Towards A Computational, Discrete Geometric Foundation for Nonlinear Dynamics

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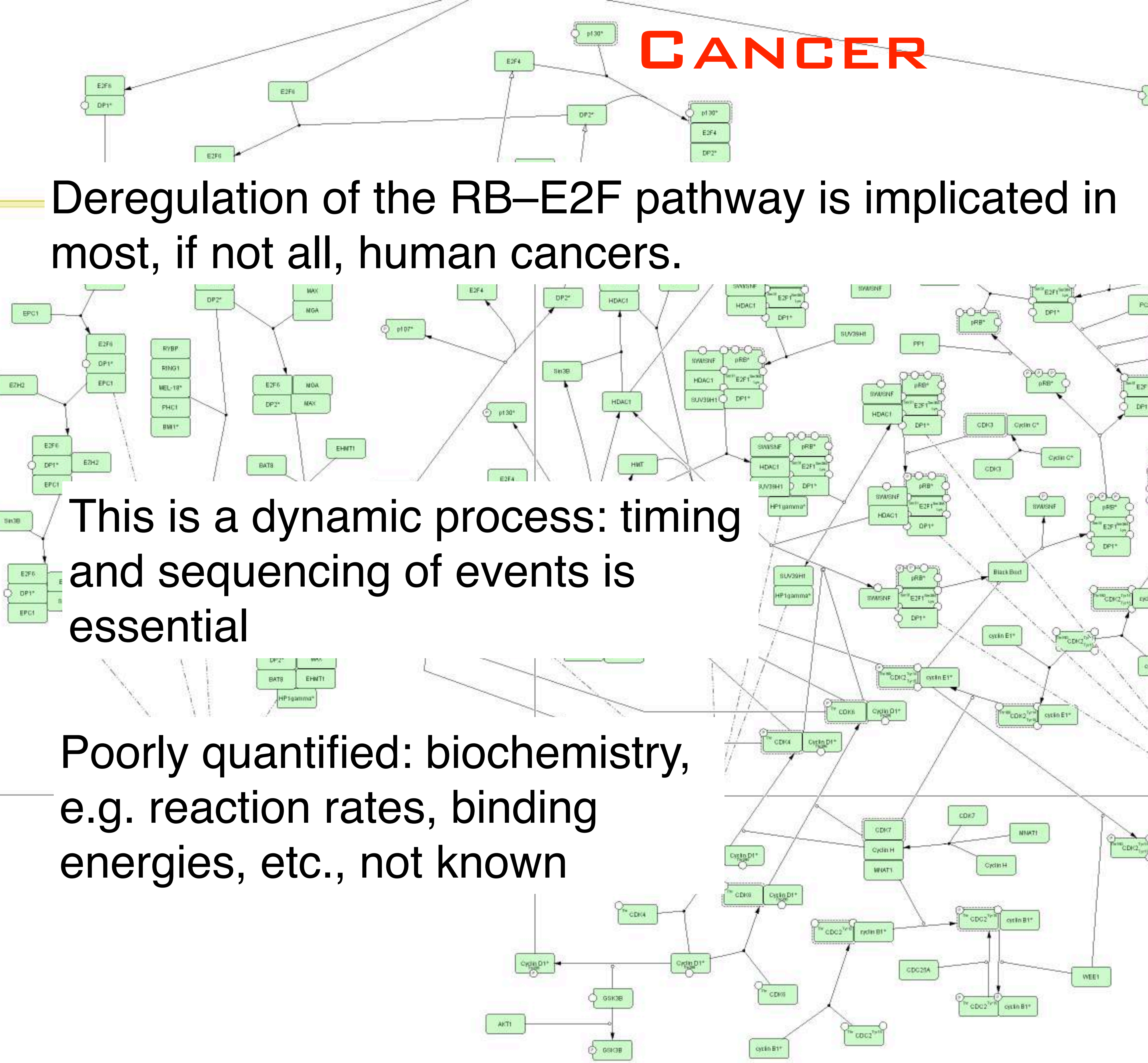
Why?

Cancer

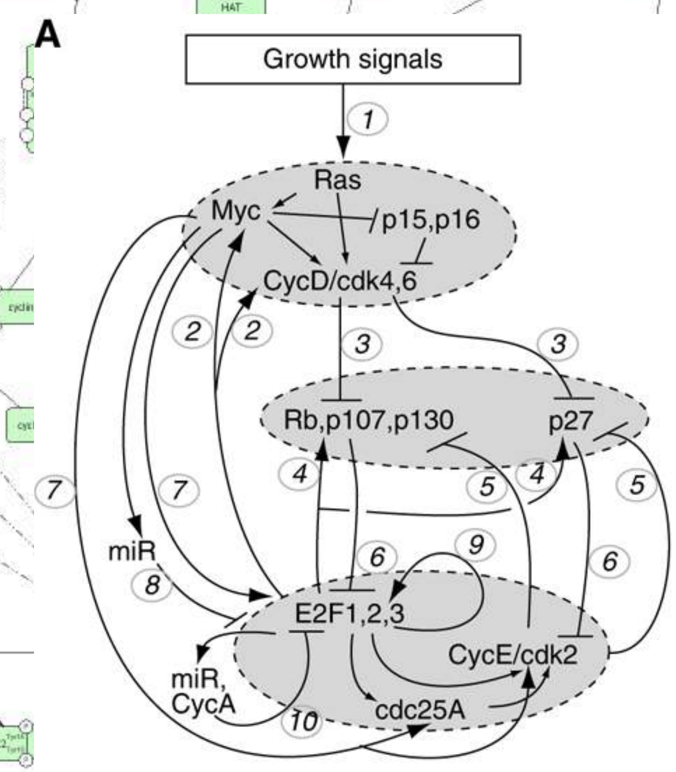
RB-E2F pathway



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

This is a dynamic process: timing and sequencing of events is essential

Poorly quantified: biochemistry, e.g. reaction rates, binding energies, etc., not known

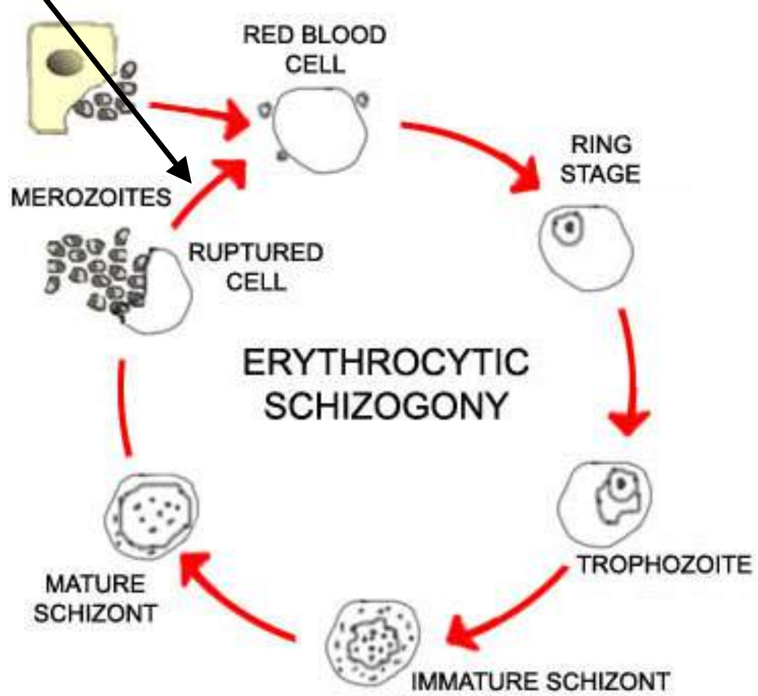


Yao, et. al., MSB, 2011

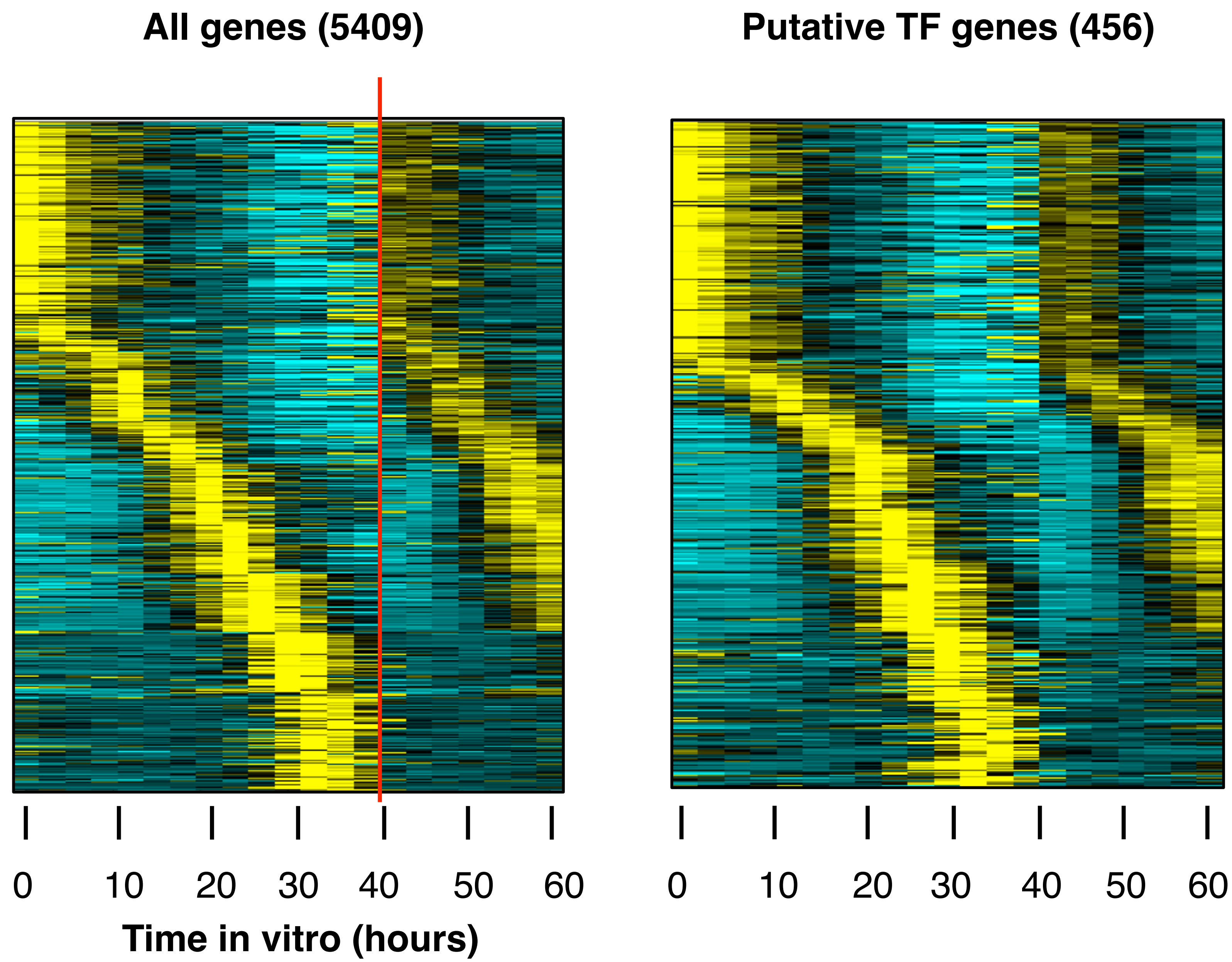
What is (are) appropriate model(s) for dynamics?

MALARIA *P. falciparum*

1-2 minutes



48 hour cycle



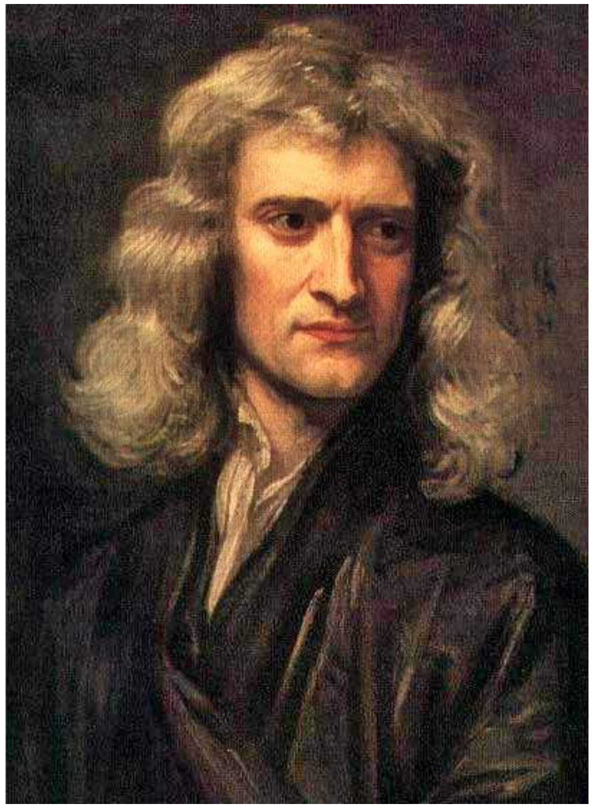
Dynamic process: timing and sequencing of events is essential

Poorly annotated: network of interactions is not known

What is (are) appropriate model(s) for dynamics?

What does it mean to solve a differential equation?

Classical Differential Equations



Isaac Newton
1643-1727

Newton's Law of Gravitation

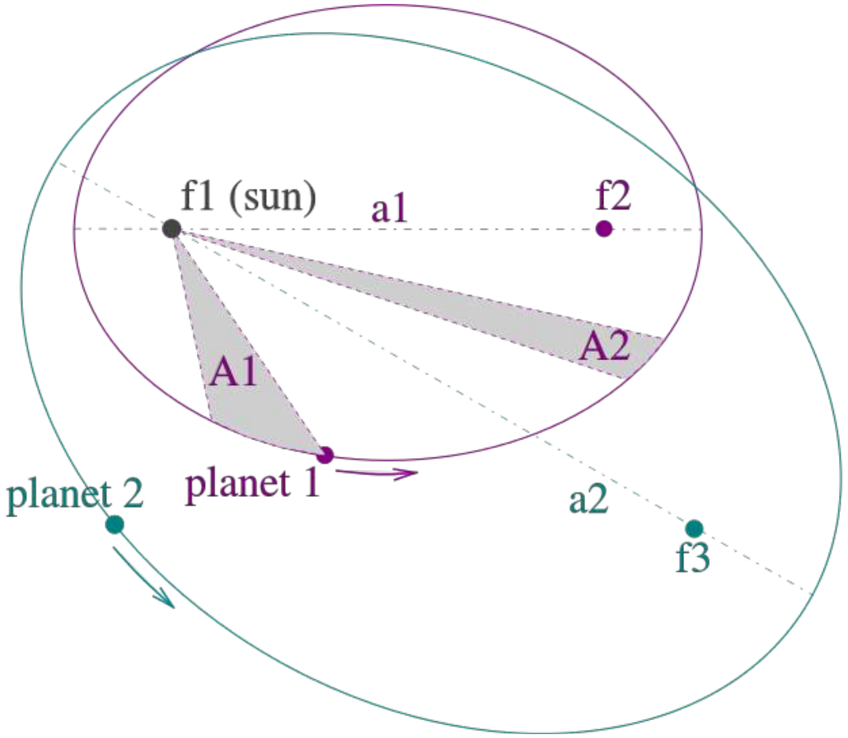
$$m_i \frac{d^2 q_i}{dt^2} = G \sum_{j \neq i} \frac{m_j m_i (q_j - q_i)}{\|q_j - q_i\|^3}$$

2-body problem

$$\frac{d^2 q_1}{dt^2} = \frac{G m_2 (q_2 - q_1)}{\|q_2 - q_1\|^3}$$

$$\frac{d^2 q_2}{dt^2} = \frac{G m_1 (q_1 - q_2)}{\|q_1 - q_2\|^3}$$

Kepler's three laws of planetary motion



Johannes Kepler
1571-1630

Jules Henri Poincare
1854-1912

Need to consider all solutions:

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

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

value of solution at time t

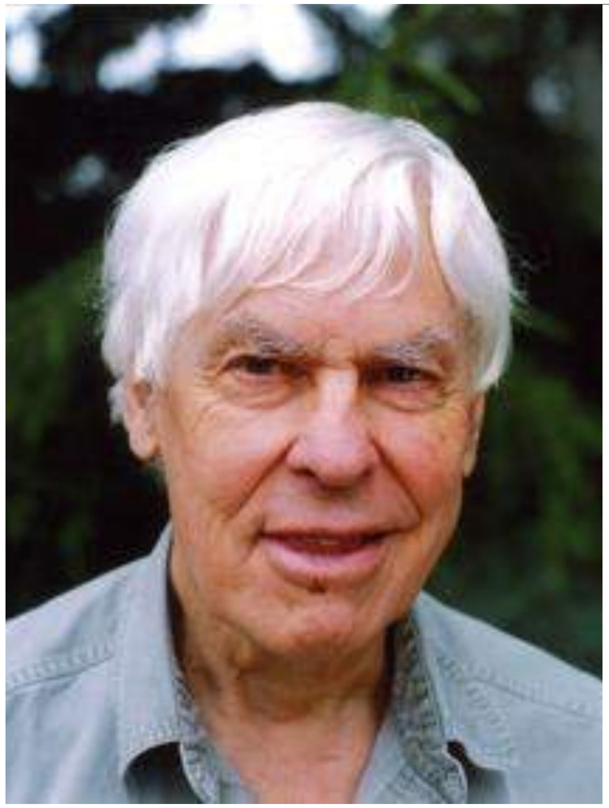
$$\text{time} \rightarrow (t, x, \lambda) \mapsto \varphi_\lambda(t, x)$$

initial condition

parameter value

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

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



Steven Smale
1930-

The objects of interest: A set S is invariant if $f_\lambda(S) = S$.

