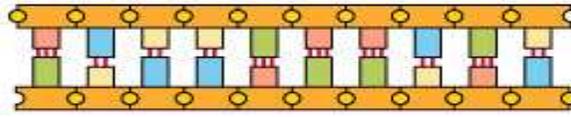

Tools for describing biological processes

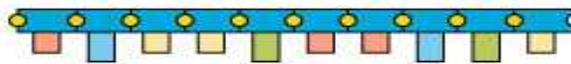
CellDesigner
BiNoM
NaviCell

Laurence Calzone
June 4th

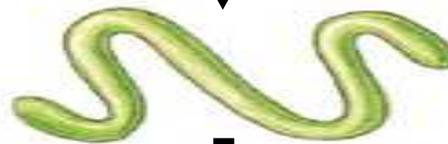
DNA



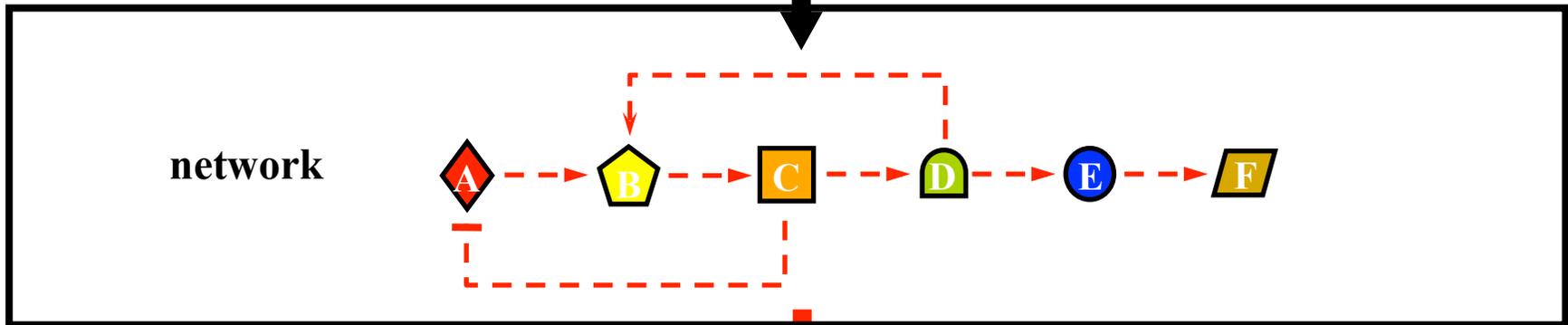
mRNA



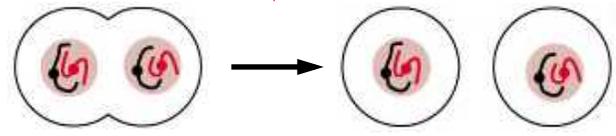
polypeptide



protein activity



physiology



Motivation: Establish a link between physiology and molecular interactions

Physiology of the cell

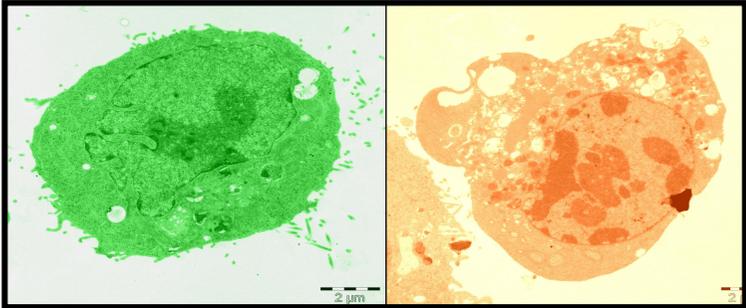
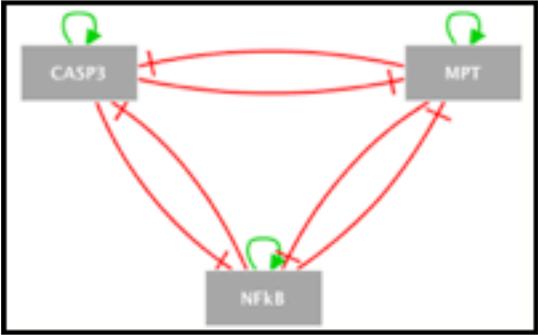
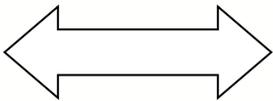
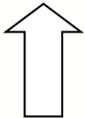
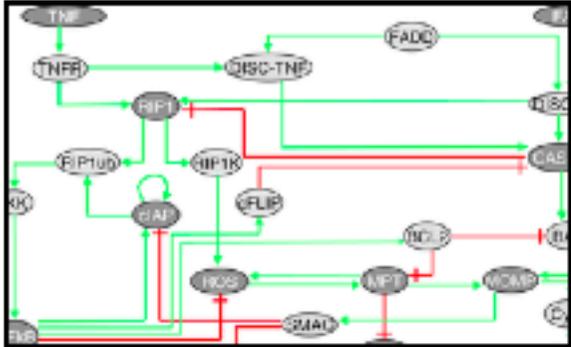
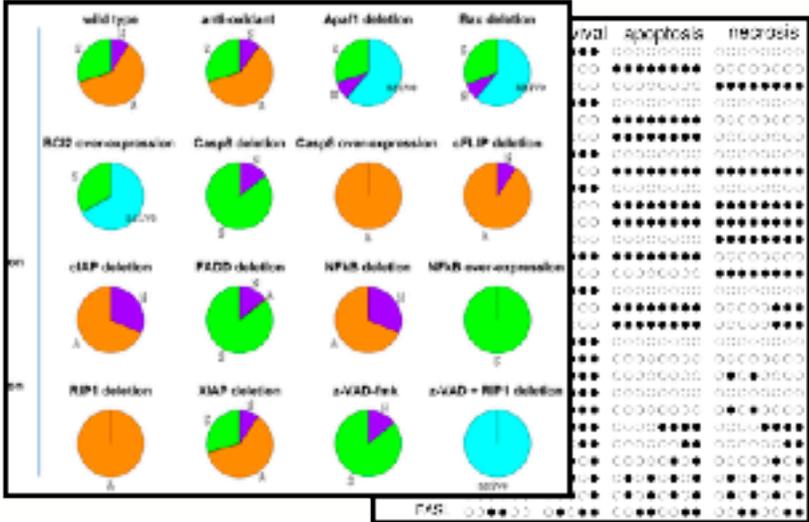


Diagram of protein interactions



Formulation of predictions
Experimental validation

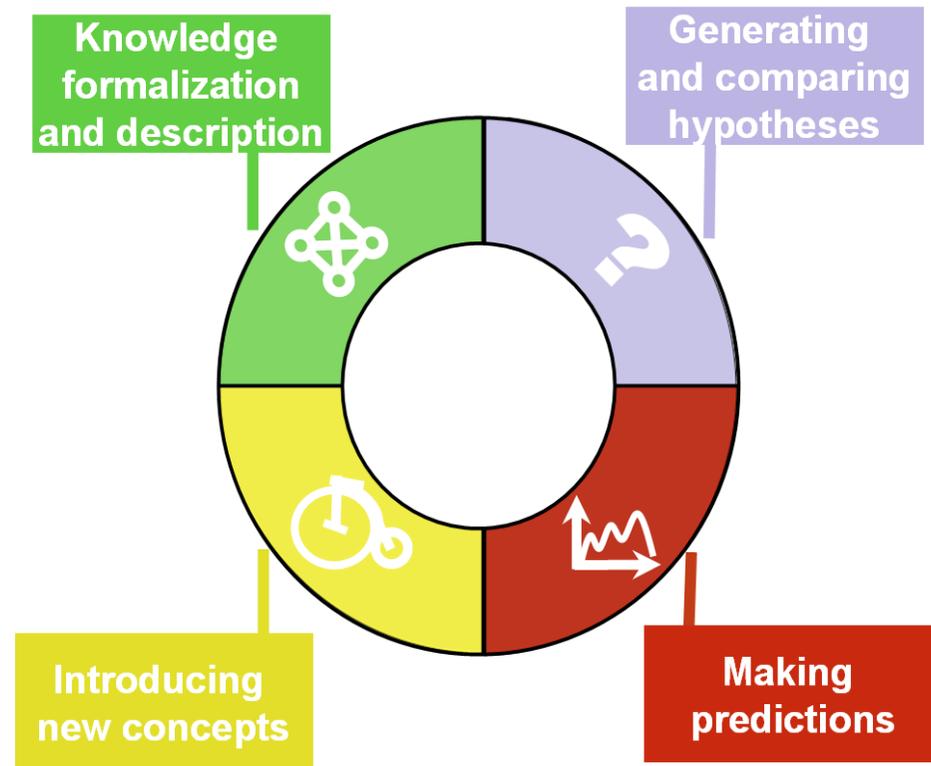


Translation in mathematical terms
Formal verification of what is known

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

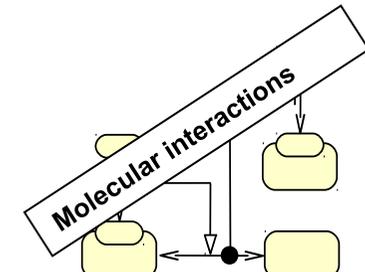
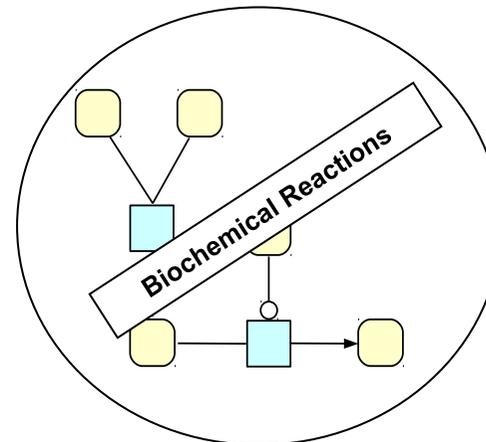
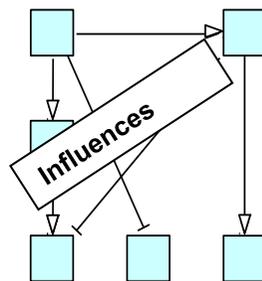
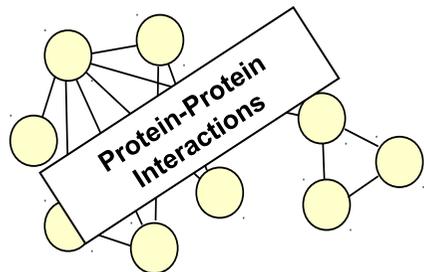
Construction of maps

- Select a biological process to describe
- Gather information

The collage includes the following text elements:

- NCBI PubMed logo
- Cell Death and Differentiation (2007) 14, 400-410
- Mathematical modeling reveals threshold mechanism in CD95-induced apoptosis
- M. Bentele,¹ I. Lavrik,² M. ...
- Modeling suppression of cell death by Bcl-2 over-expression in myeloma NS0 6A1 cells
- Kim C. O'Connor · James W. Muhitch · Daniel J. Lacks · Mohamed Al-Rubeai
- Identifying mechanisms for bistability in an apoptosis network
- M Chaves, T Eissing & F Allgöwer
- Institute for Systems Theory and Automatic Control, University of Stuttgart, Pfaffenwaldring 9, 70550 Stuttgart, Germany
- each other and these stress-in...
- RIP1-containing complexes are formed; these initiate only a limited number of cellular responses. In this review, we describe how RIP1 acts as a key integrator of signalling pathways initiated by stimulation of death receptors, bacterial or viral infection, genotoxic stress and T-cell homeostasis.
- Cell Death and Differentiation (2007) 14, 400-410. doi:10.1038/sj.cdd.4402085
- within the death-

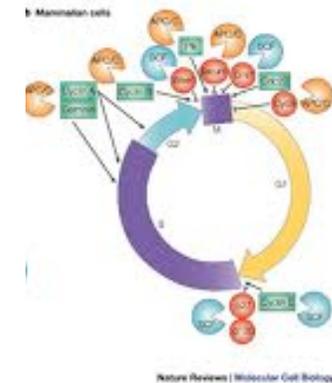
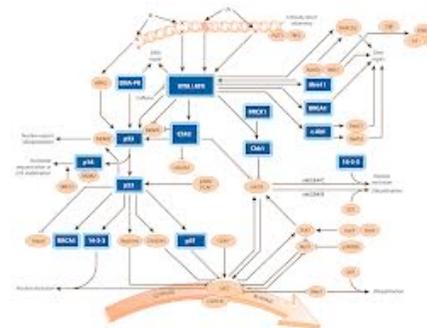
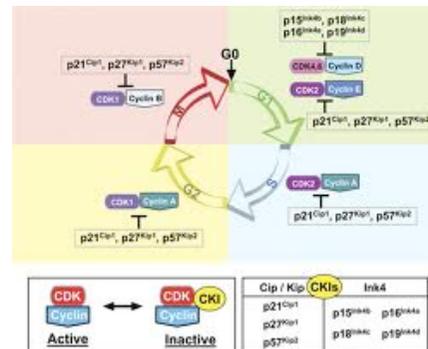
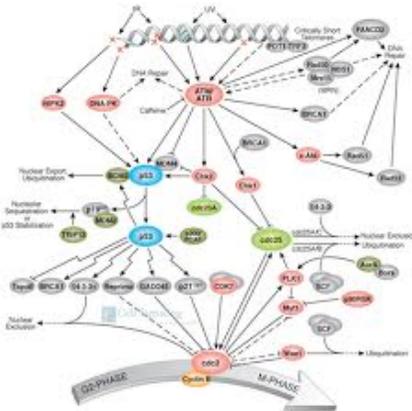
- Organize the information as the most appropriate type of diagrams



Tomorrow with
Loredana's course

The need for tools

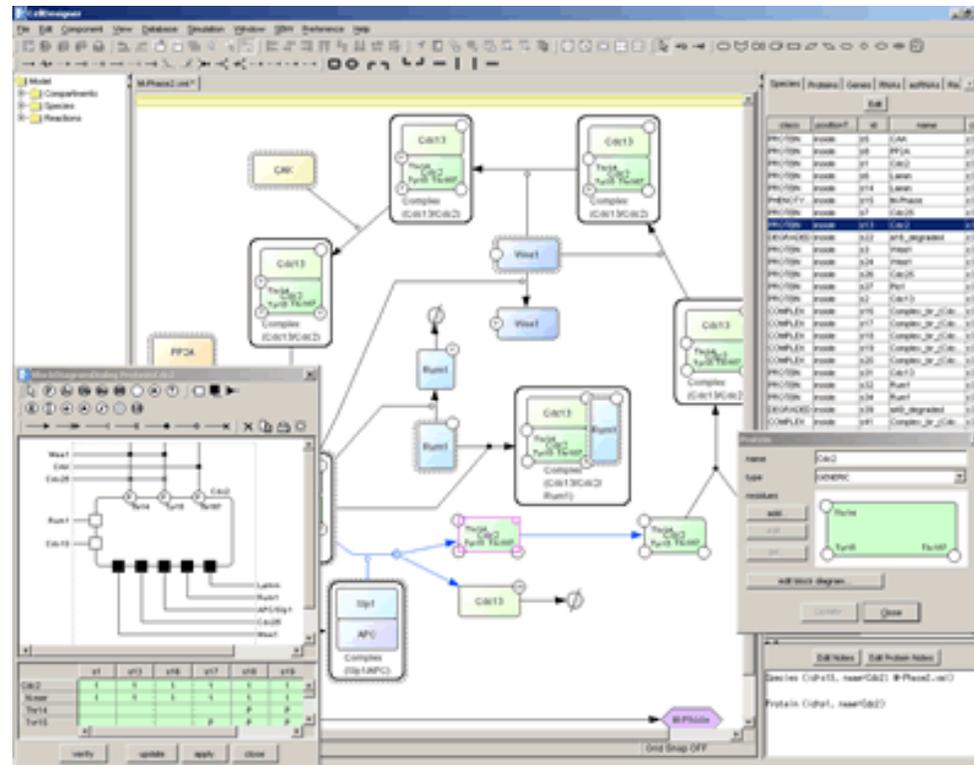
The same process can be represented in many different ways



- 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.

What is CellDesigner?

