Web-based hybrid-dimensional Visualization and Exploration of Cytological Localization Scenarios

Gökhan Kovancı², Mehmood Ghaffar¹, Björn Sommer²,³,*

¹Bio-/Medical Informatics Department, Bielefeld University, Universitätsstraße 25, 33615 Bielefeld, Germany
²Computational Life Sciences, University of Konstanz, Universitätsstraße 10, 78457 Konstanz, Germany
³Faculty of Information Technology, Monash University, 20 Research Way, 3800 Melbourne, Australia

Summary

The CELLmicrocosmos 4.2 PathwayIntegration (CmPI) is a tool which provides hybrid-dimensional visualization and analysis of intracellular protein and gene localizations in the context of a virtual 3D environment. This tool is developed based on Java/Java3D/JOGL and provides a standalone application compatible to all relevant operating systems. However, it requires Java and the local installation of the software. Here we present the prototype of an alternative web-based visualization approach, using Three.js and D3.js. In this way it is possible to visualize and explore CmPI-generated localization scenarios including networks mapped to 3D cell components by just providing a URL to a collaboration partner. This publication describes the integration of the different technologies – Three.js, D3.js and PHP – as well as an application case: a localization scenario of the citrate cycle. The CmPI web viewer is available at: http://CmPIweb.CELLmicrocosmos.org.

1 Introduction

The CELLmicrocosmos 4.2 PathwayIntegration (CmPI) is a software framework which can be used to visualize protein- and gene-related pathways in their cytological environment [1]. For this purpose, CmPI supports the localization of these pathways by connecting to different databases. The pathways can be easily imported using formats like GraphML (comprehensive file format for graphs), SBML (System Biology Markup Language), AND Visio (PubMed-based text mining data) and StringDB (Database of known and predicted protein-protein interactions) [2–4]. CmPI also contains a network editor which can be used to generate pathways and the 3D viewer supports 3D-stereoscopic visualization. Segmented cell component models are based on the VRML97 format (Virtual Reality Modelling Language). Nowadays, usually Blender or Fiji (Is Just ImageJ) are used for the model creation process [5], [6].

Gene- or protein-related identifiers can be localized by connecting to the Bio Data Warehouse (BioDWH)/DAWIS-M.D. or ANDCell [7–9]. The localization entries contained in DAWIS-M.D. are derived from databases, such as UniProt, Reactome, and the Gene Ontology [10–12]. CmPI provides a number of different approaches to analyse and visualize different localization scenarios. A single protein usually features a number of different localization entries which may

* To whom correspondence should be addressed. Email: bjoern@CELL.microcosmos.org

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differ in the publication source, as well as in the associated cell component, or even the cell component layer. For example, in our previous work we analysed the molecular environment and co-localizations of the MPDZ/MUPP1-related protein and recently protein cascades in cardiac phenotypes [13], [14]. A standard example which was used to verify the subcellular localization process is the localization of the citrate cycle and the glycolysis [1]. Each localization is based on a publication, a web link, or a text-mined abstract (in case of ANDCell). Because the analysis of each and every localization entry is time consuming, an alternative localization method was introduced: the Subcellular Localization Charts (SLC) [15].

The SLC provide a simplified way to predict common localizations among associated proteins. These proteins may be associated by their corresponding pathway, by a direct reaction or protein-protein interaction edge, or other text mining-based associations. It is possible to analyse the overall localization of a pathway, or to visualize the localizations for all proteins/genes.

Based on the localization strategy, different localization scenarios may be generated. And these localization scenarios may be the base for further discussions with other scientists.

Another common problem for the localization prediction is the fact that molecules are traveling inside cells; the cell components associated with corresponding genes/proteins often change over time. In our approach, also different localization scenarios can be used to visualize localization changes over time.

