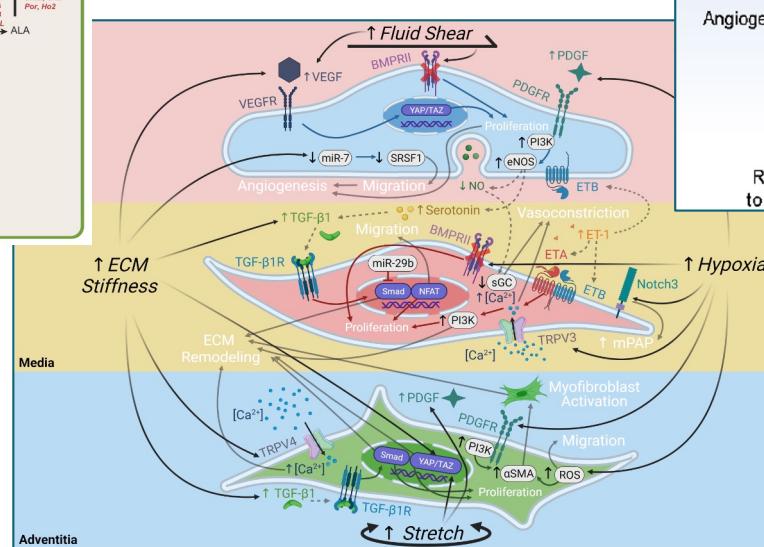
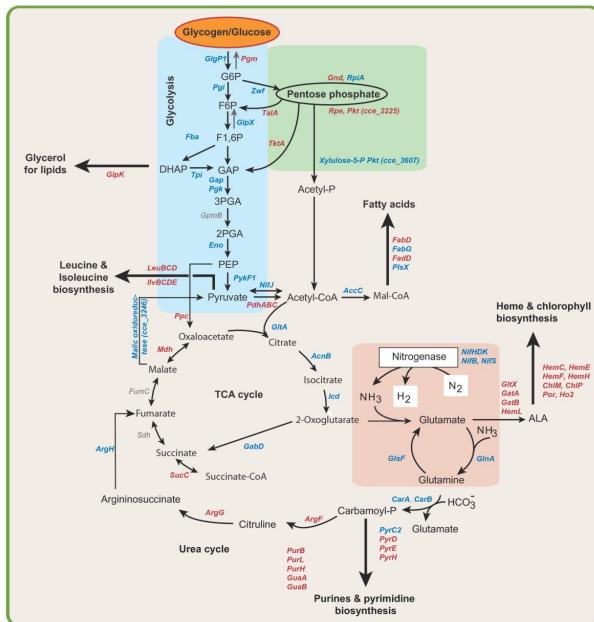
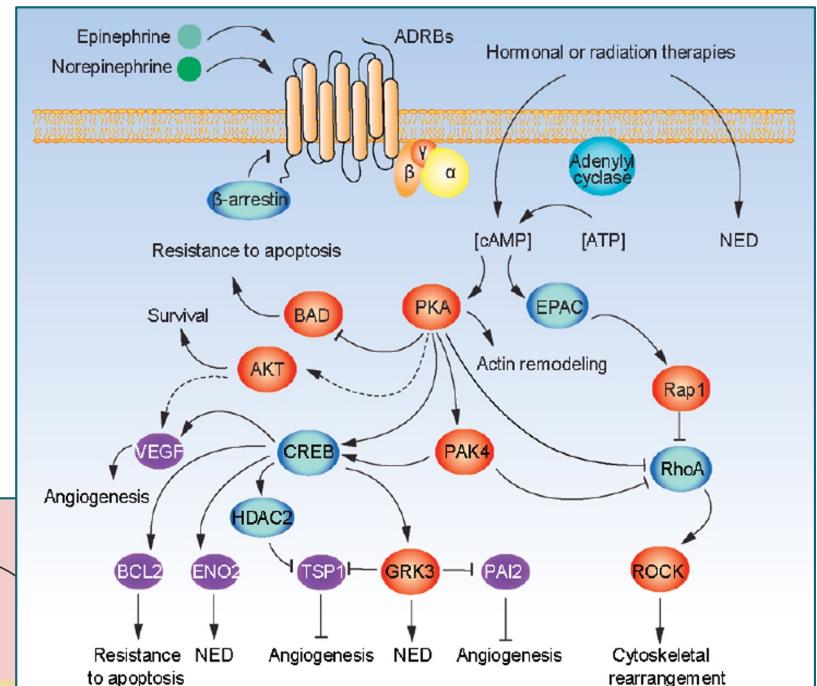


Biochemical Reaction Networks

Metabolic pathways



Intracellular signaling pathways



Intercellular signaling networks

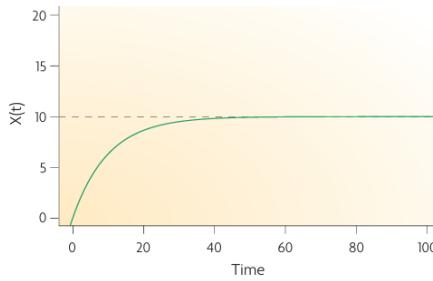
Types of Biochemical Network Model: Deterministic vs. Stochastic, Continuous vs. Discrete

Continuous deterministic model (RRE):

$$\frac{dX}{dt} = \alpha - \mu X$$

Solution: $X_t = \frac{\alpha}{\mu} (1 - e^{-\mu t})$

Equilibrium: $X_\infty = \alpha/\mu$



Discrete stochastic model:

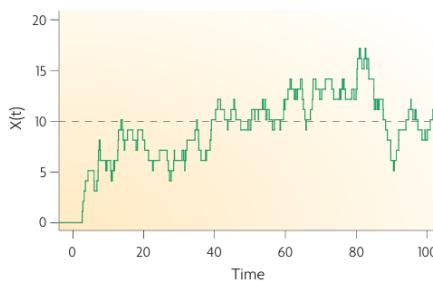
$$\Pr(X_{t+dt} = x+1 | X_t = x) = \alpha dt$$

$$\Pr(X_{t+dt} = x-1 | X_t = x) = \mu x dt$$

Solution: $X_t \sim \text{Poisson} \left(\frac{\alpha}{\mu} [1 - e^{-\mu t}] \right)$

Equilibrium distribution: $X_\infty \sim \text{Poisson} (\alpha/\mu)$

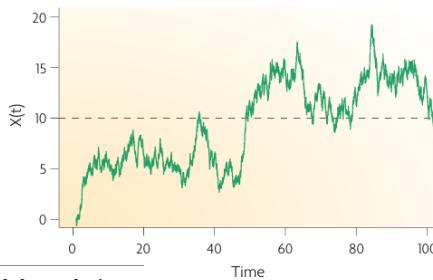
$$E(X_\infty) = \text{Var}(X_\infty) = \alpha/\mu$$



Continuous stochastic model (CLE):

$$dX_t = (\alpha - \mu X_t) dt + \sqrt{\alpha + \mu X_t} dW_t$$

At equilibrium: $E(X_\infty) = \text{Var}(X_\infty) = \alpha/\mu$



Box 1 | A simple model for protein production and degradation

Review Article | Published: February 2009

Stochastic modelling for quantitative description of heterogeneous biological systems

Darren J. Wilkinson

Nature Reviews Genetics 10, 122–133 (2009) | [Cite this article](#)

Types of Deterministic Metabolic Network Model: Mass-Action Kinetics to Steady-State Constraint-Based

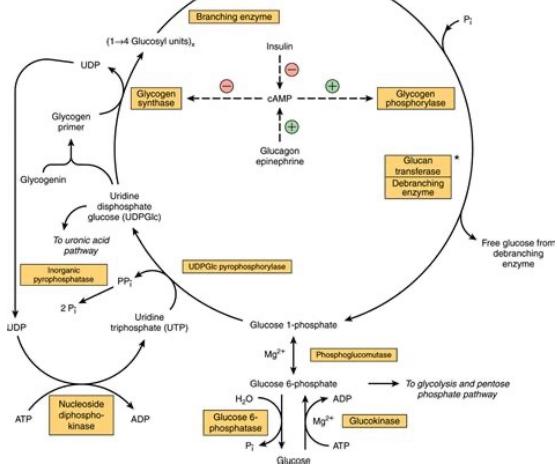
Biophysical Journal



Volume 91, Issue 4, 15 August 2006, Pages 1264-1287

Dynamics of Muscle Glycogenolysis Modeled with pH Time Course Computation and pH-Dependent Reaction Equilibria and Enzyme Kinetics

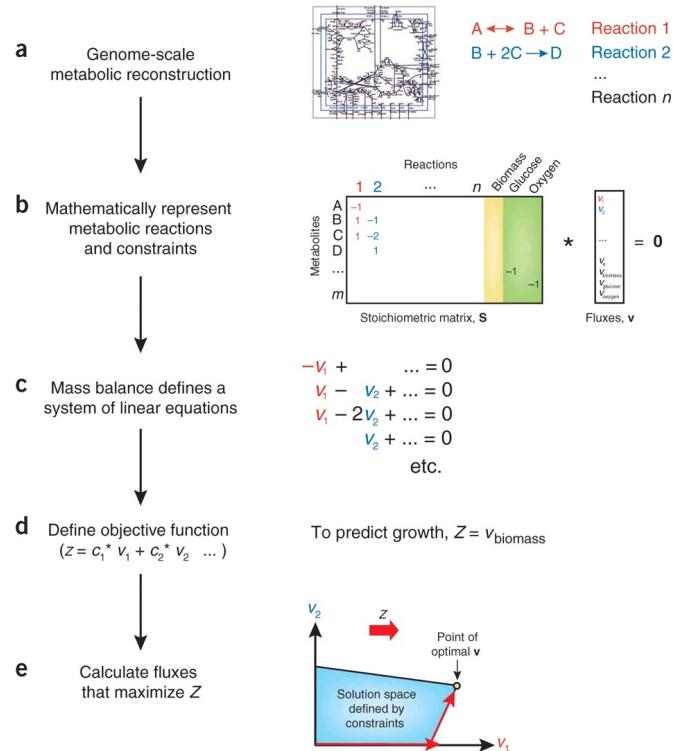
Kalyan Vinnakota *¹, Melissa L. Kemp ¶¹, Martin J. Kushnerick *†‡§, □



What is flux balance analysis?

