

Pathway Logic

Symbolic Systems Biology

Using formal systems and reasoning tools to understand

- how things work;
- why things don't work

Carolyn Talcott
Stanford Computational Biology
2013 December 11

Plan

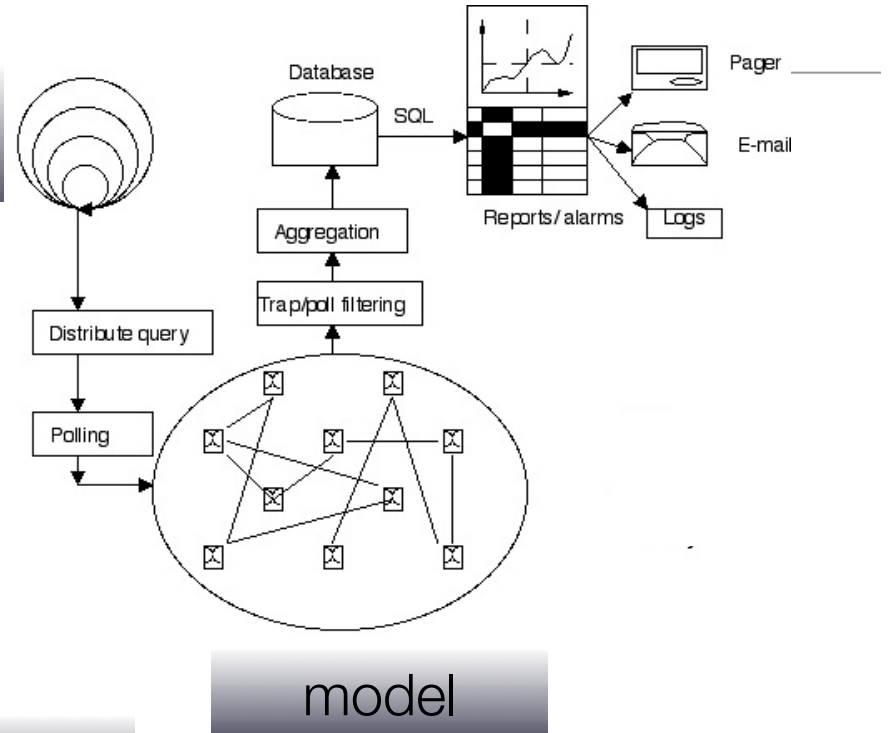
- About formal systems, formal modeling
- Pathway Logic and the STM model
- Other models
- Challenges

Formal Modeling Methodology

Curator/model builder



data



model

asking questions



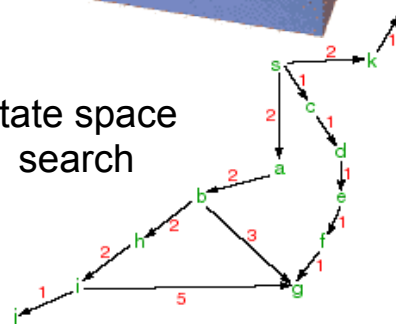
$$S \models \Phi$$

model checking



rapid prototyping

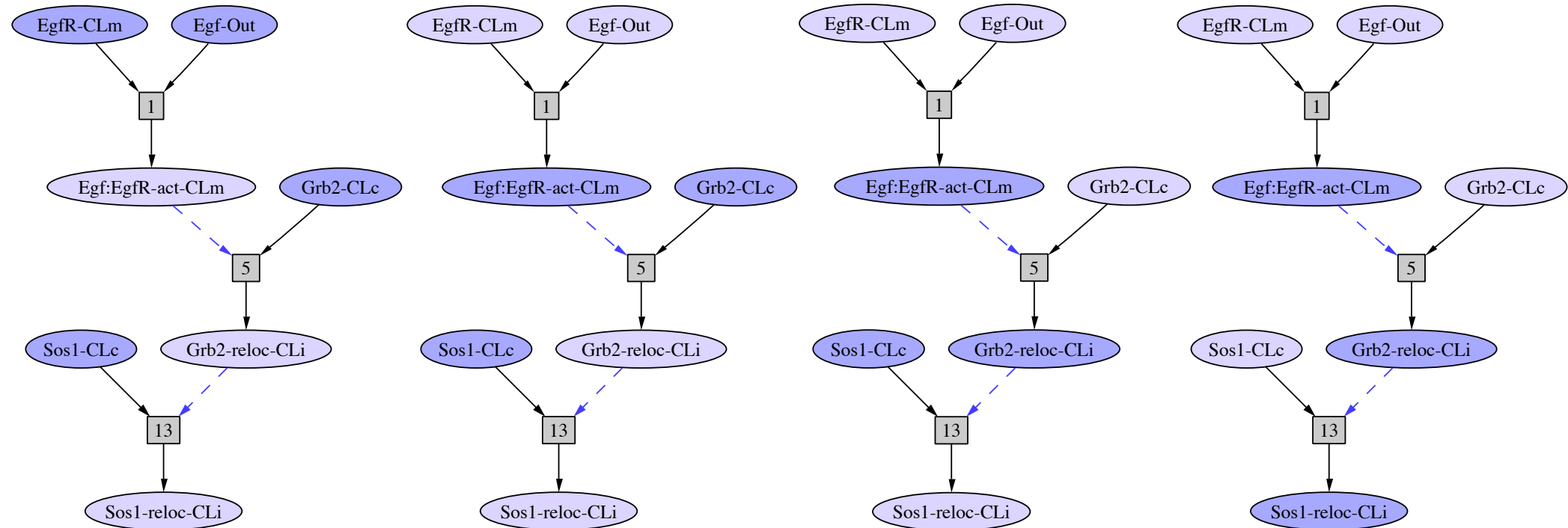
state space search



What is a formal system?

- Language: to describe system states and properties
- Semantics/System behavior: what does a description describe?
- Reasoning principles: proving/disproving properties
- Executable formal models (model train, model airplane, ..)
 - System state: collections of entities (name,location,knowledge,resources..)
 - experimental setup: cell state -- what is expressed, where; treatment
 - State transition rules
 - metabolic reaction, signal transduction step, secretion, cell mobility
 - Watch it run, poke it, do in silico experiments
- Execution: set of rule applications -- possible behavior
 - How does a signal propagate, watch things light up as modified ...
 - Find collections of cellular components that function together
 - One notion of “Pathway”

Example Execution (Petri Nets)



rasDish =rule1=> rasDish1 =rule5=> rasDish2 =rule13=> rasDish3

Ovals are occurrences -- biomolecules in locations (aka places).

Dark ovals are present in the current state (marked).

Squares are rules (aka transitions).

Dashed edges connect components that are not changed.

Symbolic analysis -- answering questions

- Forward reasoning -- what states / rules are possible
 - What is the relevant network of rules when Egf is added to a cell at rest?
- Backward reasoning -- all the ways to get to a state of interest
 - What are all the ways that Erk could be activated in response to Egf? (>150)
- Model checking -- do all executions satisfy property ϕ , find a counter example
 - Find a specific execution/pathway that activates Erk? Assert it can't be done.
- Constraint solving -- steady state analysis
 - flux balance, finding minimal nutrient sets

Pathway Logic (PL) <http://pl.csl.sri.com>

- Datum knowledge base -- formal model of experimental findings
- Rule knowledge base -- executable models of biological processes
- Pathways (sets of biomolecules that function together) and regulation effects discovered by asking questions (answered by formal reasoning)

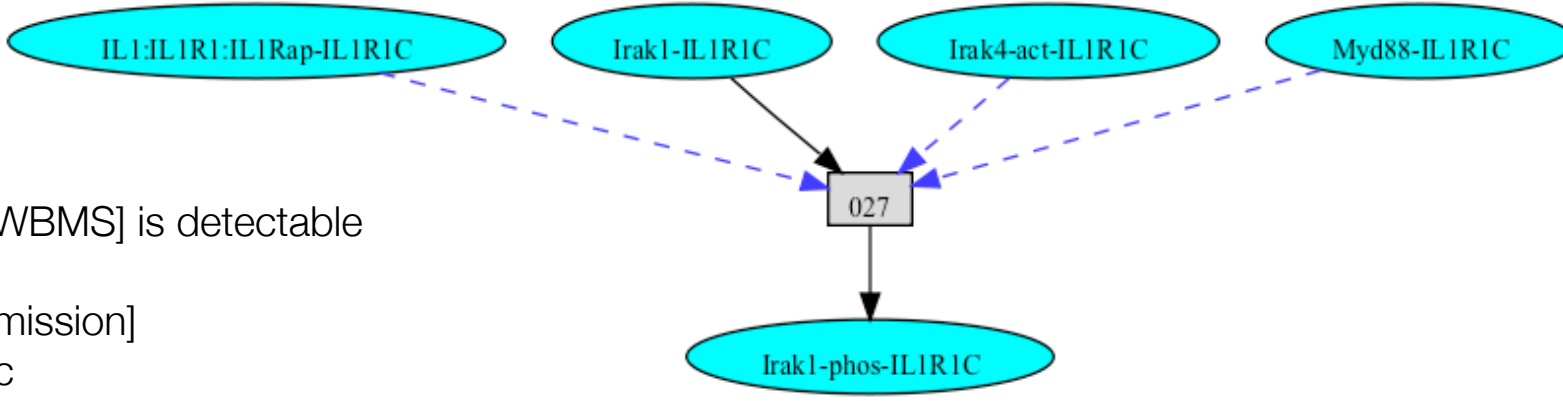
Pathway Logic Knowledge Base

- Vocabulary: Names of things, linked to standard references
 - IL1: Protein Family, members: IL1a IL1b
 - Irak1: Protein, UNIPROT:P51617, synonyms: Interleukin-1 receptor-associated kinase 1, Pelle-like kinase, PLK...
 - phos: AAMOD MOD:00696, phosphorylated

