NaviCell

Web tool for navigation, curation and maintenance of molecular interactions maps

Guide for user and map curator

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1. Introduction

1.1 Description of NaviCell

NaviCell is a web tool for exploring large maps of molecular interactions created in CellDesigner (https://celldesigner.org). The tool is characterized by the unique combination of three essential features: efficient map navigation based on Google maps engine, semantic zooming for viewing different levels of details on the map and integrated web-based blog for collecting the community curation feedbacks. In addition the tool provides a web-based service for omics data integration and analysis in the context of the maps.

NaviCell supports a collection of maps created by various groups (https://navicell.curie.fr/pages/maps.html) and the Atlas of Cancer Signaling Network (ACSN, https://acsn.curie.fr).

1.2 Guide content

The manual contains instructions for map users and map curators how to navigate (Section 2) and comment (Section 3) maps in NaviCell.

For map creators/managers that are interested to upload their own maps; NaviCell is applicable for any CellDesigner map that meets the general requirements mentioned in the Section 4. Recommended format for preparation of CellDesigner maps for NaviCell is briefly described in the Section 4. Maps maintenance description in NaviCell is found in the Sections 5. The NaviCell installation instructions redirection is found in Section 6.

For detailed NaviCell standard description, recommended procedures for maps preparation towards uploading into NaviCell and step-by-step NaviCell installation procedure see NaviCell technical guide available at:
http://navicell.curie.fr/doc/NaviCellMapperAdminGuide.pdf

Types of NaviCell investigators	
User	Explores existing collection of the maps.
Map curator	Explorers, critically analyzes and comments content of maps in the blog.
Map creator/manager	Creator of map(s) that uploads maps to NaviCell, maintains maps by collecting curators comments and updating maps accordingly.
System administrator	Installs and maintains NaviCell web-application.

| NaviCell terminology	
Map	Image of detailed molecular interactions network graphically represented using CellDesigner tool and converted to NaviCell for exploring, curation and maintenance.
Map module	Image of part of the map representing a group of molecular interactions with common functional relevance.
Map entity	Component of the map graphically depicted using SBGN standards in CellDesigner tool.
Semantic zoom	A mechanism providing several map views with different levels of details depiction achieved by gradual exclusion of details while zooming out.
Title panel	Upper panel containing map title, help and map symbols code.
Map panel	Central panel depicting the image of the map.
Selection panel	Right panel containing list of map entities grouped by type and map modules. Selection of entities is by clicking on the corresponding checkbox.
Bird-eye view panel	Window containing top-level view of the map with indication on currently centered area; adapted from Google maps.
Zooming bar	Zoom control slider; adapted from Google maps.
Marker	Symbol indicating location of chosen objects on the map; adapted from Google maps.
Callout window	Small window that opens by clicking on marker. Contains short description and hyperlinks related to the marked entity.
Blog	A web site associated with NaviCell on which maps entities annotations are displayed and where curators can leave comments about content of maps.

Annotation post	Detailed map entity annotation created in CellDesigner by map manager. The annotation is converted to annotation post and displayed in the associated blog by NaviCell.
Post icon (book)	Symbol indicating blog (post) hyperlink. Clicking on the post logo open corresponding post in a separate window.
Map icon (globe)	Symbol indicating map hyperlink. Clicking on the map logo open the map in a separate window.

2. Instructions for map navigation (Google maps)

User-friendly navigation through the map is allowed by adaptation of the Google maps engine.

