INF358 Seminar in Visualization (2011)
Ivan Viola and Július Parulek (Editors)

Interactive and Exploratory Visual Analysis In Biology

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Abstract

Interactive Visualization of Biological Data is an emerging field, which holds many interesting applications for biologist and medical researchers. Programs for visualizing data from biology are often of a varied and specialized nature. This is in part due to the large variety in the sources and formating of the data. But also because of the large variety of tasks for which the data is being used.

In this State of The Art Report (STAR) an overview and a taxonomy of the field, focusing on exploratory visualization is presented. More specifically this STAR presents a task based taxonomy and classifies a number of papers according to this taxonomy. In addition to the taxonomy there are many useful methods available to visualization researcher. One such method is the integration of many different tasks into a single tool or framework. This integration of different biological problem domains allows researchers to find solutions to more complex questions. It has therefore grown in popularity in recent years and will be explored in depth.

These factors are discussed in light of the novelty of visualization techniques, use-ability of visualization tools resulting from visualization research and the interoperability of visualization tools.

Categories and Subject Descriptors (according to ACM CCS): I.3.3 [Computer Graphics]: Applications, Miscellaneous

1. Introduction

The rapid expansion of the data acquiring ability of the bio-instrumentation and bioinformatics fields, has created a demand among biologists and medical researchers for methods of interpreting a growing amount of biological data [OGG*10]. Most of this demand is met by methods developed by the bioinformatics community. These methods include clustering and machine-learning techniques. An overview of commonly used bioinformatics methods is presented by Kapetanovic et al. [KR04]. However bioinformatics and biologist have to a large extent begun turning to visualization techniques as a method not only to show and explore their finished results, but also as a means by which to learn more about and to manipulate their data.

In the past decade a large number of visualization tools for bio-data has been made available to researchers. Some visualization methods such as Livengood et al. (metabolics vis.) [LMCE11] and the Paterson et al. (VIPER) [PGKL11], focus on assisting researchers in one specific task. While other papers such as Barsky et al. (Cerebral) [BGHM07] and Lex et al. (Caleydo) [LSKS10], combines a number of different types of tasks into a single tool or framework.

There is also great variation in the data sources. Data could come from imaging data from microscopy [SO11], gene expression data from microarrays [VS09], simulation data from bioinformatics [TPRH11], or a number of other sources. This variation is also reflected in the available repositories and formats for any given data source. For instance for gene expression data there are three different primary repositories. The Gene Expression Omnibus in the USA, the ArrayExpress in Europe and the Center for Information Biology Gene Expression Database in Japan [VS09]. The heterogeneous nature of the sources and formats of bio-data makes combining information from different sources difficult. Not only is there often redundancy in the information but they often go by different identifiers in each source as well [VS09]. This has a limiting effect on the data sources for which each visualization program can be used. The sources and data available for visualization can be expected to grow, as bio-instrumentation and bioinformatics techniques are invented and refined.

2. A taxonomy of tasks in Bioinformatics

Biologist have many different tasks or problem domains to which they wish to apply visualization techniques. These can usually be split up into different areas of studies within biology. Although the methods and data vary greatly between fields within biology, it can usually be expected that methods and data formats are somewhat uniform within one biological discipline. This allows the creation of a taxonomy, classifying visualizations according to which discipline or "task" it is being applied to.

2.1. Omics

Omics is the the division of biology into fields of studies ending in -omics. The objects of study of each field is generally referred to with the same name as the field but with the suffix -ome instead of omics. The omics category is probably the most varied category in this taxonomy. In fact two of the tasks that could be construed to be part of the omics category are so large that they have instead been defined as their own categories. These tasks are the visualization of genomics data and the visualization of pathways.

2.2. Genomics

Genomics is the study of the genetic make-up of organisms. The most common type of data to be visualized in genomics is genome sequencing data from micro-arrays. These data are usually easily translated into heatmaps, due to the design of microarrays.