[Jeffrey D Orth, Ines Thiele & Bernhard Ø Palsson](#) □

[Nature Biotechnology](#) 28, 245–248 (2010) | [Cite this article](#)

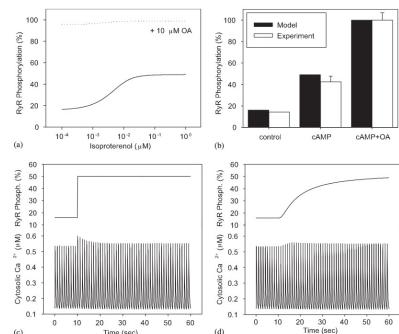
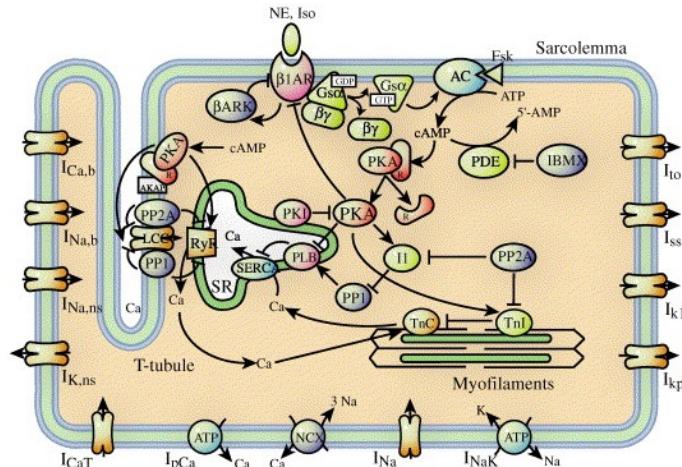


Types of Deterministic Signaling Network Model: Empirical Biochemical Kinetics to Boolean

Mechanistic systems models of cell signaling networks: a case study of myocyte adrenergic regulation

Jeffrey J. Saucerman, Andrew D. McCulloch*

Progress in Biophysics & Molecular Biology 85 (2004) 261–278



OPEN ACCESS Freely available online



Boolean Network Model Predicts Knockout Mutant Phenotypes of Fission Yeast

Maria I. Davidich, Stefan Bornholdt*

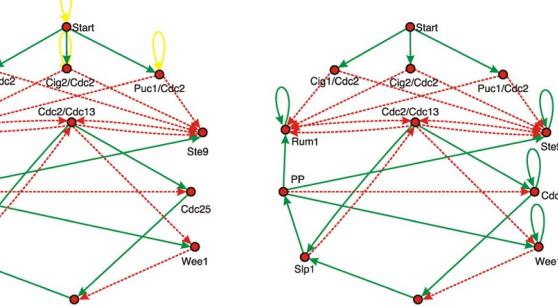
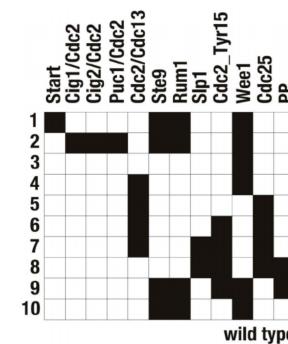
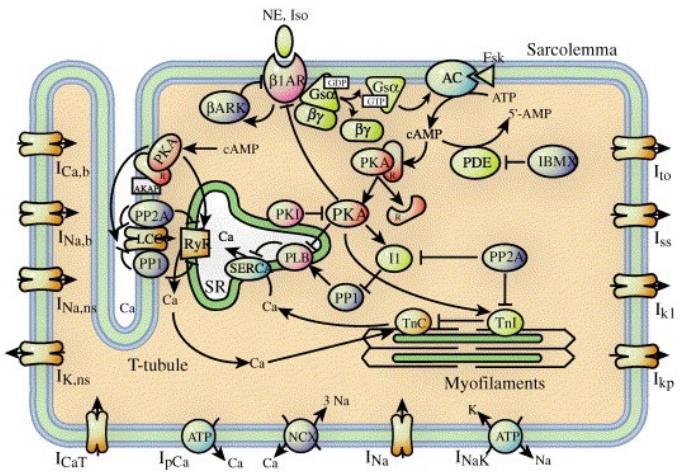


Figure 1. Boolean network model of the fission yeast cell cycle regulation. Nodes with states ON/OFF represent the presence of proteins. Arrows represent interactions between proteins as defined in the interaction matrix a_{ij} of the model (with $a_{ij} = +1$ for green/solid arrows and $a_{ij} = -1$ for red/dashed arrows). The dynamics is defined through a threshold function representing the switching behavior of regulatory proteins. Left: Network model with threshold function (1) and with self-degrading loops (yellow). Right: Simplified Boolean network model with threshold function as defined in eqn. (2). Both networks exhibit the same dynamical results discussed in this study. Thresholds for the nodes are chosen as described in the text. For annotations see Table 1.
doi:10.1371/journal.pone.0071786.g001

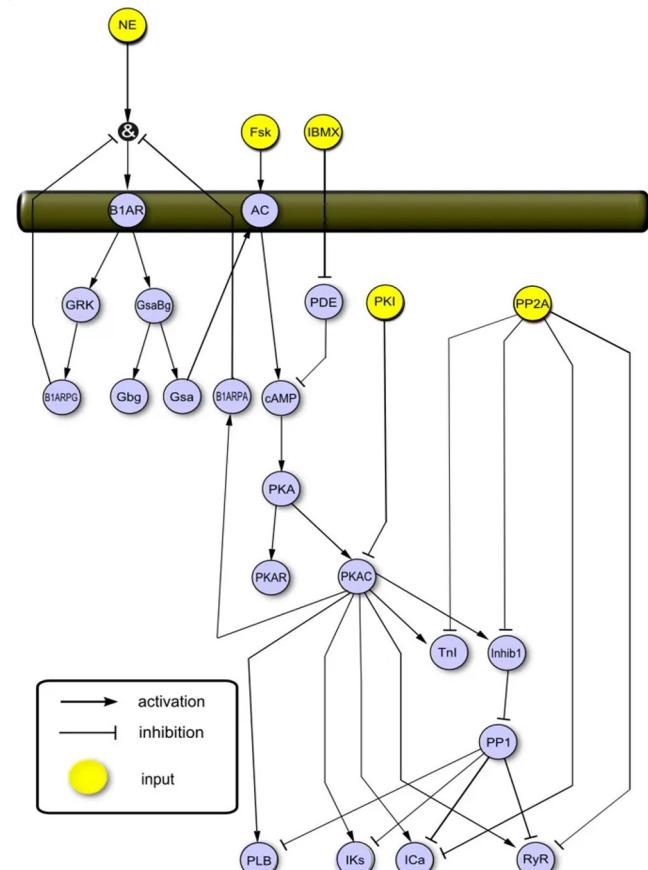
Citation: Davidich MI, Bornholdt S (2013) Boolean Network Model Predicts Knockout Mutant Phenotypes of Fission Yeast. PLoS ONE 8(9): e71786. doi:10.1371/journal.pone.0071786



Modeling Cell Signaling with Continuous Logic-Based Hill-Type Ordinary Differential Equations

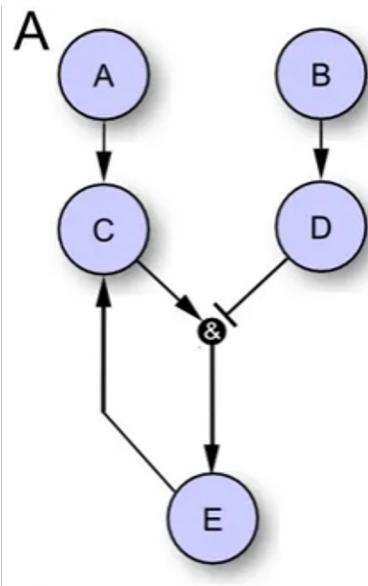


- Nodes:** species (receptor, signaling molecule, transcription factor, protein, etc.) normalized from 0 to 1
- Edges:** reactions (activation or inhibition)
- Interactions:** logical AND, OR (default) operators



Kraeutler, M.J., Soltis, A.R. & Saucerman, J.J. Modeling cardiac β -adrenergic signaling with normalized-Hill differential equations: comparison with a biochemical model. *BMC Syst Biol* 4, 157 (2010). <https://doi.org/10.1186/1752-0509-4-157>

