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Toward disease diagnosis visual support bridging classic and precision medicine

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Figure 1: *The Visual Analytics environment is composed of a Sankey diagram (B) showing connections among symptoms, anatomies, and diseases categories; a left pane (A) dedicated to symptoms and a right pane (C) dedicated to anatomies; the list of disease categories (D), the diseases similarity matrix (E), the top ten ranking of similar diseases (F) and a similarity radar chart (G) for their comparison.*

Abstract

The traditional approach in medicine starts with investigating patients' symptoms to make a diagnosis. While with the advent of precision medicine, a diagnosis results from several factors that interact and need to be analyzed together. This added complexity asks for increased support for medical personnel in analyzing these data altogether. Our objective is to merge the traditional approach with network medicine to offer a tool to investigate together symptoms, anatomies, diseases, and genes to establish a diagnosis from different points of view. This paper aims to help the clinician with the typical workflow of disease analysis, proposing a Visual Analytics tool to ease this task. A use case demonstrates the benefits of the proposed solution.

CCS Concepts

• ***Human-centered computing*** → ***Visual analytics;*** • ***Applied computing*** → ***Computational genomics; Biological networks;***

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1. Introduction

Nowadays, a large amount of data is available for biomedical research and clinical applications. However, its integration and exploitation are still complex tasks, often inaccessible to those without non-trivial computational knowledge. In particular, there are now large knowledge bases (KBs) for which exploration with Visual Analytics (VA) approaches would be very desirable and useful. Some of these KBs, such as DRKG [ISM*20] or Hetionet [HLH*17], are *hetnet*, i.e., heterogeneous information networks of biomedical knowledge. They encode relationships and associations among many different types of biomedically-relevant entities from a large number of studies into a single, integrated resource. While their advanced computational analysis has already proved very useful [SCN*22], there is still a lack of tools that can easily and intuitively navigate their data. VA potentially represents a tool of great importance, as has already been the introduction of the network paradigm and other abstract mathematical-computational concepts in biology and medicine. [BO04,TGZ*10]. Current approaches in biomedicine and clinical practices (e.g., drug repurposing) often tend to oversimplify disease mechanisms (we frame this as classic medicine support), which are in fact complex processes involving a large number of intertwined players, also exemplified by the spread, advancement and the success of computational network medicine approaches (we frame this as precision medicine support). Moreover, disease definitions are still mainly symptom- rather than mechanism-based, therapies and therapeutics being often likewise. With the perspective of framing this complexity within a systems approach, in this work, we have extracted a large amount of information from DRKG and Hetionet and built a VA tool for their exploration. We exploited the data on the association between diseases, symptoms, and anatomies, also taking into account other available information such as genetic data (gene-disease associations) and of belonging to cell signaling pathways, among others.

The contributions of this paper are: (i) an initial effort to merge the two illustrated medicine approaches for interactive analysis; (ii) a VA environment that supports the disease diagnosis task exploiting the joint classic and precision medicine approach; (iii) a use case that shows an example of how the VA environment supports this analysis.

2. Related Work

The increasing amount of data due to scientific advancements such as human genome sequencing, metagenomics, proteomics, among others the analysis of network medicine, and the advent of precision medicine to treat patients, have brought new challenges in their analysis toward supporting decision-making activities such as disease diagnoses or treatments. A possible solution that has been adopted in recent years is Visual Analytics (VA) because of its usefulness in the analysis of large quantities of data while at the same time aiding the user in visually exploring the results. Thanks to its nature, VA is applied to different fields in the healthcare domain, ranging from public health [PL20] to epidemiology [PKH*16], multi-faceted medical data [Rai19] genomics, and cancer [QLN*19]. Looking at the existing literature in this area, we have split the works into two significant groups depending on the applied strategy: classic medicine or precision medicine support.

