Conversion of mEPN pathway diagrams to SBGN in BioLayout *Express*^{3D}

Derek Wright, Tim Angus, Athanasios Theocharidis,
Tom C. Freeman
The Roslin Institute, R(D)SVS, University of Edinburgh, UK

Process Modelling of Biological Pathways

Aim

To construct models of the current consensus view of pathways of interest, useful to biologists for data interpretation and hypothesis generation

Progress to date

- **Initial and on-going interest in modelling macrophage activation pathways**
- **Interest in mapping other pathways/systems**
- **Work has involved the training and use of successive cohorts of BSc/MSc students for literature mining and pathway depiction**
- **When this work started no standard notation system available, so we developed our own (mEPN) which has evolved through meeting challenges met during the modelling process**
- **Pathway mapping project now in its 8th year**

ROSLIN

modified Edinburgh Pathway Notation scheme

Freeman et al., BMC Systems Biology 4:65, 2010

COMPONENT

- PEPTIDES, PROTEIN OR COMPLEX
- GENE
- DNA SEQUENCE (PROMOTER ELEMENT)
- SIMPLE BIOCHEMICAL
- GENERIC ENTITY
- DRUG
- ION/ SIMPLE MOLECULE

COMPONENT ANNOTATION

PROTEIN 1 [Mod] (ALIAS)	PROTEIN 1: <n> PROTEIN 2 [Mod] (ALIAS)

NODE COLOUR BASED ON:
- COMPONENT TYPE
- SUB-CELLULAR LOCATION
- EXPRESSION

Protein/Complex State

[A] ACTIVE [I] INACTIVE

<n> NUMBER OF SPECIFIC MOLECULAR SPECIES

Protein Modifications

[P] PHOSPHORYLATED
[Ub] UBIQUITINATED
[Su] SUMOLAYTED
[Ac] ACETYLATED
[Pr] PRENYLATED
[H] PROTONATED
[Pe] PEGYLATED
[Ox] OXIDISED
[Gy] GLYCOSYLATED
[Me] METHYLATED
[Pa] PALMITOYLATED
[S] SULPHATED
[My] MYRISTOYLATED
[OH] HYDROXYLATED
[Se] SELENYLATED
[t] TRUNCATED

PROCESS NODES

- B BINDING
- X CLEAVAGE
- D DISSOCIATION
- C CATALYSIS
- T TRANSLOCATION
- A ACTIVATION
- P PHOSPHORYLATION
- AP AUTO-PHOSPHORYLATION
- Ub UBIQUITISATION
- Se SELENYLATION
- Pr PRENYLATION
- At ACETYLATION
- H+ PROTONATION
- Pe PEGYLATION
- Ox OXIDISATION
- O OLIGERMISATION
- AX AUTO-CLEAVAGE
- AC AUTO-CATALYSIS
- TL TRANSCRIPTION/ TRANSLATION
- I INHIBITION
- -P DEPHOSPHORYLATION
- PT PHOSPHO-TRANSFER
- Su SUMOYLATION
- Gy GLYCOSYLATION
- Me METHYLATION
- Pa PALMITOYLATION
- S SULPHATION
- My MYRISTOYLATION
- OH HYDROXYLATION
- Sec SECRETION
- SINK (PROTEASOMAL DEGRADATION)

OTHER

- ENERGY/ MOLECLUAR TRANSFER
- CONDITIONAL SWITCH
- PATHWAY MODULE
- PATHWAY OUTPUT

BOOLEAN LOGIC OPERATORS

& AND OR OR

EDGE ANNOTATION

- INTERACTION
- DETAILS UNKNOWN
- PHYSICAL LINK
- C CATALYSES
- A ACTIVATES
- I INHIBITS
- PATHWAY INPUT
- PATHWAY OUTPUT
- TRANSLOCATION
- TRANSCRIPTION/ TRANSLATION

CELLULAR COMPARTMENTS

- ORGAN
- BLOOD VESSEL
- EXTRACELLULAR
- CELL MEMBRANE
- ENDOCYTIC VESICLE
- PHAGOSOME
- CYTOPLASM
- MITOCHONDRION
- MITOCHONDRIAL MEMBRANE
- MITOCHONDRIAL LUMEN
- NUCLEUS
- NUCLEAR MEMBRANE
- NUCLEOPLASM
- NUCLEOLUS
- GENOME
- ENDOPLASMIC RECTICULUM
- ENDOPLASMIC RECTICULUM MEMBRANE
- PEROXISOME
- GOLGI APPARATUS
- GOLGI DERIVED VESICLE
- COPII COATED VESICLE
- RETICULUM-GOLGI INTERMEDIATE COMPARTMENT
- MHC CLASS II ASSOCIATED ENDOCTYIC COMPARTMENT (MIIC)
- LYSOSOME
- ENDOSOME
- EARLY ENDOSOME
- LATE ENDOSOME

yED yWorks

http://www.mepn-pathway.org/

modified Edinburgh Pathway Notation (mEPN) 2013

PLACES

ENTITY NODES

- PROTEIN COMPLEX
- PEPTIDE, PROTEIN
- GENE
- DNA SEQUENCE (PROMOTER ELEMENT)
- GENERIC ENTITY
- ION/SIMPLE MOLECULE
- SIMPLE BIOCHEMICAL
- ENERGY TRANSFER (CO-REACTION)
- DRUG

