schneiderman, 2000).

KDT also serves as a powerful collaboration tool. By annotating items or links, users can informally share their opinions and enrich the existing contents. Furthermore, by continuously monitoring common bookmarks and users' navigation paths, the tool also can match users with similar interests.

Because the index is continuously updated, the researchers can use KDT to monitor new items and links related to a topic of interest. We also developed wizards similar to those used in setting up printers in Microsoft Windows, to automate the repetitive tasks that the users frequently do with KDT.

## 4 INSTANTIATING THE MODEL

The process used to instantiate the model is very similar to the one used for data warehousing (Fayyad et al., 1996). The data from the selected data sources is extracted and transformed into its relational form. It is then cleansed of errors using a semi-automated approach. Thesauri are created in the process. Cleansed data is then integrated. This process is described more in detail below.

### 4.1 Data Selection, Mapping and Extraction

The 13 sources used in the current implementation of KDT are: Enzyme, GeneOntology, NCBI Genome, Interpro, KEGG, LocusLink, MeSH, NLM Taxonomy, OMIM, MEDLINE, NCBI RefSeq, Swissprot, and Unigene.

First, data fields in each source are mapped onto the attributes of entities in our model. For example, NLM Taxonomy's TaxID, LocusLink's OrganismID and RefSeq's OrganismID are all mapped to the OrganismID in the model. We map all attributes of all entities and relationships defined in our model. As the above example indicates, most attributes in the knowledge model are instantiated from multiple sources. This, of course, generates conflicts and they will be addressed in section 4.3.

Second, we create a representation of each source in a local database. Once the information is in the database, some of the fields have to be parsed further. For example, the pathway description field from KEGG may contain a piece of text like "Glycolysis/Gluconeogenesis – Aquifex aeolicus" which would be parsed into two subfields: "Glycolysis/Gluconeogenesis" as the pathway's title and "Aquifex aeolicus" as the associated organism name. This secondary parsing could also result in building new hierarchies. For example, by parsing the ExPASy's EnzymeID, one can determine that the protein family with EnzymeID of "EC.2.7.1.12" is a child of EnzymeID "EC.2.7.1." We use dozens of rules to guide data extraction.

### 4.2 Schema Integration

This phase reconciles diverse schemas in the local database with the schema as defined in the knowledge model. Lenzerini (2002) describes this as the local-as-view (LAV) process. It is done in two steps. The first step handles the fact that a data source could be mapped into multiple entities in the knowledge model. This is accomplished by creating multiple database views. The second step handles

the fact that an attribute of an entity can be assembled from multiple sources. Thus we need to combine multiple database views from step one. This is accomplished by writing SQL scripts to insert the contents from the appropriate views to the target table for each entity.

### 4.3 Instance Integration

Schema integration produces a large number of redundant instances for each entity primarily due to the fact that different sources use different nomenclature or provide different set of attributes. The objective of instance integration is to remove conflicts and merge redundant data of an instance by comparing one or more of its attributes.

We start instance integration by identifying redundant records. We employ the vector space model (Fasulo, 1999) to determine the similarity among attributes through the use of two broad classes of heuristics: ID-based and text-based. In ID-based heuristics, we assume that there are one or more IDs that uniquely identify an instance. While this is the most straightforward in most cases, the process is complicated by the fact that some of these IDs may not be consistent.

The heuristics to solve ID inconsistencies were manually developed by domain experts after visually inspecting the origins of the inconsistencies. For example, we found that the combination of SwissprotID and OrganismID can be used to uniquely identify a gene for our purpose. This class of heuristics is applicable to gene, proteins, pathways, protein families and genomes where the use of IDs is quite pervasive.

The text-based heuristics are applicable to organisms, phenotypes, organizations and people where IDs are not readily available. We employ many techniques and heuristics to resolve the name similarity problem. Many of such techniques are also used in WHIRL (Cohen, 2000). They range from simple removal of punctuation (e.g., "Legionnaires' Disease" vs. "Legionnaires Disease"), to comparing last name and first initial (e.g., "A. aeolicus" vs. "Aquifex aeolicus"), to using dictionaries and synonyms to match "zebrafish" to "zebra danio".

