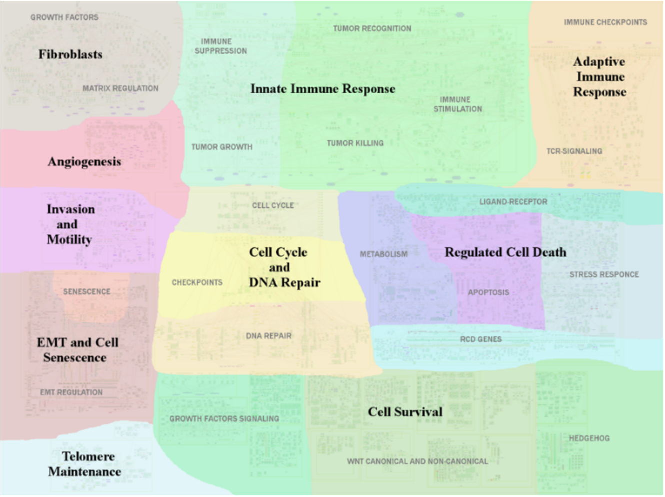
ACSN 2.0

Exploration under NaviCell platform

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

Guide for users



Updated on June 2018

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1. Introduction

1.1 Description of ACSN2.0

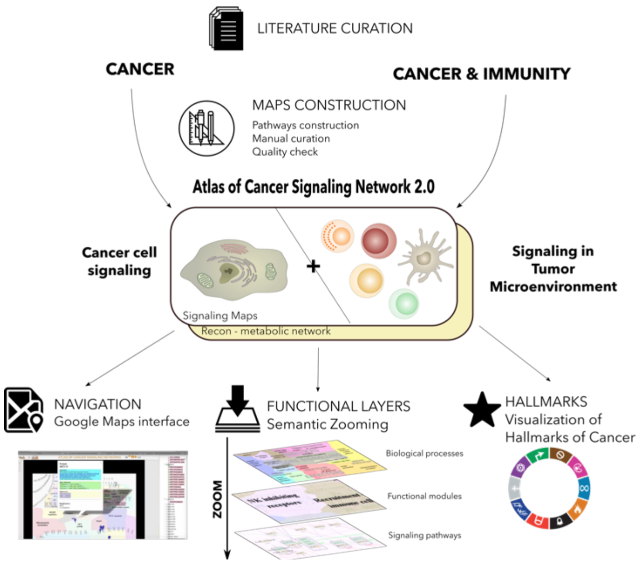
ACSN (https://acsn.curie.fr) is a web-based multi-scale resource of biological maps depicting molecular processes in the cancer cell and the tumor microenvironment. The Atlas represents interconnected cancer-related signalling and metabolic network maps. The molecular mechanisms are depicted on the maps at the level of biochemical interactions, creating a large seamless network of above 8000 reactions covering close to 3000 proteins and 800 genes and based on more than 4500 scientific publications. The Atlas is a "geographic-like" interactive "world map" of molecular interactions leading the hallmarks of cancer as described by Hanahan and Weinberg.

Molecular mechanisms within cancer cell and components of tumor microenvironment are represented in the form of comprehensive maps manually created using systems biology standards, making these maps amenable for computational analysis. The content of the maps reflects the most recent knowledge on mechanisms implicated in cancer development.

The maps of ACSN 2.0 are interconnected, the regulatory loops between cancer cell and tumor microenvironment are systematically depicted. The cross-talk between signalling mechanisms and metabolic processes in the cancer cells is explicitly depicted thanks to new feature of the Atlas: ACSN 2.0 is now connected to RECON metabolic network, the largest graphical representation of human metabolism.

ACSN 2.0 is composed of 13 maps, which are all interconnected. There are six maps covering signalling processes involved in cancer cell development and four maps describing tumor microenvironment. In addition, there are 3 cell type-specific maps describing specific signalling within different cells types found in the surrounding mullei of cancer cell. This feature of ACSN 2.0 reflects heterogeneity of tumor microenvironment.

Schematic representation of principle for construction of ACSN2.0 and major feature of the resource



1.2 Description of NaviCell

NaviCell is a web tool for exploring large maps of molecular interactions created in CellDesigner (http://celldesigner.org). This tool is currently used for navigation of the Atlas of Cancer Signalling Networks (ACSN). The NaviCell 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 tool box for data integration and visualisation in the map context.

