Using the Wentzell-Freidlin least action to direct network dynamical systems

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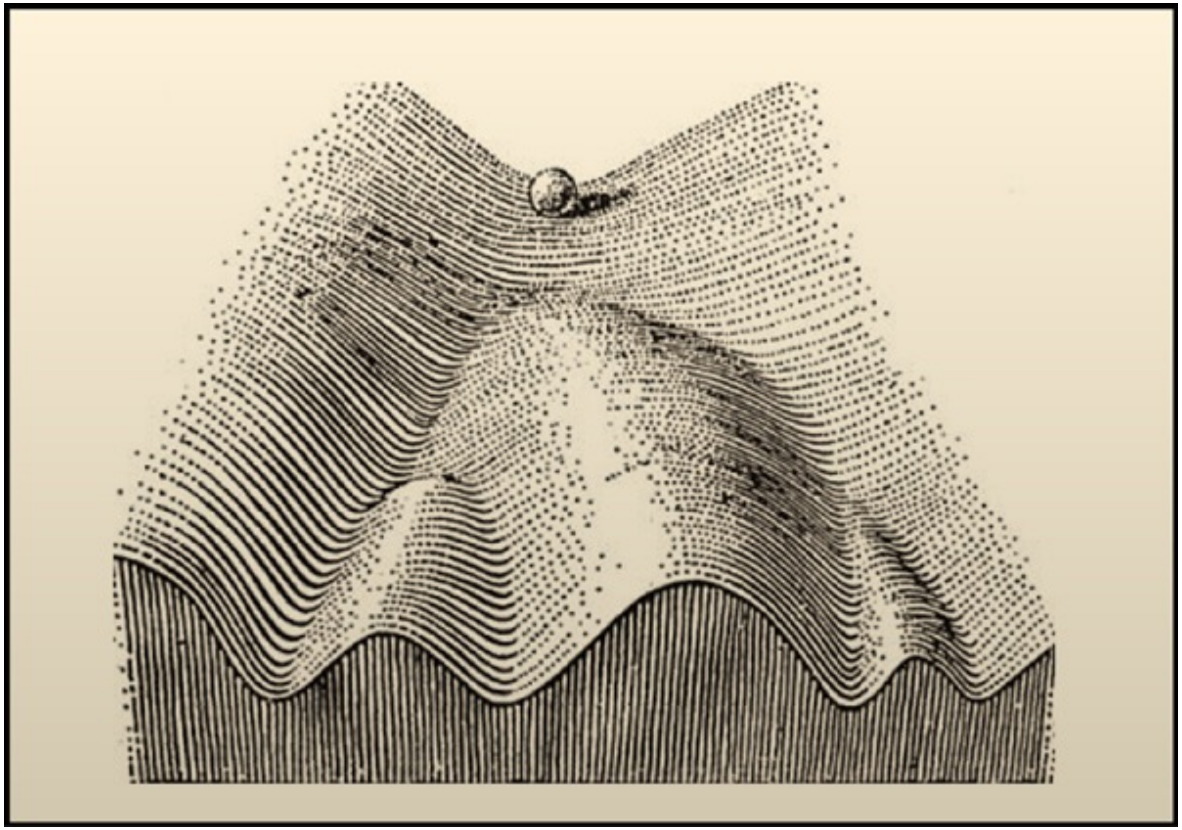
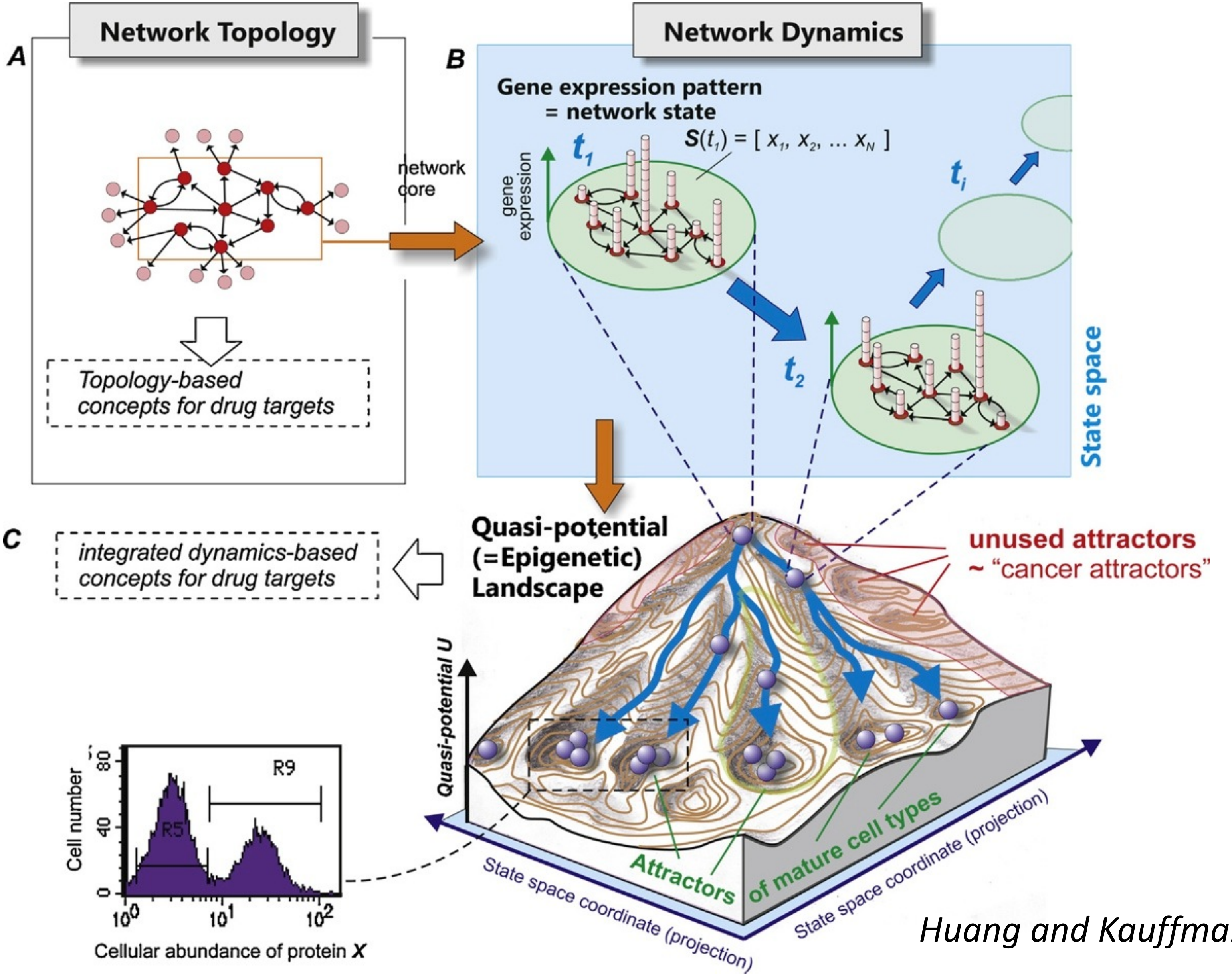
Epigenetic dynamics

Waddington's epigenetic landscape…



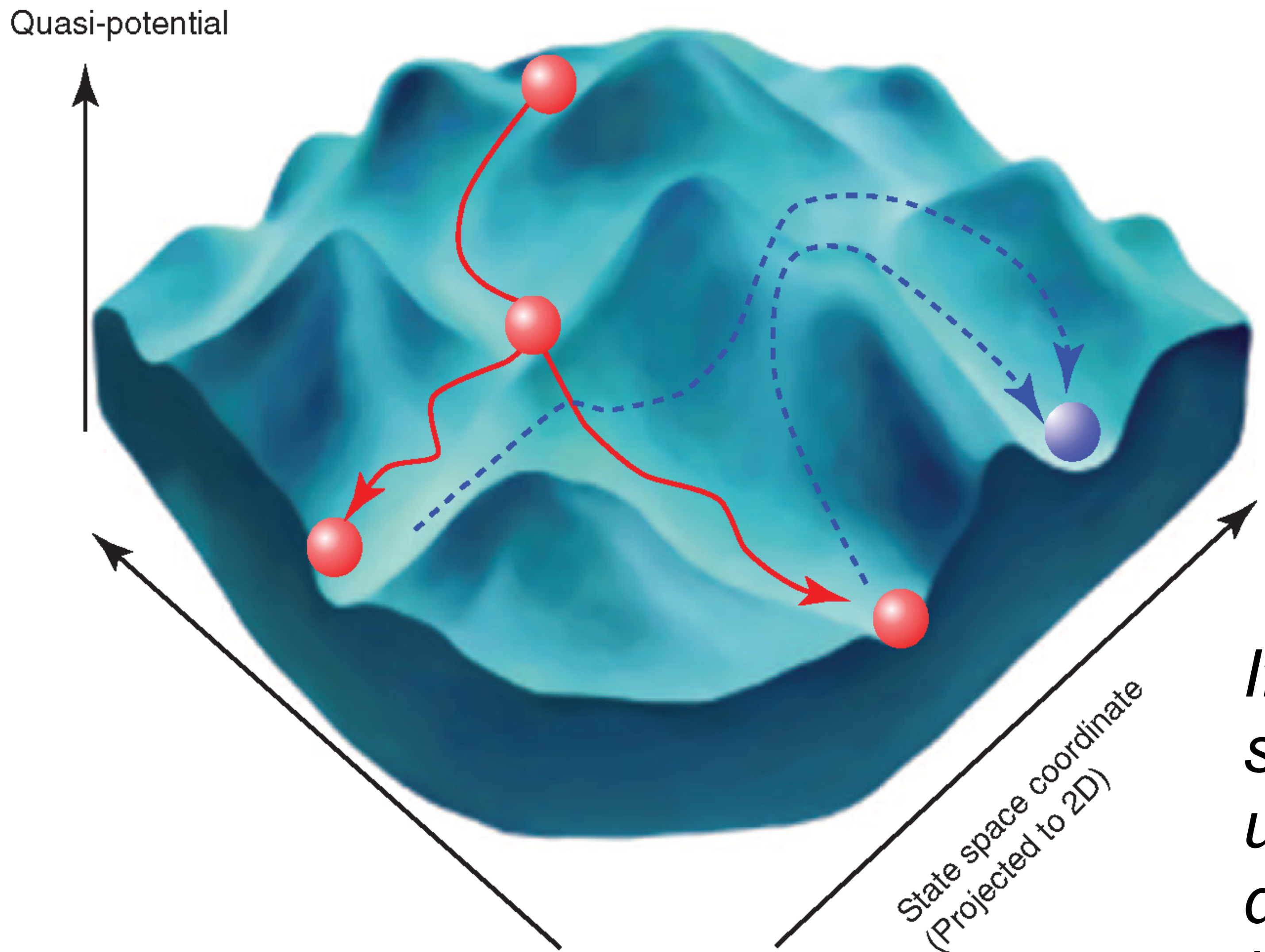
...a qualitative model of cell differentiation

