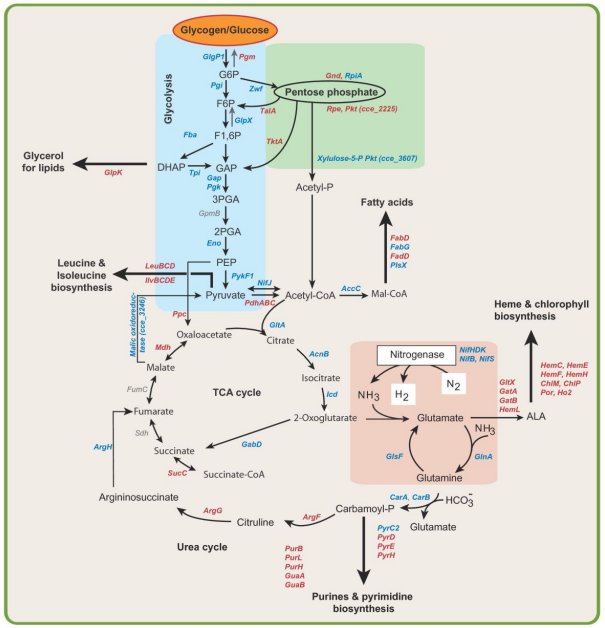
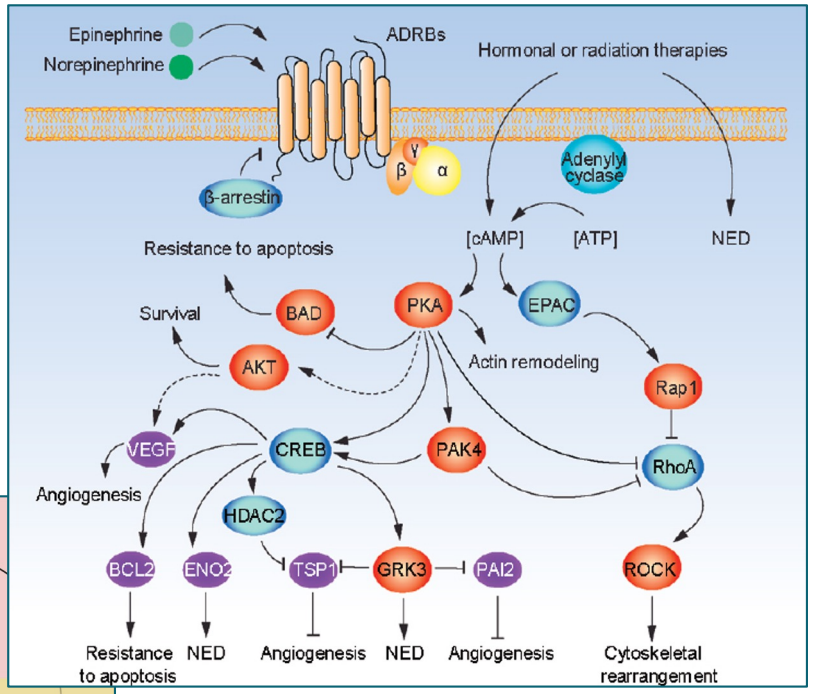
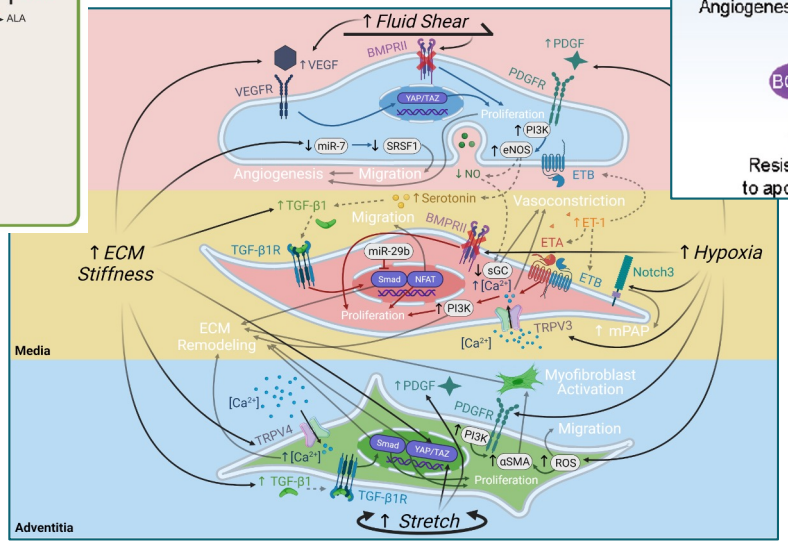
Biochemical Reaction Networks

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:

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

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

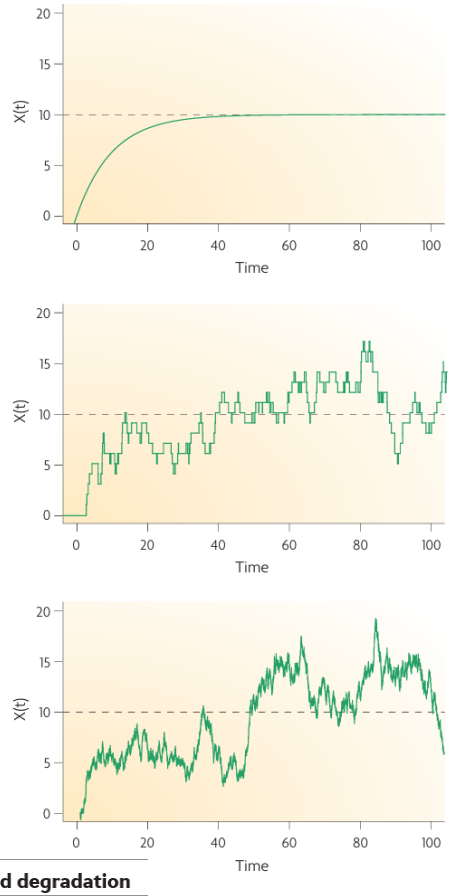
Equilibrium distribution: $X_\infty \sim \text{Poisson}(\alpha/\mu)$

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

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

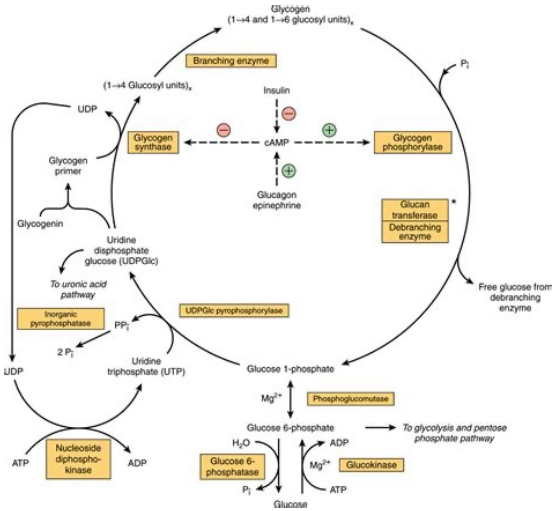
Types of Deterministic Metabolic Network Model: Mass-Action Kinetics to Steady-State Constraint-Based

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

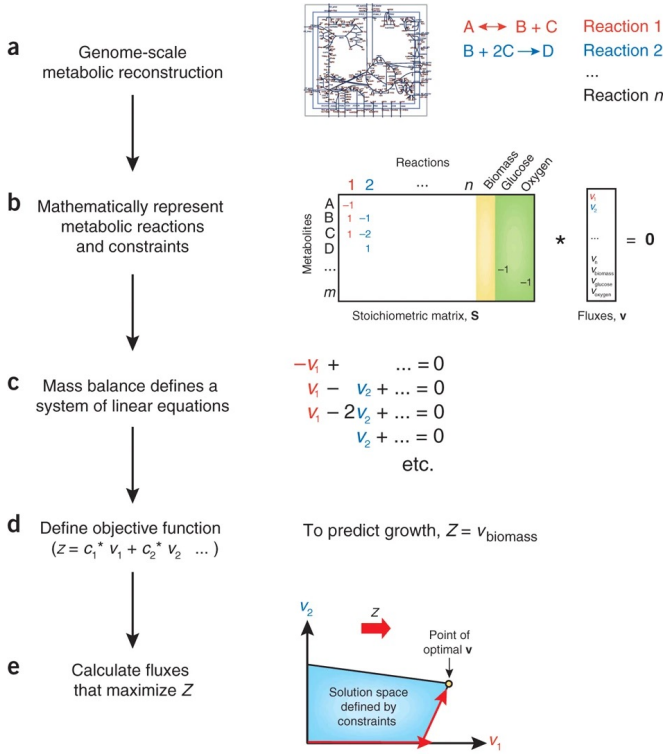
Kalyan Vinnakota [*1], Melissa L. Kemp [¶1], Martin J. Kushmerick [*†‡]



What is flux balance analysis?

