Switching networks database as a platform for parameter search in gene regulatory networks

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High dimensional/Multiparameter World

Gene regulation: tens/hundreds of variables and/or parameters
Combustion: hundreds/thousands of variables and/or parameters
Neuroscience: millions/ potentially billions of variables

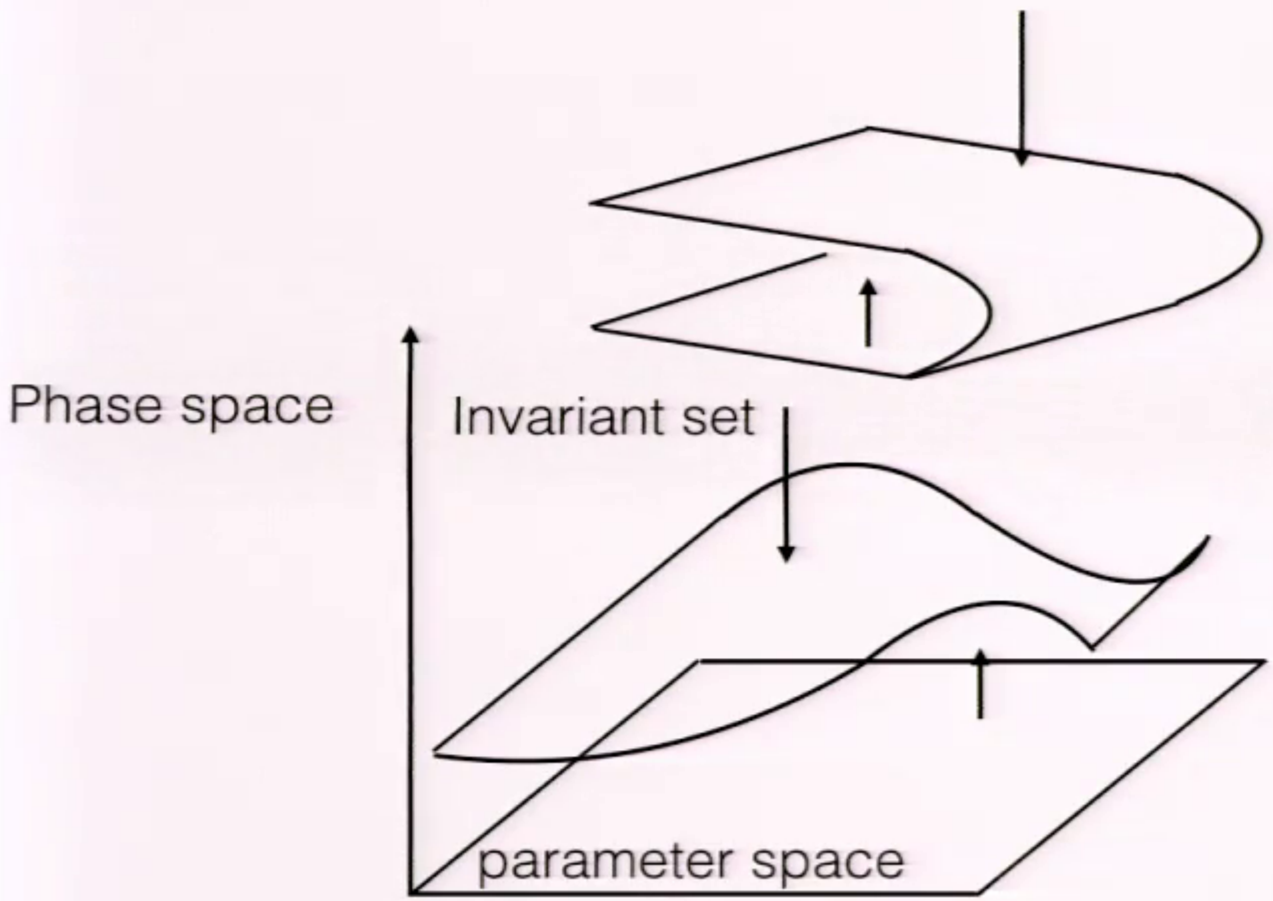
Species: Relevant species and interactions not certain
Nonlinearities: Not derived from first principles
Parameters: Poorly approximated or not known

Typical: Finite set of initial conditions at a finite set of parameter values.
Results: Fragmented, incomplete knowledge/understanding

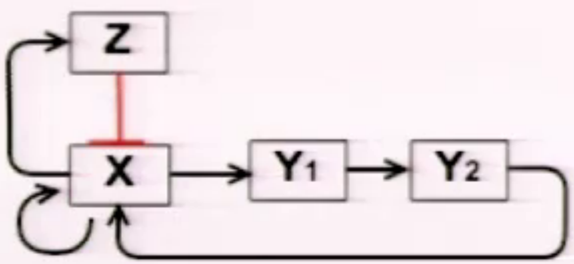
We describe a new approach that provides a finite queryable description of global dynamics for multiparameter systems

Classical paradigm in dynamical systems

- Invariant sets depends sensitively on parameters, model selection, and initial conditions
- These are **not** computable objects in high dimensions!



Switching models: computable models



Hill function model

$$
\begin{aligned}
\dot{x} &= -x + \left(\alpha_1 \frac{x^n}{K_1^n + x^n} + \alpha_{14} \frac{y_2^n}{K_{13}^n + y_2^n}\right) \frac{K_{14}^n}{K_{14}^n + z^n} \\
\dot{y}_1 &= -y_1 + \alpha_2 \frac{x^n}{K_3^n + x^n} \\
\dot{y}_2 &= -y_2 + \alpha_3 \frac{y_1^n}{K_4^n + y_1^n} \\
\dot{z} &= -z + \alpha_4 \frac{x^n}{K_5^n + x^n}
\end{aligned}
$$

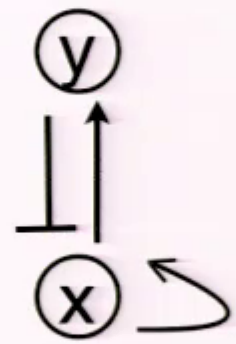
Switching model

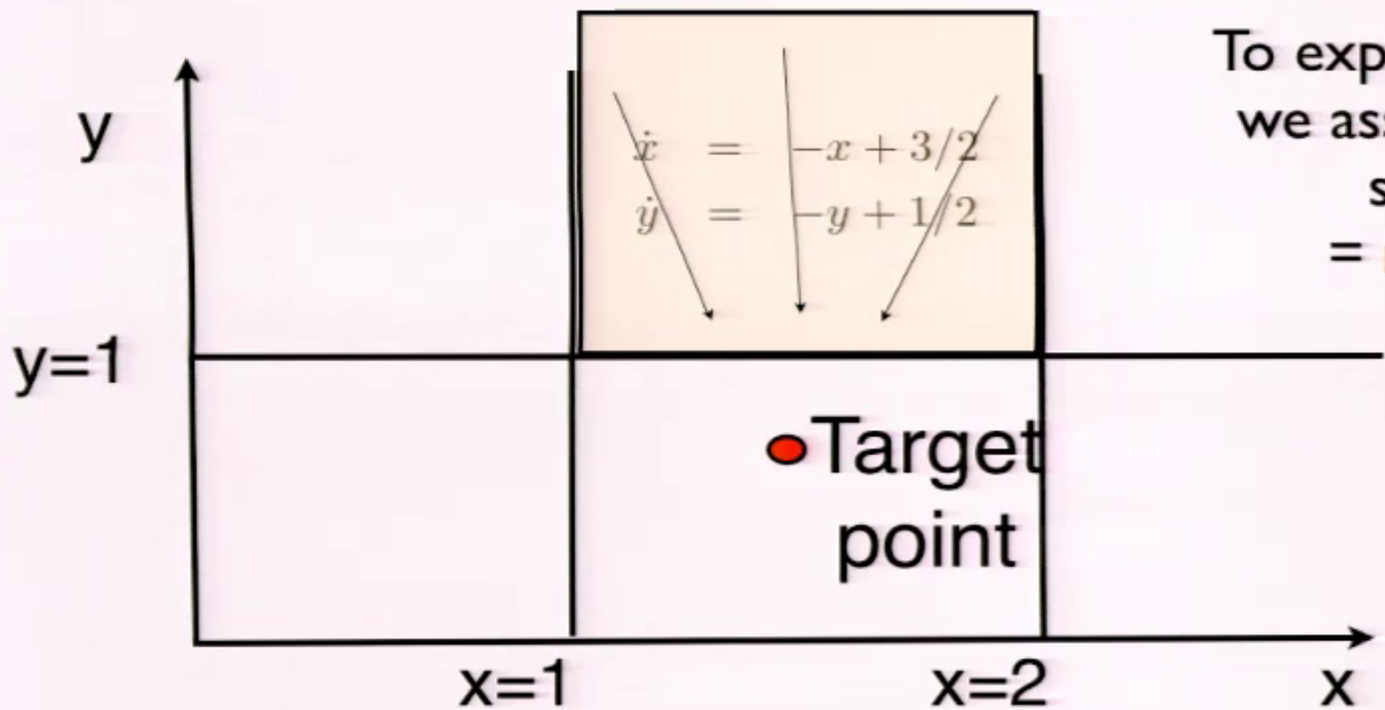
$$
\begin{aligned}
\dot{x} &= -x + \Lambda_1(X, Y_2, Z) \\
\dot{y}_1 &= -y_1 + \Lambda_2(X) \\
\dot{y}_2 &= -y_2 + \Lambda_3(Y_1) \\
\dot{z} &= -z + \Lambda_4(X) \\
X &= sign(x), Y_1 = sign(y_1) \\
Y_2 &= sign(y_2), Z = sign(z)
\end{aligned}
$$