BOOLEAN LOGIC OPERATOR

OR OR (OPERATRES AS PLACE)

SPN-SPECIFIC NODES

SPACER NODE

COMPONENT ANNOTATION

PROTEIN 1 [Mod] (ALIAS)	PROTEIN 1: <n> PROTEIN 2 [Mod] (ALIAS)

NODE COLOUR BASED ON:
- COMPONENT TYPE
- SUB-CELLULAR LOCATION
- EXPRESSION

Protein/Complex State

[A] ACTIVE [I] INACTIVE
<n> NUMBER OF DEFINED ENTITY

Protein Modifications

[P] PHOSPHORYLATED
[Ub] UBIQUITINATED
[Su] SUMOLAYTED
[Ac] ACETYLATED
[Pr] PRENYLATED
[H] PROTONATED
[Pe] PEGYLATED
[Ox] OXIDISED
[Gy] GLYCOSYLATED
[Me] METHYLATED
[Pa] PALMITOYLATED
[OH] HYDROXYLATED
[S] SULPHATED
[My] MYRISTOYLATED
[Se] SELENYLATED
[t] TRUNCATED

TRANSITIONS

PROCESS NODES

BINDING	B	O	OLIGERMISATION
CLEAVAGE	X	AX	AUTO-CLEAVAGE
DISSOCIATION	D	AC	AUTO-CATALYSIS
CATALYSIS	C	TL	TRANSCRIPTION/TRANSLATION
TRANSLOCATION	T	A	ACTIVATION
PHOSPHORYLATION	P	-P	DEPHOSPHORYLATION
AUTO-PHOSPHORYLATION	AP	PT	PHOSPHO-TRANSFER
UBIQUITISATION	Ub	Su	SUMOYLATION
SELENYLATION	Se	Gy	GLYCOSYLATION
PRENYLATION	Pr	Me	METHYLATION
ACETYLATION	Ac	Pa	PALMITOYLATION
PROTONATION	H+	Su	SULPHATION
PEGYLATION	Pe	My	MYRISTOYLATION
OXIDATION	Ox	OH	HYDROXYLATION
MUTATION	M	S	SECRETION
SINK (PROTERSOMAL DEGRADATION)	ϕ	?	UNKNOWN

AND (OPERATES AS TRANSITION) & PATHWAY MODULE/OUTPUT

SPN-SPECIFIC TRANSITIONS

TOKEN INPUT

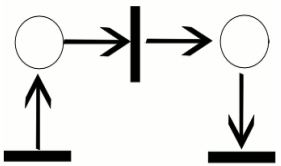
DISTRIBUTION NODE (20, 20)