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



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:



CellDesigner screen

CellDesigner

File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help

M-Phase.xml *

Model

- Compartment
- Species
 - CyclinB (id = s3)
 - PP2A (id = s5)
 - Kinase X (id = s6)
 - CAK (id = s7)
 - Nim1 (id = s10)
 - Lamin (id = s11)
 - M-Phase (id = s12)
 - Lamin (id = s21)
 - Cdc25 (id = s4)
 - Mk1 (id = s8)
 - Wee1 (id = s9)
 - Cdc25 (id = s22)
 - Wee1 (id = s24)
 - Mk1 (id = s25)
 - a33_degraded (id = s26)
 - Cdc2 (id = s2)
 - Complex(CyclinB,Cdc2)
 - Complex(CyclinB,Cdc2)
 - Complex(CyclinB,Cdc2)
 - Complex(CyclinB,Cdc2)
- Reactions

Layer

- Layer0001
- base

Species Proteins Genes RNAs asRNAs Reactions Compartments Parameters Functions Units Rules Events

class	positio...	id	name	compa...	quanti...	ini...	subs...	spat...	ha...	b.c.	...	co...
PROTEIN	inside	s3	CyclinB	c1	Amount	0.0			false	false	0	false
PROTEIN	inside	s5	PP2A	c1	Amount	0.0			false	false	0	false
PROTEIN	inside	s6	Kinase X	c1	Amount	0.0			false	false	0	false
PROTEIN	inside	s7	CAK	c1	Amount	0.0			false	false	0	false
PROTEIN	inside	s10	Nim1	c1	Amount	0.0			false	false	0	false
PROTEIN	inside	s11	Lamin	c1	Amount	0.0			false	false	0	false
PHENOT...	inside	s12	M-Phase	c1	Amount	0.0			false	false	0	false

Edit Notes Edit Protein Notes

Species (id=s7, name=CAK; M-Phase.xml)

Protein (id=p7, name=CAK)

Grid Snap OFF

General view

TREE AREA

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

DRAW AREA

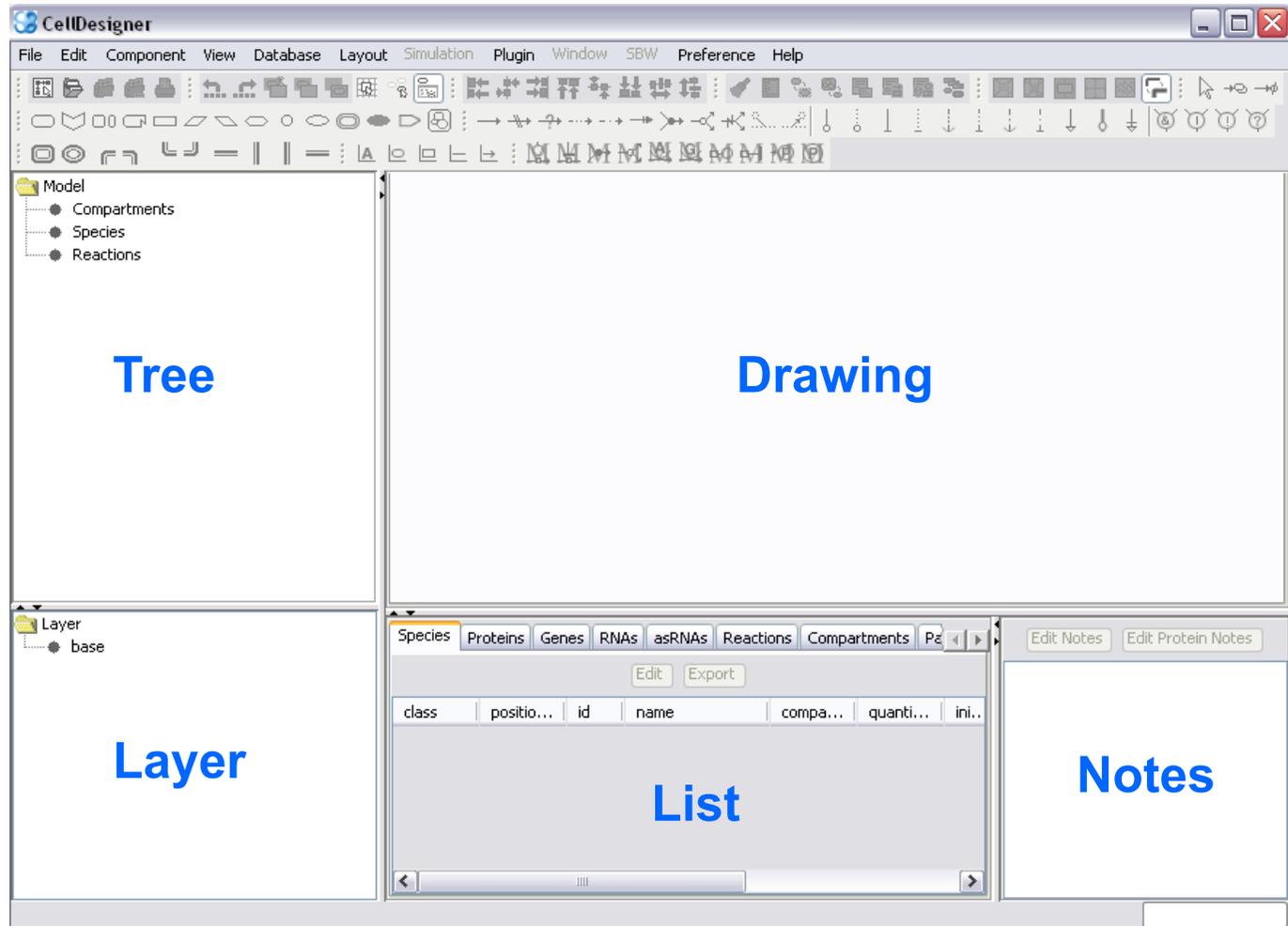
is the area where the model is built from the tool bar items.

LIST AREA

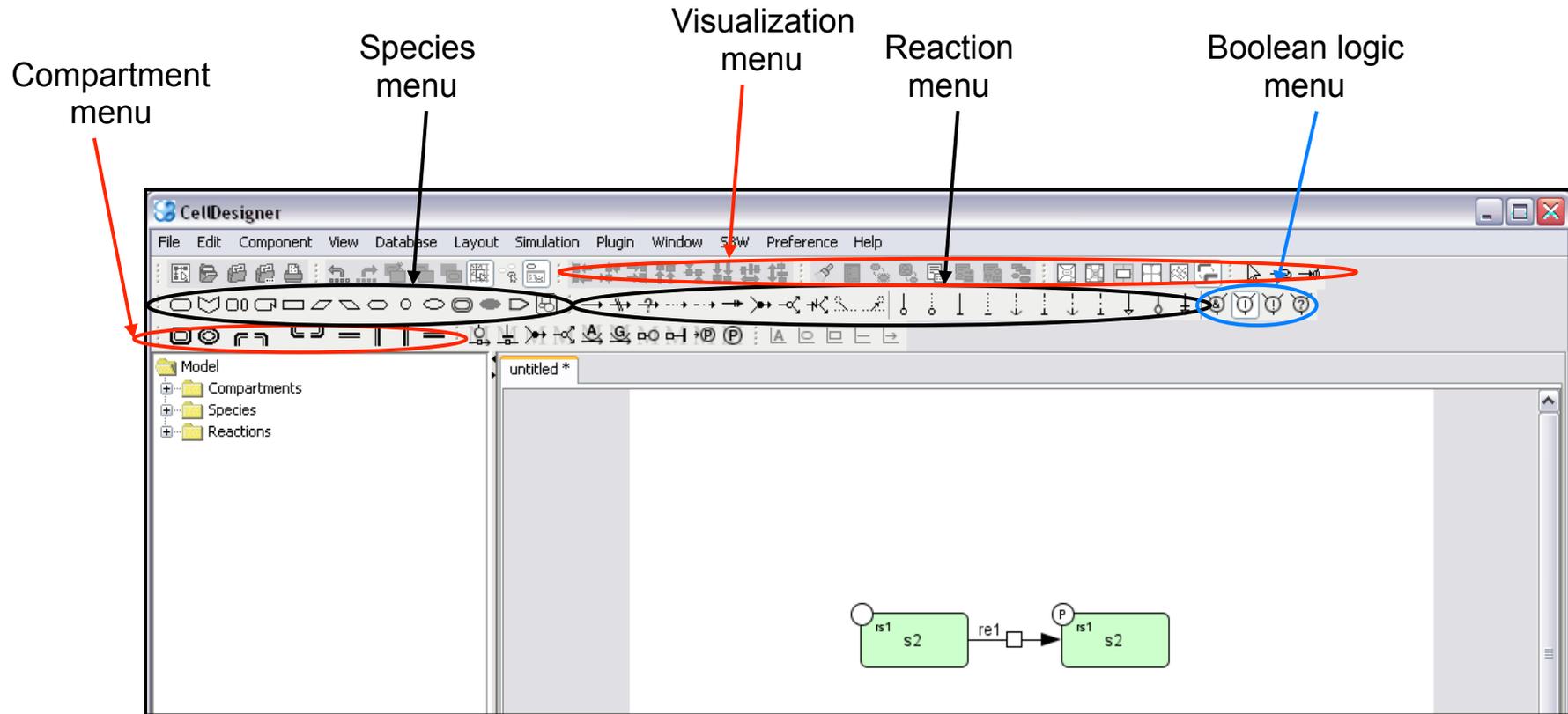
displays and edits the list of the components of the model (species, proteins, genes, RNAs, etc.)

NOTES AREA

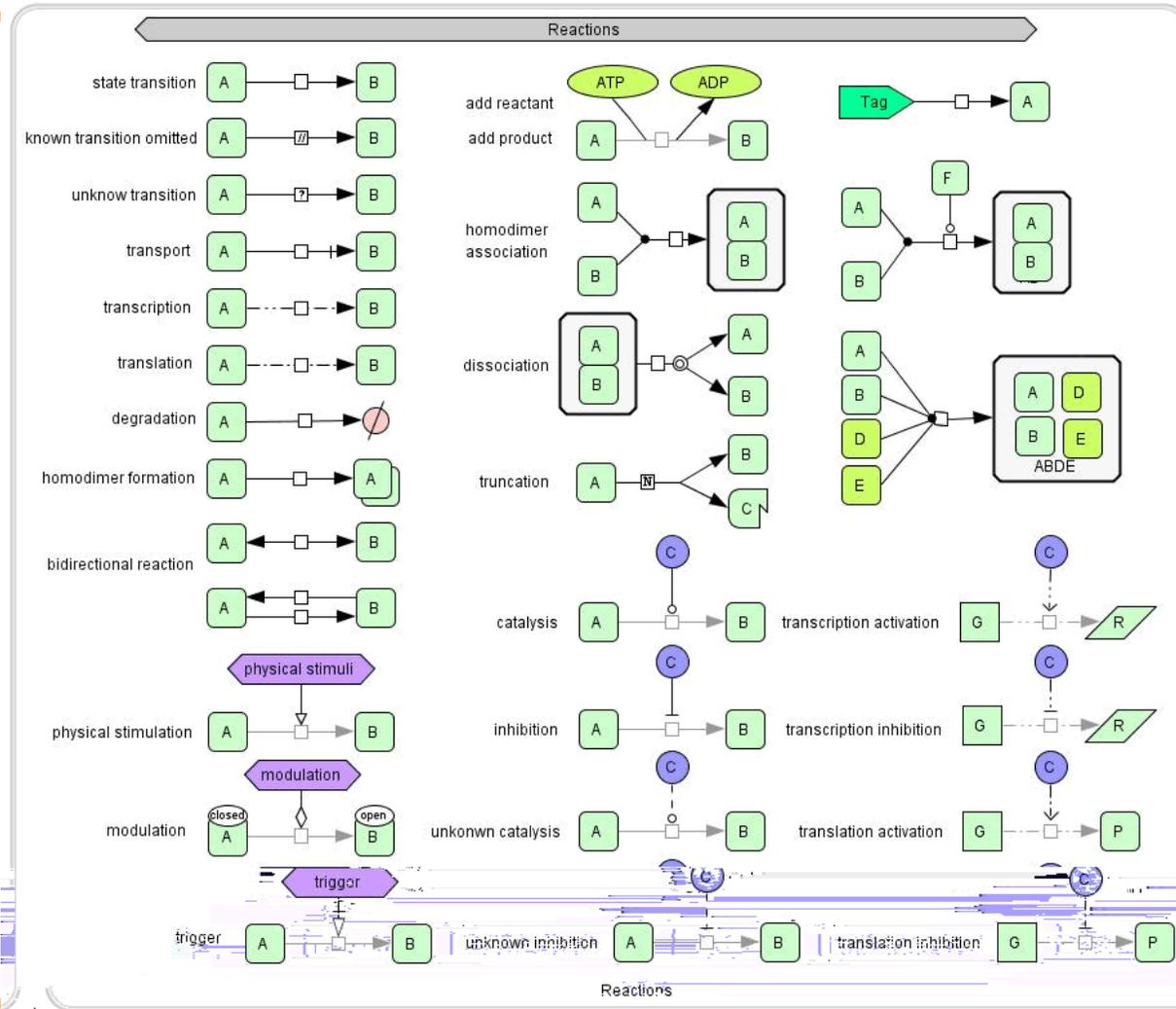
displays and edits the notes of each component (reactions, protein, complex, etc.)



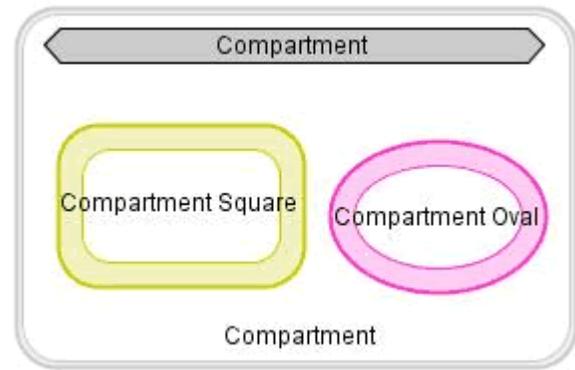
The menu



The reactions



The compartments

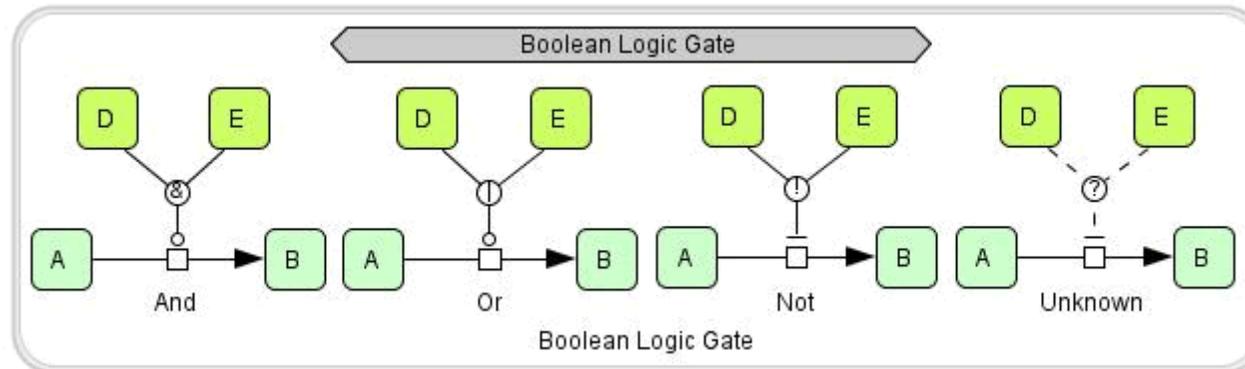


Compartments can be:

- Cytoplasm
- Nucleus
- Nucleolus
- etc.

