

BiNoM, a Cytoscape plugin for accessing and analyzing pathways using standard systems biology formats

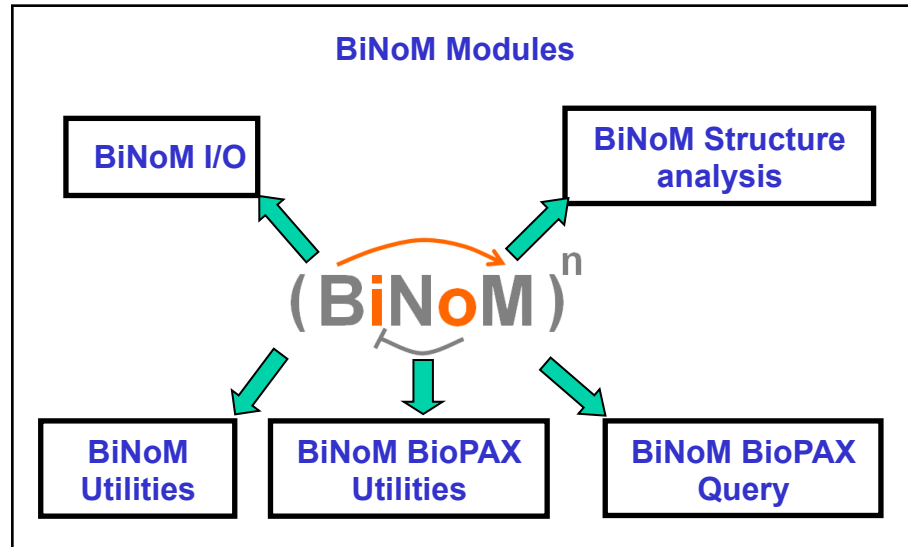
Eric Bonnet

Computational Systems Biology of Cancer
Institut Curie - INSERM U900 - Mines ParisTech