Classic medicine support Classic medicine support is based on the clinical life of patients that can be found analyzing Electronic Medical Records (EMR) or Electronic Health Records (EHR). Zhang et al. [ZBA*13] propose a visualization framework able to capture all health conditions of the past and present to serve as a quick overview and apply a reasoning chain to understand and generate a diagnosis. They use a sunburst to represent the hierarchical structures of related events, while we use a Sankey to represent the hierarchy of elements. Kwon et al. [KCK*19] apply recurrent neural networks (RNNs) on EMRs and develop RetainVis, a VA solution to increase the interpretability and interactivity of RNNs that helps users to explore real-world EMRs, gain insights, and generate new hypotheses. Also, Perer and Sun [PS12] analyze the clinical events of patients to improve disease diagnosis by providing insights for understanding disease progression using MatrixFlow and supposing the same flow for other patients. In this case, the matrix is a temporal flow matrix, whereas we use a matrix to represent the similarity of disease using different parameters. Instead, Basole et al. [BBK*15] apply process mining to analyze and investigate the care process of pediatric asthma and use the VA to gain insight. Unlike all these works, we do not use patient and temporal data, but this paper investigates the network composed of symptoms, anatomies, and diseases.

Precision medicine support Precision medicine support takes into account individual variability in genes for disease treatment and prevention, exploiting the connections obtained through the analysis of network medicine. The strength of network medicine is the heterogeneity of the data [HK20], because it allows to analyze the problem from different points of view, also exploiting the concept of multilayer network [KAB*14].
This capability led to the development of VA solutions able to support the exploration of precision and network medicine data. The visualization efforts usually target the protein-protein interaction network (interactome) [CMR*09], disease modules [RAS*21], gene pathways [MSH*05], and drugs composition [IGA20]; also analyzing the connections among different layers, as gene and diseases [ABF*19]. Focusing on the use of precision medicine, HitWalker2 [BMW16] is a reproducible and flexible VA framework for prioritization that applies to a large number of clinical, translational, and primary science use cases. The results are obtained by investigating many aspects of the genes layer and the data is not connected to a specific patient but derives from the network investigation. Unlike this approach, we reconnect the gene information to the specific disease to obtain the similarity among diseases. In contrast, ClinOmicsTrailbc [SKT*19] focuses on the breast cancer treatment stratification to assess and prioritize breast cancer drugs by investigating the specific genome of the patients. While authors propose a rich VA workflow obtaining ten blocks of decision support, we start from the opposite perspective and use only two decision support elements, an overview of specific tumor characteristics and prediction of tumor sub-type. These are mapped to symptoms and anatomies as done in the classic medicine support, and then we exploit precision medicine to work on similarity.

3. Proposed approach

The VA environment aims to help the clinician, who works on diseases diagnosis and analysis in not time-critical situation (e.g.,

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practitioner), into the investigation of disease who a patient suffers, taking into account the classic medicine and the precision medicine. To better support this workflow and obtain the requirements for the VA environment, we have worked together with two expert bioinformatics. The proposed solution followed a user-centered design paradigm [ND86], performing a set of ten meetings lasting on average 1.5 hours each over five months. They were organized in two initial brainstorming sessions, where the main problems for visual support of disease diagnosis were identified and discussed, three meetings for identifying data sources and data categorization principles, five meetings to support the iterative development of the VA environment.

The brainstorming sessions were based on a think-aloud protocol to describe the clinician's disease diagnosis workflow and how it can be merged with the precision medicine analysis. This process generated three requirements for the VA environment:

- **RQ1**: the ability to analyze data from classic medicine and precision medicine perspectives in a combined way.
- **RQ2**: support the investigation of unreliable knowledge of the patient's conditions based only on his/her symptoms.
- **RQ3**: the capability to refine the set of disease candidates and compare them.

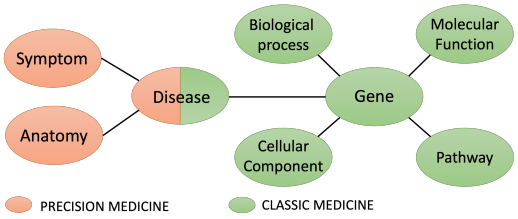

Figure 2: *Schema of the entities divided into precision medicine, in orange, and classic medicine, in green.*

During the three meetings related to the data sources, the needed data operations were arisen and discussed; due to the different types of sources, data integration was deemed mandatory to perform a combined analysis [MH22]. In this work, we targeted data coming from two KBs: DRKG and Hetionet. They contain relations among entities from classic medicine (e.g., diseases, symptoms, anatomies) and precision medicine (e.g., the genetic data such as molecular functions, pathways, cellular components, and biological processes). Figure 2 shows a simplified data schema, where the diseases are identified as the common bridging layer, while the genes are the key points for the precision medicine analysis. Moreover, Table 1 recaps the types and amount of data considered.

