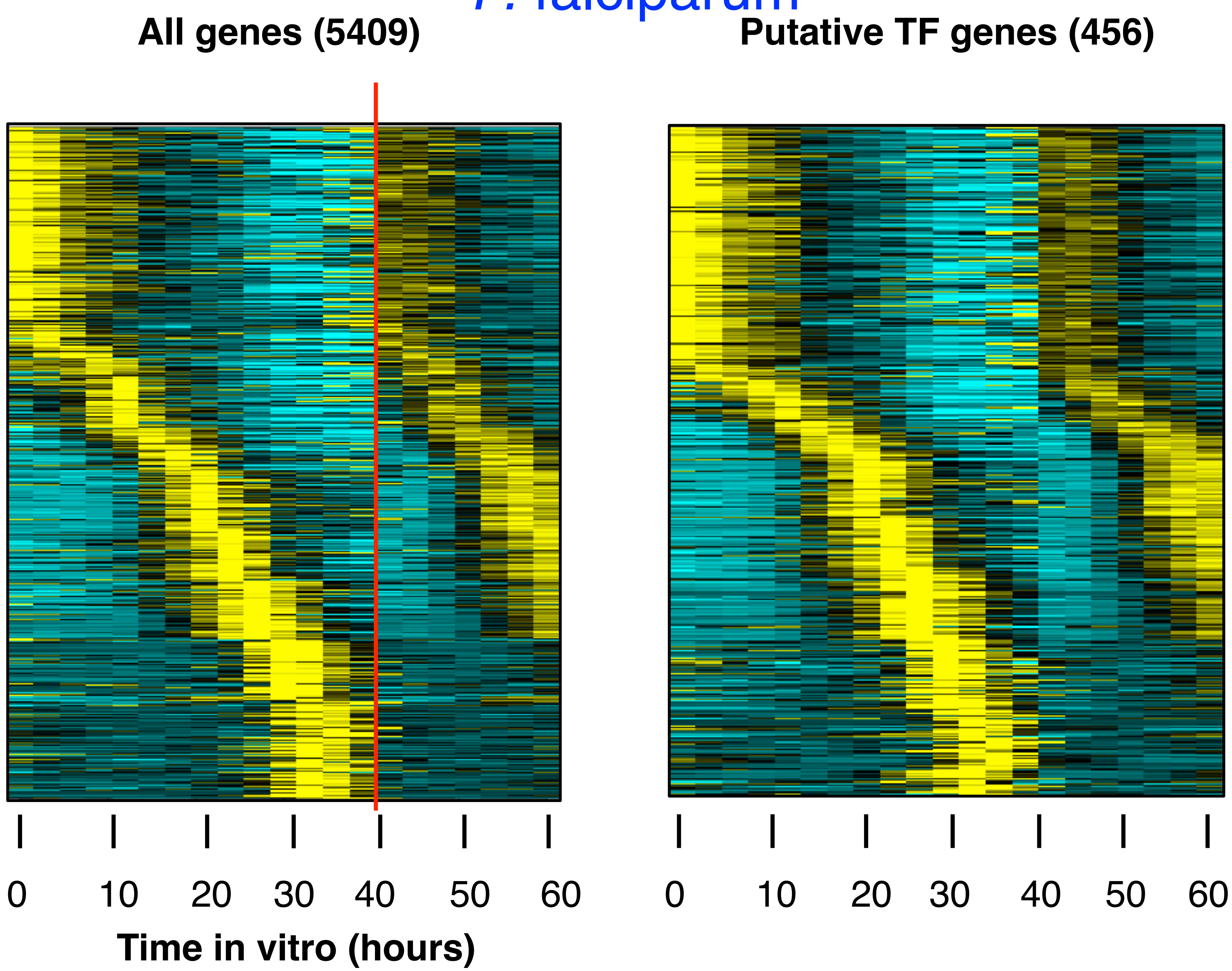
Dynamics of Gene Regulatory Networks with Unknown Parameters

T. Gedeon, B. Cummins,
Zane Huttinga
Montana State University

K. Mischaikow, S. Harker,
Rutgers University

Malaria

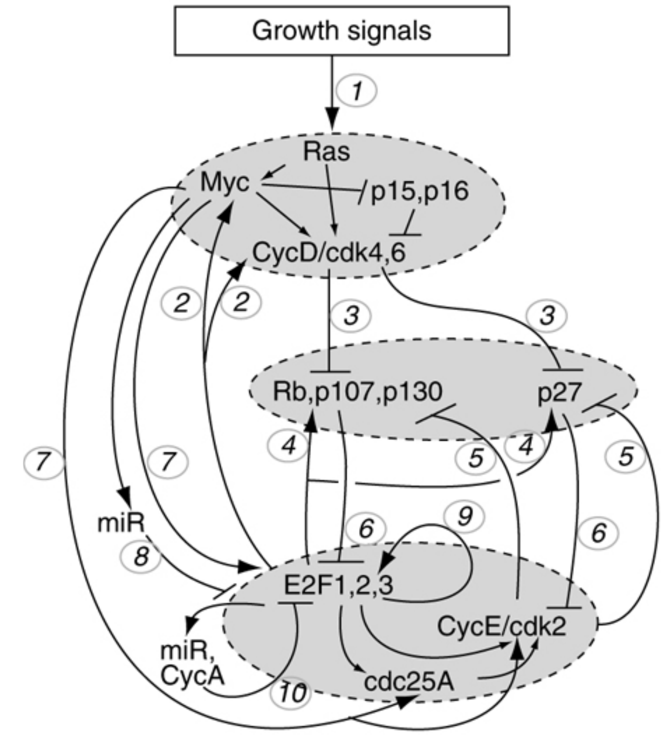
P. falciparum



Poorly annotated

Cancer

RB-E2F pathway



Poorly quantified

Dynamic processes; timing and sequencing of events is essential

What is an appropriate model for biological dynamics?

What is an appropriate model of biological dynamics?

Perhaps simplest models are ordinary differential equations

$$\frac{dx}{dt} = f(x, \lambda), \quad x \in R^n, \quad \lambda \in \Lambda$$

In order to use the model we need to "solve" the differential equation.

Challenges.

- Nonlinearity f is heuristic
- parameter space is high dimensional
- parameters are not known.

What does it mean to "solve" a differential equation in this context?

Solving differential equations

Newton: Find an analytic representation for $x(t) : R \to R^n$

Poincare,Smale,…: Qualitative theory, structural stability, bifurcation theory

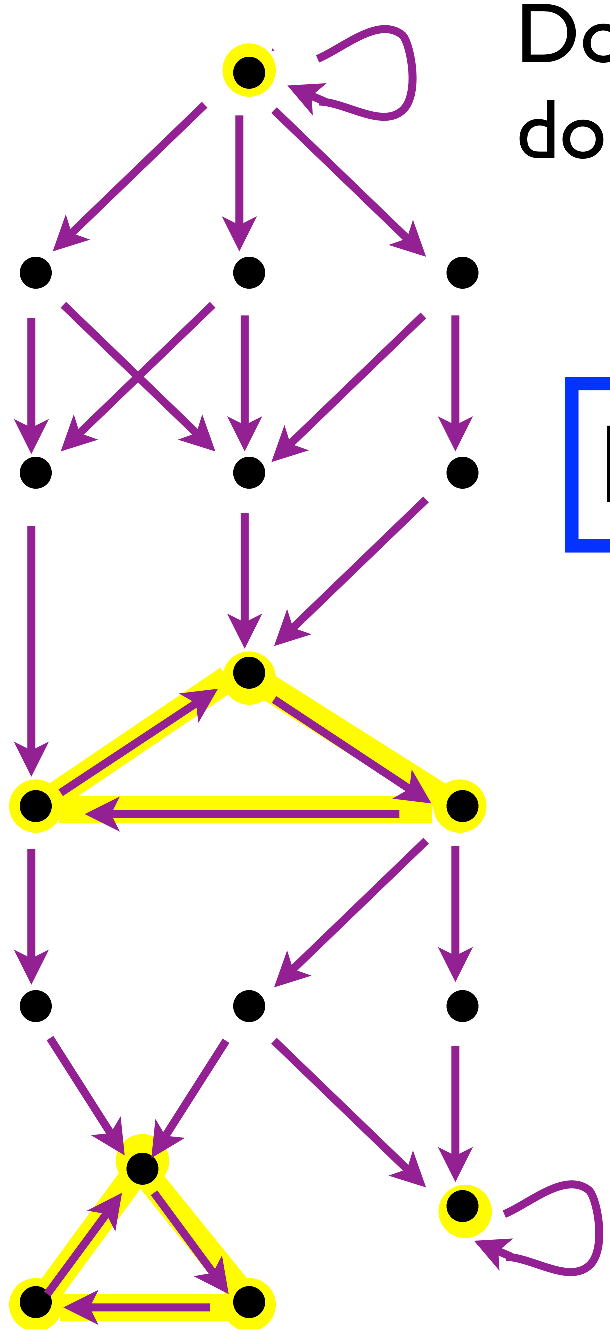
- Need analytical form of nonlinearity
- Limitation by dimension of phase space
- Limitation by dimension of the parameter space

“Solve” differential equations by describing

Lattice of attractors/Morse decompositions

How to build a Morse decomposition?

State Transition Graph



Vertices: States

Edges: Dynamics

Don’t know exact current state, so don’t know exact next state

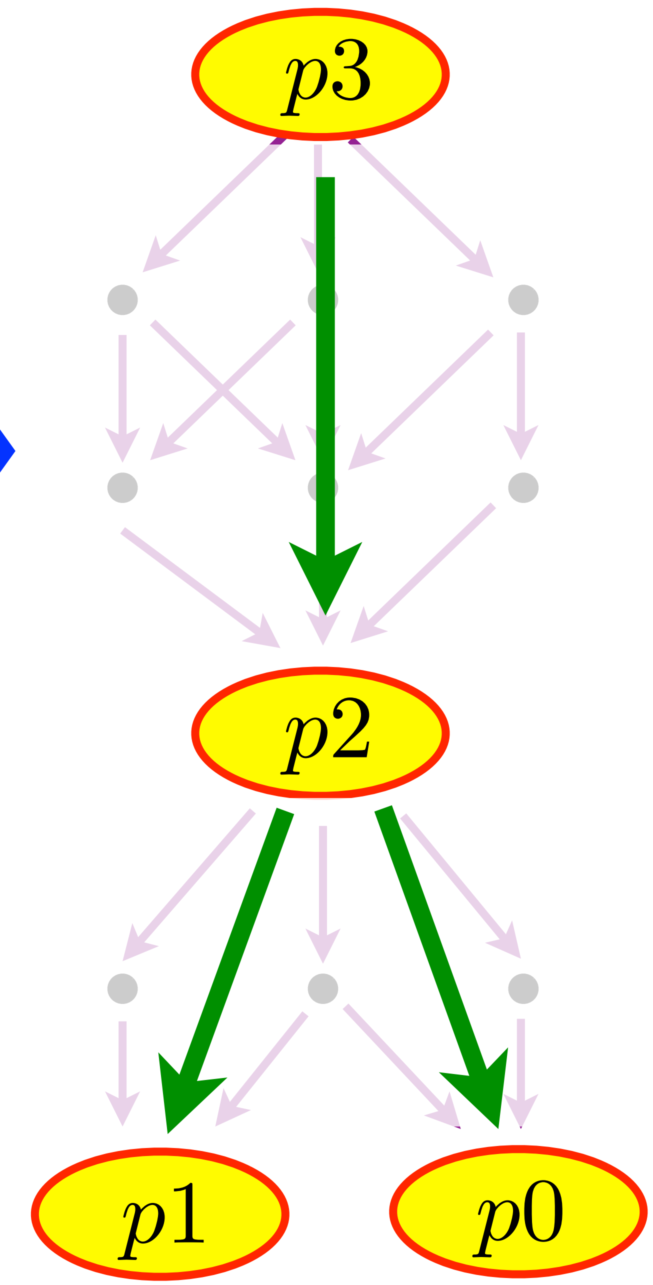
Linear time Algorithm!