Logical Network Representation



$$X \text{ OR } Y = X \vee Y = X + Y - X \times Y$$

$$X \text{ AND } Y = X \wedge Y = X \times Y$$

$$\text{NOT } X = \neg X = 1 - X$$

A **OR** E activates C

B activates D

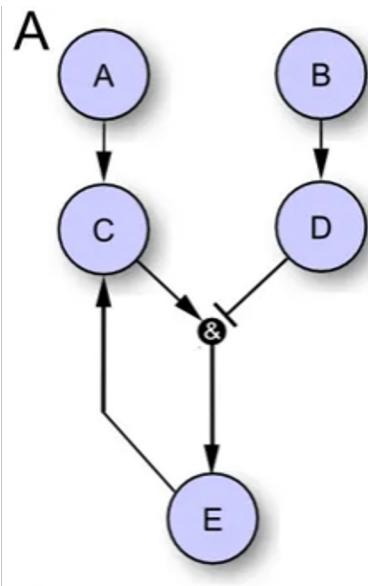
C **AND** NOT(D) activates E

Activity of E

C

| D | ON (1) | OFF (0) |
|---------|--------|---------|
| ON (1) | | |
| OFF (0) | | |

Logical Network Representation



$$X \text{ OR } Y = X \vee Y = X + Y - X \times Y$$

$$X \text{ AND } Y = X \wedge Y = X \times Y$$

$$\text{NOT } X = \neg X = 1 - X$$

A **OR** E activates C

B activates D

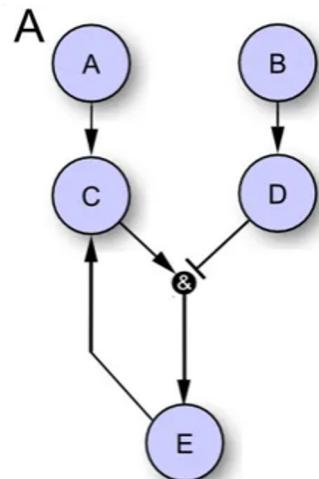
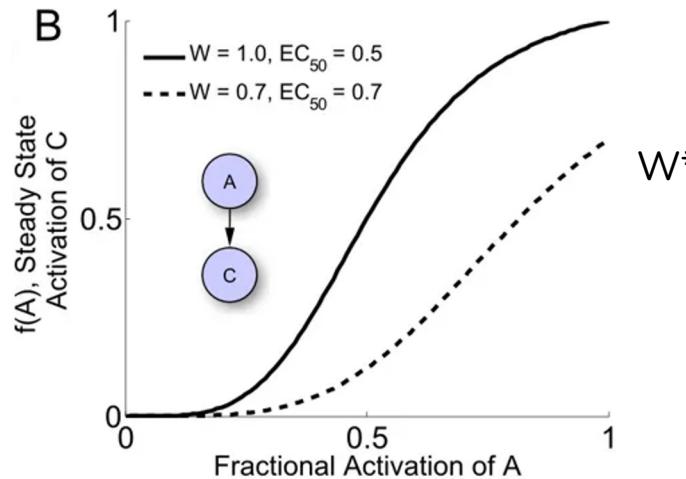
C **AND** NOT(D) activates E

Activity of E

C

| D | ON (1) | OFF (0) |
|---------|--------|---------|
| ON (1) | OFF | ON |
| OFF (0) | OFF | OFF |

Steady-State Hill-Type Activation and Inhibition Functions



Parameters:

- n (Hill coefficient): steepness of the curve
- EC_{50} : half maximal activation
- W (reaction weight): defaults to 1

$$f_{act}(X) = \frac{BX^n}{K^n + X^n} \quad f_{inhib}(x) = 1 - \frac{BX^n}{K^n + X^n}$$

$$K^n = \frac{EC_{50}^n}{1 - 2EC_{50}^n}, \quad B = K^n + 1 \quad 0 < EC_{50} < 2^{-\frac{1}{n}}$$

Kinetics ODEs

Activation

$$\frac{dy}{dt} = \frac{1}{\tau_y} (W_{xy} f_{act}(x) y_{max} - y)$$

Inhibition

$$\frac{dy}{dt} = \frac{1}{\tau_y} (W_{xy} f_{inhib}(x) y_{max} - y)$$

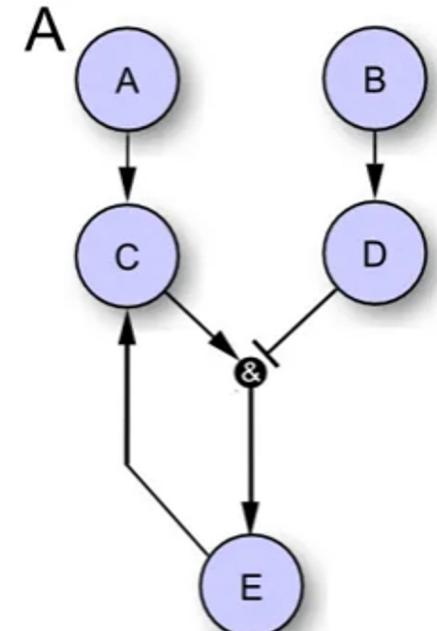
- τ_y is the time constant for y
- y_{max} is maximum fractional activation of y , (constrained to $0 \leq y_{max} \leq 1$ and defaults to 1)
- W_{xy} is the reaction weight, $0 \leq W_{xy} \leq 1$ defaults to 1

$$f_{act}(y_i) = \frac{By_i^n}{K^n + y_i^n} \quad f_{inhib}(y_i) = 1 - \frac{By_i^n}{K^n + y_i^n}$$

OR: $\frac{dC}{dt} = \frac{1}{\tau_C} [(W_{AC} f_{act}(A) + W_{EC} f_{act}(E) - W_{AC} f_{act}(A) W_{EC} f_{act}(E)) C_{max} - C]$

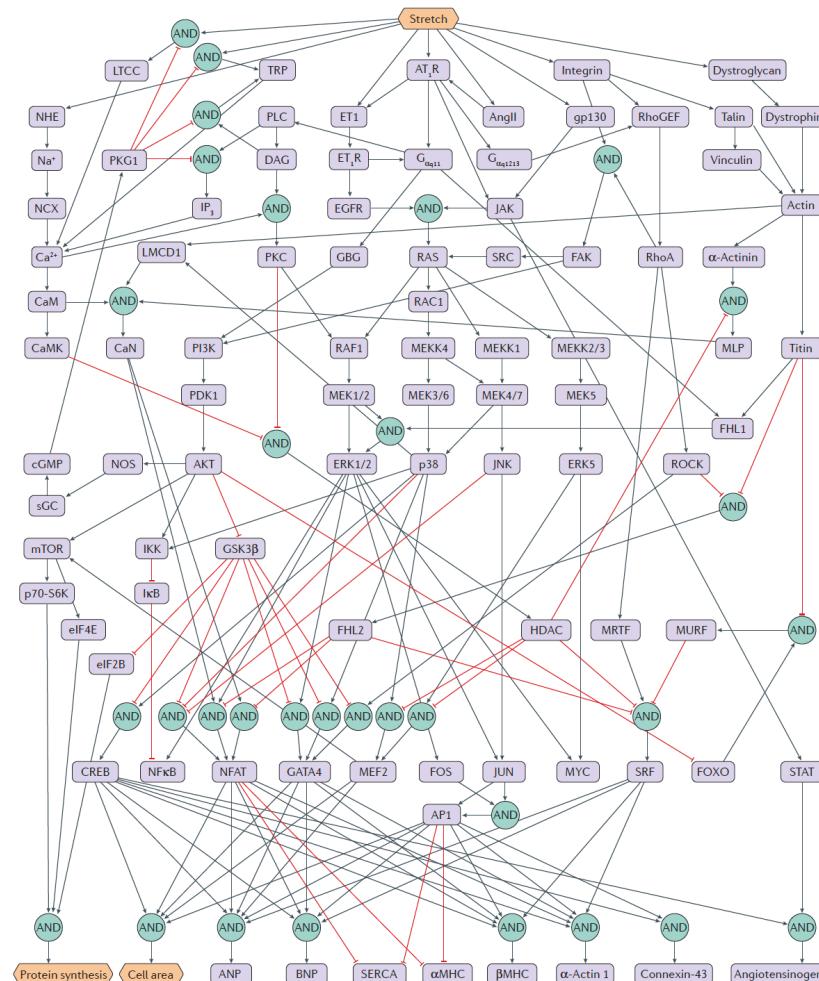
$$\frac{dD}{dt} = \frac{1}{\tau_D} (W_{BD} f_{act}(B) D_{max} - D)$$

AND: $\frac{dE}{dt} = \frac{1}{\tau_E} (W_{CDE} f_{act}(C) f_{ini}(D) E_{max} - E)$



- ◆ 172 experimental papers to define network
- ◆ 54 separate papers on *in-vitro* stretch of cardiomyocytes saved for validation
- ◆ 5 direct mechanosensors: AT1R, LTCC, TRP, integrins, dystroglycan.
- ◆ 4 mechanoresponsive nodes: gp130, NHE, Ang II, ET-1
- ◆ 65 signaling molecules
- ◆ 11 transcription factors
- ◆ 10 phenotypic outputs: protein synthesis, cell area, and expression of: ANP, BNP, SERCA, skeletal α -actin, β -MHC, Cx43 and angiotensinogen
- ◆ 94 nodes and 125 reactions