2.3. Pathways

Pathways can be defined as graphs showing the overall change in states in a biological system [NCD*10]. Visualizing these pathways is useful to the biologists as it allows them to determine how certain processes work. Methods for pathway visualizations usually involve graph and tree visualization techniques.

In the Visualization of omics data Gehlenborg et al. presents taxonomy for visualization of omics data [NCD*10]. He suggests that omics visualizations can be divided into two partly overlapping catagories. Visualizations based on the automated exploration of large biological networks, and visualizations based on assembly and curation of pathways.

In this taxonomy however pathway visualization is considered a task, and is therefore like genomics a separate classification to omics visualization.

2.4. Phylogenetics

Phylogenetics is the study of the evolutionary relatedness between groups of organisms. This is a rather new area of visualization. Methods commonly employed in this category include tree visualizations and sequence alignment methods [PTL*10]. The state of the art tree visualizations in phylogenetics often use either euclidean or hyperbolic geometric display models. See fig. 1 for an example of a hyperbolic display model.

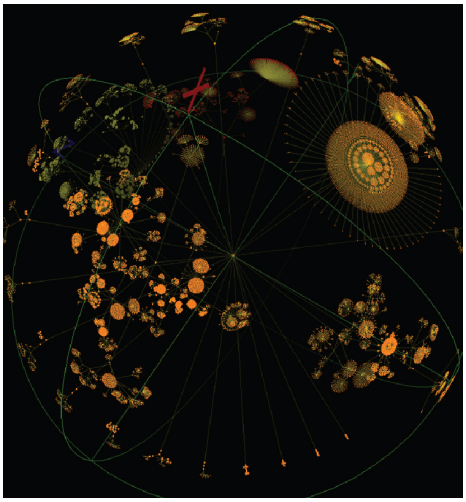

Figure 1: *A hyperbolic tree visualization of the NCBI taxonomy [PTL*10].*

3. Methods of visualization

The methods of visualization in the biological domain varies greatly based on the problem and available data. In this section an overview over the most frequently employed methods is given.

3.1. Heatmap

Heatmaps are visualization methods developed during the 19th and 20th century for the purpose of visualizing statistical data, that maintains clusters and hierarchies [IR09]. The cluster heatmap (see fig. 2) is technically a data matrix graph representation. It consists simply of color coded points (or pixels) on an X-Y axis in a matrix. Where each pixels color is decided by an intensity value. The hierarchy and cluster preserving nature of heatmaps makes it a desirable and popular visualization technique. It is especially popular with gene expression data, since the Micro-Arrays orders its results in matrices. This makes conversions to heatmaps trivial.

3.2. Graphs

Graphs are an important part of information visualization [HSMM00]. In bio-visualization graphs are useful for visualizing relations such as pathways or models. The visualization of graphs is not always a trivial task. Graphs can often be large and it is difficult to determine which parts interests the

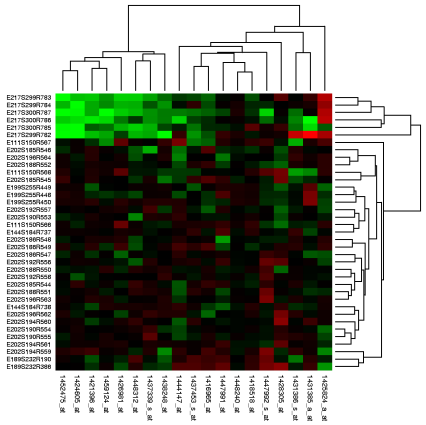

Figure 2: *A heatmap with appended dendrograms [IR09].*

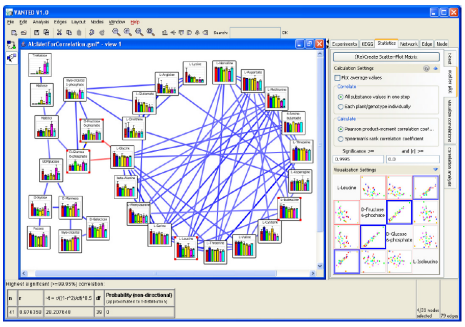

Figure 3: *VANTED: This screenshot shows a correlation graph and a corresponding scatterplot [JK06].*