To model the relations among symptoms, anatomies, and diseases and to help the user in their navigation, we categorize the entities using three ontologies. The diseases are categorized by the Human Disease Onthology [SMS*22] taking the subdivision by anatomical entities. The symptoms are labeled with the MeSH Class [ROG63], while anatomies follow the Uberon Anatomy Ontology [MTG*12] focused on anatomical systems.

The five meetings that supported the system development were focused on the presentation of mock-ups to expert users and collecting feedback on the general behavior and workflow. They informed

Table 1: *Number of nodes and edges divided for type.*

Entities	#	Relations	#
Disease	133		
Anatomy	400	Anatomy-Disease	3602
Symptom	415	Symptom-Disease	3357
Genes	11814	Gene-Disease	27963
Molecular Function	2839	Gene-Molecular Function	70845
Cellular Component	1377	Gene-Cellular Component	54662
Biological Process	11312	Gene-Biological Process	447975
Pathway	1821	Gene-Pathway	67441

the incremental refinement of prototypes, fine-tuning visual encodings, interaction means, layout, and testing simplified analyses.
The resulting VA environment, visible in Figure 1, can be divided into two main parts: classic medicine support (upper part), and precision medicine support (lower part). The choice of this layout is based on interconnecting the two perspectives, but still making visually evident their boundary, supporting a workflow that mixes the two approaches (**RQ1**).
The classic medicine support shows the overview of symptoms and anatomies categories, and it is divided into three views: a left pane (see Figure 1A) dedicated to symptoms and a right pane (see Figure 1C) dedicated to anatomies. Both follow a 2-layer hierarchical approach, either showing the list of categories or how each category is composed, using a detailed list. In the central area, an interactive Sankey diagram (see Figure 1B) [RHF05] shows the overview of connections between symptoms and anatomies, giving the possibility to add on-demand the disease categories.
The precision medicine support is focused on the refinement of disease candidates and analysis of their similarity. It is composed of four views: the list of disease categories (see Figure 1D), the diseases similarity matrix (see Figure 1E), the top ten ranking of similar diseases (see Figure 1F), and a similarity radar chart for their comparison (see Figure 1G).
Focusing on the main visual encodings, the goal of the clinician is to analyze the relations that occur among symptoms, anatomies and diseases, and for this reason we chose to represent the network through the Sankey visualization (Figure 1B). It visually encodes and focuses the attention on the flow of interest, allowing interactive exploration of the categories of interest. Moreover, the Sankey allows allows the exploitation of several visual features: each rectangle represents a category (of symptoms or anatomies respectively), where its height represents the cardinality of elements inside the category, and its color encodes the number of connections with other categories (total). This solution allows evaluating at a glance both the prominence of elements inside a category and their total interconnections with the other categories. The thickness of each ribbon quantifies the number of connections among each pair of categories, providing a breakdown of the previous total interconnections.
When the clinician selects a category due to patient health conditions, the selection of a category adds a color coding for the specific element that is dynamically picked from a ten-values ordinal color scale; in this way, each selected category is easily distinguishable from the others. The selection is also supported by a range slider, to filter the paths due to the number of connections, and a boxplot,

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which shows the distribution of the connections for each element inside a category. The use of category reinforces the hierarchy in the network medicine data and allows the clinician to interpret a set of elements with similar conditions (**RQ2**). Selecting multiple categories of symptoms and anatomies, she obtains the list of diseases connected to them.
The clinician can refine this set by also selecting a category of diseases from the category list (Figure 1D), or on the Sankey (showing the disease with the relative button). These operations support a progressive refinement of the list of potential diseases that match the reported symptoms and interested anatomies. The number of elements depends on the selection based on the categories of interest and the result of this step, which can be conducted multiple times, is then used as the base for diseases confirmatory laboratory tests. To reach this goal, analyses based on precision medicine are exploited in our solution, as they are the best fit to compute fine-grained indicators on the diseases.
We first calculate similarity among diseases, and due to the high cardinality of the data, we encode the results in the disease similarity matrix (Figure 1E), to obtain a quick overview and an easy comparison (**RQ3**). The similarity is computed using the Jaccard Similarity Score, considering disease module composition (e.g., genes) and associated symptoms. The default formula weights these components equally, while the clinician can re-weight them interactively and check the new similarity; this behavior allows to analyze the diseases connection from the genetic or the symptoms point of view, or both. In addition, the clinician can personalize the similarity definition by selecting only the components she believes important using checkboxes (e.g., molecular function, cellular component, biological process, and pathways). Each matrix cell will encode the result of the similarity with an interpolate green color scale.
In order to support a faster analysis, a disease ranking list represents the top ten similar diseases (Figure 1F), which are the darker green cells of the matrix. Mouse-hovering on the rows of the disease ranking list, the clinician can investigate the diseases, and by clicking them, she can compare multiple diseases on the radar chart (Figure 1G). Each disease selection adds a polygon on the radar chart, helping compare the breakdown on the components of their similarity. The clinician can quickly compare the most similar diseases and eventually include or exclude them, forming a new set of candidate diseases for laboratory tests.