2.1 NaviCell layout

The NaviCell interface is composed of 5 panels (Fig 1): (A) a title panel with the name of the map, 'search' box and blog, 'map symbols' and 'help' buttons, (B) the main panel showing the image of the map, (C) a selection panel with an interactive list of map's entities and modules. (D) a zoom bar and (E) data visualization and analysis tool box allowing to integrate, display and analyze data in the context of the maps. The map (B) and the list of map entities and modules (C) are interconnected in such way that entities chosen from the list will be marked on the map. The logic of navigation such as scrolling and zooming; functions such as markers, callout windows and zoom bar are adapted from the Google maps.
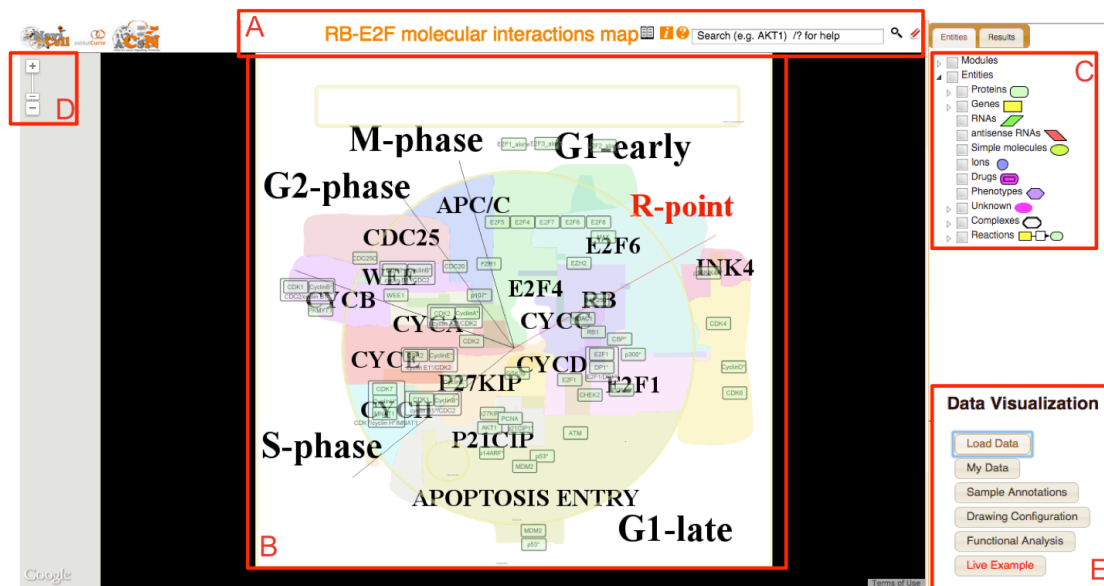

Fig1: NaviCell layout.
(A) *Title panel,* ***(B)*** *Map panel,* ***(C)*** *Selection panel,* ***(D)*** *Zoom bar,* ***(E)*** *Data visualization and analysis tool box*

2.2 Map zooming

The application of semantic zooming in NaviCell simplifies navigation through large maps of molecular interactions by providing several levels of details, resembling navigation through geographical maps. Exploring the map from a detailed towards a top-level view is achieved by gradual exclusion of details while zooming out. There are four semantic zoom levels: (A) detailed, (B) hidden details, (C) pruned and (D) top-level (Fig 2). The size of the images representing each zoom level is scaled to two times smaller than the preceding zoom level.

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- The **detailed zoom level** is the original version of the map that contains all details as created in the CellDesigner map.
- The **hidden-details zoom level** hides entities modifications, complexes names and reaction numbers.
- The **pruned zoom level** represents only major routes on the map (canonical pathways).
- The **top-level view zoom level** is a territory map. This zoom level does not contain map entities and edges, but represents localization of different map parts (modules) similar to the representation of countries' boundaries on geographical maps (see Section 4.2 for procedures of how to generate zoom levels).

(A) Detailed view   **(B) Hidden details view**

(C) Pruned view   **(D) Top-level view**
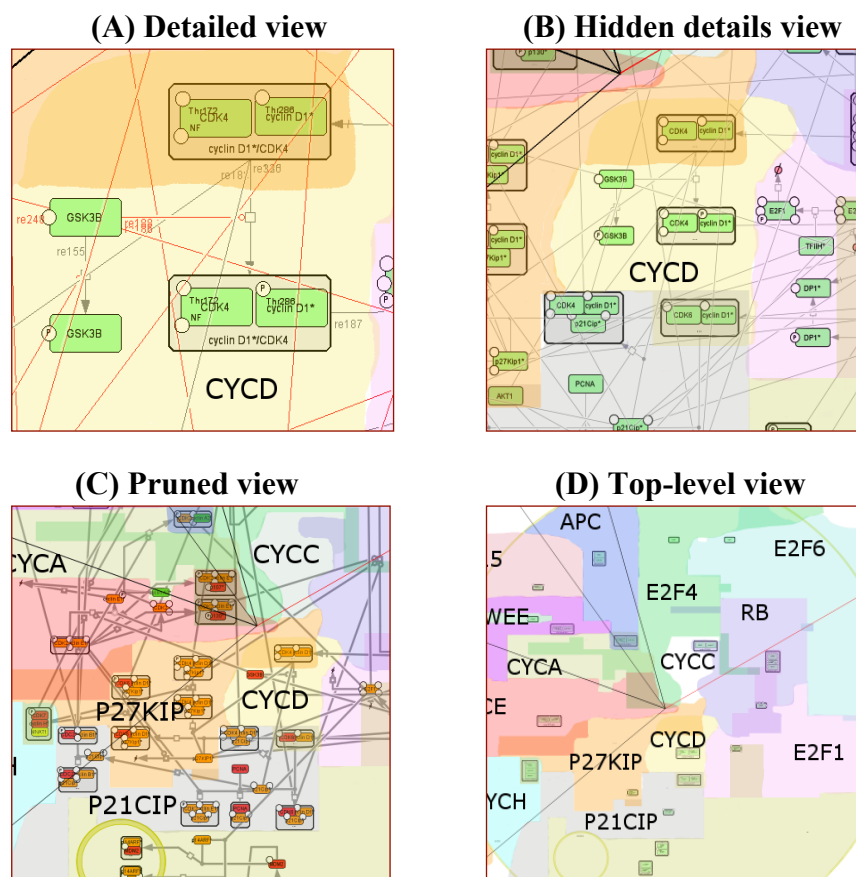
Fig2: NaviCell semantic zooming.
The same area of the map is visualized using 4 zooms; each image is twice smaller that in the preceding zoom level. (A) In the detailed view, entity names, modifications and reaction IDs are visible. (B) In the hidden details view, part of textual information is removed. (C) In the pruned view, only major routes are visible. (D) In the top-level view, boundaries of map modules are visible.

