Dynamic Signatures Generated by Regulatory Networks

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Outline

I. Motivation: why we need a new approach to Nonlinear dynamics

II. Combinatorial Model For Dynamics: This is what is computable

III. Databases of Nonlinear Dynamics: A global approach to dynamics

IV. Conley Theory: This provides the theoretical foundations and the tie to classical dynamical systems

MOTIVATION

Three Problems
Involving
Nonlinear Dynamics

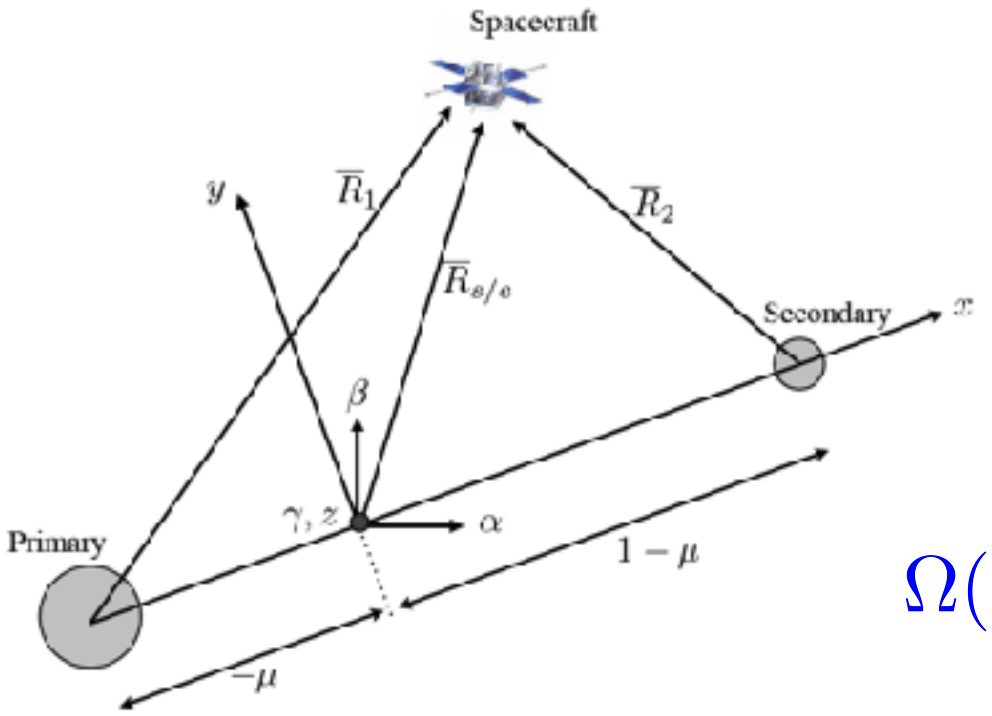
$$\frac{dx}{dt} = f(x) \qquad \frac{dx}{dt} = f(x) \qquad \frac{dx}{dt} = ??$$

DIFFERENTIAL EQUATIONS: ANALYTIC SOLUTIONS

$$\frac{dx}{dt} = f(x)$$

Restricted 3 Body Problem (Euler 1772)

$$\frac{d^2x}{dt^2} - 2\frac{dy}{dt} = \Omega_x$$
$$\frac{d^2y}{dt^2} + 2\frac{dx}{dt} = \Omega_y$$



$$\Omega(x,y) = \frac{x^2+y^2}{2} + \frac{1-\mu}{r_1} + \frac{\mu_2}{r_2} + \frac{\mu(1-\mu)}{2}$$

W.S. Koon, M. W. Lo, J. E. Marsden, S. D. Ross, Heteroclinic connections between periodic orbits and resonance transitions in celestial mechanics, *Chaos*, 2000

Motivation: “the design of trajectories for space missions such as the Genesis Discovery Mission.”

D. Wilczak, P. Zgliczynski, *Comm. Math. Phys.*, 2003

DYNAMICAL SYSTEMS:
QUALITATIVE THEORY
OF
DIFFERENTIAL EQUATIONS

The 3-body Problem ≈1890

Jules Henri Poincare
1854-1912

Chaotic dynamics exists.

→ Understanding the solution of an single initial value problem is not sufficient.

Need to consider all solutions: $\frac{dx}{dt} = g(x), \quad x \in \mathbb{R}^n$

Flow: $\varphi\colon \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$

$$(t, x) \mapsto \varphi(t, x)$$

time

initial condition

value of solution at time t

Map: $f\colon \mathbb{R}^n \to \mathbb{R}^n$

$$x \mapsto f(x) := \varphi(\tau, x)$$

$\tau > 0$ is a fixed time.

Steven Smale
1930-

$f\colon X \times \Lambda \to X$ differentiable

$(x, \lambda) \mapsto f_\lambda(x)$

The objects of interest:

A set $S \subset X$ is invariant if $f_\lambda(S) = S$.

Examples: equilibria, periodic orbits, heteroclinic orbits, strange attractors

The equivalence relation:

Two maps $f\colon X \to X$ and $g\colon Y \to Y$ are topologically conjugate if there exists a homeomorphism $h\colon X \to Y$ such that $h \circ f = g \circ h$.

The places of change:

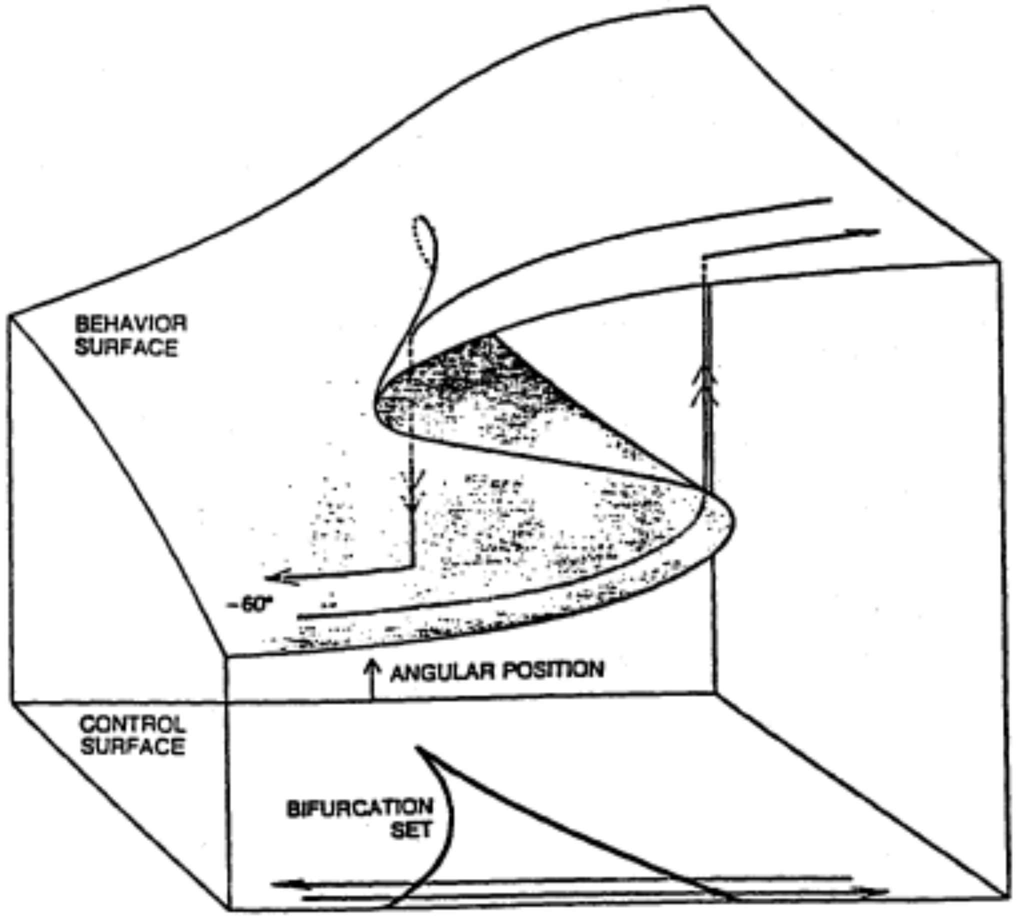
$\lambda_0 \in \Lambda$ is a bifurcation point if for any neighborhood U of λ_0 there exists $\lambda_1 \in U$ such that f_{λ_0} is not conjugate to f_{λ_1}

Given a family of dynamical systems (differential equations), what *types of dynamical structures* does one expect to see *typically*?

THEORIE DE CATASTROPHES

Rene Thom
1923-2002

What is the minimal parameter space Λ which allows us to fully explain bifurcations?



Cusp
Catastrophe

Limits to Theory: 1. Description of Fixed Points

2. Smooth theory with limits to finite classification

3. Local theory (to the best of my knowledge)

Dynamical systems approach to differential equations is incredibly fruitful.

1. Arnold Conjecture

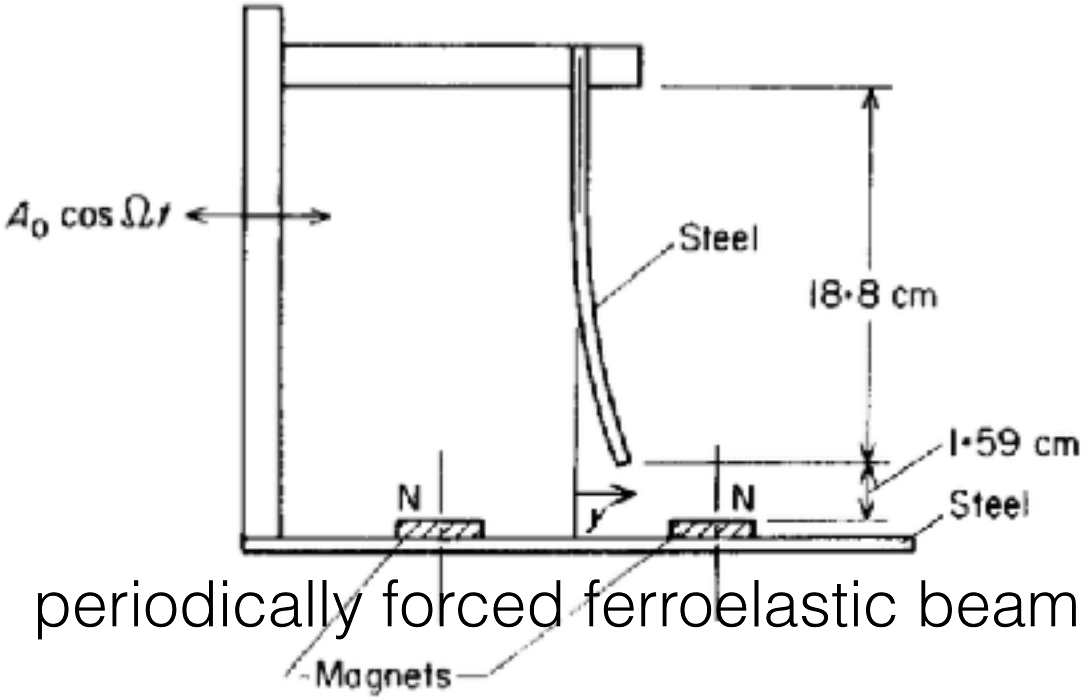
Theorem: (Conley,Zehnder) Consider the $2n$ dimensional torus with standard symplectic structure J, a 1 periodic exact Hamiltonian $H\colon S^1 \times T \to \mathbb{R}$, and the resulting differential equation

$$\dot{x} = J\nabla H(t,x).$$

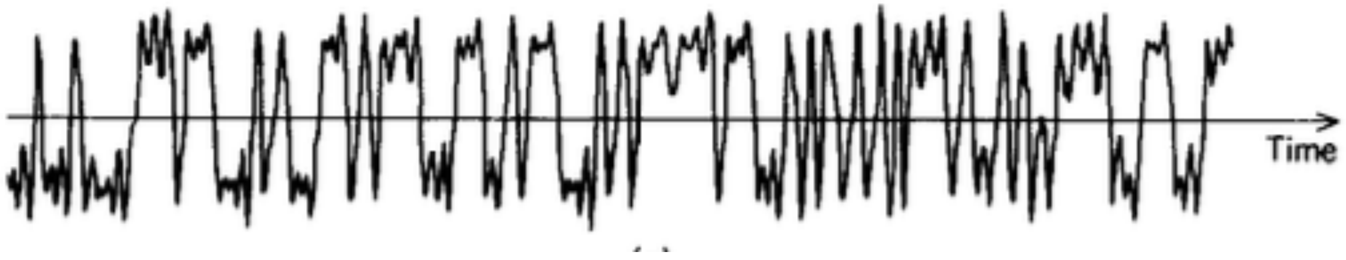
Then, there must be at least $2n+1$ periodic orbits of period 1.

Remark: A quintessential dynamical systems theorem: existence of solutions with particular geometric properties, but almost no quantitative information.

2. Analysis of nonlinear systems



periodically forced ferroelastic beam



time series data

ODE model: $\ddot{x} + \gamma \dot{x} - \frac{1}{2}(1 - x^2)x = f \cos \omega t$

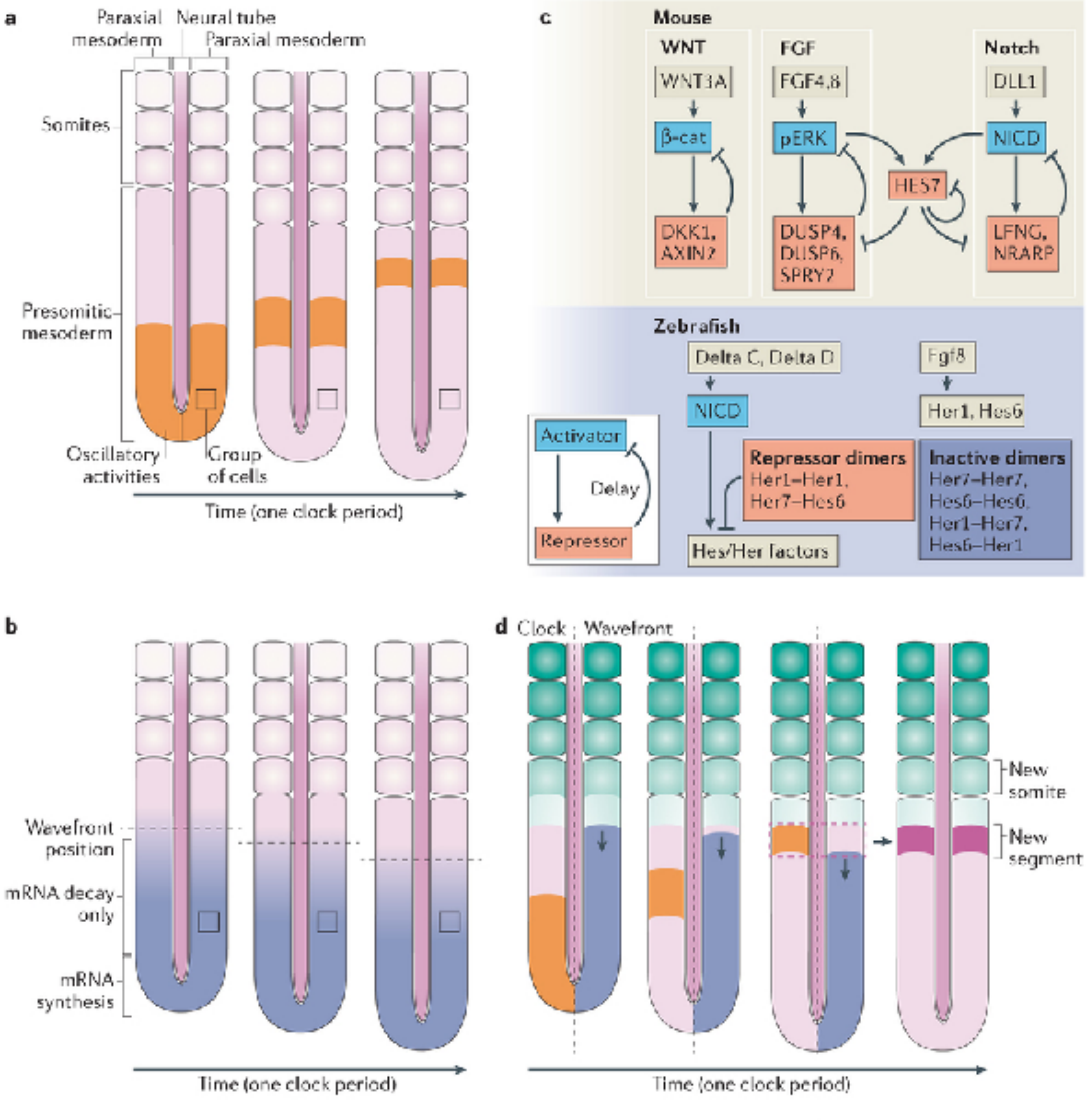
"First principles" derivation of model:

1. Magnetic forces
2. Catastrophe theory used to identify nonlinearity
3. Continuum modeling to obtain PDEs
4. Galerkin projection

Verification of model by comparing experimentally observed bifurcations with theoretical and numerical analysis of bifurcations of model.

F. C. Moon, P. J. Holmes, A Magnetoelastic Strange Attractor, *J. Sound & Vibration*, 1979

3. Conceptual generation of models



Nature Reviews | Molecular Cell Biology

A. Hubaud & O. Pourquié (2014)

"The clock-and-wavefront model first proposed the existence of an oscillator to explain the rhythmic formation of somites in the embryo. This theoretical model, inspired by the mathematical theory of catastrophes that was developed in the 1970s, postulates that somite formation results from a periodic abrupt change (a catastrophe) in cellular properties triggered by a travelling front of maturation (the wavefront)."

What's Left To Worry About?

1. Growth of population of *Paramecium caudatum* (G. Gause 1932)

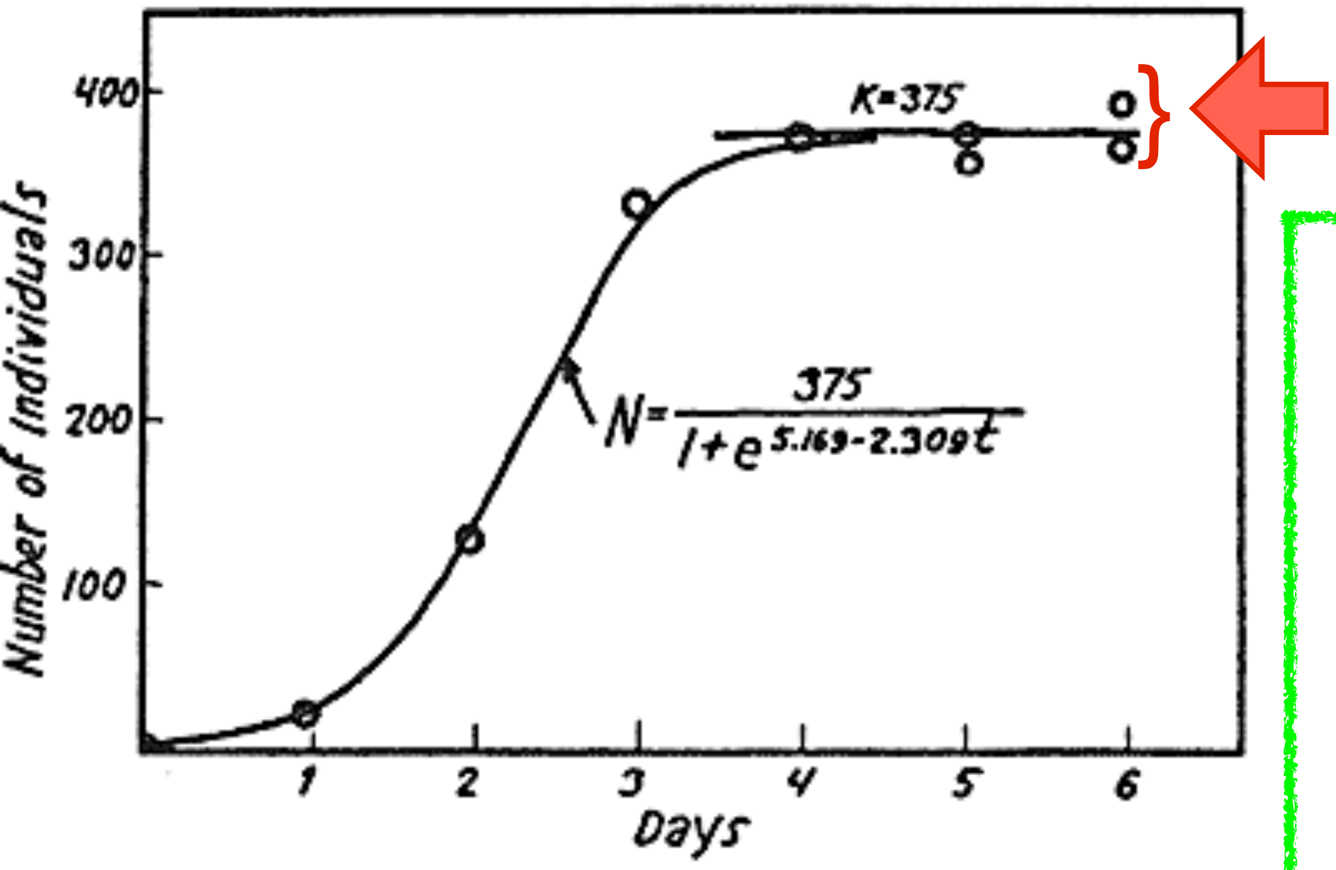
$$\frac{dN}{dt} = rN\left(\frac{K-N}{K}\right)$$

r is the birth rate.

K represents carrying capacity of the environment.

Fact: Given an initial condition $N(0) > 0$ a solution satisfies

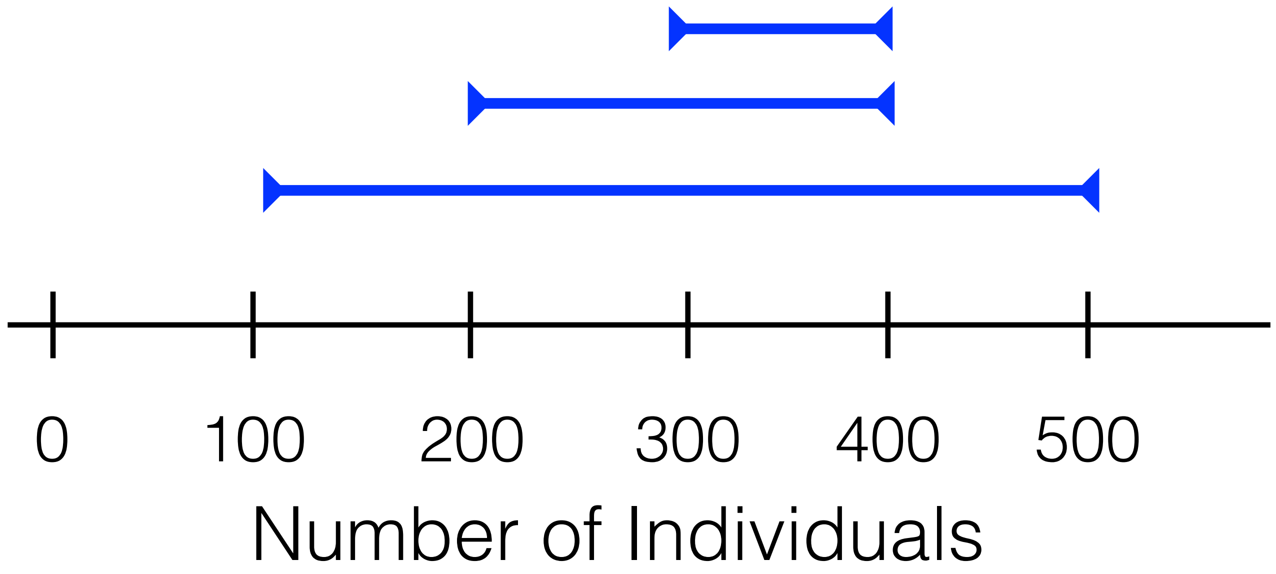
$$\lim_{t\to\infty} N(t) = K.$$



Experimental Data

Mathematical prediction is not precise

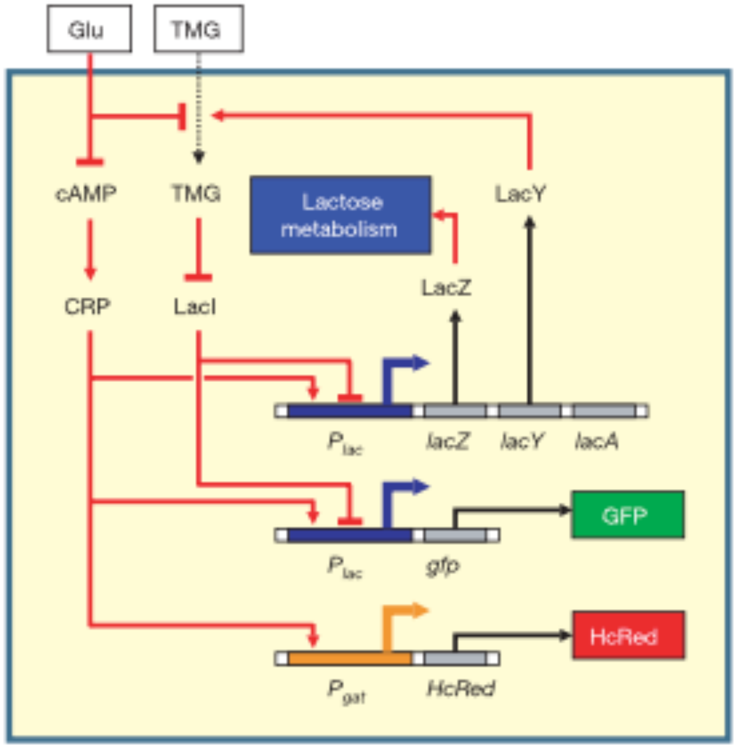
Is it enough to talk about a lattice of attracting blocks?