While the workflow has been described as a single sequential flow of analysis, its real application is not limited to one execution. The clinician can exploit the added knowledge from the candidate diseases list to include or exclude initially chosen anatomies or symptoms, affecting the disease similarity scores and the newly obtained disease ranked list, in a classic VA fashion.

4. Use case

The use case's goal is to show how a clinician can act to establish a disease diagnosis using the VA environment and how much it is useful to investigate at the same time symptoms, anatomies, and genetic data. The clinician can select the specific symptoms categories, search them in the relative search bar or investigate a disease category regarding the relative symptoms and anatomies.
For example, it is possible to visually explore the associations between a broad class of diseases, e.g., the diseases of the nervous system, the symptoms, and the specific diseases and anatomies involved. It may help enable the elaboration of new working hypotheses on a mechanistic basis to be tested experimentally.

By selecting the *Nervous System Diseases* category from the left panel, she obtains a selection of 213 symptoms. The ribbons of the associations among the symptom category and all the compartments considered are highlighted mouse-hovering on the specific category, while information among paths can be visible by a mouseover interaction. The paths can be filtered with a selected range on the menu to obtain the weighted connection of interest. In this case, the range is moved to the $[22-23000]$ interval because the clinician has interactively configured the Sankey visualization to show only the symptoms category of interest.
Now it is possible to decide the anatomies categories of interest. From the right panel, she selects the *digestive system*, *endocrine system*, and *immune system*. The resulting selection contains 45 anatomies and 213 symptoms. She obtains the diseases in common and can investigate the directed paths among them by adding disease categories to the Sankey. The clinician is interested in investigating diseases related to the same categories of anatomical entities chosen, so she selects *endocrine system disease*, *gastrointestinal system disease*, and, *immune system disease*, resulting in 32 selected diseases. She investigates the similarity among the selected diseases to all the others through the disease similarity matrix. Inspecting the disease ranking list, the most similar diseases (five) are the *malignant neoplasm of the stomach* (DO13274) with *ovarian neoplasm* (D010051), *liver neoplasm* (D008113), *glioma* (D005910), and *breast cancer familial* (C562840), all within a range of similarity $[0.7690, 0.7769]$. Raising the weight of symptoms to 0.8 brings the range of similarity for *malignant neoplasm of the stomach* to $[0.9076, 0.9108]$. By removing the symptoms from the calculation of similarity, the most similar diseases are *ulcerative colitis* (D003093) and *ileitis* (D007079) with a similarity of 0.6020. The clinician can also compare different diseases from the disease ranking list, adding them to the similarity radar chart. In this case, *ulcerative colitis* and *ileitis* are different in the gene similarity with respect to *pancreatic neoplasm* and *prostatic neoplasm*. At the end of the analysis, the clinician obtains four diseases that need a deeper investigation with laboratory tests: *malignant neoplasm of the stomach* and *ovarian neoplasm*, due to the similarity of all the features; and *ulcerative colitis* and *ileitis* due to the similarity among the gene compositions. A demonstrative video of the use case can be found at https://aware-diag-sapienza.github.io/ddva/.

5. Conclusion and future work

This paper describes an initial effort to integrate the classic and precision medicine approaches to support the diagnosis of a disease exploiting a VA environment. This preliminary work had taken into account part of the entities of existing KBs, integrated their data, and built a VA environment able to support a clinician workflow in executing the diagnosis of a disease. In future works, we plan to investigate and systematize the interconnection and differences between those approaches, having attacked only a part of the problem. Moreover, we plan to extend the degree of integration on disease diagnosis support by integrating genomic data for the anatomies.

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