Switching networks: phase space

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

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



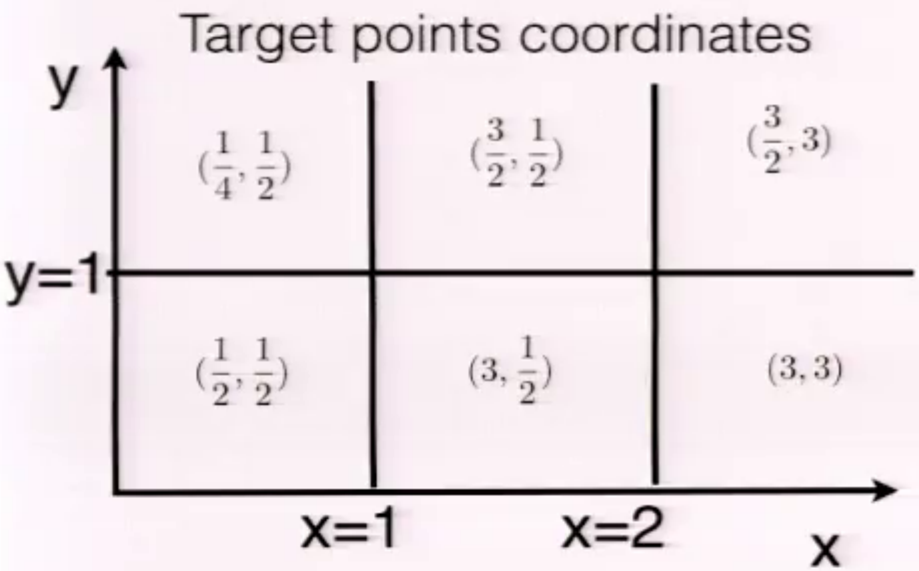


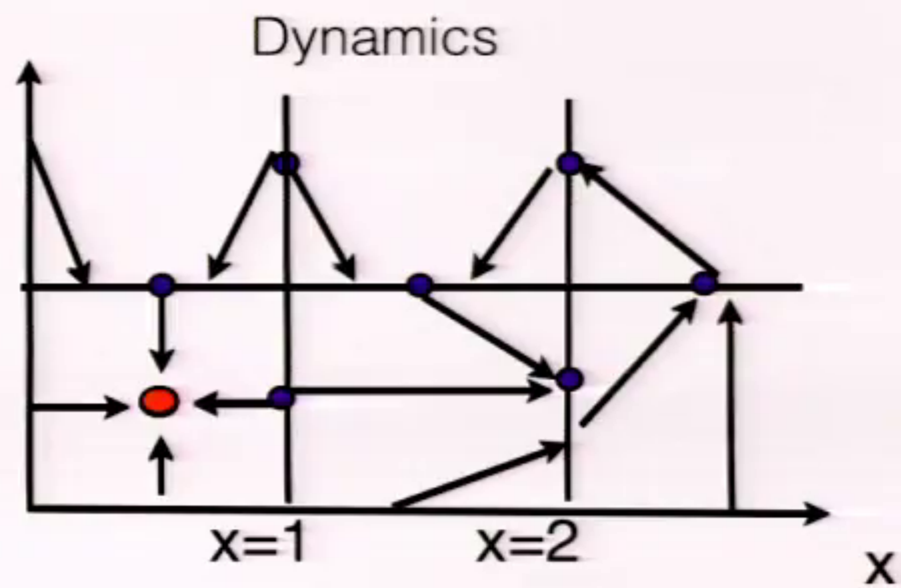
To explain the main ideas we assume no negative self-feedback = no black walls

Phase space and the dynamics

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

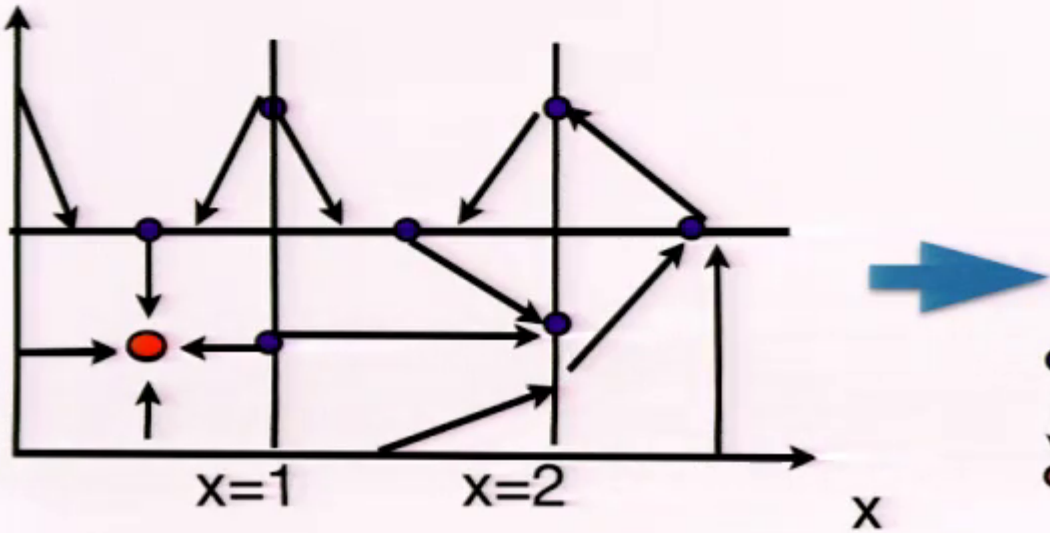
$$\dot{y} = -y + \begin{cases} 3 & x > 2 \\ 1/2 & x < 2 \end{cases}$$



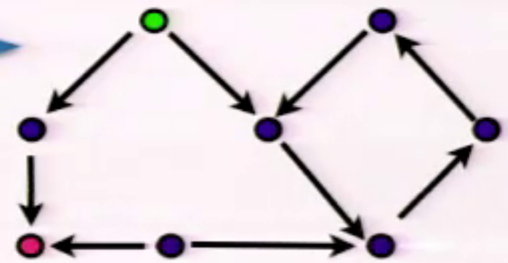


Dynamics is captured by collection of walls, special objects to represent the equilibria, and maps between them.