Simple decomposition of Dynamics:

Recurrent

Strongly connected path components

Nonrecurrent (gradient-like)

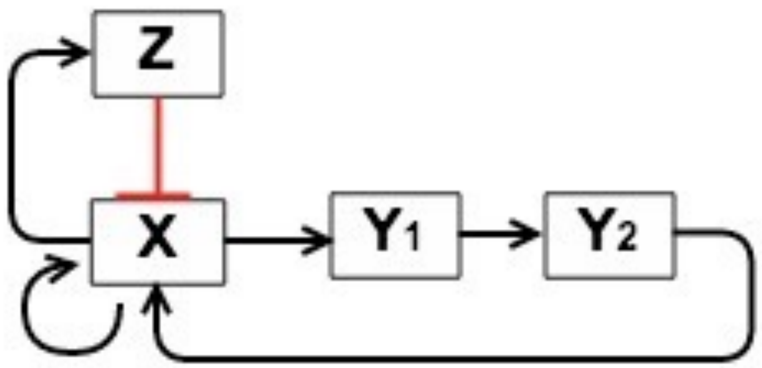


Morse Graph of state transition graph

How to define a State Transition Graph?

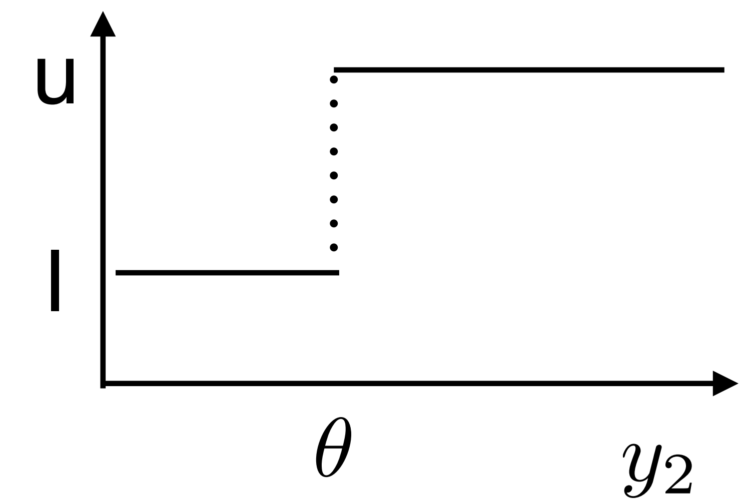
Switching systems

(Glass, Snoussi, Thomas, Edwards, Plahte, Mestl, Chaves, Gouze,…)



Every interaction mediated by a piece-wise constant function

$\sigma_{y_2 \to x}(y_2)$



Switching model

$$\dot{x} = -x + \Lambda_1(\sigma_{x\to x}, \sigma_{y_2 \to x}, \sigma_{z \to x})$$

$$\dot{y}_1 = -y_1 + \Lambda_2(\sigma_{x \to y_1})$$

$$\dot{y}_2 = -y_2 + \Lambda_3(\sigma_{y_1 \to y_2})$$

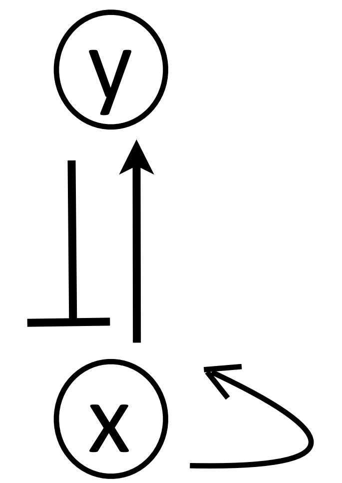
$$\dot{z} = -z + \Lambda_4(\sigma_{x \to z})$$

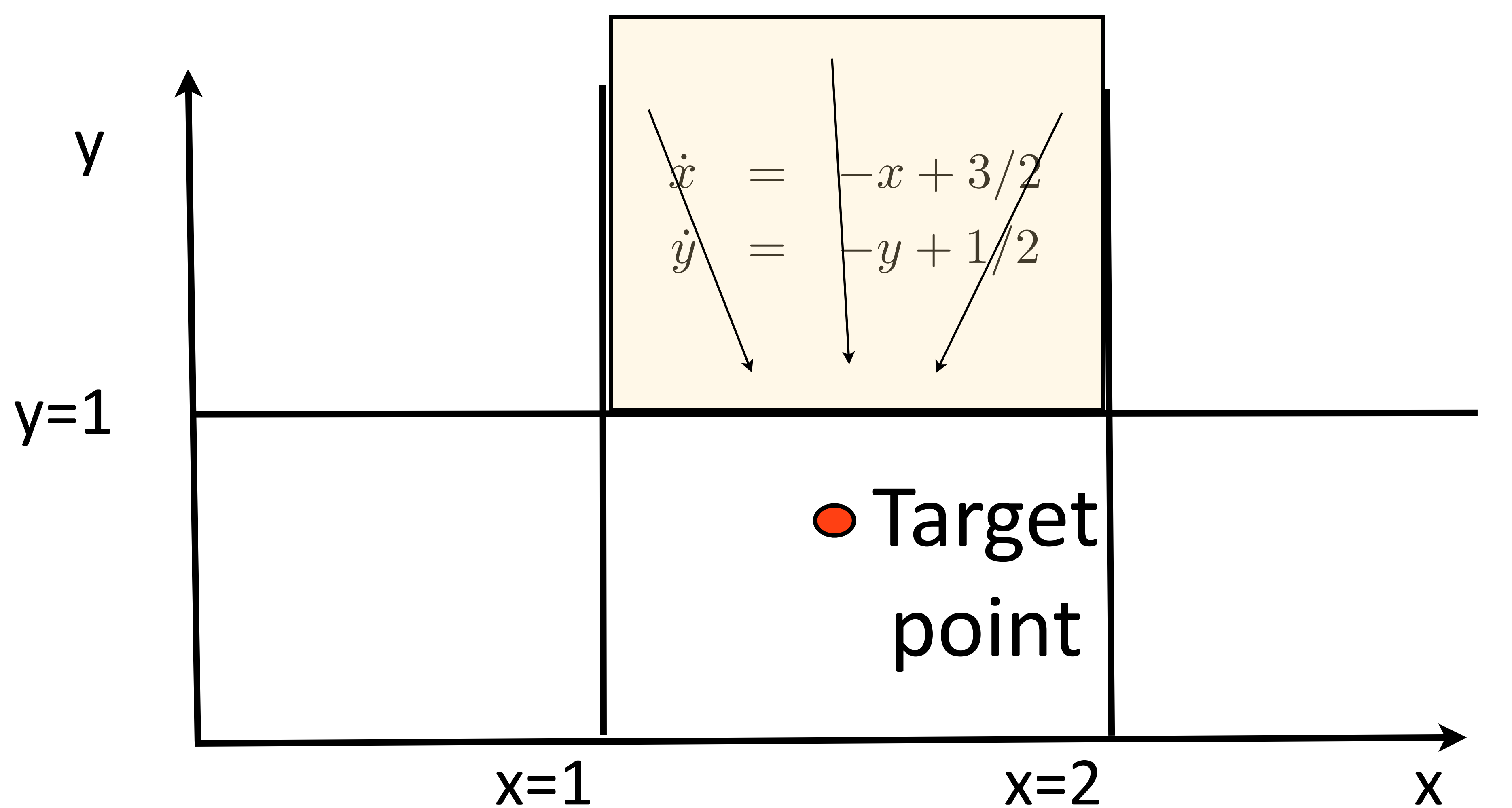
Logic of interaction is embedded in

$$\Lambda_1 = \Lambda_1(X, Y_2, Z) = (X + Y_2)Z$$

Phase space

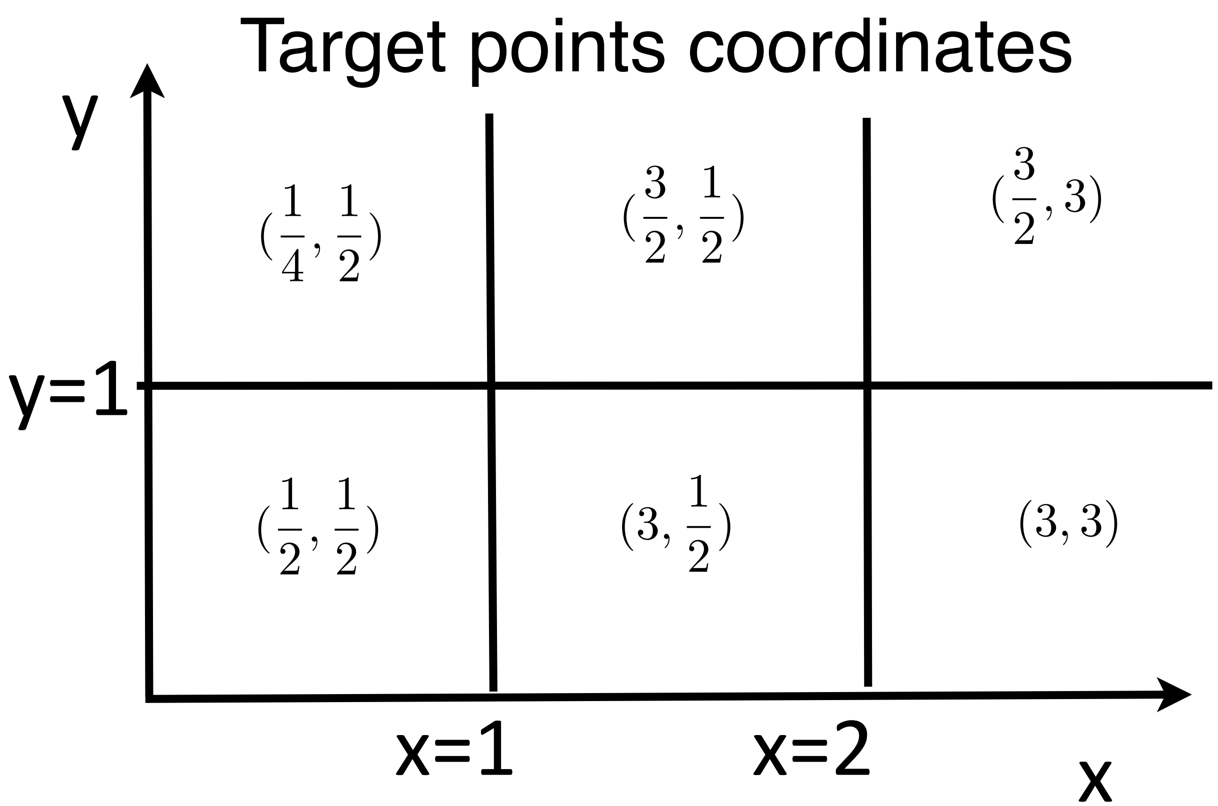
$$
\begin{aligned}
\dot{x} &= -x + \left(\begin{cases} 3 & x > 1 \\ 1/2 & x < 1 \end{cases} \right) \begin{cases} 1/2 & y > 1 \\ 1 & y < 1 \end{cases} \\
\dot{y} &= -y + \begin{cases} 3 & x > 2 \\ 1/2 & x < 2 \end{cases}
\end{aligned}
$$

