



institut**Curie**



**Biological NetwOrk Manager
Cytoscape plugin**

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**U900 Institut Curie/INSERM/Ecole de Mines
“*Computational Systems Biology of Cancer*”**

<http://bioinfo.curie.fr/sysbio>



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Director of the U900 Institut Curie/INSERM/Ecole de Mines ParisTech
Data integration, Systems Biology of Cancer, Dynamics of network motifs



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SITCON project, next generation sequencing
Genomic sequence analysis



Laurence Calzone, PhD
APO-SYS and CALAMAR projects
Cell-cycle modeling



Gautier Stoll, PhD
SITCON project
Pathway qualitative modeling



Thomas Fink, PhD
Dynamics of network motifs
Information theory for data analysis



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APO-SYS project
Systems Biology of Apoptosis



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SITCON project
Regulatory sequence analysis



Antonio Cappuccio, PhD
ANR 'Skin TSLP' project
Systems Immunology



Inna Kuperstein, PhD
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Systems biology of cancer



Paola Vera-Licona, PhD
Curie-Servier alliance on basal breast cancer
Mathematical modeling of biological networks



Andrei Zinovyev, PhD
Scientific coordinator of the Systems Biology team
Systems Biology of Cancer, Complexity and Model reduction

We are rather standards consumers than creators

Modeling cancers
(breast cancer, bladder cancer, Ewing's sarcoma)

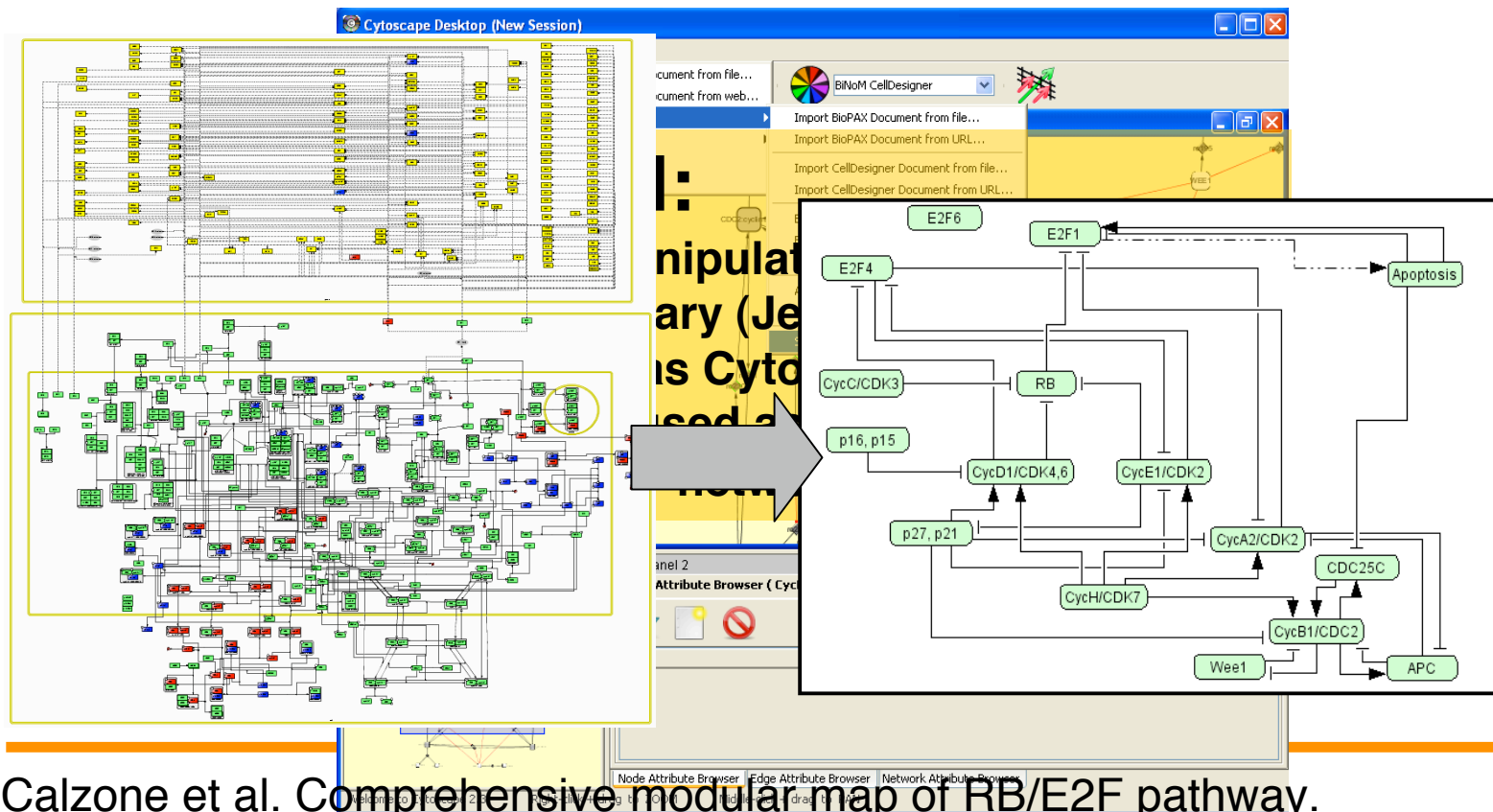
Modeling molecular mechanisms
(cell cycle, DNA repair, apoptosis)

Creating big comprehensive maps (~1000 chemical species)



facilitates model building in the bottom-up approach

Comprehensive network -> Biological question -> Network manipulations -> Small model



Calzone et al. Comprehensive modular map of RB/E2F pathway. Molecular Systems Biology, 2008

Evolution of (BiNoM)ⁿ (2006-2010)

2006: RB/E2F pathway map in CellDesigner – what to do with it?

2006: CellDesigner -> Cytoscape converter

2007: CellDesigner -> BioPAX converter

2007: BioPAX -> Cytoscape converter (different from the standard one)