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.
Pop-up bubble	Small window that opens by clicking on marker. Contains short description and hyperlinks related to the marked entity.
Annotation post	Detailed map entity annotation created in CellDesigner by map manager. The annotation is converted to annotation post and displayed 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 several 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 panel. 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, pop-up bubbles and zoom bar are adapted from the Google maps.

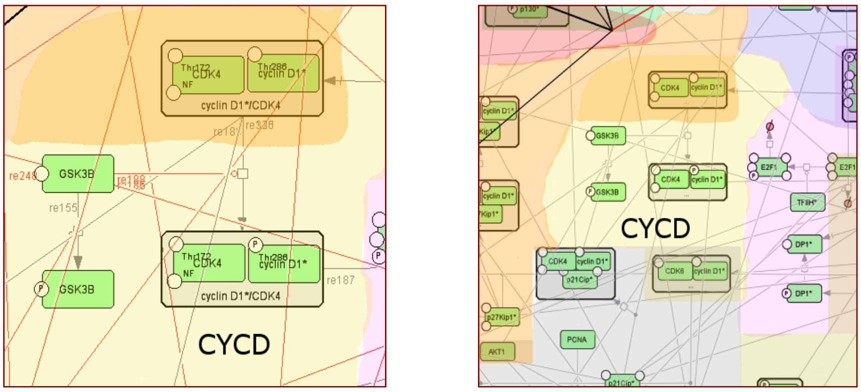
Fig1: NaviCell layout.
*(A) Title panel, **(B)** Map panel, **(C)** Selection panel, **(D)** Zoom bar, **(E)** Data visualization panel*

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.

- 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**

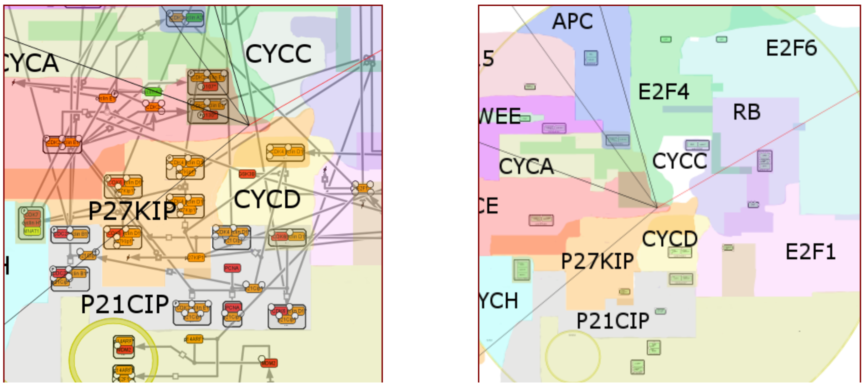


Fig2: NaviCell semantic zooming.
The same area of the map is visualized using 4 zooms; each image is twice smaller that in the preceding zoom level. ***(A)*** *In the detailed view, entity names, modifications and reaction IDs are visible.* ***(B)*** *In the hidden details view, part of textual information 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).