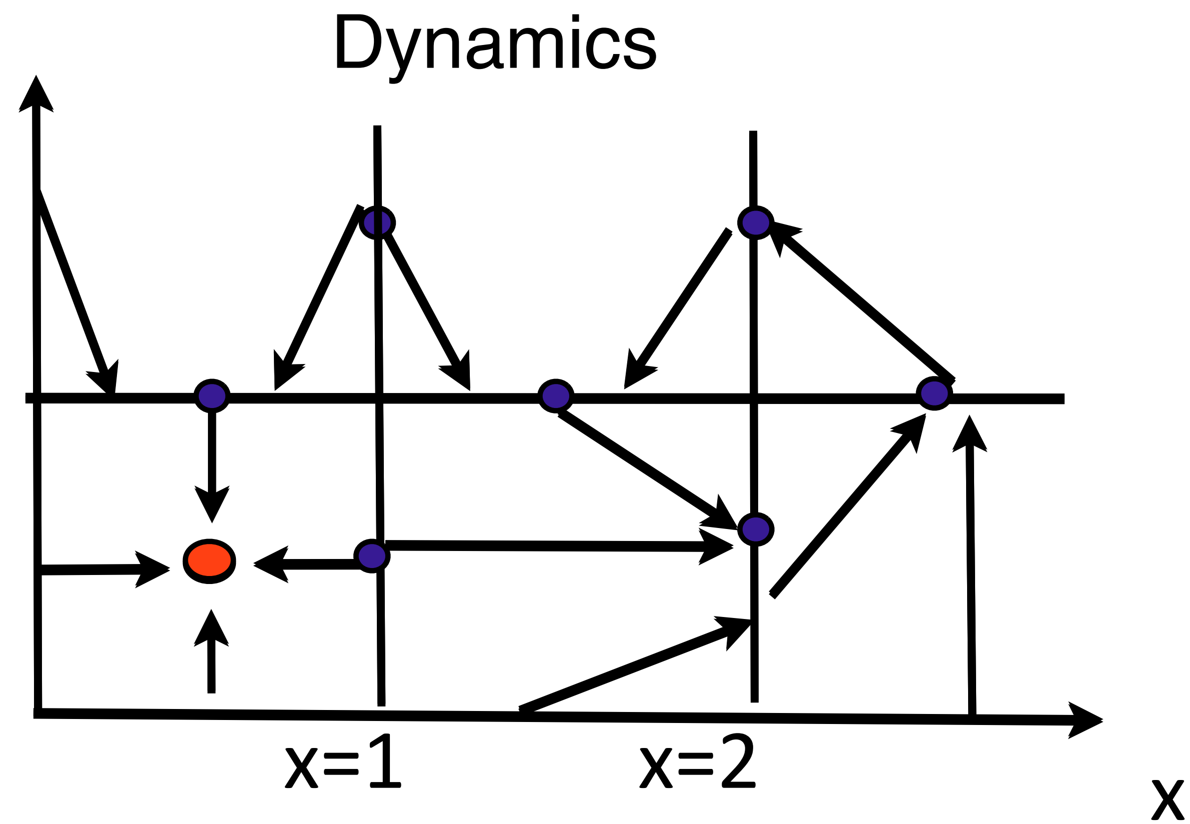




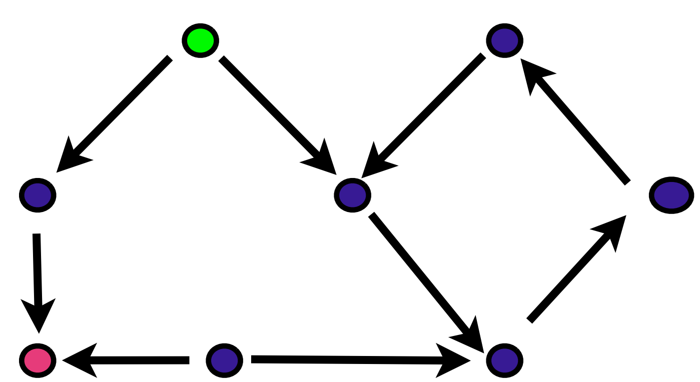
$$\dot{x} = -x + \left(\begin{cases} 3 & x > 1 \\ 1/2 & x < 1 \end{cases} \right) \begin{cases} 1/2 & y > 1 \\ 1 & y < 1 \end{cases}$$

$$\dot{y} = -y + \begin{cases} 3 & x > 2 \\ 1/2 & x < 2 \end{cases}$$

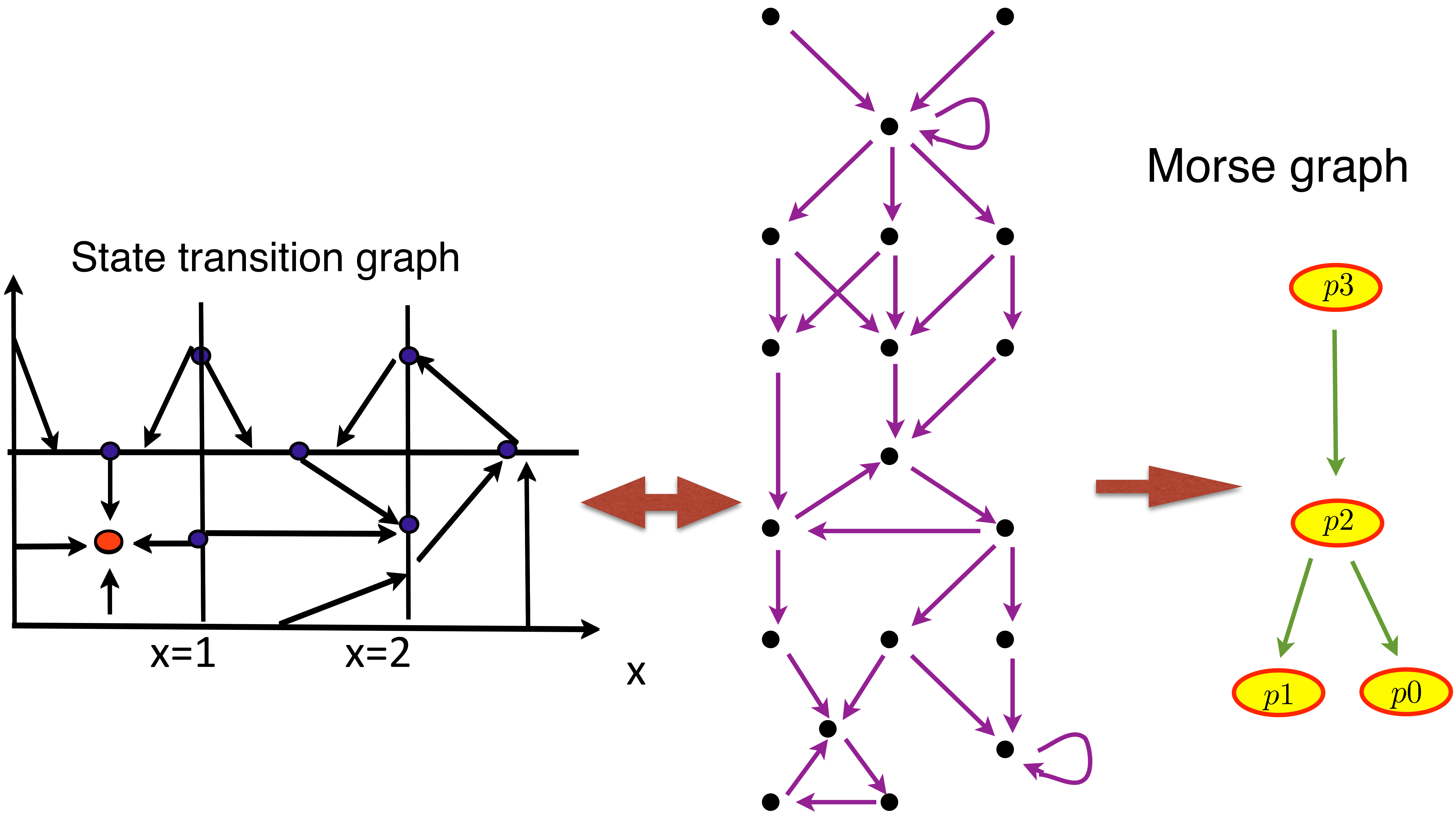




State transition graph



Switching systems give rules to construct state transition graph



Vertices: States

Edges: Dynamics

Parameter space (Combinatorial bifurcation theory)

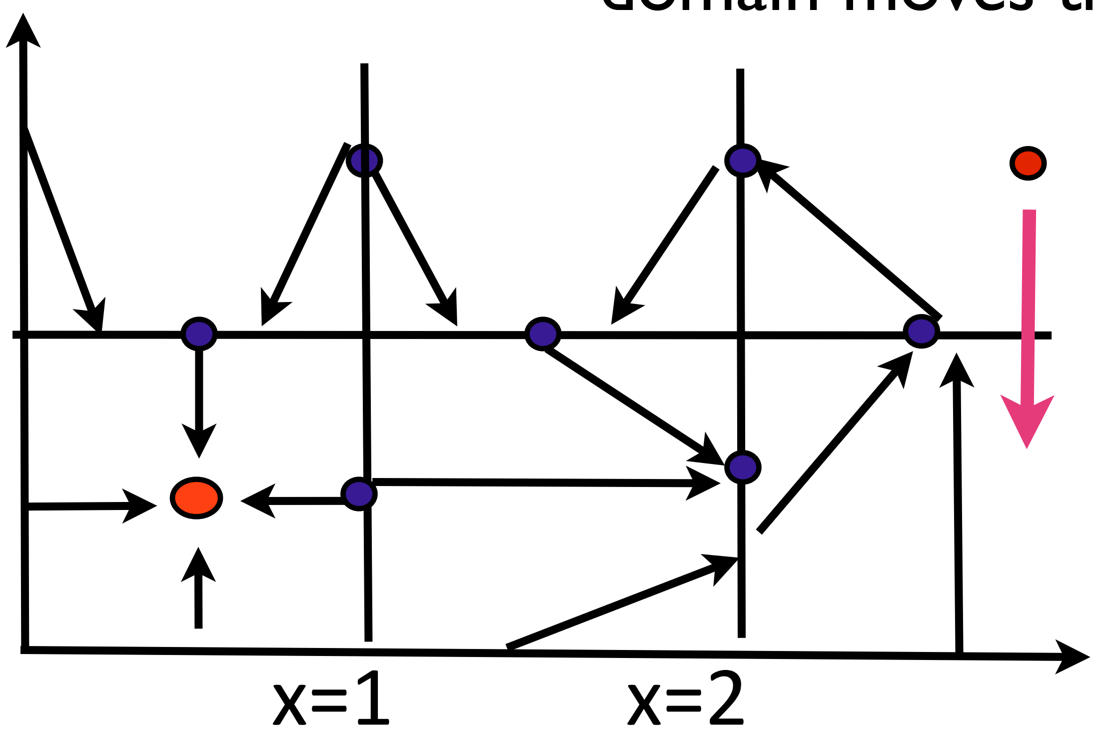
$$
\begin{aligned}
\dot{x} &= -x + \left(\begin{cases} 3 & x > 1 \\ 1/2 & x < 1 \end{cases}\right) \begin{cases} 1/2 & y > 1 \\ 1 & y < 1 \end{cases} \\
\dot{y} &= -y + \begin{cases} 3 & x > 2 \\ 1/2 & x < 2 \end{cases}
\end{aligned}
$$