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:

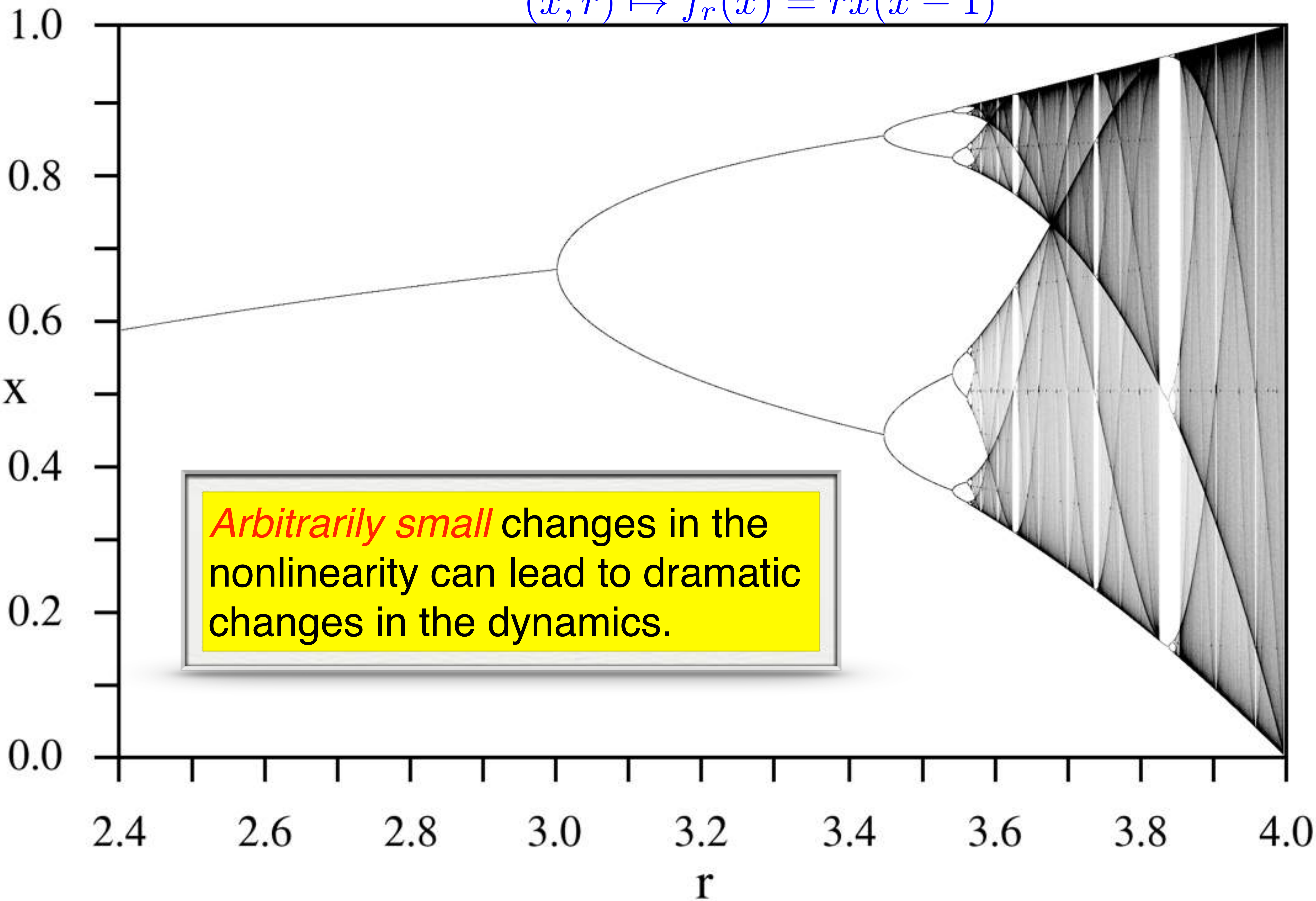
$\lambda_0 \in \Lambda$ is a bifurcation point if for any neighborhood U of λ_0 there exists $\lambda_1 \in U$ such that f_{λ_0} is not conjugate to f_{λ_1}

The challenge of Bifurcations

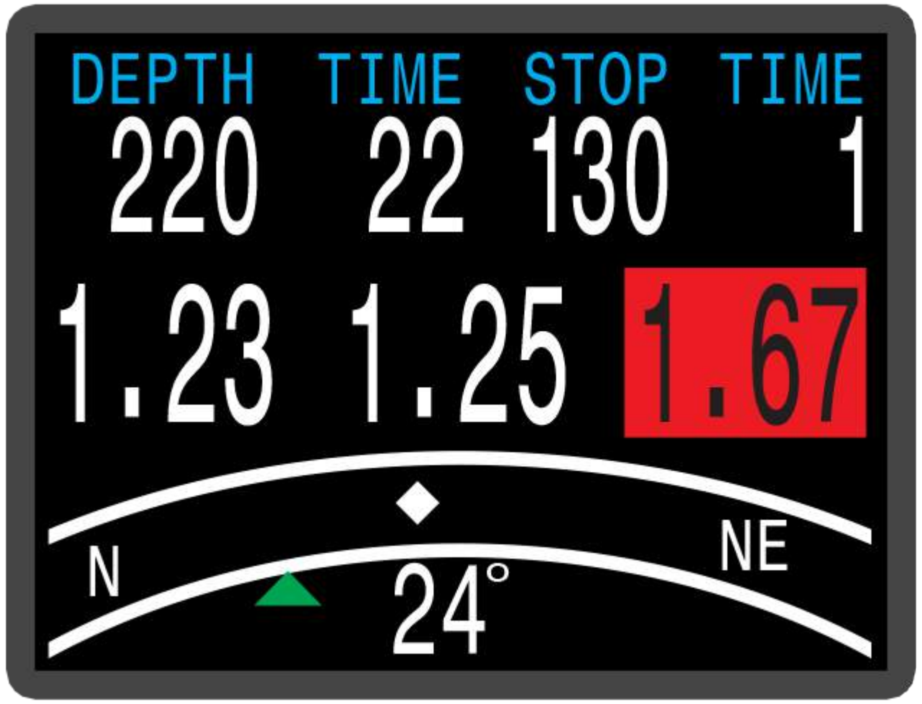
$$f\colon [0,1]\times[2.4,4]\to[0,1]$$

$$(x,r)\mapsto f_r(x)=rx(x-1)$$

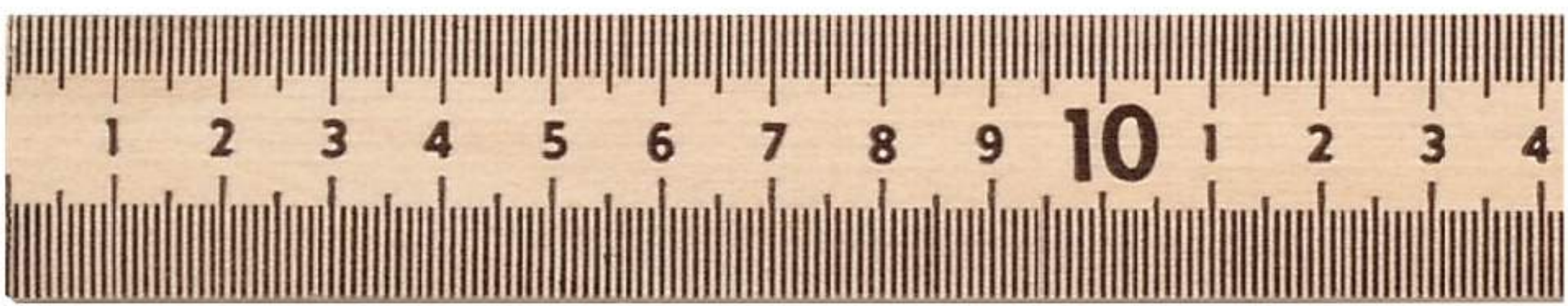
logistic map



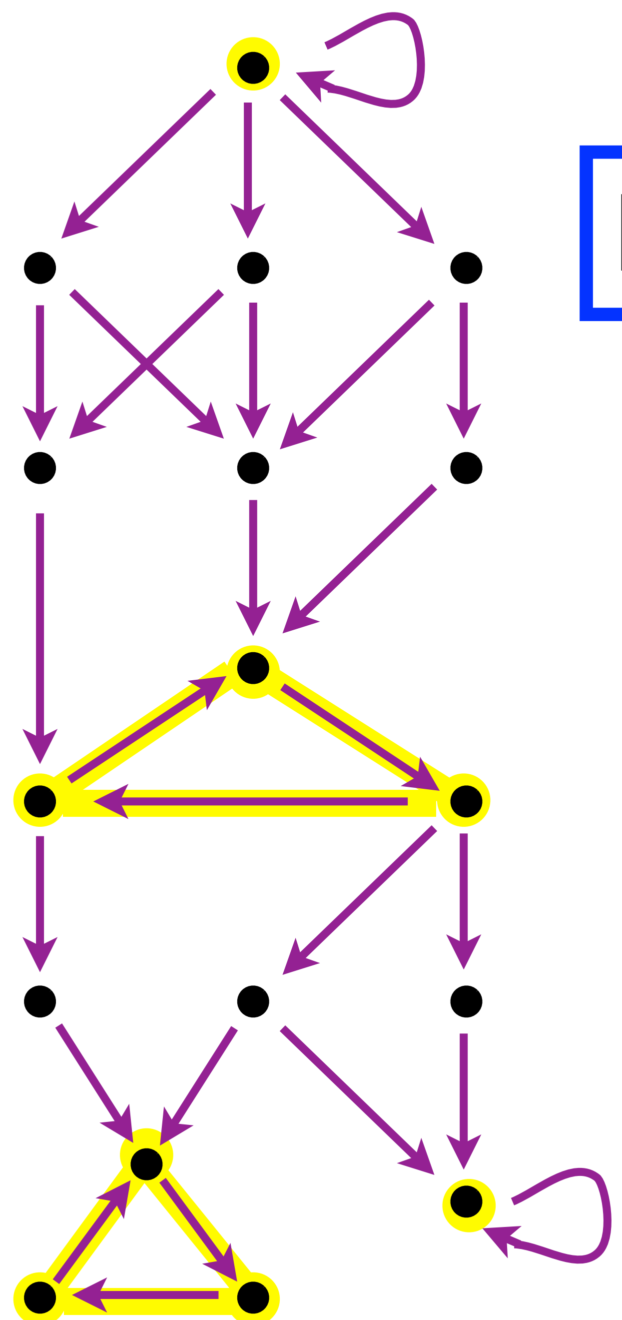
Arbitrarily small changes in the nonlinearity can lead to dramatic changes in the dynamics.



Combinatorial Dynamics



State Transition Graph $\mathcal{F}: \mathcal{X} \rightrightarrows \mathcal{X}$

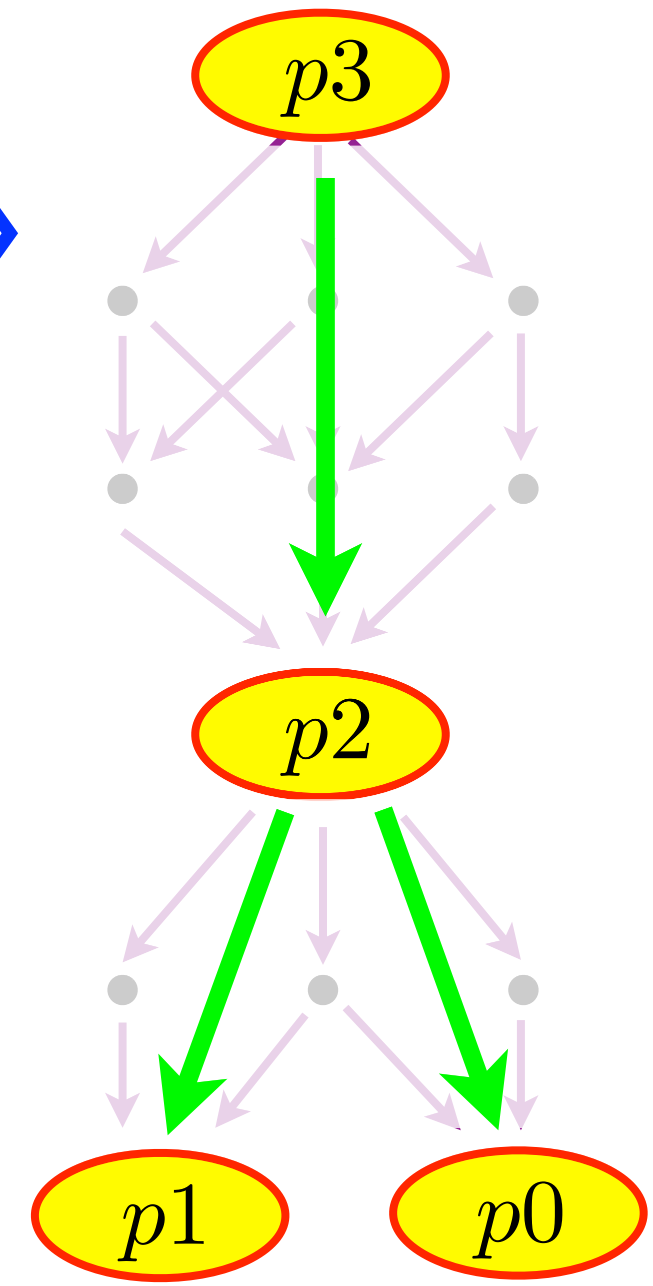


Linear time Algorithm!

Simple decomposition of Dynamics:

Recurrent

Nonrecurrent (gradient-like)



Vertices: States
Edges: Dynamics

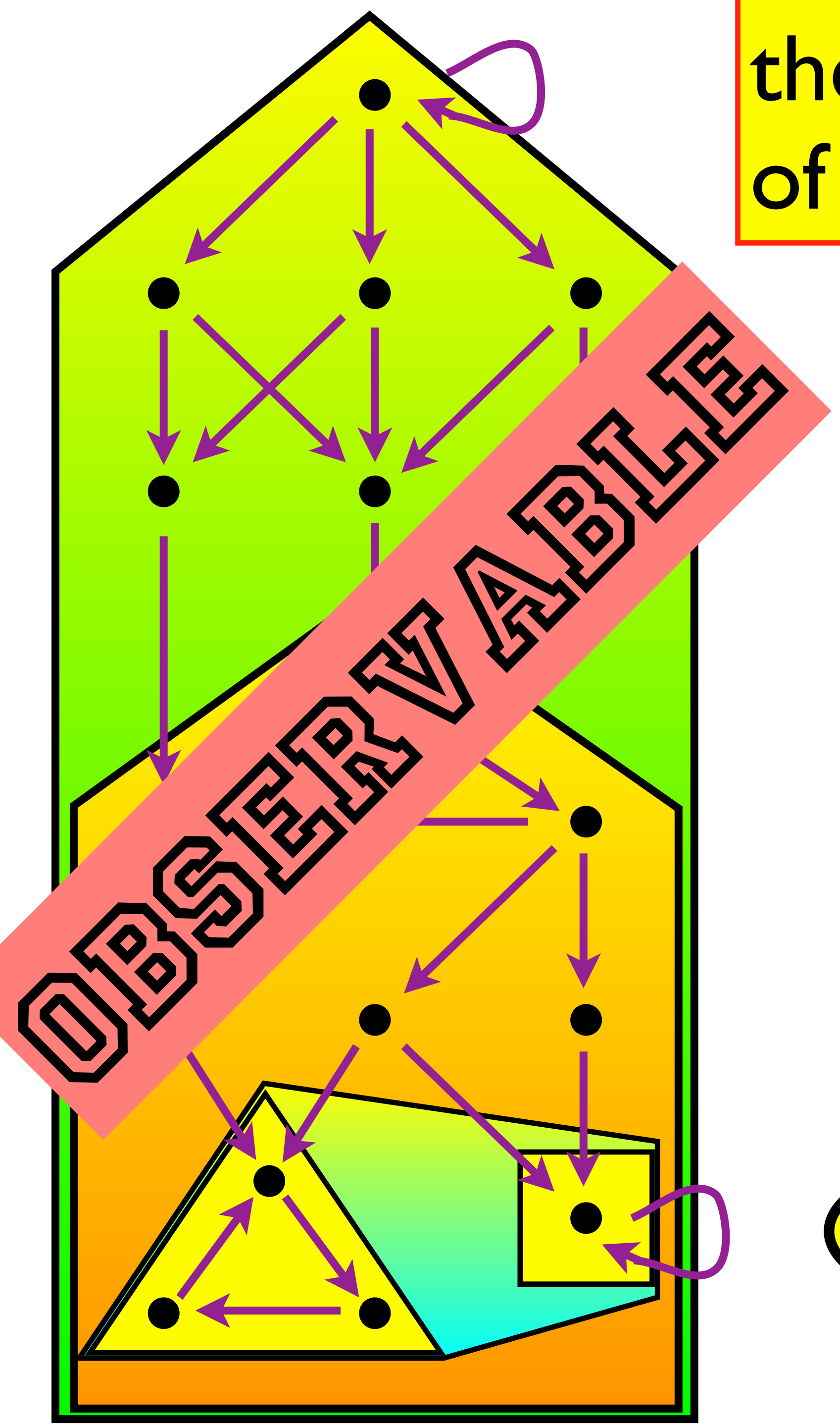
Don't know exact current state, so don't know exact next state