2007: BioPAX -> SBML converter

2007: BioPAX editor for Cytoscape

2007: Structural analysis of RB/E2F map – set of graph theory algorithms

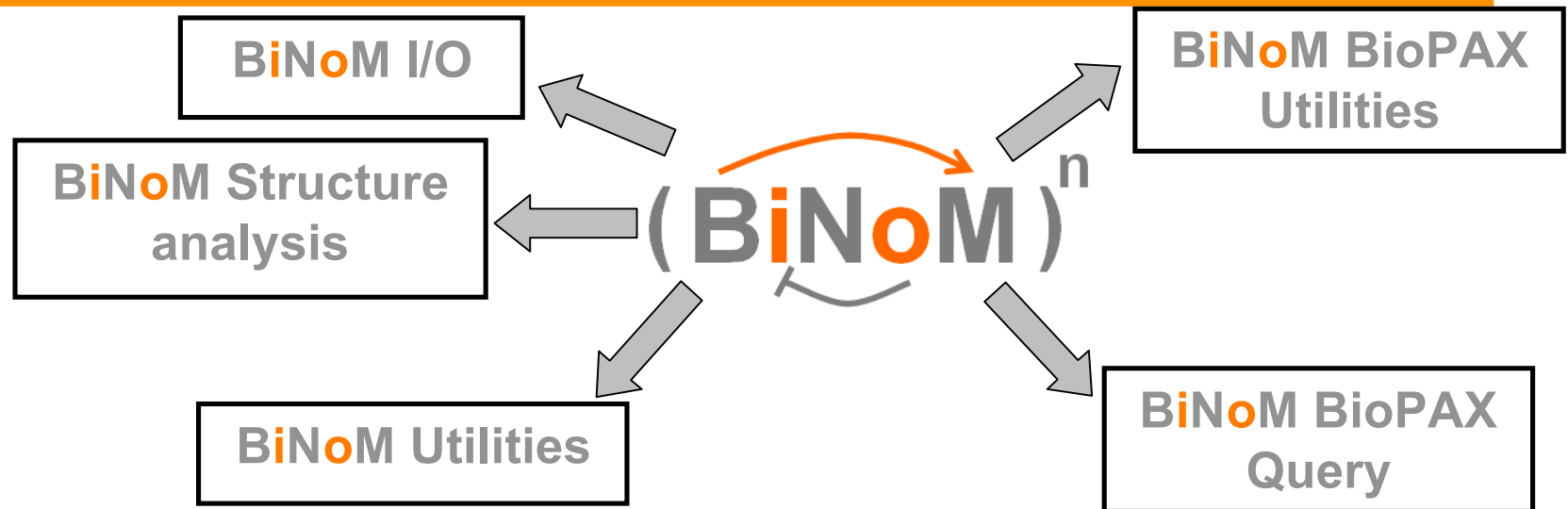
2008: Improving Cytoscape functions (clipboard, graph merging and decomposition)

2008: Indexing and querying large BioPAX files
(Reactome, Transpath) to compare maps with databases

2009: Algorithms for analyzing path distributions

2010: CSML -> Cytoscape converter (to work with Biobase Explain)

BiNoM (Zinovyev et al., Bioinformatics, 2008)



Some Functions of the version 1.0:

Import of BioPAX, SBML, CellDesigner and simple influence network formats

Export to BioPAX, SBML and CellDesigner formats after user manipulations

Network clipboard

Conversion between standards (CellDesigner->BioPAX, BioPAX->SBML)

Full support of BioPAX information

(reaction network, interaction network, pathway structure, references)

Editing BioPAX content

Structural analysis of the networks (extracting strongly connected components, clustering relevant cycles, structural pathway analysis, modular network representation, path analysis)

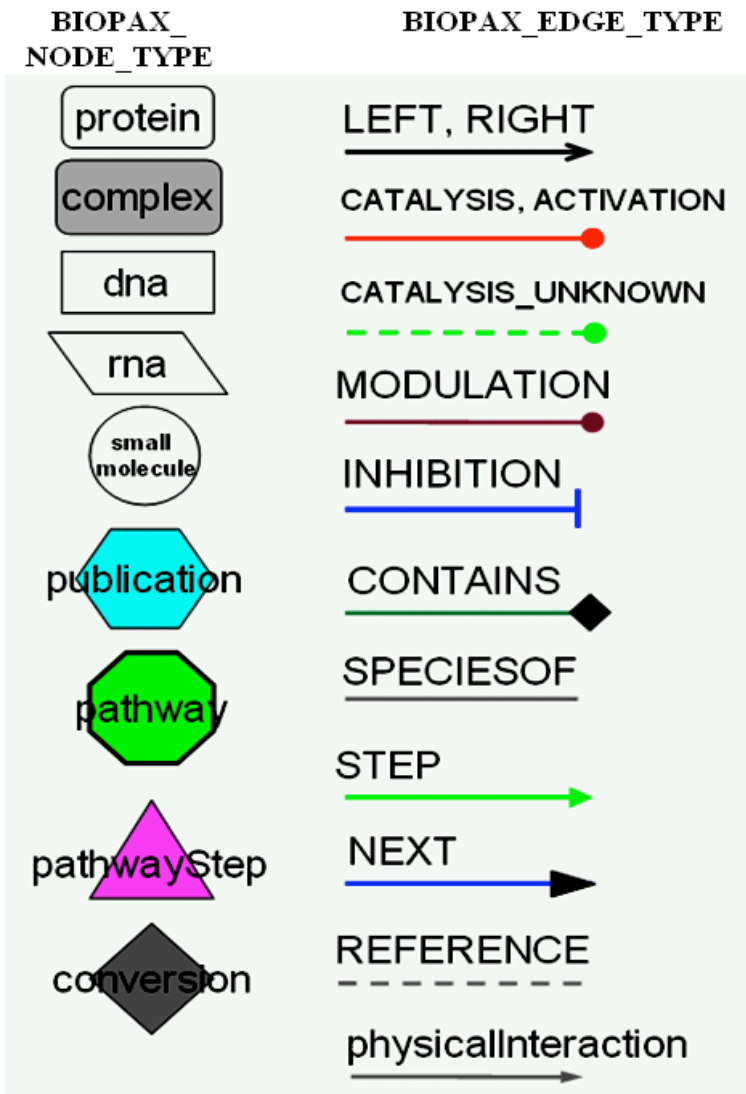
Biological network databases query system

Typical scenarios

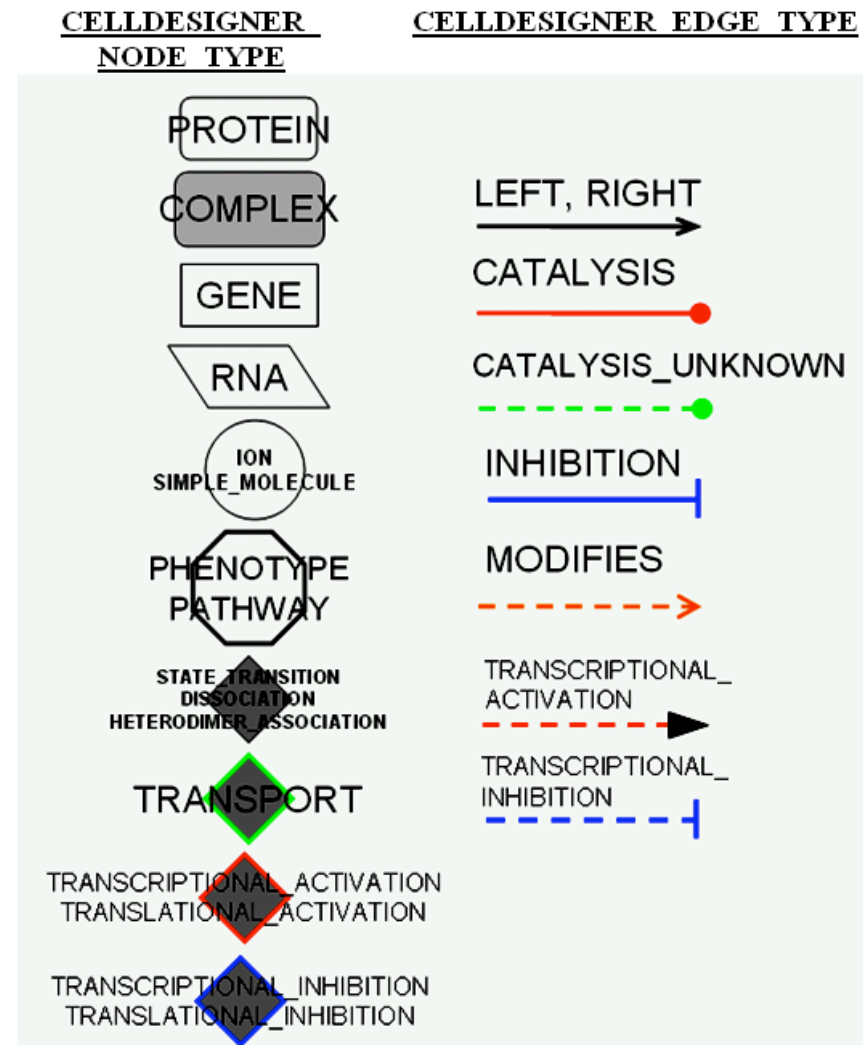
- 1) Import CellDesigner diagram, manipulate, convert to BioPAX
 - 2) Import CellDesigner diagram, put colors and save it back
 - 3) Import CellDesigner diagram, analyze, decompose into modules, create a modular view of the diagram
 - 4) Import CellDesigner diagram, create a clickable web page
 - 5) Import BioPAX file, extract a part, export to SBML, create a model
 - 6) Import BioPAX file, edit, save it back
 - 7) Create a BioPAX file from simple factsheet (managing families, implicit reactions)
 - 8) Index huge BioPAX file (i.e., whole Reactome), make a query, save result as small BioPAX file
- etc.