Cardiac Myocyte Mechano-Signaling

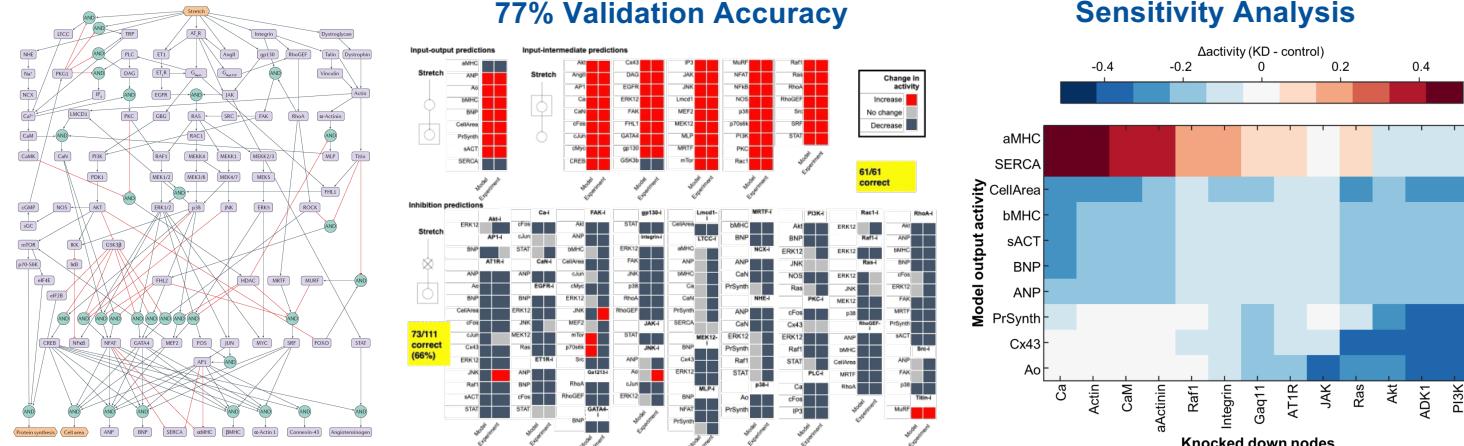


Tan et al, (2017)
Systems analysis identifies key network regulators of cardiomyocyte mechano-signalling. PLoS Comp Biol 13(11): e1005854