Jeffrey D Orth, Ines Thiele & Bernhard Ø Palsson

Nature Biotechnology **28**, 245–248 (2010) | Cite this article

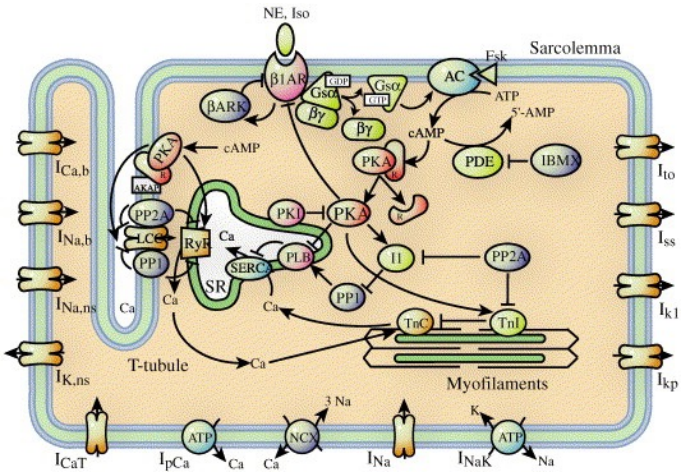


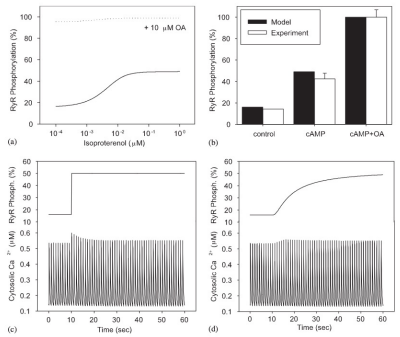
Types of Deterministic Signaling Network Model: Empirical Biochemical Kinetics to Boolean

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

PLOS ONE

Boolean Network Model Predicts Knockout Mutant Phenotypes of Fission Yeast

Maria I. Davidich, Stefan Bornholdt*

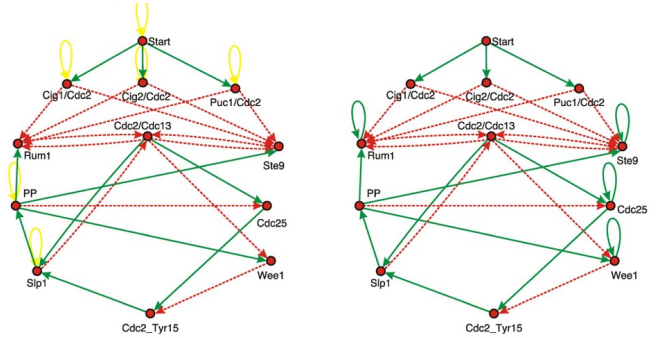
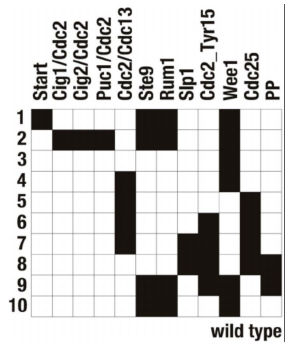
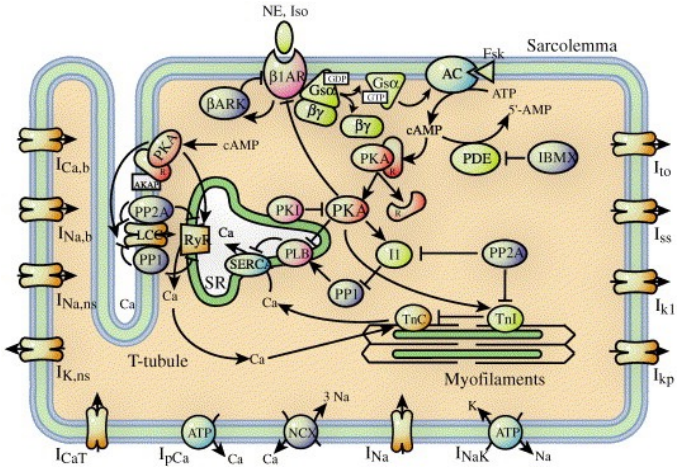


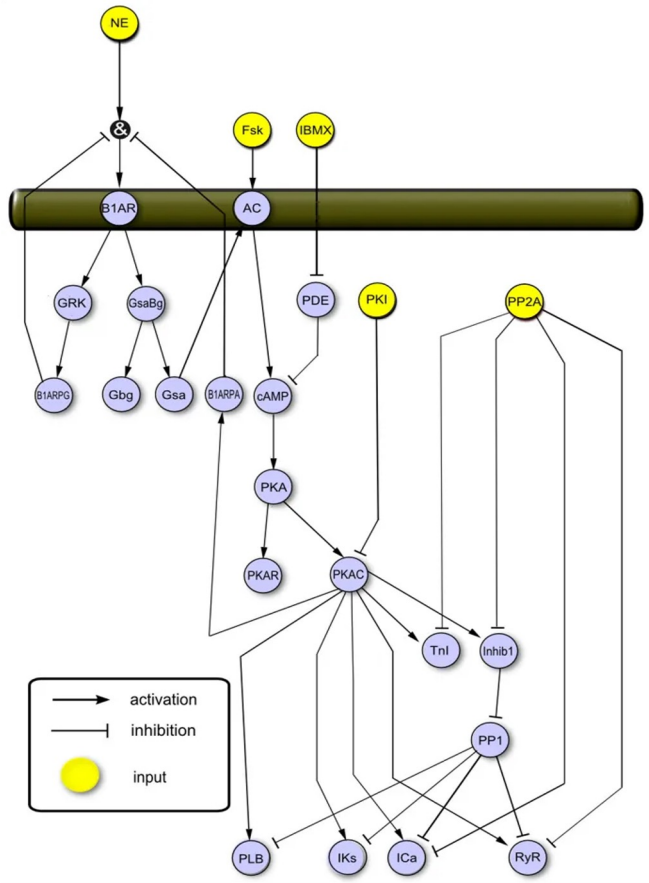
Figure 1. Boolean network model of the fission yeast cell cycle regulation. Nodes with states ON/OFF represent the presence of proteins. Arrows represent interactions between proteins as defined in the interaction matrix a_{ij} of the model (with $a_{ij} = +1$ for green/solid arrows and $a_{ij} = -1$ 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

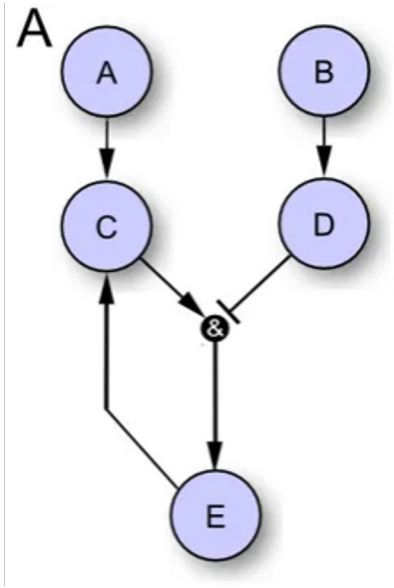




- **Nodes**: species (receptor, signaling molecule, transcription factor, protein, etc.) *normalized from 0 to 1*
- **Edges**: reactions (*activation* or *inhibition*)
- **Interactions**: logical *AND*, *OR* (default) operators

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



A **OR** E activates C

B activates D

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

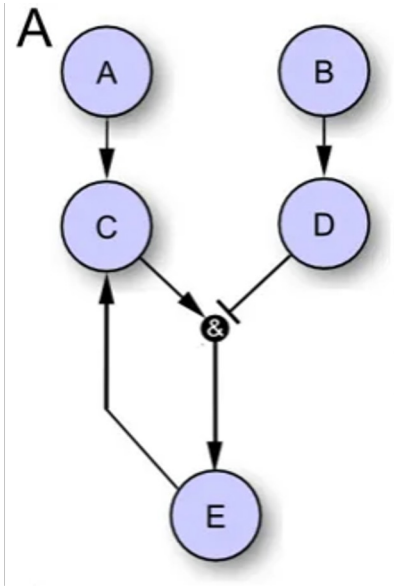
X **OR** Y = X ∨ Y = X + Y − X×Y

X **AND** Y = X ∧ Y = X×Y

NOT X = ¬X = 1 − X

		Activity of E	
		D	
		ON (1)	OFF (0)
C	ON (1)		
	OFF (0)		