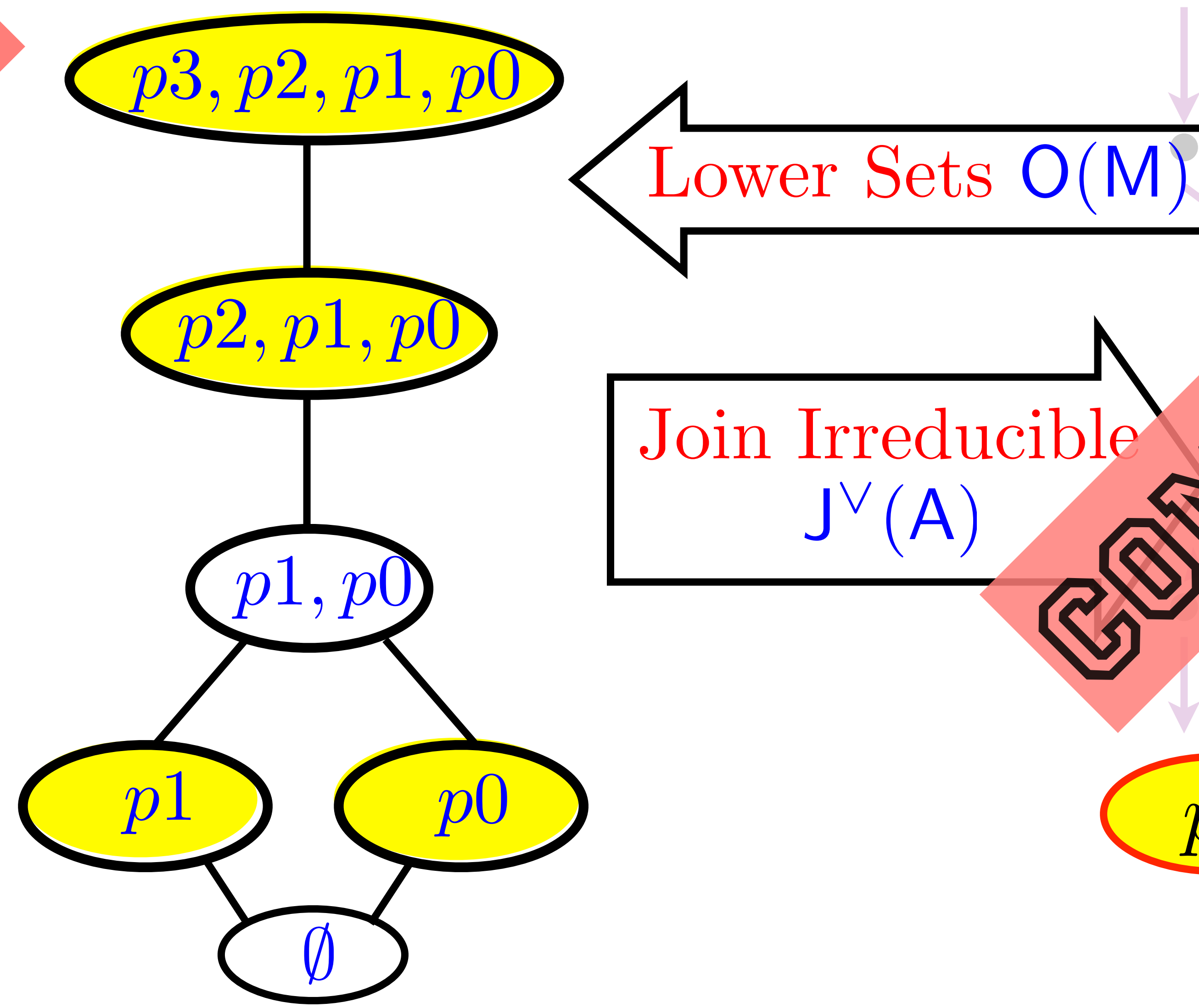
Morse Graph of state transition graph

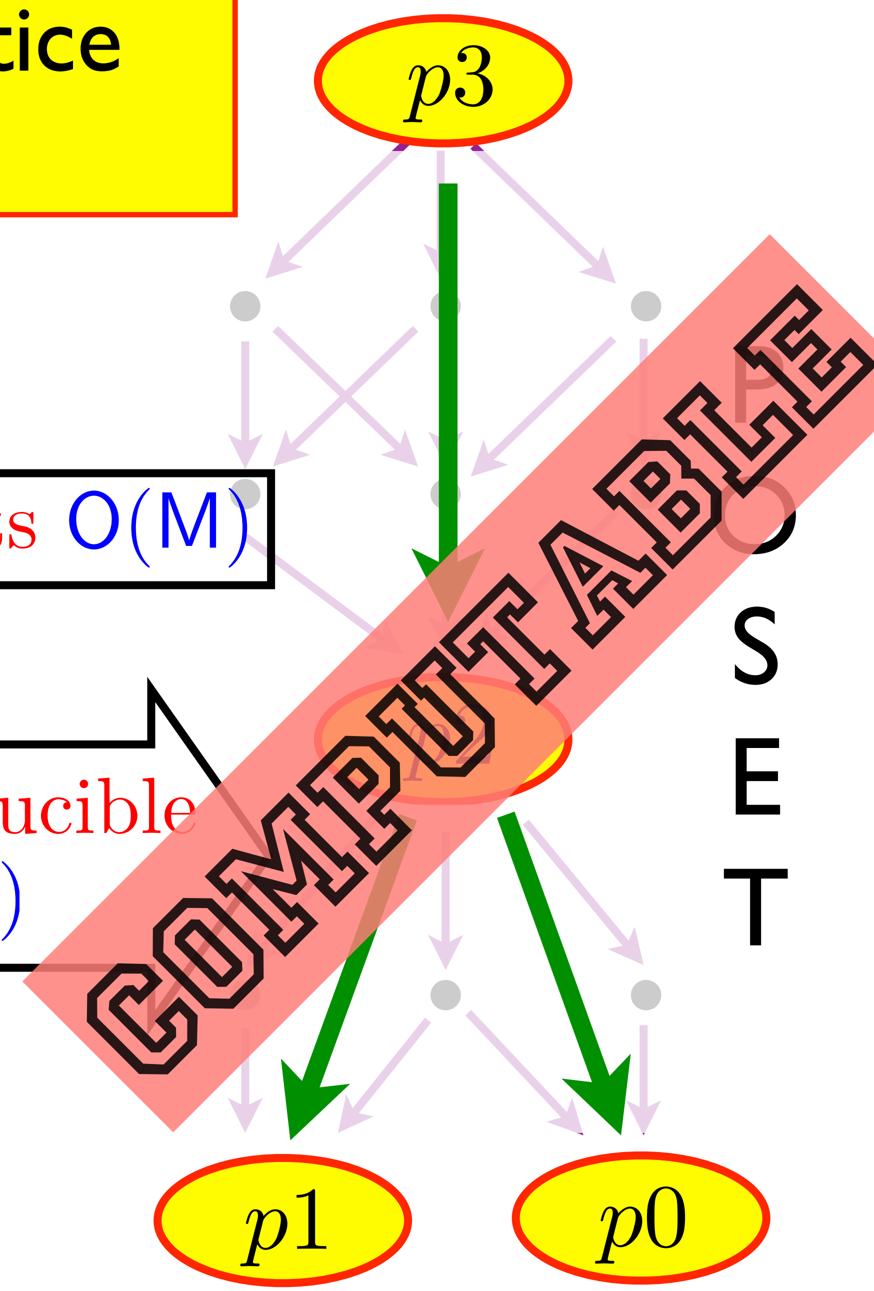
Poset

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.





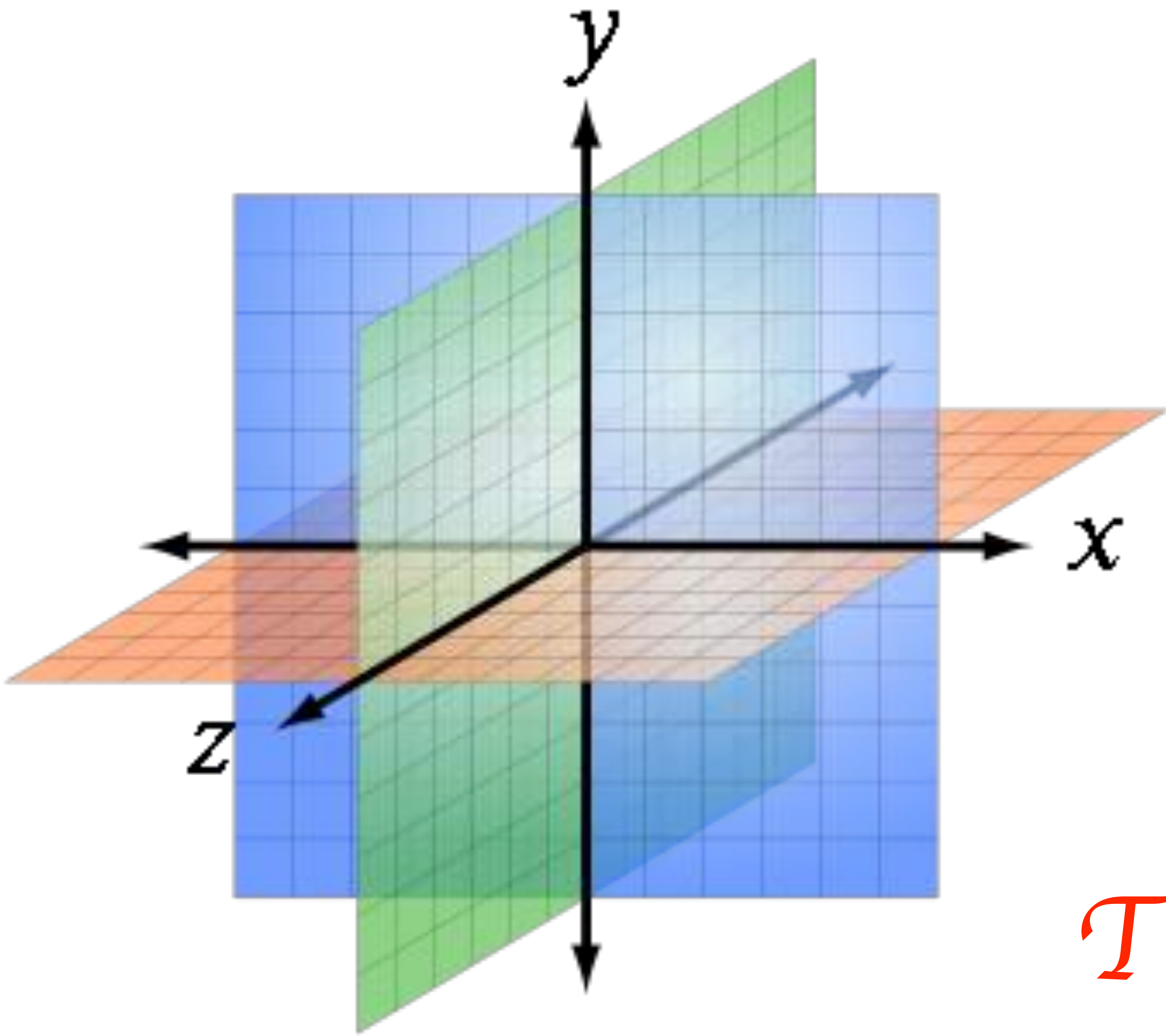


Lattice of Attractors of $\mathcal{F}\colon \mathcal{X} \rightrightarrows \mathcal{X}$

$\vee = \cup$

$\wedge =$ maximal attractor in $\cap$

Morse Graph of $\mathcal{F}\colon \mathcal{X} \rightrightarrows \mathcal{X}$



Topology

(differential equations are not defined on finite sets)

Topology

Let X be a compact metric space. — phase space

Let $\mathsf{R}(X)$ denote the lattice of regular closed subsets of X. — Infinite unbounded lattice

Let L be a finite bounded sublattice of $\mathsf{R}(X)$. — Level of measurement; Applicable scale for model

$\mathcal{G}(L)$ denoted atoms of L — "smallest" elements of **L**

Dynamics

Declare a bounded sublattice $\mathsf{A} \subset \mathsf{L}$ to be the lattice of attractors

Use Birkhoff to define poset $(\mathsf{P} := \mathsf{J}^{\vee}(\mathsf{A}), <)$

For each $p \in \mathsf{P}$ define a Morse tile $\mathsf{M}(p) := \mathrm{cl}(A \setminus \mathsf{pred}(A))$

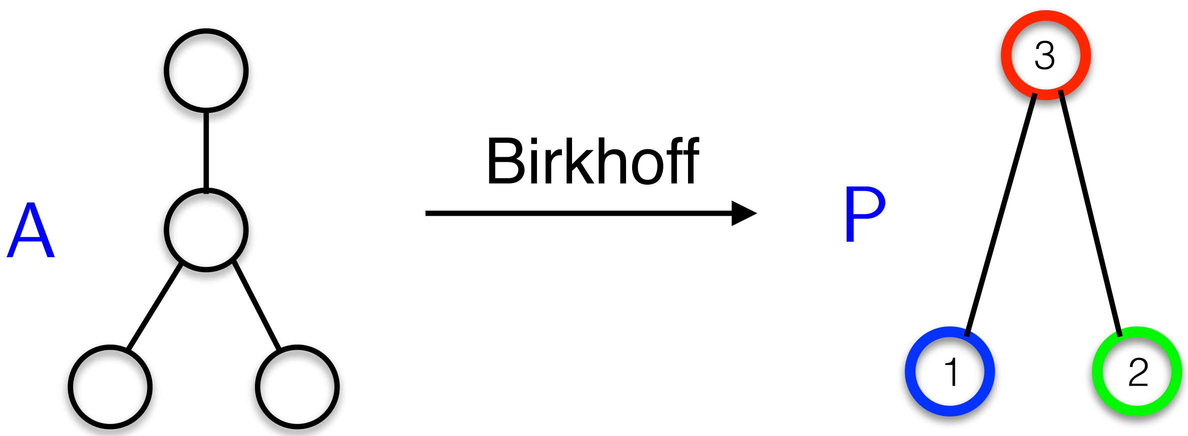
Remark: I have purposefully ignored the relation between L and $\mathcal{F}\colon \mathcal{X} \rightrightarrows \mathcal{X}$

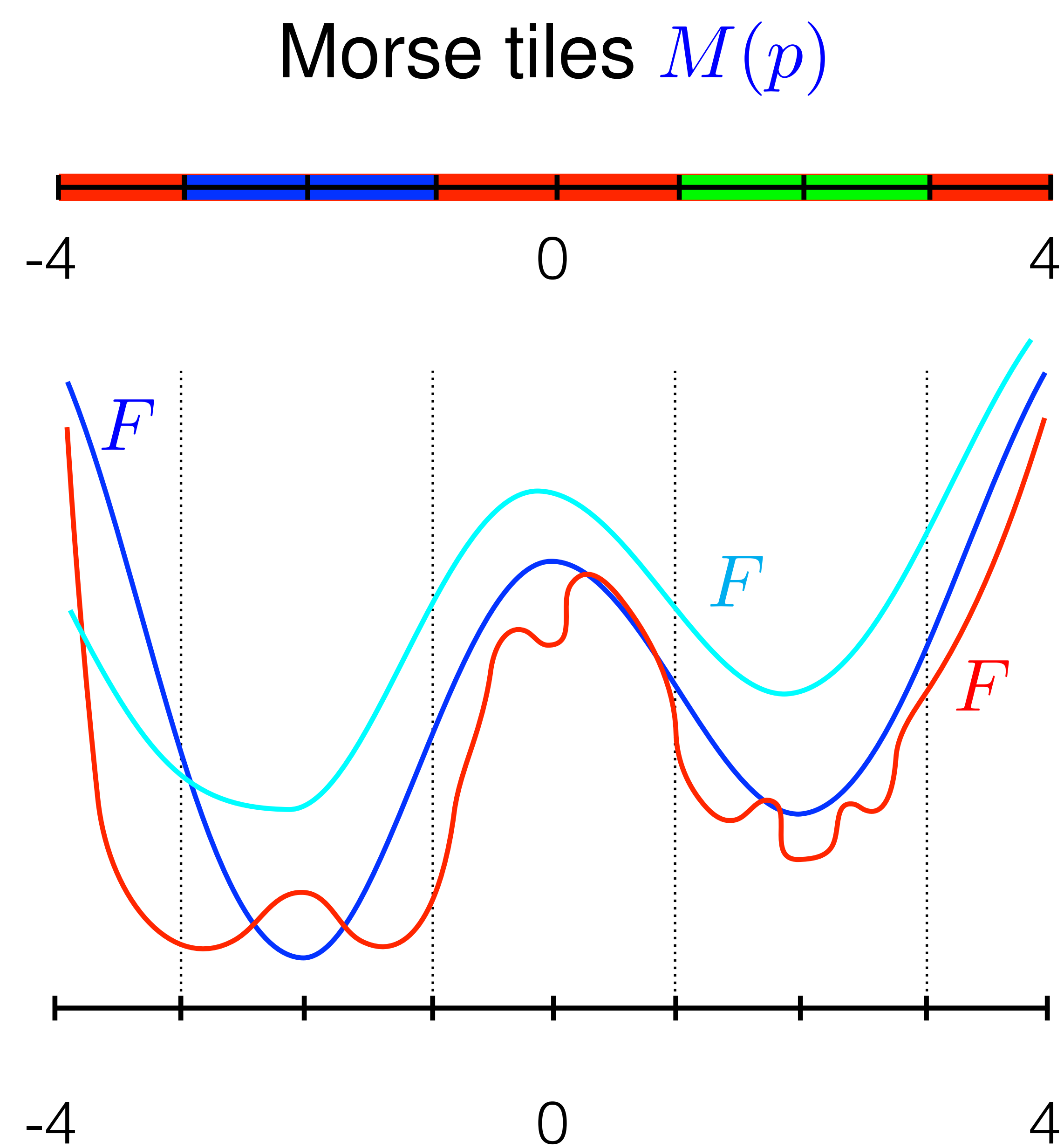
Example

Phase space: $X = [-4, 4] \subset \mathbb{R}$

Atoms of lattice: $\mathcal{G}(\mathsf{L}) = \{[n, n+1] \mid n = -4, \ldots, 3\}$

Lattice of attractors: $\mathsf{A} = \{[-3,-1], [1,3], [-3,-1] \cup [1,3], [-4,4]\}$





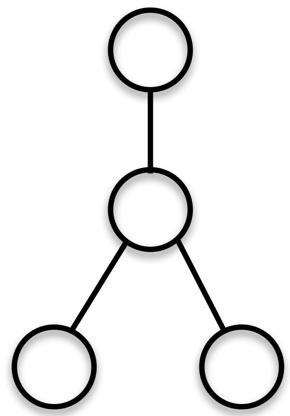
How does this relate to a differential equation $\frac{dx}{dt} = f(x)$?