But usually it is not required that all scientists involved in the discussion install CmPI on their computer. This is a redundant process in case the user only wants to visualize and explore a distinct localization scenario without modifying it. To tackle this issue, a simple web-based tool was developed which is able to visualize the localization scenarios in a convenient and easy way. These Localization Scenarios can be used for the following purposes:

- discussion of different potential localization scenarios for particular gene/protein networks among scientists, combining functional and structural information,
- representation of different time stamps of localization scenarios,
- illustration of intracellular pathways for educational purposes, or
- initial discussion of complex tours using the Space Map [16].

In summary, the main target group of the here introduced online tool are researchers who want to explore specific localization scenarios created with CmPI.

2 Related Work

Related approaches which should be shortly discussed in this context are focusing 1) at the visualization of cell models inside the browser, and 2) and the visualization of cytological localizations of protein-/gene-related networks.

2.1 Browser-based Cell Visualization

As previously mentioned, our in-house tool CmPI is focusing at the visualization of cell maps. A related approach is cellPACK, a software project which can be used in combination with different 3D modelling tools, such as Blender or Cinem4D®, to develop complex mesoscopic cell models [6]. But it is not focusing on the abstract visualization of networks in correlation with cell models, its main purpose is to support 3D modellers during the modelling of cells by combining different packing algorithms to create filled cells. cellVIEW is a tool based on the commercial Unity3D® engine which can be used to visualize the models created with cellPACK, but it is currently not available for the web browser and was not developed based on WebGL [17].
Recently, a number of 3D web visualizations on the molecular level are being developed. Jmol/JSmol or Jolecule are tools which can be used to visualize PDB files [18–20]. Also, the related Protein Data Bank which provides the PDB files includes different 3D viewers supporting the molecular level [18]. Other tools, such as Aquaria, provide hybrid-dimensional visualizations, just like the tool discussed in this publication. Aquaria is combining 2D with 3D visualization [21] with the subjective to visualize and analyse proteins based on the PDB format in combination with their sequences [22]. Hybrid-dimensional browser visualization recently gains growing popularity among biomedical scientists [23], [24].

2.2 Browser-based Localization Visualization of Biological Networks

All these third-party tools are focusing on the visualization of cellular structures, but our CmPI additionally combines these cellular structures with subcellular localization information in 3D space. Whereas there is – to our knowledge – no web-based tool available to visualize networks in 3D cell environments, there is a tool supporting the visualization of localized 2D networks: the previously-mentioned CellWhere [25]. Similar to the Cytoscape plugin Cerebral, CellWhere uses 2D layouts to visualize gene-related networks in multiple abstract layers representing cell components [26]. While CmPI is a tool which tries to support many different organisms and is tissue-independent, CellWhere focusses on the localization of muscle-related research. The localization process in CmPI is done semi-automatically by using the previously-mentioned SLC, but the localization process in CellWhere is fully automatized by providing confidence scores, which are also known from, e.g., COMPARTMENTS. The large advantage of CellWhere is that the user is directly provided with the prediction of a single potential localization scenario, but is it not possible to explore alternative localization scenarios. The generation of different localization scenarios, especially in 3D space, is a unique feature of CmPI, and CmPIweb is the first web tool which can be used to visualize these scenarios in the browser.

3 Architecture/Implementation

To enable the visualization and exploration of the generated cell models associated with localized pathways, the CELLmicrocosmos 4.2 PathwayIntegration web viewer (CmPIweb) was developed.

CmPIweb required the following basic functionalities:

- loading of cell models in .Cm3 and .Cm4 format,
- visualization of 3D cell models associated with pathways in the browser,
- visualization of 2D networks in the browser, and
- visualization of a subset of Subcellular Localization Charts in the browser.

3.1 CmPIweb: Three-tier Architecture

To enable the integration of all previously described features in a simple way, a three tier architecture was realized. Figure 1 illustrates the architecture.

PHP is used for transferring the files from the server to the client, decompressing ZIP archives and local file handling (Figure 1). A particular requirement was the support for 100 MB+ files via web, and here PHP was chosen as an appropriate technology. Moreover, the original CELLmicrocosmos.org website which is hosting CmPIweb is also being developed in PHP. Therefore, a seamless integration in the future will be possible.