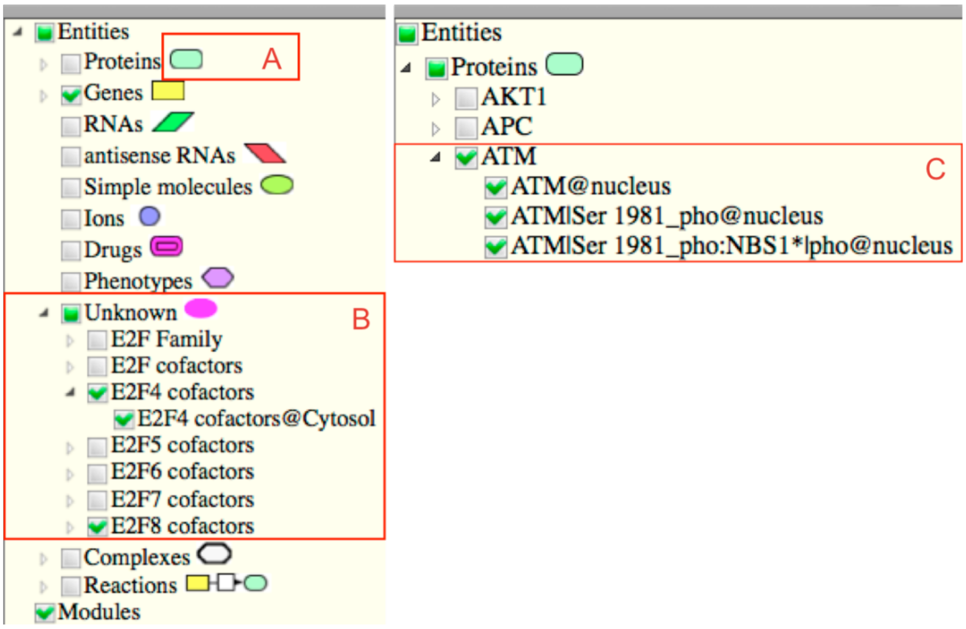
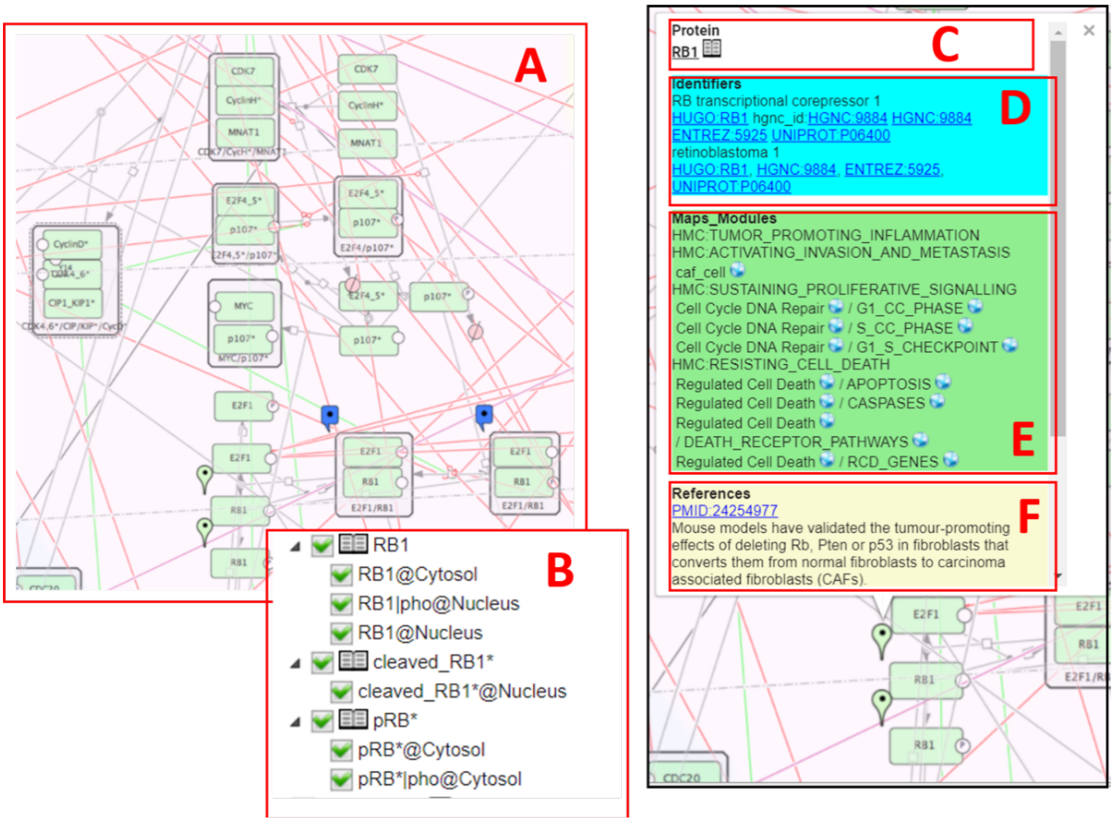


Fig3: NaviCell selection panel with list of map entities ordered per entity type.
(A) *Entity symbol,* ***(B)*** *List of entities for entity type 'Unknown',* ***(C)*** *List of modifications for entity Protein 'ATM': ATM found in particular cellular compartment, ATM with post-translational modification and ATM as part of complex.*

2.4 Markers and pop-up bubbles

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 pop-up bubble. The **pop-up bubble** contains a short description about the selected component of the map. Hyperlinks are accessible from the pop-up bubble. There are **external hyperlinks** (databases) and **internal hyperlinks** (map entity modifications, reactions and modules). Clicking on the names of the entities in the bubble 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 or reaction 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 pop-up bubbles can be opened simultaneously on the same map (Fig 4).