The epigenetic landscape and cancer attractors



Huang and Kauffman, 2013

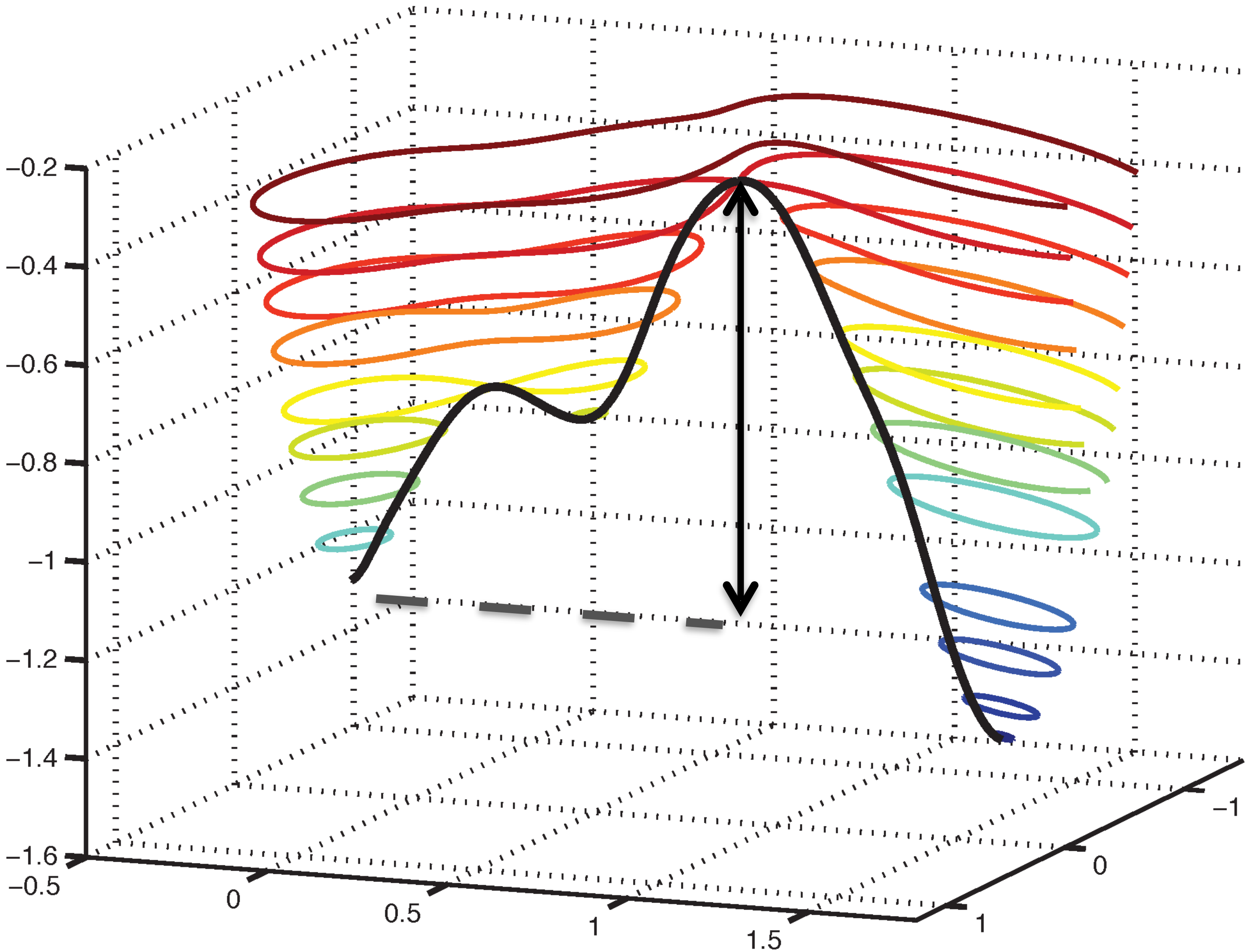
The aim: a rational basis for cell reprogramming



If the blue state is undesirable, direct system back

Zhou and Huang, 2011

Need barrier height in the quasipotential landscape



Determining the barrier height

Barrier height can be determined from a stochastic model. If the system is

$$d\vec{X} = \vec{F}(\vec{X};\vec{P})\,dt + \sqrt{\varepsilon}\,d\vec{W}$$

(with $\vec{P}$ a vector of parameters, and ε small)

then the Wentzell-Freidlin least action measures it

$$S[\vec{\phi}^{*}_{i,j};\vec{P}] = \min_{\substack{\vec{\phi}(t) \\ \vec{\phi}(T_1)=\vec{a}_i \\ \vec{\phi}(T_2)=\vec{a}_j}} \frac{1}{2}\int_{T_1}^{T_2} \left\| \frac{d\vec{\phi}}{dt} - \vec{F}(\vec{\phi}(t);\vec{P}) \right\|^2 dt$$

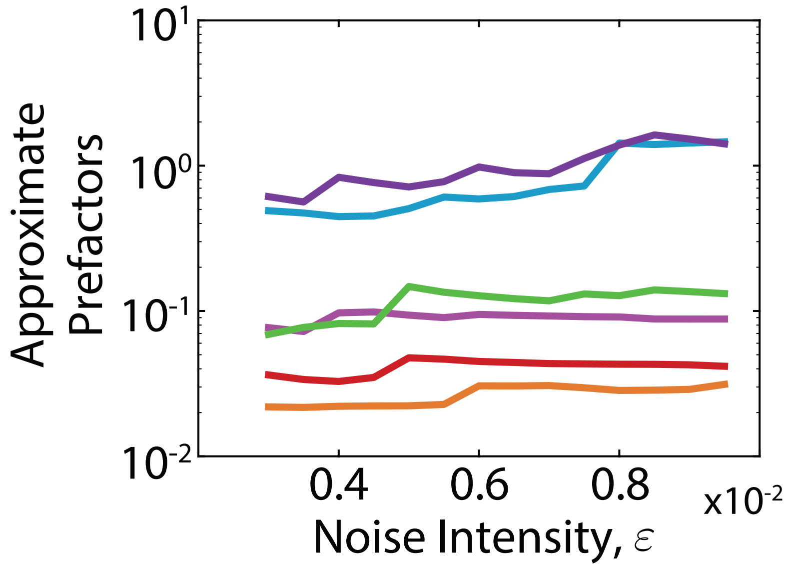
The minimization is over paths from one state to another

The minimum action sets the transition rate

$$R^{\varepsilon}_{i,j}(\vec{P}) \sim C(\varepsilon)\exp\left(-\frac{1}{\varepsilon}S[\phi^{*}_{i,j};\vec{P}\,]\right)$$

Freidlin & Wentzell

- Asymptotic form of coefficient is more difficult to determine
- But main behavior determined by action and exponential
- If necessary, can compute prefactor with importance sampling



For details: see some of the *extensive* literature

Kramers, Physica 7 (1940) 284

Freidlin and Wentzell, Random Perturbations of Dynamical Systems, 1984

Dupuis and Kushner, SIAM J. Appl. Math 47 (1987) 643

Maier and Stein, Phys. Rev. E 48 (1993) 931

Dykman, Mori, Ross and Hunt, J. Chem. Phys. 100 (1994) 5735

E, Ren and Vanden-Eijnden, Comm. Pure Appl. Math 7 (2004) 637

Yin and Ao, J. Phys. A 39 (2006) 8593

Zhou, Ren and E, J. Chem. Phys. 128 (2008) 104111

Schwartz, Billings, Dykman and Landsman, J. Stat. Mech. P01005 (2009)

Berglund and Gentz, J. Phys. A 42 (2009) 052001

Keener and Newby, Phys. Rev. E. 84 (2011) 011918

Vanden-Eijnden and Weare, Comm. Pure Appl. Math 65 (2012) 1770

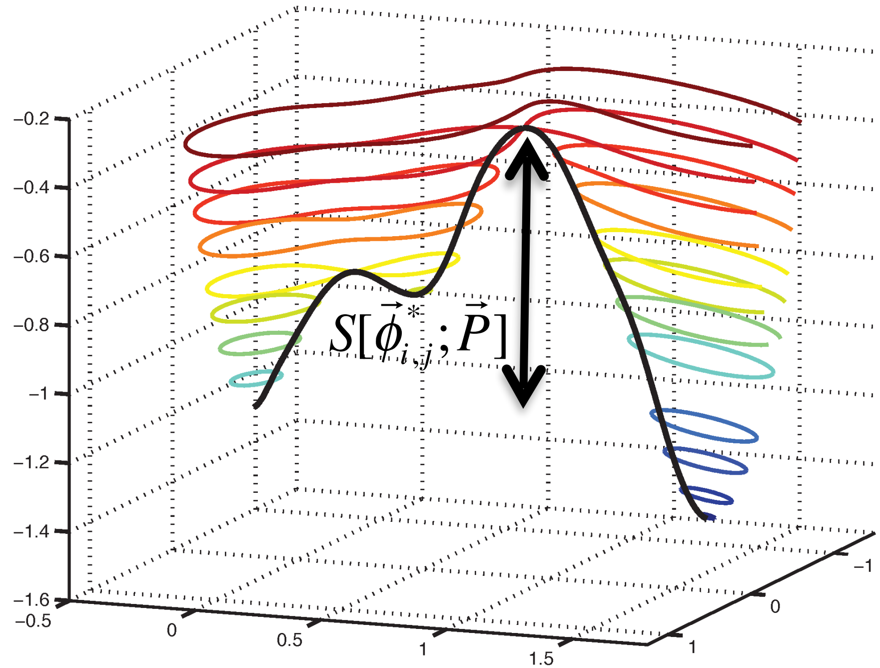
Cameron, Phys. D 241 (2012) 1532

Lindley and Schwartz, Physica D 255 (2013) 22

Key idea: minimize barrier height w.r.t. parameters

$$\min_{\vec{P}} S[\vec{\phi}^*_{i,j}; \vec{P}]$$

…to make transition from one state to another more likely



- Only need fixed points of interest
- Problem is basically 1D, even if full problem has high dimension
- Takes into account *some* non-local system information
- Minimize over paths (there are good methods for this), and then minimize with respect to parameters (good methods for this, too)
- **Use to predict the optimal combination (possibly constrained) of system parameters (e.g., gene expression rates) inducing a desired state**