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

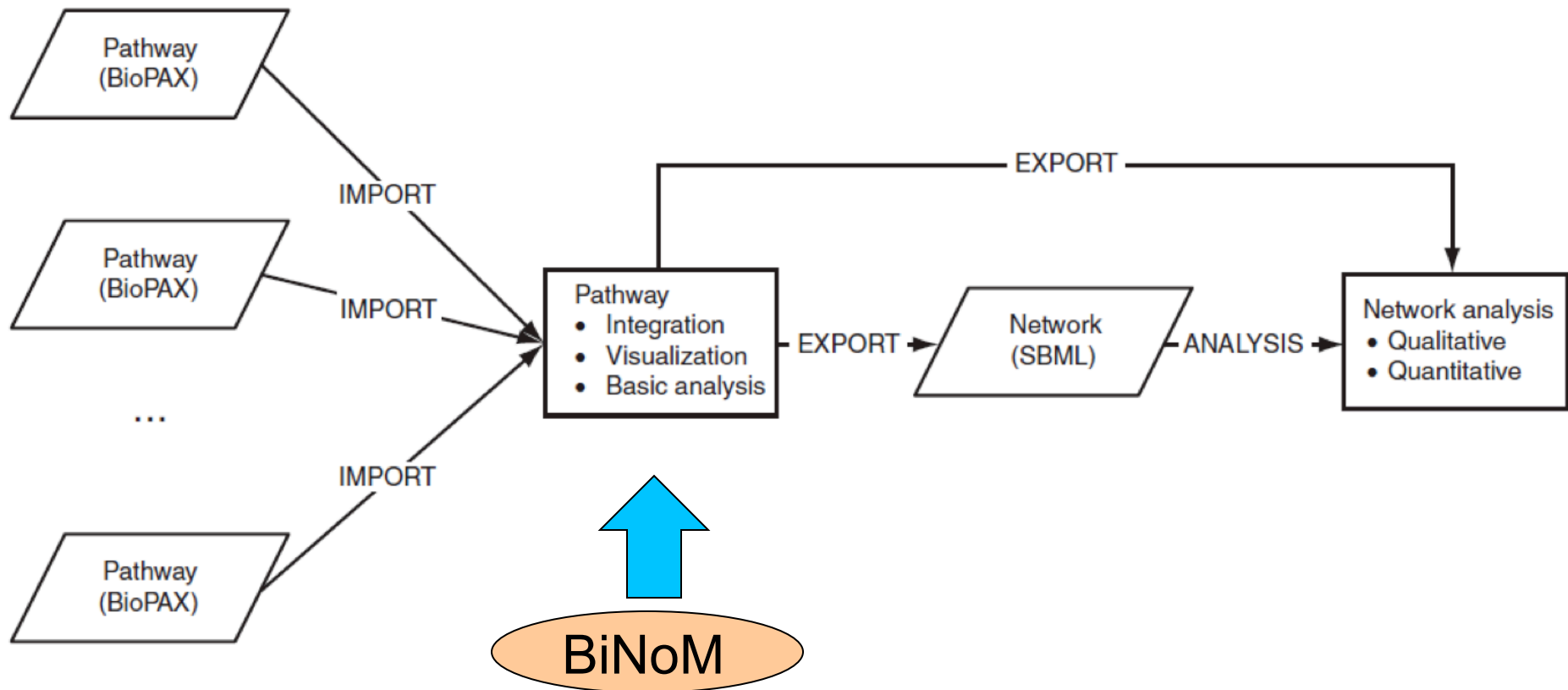
COMBINE 2012 – Toronto

BiNoM, a Biological Network Manager



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

BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. Zinovyev A, Viara E, Calzone L, Barillot E. Bioinformatics. 2008 Mar 15;24(6):876-7.

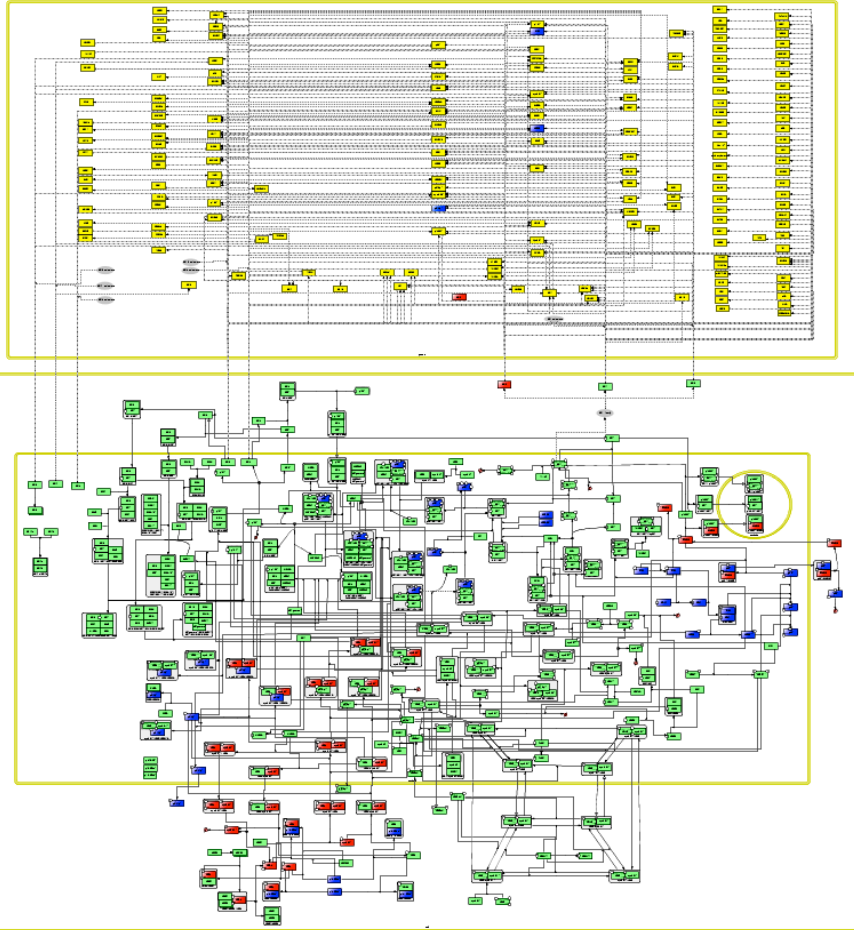


Use of data from public pathway databases for modelling purposes (from Bauer-Mehren et al., Pathway databases and tools for their exploitation: benefits, current limitations and challenges. 2009 Molecular Systems Biology 5:290).

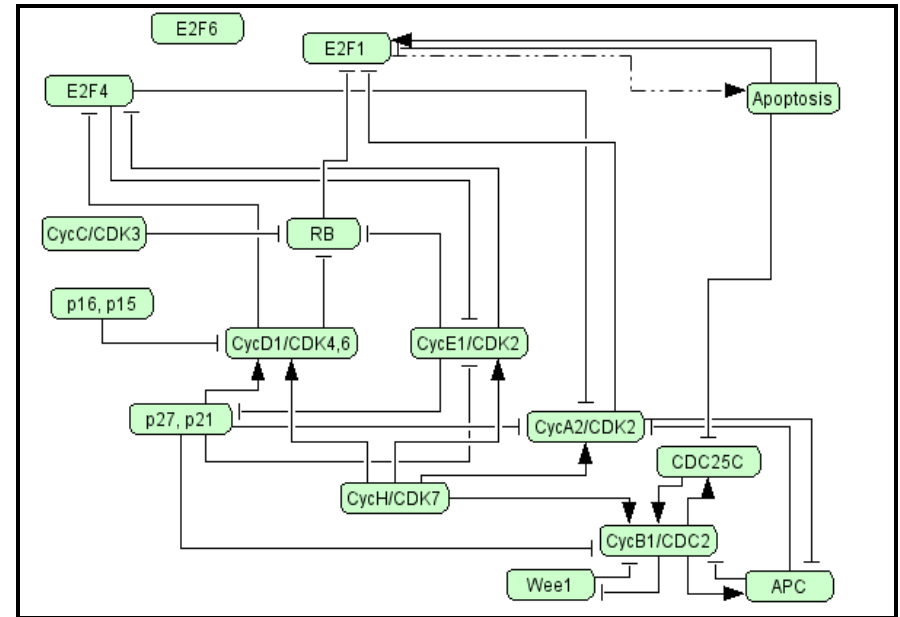
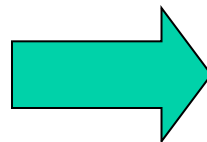
BiNoM typical scenarios