2.3 Using the selection panel

The selection panel contains the list of entities grouped per type, reactions and modules of the map (see Section 7.1 for the map structure, content and symbols explanation). Each **entity type** is indicated by the corresponding symbol on the right side of the entity names. For each entity type, there is a list of corresponding **entities** found in the map; for each entity, there is a list of its **modifications** found in the map (Fig 3).

Any component of the map can be selected from the selection panel by clicking on the corresponding **checkbox**. This action shows new markers on the map in such way that all items with ticked checkboxes in the selection panel are shown on the map by **markers**. Ticking off a marked checkbox de-selects it and the corresponding marker

is removed from the map (for organization and logic of changing states of the checkboxes see FatJar Eclipse interface (http://fjep.sourceforge.net).
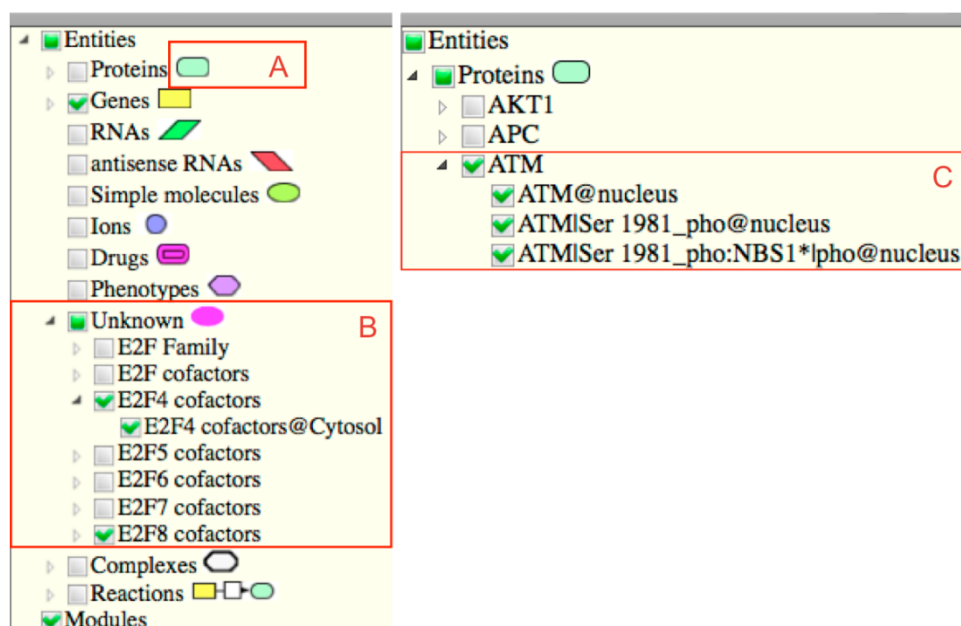
Fig3: NaviCell selection panel with list of map entities ordered per entity type.
(A) Entity symbol, (B) List of entities for entity type 'Unknown', (C) List of modifications for entity Protein 'ATM': ATM found in particular cellular compartment, ATM with post-translational modification and ATM as part of complex.