An old (illustrative) method to find the path

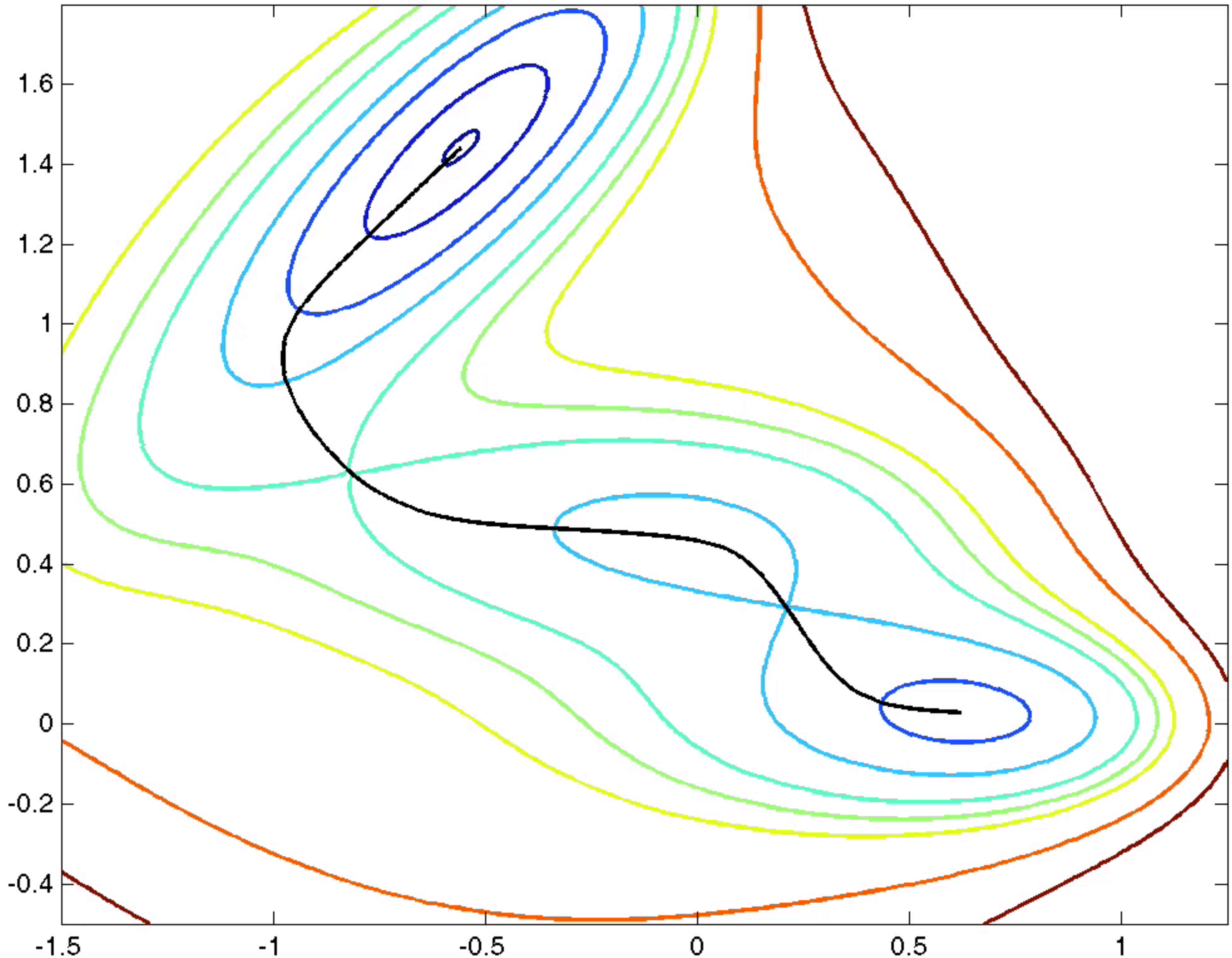
$$S(\lambda) = \int_{-\infty}^{\infty} \left[d\vec{X} / dt - \vec{F}(\vec{X}) \right]^2 dt = \int_{-\infty}^{\infty} L(\vec{X}(\lambda), \dot{\vec{X}}(\lambda)) dt$$

If choose

$$\frac{\partial \vec{X}}{\partial \lambda} = -\frac{1}{2} \left[\frac{\partial L}{\partial \vec{X}} - \frac{d}{dt} \left(\frac{\partial L}{\partial \dot{\vec{X}}} \right) \right]$$

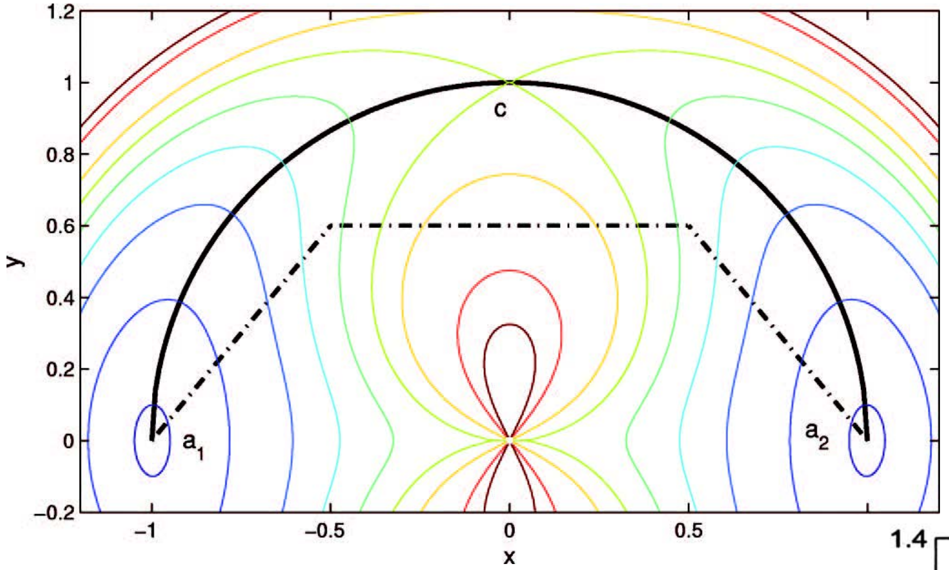
$$\Rightarrow \frac{\partial S}{\partial \lambda} = -\frac{1}{2} \int_{-\infty}^{\infty} \left[\frac{\partial L}{\partial \vec{X}} - \frac{d}{dt} \left(\frac{\partial L}{\partial \dot{\vec{X}}} \right) \right]^2 dt \leq 0$$

R. Courant, Variational methods for the solution of problems of equilibrium and vibrations, Bull. Amer. Math. Soc., 49:1-23, 1943.



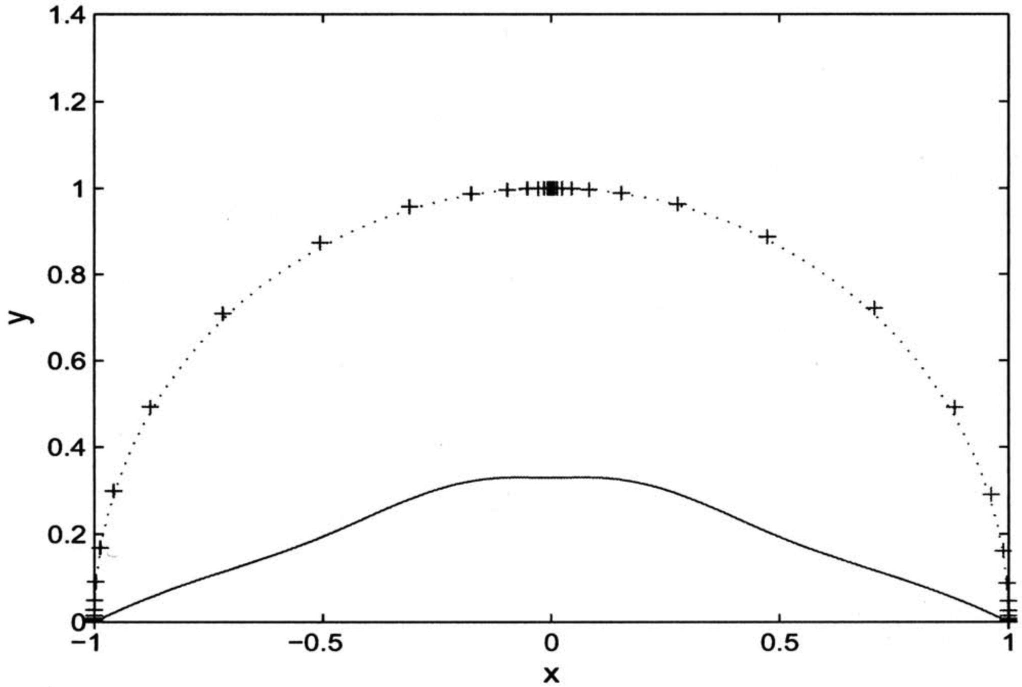
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-1.5
-1
-0.5
0
0.5
1