Protein
RB1

Identifiers
RB transcriptional corepressor 1
HUGO:RB1 hgnc_id:HGNC:9884 HGNC:9884
ENTREZ:5925 UNIPROT:P06400
retinoblastoma 1
HUGO:RB1, HGNC:9884, ENTREZ:5925,
UNIPROT:P06400

Maps_Modules
HMC:TUMOR_PROMOTING_INFLAMMATION
HMC:ACTIVATING_INVASION_AND_METASTASIS
caf_cell
HMC:SUSTAINING_PROLIFERATIVE_SIGNALLING
Cell Cycle DNA Repair / G1_CC_PHASE
Cell Cycle DNA Repair / S_CC_PHASE
Cell Cycle DNA Repair / G1_S_CHECKPOINT
HMC:RESISTING_CELL_DEATH
Regulated Cell Death / APOPTOSIS
Regulated Cell Death / CASPASES
Regulated Cell Death
/ DEATH_RECEPTOR_PATHWAYS
Regulated Cell Death / RCD_GENES

References
PMID:24254977
Mouse models have validated the tumour-promoting effects of deleting Rb, Pten or p53 in fibroblasts that converts them from normal fibroblasts to carcinoma associated fibroblasts (CAFs).

Fig 4: Markers and pop-up bubbles.
*(**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 pop-up bubble 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 a separate window (internal link). (**D**) Identifiers: clicking on hyperlinks opens corresponding databases (external link). (**E**) Maps, Modules, Hallmarks of cancer (HMC): 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).*

2.5 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 pop-up bubble as 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 pop-up bubble are 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).

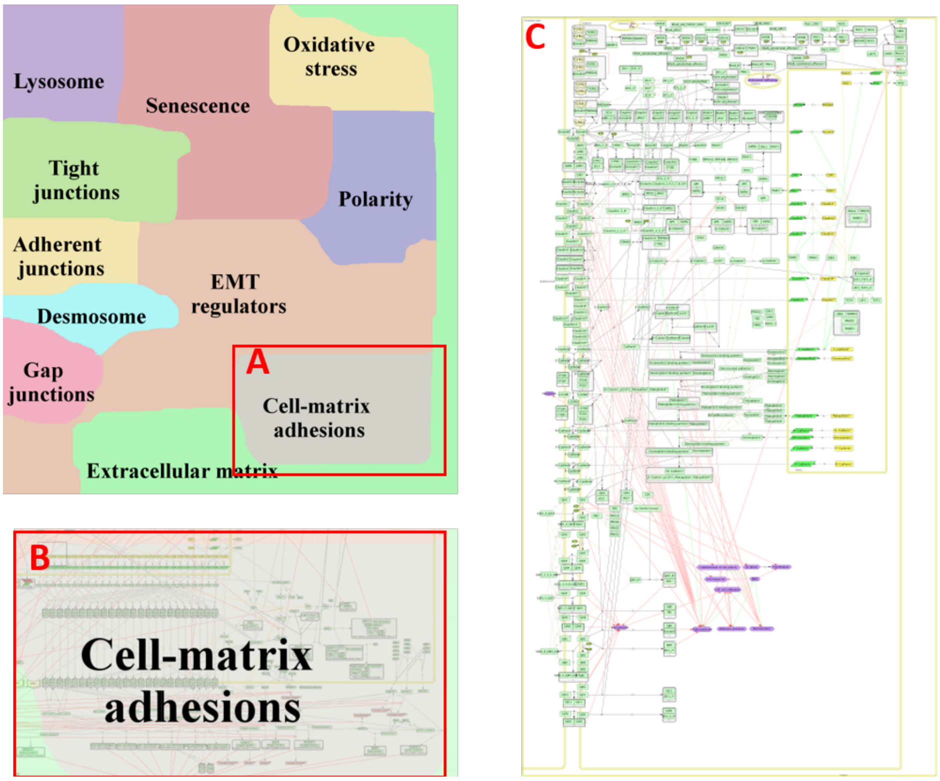


Fig 5: Modular maps.
(A) *Cell-matrix adhesion module on the Top-level view zoom of EMT map,* ***(B)*** *Cell-matrix adhesion module on the hidden-details view zoom,* ***(C)*** *Isolated Cell-matrix adhesion module*

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 6).