Wall graphs capture the dynamics



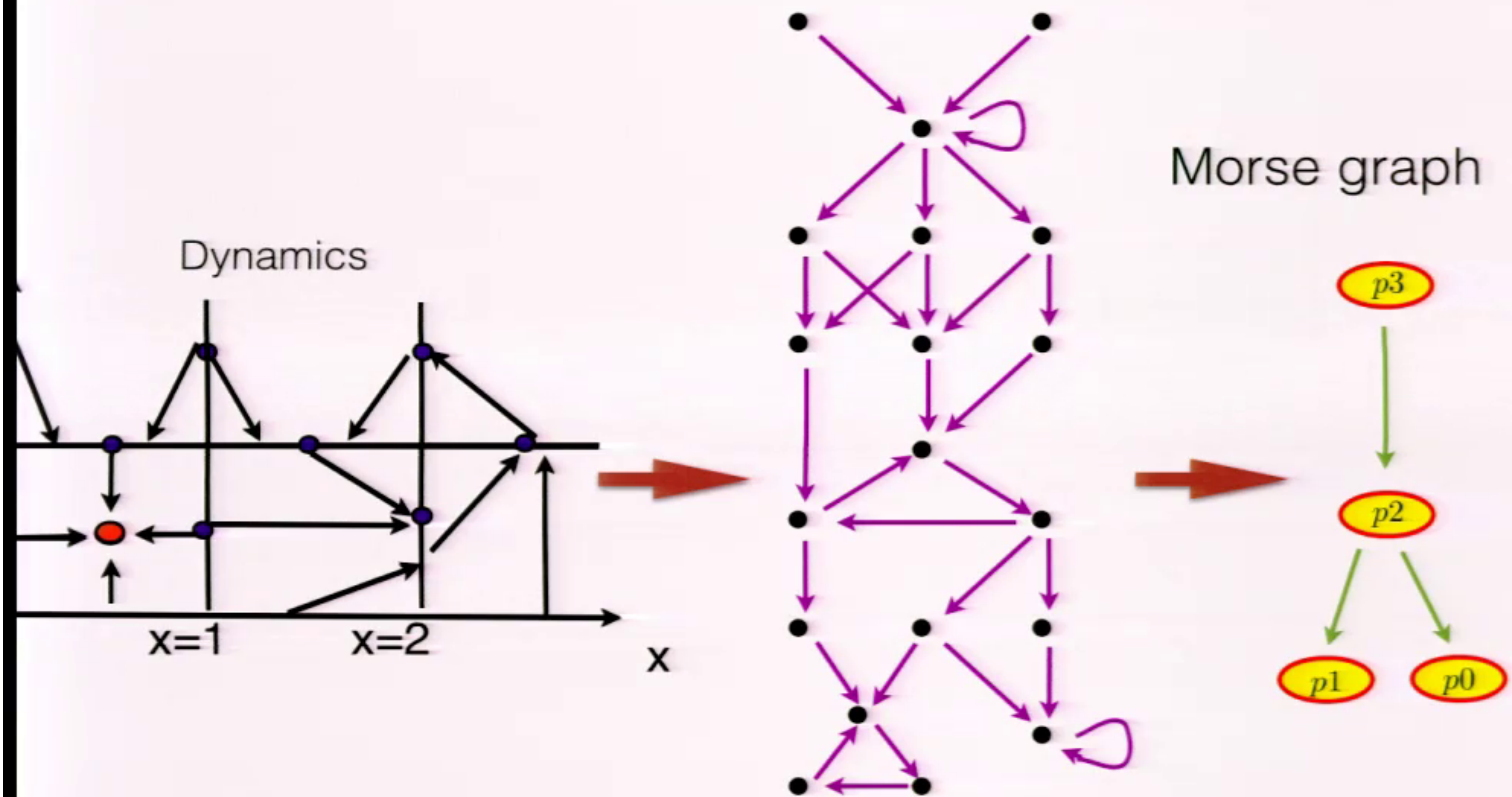
Wall graph
0-level resolution



Recurrent set

Morse sets

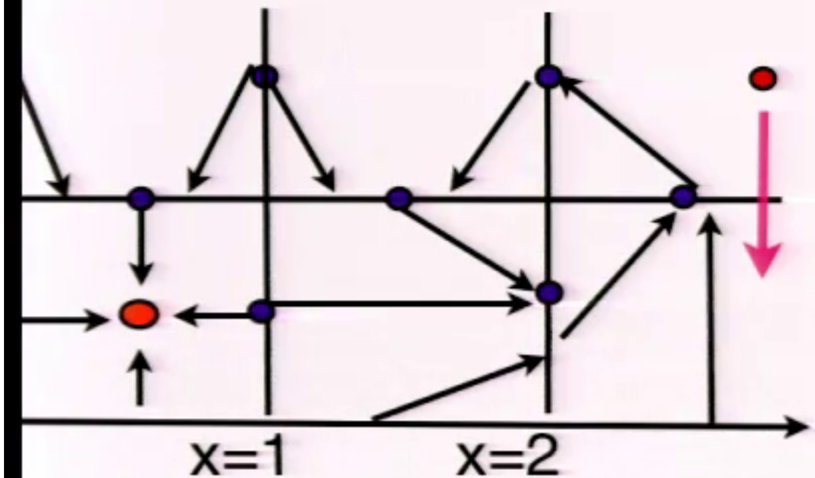
Computable Dynamics (phase space)



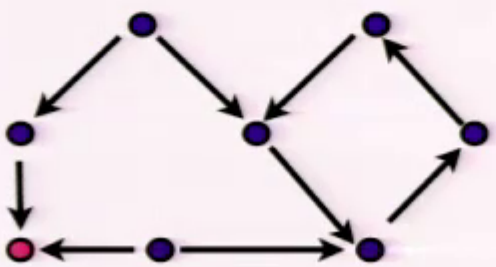
Vertices: States
Edges: Dynamics

When does the wall graph change?