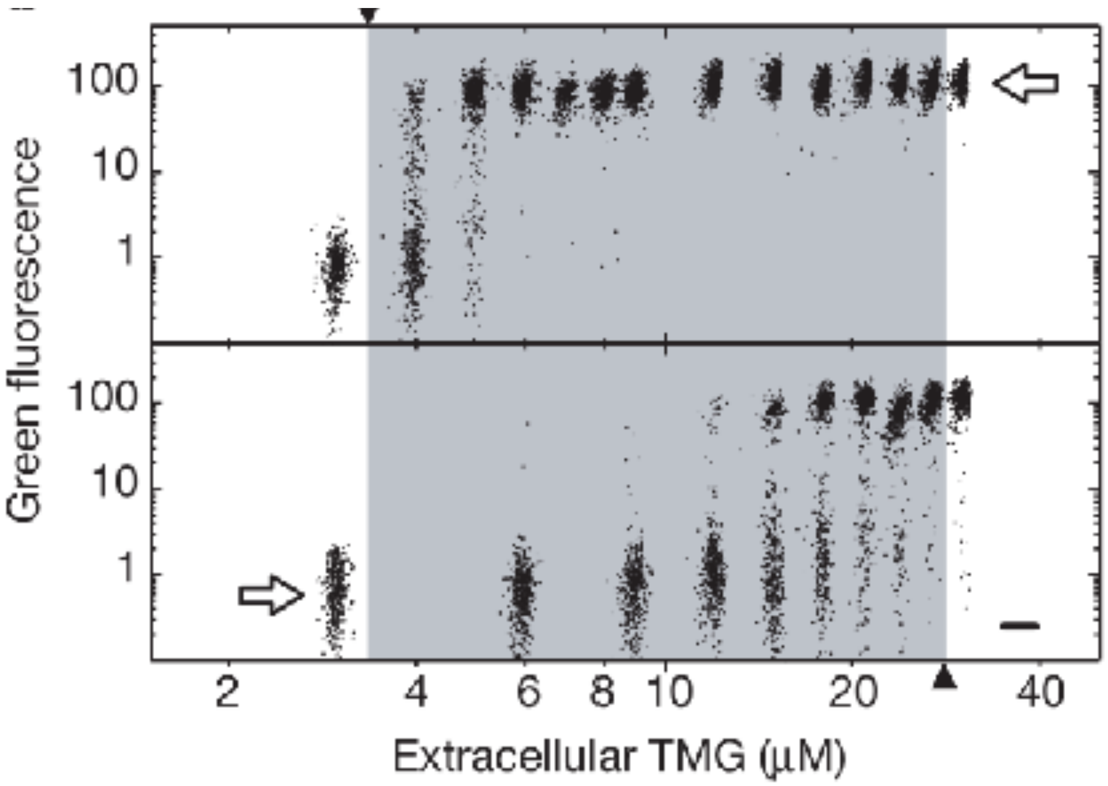
2. Lac Operon

Ozbudak et al. Nature 2004

ODES are great modeling tools, but should be handled with care.



Network Model



Data

$$\frac{1}{\tau_y}\dot{y} = \alpha\frac{R_T}{R_T + R(x)} - y$$

$$\frac{1}{\tau_x}\dot{x} = \beta y - x$$

$$R(x) = \frac{R_T}{1 + \left(\frac{x}{x_0}\right)^n}$$

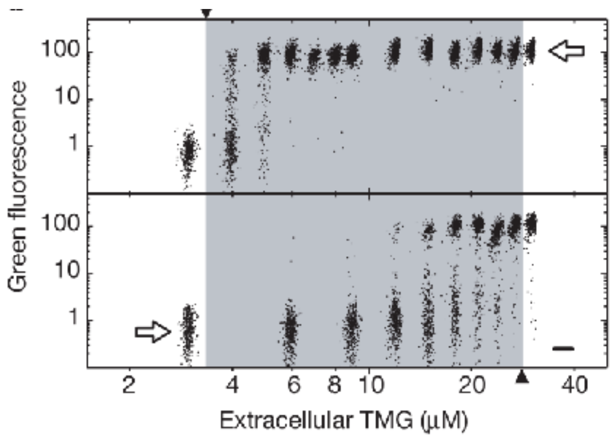
ODE Model

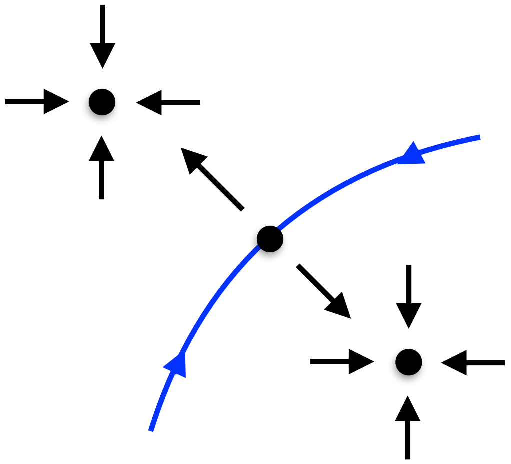
$$\alpha = \frac{84.4}{1 + (G/8.1)^{1.2}} + 16.1$$

$$\beta = \ldots$$

parameter values

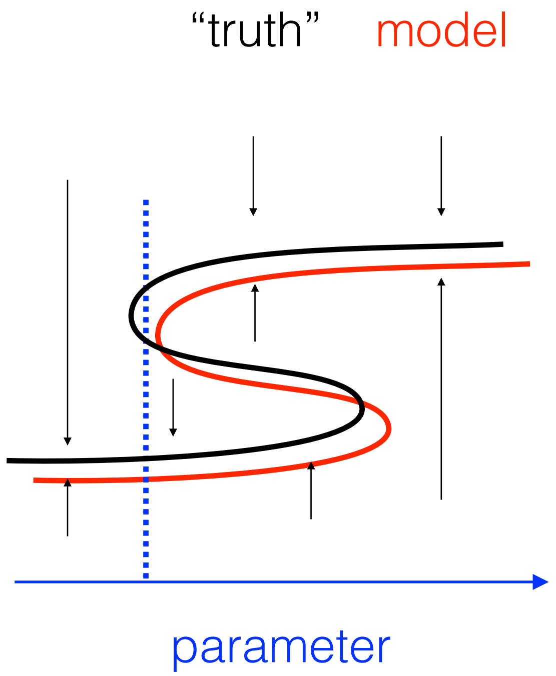
What does it mean to solve an ODE?

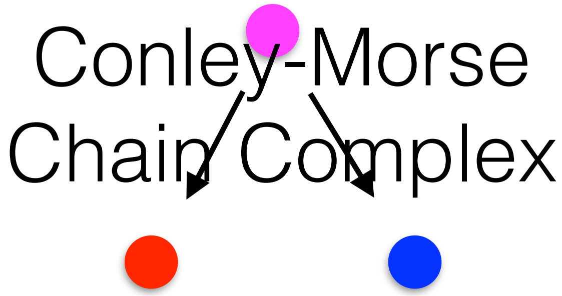




Classical Qualitative
Representation
of Dynamics

Precise
Not Accurate
Not Rigorous

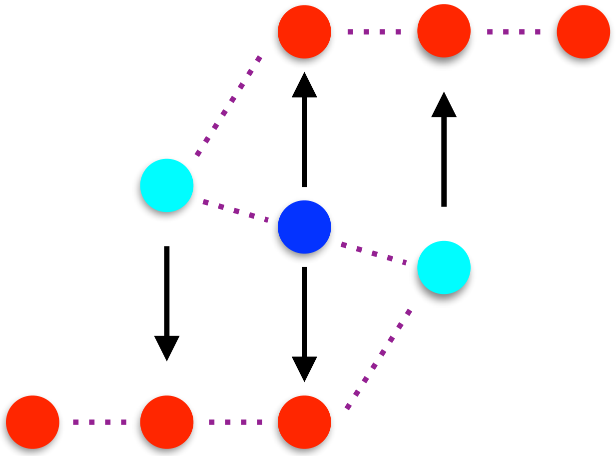




Conley-Morse
Chain Complex

Dynamic
Signature
(Morse Graph)

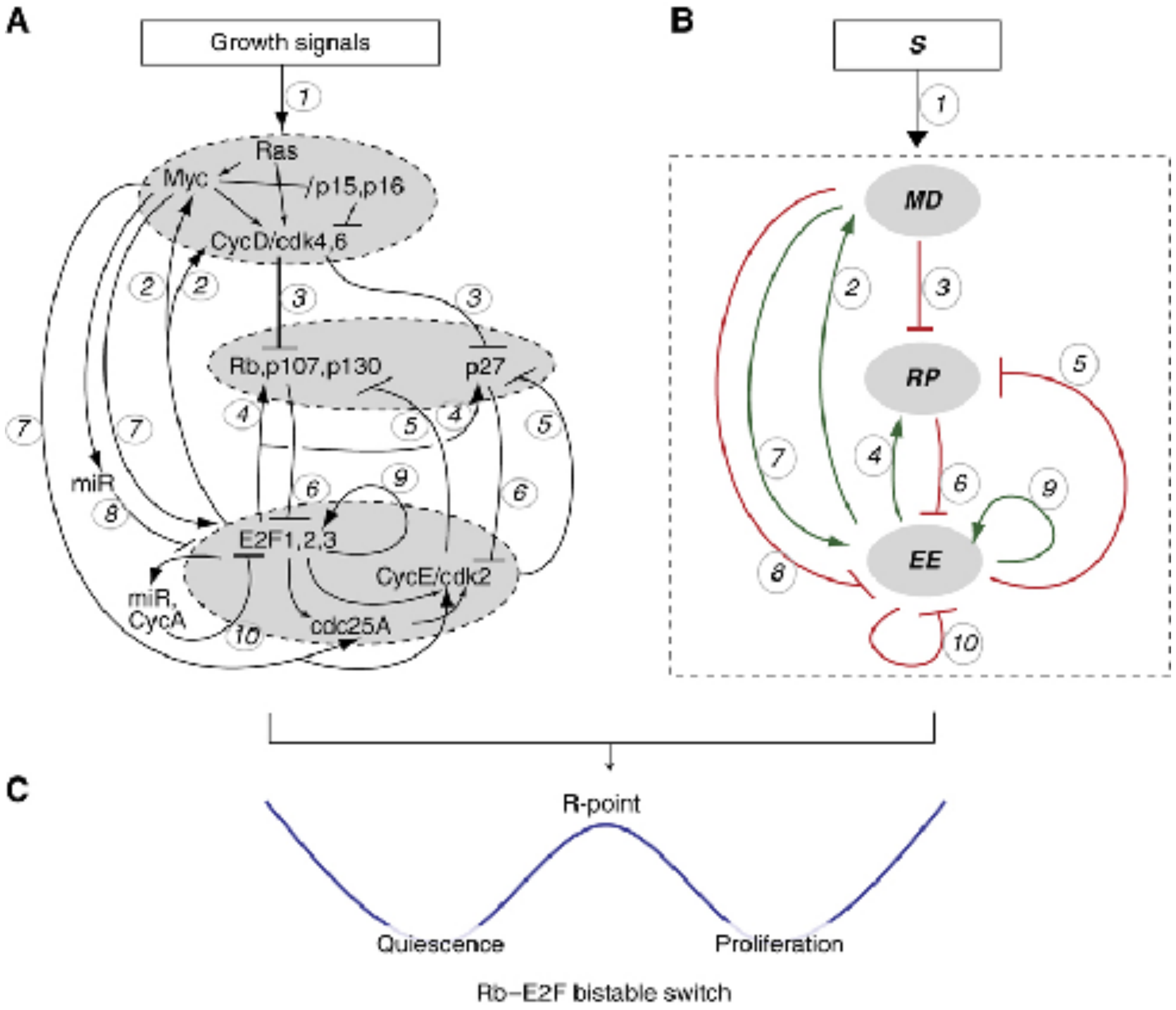
Not Precise
Accurate
Rigorous



3. Cancer

$$\frac{dx}{dt} = ??$$

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

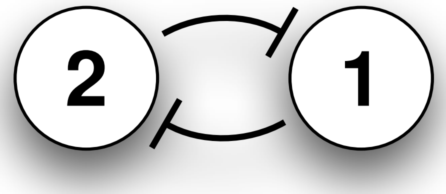
A is stable if MD ON

B is stable if MD OFF

Resettable:

MD: ON -> OFF

System moves from A to B

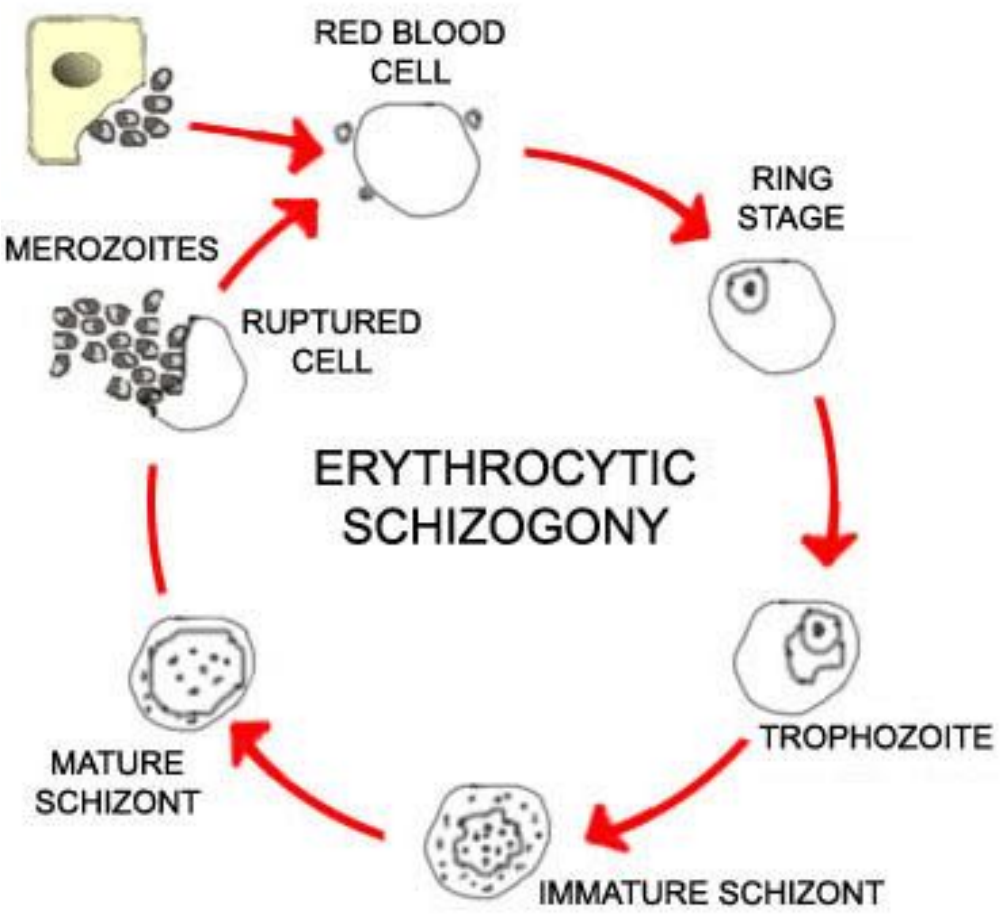


Toggle Switch

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

4. Malaria

P. falciparum



48 hour cycle

Once a liver schizont has matured, it ruptures, and the merozoites spill into the bloodstream. Within 1-2 minutes, each merozoite has invaded an erythrocyte. Once in the erythrocyte, the merozoite consumes hemoglobin to use for energy, at which point it becomes known as a trophozoite. It uses this energy to form schizonts and begin another round of asexual amplification, producing up to 36 merozoites per schizont. When this schizont ruptures, the merozoites are released into the bloodstream once again and infect other red blood cells.

This cycle of infection, multiplication, and bursting continues until it is brought under control by the immune system or by antimalarial drugs. These erythrocitic merozoites are responsible for the clinical manifestations of malaria.

Estimated number of malaria cases in 2010: between 219 and 550 million

Estimated number of deaths due to malaria in 2010: 600,000 to 1,240,000

Malaria may have killed half of all the people that ever lived. And more people are now infected than at any point in history. There are up to half a billion cases every year, and about 2 million deaths - half of those are children in sub-Saharan Africa.

J. Whitfield, Nature, 2002

Malaria is of great public health concern, and seems likely to be the vector-borne disease most sensitive to long-term climate change.

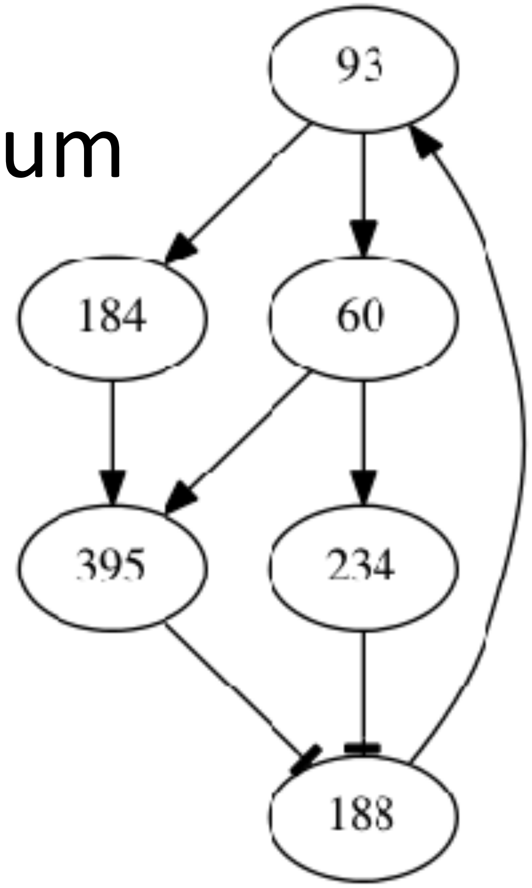
World Health Organization

Resistance is now common against all classes of antimalarial drugs apart from artemisinins. … Malaria strains found on the Cambodia–Thailand border are resistant to combination therapies that include artemisinins, and may therefore be untreatable.

Hypothesis: desynchronization of erythrocytic cycle will allow for the development of novel effective treatments of malaria.

Goals: 1. Identify the regulatory network in *P.* falciparum that governs the synchronization.

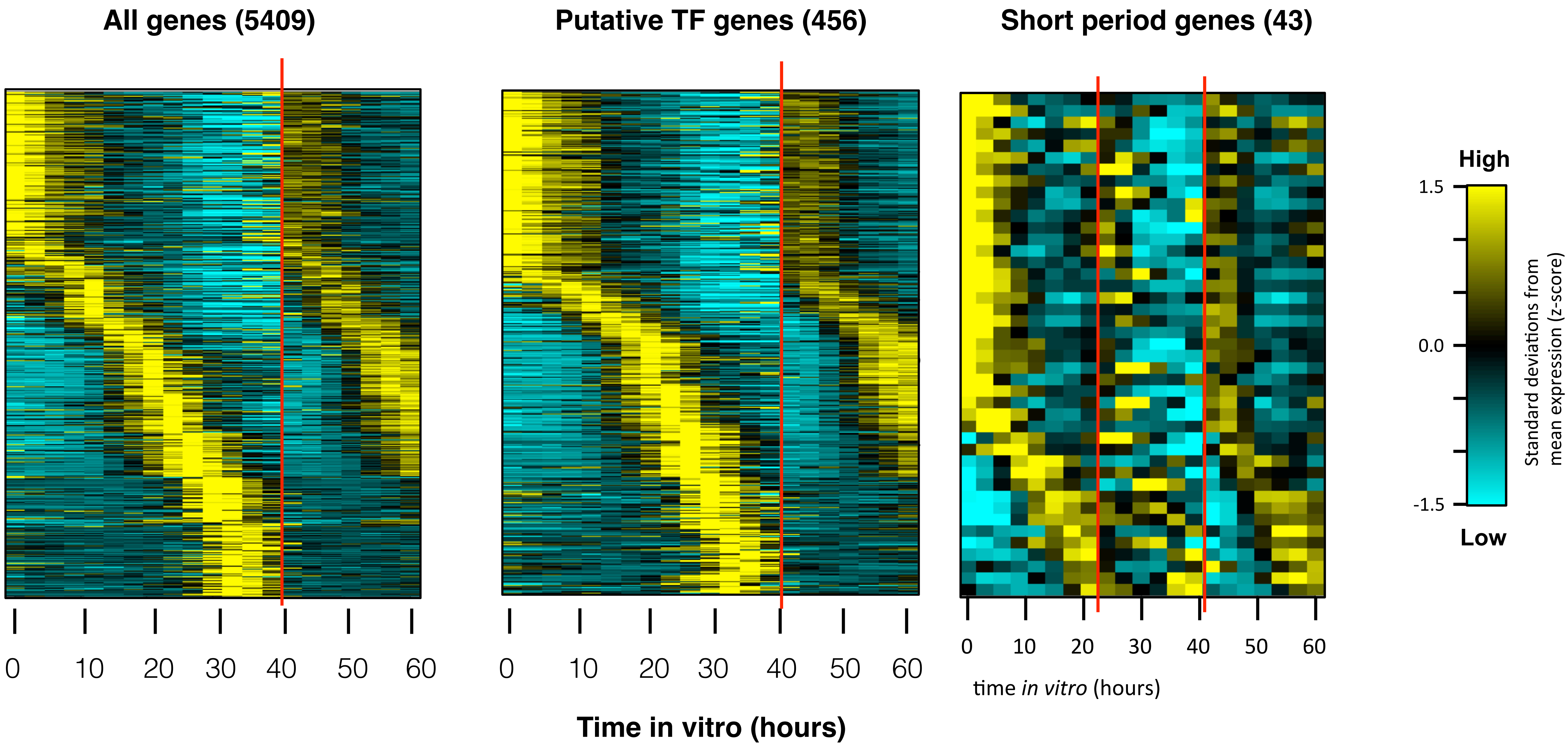
2. Identify variety of control mechanisms that when applied to the regulatory network will disrupt the synchronous behavior.



Remarks: To efficiently achieve 2 requires that we achieve 1.

Achieving 1, but not being able to attain 2 would be very disappointing.

P. falciparum



Sequenced, but poorly annotated

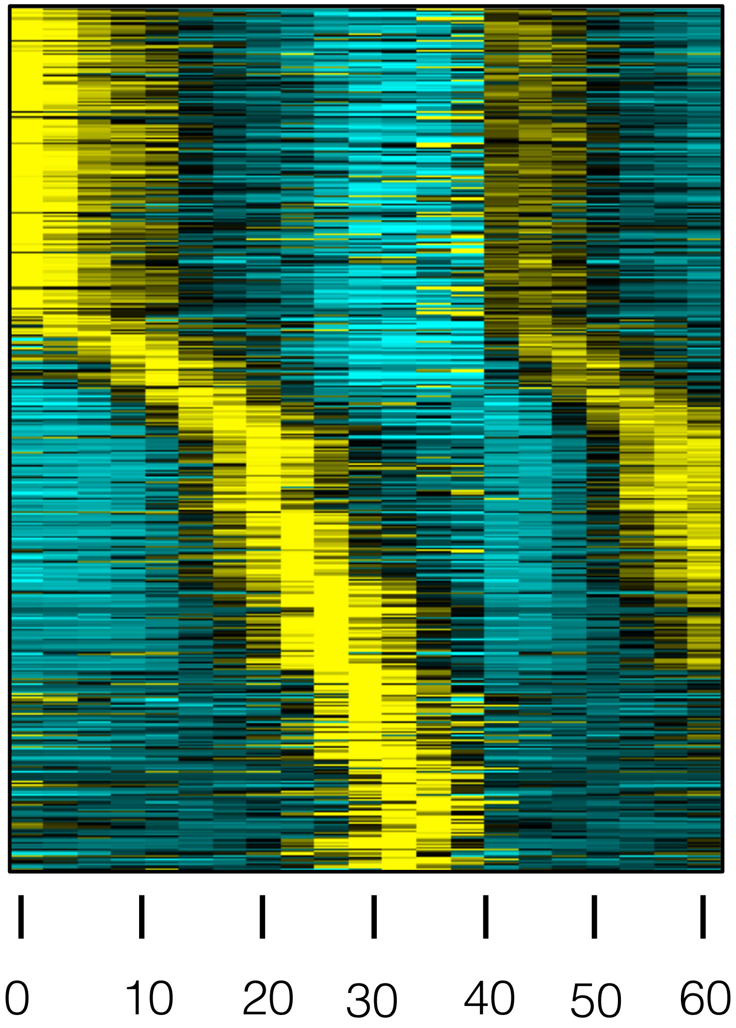
Walter Reed Army Institute of Research
Duke

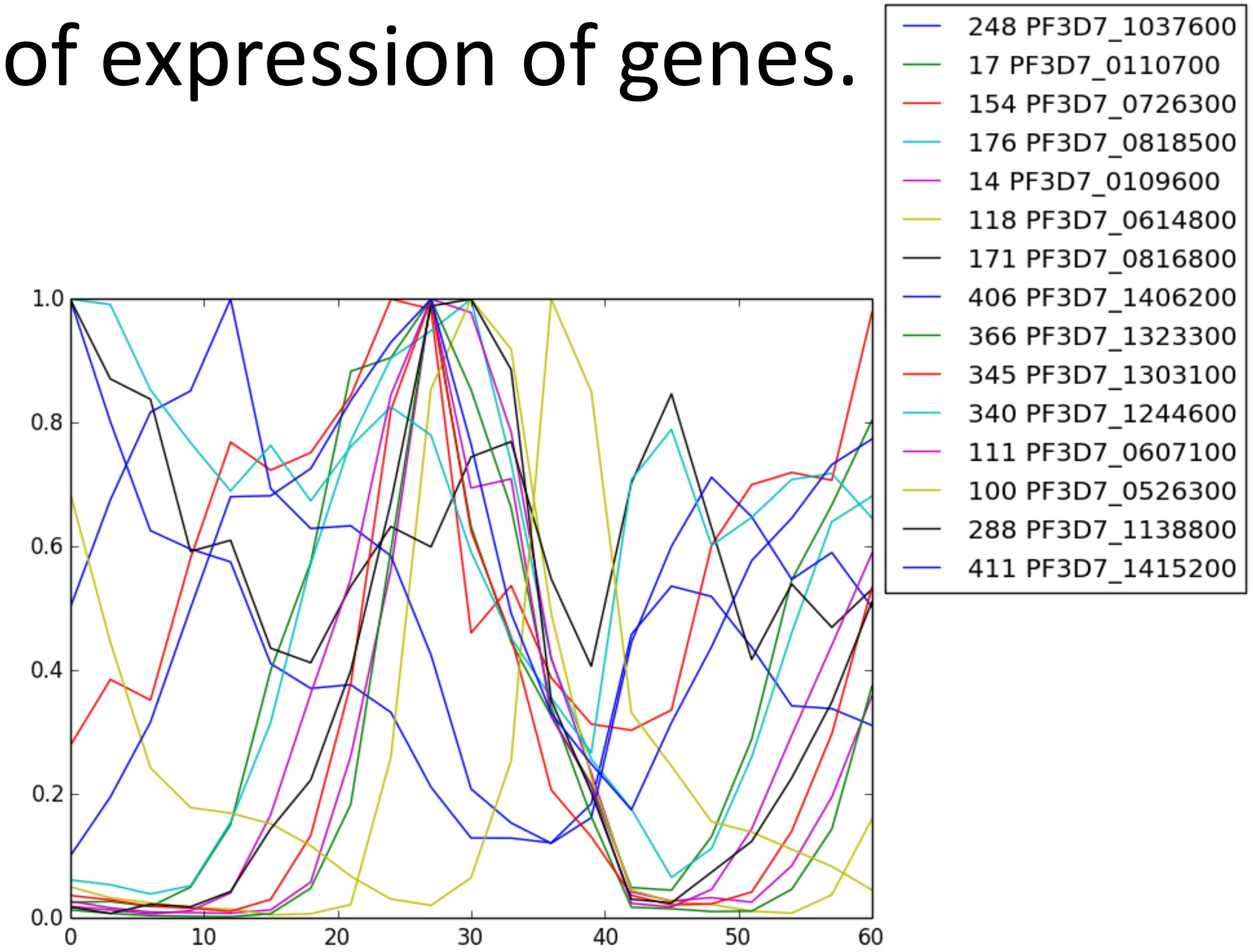
Regulatory Network

$$\frac{dx}{dt} = ??$$

Summary of Dynamics:

1. Gene expression is recurrent in nature.
2. Length of cycles appear to be approximately 20 or 40 hours.
3. Can identify a partial order of expression of genes.





