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# CellPublisher: a web platform for the intuitive visualization and sharing of metabolic, signalling and regulatory pathways

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**ABSTRACT**

**Summary:** Systems biology relies increasingly on collaborations between several groups with different expertise. Therefore, the systems biology community is adopting standards that allow effective communication of concepts, as well as transmission and processing of pathway information. The Systems Biology Graphical Notation (SBGN) is a graphical language for biological pathways that has both a biological as well as a computational meaning. The program CellDesigner allows the codification of biological phenomena in an SBGN compliant form. CellPublisher is a web server that allows the conversion of CellDesigner files to web-based navigatable diagrams based on the user interface of Google maps. Thus, CellPublisher complements CellDesigner by facilitating the understanding of complex diagrams and by providing the possibility to share any CellDesigner diagram online with collaborators and get their feedback. Due to the intuitive interface of the online diagrams, CellPublisher serves as a basis for discovery of novel properties of the modelled networks.

**Availability:** The freely available web server and the documentation can be accessed at: http://cellpublisher.gobics.de/. The source code and the offline version for Microsoft Windows are freely available at http://sourceforge.net/projects/cellpublisher/.

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**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

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## 1 INTRODUCTION

The detailed understanding of biological pathways and the design of novel molecular pathways with engineered properties lies at the core of systems biology. To meet these goals, two complementary approaches are combined in modelling: simulation and graphical representation. While the former aims to mimic the behaviour of the pathway *in silico*, the latter aims to make the pathway properties and structure understandable to humans.

The pace of discovery in systems biology has been greatly accelerated by the adoption of standards by the community (e.g. SBML). The Systems Biology Graphical Notation (SBGN, Le Novère *et al*., 2009) is likely to become the standard for graphical representation. Adequate software tools such as CellDesigner (Funahashi *et al*., 2008) are freely available and actively used.

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While several online databases such as KEGG, BioCyc, Reactome, Panther, Pathway projector or *Subti*Pathways exist for visualizing centrally curated pathways (Bauer-Mehren *et al*., 2009; Kono *et al*., 2009), only few of them are adopting a standard graphical language (e.g. Panther and *Subti*Pathways; Lammers *et al*., 2010; Mi *et al*., 2010). Moreover, as novel pathways are constantly discovered or designed, there is a specific need for presenting custom pathways and receiving feedback from other scientists.

So far, authoring diagrams for online sharing is possible using the web servers BioPP, Payao and WikiPathways (Kelder *et al*., 2009; Matsuoka *et al*., 2010; Viswanathan *et al*., 2007). However, these servers do not allow the generation of easily navigatable diagrams which are required for the evaluation of pathway maps by the non-specialist busy lab scientist. With the advent of Asynchronous JavaScript and XML (AJAX) technologies in the web, which have given rise to applications such as Google maps, the possibilities for navigation of graphical information have been greatly improved.

To complement the powerful authoring capabilities of CellDesigner with an improved visualization interface and to overcome the limitations of the existing pathway presentation tools, we have developed CellPublisher, a web server for the intuitive visualization, sharing and discussion of metabolic, signalling and regulatory pathways based on the interface of Google maps.

## 2 THE WEB SERVER

### 2.1 User input

In the design of the input screen, we have focused on making the submission procedure as fast, simple and intuitive as possible. Apart from entering the author and title of the pathway, the user is asked to upload the CellDesigner file and an image of it. The image can be exported easily from CellDesigner and can be modified with other programs before uploading (see below). Moreover, the user has the option to enter an e-mail address, to get notified when the conversion is finished.

Upon submission, the user is directed to an admin page with links to download a local copy of the interactive pathway, and to the online version of the diagram. Both versions are basically identical, but the local copy can be modified further and shared on any web server. In addition, the admin page includes a link to delete the pathway, together with all user input. The link to the admin page can be bookmarked. It is also accessible from the e-mail sent to the user.

The same functionality of the web server is also available as a standalone, 'offline' version (Supplementary Material).