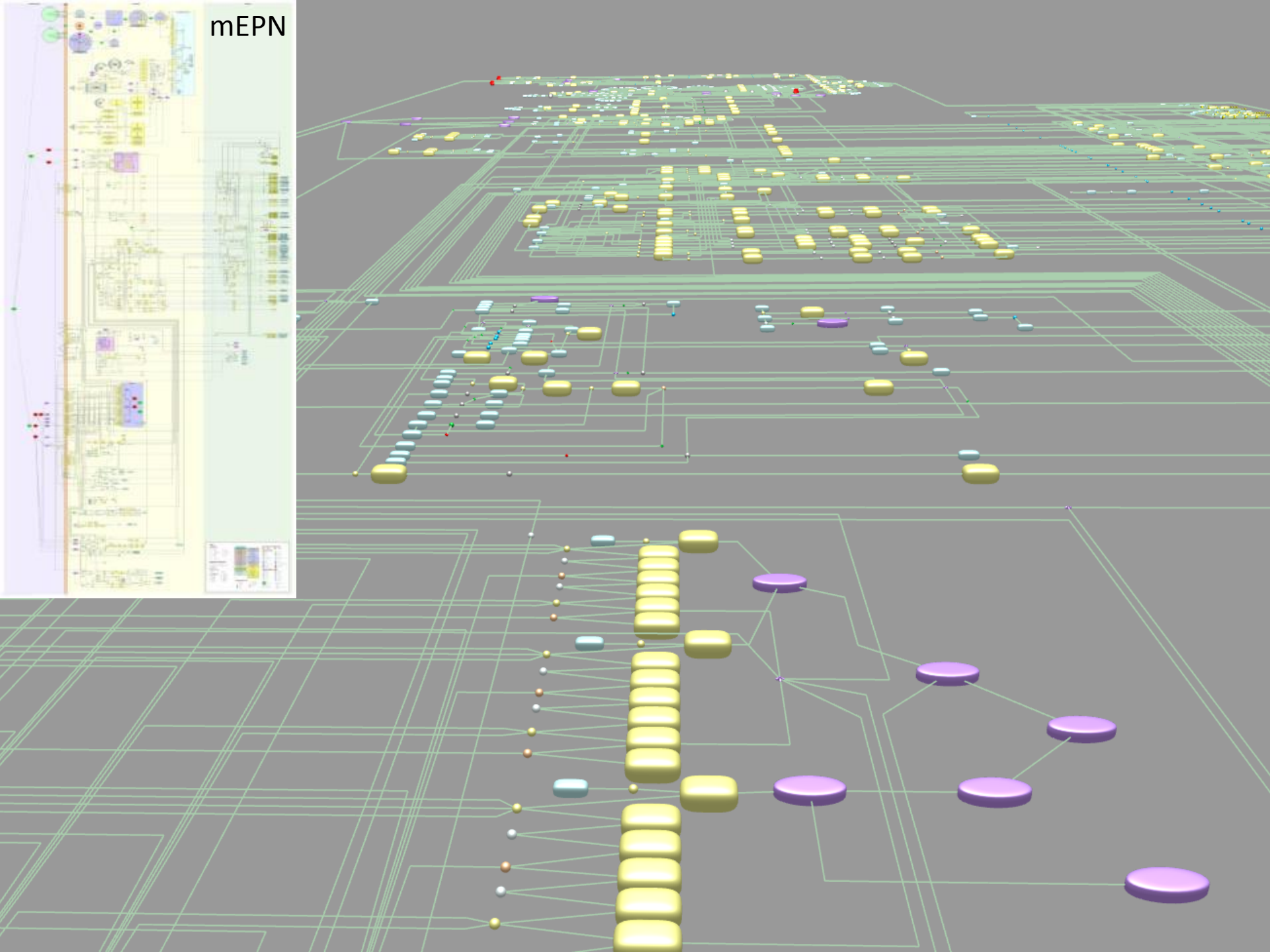
SPACER NODE/TOKEN OUTPUT (10, 10)

EDGES

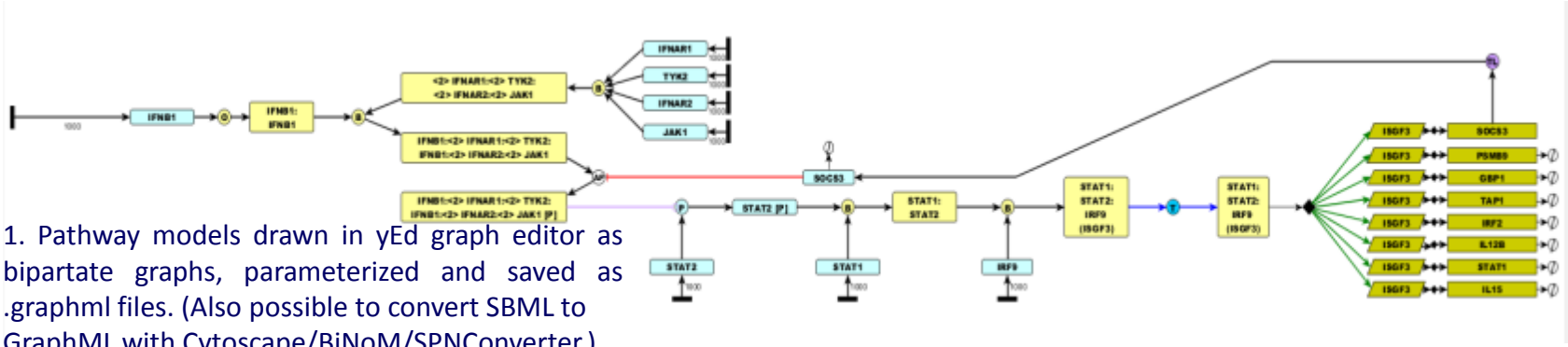
EDGE ANNOTATION

- INTERACTION
- CATALYSIS
- INHIBITION
- INHIBITION (NON-COMPETITIVE)
- INHIBITION (COMPETITIVE)