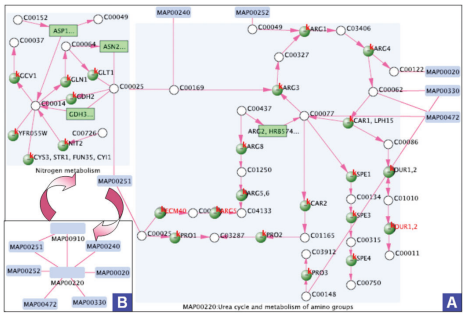

Figure 4: *VisANT in metagraph mode. This mode allows for the visualization of the data on multiple scales [HNY*07].*

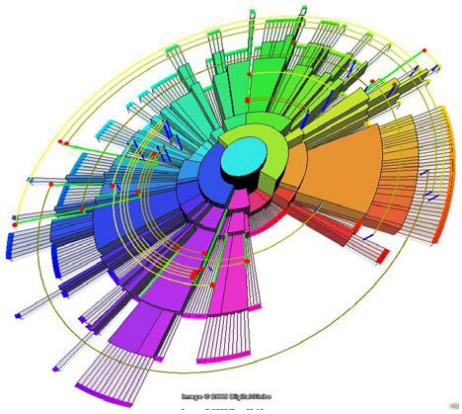

Figure 5: *A tree visualization of pathways shown in google earth, and generated in MetNetGE. The root node is the circle in centre. The children nodes are directly connected to the parents. With each level outward from the center, representing one incrementation in the trees depth [JSWD09].*

user at any given time. To solve these problems techniques relying on clustering parts of the graph together, has been developed. The user can then use either zooming or selection (brushing) techniques to find the desired data [HSMM00]. Examples of bio-visualization tools that implement some of these techniques are VANTED (see fig. 3) [JK06] and VisANT (see fig. 4) [HNY*07].

3.3. Trees

A special case in graph visualization is tree-visualization. Trees are undirected acyclic graphs. The fact that trees are acyclic means that it can be divided hierarchically from the root node. This hierarchy is a feature which tree-visualizations often tries to preserve. There are many different types of tree visualizations available for biological visualizations. An example of a novel tree visualization for pathways in MetNetGE [JSWD09] is shown in fig. 5. Fig. 2 shows how dendrograms can be added to heatmaps to increase the expressibility of the visualization. For a more thorough introduction to tree and graph visualization see a survey by Herman et al. [HSMM00].

3.4. Scatter Plots and Parallel Coordinates

Scatterplot and related spatial mappings such as heatmaps, can be useful for identifying clusters in the data. Classical examples of this includes the matlab clustering visualization in fig. 6 [FDSE11] or the clustered heatmap for visualizing gene expression data discussed earlier. Parallel coordinates are often used for expressing high dimensional data. Examples include the Hierarchical Clustering Explorer (HCE), use of parallel coordinates to visualize multidimensionality in clustering data [SS02].

3.5. Volume and Surface Rendering

Volume and surface rendering methods are often used in proteomics and other structure domains. Since these are pure