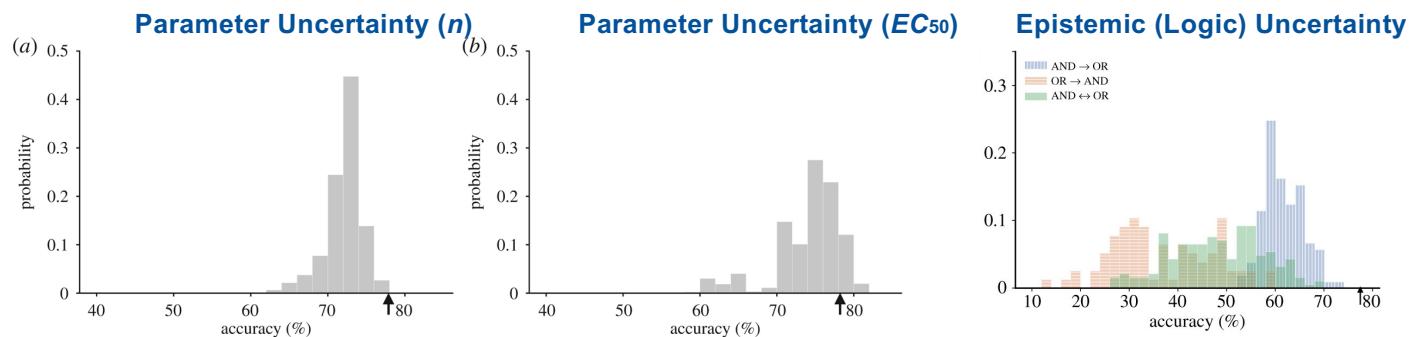
| Species Information | | | | | | | | | | Reaction Information | | | | | | | | | | | |
|---------------------|----------|--|-------|------|-----|---------------|----------|-----------------------|--------|----------------------|----------------------------------|--------|-----|------|------|---|---|---------|---------|-------|------|
| module | ID | name | Yinit | Ymax | tau | type | location | alternate names | module | ID | rule | weight | n | EC50 | code | notes | PMID | author | species | sourc | PMID |
| integrin | aActinin | alpha-actinin | 0 | 1 | 1 | protein | | | input | i1 | => Stretch | 0 | 1.4 | 0.5 | 3 | Stretch input | | | | | |
| integrin | Actin | Actin | 0 | 1 | 1 | protein | | | input | i2 | => AngII | 0 | 1.4 | 0.5 | 3 | AngII addition | | | | | |
| PI3K | Akt | Protein kinase B | 0 | 1 | 1 | protein | | PKB, protein kinase B | input | i3 | => AT1R | 0 | 1.4 | 0.5 | 3 | AT1R activation (without AngII) | | | | | |
| outputs | aMHC | Alpha-myosin heavy chain | 1 | 1 | 1 | geneExpr | | | input | i4 | => Dysgl | 0 | 1.4 | 0.5 | 3 | Dysgl activation | | | | | |
| g-coupled | AngII | Angiotensin II | 0 | 1 | 1 | protein | | | input | i5 | => ET1 | 0 | 1.4 | 0.5 | 3 | ET1 addition | | | | | |
| outputs | ANP | Atrial natriuretic protein | 0 | 1 | 1 | geneExpr | | ANF | input | i6 | => gp130 | 0 | 1.4 | 0.5 | 3 | gp130 activation | | | | | |
| outputs | Ao | Angiotensinogen | 0 | 1 | 1 | geneExpr | | | input | i7 | => Integrin | 0 | 1.4 | 0.5 | 3 | Integrin activation | | | | | |
| transcript | AP1 | Activator protein 1 | 0 | 1 | 1 | protein | | | input | i8 | => LTCC | 0 | 1.4 | 0.5 | 3 | LTCC activation | | | | | |
| g-coupled | AT1R | Antiotensin type 1 receptor | 0 | 1 | 1 | protein | | | input | i9 | => NHE | 0 | 1.4 | 0.5 | 3 | NHE activation | | | | | |
| outputs | bMHC | Beta-myosin heavy chain | 0 | 1 | 1 | geneExpr | | | input | i10 | => TRP | 0 | 1.4 | 0.5 | 3 | TRP activation | | | | | |
| outputs | BNP | Brain natriuretic protein | 0 | 1 | 1 | geneExpr | | | input | i11 | => sGC | 0 | 1.4 | 0.5 | 3 | sGC activation | | | | | |
| calcium | Ca | Calcium | 0 | 1 | 1 | smallMolecule | | Ca2+ | middle | r1 | Stretch => AngII | 0.9 | 1.4 | 0.5 | 2 | Stretch induces AngII | 8831108 Miyata Eur J NRVM | Stretch | 95255 | | |
| calcium | CaM | Calmodulin | 0 | 1 | 1 | protein | | | middle | r2 | Stretch => AT1R | 0.9 | 1.4 | 0.5 | 3 | Stretch activates AT1R | 15146194 Zou Nat Cell HEK293T AT1R | 205308 | | | |
| calcium | CaMK | CaM kinase | 0 | 1 | 1 | protein | | | middle | r3 | Stretch => Dysgl | 0.9 | 1.4 | 0.5 | 3 | Stretch exerts force | 8349731 Ervasti JBC Purifcation of the | 14472 | | | |
| calcium | CaN | Calcineurin | 0 | 1 | 1 | protein | | | middle | r4 | Stretch => ET1 | 0.9 | 1.4 | 0.5 | 2 | Stretch induces ET1 | 8621724 Yamazaki JB NRVM | Stretch | 97767 | | |
| outputs | CellArea | Cell area | 0 | 1 | 1 | phenotype | | | middle | r5 | Stretch => gp130 | 0.9 | 1.4 | 0.5 | 2 | Stretch activates gp130 | 10219240 Hirota Cell Mouse gp130 | 112624 | | | |
| transcript | cFos | Proto-oncogene c-Fos | 0 | 1 | 1 | protein | | | middle | r6 | Stretch => Integrin | 0.9 | 1.4 | 0.5 | 3 | Stretch activates Integrin | 7684161 Wang Scien Capilla Stret | 94785 | | | |
| PI3K | cGMP | Cyclic guanosine monophosphate | 0 | 1 | 1 | smallMolecule | | | middle | r7 | !PKG1 & Stretch => LTCC | 0.9 | 1.4 | 0.5 | 3 | Stretch activates L-T | 12176756 Lyford Am J CHO Trans | 159107 | | | |
| transcript | cJUN | Proto-oncogene c-Jun | 0 | 1 | 1 | protein | | | middle | r8 | Stretch => NHE | 0.9 | 1.4 | 0.5 | 2 | Stretch activates NHE | 12650883 von Lewinski P J Biol SFR | 151052 | | | |
| transcript | cMyc | Proto-oncogene c-Myc | 0 | 1 | 1 | protein | | | middle | r9 | !PKG1 & Stretch => TRP | 0.9 | 1.4 | 0.5 | 3 | Stretch activates Trp | 17056714 Spassova P CHO ar Stret | 206057 | | | |
| transcript | CREB | cAMP response element binding | 0 | 1 | 1 | protein | | | middle | r10 | Actin => aActinin | 0.9 | 1.4 | 0.5 | 2 | Actin links to aActinin | 14983059 Kwan PNAS Human PKG p | 199618 | | | |
| growth fac | DAG | Diacylglycerol | 0 | 1 | 1 | phospholipid | | | middle | r11 | Actin => Lmcd1 | 0.9 | 1.4 | 0.5 | 3 | Actin activates Lmcd1 | 10662546 Bespalova G Purification of the | 152465 | | | |
| integrin | Dysgl | Dystroglycan | 0 | 1 | 1 | protein | | | middle | r12 | Actin => Titin | 0.9 | 1.4 | 0.5 | 3 | Actin links to Titin | 11701614 Kulke Circ Purification of the | 252465 | | | |
| growth fac | EGFR | Epidermal growth factor receptor | 0 | 1 | 1 | protein | | | middle | r13 | !Akt => FoxO | 0.9 | 1.4 | 0.5 | 3 | Akt phosphorylates FoxO | 1577864 Lu J Cell Bio Chick aActinin is loca | 1577864 | | | |
| PI3K | eIF4E | Eukaryotic translation initiation factor 4E | 0 | 1 | 1 | protein | | | middle | r14 | !Akt => GSK3b | 0.9 | 1.4 | 0.5 | 3 | Akt phosphorylates GSK3b | 11715022 Rommel Mol HEK293T | 230005 | | | |
| PI3K | eIF2B | Eukaryotic translation initiation factor 2B | 0 | 1 | 1 | protein | | | middle | r15 | Akt => IKK | 0.9 | 1.4 | 0.5 | 3 | Akt activates IKK | 10485710 Ozez Nature HEK293T | | | | |
| MAPK | ERK12 | Extracellular signal-related kinases 1 or 2 | 0 | 1 | 1 | protein | | | middle | r16 | Akt => mTor | 0.9 | 1.4 | 0.5 | 3 | Akt activates mTor | 11715022 Rommel Mol HEK293T | | | | |
| MAPK | ERK5 | Extracellular signal-related kinase 5 | 0 | 1 | 1 | protein | | | middle | r17 | Akt => NOS | 0.9 | 1.4 | 0.5 | 3 | Akt activates NOS | 10376603 Dimmeler Mol HUVEC | | | | |
| g-coupled | ET1 | Endothelin-1 | 0 | 1 | 1 | protein | | | middle | r18 | AngII => AT1R | 0.9 | 1.4 | 0.5 | 3 | AngII binds to AT1R | 8348686 Sadoshima J NRVM | | | | |
| g-coupled | ET1R | Endothelin-1 receptor | 0 | 1 | 1 | protein | | | middle | r19 | AP1 & CREB & GATA4 & MEF2 & SAKP | 0.9 | 1.4 | 0.5 | 3 | AP1 is necessary for AP1 | 11799083 Omura Hyp NRVM | 157953 | | | |
| integrin | FAK | Focal adhesion kinase | 0 | 1 | 1 | protein | | | middle | r20 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | CREB is necessary for ANP transcription | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| integrin | FHL1 | Four-and-a-half LIM domains protein 1 | 0 | 1 | 1 | protein | | | middle | r21 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | GATA4 is necessary for AP1 | 21746915 van Berlo P Mouse adult heart | | | | |
| integrin | FHL2 | Four-and-a-half LIM domains protein 2 | 0 | 1 | 1 | protein | | | middle | r22 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | MEF2 is necessary for AP1 | 10531040 Kolodziejczyk J Mouse adult heart | | | | |
| transcript | FoxO | Forkhead box O | 1 | 1 | 1 | protein | | | middle | r23 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | NFAT is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| g-coupled | Ga1213 | G 12/13 alpha subunit | 0 | 1 | 1 | protein | | | middle | r24 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | SRF is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| g-coupled | Gaq11 | G q/11 alpha subunit | 0 | 1 | 1 | protein | | | middle | r25 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | CREB is necessary for AP1 | 15795322 Jeong Circ 2 NRVM | | | | |
| transcript | GATA4 | GATA-binding protein 4 | 0 | 1 | 1 | protein | | | middle | r26 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | GATA4 is necessary for AP1 | 9568714 Molkentin C Mouse adult heart | | | | |
| g-coupled | Gbg | G beta/gamma subunit | 0 | 1 | 1 | protein | | | middle | r27 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | NFAT is necessary for AP1 | 10531040 Kolodziejczyk J Mouse adult heart | | | | |
| cytokine | gp130 | Glycoprotein 130 | 0 | 1 | 1 | protein | | | middle | r28 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | SRF is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| PI3K | GSK3b | Glycogen synthase kinase 3 beta | 1 | 1 | 1 | protein | | | middle | r29 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | CREB is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| transcript | HDAC | Histone deacetylase | 1 | 1 | 1 | protein | | | middle | r30 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | GATA4 is necessary for AP1 | 15795322 Jeong Circ 2 NRVM | | | | |
| PI3K | IkB | Nuclear factor of kappa light polypeptide gene enhancer in B cells | 1 | 1 | 1 | protein | | | middle | r31 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | IkB is necessary for AP1 | 9568714 Molkentin C Mouse adult heart | | | | |
| PI3K | IKK | Inhibitor of kappa light polypeptide gene enhancer in B cells | 0 | 1 | 1 | protein | | | middle | r32 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | CREB is necessary for AP1 | 12370307 Wilkins Mol Cell NRVM, Mouse adult heart | | | | |
| integrin | Integrin | Integrin | 0 | 1 | 1 | protein | | | middle | r33 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | GATA4 is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| g-coupled | IP3 | Inositol triphosphate | 0 | 1 | 1 | phospholipid | | | middle | r34 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | IP3 is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| cytokine | JAK | Janus kinase 1 or 2 | 0 | 1 | 1 | protein | | | middle | r35 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | CREB is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| MAPK | JNK | c-Jun N-terminal kinase | 0 | 1 | 1 | protein | | SAPK | middle | r36 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | GATA4 is necessary for AP1 | 21746915 van Berlo P Mouse adult heart | | | | |
| MAPK | Lmcd1 | LIM and cysteine-rich domains 1 | 0 | 1 | 1 | protein | | Dyxin | middle | r37 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | NFAT is necessary for AP1 | 21746915 van Berlo P Mouse adult heart | | | | |
| calcium | LTCC | L-type calcium channel | 0 | 1 | 1 | protein | | | middle | r38 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | SRF is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| transcript | MEF2 | Myocyte enhancer factor 2 | 0 | 1 | 1 | protein | | | middle | r39 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | AP1 is necessary for AP1 | 11799083 Omura Hyp NRVM | | | | |
| MAPK | MEK12 | MAPK/ERK kinase 1 or 2 | 0 | 1 | 1 | protein | | MAPKK12 | middle | r40 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | CREB is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| | | | | | | | | | middle | r41 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | GATA4 is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |
| | | | | | | | | | middle | r42 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 1 | MEF2 is necessary for AP1 | 10531040 Kolodziejczyk J Mouse adult heart | | | | |
| | | | | | | | | | middle | r43 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 2 | NFAT is necessary for AP1 | 9568714 Molkentin C Mouse adult heart | | | | |
| | | | | | | | | | middle | r44 | AP1 & CREB & GATA4 & NFAT & SAPK | 0.9 | 1.4 | 0.5 | 3 | AP1 is necessary for AP1 | 15950986 Nelson JMC NRVM, Mouse adult heart | | | | |

species reactions

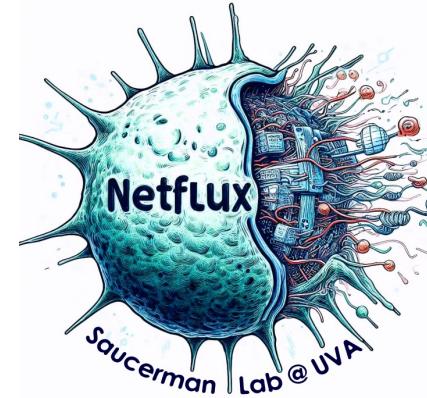
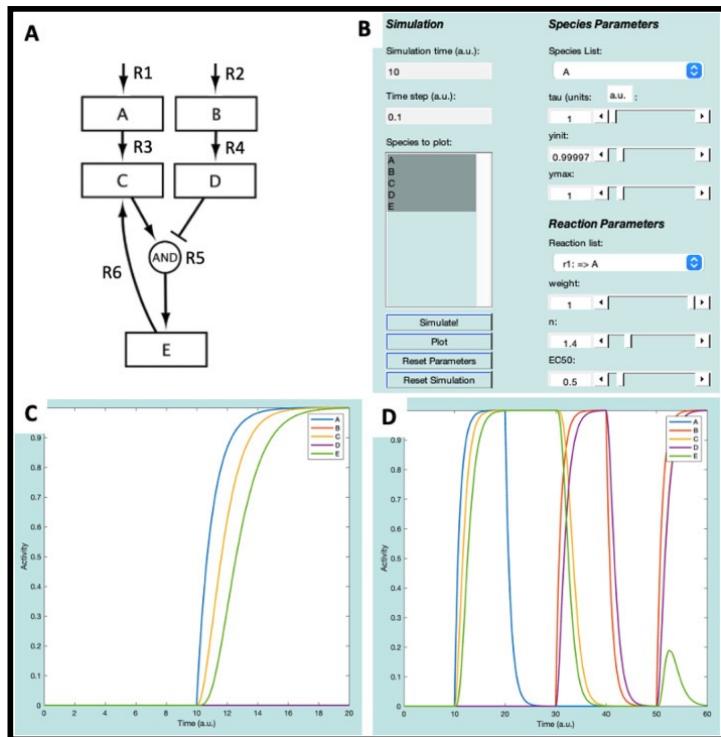
Validation, Sensitivity & Uncertainty Quantification



