

A tutorial for using OmniPath App in Cytoscape

supplementary material for

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Bringing data from curated pathway resources to Cytoscape with OmniPath



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Case study 2: Training network model to data





- Here we combine Omnipath App with PathLinker and Cytocopter
- Problem statement:
 - we want to investigate the signal propagation in the MAP-kinase pathway upon treatment with EGF and TNFa stimulation and PI3K and RAF1 inhibition
 - We have measurements for the following nodes:
 - RAF1, MAPK3, JUN, GSK3b, MAPK14, NFkB1
- Pipeline:
 - we query signaling interactions from Omnipath App
 - select a subnetwork by finding shortest path between the perturbed node and measured phosphoproteins. We use PathLinker for this job
 - Turn the network into a Boolean logic model and train the model to the data using Cytocopter.



Requirements

- Install
 - Omnipath App (<https://apps.cytoscape.org/apps/omnipath>)
 - CytoCopttr (<https://apps.cytoscape.org/apps/cytoCopttr>)
 - PathLinker (<https://apps.cytoscape.org/apps/pathlinker>)
- user data is provided on Github
 - (https://github.com/saezlab/Omnipath_Cytoscape/tree/master/tutorial)



Import signaling network from Omnipath

1. human species

2. prot.-prot. interaction

3. Signor & Signalink

4. Directed & Signed

5. Hit confirm

6. switch to node attributes!

7. switch to source/target node!

source	target	source_genesymbol	target_genesymbol	is
P12931	P60484	SRC	PTEN	
P06239	P60484	LCK	PTEN	
P60484	P63000	PTEN	RAC1	
P60484	Q9Y243	PTEN	AKT3	
P60484	P35813	PTEN	PPM1A	
P37231	P60484	PPARG	PTEN	
Q15831	P60484	STK11	PTEN	



Imported network with organic layout

Session: New Session

Control Panel

Network Style Select Cytocopter **Omnipath**

Omnipath Control Panel

Info: [Omnipath](#)

Select Organism

☒ Human ☐ Mouse ☐ Rat

Select Dataset

Signaling networks

Select TF Confidence Level

☐ A ☐ B ☐ C ☐ D ☐ E ☐ All

Database Selection

Available choices: ReMap, Reactome, ProtMa..., RegNetwork, SPIKE, Signor, ProtMapper, Sparsar, ProtMap..., TFacts, TFe

Your choices: SignaLink3, Signor

Add >> << Remove

Select all Deselect all

☒ Directed interactions only ☒ Signed interactions only

Launch query

Annotation

Resources: Adhesome/mainclass, CPAD/cancer, CPAD/effect_on_cancer, CPAD/pathway, CancerSEA/state, ComPPI/location, Exocarta/vesicle, GO_Intercell/mainclass

Features

Query annotations Annotate network

Results Panel

cy3sbml

No information

No SBMLDocument associated with the current network.

Table Panel

Signalingnetworks_Human_2019-12-16_08-01-07.txt

shared name	name	source	target	isExcludedFromPaths	isInPath	gene_sym	nc
SRC	SRC	P12931	P12931	<input type="checkbox"/>	<input type="checkbox"/>	prot	
PTEN	PTEN	P60484	P60484	<input type="checkbox"/>	<input type="checkbox"/>	prot	
LCK	LCK	P06239	P06239	<input type="checkbox"/>	<input type="checkbox"/>	prot	
RAC1	RAC1	P63000	P63000	<input type="checkbox"/>	<input type="checkbox"/>	prot	
AKT3	AKT3	Q9Y243	Q9Y243	<input type="checkbox"/>	<input type="checkbox"/>	prot	
PPM1A	PPM1A	P35813	P35813	<input type="checkbox"/>	<input type="checkbox"/>	prot	

Node Table Edge Table Network Table Cytocopter

Memory



PathLinker: find relevant subnetwork

Session: New Session

Control Panel

Network Style Select Omnipath Cytocopter PathLinker

PathLinker

Help About

Network

Select network: 1. Signalingnetworks_Human_2019-08-21_09-...
☐ Treat network as undirected