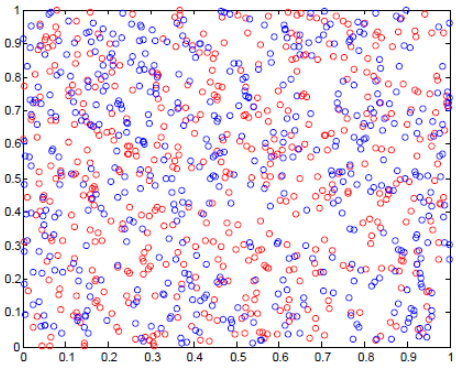

Figure 6: *A scatterplot representation in matlab [FDSE11].*

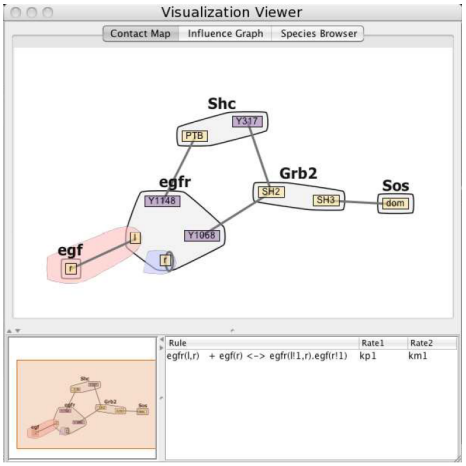

Figure 7: *The visualization tool in the RuleBender rule based modeling tool [XSFM11].*

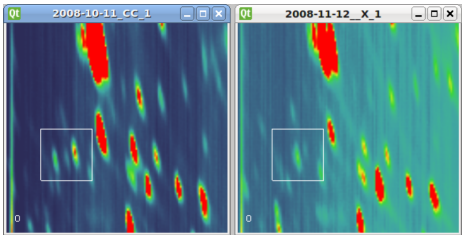

Figure 8: *A Visual System for Matabolomics Data. This figure shows a cancerous sample on the from a canine on the left side and a healthy one on the right side [LMCE11].*

visualization techniques and the focus of this paper is exploratory visualization techniques, they lay outside the scope of this paper. However, they are useful for highlighting structural effects of data found through exploratory visualization. These techniques are therefore sometimes used in concert with exploratory visualization techniques. An example of this would be the tool developed by Steffen Oeltze et al. that is to be presented in the paper Interactive Visual Analysis of Multi-parameter Fluorescence Microscopy Data in Toponomics [SO11].

4. Classification of visualization tools

Previously in this paper a task based taxonomy was presented. In this section an overview of each classification within the taxonomy is presented. Several bio-visualization tools are then discussed and classified according to this taxonomy.

4.1. Omics

The visualization techniques and problems explored in the visualization of omics data varies greatly. Some problems require sophisticated modeling techniques where the visualization techniques are simply used as an aid. Whereas other problem might use a combination information visualization techniques or imaging techniques.

RuleBender is a tool made for solving proteomics problems through a process called rule based modeling [XSFM11]. Rule based modeling is technically a bioinformatics technique. However, it also includes graph based visualizations of the network as shown in fig. 7. This visualization shows molecules in the model and allows for rapid debugging of the model. Programs such as RuleBender are examples of visualization methods being integrated into bioinformatics simulations to enhance usability.

Livengood et al. presented several methods for visualizing metabolics data one of which is shown in fig. 8 [LMCE11]. The methods are are especially useful for cancer researchers interested in bio-markers. The visualizations use methods known from statistics and image processing to identify meaningful differences between healthy and unhealthy gas chromatography-mass spectrometry samples. A more novel technique presented in the paper are different height maps of the data instead of simple 2 dimensional color coded images seen in fig. 8 (see the original paper for examples).

4.2. Genomics

Visualizations and problems in genomics focus on gene expression and gene sequencing data. Genomics is a very fundamental discipline in biology and the problems often affect other biological disciplines. Common problems relates to for instance Single Nucleotide Polymorphisms (SNP) or other gene mutation issues. This is often interesting in relation to understanding biological processes such as diseases, as well as finding new methods for treatment.