- Evidence and Rules

Irak1[Ab] upshift[WBMS] is increased irt IL1b (times)
cells: hFibros in BMS
times: 0 30+ 60+ min
reqs: xIrak4 [omission]
source: 15084582-Fig-5

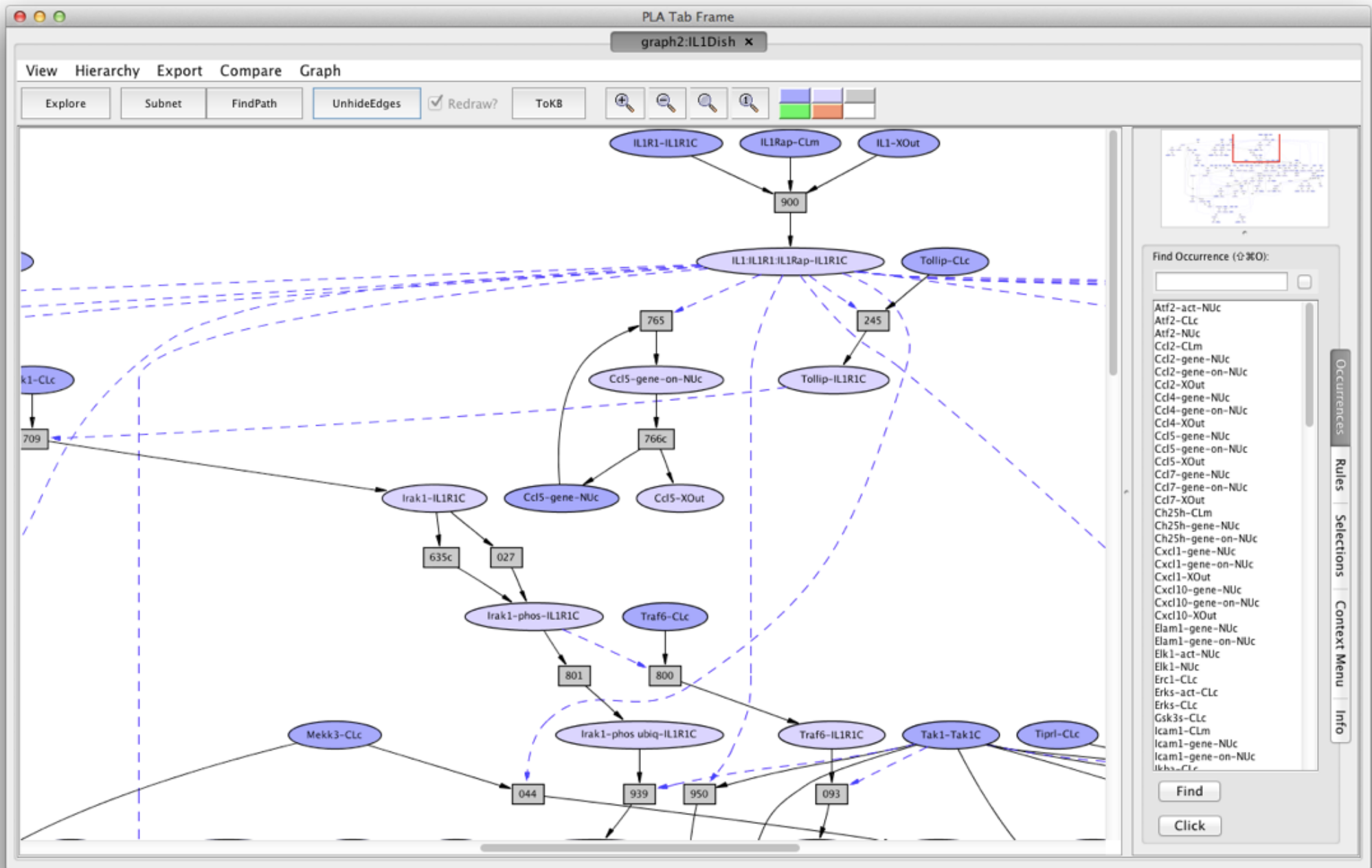
xIrak1(T66A)[Ab] upshift[WBMS] is detectable
cells: HEK293T in BMS
partially reqs: xMyd88 [omission]
source: 10854325-Fig-4c