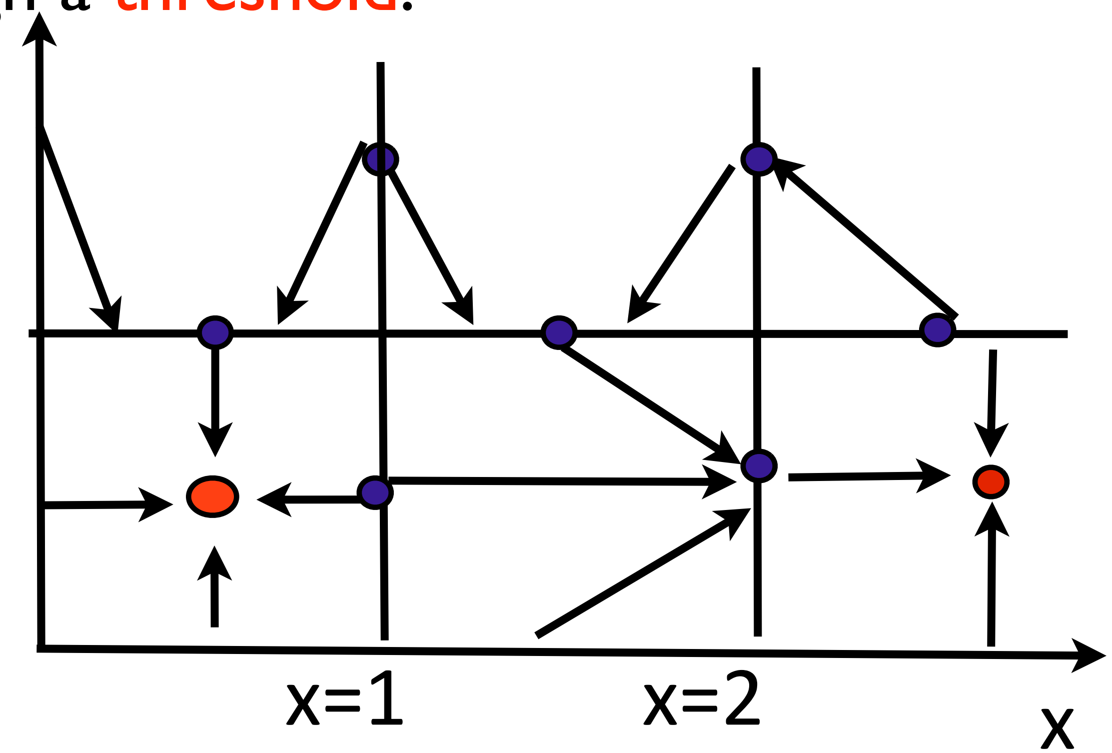
Study general system where parameters describe expression levels, and thresholds

$$
\begin{aligned}
\dot{x} &= -x + \left(\begin{cases} b_1 & x > 1 \\ a_1 & x < 1 \end{cases}\right) \begin{cases} a_2 & y > 1 \\ b_2 & y < 1 \end{cases} \\
\dot{y} &= -y + \begin{cases} b_3 & x > 2 \\ a_3 & x < 2 \end{cases}
\end{aligned}
$$

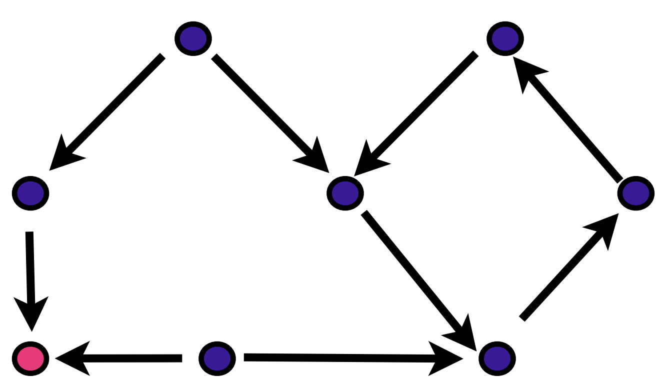
Combinatorial bifurcation theory

State transition diagram changes only when a target point of a domain moves through a threshold:

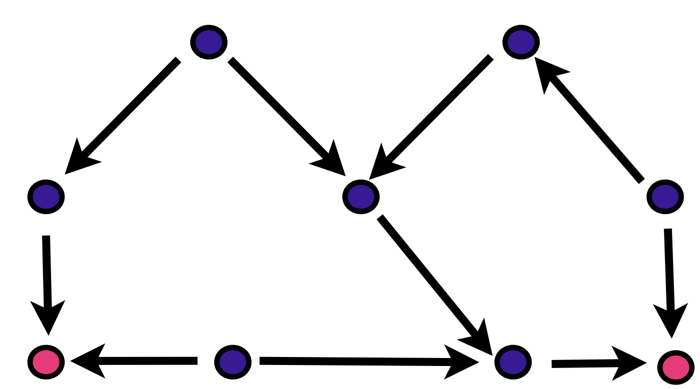




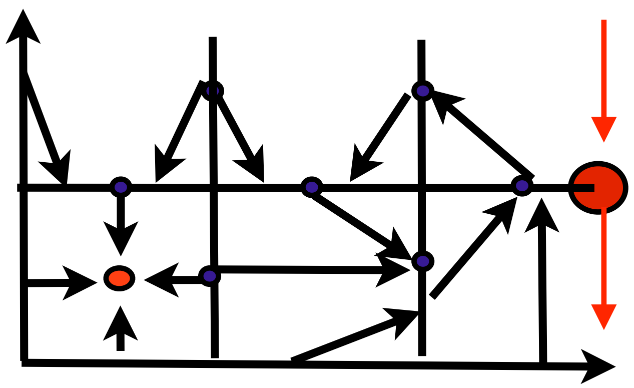
State transition graph



State transition graph

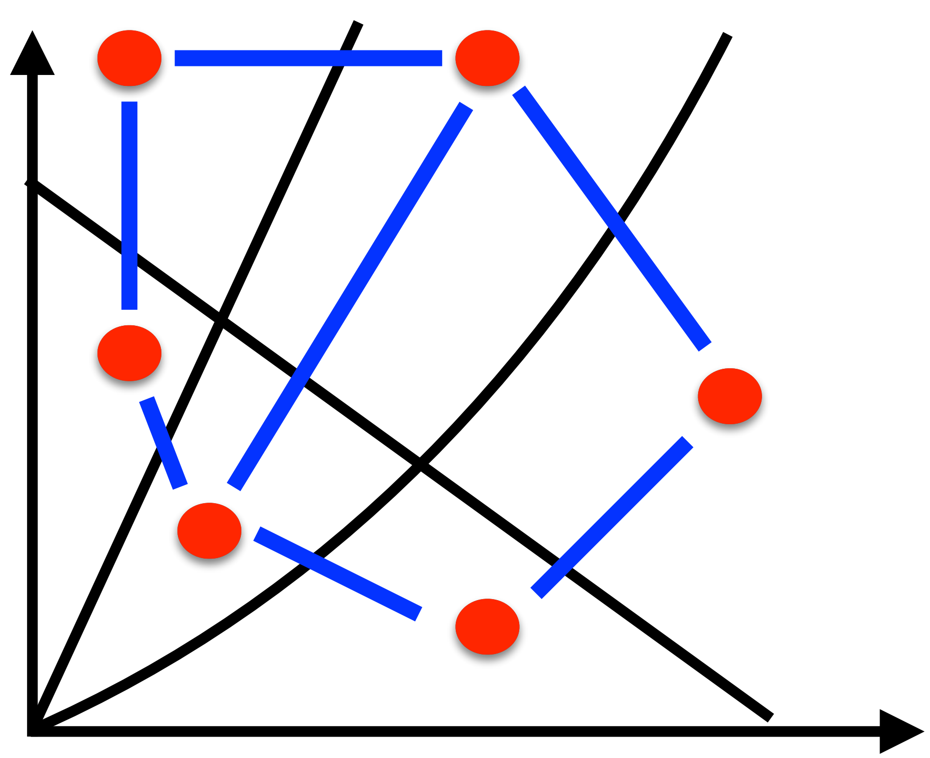


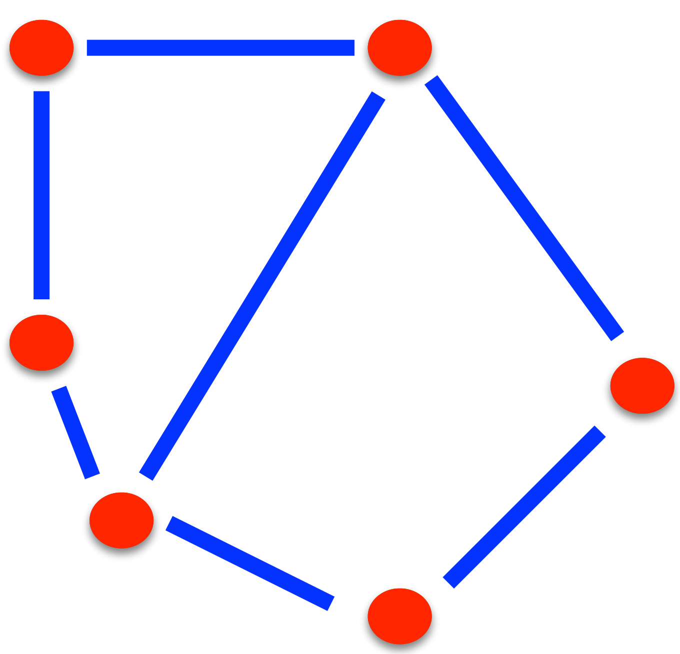
Geometry of the parameter space



Changes in STG when : $\{(\text{Target point})_i = \theta_j\}_{i,j}$

In each region bounded by these hyper surfaces
the Morse graph is the same.

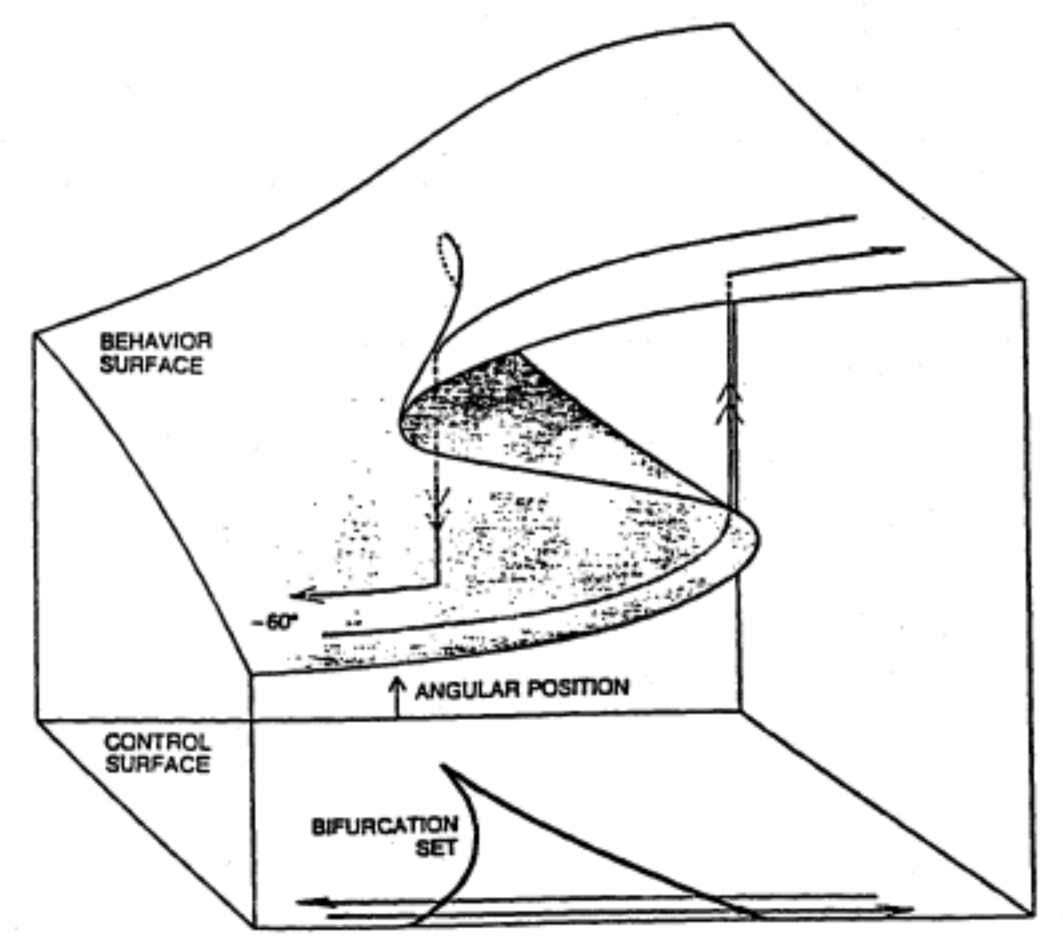




Geometric parameter graph

Combinatorial description of multi parameter dynamical system (computable!)