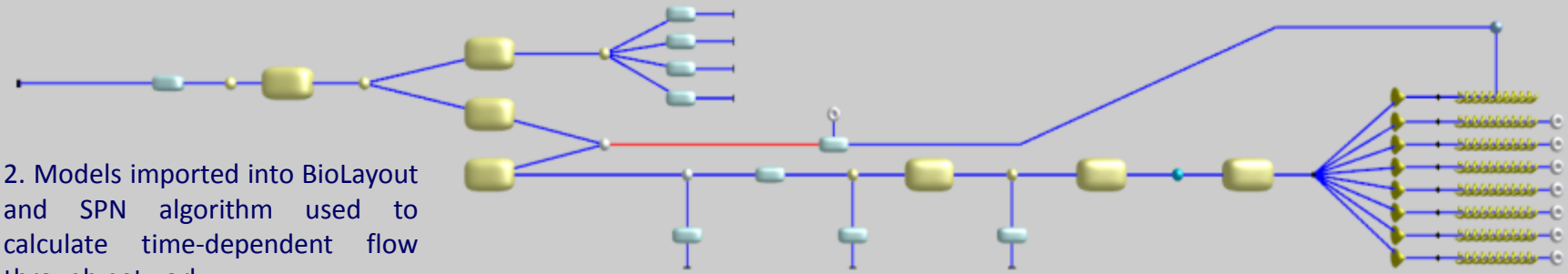



mEPN

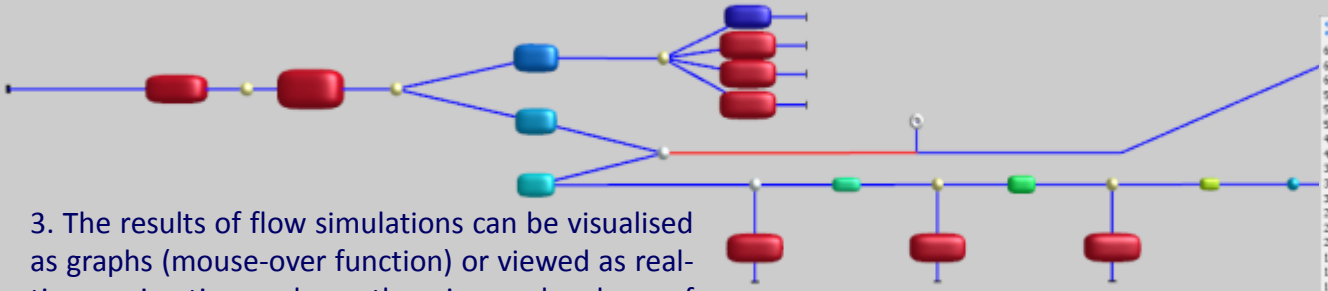
Analysis and visualisation of rule-based stochastic flow through models of biological pathways

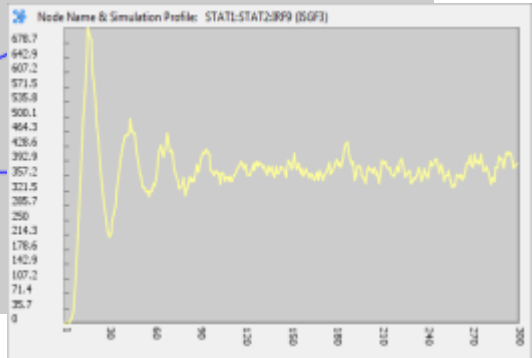


1. Pathway models drawn in yEd graph editor as bipartate graphs, parameterized and saved as .graphml files. (Also possible to convert SBML to GraphML with Cytoscape/BiNoM/SPNConverter.)