Sources/Targets

Sources separated by spaces (e.g., S1 S2 S3)
Must match the 'name' column in the Node Table

EGF TNF
Add selected source(s)

Targets separated by spaces (e.g., T1 T2 T3)
PIK3CA RAF1 MAPK3 JUN GSK3B MAPK14 NFKB1
Add selected target(s)

☒ Allow sources and targets in paths
☐ Connect sources to each other Clear

Algorithm

k (# of paths): 50
Edge penalty:
☐ Include tied paths

Edge Weights

☒ Unweighted
☐ Weights are additive
☐ Weights are probabilities
Edge weight column:
Submit Close

Results Panel

cy3sbml

No information
No SBMLDocument associated with the current network.

Table Panel

Signalingnetworks_Human_2019-08-21_09-31-14.txt

shared name	name	source	target	isExcludedFromPaths	isInPath	gene_sym
PIAS4	PIAS4	Q8N2W9		<input type="checkbox"/>	<input type="checkbox"/>	
PICALM	PICALM	Q13492	Q13492	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3AP1	PIK3AP1	Q6ZUJ8		<input type="checkbox"/>	<input type="checkbox"/>	
PIK3C2A	PIK3C2A		O00443	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3C2B	PIK3C2B		O00750	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3C3	PIK3C3	Q8NEB9	Q8NEB9	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3CA	PIK3CA	P42336	P42336	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3CB	PIK3CB		P42338	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3CD	PIK3CD		O00329	<input type="checkbox"/>	<input type="checkbox"/>	
PIK3CG	PIK3CG	P48736	P48736	<input type="checkbox"/>	<input type="checkbox"/>	

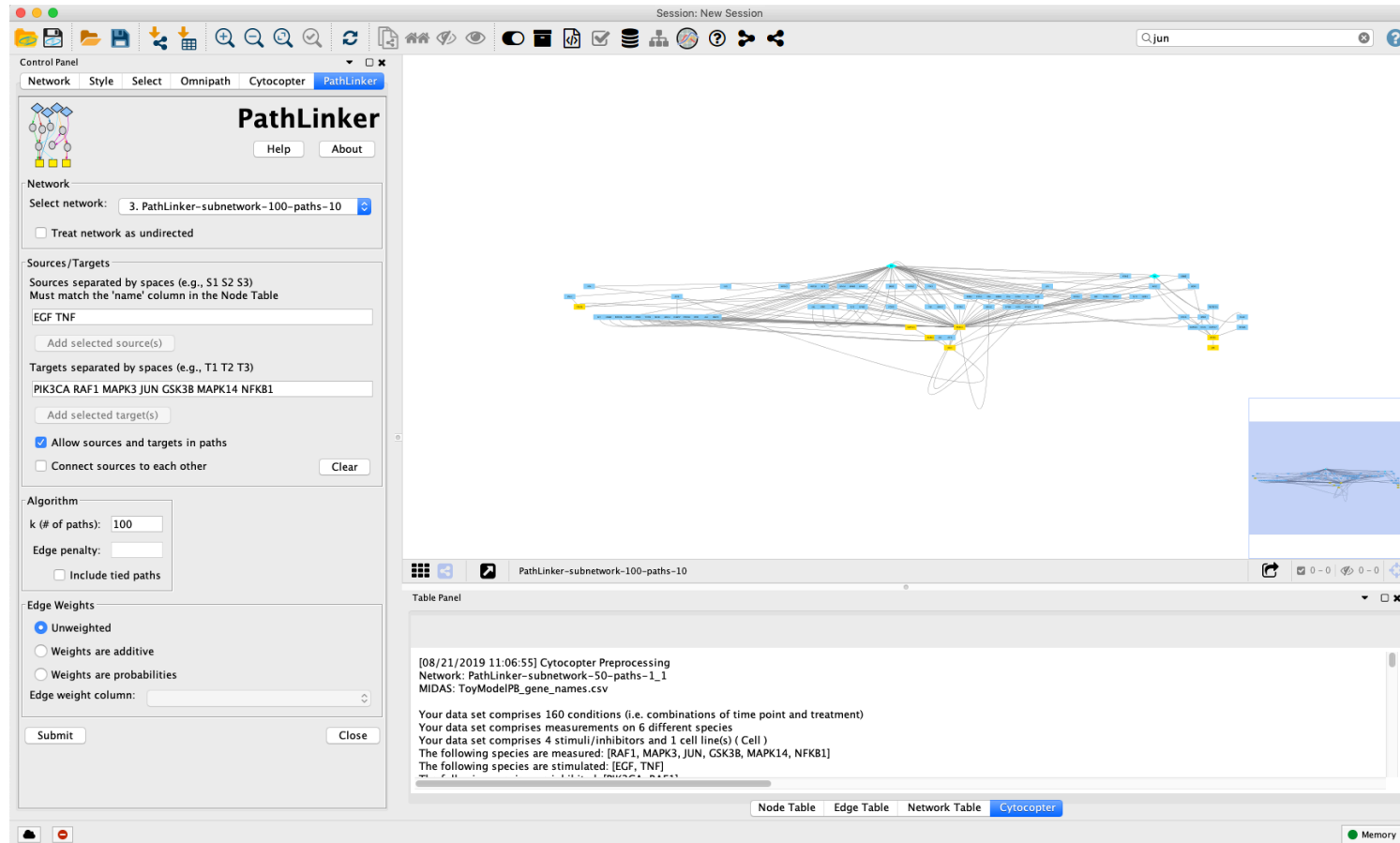
Node Table Edge Table Network Table Cytocopter