Let $F'(x) = -f(x)$.

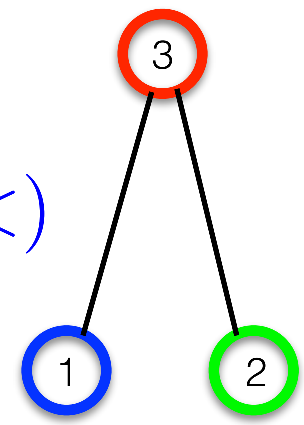
Combinatorial attractors represent regions of phase space that are forward invariant with time.

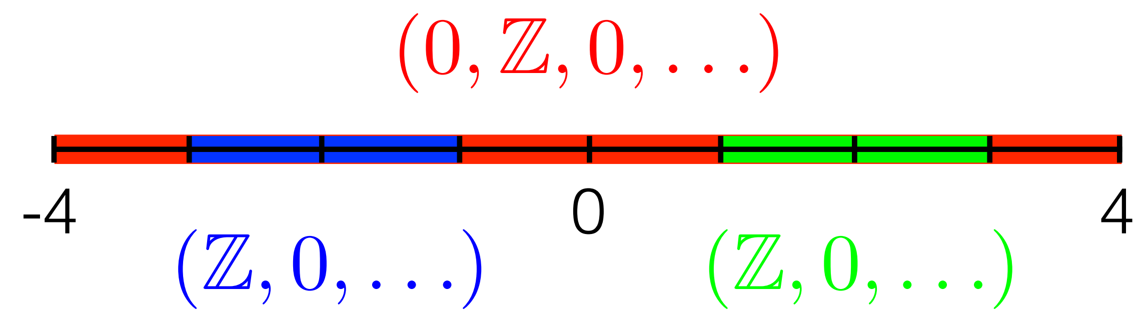
Example (continued) $X = [-4, 4] \subset \mathbb{R}$

A



$(\mathsf{P}, <)$





For flows the homology Conley index of $\mathsf{M}(p)$ is

$$CH_*(p) := H_*(A, \mathsf{pred}(A))$$

For maps the homology Conley index of $\mathsf{M}(p)$ is the shift equivalence class of

$$f_*\colon H_*(A, \mathsf{pred}(A)) \to H_*(A, \mathsf{pred}(A))$$

Remark: f_* can be computed (rigorously) from an outer approximation $\mathcal{F}\colon \mathcal{X}(\mathsf{L}) \rightrightarrows \mathcal{X}(\mathsf{L})$ without knowing f.

S. Harker, K.M., M. Mrozek, V. Nanda, FoCM, 2013

S. Harker, H. Kokubu, K.M., P. Pilarczyk, Proc. AMS, 2016

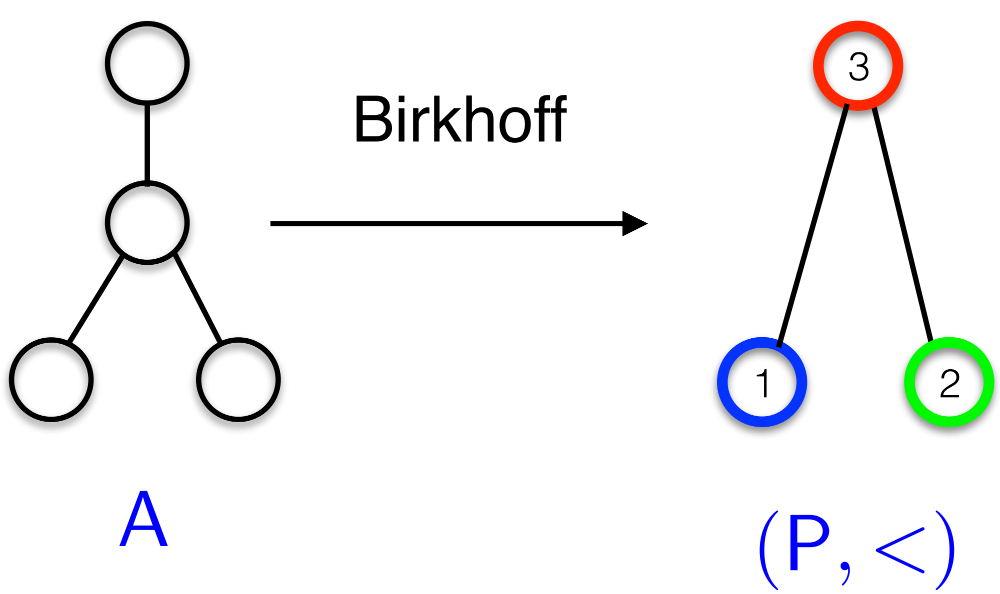
Theorem: (C. Conley; M. Mrozek; J. Robbin, D. Salamon) If Conley index of the Morse tile $M(p)$ is nontrivial, then there exists a non-empty invariant set in $\mathrm{cl}(A \setminus \text{pred}(A))$.

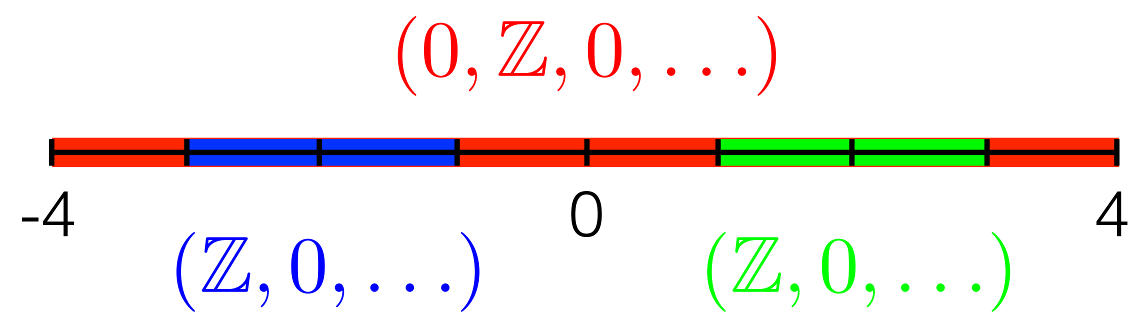
Recall Example:

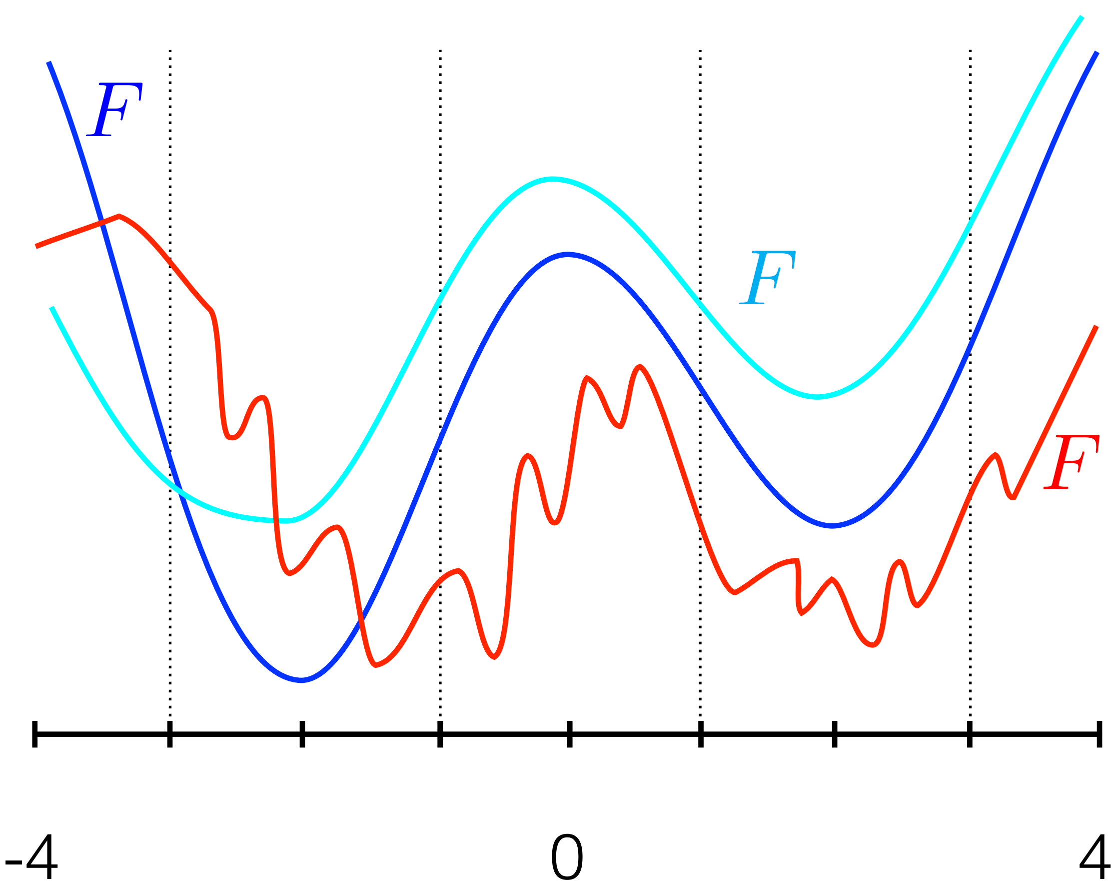
Phase space: $X = [-4, 4] \subset \mathbb{R}$

Lattice of Attractors

$\mathsf{A} = \{[-3,-1], [1,3], [-3,-1] \cup [1,3], [-4,4]\}$







Moral: We can make nontrivial statements about dynamics without having an analytic representation of the dynamical system.

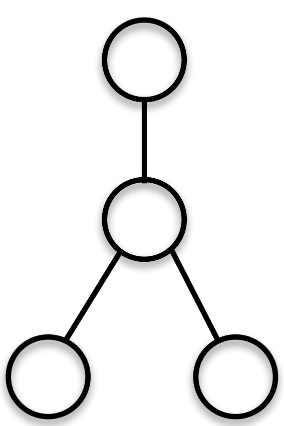
Conley index can be used to guarantee existence of equilibria, periodic orbits, heteroclinic and homoclinic orbits, and chaotic dynamics.

Theorem: (R. Franzosa) There exists a strictly upper triangular (with respect to $<$) boundary operator

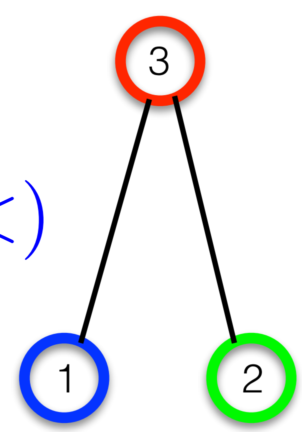
$$\Delta \colon \bigoplus_{p \in \mathsf{P}} CH_*(p) \to \bigoplus_{p \in \mathsf{P}} CH_*(p)$$

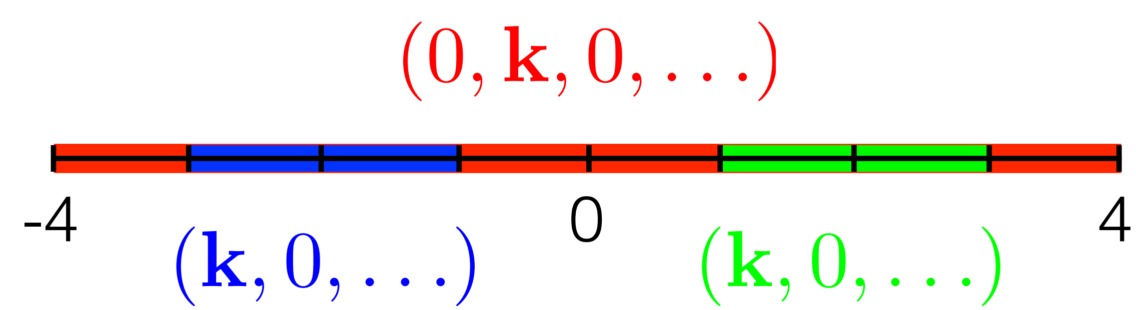
such that the induced homology is isomorphic to $H_*(X)$.

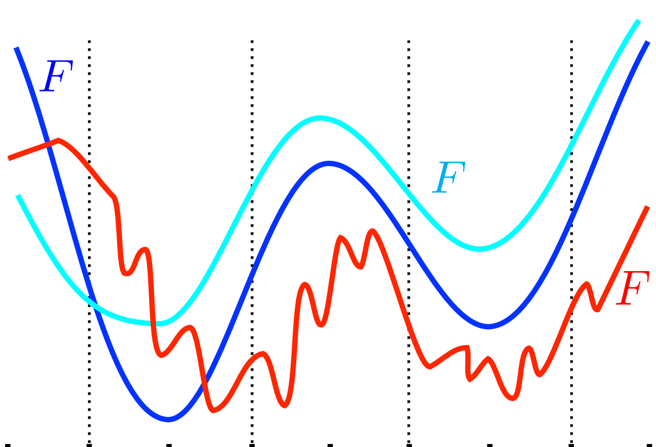
A



(P, $<$)







$$\Delta = \begin{bmatrix} 0 & 0 & 1 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix} : \bigoplus_{p=1}^{3} CH_*(p) \to \bigoplus_{p=1}^{3} CH_*(p)$$

Claim: (S. Harker, K. Spendlove, K.M.)
Δ can be computed efficiently.

Switching Systems

(an example of how to use these ideas)

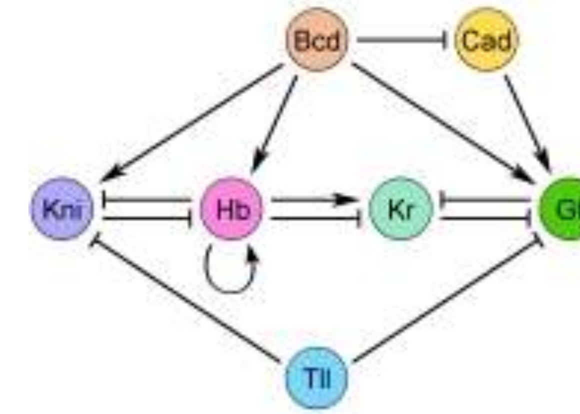
Choosing L and $\mathcal{F} \colon \mathcal{X} \rightrightarrows \mathcal{X}$

Biological Model

How do I want to interpret this information?

What differential equation do I want to use?

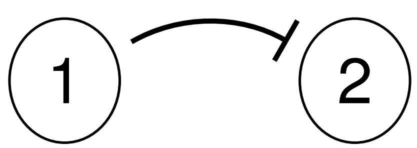
x_i denotes amount of species i.



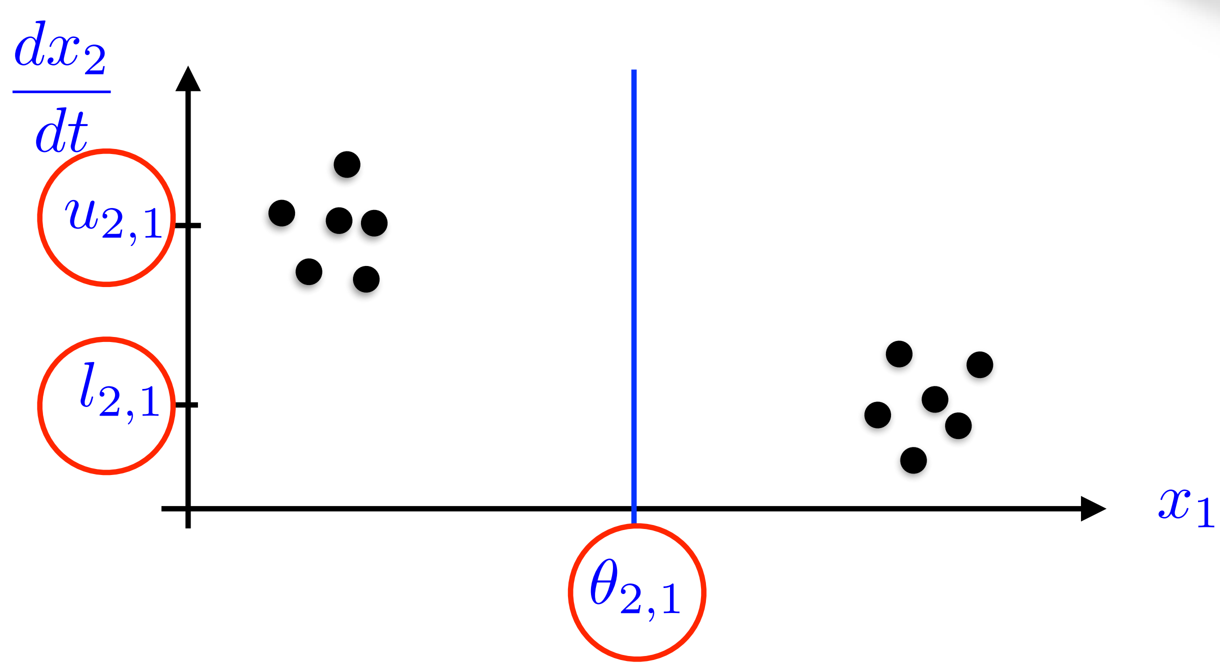
Assume x_i decays. $\frac{dx_i}{dt} = -\gamma_i x_i$

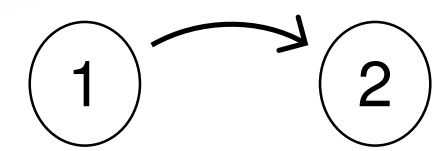
Parameters
1/node
3/edge

Proposed model: $\frac{dx_i}{dt} = -\gamma_i x_i + \Lambda_i(x_j)$



x_1 represses the production of x_2.





x_1 activates the production of x_2.

