Computing dynamics of (gene) regulatory networks

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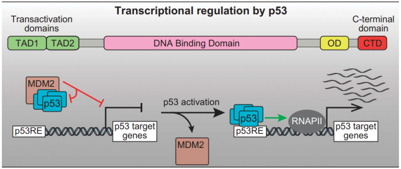
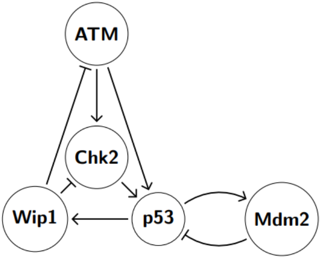
Outline

Gene regulation



Graphical Abstract

(a) p53

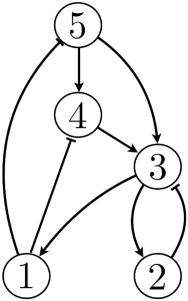


(b) Subnetwork of key species of the p53 signaling network

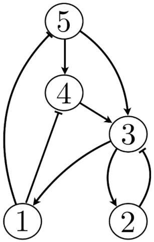
(Gene) Regulatory Networks

Definition

A regulatory network is a directed graph $G = (V, E, W)$ with a set of vertices V, edges E and a sign function $W : E \to \{+1, -1\}$.

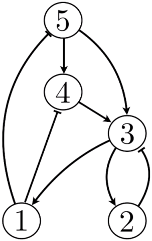


Goal



$$\dot{x} = f(x, \lambda)$$

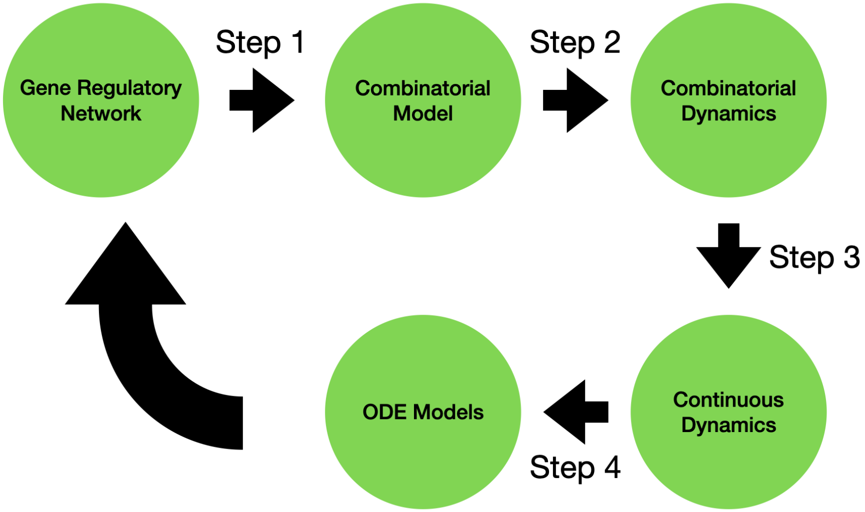
Goal



$\longleftrightarrow$ DSGRN $\longleftrightarrow$ $\dot{x} = f(x, \lambda)$

Dynamic Signatures Generated by Regulatory Networks (DSGRN)

Main steps


Gene Regulatory Network
Step 1
Combinatorial Model
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Step 3
Continuous Dynamics
Step 4
ODE Models

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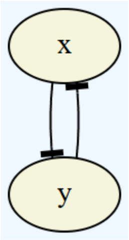
Cubical Cell Complex



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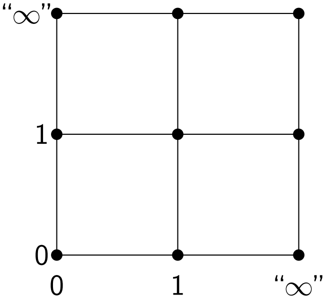

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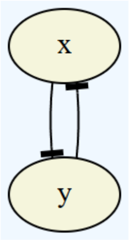

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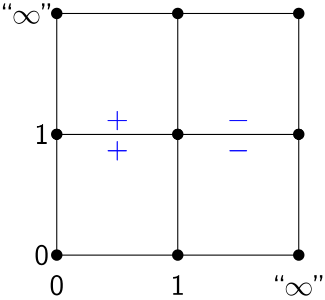

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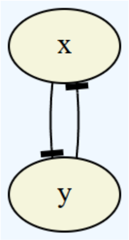

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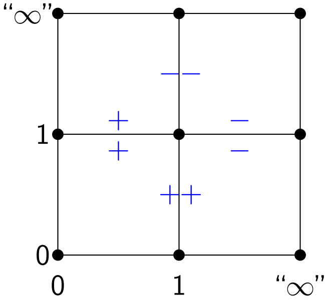
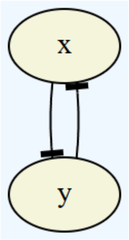


Cubical Cell Complex



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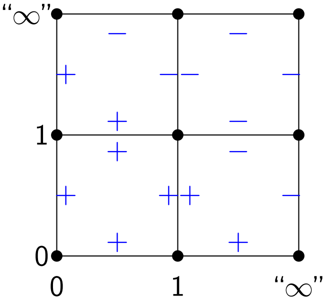
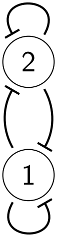
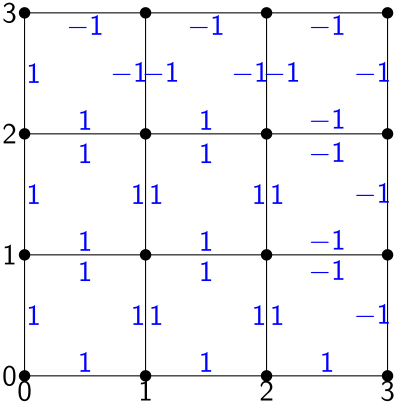