1. When a target point moves through a threshold:

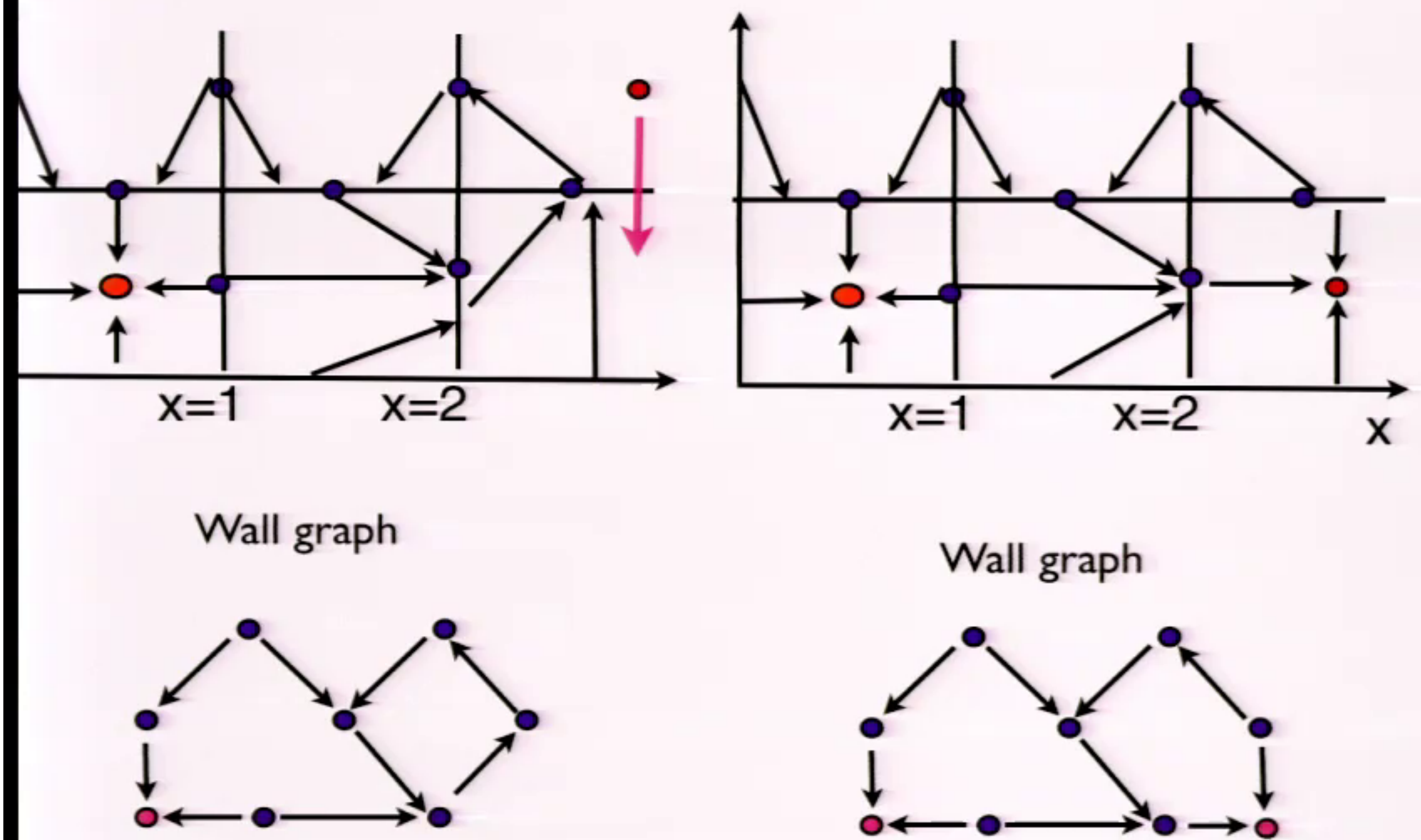


Wall graph



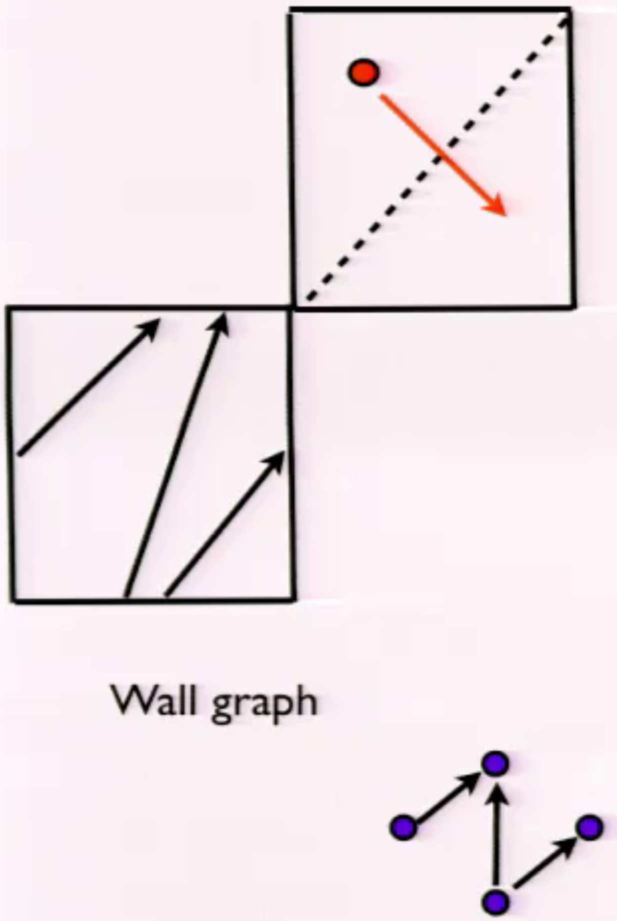
When does the wall graph change?

1. When a target point moves through a threshold:

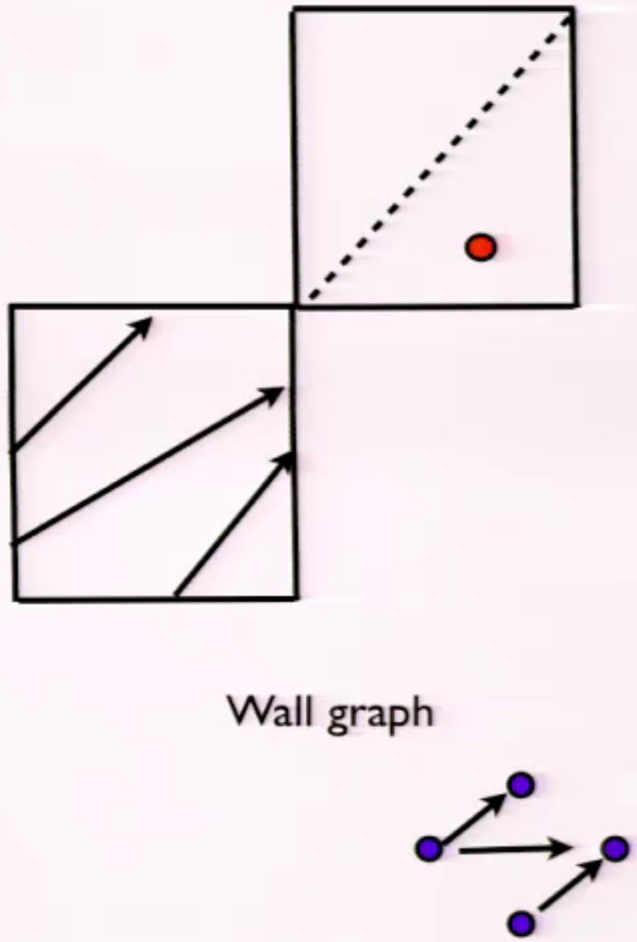


When does the wall graph change?