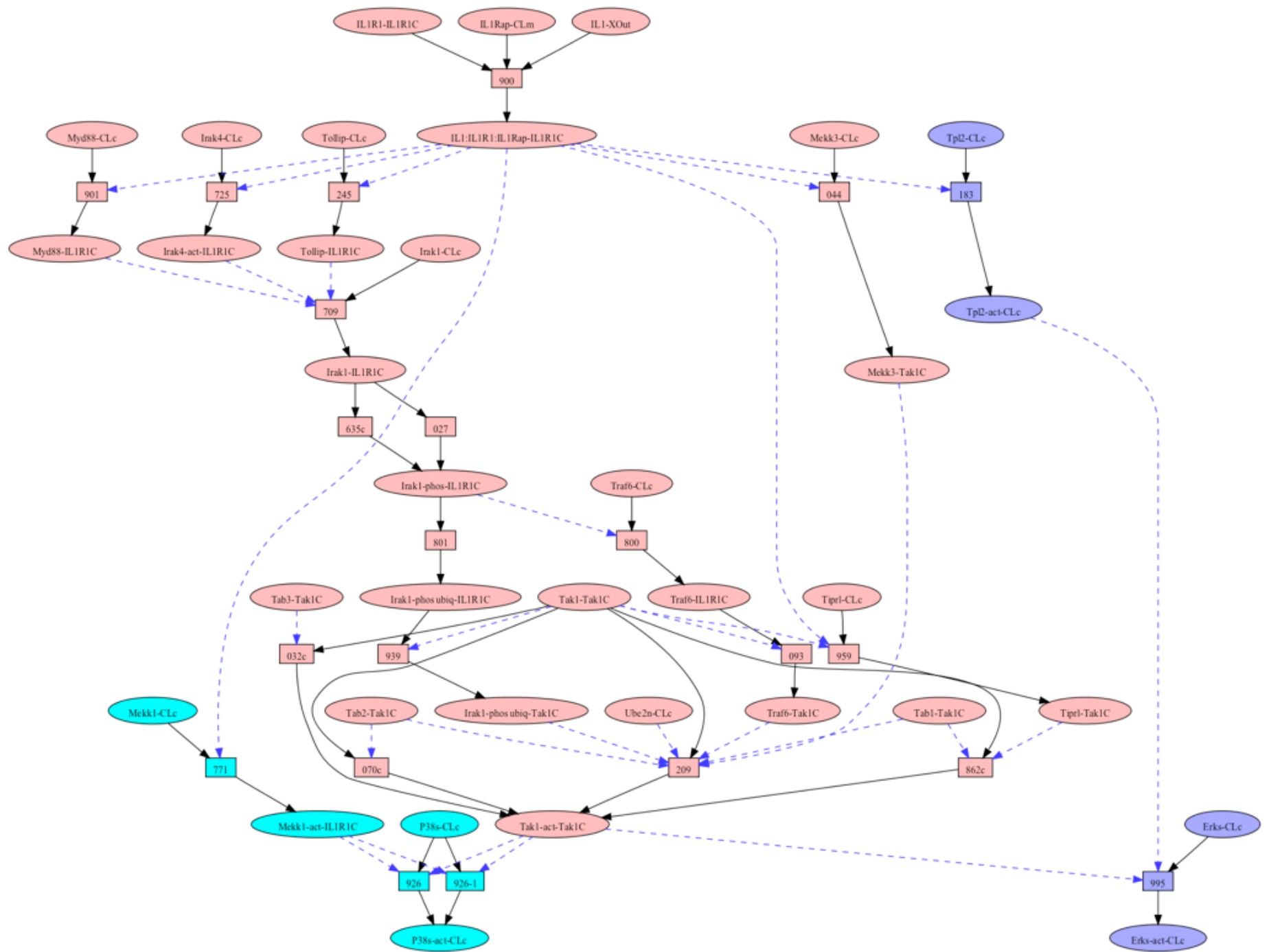


Pathway Logic Assistant: Features

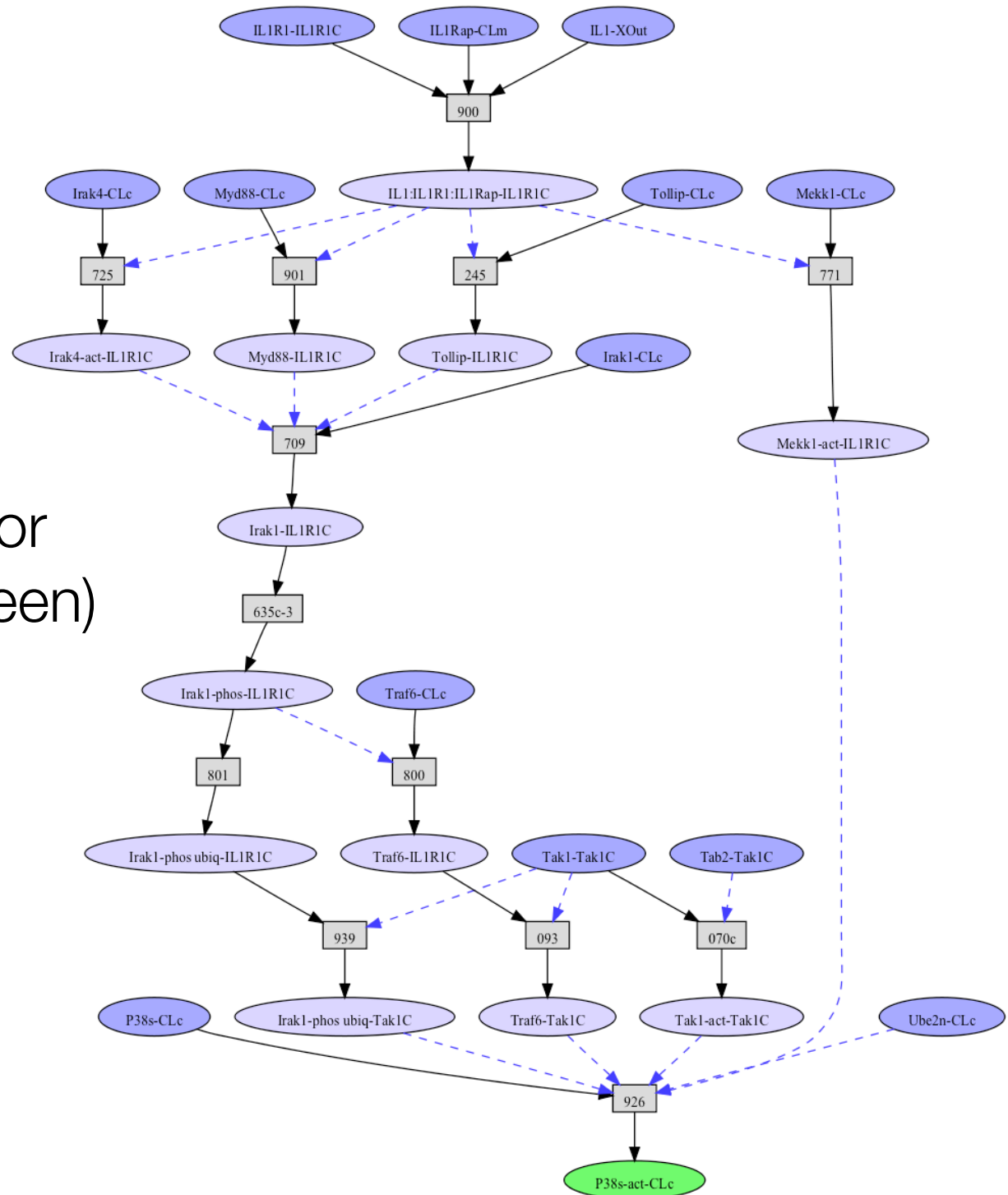
- Derive the network of rules modeling response to a stimulus
 - STM Model: CD40 Csf1 Egf Igf1 **IL1** Ins LPS Tgfb Tnf
- Find Erk activated in the picture (where is waldo?)
- Compute subnet activating Erk/P38,
- Compare subnets,
- Find an execution Path
- Explore -- what is upstream/downstream of X

Network modeling response to IL1



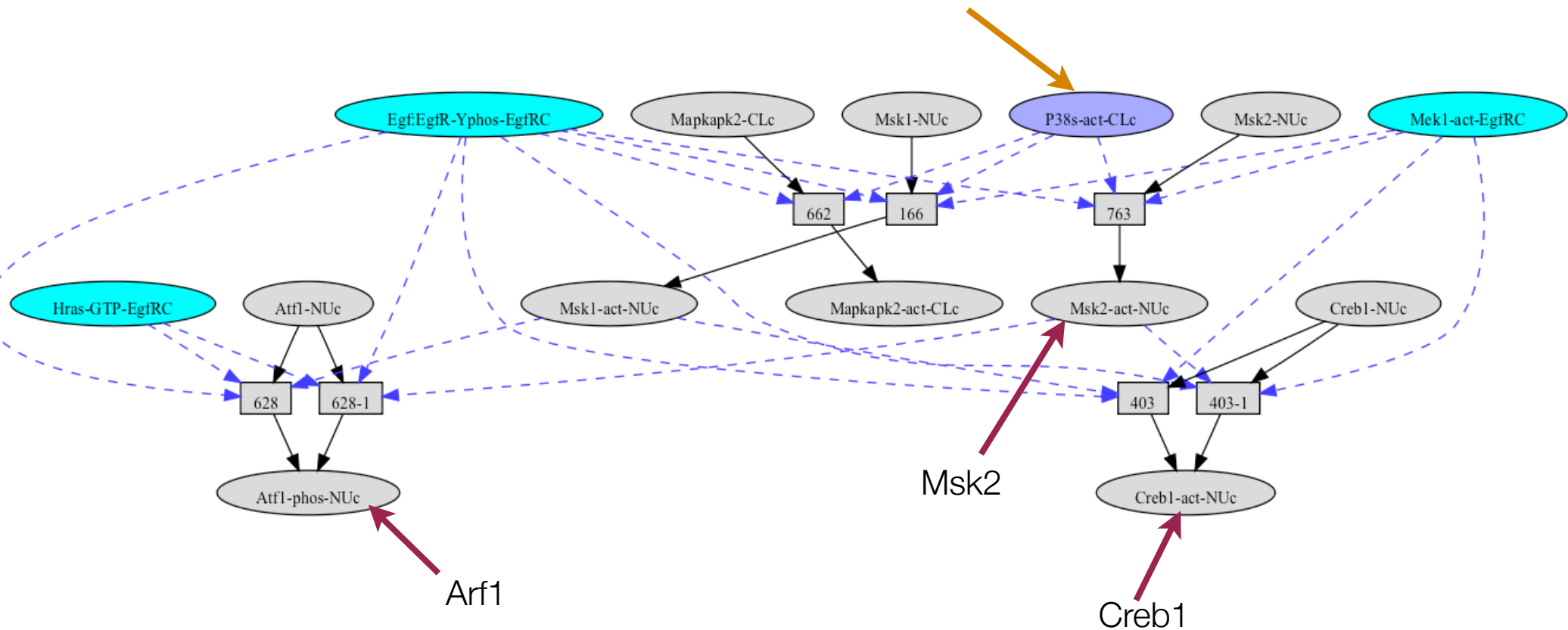


Comparing subnets for P38 (cyan) and Erk (blue) activation



Execution pathway for activation of P38 (green) in response to IL1

What if P38 has a mutation affecting its function?
Here are downstream elements in the Egf stimulation model.