Logical Network Representation



A **OR** E activates C

B activates D

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

X **OR** Y = X ∨ Y = X + Y − X×Y

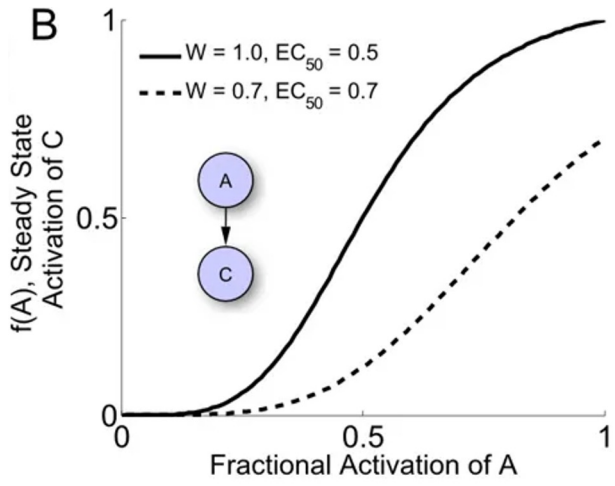
X **AND** Y = X ∧ Y = X×Y

NOT X = ¬X = 1 − X

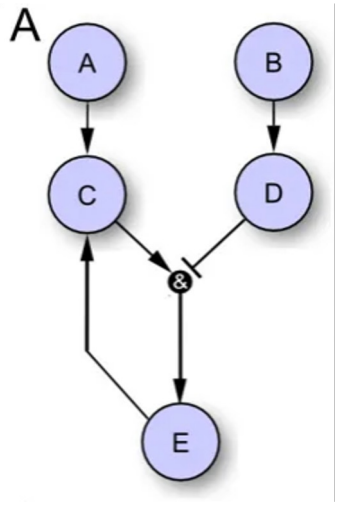
Activity of E

C \ D	ON (1)	OFF (0)
ON (1)	OFF	ON
OFF (0)	OFF	OFF

Steady-State Hill-Type Activation and Inhibition Functions



W*f(A)



Parameters:

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

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

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

Kinetics ODEs

Activation

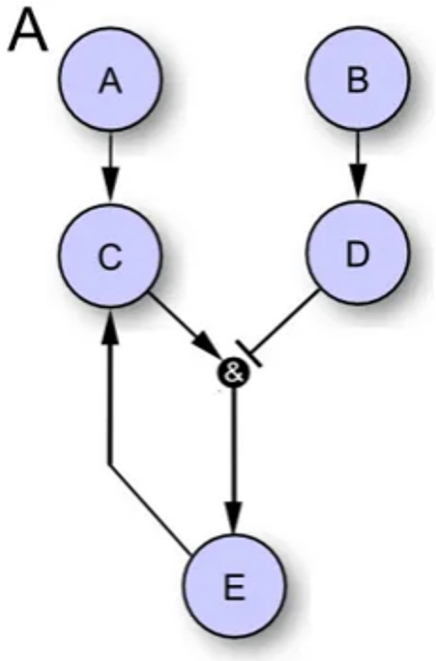
$$\frac{dy}{dt} = \frac{1}{\tau_y}\left(W_{xy} f_{\text{act}}(x) y_{\max} - y\right)$$

Inhibition

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

- 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

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



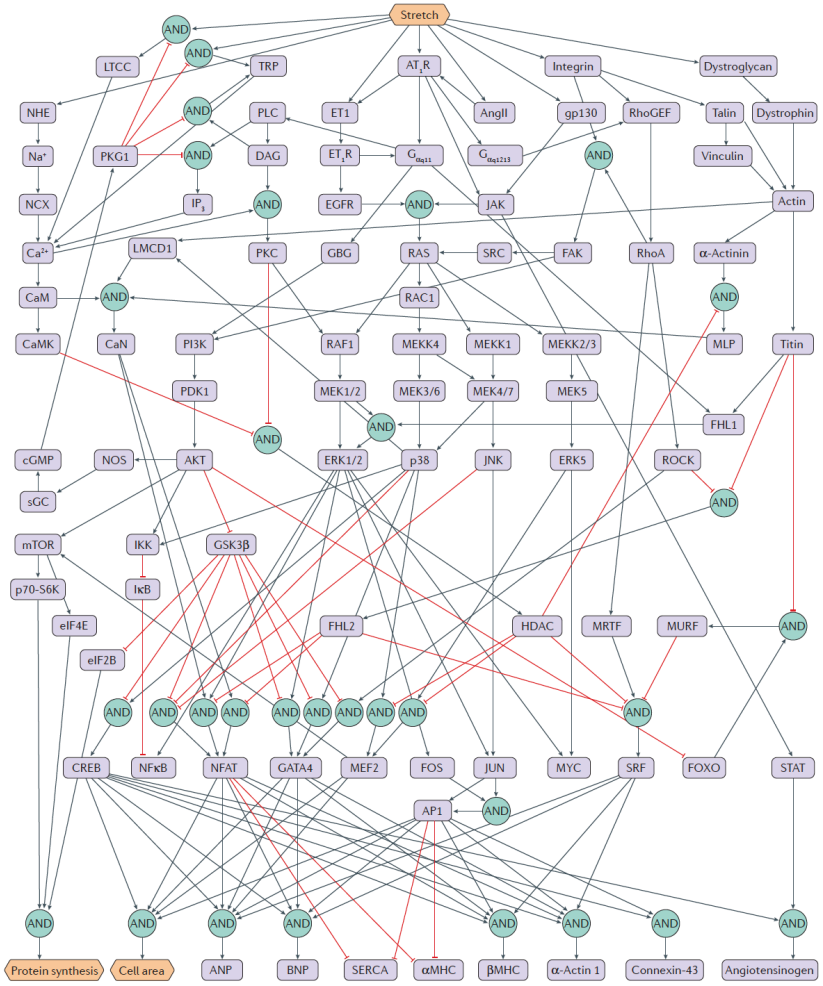
OR: $$\frac{dC}{dt} = \frac{1}{\tau_C}\left[\left(W_{AC} f_{act}(A) + W_{EC} f_{act}(E) - W_{AC} f_{act}(A) W_{EC} f_{act}(E)\right) C_{max} - C\right]$$

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

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

Cardiac Myocyte Mechano-Signaling

- 172 experimental papers to define network
- 54 separate papers on *in-vitro* stretch of cardio-myocytes 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