2. When a target point moves through a computable hyperplane.

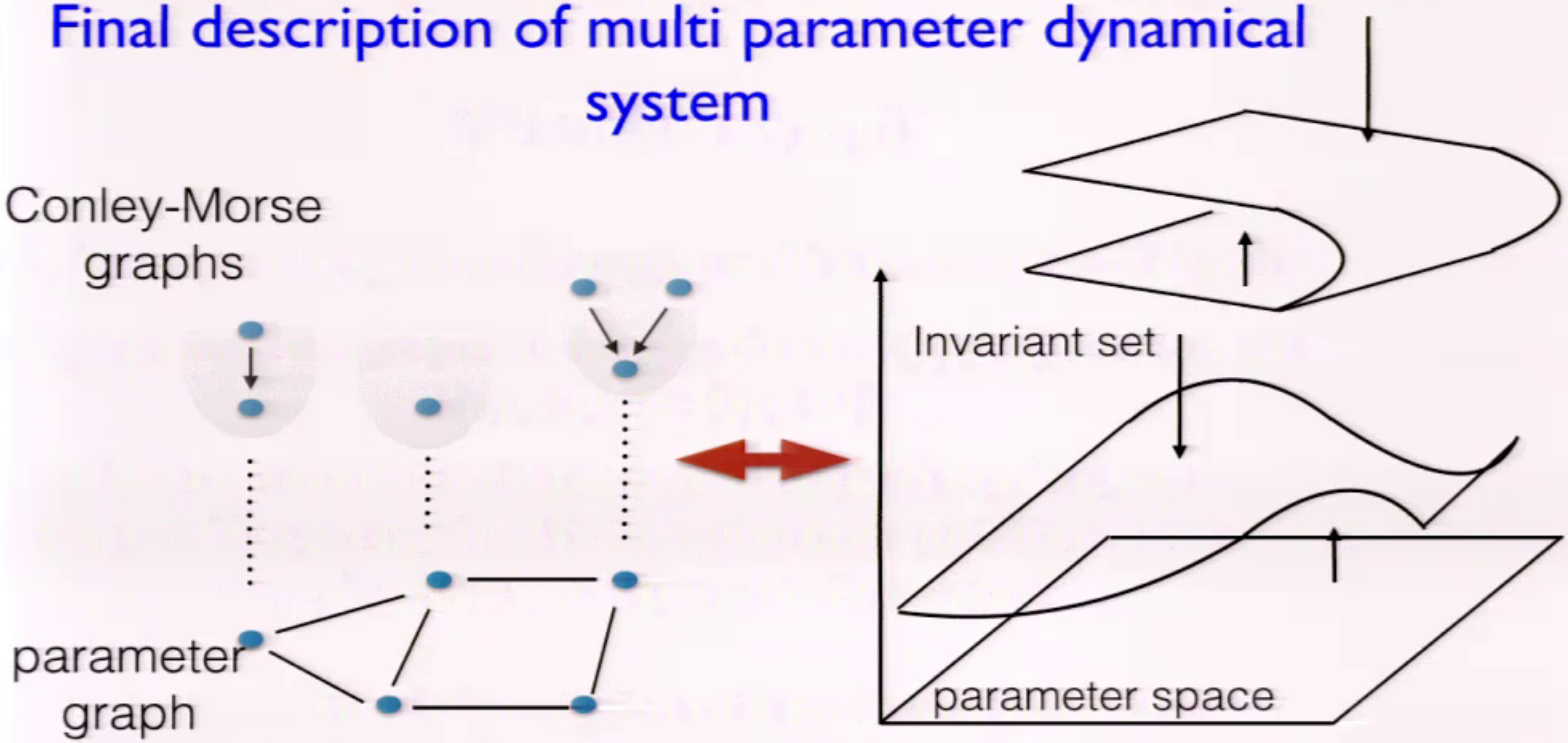


Wall graph

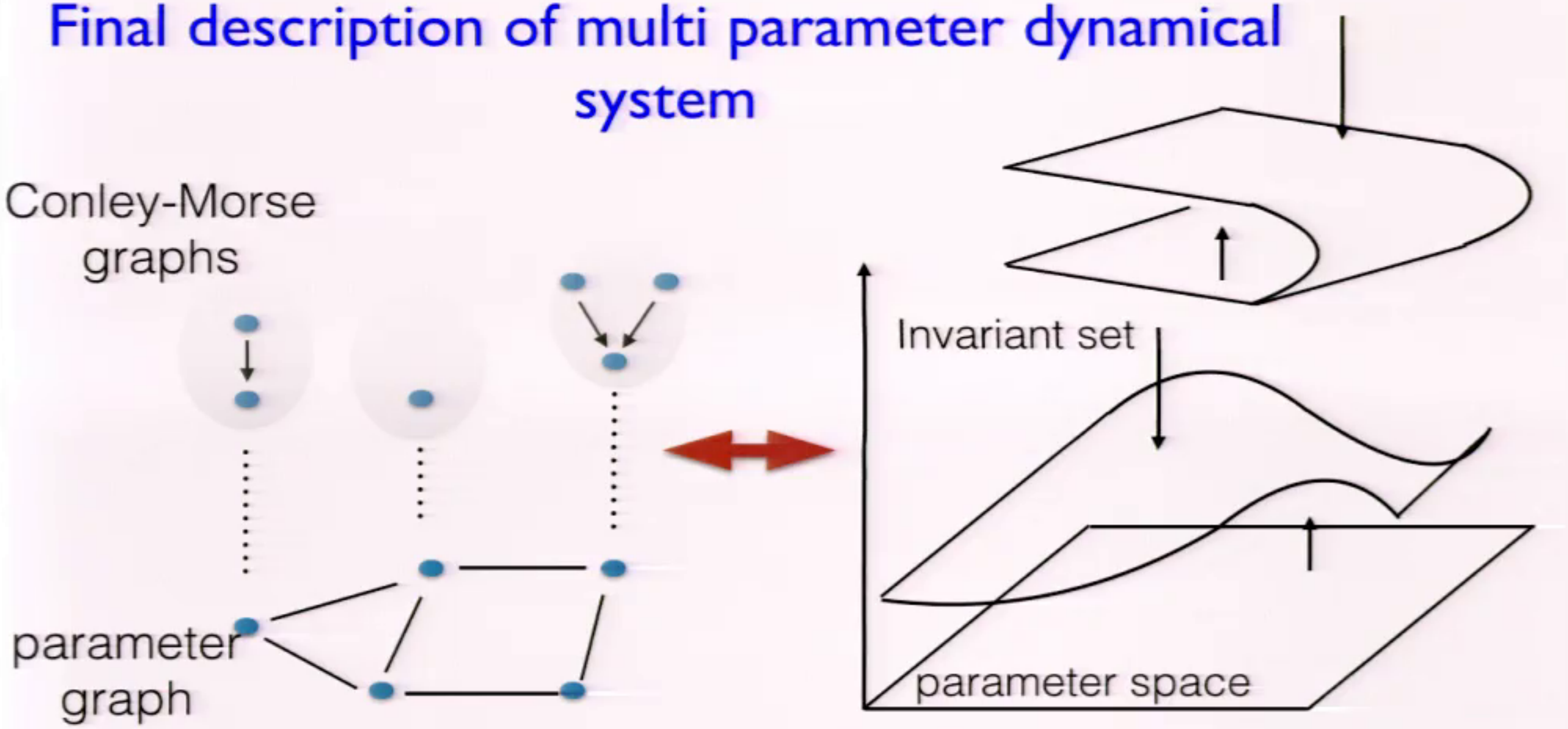


Wall graph

Final description of multi parameter dynamical system



Final description of multi parameter dynamical system

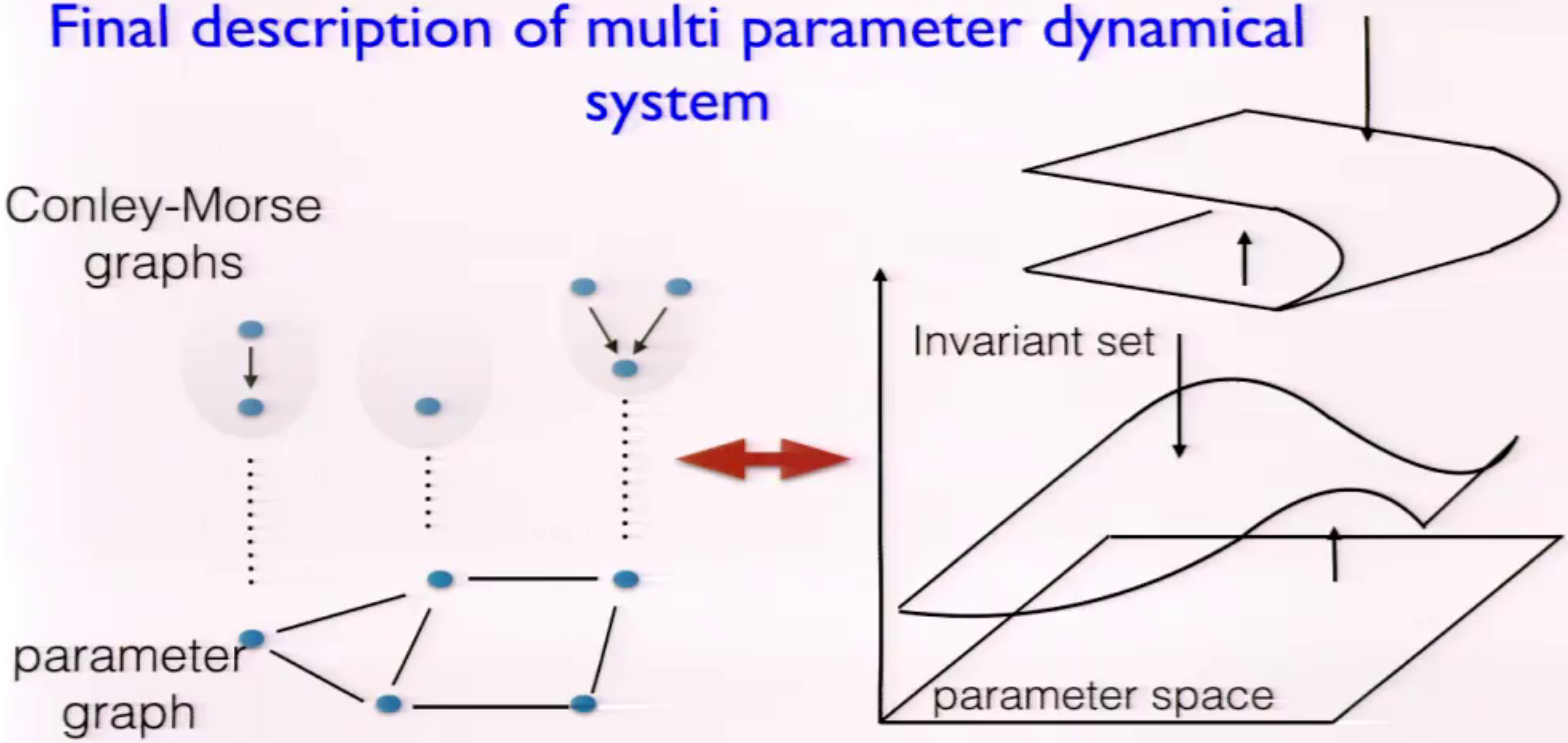


We can first construct the parameter graph, then compute Conley Morse graph at each vertex of parameter graph, and only later determine parameters that each vertex represents!