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Three.js is a WebGL framework providing a scene graph–based API and visualization and exploration in most browsers, such as Chrome®, Firefox, Internet Explorer®, or Safari® [27]. The huge advantage of WebGL is the fact that all recent popular browsers support this standard without any need to install additional browser plugins. Three.js supports also the VRML97 format, which is used by CmPI to import/export 3D cell models. In comparison to Java3D, Three.js is a very recent technology which is more flexible and easy to use. Three.js is also available with a number of stereoscopic 3D-related features, such as anaglyph, cross-eyed and parallax barrier. We showed in a recent publication that the 3D-stereoscopic exploration is a valuable approach to increase the insight into the structure of a cell [28]. For this reason, the future extension of this tool into the third dimension could be a valuable approach. Moreover, it is already implemented in CmPI. In addition, Three.js supports the import of different file formats, such as binary code, images, scenes, and of course JSON. Three.js, Java3D as well as VRML97 use a scene graph model to abstracting the 3D structures. Although VRML is a quite old format, going back to 1995 (version 1.0) and 1997 (version 2.0), it is still often used as it is a standard format which is supported by most 3D modelling packages such as Blender [[6], [29]. The scene graph-based structure is, however, used by many other formats. It is also used to create the cell models. Each cell component is represented by a 3D structure which is positioned in 3D space by using the depicted structure. This similarity between Java3D, VRML and Three.js was an important reason why Three.js for the development of CmPIweb.

D3.js (Data-Driven Documents) is a JavaScript–based visualization library providing fast browser-based 2D visualization [30]. Many biomedical tools are nowadays using D3.js and related approaches [31]. It can be used to create SVG objects which can further be useful for large datasets that uses D3.js functions to generate rich text/graphic charts and diagrams. Nowadays it is used by a wide range of visualization and analysis approaches which are found at the corresponding webpage [32]. In CmPIweb it is used to visualize the 2D networks of the biomedical pathways, as well as to visualize the localization charts shown on the bottom of Figure 1. These charts are based on the previously discussed subcellular localization charts.

![Figure 1: The three-tier Architecture of CmPIweb: PHP, Three.js, and D3.js. Details on the file loading process can be found in Figure 2.](http://journal.imbio.de/)
3.2 CmPIweb: Loading of Localization Scenarios

There are two ways to load different cell models containing cytological pathways into CmPIweb, as shown in Figure 2:

1) loading an external file by using a URL (GET parameter), or
2) loading a local file by using a file chooser.

Using the first approach, the .Cm3 file (containing only a 3D cell model) or the .Cm4 file (containing a 3D cell model plus the localized network) have to be packed as a ZIP file. The ZIP file has to be uploaded to a server from where it is available via URL.

In case the file is loaded locally, the File-API is used. In this case, the user can select the local files to be loaded into the browser application. It is possible to use the CmPI standard files, consisting of .Cm3/.Cm4 and VRML 97 files, or by selecting a ZIP package containing all files.

Figure 2 (right) shows the online loading process. First, the ZIP file is downloaded to the server of the web application. Then, it is unpacked on the server and then loaded into the memory of the local computer. Once the loading is done, the file is deleted from the server.

In case the file is locally loaded, the loading process is only started on the local computer. As unpacking and processing of a file is all done locally, no deletion operation takes place on the server. The loading process of locally-stored files is much faster than for external files.

Figure 2: Server-Client approach during loading: loading of online-available files (left) and local files (right).
3.3 CmPIweb: Navigation

Because navigation is crucial in 3D environments, CmPIweb provides three navigation modes based on the modes implemented in CmPI, but they are strongly simplified and optimized for browser compatibility:

- **Floating Mode**: The user 'floats' in the cell environment by using WASD-keys or the mouse wheel to move forward/backwards. In addition, the following mode can be initiate via double click:
  - **Object-Bound Mode**: The selected cell component or node is centred and the movement occurs around its centre by mouse movement while the left mouse button is pressed. Again with the mouse wheel forward/backward movement is triggered. This mode is suspended by double-clicking into an empty area.
  - **Flight Mode**: By holding the CTRL key down, the user can fly forward by using the left mouse button, and fly backward, by using the right mouse button, whereas the mouse movement changes the direction.