The Interactive Hierarchical Aggregation Table is a visualization tool for finding SNPs [VHBW11]. The visual-

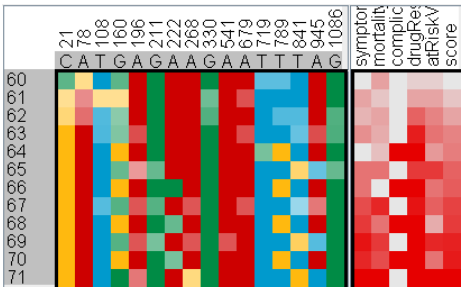

Figure 9: *The color-coded table from iHat [VHBW11].*

ization uses a color coded table system similar to heatmaps (see fig. 9). To explore the aggregation of the data the visualization also includes a tree view. iHAT also distinguishes between ordinal, nominal, interval and ratio data. The aggregation of nominal and interval data is visualized by using multi-hued colormaps, which indicate class membership and map saturation. Interval and ratio data aggregation is shown through perceptually uniform colormaps.

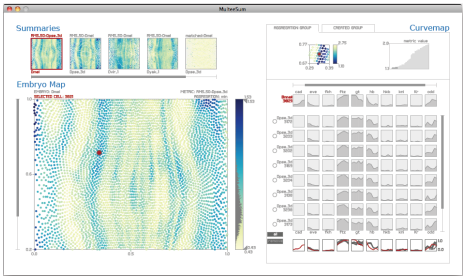

Figure 10: *Multeesum, on the right side is a spatial mapping of a Virtual Embryo. On the left side is temporal gene expression data shown as curve maps [MMDP10].*

Multeesum is a visualization tool developed by Meyer et al. (see fig. 10) [MMDP10]. It presents a novel new visualization technique combining 2D spatial mapping of a Virtual Embryo (VE) with the curve map visualization technique presented earlier by Meyer et al. [MWS*10]. Curve maps visualizes the gene expression levels of a single cell or a group of cell over time. The advantage of this method is that it allows the user to analyze the gene expression levels of parts of VE's over time. This should help researchers determine differences in gene expressions between different embryonic organisms and cell groups.

4.3. Pathways

Pathway visualization remains one of the most important applications of visualizations to biology and bioinformatics. Since pathways are the expression of processes in biology they can be expressed as graphs this makes graph and tree visualizations important tools.

MetNetGE is a tool for visualizing pathways data [JSWD09]. It focuses on tree visualizations such as the example in fig. 5. However it also has a limited support for graph-edges. The visualization method itself is rather novel and uses the direct physical link of each parent node to its children to denote the parent child relationship.

VisANT is a pathway visualization tool, wich features different types of visualization modes [HNY*07]. The metagraph mode shows an overview of a pathway where smaller sub- processes can be hidden from the users (see fig. 4). These processes can then be expanded by going into the expanded view. VisANT also supports KGML files, which contains graph representations of metabolic pathways. This increases interoperability with other programs and allows researchers to search through databases to match their own pathways to pathways already discovered.

VANTED is a visualization tool for exploring and interpreting bio-chemical experimental data, to identify pathways (see fig. 3) [JK06]. It uses MS excel forms to load the data into the program. The program then applies statistical methods and graph visualizations to the data to assist in analyzing it. A normal workflow in the program would involve using visualization methods to determine whether there are clustering information that needs addressing.

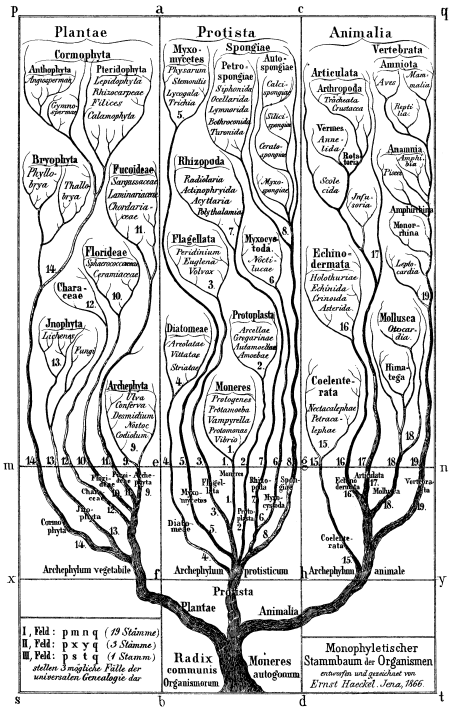

Figure 11: *Monophyletischer Stambaum der Organimsen (eng. monophyletic pedigree for the organisms), is an example of traditional tree-representations in phylogenetics [Hae66].*