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

Species Information

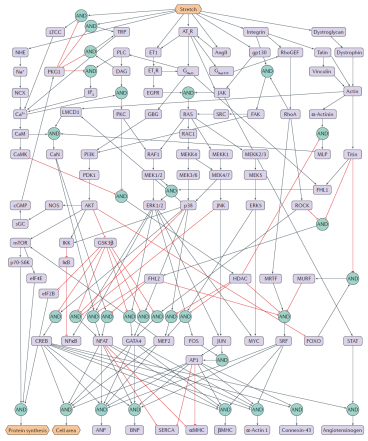
module	ID	name	Yinit	Ymax	tau	type	location	alternate names
integrin	aActinin	alpha-actinin	0	1	1	protein		
integrin	Actin	Actin	0	1	1	protein		
PI3K	Akt	Protein kinase B	0	1	1	protein		PKB, protein kinase B
outputs	aMHC	Alpha-myosin heavy chain	1	1	1	geneExpr		
g-coupled	AngII	Angiotensin II	0	1	1	protein		
outputs	ANP	Atrial natriuretic protein	0	1	1	geneExpr		ANF
outputs	Ao	Angiotensinogen	0	1	1	geneExpr		
transcriptio	AP1	Activator protein 1	0	1	1	protein		
g-coupled	AT1R	Antiotensin type 1 receptor	0	1	1	protein		
outputs	bMHC	Beta-myosin heavy chain	0	1	1	geneExpr		
outputs	BNP	Brain natriuretic protein	0	1	1	geneExpr		
calcium	Ca	Calcium	0	1	1	smallMolecule		Ca2+
calcium	CaM	Calmodulin	0	1	1	protein		
calcium	CaMK	CaM kinase	0	1	1	protein		
calcium	CaN	Calcineurin	0	1	1	protein		
outputs	CellArea	Cell area	0	1	1	phenotype		
transcriptio	cFos	Proto-oncogene c-Fos	0	1	1	protein		
PI3K	cGMP	Cyclic guanosine monophosphate	0	1	1	smallMolecule		
transcriptio	cJun	Proto-oncogene c-Jun	0	1	1	protein		
transcriptio	cMyc	Proto-oncogene c-Myc	0	1	1	protein		
transcriptio	CREB	cAMP response element binding	0	1	1	protein		
outputs	Cx43	Connexin 43	0	1	1	geneExpr		
g-coupled	DAG	Diacylglycerol	0	1	1	phospholipid		
integrin	Dysgl	Dystroglycans	0	1	1	protein		
integrin	Dysph	Dystrophin	0	1	1	protein		
growth fac	EGFR	Epidermal growth factor receptor	0	1	1	protein		
PI3K	eIF4E	Eukaryotic translation initiation factor 4E	0	1	1	protein		
PI3K	eIF2B	Eukaryotic translation initiation factor 2B	0	1	1	protein		
MAPK	ERK12	Extracellular signal-related kinases 1 or 2	0	1	1	protein		p42/p44 MAPK
MAPK	ERK5	Extracellular signal-related kinase 5	0	1	1	protein		BMK1
g-coupled	ET1	Endothelin-1	0	1	1	protein		
g-coupled	ET1R	Endothelin-1 receptor	0	1	1	protein		
integrin	FAK	Focal adhesion kinase	0	1	1	protein		
integrin	FHL1	Four-and-a-half LIM domains protein 1	0	1	1	protein		
integrin	FHL2	Four-and-a-half LIM domains protein 2	1	1	1	protein		
transcriptio	FoxO	Forkhead box O	1	1	1	protein		
g-coupled	Ga1213	G 12/13 alpha subunit	0	1	1	protein		
g-coupled	Gaq11	G q/11 alpha subunit	0	1	1	protein		
transcriptio	GATA4	GATA-binding protein 4	0	1	1	protein		
g-coupled	Gbg	G beta/gamma subunit	0	1	1	protein		
cytokine	gp130	Glycoprotein 130	0	1	1	protein		
PI3K	GSK3b	Glycogen synthase kinase 3 beta	1	1	1	protein		
transcriptio	HDAC	Histone deacetylase	1	1	1	protein		
PI3K	IkB	Nuclear factor of kappa light polypeptide ge	1	1	1	protein		
PI3K	IKK	Inhibitor of kappa light polypeptide gene en	0	1	1	protein		
integrin	Integrin	Integrin	0	1	1	protein		
g-coupled	IP3	Inositol triphosphate	0	1	1	phospholipid		
cytokine	JAK	Janus kinase 1 or 2	0	1	1	protein		
MAPK	JNK	c-Jun N-terminal kinase	0	1	1	protein		SAPK
MAPK	Lmcd1	LIM and cystein-rich domains 1	0	1	1	protein		Dyxin
calcium	LTCC	L-type calcium channel	0	1	1	protein		
transcriptio	MEF2	Myocyte enhancer factor 2	0	1	1	protein		
MAPK	MEK12	MAPK/ERK kinase 1 or 2	0	1	1	protein		MAPKK12

Reaction Information

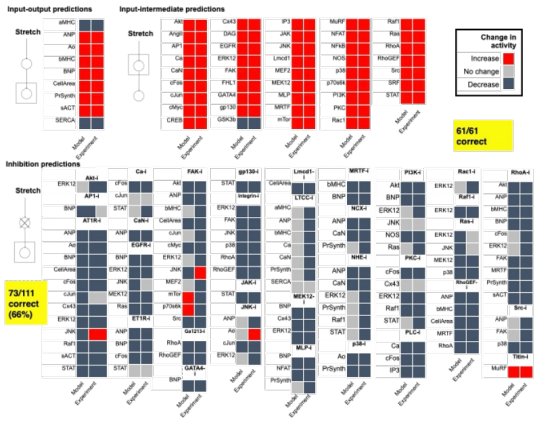
module	ID	rule	weight	n	EC50	code	notes	PMID	author	specie	sour	PMID
input	i1	=> Stretch	0	1.4	0.5	3	Stretch input					
input	i2	=> AngII	0	1.4	0.5	3	AngII addition					
input	i3	=> AT1R	0	1.4	0.5	3	AT1R activation (without AngII)					
input	i4	=> Dysgl	0	1.4	0.5	3	Dysgl activation					
input	i5	=> ET1	0	1.4	0.5	3	ET1 addition					
input	i6	=> gp130	0	1.4	0.5	3	gp130 activation					
input	i7	=> Integrin	0	1.4	0.5	3	Integrin activation					
input	i8	=> LTCC	0	1.4	0.5	3	LTCC activation					
input	i9	=> NHE	0	1.4	0.5	3	NHE activation					
input	i10	=> TRP	0	1.4	0.5	3	TRP activation					
input	i11	=> sGC	0	1.4	0.5	3	sGC activation					
middle	r1	Stretch => AngII	0.9	1.4	0.5	2	Stretch induces Angl	8831108	Miyata Eur J	NRVM	Stret	9525
middle	r2	Stretch => AT1R	0.9	1.4	0.5	3	Stretch activates AT1	15146194	Zou Nat Cel	HEK29	AT1R	20530
middle	r3	Stretch => Dysgl	0.9	1.4	0.5	3	Stretch exerts force	8349731	Ervasti JBC	Purifie	The d	1447
middle	r4	Stretch => ET1	0.9	1.4	0.5	2	Stretch induces ET1	8621724	Yamazaki JB	NRVM	Stret	9776
middle	r5	Stretch => gp130	0.9	1.4	0.5	2	Stretch activates gp	10219240	Hirota Cell 1	Mouse	gp13	11262
middle	r6	Stretch => Integrin	0.9	1.4	0.5	3	Stretch activates Int	7684161	Wang Scien	Capilla	Stret	9478
middle	r7	!PKG1 & Stretch => LTCC	0.9	1.4	0.5	3	Stretch activates L-ty	12176756	Lyford Am J	CHO	Trans	15910
						3	PKG1 inhibits LTCC	12177418	Fielder PNAS	NRVM	cGMP inhibits L	
middle	r8	Stretch => NHE	0.9	1.4	0.5	2	Stretch activates NH	12650883	von Lewinsk	Rabbit	SFR i	15105
middle	r9	!PKG1 & Stretch => TRP	0.9	1.4	0.5	3	Stretch activates Trp	17056714	Spassova PN	CHO a	Stret	20605
						3	PKG1 phosphorylates	14983059	Kwan PNAS	Human	PKG p	19961
middle	r10	Actin => aActinin	0.9	1.4	0.5	2	Actin links to aActinin	1577864	Lu J Cell Bio	Chick	aActinin is loca	
middle	r11	Actin => Lmcd1	0.9	1.4	0.5	3	Actin activates Lmcd	10662546	Bespalova G	Purifie	Lmcd1 is part	
middle	r12	Actin => Titin	0.9	1.4	0.5	3	Actin links to Titin	11701614	Kulke Circ R	Purifie	Actin	25246
middle	r13	!Akt => FoxO	0.9	1.4	0.5	3	Akt phosphorylates a	15781459	Skurk JBC 2	NRVM		
middle	r14	!Akt => GSK3b	0.9	1.4	0.5	3	Akt phosphorylates a	11715022	Rommel Na	C2C12		23000
middle	r15	Akt => IKK	0.9	1.4	0.5	3	Akt activates IKK	10485710	Ozes Nature	HEK293		
middle	r16	Akt => mTor	0.9	1.4	0.5	3	Akt activates mTor	11715022	Rommel Na	C2C12		
middle	r17	Akt => NOS	0.9	1.4	0.5	3	Akt activates NOS	10376603	Dimmeler N	HUVEC		
middle	r18	AngII => AT1R	0.9	1.4	0.5	3	AngII binds to AT1R	8348686	Sadoshima	NRVM		
middle	r19	AP1 & CREB & GATA4 & MEF2	0.9	1.4	0.5	3	AP1 is necessary for	11799083	Omura Hyp	NRVM		15795
						1	CREB is necessary for ANP transcription					
						3	GATA4 is necessary fo	21746915	van Berlo P	Mouse	adult heart	
						3	MEF2 is necessary for	10531040	Kolodziejczy	Mouse	adult heart	
						1	NFAT is necessary for ANP transcription					
						3	SRF is necessary for	15950986	Nelson JMC	NRVM,	Mouse adult he	
middle	r20	AP1 & CREB & GATA4 & NFAT &	0.9	1.4	0.5	3	AP1 is necessary for	15795322	Jeong Circ 2	NRVM		
						2	CREB is necessary for	9568714	Molkentin C	Mouse	adult heart	
						1	GATA4 is necessary for bMHC transcription					
						2	NFAT is necessary for	12370307	Wilkins Mol	Mouse	adult heart	
						3	SRF is necessary for	15950986	Nelson JMC	NRVM,	Mouse adult he	
middle	r21	AP1 & CREB & GATA4 & NFAT &	0.9	1.4	0.5	3	AP1 is necessary for	11799083	Omura Hyp	NRVM		15795
						1	CREB is necessary for BNP transcription					
						3	GATA4 is necessary fo	21746915	van Berlo P	Mouse	adult heart	
						2	NFAT is necessary for	21746915	van Berlo P	Mouse	adult heart	
						3	SRF is necessary for	15950986	Nelson JMC	NRVM,	Mouse adult he	
middle	r22	AP1 & CREB & GATA4 & MEF2	0.9	1.4	0.5	3	AP1 is necessary for	11799083	Omura Hyp	NRVM		
						1	CREB is necessary for CellArea increase					
						3	GATA4 is necessary fo	21746915	van Berlo P	Mouse	adult heart	
						3	MEF2 is necessary for	10531040	Kolodziejczy	Mouse	adult heart	
						2	NFAT is necessary for	9568714	Molkentin C	Mouse	adult heart	
middle	r23	AP1 & CREB & GATA4 & NFAT &	0.9	1.4	0.5	3	AP1 is necessary for	15795322	Jeong Circ 2	NRVM		