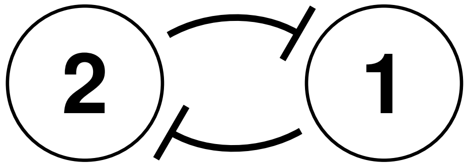
For $x_1 < \theta_{2,1}$ we ask about **sign** $(-\gamma_2 x_2 + u_{2,1})$.

For $x_1 > \theta_{2,1}$ we ask about **sign** $(-\gamma_2 x_2 + l_{2,1})$.

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

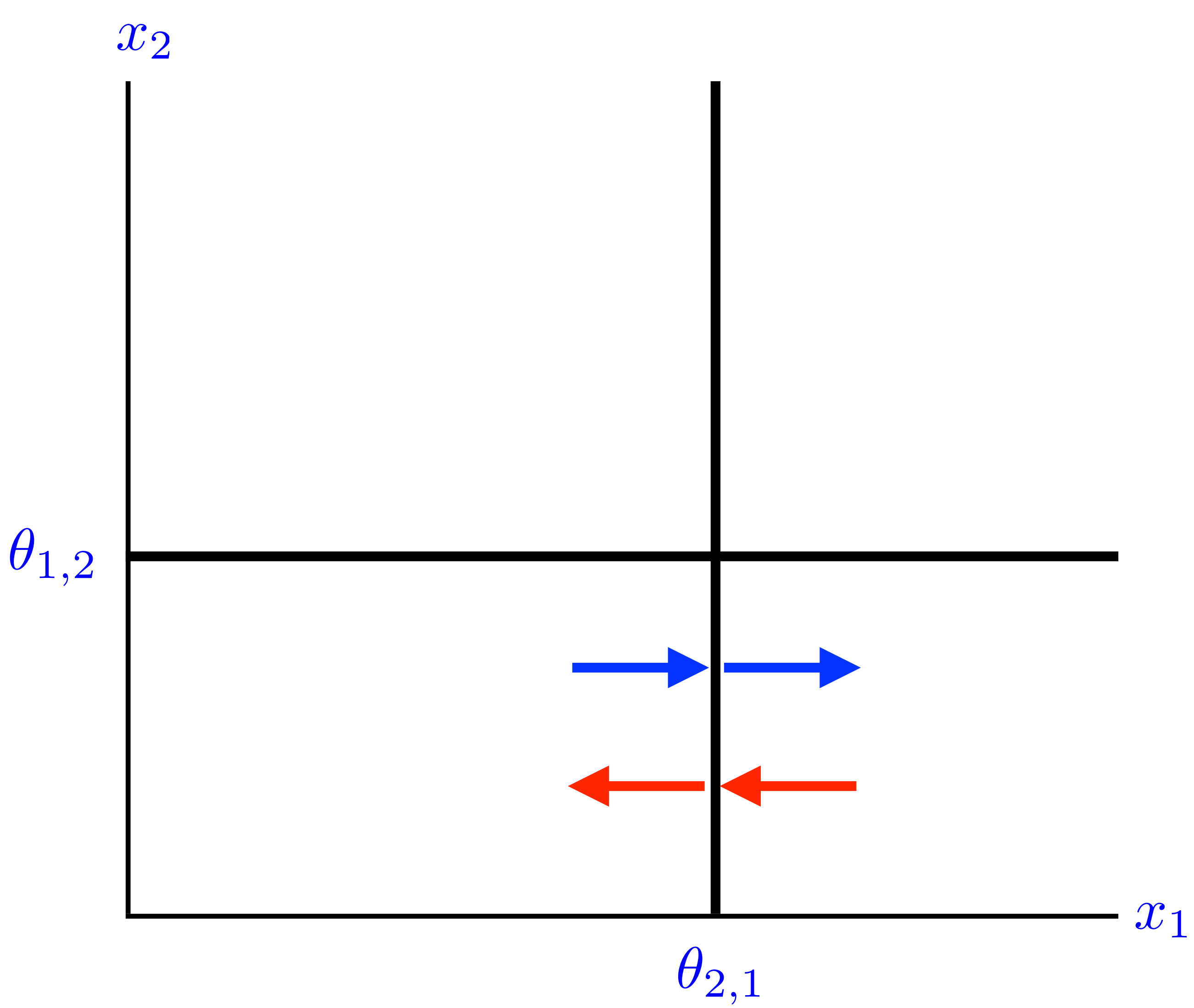
Focus on sign of $-\gamma_i x_i + \sigma^-_{i,j}(x_j)$

Example (The Toggle Switch)



Parameter space is a subset of $(0, \infty)^8$

Fix z a regular parameter value.



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

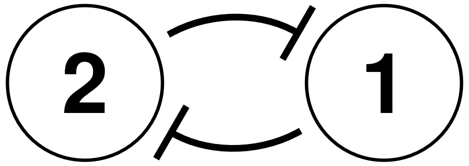
If $-\gamma_1\theta_{2,1} + \sigma^-_{1,2}(x_2) > 0$

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

z is a regular parameter value if

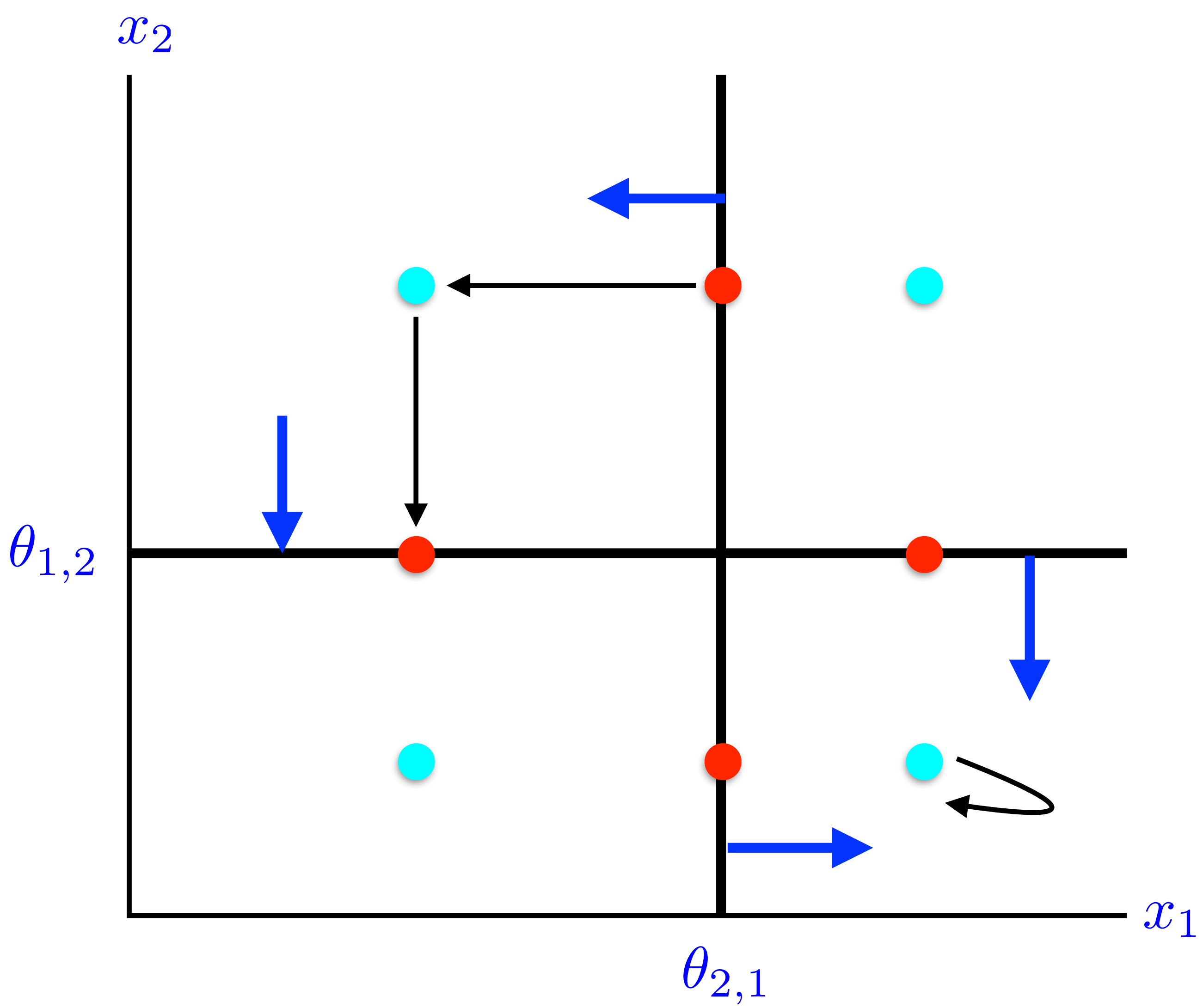
$$0 < \gamma_i$$
$$0 < \ell_{i,j} < u_{i,j},$$
$$0 < \theta_{i,k} \neq \theta_{j,k}, \quad \text{and}$$
$$0 \neq -\gamma_i\theta_{j,i} + \Lambda_i(x)$$

Example (The Toggle Switch)



Fix z a regular parameter value.

Need to Construct State Transition Graph $\mathcal{F}_z : \mathcal{X} \rightrightarrows \mathcal{X}$



Vertices

$\mathcal{X}$ corresponds to all rectangular domains and co-dimension 1 faces defined by thresholds θ.

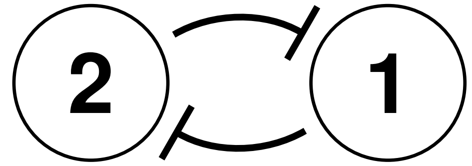
Edges

Faces pointing in map to their domain.

Domains map to their faces pointing out.

If no outpointing faces domain maps to itself.

The Toggle Switch

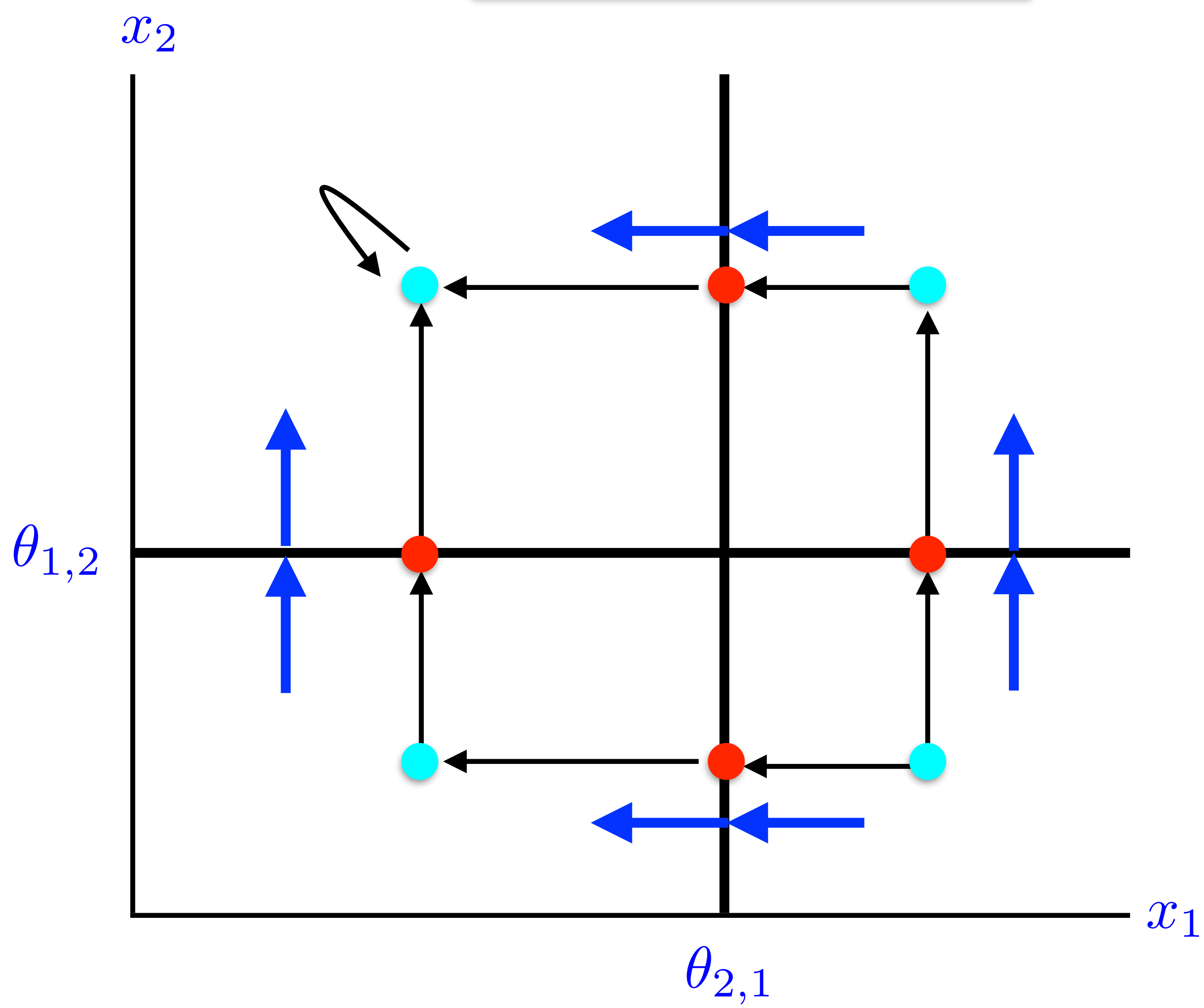


Constructing state transition graph $\mathcal{F}_z : \mathcal{X} \rightrightarrows \mathcal{X}$

Fix z a regular parameter value.

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

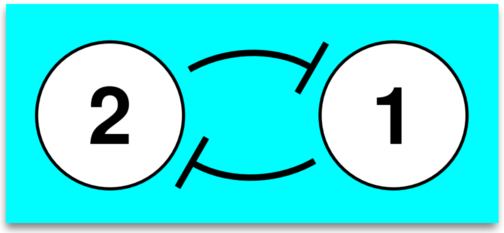
Check signs of $-\gamma_i\theta_{j,i} + \sigma^-_{i,j}(x_j)$



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

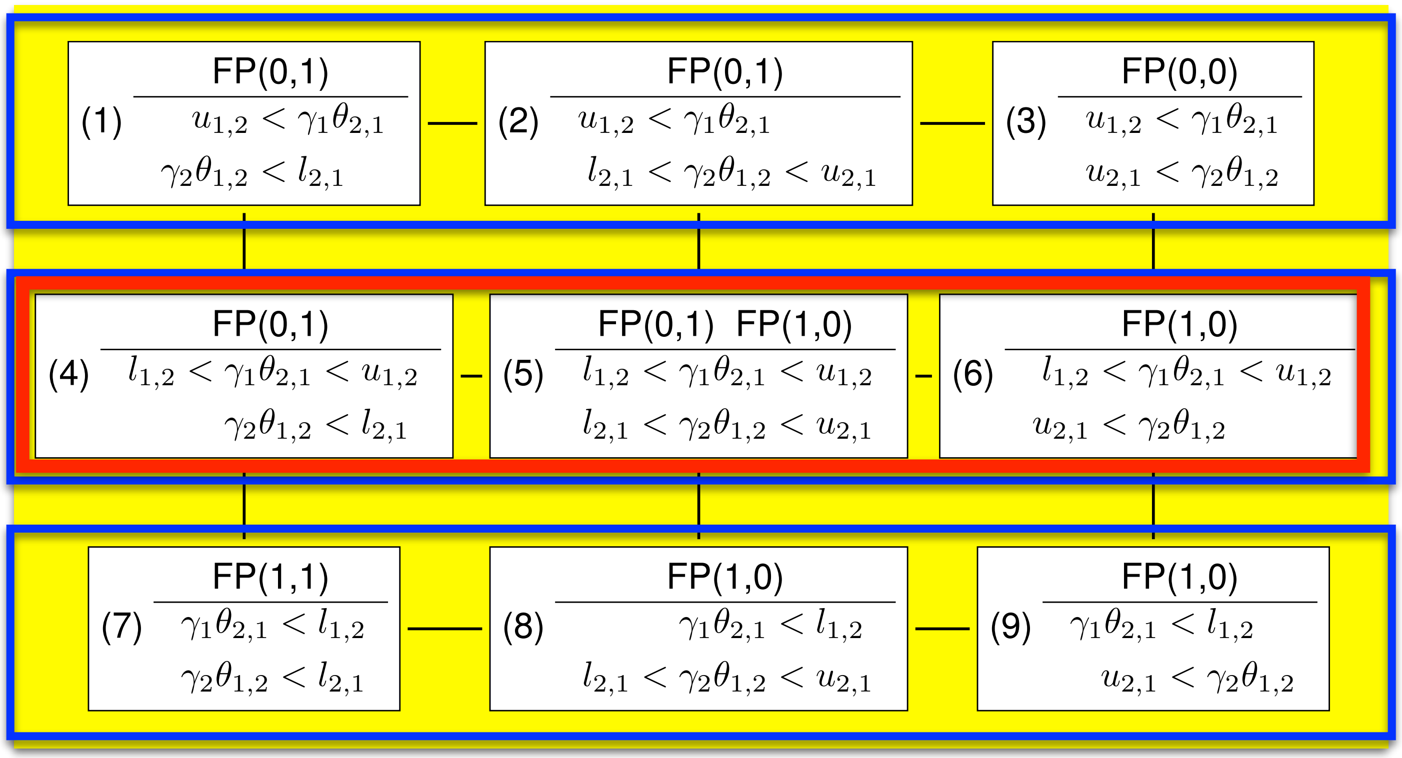
(8) FP(1,0)
$$\gamma_1\theta_{2,1} < l_{1,2}$$
$$l_{2,1} < \gamma_2\theta_{1,2} < u_{2,1}$$