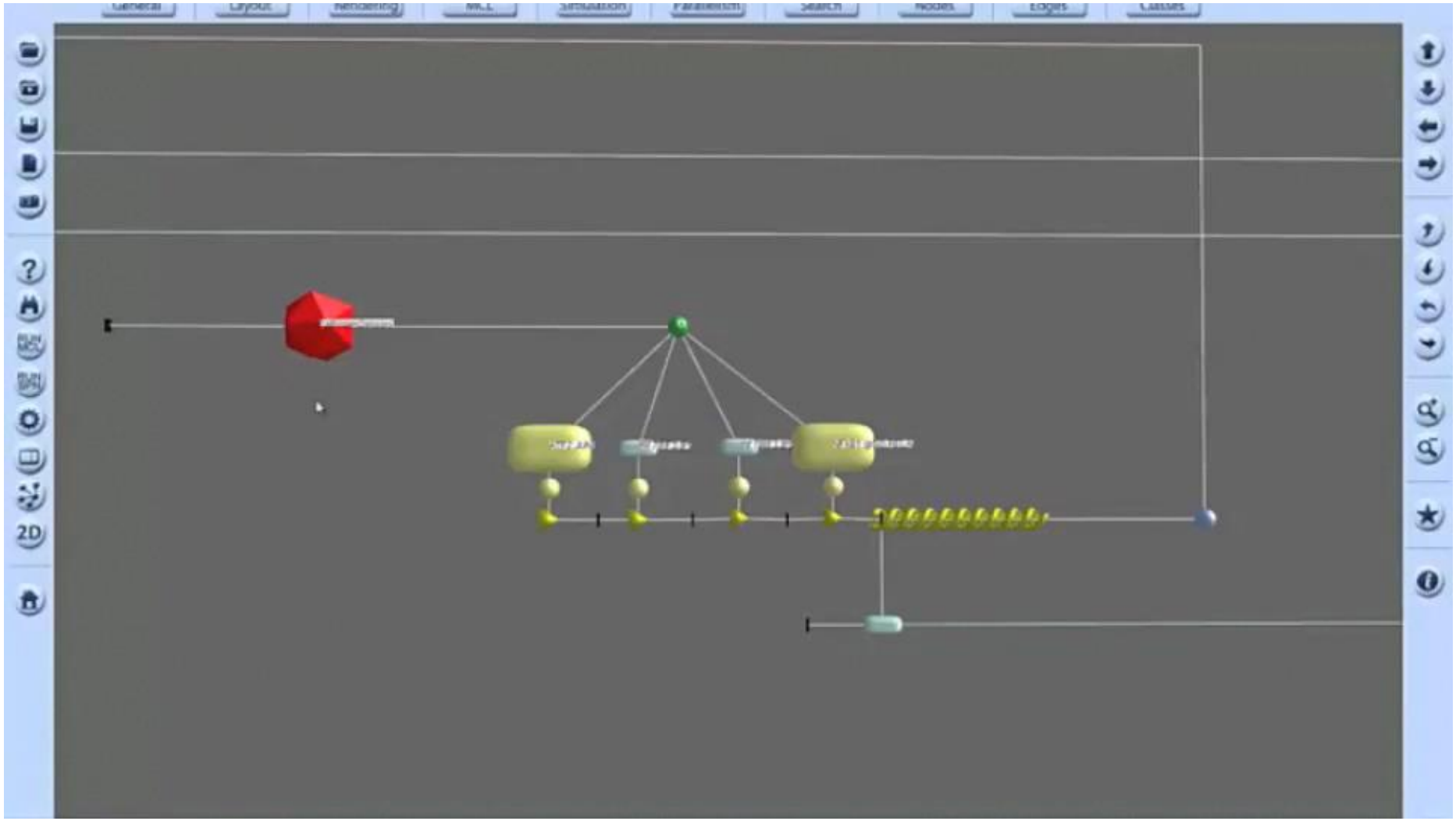
2. Models imported into BioLayout and SPN algorithm used to calculate time-dependent flow through network.





3. The results of flow simulations can be visualised as graphs (mouse-over function) or viewed as real-time animations where the size and colour of nodes is used to represent their activity/amount.

Signalling Petri Net Simulation



Conversion of mEPN diagrams to SBGN

Why?

- To provide a bridge to the current standard

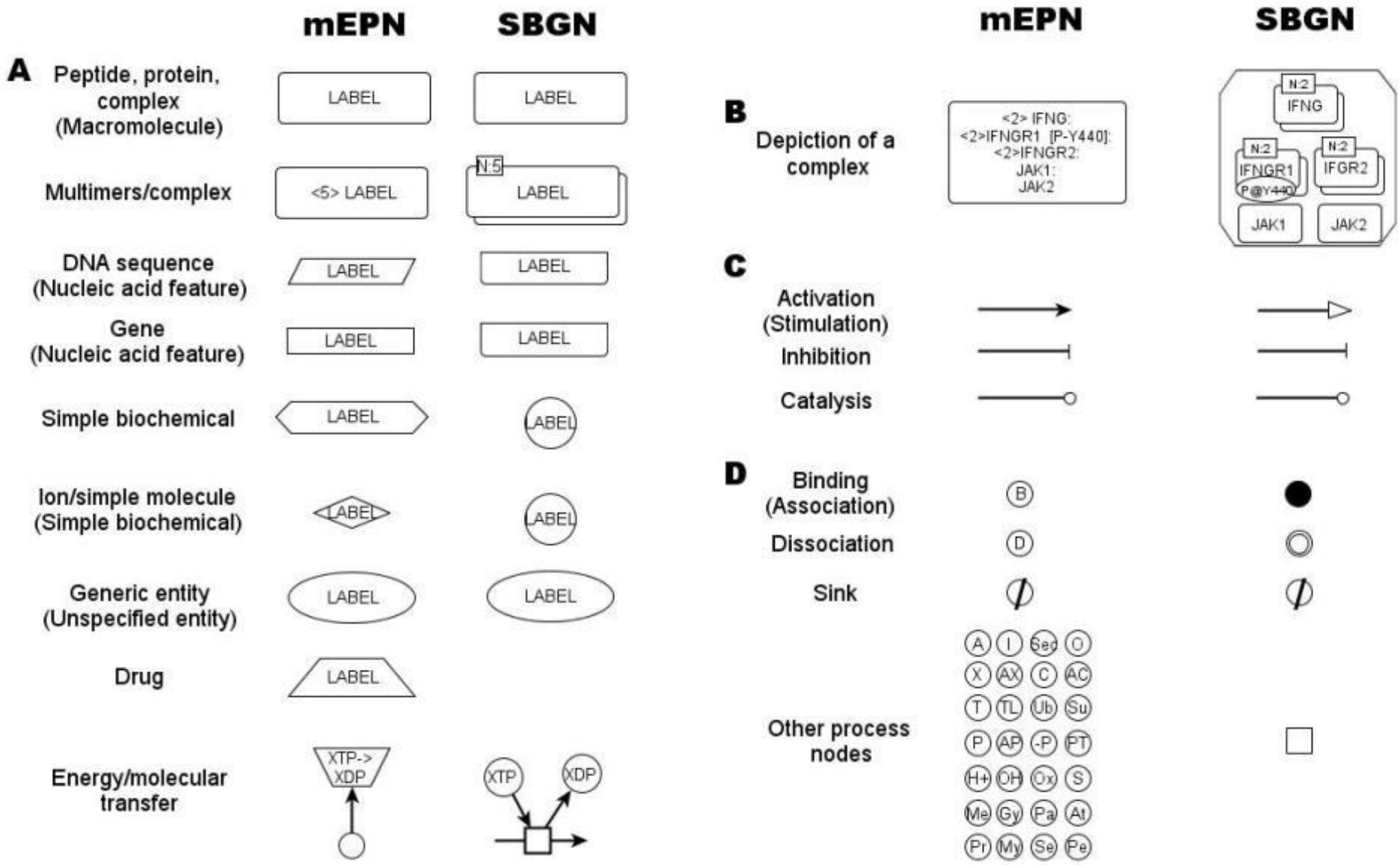
How?