Repressilator

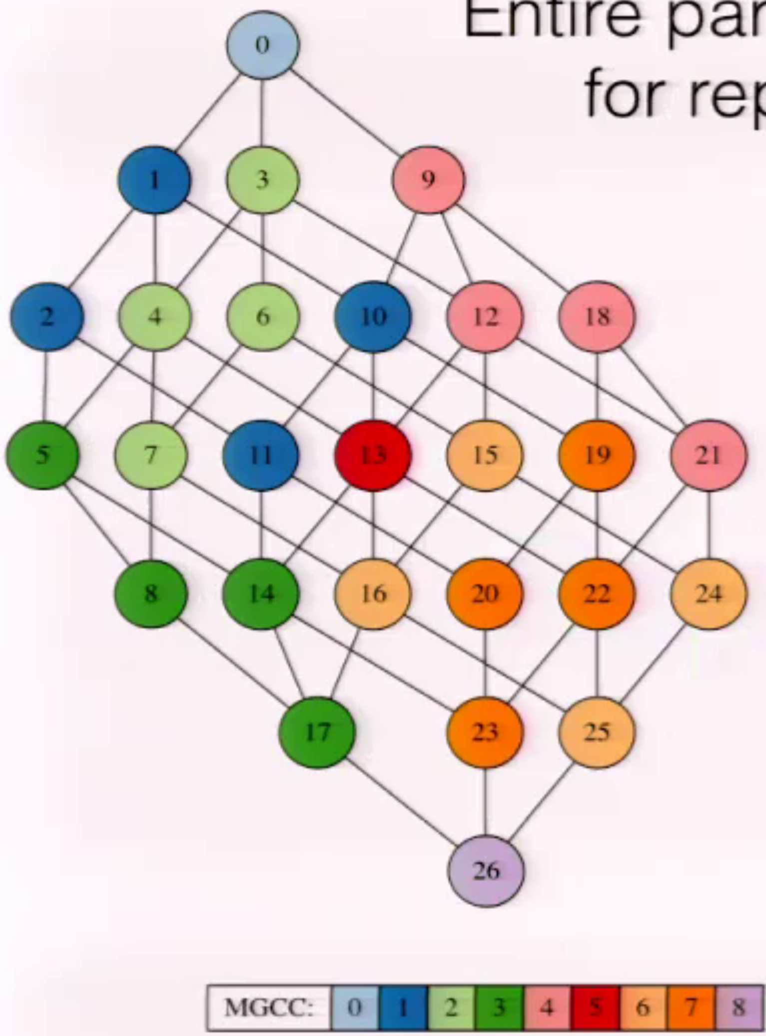
Example

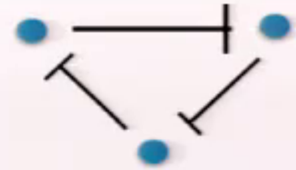
Final description of multi parameter dynamical system



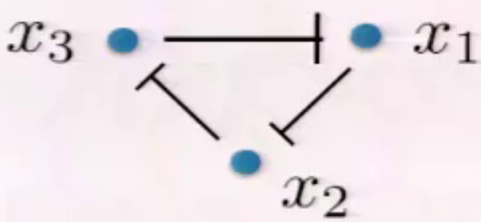
We can first construct the parameter graph, then compute Conley Morse graph at each vertex of parameter graph, and only later determine parameters that each vertex represents!

Entire parameter graph for repressilator



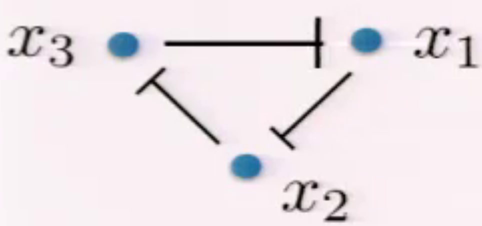


13



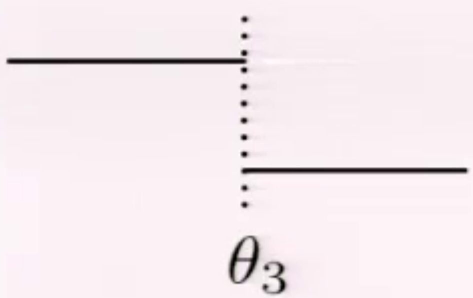
$$
\begin{aligned}
\dot{x}_1 &= -\gamma_1 x_1 + \sigma_3(x_3) \\
\dot{x}_2 &= -\gamma_2 x_2 + \sigma_1(x_1) \\
\dot{x}_3 &= -\gamma_3 x_3 + \sigma_2(x_2)
\end{aligned}
$$

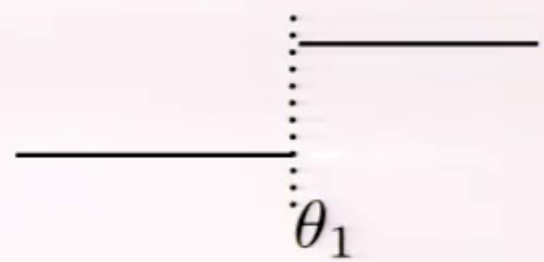
13



$$\begin{aligned}
\dot{x}_1 &= -\gamma_1 x_1 + \sigma_3(x_3) \\
\dot{x}_2 &= -\gamma_2 x_2 + \sigma_1(x_1) \\
\dot{x}_3 &= -\gamma_3 x_3 + \sigma_2(x_2)
\end{aligned}$$

$$\sigma_3(x_3) := \begin{cases} u_3 & \text{if } x_3 < \theta_3; \\ l_3 & \text{if } x_3 > \theta_3, \end{cases} \qquad \sigma_1(x_1) := \begin{cases} l_1 & \text{if } x_1 < \theta_1; \\ u_1 & \text{if } x_1 > \theta_1, \end{cases}$$

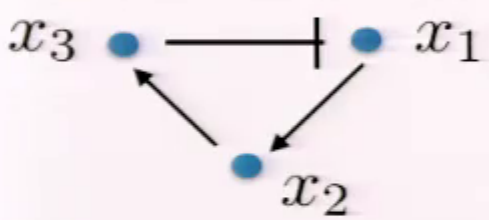




$$13 = \begin{aligned} l_3 < \theta_1 < u_3 \\ l_1 < \theta_2 < u_1 \\ l_2 < \theta_3 < u_2. \end{aligned}$$

Parameter node 13 is a condition on parameters producing periodic orbit

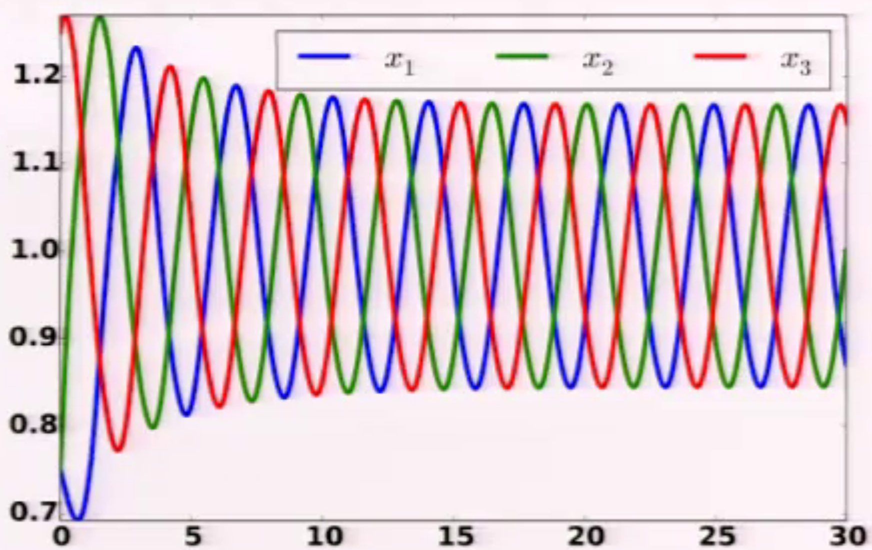
13



$$\begin{aligned}\dot{x}_1 &= -\gamma_1 x_1 + \sigma_3(x_3)\\ \dot{x}_2 &= -\gamma_2 x_2 + \sigma_1(x_1)\\ \dot{x}_3 &= -\gamma_3 x_3 + \sigma_2(x_2)\end{aligned}$$