Better path finding: adaptive minimum action method



Adaptive discretization
+ minimize with L-BFGS

Zhou, Ren and E
J. Chem Phys. 128 (2008) 10411



Optimal Least Action Control (OLAC): find minimum path, then minimize over parameters

1. Takes account of nonlinear interaction between nodes

2. Modular, scalable
- Effort proportional to the number of transitions, not size of system (upper bound: the square of the number of stable fixed points)

3. Able to incorporate flexible constraints
- Not all interventions may be possible
- Can add sparsity constraints

4. Implementation can be state agnostic
- If know all stable states, can increase occupancy of desired state (alternatively, just lower barriers *into* the desired state)
- Then predicted interventions apply in parallel to cells in different states

OLAC can identify system interventions that change the landscape to bring about a desired network state

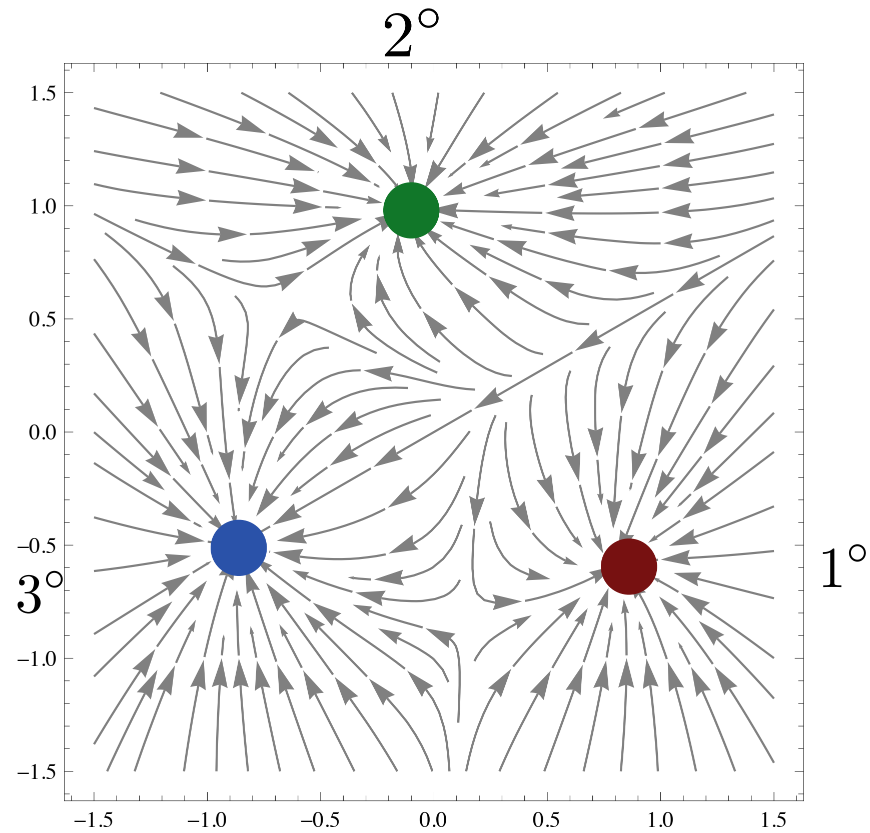
Example: an intervention to enhance lineage respecification

The model: *C. elegans* vulval precursor cells (VPC); competent to adopt three fates.

$$\frac{d\vec{r}}{dt} = \vec{\sigma}(\vec{r}, l_1, l_2)$$

Fate is determined by two signaling pathways, EGF and Notch, whose strengths are determined from ℓ_1 and ℓ_2.

low ℓ_1, low ℓ_2: bias towards 3° (blue)
high ℓ_1, low ℓ_2: bias towards 1° (red)
low ℓ_1, high ℓ_2: bias towards 2° (green)



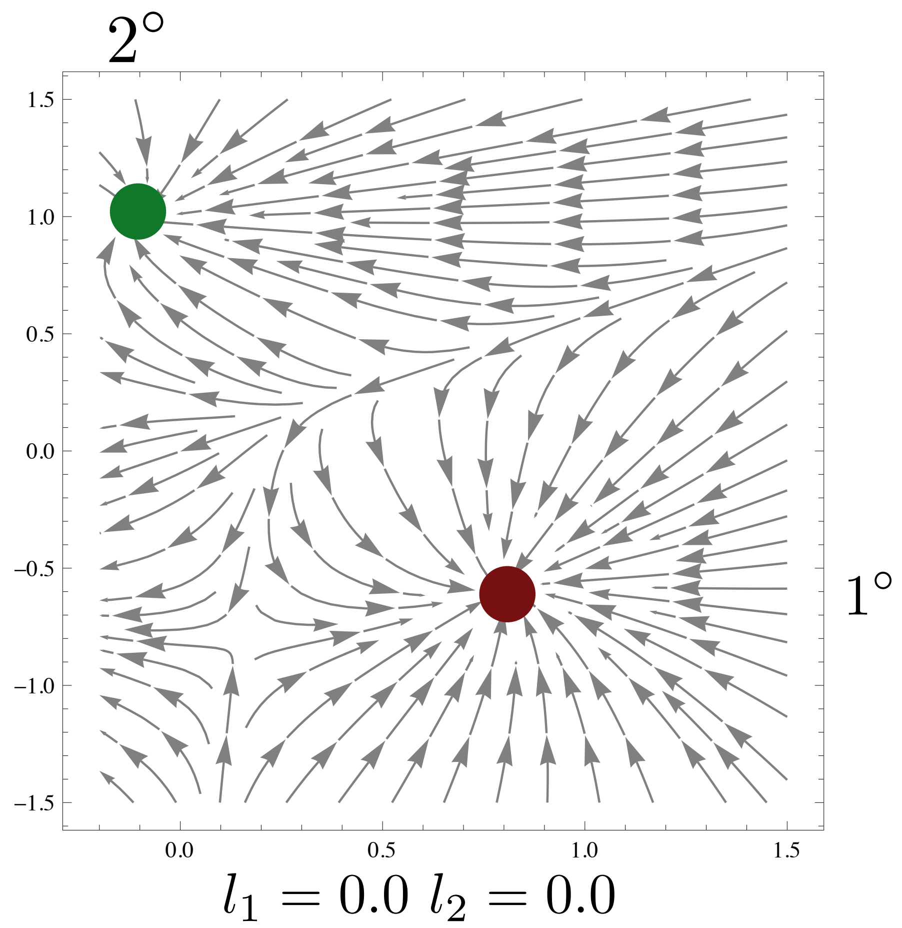
$$l_1 = 0.0 \; l_2 = 0.0$$

Corson F., and Siggia, E. PNAS (2012)

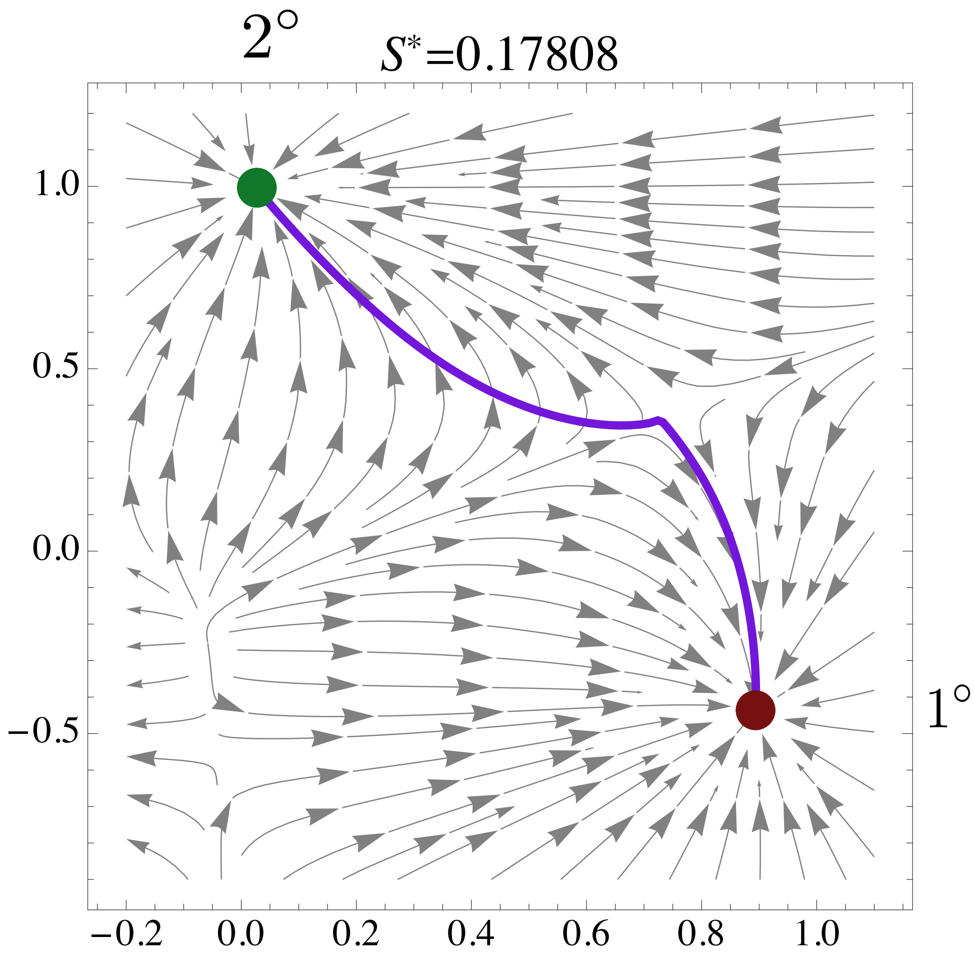
Choose the particular "desired" state

Goal: optimize transition rate (minimize S^*) from 2° (green) to 1° (red).

It is known this occurs for high EGF (l_1) and low Notch (l_2) signaling.

