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)
BiNoM:

1) Easy manipulations of SB standards
2) Java library (Jena + XMLBeans)
3) Is used as Cytoscape plugin
4) Can be used as CellDesigner plugin
5) Tools for network analysis


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

facilitates model building in the bottom-up approach
Evolution of \( \text{BiNoM}^n \) (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**

<table>
<thead>
<tr>
<th>BIOPAX NODE_TYPE</th>
<th>BIOPAX EDGE_TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>protein</td>
<td>LEFT, RIGHT</td>
</tr>
<tr>
<td>complex</td>
<td>CATALYSIS, ACTIVATION</td>
</tr>
<tr>
<td>dna</td>
<td>CATALYSIS_UNKNOWN</td>
</tr>
<tr>
<td>rna</td>
<td>MODULATION</td>
</tr>
<tr>
<td>small molecule</td>
<td>INHIBITION</td>
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<tr>
<td>publication</td>
<td>CONTAINS</td>
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<td>pathway</td>
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<tr>
<td>pathwayStep</td>
<td>STEP</td>
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<tr>
<td>conversion</td>
<td>NEXT</td>
</tr>
<tr>
<td></td>
<td>REFERENCE</td>
</tr>
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<td></td>
<td>physicalInteraction</td>
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**BiNoM CellDesigner visual mapper**

<table>
<thead>
<tr>
<th>CELLDESIGNER NODE_TYPE</th>
<th>CELLDESIGNER EDGE_TYPE</th>
</tr>
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<tbody>
<tr>
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<td>LEFT, RIGHT</td>
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<tr>
<td>COMPLEX</td>
<td>CATALYSIS</td>
</tr>
<tr>
<td>RNA</td>
<td>CATALYSIS_UNKNOWN</td>
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<tr>
<td>SIMPLE MOLECULE</td>
<td>INHIBITION</td>
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<tr>
<td>PHENOTYPE PATHWAY</td>
<td>MODIFIES</td>
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<tr>
<td>STATE TRANSITION</td>
<td>TRANSCRIPTIONAL ACTIVATION</td>
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<tr>
<td>DISASSOCIATION</td>
<td>TRANSCRIPTIONAL INHIBITION</td>
</tr>
<tr>
<td>HETERO DIMER ASSOCIATION</td>
<td></td>
</tr>
<tr>
<td>TRANSPORT</td>
<td>TRANSCRIPTIONAL ACTIVATION</td>
</tr>
<tr>
<td></td>
<td>TRANSCRIPTIONAL INHIBITION</td>
</tr>
</tbody>
</table>
Naming convention:
Need for a standard for a textual glyph encoding (SBTN? :)

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

E2F1|Ser403_phot@nucleus

CDC2|Tyr15_phot|Thr14_phot:cyclinB1*@cytoplasm

(lion:(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?

+ 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
Pathway Database -> BioPAX -> BiNoM query

- Reactome
- Cancer Cell Map
- INOH
- Nature/NCI Pathway Interaction
- BioCyc
- Pathway Commons
- BioBase

Big BioPAX file

(BiNoM)^n

Mapping on a graph

.xgmml file

Reactome Index

Query

Network
... Give the shortest and suboptimal paths connecting given proteins
Create BioPAX file from a simple text file (Facts sheet)

1) Defining families

<table>
<thead>
<tr>
<th>Link</th>
<th>ReviewRef</th>
<th>ChemType</th>
<th>Tissue</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>MAPK1, MAPK2, MAPK10 -&gt; MAPK1, MAPK2, MAPK10</td>
<td>PMID: 9809183</td>
<td>Influence</td>
<td>U-937 cells</td>
<td>seems more persistent than TNF activation. (Other name for MAPK8, MAPK9, MAPK10: JNK), (other name for TNFSP15: VEG1)</td>
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<tr>
<td>MAPK1, MAPK2 -&gt; MAPK1, MAPK2</td>
<td>PMID: 120200800</td>
<td>Phosphorylation</td>
<td>All</td>
<td>pro-apoptotic effects of MAP kinases in case of DNA damage</td>
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<tr>
<td>MAPK2 -&gt; PS3</td>
<td>PMID: 120200801</td>
<td>Phosphorylation</td>
<td>mutant</td>
<td>Phosphorylate p53 at Thr55, which increase transcriptional activity (other name for IER3: IEX-1)</td>
</tr>
<tr>
<td>IER3 -&gt; MAPK1, MAPK2</td>
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<td>PRKD1 -&gt; MAPK</td>
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<td>PRKD1 -&gt; RB1,p</td>
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<td>Phosphorylation</td>
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<td>.</td>
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<tr>
<td>(RB1: E2F5) -&gt; cell_cycle</td>
<td>PMID: 120200804</td>
<td>Phosphorylation</td>
<td>.</td>
<td>.</td>
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<tr>
<td>(RB1: E2F1, E2F2, E2F3) -&gt; cell_cycle</td>
<td>.</td>
<td>Transcriptional</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

2) Consistency check

Select constitutive reactions to add

- IER3 -&gt; IER3,p
- RB1 -&gt; RB1,p
- RB1 + E2F5 -&gt; RB1:E2F5
- RB1 + (E2F1, E2F2, E2F3) -&gt; RB1: (E2F1, E2F2, E2F3)

[Select All] [Deselect All] [OK] [Cancel]
### Create BioPAX file from a simple text file (Facts sheet)

<table>
<thead>
<tr>
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<th>ChemType</th>
<th>Tissue</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF15→(MAPK9,MAPK9,MAPK10)</td>
<td>PMID: 9069183</td>
<td>Influence</td>
<td>U-937 cells</td>
<td>seems more persistent than TNF activation. (Other name for (MAPK9,MAPK9,MAPK10): JNK, (other name for THF15: VEGF)</td>
</tr>
<tr>
<td>(MAPK1,MAPK2)→(MAPK1,MAPK2)</td>
<td>PMID: 1200800</td>
<td>Phosphorylation</td>
<td>All</td>
<td>pro-apoptotic effects of MAP kinases in case of DNA damage</td>
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<td>IEK3→(MAPK1,MAPK2)</td>
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<td>Transcriptional</td>
</tr>
</tbody>
</table>

[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
Laurence Calzone
Gautier Stoll
Emmanuel Barillot
Daniel Rovera