Cytoscape and Sysbio standards: Only some features of SBGN notation

BiNoM BioPAX visual mapper

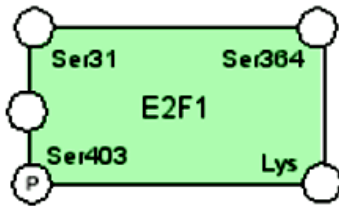


BiNoM CellDesigner visual mapper

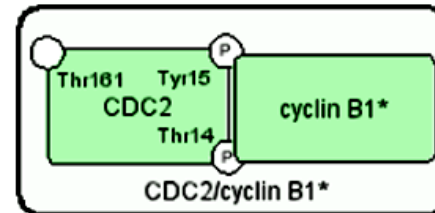


Naming convention: Need for a standard for a textual glyph encoding (SBTN? :)

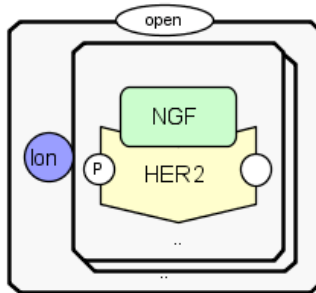
Entity1_name|Modification1|Modification2|...: Entity2_name|Modifications...[_active|_hmN]@compartment



E2F1|Ser403_pho@nucleus

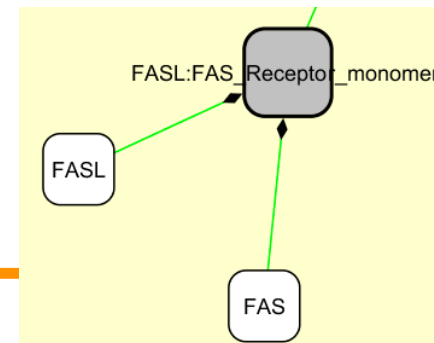
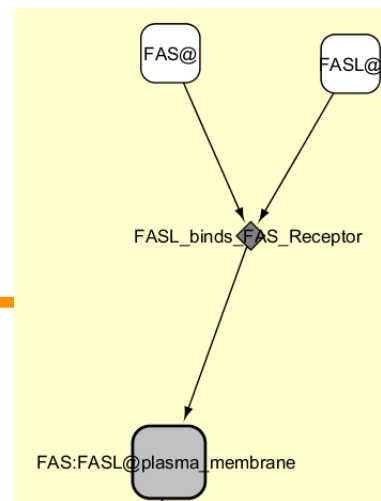


CDC2|Tyr15_pho|Thr14_pho:cyclinB1*@cytoplasm



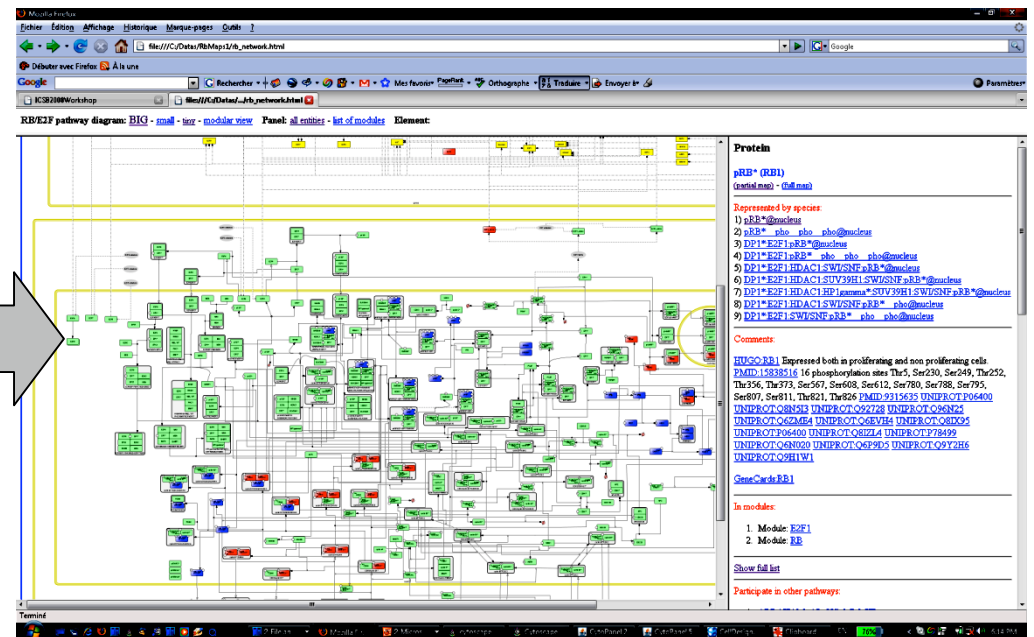
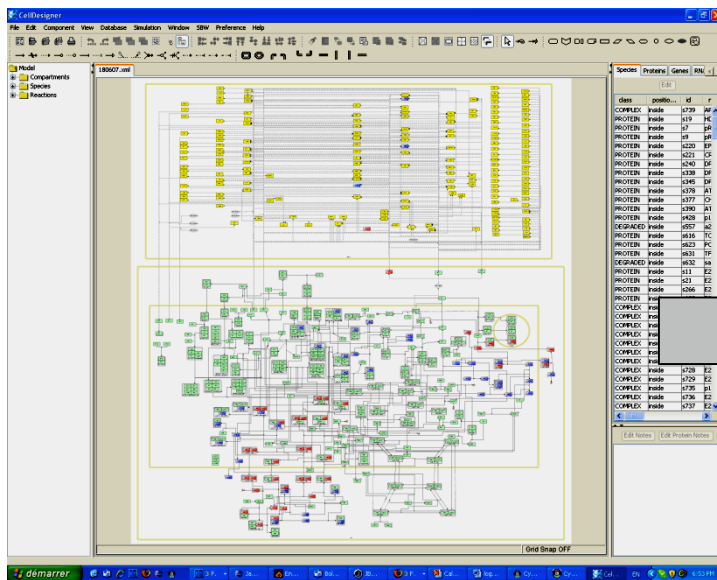
(ION:(HER2|phol:NGF)|hm2)lopen@plasma_membrane

Using “@” distinguishes entities from chemical species



Generation of web pages for browsing CellDesigner diagrams online

<http://bioinfo.curie.fr/projects/rbpathway>



Working with BioPAX files: Need for a standard mapping onto a graph?