Goals: 1. Generate models that can be quantitatively matched to data.

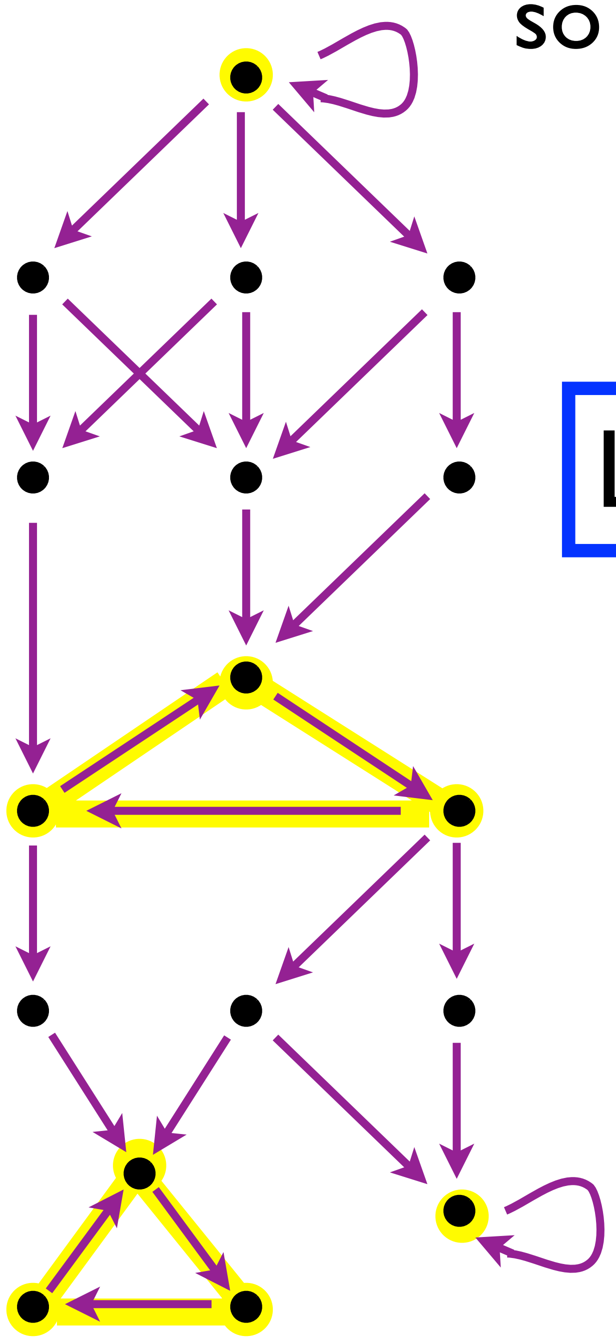
2. Identify essential parameters.

3. Help optimize future experiments.

COMBINATORIAL DYNAMICS

See Rob Vandervorst’s talk

State Transition Graph



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

Linear time Algorithm!

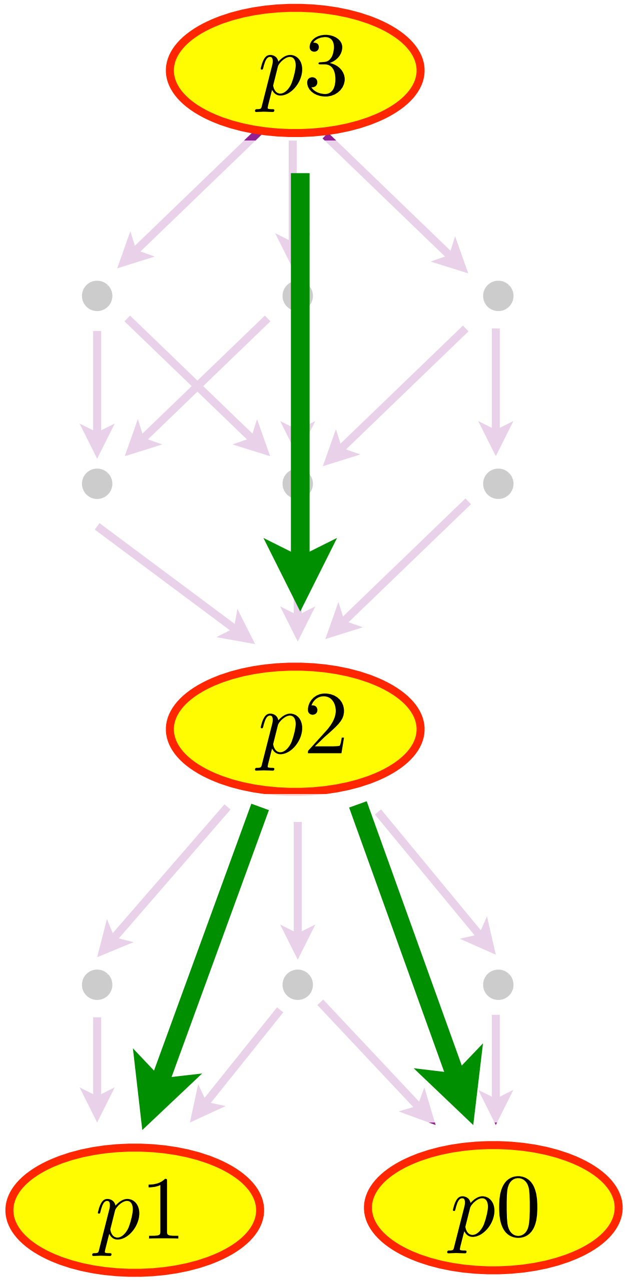
Simple decomposition
of Dynamics:

Recurrent

Strongly connected
path components

Nonrecurrent
(gradient-like)

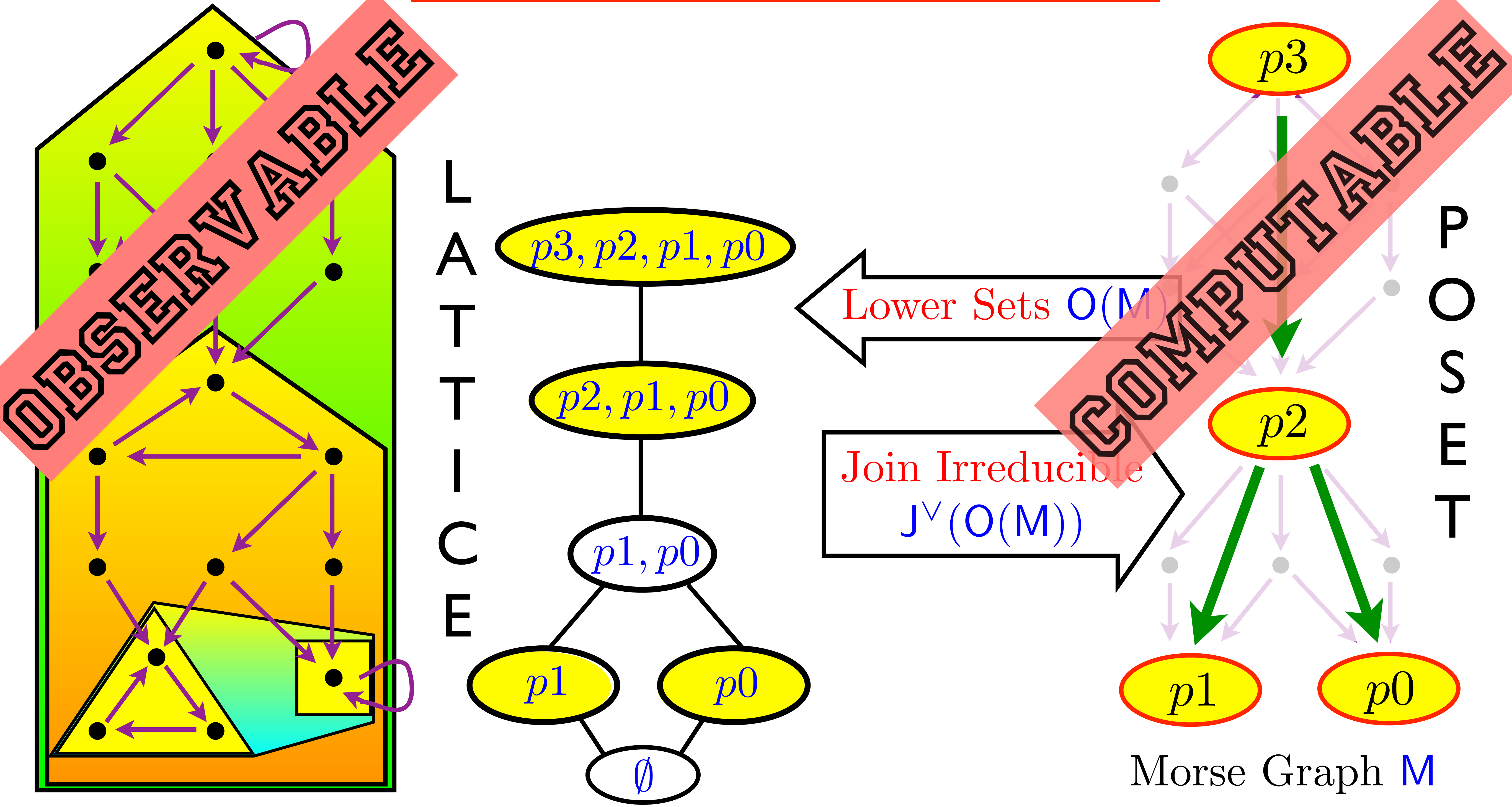
Vertices: States
Edges: Dynamics



Morse Graph
of state transition graph

What is observable? $\mathcal{A} \subset \mathcal{X}$ is an attractor if $\mathcal{F}(\mathcal{A}) = \mathcal{A}$

Birkhoff's Theorem implies that the Morse graph and the lattice of Attractors are equivalent.



Lower Sets O(M)

Join Irreducible $J^{\vee}$(O(M))

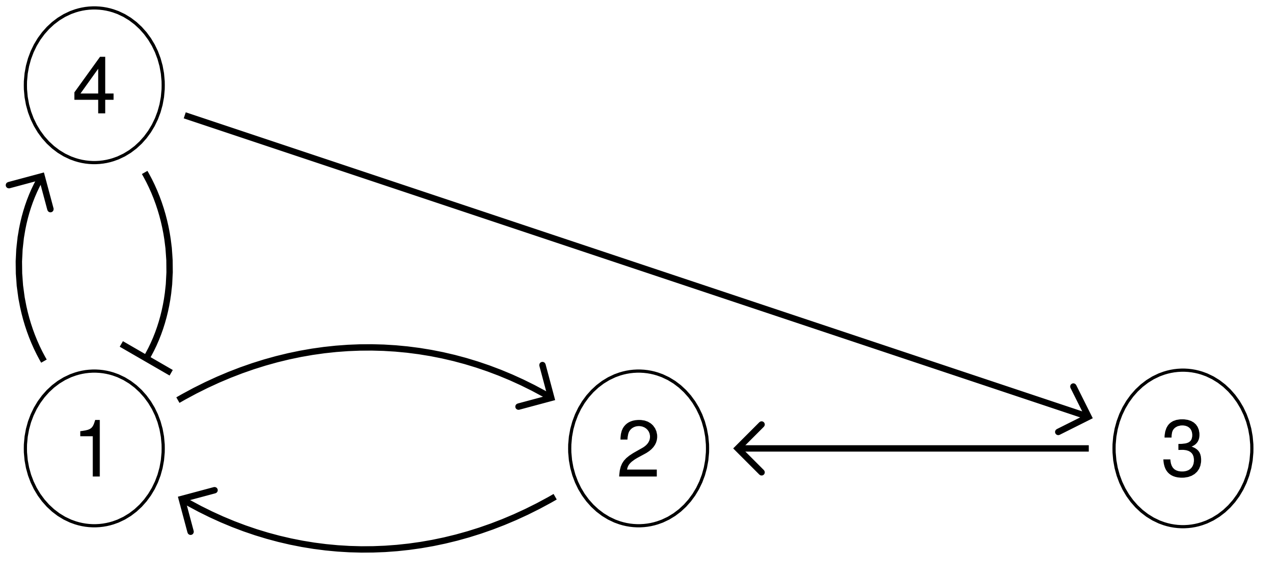
Morse Graph M

DATABASE OF NONLINEAR DYNAMICS

Dynamic Signatures Generated by Regulatory Networks

DSGRN

Regulatory networks are biological models.



Remark: For technical reasons we do not allow repressive self loops

Mathematical Definitions:

A regulatory network $RN = (V, E, M)$ consists of vertices $V = \{1, \ldots, N\}$ called network nodes, annotated directed edges $E \subset V \times V \times \{\rightarrow, \dashv\}$ called interactions, and node logics M_k for each $k \in V$.

The annotated edge $\rightarrow$ is referred to as an activation and the annotated edge $\dashv$ is called a repression.

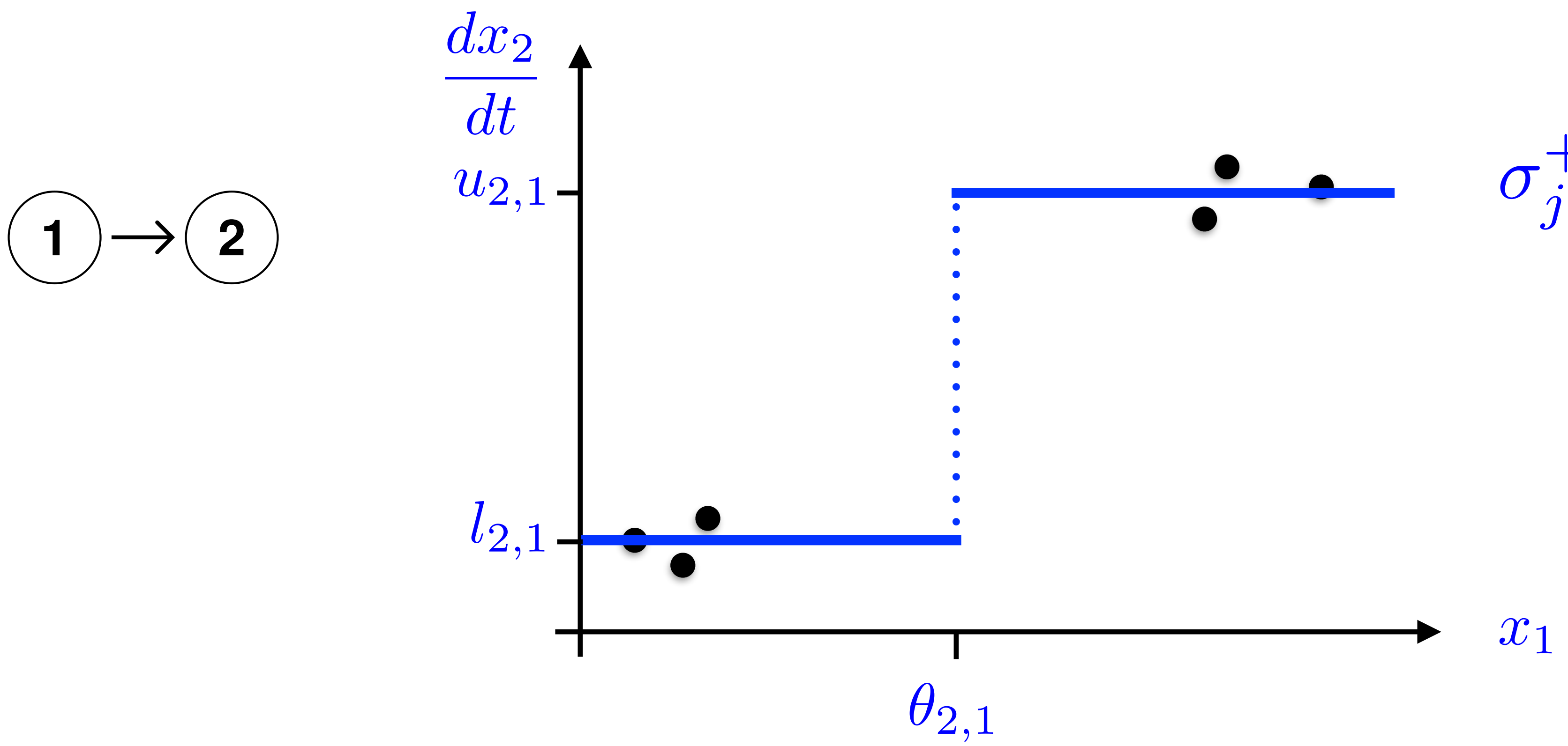
The Nodes

To each node $j \in V$ in the regulatory network we assign a non-negative real valued variable x_i, e.g. concentration.

We assume the variable decays with decay rate $\gamma_i > 0$.

The Edges

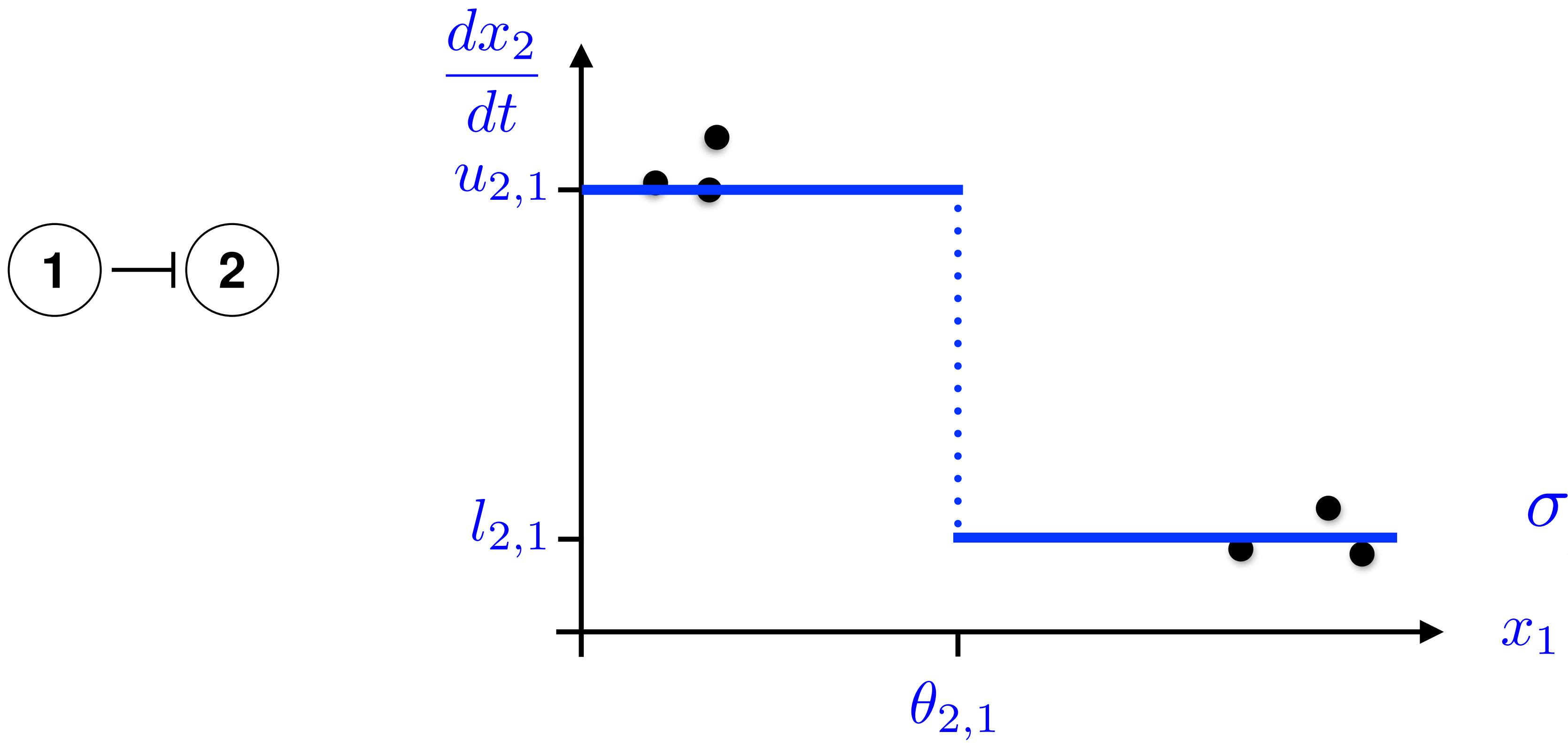
Assume regulation is observed to have a switch like behavior



$$\sigma^+_{j,i}(x_i) = \begin{cases} \ell_{j,i} & \text{if } x_i < \theta_{j,i} \\ u_{j,i} & \text{if } x_i > \theta_{j,i} \end{cases}$$

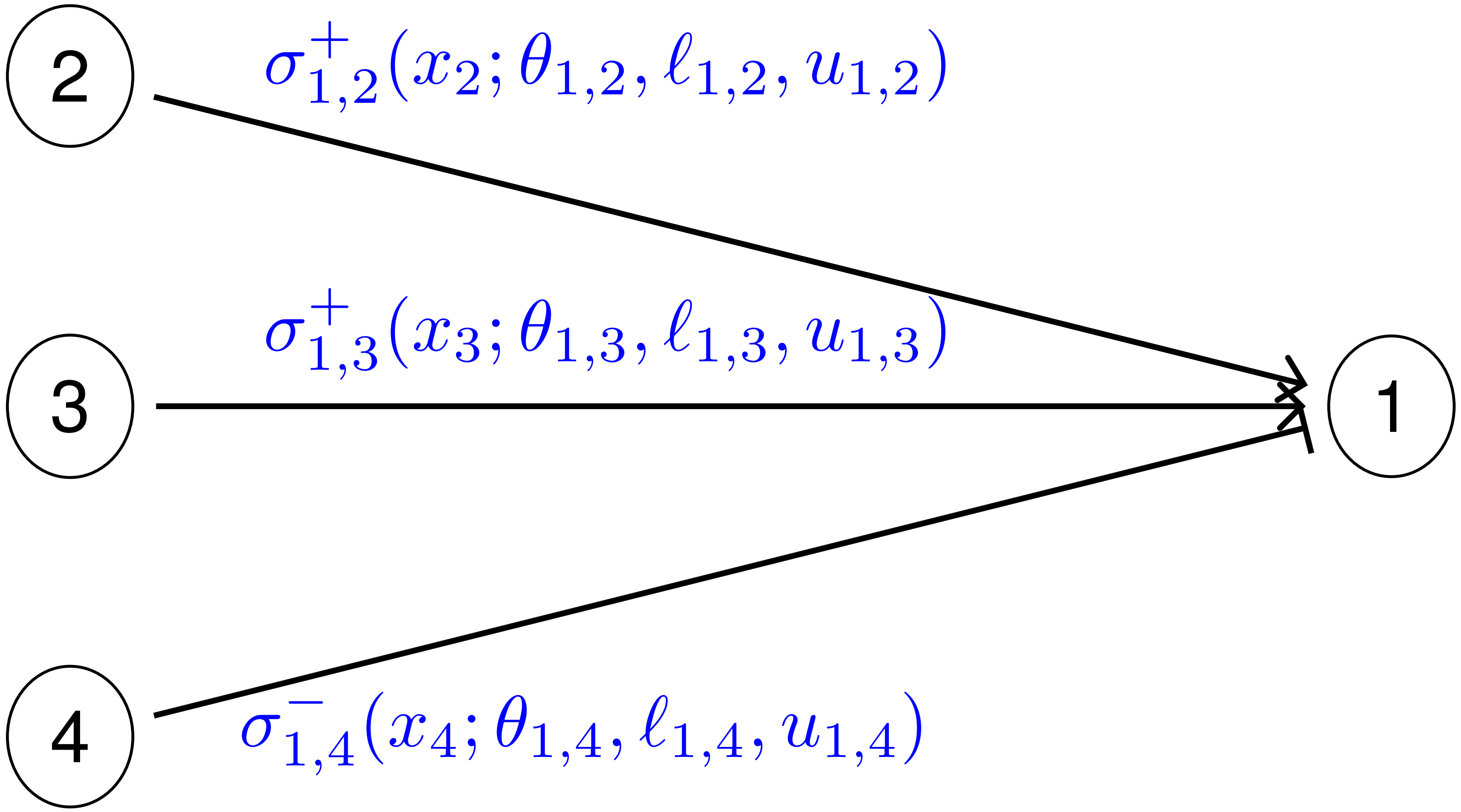
We associate to each edge (i, j) three parameters

- Threshold $\theta_{j,i}$
- Lower Activation $\ell_{j,i}$
- Upper Activation $u_{j,i}$



$$\sigma^-_{j,i}(x_i) = \begin{cases} u_{j,i} & \text{if } x_i < \theta_{j,i} \\ \ell_{j,i} & \text{if } x_i > \theta_{j,i} \end{cases}$$

The Logic



$+ \quad \Leftrightarrow$ or

$\cdot \quad \Leftrightarrow$ and

M_1 indicates how node 1 processes inputs from nodes 2, 3, and 4.

$$\Lambda_i(x) := M_i(\sigma(x))$$

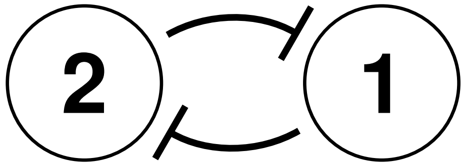
$$\left(\sigma^{+}_{1,2}(x_2) + \sigma^{+}_{1,3}(x_3)\right) \cdot \sigma^{-}_{1,4}(x_4)$$

$$\sigma^{+}_{1,2}(x_2) + \sigma^{+}_{1,3}(x_3) + \sigma^{-}_{1,4}(x_4)$$

$$\sigma^{+}_{1,2}(x_2) \cdot \sigma^{+}_{1,3}(x_3) \cdot \sigma^{-}_{1,4}(x_4)$$

