Tools for describing biological processes

CellDesigner
BiNoM
NaviCell

Laurence Calzone
June 4th

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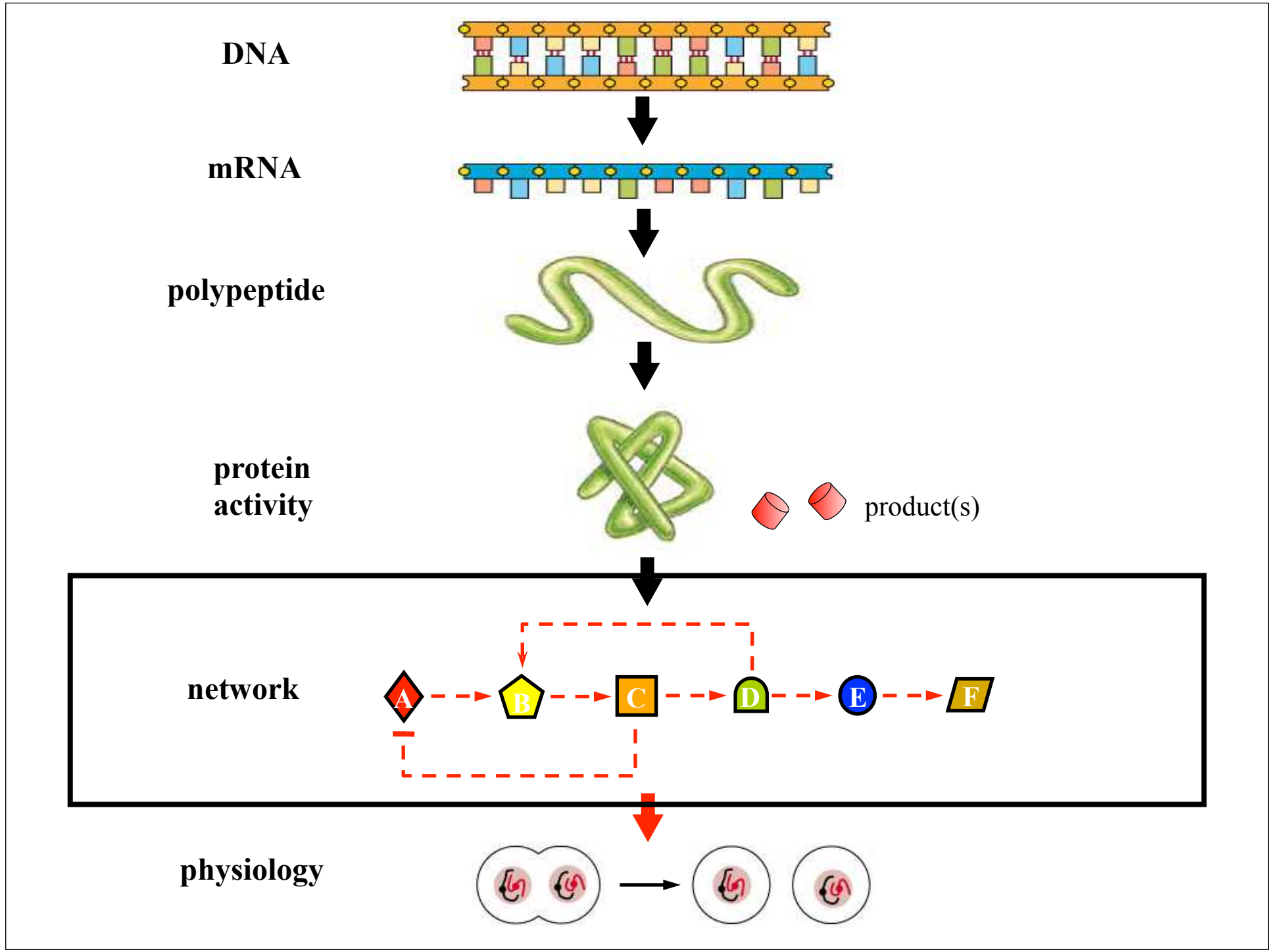

DNA
mRNA
polypeptide
protein
activity
product(s)
network
A
B
C
D
E
F
physiology

Motivation: Establish a link between physiology and molecular interactions

Physiology of the cell

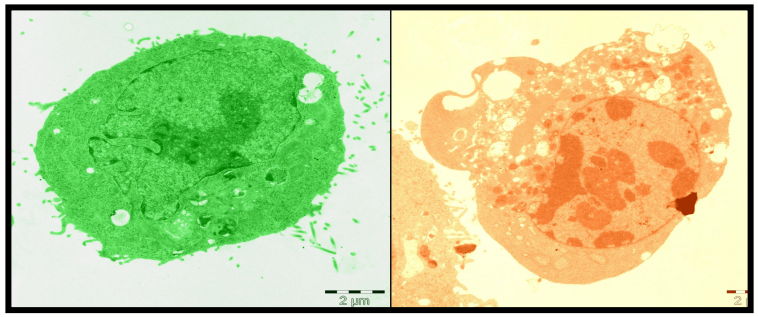
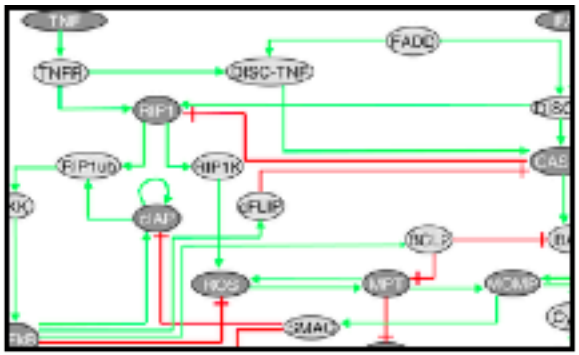
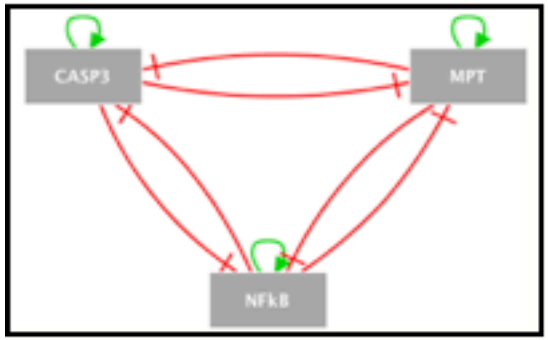
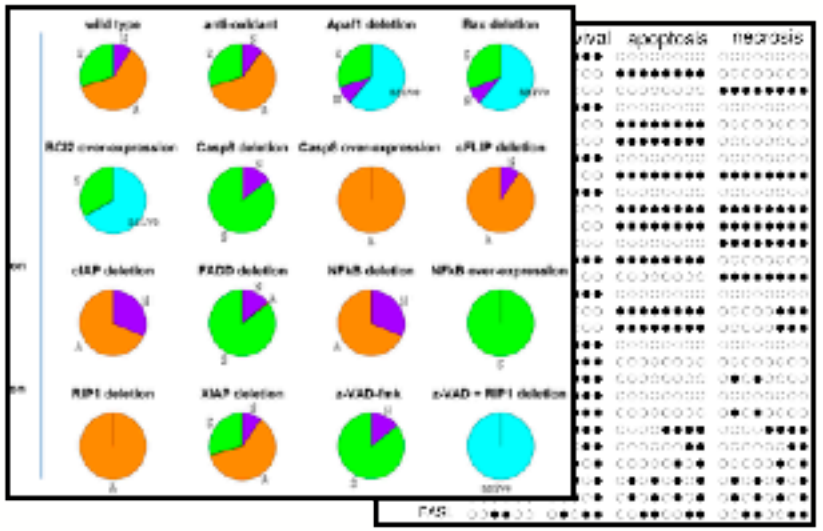


Diagram of protein interactions





Formulation of predictions
Experimental validation

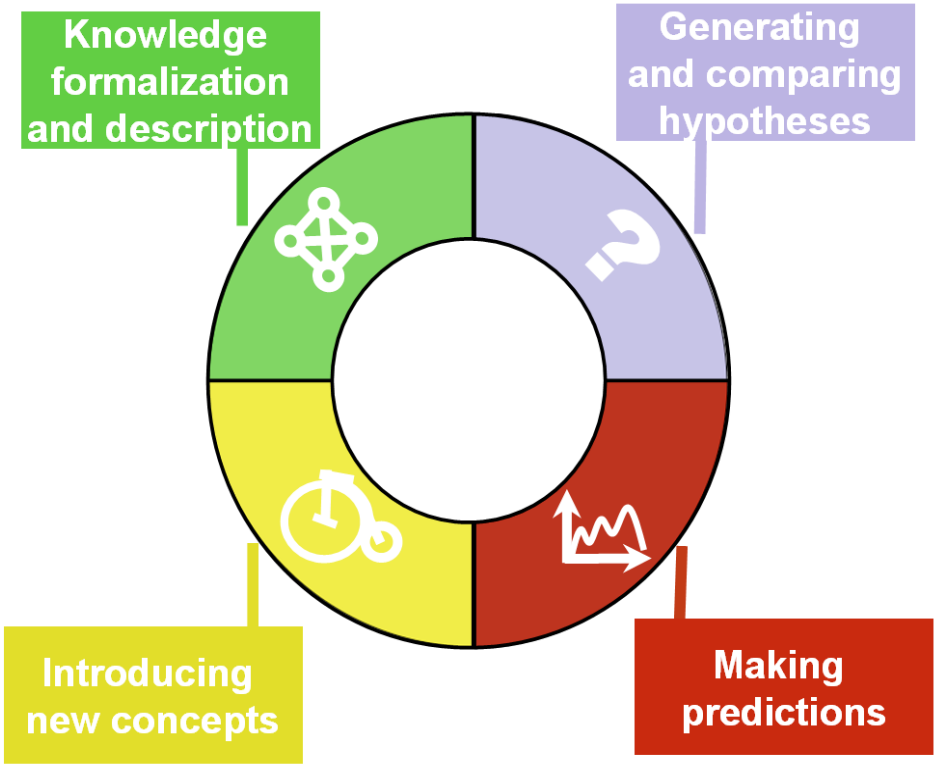


Translation in mathematical terms
Formal verification of what is known

The role of bioinformatics and systems biology

The goal is to:

- provide a consensus picture of the cell functioning & integrate information from many experiments and publications
- help confirm or infirm hypotheses: check that the mechanism is correct
- propose experiments to experimentalists
- introduce new concepts



Four hallmarks of mathematical modelling

OUTLINE

1. **CellDesigner**:
   Constructing reaction maps

2. **BiNoM**:
   Manipulating reaction maps

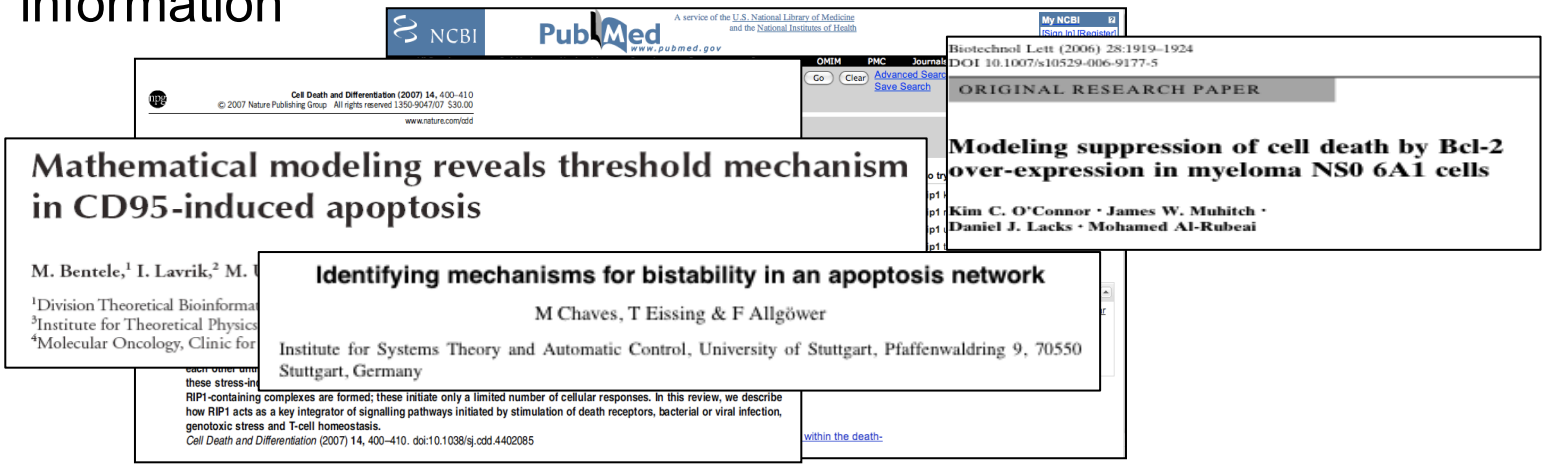
3. **NaviCell**:
   Navigating through reaction maps

1. CellDesigner

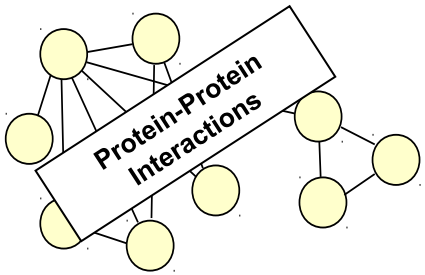
Constructing reaction maps

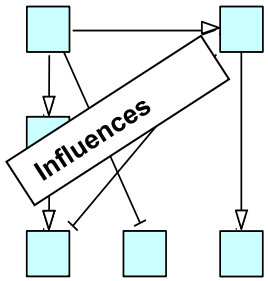
Construction of maps

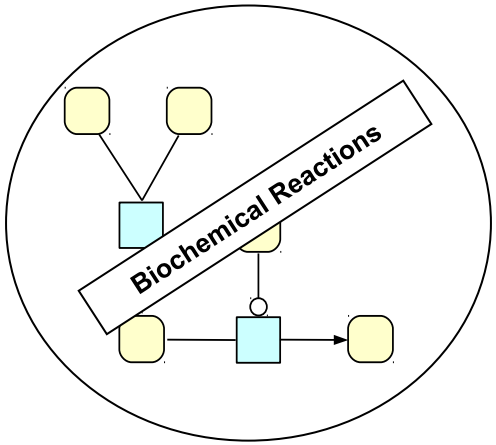
- Select a biological process to describe
- Gather information

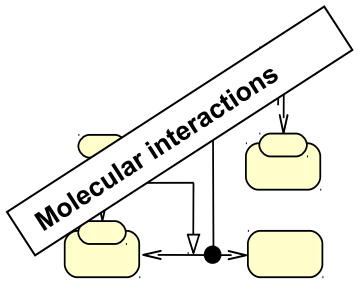


- Organize the information as the most appropriate type of diagrams







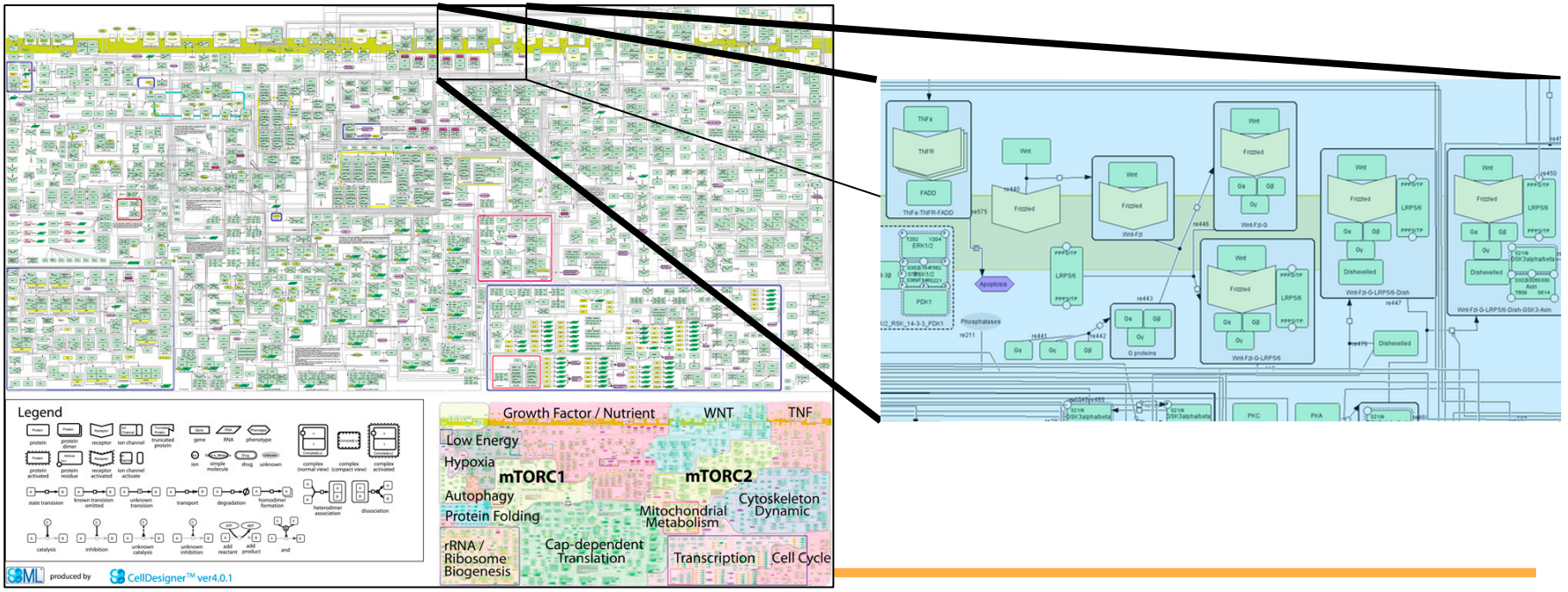


Tomorrow with Loredana's course

SBGN – Systems Biology Graphical Notation

Biochemical reaction maps

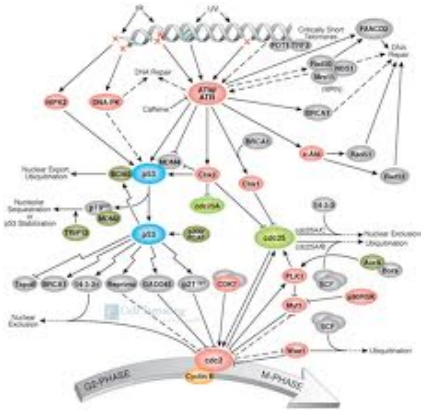
- Composed of biochemical reactions: syntheses, degradations, complexations, phosphorylations, acetylations, etc.
- Mean to summarize hundreds of scientific facts
- Description of reactions in a standard format

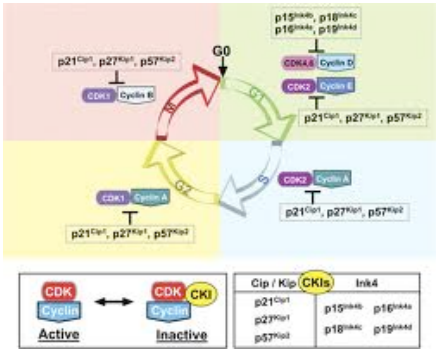


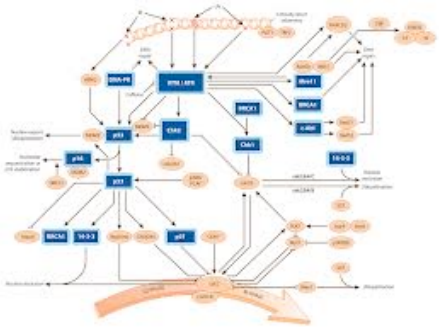
A comprehensive map of the mTOR signaling network
Etienne Caron, Samik Ghosh, Yukiko Matsuoka, Dariel Ashton-Beaucage, Marc Therrien, Sébastien Lemieux, Claude Perreault, Philippe P Roux & Hiroaki Kitano
Molecular Systems Biology **6** Article number: 453

The need for tools

The same process can be represented in many different ways







- Each biologist uses its own representation
- Need to read the paper to understand the process / reaction map
- Need to understand the symbols before understanding
- Need for a standard format to extract information from the map, to use the map, compose maps, etc.