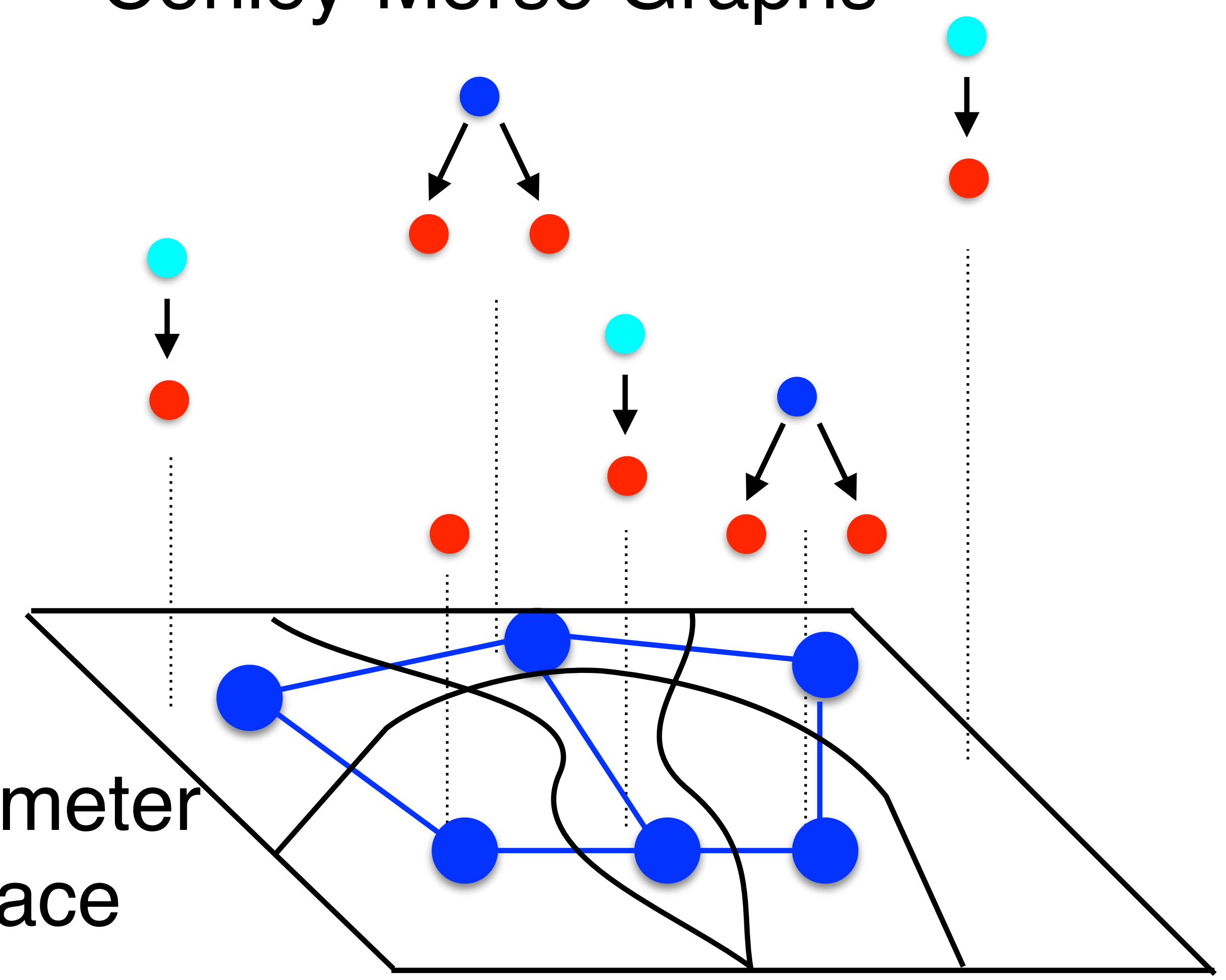
Description in classical dynamics



Cusp Catastrophe

DSGRN database

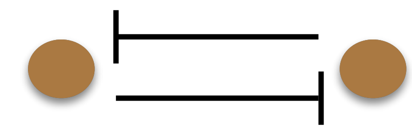
Conley-Morse Graphs



Parameter space

Parameter Graph

A simple example- a toggle switch



(Gardner, Cantor, Collins; Nature 2000)

$$\dot{x}_1 = -\gamma_1 x_1 + \begin{cases} u_{12} & x_2 < \theta_{12} \\ l_{12} & x_2 > \theta_{12} \end{cases}$$

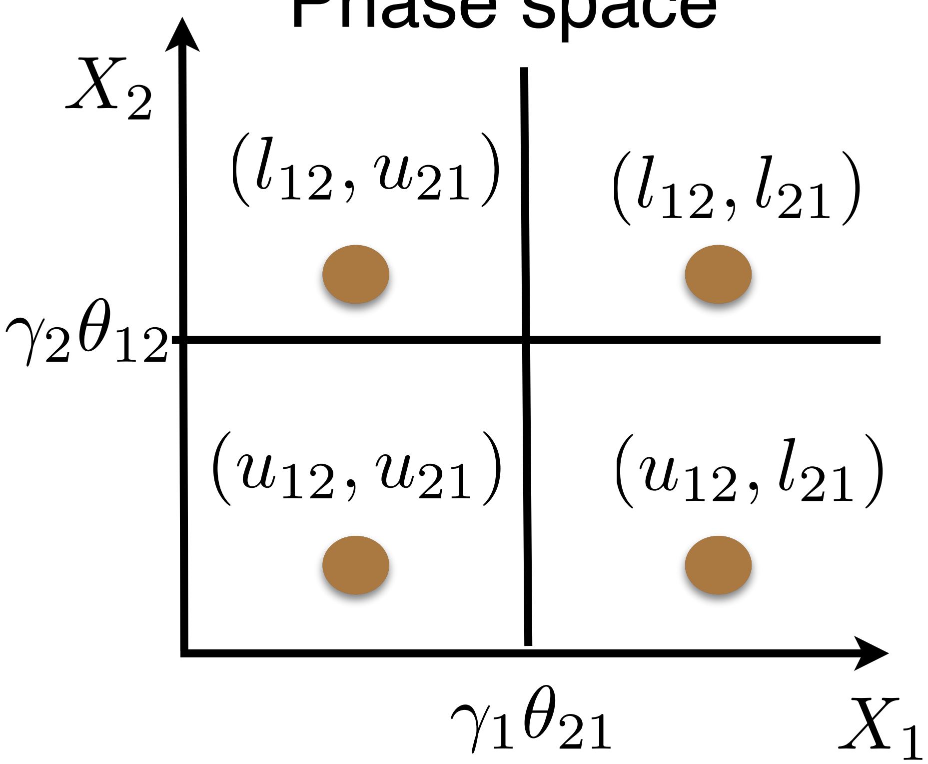
$$\dot{x}_2 = -\gamma_2 x_2 + \begin{cases} u_{21} & x_1 < \theta_{21} \\ l_{21} & x_1 > \theta_{21} \end{cases}$$

$$\dot{X}_1 = -X_1 + \begin{cases} u_{12} & X_2 < \gamma_2\theta_{12} \\ l_{12} & X_2 > \gamma_2\theta_{12} \end{cases}$$

$$\dot{X}_2 = -X_2 + \begin{cases} u_{21} & X_1 < \gamma_1\theta_{21} \\ l_{21} & X_1 > \gamma_1\theta_{21} \end{cases}$$

$$X_1 := \gamma_1 x_1, X_2 := \gamma_2 x_2$$

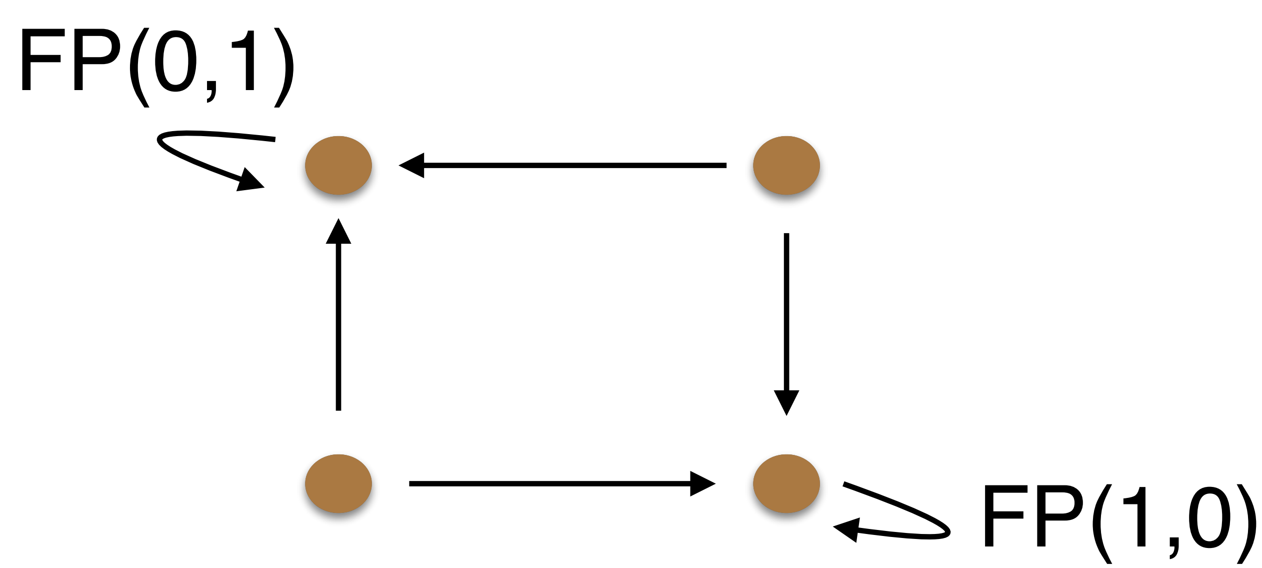
Phase space



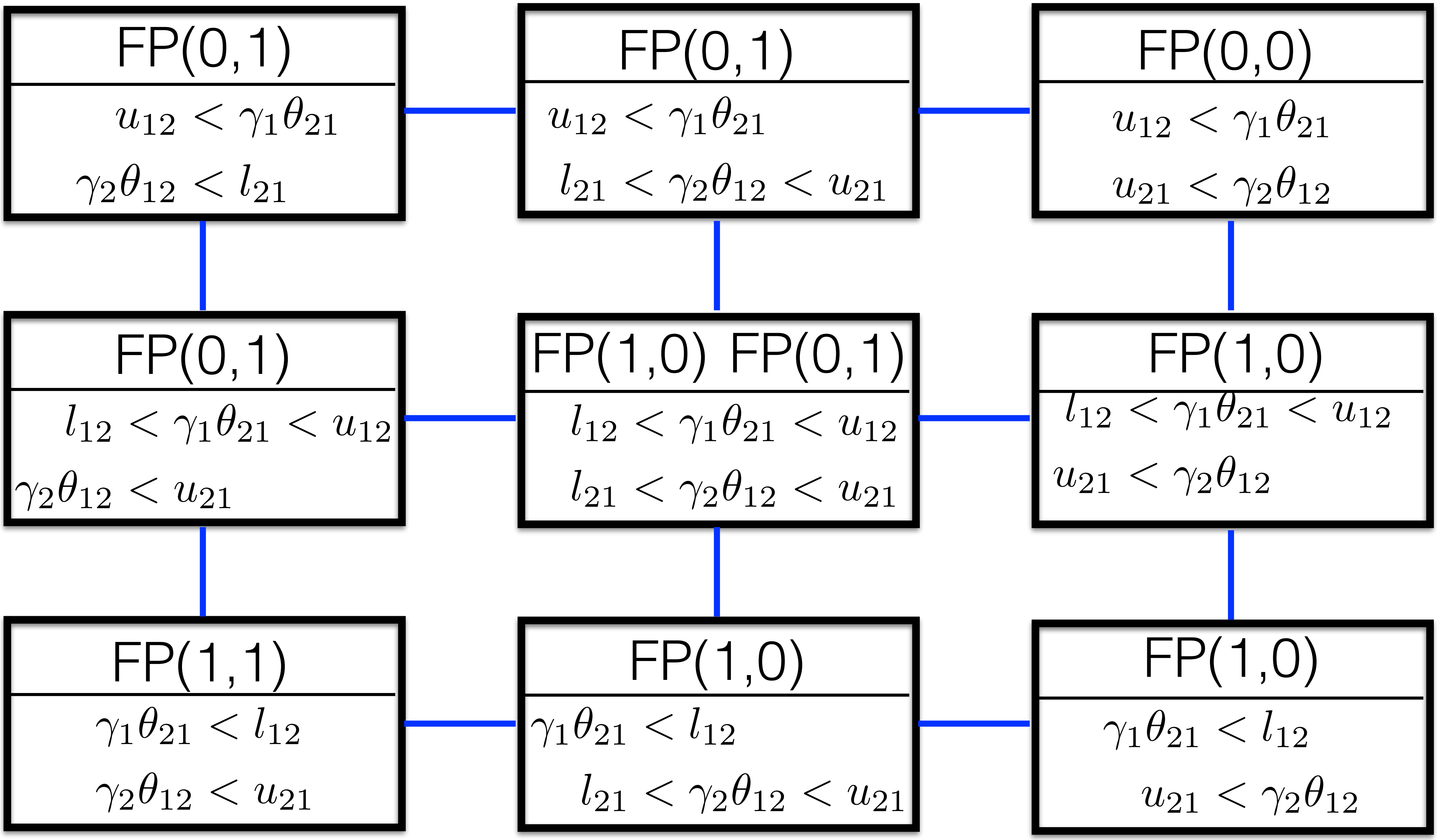
Parameter selection (node in the parameter graph)