The Dynamics (via an example)

The Toggle Switch

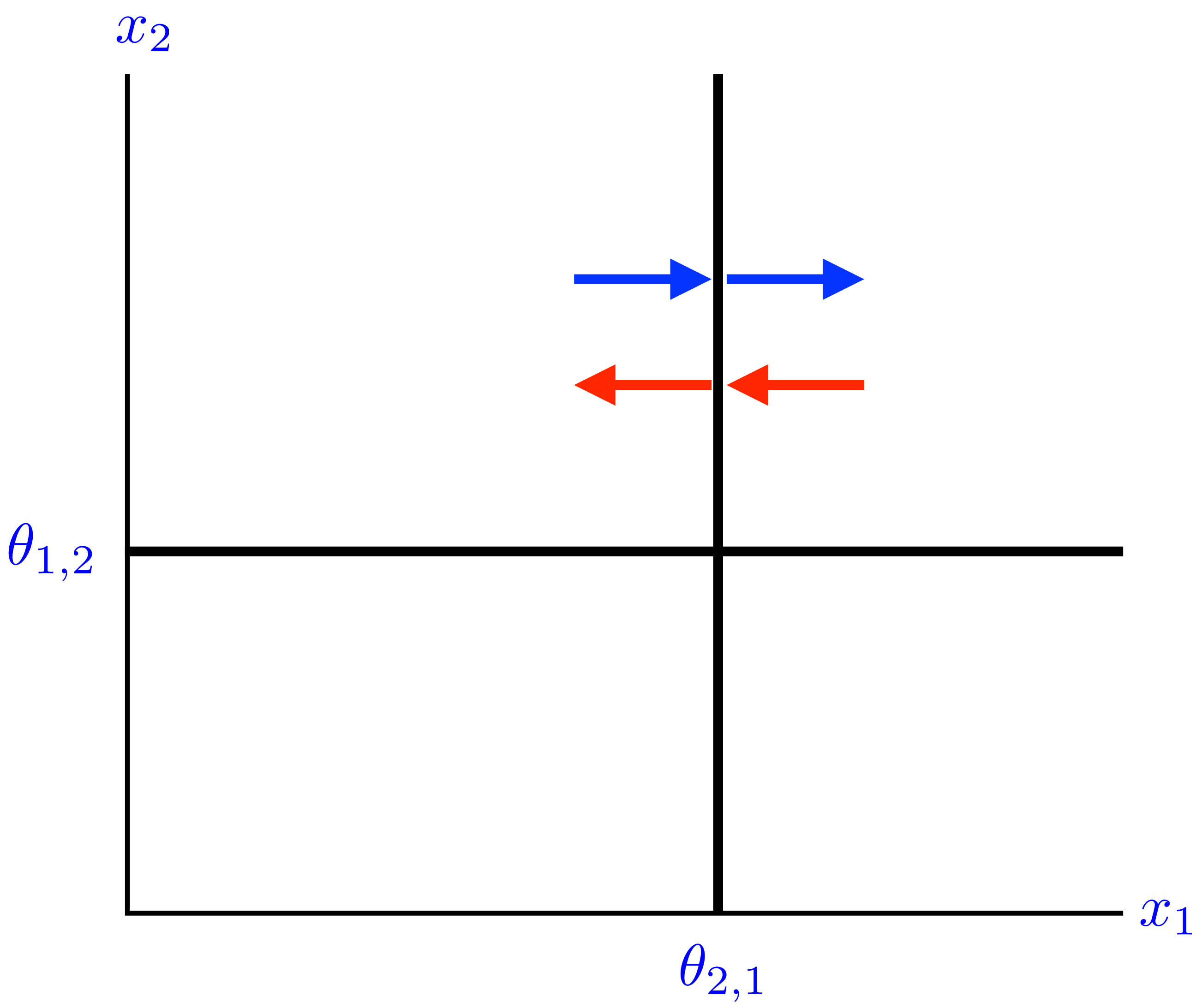


Parameter space: $Z \subset \bar{Z} \subset (0,\infty)^8$

$$\frac{dx_1}{dt} = -\gamma_1 x_1 + \sigma^-_{1,2}(x_2; \theta_{1,2}, \ell_{1,2}, u_{1,2})$$

decay rate   repression relation

Fix $z \in Z$



If $-\gamma_1\theta_{2,1} + \sigma^-_{1,2}(x_2) > 0$

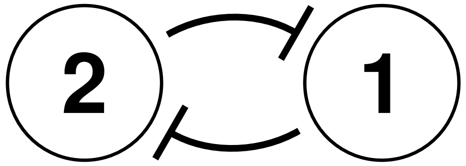
If $-\gamma_1\theta_{2,1} + \sigma^-_{1,2}(x_2) < 0$

Phase space: $X = (0,\infty)^2$

z is a regular parameter value if

$$0 < \gamma_i$$
$$0 < \ell_{i,j} < u_{i,j},$$
$$0 < \theta_{i,j} \neq \theta_{i,k}, \quad \text{and}$$
$$0 \neq -\gamma_i\theta_{j,i} + \Lambda_i(x)$$

The Toggle Switch

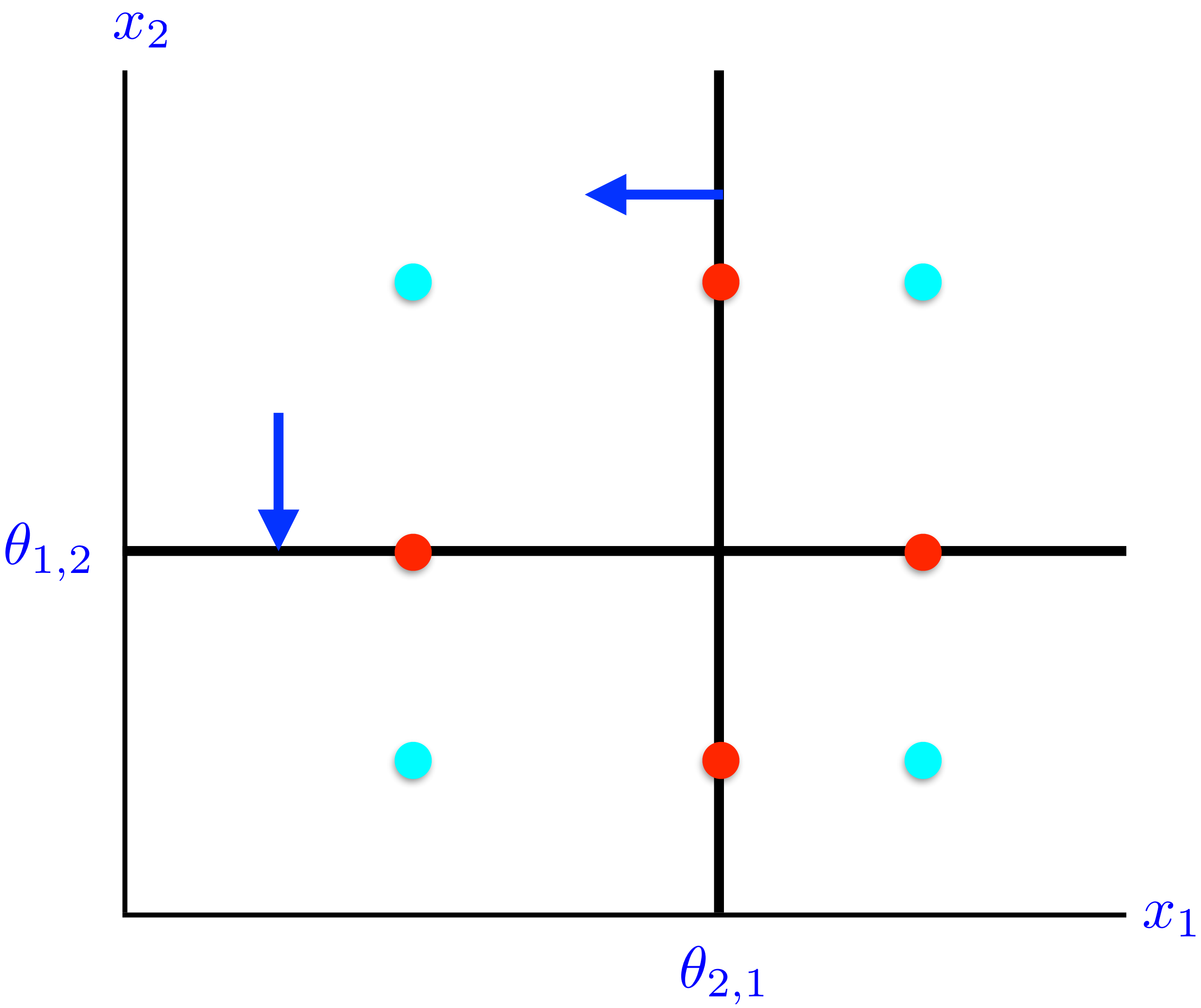


Constructing Combinatorial Dynamics

$\mathcal{F}_z : \mathcal{V} \rightrightarrows \mathcal{V}$

State Transition Graph

Fix $z \in Z$



Vertices

$\mathcal{V}$ corresponds to all rectangular domains and faces defined by thresholds

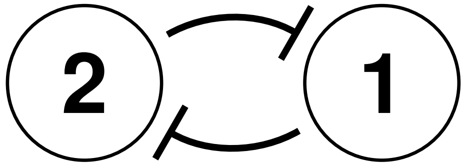
Edges

Faces pointing in map to their domain.

Domains map to their faces pointing out.

If no outpointing faces domain map to itself.

The Toggle Switch



Constructing Combinatorial Dynamics

Fix $z \in Z$

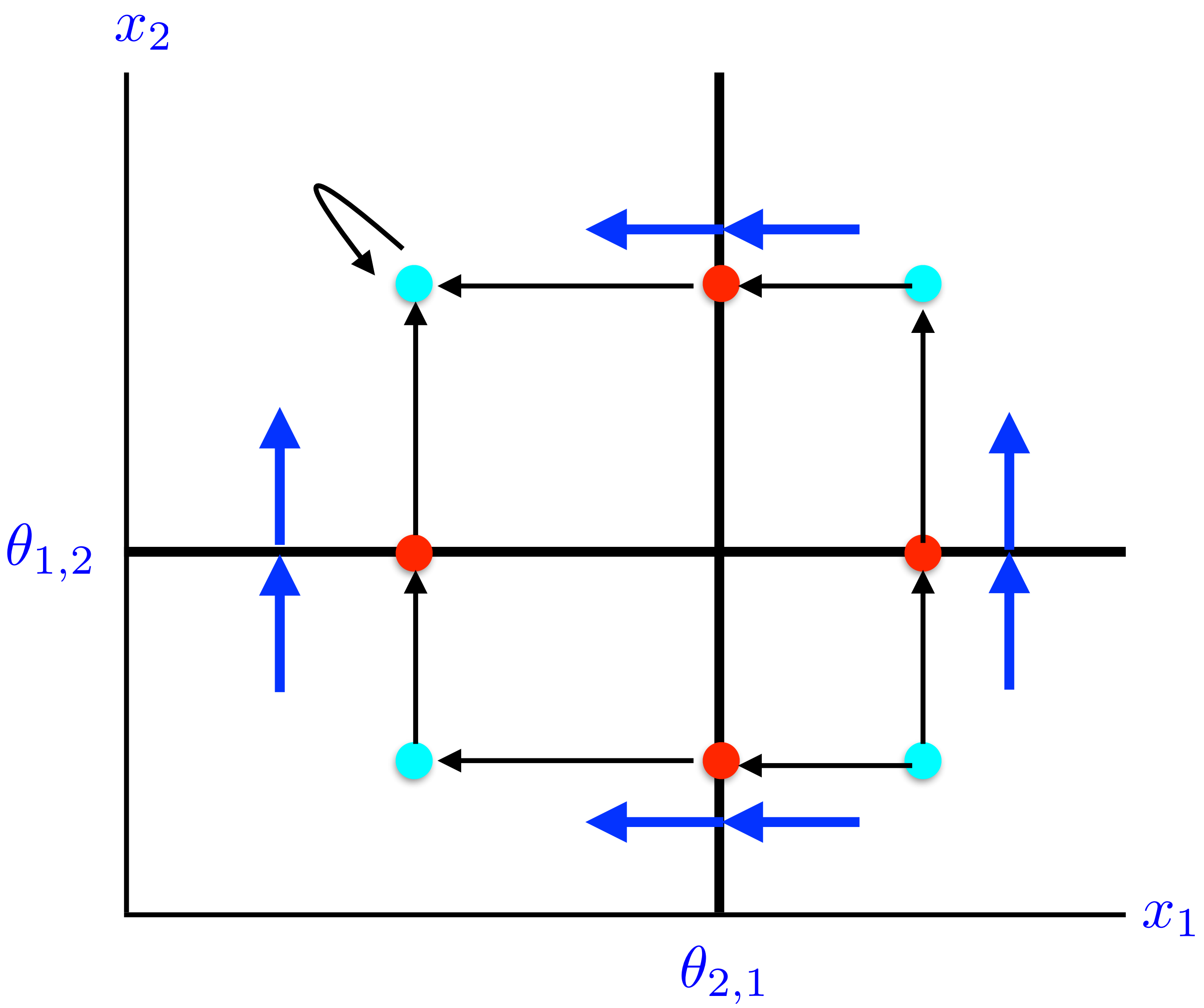
Assume:

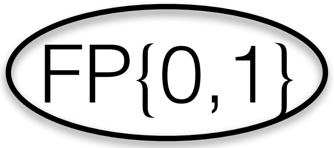
$$\boxed{\begin{array}{r} l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2} \\ \gamma_2\theta_{1,2} < l_{2,1} \end{array}}$$

$\mathcal{F}_z : \mathcal{V} \rightrightarrows \mathcal{V}$ State Transition Graph

z is a regular parameter value if

$$0 < \gamma_i$$
$$0 < \ell_{i,j} < u_{i,j},$$
$$0 < \theta_{i,j} \neq \theta_{i,k}, \quad \text{and}$$
$$0 \neq -\gamma_i\theta_{j,i} + \Lambda_i(x)$$

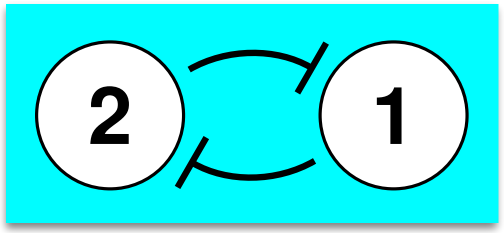




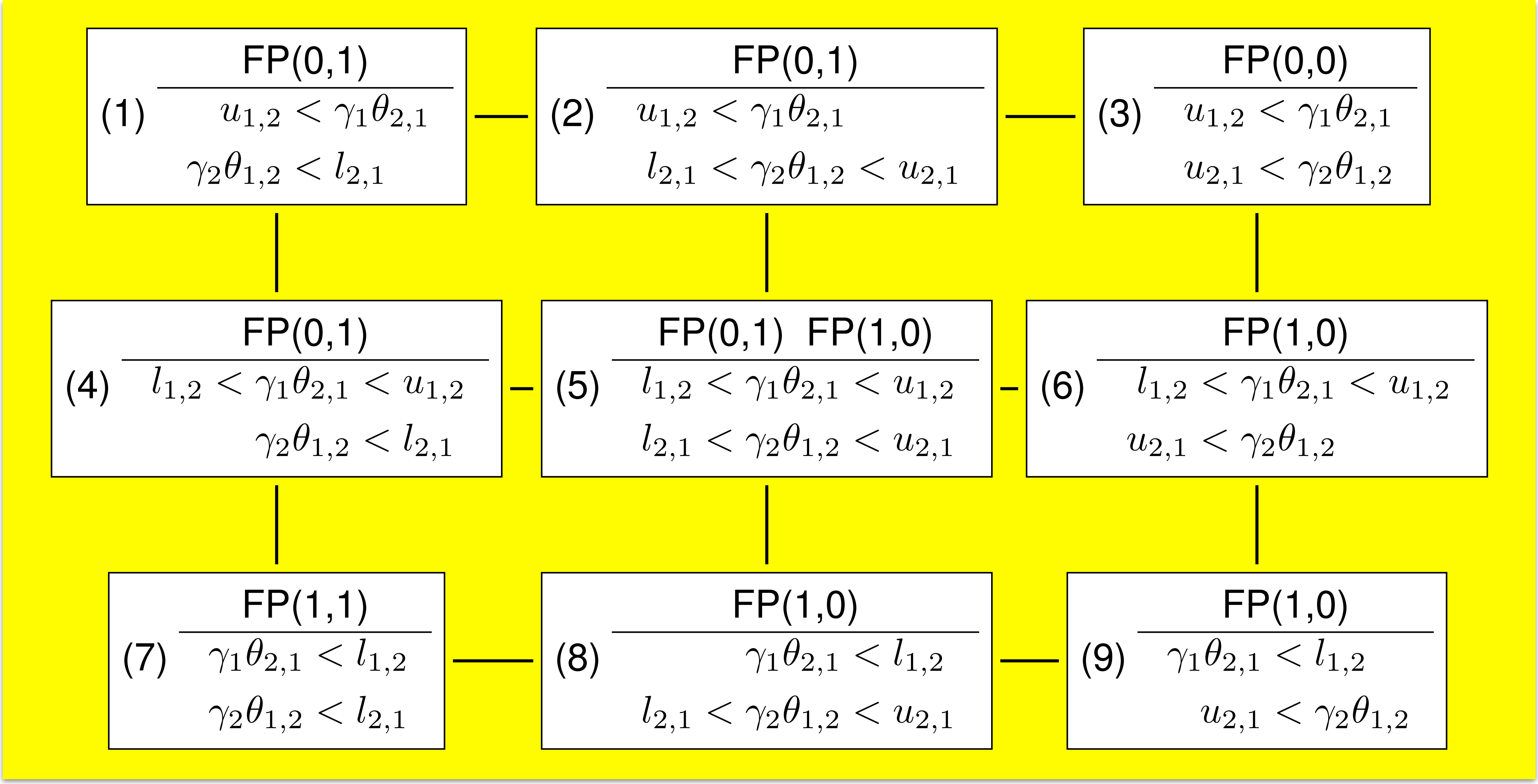
Morse Graph

DSGRN DATABASE FROM GENETIC TOGGLE SWITCH

Input:
Regulatory Network



Output:
DSGRN database



(1) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(2) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(3) FP(0,0)
$u_{1,2} < \gamma_1\theta_{2,1}$
$u_{2,1} < \gamma_2\theta_{1,2}$

(4) FP(0,1)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(5) FP(0,1) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(6) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

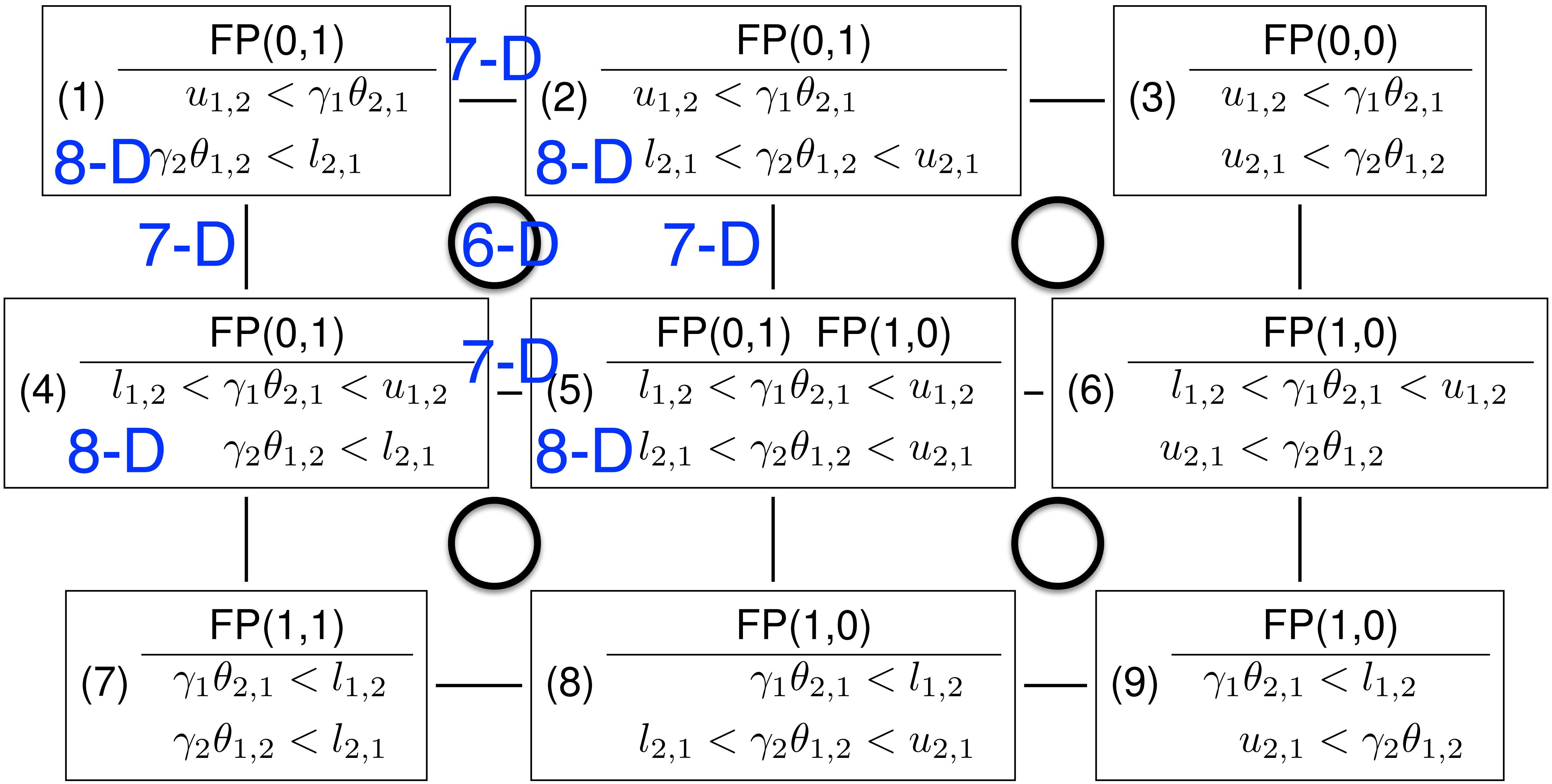
(7) FP(1,1)
$\gamma_1\theta_{2,1} < l_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(8) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(9) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

Parameter graph provides explicit partition of entire 8-D parameter space.

Observe that we can query this database for local or global dynamics.



(1) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(2) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(3) FP(0,0)
$u_{1,2} < \gamma_1\theta_{2,1}$
$u_{2,1} < \gamma_2\theta_{1,2}$

(4) FP(0,1)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(5) FP(0,1) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(6) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

(7) FP(1,1)
$\gamma_1\theta_{2,1} < l_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(8) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(9) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

Remark: Each node in parameter graph is a non-empty, connected region

Remark: This defines a complex, so in principle we can use this to determine homology of regions of parameter space that express dynamic phenotypes.

Recovering Classical Dynamics

Let $\varphi\colon \mathbb{R}\times X \to X$ be a flow with a compact global attractor S. A Morse decomposition of S under φ consists of a finite poset $(\mathsf{P},<)$ that labels a collection of mutually disjoint compact invariant sets $M(p)$ called Morse sets with the property that if $x \in S \setminus \bigcup_{p\in P} M(p)$ then there exists $p, q \in P$ such that

$$\alpha(x,\varphi) \subset M(p) \quad \text{and} \quad \omega(x,\varphi) \subset M(q)$$

and $q < p$.

Recovering Classical Dynamics

We have a *formal* ODE model for DSGRN

$$\frac{dx_1}{dt} = -\gamma_1 x_1 + \begin{cases} u_{1,2} & \text{if } x_2 < \theta_{1,2} \\ l_{1,2} & \text{if } x_2 > \theta_{1,2} \end{cases}$$

$$\frac{dx_2}{dt} = -\gamma_2 x_2 + \begin{cases} u_{2,1} & \text{if } x_1 < \theta_{2,1} \\ l_{2,1} & \text{if } x_1 > \theta_{2,1} \end{cases}$$

Remark: To move from this formal system to an appropriate set of ordinary differential equations is problem/context specific.

Open problem: Develop a natural methodology for doing this.