1. Import a CellDesigner diagram, manipulate, convert to BioPAX.
2. Import a CellDesigner diagram, analyze, decompose into modules, create a network modular view.
3. Import BioPAX file, extract a part, export to SBML, create a mathematical model.
4. Create a BioPAX file from simple factsheet text file.
5. Index huge BioPAX file (i.e., whole Reactome), make a query, save result as a smaller BioPAX file.

Knowledge extraction

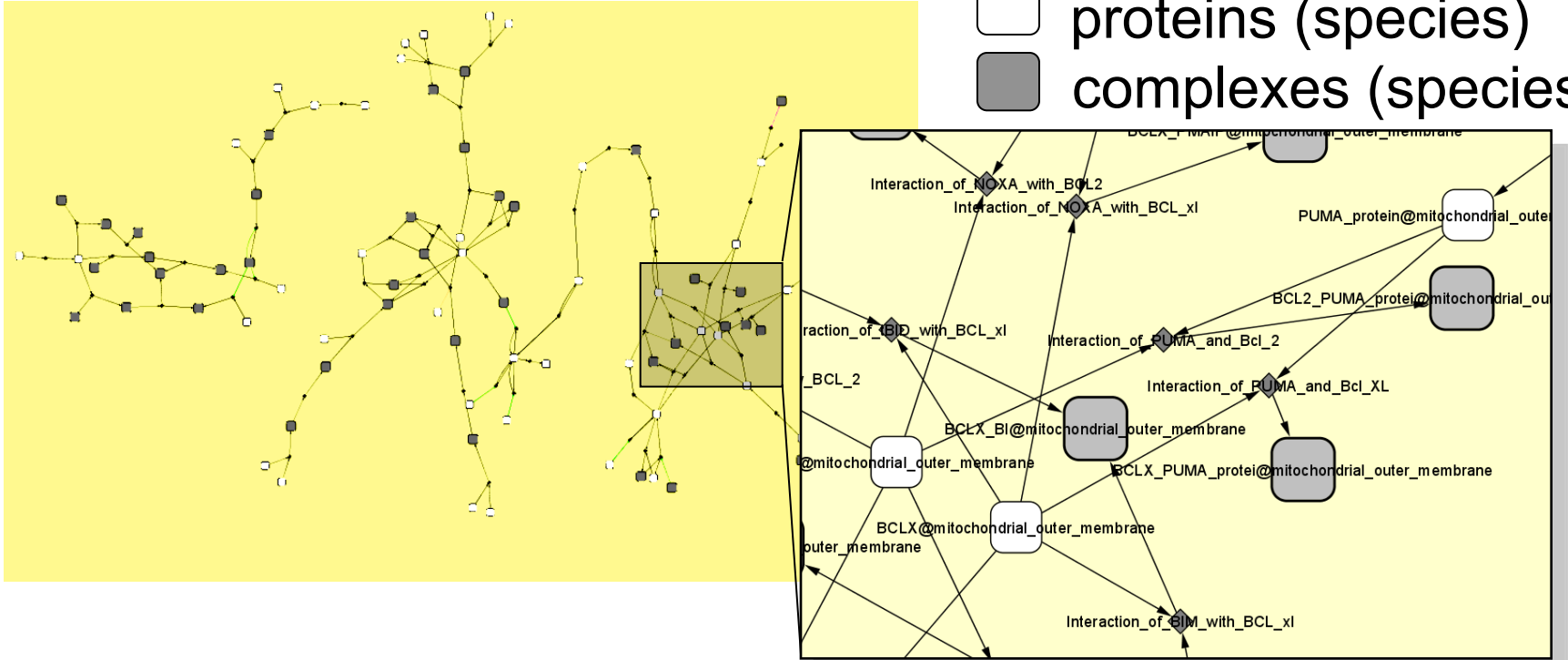
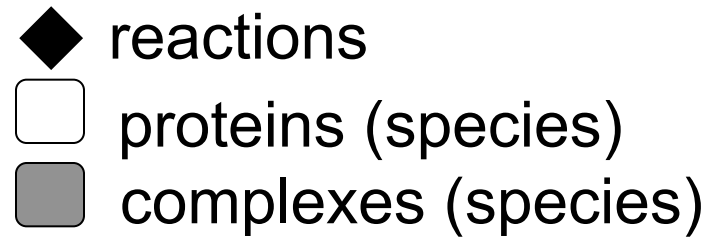