2.4 Markers, callout windows and confidence score

Marker design and functionalities resemble of those used in Google maps. Markers appear on the entity's modifications, reactions and modules of the map by choosing the corresponding item from the list in the selection panel as explained in the Section 2.3. The set of chosen markers is kept does not change for all four views. Clicking on one of the markers opens the sectioned **callout window for an entity**. The **callout window** is structures in four sections that contain a short description about the selected component of the map. Hyperlinks are accessible from the callout window. There are **external hyperlinks** (databases, PMIDs) and **internal hyperlinks** (map entity modifications, reactions and modules). Clicking on the names of the entities in the callout window drops markers corresponding to all modification of the selected entity on the map (internal link). Clicking on the **post icon (book)** on the right of the entity name, opens the corresponding annotation post in the blog where comments can be left behind (internal hyperlink) (see Section 3 for blog explanation). Unlimited number of callout windows can be opened simultaneously on the same map (Fig 4).
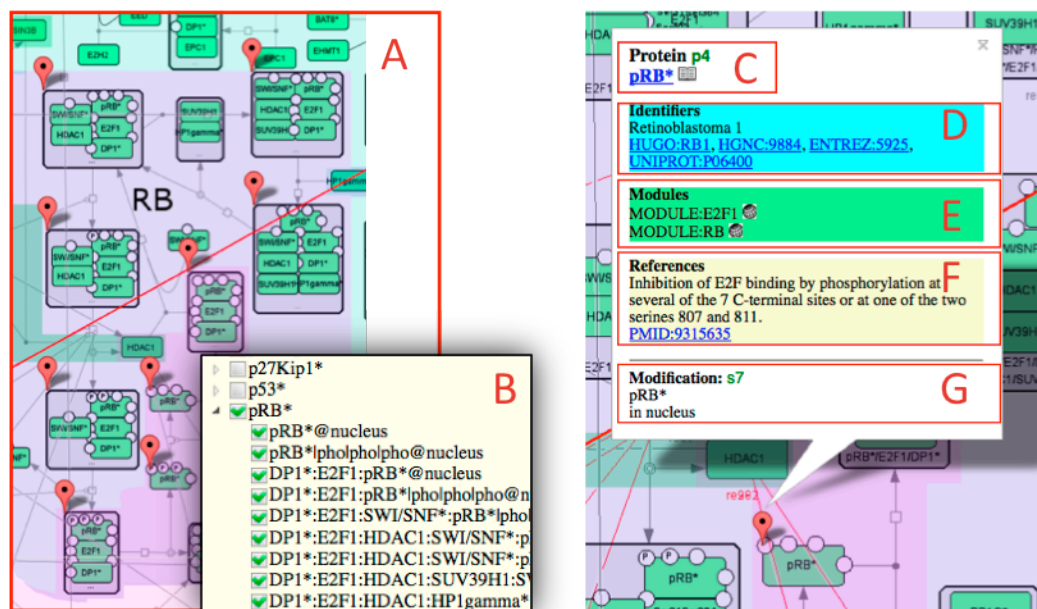
Fig 4: Markers and callout windows for an entity.
(A) Markers indicating map component, (B) List of modifications for entity protein 'pRB' selected by checking on boxes in the selection panel. The number of markers that appear on the map (9 markers in A) corresponds to the number of protein 'pRB' modifications chosen in selection panel (9 modifications in B). Clicking on a marker opens a callout window that contains (C) Entity type and name: clicking on the hyperlink shows markers for protein modifications (internal link). Clicking on the post logo (book) opens annotation post in the blog in a separate window (internal link). (D) Identifiers: clicking on hyperlinks opens corresponding databases (external link). (E) Modules: clicking on hyperlinks opens the corresponding map module (internal link). (F) References: map creator notes and literature, clicking on hyperlinks opens corresponding article in PubMed (external link). (G) Description of the modification that is currently selected.

Reaction edges are clickable; the sectioned **callout window for a reaction** will be opened while clicking on the marker indicating a reaction. The callout window of a reaction contains the description of the reaction type, the reactants, products and the regulators of the reaction. In similar to the entity callout window, there are **external hyperlinks** (PMIDs) and **internal hyperlinks** (entities and reactions). Clicking on the names of the entities in the callout window drops markers corresponding to all modification of the selected entity on the map (internal link). Clicking on the post **icon (book)** on the right of the reaction type name opens the corresponding annotation post of the reaction in the blog where comments can be left.

The unique feature of the reaction's callout windows is the section named **'Confidence'**. This section included **confidence score** for the reaction calculated automatically and displayed in the form of stars and text (see the principle of the score calculation below). In addition, the notes related to the confidence of the reaction can be added by the map manager in a form of free text.

The principle of confidence scores calculation used in ACSN is the following: there are two values that define the confidence score, the reference score (REF) and the functional proximity score (FUNC). The number of filled stars shows number of articles confirming the interaction (one experimental article = one filled star, one review = 3 stars). The background star color corresponds to the confidence score based on the average functional distance between interacting proteins calculated from HPRD (Human Protein Reference Database, http://www.hprd.org), curated protein-protein interaction network. The star color changes from grey/black (value «0» reserved for reactions for which the confidence is not possible to establish such that

self-interacting proteins, transport reactions, etc) through green (value «3» means that interaction between the proteins is indirect and mediated by other proteins) to rose/red (value «5» corresponds to direct physical contact of macromolecules, as it is documented in the HPRD interaction network).