Special Case: Hill functions.

$$f^+(x) = \frac{x^n}{\theta^n + x^n}$$

$$f^-(x) = \frac{\theta^n}{\theta^n + x^n}$$

Recovering Classical Dynamics

$$\frac{du}{dt} = -u + \frac{\alpha_1}{1 + v^\beta}$$
$$\frac{dv}{dt} = -v + \frac{\alpha_2}{1 + u^\gamma}$$

Gardner, et. al., Construction of a genetic toggle switch in *E. coli*, Nature, 2000

General Hill Functions

$$\frac{dx_1}{dt} = -\gamma_1 x_1 + l_{1,2} + \frac{(u_{1,2} - l_{1,2})\theta^n_{1,2}}{\theta^n_{1,2} + x_2^n}$$
$$\frac{dx_2}{dt} = -\gamma_2 x_2 + l_{2,1} + \frac{(u_{2,1} - l_{2,1})\theta^n_{2,1}}{\theta^n_{2,1} + x_2^n}$$

$$n \to \infty$$

$$\frac{dx_1}{dt} = -\gamma_1 x_1 + \begin{cases} u_{1,2} & \text{if } x_2 < \theta_{1,2} \\ l_{1,2} & \text{if } x_2 > \theta_{1,2} \end{cases}$$

$$\frac{dx_2}{dt} = -\gamma_2 x_2 + \begin{cases} u_{2,1} & \text{if } x_1 < \theta_{2,1} \\ l_{2,1} & \text{if } x_1 > \theta_{2,1} \end{cases}$$

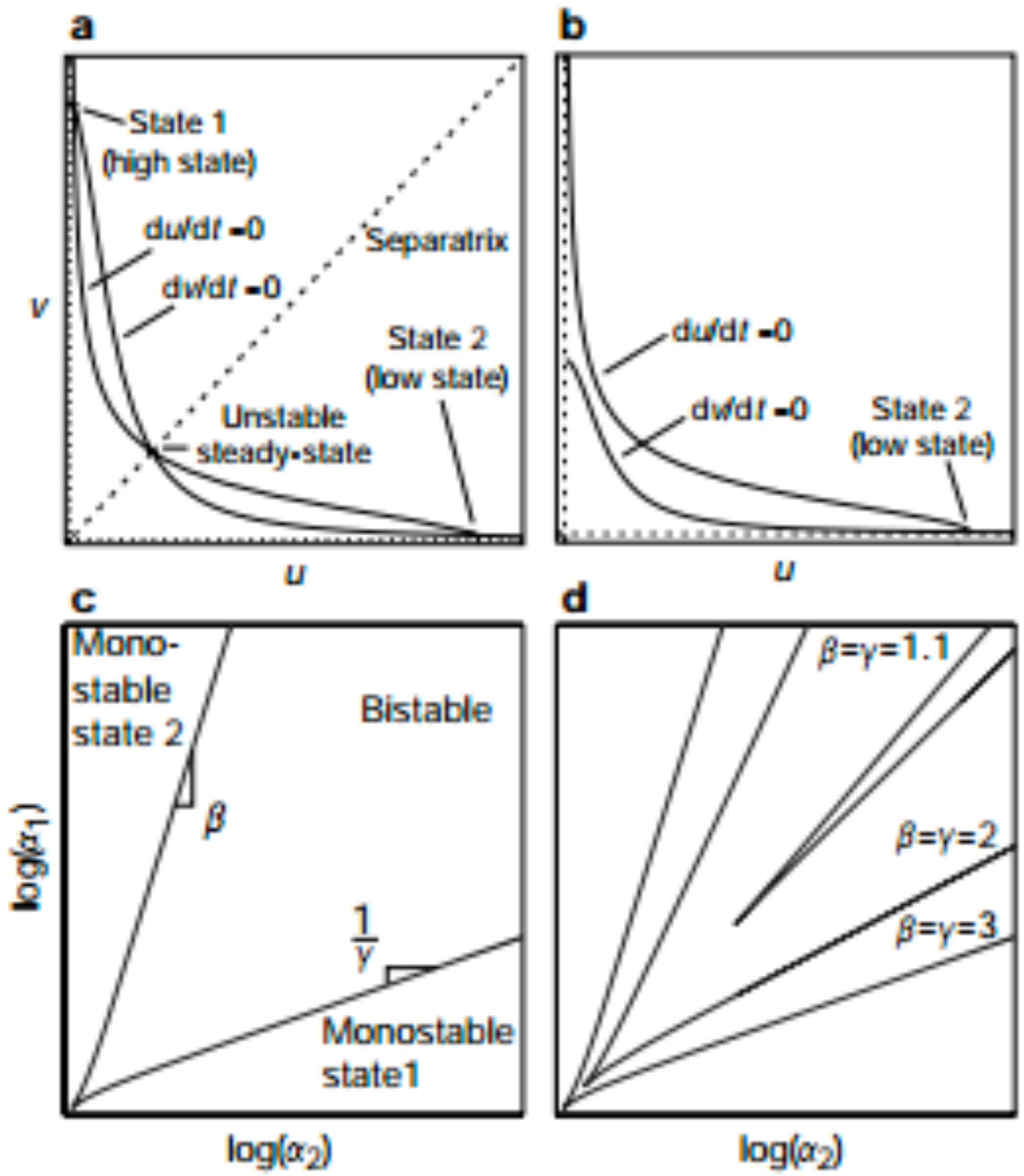


Figure 2 Geometric structure of the toggle equations. **a**, A bistable toggle network with balanced promoter strengths. **b**, A monostable toggle network with imbalanced promoter strengths. **c**, The bistable region. The lines mark the transition (bifurcation) between bistability and monostability. The slopes of the bifurcation lines are determined by the exponents β and γ for large α_1 and α_2. **d**, Reducing the cooperativity of repression (β and γ) reduces the size of the bistable region. Bifurcation lines are illustrated for three different values of β and γ. The bistable region lies inside of each pair of curves.

$$\frac{du}{dt} = -u + \frac{\alpha_1}{1+v^{\beta}}$$
$$\frac{dv}{dt} = -v + \frac{\alpha_2}{1+u^{\gamma}}$$

	FP(0,1)	FP(1,0)
(5)	$l_{1,2} < \gamma_1 \theta_{2,1} < u_{1,2}$ $l_{2,1} < \gamma_2 \theta_{1,2} < u_{2,1}$	

$$\gamma_1 = \gamma_2 = 1$$

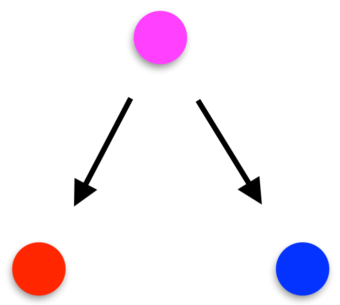
$$\ell_{1,2} = \ell_{2,1} = 0$$

$$\frac{dx_1}{dt} = -\gamma_1 x_1 + l_{1,2} + \frac{(u_{1,2} - l_{1,2})\theta^n_{1,2}}{\theta^n_{1,2} + x^n_2}$$
$$\frac{dx_2}{dt} = -\gamma_2 x_2 + l_{2,1} + \frac{(u_{2,1} - l_{2,1})\theta^n_{2,1}}{\theta^n_{2,1} + x^n_2}$$

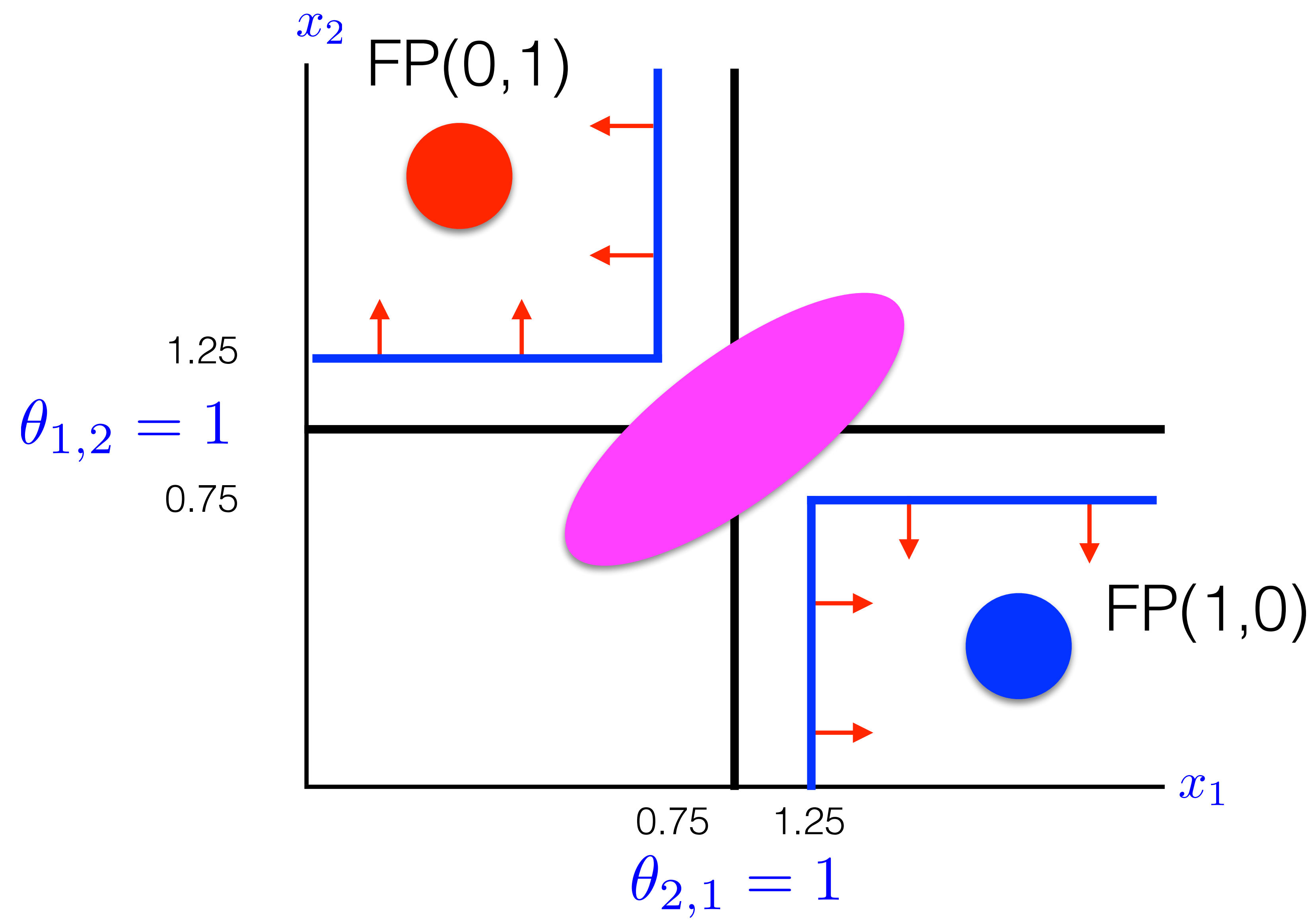
	FP(0,1)	FP(1,0)
(5)	$1 < u_{1,2}$ $1 < u_{2,1}$	

Consider what happens if we choose $u_{1,2} = u_{2,1} = 2$.

$$\frac{dx_1}{dt} = -x_1 + \frac{2}{1+x_2^n}$$
$$\frac{dx_2}{dt} = -x_1 + \frac{2}{1+x_1^n}$$



Poset for a Morse decomposition for the flow



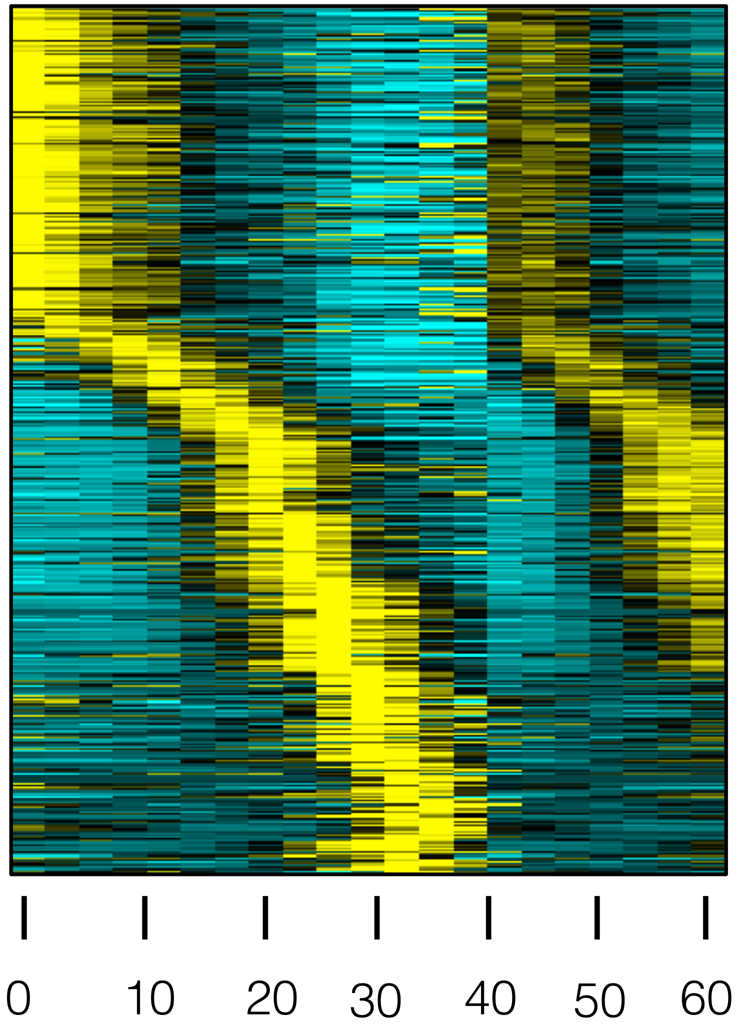
(5) FP(0,1) FP(1,0)

$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$

$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

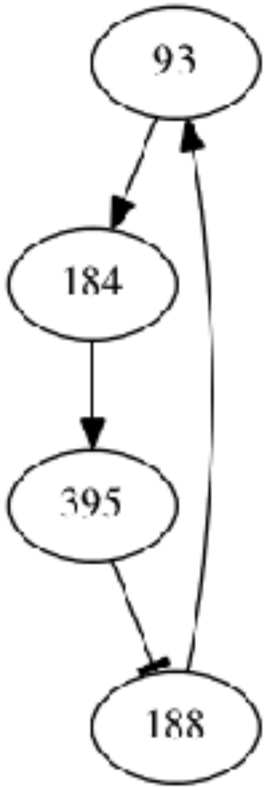
For $n \geq 4.5$ vector field is transverse to blue regions.

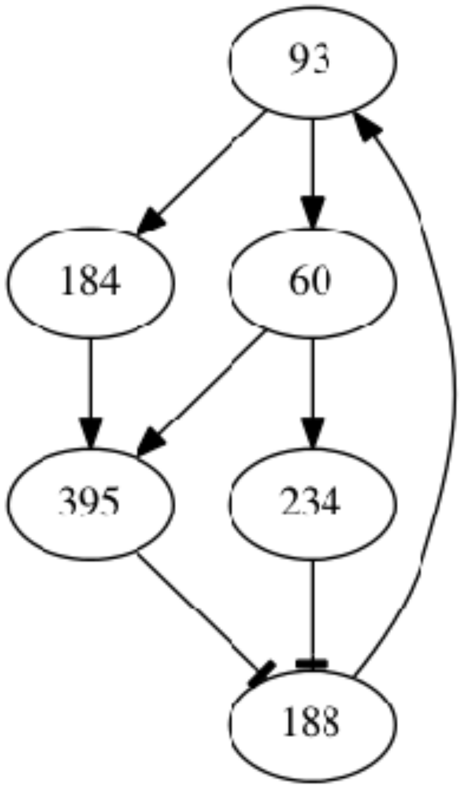
Malaria

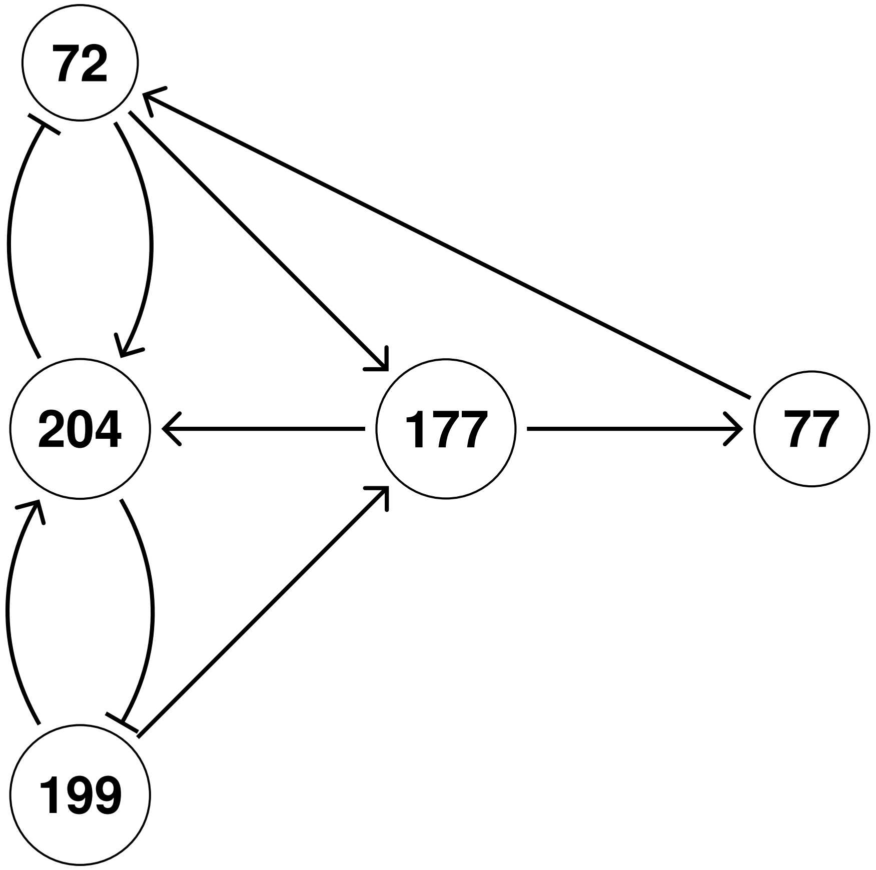


Putative TF genes (456)

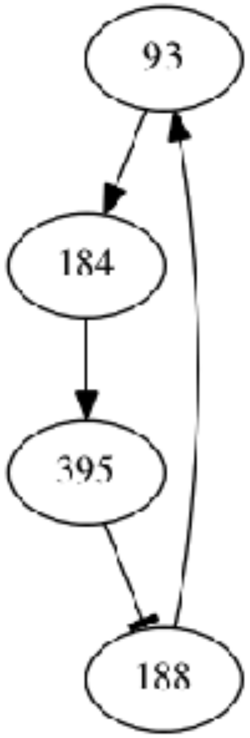
Can any of the following networks support the time series data?



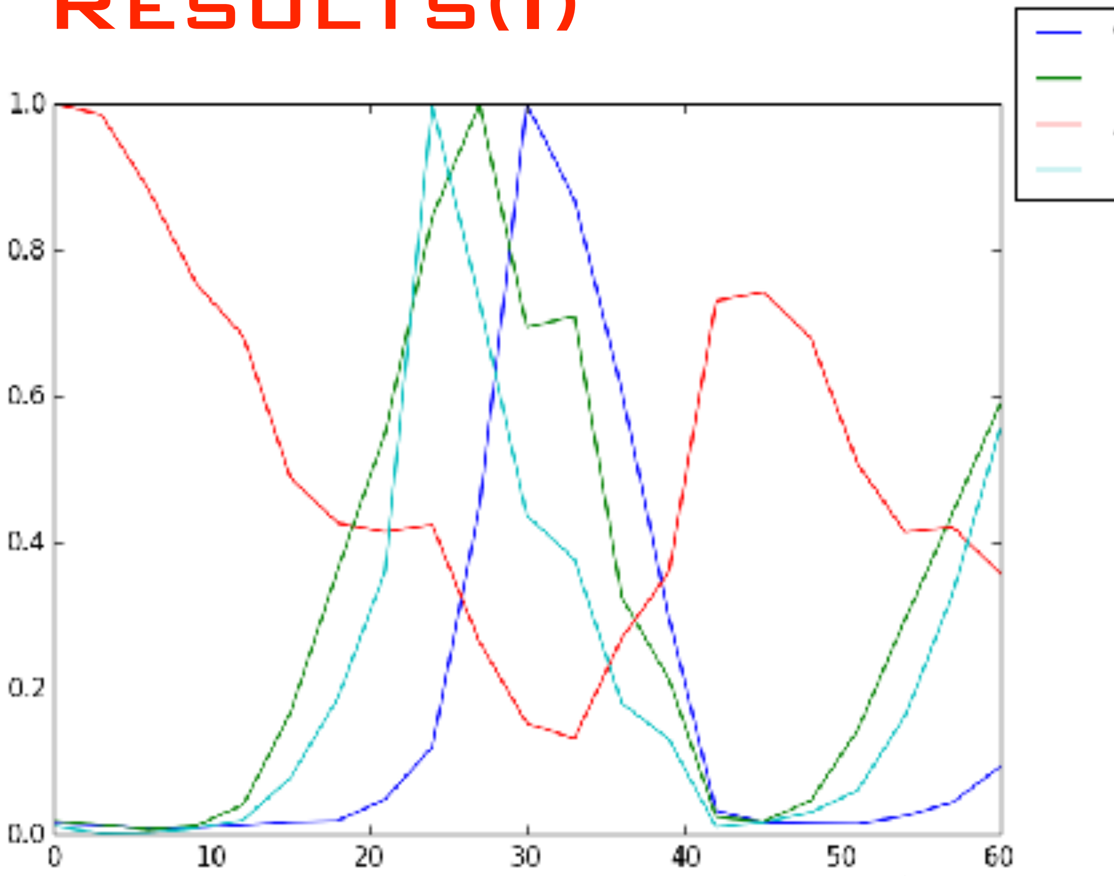




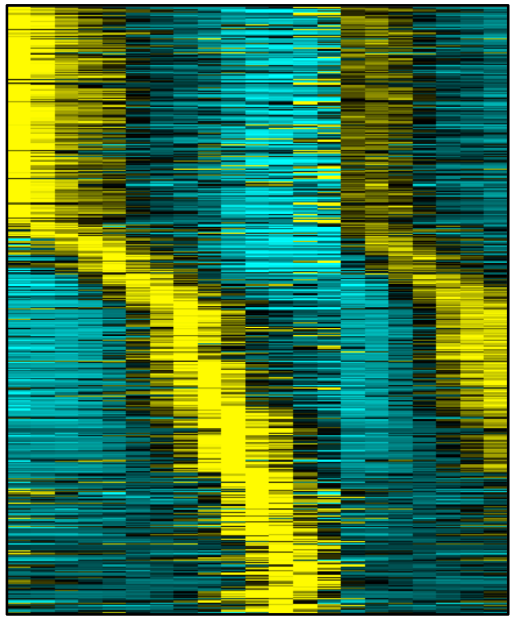
RESULTS(I)



Cyclic feedback system well understood using classical dynamical systems.



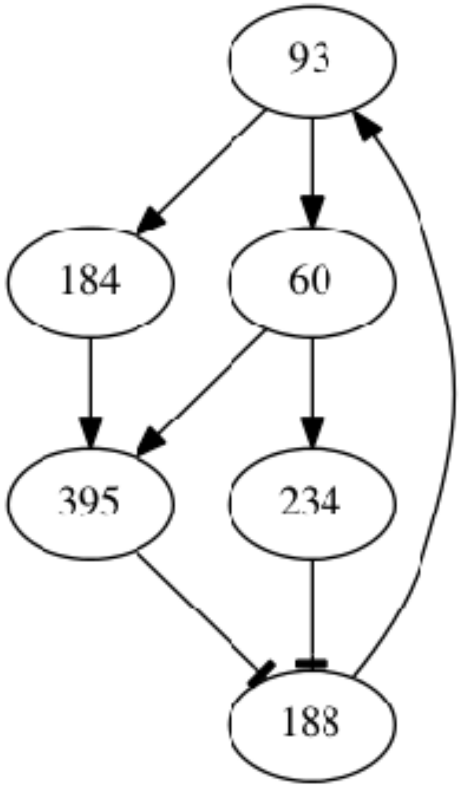
Experimental time series for associated genes



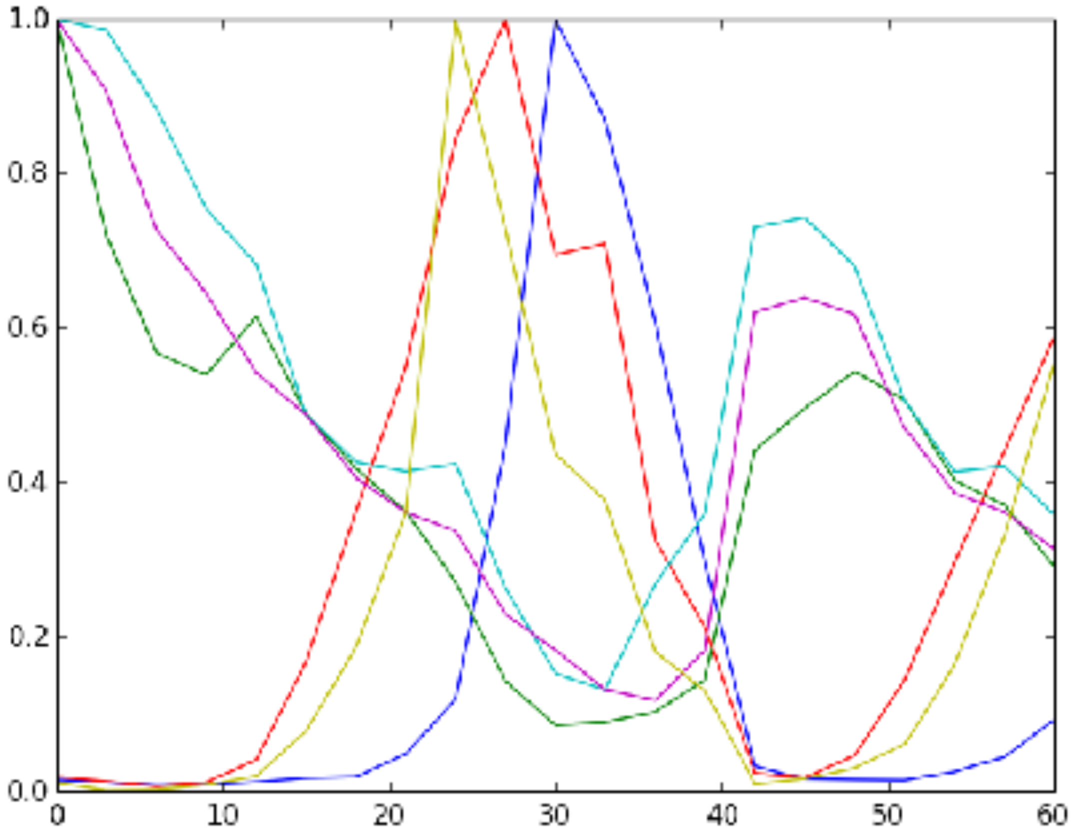
Under the assumption of monotone switches if parameter values are chosen such that there exists a stable periodic orbit, then the maxima in the network must occur in the order: (188,93,184, 395) (green, blue, cyan,red)

Conclusion: This network does not generate observed dynamics

DSGRN ANALYSIS (I): EXISTENCE OF OSCILLATIONS



No mathematical theory



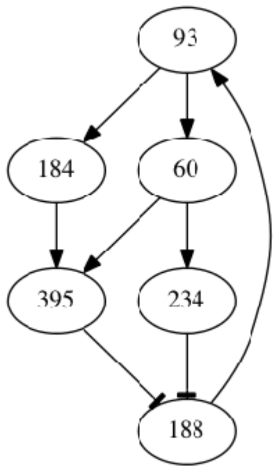
Time series for associated genes

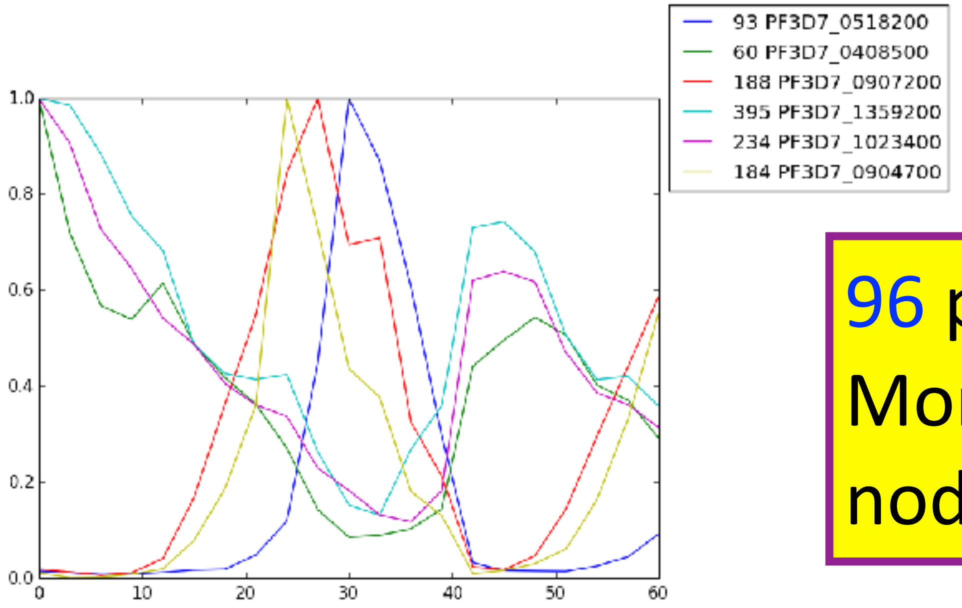
DSGRN computation produces a parameter graph with approximately 45,000 nodes.