4 Application

The following example was already discussed in the first version of CmPI: the combination of the citrate cycle and the glycolysis [1]. It is a standard example because it is common knowledge that the citrate cycle is attributed to mitochondria, and the glycolysis to the cytosol. By using the previously-introduced SCL, it is a straight forward to predict the localization to the corresponding localizations. This process is discussed in detail in the book chapter: “Network Analysis and Integration in a Virtual Cell Environment” [33].

By using the following URL, the application is started in the browser by simultaneously loading the given file:

http://CmPIweb.CELLmicrocosmos.org/?url=http://www.cellmicrocosmos.org/cm4files/Animal_Cell_1_72_hsa00010-20_1_4_2014[Cm4].zip

The first part of the URL represents the locations of the CmPIweb application, the second part (non-bold font, starting with “?url”), represents the absolute path of the ZIP file to be loaded.

Figure 5 shows the loaded cell model. Here, the KEGG citrate cycle and the glycolysis are shown (hsa00010 and has00020) [34]. The localization was previously done by using CmPI. All localization results are visible to the user by using the bottom table on Figure 3 Top. But in contrast to CmPI it is not possible to modify this table in CmPIweb – only the result can be explored.

It is possible to change the colour of the different entries – for this purpose, it is just required to click on the corresponding table entry representing a cell component on the right side of the application shown in Figure 5. The colours of the citrate cycle as well as glucose cycle can also be changed by clicking on the pathway table at the bottom of the application.

Obviously, the citrate cycle is localized at the mitochondrial region, whereas the glycolysis is localized at the cytosol. This localization is a very straightforward task by using CmPI and the result covers basic biological knowledge.

Figure 3 Top shows the complete cell environment associated with the metabolic network. The 3D view on the right side shows both pathways in 2D, drawn using the original KEGG layout and depicting both pathways-connecting enzymes by inter-pathway edges.
Figure 3: CmPIweb visualizing the citrate cycle and the glycolysis pathway inside an animal cell. Top: The complete cell is shown in the centre and on the left side the complete pathway is shown. Centre: The mitochondrion is focused which contains the citrate cycle (red), whereas the glycolysis is located in the cytosol (yellow); Bottom: Focusing at the enzyme 4.1.1.32, which is part of the citrate cycle as well as the glycolysis pathway and located on the surface of the mitochondrion.
Figure 4: CmPIweb provides a simplified version of the Subcellular Localization Charts. The actually chosen localization for the specific localization scenario is indicated by the colour of the enzyme nodes in Figure 3, in the 2D as well as 3D view. The cell components’ colours are based on the localization colours which are also used for the charts. Top: visual summary of all enzyme localization entries as derived from the databases of CmPI; Bottom Left: The SLC for enzyme 4.1.1.32 selected in Figure 3 Bottom; Bottom Right: The Localization Table entry for 4.1.1.32 including the alternative localization entries triggered by mouse click on the corresponding entry.

By moving towards the cell using the previously-discussed Floating Mode methods, the close-up view of the mitochondrion associated with the citrate cycle (red colour) is created, as seen in Figure 3 Centre. In the neighbourhood of the mitochondrion the glycolysis pathway associated with the cytosol is visible.

Now, by zooming into the pathways using the 2D view, specific nodes become visible – here, the enzyme 4.1.1.32. Now, a force-directed layout is used to mix both pathways, providing a better overview concerning inter-pathway enzymes like 4.1.1.32. Now, a double click is performed on this node in the 2D viewer, and the view automatically centres the corresponding enzyme and the user can move towards the node by using the already discussed methods of the Object-Bound Mode. Figure 3 Bottom shows the resulting view. On the right side the selected and/or focused node is indicated in the 2D view by increased size.