RB / E2F network, 70+ proteins,
160+ reactions, 350 publications

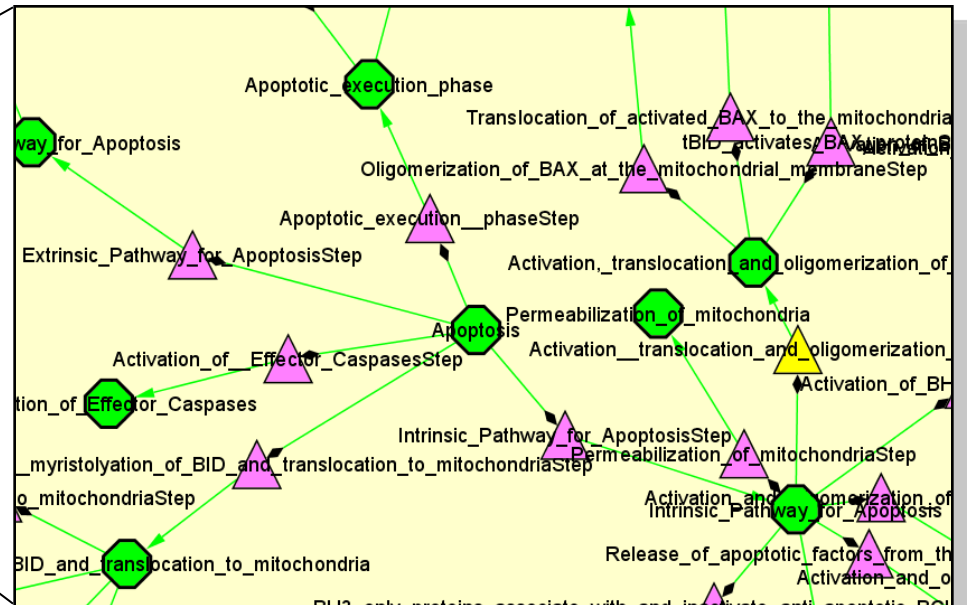
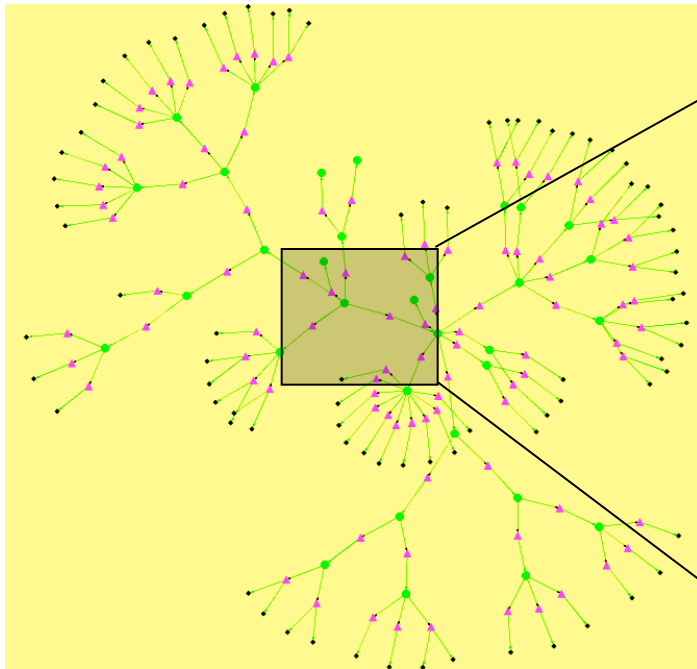
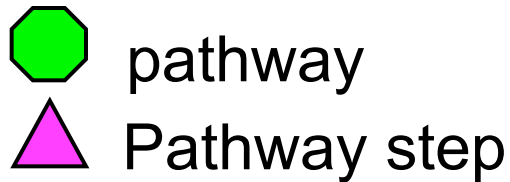