SQL Query: A stable cycle involving oscillations in all genes

Computation time on laptop approximately 1 second.

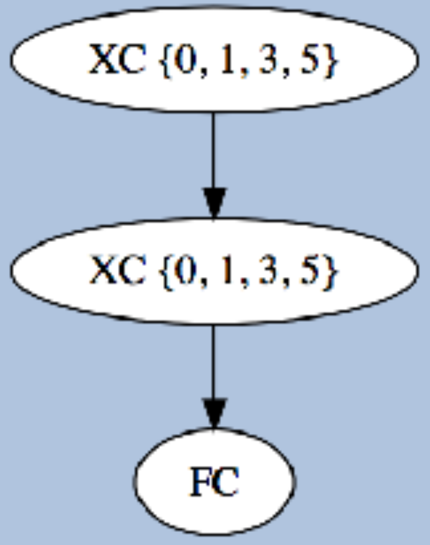
96 parameter graph nodes with Morse graph that has a minimal node consisting of a Full Cycle (FC).

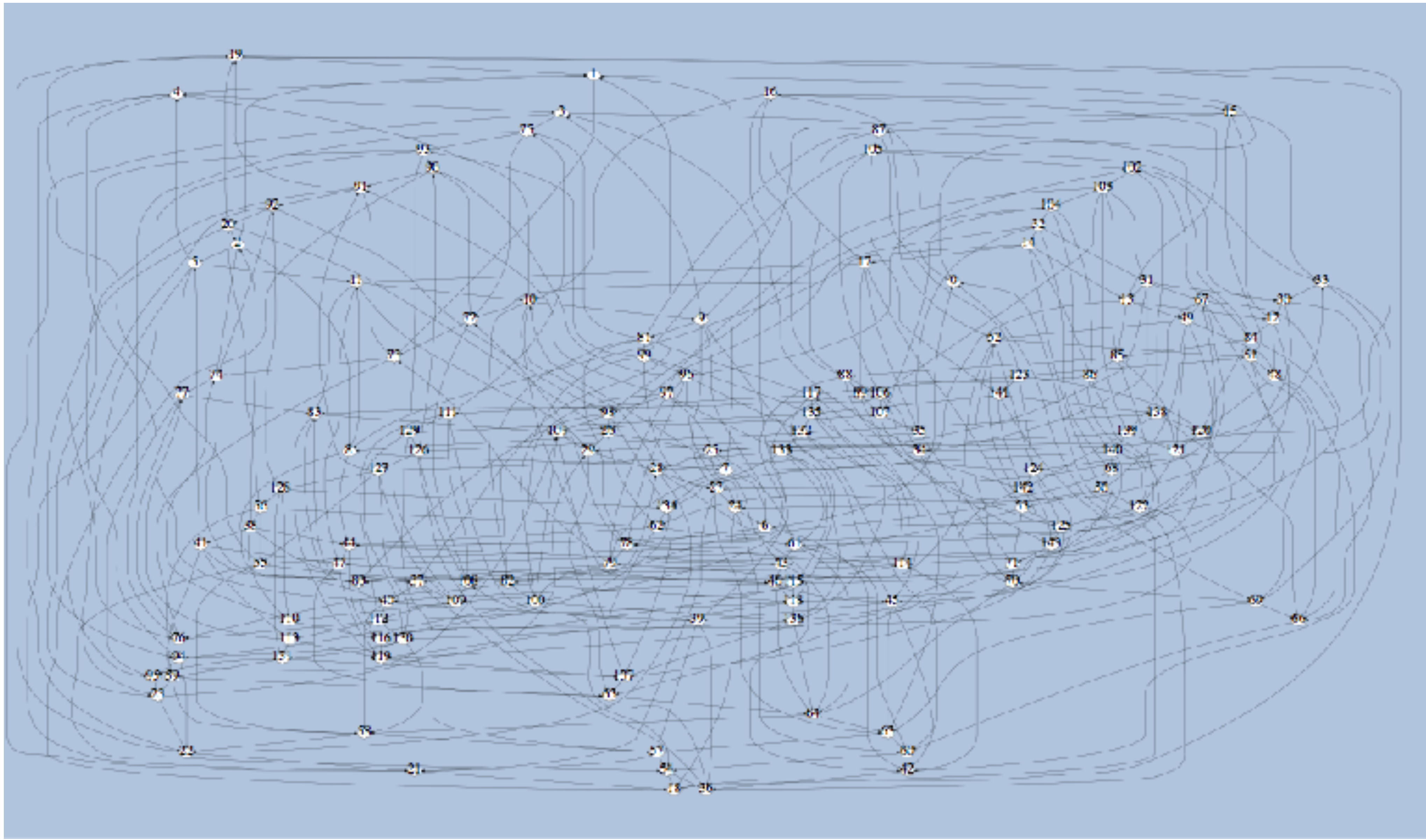




96 parameter graph nodes with Morse graph that has a minimal node consisting of a Full Cycle (FC).

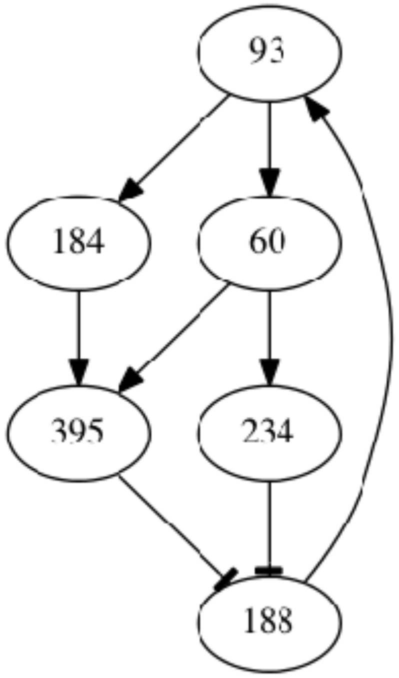
Morse Graph 47
Parameters: 8

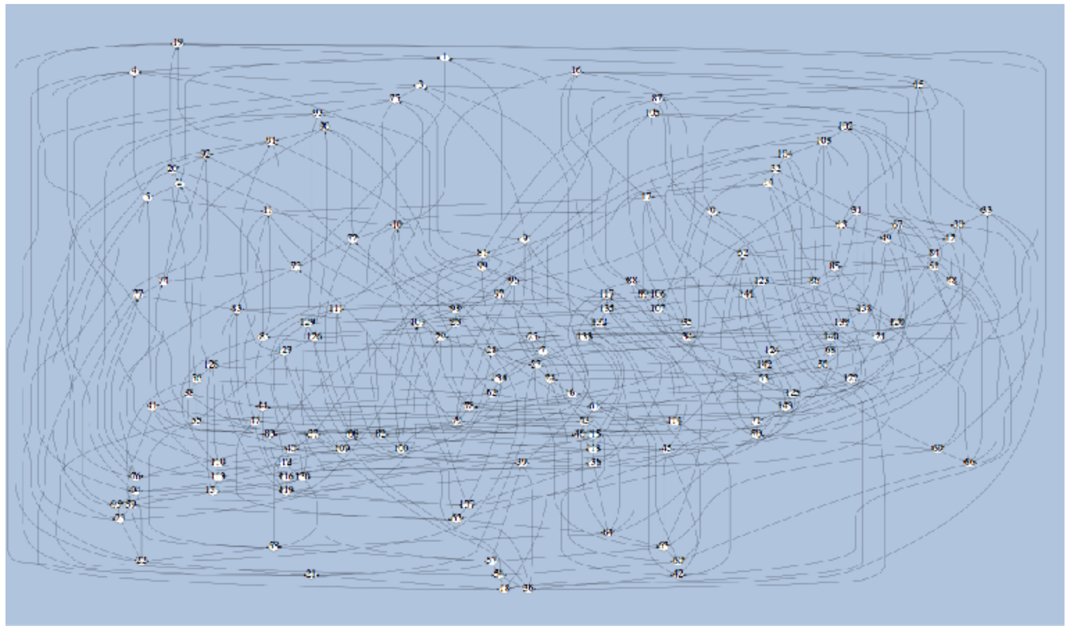


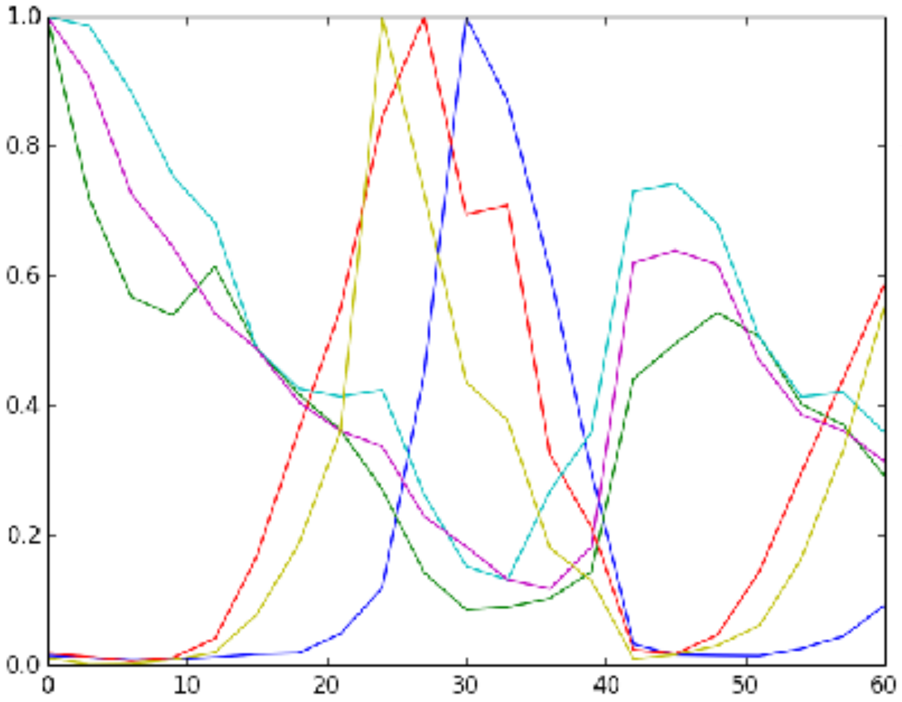


phase space dynamics (domain graph)

DSGRN ANALYSIS (II): MAX-MIN MATCHING





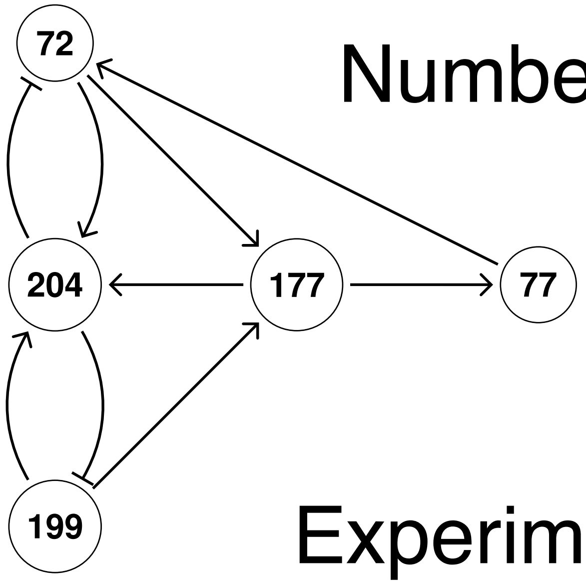


M m m
M m → M → M → M m
M m m

Have developed polynomial time algorithm that take paths in state transition graph and identifies sequences of possible maxima and minima.

Tested all max-min sequences from state transition graphs from all 96 parameter graph nodes against 17,280 experimental patterns. No Match

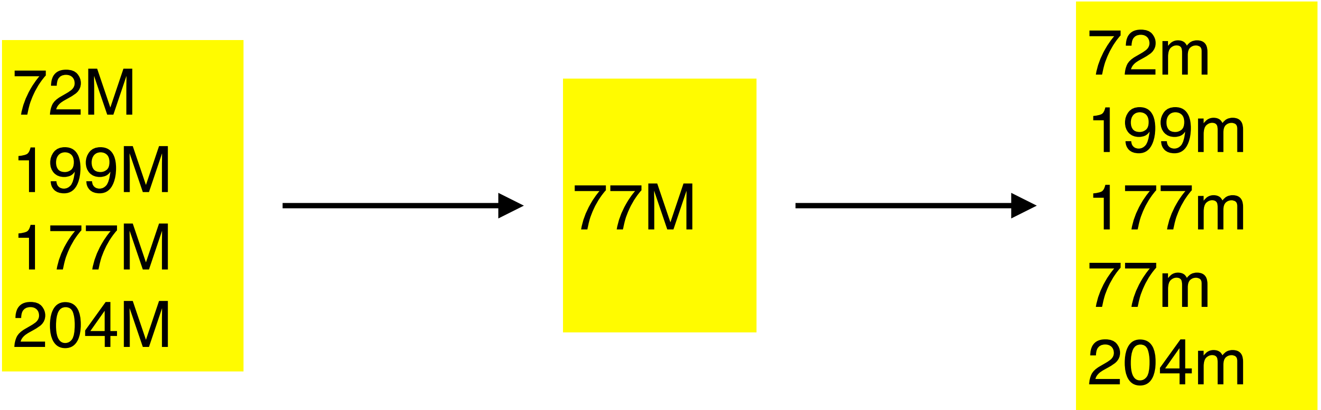
Conclusion: This network does not generate observed dynamics



Number of regions in parameter space: 17,280,000 (20 min)

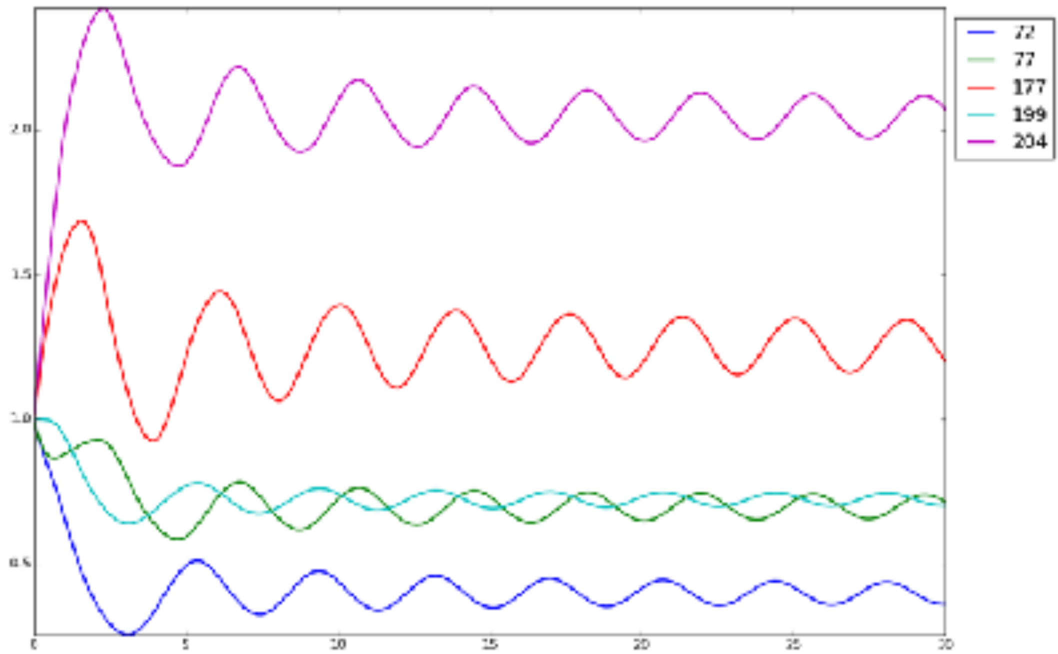
Number of regions for which Morse graph exhibits stable FC (cycle all elements oscillate): 342,800

Experimentally possible Max-Min ordering (2880)

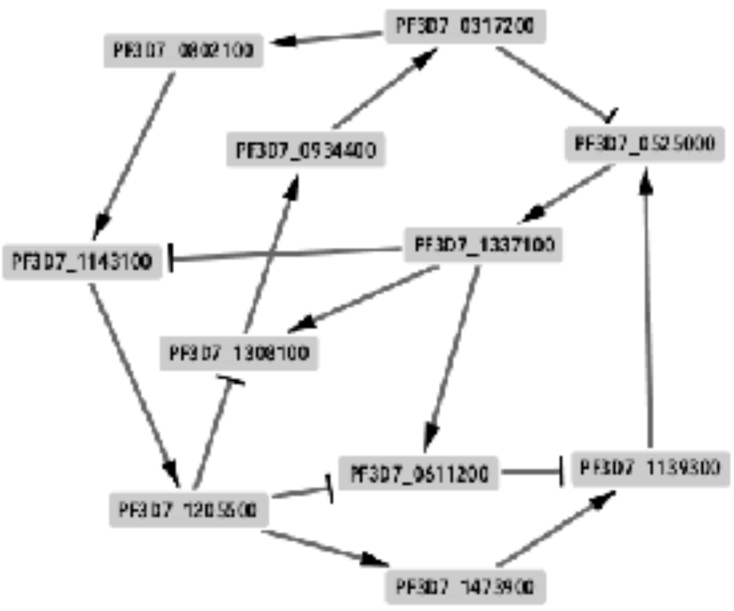


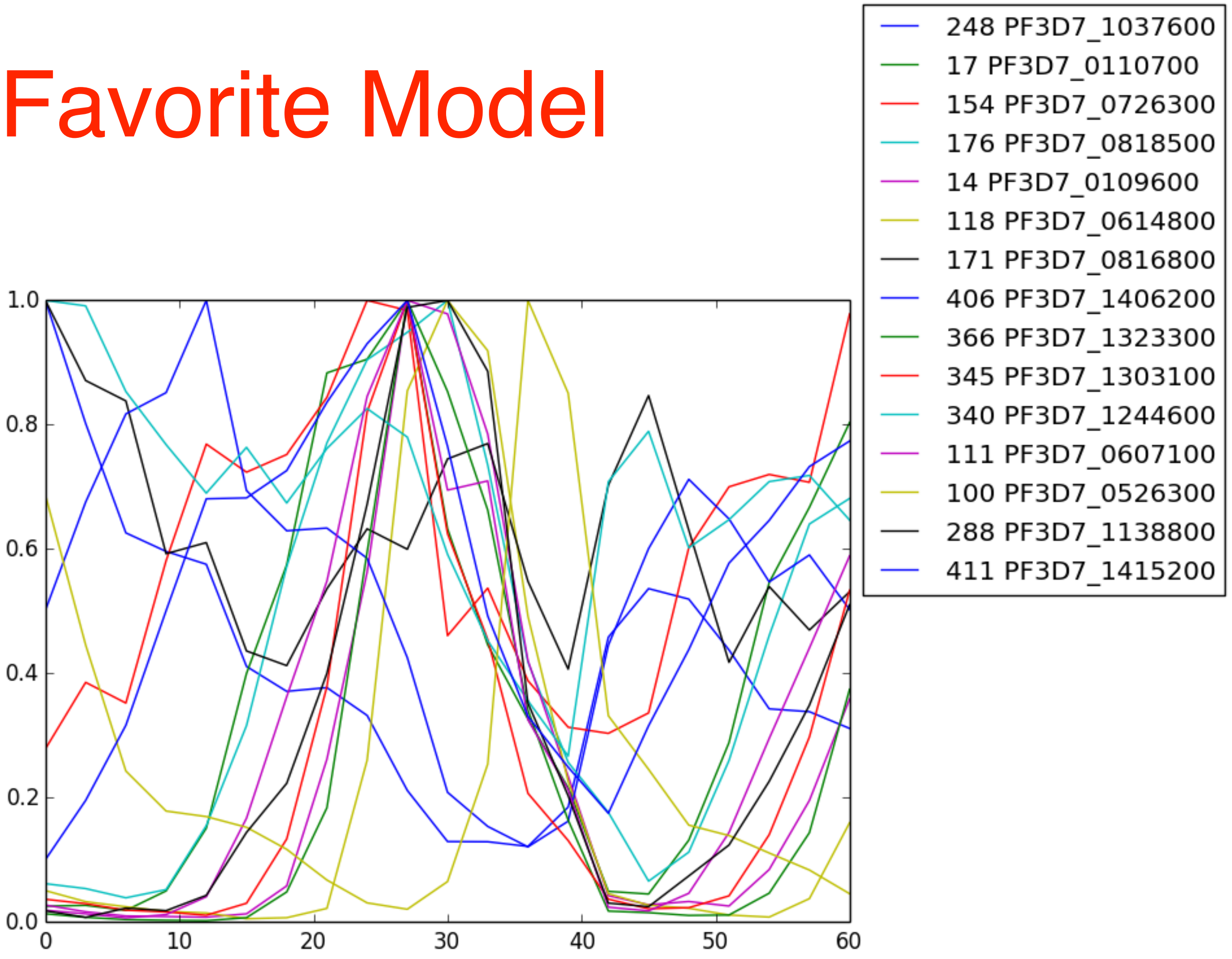
Number of regions where state transition graph produces experimentally possible Max-Min ordering: 100,346 (1 min)

Choose a parameter point from one of these regions. Numerically simulate an ODE with Hill function nonlinearities at the parameter value with Hill exponent n=10.



Current Favorite Model





Network dynamics matches experimental data for 49.7% of 9,069,926,400* parameter regions.

Parameter space is a subset of $(0, \infty)^{59}$.

*Essential Network:

Only consider parameter values such that each node talks to and is talked to by another node.

Summary

Lecture 1: Why we need a new paradigm for dynamics.

Lecture 2: DSGRN, an instantiation of a new approach to dynamics.

Used the toggle switch as an example.

Dynamics were formulated in language of posets (Morse graphs).

Did not need to use concepts of flows, invariant sets, etc.

Used Malaria data to show that DSGRN can perform nontrivial computations efficiently.

Lecture 3: Mathematical challenges.

4 Fundamental Challenges

I. Relation to classical Dynamics: How do we translate DSGRN results into the language of dynamical systems

Ii. Parameter Space: How do we understand geometry associated with parameter graph?

III. Refinements: How do we do finer approximations?

IV. Size of Parameter Graph: How to reduce stored data?

I. RELATION TO CLASSICAL DYNAMICS:

For each parameter value $z \in Z$ we produce a state transition graph $\mathcal{F}\colon \mathcal{V} \rightrightarrows \mathcal{V}$.

The associated Morse graph is the Hasse diagram for the poset P of recurrent components of $\mathcal{F}\colon \mathcal{V} \rightrightarrows \mathcal{V}$.

The lattice of downsets $\mathsf{O}(\mathsf{P})$ is isomorphic to the lattice of attractors of $\mathcal{F}\colon \mathcal{V} \rightrightarrows \mathcal{V}$.

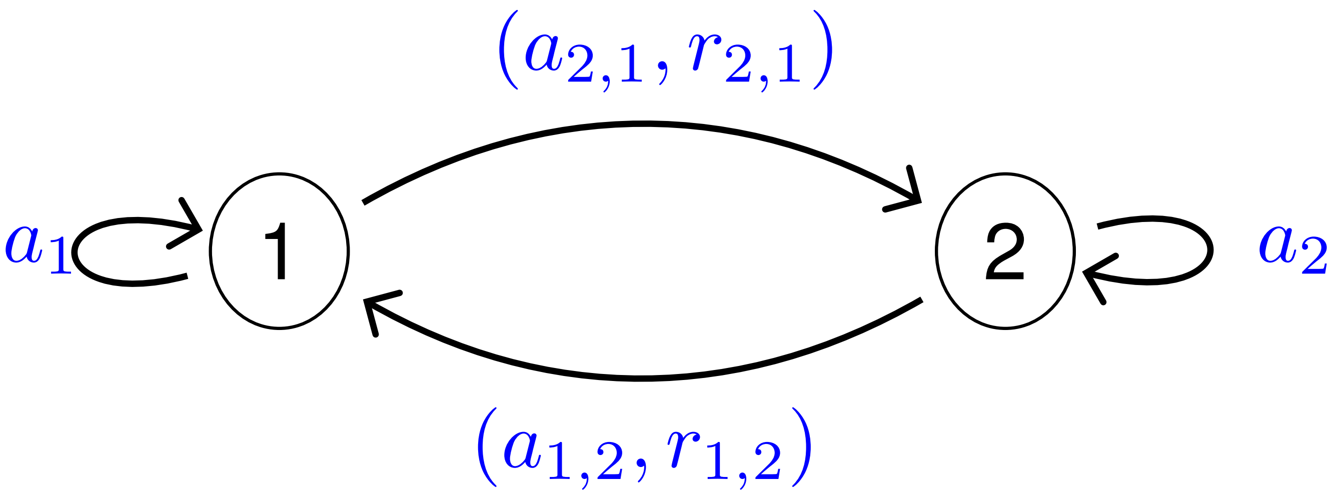
DSGRN

Let A be a finite lattice of attracting blocks for a dynamical system $\varphi\colon \mathbb{R}^+ \times X \to X$.

Then $\mathsf{P} := \mathsf{J}(\mathsf{A})$ is a poset order for a Morse decomposition of X under φ.