*Fig 4a: Markers and callout windows for a reaction.*
*Clicking on the post logo (book) opens annotation post in the blog in a separate window (internal link). The reactants, products and reaction regulators are internal hyperlinks, clicking on the names opens the corresponding maps and displays markers on the corresponding entities. **References**: map creator notes and literature, clicking on hyperlinks opens corresponding article in PubMed (external link). **Confidence:** The number of filled stars depicts **reference confidence score** demonstrating number of articles confirming the interaction (corresponds to 'REF'). The background color of the stars **depicts functional proximity confidence score** demonstrating the functional closeness of the entities participating in the reactions according to the functional distance calculated using the HPRD (Human Protein Reference Database (corresponds to 'FUNC').*

2.5 Selection and highlighting of map objects

To facilitate exploration of individual entities of the map, the function of selecting and highlighting only species of interest is available. (Figure 4a).
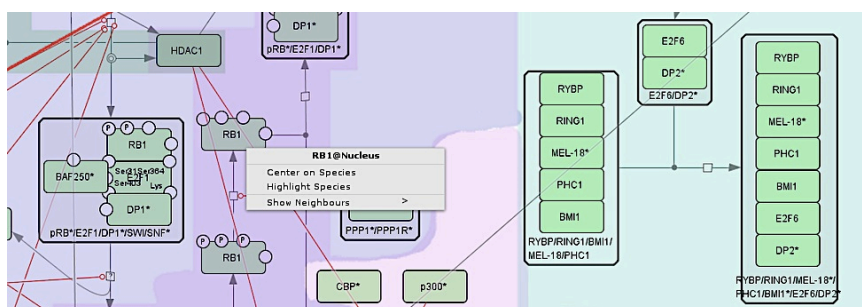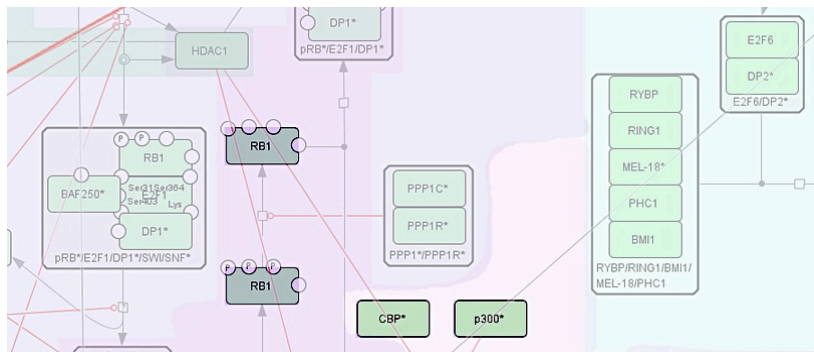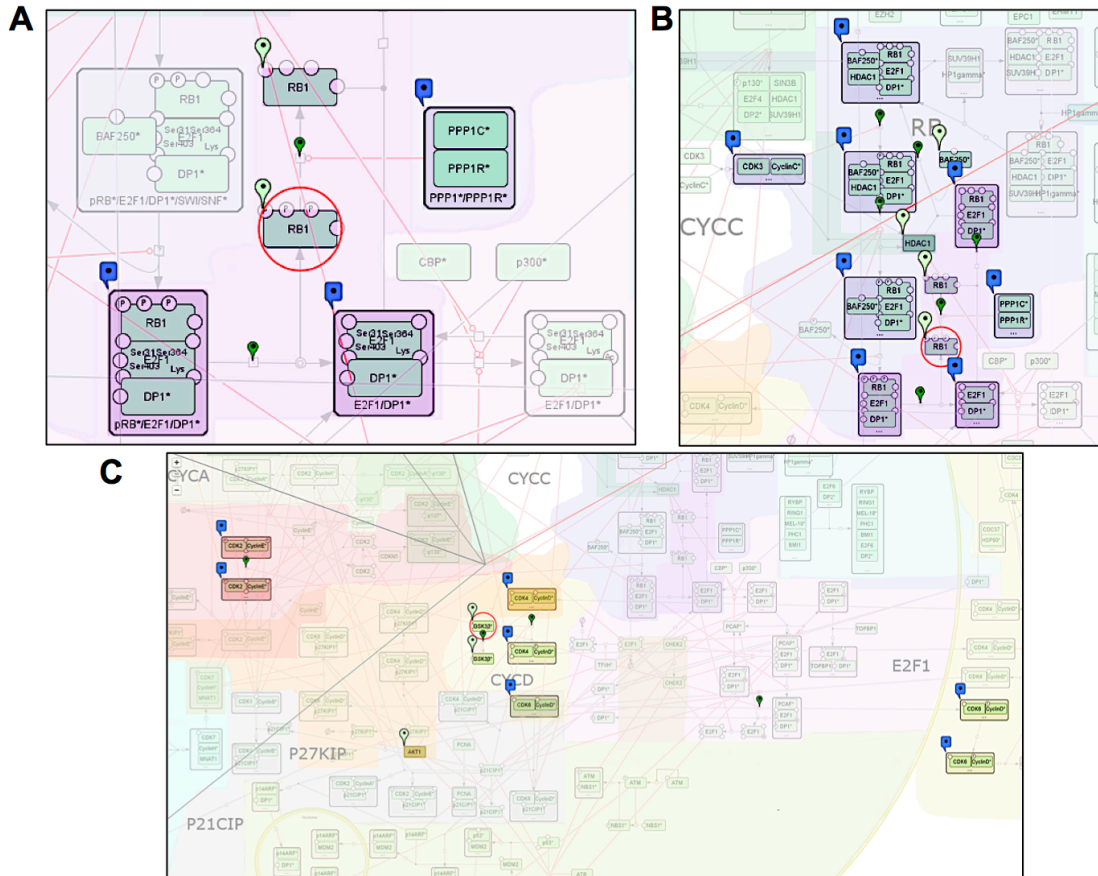
Fig 4b: Highlight entity of interest.