The screenshot shows the Cytoscape Desktop interface. The 'Plugins' menu is open, displaying options such as 'Merge networks', 'BiNoM I/O', 'BiNoM Analysis', 'BiNoM BioPAX Utils', 'BiNoM BioPAX Query', and 'BiNoM Utilities'. The 'BiNoM I/O' sub-menu is expanded, showing options like 'Import BioPAX Document from file...', 'Import BioPAX Document from URL...', 'Import CellDesigner Document from file...', 'Import CellDesigner Document from URL...', 'Import influence network from AIN file...', 'Export current network to BioPAX...', 'Export current network to CellDesigner...', 'Export current network to SBML...', 'Associate BioPAX Source...', 'Save whole associated BioPAX as...', 'Associate CellDesigner Source...', 'List all reactions...', and 'List all nodes...'. The 'BiNoM Parameters' dialog box is open, showing checked options for 'Reaction Network', 'Pathway Hierarchy', 'Include Pathways', 'Include Interactions', and 'Protein-protein interactions'. There are also unchecked options for 'Make Root Pathway Node', 'Include Next Links', and 'Include Pathways'. The background shows a network graph with various nodes and edges.

BiNoM Parameters

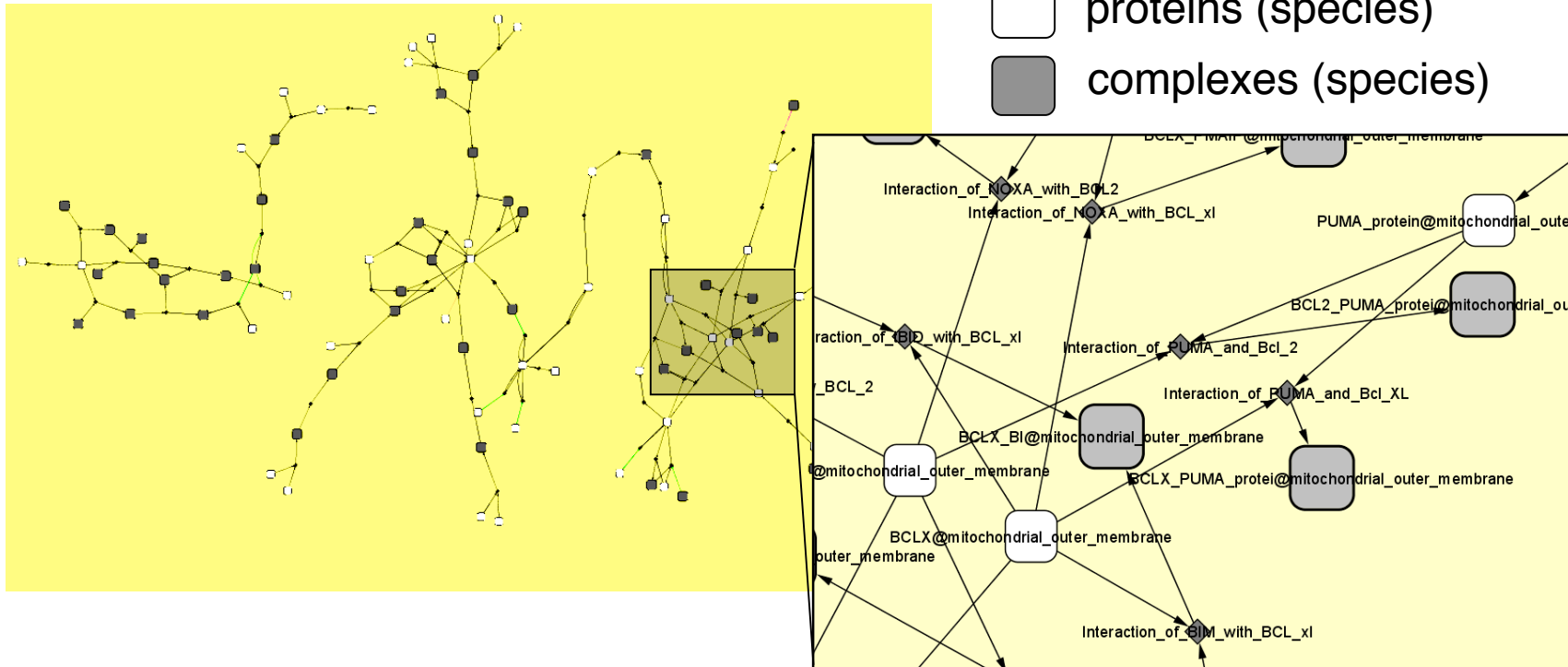
- Reaction Network
- Pathway Hierarchy
 - Make Root Pathway Node
 - Include Next Links
- Include Pathways
- Include Interactions
- Protein-protein interactions