 

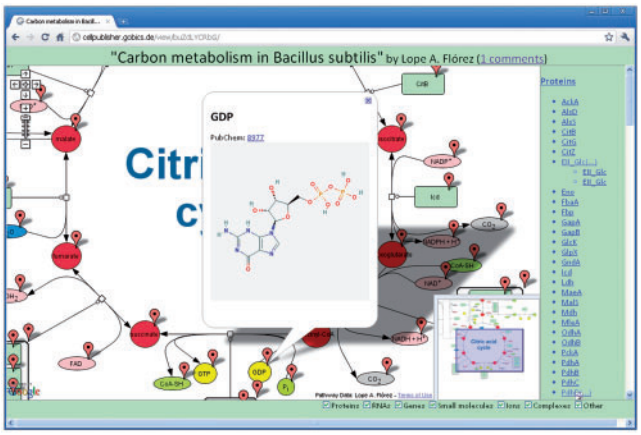


**Fig. 1.** Screenshot of an online diagram. The CellDesigner-based representation can be navigated like a Google map. Clickable markers appear on the species at the highest magnification, which contain the information in the CellDesigner notes and external links for selected databases.

### 2.2 Features of the computed diagram

In the pathway navigation interface (Fig. 1), the majority of the screen is devoted to the interactive pathway map. It can be zoomed in and out with the mouse, and navigated as is known from Google maps. A bird's eye view on the lower right provides orientation on higher magnifications. At the highest magnification, all the species include a clickable marker that opens a pop-up window with additional information on the species. The content of the window is directly taken from the notes entered in CellDesigner.

For the PDB, PubChem Compound, PubMed and Uniprot databases, an ID entered in the CellDesigner notes will automatically be linked to the external resource. Moreover, the molecular structure of species linked to PubChem Compound will be incorporated in the info window (Fig. 1). Likewise, under Mozilla Firefox, PDB references will also include a Jmol applet with the 3D structure.

The map is framed on the right with an ordered list of all species in it. Clicking on a link in this list will open the pop-up window of the corresponding species in the map. This is useful to explore the various places where a species participates in the diagram.

A forum for each pathway can be accessed through the link on the top right of the page. In this forum, every viewer can give feedback to all other viewers.

### 2.3 Sharing of the diagrams

The main purpose of CellPublisher is to provide an easier way to navigate SBGN compliant diagrams and share them with a wider audience. We envision at least two scenarios where the use of CellPublisher is of particular convenience: publishing and discussion among colleagues and collaborators.

For instance, a publication can cite the link to the online diagram and it will be immediately accessible to everyone without the need of installing programs; the use of any modern web browser is sufficient. The species notes can be enriched with references to other external sources, such as online databases or web pages with extended information. As novel information is discovered, the diagrams can be enriched with comments from the community.

Moreover, the enhanced navigation makes it easier to analyse and discuss a diagram. For instance, it is easier to upload a diagram with need of discussion to CellPublisher, and send the URL to the collaborators, instead of attaching the full CellDesigner file.

As mentioned above, the image of the diagram can be processed with additional programs (e.g. Adobe Photoshop®) before uploading it to CellPublisher. While preparing a discussion, it could be useful to mark in some way uncertain areas of the diagram. These marks will be visible in the online diagram, something that is not possible in current CellDesigner versions.

These features can be especially useful in the early phases of discussion, where an agreement on the pathway connectivity is necessary. In contrast, Payao (Matsuoka *et al*., 2010) could be most useful in later phases, involving the meta-annotation of the individual components by curation experts.

An additional level of customization can be achieved with the local version, which can be obtained from the admin page or the offline version. The look-and-feel and the interactivity can be adapted to specific needs and the resulting pathway can be uploaded to any server. This customization of CellPublisher diagrams is exemplified by *Subti*Pathways, a collection of diagrams covering metabolism and gene regulation in the bacterium *Bacillus subtilis* (http://subtipathways.uni-goettingen.de; Lammers *et al*., 2010).

## 3 CONCLUSION

As the complexity of the studied pathways increases, the encoded diagrams themselves will increase in size and complexity. This requires software that makes the diagrams understandable in spite of their size. In addition, sharing pathway information with collaborators in a graphical way becomes increasingly important, as well as receiving comments by the community.

CellPublisher is perfectly suited for this task due to its combination of intuitive visualization, the possibility to process custom-made diagrams, the forum for each pathway and free availability via a web browser.

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