$$l_{12} < \gamma_1\theta_{21} < u_{12}$$

$$l_{21} < \gamma_2\theta_{12} < u_{21}$$



DSGRN database for toggle switch



Application to cell cycle progression switch

For larger networks visual inspection of the parameter graph is not possible

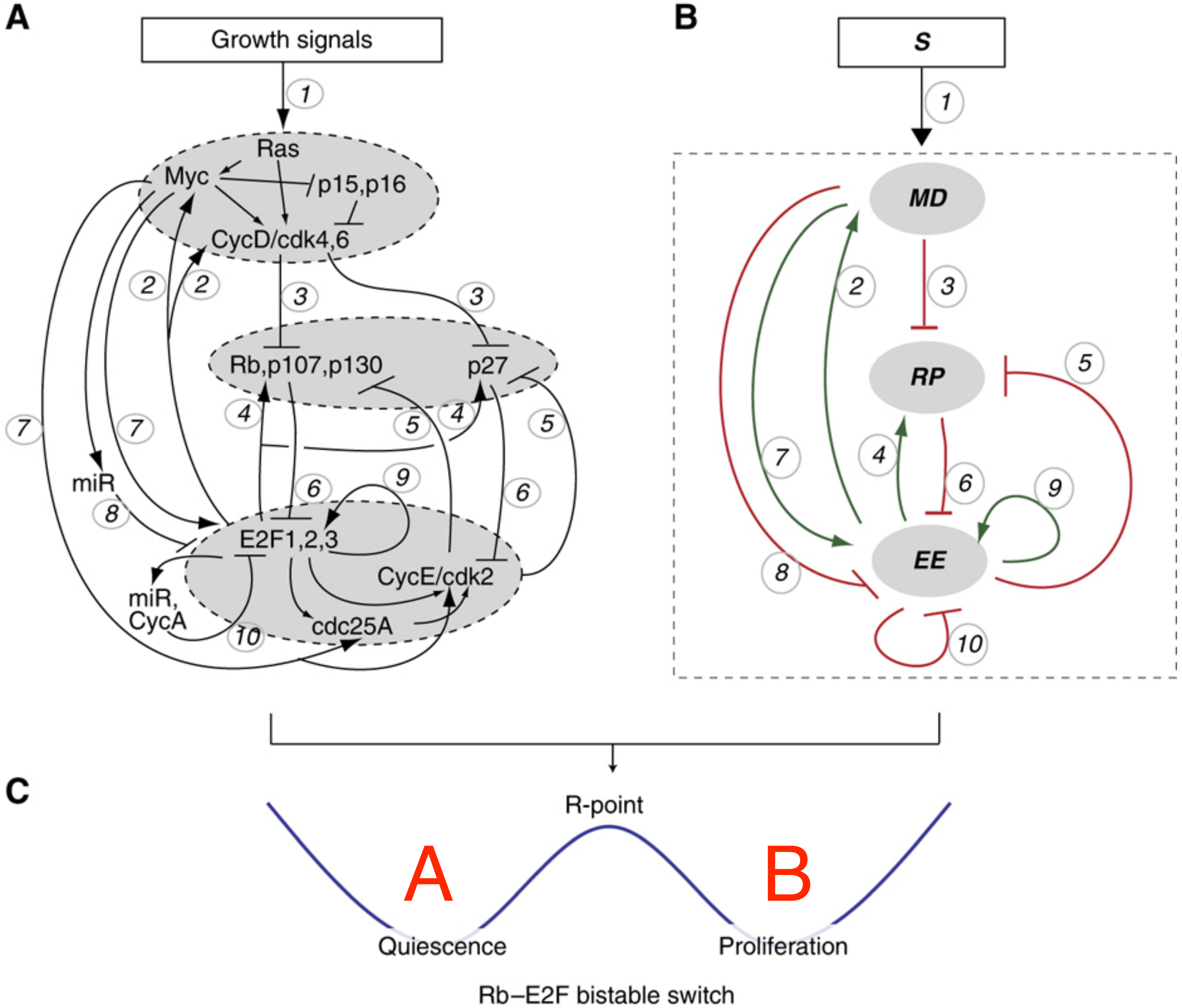
Use summary descriptions:

- percentage of the parameter graph that admits certain dynamics
- percentage of the reduced parameter graph that admits certain sequence of dynamic behaviors as input changes

Evaluate multiple networks - search in the space of networks

Cancer

Yao, et. al., Origin of bistability underlying mammalian cell cycle entry, MSB, 2011



Deregulation of the RB–E2F pathway is implicated in most, if not all, human cancers.

Goal: minimal network that exhibits *resettable bistability*

Bistability:
Two equilibria:
(A) Rb ON, E2F OFF = quiescence
(B) Rb OFF, E2F ON = proliferation

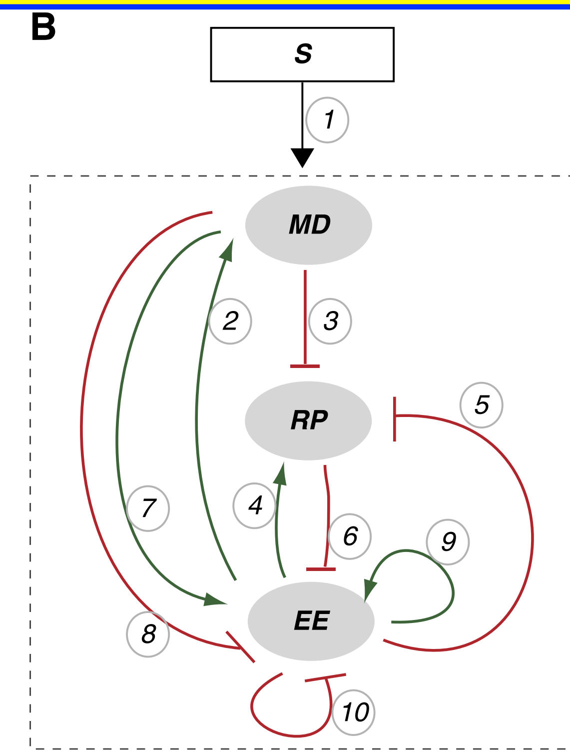
MD

Resettable bistability:
MD: ON -> OFF
System moves from B to A

Yao et. al. tested 3-node networks on 20,000 random parameter choices for bistability, and resettable bistability to find minimal network(s).

Test networks for dynamics phenotype

Yao, et. al., Origin of bistability underlying mammalian cell cycle entry, MSB, 2011



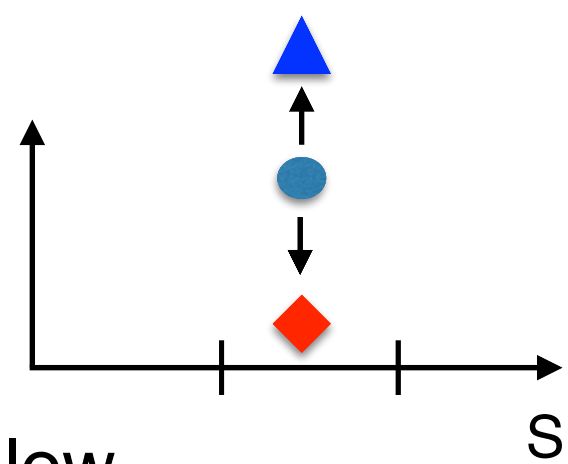
Construct all subnetworks with 4 nodes that:

- Has input node S
- only one edge between two nodes

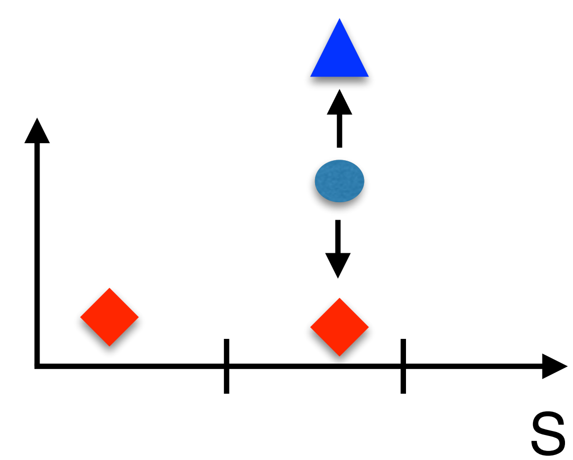
(49 networks satisfy this requirement)

Evaluate each network on prevalence in its parameter graph of:

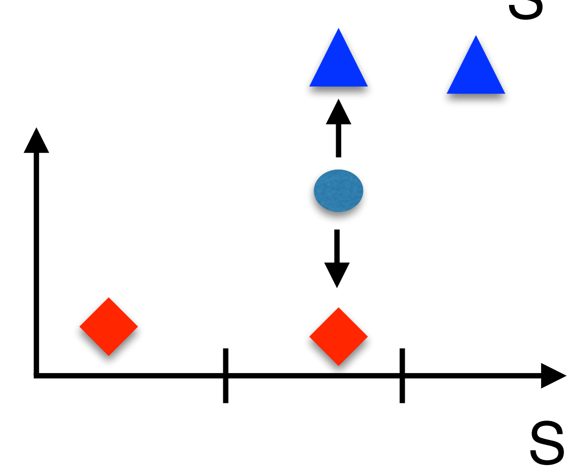
1. bistability with S in the middle of its range.