OK Cancel

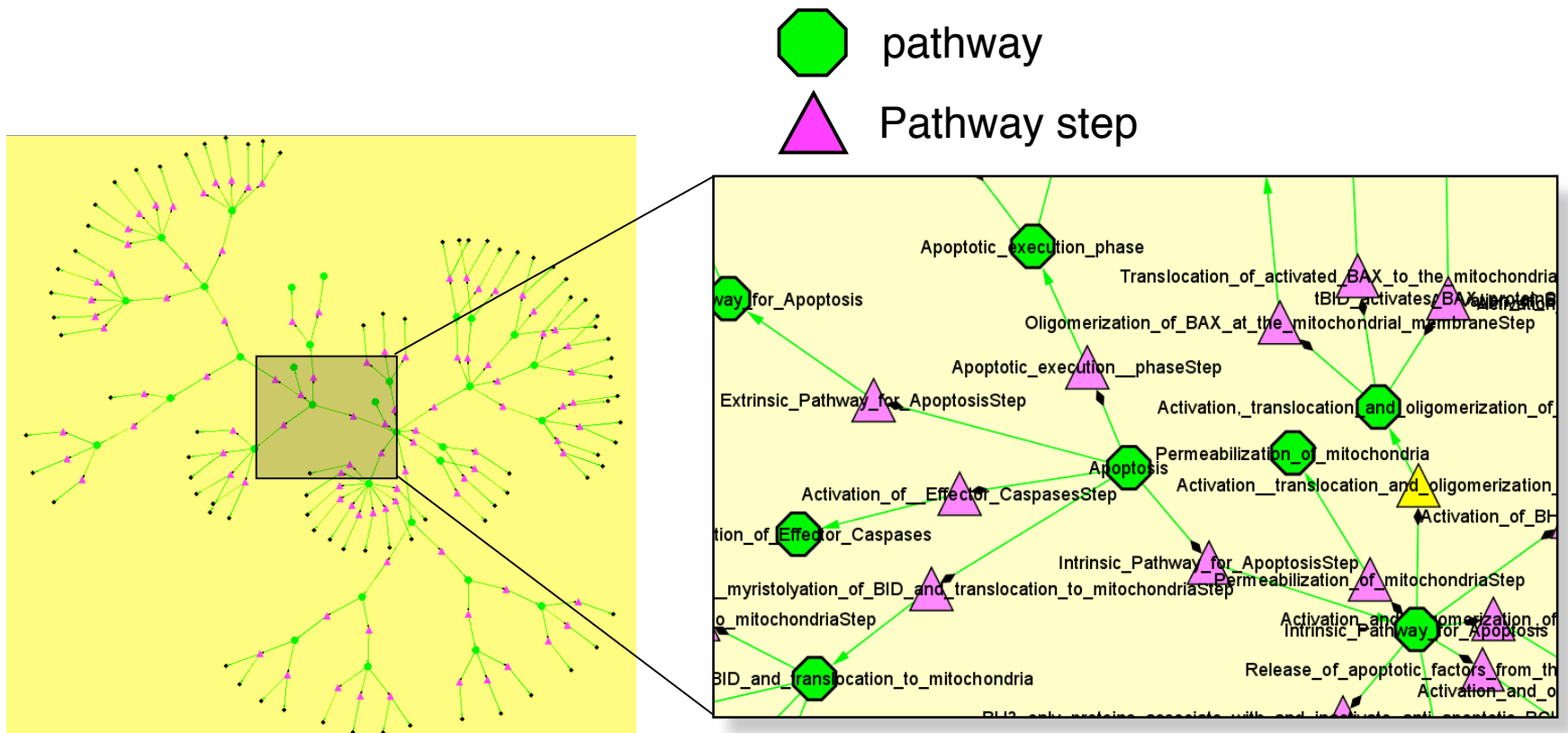
+ other, like co-citation network

Reaction network representation

- ◆ reactions
- proteins (species)
- complexes (species)



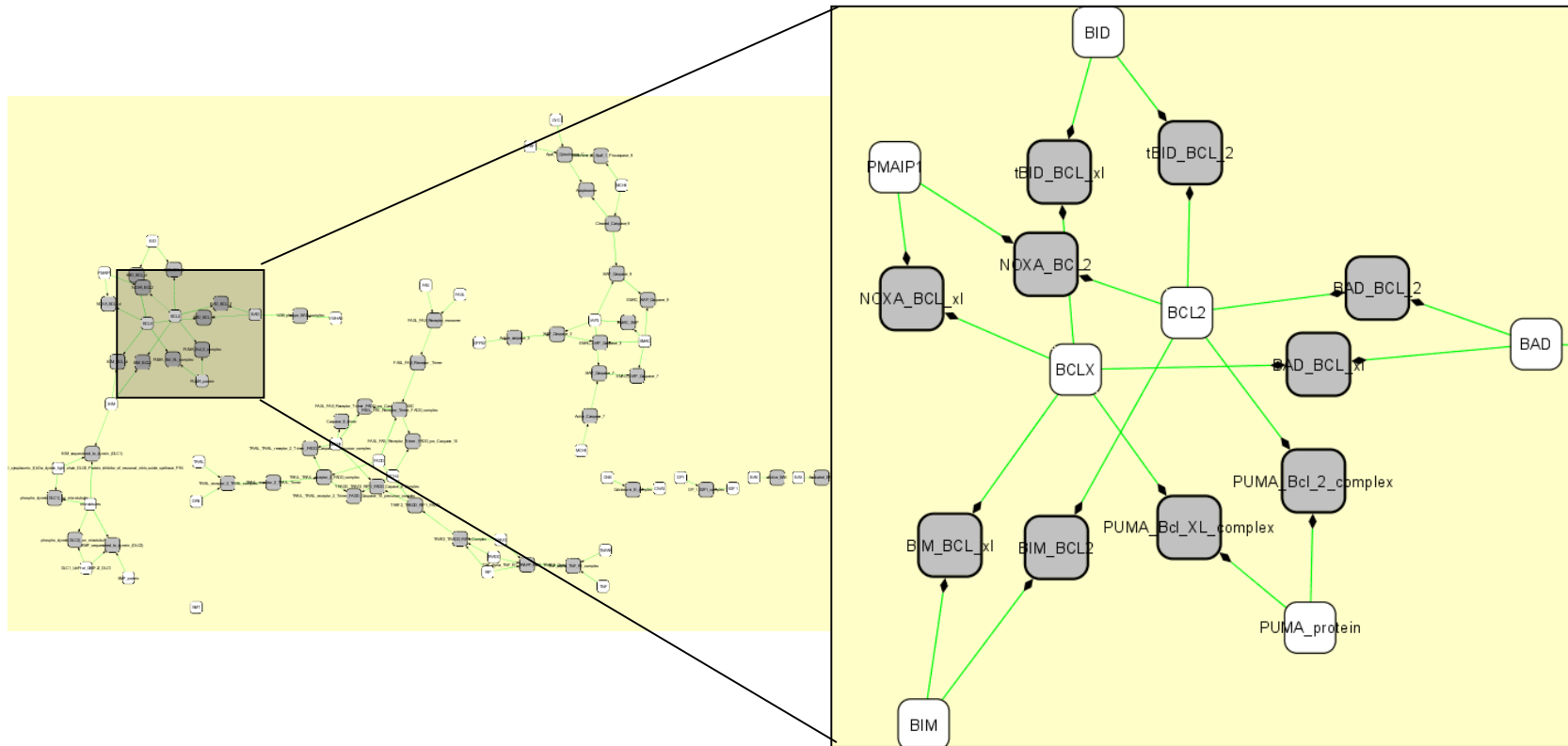
Pathway structure representation



'Protein interactions' representation

□ proteins (entities)

■ complexes (entities)



Basic BioPAX editor

The screenshot displays the Cytoscape Desktop environment with the BioPAX editor open. The main window shows a network diagram with nodes representing proteins and interactions. The BioPAX Property Editor is open for the 'SMAC' protein, showing its class, object, function, and other attributes. The BioPAX Class Tree: Apoptosis PP is also visible, showing a hierarchical view of the class structure.