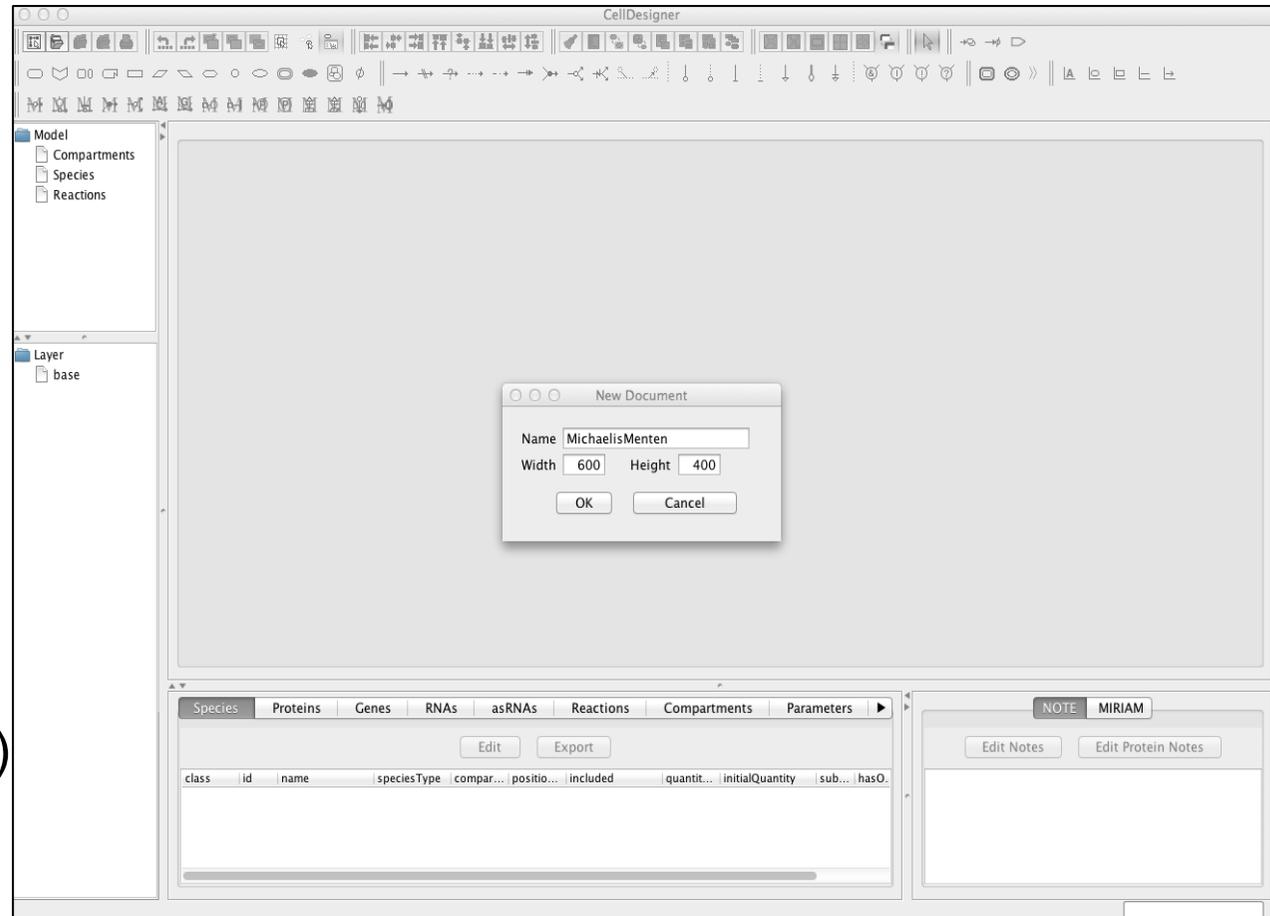
Boolean gates

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)

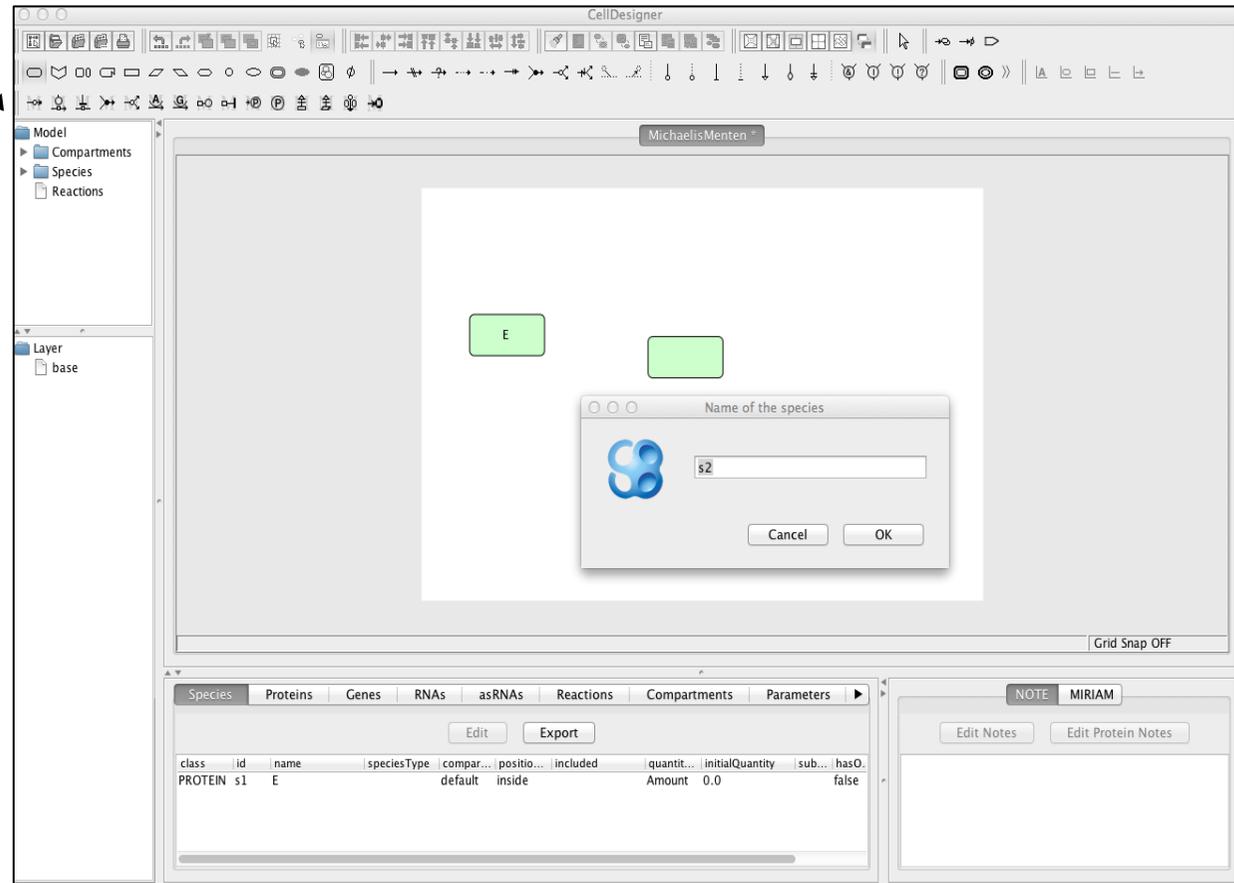


Add proteins

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

- A pop-up window opens: name your protein

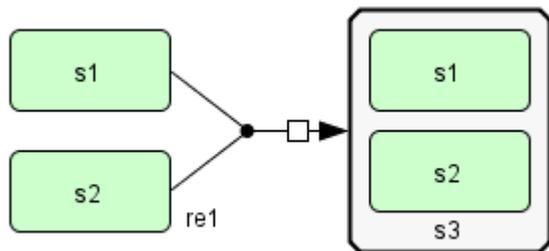
- Repeat the process as many times as needed



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



The screenshot shows the CellDesigner software interface. The main window displays a Michaelis-Menten reaction diagram with species E and S reacting to form a complex ES. The interface includes a toolbar, a model tree on the left, and a species table at the bottom.

class	id	name	speciesType	compar...	positio...	included	quantit...	initialQuantity	sub...	hasO...
PROTEIN	s1	E	default	default	inside		Amount	0.0	false	
PROTEIN	s2	S	default	default	inside		Amount	0.0	false	
COMPLEX	s3	ES	default	default	inside	s3(s5 s4)	Amount	0.0	false	

Annotate species

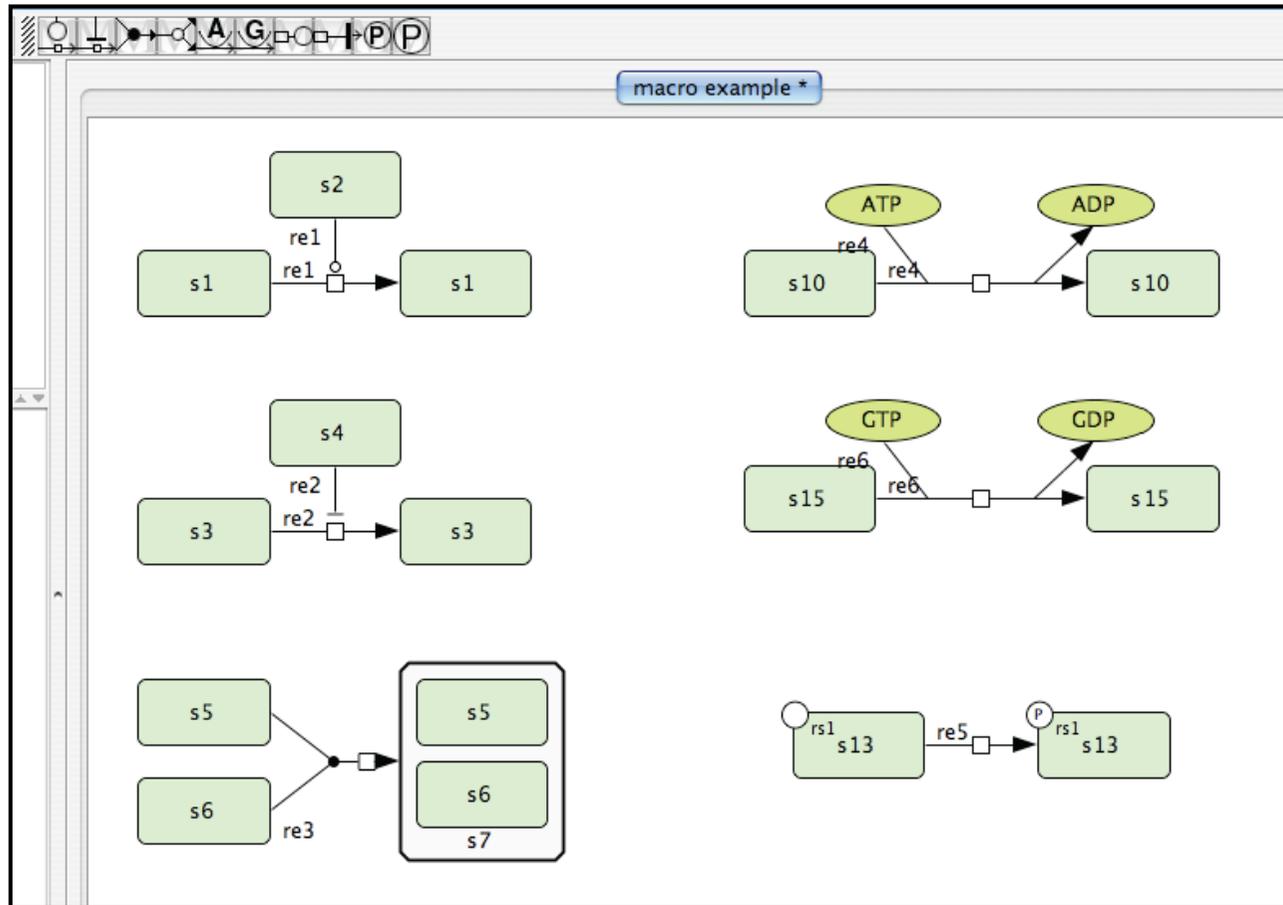
The screenshot shows the CellDesigner interface with a Michaelis-Menten reaction diagram. The diagram consists of three species: E (Enzyme), S (Substrate), and ES (Enzyme-Substrate complex). E and S are shown as separate boxes on the left, with arrows pointing to a larger box on the right containing E and S, representing the ES complex. The interface includes a toolbar at the top, a left sidebar with 'Model' (Compartment, Species, Reactions) and 'Layer' (base) sections, and a bottom panel with a table and a notes section.

class	id	name	speciesType	compar...	positio...	included	quantit...	initialQuantity	sub...	hasO...
PROTEIN	s1	E		default	inside		Amount	0.0		false
PROTEIN	s2	S		default	inside		Amount	0.0		false
COMPLEX	s3	ES		default	inside	s3(s5 s4)	Amount	0.0		false

NOTE MIRIAM
Edit Notes Edit Protein Notes

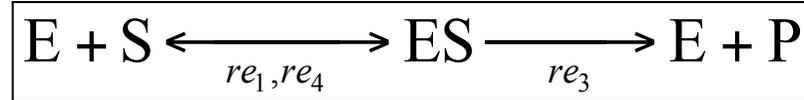
Write Notes about species, reactions, etc.

Examples of macros

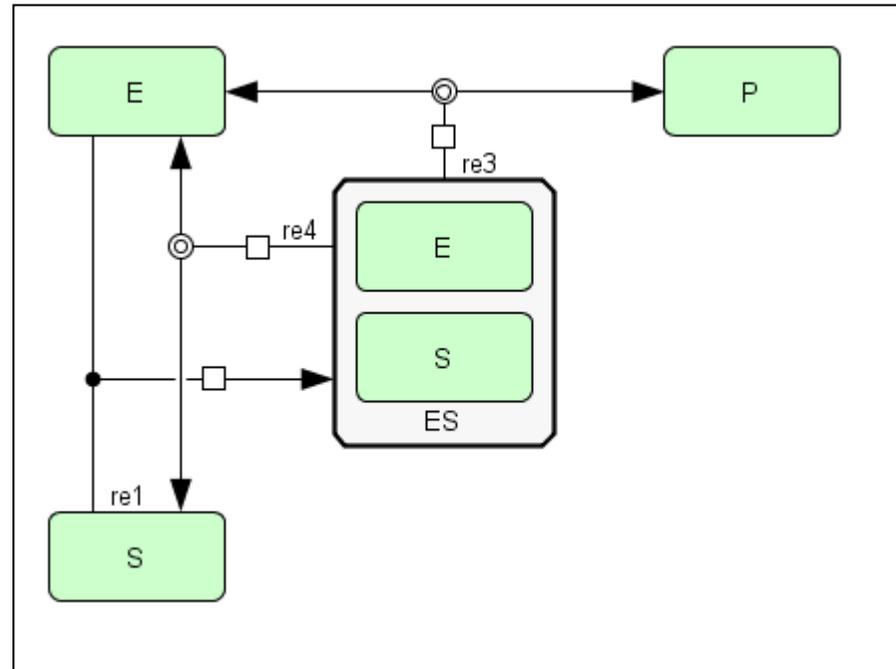


Small network

This biochemical reaction



is translated into this diagram



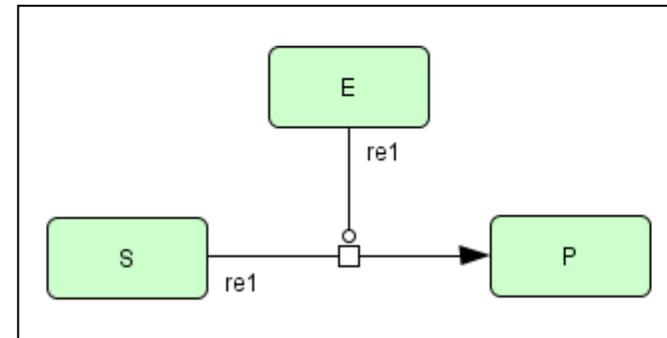
Note: There is a possibility to include dynamics into the diagram by defining the parameters re_1 , re_4 , re_3 ... We will not describe this process today...

Or more simply...