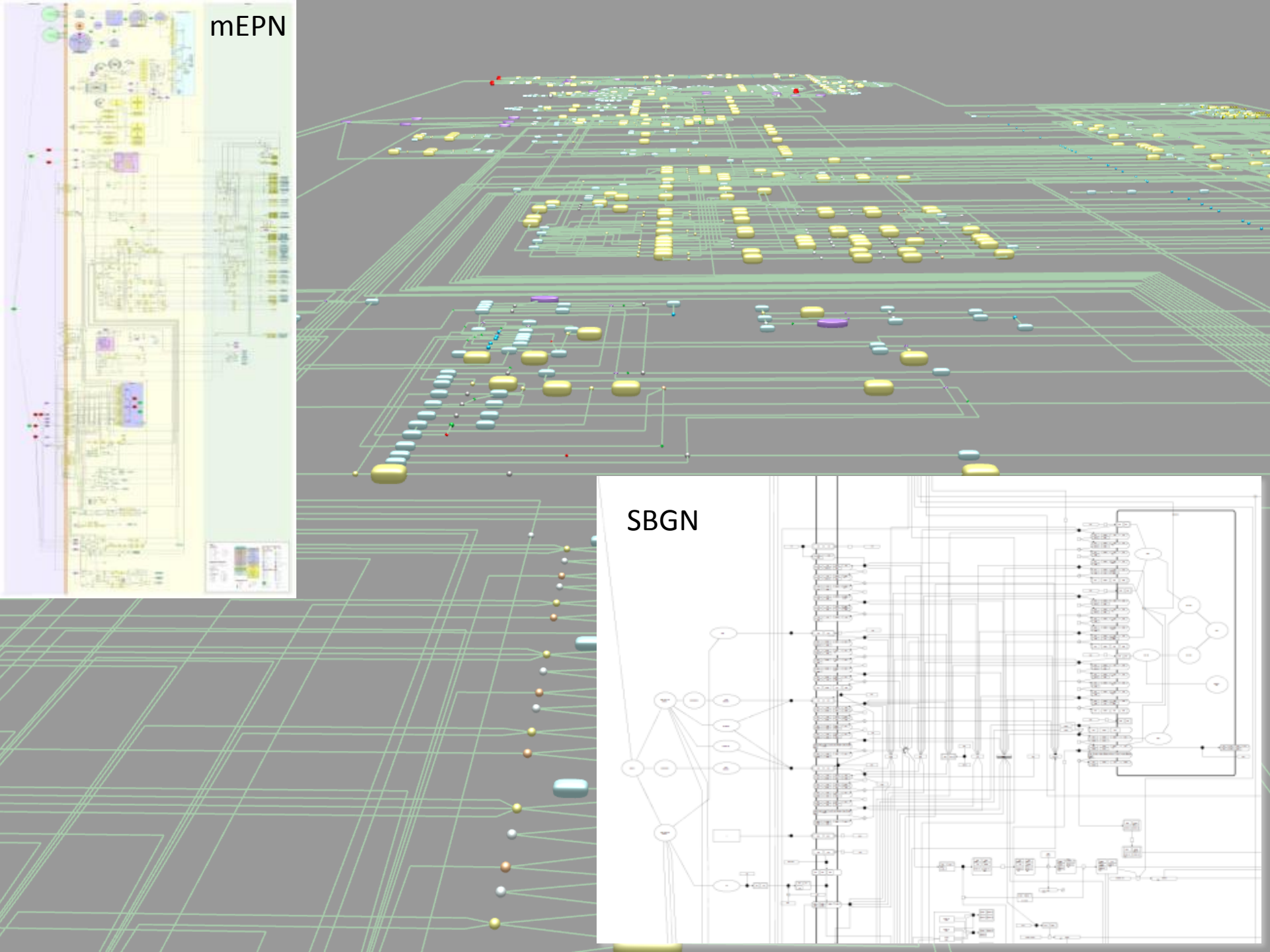
- Map mEPN – SBGN types
  - Creates glyphs from nodes
  - Create arcs from edges
- Preserve geometry + apply scaling
- Create compartments
- Serialize to SBGN-ML using LibSBGN Java library