species | reactions

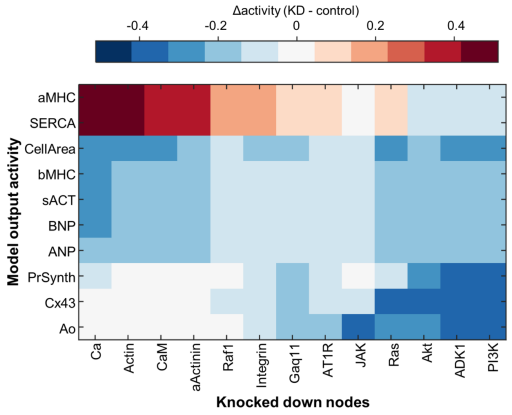
Validation, Sensitivity & Uncertainty Quantification



77% Validation Accuracy

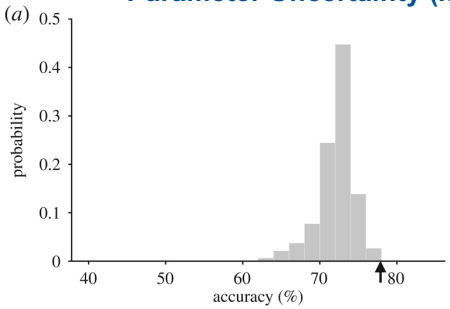


Sensitivity Analysis

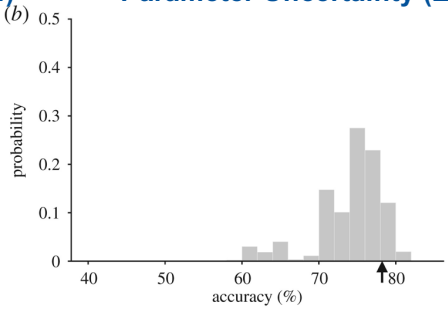


Tan *et al.*, (2017) Systems analysis identifies key network regulators of cardiomyocyte mechano-signalling. *PLoS Comp Biol*

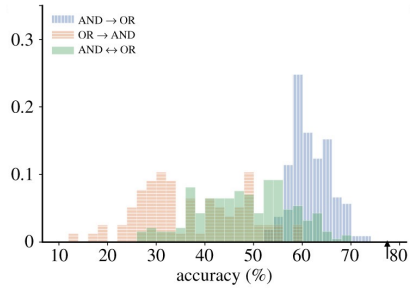
Parameter Uncertainty (*n*)



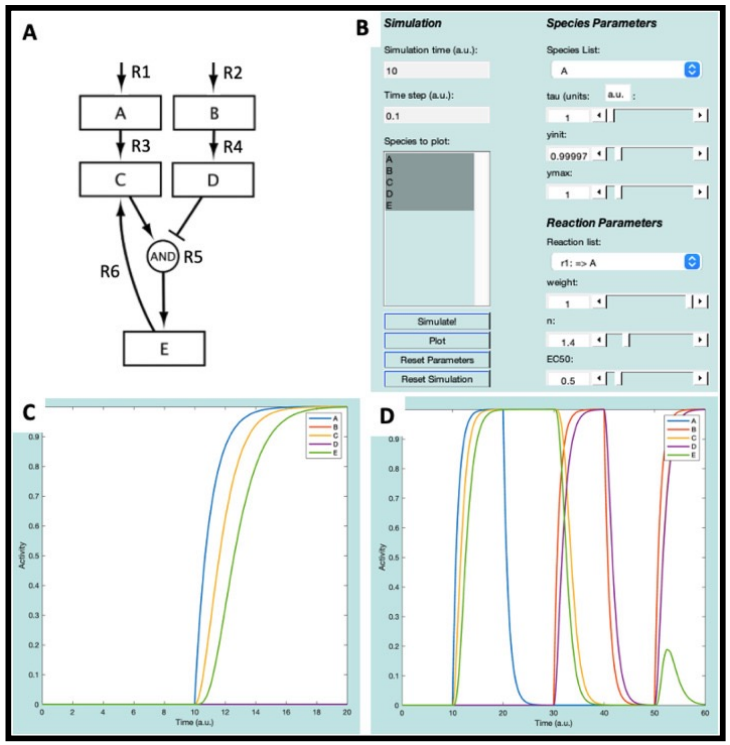
Parameter Uncertainty (EC_{50})