Cytoscape Desktop (Session: data)
File Edit View Select Layout Plugins Help

BioPAX Property Editor
Valid attributes displayed | Display all attributes | << | >> | Close current tab | Close all tabs | Edit

SMAC@cytosol_SMAC3	SMAC@mitochondrial_intermembrane_space	API3_CPP32_CPP32@cytosol_XIAP_Caspase_3_cytosol
API3_MCH6_MCH6_SMAC@cytosol_SMAC_XIAP_Caspase_9_cytosol_2	API3_MCH6_MCH6@cytosol_XIAP_Caspase_9_cytosol	
XIAP_Caspase_7	SMAC_XIAP_Caspase_7	SMAC_XIAP_Caspase_3
SMAC_binds_XIAP_Caspase_9	SMAC_binds_XIAP_Caspase_3	Release_of_SMAC_from_mitochondria
		SMAC

Class protein
Object SMAC

COMMENT
FUNCTION: Promotes apoptosis by activating caspases in the cytochrome c/Apaf-1/caspase-9 pathway. Acts by opposing the inhibitory activity of inhibitor of apoptosis proteins (IAP). SUBUNIT: Homodimer. Interacts with BIRC2, BIRC3, BIRC4/XIAP and BIRC7. SUBCELLULAR LOCATION: Mitochondrial but released into the cytosol when cells undergo apoptosis. ALTERNATIVE PRODUCTS: Event=Alternative splicing; Named isoforms=2; Name=1; Isold=Q9NR28-1; Sequence=Displayed; Name=2; Synonyms=Diablo-S; Isold=Q9NR28-2; Sequence=VSP_004397; TISSUE SPECIFICITY: Ubiquitously expressed with highest expression in testis. Expression is also high in heart, liver, kidney, spleen, prostate and ovary. Low in brain, lung, thymus and peripheral blood leukocytes. DOMAIN: The mature N-terminus mediates interaction with BIRC4/XIAP.

DATA_DASH_SOURCE [ReactomeDataSource](#)

NAME
UniProt:Q9NR28-1 Diablo homolog, mitochondrial precursor (Second mitochondria-derived activator of caspase) (Smac protein) (Direct IAP binding protein with low pI)

ORGANISM [Homo_sapiens](#)

SYNONYMS
DIABLO
SMAC

XREF [Q9NR28@UniProt](#)

BioPAX Class Tree: Apoptosis PP
Strict instances displayed | Display sub instances | New instance | protein

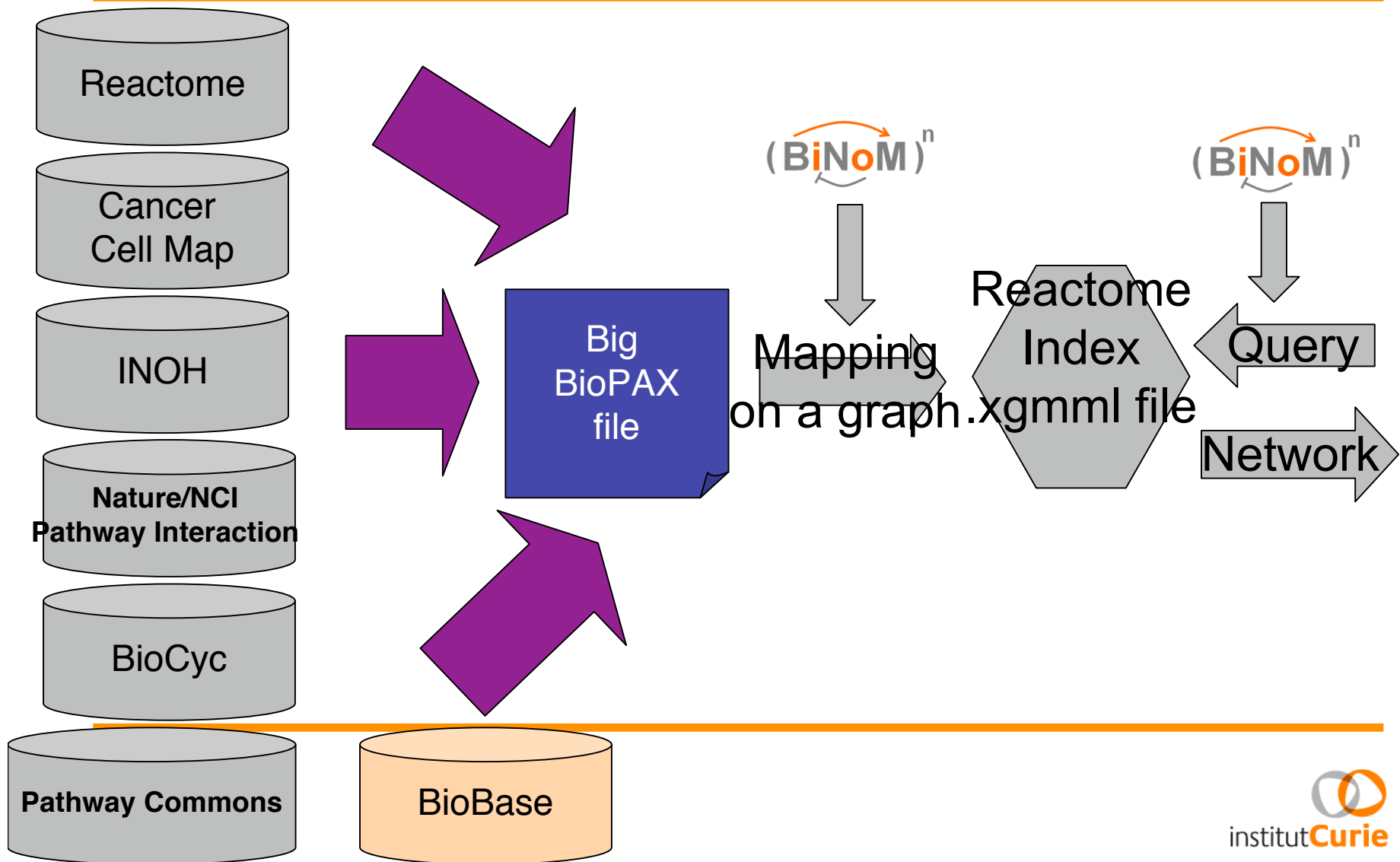
- interaction (0)
 - physicalInteraction (0)
 - control (0)
 - catalysis (10)
 - modulation (5)
 - conversion (0)
 - biochemicalReaction (66)
 - pathway (32)
 - physicalEntity (1)
 - complex (48)
 - protein (41)
 - utilityClass (0)
 - confidence (0)
 - deltaGrimeO (0)
 - evidence (0)

Node Attribute Browser | **Edge Attribute Browser** | **Network Attribute Browser**