Modular representation

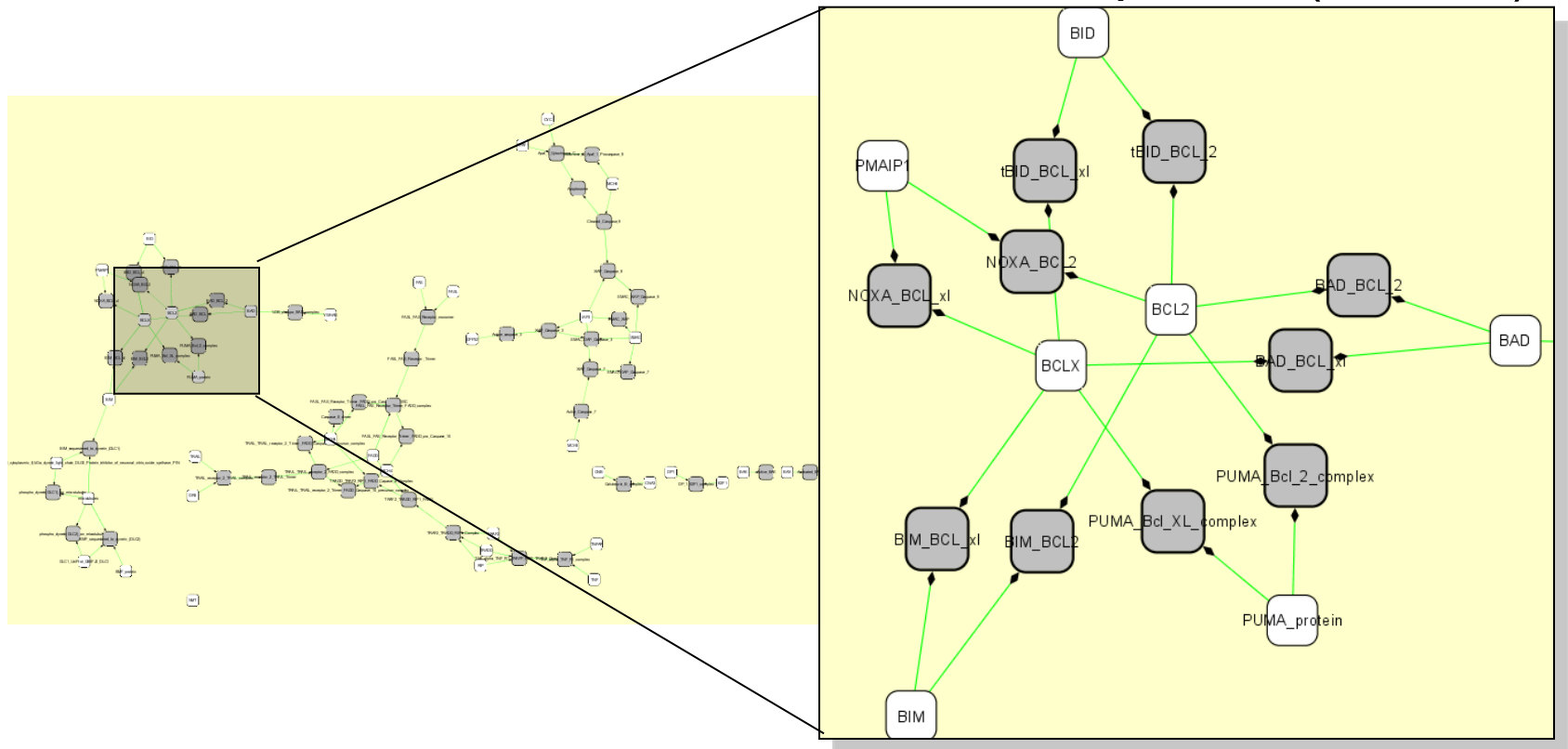
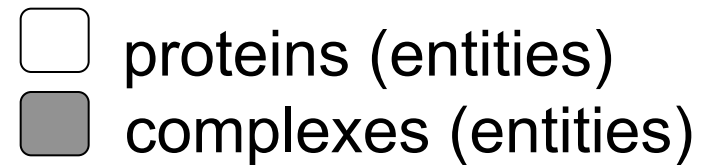
BioPAX -> Reaction Network



BioPAX -> Pathway Structure



BioPAX -> Protein Interactions



Cytoscape Desktop (Session: data)

File Edit View Select Layout Plugins Help

BIoNoM BioPAX Search:

CytoPanel 1

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

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](#)

CytoPanel 2

ID

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

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)

protein (41)

- protein UniProt_P10415_1_Apoptosis_regulator_Bcl_2
- protein TNFAR
- protein FAS
- protein NMT
- protein RAC
- protein YWHAB
- protein CPP32
- protein JNK1
- protein FASL
- protein CNA3
- protein TRAIL
- protein MCH3
- protein MCH6
- protein UniProt_P55957_BH3_interacting_domain_death_agonist_(f