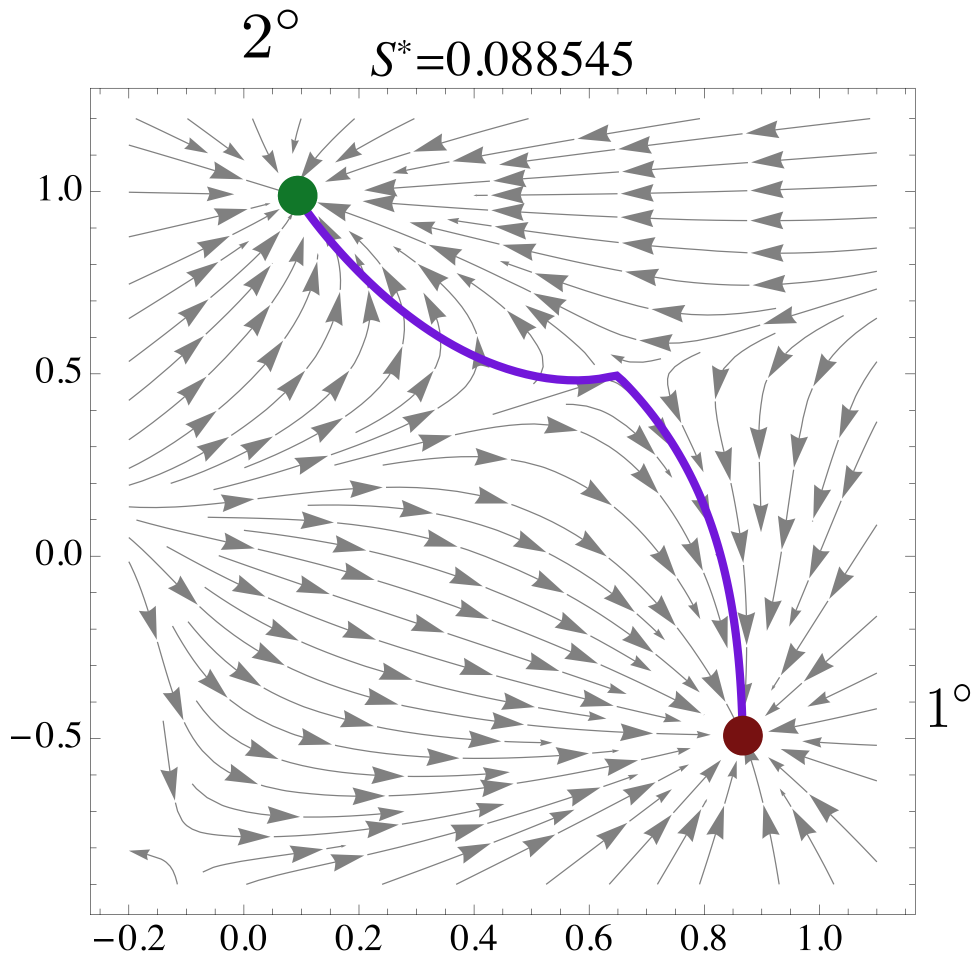


Find least action path, iterate over parameters



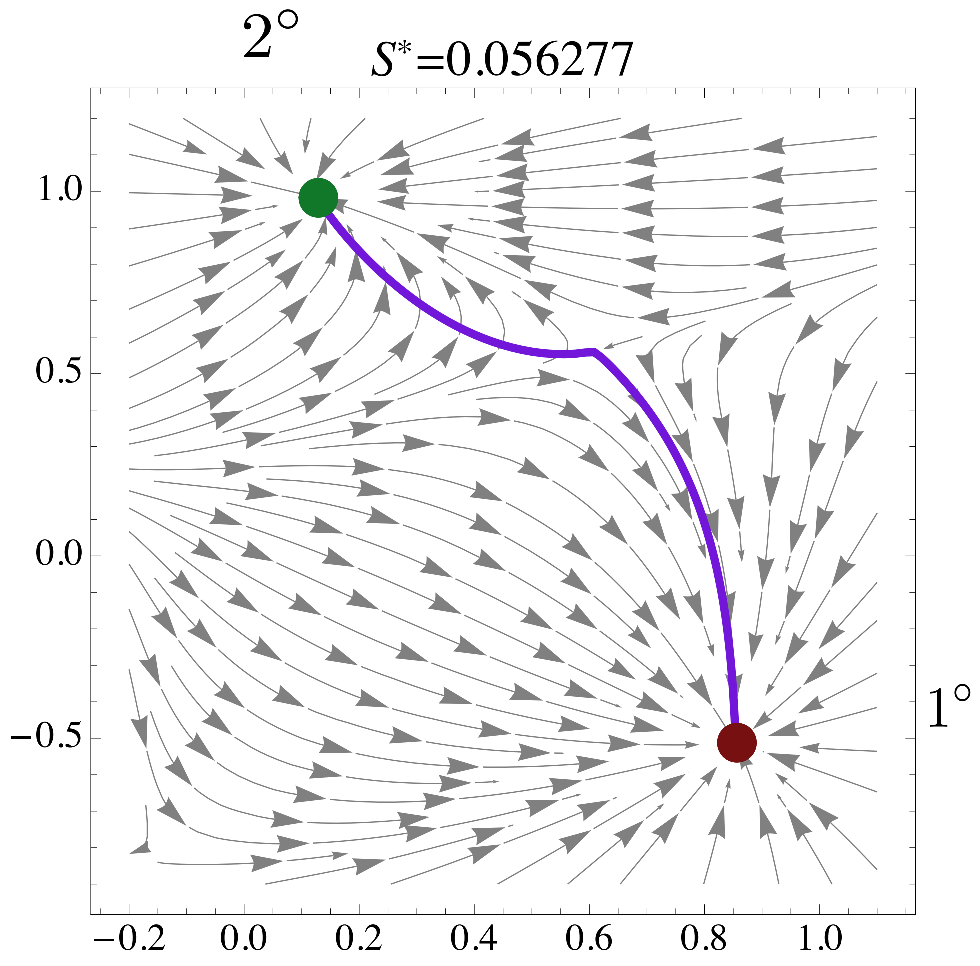
$$l_1 = 0.1 \; l_2 = 0.1$$

Find least action path, iterate over parameters



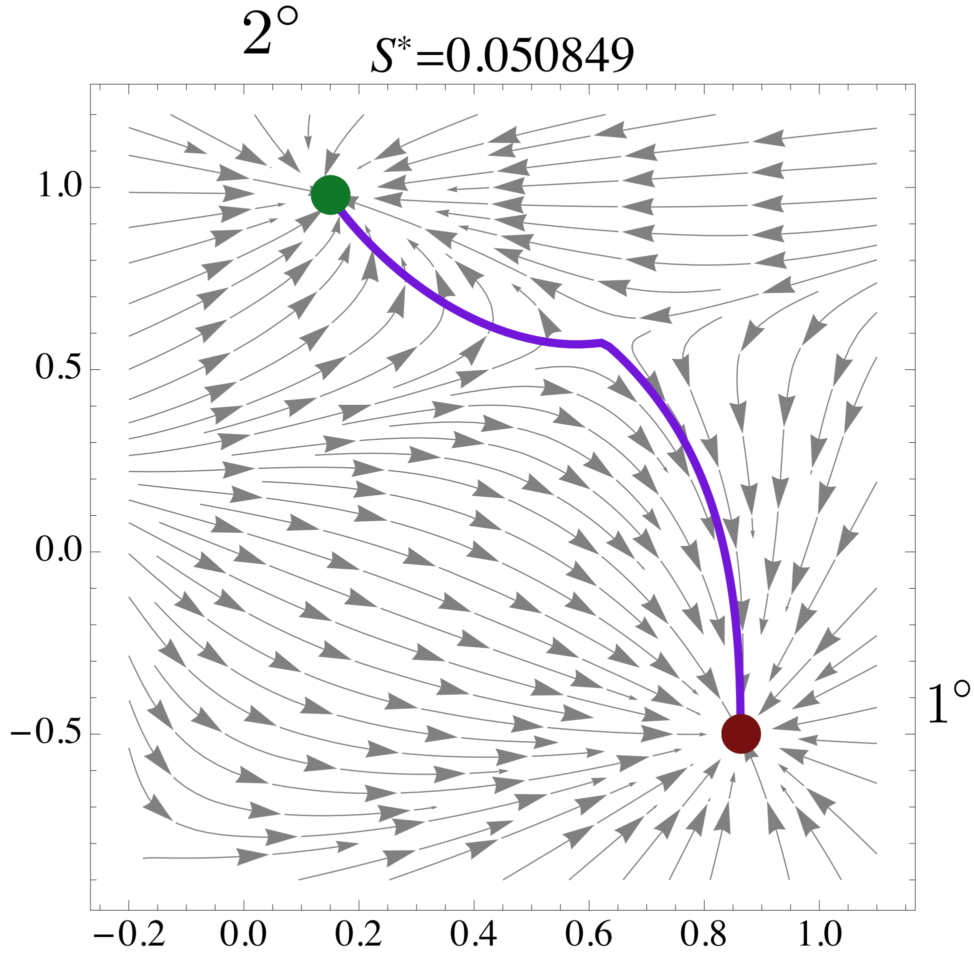
$$l_1 = 0.1437 \; l_2 = 0.0649$$

Find least action path, iterate over parameters



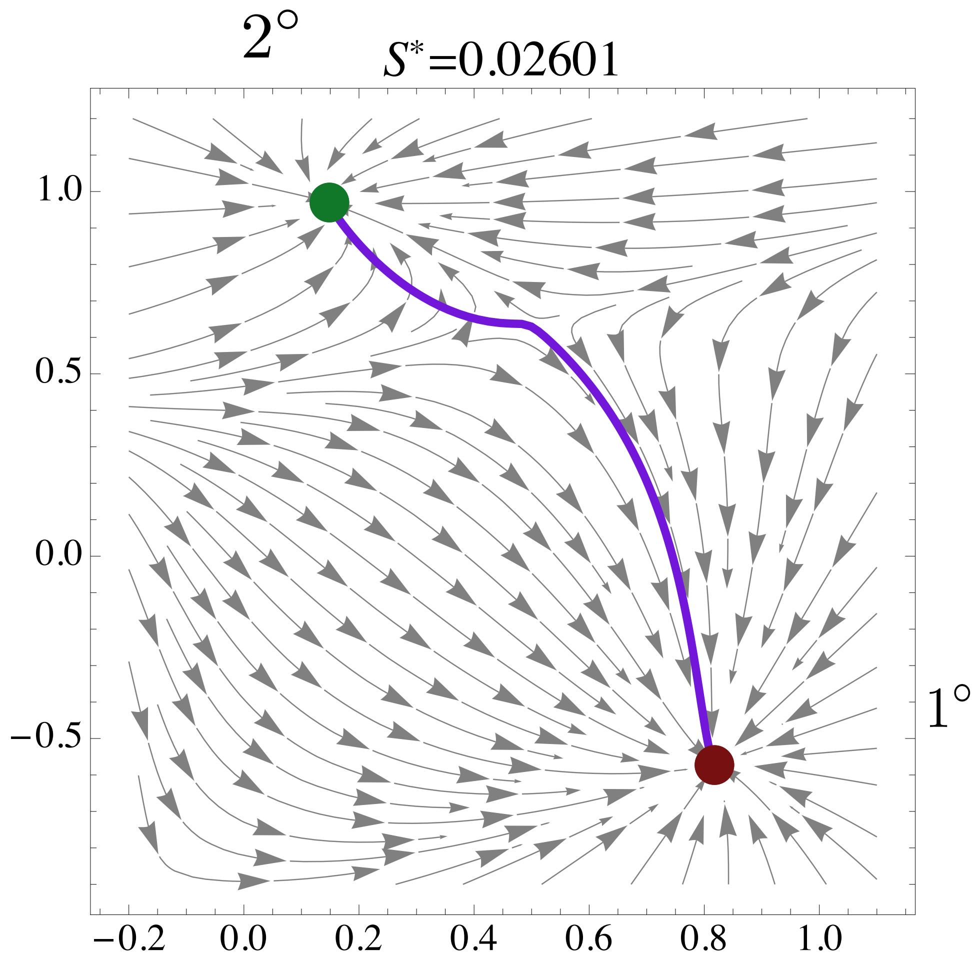
$$l_1 = 0.1642 \; l_2 = 0.0486$$