2. bistability AND Off FP when S is low = resettable bistability



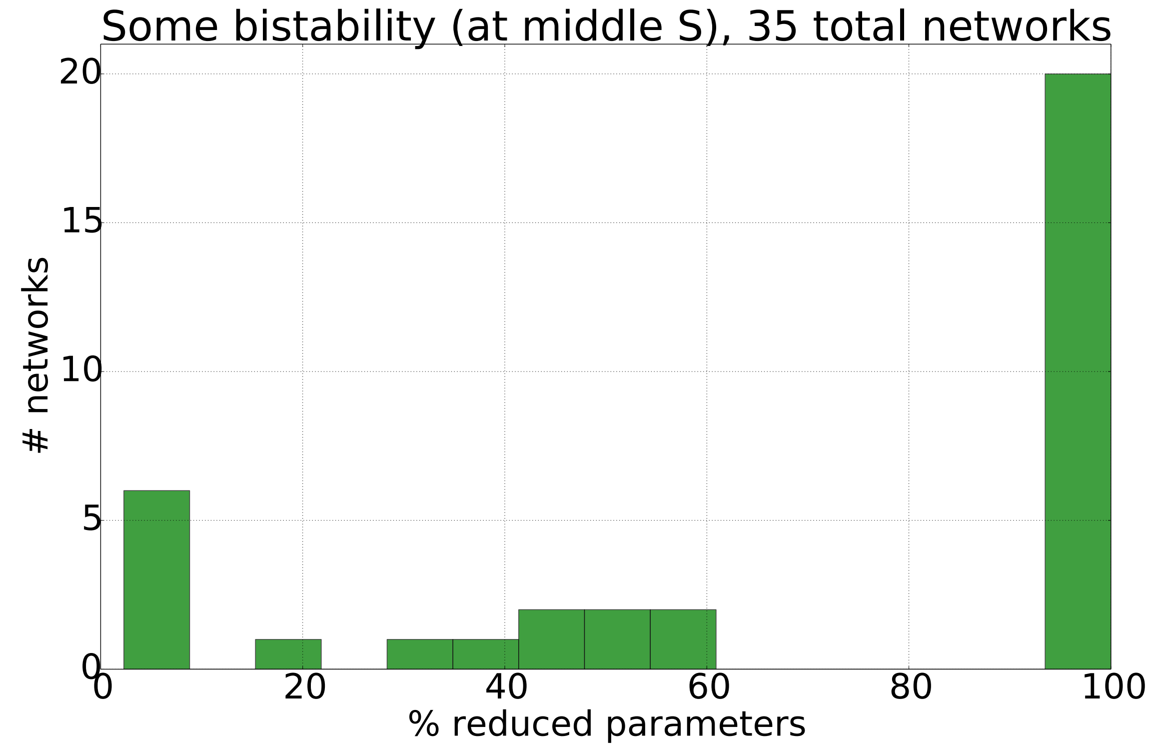
3. resettable bistability AND On FP when S is high = hysteresis



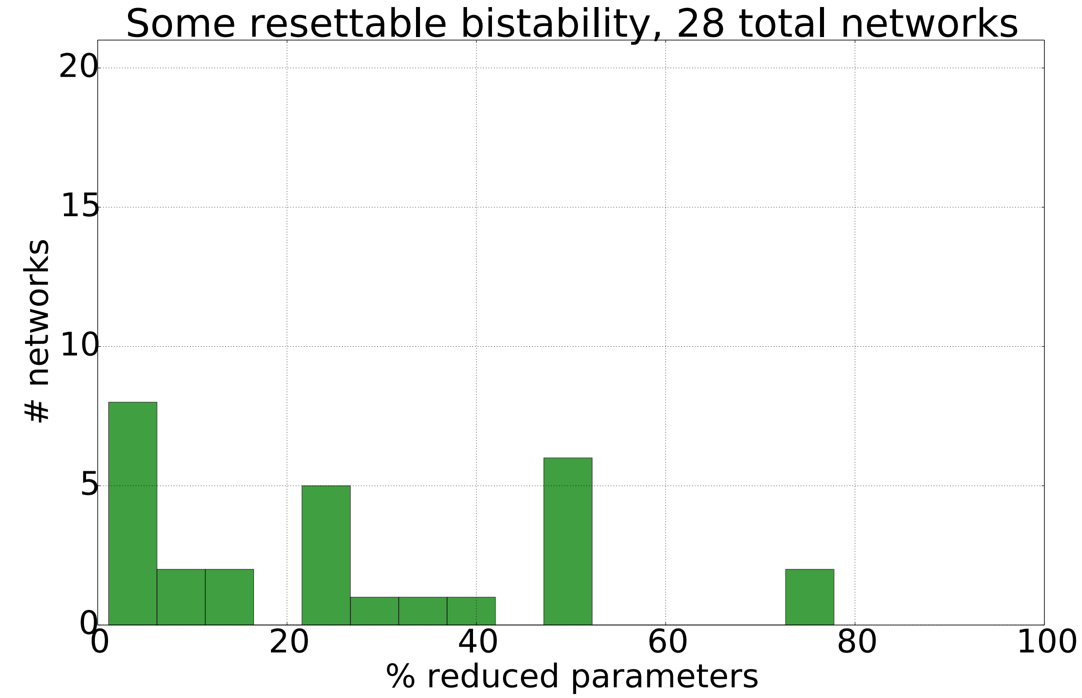
Results

When S is in the middle range:

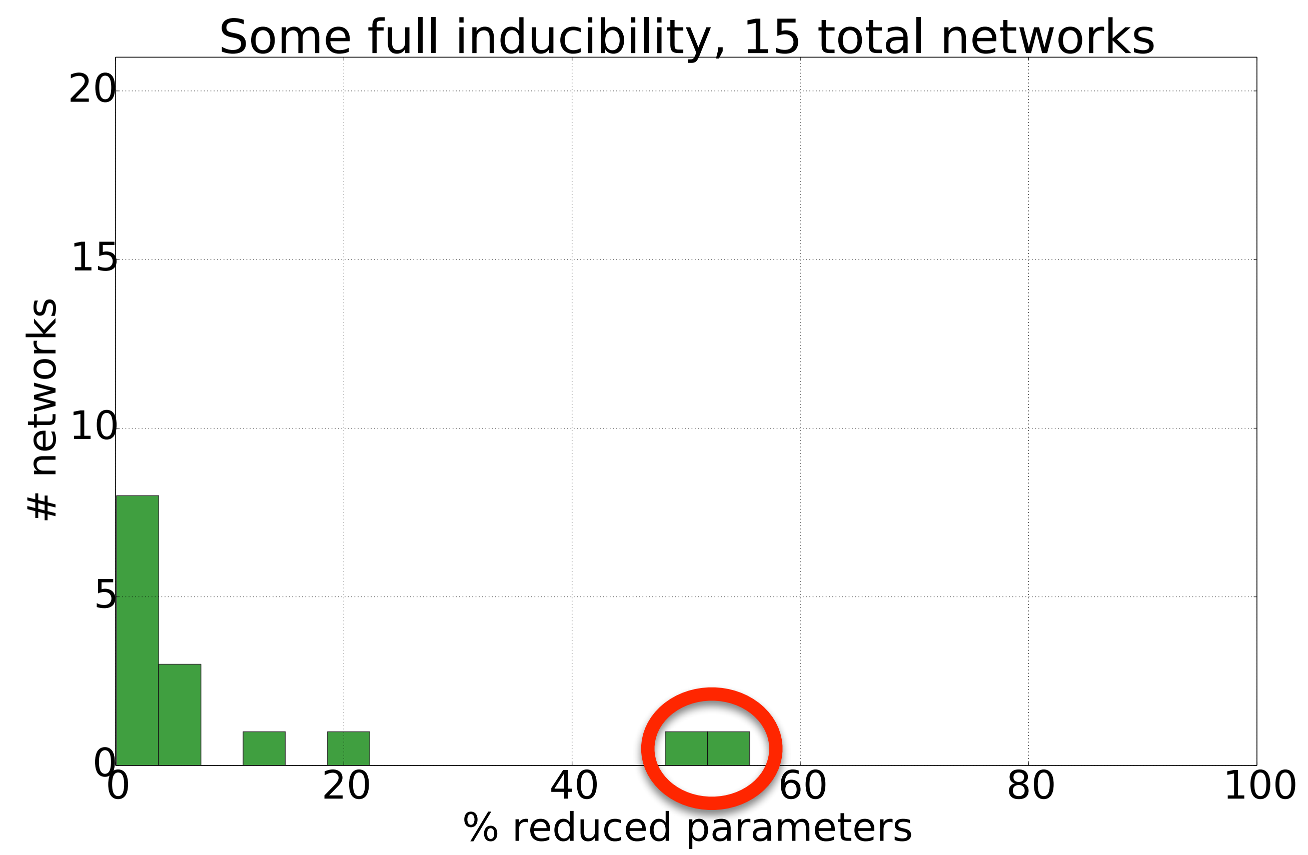
35 networks have some bistability

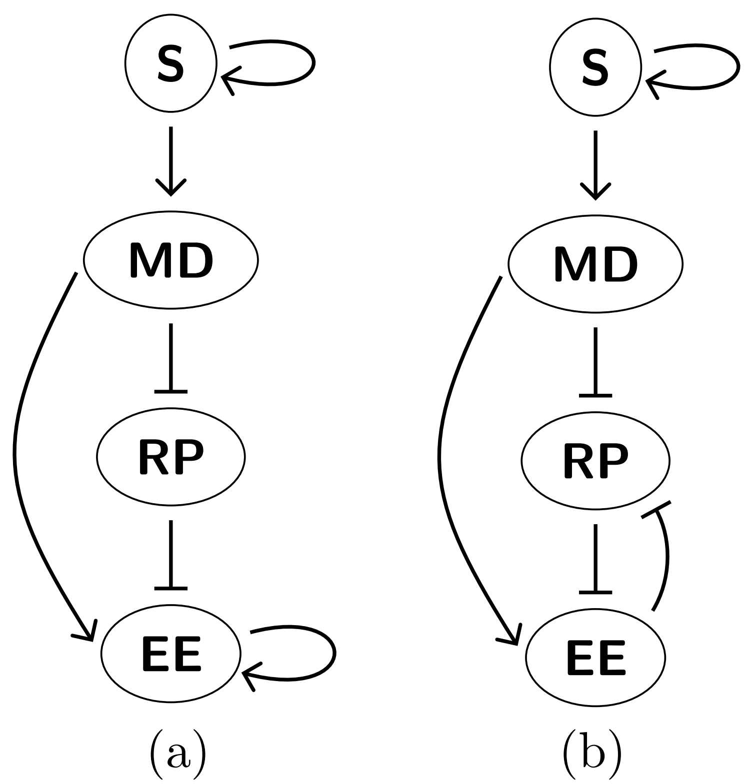


Out of these 28 have some resettable bistability



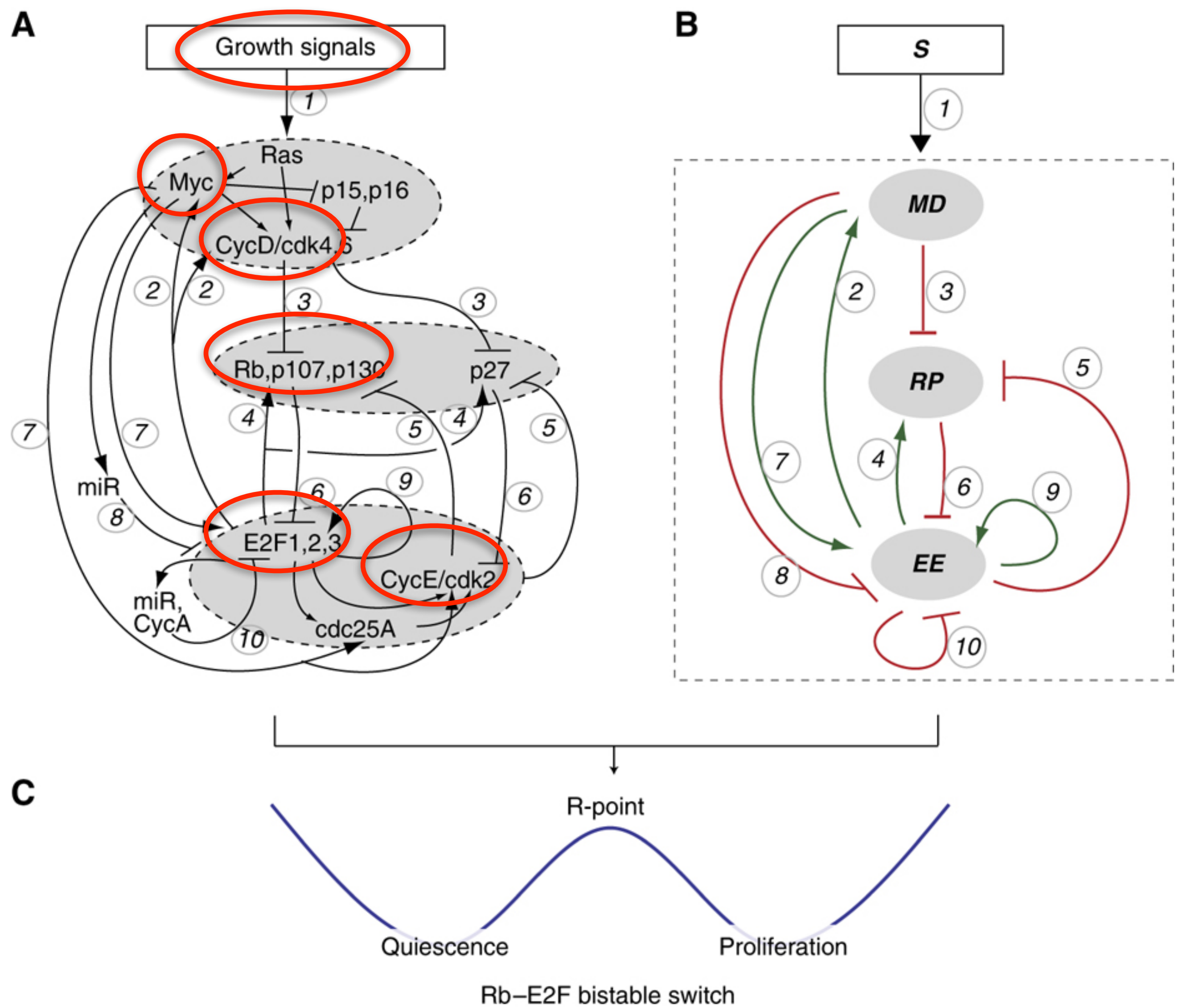
Hysteresis:
two networks where
full hysteresis
occupies more than half
of the parameter graph