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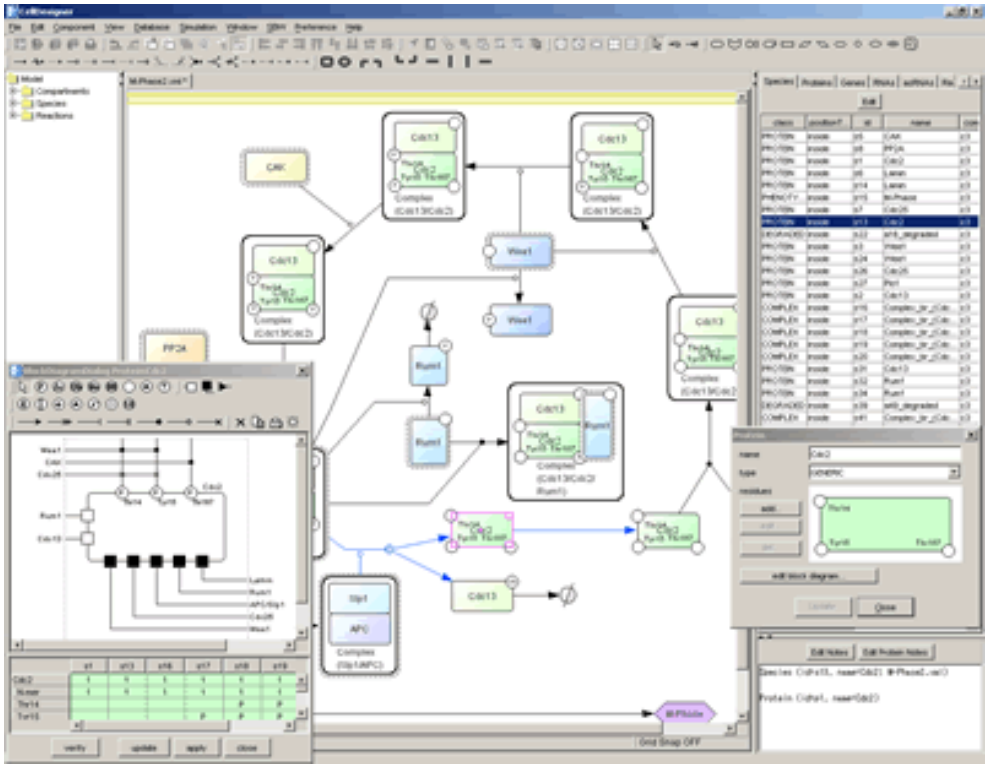
What is CellDesigner?

CellDesigner is a structured diagram editor for drawing gene-regulatory and biochemical networks that uses standard formats.



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What is CellDesigner good for?

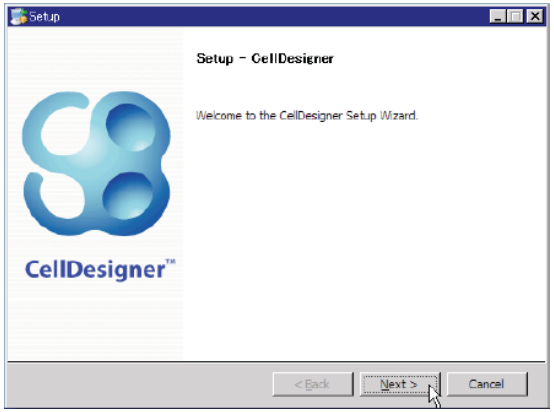
- Offers an « easy-to-use » graphical representation of a network
- Facilitates exchange of models developed by different groups, using a standard language (SBML: Systems Biology Markup Language)
- Allows to annotate the reactions, proteins, genes, etc.
- Proposes links to other databases (PubMed, IHOP, BioModels, KEGG, etc.)
- Organizes a lot of information in a unique diagram
- Allows an exchange with other modeling tools

Install and Start CellDesigner

Download CellDesigner version 4.3 from http://celldesigner.org

Download:

Setup:



Launch:

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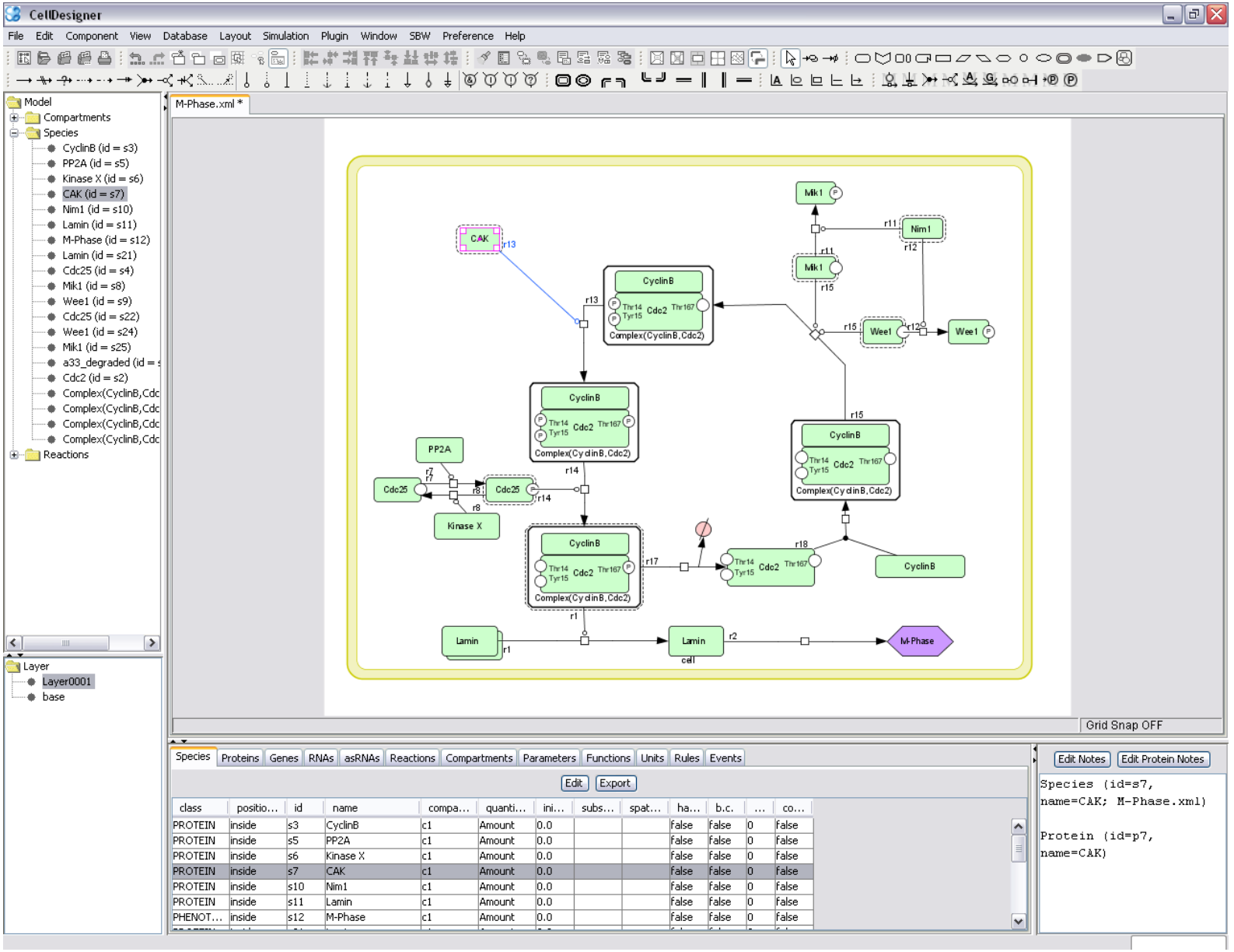
CellDesigner screen



General view

TREE AREA

displays all the list of the components in a tree structure.

DRAW AREA

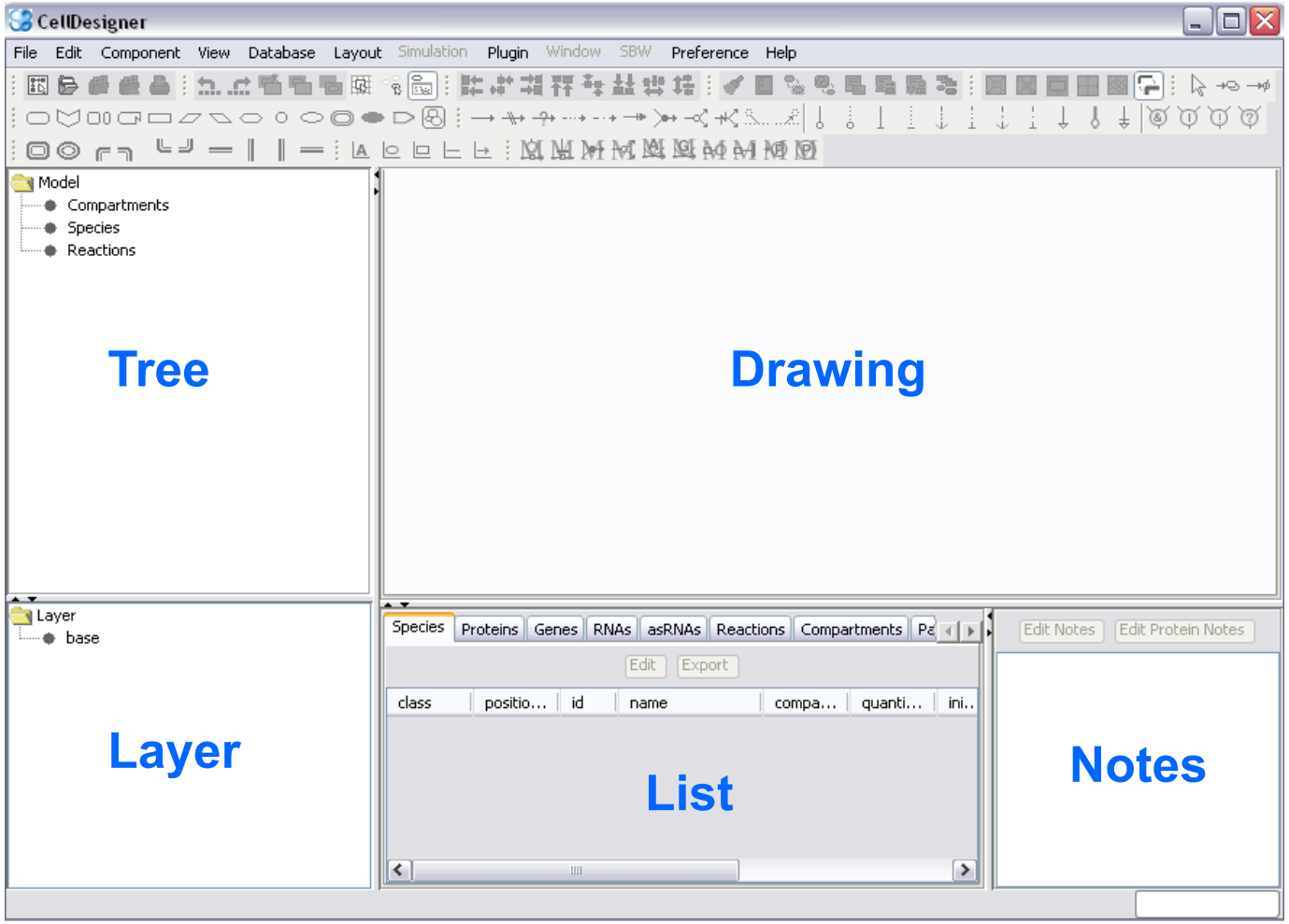
is the area where the model is built from the tool bar items.

LIST AREA

displays and edits the list of the components of the model (species, proteins, genes, RNAs, etc.)

NOTES AREA

displays and edits the notes of each component (reactions, protein, complex, etc.)



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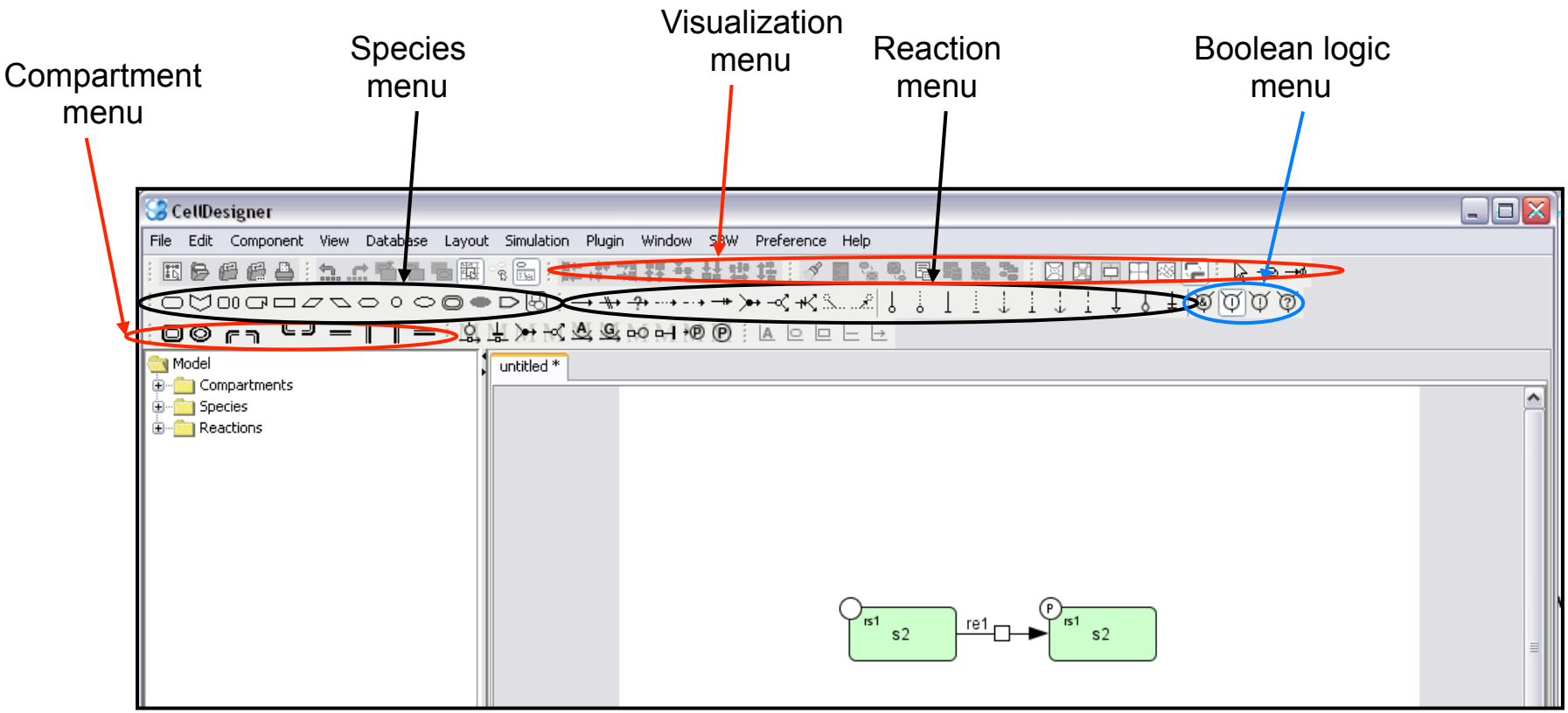
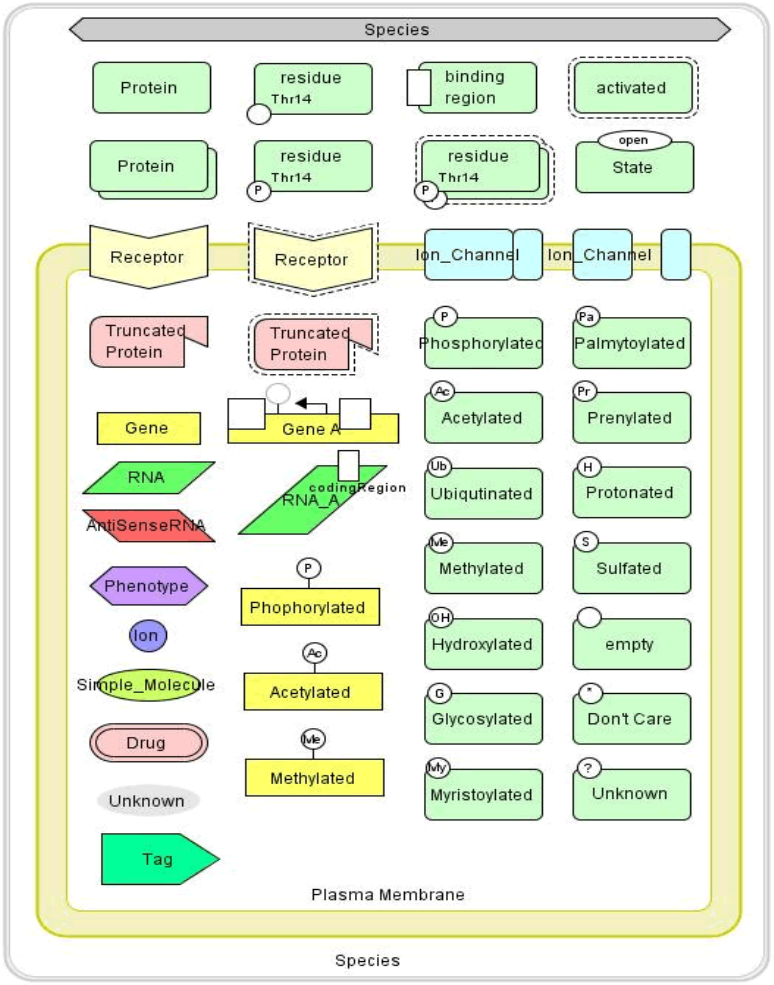
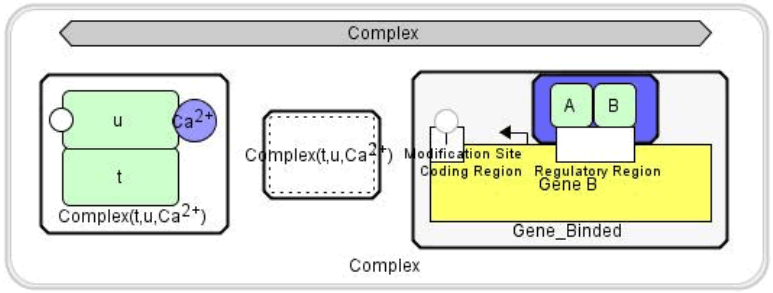
The menu


Compartment menu
Species menu
Visualization menu
Reaction menu
Boolean logic menu
CellDesigner
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
Model
Compartments
Species
Reactions
untitled *
rs1
s2
re1
P
rs1
s2

The species





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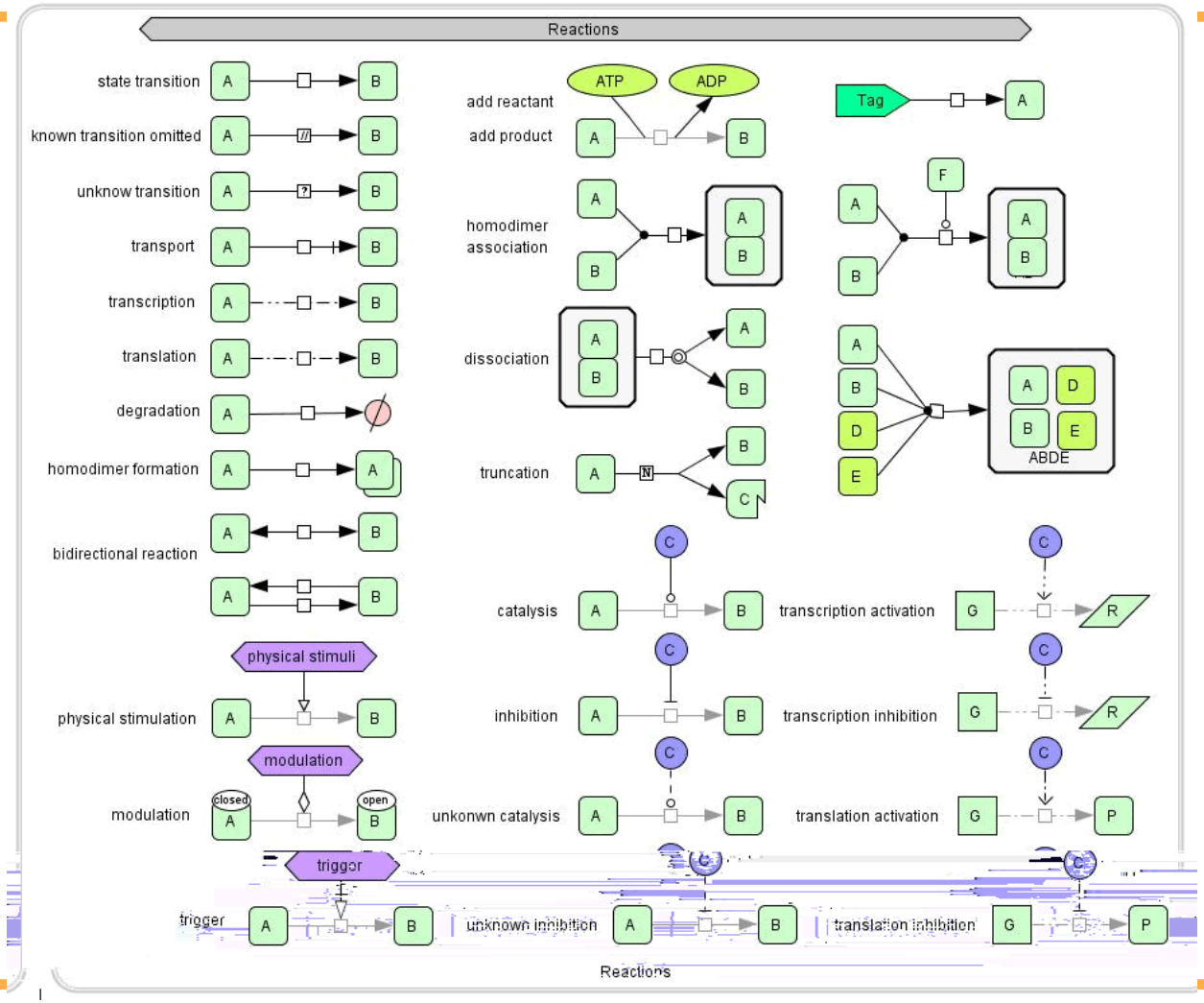
The reactions