Tan et al., (2017) Systems analysis identifies key network regulators of cardiomyocyte mechano-signalling. *PLoS Comp Biol*



Cao S, Aboelkassem Y, Wang A, Valdez-Jasso D, Saucerman JS, Omens JH, McCulloch AD (2020) [Quantification of model and data uncertainty in a network analysis of cardiac myocyte mechanosignaling](#). *Phil. Trans. R. Soc. A.* 378:20190336



<https://github.com/saucermanlab/Netflux>

A

B

| | A | B | C | D | E | F | G | H | I | J |
|---------------------|--------|-------|------------|-------|------|-----|---------|----------|-----|-------|
| Species information | module | ID | name | Yinit | Ymax | tau | type | location | ref | notes |
| | 1 | GATA6 | spec_GATA6 | 0 | 1 | 1 | protein | | | |
| | 2 | NKX25 | spec_NKX25 | 0 | 1 | 1 | protein | | | |
| | 3 | TBX1 | spec_TBX1 | 0 | 1 | 1 | protein | | | |
| | 4 | ISL1 | spec_ISL1 | 1 | 1 | 1 | protein | | | |
| | 5 | PITX2 | spec_PITX2 | 0 | 1 | 1 | protein | | | |

C

| | A | B | C | D | E | F | G |
|----------------------|--------|----|----------------|--------|------|----------|---|
| Reaction Information | module | ID | Rule | Weight | EC50 | location | |
| 1 | inputs | r1 | => GATA6 | 0 | 1.4 | 0.5 | |
| 2 | middle | r2 | GATA6 => NKX25 | 1 | 1.4 | 0.5 | |
| 3 | middle | r3 | GATA6 => TBX1 | 1 | 1.4 | 0.5 | |
| 4 | middle | r4 | NKX25 => TBX1 | 1 | 1.4 | 0.5 | |
| 5 | middle | r5 | TBX1 => PITX2 | 1 | 1.4 | 0.5 | |
| 6 | middle | r6 | NKX25 => PITX2 | 1 | 1.4 | 0.5 | |
| 7 | middle | r7 | !NKX25 => ISL1 | 1 | 1.4 | 0.5 | |



Logic-based modeling of biological networks with Netflix

Alexander P. Clark, Mukti Chowkale, Alexander Paap, Stephen Dang, Jeffrey J. Saucerman

Published: April 4, 2025 • <https://doi.org/10.1371/journal.pcbi.1012864>

The screenshot shows a GitHub repository page for 'saucermanlab/Netflix'. The main heading is '1. Download Netflix'. Below it, there's a navigation bar with links like 'Code', 'Issues 9', 'Pull requests', 'Actions', 'Projects', 'Wiki', 'Security', and 'Insights'. A dropdown menu for the 'Code' button is open, showing options for 'Clone' via 'HTTPS' or 'GitHub CLI', and 'Download ZIP'. A callout bubble points to this 'Download ZIP' option with the text: 'Click on <> Code button and choose Download Zip'. To the right of the clone menu, there's a summary of the repository: 'jsaucerman more tips for Mac installation', '3 Branches', '2 Tags', '4 months ago', '10 years ago', and a list of files including 'Autogenerated models', 'Netflix Compiled', 'Netflix', '.gitattributes', '.gitignore', 'README.md', and 'license.txt'. On the far right, there are sections for 'About', 'Custom properties' (25 stars, 10 watching, 8 forks), 'Report repository', 'Releases 1' (v1.0.1 Latest on Aug 17, 2015), and a 'Notifications' section.

1. Download Netflix

Code Issues 9 Pull requests Actions Projects Wiki Security Insights

master 3 Branches 2 Tags

Clone

HTTPS GitHub CLI

<https://github.com/saucermanlab/Netflix.git>

Clone using the web URL.

Open with GitHub Desktop

Download ZIP

Custom properties

25 stars 10 watching 8 forks

Report repository

Releases 1

v1.0.1 Latest on Aug 17, 2015

Notifications Fork 8 Star 25

Click on <> Code button and choose Download Zip

more tips for Mac installation

Autogenerated models Change folder name

Netflix Compiled updated Netflix co

Netflix Fix bug in exportPy

.gitattributes Added .gitattribute

.gitignore updated README

README.md more tips for Mac insta

license.txt

README License

Netflix

Netflix is a user-friendly software for developing dynamic computational models of biological networks. Models are created in Excel format and then simulated using the Netflix graphical interface. No computer programming is required. Netflix is written in MATLAB, but binary versions are available for Windows and MacOS for those that do not have MATLAB installed.

2. Install Netflix (Users with MATLAB)

A. You can use the UCSD site license to install MATLAB:

<https://www.mathworks.com/academia/tah-portal/university-of-california-san-diego-1144083.html>

B. With MATLAB installed: Extract the “Netflix” folder from within the ZIP file and move it to your desired location. Run Netflix.m in MATLAB.

2. Install Netflix (Users without MATLAB)

- A. Windows:** Open the “Netflix Compiled” folder and run “Netflix Installer Windows.exe”. Netflix will be installed to the C:\Program Files\Netflix folder
- B. MacOS with Apple Silicon (only):** Open the “Netflix Compiled” folder, extract “Netflix_Installer_MacOS”, and run ./Netflix_Installer_macOS.app in the terminal. Run Netflix.app from the terminal
- C. Apporto:** MATLAB is installed on the Apporto cloud computing environment where you can download Netflix to using the instructions on the previous slide.
<https://ucsd.apporto.com/home>

3. YouTube Videos

Introduction to Netflix:

<https://youtu.be/tU2gU8d5hvQ?si=LLYdF1uHuDUKAozo>

Netflix Tutorial: Basic Simulations

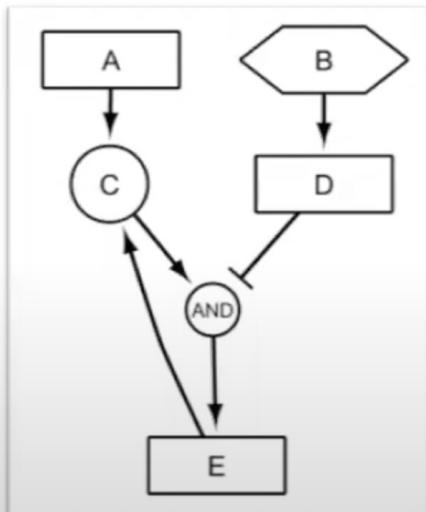
<https://youtu.be/susMLNhQjig?si=WaEhECpyrMIZFs7r>

Netflix Tutorial: Visualization with Cytoscape

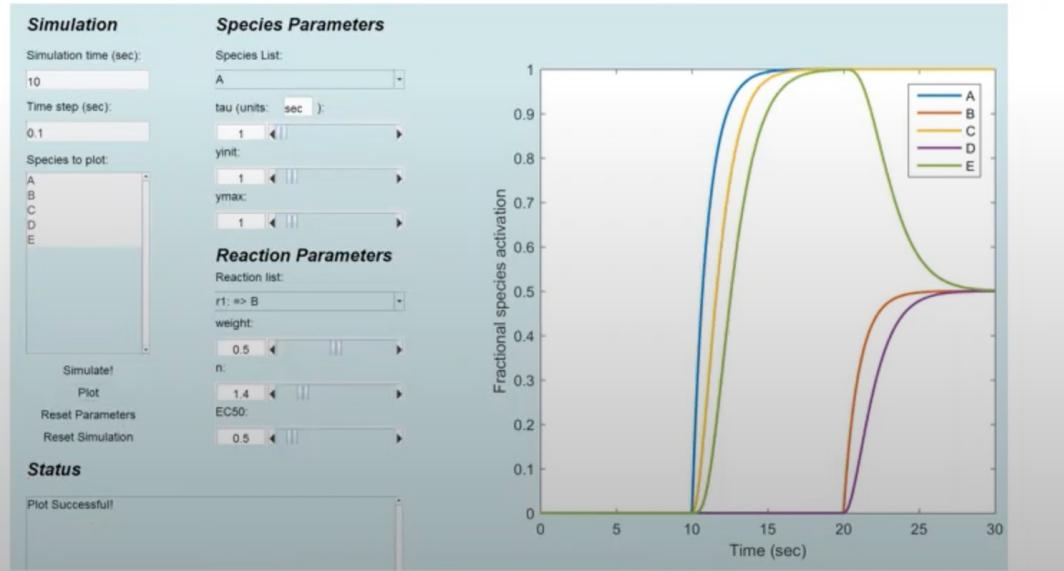
https://youtu.be/lHrV5SOV7jA?si=ZgxOBighbh_kCVgG