Classical

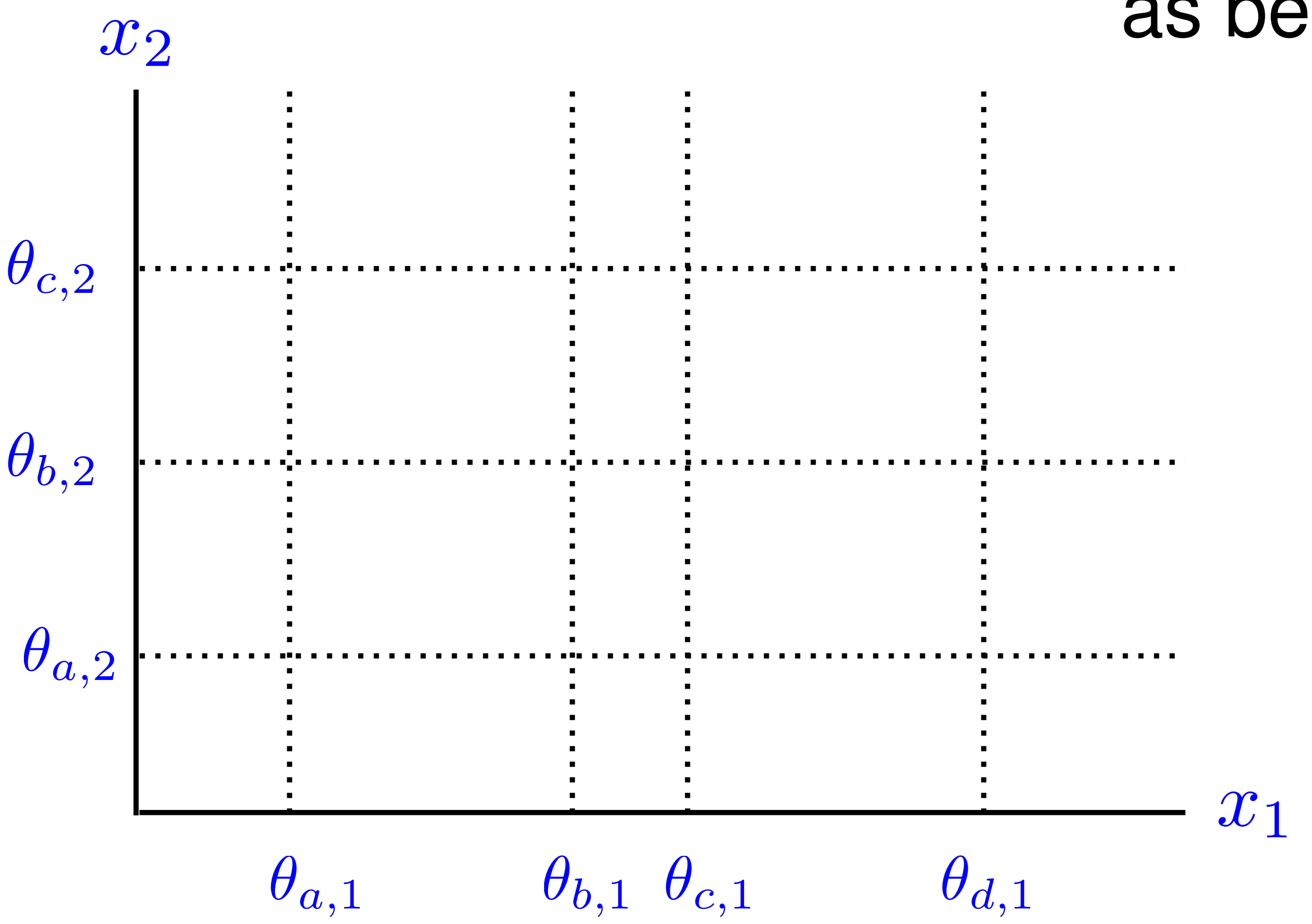
Multigraph

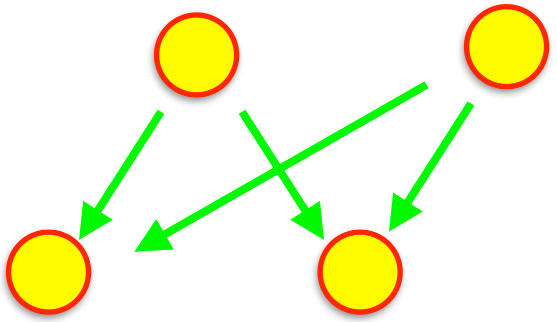


$$\boxed{\Lambda_i(x) := M_i(\sigma(x))}$$

For fixed $z \in Z$ we have a rectangular decomposition of phase space.

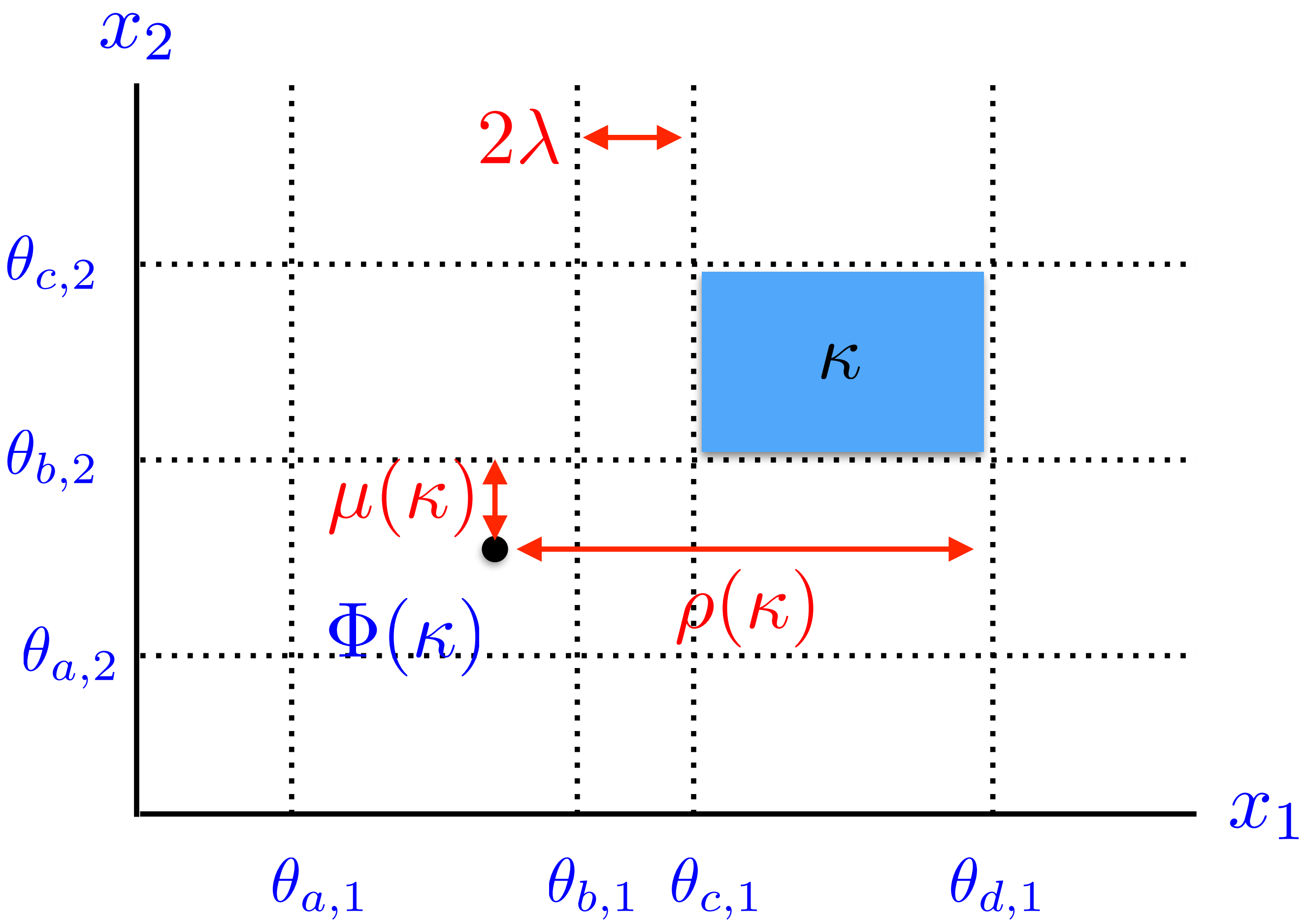
Define state transition graph $\mathcal{F} \colon \mathcal{V} \rightrightarrows \mathcal{V}$ as before.

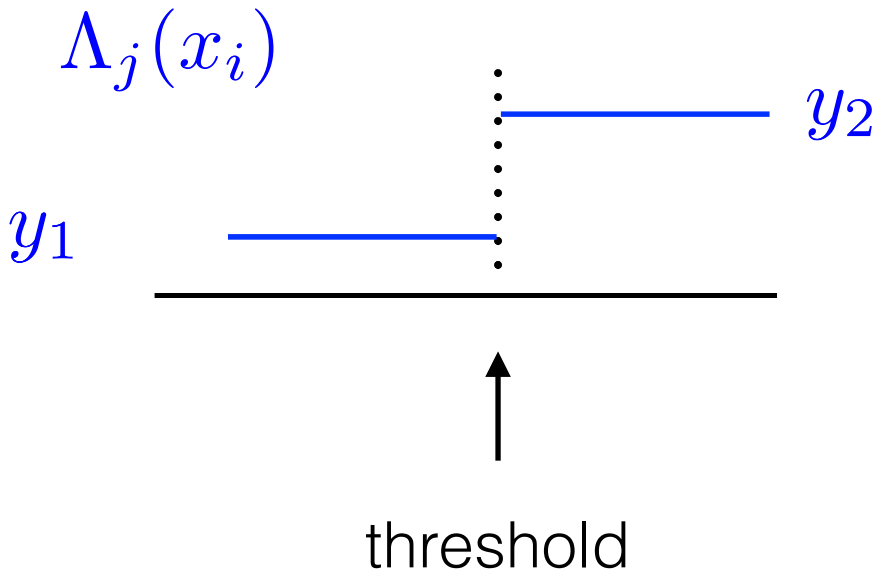




Morse Graph

Question: For what differential equations $\dot{x} = f(x)$, $x \in (0,\infty)^2$, is this Morse graph information relevant?





Set

$$\Phi(\kappa) := \begin{pmatrix} \gamma_1^{-1}\Lambda_1(\kappa) \\ \gamma_2^{-1}\Lambda_2(\kappa) \end{pmatrix}$$

Define:

$$\mu = \min_{\kappa} \mu(\kappa)$$

$$\rho = \max_{\kappa} \rho(\kappa)$$

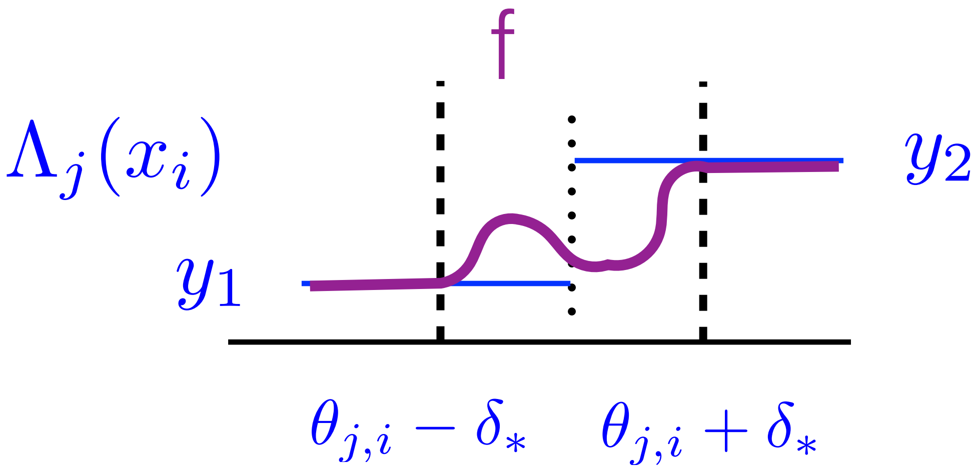
$$\bar{\gamma} = \min\left\{\frac{\gamma_1}{\gamma_2}, \frac{\gamma_2}{\gamma_1}\right\}$$

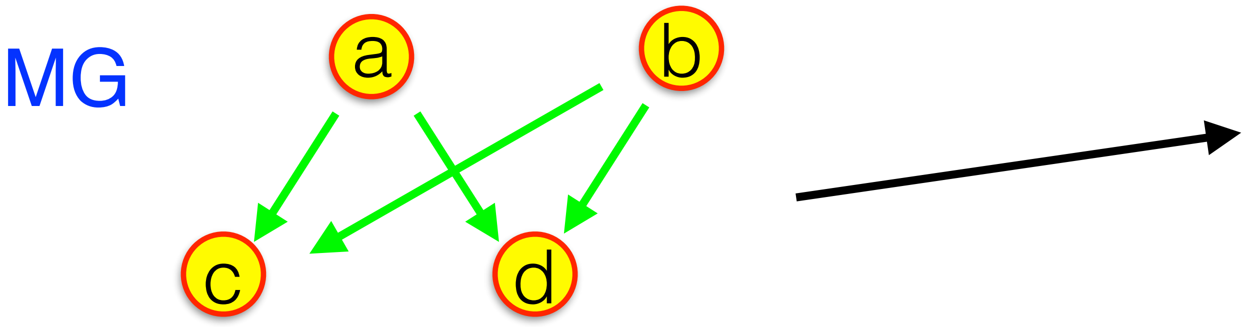
$$\delta_* := \min\left\{\frac{\lambda\mu\bar{\gamma}}{\sqrt{2}(2\lambda + 3\rho)}, \sqrt{\frac{\lambda\mu\bar{\gamma}}{32}}\right\}$$

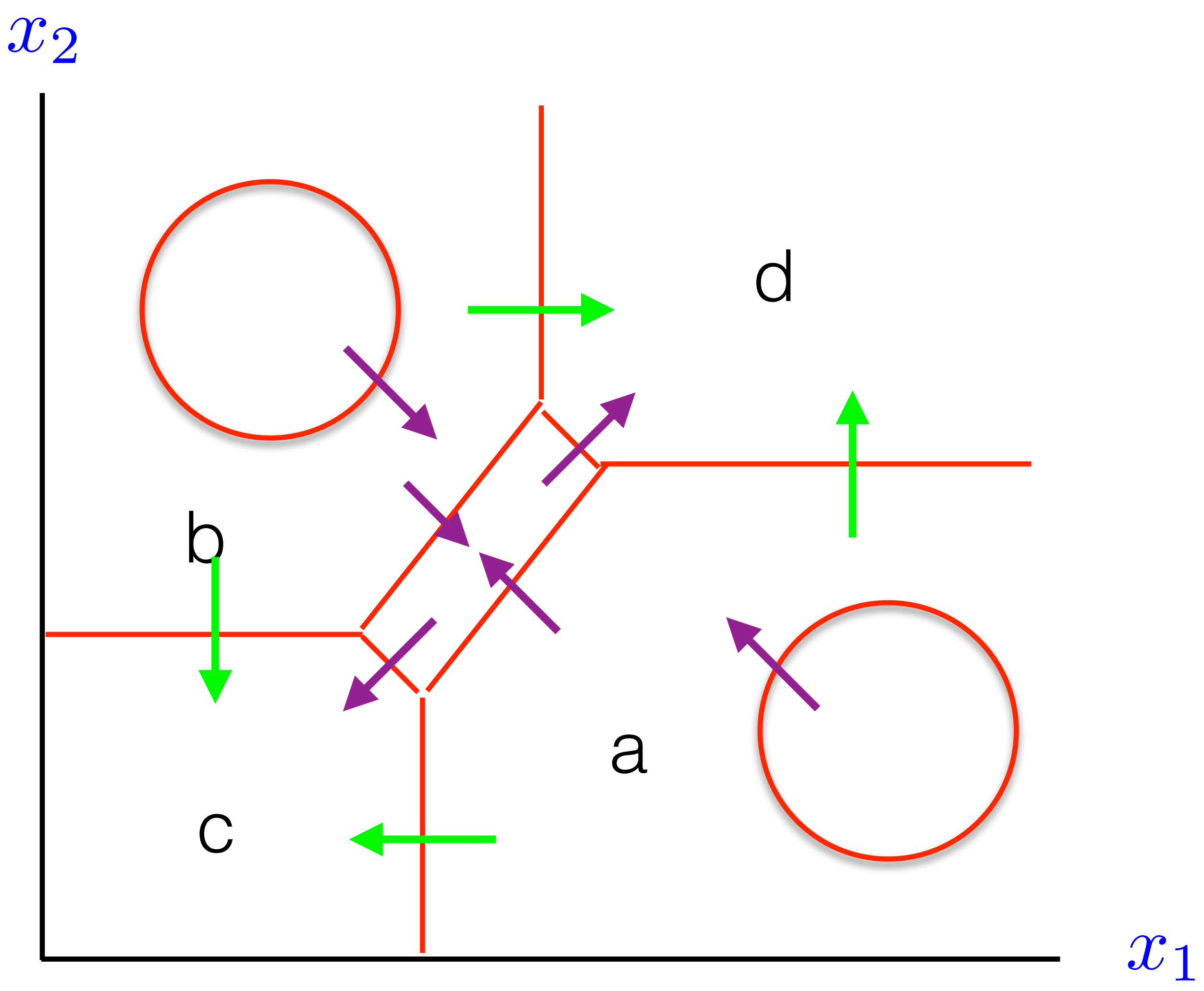
Theorem: (T. Gedeon, S. Harker, H. Kokubu, K.M., H. Oka) There exists a Morse decomposition (invariant sets associated with a filtration of phase space indexed by a poset P) for

$$\dot{x}_j = -\gamma_j x_j + f_j(x), \quad j = 1, 2,$$

such that there is an order preserving injection MG → P.

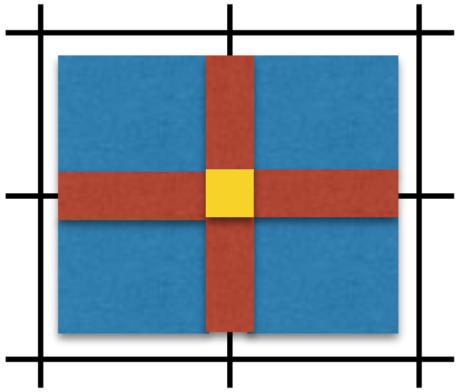






Idea of proof: Consider four regions.

Define five types of tiles.



Given an attractor $\mathcal{A}$ of $\mathcal{F}\colon \mathcal{V} \rightrightarrows \mathcal{V}$, for each set of four regions, one applied 6 rules that indicate which tiles should be used.

This defines a map $N\colon \mathsf{Att}(\mathcal{F}) \to \mathcal{P}(X)$

Prop: $N\colon \mathsf{Att}(\mathcal{F}) \to \mathsf{ANbhd}$ is a join semi-lattice morphism.

$$N(A_0 \wedge A_1) = N(A_0) \cap N(A_1) \in \mathsf{ANbhd}$$

$$\begin{tikzcd}
(\mathsf{P}(\mathcal{F}), <_{\mathsf{P}(\mathcal{F})}) \arrow[r, "\text{Birkhoff}"] \arrow[drr, dotted] & \mathsf{Att}(\mathcal{F}) \arrow[r, "N"] & \mathsf{L}(N(\mathsf{Att}(\mathcal{F}))) \arrow[d, "\text{Birkhoff}"'] & \\
 & & (\mathsf{J}^{\vee}(\mathsf{L}(N(\mathsf{Att}(\mathcal{F})))), <) \arrow[r, "\mu"] & MD(\varphi)
\end{tikzcd}$$

II. PARAMETER SPACE (PARAMETER GRAPHS)

Given a regulatory network $RN = (V, E)$ the associated parameter space is $\bar{Z} \subset [0, \infty)^D$ where $D = \#(V) + 3 \cdot \#(E)$ and a parameter $z = (\ell, u, \theta, \gamma) \in \bar{Z}$ satisfies the following constraints:

$$0 \leq \theta_{i,j}, \qquad 0 \leq \ell_{i,j} \leq u_{i,j}, \qquad 0 \leq \gamma_i.$$

The set of regular parameter values $Z \subset \bar{Z}$ is defined to be the complement of the set of parameter values that satisfy the following equalities:

1. $0 = \theta_{i,j}$, $0 = \ell_{i,j}$, $0 = u_{i,j}$, $0 = \gamma_i$,
2. $0 = u_{i,j} - \ell_{i,j}$,
3. $0 = \theta_{i,j} - \theta_{k,i}$,
4. $0 = \gamma_j \theta_{i,j} - \Lambda_j(\kappa)$,

A parameter value $z \in \bar{Z}$ is k-deficient if exactly k of the equalities are satisfied.

where $\kappa \subset (0, \infty)^{\#(V)}$ is a $\#(V)$-dimensional rectangular domain defined by the thresholds θ and $\theta_{i,j}$ defines a face of κ.

Mathematically we view the DSGRN database as a map.

The nodes of the parameter graph, denoted by $\mathcal{Z}$, are regions of parameter space and the edges indicate geometric relations between the regions.

The map is

$$DB\colon \mathcal{Z} \to AMG$$

where AMG denotes the collection of annotated Morse graphs.

There are (at least) two reasonable ways to define $\mathcal{Z}$.

The Geometric Parameter Graph GPG is defined as follows. Let $\mathcal{Z}$ denote the set of connected components of Z. Given $\zeta_0, \zeta_1 \in \mathcal{Z}$, the parameter graph has an edge (ζ_0, ζ_1) if there exists $z \in \mathrm{cl}(\zeta_0) \cap \mathrm{cl}(\zeta_1)$ such that k is 1-deficient.

Prop: The GPG is connected.

The definition of the Combinatorial Parameter Graph CPG is technical. Heuristically, $\mathcal{Z}$ denotes the set of algebraic relations defined by the complement that lead to non-empty sets of parameters. Given $\zeta_0, \zeta_1 \in \mathcal{Z}$, the parameter graph has an edge (ζ_0, ζ_1) if exactly one of the algebraic constraints differ.

For each $i \in V$ the nodes of the geometric factor graph GPG_i is defined to be the connected components of the complement of the set of parameter values that satisfy the following equalities:

1. $0 = \theta_{j,i}$, $0 = \ell_{j,i}$, $0 = u_{j,i}$, $0 = \gamma_i$,
2. $0 = u_{j,i} - \ell_{j,i}$,
3. $0 = \theta_{j,i} - \theta_{k,i}$,
4. $0 = \gamma_i \theta_{j,i} - \Lambda_i(\kappa)$,

where $\theta_{j,i}$ defines a face of κ. Two nodes share an edge if they admit a 1-deficient point in their common boundary.

Prop: $GPG = \prod_{i \in V} GPG_i$

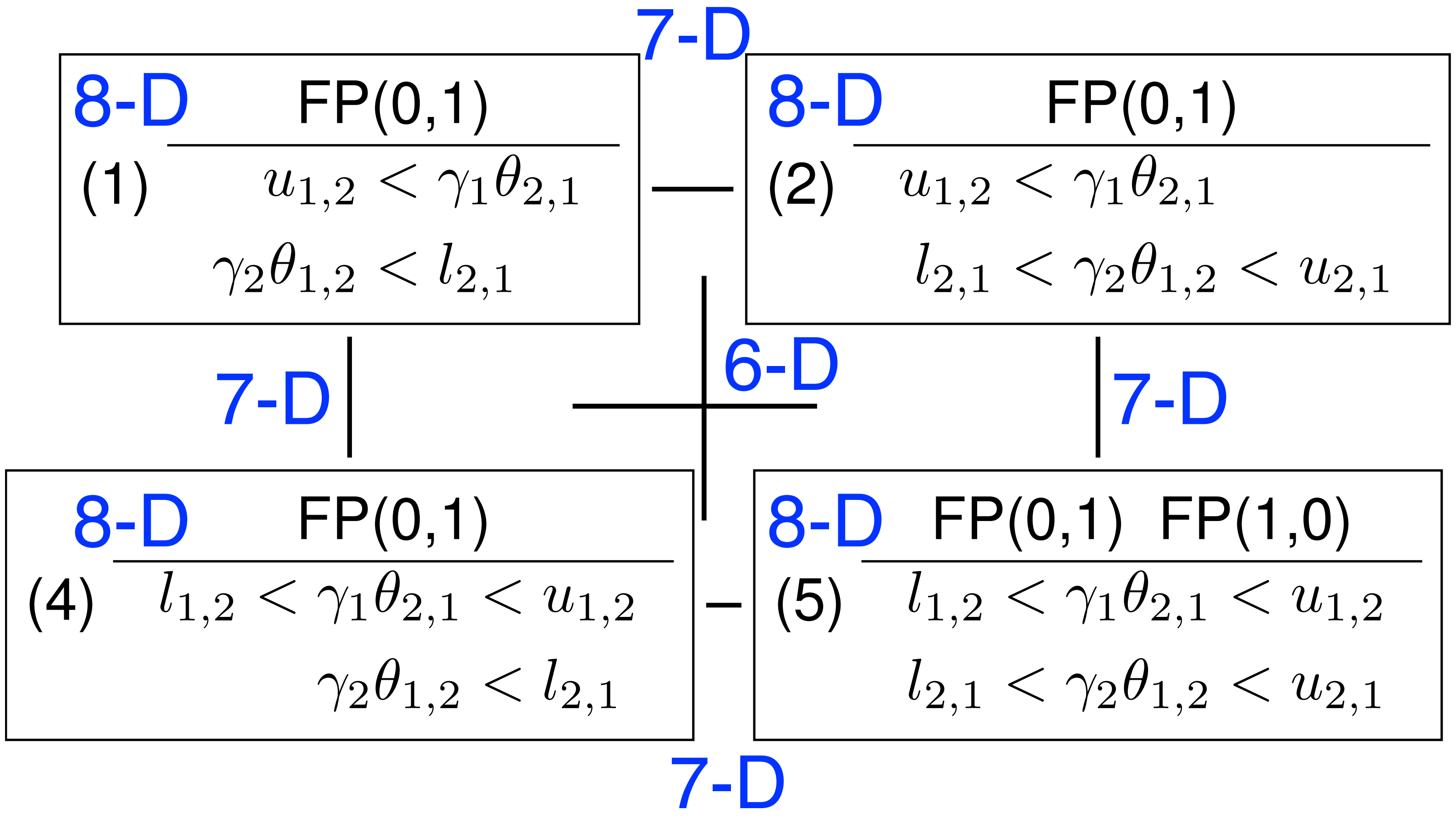
Same result for CPG.

Thm: GPG and CPG are isomorphic in the following cases.

$\#$Sources(i)	$\#$Targets(i)	M_i	$\#PG_i/\#$Targets$(i)!$
1	1	x	3
1	2	x	6
1	3	x	10
2	1	$x+y$	6
2	1	xy	6
2	2	$x+y$	20
2	2	xy	20
2	3	$x+y$	50
2	3	xy	50
3	1	$x+y+z$	20
3	1	xyz	20
3	1	$x(y+z)$	20
3	2	$x+y+z$	150
3	2	xyz	150
3	2	$x(y+z)$	155
3	3	$x+y+z$	707
3	3	xyz	707
3	3	$x(y+z)$	756

Open Question: How can one can one compute the homology of regions of parameter space defined by unions of nodes of parameter graph?