Find least action path, iterate over parameters



$$l_1 = 0.1793 \; l_2 = 0.0591$$

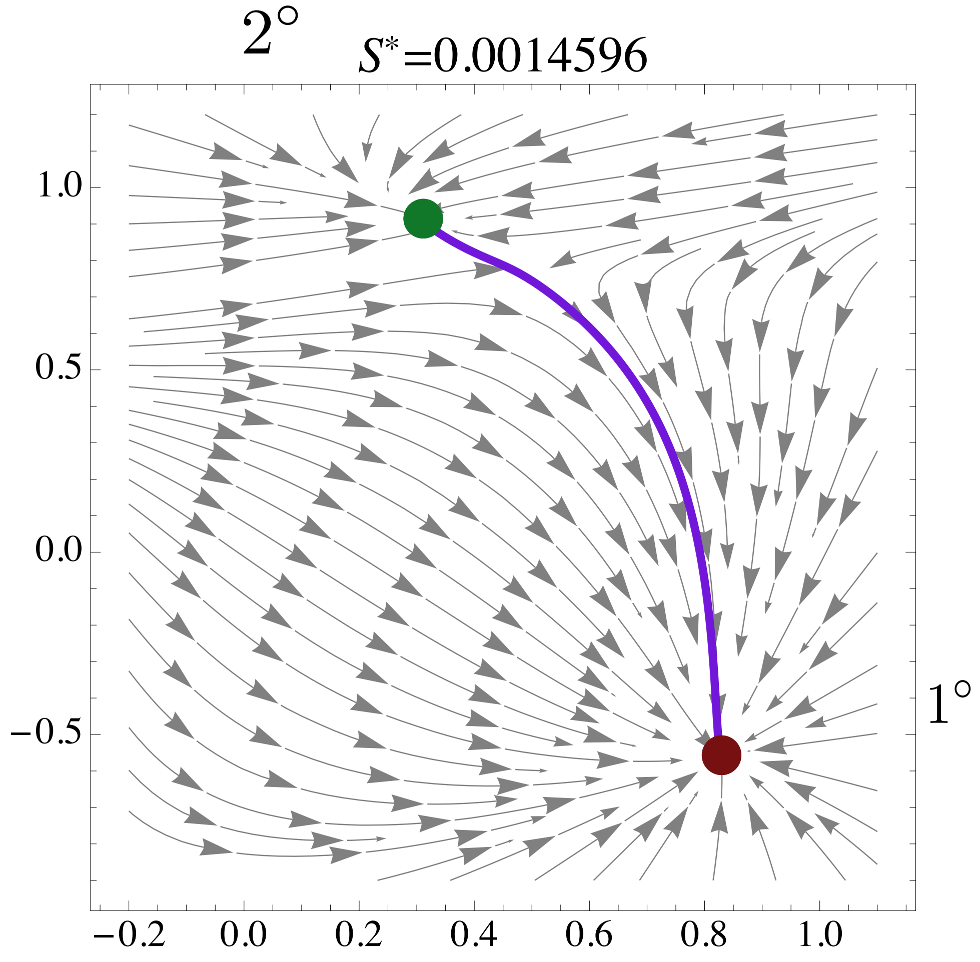
Find least action path, iterate over parameters



$$l_1 = 0.1642 \; l_2 = 0.002$$

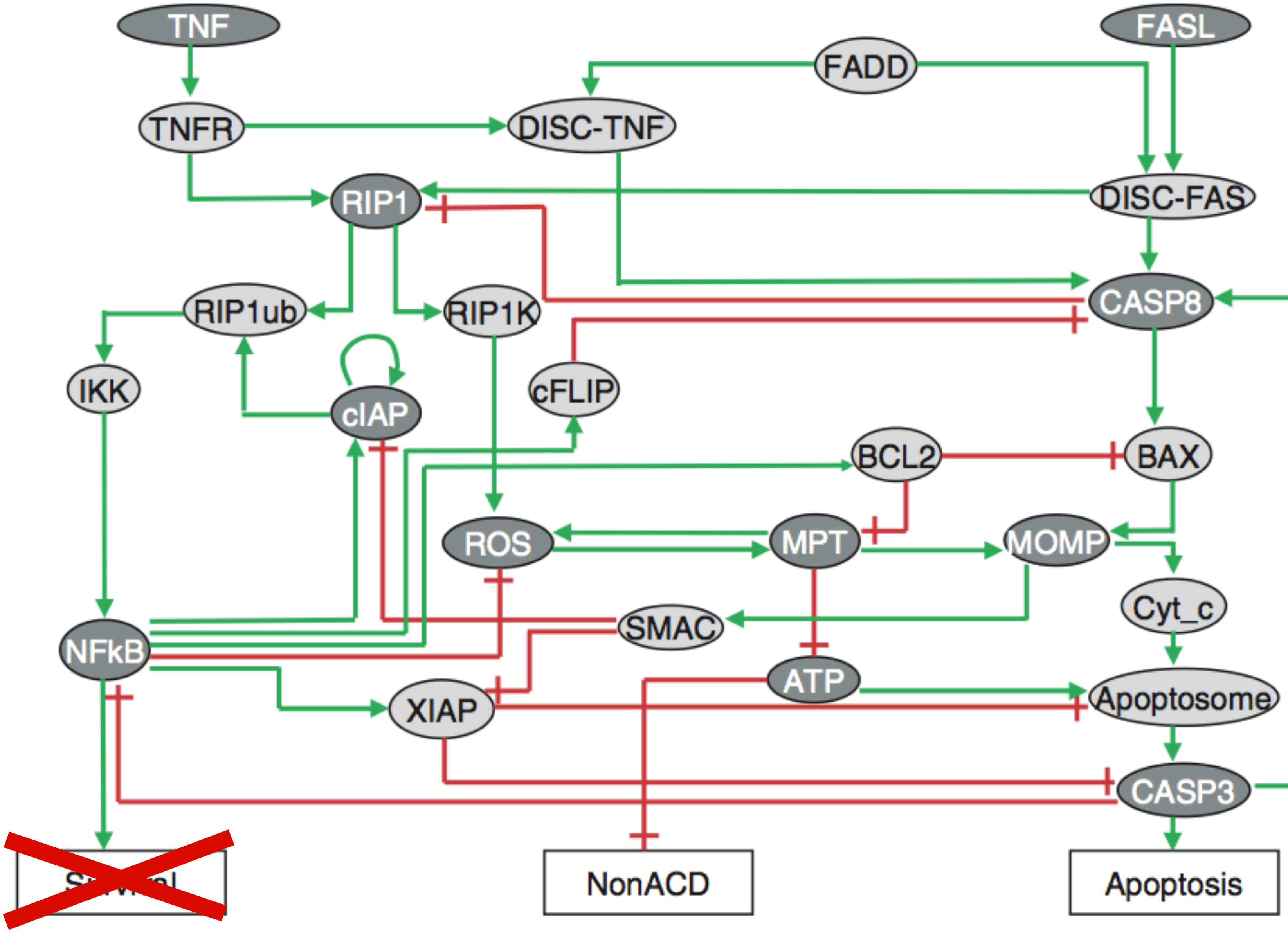
Final answer agrees with biological result

Note that the fixed point and saddle point have almost merged; the iteration has pushed the system close to a bifurcation