This reaction



is translated into this diagram

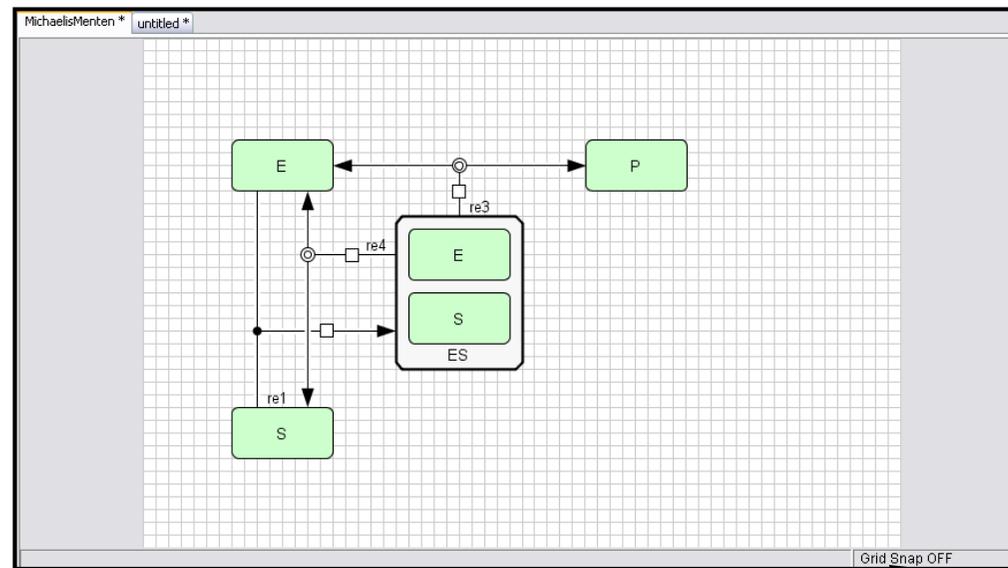
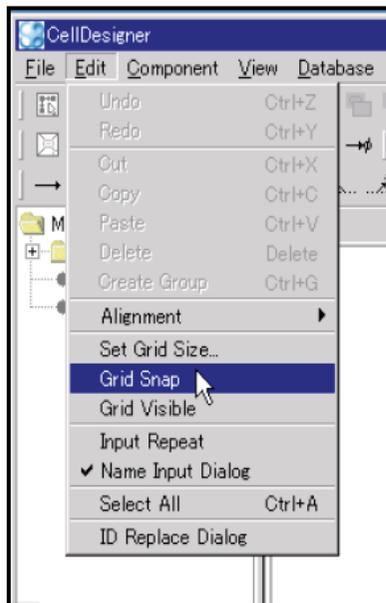


You choose the level of details...

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/gnp/pub/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

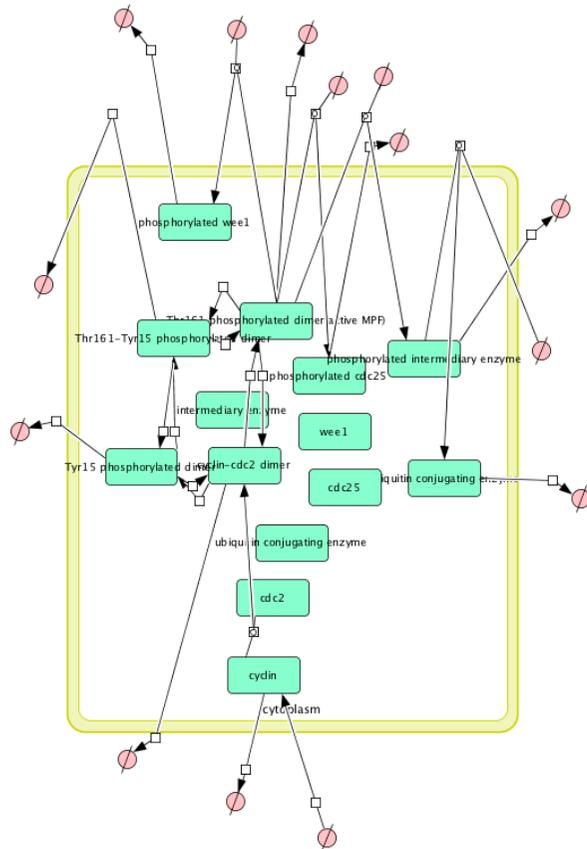
The image shows two overlapping windows. The top window is the BioModels.net interface, displaying a list of models with columns for ID and Name. The bottom window is a web browser showing the NCBI Entrez Gene search results for the query 'wee1'. The search results list several entries, including 'WEE1 - WEE1 homolog (S. pombe)' and 'WEE1 - M phase inhibitor protein kinase Wee1 [Schizosaccharomyces pombe 972h-]'. Arrows from the table in the left image point to the BioModels.net window and the search results in the browser window.

Existing models

1. Import model from a database:

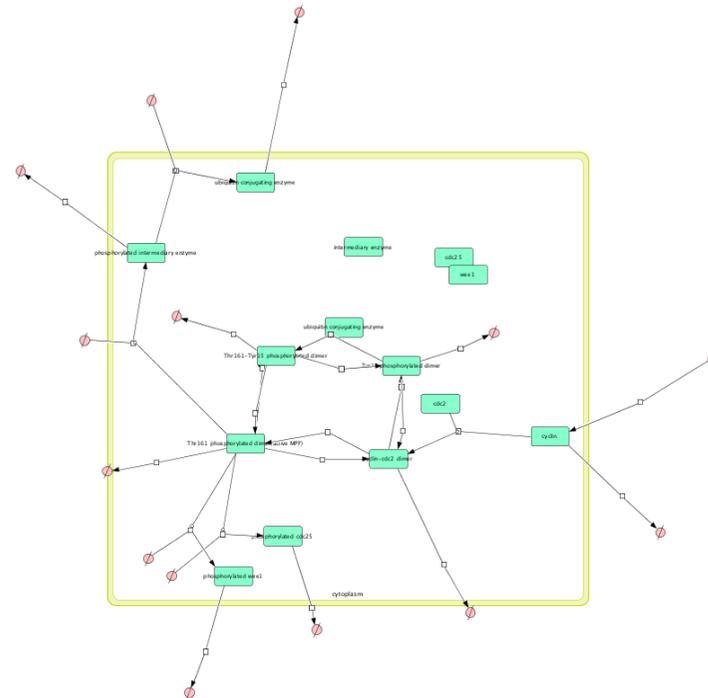
[Database] => [Import a model from BioModels.net]:

BIOMD0000000111 (Novak2001)

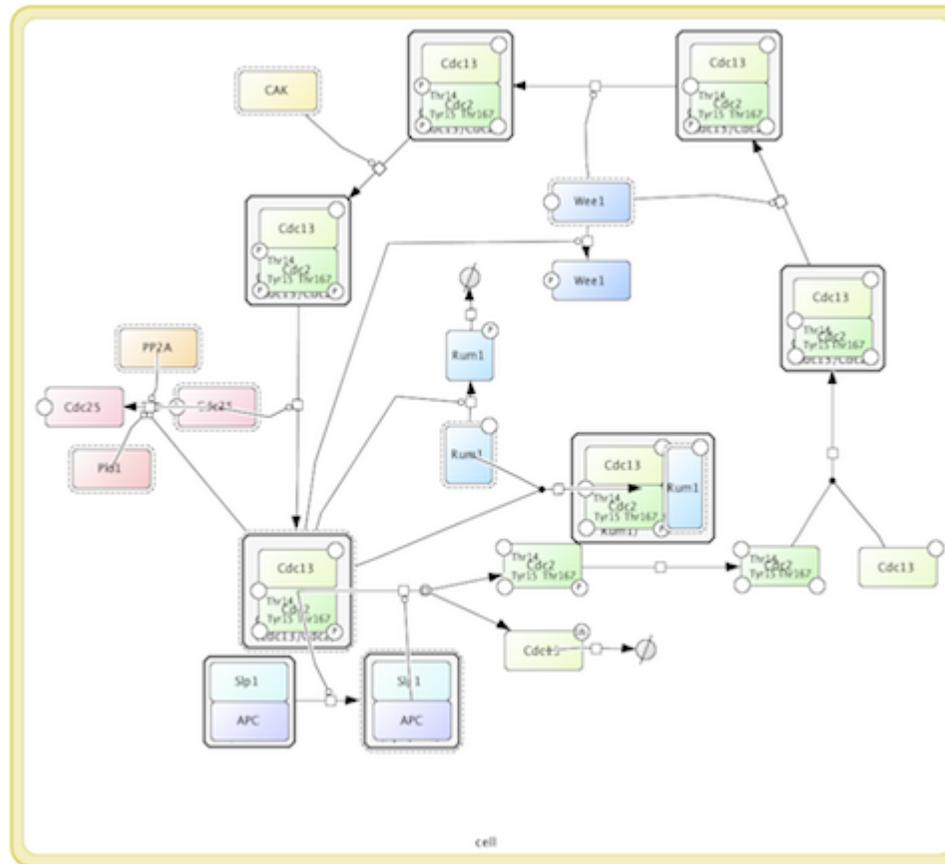


2. Change layout:

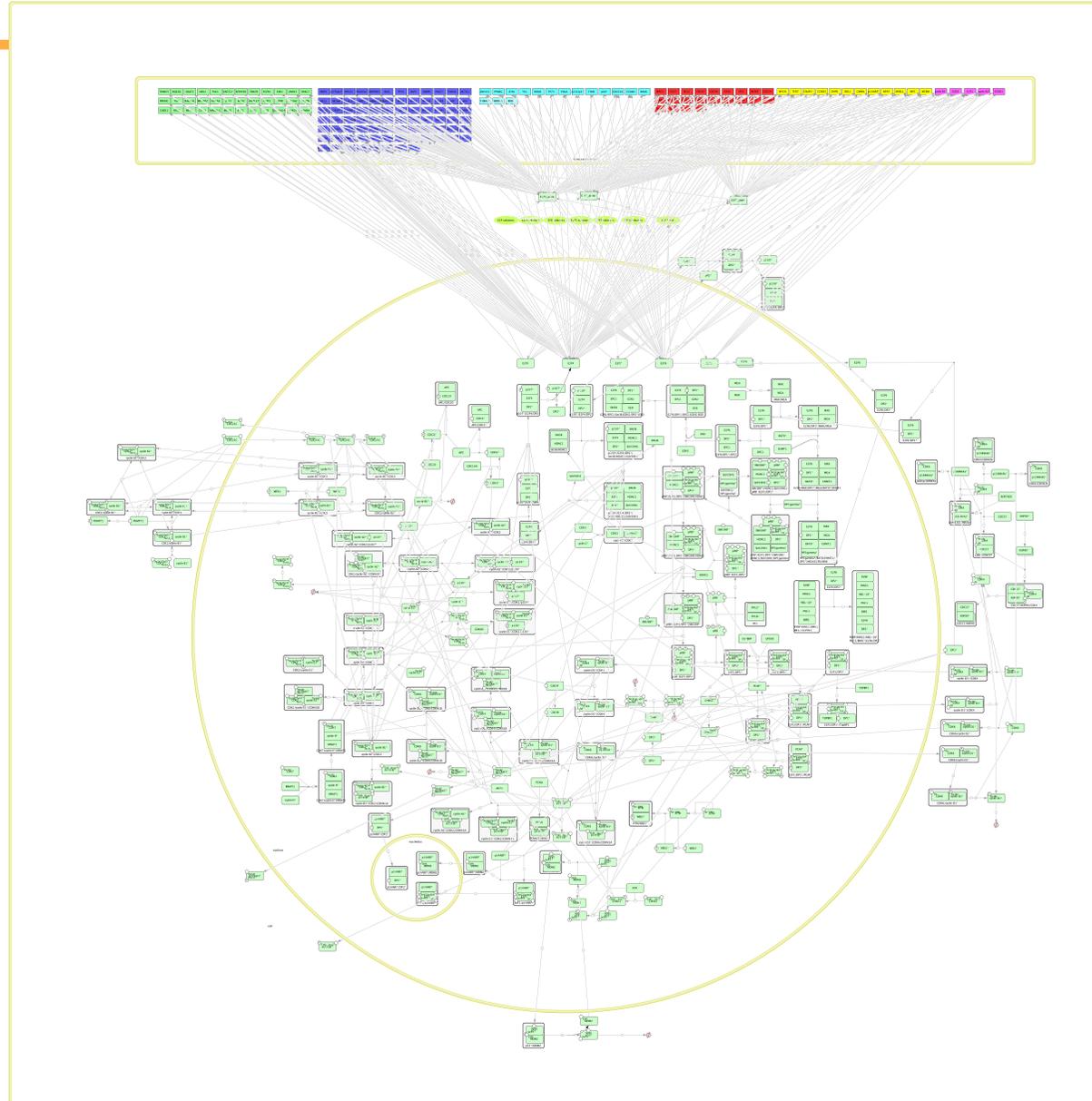
[Layout] => [Organic layout]



M-Phase.xml



rbe2f.xml

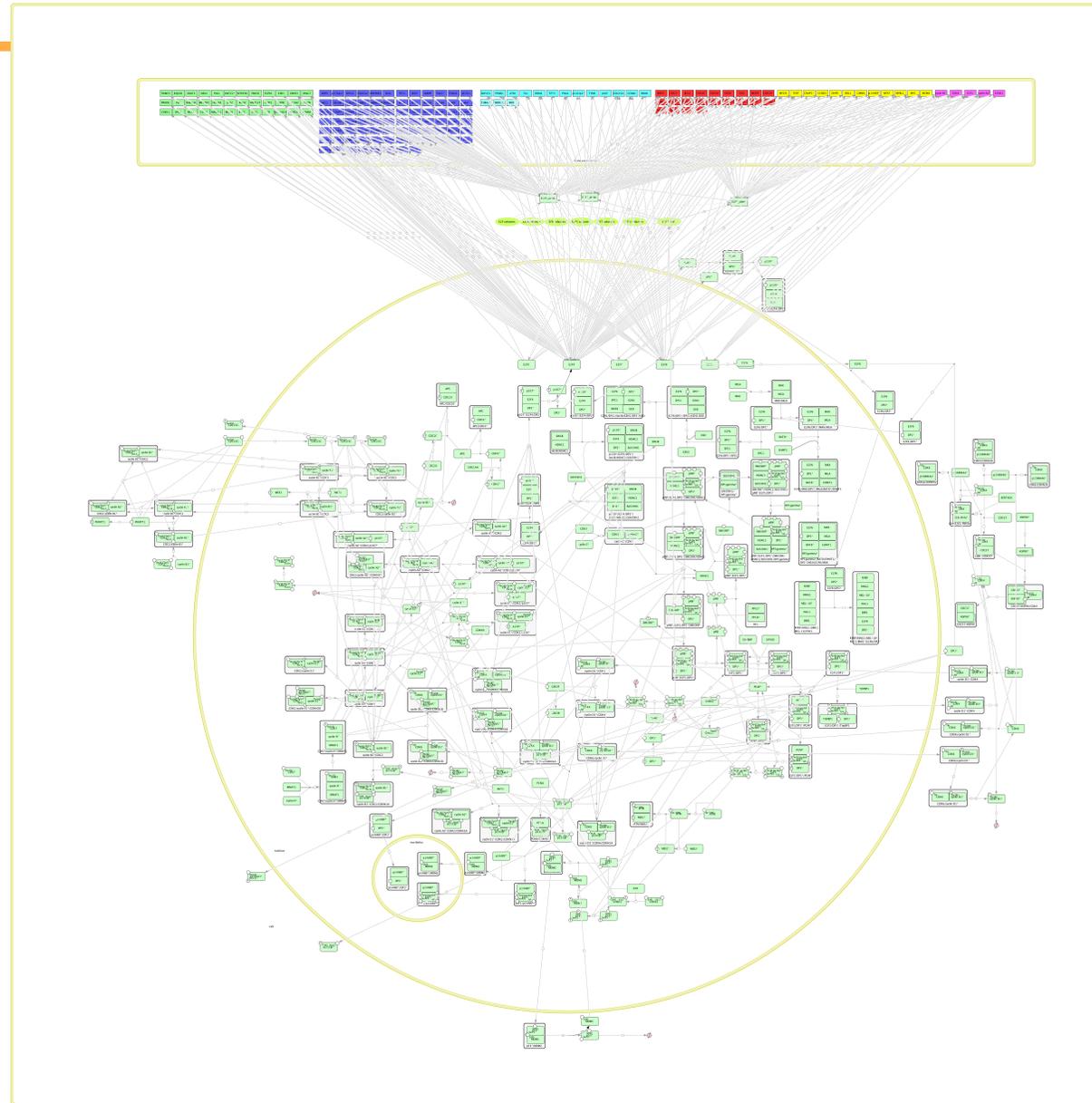


QUESTIONS??