Conjecture: It has a CW type structure that leads to a computable cell complex.



7-D

8-D FP(0,1)

(1) $u_{1,2} < \gamma_1\theta_{2,1}$

$\gamma_2\theta_{1,2} < l_{2,1}$

8-D FP(0,1)

(2) $u_{1,2} < \gamma_1\theta_{2,1}$

$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

7-D

6-D

7-D

8-D FP(0,1)

(4) $l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$

$\gamma_2\theta_{1,2} < l_{2,1}$

8-D FP(0,1) FP(1,0)

(5) $l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$

$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

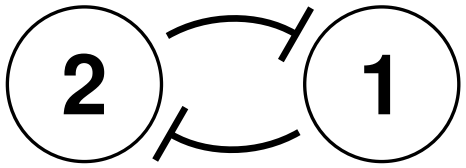
7-D

III. Refinements: How do we do finer approximations?

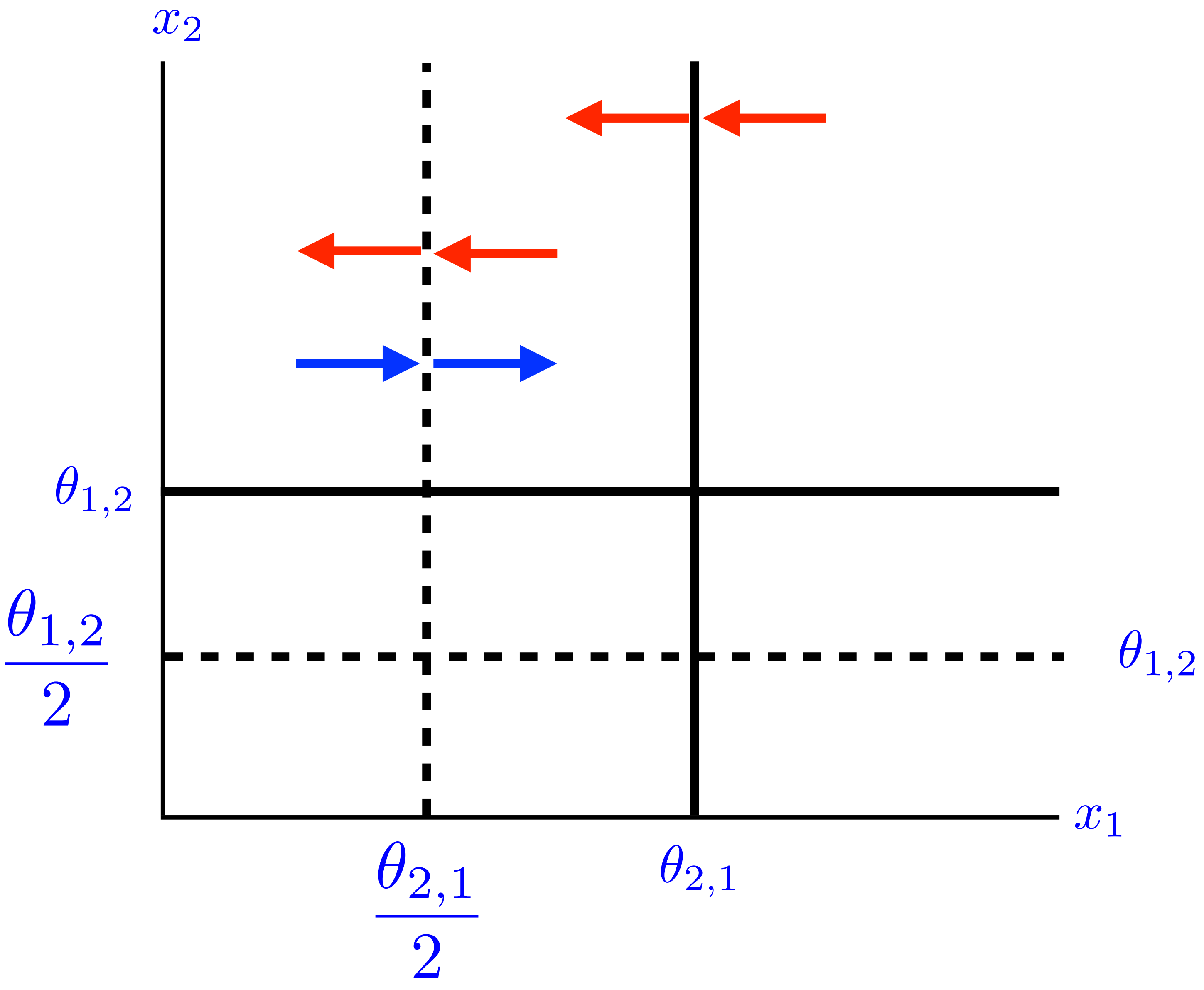
III. REFINEMENTS: BISECTION

The Toggle Switch

Parameter space: $Z \subset \bar{Z} \subset (0,\infty)^8$



Fix $z \in Z$



If $-\gamma_1\theta_{2,1} + \sigma^{-}_{1,2}(x_2) < 0$

If $-\gamma_1\frac{\theta_{2,1}}{2} + \sigma^{-}_{1,2}(x_2) < 0$

If $-\gamma_1\frac{\theta_{2,1}}{2} + \sigma^{-}_{1,2}(x_2) > 0$

1. Number of parameter nodes increases rapidly

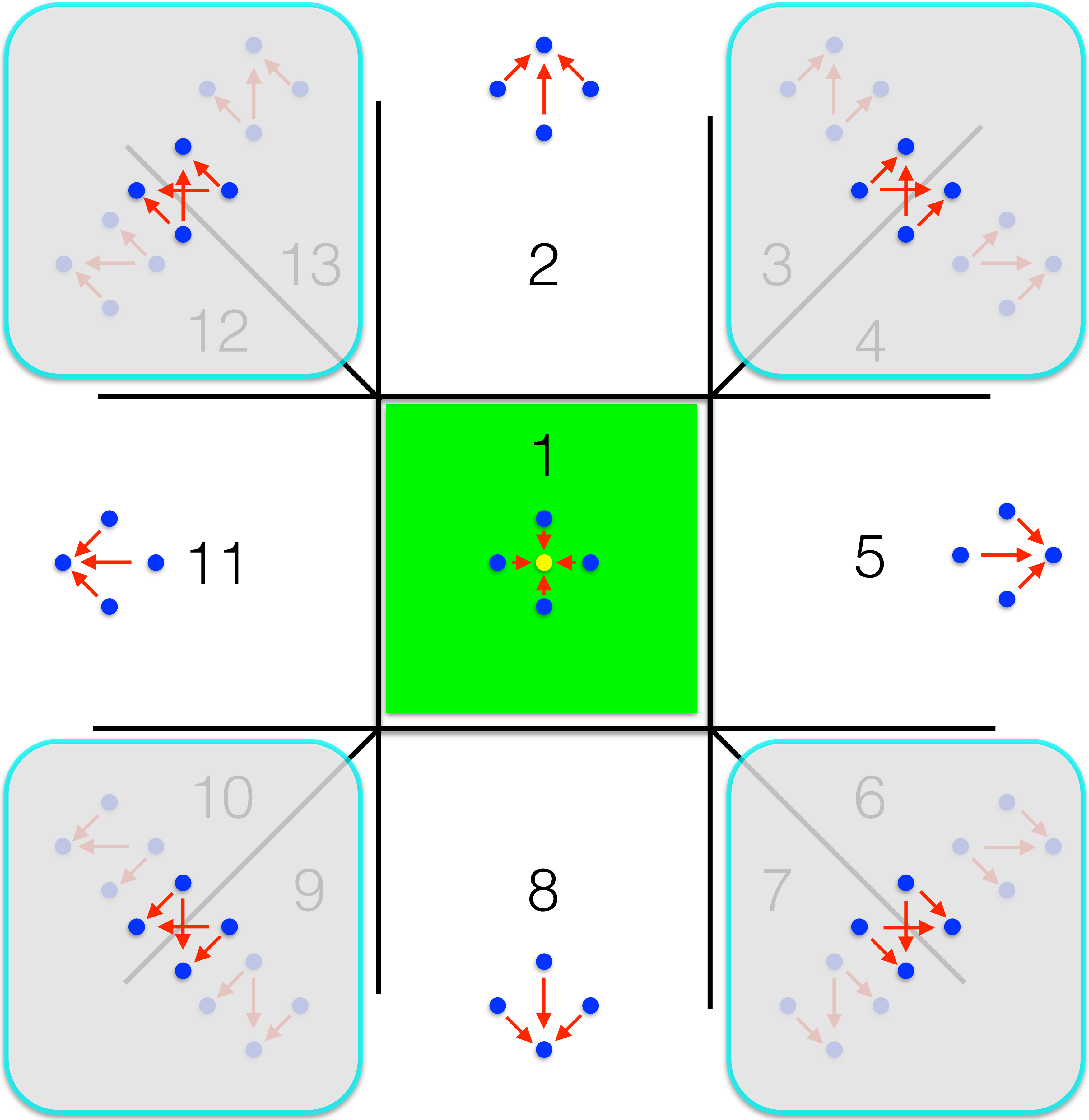
2. I don’t think we get rapid convergence of approximation of dynamics

III. REFINEMENTS: DIAGONALIZATION

A finer resolution of $\mathcal{F} \colon \mathcal{V} \rightrightarrows \mathcal{V}$

$$\Phi(\kappa) := \Gamma^{-1}\Lambda(\kappa)$$

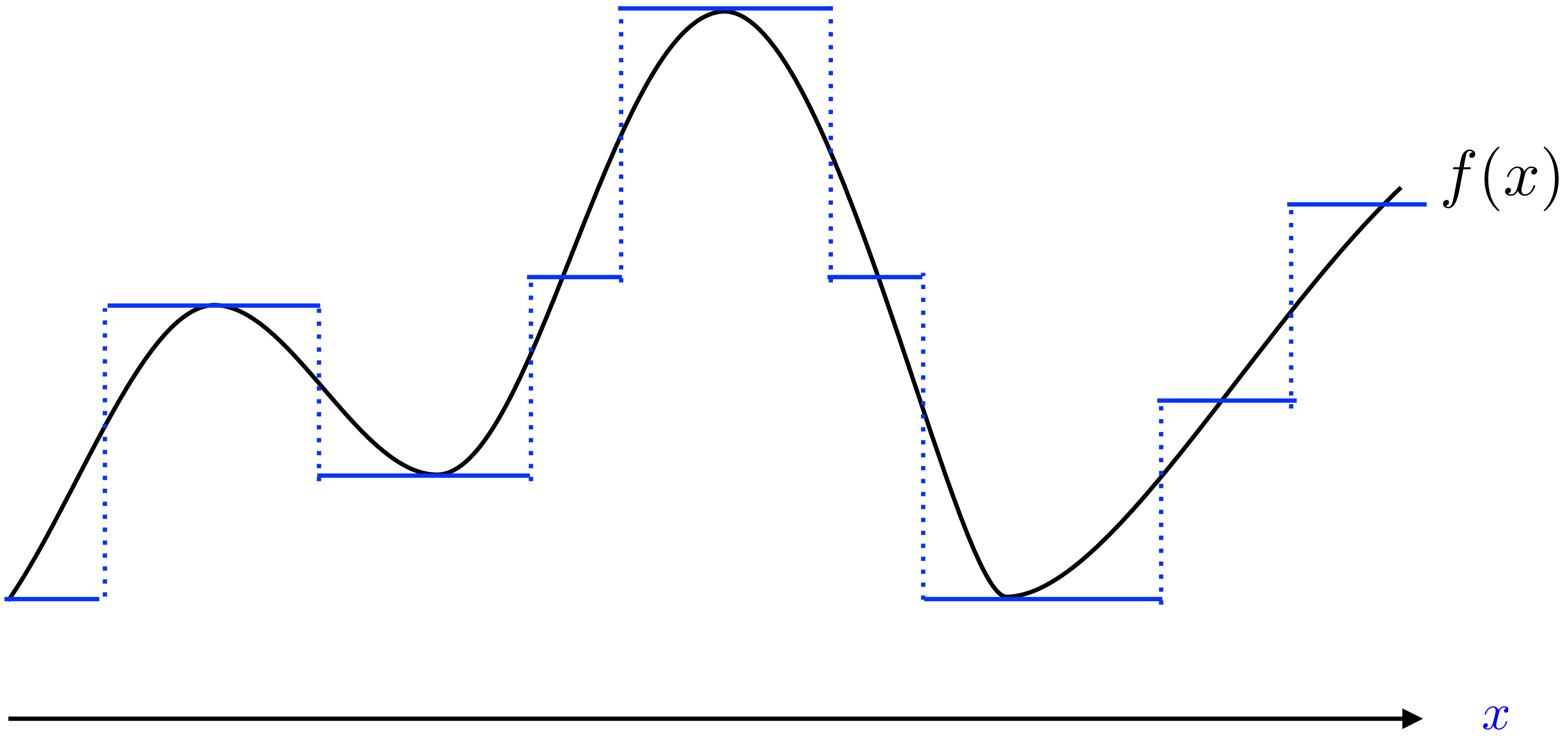
Parameter graph is no longer a product graph.



POSSIBLE LOCAL GRAPHS

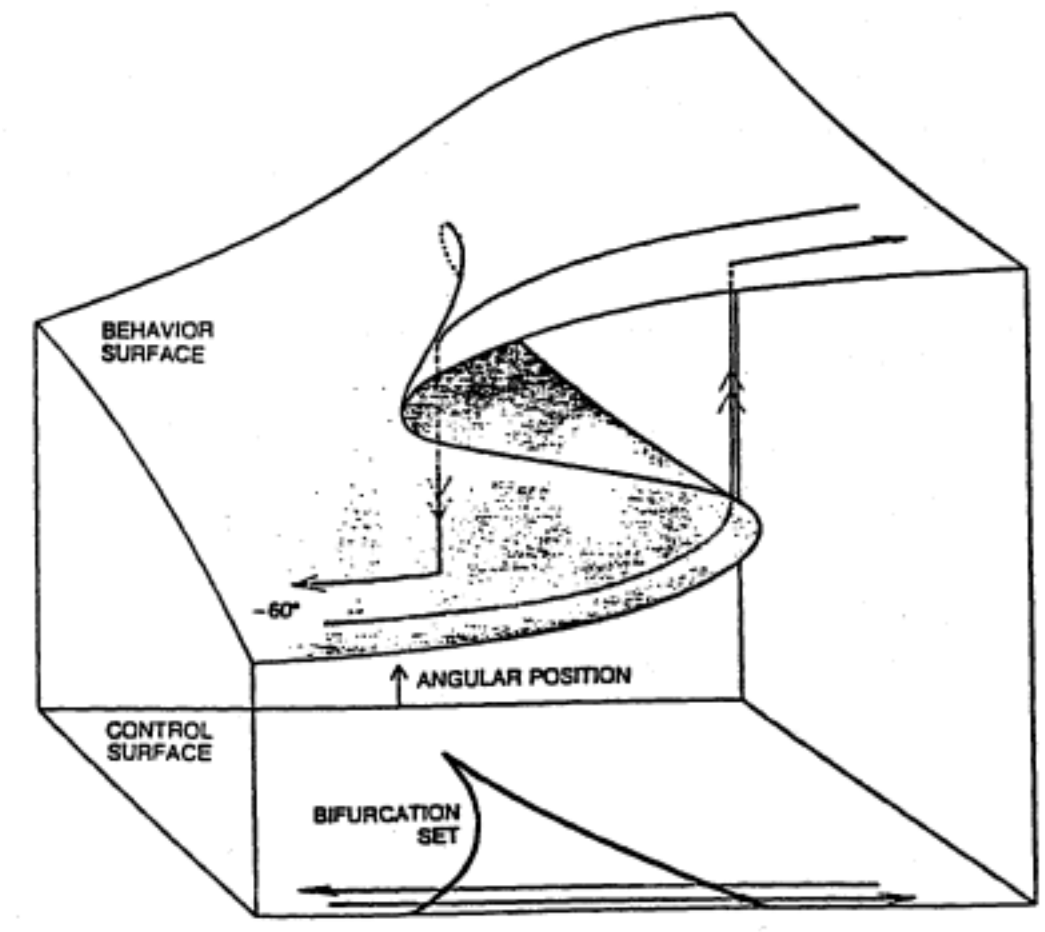
III. REFINEMENTS: NUMERICAL METHOD

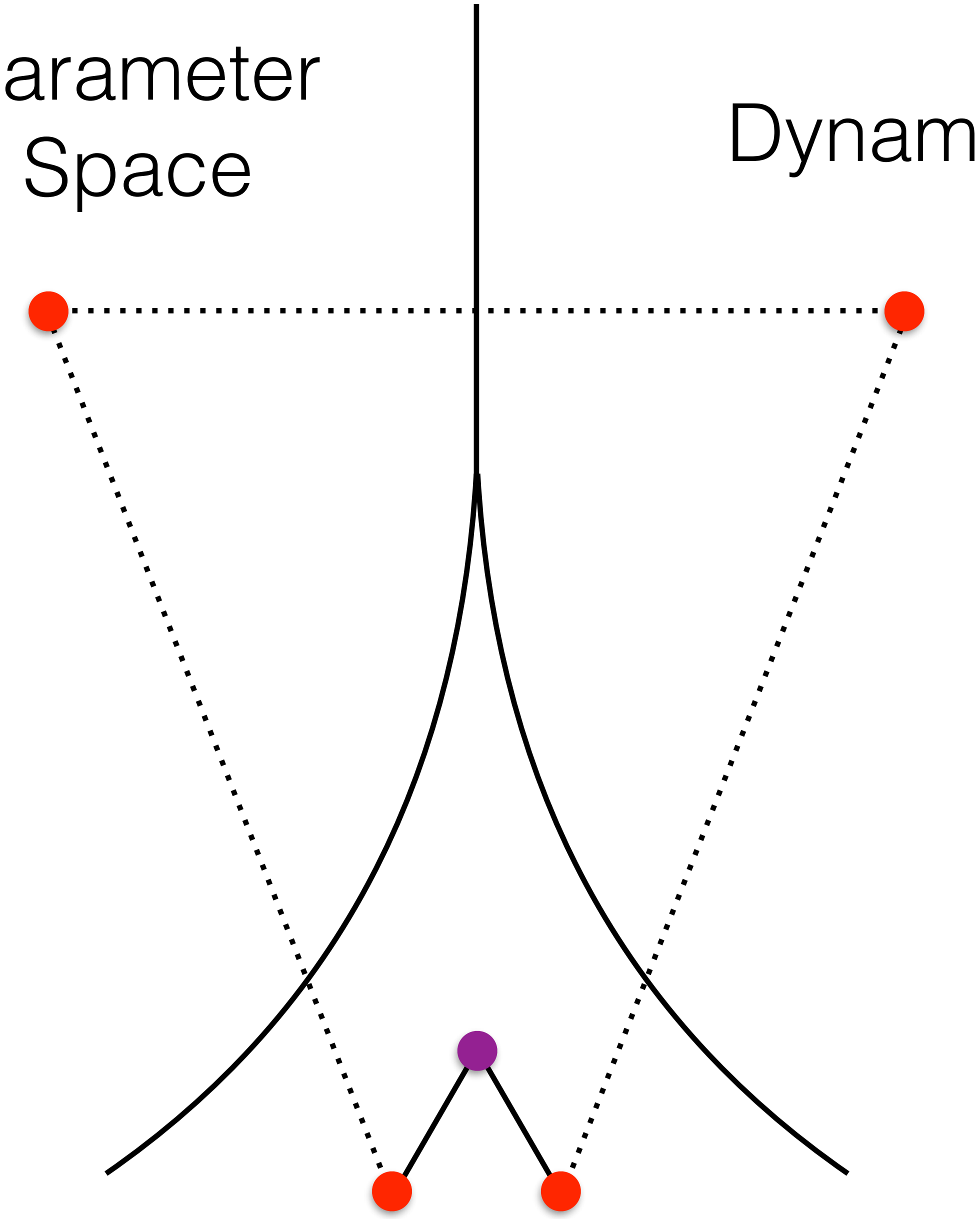
$$\frac{dx}{dt} = f(x, \lambda)$$



IV. SIZE OF PARAMETER GRAPH: HOW TO REDUCE STORED DATA?

Cusp
Catastrophe

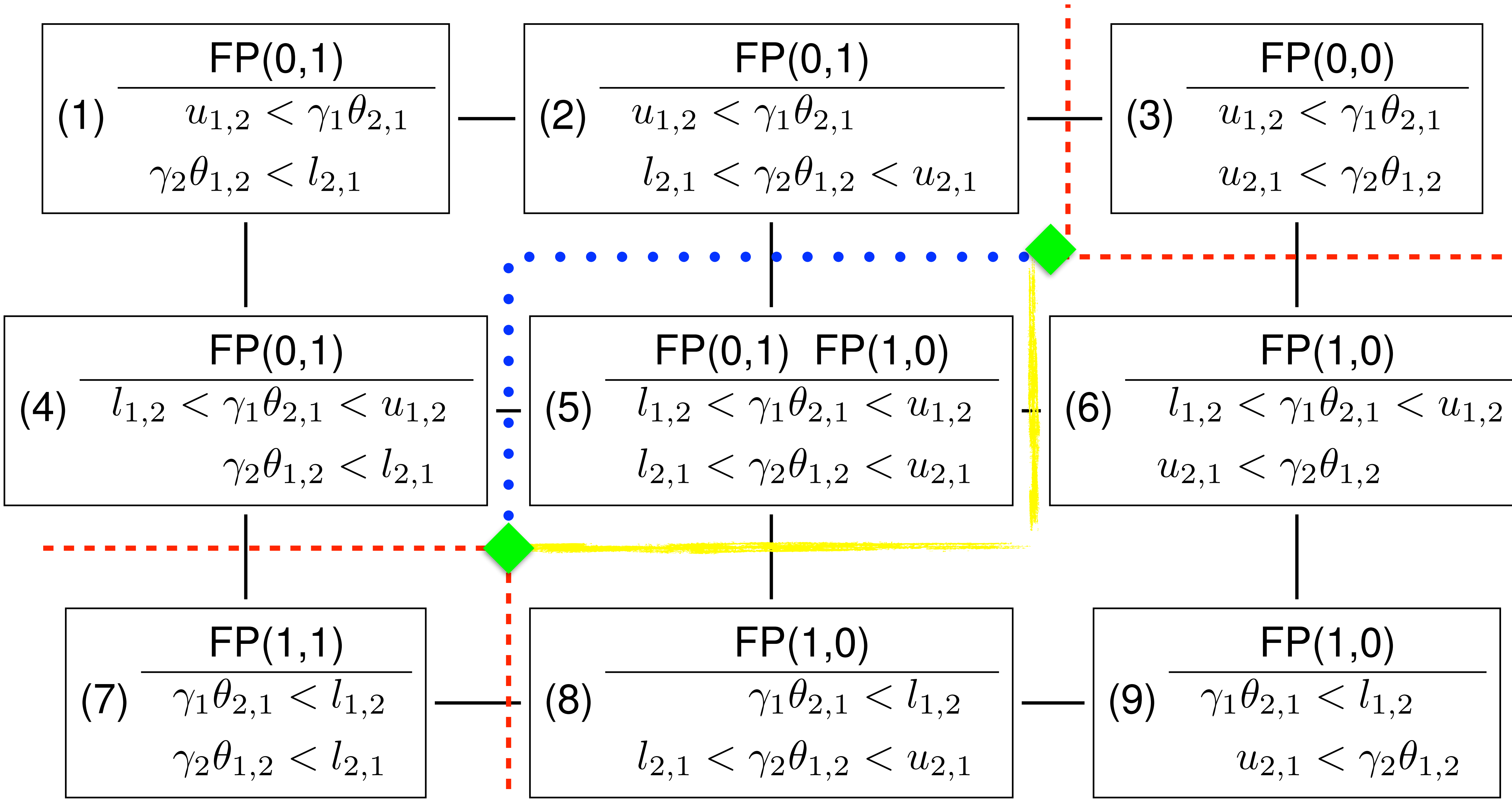




Parameter
Space

Dynamics

DSGRN DATABASE FROM GENETIC TOGGLE SWITCH



(1) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(2) FP(0,1)
$u_{1,2} < \gamma_1\theta_{2,1}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(3) FP(0,0)
$u_{1,2} < \gamma_1\theta_{2,1}$
$u_{2,1} < \gamma_2\theta_{1,2}$

(4) FP(0,1)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(5) FP(0,1) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

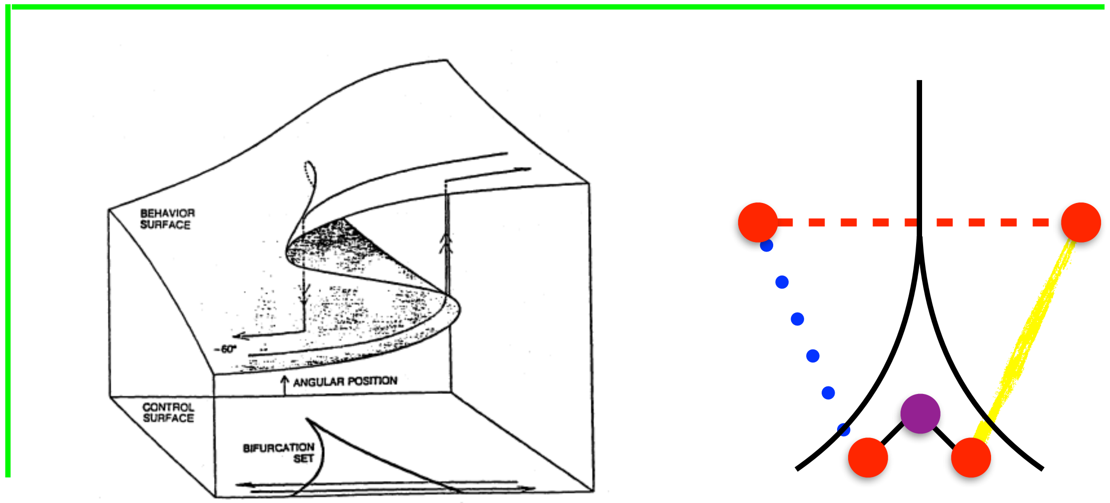
(6) FP(1,0)
$l_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

(7) FP(1,1)
$\gamma_1\theta_{2,1} < l_{1,2}$
$\gamma_2\theta_{1,2} < l_{2,1}$

(8) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$

(9) FP(1,0)
$\gamma_1\theta_{2,1} < l_{1,2}$
$u_{2,1} < \gamma_2\theta_{1,2}$

Observe: We can capture the structure in parameter space by giving two codimension 2 points and four codimension 1 edges.



Thank-you for your Attention

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