user-friendly software for logic-based network modeling



Network
defined in
MS Excel

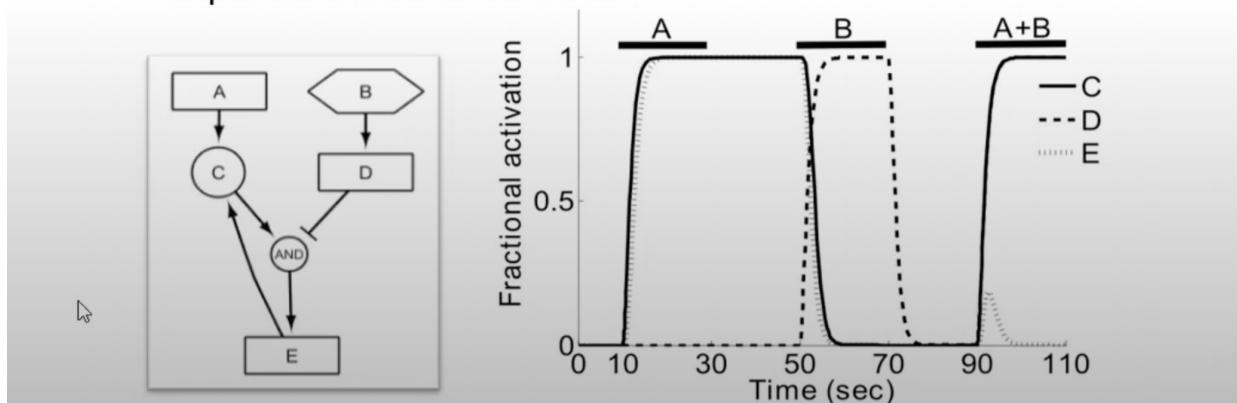


Demo



Exercises 1: basics

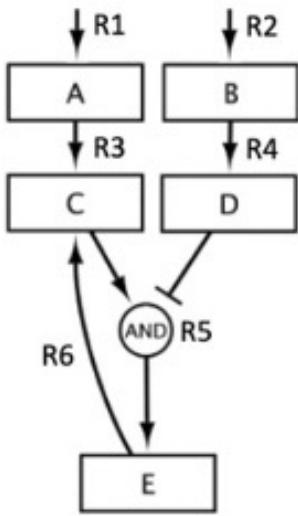
1. Open “Netflix documentation.docx” and open Netflix
2. Open “exampleNet.xlsx” in both Netflix and Excel
3. Run simulations to predict the response to activation of A.
Do the results make sense?
4. Run simulations to reproduce the more complicated
experiment shown below.





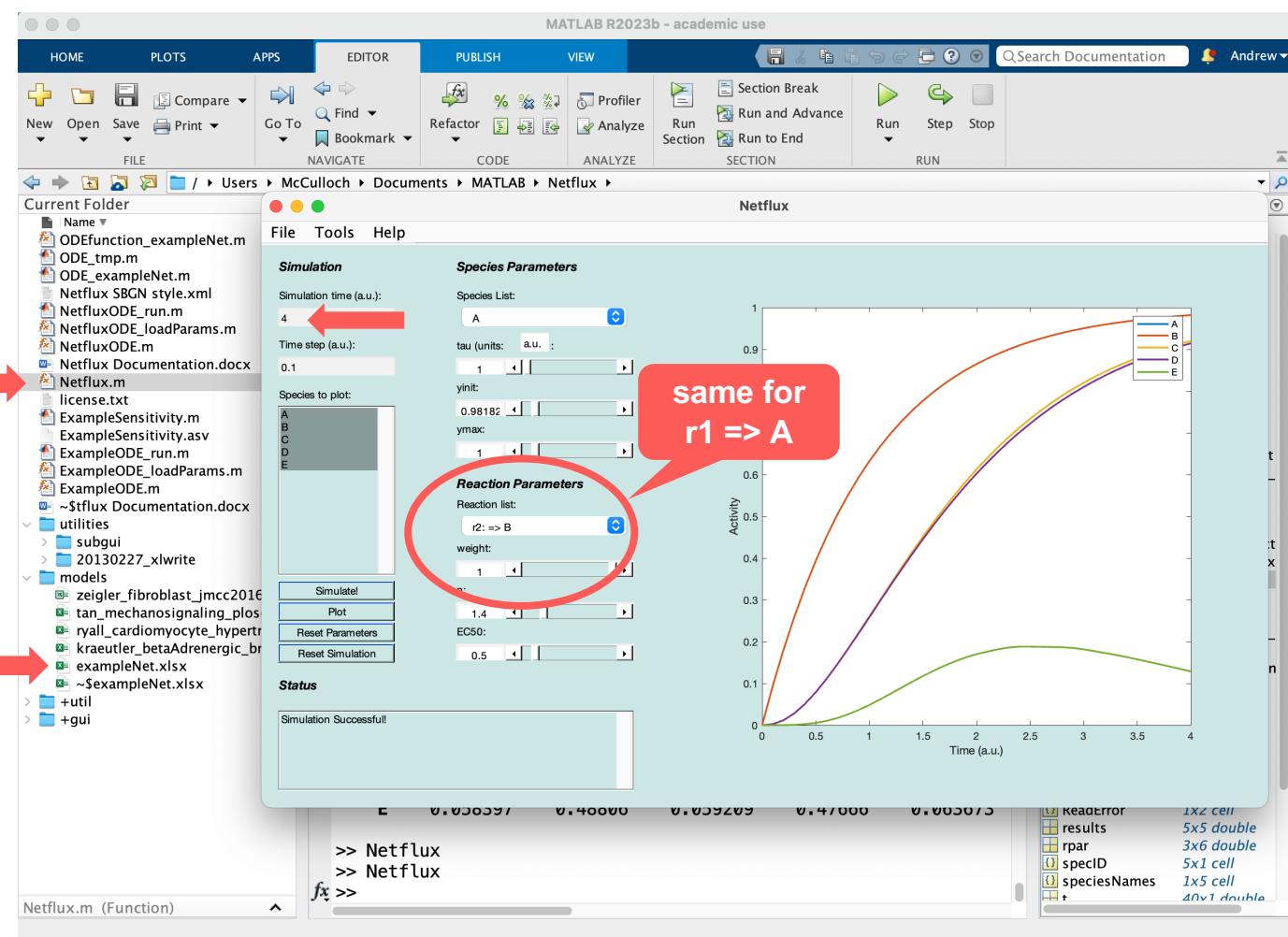
Exercises 2: extending

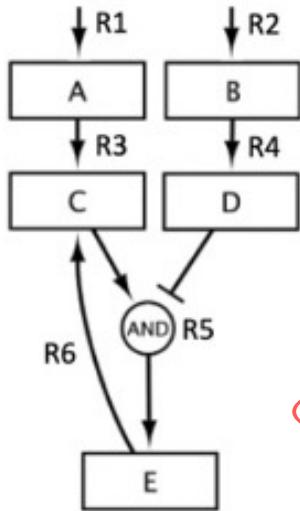
1. Test how changing various parameters affect the result.
2. Design an experiment to block activation of E. Test if the network responds as you predicted.
3. Modify the network in Excel by adding a new reaction, save the changes, then reload the model
4. Test out the exporting features:
 1. Exporting Data, load in Excel to plot
 2. Exporting MATLAB ODE files
 3. Export Cytoscape> As XGMML (just type network name)
5. Implement a simple model of a biological pathway of your choice (use Google Image search to find a schematic)



40 time steps
 $R1=1$
 $R2=1$

Analysis of Example Network





Exporting and using MATLAB model code

The screenshot illustrates the process of exporting a reaction network from a tool like Netflix to MATLAB.

Left Panel: A file browser window showing a directory structure. A red oval highlights the 'models' folder, which contains several MATLAB files. One file, 'ExampleODE_loadParams.m', is circled in red.

Middle Panel: A screenshot of a MATLAB interface titled 'NETFLUX'. The 'File' menu is open, showing options: Open Model, Export Data, Export Cytoscape, Export MATLAB ODE (which is highlighted with a red arrow), Export Python ODE, and Exit.