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 (Biological 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

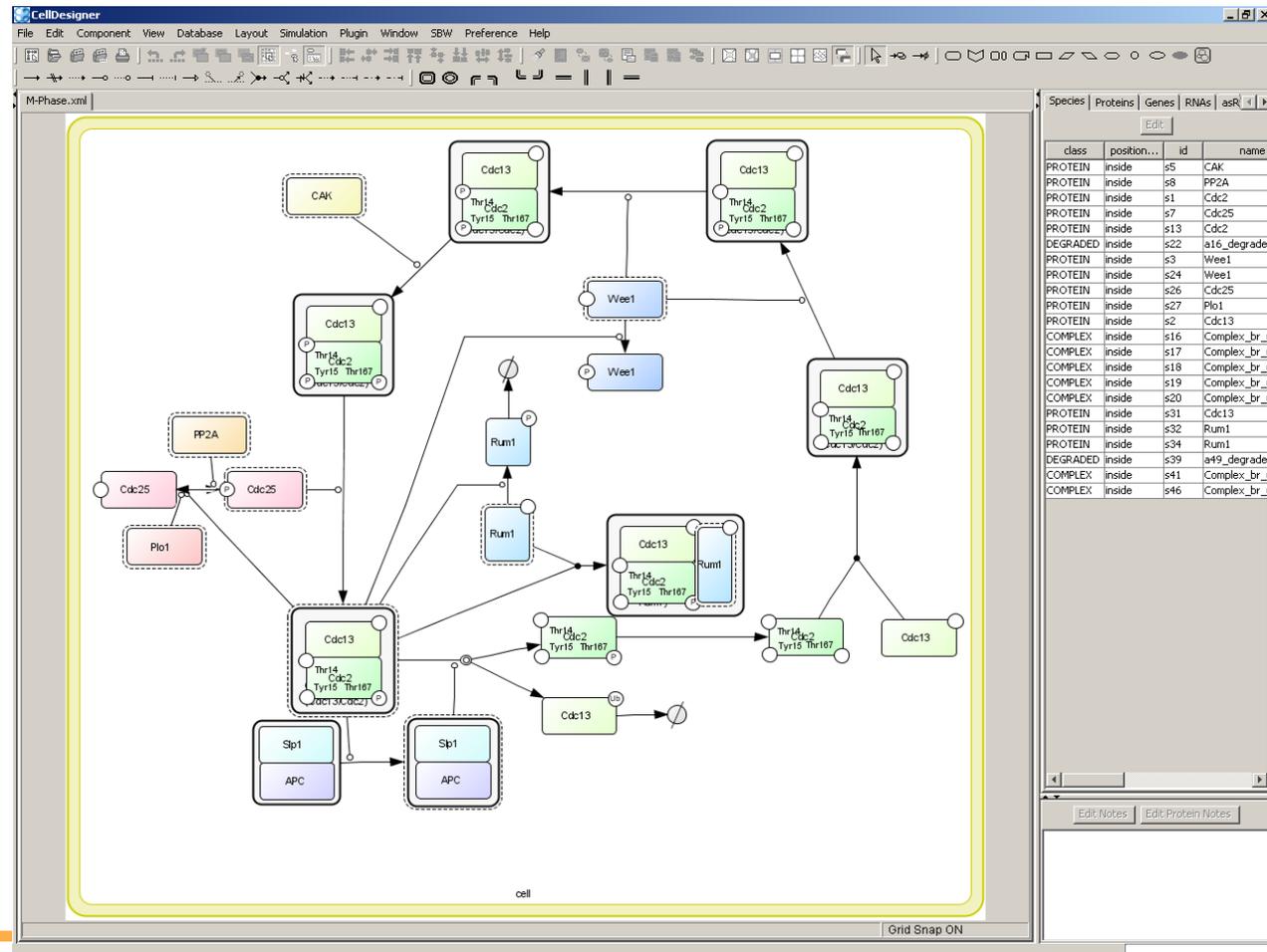
- Download Cytoscape from:
<http://www.cytoscape.org/>
- Download BiNoM from:
<http://binom.curie.fr/>
- Copy the jar file (BiNoM_all.jar) in the plugins folder of Cytoscape
- Launch Cytoscape

Our toy example

CellDesigner file of M-Phase model

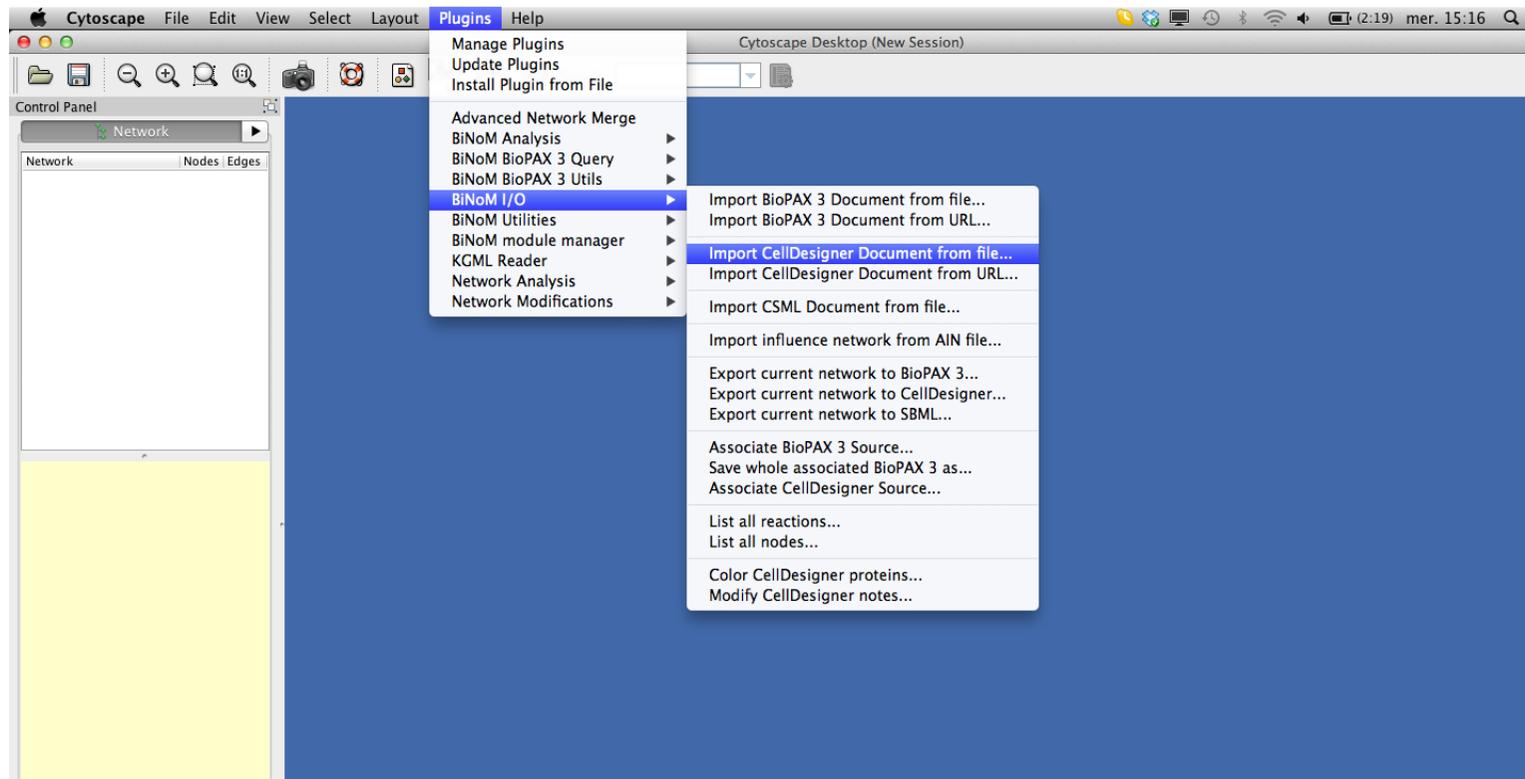
Simple example:

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

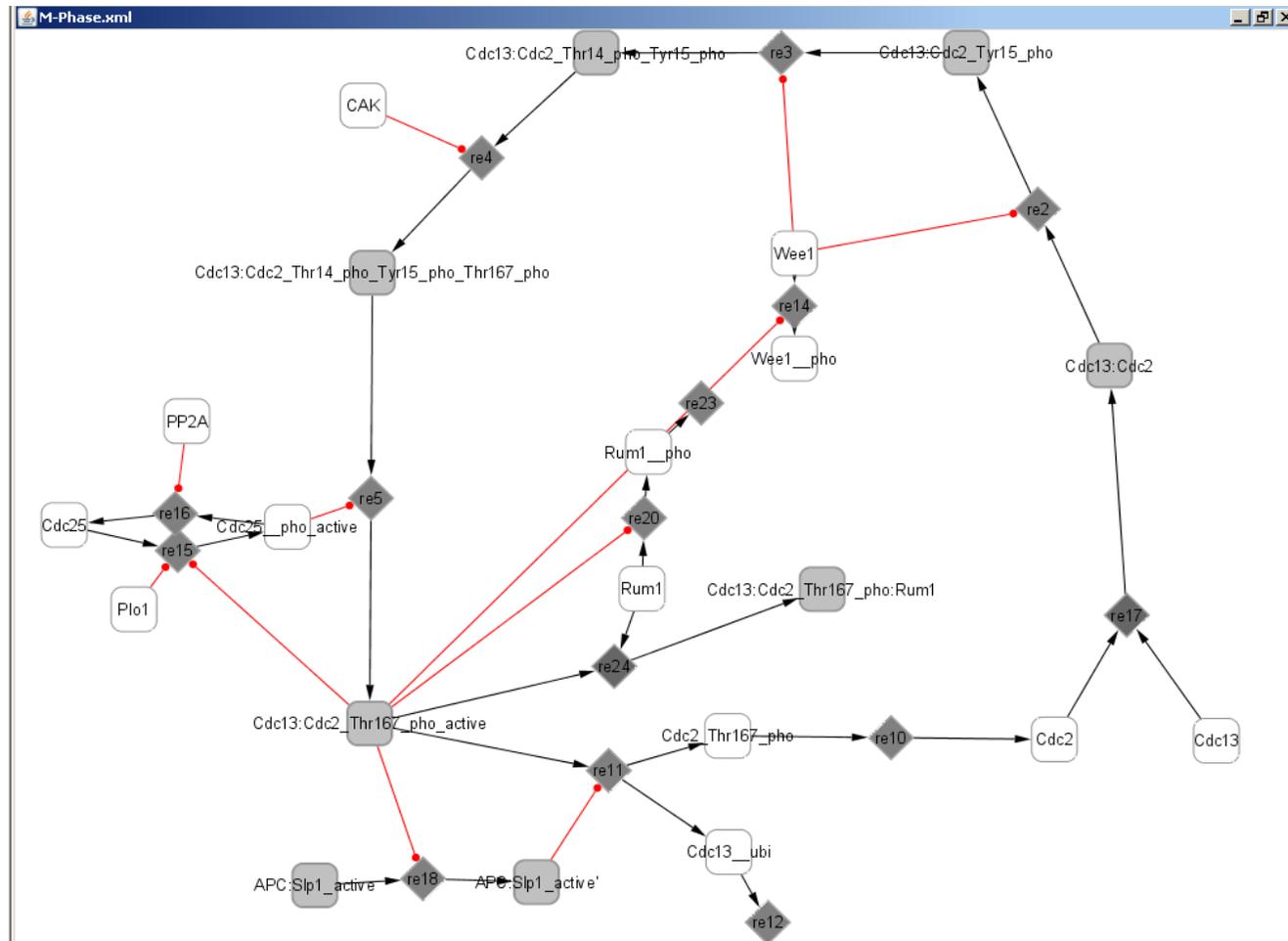


1. Import the toy example in Cytoscape

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

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...

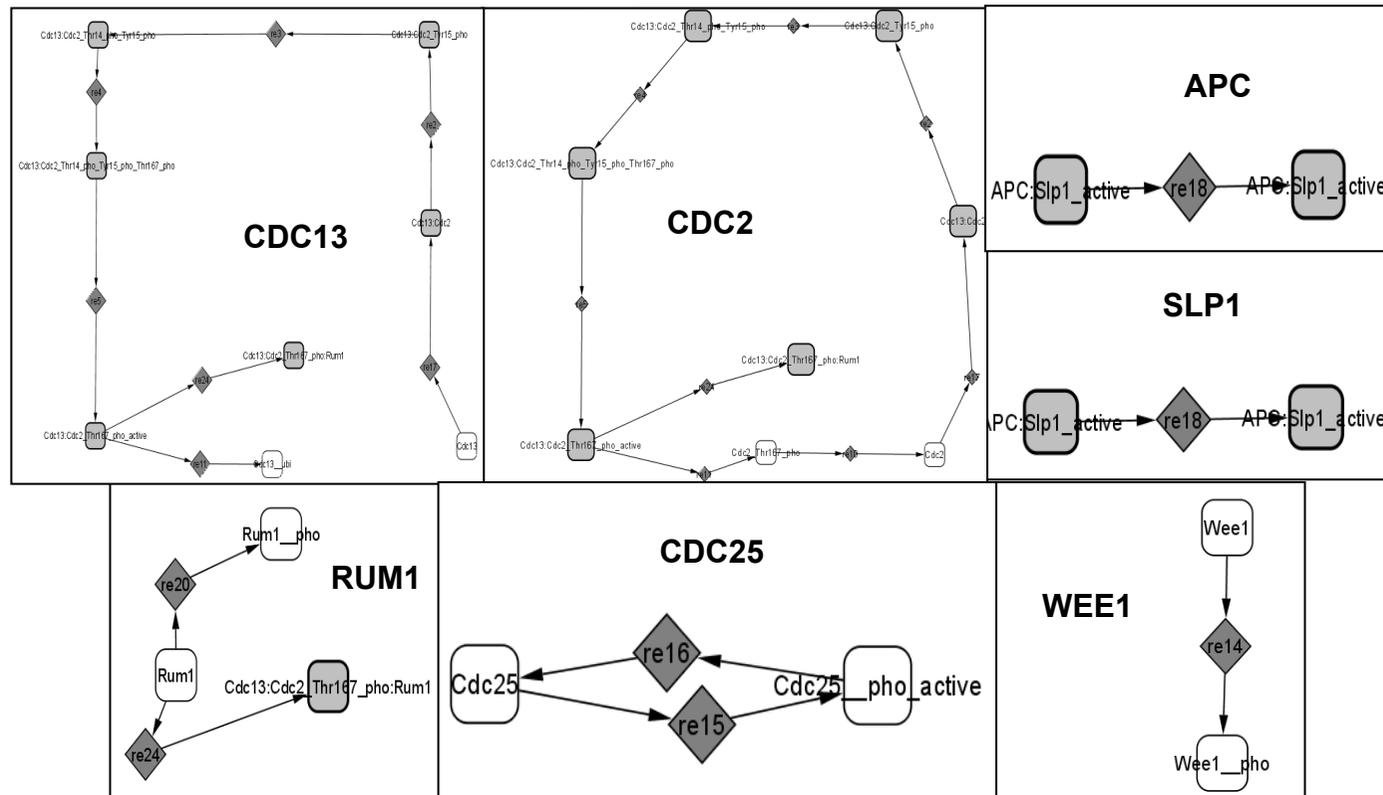
Solution:

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

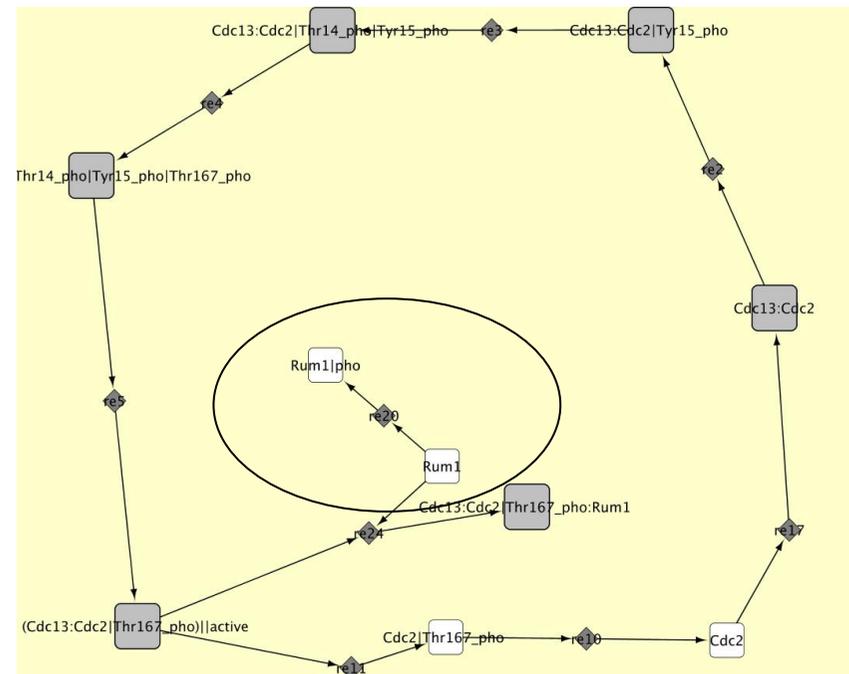
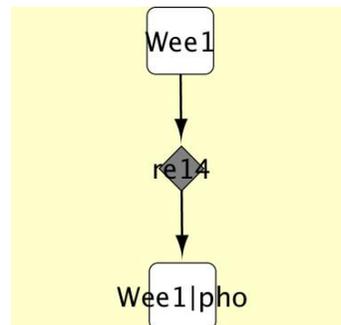
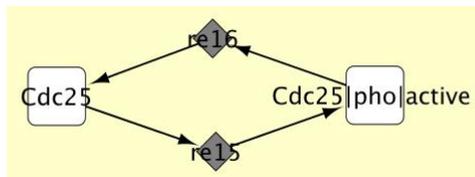
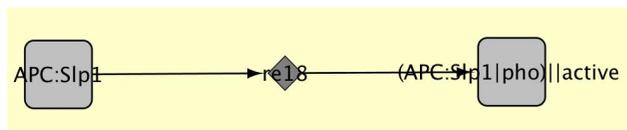
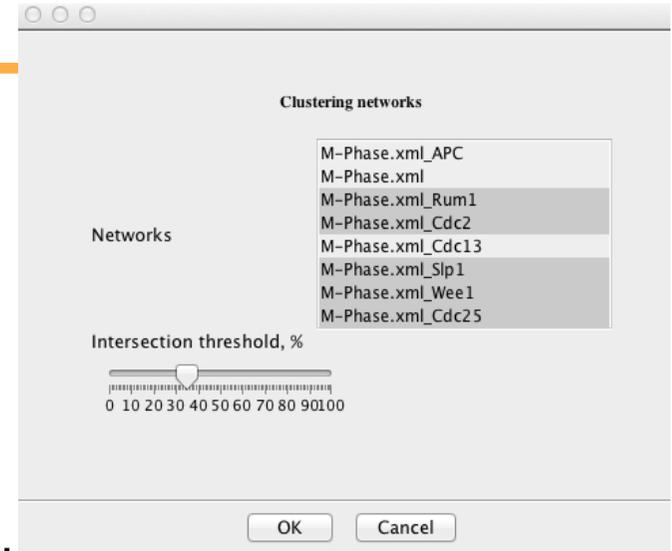
This step is necessary if the network is big.
Not necessary here, but let's try anyway.

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...



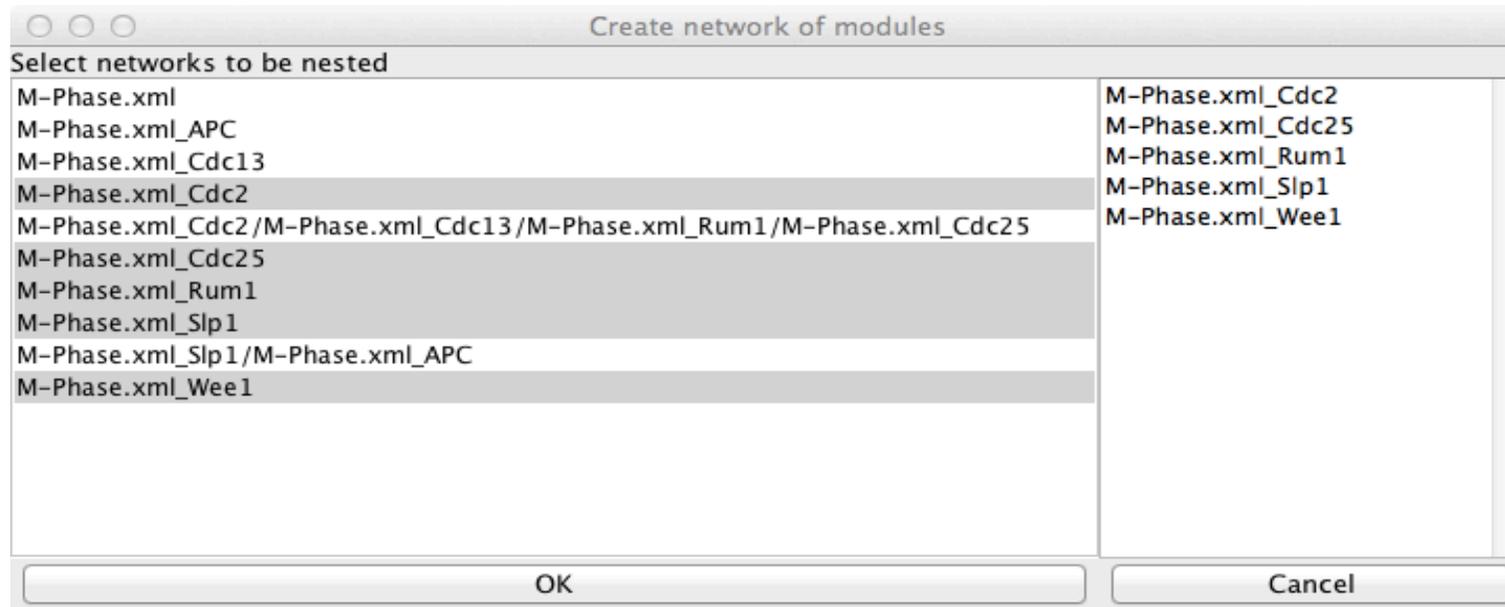
2. Reducing complexity of the map

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)

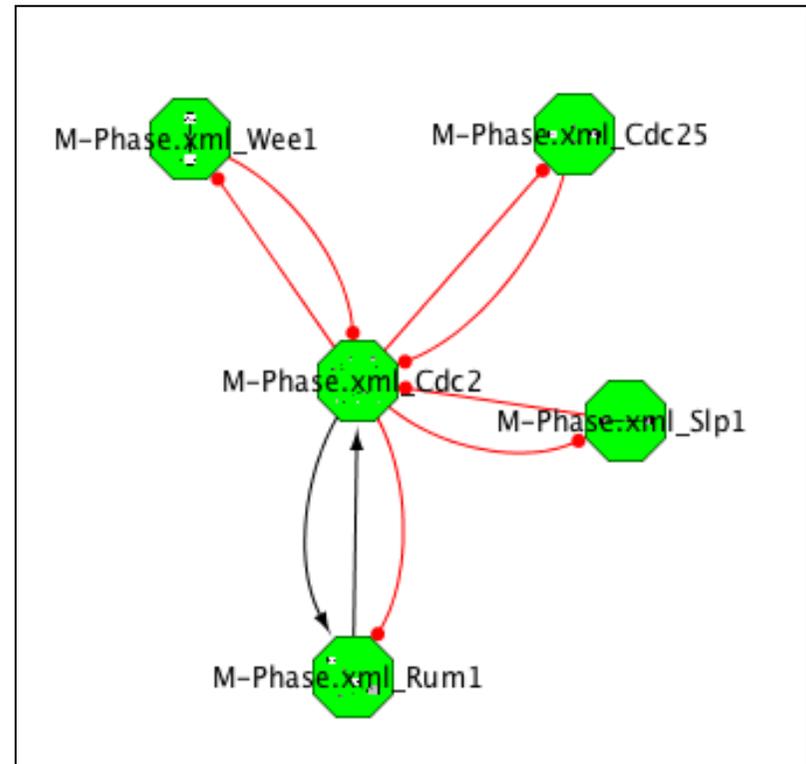
Create modular view (2)

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

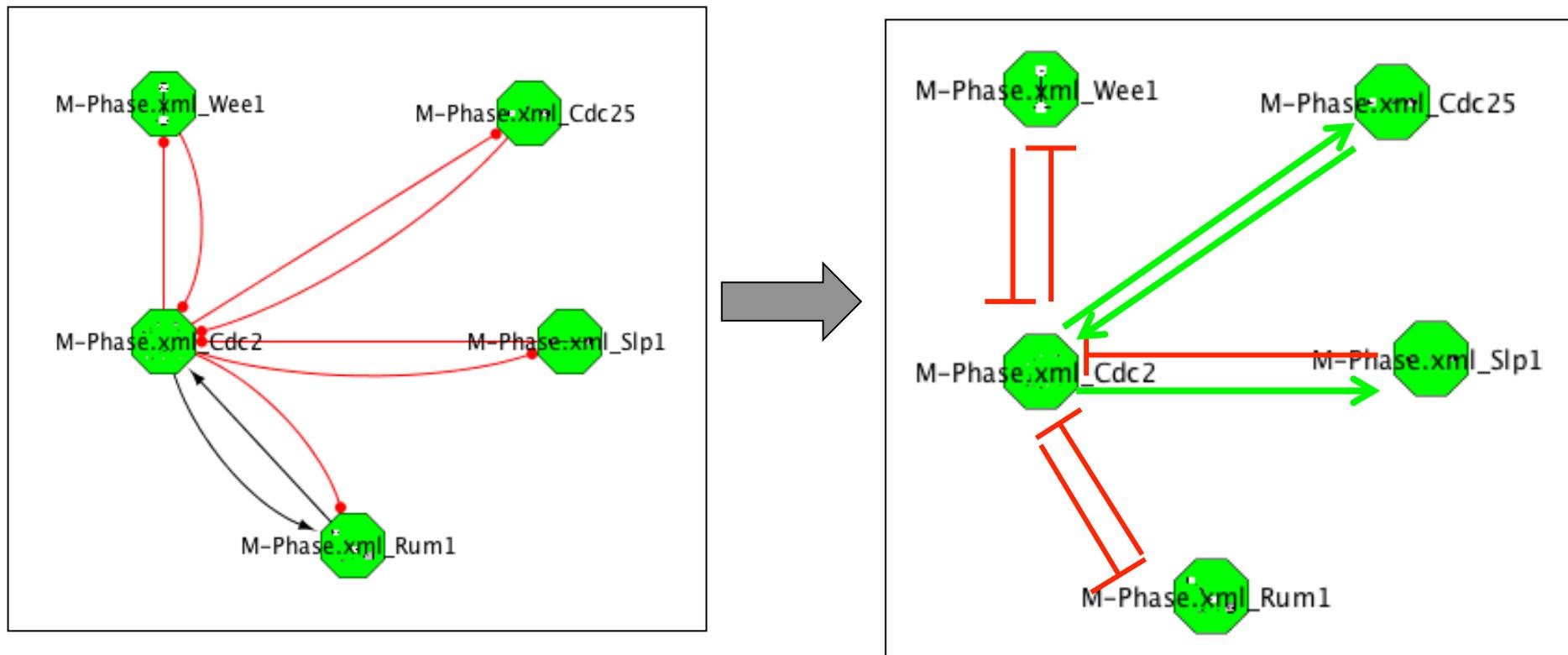
The arrows shows different types of interactions between the modules



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

The screenshot displays the Cytoscape Desktop interface with a new session titled "Cytoscape Desktop (New Session)". The main window shows a complex network graph with nodes and edges, primarily colored in black and red. The network is dense and hierarchical, with a large cluster of nodes at the top and a more dispersed structure below. The interface includes a Control Panel on the left with a "Network" tab and a table showing the loaded file "rbe2f.xml" with 922 nodes and 122 edges. A Data Panel at the bottom provides access to "Node Attribute Browser", "Edge Attribute Browser", and "Network Attribute Browser".

Network	Nodes	Edges
rbe2f.xml	922...	122...

Path Analysis

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

2. **BiNoM 2.3 => BiNoM Analysis => Path Analysis**

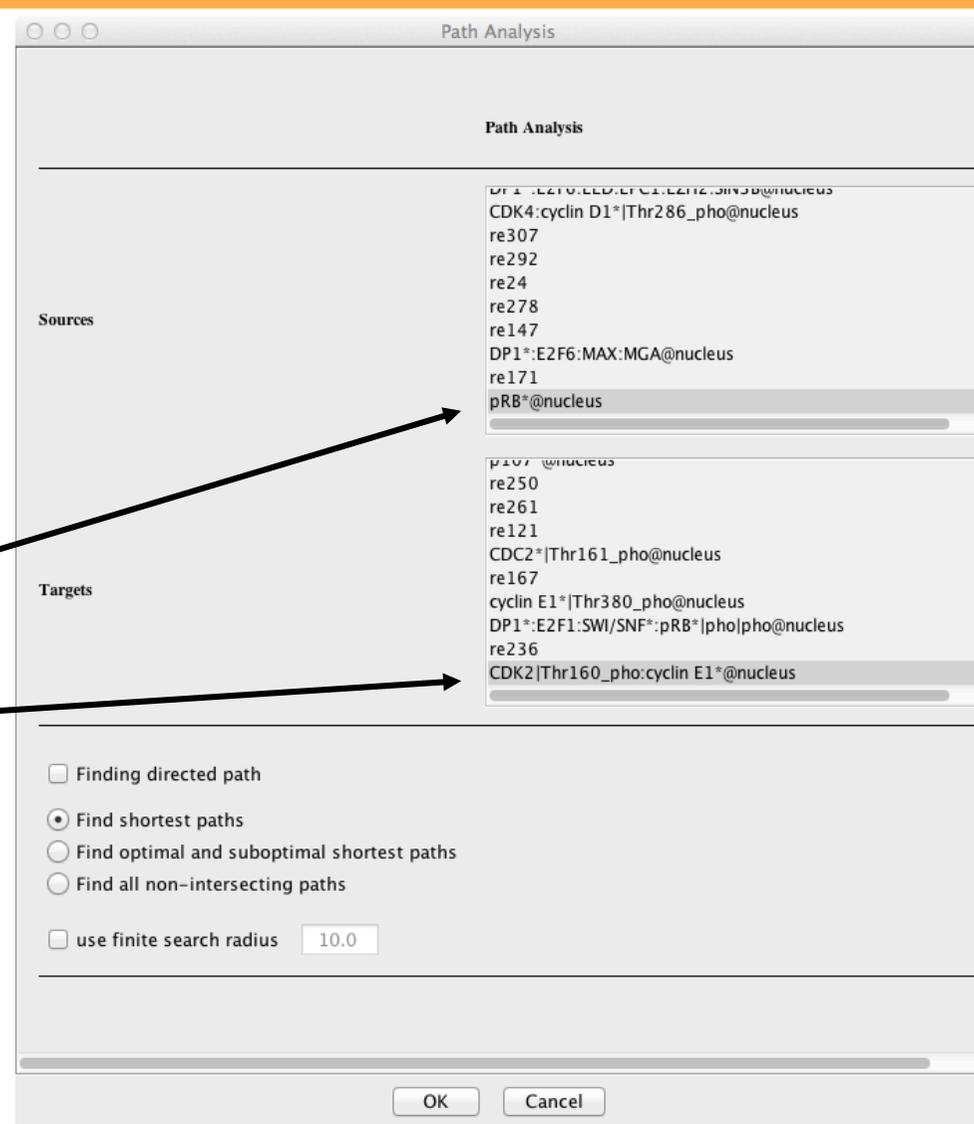
A window pops up

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

The screenshot displays the Cytoscape Desktop interface with a network visualization. The main window shows a dense network of nodes and edges, with a specific path highlighted in red. A black arrow points to this highlighted path. The interface includes a Control Panel on the left with a table of network files, a Data Panel at the bottom, and a search bar at the top right.