BiNoM v2.0 (2012): New functionalities

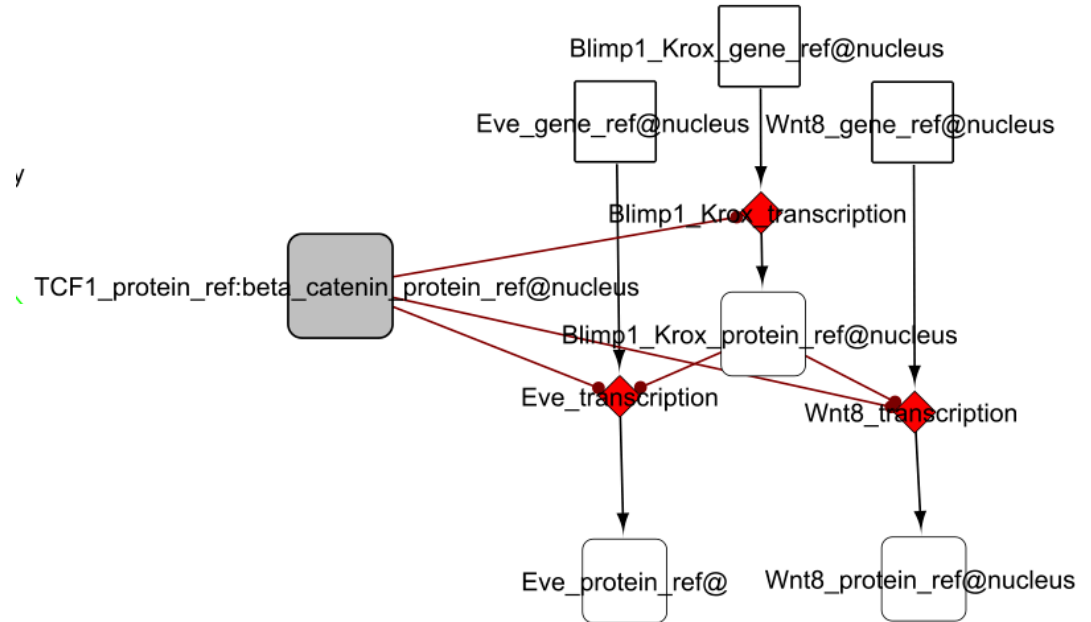
1. BioPAX level 3.0 support.
2. CellDesigner format 4.1 support.
3. Cytoscape 2.7.0+ support.
4. Pathway Quantification algorithm.
5. Minimal Cut Set algorithm.
6. Creation of interactive, “google maps” like molecular maps.

Support for BioPAX Level 3

- BioPAX is a standard language for representation of pathways.
- Latest specification (BioPAX level 3) released in 2010.
 - Metabolic pathways.
 - Signaling pathways.
 - Gene regulatory networks
 - Molecular interactions
 - Genetic interactions

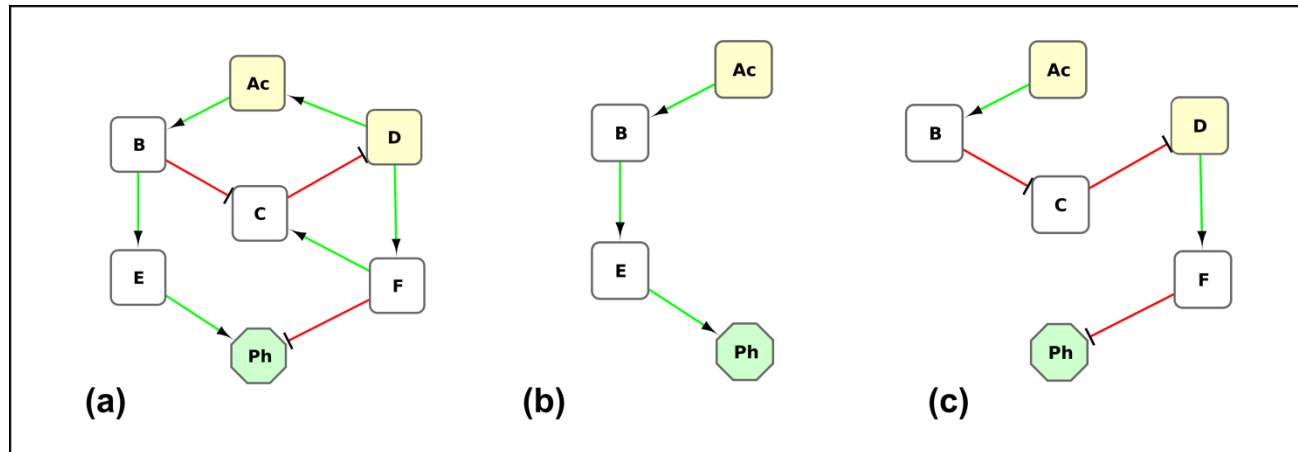


genetic-interaction



template-reaction
Reaction Network

Pathway Influence Quantification (PIQuant)