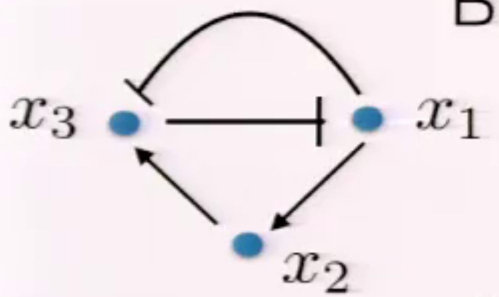
Pick smooth functions  that satisfy

$$l_3 < \theta_1 < u_3$$
$$l_1 < \theta_2 < u_1$$
$$l_2 < \theta_3 < u_2.$$

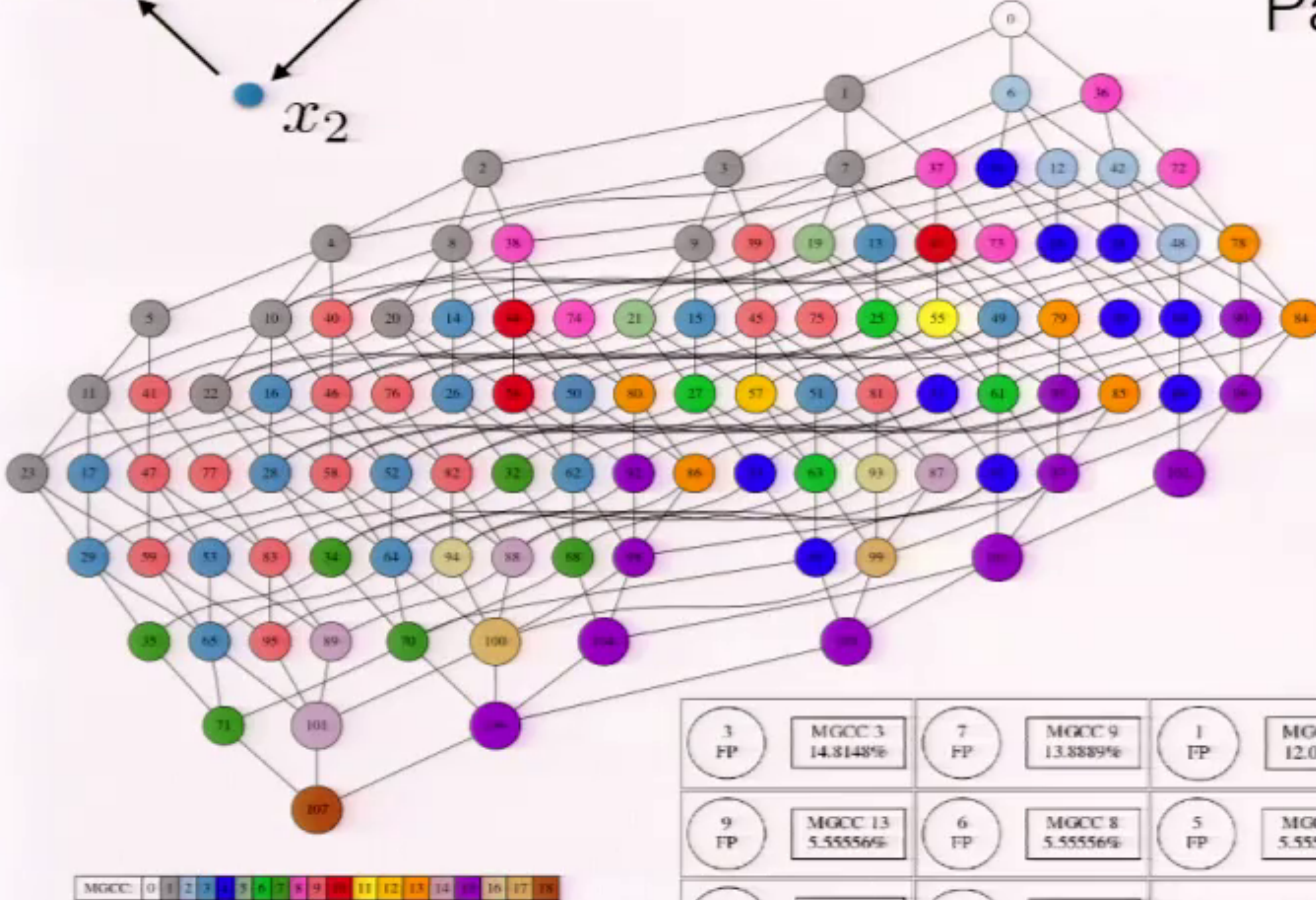


Bistable Repressilator

Bistable repressilator



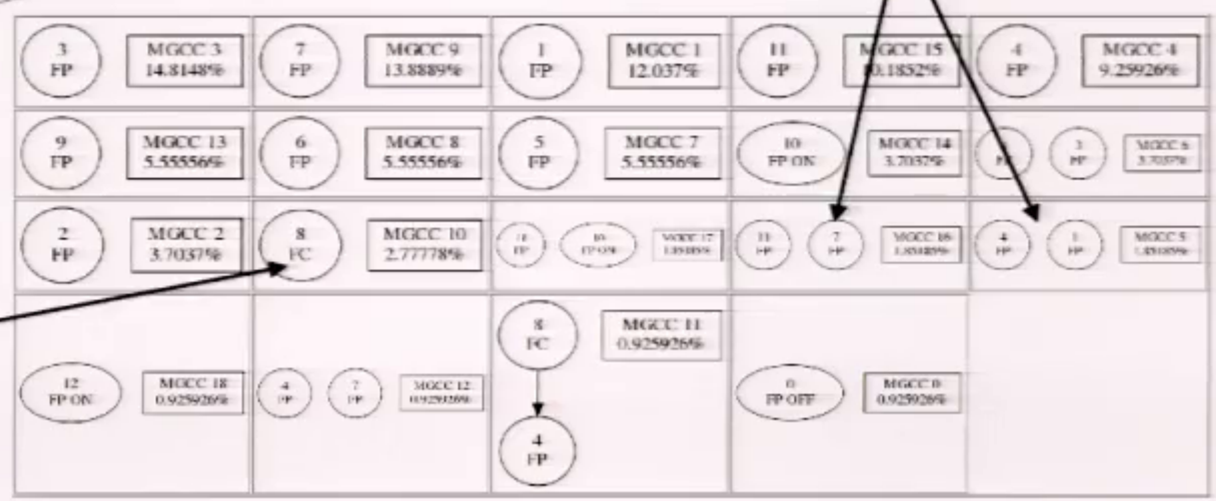
Parameter graph

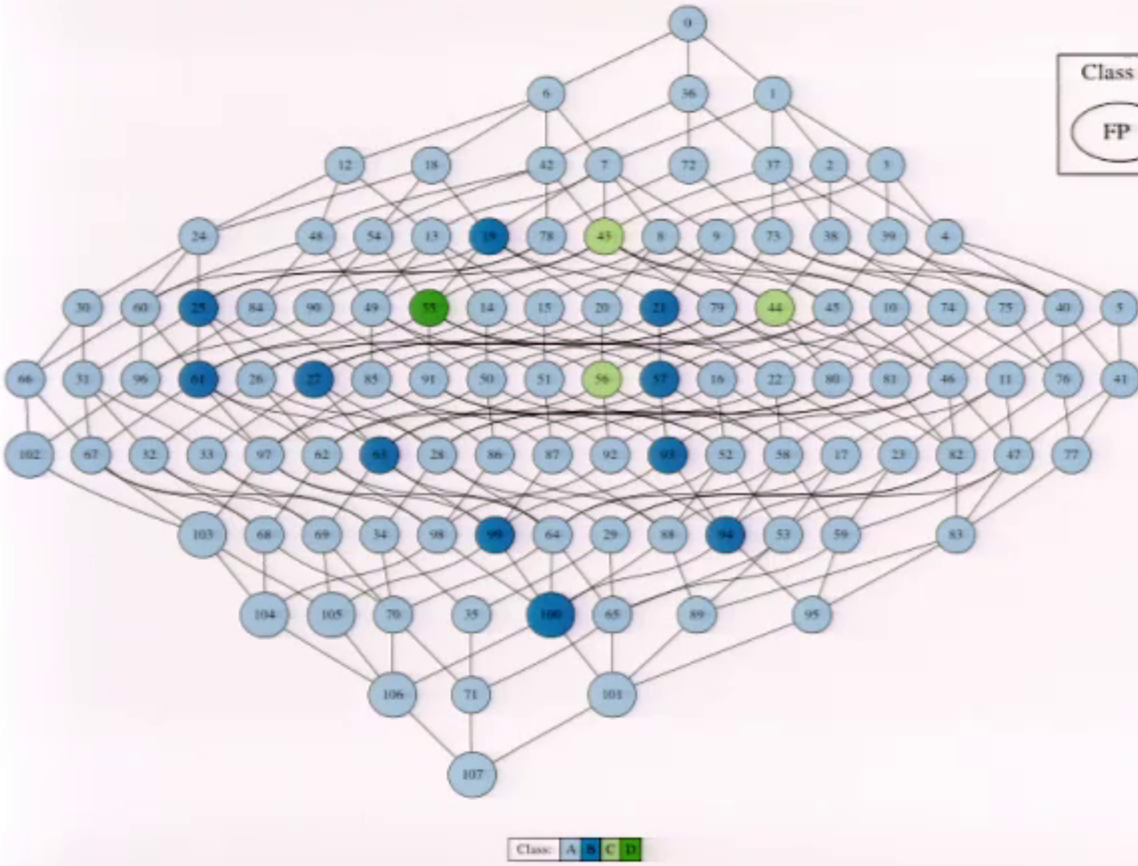


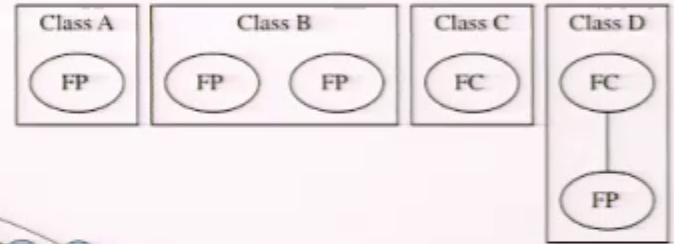
FP=fixed point
FC=periodic orbit

Bistability

Periodic orbit

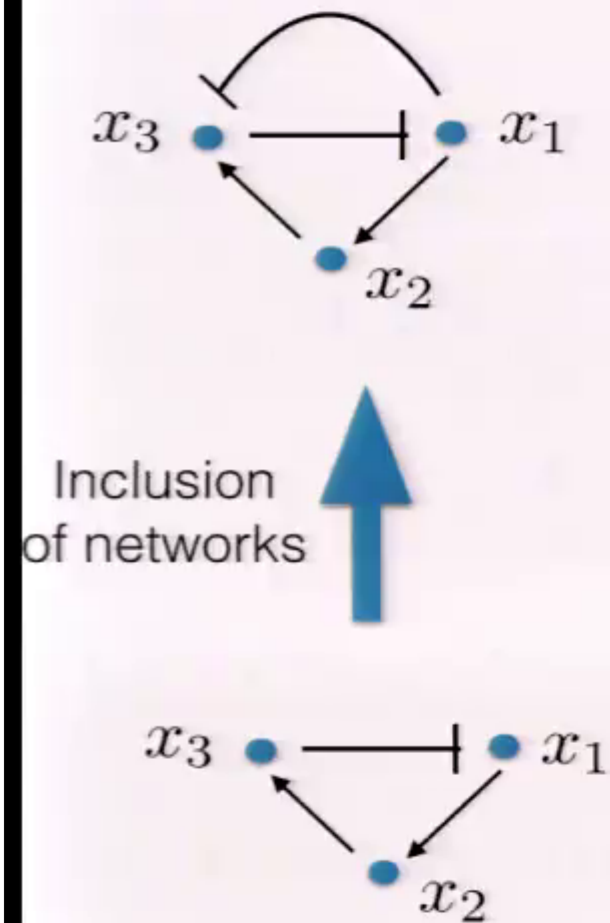




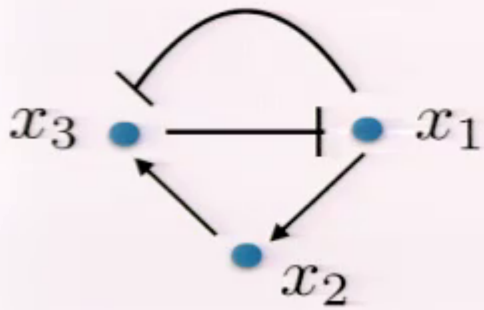