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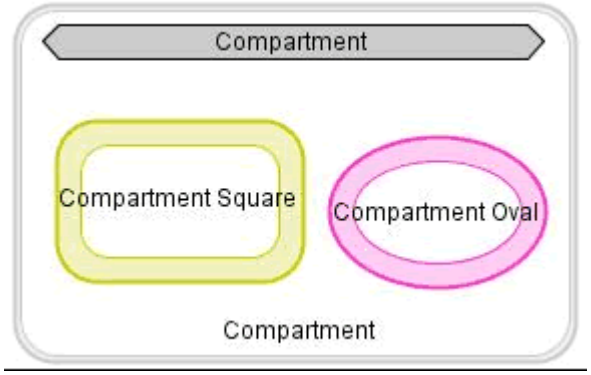
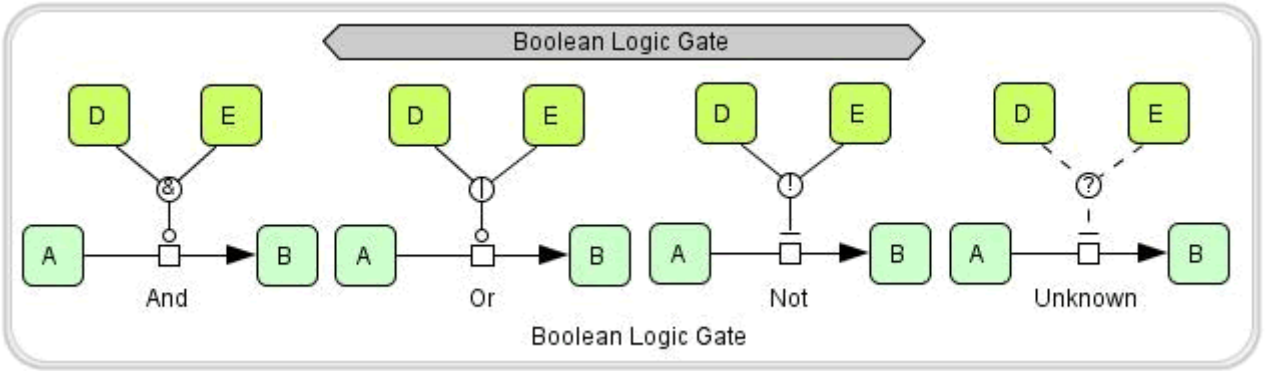
The compartments



Compartments can be:
- Cytoplasm
- Nucleus
- Nucleolus
- etc.

Boolean gates

Introduce boolean logic information into the diagram

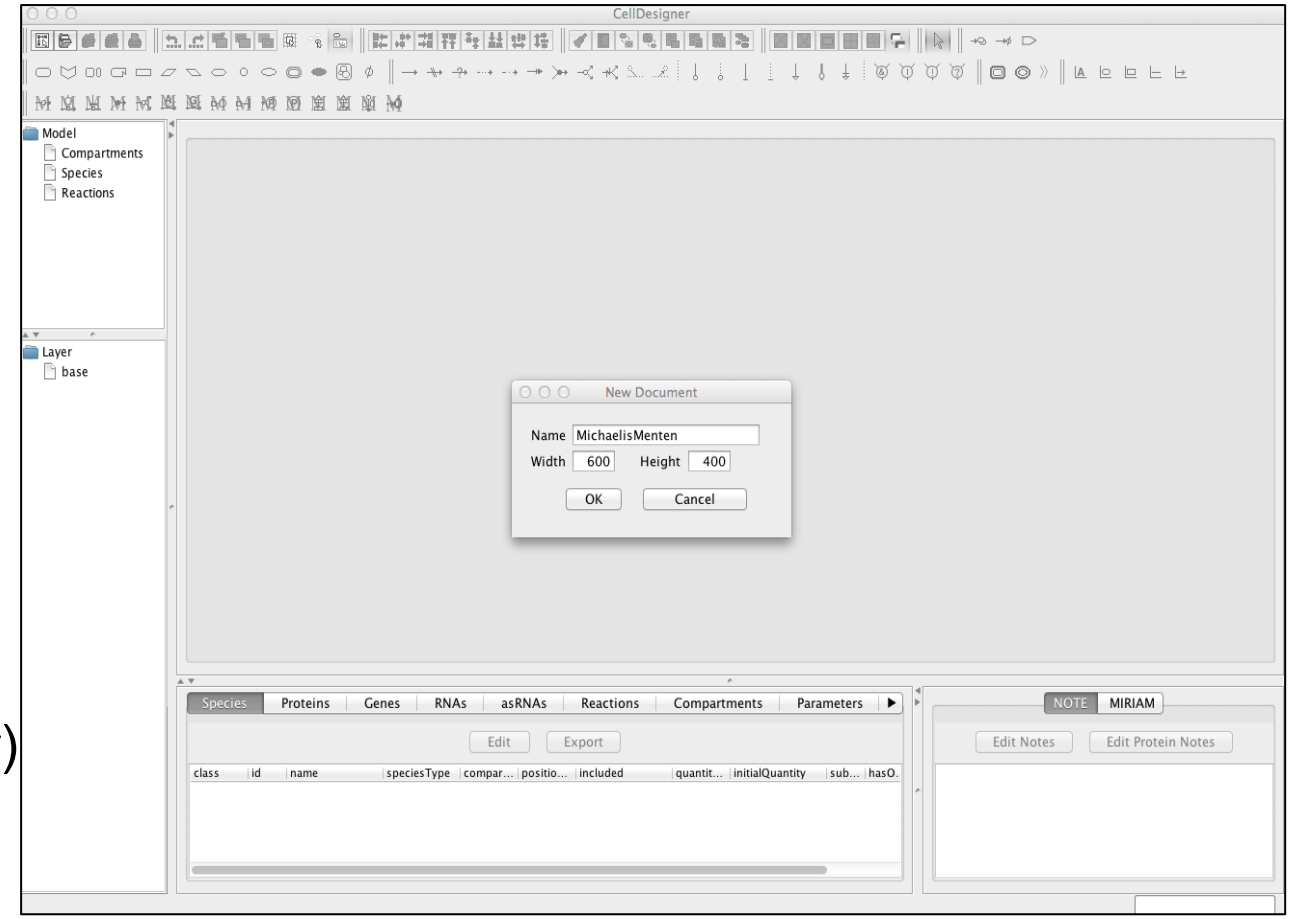


Start with a simple network

- Open a new document:
[File] => [New]

- Name your network
(MichaelisMenten)

- Choose the dimension of the graph
(by default: 600 by 400 but can be changed later)



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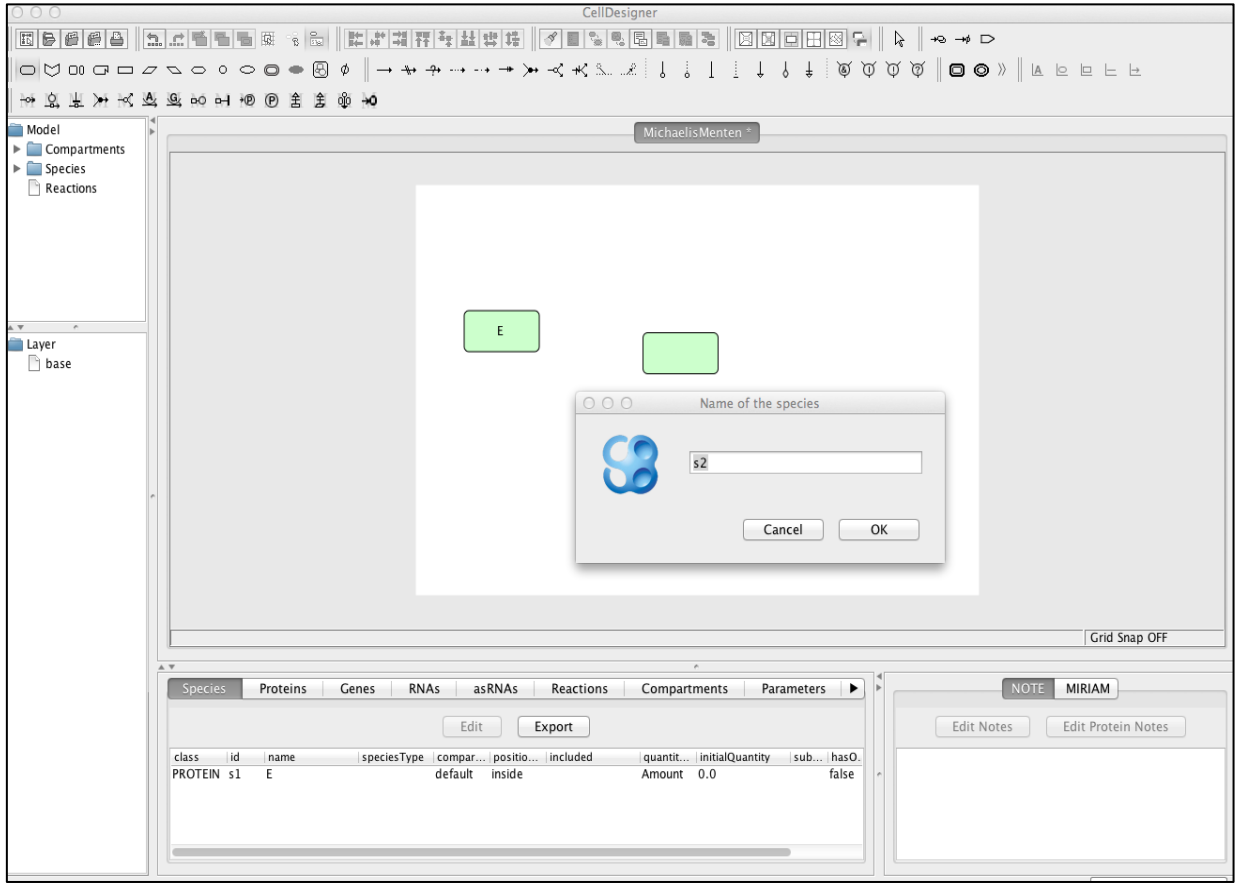
Add proteins

- Choose to add a protein from the *Species* menu

- A pop-up window opens: name your protein

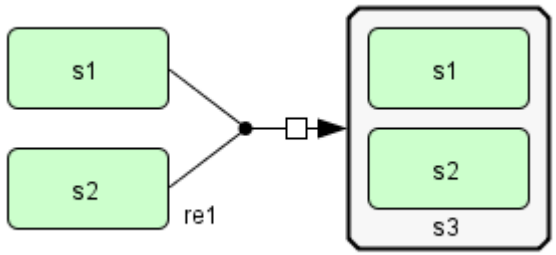
- Repeat the process as many times as needed

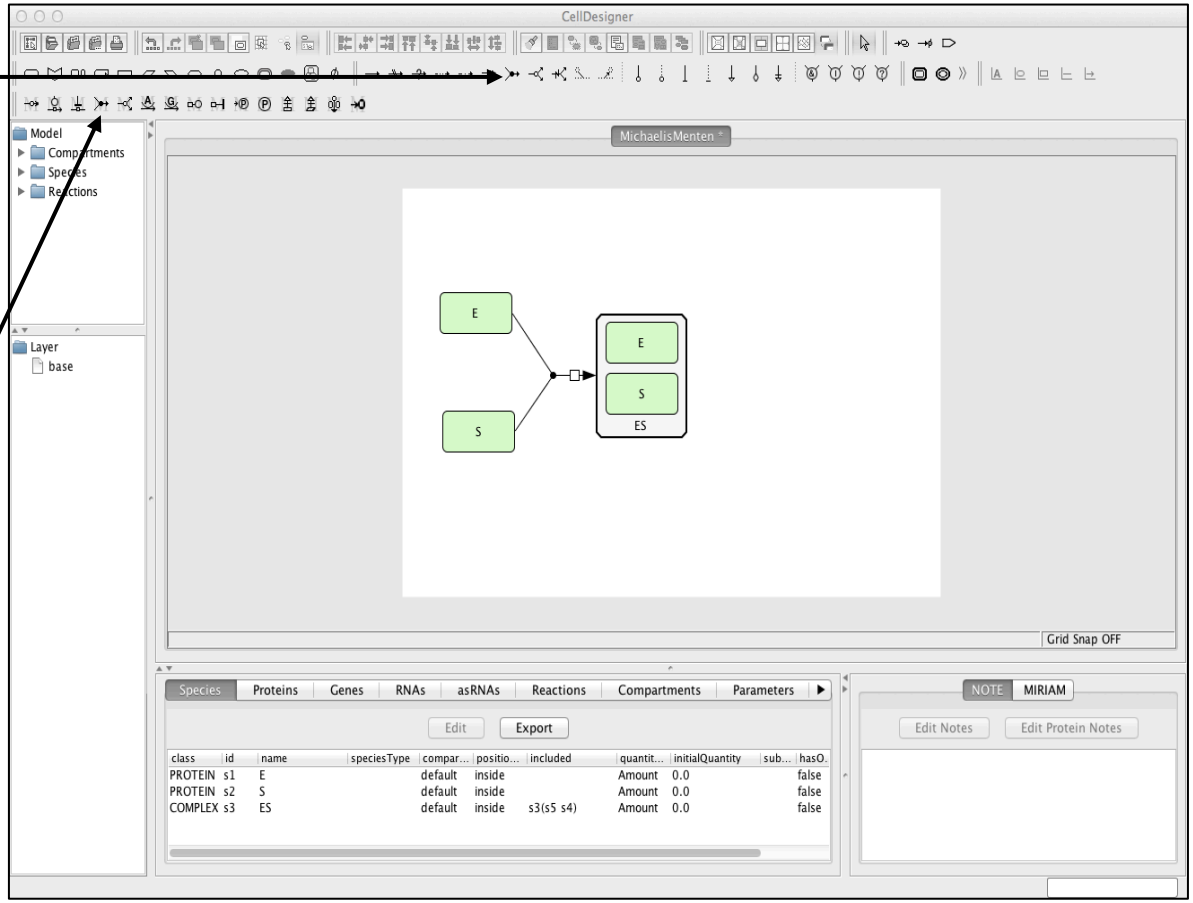


Connect species

- Choose the heretodimer association to connect the proteins E, S and the complex ES (there are many reaction types to link two species)

- An alternative: a *macro*, allows to do all these steps in just one step





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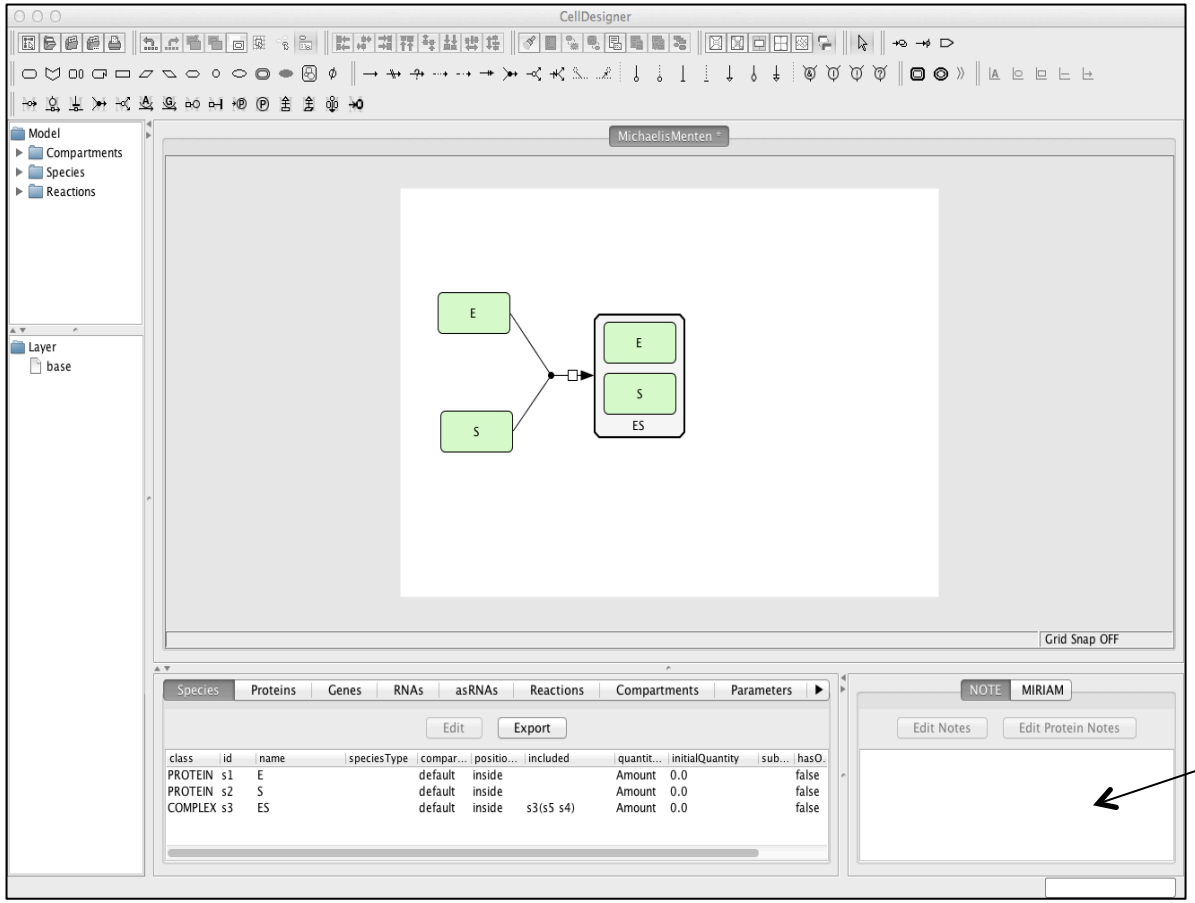
Annotate species



Write Notes about species, reactions, etc.