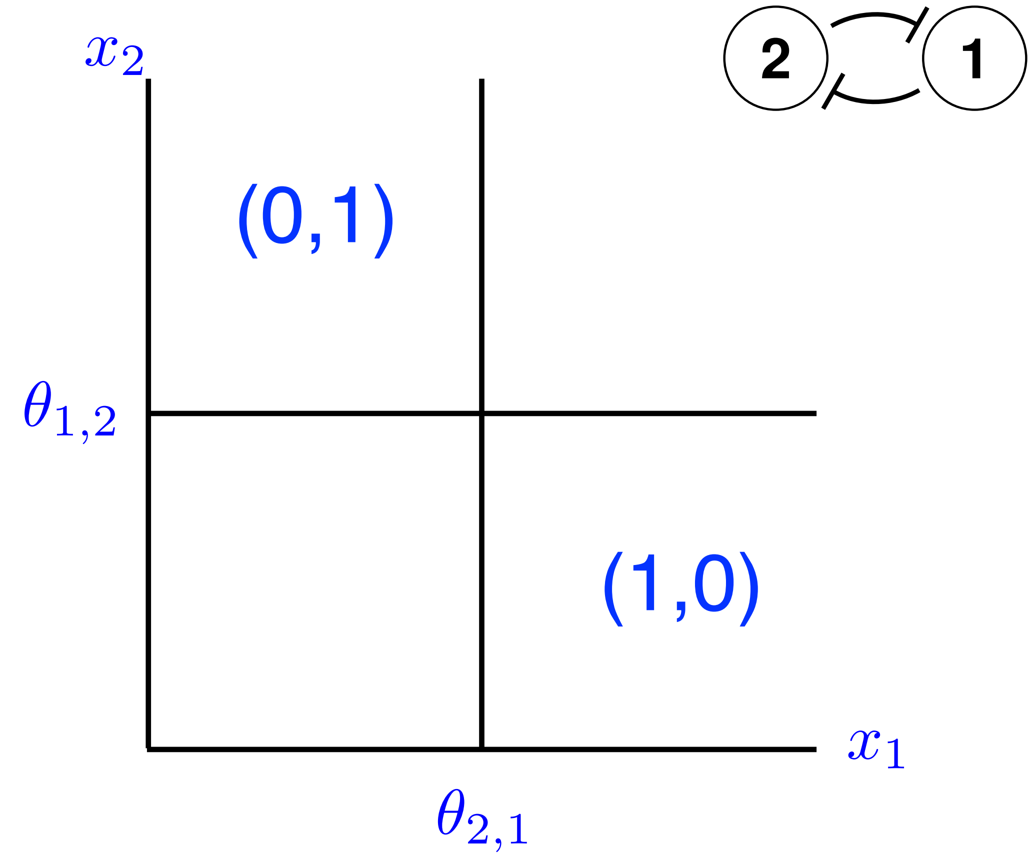
(9) FP(1,0)
$$\gamma_1\theta_{2,1} < l_{1,2}$$
$$u_{2,1} < \gamma_2\theta_{1,2}$$

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

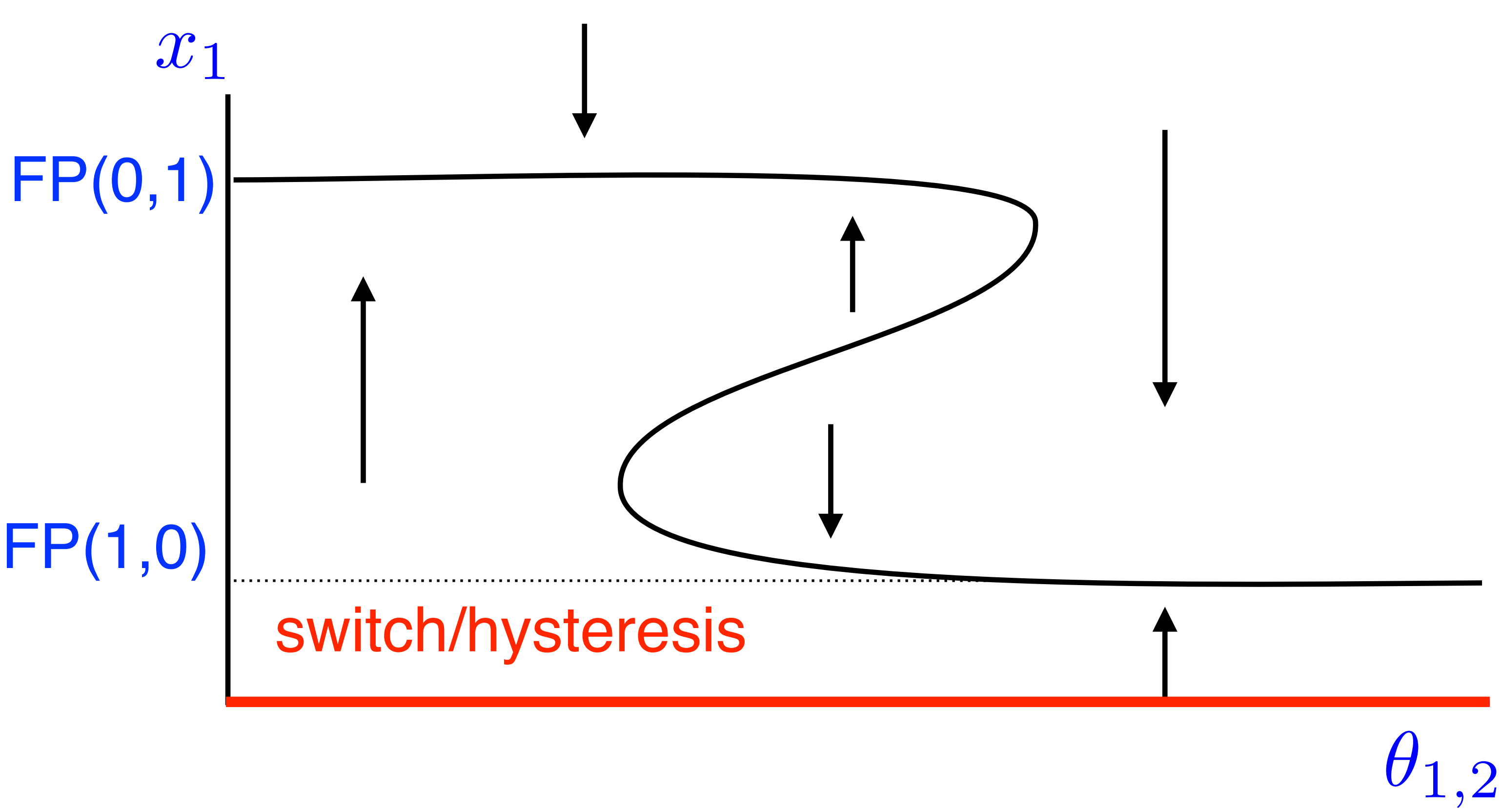
We can query this database for local or global dynamics.

Why is the Toggle Switch a Switch?



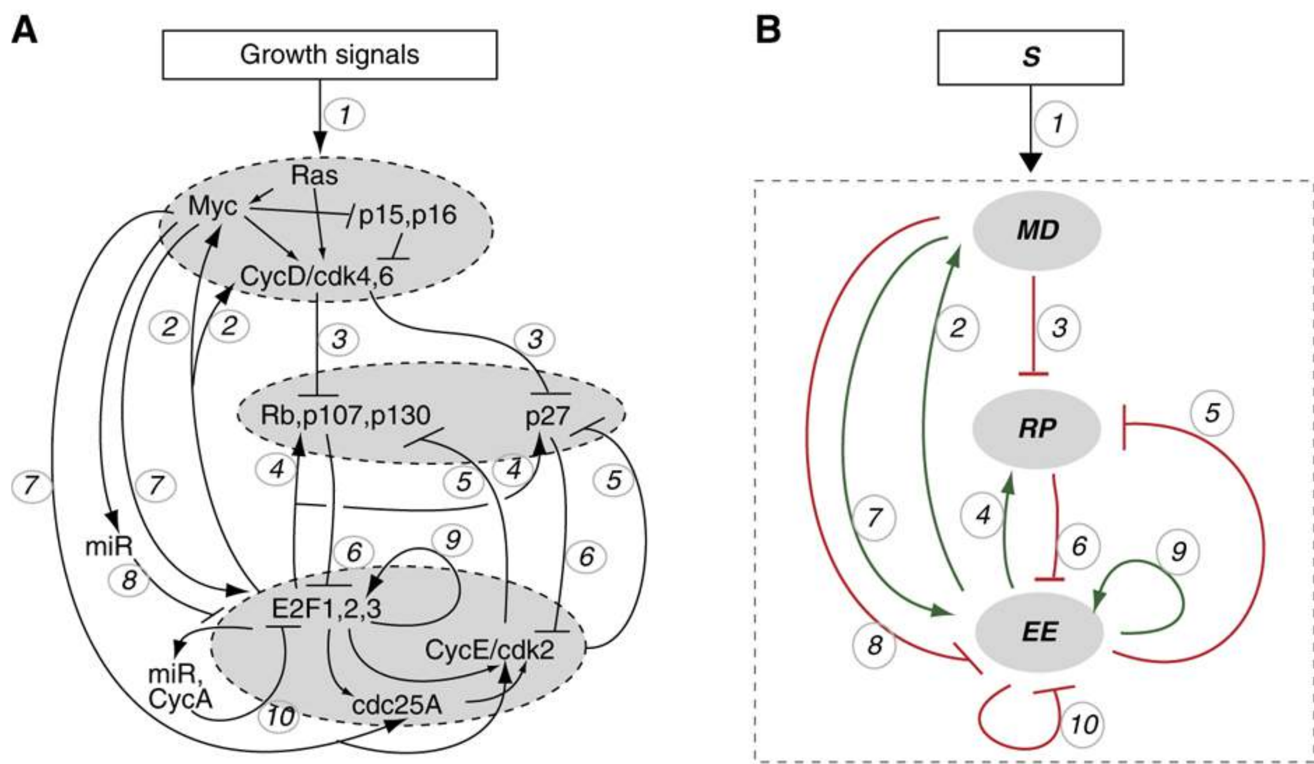


Paths defined by varying $\theta_{1,2}$

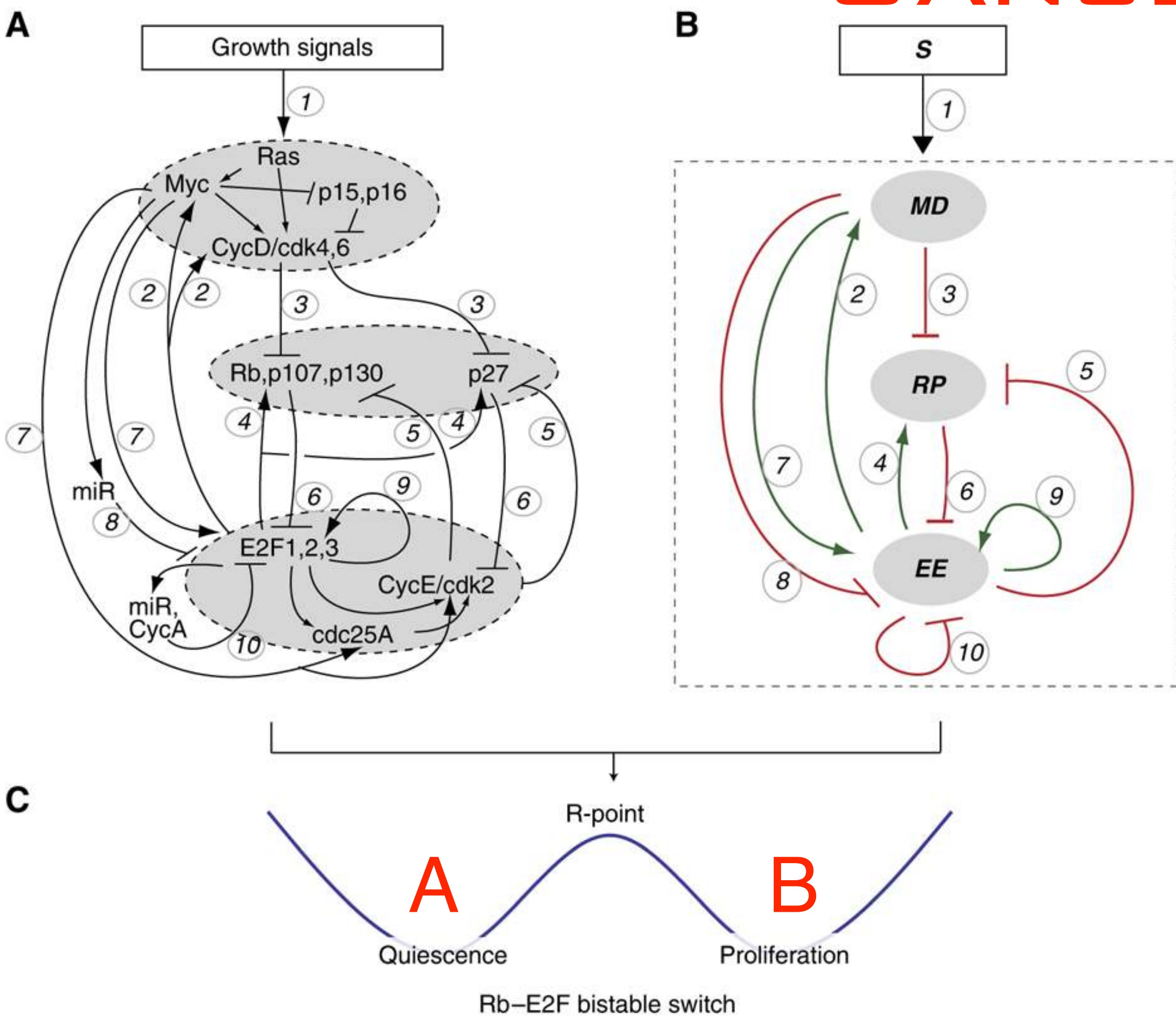


Hysteresis can be identified by tracking changes in Morse graphs over paths in parameter graph.

Choosing Models



Cancer



Goal: minimal network that exhibits hysteresis

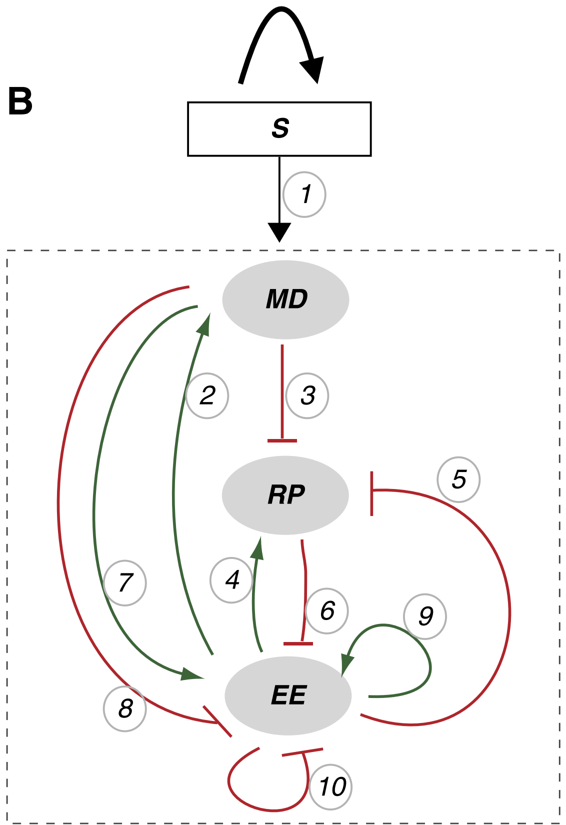
(Hysteresis) Two equilibria:
(A) Rb ON, E2F OFF = quiescence
(B) Rb OFF, E2F ON = proliferation

Yao et. al. tested 3-node networks (with Hill function nonlinearities to define dynamics) to identify frequency of hysteresis based on choice of 20,000 random parameters.

$$\text{Quality of model} = \text{QM} = \frac{\text{\# parameters with bistability}}{20{,}000}$$

Yao, et. al., MSB, 2011

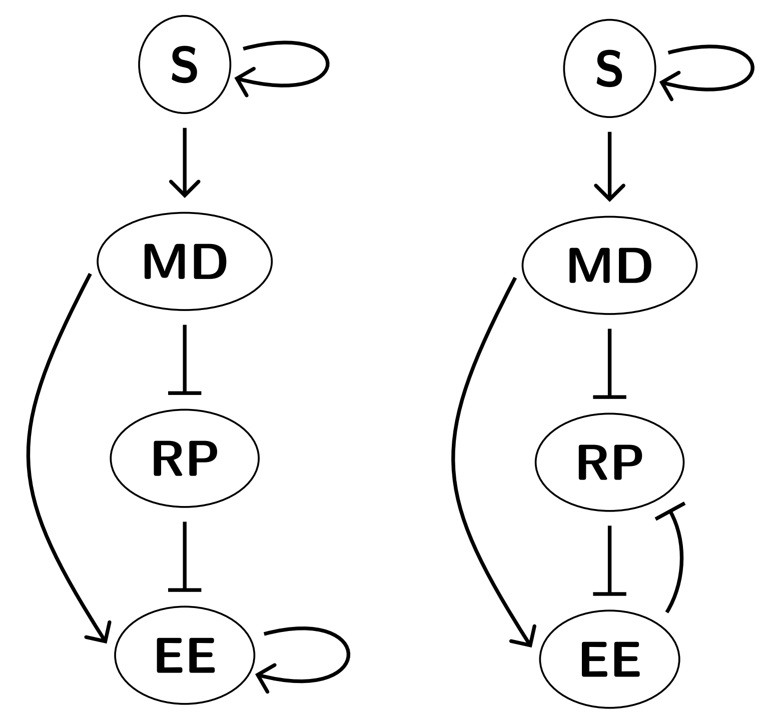
DSGRN Approach



For each possible regulatory network compute database.