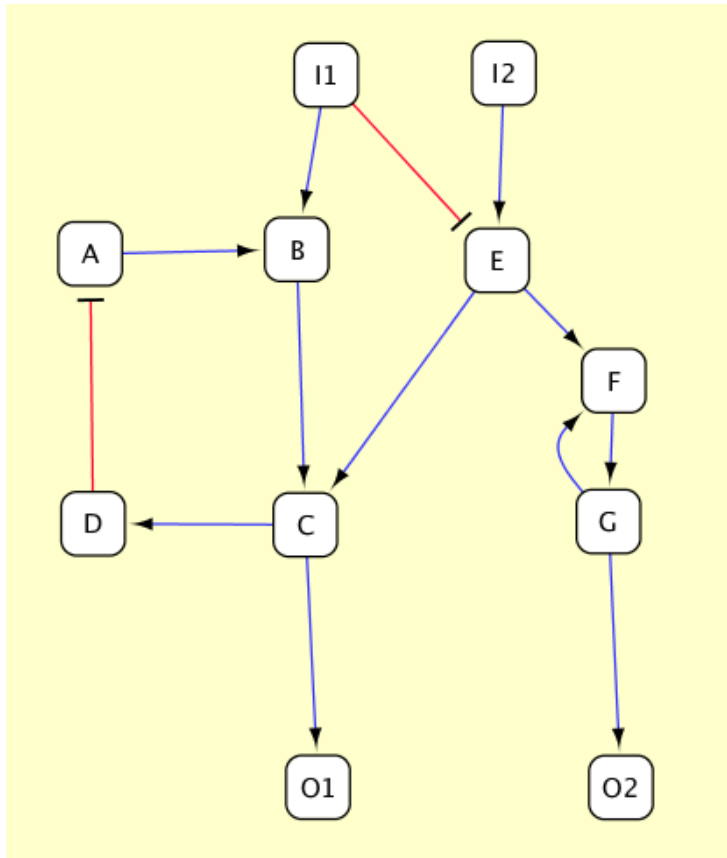


$$PIQuant_{score} = \sum_{k=1}^q \alpha_k \sigma_k \frac{1}{\lambda_k}$$

Alpha: activity of the path
Sigma: sign of the path
Lambda: length of the path

$$PIQuant_{score} = 2 \cdot 1 \cdot \frac{1}{3} + 2 \cdot (-1) \cdot \frac{1}{5} = 0.27$$

Minimal cut sets



- Influence graph G.
- Input nodes I1, I2.
- Output (target) nodes O1, O2.

I1 → B → C → O1

I1 → E → C → O1

I2 → E → C → O1

- Cut sets: {C}, {E, B}, {I1, I2}
- Minimal:
 - {E, C} is a cut set, but is not minimal.
- Application: define novel candidate drug targets.

MCS Algorithms

- Berge's algorithm (1989)
 - Based on hypergraph theory.
 - Do not scale well for networks 50+ nodes.

```
for  $i = 2, \dots, m$  do
  Find  $Tr(\mathcal{H}_{i-1})$ 
  Compute  $Tr(\mathcal{H}_i) = Min(Tr(\mathcal{H}_{i-1}) \vee \{\{v\}, v \in \mathcal{E}_i\})$ 
end for
Return  $Tr(\mathcal{H}_m)$ 
```

Algorithm 1: The algorithm of Berge

- Partial enumeration
 - Selection of a subset of nodes, by using a score based on path length and sign.
 - Enumerate subset of all possible solutions.
 - Check if they are cut sets and if they are minimal.