Right-click of the computer mouse on the entity of interest opens the menu for individual entities exploration. The entities of interest can be selected to visualize only the subset of interest of the user.

In addition, there is more elaborated function of selecting and highlighting neighbours of an entity of interest. This way, the connectivity of selected entities through the map can be studied. Step-wise enlarging of the neighbourhood coverage can help to follow the propagation of signaling from one molecular entity to another (Figure 4c)


Figure 4c. Entity neighborhood explorations

The right-click button of computer mouse on the entity of interest (RB1) opens a menu for exploration of individual map entities. The function 'Select and Highlight Neighbours' highlights local interactions of (A) Map objects interacting with the entity of interest (RB1). (B) Repeating the action highlights extended neighbourhood of the entity of interest (RB1). (C) The function allows highlighting more « distant » interactions of entity of interest (GSK3β*).

2.6 Modular maps

An easier navigation through the map is achieved by a modular representation of the map (Fig 5). The map is divided into separate but interconnected modules depending on the procedure of modular map preparation. Each module from the modular top-level view can be visualized individually by selecting the corresponding module in the selection panel or by clicking on the module's internal link in the callout windowas explained in the Section 2.4. Each modular map has the same number of zoom levels as the detailed map, however zoom views are generated by reducing the size of the detailed modular map. Semantic zooming is not available for the modular map representation. Each modular map is annotated in CellDesigner while map construction and the callout windoware generated as explained in the Section 2.4. The content of the annotation post in the blog for each modular map is created as well (see Section 3).
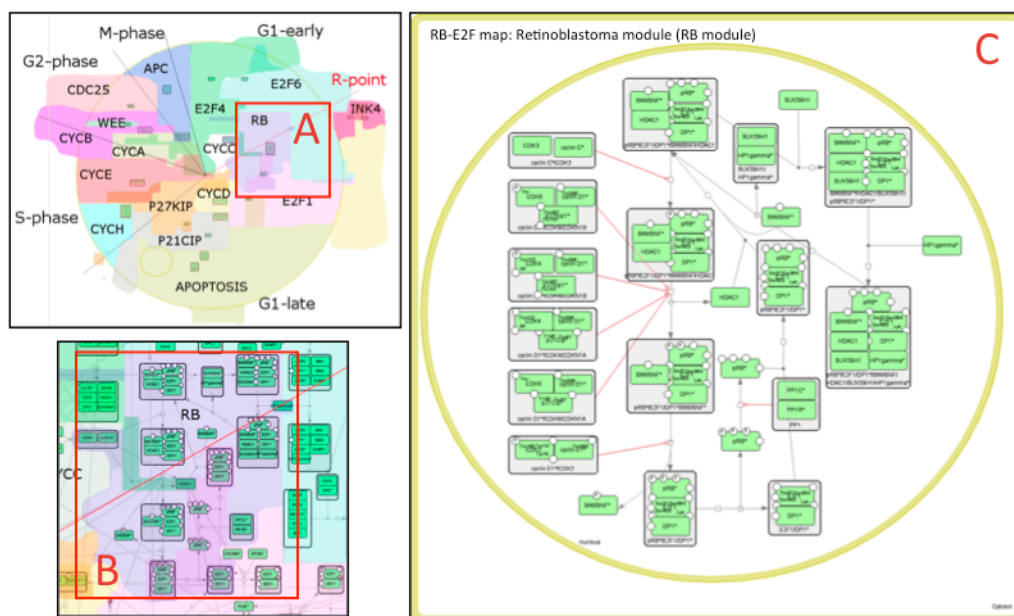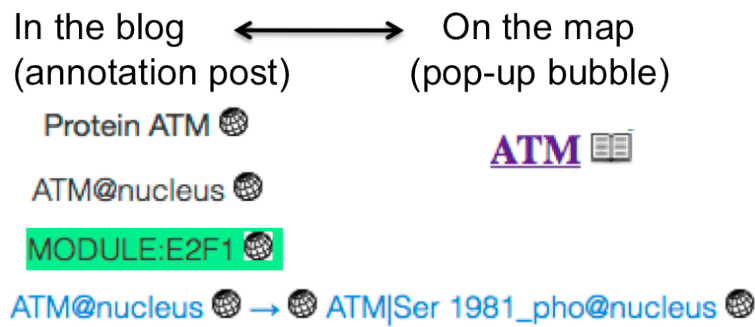