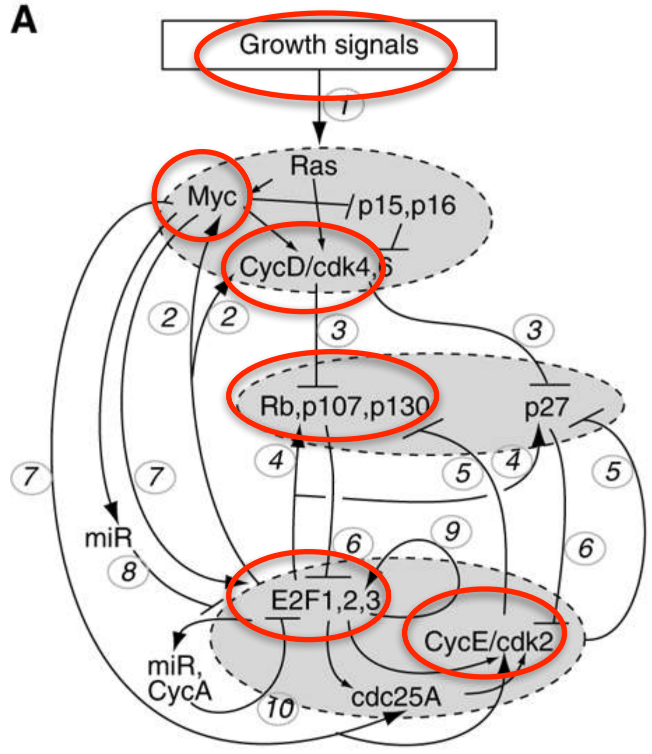
$$\text{QM} = \frac{\#\text{ paths varying } \theta_{S,S} \text{ with hysteresis}}{\#\text{ paths varying } \theta_{S,S}}$$

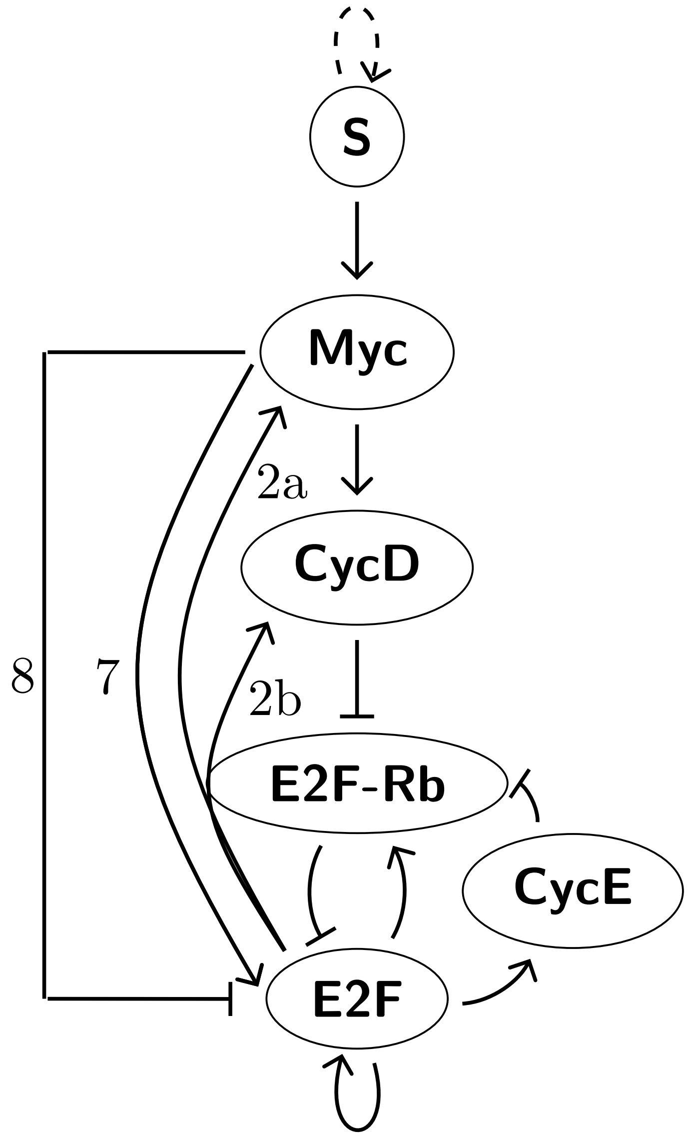
Two networks where QM $> 50\%$
(match top two networks of Yao et. al.)



(a) (b)

More Detailed Models



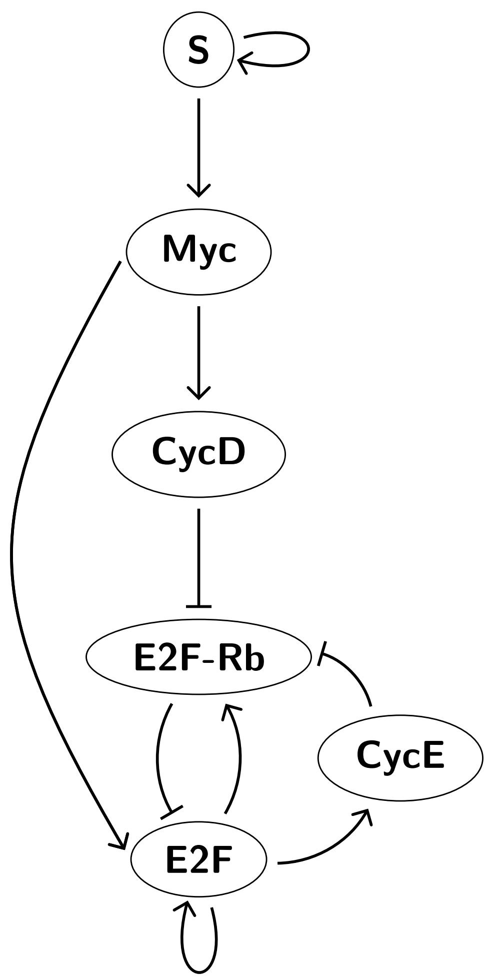


For each possible regulatory network compute database.

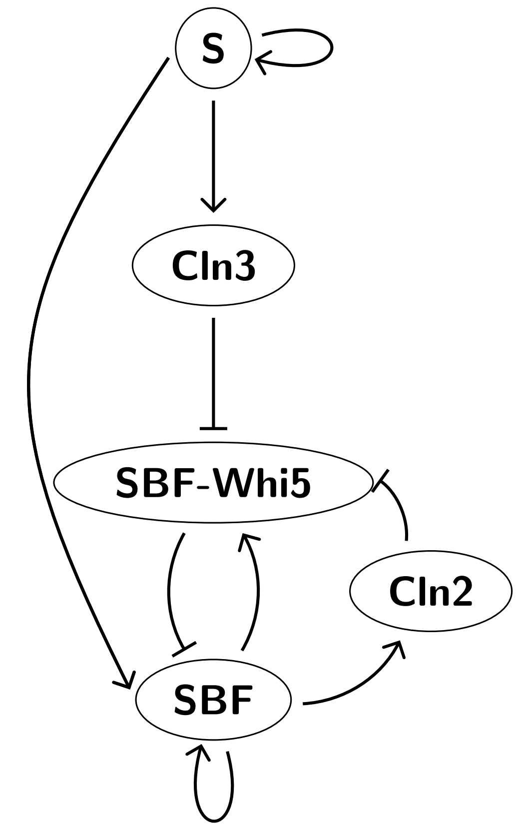
$$\text{QM} = \frac{\#\text{ paths varying } \theta_{S,S} \text{ with hysteresis}}{\#\text{ paths varying } \theta_{S,S}}$$

Cross Species Comparison

DSGRN best network (human):



Yeast cell cycle entry:

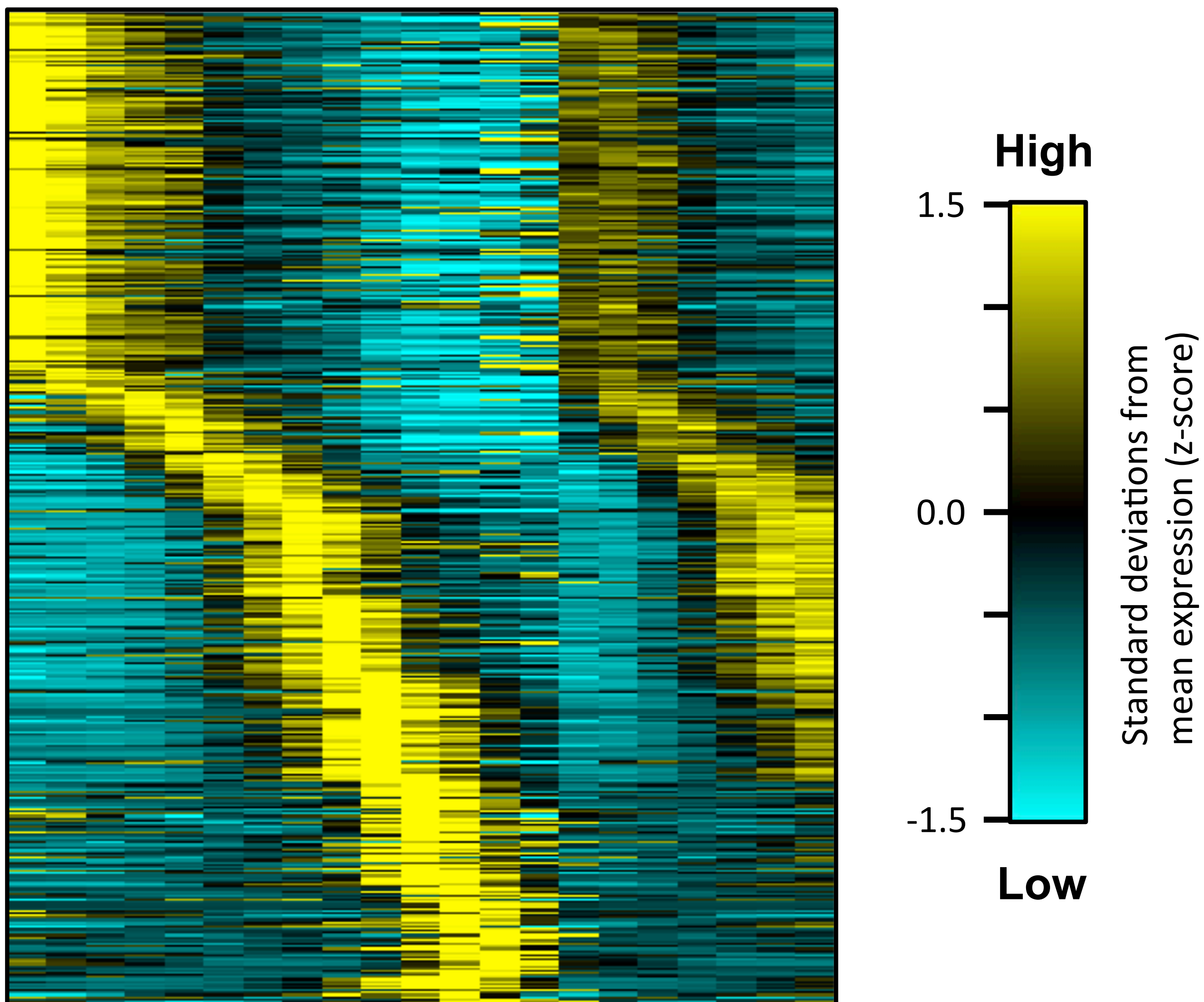


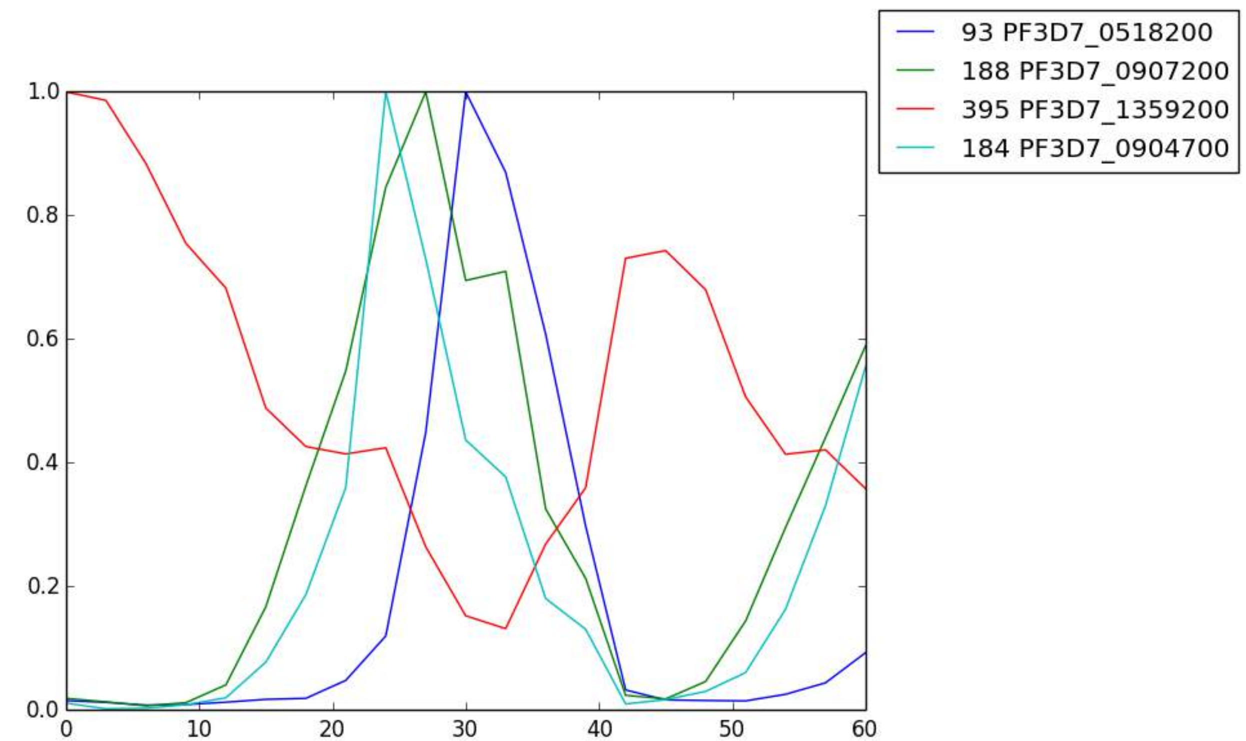
No homology between individual genes!
Only network structure is similar.

Is the structure selected for its dynamical property i.e. a robust bistable switch?

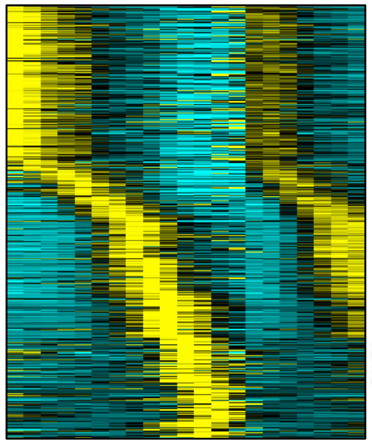
Malaria

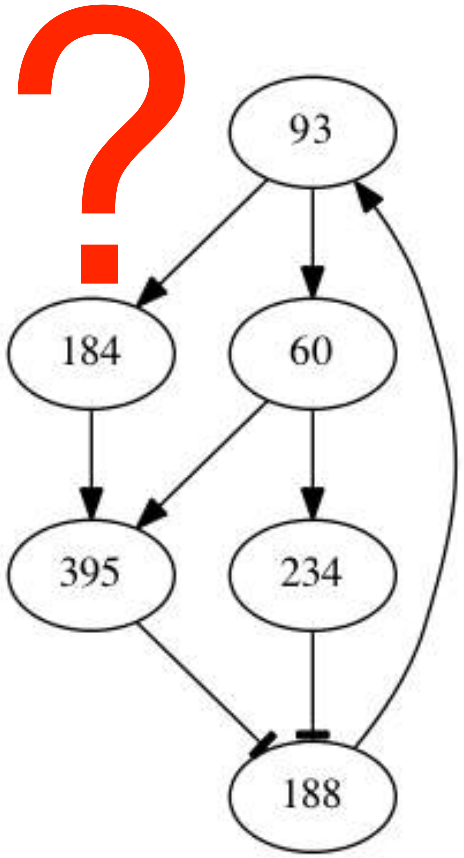
(what are the models?)