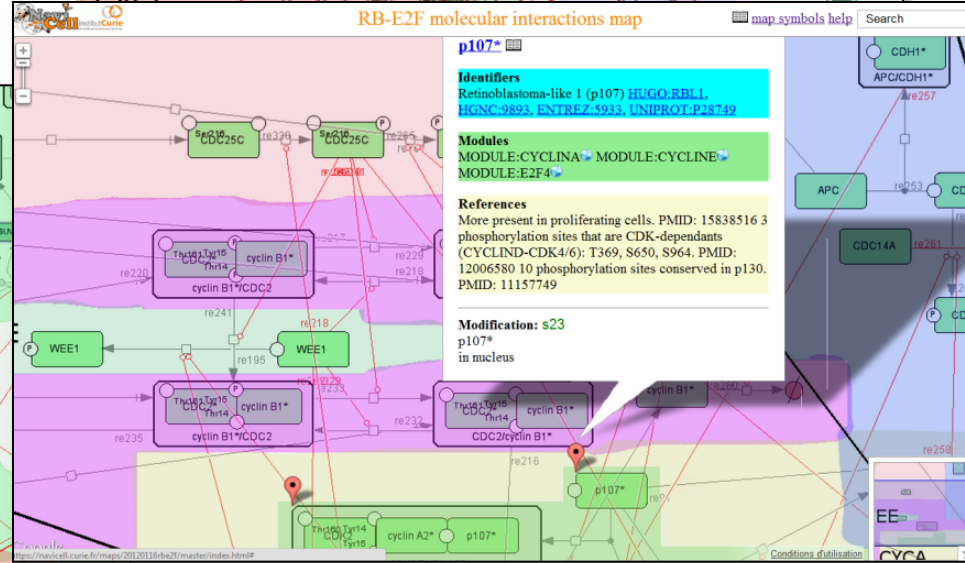
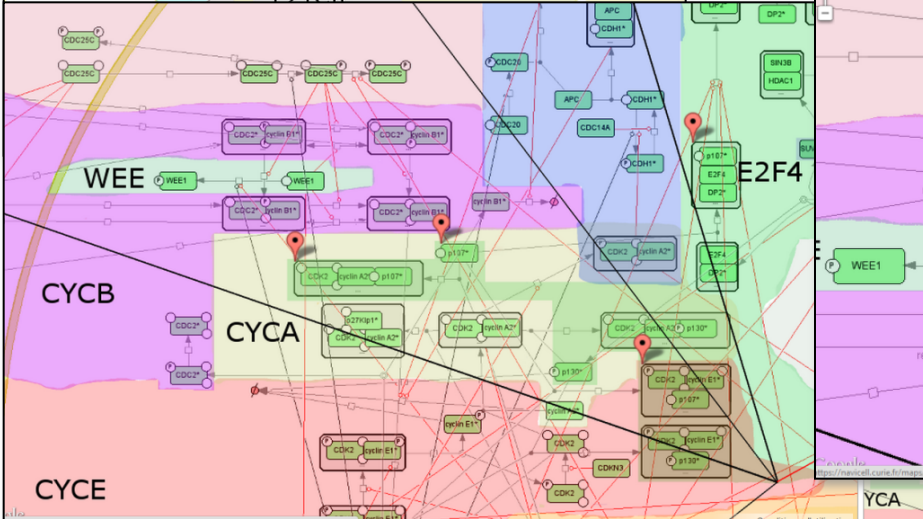
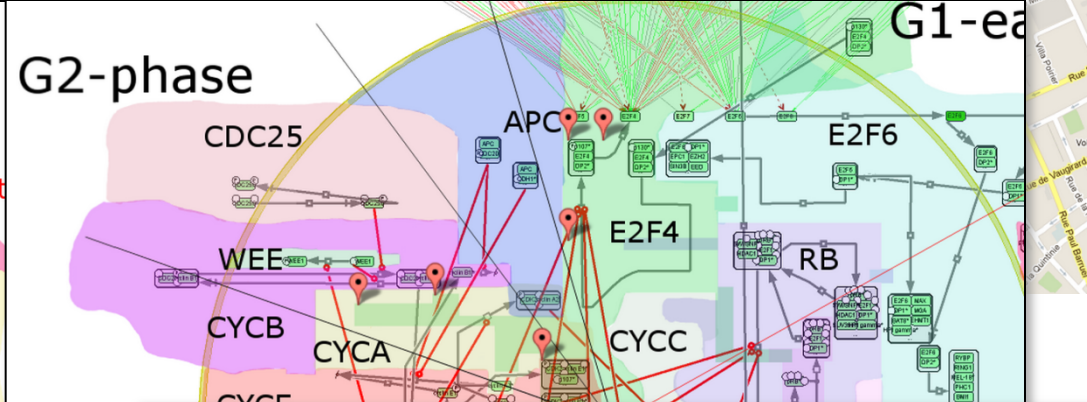
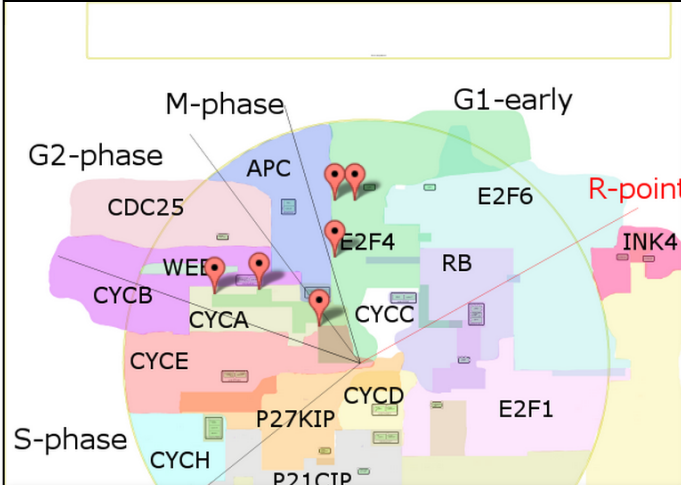


Blog for commenting





Semantic zooming



BiNoM v2.0

- Cytoscape plugin manager.
- <http://binom.curie.fr>
 - BiNoM jar file
 - BiNoM source code & doc
 - BiNoM manual (~100 pages)
 - BiNoM tutorial (book chapter)
 - BiNoM v1.0

Acknowledgements



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