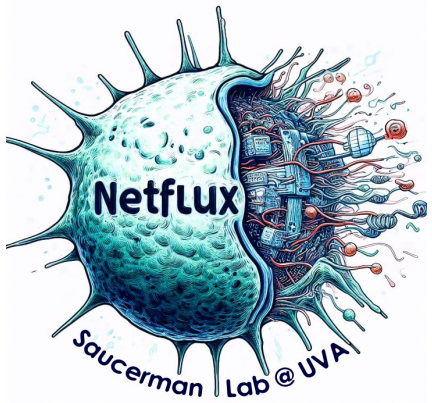


Epistemic (Logic) Uncertainty



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.* 37820190336





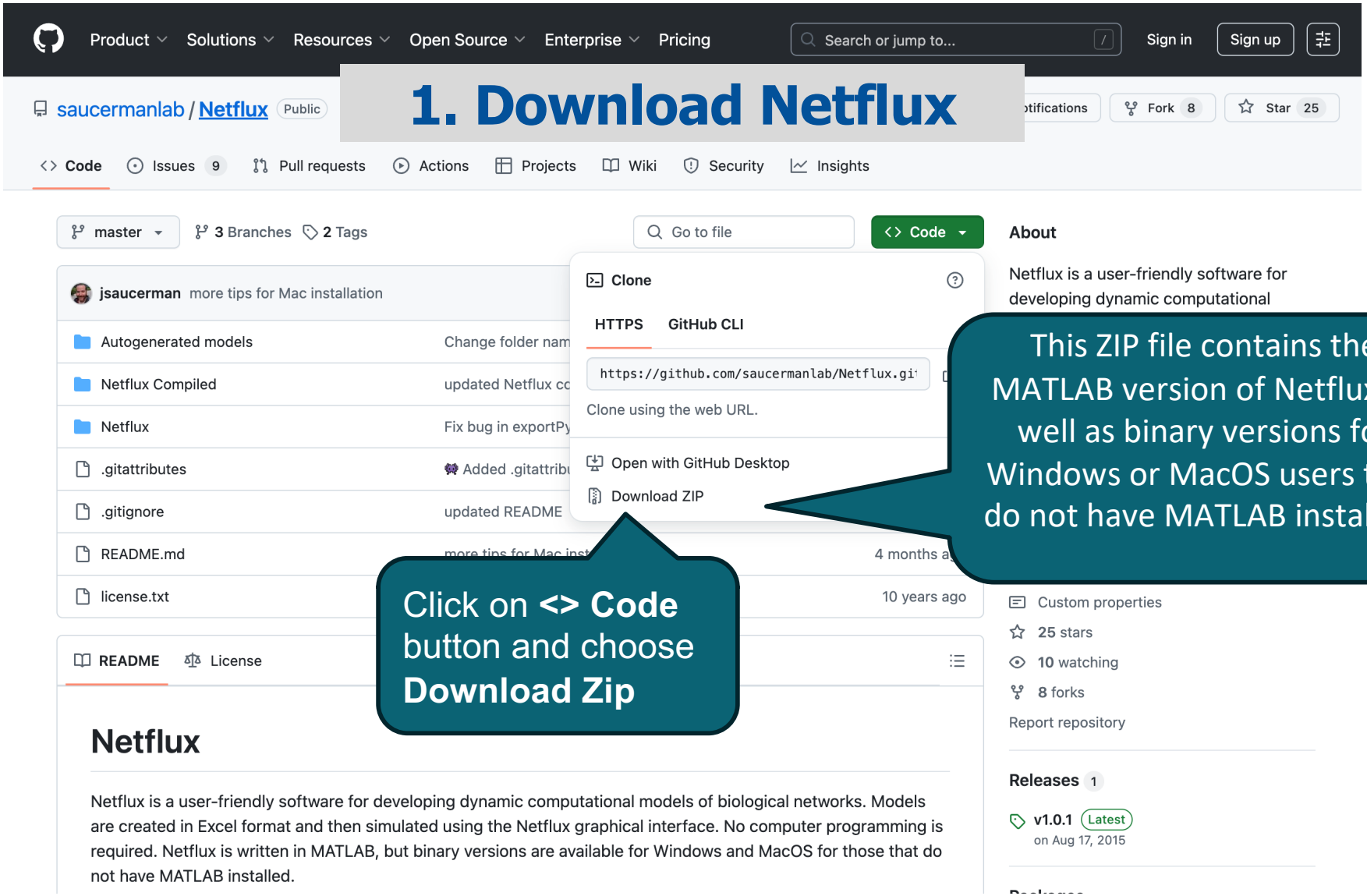
https://github.com/saucermanlab/Netflux

PLOS Computational Biology

Logic-based modeling of biological networks with Netflux

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

Published: April 4, 2025 • https://doi.org/10.1371/journal.pcbi.1012864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Go to file
Code
About
Netflux is a user-friendly software for developing dynamic computational
jsaucerman more tips for Mac installation
Autogenerated models
Change folder nam
Netflux Compiled
updated Netflux cc
Netflux
Fix bug in exportPy
.gitattributes
Added .gitattribu
.gitignore
updated README
README.md
more tips for Mac inst
4 months a
license.txt
10 years ago
Clone
HTTPS
GitHub CLI
https://github.com/saucermanlab/Netflux.gi
Clone using the web URL.
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This ZIP file contains the MATLAB version of Netflux as well as binary versions for Windows or MacOS users that do not have MATLAB installed.
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README
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Netflux
Netflux is a user-friendly software for developing dynamic computational models of biological networks. Models are created in Excel format and then simulated using the Netflux graphical interface. No computer programming is required. Netflux is written in MATLAB, but binary versions are available for Windows and MacOS for those that do not have MATLAB installed.
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on Aug 17, 2015

2. Install Netflux (Users with MATLAB)

A. You might be able to use your institutional site license to install MATLAB from their academic portal:
https://www.mathworks.com/search.html?c%5B%5D=entire_site&q=TAH+portal&page=1

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

2. Install Netflux (Users without MATLAB)

A. Windows: Open the “Netflux Compiled” folder and run “Netflux Installer Windows.exe”. Netflux will be installed to the C:\Program Files\Netflux folder

B. MacOS with Apple Silicon (only): Open the “Netflux Compiled” folder, extract “Netflux_Installer_MacOS”, and run ./Netflux_Installer_macOS.app in the terminal. Run Netflux.app from the terminal

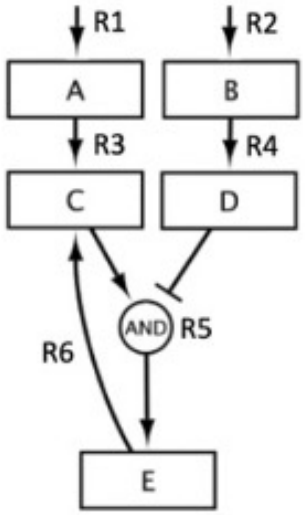
3. YouTube Videos

Introduction to Netflux:
https://youtu.be/tU2gU8d5hvQ?si=LLYdF1uHuDUKAozo

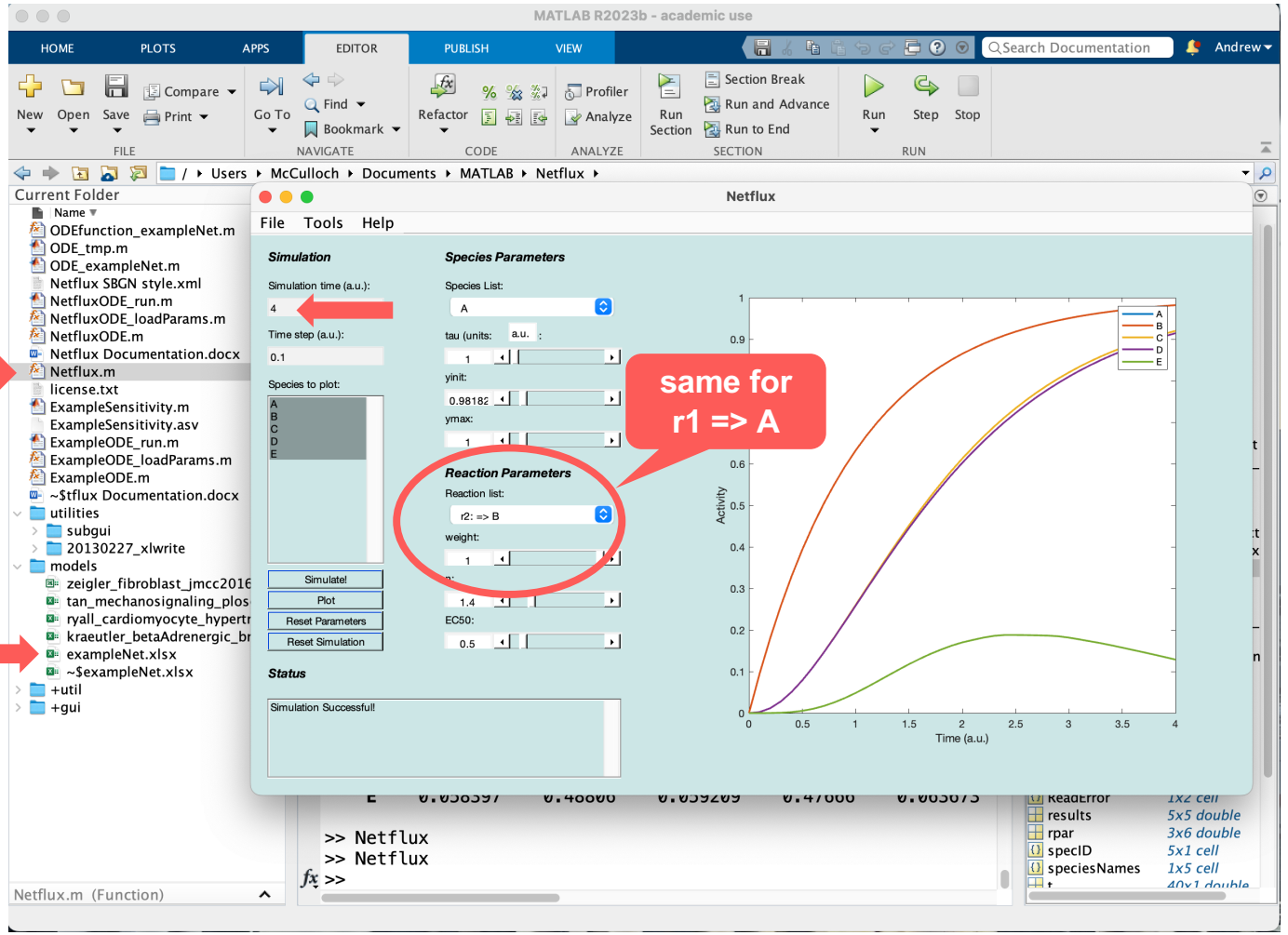
Netflux Tutorial: Basic Simulations
https://youtu.be/susMLNhQjig?si=WaEhECpyrMIZFs7r

Netflux Tutorial: Visualization with Cytoscape
https://youtu.be/IHrV5SOV7jA?si=ZgxOBighbh_kCVgG

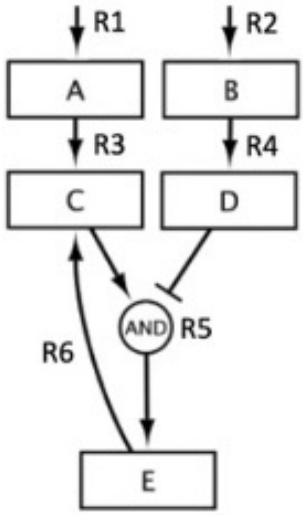
Running Example Network (exampleNetwork.xlxs)