Exactly How?

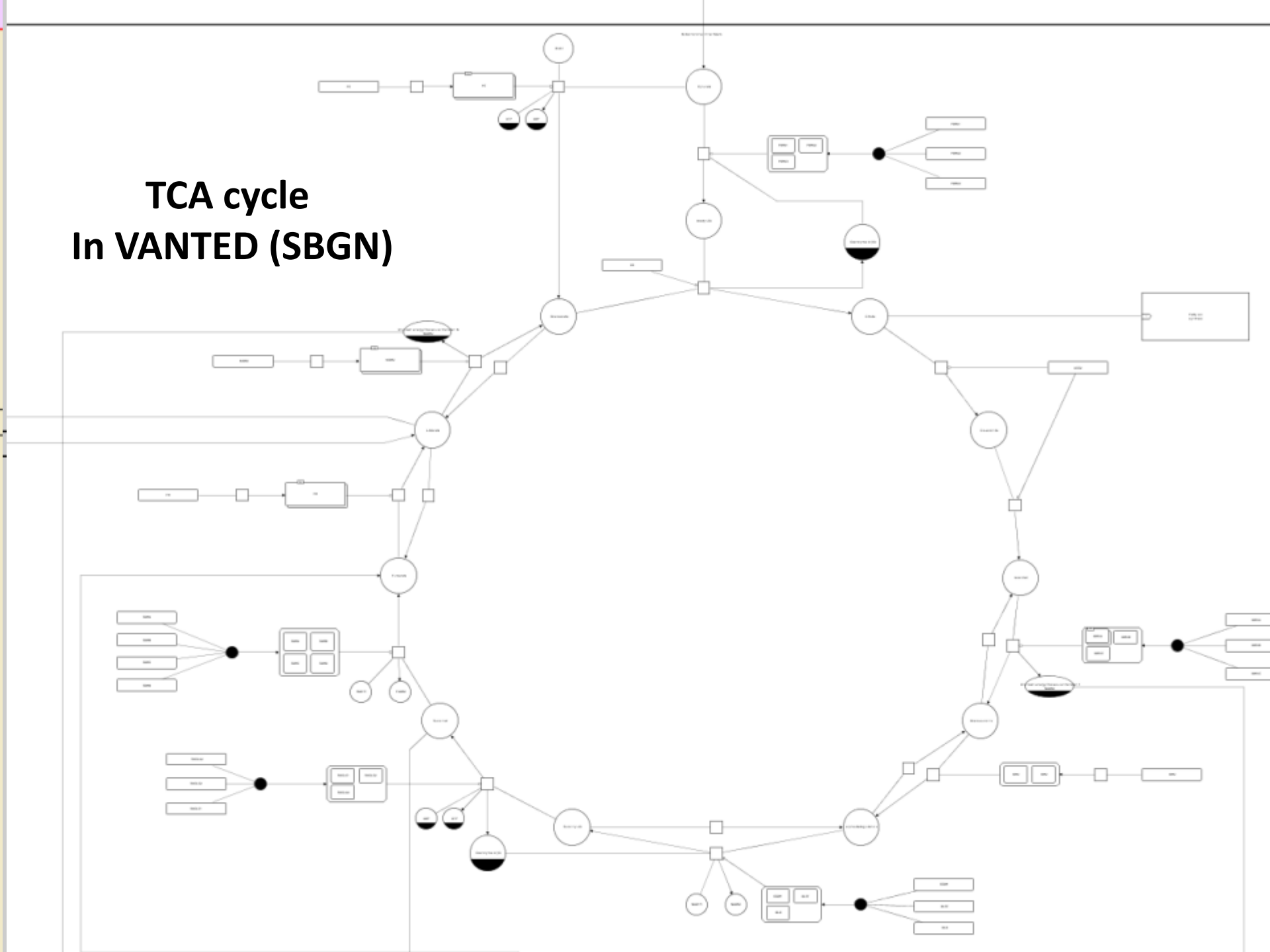
- Source code available at www.biolayout.org