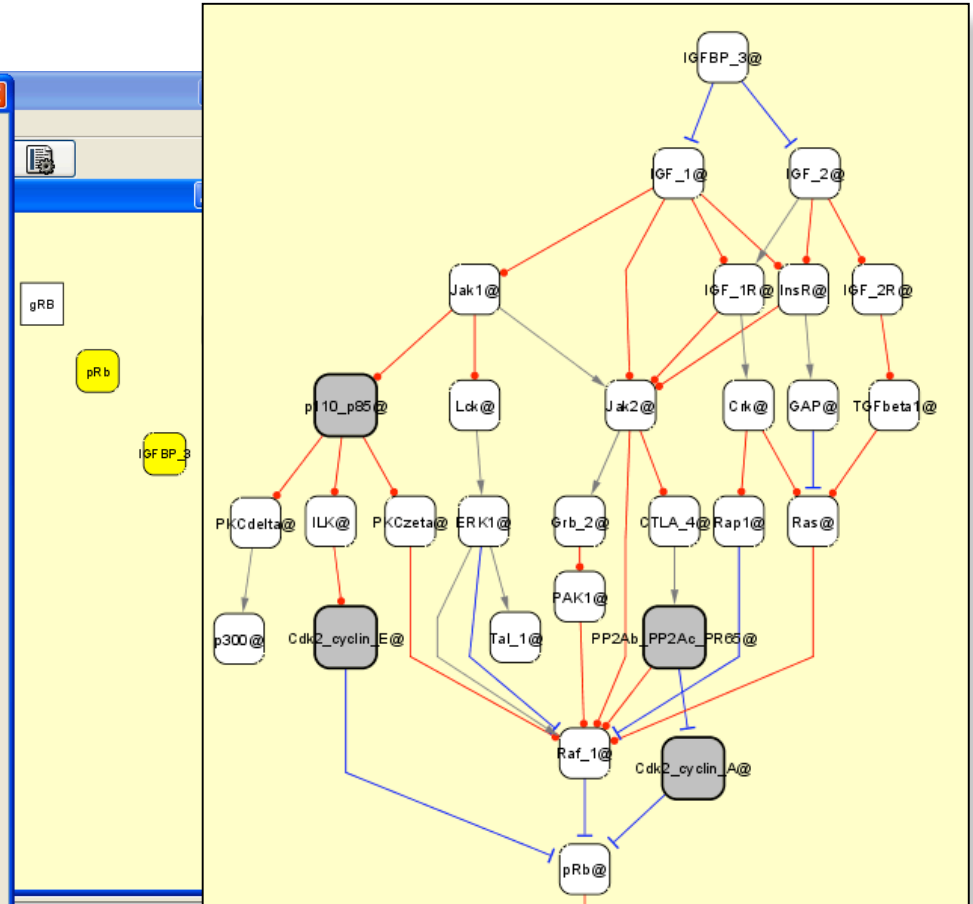
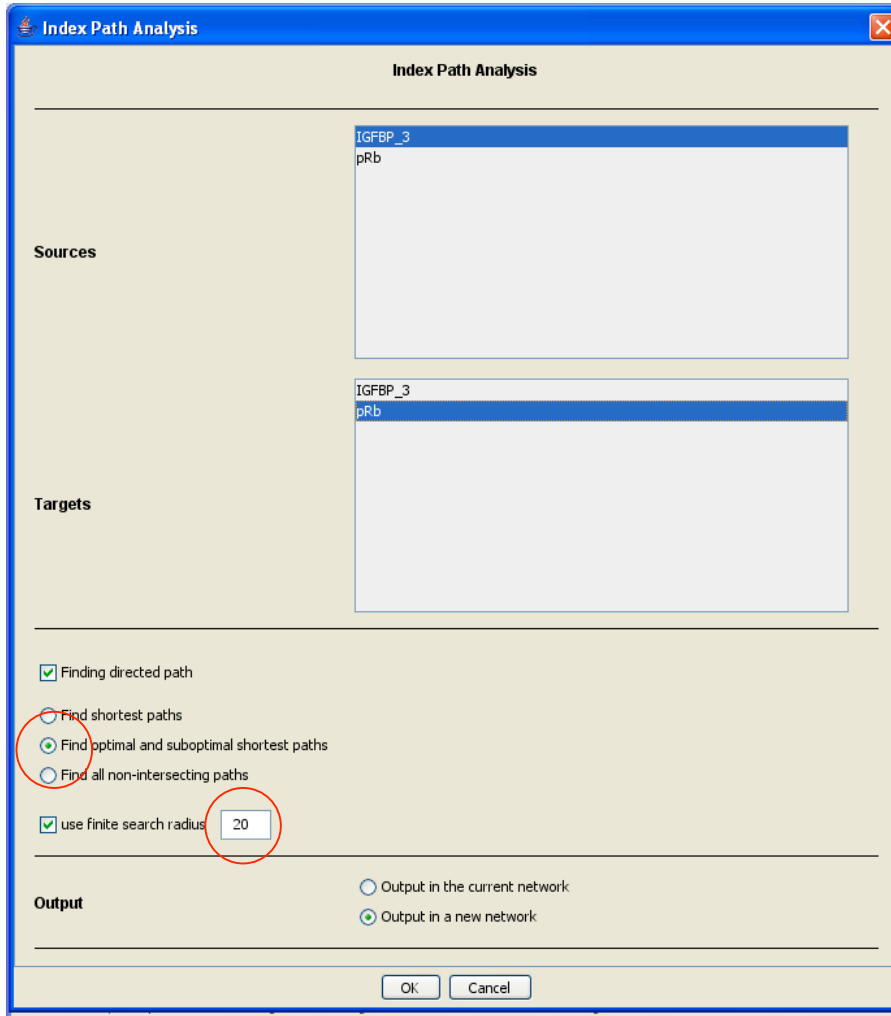
Welcome to Cytoscape 2.4.0 | Right-click + drag to ZOOM | Middle-click + drag to PAN

6:42 PM

Pathway Database -> BioPAX -> BiNoM query



... Give the shortest and suboptimal paths connecting given proteins

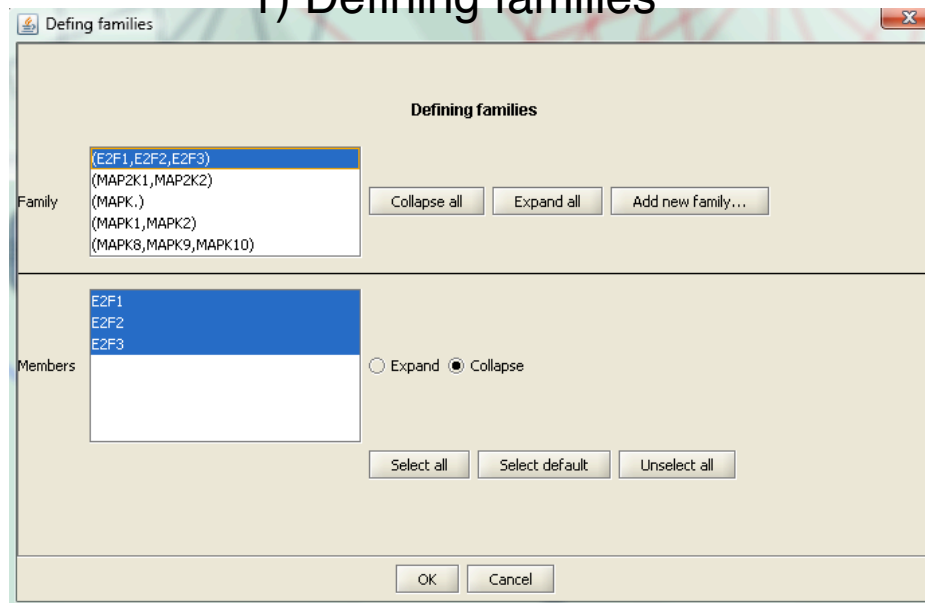


Export to BioPAX
Export to SBML

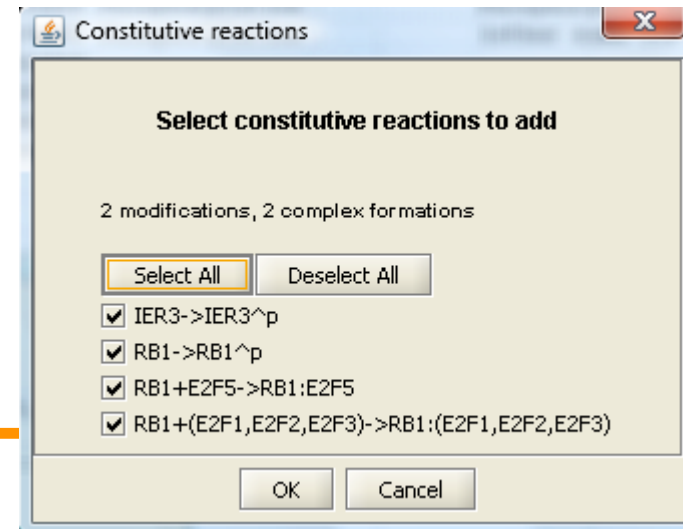
Create BioPAX file from a simple text file (Facts sheet)