Right Panel: An MATLAB editor window titled 'Editor - /Users/McCulloch/Documents/MATLAB/Netflix/ExampleODE_loadParams.m'. The code is as follows:

```

function [params,y0] = ExampleODE_loadParams()
% ExampleODE_loadParams.m
% Automatically generated by Netflix on 09-May-2025

% species parameters
speciesNames = {'A','B','C','D','E',};
tau = [1, 1, 1, 1, 1, ];
ymax = [1, 1, 1, 1, 1, ];

% reaction parameters
w = [1, 1, 1, 1, 1, 1, ];
n = [1.400000e+00, 1.400000e+00, 1.400000e+00, 1.400000e+00, 1.400000e+00, 1.400000e+00];
EC50 = [5.000000e-01, 5.000000e-01, 5.000000e-01, 5.000000e-01, 5.000000e-01, 5.000000e-01];
rpar = [w;n;EC50];

params = {rpar,tau,ymax,speciesNames};

y0 = [0, 0, 0, 0, 0, ];

```

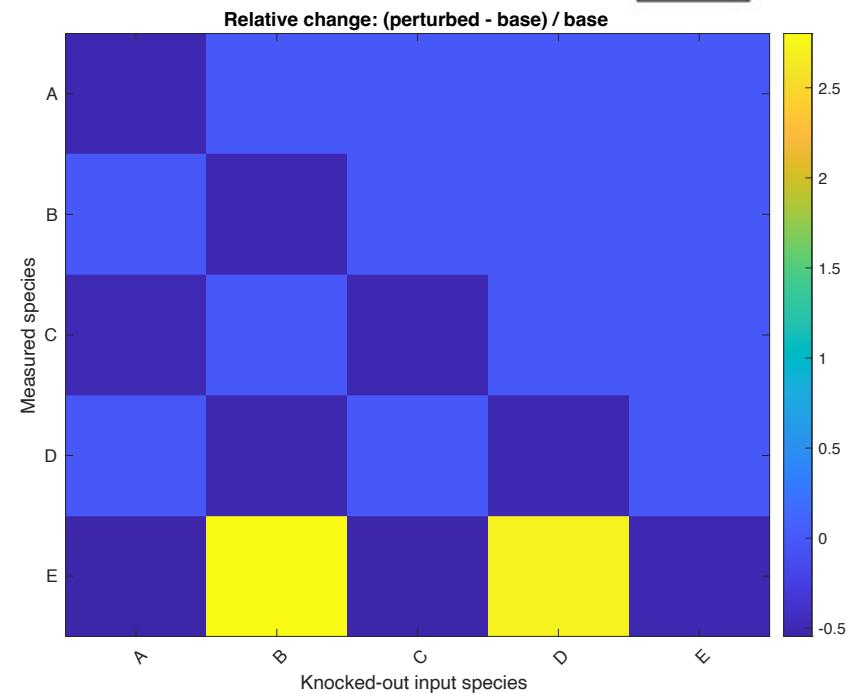
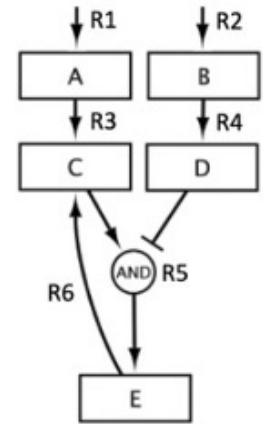
A red arrow points to the 'w' parameter line, and another red circle highlights the 'reaction parameters' section of the code.

Sensitivity Analysis

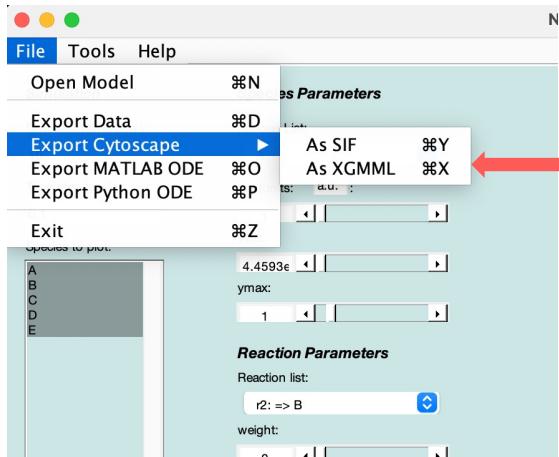
```

Editor - /Users/McCulloch/Documents/MATLAB/Netflux/ExampleSensitivity.m
+7 ExampleODE_loadParams.m ExampleODE.m ExampleODE_run.m ExampleSensitivity.m
1 % ExampleODE_sensitivity.m - Knockout Ymax sensitivity analysis
2
3 % Load baseline parameters
4 [params, y0] = ExampleODE_loadParams();
5 [rpar, tau, ymax, speciesNames] = params{::};
6 nSpecies = numel(y0);
7 nTimepoints = 40;
8 tspan = linspace(0, 4, nTimepoints); ←
9 results = zeros(nSpecies, nSpecies); % rows: species, cols: knockout
10
11 % Baseline simulation
12 params_base = {rpar, tau, ymax, speciesNames};
13 [t, y_base] = ode15s(@(t, y) ExampleODE(t, y, params_base), tspan, y0);
14 y_base_final = real(y_base(end, :)); % ensure real values
15
16 % Loop over each species
17 for i = 1:nSpecies
18     ymax_perturbed = ymax;
19     ymax_perturbed(i) = 0.5; % Knock down this species ←
20     % Create new param set
21     perturbed_params = {rpar, tau, ymax_perturbed, speciesNames};
22     % Simulate
23     [t, y] = ode15s(@(t, y) ExampleODE(t, y, perturbed_params), tspan, y0);
24     % Save final state for heatmap
25     y_final = real(y(end, :)); % final state, cleaned of roundoff
26     % Avoid divide-by-zero with a small epsilon
27     eps_val = 1e-12;
28     relative_change = (y_final - y_base_final) ./ max(abs(y_base_final), eps_val); ←
29     if isempty(y) || size(y, 1) < 1
30         warning("Simulation failed for K0 %s", speciesNames{i});
31         results(:, i) = NaN;
32         continue;
33     end
34     results(:, i) = relative_change;
35 end
36 results = real(results); % suppresses an infinitesimal imaginary number float error
37 % Print numerical sensitivity matrix
38 disp('==> Sensitivity Results (Final Values) ==>');
39 T = array2table(results, 'RowNames', speciesNames, 'VariableNames', matlab.lang.make
40 disp(T);

```

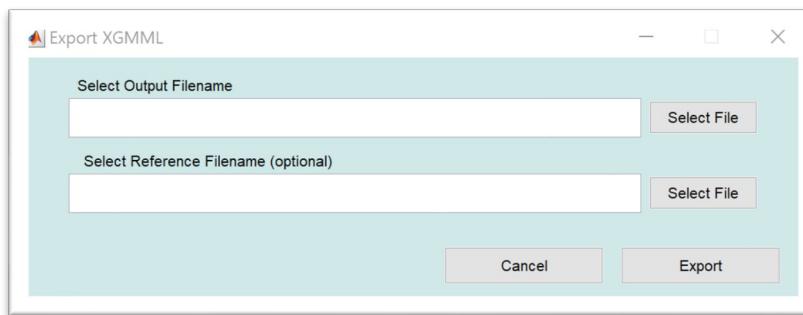


Visualization with Cytoscape

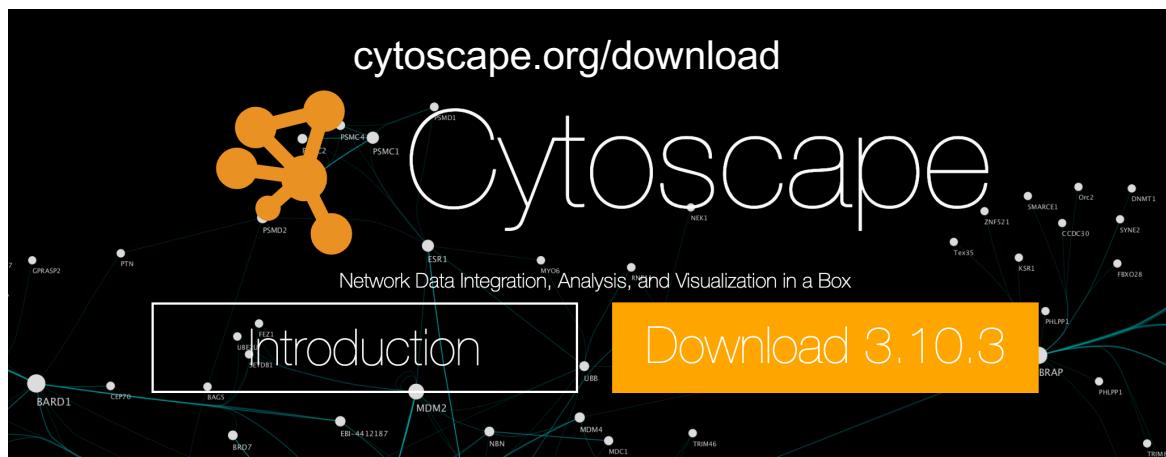


In Netflix

Select File → Export Cytoscape → As XGMML



- Under "Select Output Filename", **Select File** to specify the name and location of the XGMML file to be exported.
- Only if this is a revised visualization based on an existing XGMML file, select that file at "Select Reference Filename".
- Select **Export**. You will see a "Model exported to:" message in the status window.



Network Visualization with Cytoscape

In Cytoscape:

- Select File → Import → **Network from File...** and select the XGMML file that you exported from Netflix.
- Import the SBGN layout style by selecting File → Import → **Styles from File...**, and select “**Netflix SBGN styles.xml**” from the installed Netflix directory.
- Apply the “Netflix SBGN” style by going to the **Style** tab within the Control Panel. Click on the dropdown menu that says “**default**” and change to “**Netflix_SBGN**”.
- Apply the desired layout to the network from the **Layout menu**. Use **Layout → “yFiles Hierarchic Layout”**, manually reposition the nodes. Note the type of box is determined by the **species type** column imported from Netflix.
- **Layout → Layout Tools** will place layout tools in the control panel.
- **Save** your Cytoscape session as a .cys file.
- If you would like to use this network visualization as a Reference for a future model revision, be sure to also export your network in XGMML format using File → Export → **Network to File...** select XGMML and the desired filename.