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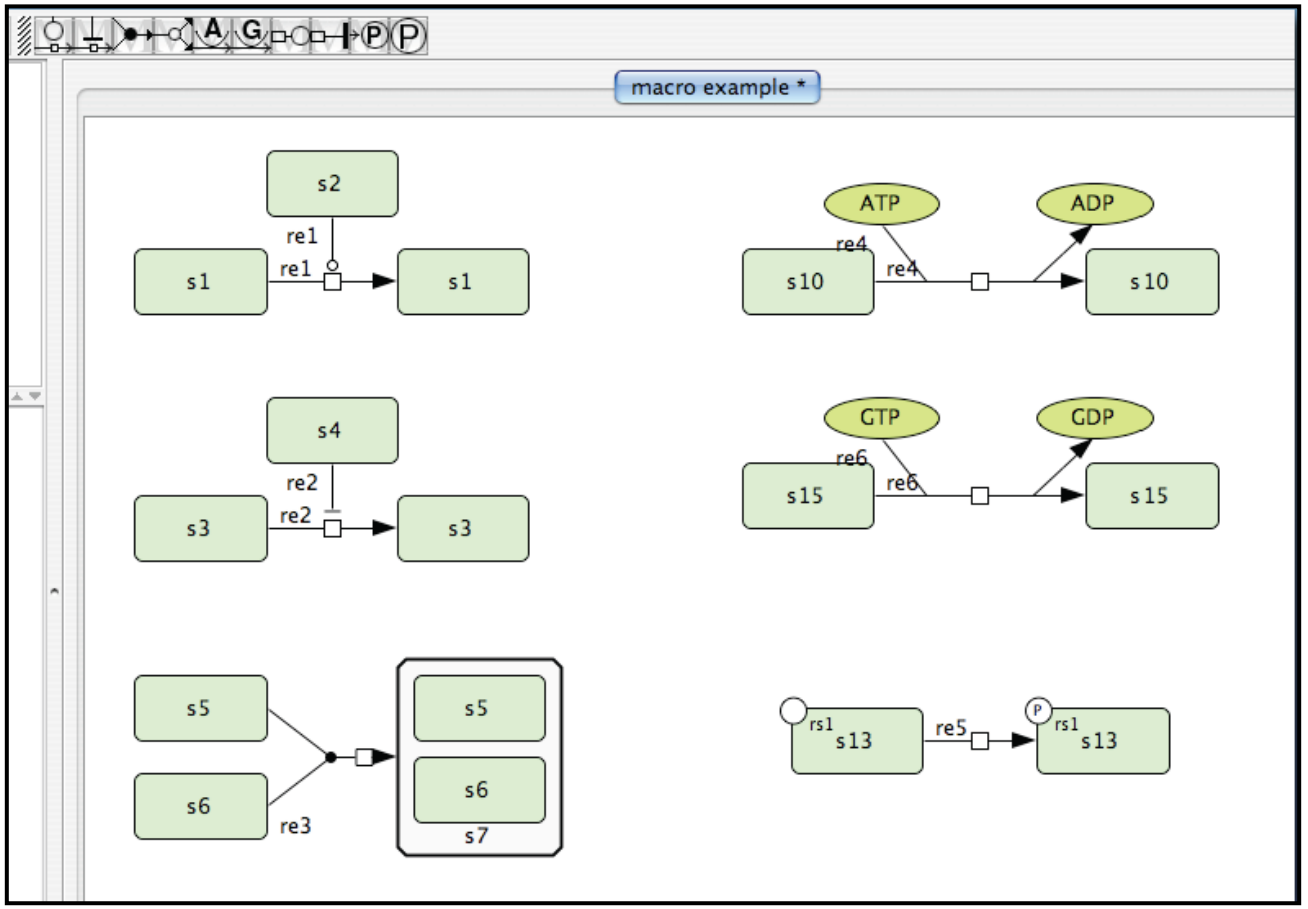
Examples of macros

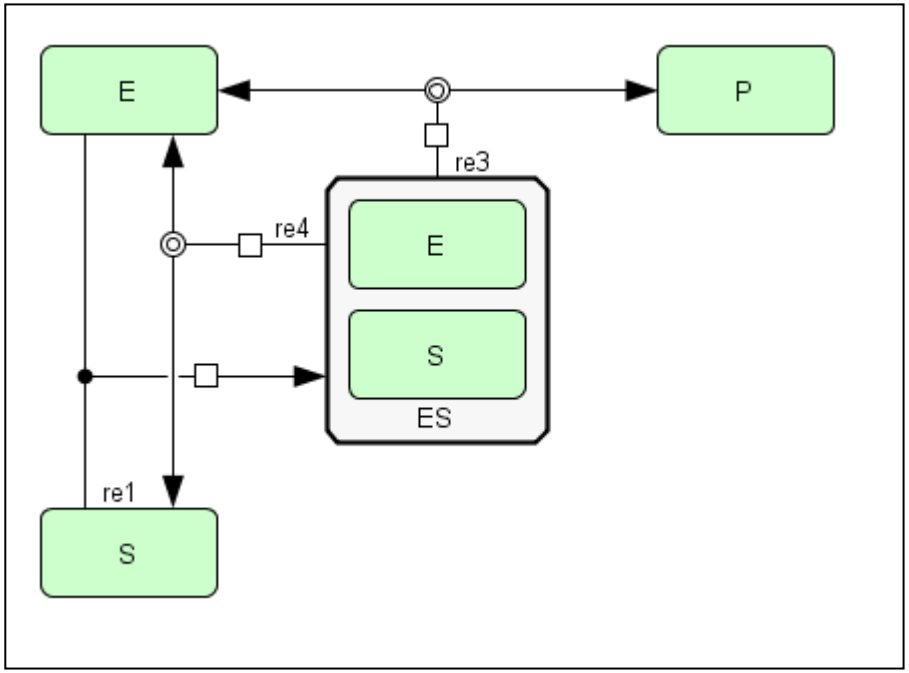


Small network

This biochemical reaction

$$E + S \underset{re_1, re_4}{\longleftrightarrow} ES \xrightarrow[re_3]{} E + P$$

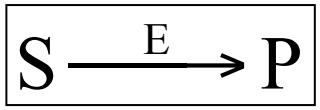
is translated into this diagram



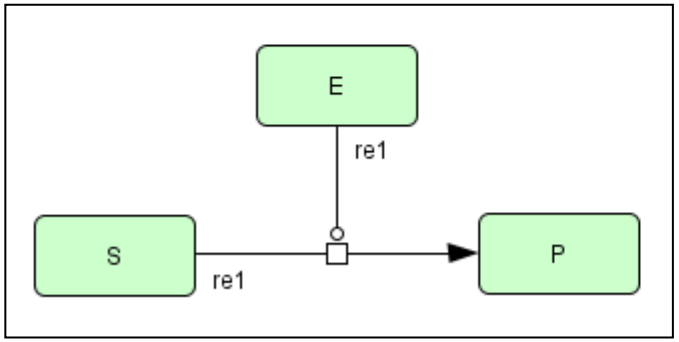
Note: There is a possibility to include dynamics into the diagram by defining the parameters re1, re4, re3… We will not describe this process today…

Or more simply…

This reaction



is translated into this diagram

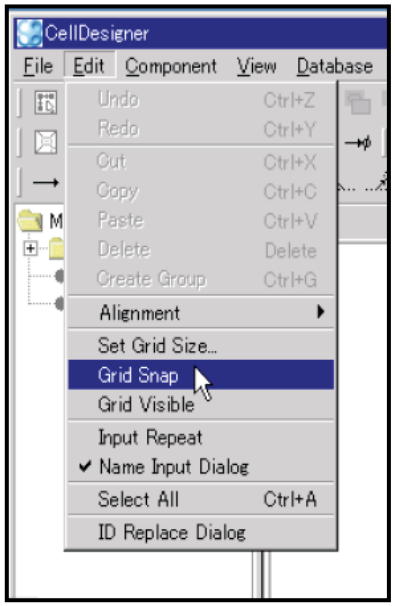


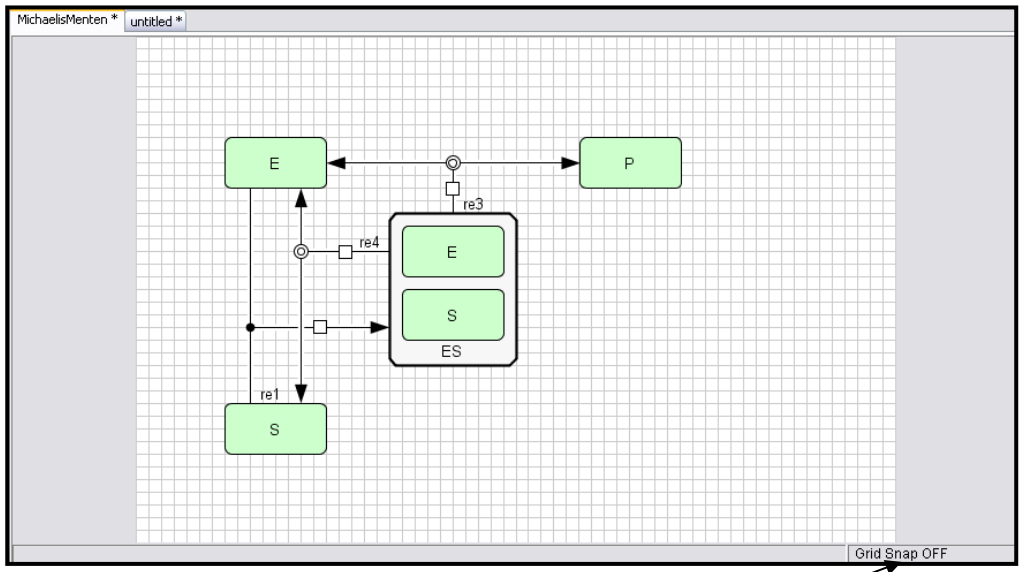
You choose the level of details…

Some functions

Drawing tips:

- Choose from the [Edit] menu, Grid Snap, to help you draw your network.
- You can also make the grid visible

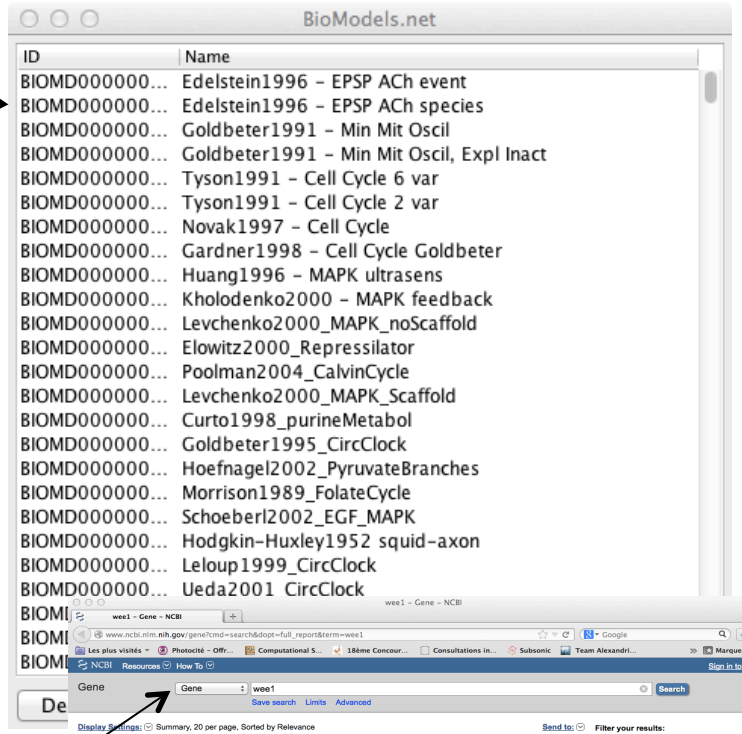




Grid Snap On or OFF indicated here

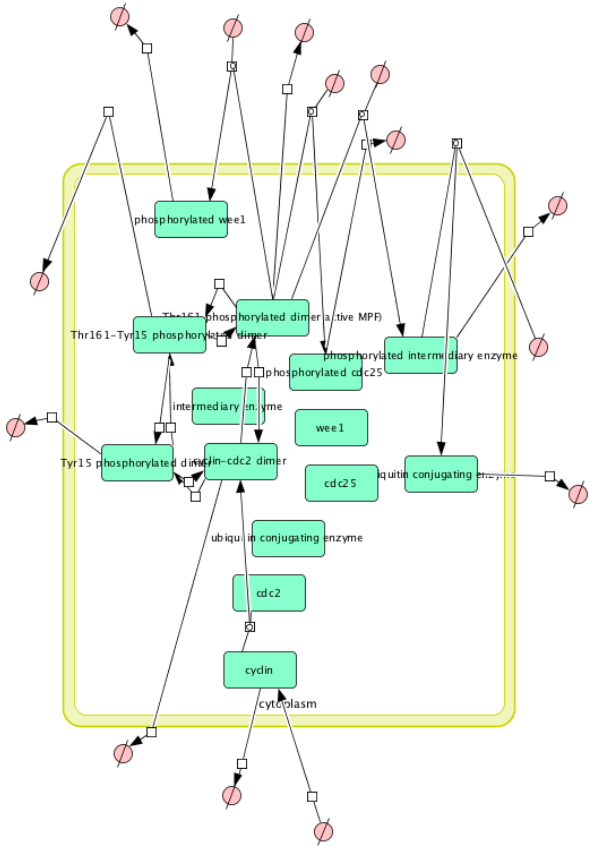
Database Connection

Importing models and information	
BioModels.net	http://www.biomodels.net, http://www.ebi.ac.uk/biomodels/
JWS Online	http://jjj.biochem.sun.ac.za/
PANTHER Pathways database	http://www.pantherdb.org/pathway/
SABIO-RK	http://sabio.villa-bosch.de/
Use Species Names for query	
DBGET	http://www.genome.jp/dbget/
SGD	http://yeastgenome.org/
iHOP	http://www.ihop-net.org/UniPub/iHOP/
Genome Network Platform	http://genomenetwork.nig.ac.jp/public/sys/gnppub/portal.do
Use IDs for query	
PubMed	http://www.ncbi.nlm.nih.gov/sites/entrez
Entrez Gene	http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene
UniProt	http://www.uniprot.org
MetaCyc	http://www.metacyc.org/
Gene Wiki	http://en.wikipedia.org/wiki/Portal:Gene_Wiki
Panther Web	http://www.pantherdb.org

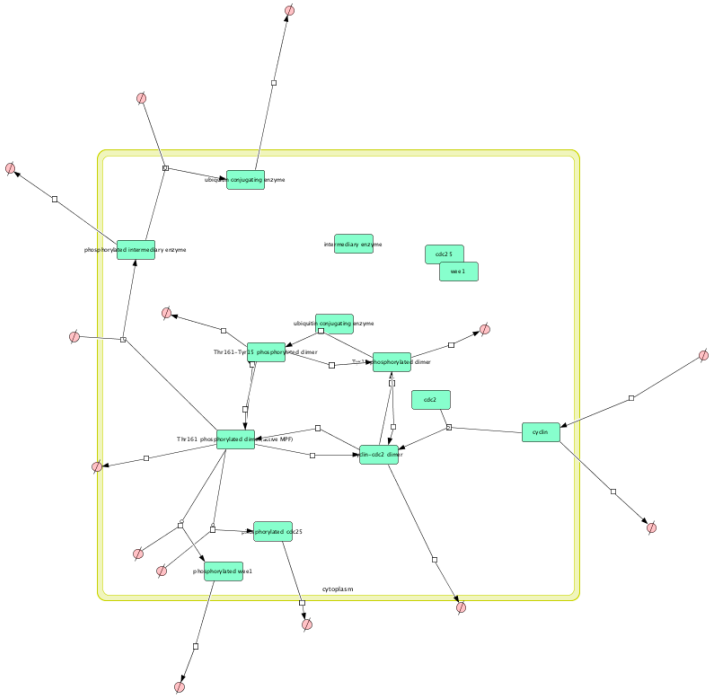


Existing models

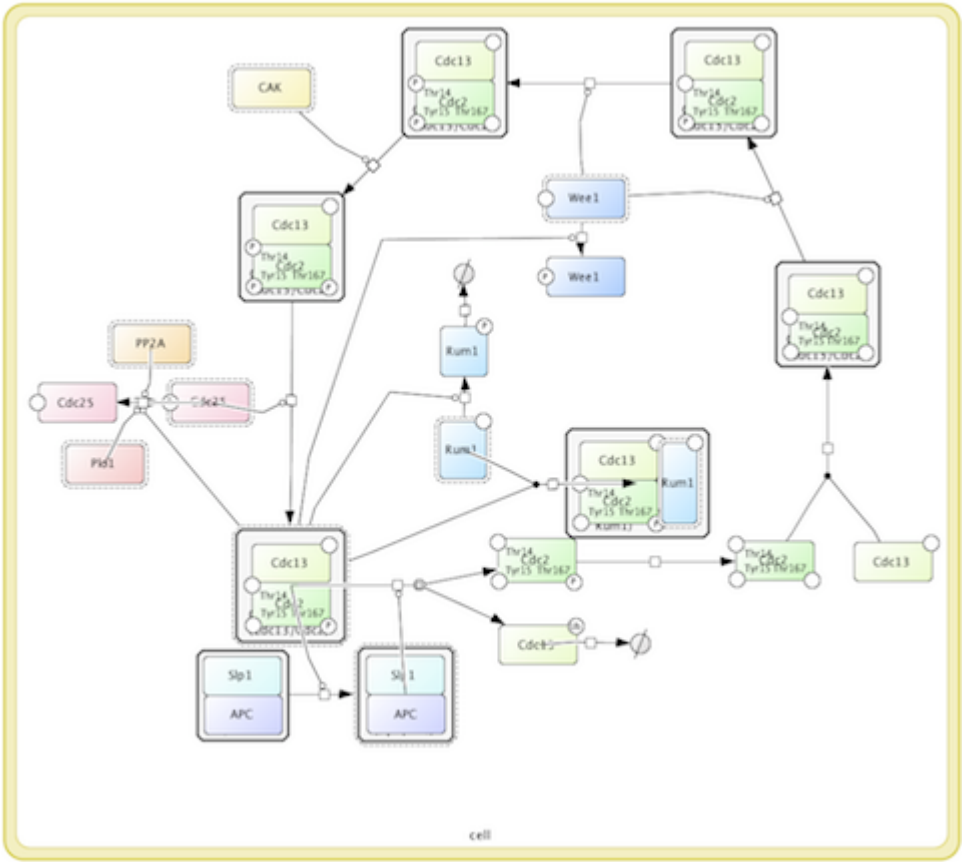
1. Import model from a database:
[Database] => [Import a model from BioModels.net]:
BIOMD0000000111 (Novak2001)



2. Change layout:
[Layout] => [Organic layout]



M-Phase.xml



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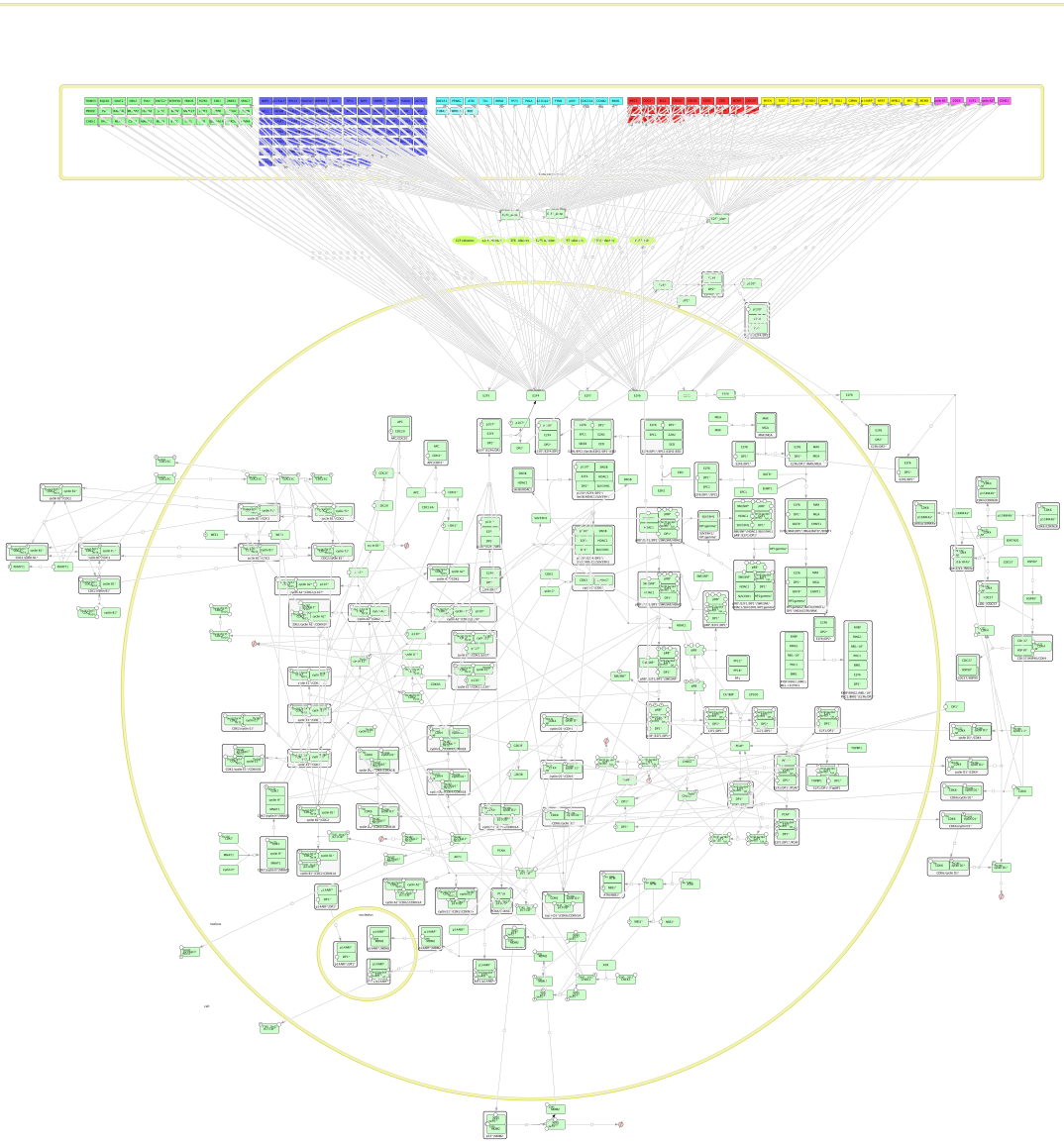
rbe2f.xml

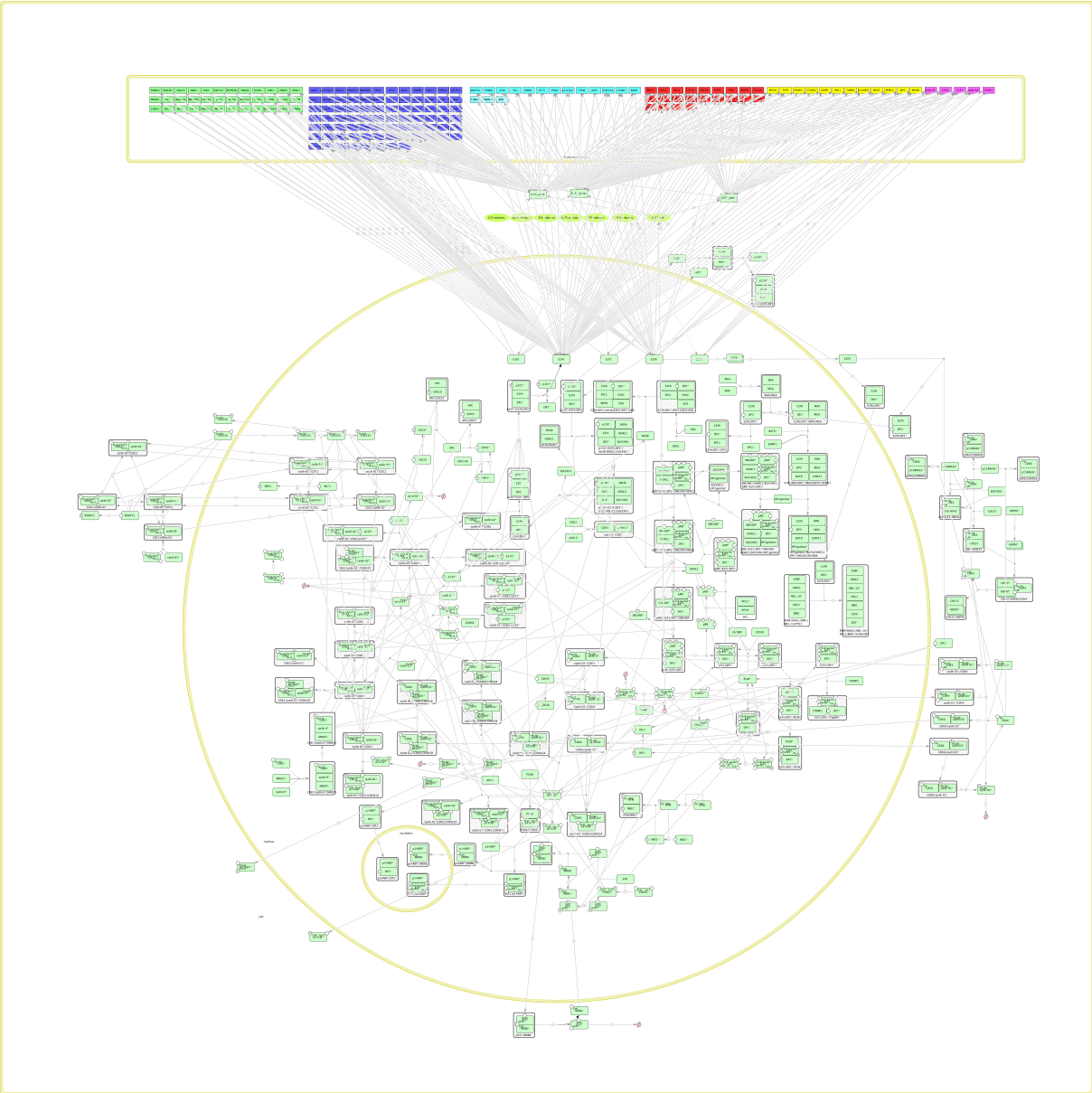


QUESTIONS??