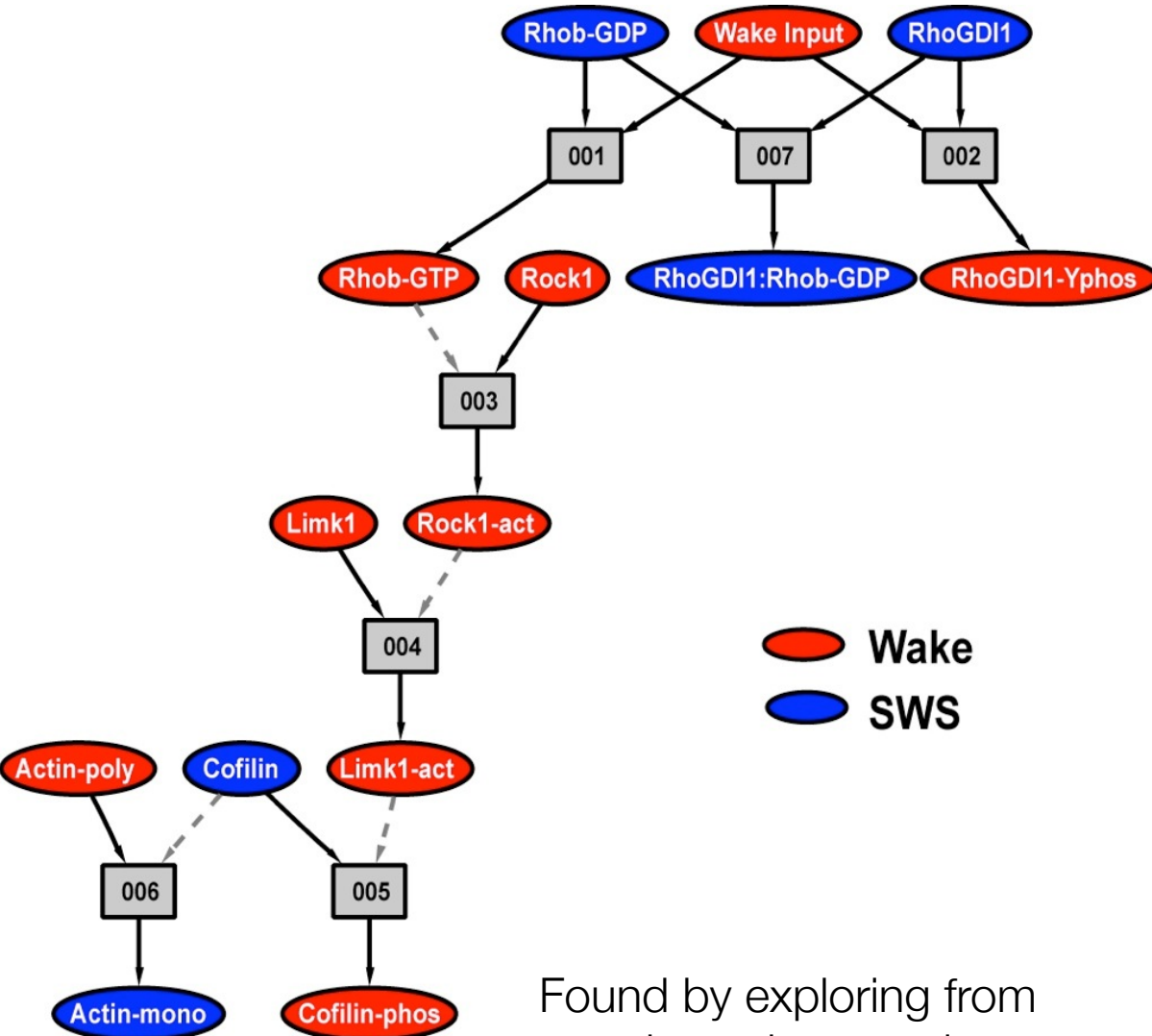


Beyond STM

- Sleep
- Protease network
- Metabolism -- Mycolic acid synthesis
- Glycosylation
- Immune system
- Diet Planning
- Drug discovery

A Hypothetical Model Pathway

Relating State and Synaptic Plasticity



Found by exploring from proteins unique to sleep state (Rhob, Actin)

Wake state:

unknown signal(s)

=> phosphorylation of Rock1

=> activation of Limk1

=> phosphorylation of cofilin

=> increase in polymerized actin
(Phosphorylated cofilin is unable to depolymerize actin)

SWS:

RhoGDI1 binds Rhob-GDP

(is not phosphorylated)

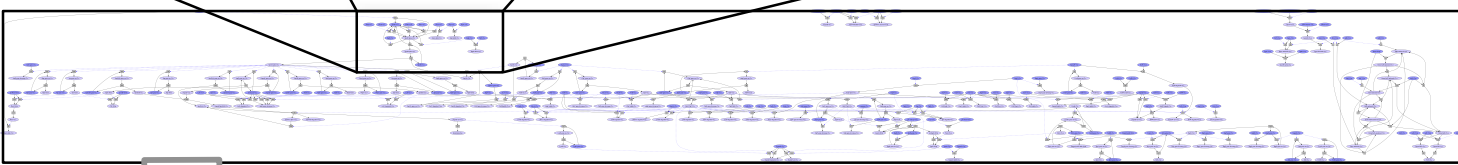
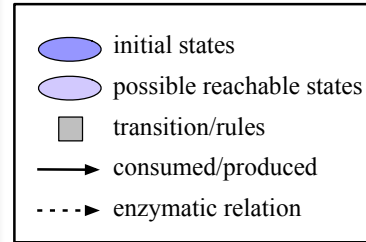
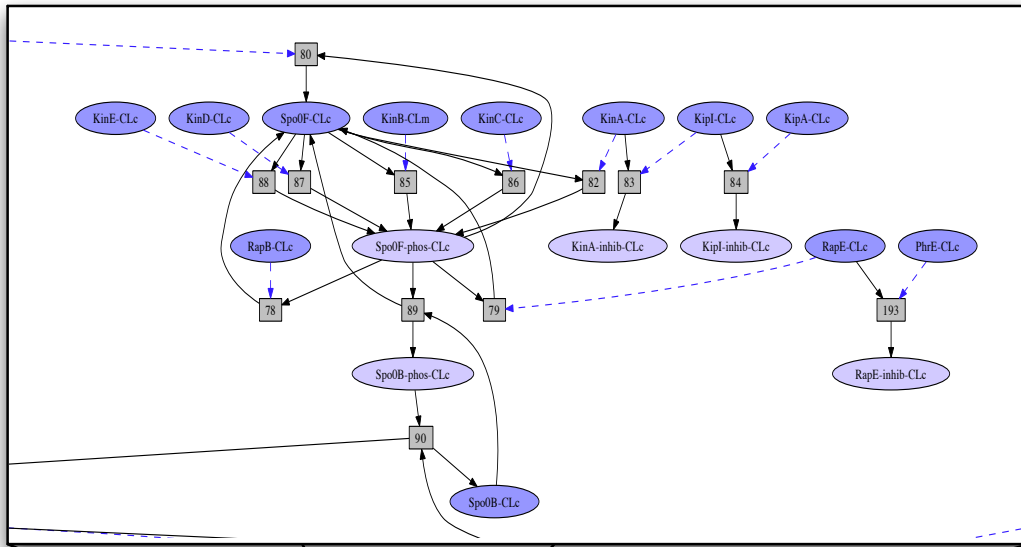
=> Rock1, Limk1, and cofilin would not be phosphorylated and