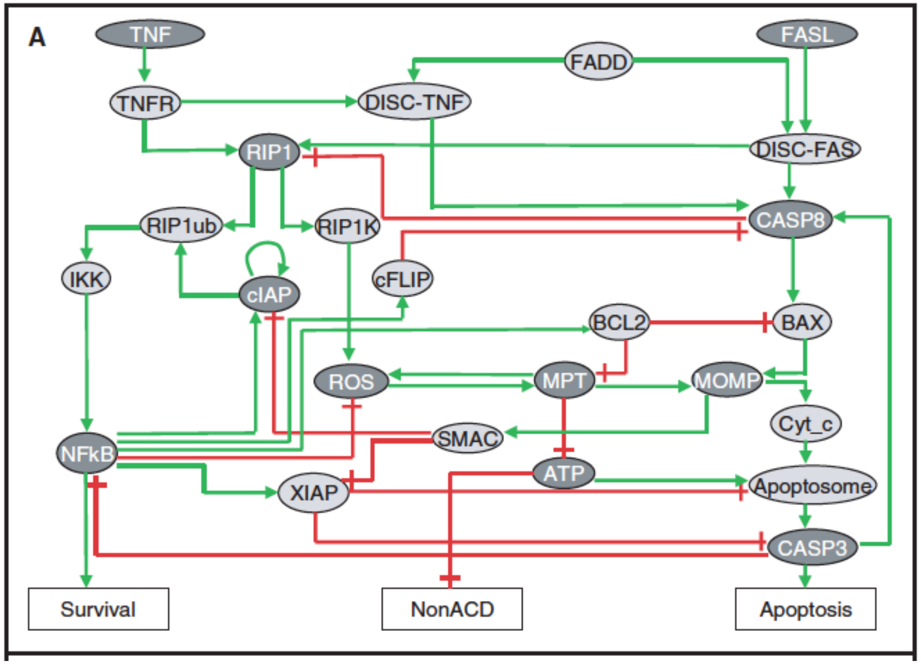


$$l_1 = 0.230 \; l_2 = 0.008$$

Another, bigger example: the cell death pathway



Details of the signaling model



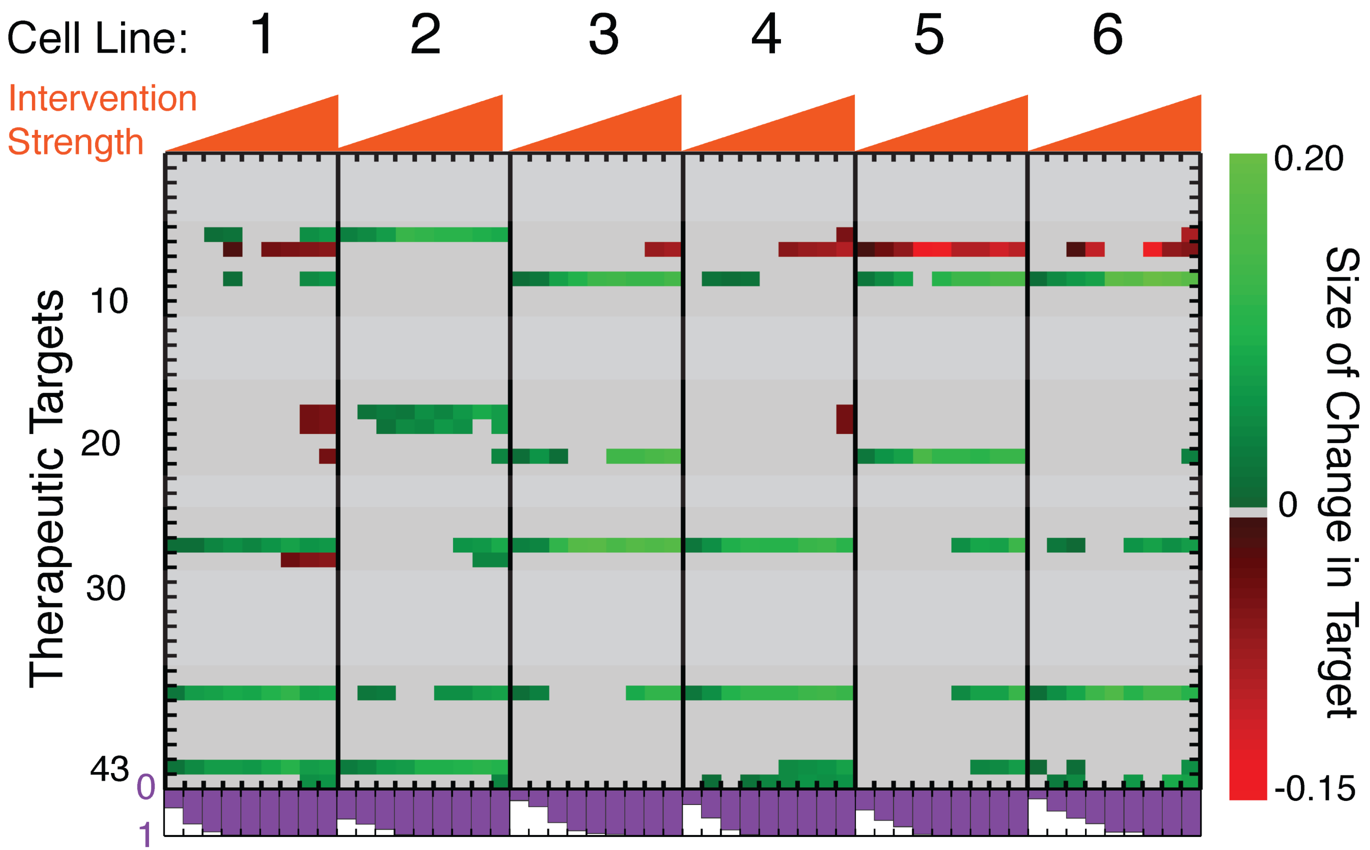
- 22 genes, 43 adjustable parameters (protein-protein interaction rate constants).
- Four stable states:
  - **Naïve**: apoptosis not induced; cell is healthy.
  - **Apoptotic**: Cell dies via apoptosis
  - **Necrotic**: Cell dies via necrosis.
  - **Proliferative**: Cell survives the apoptotic signal, is potentially proto-cancerous

Goal: Find the optimal intervention (combination of therapeutic targets) to maximize the rate of transition out of the proliferative state and into the apoptotic state.

- Intervention should be of a pre-specified dosage strength.
- Should preserve the stability of the healthy (naïve) cell state.

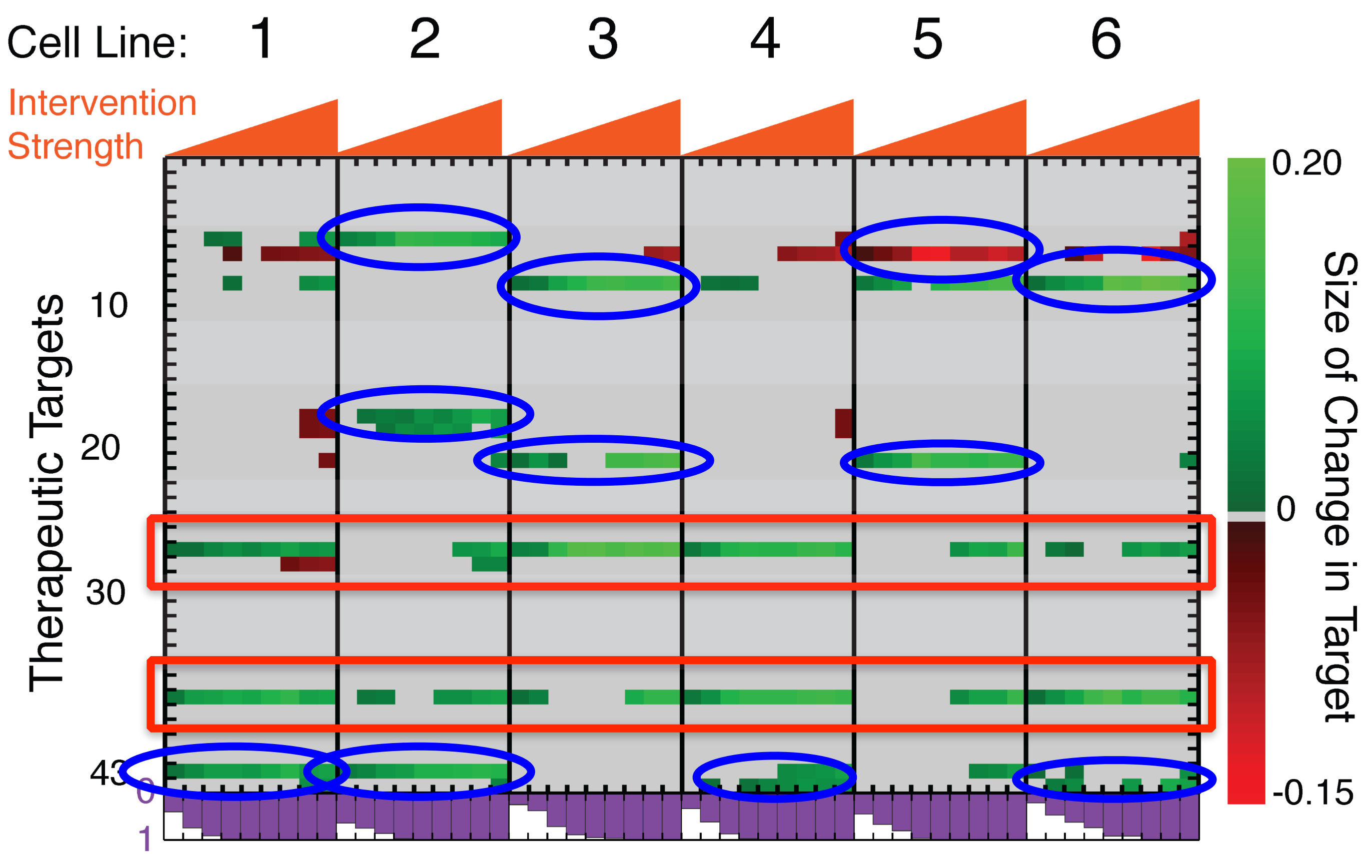
Calzone et. al. PLoS Computational Biology 2011

Method predicts optimal multiplexed therapeutic strategies



- 6 different proliferative cell lines, 9 possible dosage strengths
- Green: interaction rate decreased; Red: interaction rate increased
- Optimal therapeutic combinations comprised of 4-8 perturbations
- Eliminating proliferative state w/o significant harm to naïve state possible in all cases

Therapeutic combinations not unique, but have commonalities



Two therapeutic targets are robust for all cell lines.