2. BiNoM

Manipulating reaction maps

Example of a complex map: RB/E2F



What to do with such a complex map?

How to make sense out of the gathered information?

How to use this map to extract biological knowledge?

BiNoM (Biologial NetwOrk Manager) is a cytoscape* plugin.

BiNoM makes the link between the softwares.

It also:

- Facilitates the visualisation and manipulation of biological networks
- Supports standard systems biology formats (BioPAX, SBML, etc.)
- Assists the user in the analysis of networks
- Extracts specific information from databases such as Reactome
- …

* Cytoscape will be explained tomorrow in Loredana's course

Four tasks in BiNoM

1. Isolating modules from the map
2. Reducing the complexity of the map
3. Extracting a particular path from the map
4. Coloring the map

Tutorial

- Download Cytoscape from:

http://www.cytoscape.org/

- Download BiNoM from:

http://binom.curie.fr/

- Copy the jar file (BiNoM_all.jar) in the plugins folder of Cytoscape

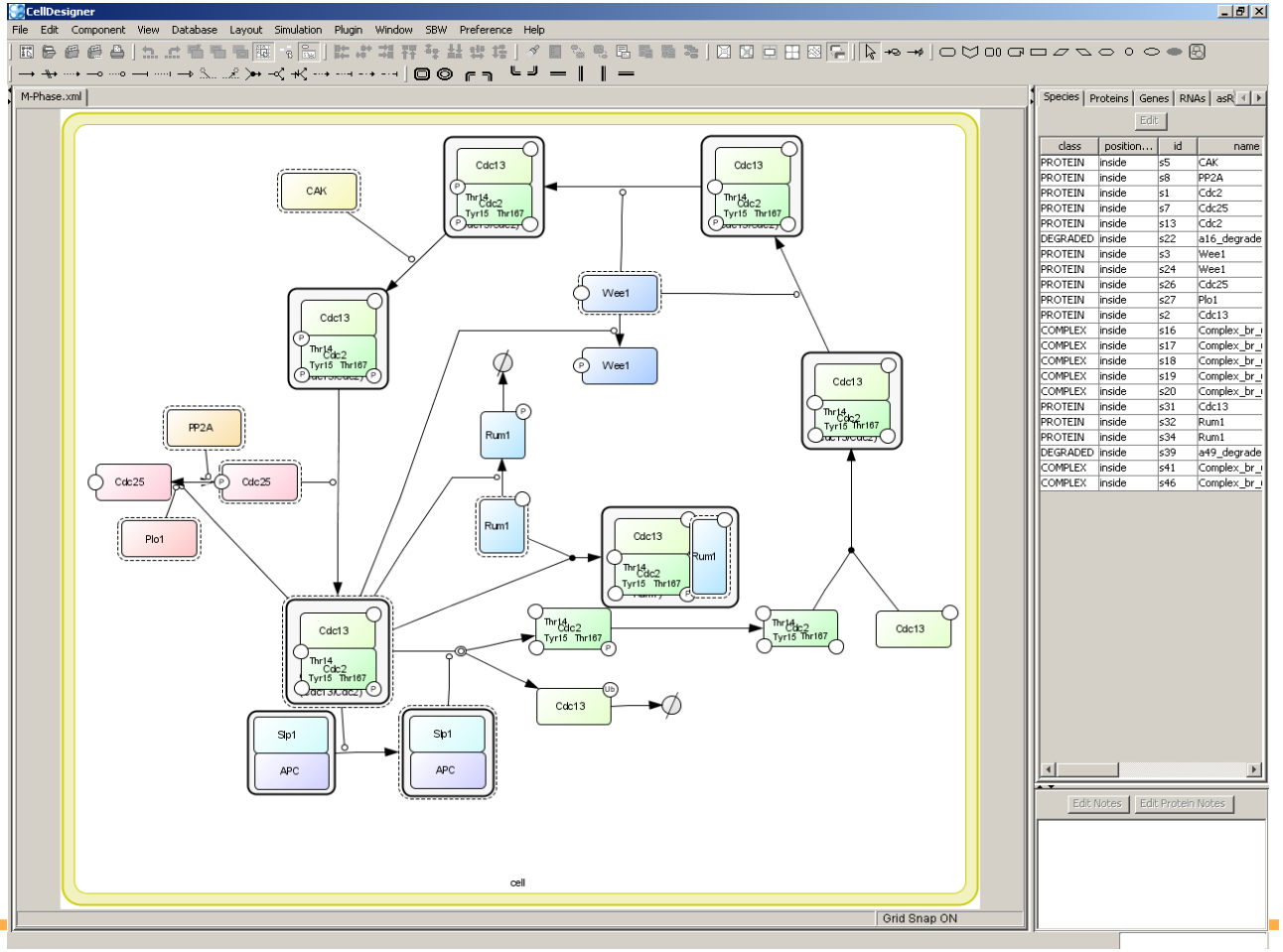
- Launch Cytoscape

Our toy example

CellDesigner file of M-Phase model

Simple example:

Model of MPF cell cycle in fission yeast – Novak *et al.*



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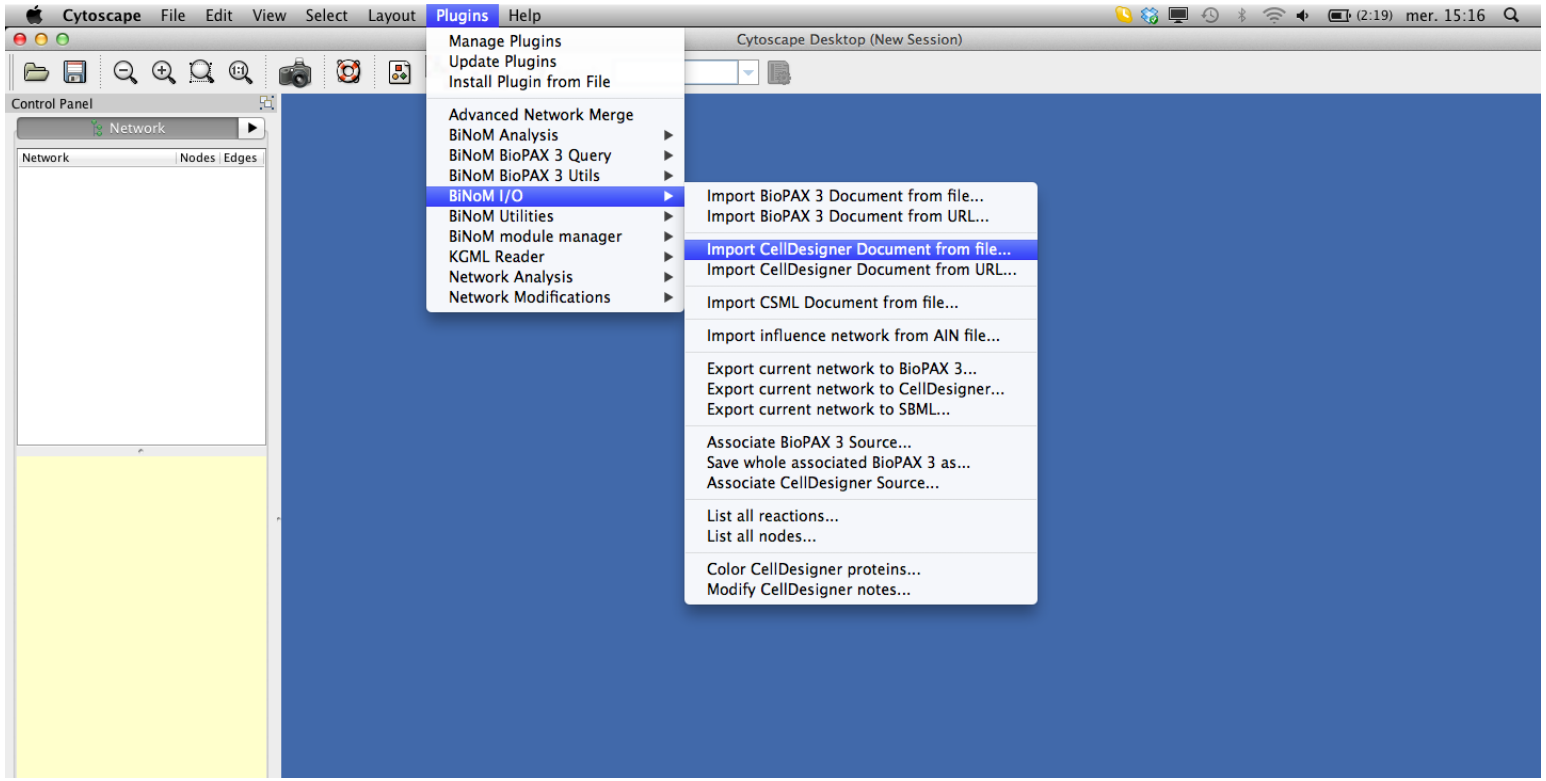
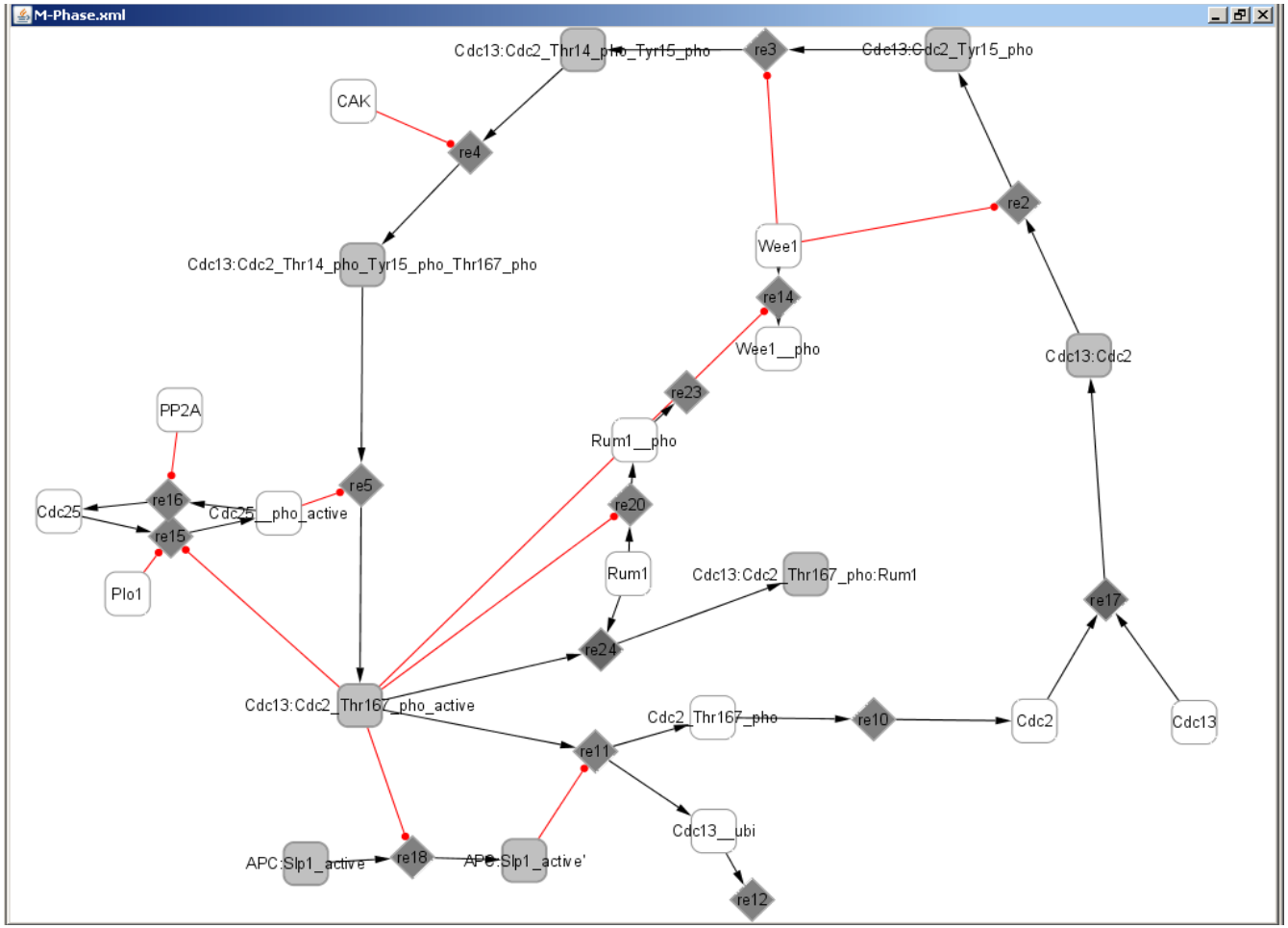
1. Import the toy example in Cytoscape

Plugins => BiNoM I/O => Import CellDesigner document from file



- Choose **M-Phase.xml** from BiNoM tutorial folder
- File imported : 36 nodes, 42 edges



Note: CellDesigner layout is conserved

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Problem:

Here the map is manageable because the network is simple enough that it can be read. But it is rare.

Imagine that the file is very big (e.g. RB/E2F map, Reactome pathways, etc.), not easy to read or to make any sense out of it…

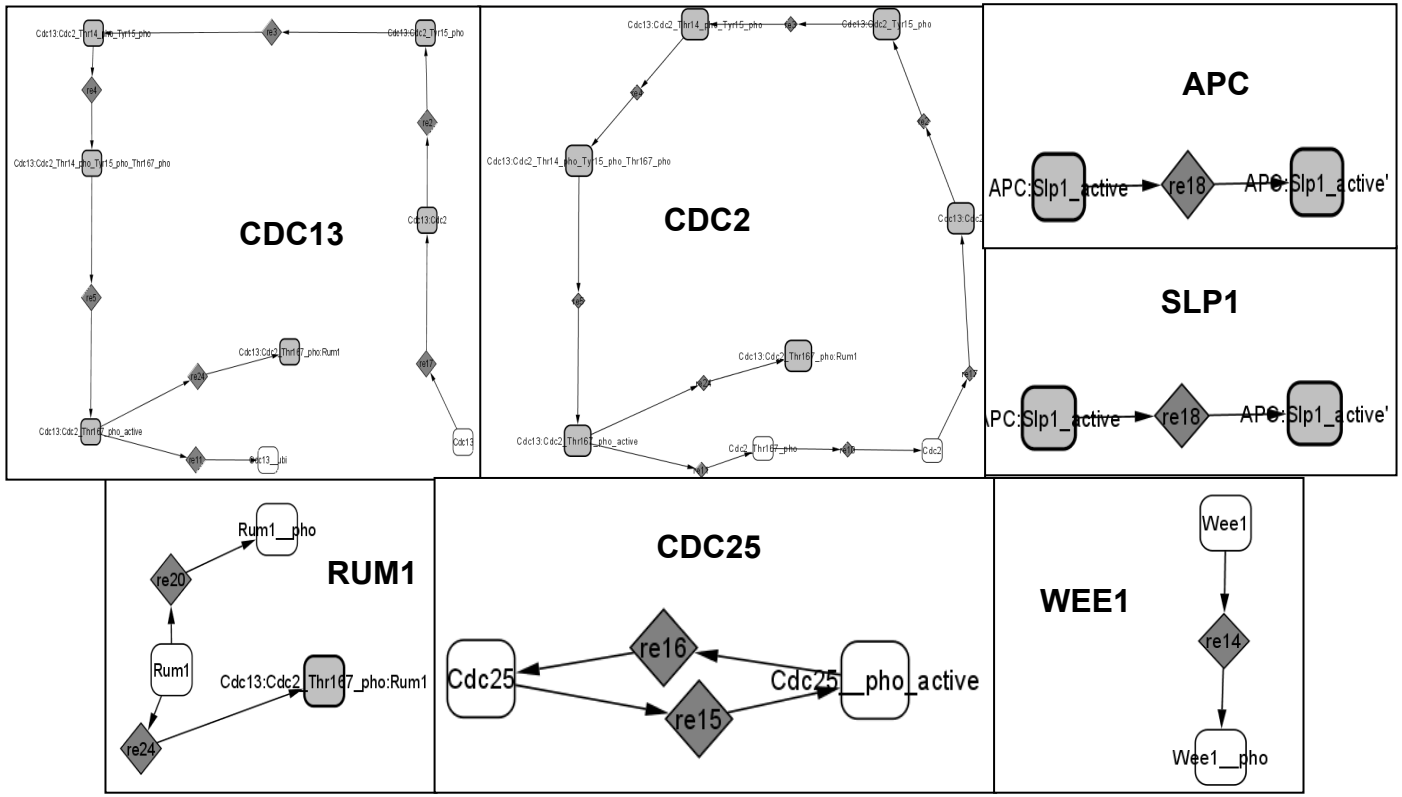
Solution:

Generate a modular version of the big map to navigate more intelligently in the complex map

1. Isolating modules from the map

Decompose the graph into species

Plugins => BiNoM 2.3 => BiNoM Analysis => Get material components



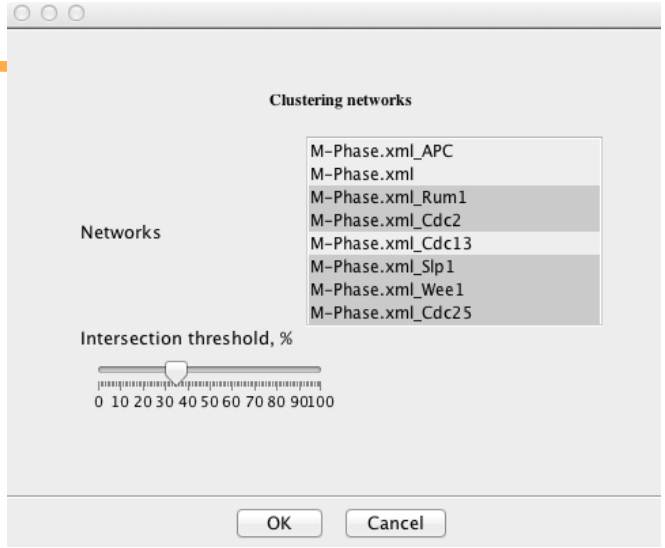
Note that:

1. Cdc13 is completely included in Cdc2. Choose only Cdc2
2. APC and SLP1 are identical. Choose only SLP1

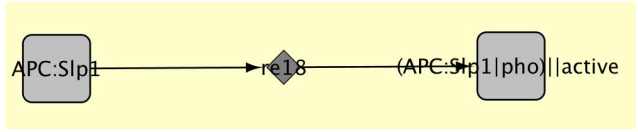
Cluster networks

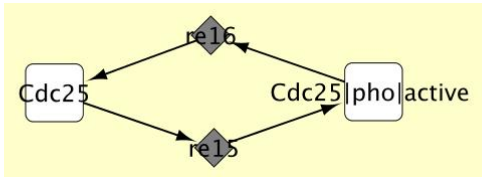
This step is necessary if the newtork is big.
Not necessary here, but let's try anyway.