4.4. Phylogenetics

The application of visualization to phylogenetics, has only recently become a priority. Since phylogenetics deals with inheritance and relatedness, graph visualizations and in particular tree visualizations are often employed. The parent-child relationship, and the generational hierarchies are preserved well by tree visualizations. It should be noted that traditional phylogenetics illustrations have used a tree growing from the bottom to top as in a real tree (see fig. 11) [PTL*10]. Rather than the traditional computer science representation of top to bottom.

VIPER is a visualization tools which allows researchers to explore large animal pedigrees and their associated genotype data [PGKL11], where pedigrees can be defined as the genealogical descent of organisms. VIPER employs a family centered model of visualization. The visualization features a sandwich view of each generation in the family, where the top part of the sandwich represents the males in a generation and the bottom the females. It also support an aggregated as well as the non-aggregated view of each pedigree.

4.5. Integrated tools

The integration classification constitutes the combination of more than one single task or field of study into a single tool. As the bioinformatics and bio-visualization fields matured, more complex problems have been explored. Some of these problems require combination of knowledge and information from several biological domains or tasks. To solve this visualizers have started incorporating many different visualization methods, or views into the same tools. By linking the data taken from many different sources and allowing many different approaches, biologists can accomplish more tasks with fewer programs. Since the different views in these integrated tools are often connected by brushing techniques it allows researchers to discover correlations in the data across domains.

Integrated visualization tools are a rather new concept. Research in this field has been conducted by Lex et al. [LSKS10] and Puff et al. [WPL*10]. This research led directly to the creation of the Caleydo application discussed below. However, there are also some visualization tools that predate this research that falls into this classification such as VitaPad and Cerebral (also discussed below). Most work in this field seems to have focused on solving problems relating to the connection between pathways and genomics.

Caleydo is a tool for analyzing gene expression data [LSKS10]. It integrates views of both the pathway and genomics classifications. The purpose of Caleydo is to allow researchers to analyze gene expression data in the broader context of biological processes, which are represented through pathways. The default view of Caleydo is a bucket view shown in fig. 12, with a graph linking data from different taxonomies superimposed on it. It is also possible

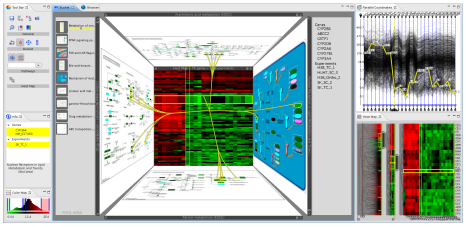

Figure 12: *Caleydo.*

to zoom in on specific views in the bucket. This allows the user to quickly switch the context of the visualization, which allows for more in depth analysis of the data. As well as the greater overview provided by the bucket view.

Cerebral is a Java plug-in that extends the Cytoscape [SMO*03] bimolecular viewer to support pathways [BGHM07]. This tool integrates pathways with biological networks and genomics, which is useful for understanding the interaction of genomes and biological processes. Since the plug-in adds pathways methods to the base application it focuses mostly on graph visualizations. These graphs are mostly of a static nature however nodes can be selected and grouped, which brings them to the foreground and changes their coloring scheme.

VitaPad is a visualization tool designed to allow the incorporation of micro-array data into pathway visualizations [HLNZ05]. Like the cerebral plug-in this is advantageous for researchers interested in the link between gene expression and biological processes.