- With larger dosage strengths, these four target alone can eliminate the proliferative state in all cases.

Individualized therapeutic combinations can be more efficient.

OLAC identifies 2 robust therapeutic targets in all cell lines, and others in individual cell lines

1. Decrease NFkB activation of cFLIP (5/6)

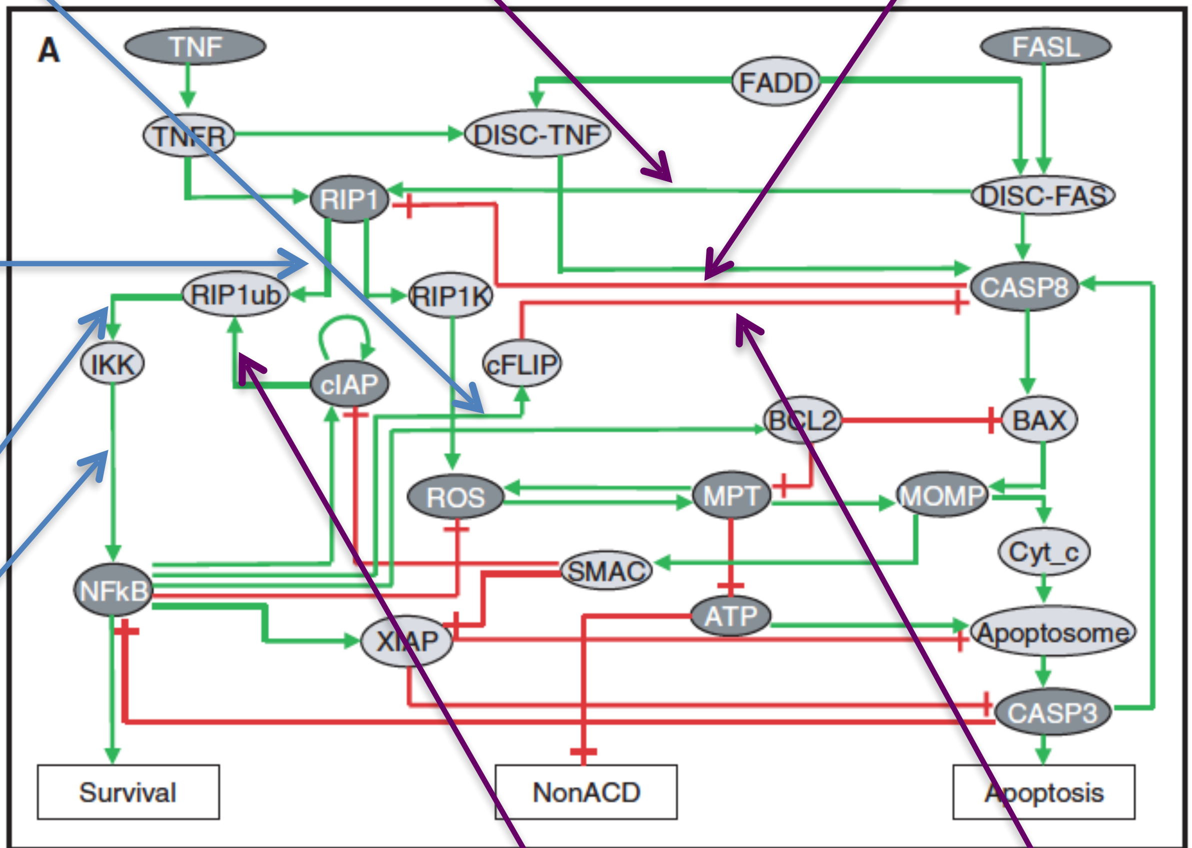
2. Decrease RIP1 activation of RIP1ub (5/6)

1. Decrease RIP1ub activation of IKK (6/6)

2. Decrease IKK activation of NFkB (6/6)

3. Decrease DISC-FAS activation of RIP1

4. Increase CASP8 inhibition of RIP1



5. Decrease cIAP activation of RIP1ub

6. Decrease cFlip inhibition of CASP8

Summary

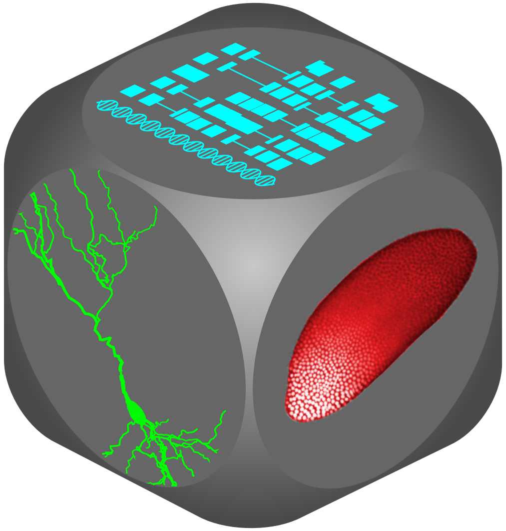
- Optimal least action control:
  manipulate the system landscape to promote an outcome
- Wentzell-Freidlin least action is a natural metric for this
- Find the minimum action path[s] between fixed points;
  reduce barrier heights associated with desired transitions
- Can push the system to a bifurcation
- Example: lineage respecification in a cell line
- Example: a signaling model of the cell death pathway;
  possible targets promoting apoptosis of proliferating cells

Positions in Applied Math at Northwestern

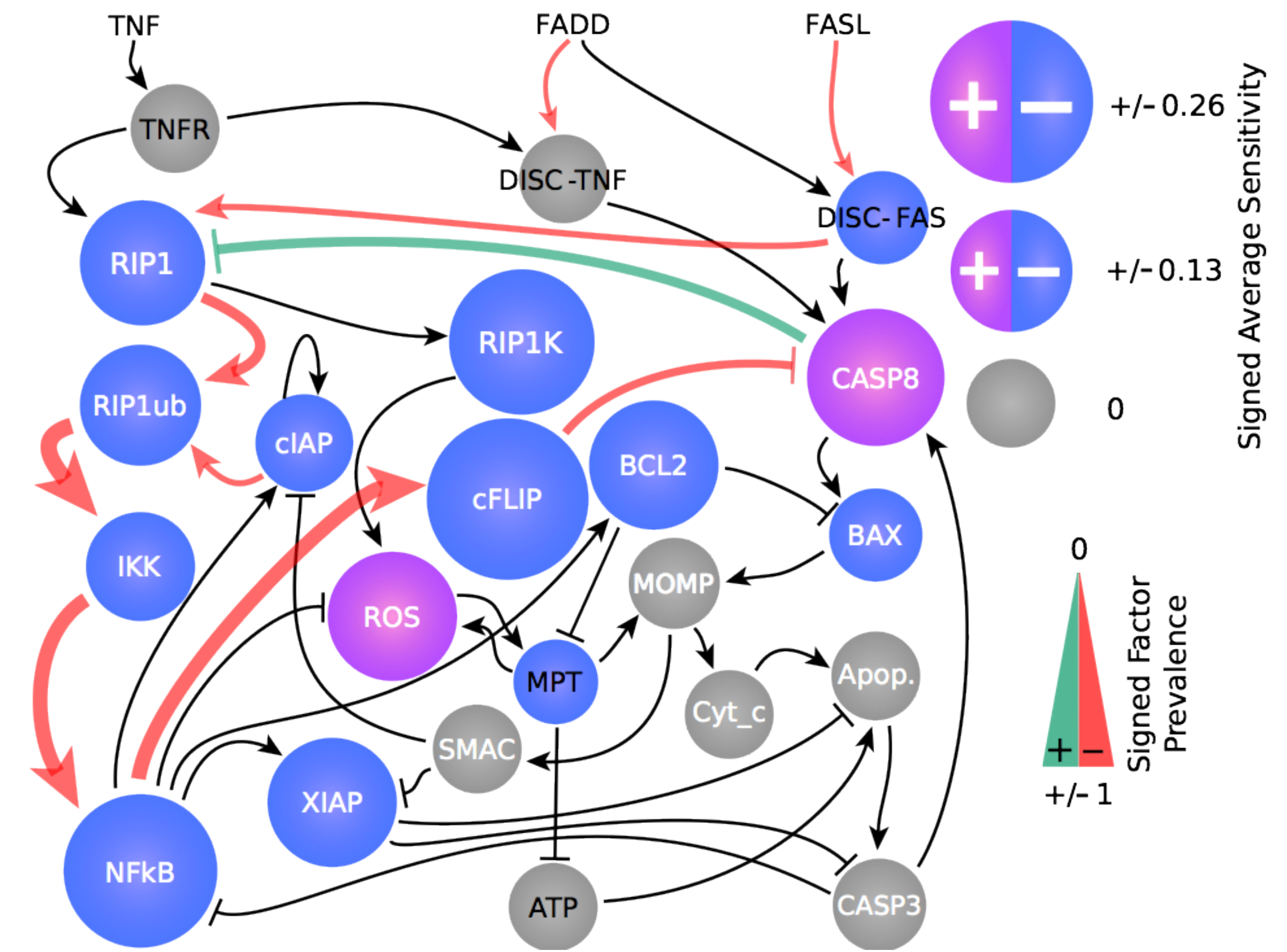
- Postdoctoral Fellows (U.S. Citizens) — part of a NSF-funded Research Training Grant in Quantitative Biological Modeling

NQuB

Northwestern University
Quantitative Biology
Research Training Program



- Tenure-track Faculty Positions — 2 anticipated for Fall 2017


TNF
FADD
FASL
TNFR
DISC-TNF
DISC-FAS
RIP1
RIP1ub
RIP1K
CASP8
cIAP
cFLIP
BCL2
BAX
IKK
ROS
MOMP
MPT
Cyt_c
Apop.
SMAC
XIAP
NFkB
ATP
CASP3
+/- 0.26
+/- 0.13
0
Signed Average Sensitivity
0
+ −
+/- 1
Signed Factor Prevalence

Indicators of progression to apoptosis