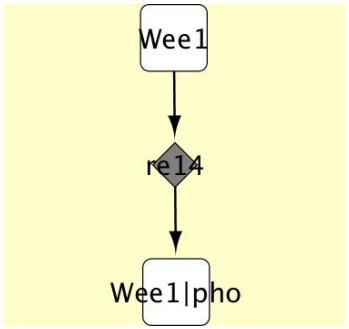
BiNoM 2.3 => BiNoM Analysis => Cluster networks
Choose 35% for instance
Select the modules to cluster: (hold ctrl)

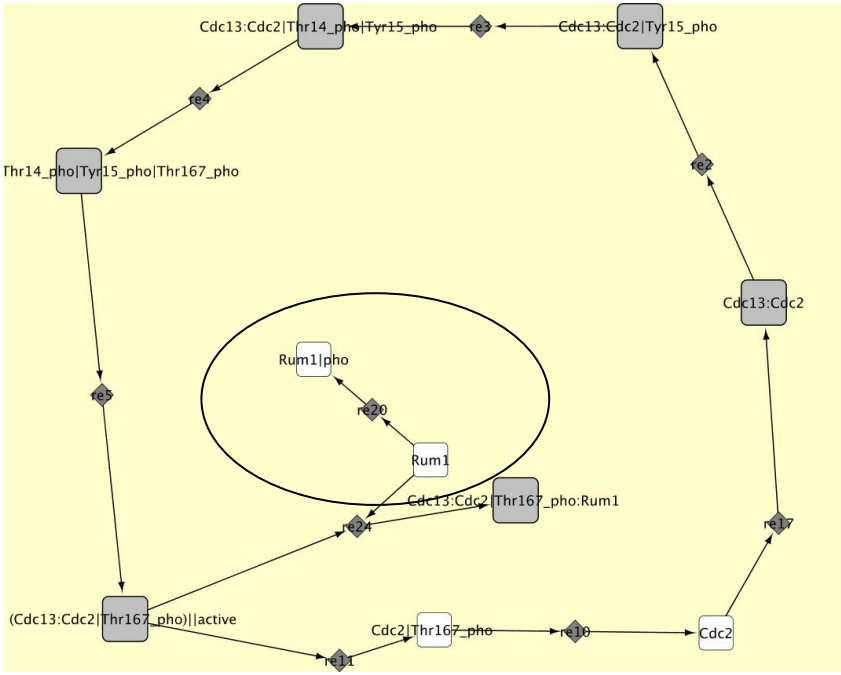


The clustering of our small network will lead to 4 modules, one of them including too many components…









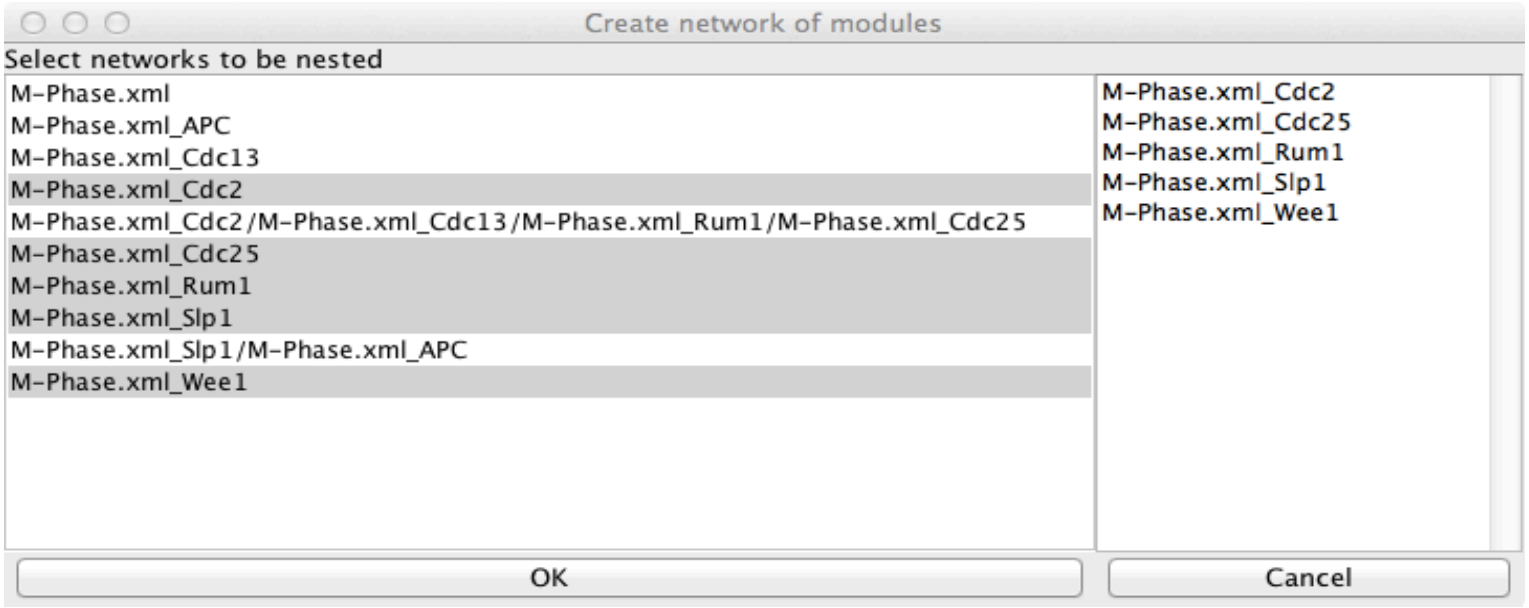
2. Reducing complexity of the map

Create modular view (1)

- Use the initial 5 sub-networks

BiNoM 2.3 => BiNoM module manager => create network of modules

In the pop-up window,
Choose the networks from the list.
Click OK



The network modular0 is created
(5 nodes, 0 edges)

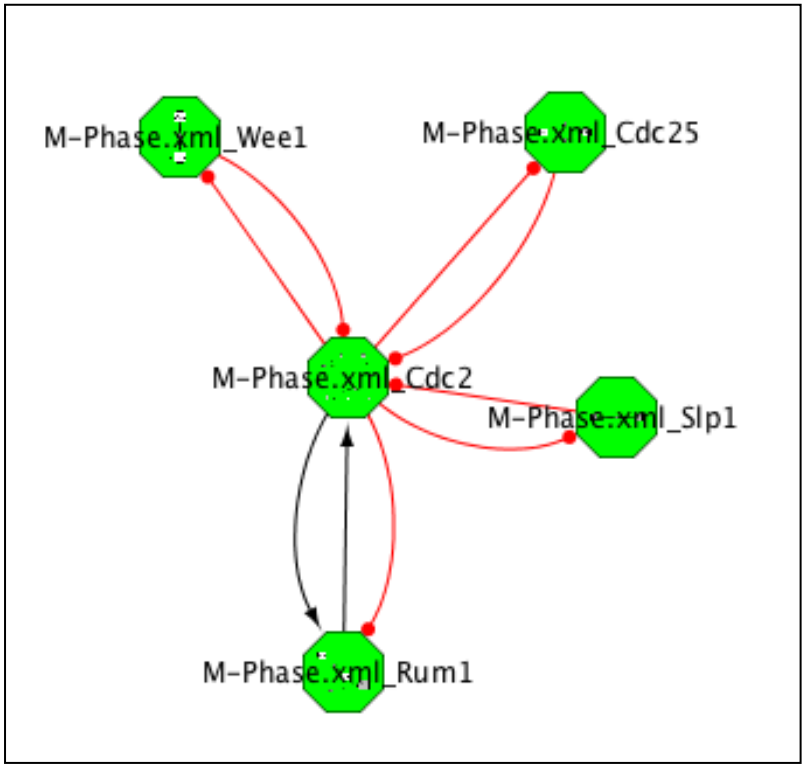
Create modular view (2)

BiNoM 2.3 => BiNoM module manager => create connections between modules

Select M-Phase.xml as a network of reference

Choose M-phase.xml as a network Reference

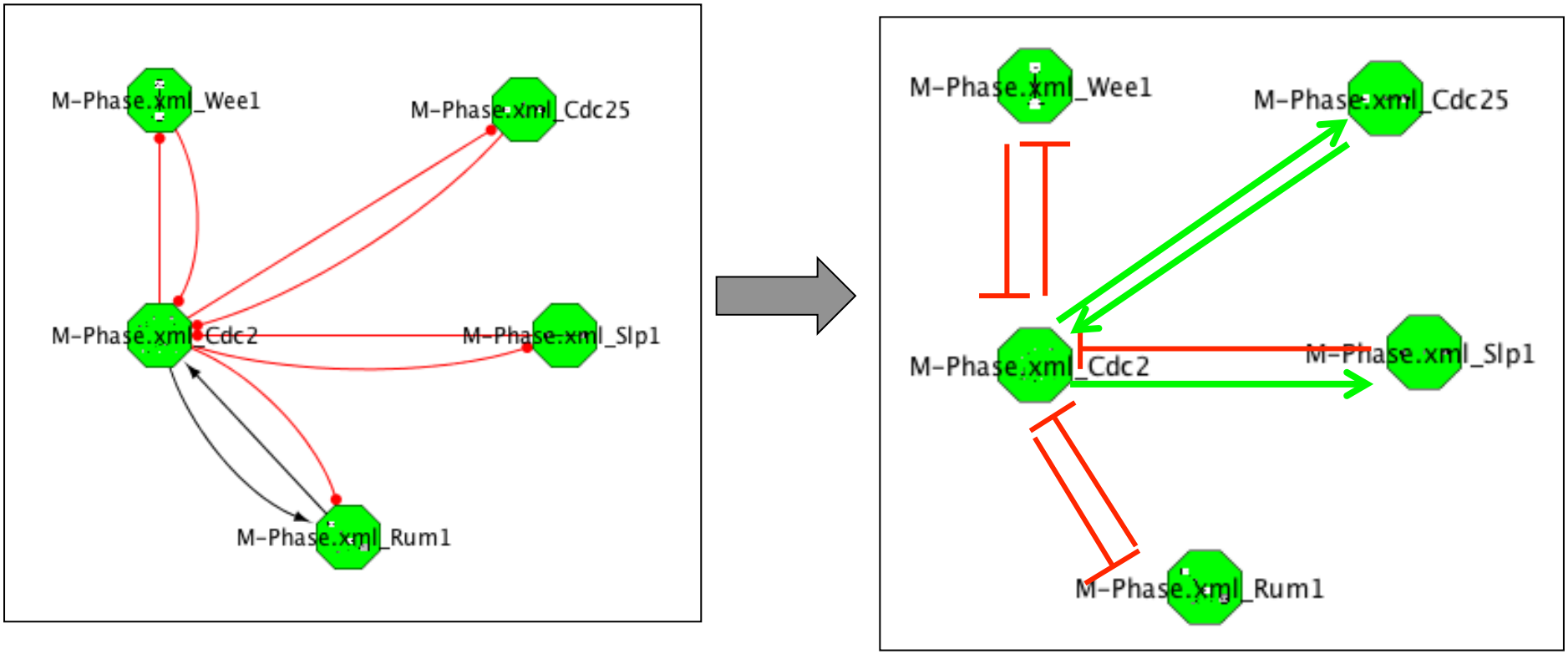
The arrows shows different types of interactions between the modules



Create modular view (3)

Interpret the arrows as influences

⇒ Manual modeller curation



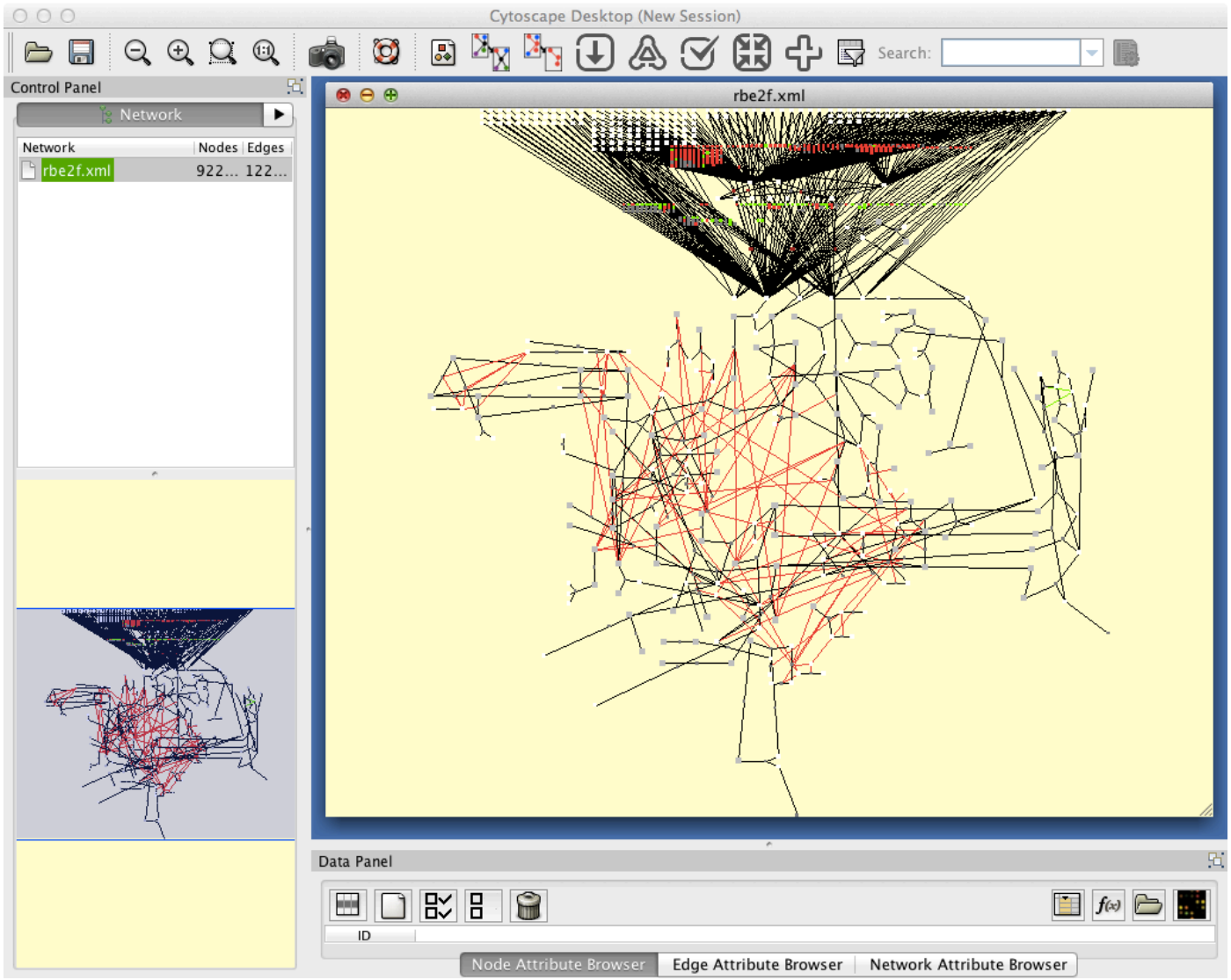
⇒ 3 positive feedback loops + 1 negative feedback loop

3. Extracting a particular path from the CellDesigner map

Import the RB/E2F network in Cytoscape

Plugins => BiNoM I/O => Import CellDesigner document from file

Choose rbe2f.xml



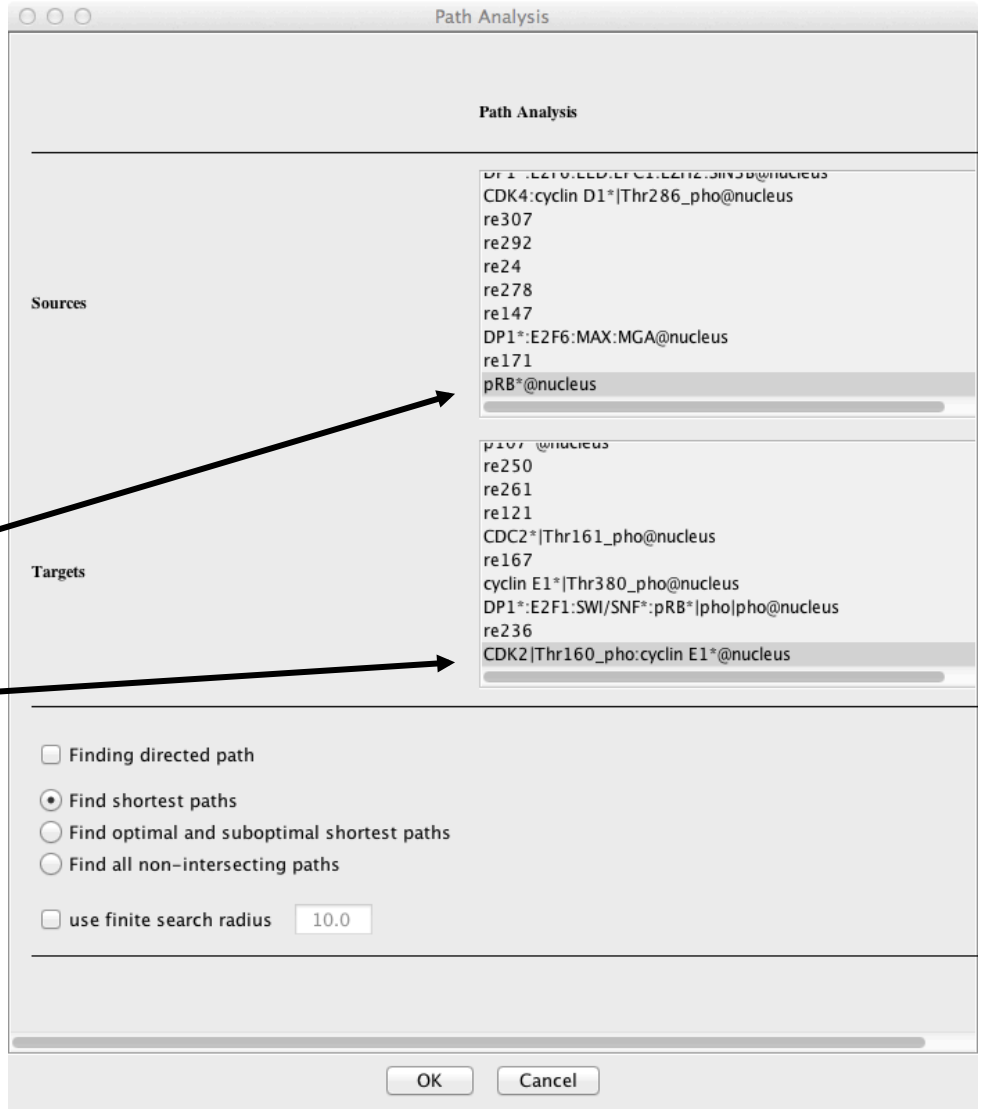
Path Analysis

1. Select with the mouse the whole (or part of) diagram (lower part here)

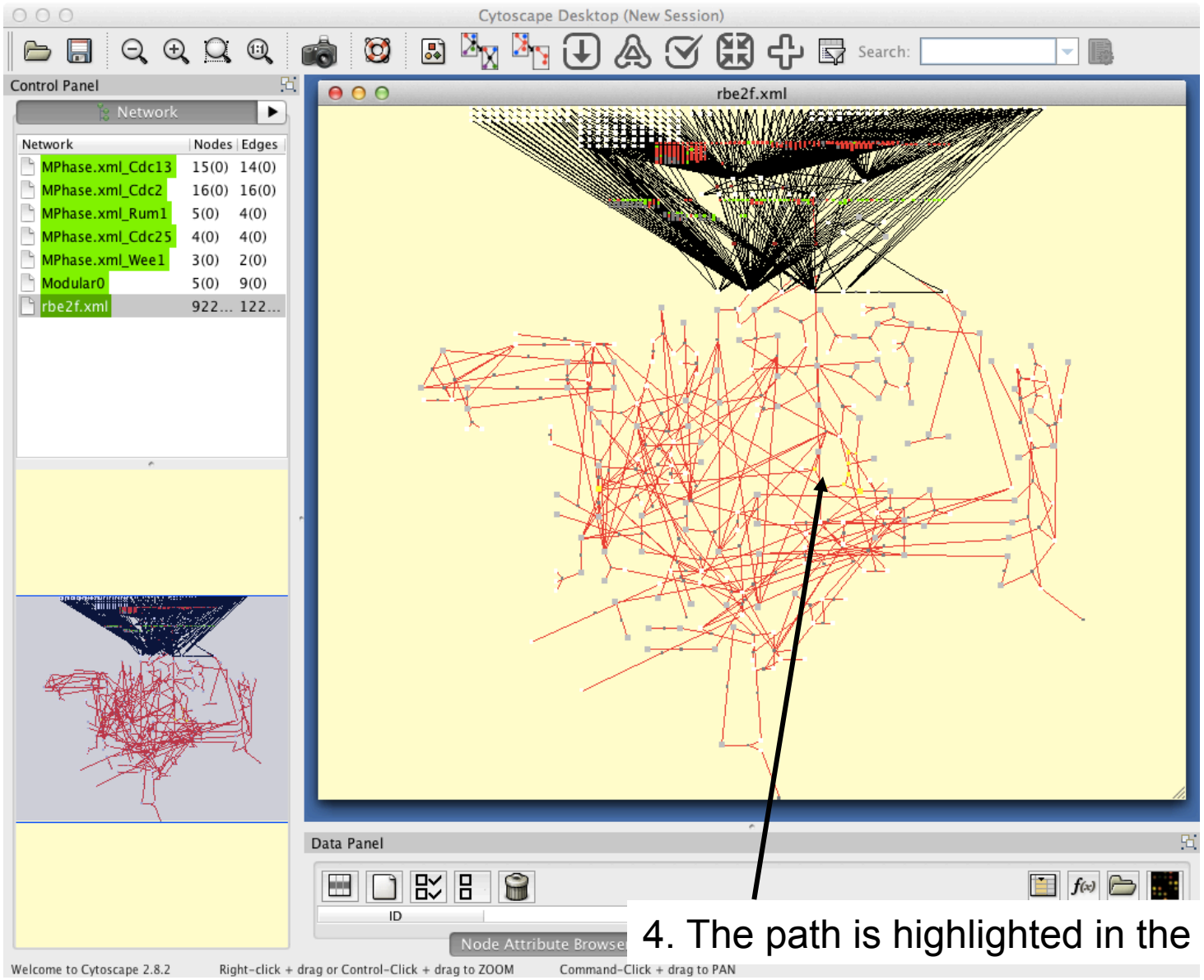
2. **BiNoM 2.3 => BiNoM Analysis => Path Analysis**
A window pops up