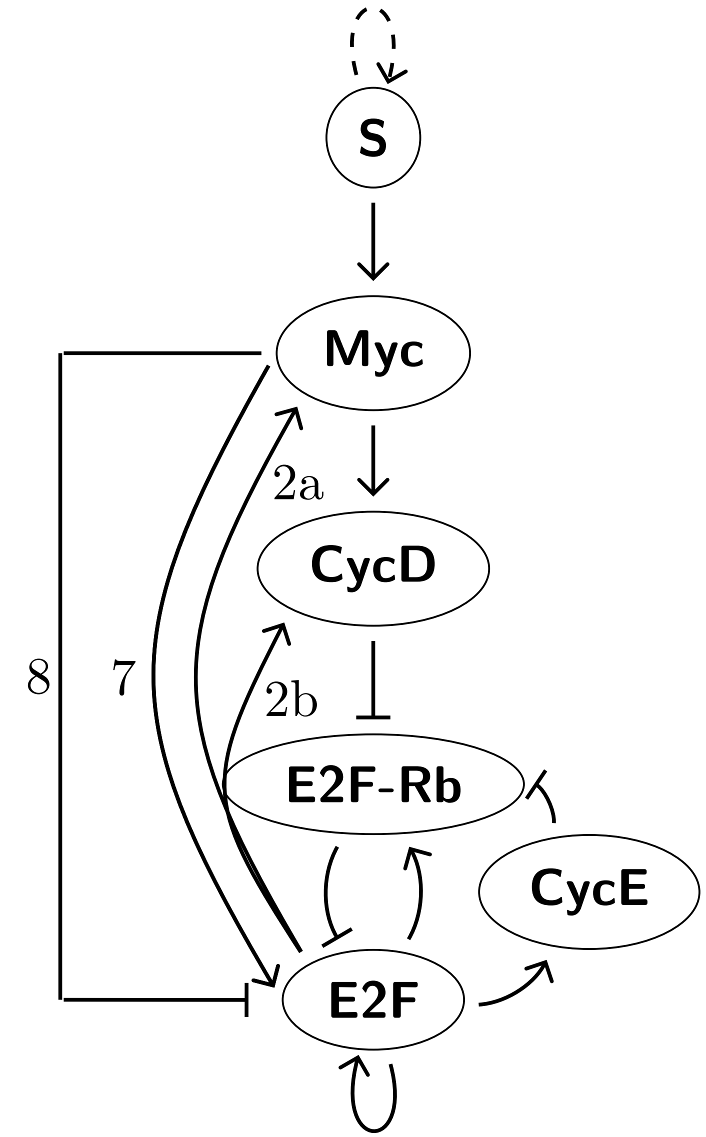




These match top two networks of Yao 2011

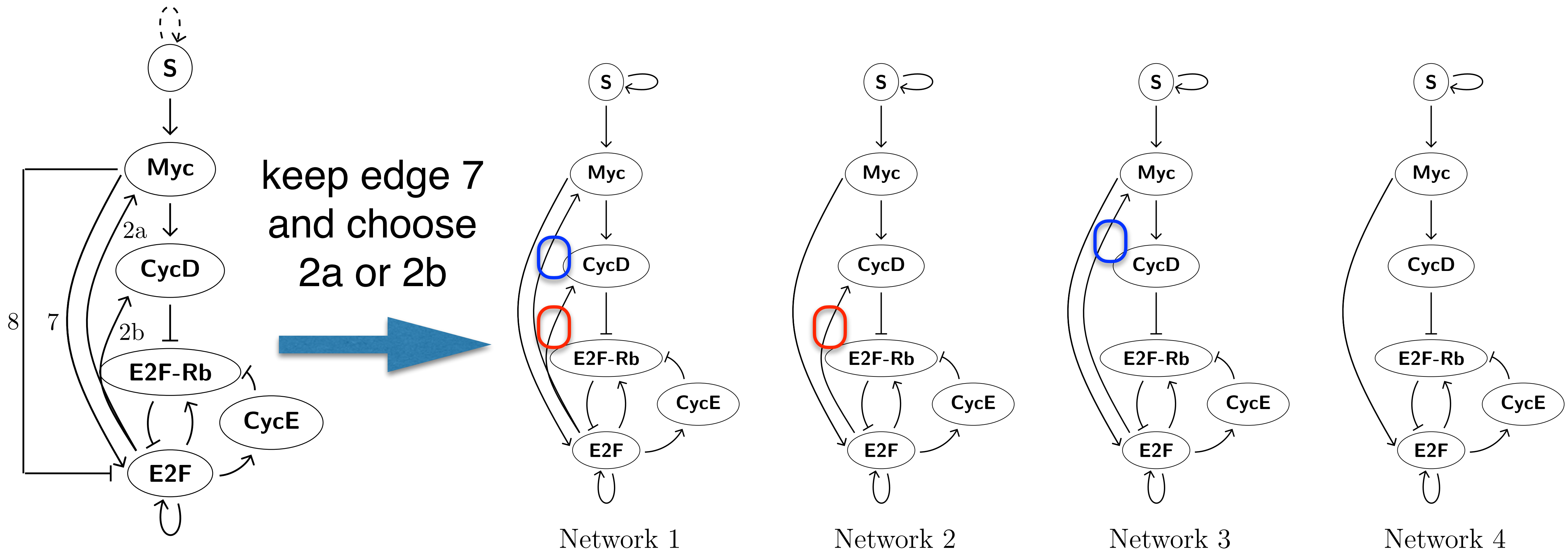
6 node network analysis





Question: How good and robust is this network at providing a clear resettable on/off signal and support hysteresis?

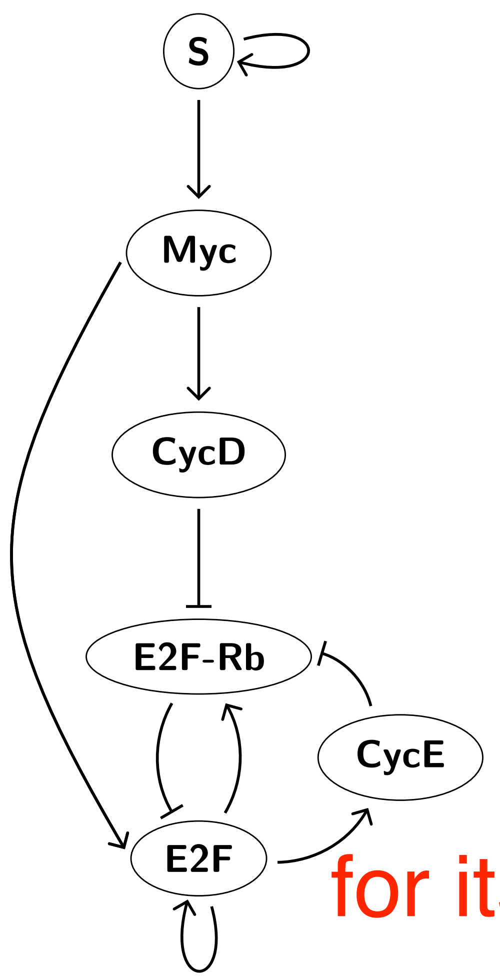
Test subnetworks



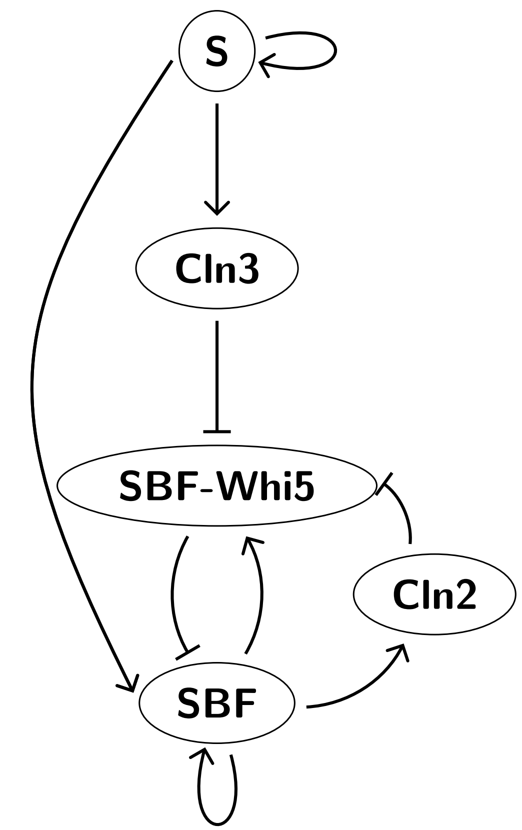
Network	Bistability	Resettable	Hysteresis
1	59%	18.8	0.9%
2	59.7%	32.9%	7.0%
3	58.9%	26.3%	1.8%
4	58.7%	43.3%	14%

Comparison across species

In our small search we find this as the best network (human):



Yeast cell cycle entry:



No homology between individual genes only network structure very similar

Is the structure selected for its dynamics i.e. for being a robust bistable switch?

Resettable Bistability	Hysteresis
43.3 %	14 %

Resettable Bistability	Hysteresis
42.3%	5.6%

Discussion

- Switching systems provide rules to construct state transition graphs
- DSGRN database describes Morse decomposition for all parameters.
- The results are rigorous and encourage refinement
- Our results illustrate usefulness of lattices of attractors/Morse decompositions as primary descriptors of dynamics in biological systems.

Cummins, Gedeon, Harker, Mischaikow, Mok,
Combinatorial representation of parameter space for switching networks,
SIAM Journal on Applied Dynamical Systems, Vol. 15,No. 4, (2016) pp. 2176-2212.

Gedeon, Harker, Kokubu, Oka, Mischaikow,
Global dynamics for steep nonlinearities in two dimensions,
Physica D 339, pp. 18-38 (15 Jan 2017)

Cummins, Gedeon, Harker, Mischaikow,
From gene networks to their dynamic phenotypes, in preparation

Cummins, Gedeon, Harker, Mischaikow,
Matching time series to symbolic dynamics using labeled graph, in preparation

Thank you.

- DARPA D12AP200025
- NSF DMS-1226213, DMS-1361240
- NIH R01 grant 1R01AG040020-01