=> actin depolymerization

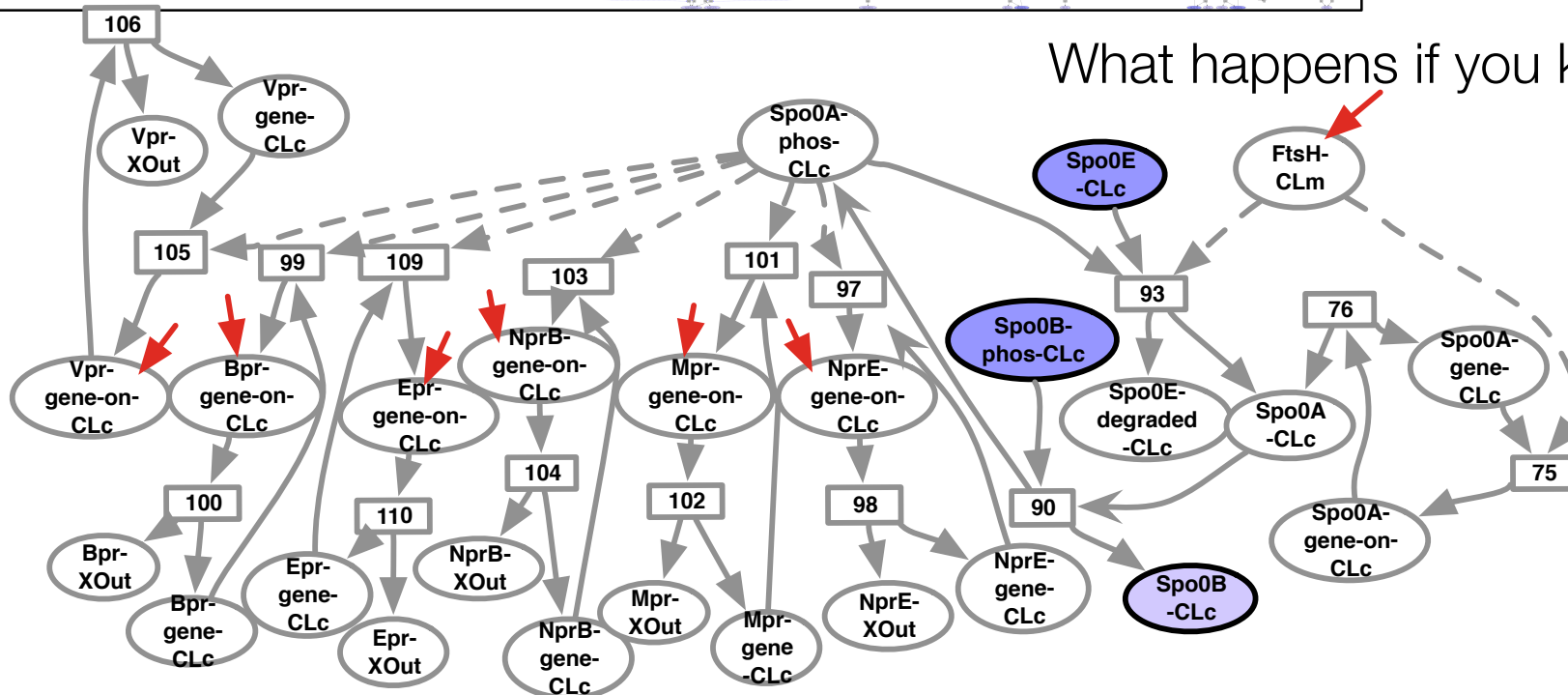
=> decrease in synaptic weight

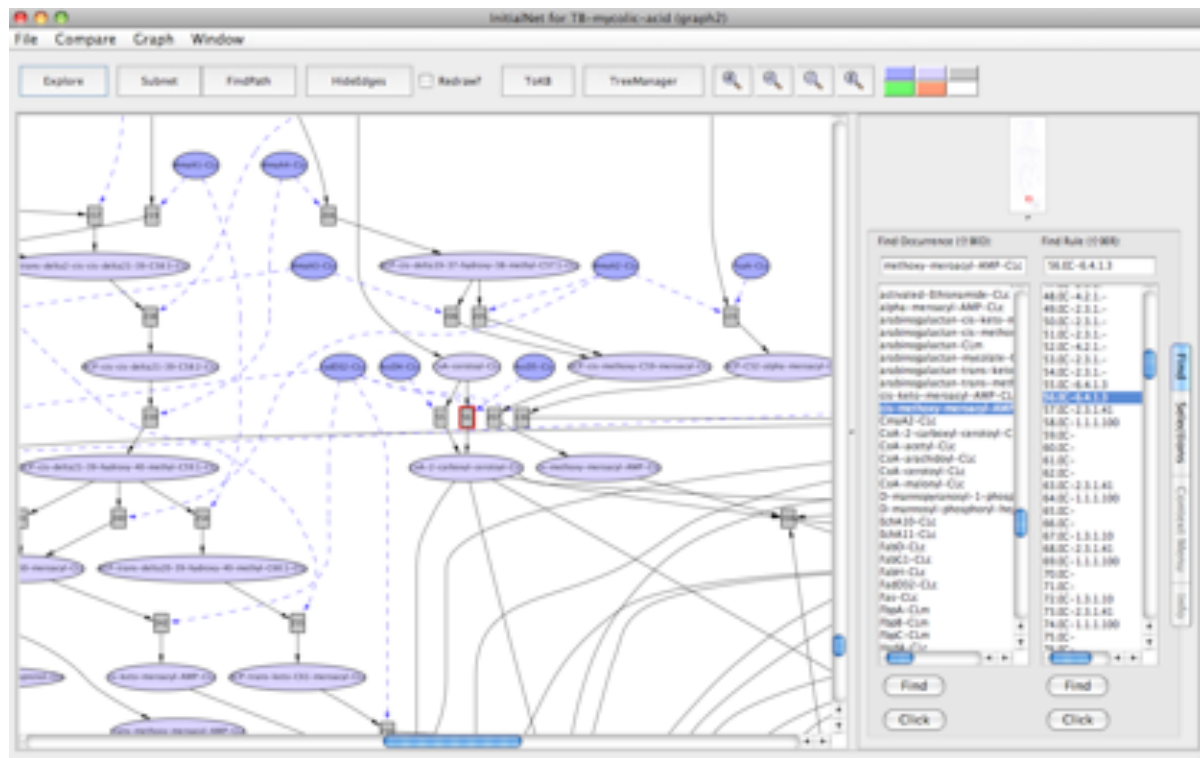
Protease interaction network (Gram Positive Bacteria) (Anupama)

What regulates a protease, what does it regulate



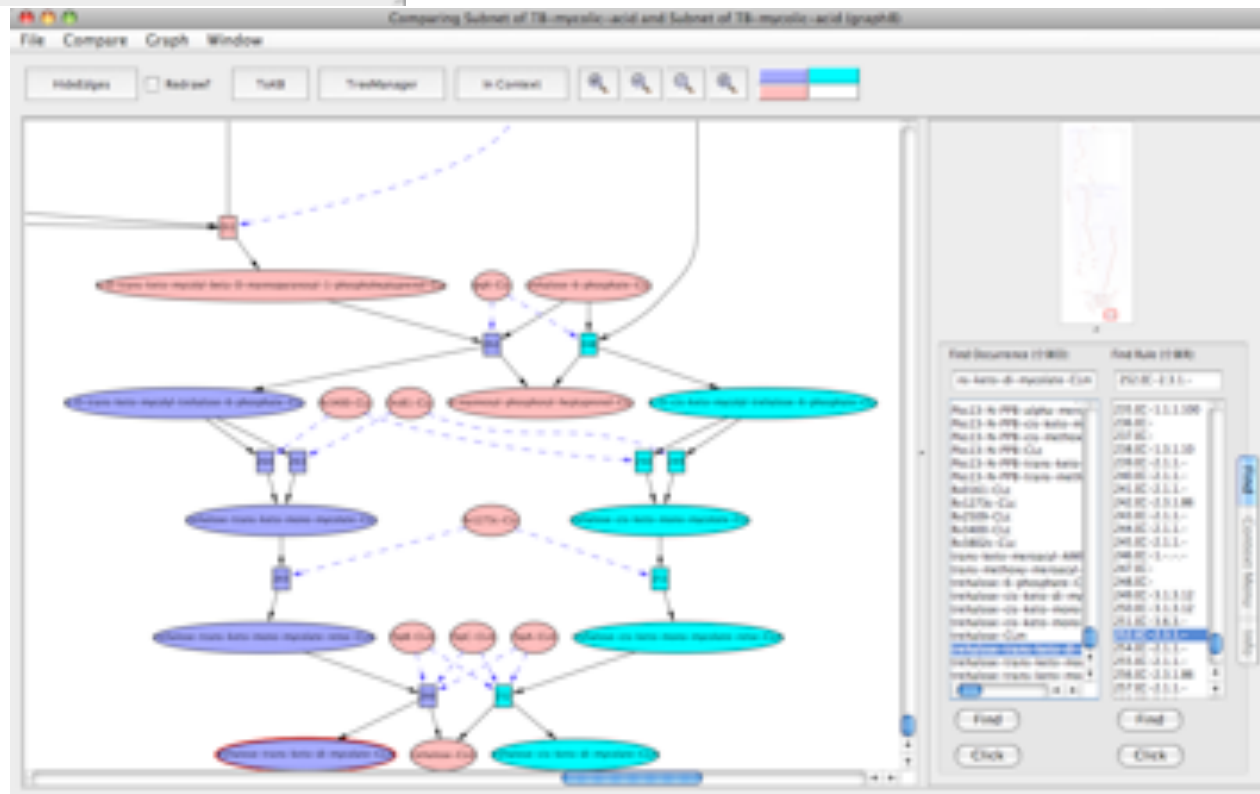
What happens if you knockout FtsH?