3. Choose the source: **pRB*@nucleus** and the target **CyclinB1@nucleus**
To look for your protein, type first letters holding shift

Choose appropriate options



Path Analysis



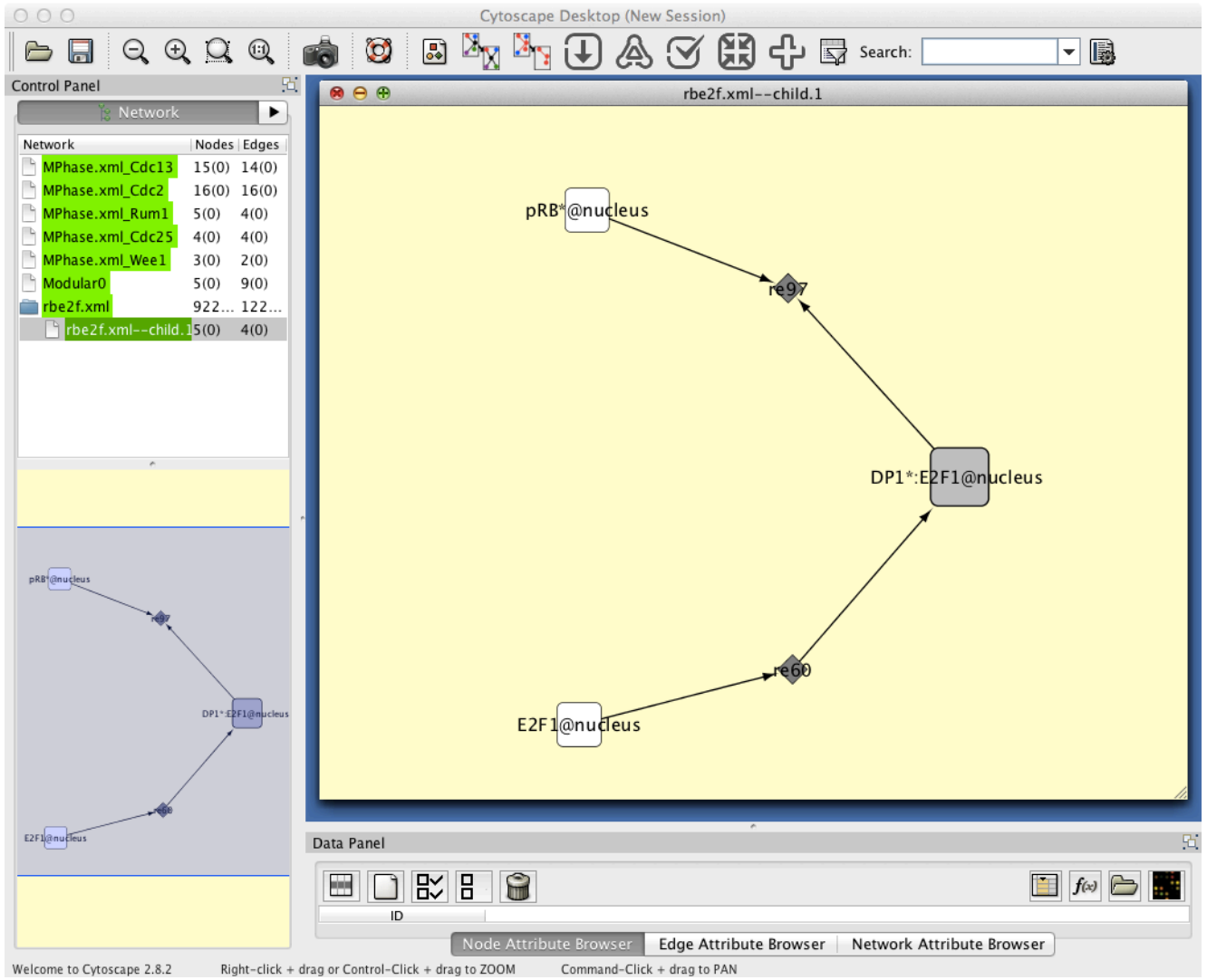
4. The path is highlighted in the network

Path Analysis

5. The path can be extracted and analyzed independently

File => New => Network => From selected nodes, all edges

If you don't like the layout, in the control panel and in the VizMapper tab, choose « Current Visual Style » and select « BiNoM BioPAX »



4. Coloring the map

Scenario for coloring M-Phase

NODE_NAME	CONCENTRATION
(APC':Slp1')||active'	0.894653733
(APC:Slp1)||active	0.886353044
Cdc13:Cdc2|Thr167_pho:Rum1	0.692614632
Rum1|pho	0.823097632
Rum1	0.729486548
Cdc13|ubi	0.258665898
(Cdc13:Cdc2|Thr167_pho)||active	0.518069104
Cdc13:Cdc2|Thr14_pho|Tyr15_pho|Thr167_pho	0.726050301
Cdc13:Cdc2|Thr14_pho|Tyr15_pho	0.542243421
Cdc13:Cdc2|Tyr15_pho	0.088092727
Cdc13:Cdc2	0.468943614
Cdc13	0.518863385
Plo1	0.886928403
Cdc25|pho|active	0.415825048
Wee1|pho	0.230049232
Wee1	0.646378149
Cdc2|Thr167_pho	0.824925337
Cdc25	0.128518345
M-Phase	0.882425015
Lamin|pho	0.01876147
Lamin|hm8	0.449188649
Cdc2	0.791098517
PP2A	0.047933604
CAK	0.427374819

1. Import CellDesigner M-Phase.xml file

2. Import text file with (hypothetical random assigned values) concentration value for each species
   File => Import => Attribute from Table (Text/Excel, …)

3. Select the input file M-Phase-expression.txt

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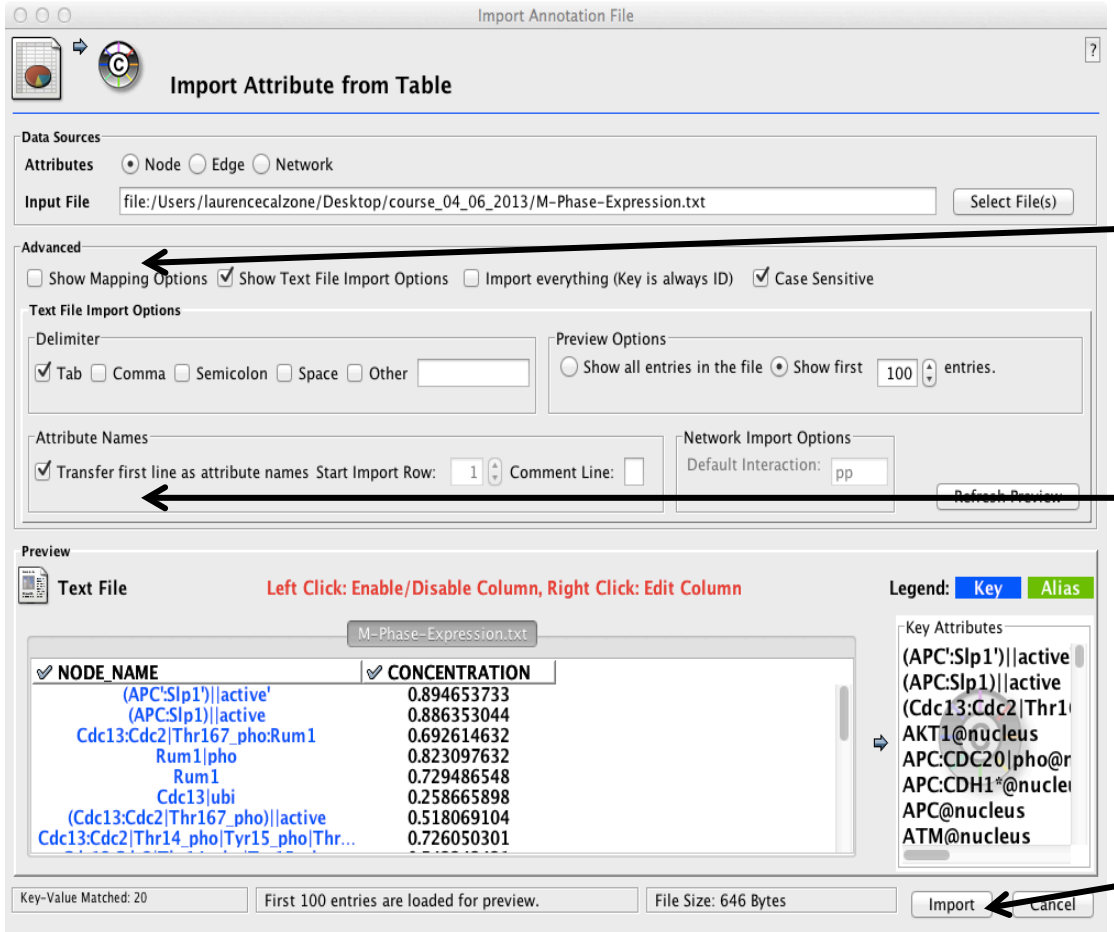

4. In the ‘Advanced’ box, click on ‘Show text file import options’

5. In the ‘Attributes’ box, click on ‘Transfer first line as attribute name (here: ‘Node_name’ and ‘concentration’)

6. Click on ‘Import’

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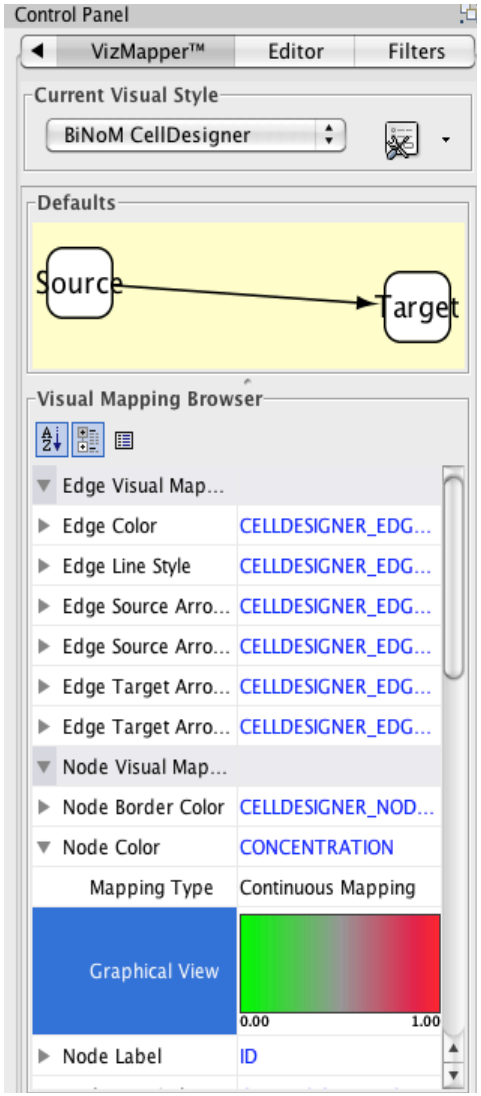
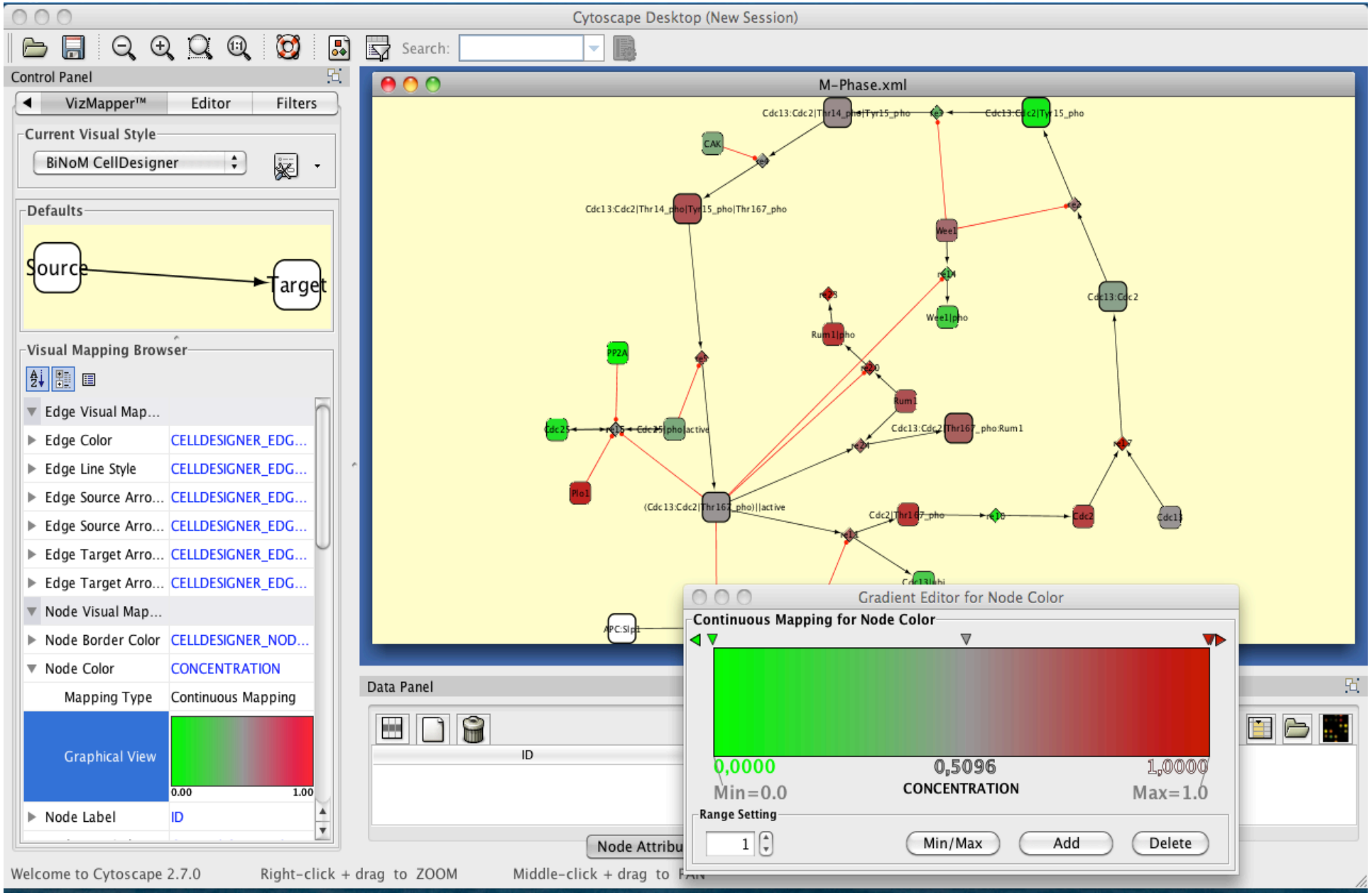
In the Vizmapper:

7. Change ‘CellDesigner node’ to ‘Concentration’

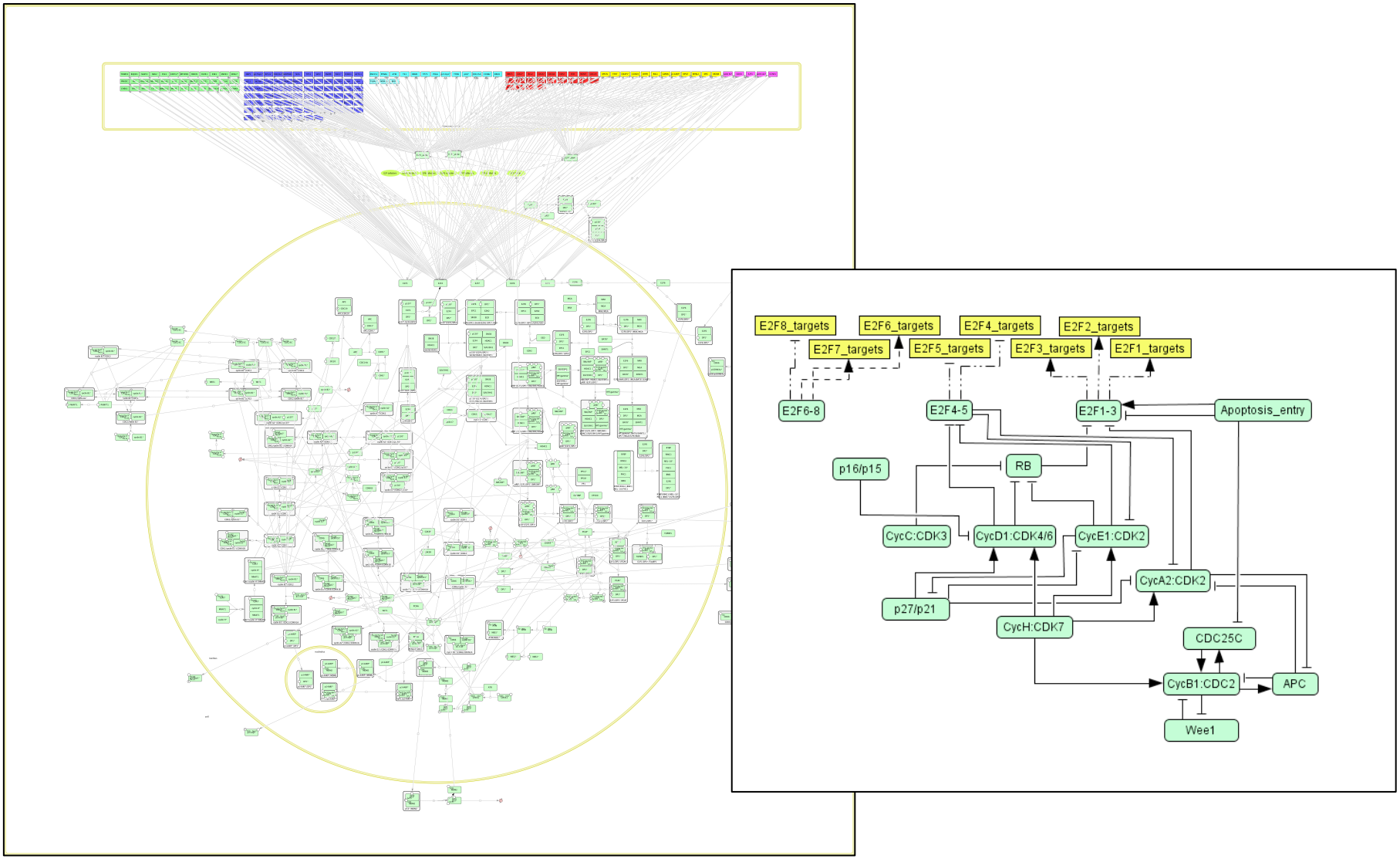
8. Modify the node color
   In Mapping type, change discrete mapper to continuous mapper (if it does not work choose first passthrough mapper then continuous mapper => this is a bug)