Network	Nodes	Edges
MPhase.xml_Cdc13	15(0)	14(0)
MPhase.xml_Cdc2	16(0)	16(0)
MPhase.xml_Rum1	5(0)	4(0)
MPhase.xml_Cdc25	4(0)	4(0)
MPhase.xml_Wee1	3(0)	2(0)
Modular0	5(0)	9(0)
rbe2f.xml	922...	122...

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 »

The screenshot displays the Cytoscape Desktop interface. The main window shows a network diagram with nodes and edges. The nodes are labeled: pRB1@nucleus, re97, DP1*:E2F1@nucleus, re60, and E2F1@nucleus. The edges connect pRB1@nucleus to re97, re97 to DP1*:E2F1@nucleus, DP1*:E2F1@nucleus to re60, and re60 to E2F1@nucleus.

The Control Panel on the left shows a list of networks with columns for Nodes and Edges:

Network	Nodes	Edges
MPhase.xml_Cdc13	15(0)	14(0)
MPhase.xml_Cdc2	16(0)	16(0)
MPhase.xml_Rum1	5(0)	4(0)
MPhase.xml_Cdc25	4(0)	4(0)
MPhase.xml_Wee1	3(0)	2(0)
Modular0	5(0)	9(0)
rbe2f.xml	922...	122...
rbe2f.xml--child.1	5(0)	4(0)

The Data Panel at the bottom shows the Node Attribute Browser, Edge Attribute Browser, and Network Attribute Browser. The Node Attribute Browser is currently selected, showing the ID of the selected node.

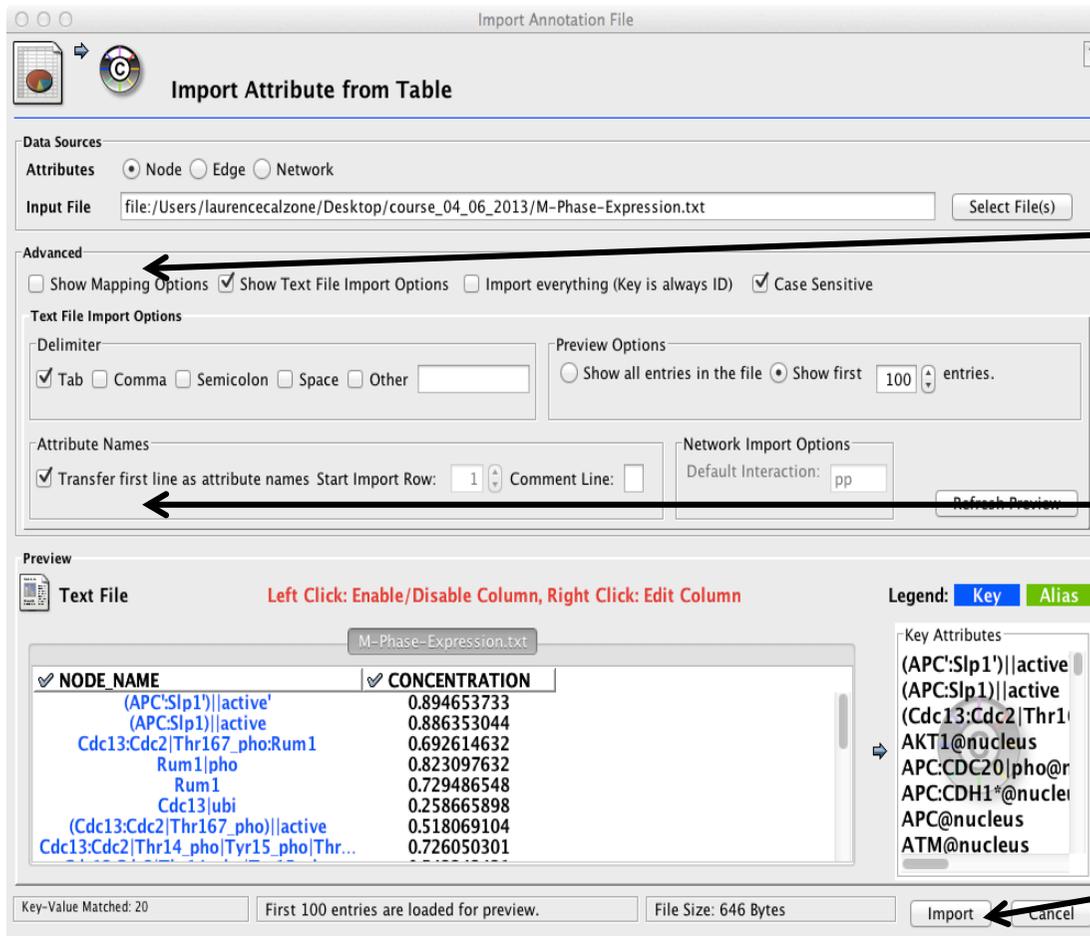
At the bottom of the window, there is a status bar with the following text: "Welcome to Cytoscape 2.8.2 Right-click + drag or Control-Click + drag to ZOOM Command-Click + drag to PAN"

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



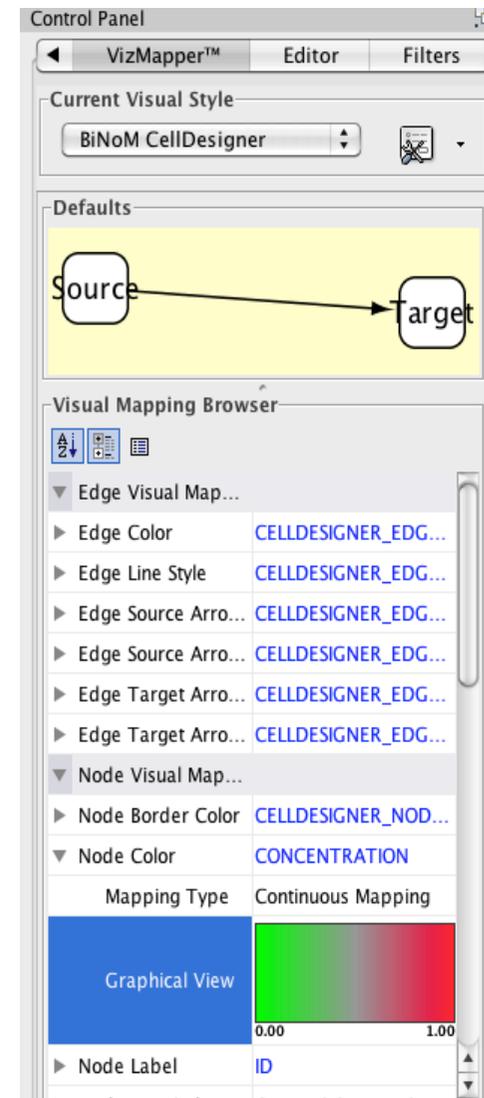
4. In the 'Advanced' box, click on 'Show text file import options'