Fig 5: Modular maps.
(A) *RB module on the Top-level view zoom,* *(B)* *RB module on the hidden-details view zoom,* *(C)* *Isolated RB module*

3. Instructions for map commenting (blog)

NaviCell contains a web-based blog system WordPress (http://wordpress.org) for collecting feedbacks from the community about the map. Comments and suggestions can be added by NaviCell curators in the annotation posts in the blog and subsequently the maps and annotation posts are updated by the NaviCell managers following the suggestions.

3.1 Shuttling between map and blog

NaviCell facilitates the link between the map and the blog (Fig 6). The annotation posts in the blog for all components of the map are accessible by clicking on the **post icon (book)** in callout windows. The map is accessible from the posts by clicking on the **map icon (globe)** on the right of the names of the map entities. Parallel use of the map and the blog is recommended when the map and the blog are open in separate windows in an Internet browser.

In the blog ⟷ **On the map**
(annotation post) (pop-up bubble)

Protein ATM 🌐

ATM 📖

ATM@nucleus 🌐

MODULE:E2F1 🌐

ATM@nucleus 🌐 → 🌐 ATM|Ser 1981_pho@nucleus 🌐

Fig 6: Icons of map and post.
The map icon (globe): found on the right to the names of map components in the annotation post. Clicking on the globe drops markers on the corresponding component on the map. The post icon (book) found on the right to the names of map components in the pop-up bubble. Clicking on the book opens the corresponding post in the blog.

3.2 Organization and content of annotation posts

Each entity of the map (i.e. genes, proteins, complexes, reactions, modules etc.) is accompanied by an annotation that is included into the map during construction in the CellDesigner by map managers. The annotation contains detailed description of the entity including its official names (HUGO, HGNC, ENTREZ, UNIPROT); map manager notes and links for the corresponding references in PubMed and internal links to related parts of the map. Entities' annotations are converted to annotation posts by NaviCell and displayed in the blog. In addition, the post contains a list of complexes and reactions in which the entity is involved (internal links). The last section of each annotation post in the blog is dedicated to the communication between map curators and map managers (Fig 7).

ATM

Protein ATM 🌐 p47

Identifiers
Ataxia telangiectasia mutated
HUGO:ATM, HGNC:795, ENTREZ:472, UNIPROT:Q13315

Modules
MODULE:APOPTOSIS_ENTRY 🌐
MODULE:CYCLINB 🌐
MODULE:E2F1 🌐

References

Modifications:
In compartment: nucleus
1. ATM@nucleus
2. ATM|Ser 1981_pho@nucleus

Participates in complexes:
In compartment: nucleus

1. ATM|Ser 1981_pho:NBS1*|pho@nucleus

Participates in reactions:
As Reactant or Product:

1. ATM@nucleus → ATM|Ser 1981_pho@nucleus

2. ATM|Ser 1981_pho@nucleus + NBS1*|pho@nucleus → ATM|Ser 1981_pho:NBS1*|pho@nucleus

As Catalyser:

1. CHEK2@nucleus → CHEK2|Thr68_pho@nucleus

2. p53*@nucleus → p53*|Ser15_pho@nucleus
3. ATM@nucleus → ATM|Ser 1981_pho@nucleus
4. MDM2@nucleus → MDM2|S395_pho@nucleus
5. NBS1*@nucleus → NBS1*|pho@nucleus
6. DP1*:E2F1|Lys_ace:PCAF*@nucleus → DP1*:E2F1|Lys_ace| Ser31_pho@nucleus + PCAF*@nucleus

This entry was posted in **protein** by **binom**. Bookmark the **permalink**.

Leave a Reply
You must be logged in to post a comment.

Fig 7: Annotation post of an entity.
The entity type, name and sections 'Identifiers', 'Modules', 'References' are also visible in the callout windowon the map. The detailed information about entity modifications, complexes and reactions is listed. The section 'Leave reply' is accessible for users. Comments in the form of hypertexts, hyperlinks and images can be uploaded.

3.3 How to leave comment in the annotation post

The curators can leave comments on the map component's posts in the form of hypertext enriched with images and hyperlinks, if desired. The access is login and password-protected. The suggestions given by curators are to be analyzed by the NaviCell managers; maps and annotation posts are modified accordingly and updated versions are then uploaded in NaviCell.