5. Discussion

When making a visualization tool there are many things to consider. One of them is the novelty of the technique used. Does the tool you are making add to the set of applications that the end-user can apply to his data? Take for instance the Grundys et al. spherical scatter plot visualization of sensor data from animal movement [GJL*09]. The normal way of visualizing this data is by using multiple line-graphs, one for each component signal. Grundys method makes determining the body postures of the animals easier and allows an intuitive understanding of the data, where previously complex statistical analysis was necessary.

Besides the visualization techniques user interface and usability should also be considered. For instance in Helping Users Recall Their Reasoning Process Lipford et al. conducts two experiments, testing users memory of the conclusions and processes they used during visualization [LSD10]. The first experiment showed that simply writing down the results of the analysis of the data resulted in a significant loss of information regarding the reasoning behind the conclusion drawn. The second experiment demonstrated that good logging software allows the user to recall to a greater extent

the methodology and rationale behind their findings. This demonstrates the usefulness of user interface and usability methods for visualization software.

Other important things for researchers wanting to do bio-visualization to take into account are the interoperability of visualization tools with each other, the integration of visualizations into bioinformatics programs and the multi-modality of biological data. Puff et al. created a tool for maintaining links across applications [WPL*10]. Here, they show that links across applications can assist in information visualization. Research such as this is interesting because the end users might want to use information or visualizations from many different tools together. A lack of interoperability between applications can result in the users ability to apply certain tools to certain problems being limited.

An example of a visualization tool has been integrated into a bioinformatics application would be the RuleBender system [XSFM11]. Integrations such as these are useful because they often add to what the user can do with systems while feeling consistent to the user.

Biological data often come from many different modalities this can often mean that integrating them together into a single visualization tool can be difficult. However, the benefit to researchers is that they can often see more interesting correlations across different modalities. This gives researchers new opportunities to learn from their data instead of isolating them to single modalities at a time. Lipford et al. showed that users often will work concentrate more on the visualization itself than the problem domain [LSD10]. Although his tests were conducted using lay people, his results seems to indicate that limiting the applications of visualizations could limit the persons ability to properly explore the domain.

6. Conclusion

The field of bio-visualization is maturing rapidly, and this is resulting demand for tools that solve more complex problems. This demand is being met both with new novel visualization techniques and the integration of multiple problem domains into single tools. Both these approaches add to the field and result in better research tools for biologists and medical researchers.

In this star a task-based taxonomy of bio-visualization in the context of bioinformatics has been presented. This taxonomy divides the field into tasks which biologist would like to accomplish. These tasks are the visualization omics, genomics, pathways and phylogenetics data. Modern and historical bio-visualization research was presented and classified according to this taxonomy. Common methods in bio-visualization were reviewed and more complex methods were discussed in light of their application to the development of new bio-visualization tools.

New methods should add to the best practice of the field and the resulting tools must take into considered usability and user friendliness for end users. A third factor discussed in this STAR is an increased focus on interoperability between different visualization tools.

7. Acknowledgments

Fig. 1 is from Procter et al. [PTL*10]. Fig. 2 is from Andrade M. (2008), "Heatmap," available at en.wikipedia.org. Fig. 3 is from Hu et al. [HNY*07]. Fig. 4 is from Junker et al. [JK06]. Fig. 5 is from Jia et al. [JSWD09]. Fig. 6 is from Falk et al. [FDSE11]. Fig. 7 is from Xu et al. [XSFM11]. Fig. 8 is from Livengood et al. [LMCE11]. Fig. 9 is from Vehlow et al. [VHBW11]. Fig. 10 is from Meyer et al. [MMDP10]. Fig. 11 is from Haeckel [Hae66]. Fig. 12 is from Lex et al. [LSKS10].

Special thanks goes out to Cagatay Turkay for supervising this project.

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