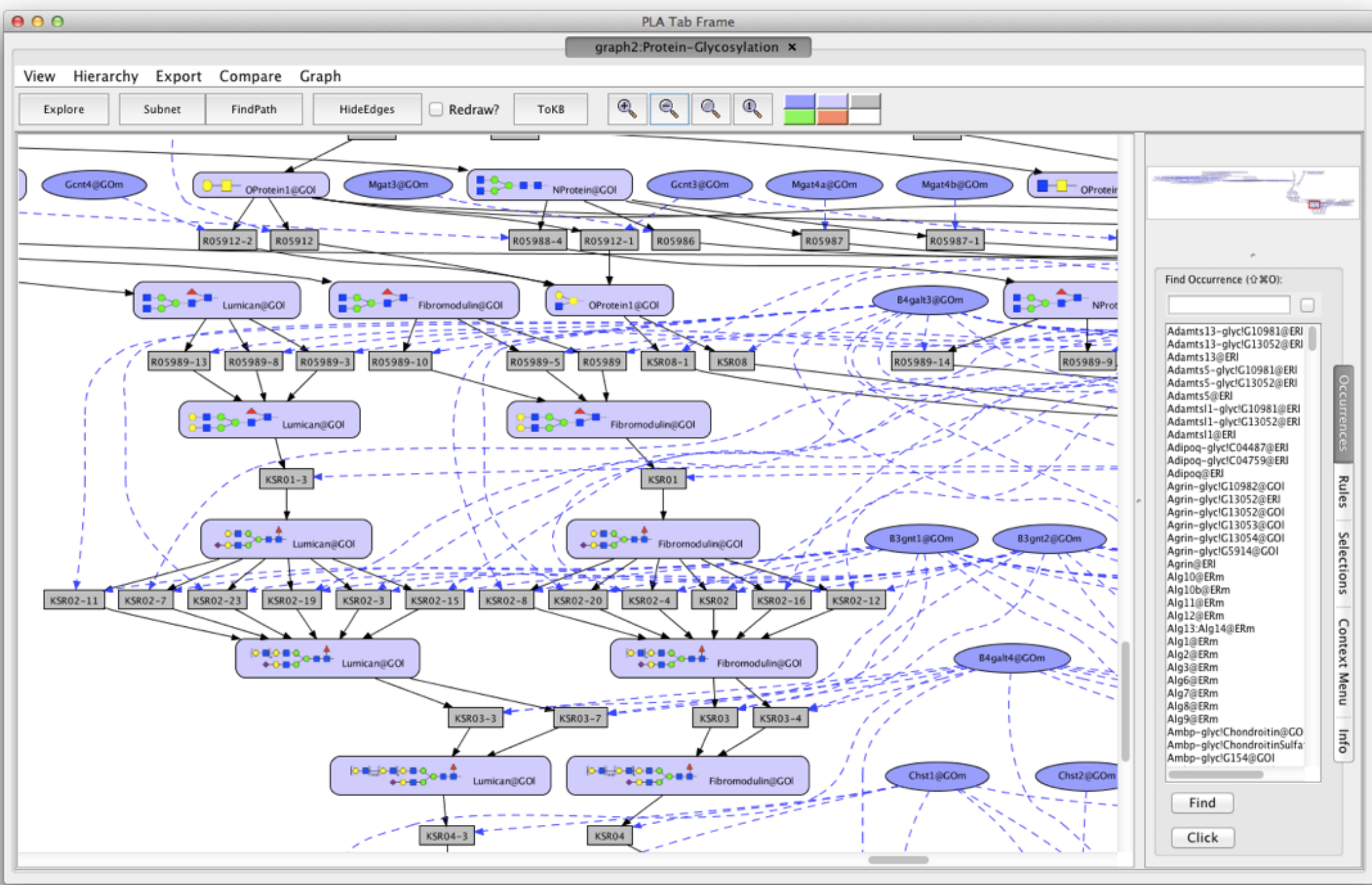


TB-mycolic-acid synthesis
(Malabika)