4. Preparing and annotating CellDesigner map for NaviCell

NaviCell is applicable for any given CellDesigner map that meets the general requirements. There are three requirements for uploading CellDesigner maps to the NaviCell: **(1)** the map should be in xml format, **(2)** the corresponding image of the map should be in png format and **(3)** the config file should accompany the map.

However, following the recommended format for preparing CellDesigner maps for NaviCell will ensure the best performances of NaviCell. The description of NaviCell format and detailed procedures for map preparation, entities annotation, deriving map modules and creating semantic zooms are found in the NaviCell technical guide at http://navicell.curie.fr/doc/NaviCellMapperAdminGuide.pdf.

5. Maintaining maps

The blog system facilitates exchanges between curators and maps managers in NaviCell. The map managers regularly collect curators comments and update the maps accordingly. In turn, NaviCell automatically updates the blog and archives older versions of posts including curators' comments, thus providing traceability of all changes on the map. The suggestions by curators are analyzed by the NaviCell managers. The maps and annotation posts are modified accordingly. The maps are re-generated and updated versions are uploaded in NaviCell.

6. NaviCell installation

For NaviCell installation instructions please download and follow NaviCell technical guide available at http://navicell.curie.fr/doc/NaviCellMapperAdminGuide.pdf.

7. Appendix

7.1 Symbols for map entities representation (SBGN)
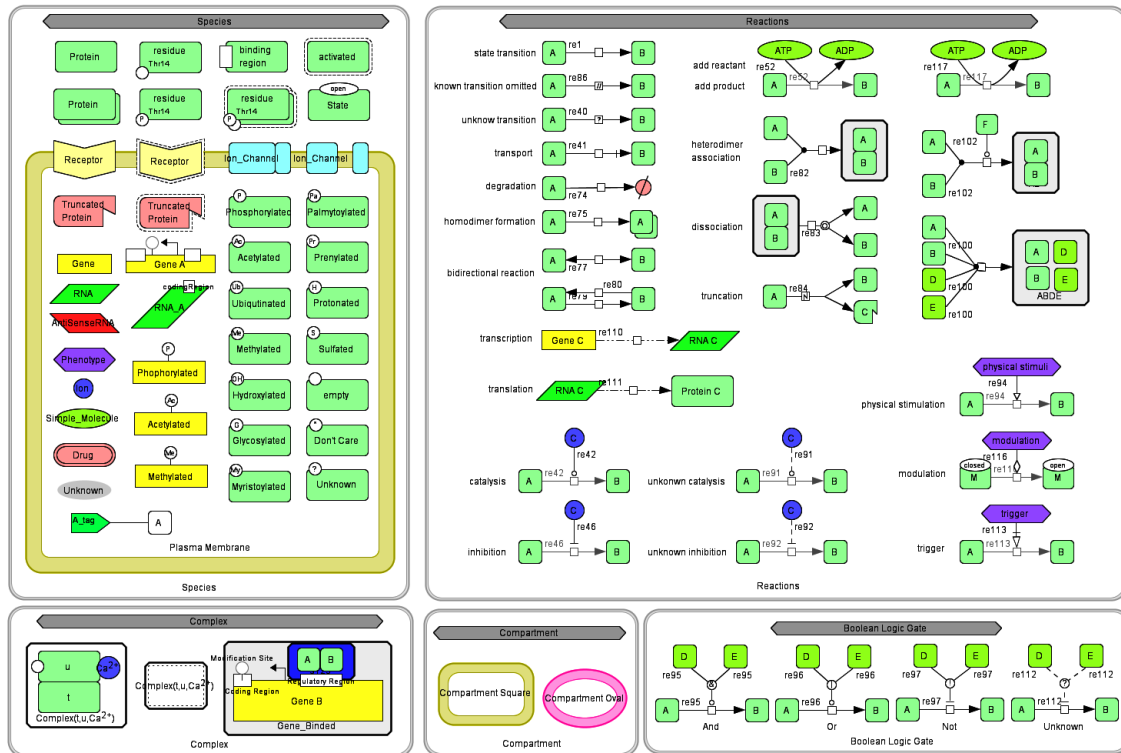
Table 1: Symbols for map entities representation
Symbols used for map entities representation are adopted by CellDesigner from Systems Biology Graphical Notation (SBGN) standards for cell molecules representation.

7.2 Map structure and content

The map schematically represents cell signaling processes. The map contains entities representing cell, molecules and compartments and edges representing reactions and catalysis. Each entity may contain modifications.

List of map entity types
-Proteins, receptor, ion channel, truncated protein
-Genes
-RNA
-asRNA
-Complexes
-Simple molecules
-Ions
-Drugs
-Unknowns
-Phenotypes
-Reactions

To learn more about SBGN please visit http://www.sbgn.org and for using CellDesigner tool for map drawing consult http://www.celldesigner.org.