Our synonym tables are created in three ways. First, there are several sources such as NLMTaxonomy that contain synonym information explicitly and we simply import them. Second, some sources contain implicit synonym information that we have to extract. For example, Swissprot's protein name may contain text like "Alzheimer's disease amyloid A4 protein precursor (Fragment) (Protease nexin-II) (PN-II) (APPI)". From this piece of text we

extract "PN-II" and "APPI" as the synonyms of "Protease nexin-II". The third way is described in conflict resolution below.

In conflict resolution, we tag each attribute with the source from which the value was extracted. Each source is associated with a *confidence value* between 0 and 10 by a domain expert. An attribute with a higher confidence value can overwrite those with lower confidence values. However, for the attributes that signify the names of an object, we mark them as potentially synonymous instead of overwriting them.

The merge step involves a domain expert to confirm that the identified redundant records are indeed redundant and that the suggested merged record is correct. We developed a small application called Thesaurus Builder to assist a domain expert in this task. This application also allows the domain expert to manually identify instances to merge. While this manual step is time consuming, it is important to have an expert to validate this step as the quality of the entire integration result is highly dependant on it. The decisions made by the domain expert are captured so that they can be automatically re-applied in the future.

### 4.4 Post-Integration

While published articles in MEDLINE form one of the richest sources of bio-medical information to date, automatically extracting semantic information from them is hard (Jacquemin, 2001). Currently, we use these articles to create weak unlabelled links between the entities in the knowledge model through the co-occurrences of terms in the articles. The more articles that link the two entities, the stronger the link is. The strength value is then used to rank and sort the query results.

Another factor in determining the strength value is the length of inferred relationships. For example, a gene can be related to a disease through its proteins and variants. As each intermediate step introduces further uncertainty, we assigned lower strength to the relationships inferred using longer paths.

## 5 OUTCOME AND BENEFIT

As shown in section 3, a KDT user is able to explore thematically related information across multiple data sources as if it were a single richly connected knowledge space. The user does not have to be concerned with the details of the underlying databases, their formats, or their access methods. Exploration of a potential link between two entities as shown in Figure 3b that takes minutes with KDT would require hours or perhaps days using the

access methods provided by the 13 knowledge sources we cover.

We developed the components used to instantiate the knowledge model using Microsoft-based technologies including Microsoft Windows 2000 Server and Microsoft SQL Database. KDT was written entirely in Java as a Java applet. This eases the deployment of the tool as it can run in most Internet browsers that support Java.

From the thirteen sources we have selected, the instantiated knowledge model contains over 1.1 million genes, 1.6 million proteins, 200,000 organisms, 12,000 pathways, 6,000 diseases, 12 million articles and over 4 billion relationships across these biological entities. Prior to the post-integration phase, the instantiated knowledge model is about 70GB in size. Once the indices and pre-calculated relationships are created, the size of the database grows to 400GB.

While we have not conducted a formal evaluation of KDT's effectiveness as compared to the current access methods, bio-medical researchers who have tried KDT have given us very positive feedback and expressed a strong desire to use the tool in their daily activities. In one particularly gratifying case, the senior leader of a heart failure research project tried it during a ten-minute demonstration and discovered a valuable relationship between heart failure and leukemia of which he had not been aware. In another case, a post-doctoral biologist discovered a new link between Lou Gehrig's disease and genital diseases suggesting that a drug for one disease can be modified for the treatment of the other.

Currently, we are working with several pharmaceutical companies, the University of Colorado Health Sciences Center in Denver and the Integrative Neuroscience Initiative on Alcoholism – an initiative sponsored by the National Institute of Alcohol Abuse and Alcoholism – to formally evaluate the effectiveness of KDT. We have over 30 people who have signed up for our initial pilot. We estimate the formal evaluation will be done in Spring 2004.

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