Protein RB1

Identifiers
RB transcriptional corepressor 1
HUGO:RB1 hgnc_id:HGNC:9884 HGNC:9884 ENTREZ:5925 UNIPROT:P06400
retinoblastoma 1
HUGO:RB1, HGNC:9884, ENTREZ:5925, UNIPROT:P06400

Maps_Modules
HMC:TUMOR_PROMOTING_INFLAMMATION
HMC:ACTIVATING_INVASION_AND_METASTASIS
caf_cell
HMC:SUSTAINING_PROLIFERATIVE_SIGNALLING
Cell Cycle DNA Repair / G1_CC_PHASE
Cell Cycle DNA Repair / S_CC_PHASE
Cell Cycle DNA Repair / G1_S_CHECKPOINT
HMC:RESISTING_CELL_DEATH
Regulated Cell Death / APOPTOSIS
Regulated Cell Death / CASPASES
Regulated Cell Death / DEATH_RECEPTOR_PATHWAYS
Regulated Cell Death / RCD_GENES

References
PMID:24254977
Mouse models have validated the tumour-promoting effects of deleting Rb, Pten or p53 in fibroblasts that converts them from normal fibroblasts to carcinoma associated fibroblasts (CAFs).
PMID:18458534
Human breast cancer-associated fibroblasts (CAFs) show caveolin-1 downregulation and RB tumor suppressor functional inactivation
PMID:18590585, PMID:17303408, PMID:17660363, PMID:7575488, PMID:15279786, PMID:7935440

Modifications:
In compartment: Cytosol

1. RB1@Cytosol

In compartment: Nucleus

1. RB1@Nucleus
2. RB1|pho@Nucleus

Participates in complexes:
In compartment: Nucleus

1. E2F1:RB1@Nucleus
2. E2F1:RB1|pho@Nucleus
3. BRCA1|S988_pho|S1387_pho|S1423_pho|S1497_pho|S1524_pho:E2F1:RB1@Nucleus
4. CTBP*|S181_pho|T179_pho|S185_pho:CTIP*|emp|S372_pho|T847_pho|S267_pho:RB1@Nucleus

Participates in reactions:
As Reactant or Product:

1. RB1@Cytosol → NEGATIVE_REGULATORS_OF_CAF@Cytosol
2. E2F1@Nucleus + RB1@Nucleus → E2F1:RB1@Nucleus
3. E2F1:RB1@Nucleus → E2F1:RB1|pho@Nucleus
4. E2F1:RB1|pho@Nucleus → RB1|pho@Nucleus + E2F1@Nucleus
5. E2F1:RB1@Nucleus → E2F1@Nucleus + RB1@Nucleus
6. RB1|pho@Nucleus → degraded
7. E2F1:RB1|pho@Nucleus → E2F1:RB1@Nucleus
8. CTBP*|S181_pho|T179_pho|S185_pho:CTIP*|emp|S372_pho|T847_pho|S267_pho@Nucleus + RB1@Nucleus → CTBP*|S181_pho|T179_pho|S185_pho:CTIP*|emp|S372_pho|T847_pho|S267_pho:RB1@Nucleus
9. E2F1:RB1@Nucleus + BRCA1|S988_pho|S1387_pho|S1423_pho|S1497_pho|S1524_pho|active@Nucleus → BRCA1|S988_pho|S1387_pho|S1423_pho|S1497_pho|S1524_pho:E2F1:RB1@Nucleus
10. RB1@Nucleus → cleaved_RB1*@Nucleus

As Catalyser:

1. G1_phase@Nucleus → S_phase@Nucleus
2. E2F1@Nucleus → E2F1@Nucleus

Fig 6: Annotation post.
The entity type, name and sections 'Identifiers', 'Modules', 'References' are also visible in the pop-up bubble on 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.