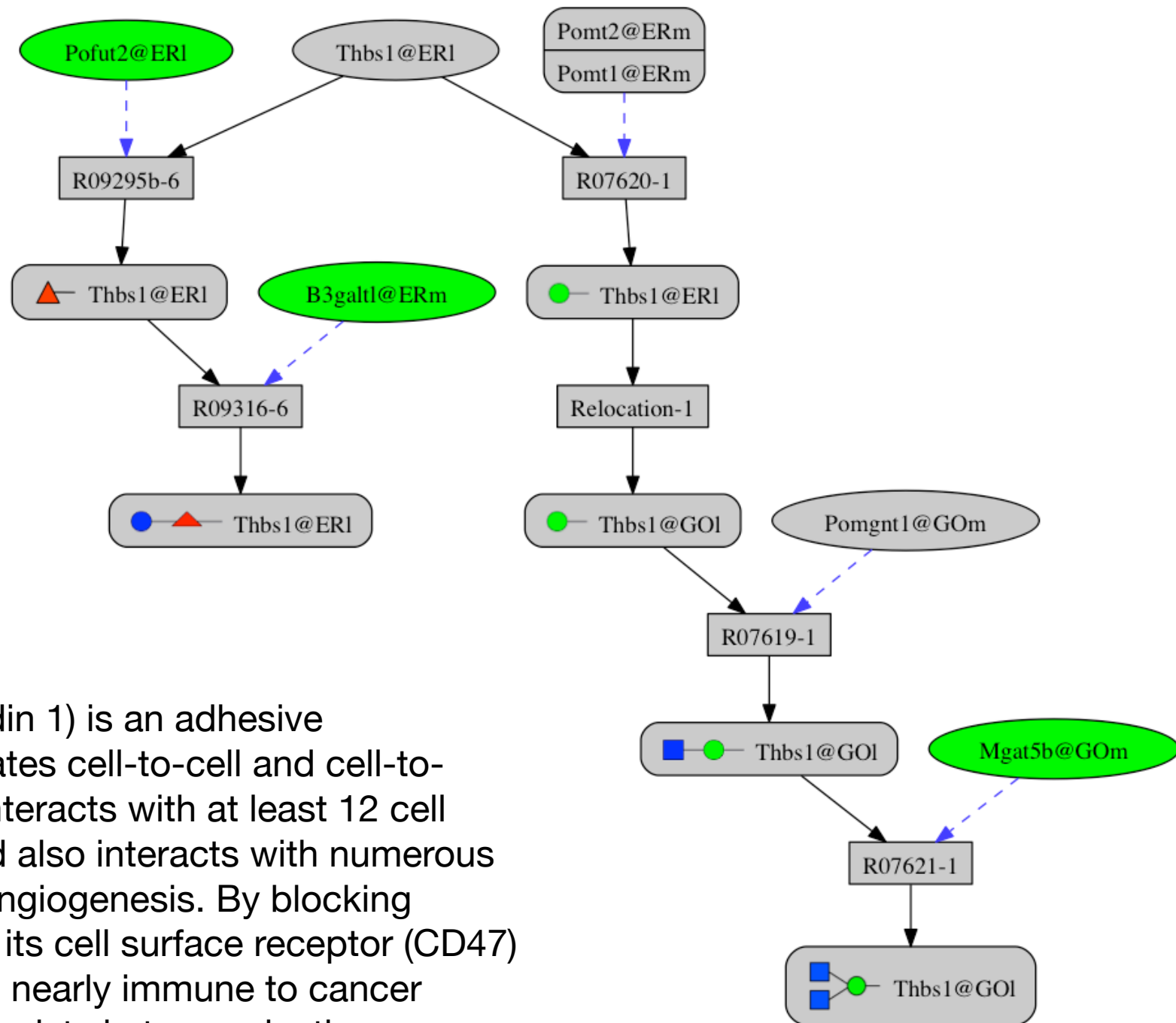
Multiple synthesis routes



Protein Glycosylation KEGG + Uniprot



Exploring Glycosylation of TBS1

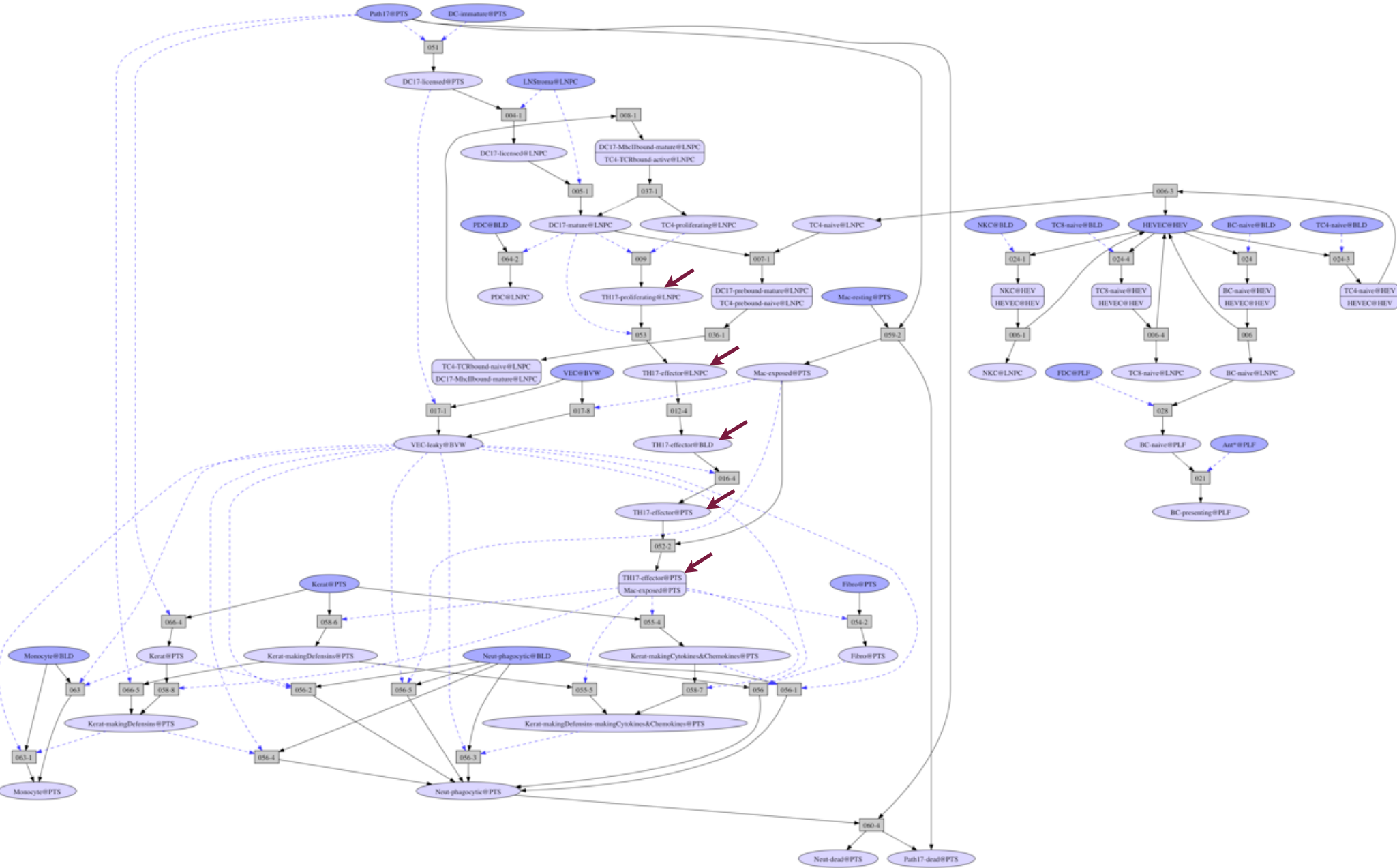


THSP1 (Thrombospondin 1) is an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. It interacts with at least 12 cell adhesion receptors and also interacts with numerous proteases involved in angiogenesis. By blocking THSP1 from binding to its cell surface receptor (CD47) normal tissue becomes nearly immune to cancer radiation therapy and assists in tumor death.

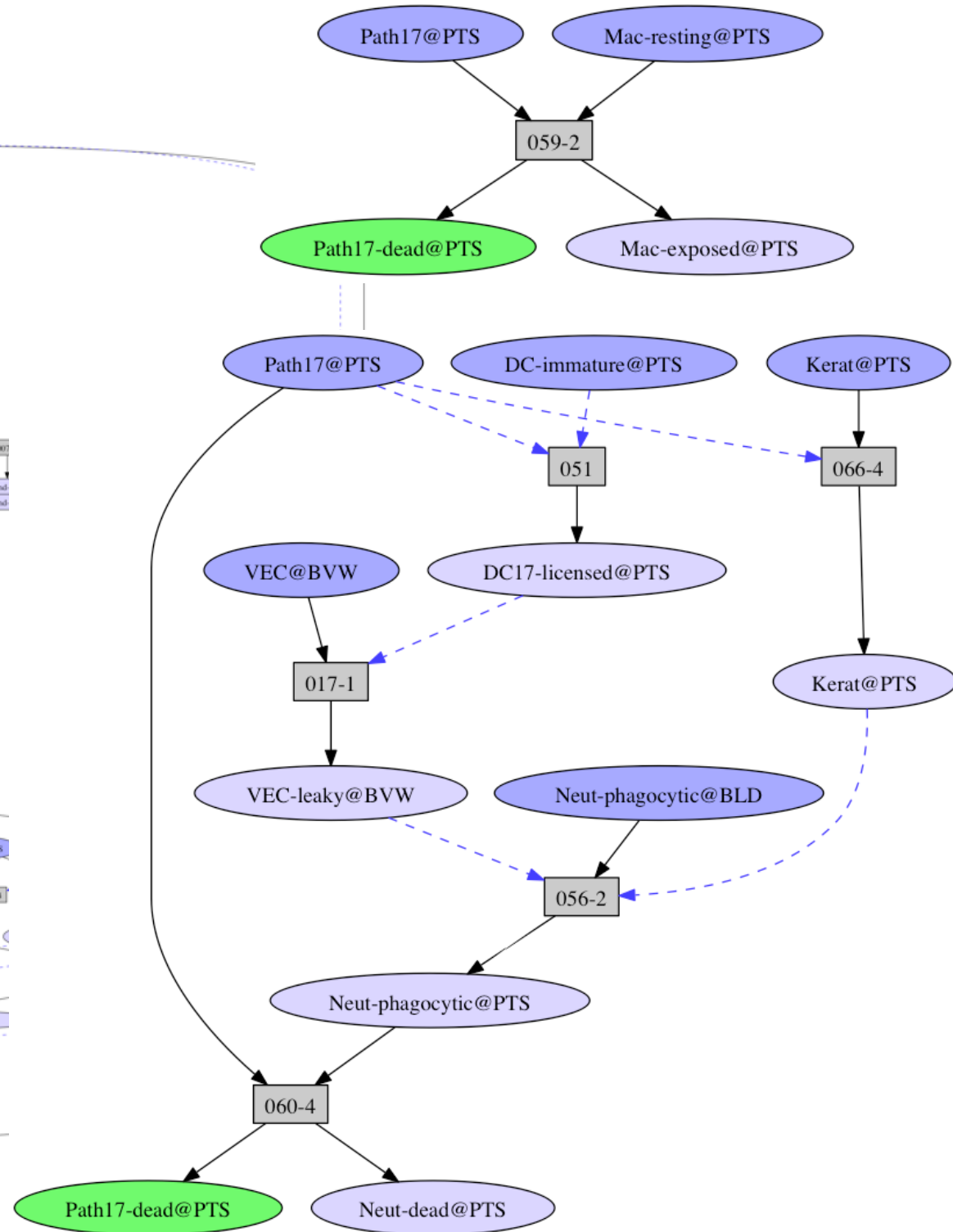
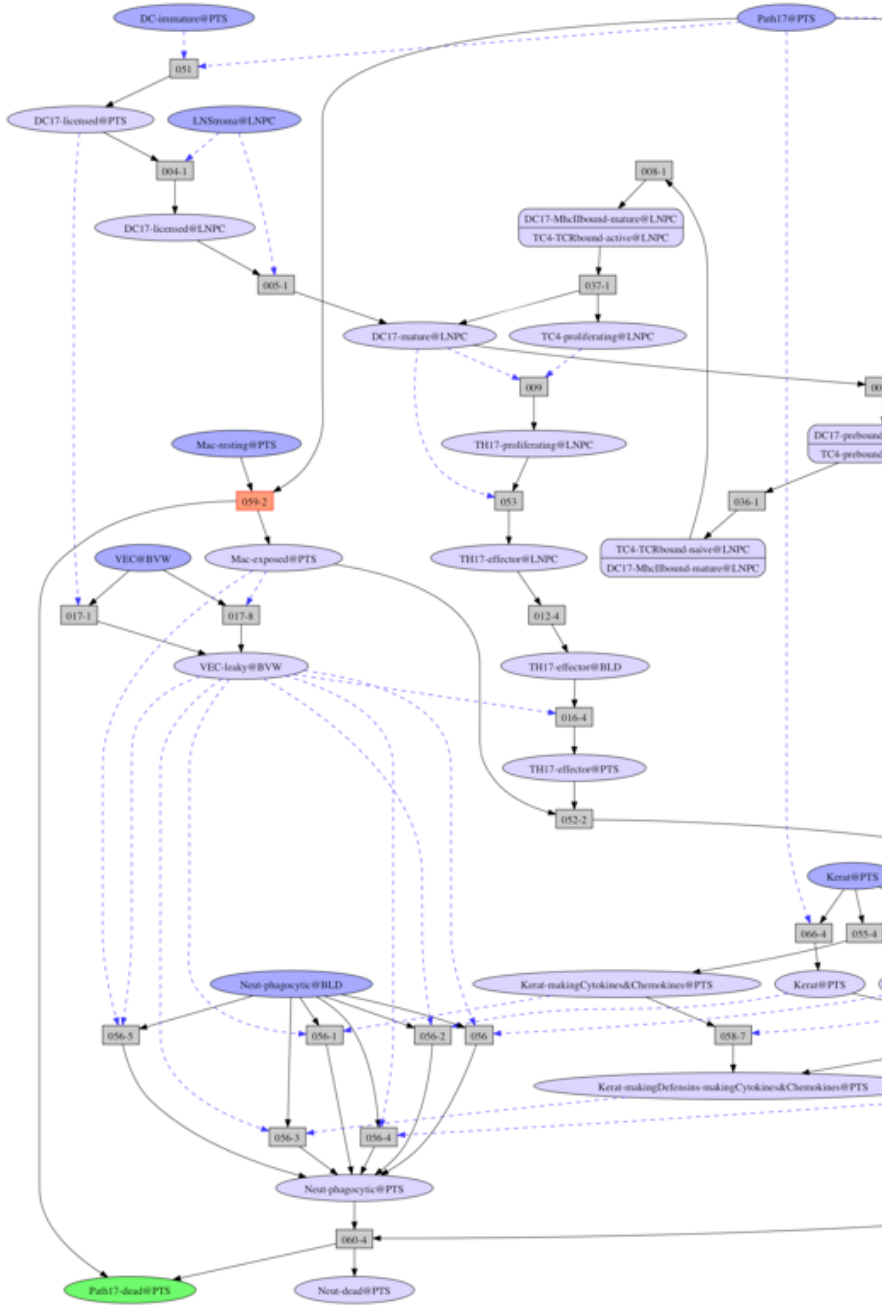
Model of the Immune System ala Janeway

- Different classes of challenge
 - Listeria: Intracellular bacterium *Listeria monocytogenes*
 - Path1: Pathogens that lead to TH1
 - Path2: Pathogens that lead to TH2
 - Path8: Pathogens killed by Cd8 cytotoxic cells
 - Path17: Pathogens that lead to TH17
 - PathFH: Pathogens that lead to THfh
 - Virus
 - NoPathogen
- 258 rules

Response to Path17



Killing Path17



Diet planning for Ecoli (aka finding minimal nutrient sets)

- Metabolic network, transportables, and growth conditions, represented as constraints.
- Find all minimal nutrient set solutions
- OOPS there are ~8560
- Partition nutrients into equivalence classes (replacable)
- 19 sets with 12 classes
- Surprise! E.Coli can grow on cyanate (and several other novel nutrient sets).