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

6. Click on 'Import'

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

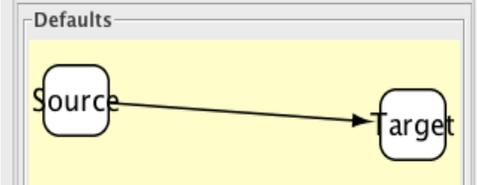




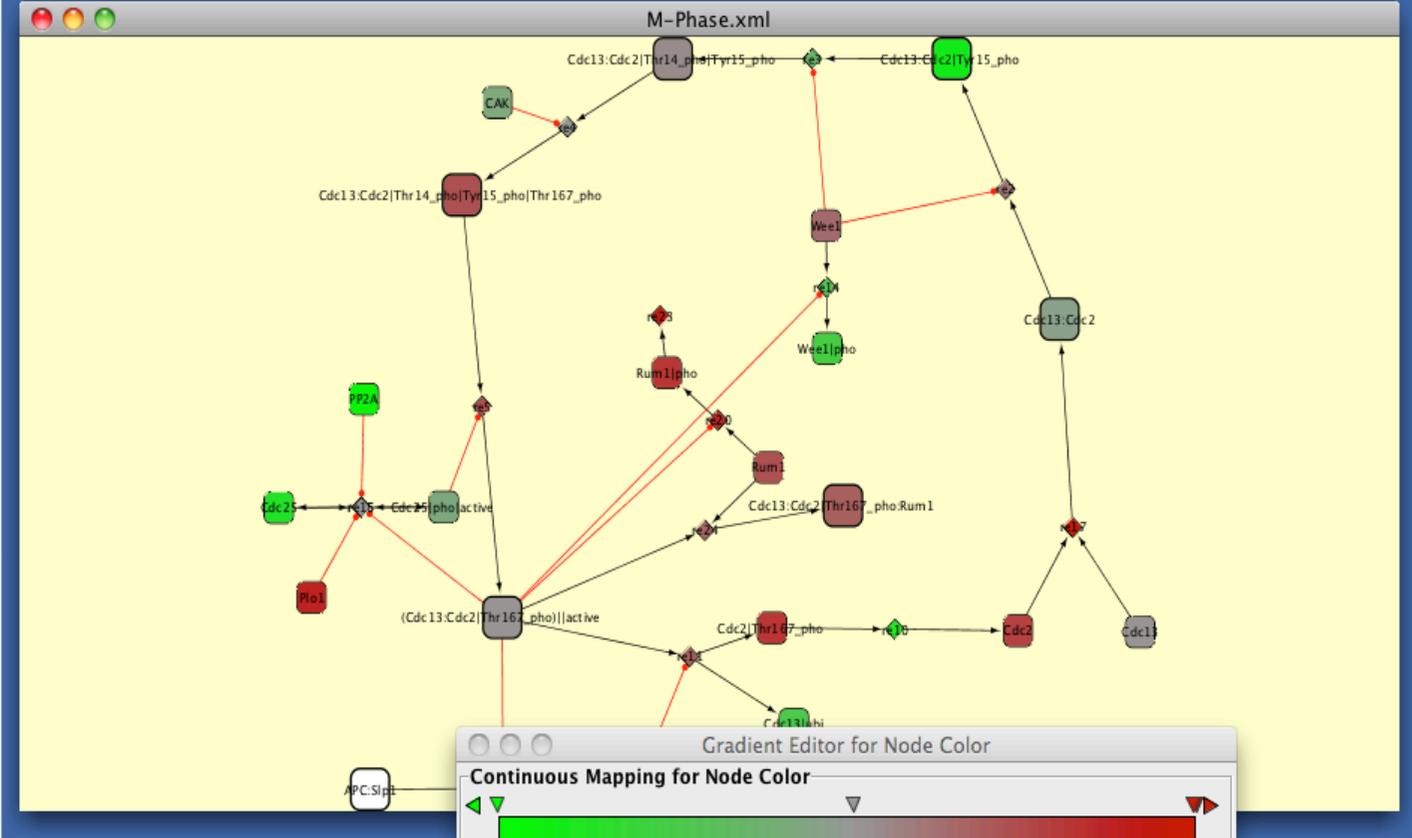
Control Panel

VizMapper™ Editor Filters

Current Visual Style
BiNoM CellDesigner



- 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:
 - Node Label: ID



Data Panel

ID

Gradient Editor for Node Color

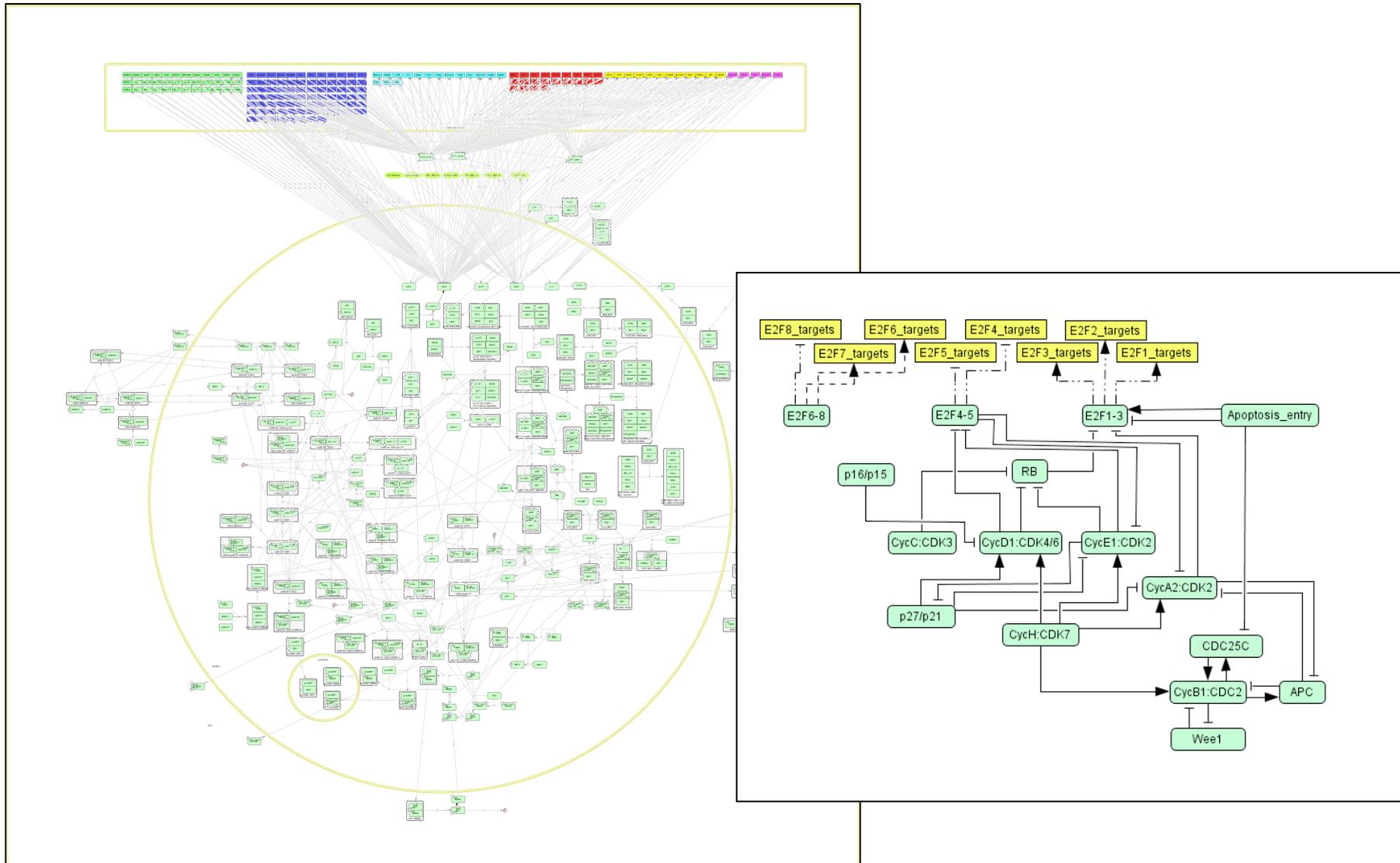
Continuous Mapping for Node Color

Min=0.0 CONCENTRATION Max=1.0

Range Setting: 1

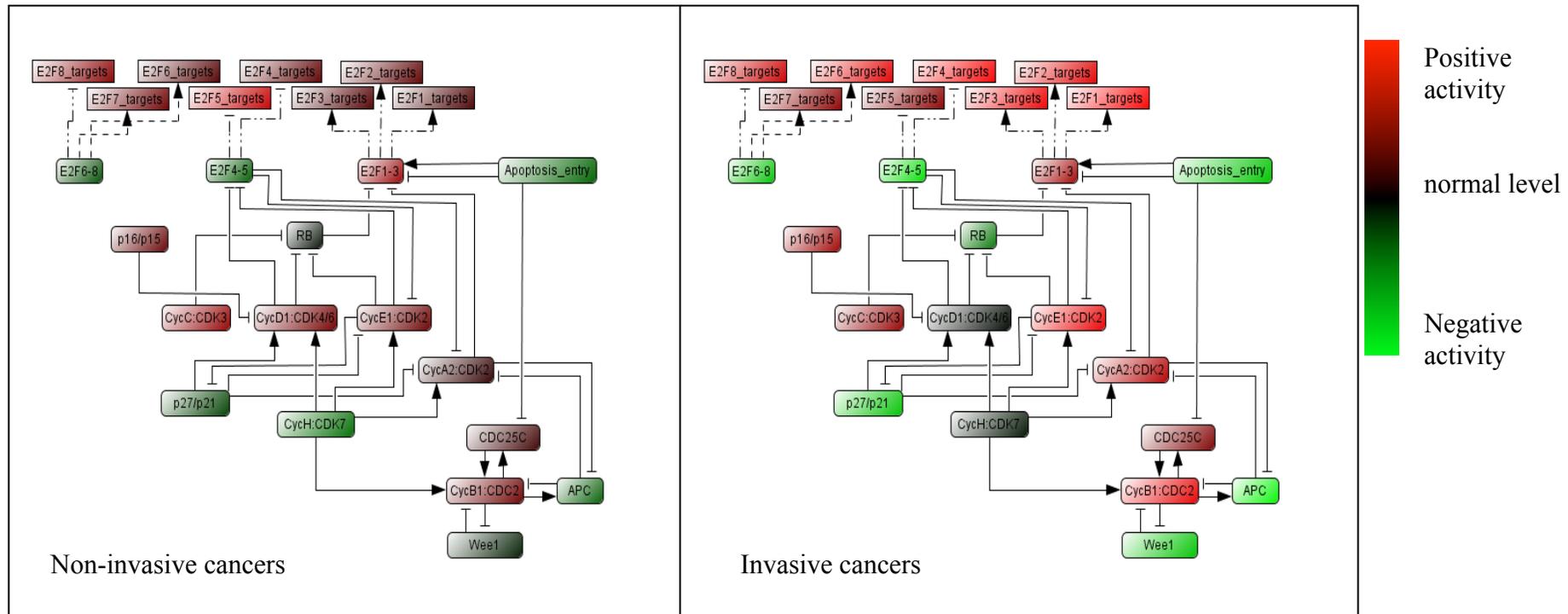
Buttons: Min/Max, Add, Delete

Coloring RB/E2F map



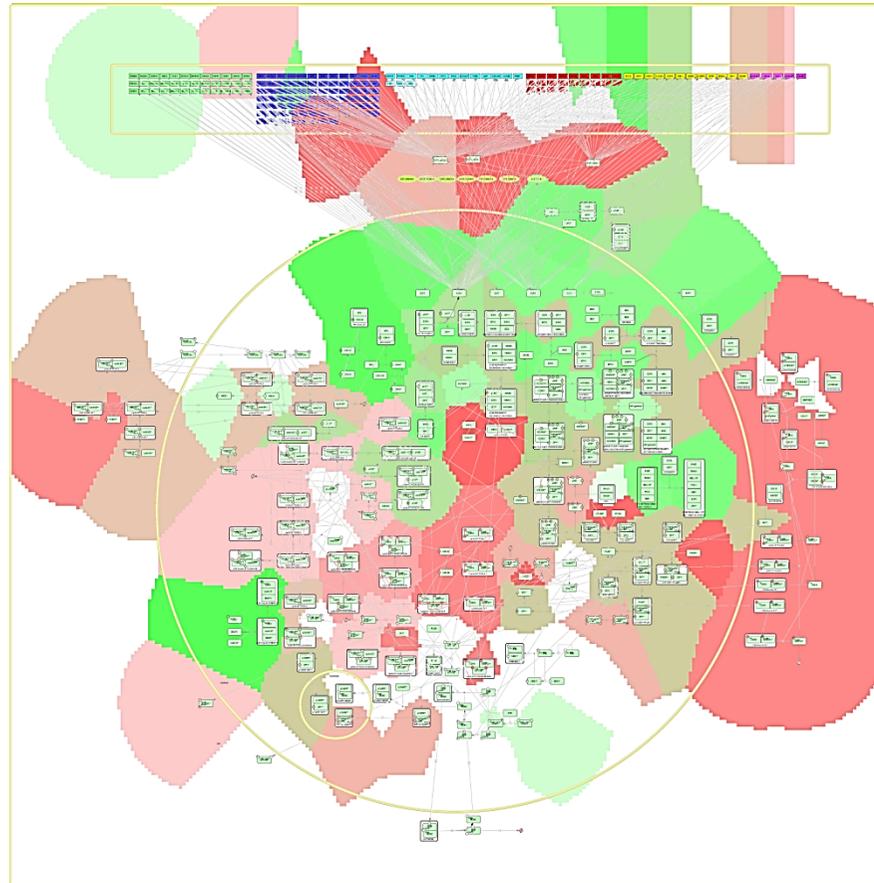
Example of bladder tumour data: invasive vs. non-invasive samples

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)

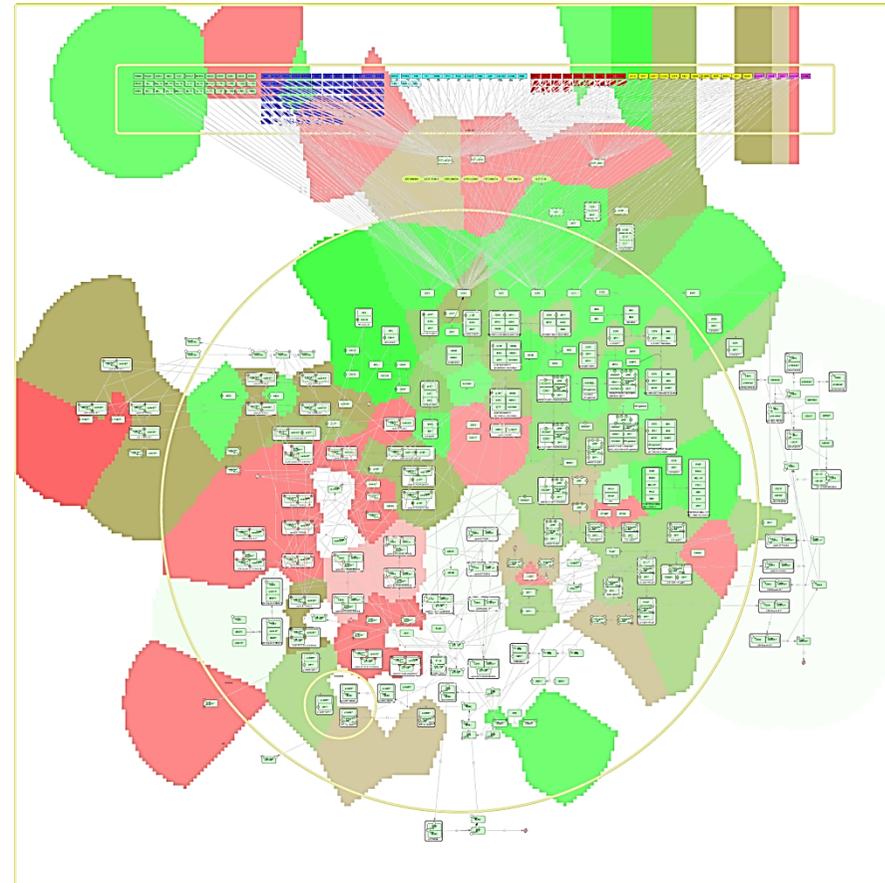


RB/E2F map colour staining

non-invasive



invasive



3. NaviCell

Navigating through reaction maps

<http://navicell.curie.fr>



Navigation, curation and maintenance of molecular interactions maps

HOME

MAPS

FEATURES

USER'S GUIDE

VIDEO TUTORIAL

INSTALL NAVICELL

UPLOAD YOUR MAP

FAQ

CONTACTS

PUBLICATIONS

HOW TO CITE US

PEOPLE

ACKNOWLEDGEMENT

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:

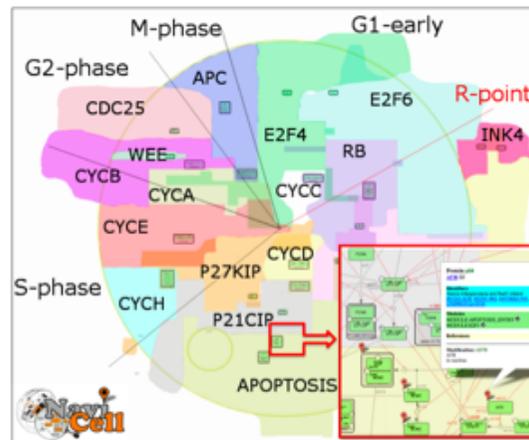
Map browsing by Google map™ engine

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



Resources

ACSN ATLAS OF CANCER
SIGNALLING NETWORKS

CELLESDIGNER

SBGN SYSTEMS
BIOLOGY GRAPHICAL
NOTATION

CYTOSCAPE

BINOM

LITERATURE

Databases

CELL SIGNALING

KEGG

PANTHER

REACTOME

REPAIRTOIRE

SPIKE

WIKIPATHWAYS

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

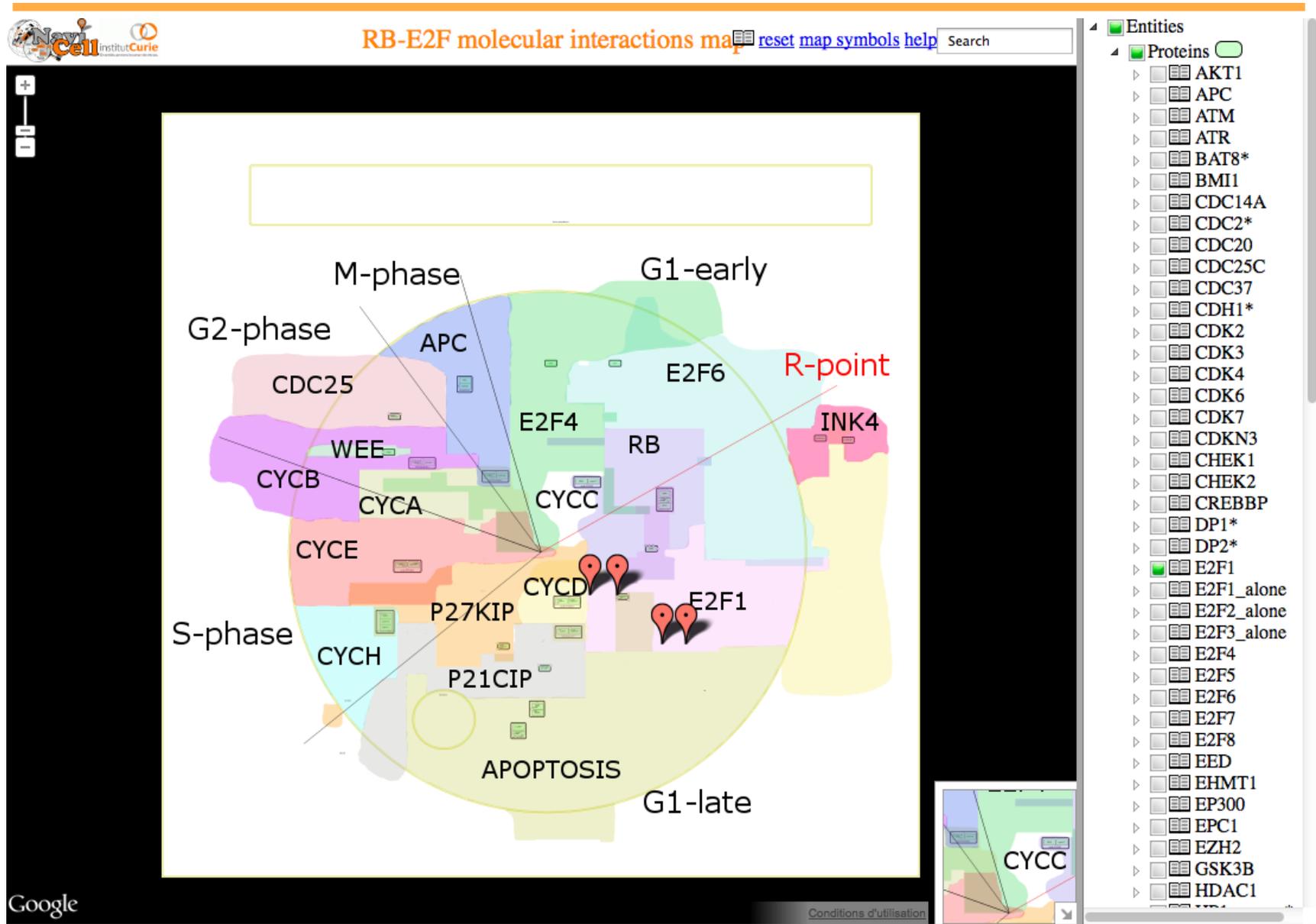
Signaling pathways of Alzheimer's disease

Sample examples

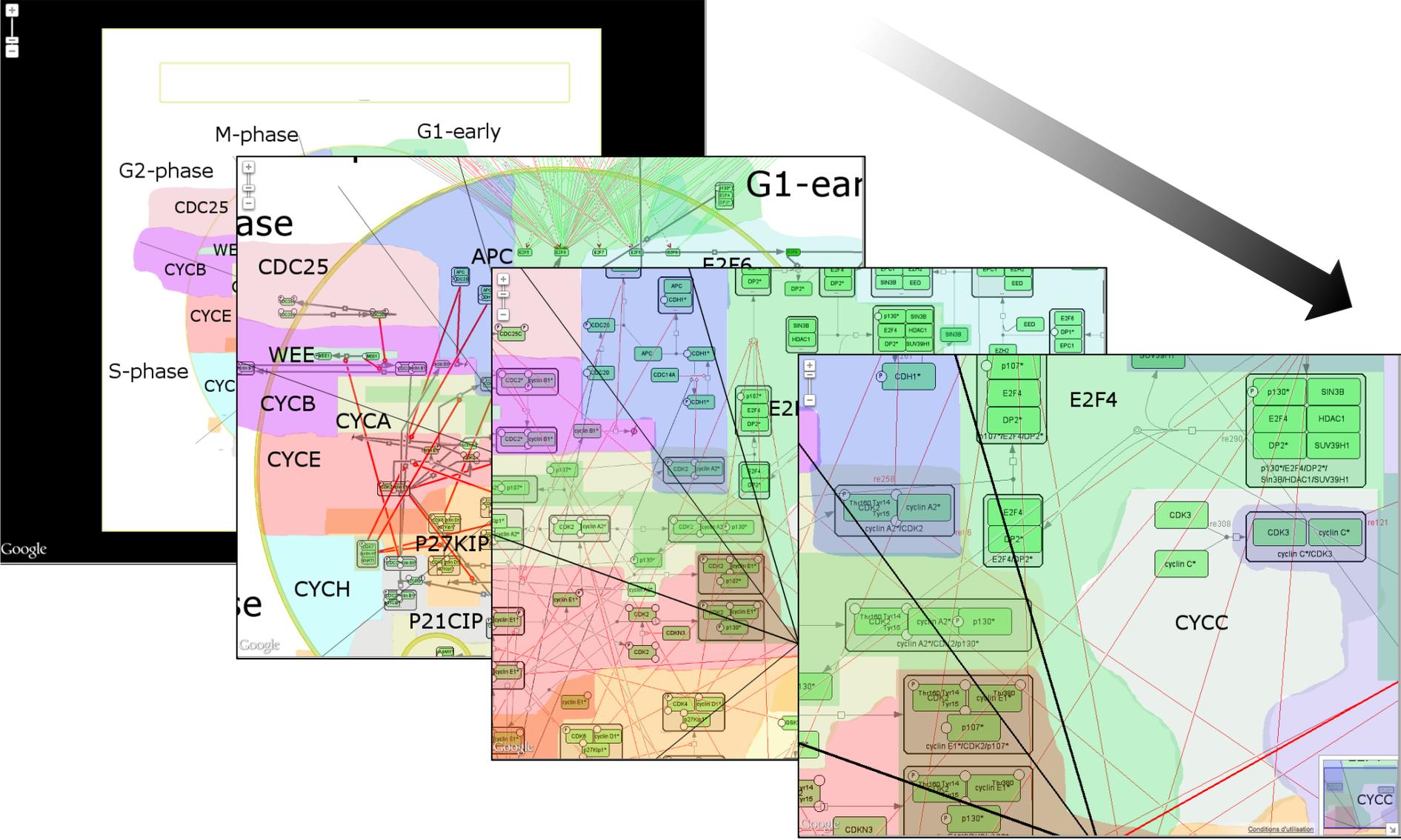
MPhase map from CellDesigner sample set



RB/E2F map



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