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, creating semantic zooms and essential scripts are found at https://github.com/sysbio-curie/NaviCell/tree/master/map_construction_procedures

5. NaviCell factory

For NaviCell Factory package allowing to convert a CellDesigner map into NaviCell Google Maps-based environment see https://github.com/sysbio-curie/NaviCell

6. References

Maria Kondratova, Nicolas Sompairac, Emmanuel Barillot, Andrei Zinovyev, Inna Kuperstein; Signalling maps in cancer research: construction and data analysis, Database, Volume 2018, bay036, https://doi.org/10.1093/database/bay036.

Eric Bonnet, Eric Viara, Inna Kuperstein, Laurence Calzone, David P. A. Cohen, Emmanuel Barillot, Andrei Zinovyev; NaviCell Web Service for network-based data visualization, Nucleic Acids Research, Volume 43, Issue W1, Pages W560–W565, 2015, https://doi.org/10.1093/nar/gkv450

Inna Kuperstein, David Cohen, Stuart Pook, Eric Viara , Laurence Calzone, Emmanuel Barillot, Andrei Zinovyev. NaviCell: a web-based environment for navigation, curation and maintenance of large molecular interaction maps. BMC Syst Biol., 7:100 ,2013, https://doi.org/10.1186/1752-0509-7-100

7. Appendix

7.1 Symbols for map entities representation (SBGN)

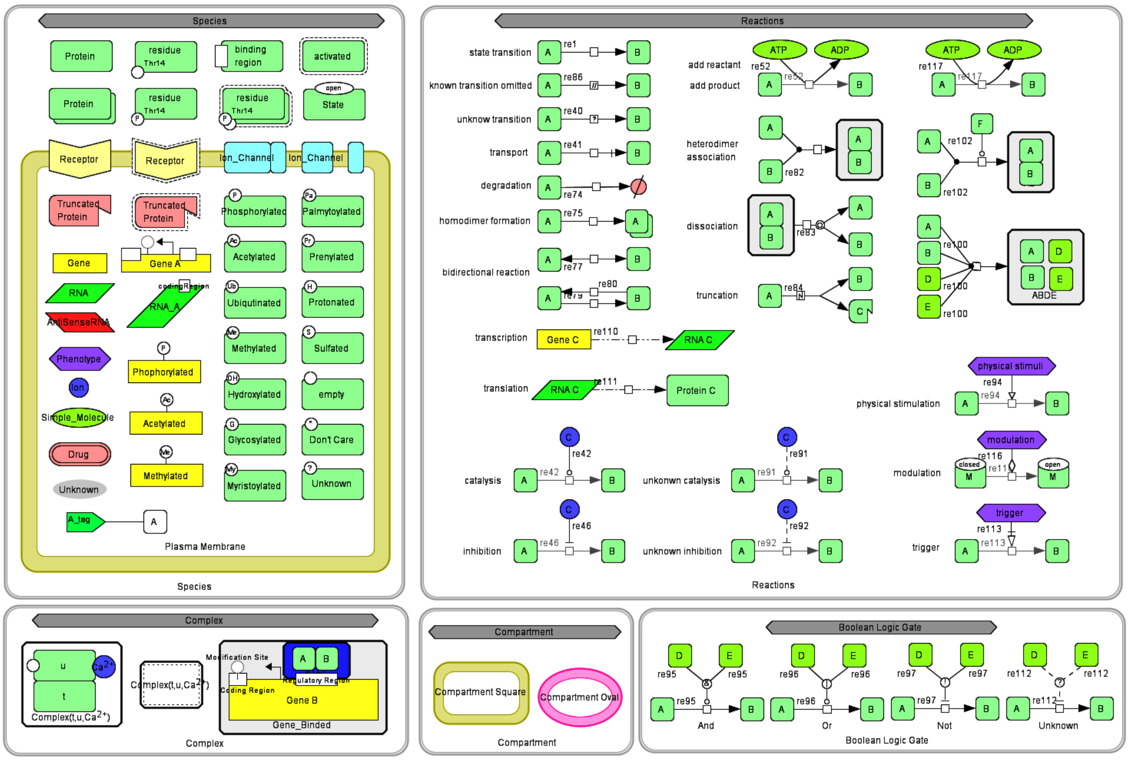


Table 1: Symbols for map entities representation

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.