Link	ReviewRef	ChemType	Tissue	Comments
TNFSF15->(MAPK8,MAPK9,MAPK10)	PMID:9889183	Influence	U-937 cells	seems more persistant than TNF activation. (Other name for (MAPK8,MAPK9,MAPK10): JNK), (other name for TNFSF15: VEGI)
(MAP2K1,MAP2K2)->(MAPK1,MAPK2)	PMID:12020800	Phosphorylation	All	
(MAPK1,MAPK2)->BAX	PMID:12020801	Influence	mutant	pro-apoptotic effects of MAP kinases in case of DNA damage
MAPK2->TP53	PMID:12020802	Phosphorylation	.	Phosphorylate p53 at Thr55, which increase transcriptional activity
(MAPK1,MAPK2)->IER3^p	PMID:12020803	Phosphorylation	.	(other name for IER3: IEX-1)
IER3->(MAPK1,MAPK2)	PMID:12020804	.	.	.
PRKCB1->(MAPK.)	PMID:12020804	.	.	.
PRKCB1->RB1^p	PMID:12020804	.	.	.
(RB1:E2F5)- [cell_cycle]	PMID:12020804	.	.	.
(RB1:(E2F1,E2F2,E2F3))->[cell_cycle]	.	Transcriptional	.	.
BAX->CYCS				

1) Defining families

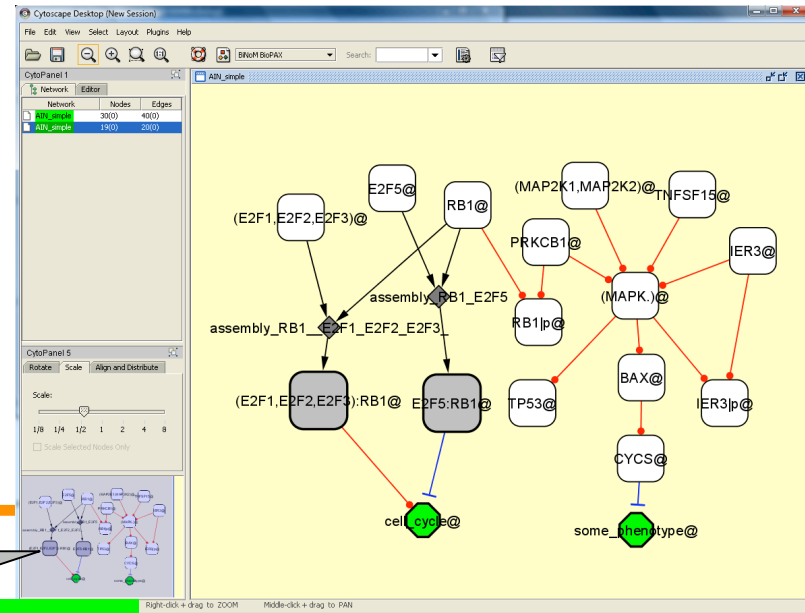
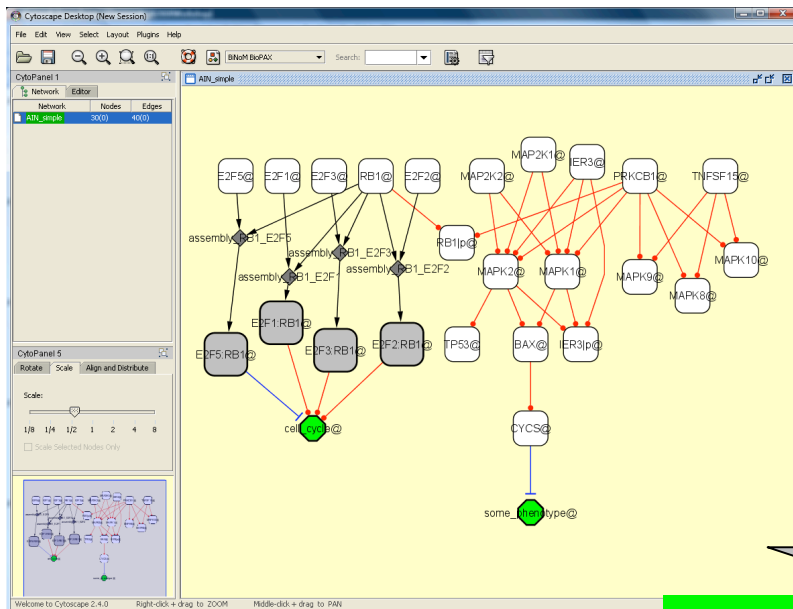


2) Consistency check



Create BioPAX file from a simple text file (Facts sheet)

Link	ReviewRef	ChemType	Tissue	Comments
				seems more persistent than TNF activation. (Other name for (MAPK8,MAPK9,MAPK10): JNK), (other name for TNFSF15: VEGI)
TNFSF15->(MAPK8,MAPK9,MAPK10)	PMID:9889183	Influence	U-937 cells	
(MAP2K1,MAP2K2)->(MAPK1,MAPK2)	PMID:12020800	Phosphorylation	All	
(MAPK1,MAPK2)->BAX	PMID:12020801	Influence	mutant	pro-apoptotic effects of MAP kinases in case of DNA damage
MAPK2->TP53	PMID:12020802	Phosphorylation	.	Phosphorylate p53 at Thr55, which increase transcriptional activity
(MAPK1,MAPK2)->IER3^p	PMID:12020803	Phosphorylation	.	(other name for IER3:IEX-1)
IER3->(MAPK1,MAPK2)	PMID:12020804	.	.	.
PRKCB1->(MAPK.)	PMID:12020804	.	.	.
PRKCB1->RB1^p	PMID:12020804	.	.	.
(RB1:E2F5)-[cell_cycle]	PMID:12020804	.	.	.
(RB1:(E2F1,E2F2,E2F3))->[cell_cycle]	.	Transcriptional	.	.
BAX->CYCS				



Export to BioPAX
Export to SBML

Nearest future

- 1) BioPAX 3.0 support
- 2) ~~CellDesigner format 4.1 support~~ done!
- 3) ~~Cytoscape 2.7.0 support~~ done!
- 4) Publication with a case study

Acknowledgements

Eric Viara

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Daniel Rovera