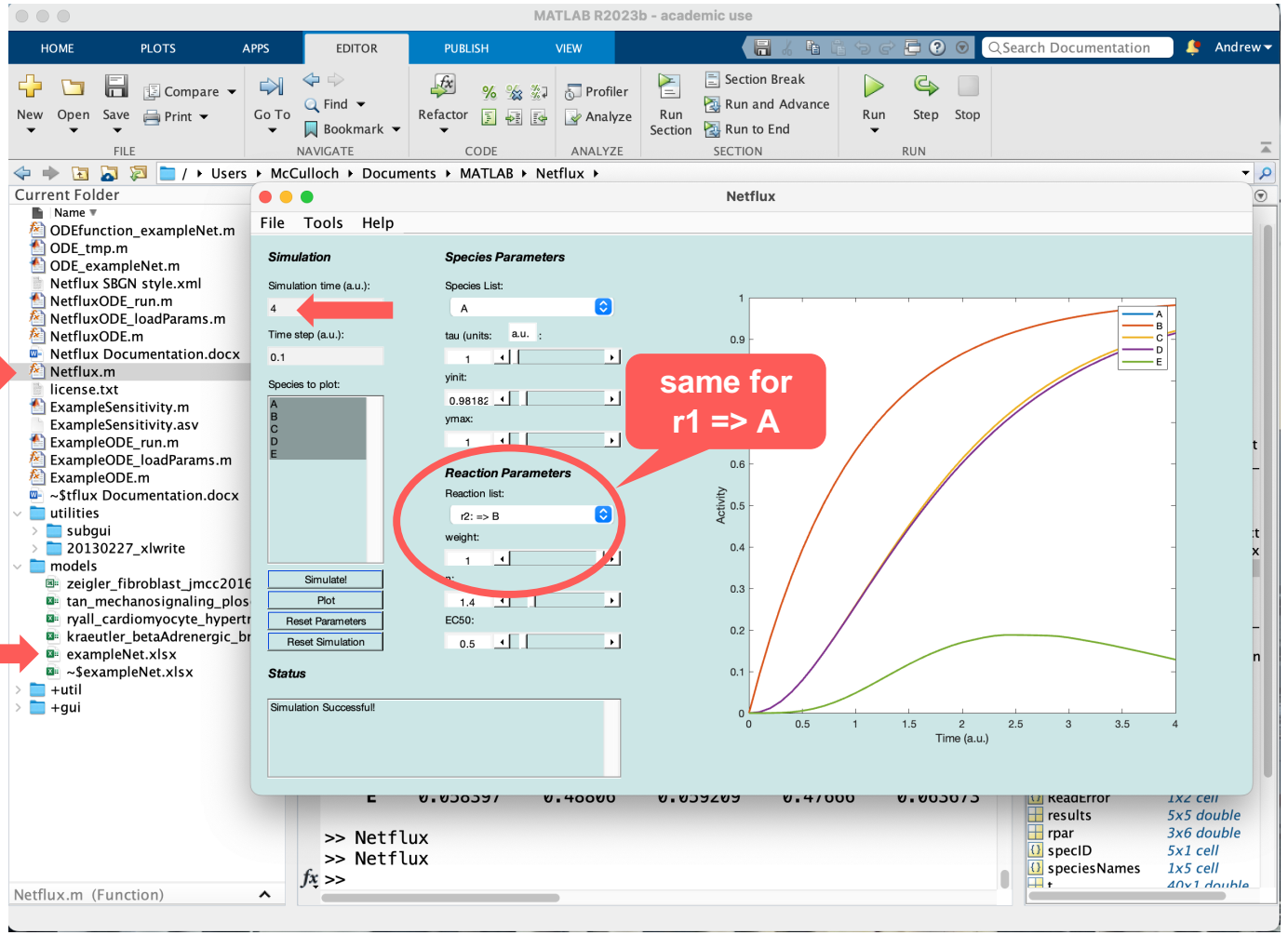
Simulation time: 10
R1=0; R2=0
R1=1; R2=0
R1=0; R2=0
R1=0; R2=1
R1=0; R2=0
R1=1; R2=1