9. Choose the color corresponding to the max and the min value by double clicking on the arrow above the max and the min



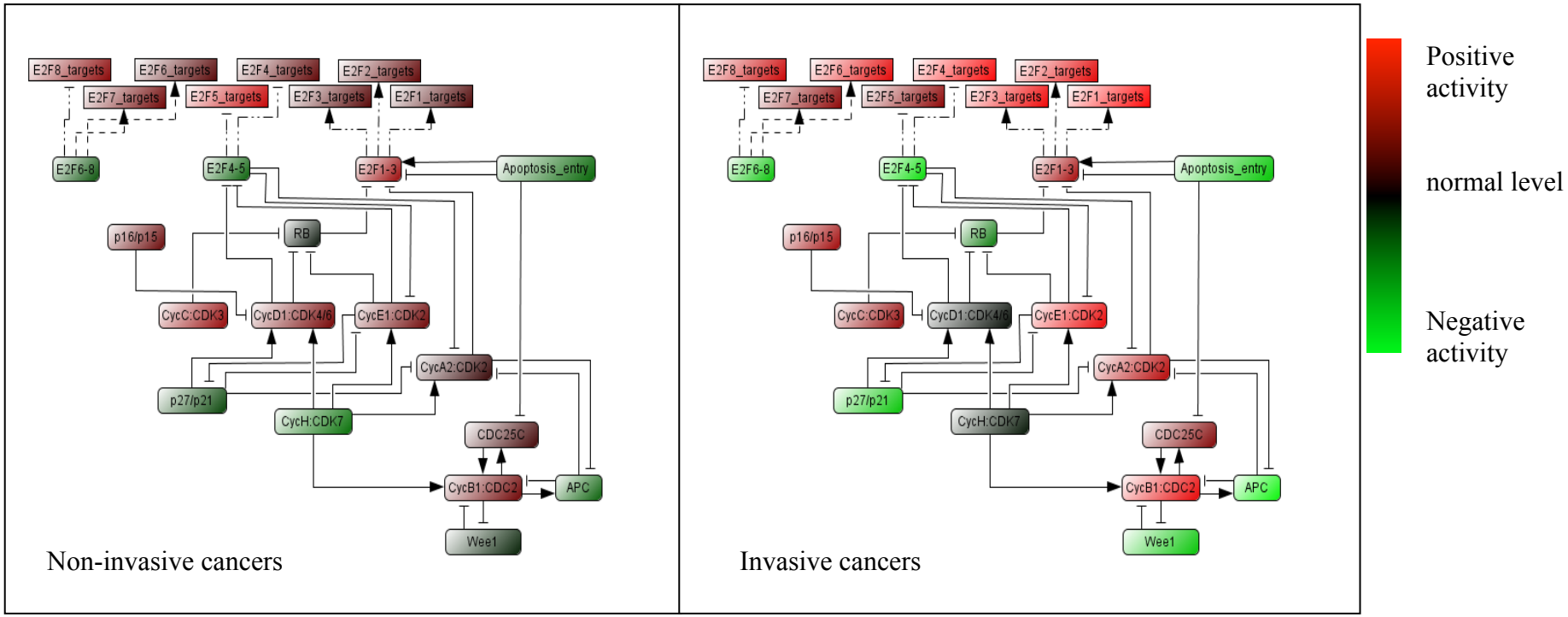

Cytoscape Desktop (New Session)
Search:
Control Panel
VizMapper™
Editor
Filters
Current Visual Style
BiNoM CellDesigner
Defaults
Source
Target
Visual Mapping Browser
Edge Visual Map...
Edge Color
CELLDESIGNER_EDG...
Edge Line Style
CELLDESIGNER_EDG...
Edge Source Arro...
CELLDESIGNER_EDG...
Edge Source Arro...
CELLDESIGNER_EDG...
Edge Target Arro...
CELLDESIGNER_EDG...
Edge Target Arro...
CELLDESIGNER_EDG...
Node Visual Map...
Node Border Color
CELLDESIGNER_NOD...
Node Color
CONCENTRATION
Mapping Type
Continuous Mapping
Graphical View
0.00
1.00
Node Label
ID
M-Phase.xml
Cdc13:Cdc2|Thr14_pho|Tyr15_pho|Thr167_pho
CAK
Wee1
Wee1|pho
Rum1|pho
PP2A
Cdc25
Cdc25|pho|active
Rum1
Cdc13:Cdc2|Thr167_pho:Rum1
Plo1
(Cdc13:Cdc2|Thr167_pho)||active
Cdc2|Thr167_pho
Cdc2
Cdc13:Cdc2
APC:Slp1
Data Panel
ID
Node Attribu
Gradient Editor for Node Color
Continuous Mapping for Node Color
0,0000
Min=0.0
0,5096
CONCENTRATION
1,0000
Max=1.0
Range Setting
1
Min/Max
Add
Delete
Welcome to Cytoscape 2.7.0
Right-click + drag to ZOOM
Middle-click + drag to

Coloring RB/E2F map



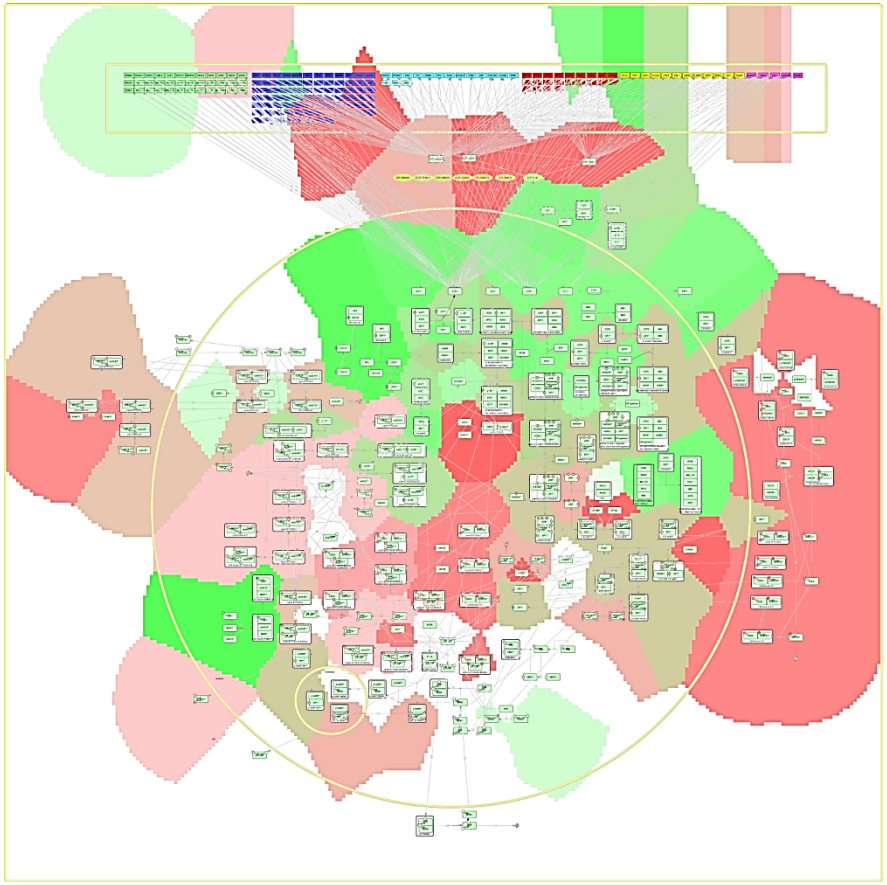
Example of bladder tumour data: invasive vs. non-invasive samples

The activity of a module is a weighted sum of expression of genes composing the module (positive vs. negative activities are compared to normal samples)

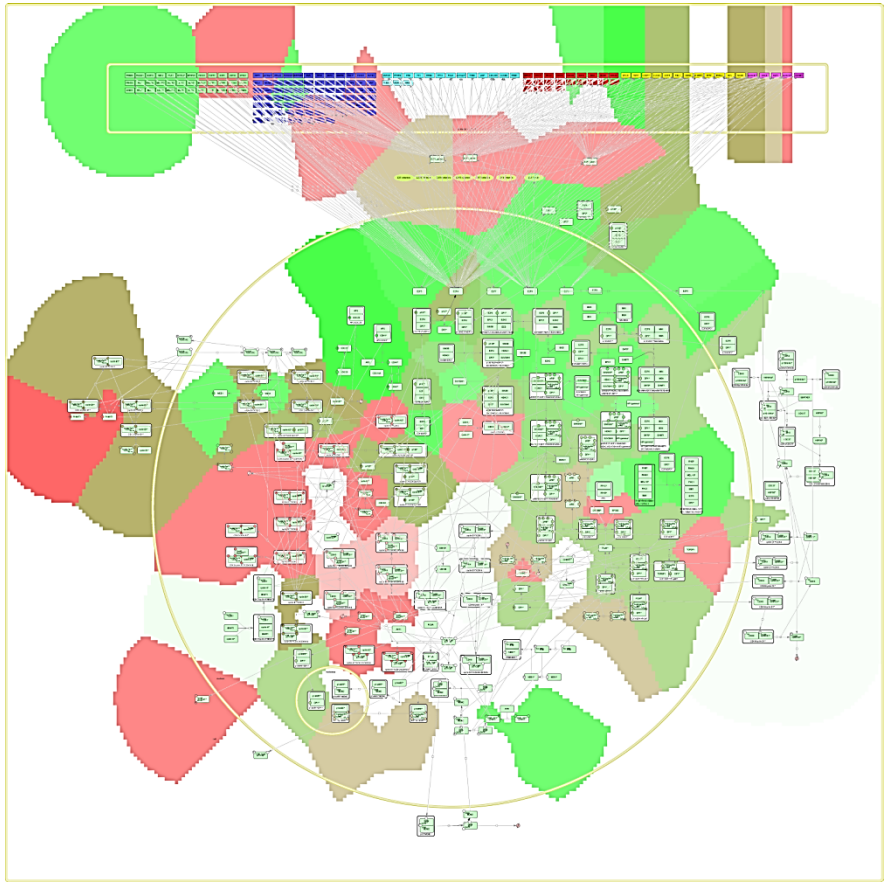


RB/E2F map colour staining

non-invasive



invasive



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3. NaviCell

Navigating through reaction maps

http://navicell.curie.fr

NaviCell

Navigation, curation and maintenance of molecular interactions maps

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What is NaviCell?

A web tool for exploring large maps of molecular interactions created by the group of Computational Systems Biology of Cancer at Institut Curie.

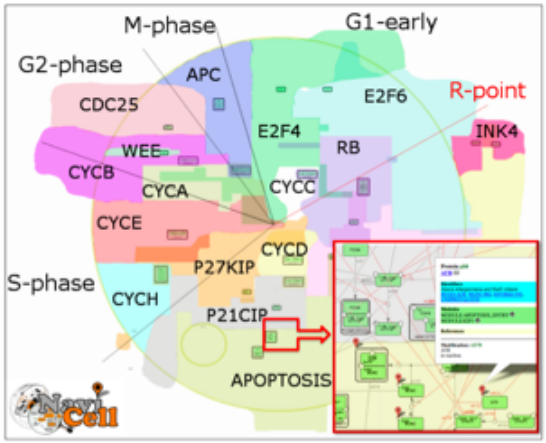
Why NaviCell is unique?

Combination of three essential features:

Map browsing by Google map™ engine
Semantic zoom for viewing different levels of details on the map
Web blog for collecting community feedback

ACCESS TO COLLECTION OF MAPS AVAILABLE AT NAVICELL

Browsers: Firefox, Safari, Chrome and IE8



Existing maps

Collection of Maps

Institut Curie Collection

Cell Cycle (RB-E2F) molecular interaction map

Cross-talk Notch/p53

DNA Repair

Cell Survival

EMT and Cell Motility

MapK pathway

External Collection

mTOR signalling network

Toll-like receptor signalling network

EGFR signalling network

Dendritic cells signalling network

Signaling pathways of Alzheimer's disease

Sample examples

MPhase map from CellDesigner sample set

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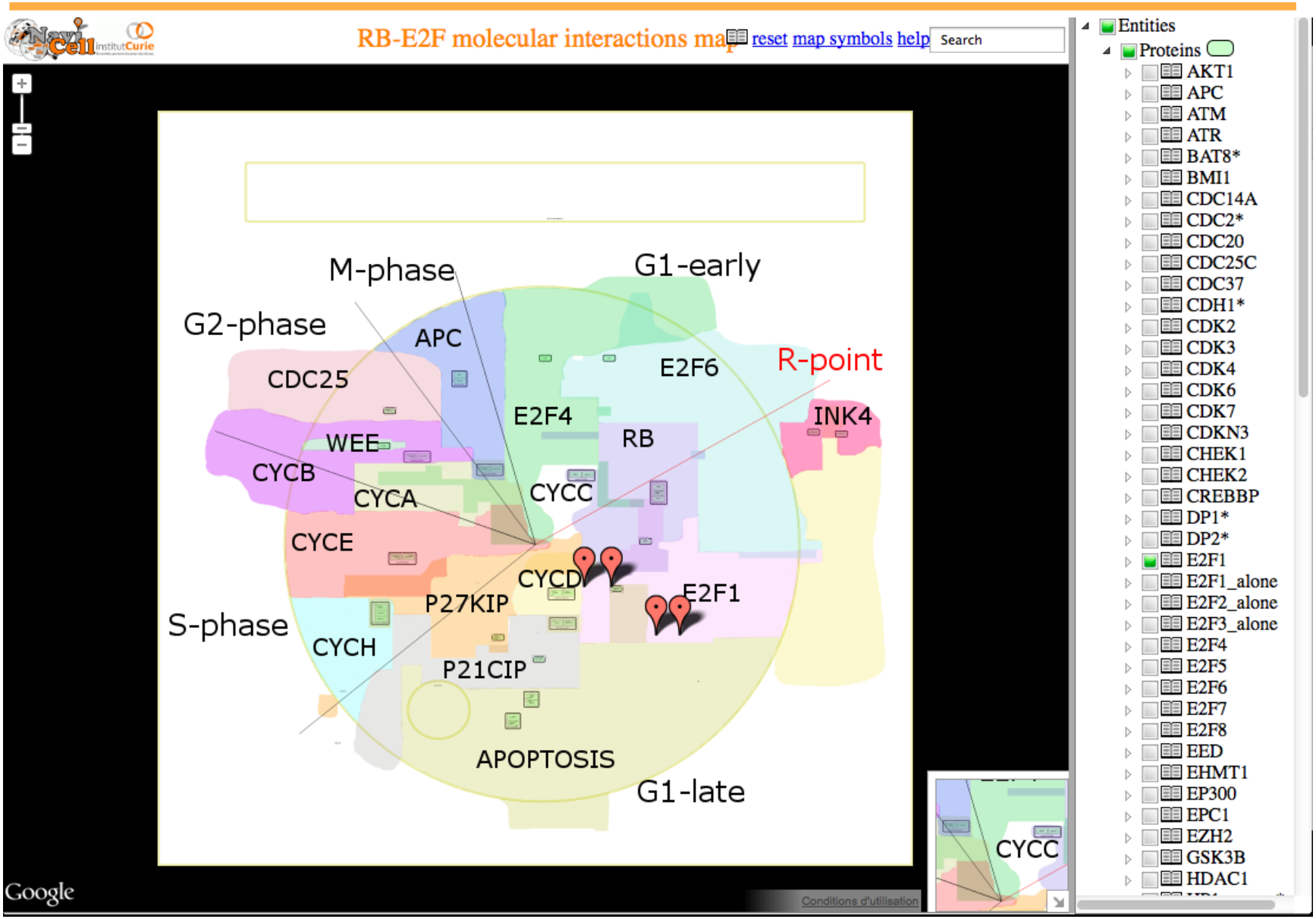
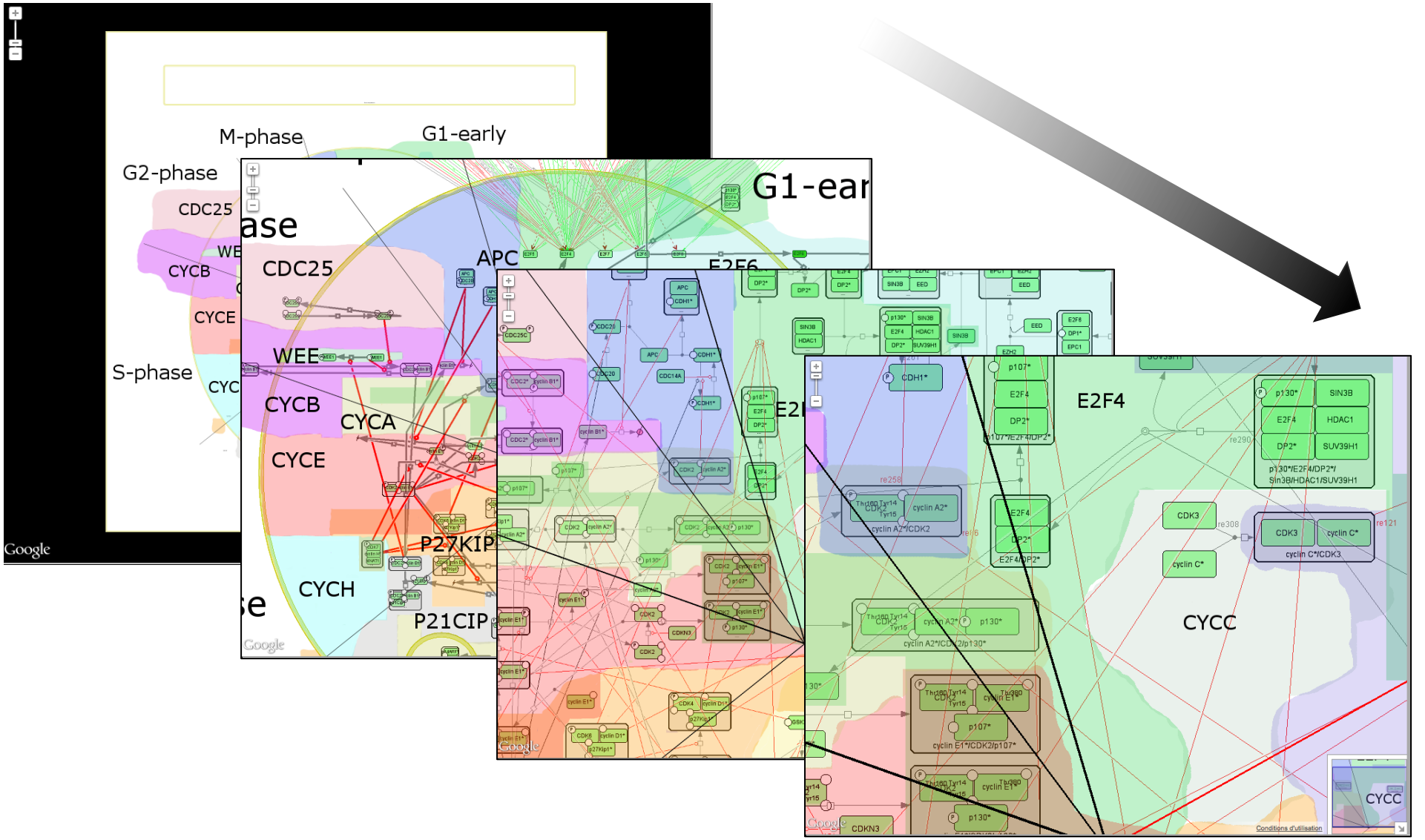
RB/E2F map


RB-E2F molecular interactions map
reset
map symbols
help
Search
M-phase
G1-early
G2-phase
APC
CDC25
E2F6
R-point
E2F4
INK4
RB
WEE
CYCB
CYCA
CYCC
CYCE
CYCD
E2F1
P27KIP
S-phase
CYCH
P21CIP
APOPTOSIS
G1-late
Entities
Proteins
AKT1
APC
ATM
ATR
BAT8*
BMI1
CDC14A
CDC2*
CDC20
CDC25C
CDC37
CDH1*
CDK2
CDK3
CDK4
CDK6
CDK7
CDKN3
CHEK1
CHEK2
CREBBP
DP1*
DP2*
E2F1
E2F1_alone
E2F2_alone
E2F3_alone
E2F4
E2F5
E2F6
E2F7
E2F8
EED
EHMT1
EP300
EPC1
EZH2
GSK3B
HDAC1
CYCC
Google
Conditions d'utilisation

Semantic zoom: Four levels of details



Navigating through a map

1. Choose RB/E2F map
2. Click on Proteins in Entities on the right panel
3. Choose E2F1, de-select the other proteins
4. Click on 
5. Choose a link in the **Identifiers** box (HUGO, ENTREZ, …)
6. Choose a link in the **Modules** box