A.



B.

	reaction 1	reaction 2
A	-1	0
B	-1	1
C	1	-1
D	1	0
E	0	1
F	0	-1

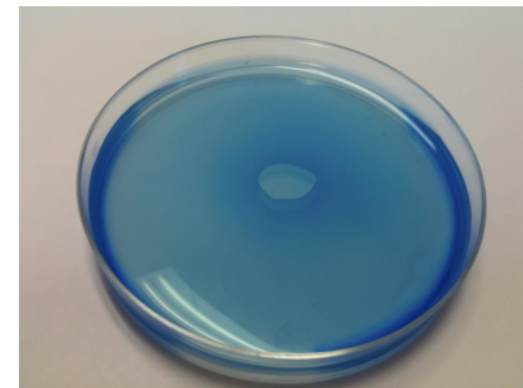
C.

(2R,3R,6S)-3-fluoro-2,4-diaminopimelate
 (2R,3S)-2-methylisocitrate
 (2R,3S)-3-isopropylmalate
 (2R,3S,6S)-2,6-diamino-3-hydroxy-diaminopimelate
 (2R,3S,6S)-3-fluoro-2,4-diaminopimelate
 (2R,4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran
 (2R,4S)-2-methyl-2,4-dihydroxydihydrofuran-3-one
 (2S)-2-amino-3-oxo-4-phosphonooxybutanoate
 (2S)-2-isopropyl-3-oxosuccinate
 (2S)-2-isopropylmalate
 (2S,3R,6S)-2,4-diamino-3-hydroxydiaminopimelate
 (2S,3R,6S)-3-fluoro-2,4-diaminopimelate
 (2S,3S)-2-methylcitrate
 (2S,3S,6S)-3-fluoro-2,4-diaminopimelate
 (4-hydroxyphenyl)acetaldehyde
 (4R,5S)-4,5,6-Trihydroxy-2,3-dioxohexanoate
 (6R)-6-fluoro-EPSP
 (6S)-6-fluoro-EPSP
 (E)-alpha-monofluoromethyldehydroarginine
 (E)-3-(methoxycarbonyl)pent-2-enedioate
 (enterobacterial common antigen)2 undecaprenyl-diphosphate
 (enterobacterial common antigen)3 undecaprenyl-diphosphate
 (enterobacterial common antigen)4 core oligosaccharide lipid A
 (enterobacterial common antigen)4 undecaprenyl-diphosphate
 (KDO) lipid NA
 (O16 antigen)2 undecaprenyl diphosphate
 (O16 antigen)3 undecaprenyl diphosphate
 (O16 antigen)4 core oligosaccharide lipid A



succinate

D.

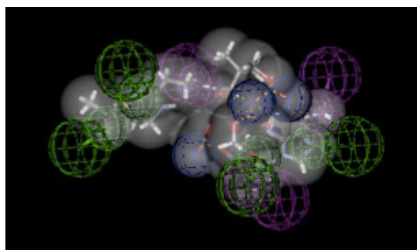


Combining Cheminformatics and Pathway Analysis

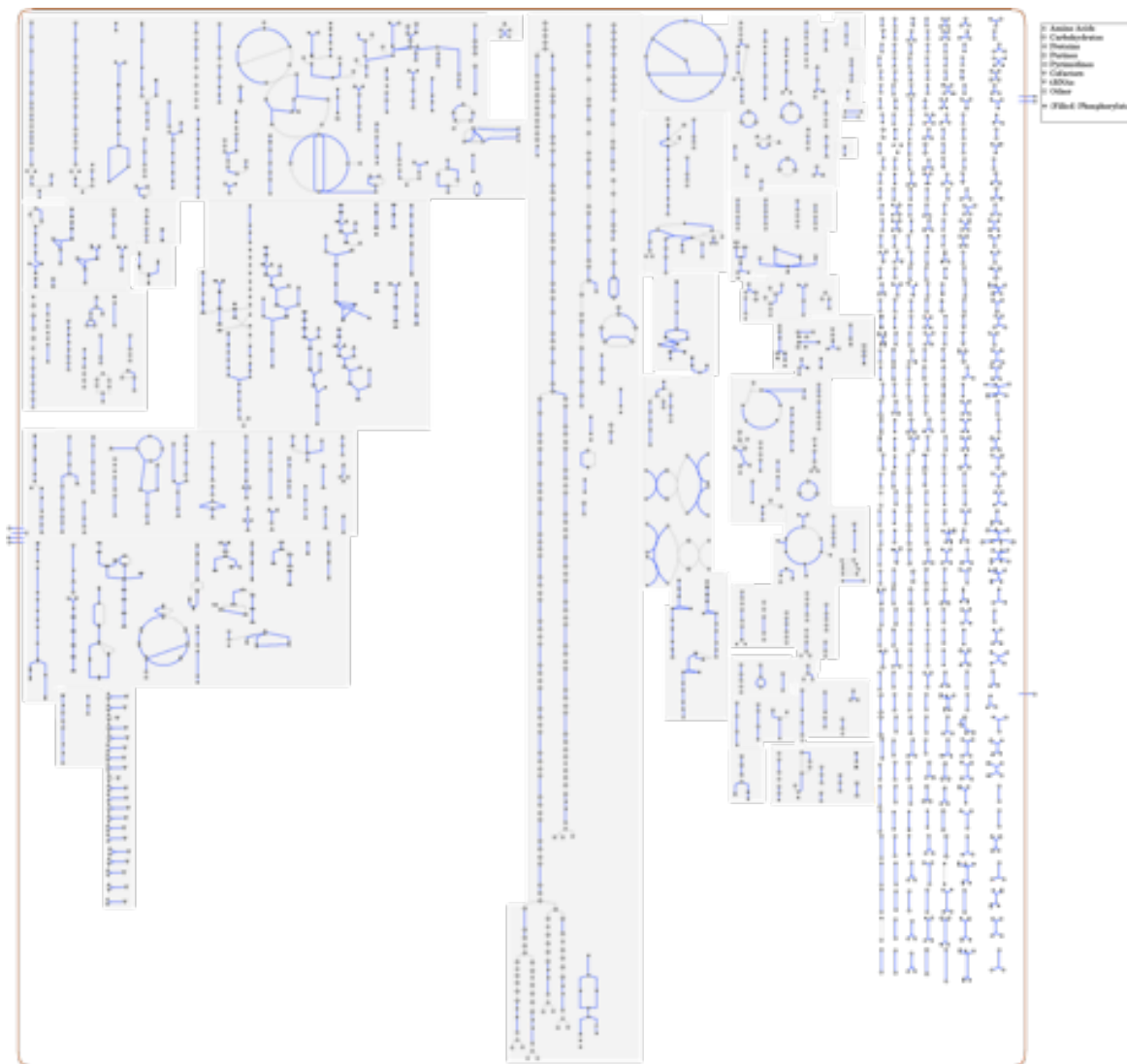
Finding TB drug candidates

NIH STTR with Collaborative Drug Design (CDD)

- Identify essential genes/enzymes
- Select substrates of highly connected enzymes
- Generate pharmacophores (abstract model of metabolite)



- Look for matches in drug catalog
- Predicted 30 candidate drugs, tested 20, 3 had activity
- Phase II STTR submitted.



Challenges

- Integrating pathways from different databases
- Integrating metabolism and signaling
- Integrating intra/inter cellular signaling
- Capturing existing experiments/data in computable form
- Getting the right experiments done
-

PL extended team*

- Anya Bida (free lance immunologist)
- Robin Donaldson (Glasgow/Stanford)
- Steven Eker
- Merrill Knapp
- Keith Laderoute
- Pat Lincoln
- Ian Mason
- Huaiyu Mi (USC, PANTHER)
- Anupama Panikkar (SV)
- Andy Poggio
- Malabika Sarker (DC)
- Carolyn Talcott
- Maneesh Yadav

*Alphabetical order