Figure 4 Top shows the overview of the Subcellular Localization Charts. In this way, all enzymes’ subcellular localizations are visible and comparable. Figure 4 Bottom shows exclusively all localization entries for 4.1.1.32. The actually-selected localization is shown: the “mitochondrion”, more precisely: its “Outer Membrane” of the species “homo sapiens”. “4/5” indicates that this is the fourth of five localization layers (matrix, inner membrane, intermembrane space, outer membrane, and the cloud). The result comes from the curated BRENDA database [36]. Also, the localization references are shown which are linked to the corresponding publications. By clicking on the actually-selected localization entry, the list of all available entries is shown. In this way it is possible to explore alternatives. However, in contrast to CmPI it is not possible at the moment to change the localization scenario based on the changes in the table, as CmPIweb is only intended as a viewer.
5 Discussion and Outlook

Here, a simple approach was presented to visualize intracellular localized pathways by combining web-based 2D and 3D visualization. In this way, hybrid-dimensional visualization approaches was realized by using just a web browser (Figures 3 and 4) [21]. Since the localization are based on often online-available data, they can be easily evaluated by clicking on the corresponding localization sources at the bottom part of the Localization Table in Figure 4. Moreover, different localization scenarios can be discussed which might be especially interesting in case the 3D structure of the cell is relevant for specific scenarios, like in case of more complex protein cascades [14]. A big advantage would be also if explicit 3D coordinates of molecular data could be provided, e.g. based on 3D MALDI technology [35]. An additional important feature in this context would be the representation of cell structures by using volumetric rendering. However, this will be a demanding task because the 3D rendering performance of a browser is still quite limited. This limitation of a browser is also relevant for CmPlweb, because it is recently not optimized for loading files with a size of multiple hundreds of megabytes. Here, the standalone tool CmPl is the better option.

Also, other relevant visualization aspects can be observed. In Figure 3 Top, the whole cell is shown, in Figure 3 Bottom, a detail is shown, focussing at the enzyme 4.1.1.32. This aspect is called the Focus+Context paradigm which is often used for the presentation of biological data [36]. While in the foreground, the actually relevant enzyme is shown in the focus, the background – the context – shows the remaining reactions of the two metabolic pathways. Moreover, the 2D view (Figures 3 right) is able to provide the complete overview of the discussed pathways.

Related approaches, such as COMPARTMENTS and CellWhere provide statistical approaches to predict protein-related localizations [16], [17]. Although these resources provide fast access and explicit predictions of subcellular localizations, often the processes behind the localization prediction are not fully transparent. SLC provide an alternative of applying Visual Analytics-related approaches to localization data provided by databases. But in near future it would be preferable to combine both approaches: statistical prediction with user-in-the-loop analysis.

Because the localization scenarios only provide static snapshots of a cell, another important feature in the future would be the support of dynamic data, enabling the illustration of changes over time.

Scientists can utilize this tool as a source for their future research. In the future, it could be also used as a part of a virtual graphical database network for biology and related fields. Based on this web tool a web component could be developed to explore every possible biochemical activity. Another important goal could be the future use to teach school and undergraduate students the inner cell composition in an interactive way, associating the cellular structure with 3D networks. For this purpose, we are planning to optimize this tool in the near future for mobile devices.

This can be on a cognitive basis highly effective, as the internal structure of a cell is spatially spread and quite complex, comparable to a small universe. A future approach could be to use the stereoscopic capabilities of Three.js to achieve better learning outcomes, as well as invoking the interest in this technology in Bioinformatics [28].

This tool is meant to be a starting point for an improved understanding of microscopic mechanisms in a more convenient and easy way.
6 Availability and Requirements

The CmPI software is available at: http://Cm4.CELLmicrocosmos.org

The CmPIweb is available at: http://CmPIweb.CELLmicrocosmos.org

To load files from your webpage with CmPIweb, please use the following syntax:
http://CmPIweb.CELLmicrocosmos.org/?url=http://www.your-url.org/full-path/Cm4-file.zip

The file discussed in the context of this publication can be found here:
http://CmPIweb.CELLmicrocosmos.org/?url=http://www.cellmicrocosmos.org/cm4files/Animal_Cell__1_72__hsa00010-20__1_4_2014[Cm4].zip

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