Memory

Sources: EGF and TNFa stimulation nodes
Targets: measured proteins



Results of PathLinker from Omnipath



This network is translated to a Boolean model in the next step using Cytocopter.



Define interaction type for the Boolean model

Table Panel

⚙️ 📄 + 🗑️ 📊 $f(x)$ ↻

shared name	shared interaction	name	interaction	is_directed	is_stimulation	is_inhibition	consensus_direction
EPHA3 (interacts wit...	1	EPHA3 (int...	=IF(ABS(\$conse	1	1	0	1
ROR2 (interacts wit...	1	ROR2 (int...	nsus_stimulatio	1	1	0	1
ROR2 (interacts wit...	1	ROR2 (int...	n)>0,"1","-1")	1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1
EGF (interacts with) ...	1	EGF (inter...		1	1	0	1

Node Table Edge Table Network Table Cytocopter

Cytocopter requires that the sign of each edge is defined in the edge table / interaction column:

➡️ 1 for activation

➡️ -1 for inhibition

Therefore, interaction field has to be updated,

IF(ABS(\$consensus_stimulation)>0,"1","-1")

Then right click on the cell and select *"apply to the entire column"*.



Setup the Boolean model in Cytocopter

Session: New Session

Control Panel

Network Style Select Omnipath Cytocopter PathLinker

Import from SBML

Netw... PathLinker-subnetwork-100-paths-10_1

Data ToyModelPB_gene_names.csv

☐ Expand gates

Preprocess

Form... boolean

Time point 12.0

Export to SBML Optimise

Configurations

Size fac	1.0E-4	NA fac	1.0
Pop size	50.0	Max time	15.0
Max gen	500.0	Rel tol	0.1

1. select network

2. load data

3. apply preprocess

PathLinker-subnetwork-100-paths-10_1

Table Panel

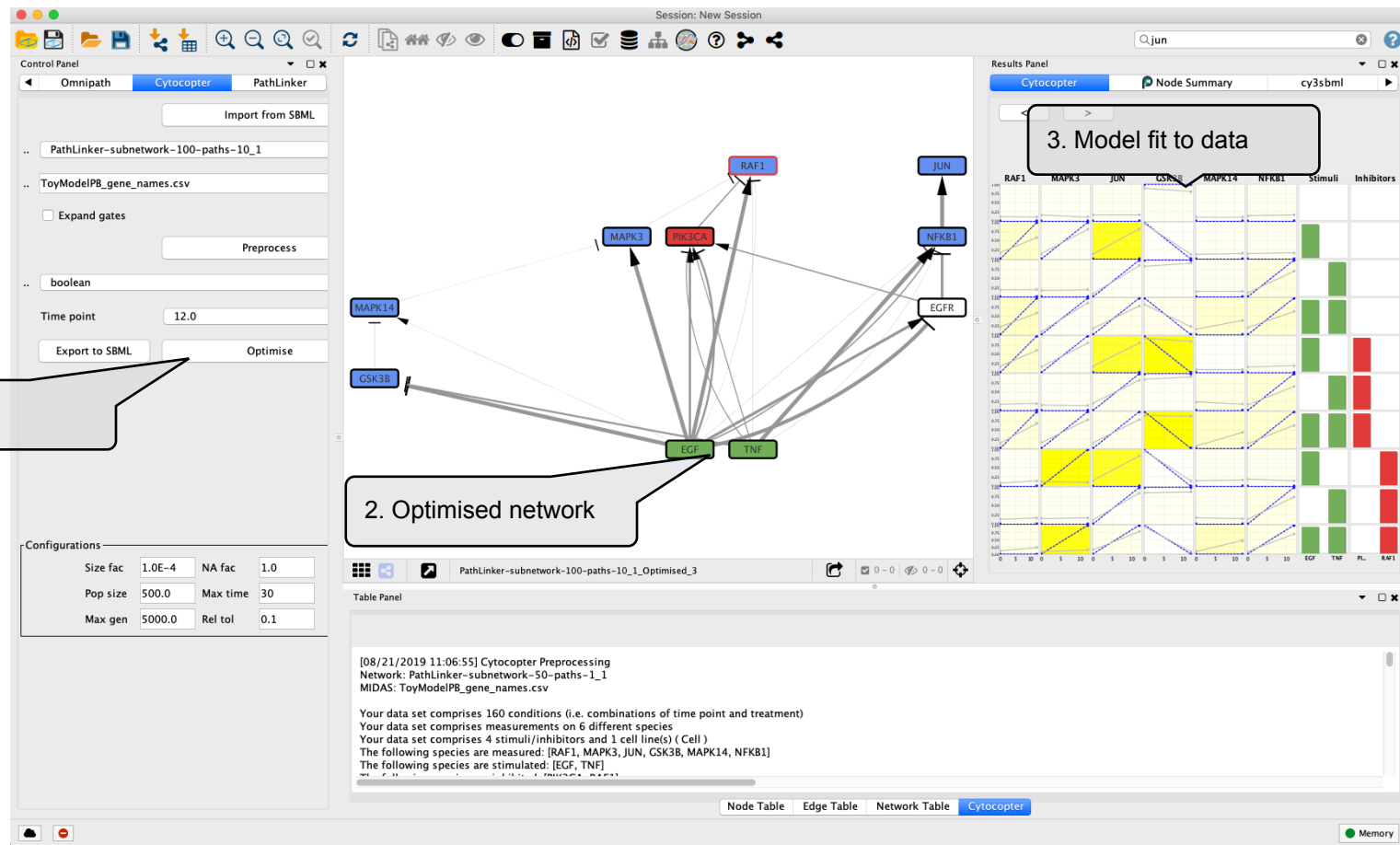
shared name	shared interaction	name	interaction	is_directed	is_stimulation	is_inhibition	consensus_direction	consensus_stimulat
EPHA3 (interacts wit...	1	EPHA3 (int...	1	1	1	0	1	1
ROR2 (interacts wit...	1	ROR2 (int...	1	1	1	0	1	1
ROR2 (interacts wit...	1	ROR2 (int...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1
EGF (interacts with)	1	EGF (inter...	1	1	1	0	1	1

Node Table Edge Table Network Table Cytocopter

Memory



Build model and optimise the network



Optimisation finds a set of models that fits the data equally good. The strength of the edges is proportional to the number of models where the edge present. Light edge shows unlikely interactions.