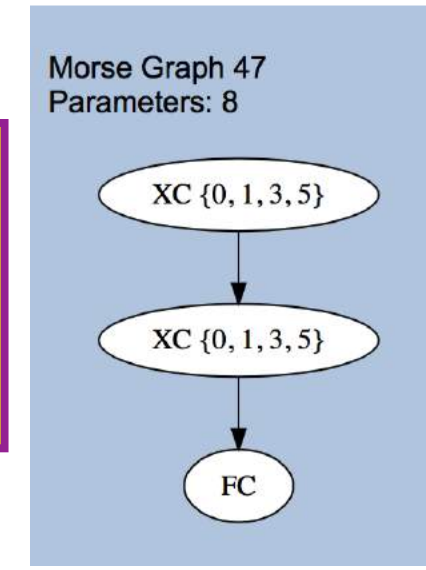
Can a Network (model) Support Experimental Data?





SQL Query: Minimal node in Morse graph containing cycle involving all variables.

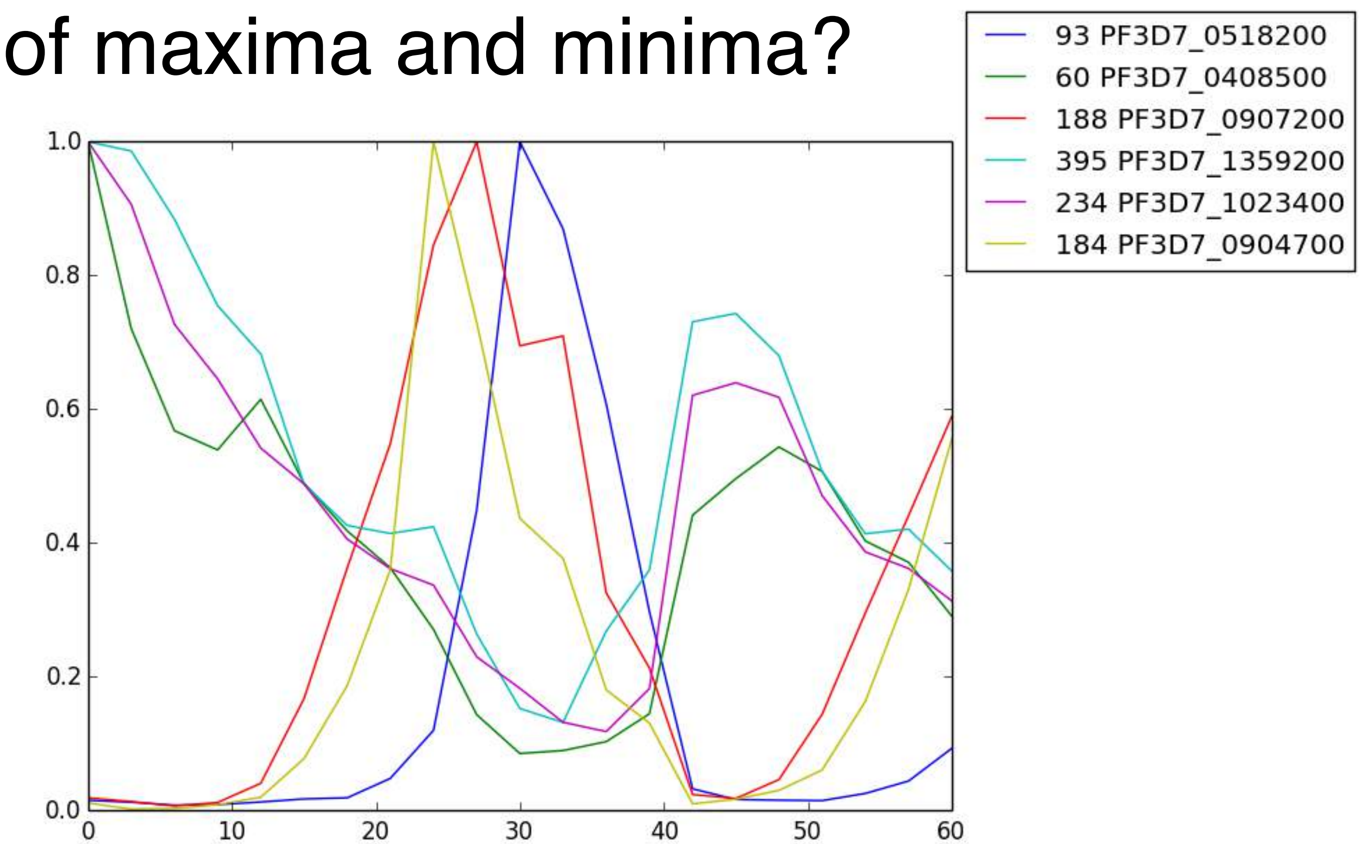
96 parameter graph nodes with Morse graph that has a minimal node consisting of a Full Cycle (FC).



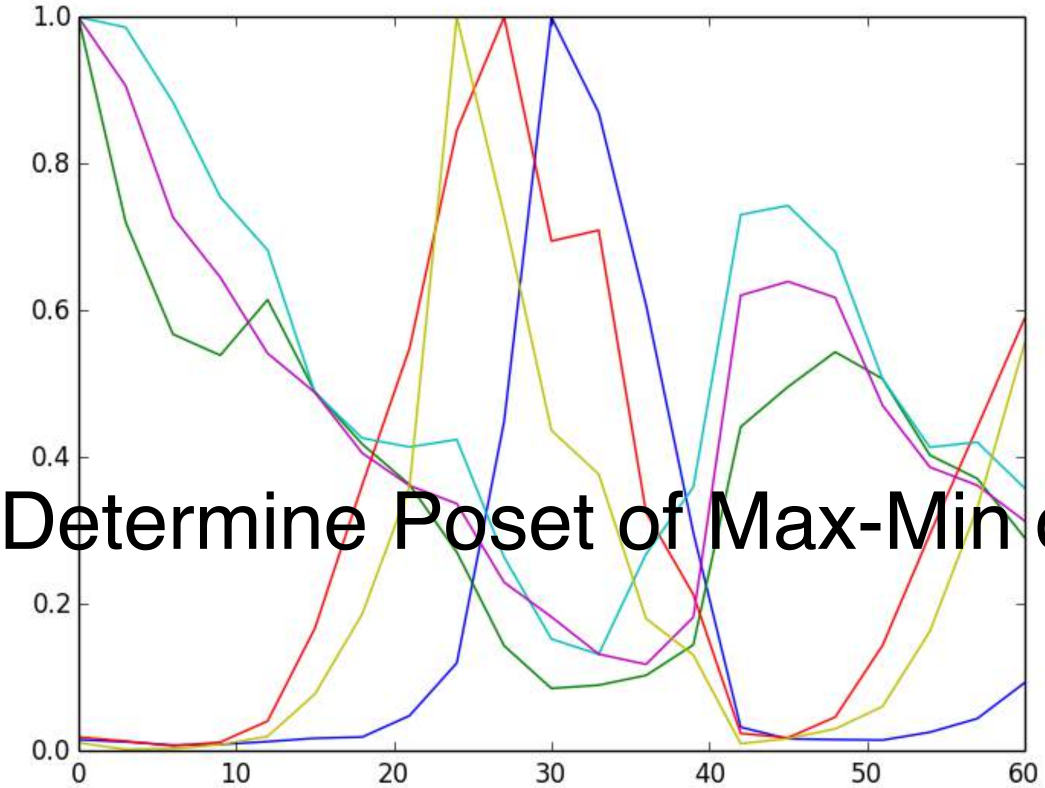
DSGRN computation produces parameter graph with ≈ 45,000 nodes.

Computation time on laptop ≈ 1 second.

Can we reproduce relative order of maxima and minima?

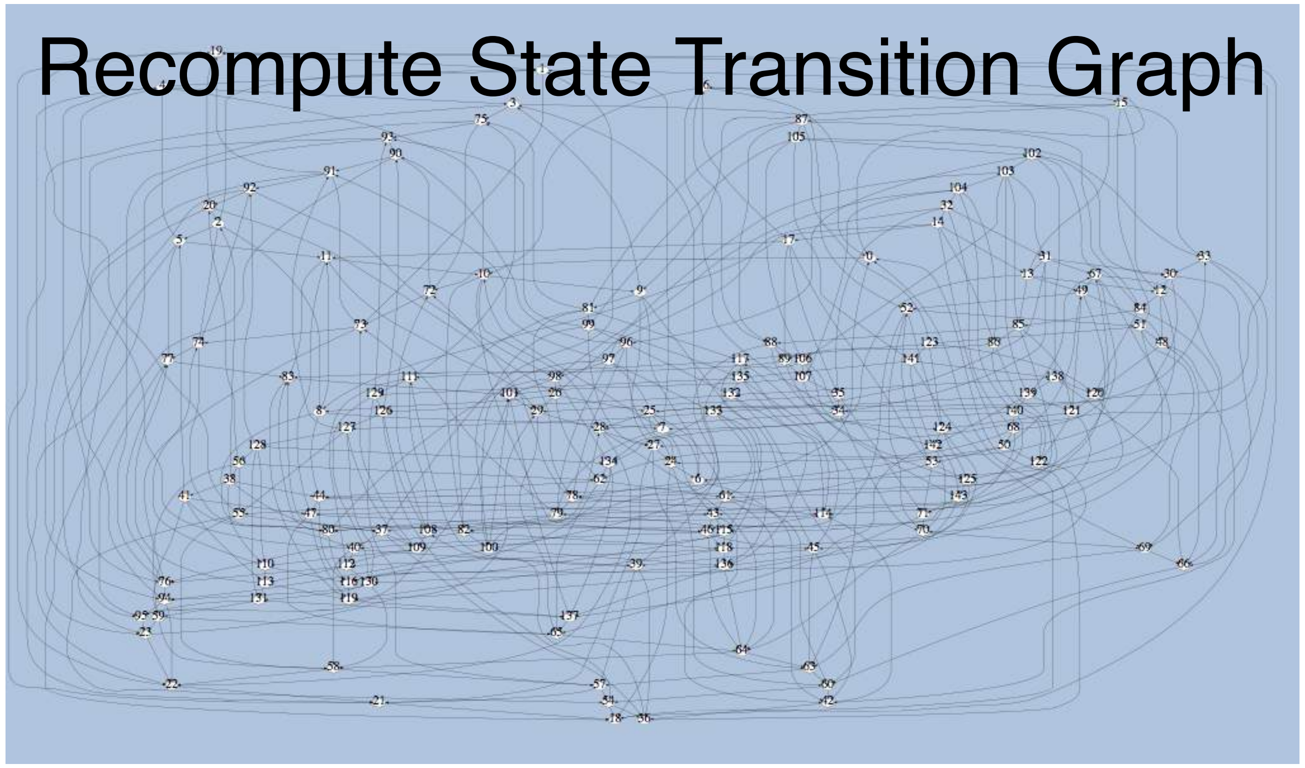


DSGRN Strategy for Matching Max-Min



Determine Poset of Max-Min orders

Recompute State Transition Graph



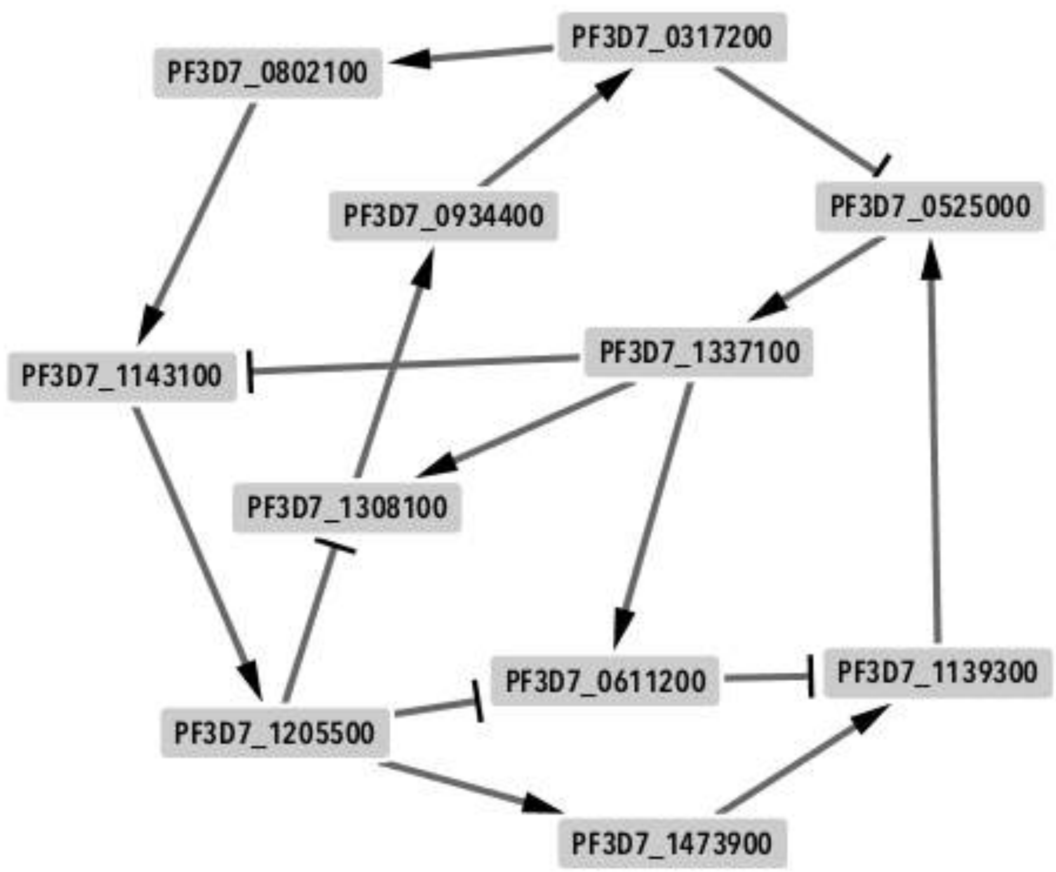
M m   m
M m ⟶ M ⟶ M ⟶ M m
M m   m

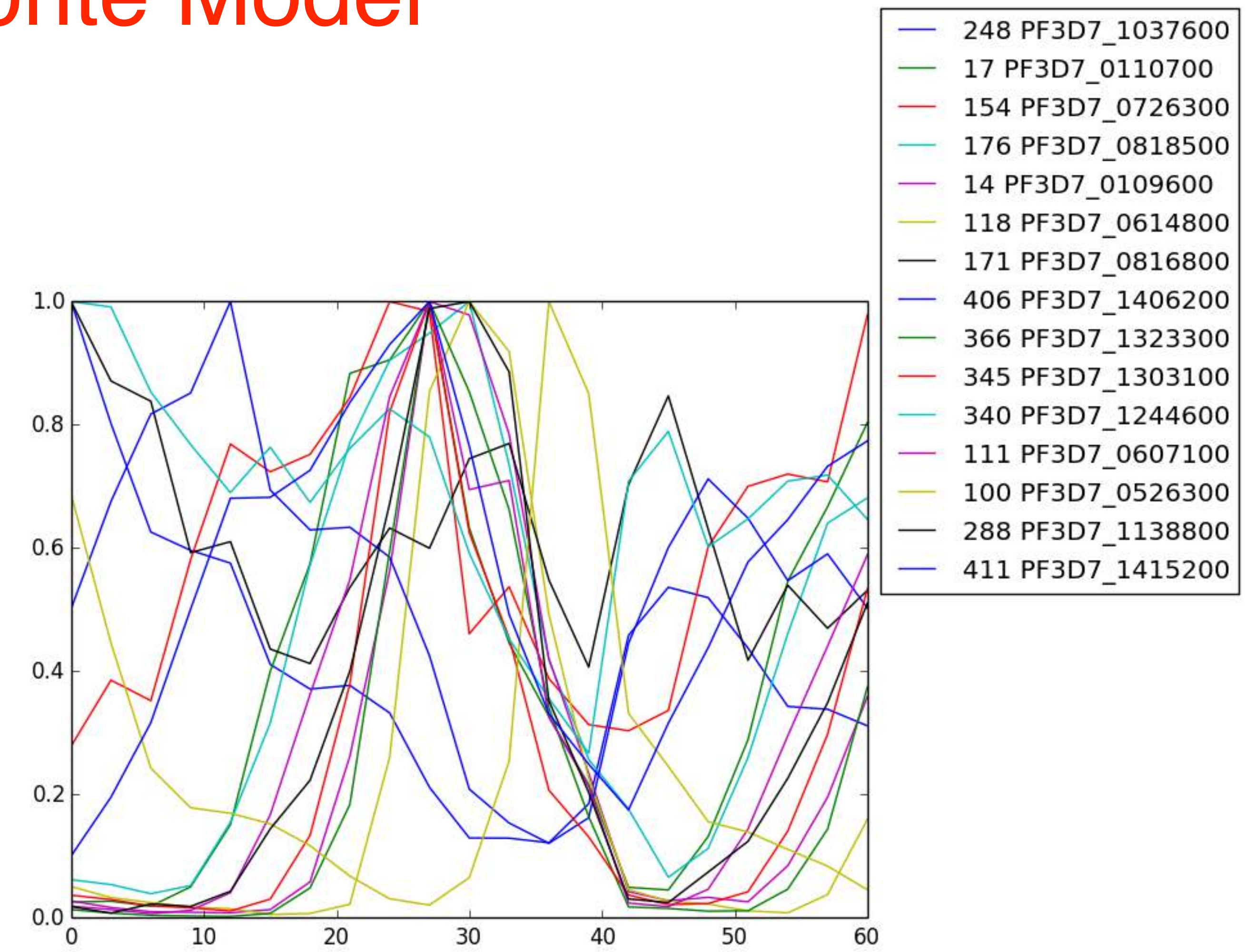
Polynomial time algorithm compares possible max-min orderings of state transition graph paths with max-min orderings of experimental data.

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

Current Favorite Model





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

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

Thank-you for your Attention

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