Visualization and Analysis of a Cardio Vascular Disease- and MUPP1-related Biological Network combining Text Mining and Data Warehouse Approaches

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Summary

Detailed investigation of socially important diseases with modern experimental methods has resulted in the generation of large volume of valuable data. However, analysis and interpretation of this data needs application of efficient computational techniques and systems biology approaches. In particular, the techniques allowing the reconstruction of associative networks of various biological objects and events can be useful. In this publication, the combination of different techniques to create such a network associated with an abstract cell environment is discussed in order to gain insights into the functional as well as spatial interrelationships. It is shown that experimentally gained knowledge enriched with data warehouse content and text mining data can be used for the reconstruction and localization of a cardiovascular disease developing network beginning with MUPP1/MPDZ (multi-PDZ domain protein).

1 Introduction

More than 4000 human diseases are known and defined [1]. Regarding the medical characteristics or main features one can see that any disease is defined or specified by particular symptoms and/or laboratory parameters. In practice the diagnosis problem is based on the fact that a lot of symptoms, such as fever, are related to many diseases. Therefore, the diagnostic procedure will always be a differential process which will produce a set of possible diseases. Furthermore, the so-called personalized medicine makes the problem of finding the patient-relevant diagnosis and recommendation for its treatment much more difficult. Based on the data of molecular biology, the development of new and more efficient tools for medical diagnosis and therapy process is becoming possible.

Today, more and more diseases can be reduced to simple metabolic processes, which more or less are based on mutations in related genes. OMIM [2] examplifies of well-known information systems which exactly represent this kind of knowledge. Overall, there are more than 1000 molecular database and information systems which represent various molecular and phenotypic data. These information resources were designed on the basis of either automatic data extraction or manual

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annotation and curation. Behind these information systems there is one more specific and powerful information system which will present molecular and medical disease knowledge. The MEDLINE information system represents all relevant publications (abstracts and in the near future a complete listing of papers) which are relevant for molecular medicine or biomedicine. Overall one have access to more than 1000 powerful database and information systems which will help identify molecular knowledge about any disease. Furthermore, this data can be supported, enriched or fused by the extension of text and data mining techniques which allow the automatic extraction of medical and molecular knowledge from the PubMed system, which includes all relevant scientific results. Therefore, it is possible to construct or predict the metabolic network for any disease. This kind of work is relatively new and during the last years different database integration and data mining systems have been implemented. However, the problem of all these systems is, that data integration and mining tools will produce networks, which are too complex. Therefore, the development of special filter systems or visualization tools is a necessary step in understanding and analyzing these complex metabolic disease-related networks. In this paper it will be demonstrated how the data integration and data mining tools can be used to gather the molecular knowledge on diseases.

The focus of this application is on Cardiovascular diseases (CVDs), and more precisely the dilated cardiomyopathy, which is the leading cause of death in developed countries. Based on the experimental identification of a CVD relevant protein, two protein-protein interaction networks were constructed by using the network visualization and analysis tool VANESA [3] and the text mining tool ANDVisio [4], which is also able to identify the localization of network components. This localization information was extended, combined with the created networks and finally visualized in 3D by the CELLmicrocosmos 4.2 PathwayIntegration (CmPI) [5].

2 Basics

2.1 Metabolic disease networks

Much attention has been recently focused on the metabolic aspects of Cardiovascular diseases (CVDs). The discovery of new CVDs specific molecular targets promoted the investigation of proteins functional roles in their specific pathways. It is quite complex to evaluate the weight of each trigger factor (metabolism, hormones, exogenous factors, etc.) on CVDs emergence. Epidemiological studies constitute the starting point for molecular medicine screening. The advent of high throughput analytical techniques (DNA chip, protein arrays, molecular imaging) has improved the capability to screen new candidate target proteins (genes). The relations of metabolic pathways of a sample coming from patients affected with dilated cardiomyopathy (DCM) was the basis of study for this publication. The proteome analysis is based on experimental data on which integrative bioinformatics approaches have been applied to characterize a specific functional pathway deregulated in the pathological sample. In this study, the combination of data warehouse with text mining approaches is demonstrated by using different software applications.

2.2 Data integration

Since industrial research of molecular biology questions starting with the Human Genome Project, one of the main challenges in bioinformatics is the integration of molecular data. Today high throughput analysis delivers data of complete genomes, for instance short sequences of all genes in an organism or expression patterns of thousands of a cell in shortest time. Analysis of these high throughput data by manual investigation using publications or relevant databases is no longer

possible. Consequently, biologist has to be supported by tools and methods that can accumulate experimental data with complementary data sources, estimate the data and compare or classify these data. This challenge leads us to the problem of database integration.

Typically, data of genomes, genes, proteins, enzymes, chemical compounds, diseases, etcetera is stored in databases with worldwide availability. A good overview of important databases is provided by the annual special issue of Nucleic Acids Research [6]. The number of molecular databases is continuously increasing in the last decade. Molecular biological data has a high semantic heterogeneity that is caused by (experimental) data extracted from a series of experiments. Molecular biology deals with complex problems, hence enormous and versatile data is produced. The total number of databases, as well the data itself, is continuously increasing, as is the distribution and heterogeneity of the data. Particularly, data heterogeneity causes big problems in molecular biological data integration. Technical heterogeneity is caused by a high number of different formats and interfaces of the different data sources. Furthermore, the data is usually not available in a standard format which causes structural heterogeneity. Moreover, there is a level of semantic heterogeneity, because of missing standards and consensus for basic biological terms. In addition to the problems of molecular biological databases there are some more in data integration. Usually, data sources of an integrated system are distributed. That means, each and every source is located on separate systems and different locations. The distribution of several data sources leads automatically to the problem of autonomy. Regarding data integration, autonomy means independence of the data source that refers to access, configuration, development and administration.

The major problem of data integration is heterogeneity that is caused by autonomy. Moreover, distribution can also cause heterogeneity, but not generally. The development of an integrated database system is a complex task. Particularly, if a large number of heterogeneous databases have to be integrated. Data warehouses (DWH) are one of the widely used structures for database integration. For that purpose a software infrastructure for building life science data warehouses using different common relational database management systems is introduced. The BioDWH [7] system is realized as a Java-based open source application that is supported on different platforms with an installed Java Runtime Environment (JRE). BioDWH is a flexible DWH infrastructure for bioinformatics; it is independent from the underlying RDBMS. Furthermore, the data warehouse approach provides an easy-to-use graphical user interface for administration and configuration. The main feature of the BioDWH tool-kit is the automatic storage and visualization of data content and information from different public databases into a homogeneous and consistent data warehouse. It provides integrated data from different widely-used life science databases, such as BRENDA [8], EMBL [9], ENZYME [10], GO [11], HPRD [12], KEGG [13], OMIM [2], Reactome [14], SCOP [15], Transfac [16], Transpath [17] and UniProt [18] and microarray data. Additionally, configuration of the infrastructure and its tools is also possible via XML, because it is human readable, well-formatted, easy accessible and standardized. A logging mechanism observes the integration process and begins a simple recovery process to guarantee a consistent state of the data warehouse. The data warehouse BioDWH addresses the aforementioned aspects of data integration.

Based on the data from the warehouse infrastructure, the CardioVINEdb [19], a data warehouse approach, was developed to browse and explore life science data. Furthermore, a DWH system to search integrated life science data and simple navigation called DAWIS-M.D. was implemented based on the life science data from the BioDWH toolkit. In addition, the network editor VANESA uses the data from DAWIS-M.D to generate biological networks and enrich them with additional information.