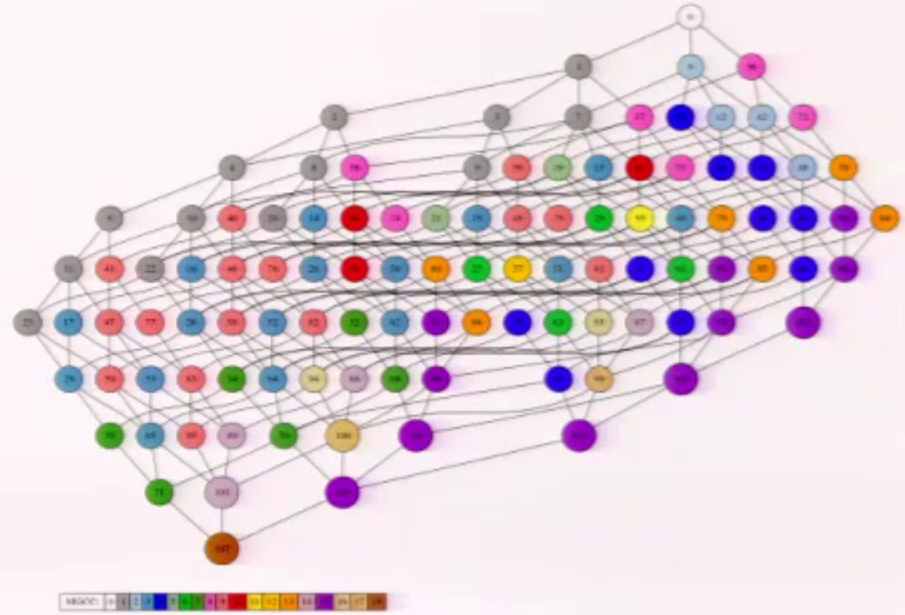
A: monostability
B: bistability
C: periodic orbit
D: cycle

Comparison of Databases



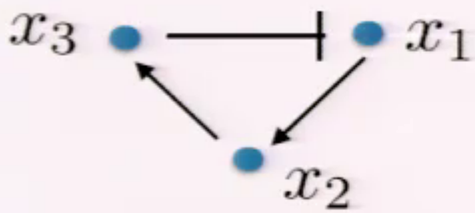
Comparison of Databases





Inclusion of networks

Inclusion of databases



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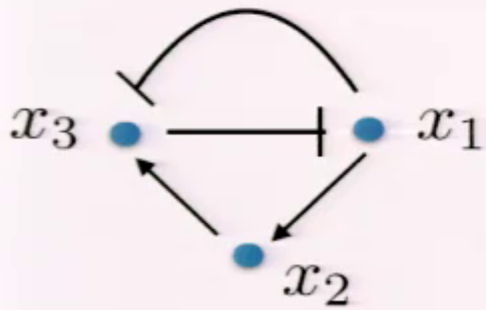
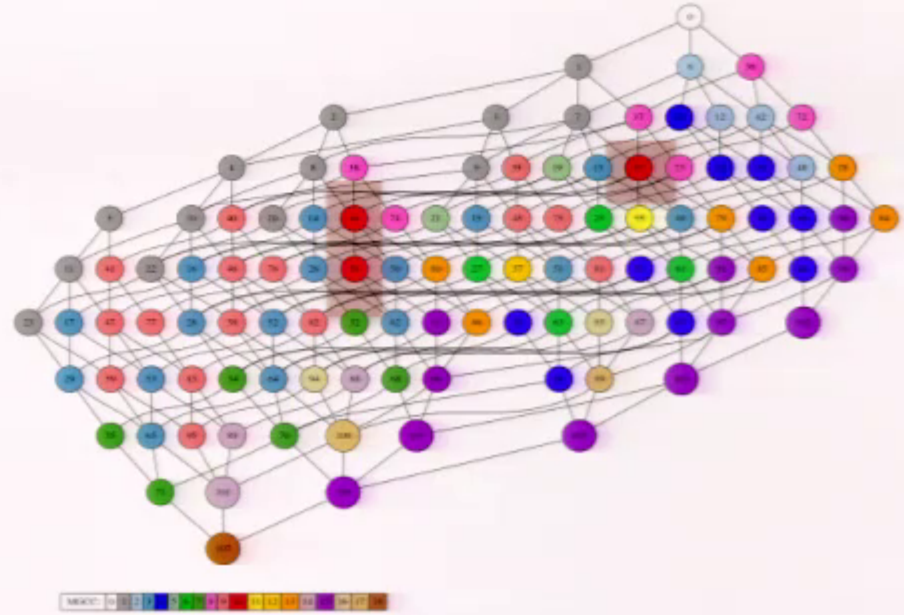
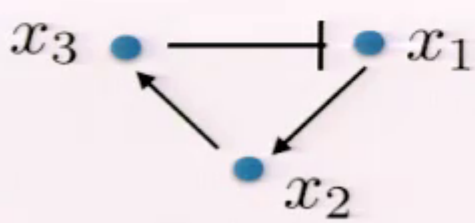




Inclusion of networks

Inclusion of databases



Database for switching networks

Provides combinatorization of dynamics over parameter spaces