Mapping mEPN to SBGN




mEPN
SBGN

TCA cycle
In VANTED (SBGN)



example pathways

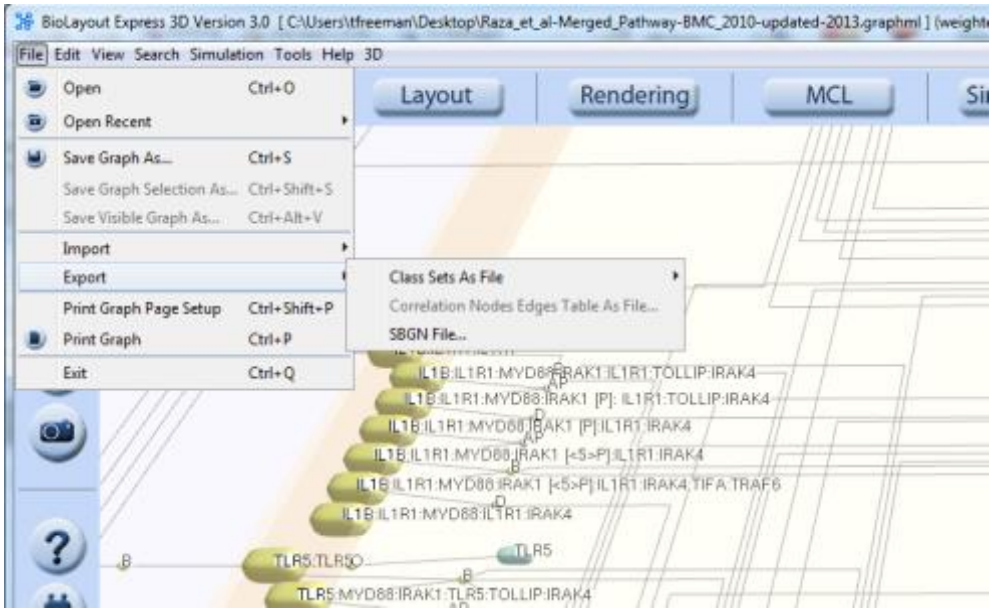
http://www.macrophages.com/macrophage-pathways

Title	Biolayout webstart	Open in yEd Editor
Macrophage Activation Pathways (integrated)		yWorks
Macrophage Activation Extended		yWorks
Toll Like Receptor & Kinase Pathways		yWorks
Non-TLR Pathogen Detection		yWorks
Dectin Pathway		yWorks
Interleukin-4 -10 & -13 Pathways		yWorks
Proteosome and Antigen Presentation		yWorks
VEGF and TGFB Pathways		yWorks
Complement Pathways		yWorks
NF-kappa-B Signalling		yWorks
TNF Promoter Model		yWorks
B-Cell Signalling		yWorks
Cholesterol Metabolism		yWorks
Oxidative Phosphorylation, TCA & Glycolysis		yWorks
p53 Signalling Pathway		yWorks
Glucocorticoid Pathway		yWorks
Oxytocin & Prolactin Signalling		yWorks

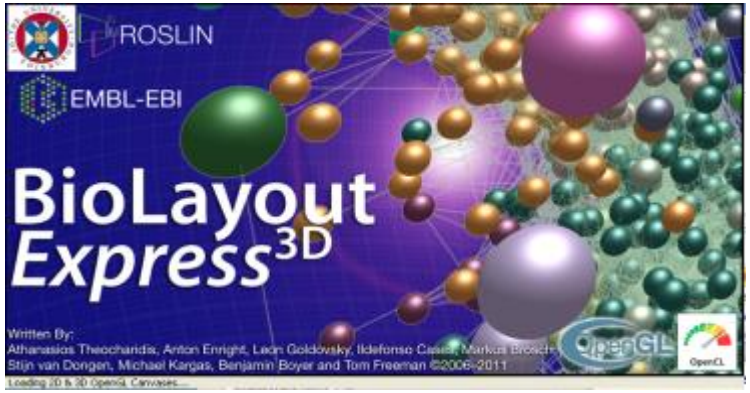
ROSLIN

macrophages.com

The Macrophage Community Website



BioLayout *Express*^{3D} Team



Roslin Institute

Tom Freeman

Thanasis Theocharidis

Ben Boyer

Tim Angus

Derek Wright

www.biolayout.org
support@biolayout.org

EMBL-EBI

Anton Enright

Stijn van Dongen

Division of PATHWAY MEDICINE

wellcome trust sanger institute

EMBL-EBI

THE UNIVERSITY OF EDINBURGH

ROSLIN

R(D)SVS

BBSRC bioscience for the future