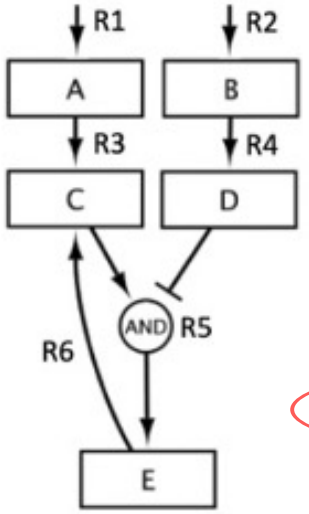
Sensitivity Analysis of Example Network

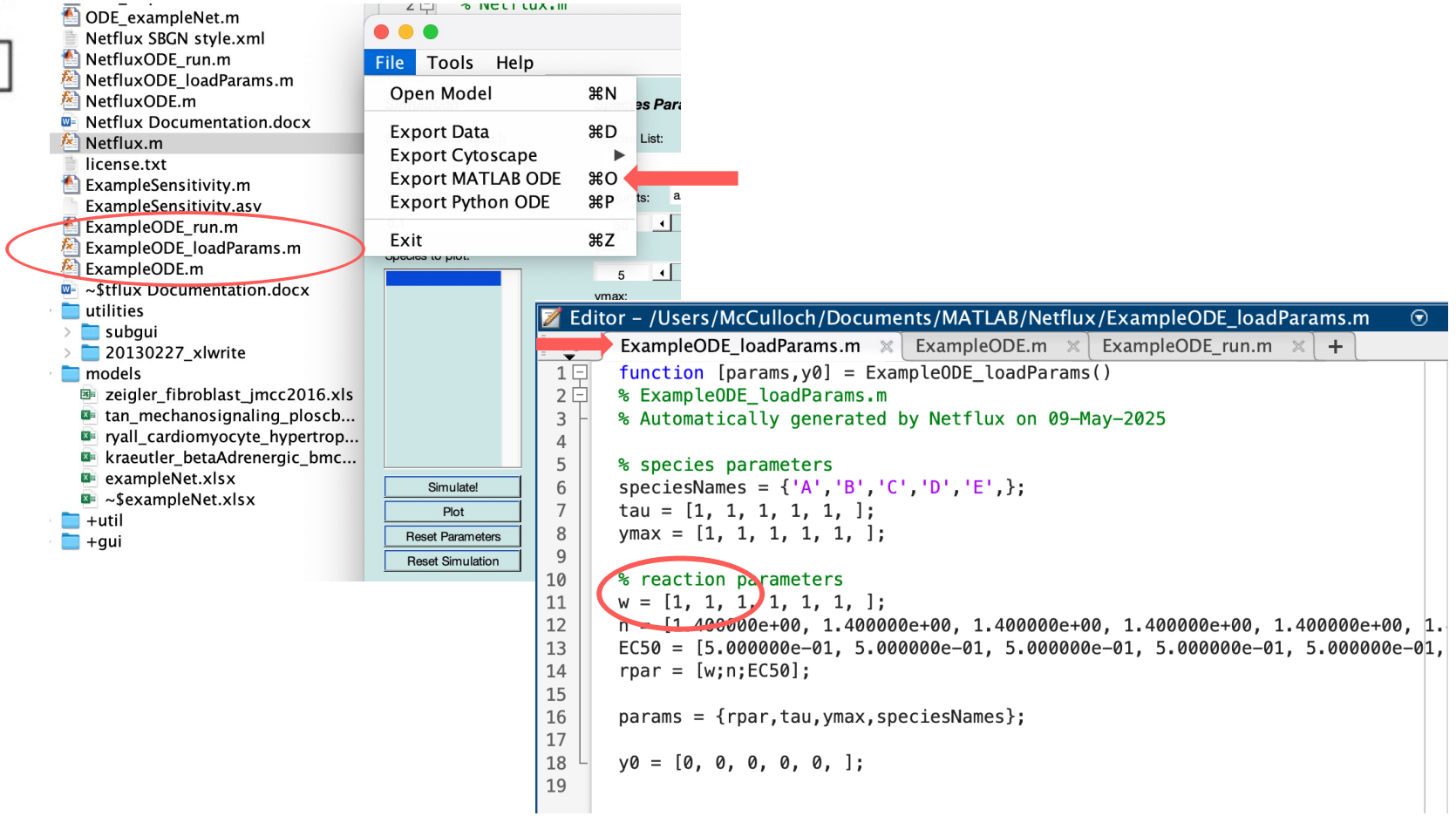


Simulation time: 4
R1=1; R2=1



Exporting and using MATLAB model code



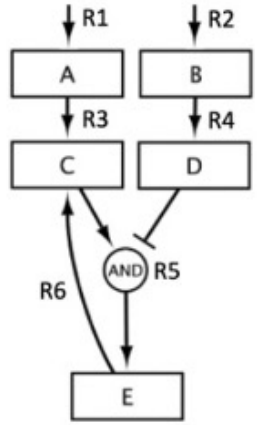


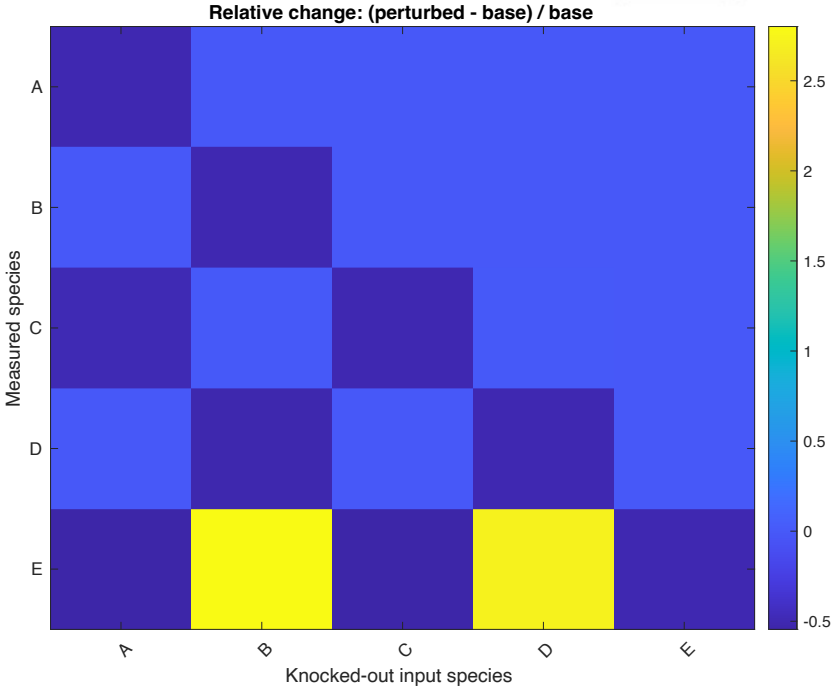
Sensitivity Analysis

Editor - /Users/McCulloch/Documents/MATLAB/Netflux/ExampleSensitivity.m

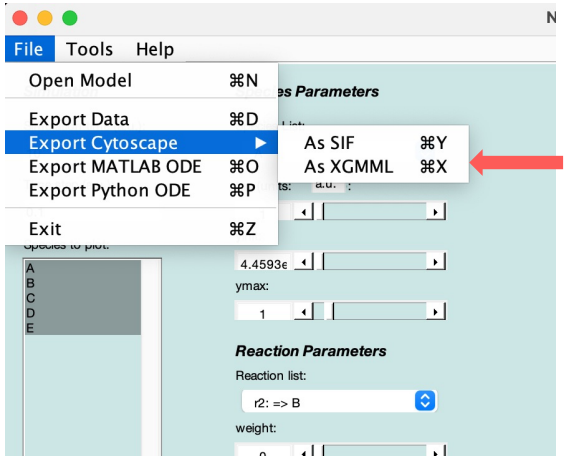
+7 | ExampleODE_loadParams.m | ExampleODE.m | ExampleODE_run.m | ExampleSensitivity.m

```
% ExampleODE_sensitivity.m — Knockout Ymax sensitivity analysis

% Load baseline parameters
[params, y0] = ExampleODE_loadParams();
[rpar, tau, ymax, speciesNames] = params{:};
nSpecies = numel(y0);
nTimepoints = 40;
tspan = linspace(0, 4, nTimepoints);
results = zeros(nSpecies, nSpecies);  % rows: species, cols: knockout

% Baseline simulation
params_base = {rpar, tau, ymax, speciesNames};
[t, y_base] = ode15s(@(t, y) ExampleODE(t, y, params_base), tspan, y0);
y_base_final = real(y_base(end, :)');  % ensure real values

% Loop over each species
for i = 1:nSpecies
    ymax_perturbed = ymax;
    ymax_perturbed(i) = 0.5;  % Knock down this species
    % Create new param set
    perturbed_params = {rpar, tau, ymax_perturbed, speciesNames};
    % Simulate
    [t, y] = ode15s(@(t, y) ExampleODE(t, y, perturbed_params), tspan, y0);
    % Save final state for heatmap
    y_final = real(y(end, :)');  % final state, cleaned of roundoff
    % Avoid divide-by-zero with a small epsilon
    eps_val = 1e-12;
    relative_change = (y_final - y_base_final) ./ max(abs(y_base_final), eps_val);
    if isempty(y) || size(y,1) < 1
        warning("Simulation failed for KO %s", speciesNames{i});
        results(:, i) = NaN;
        continue;
    end
    results(:, i) = relative_change;
end
results = real(results); % suppresses an infinitessimal imaginary number float error
% Print numerical sensitivity matrix
disp('=== Sensitivity Results (Final Values) ===');
T = array2table(results, 'RowNames', speciesNames, 'VariableNames', matlab.lang.make
disp(T);
```



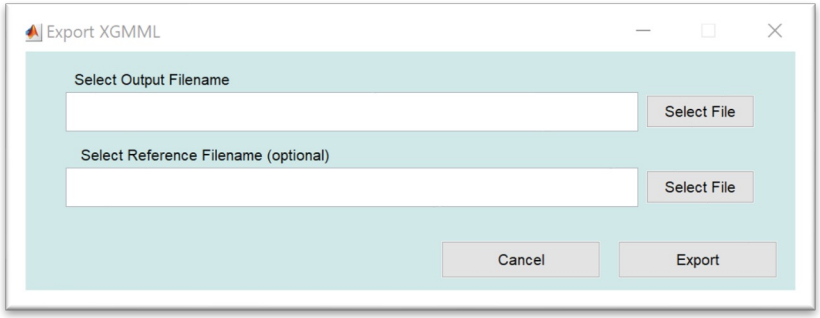


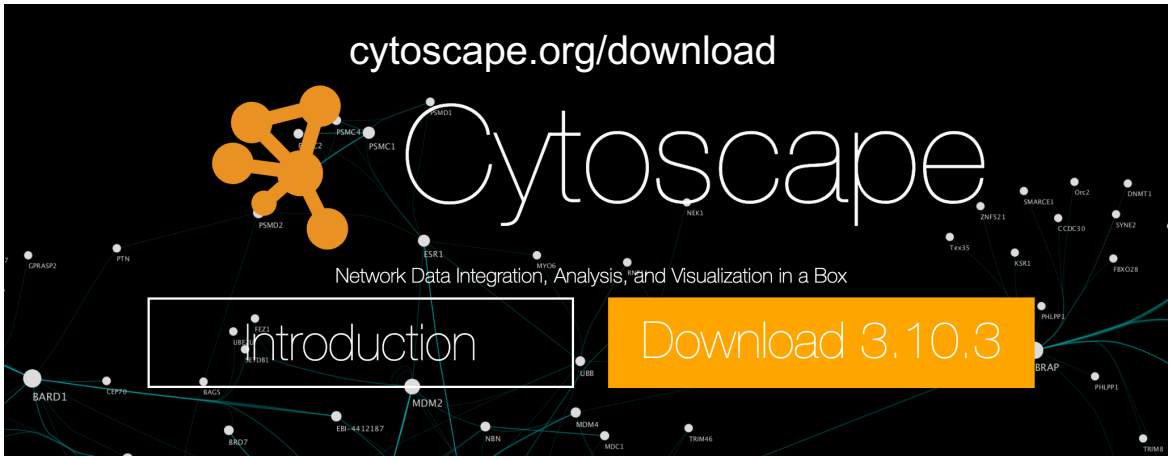
Visualization with Cytoscape



In Netflux

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 Netflux.
- Import the SBGN layout style by selecting File → Import → **Styles from File…,** and select "**Netflux SBGN styles.xml**" from the installed Netflux directory.
- Apply the "Netflux SBGN" style by going to the **Style** tab within the Control Panel. Click on the dropdown menu that says "**default**" and change to "**Netflux_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 Netflux.
- **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.