Definition

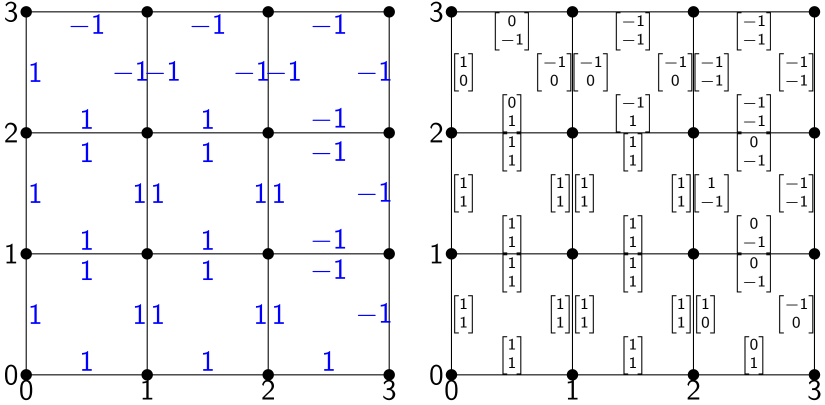
A *wall labeling* on a N-dimensional cubical complex $\mathcal{X}$ consists of

- a function $\omega\colon \mathrm{TP}(\mathcal{X}) \to \{-1, +1\}$
- for each vertex $\xi \in \mathcal{X}^{(0)}$, a map $o_\xi : \{1, \ldots, N\} \to \{1, \ldots, N\}$ that tracks changes of ω about vertices ξ.

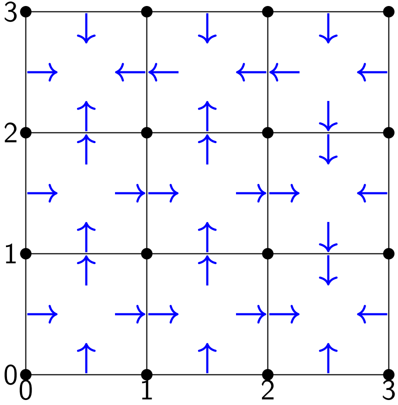


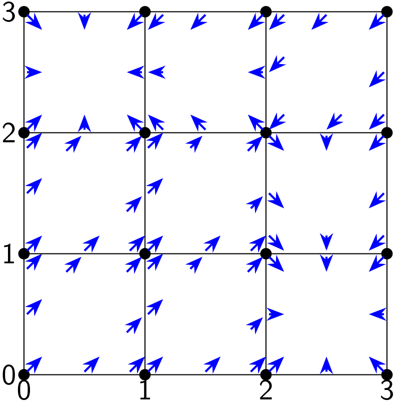


Wall labeling vs Rook Field

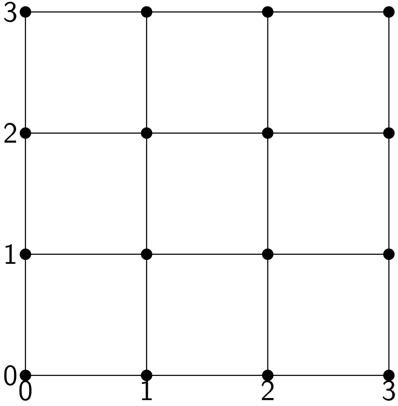


Wall labeling vs Rook Field: vector representation

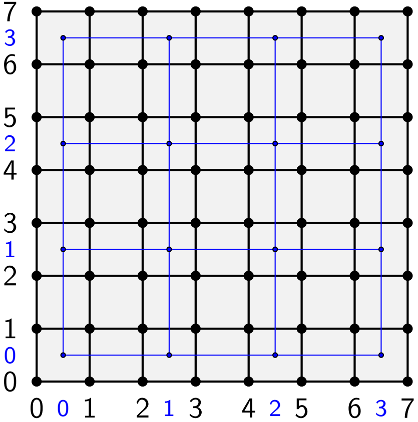




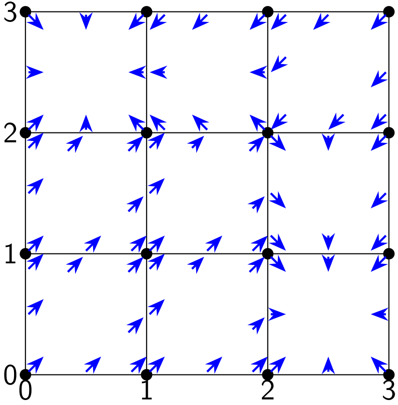
Visualizing $\mathcal{F} : \mathcal{X} \rightrightarrows \mathcal{X}$ on the blow-up complex $\mathcal{X}_b$



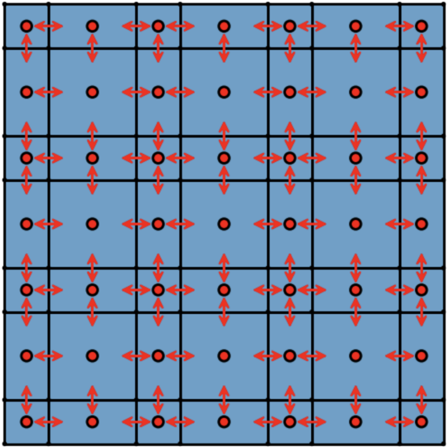
Cubical complex $\mathcal{X}$



$\mathcal{X}$ in blue, $\mathcal{X}_b$ in black.

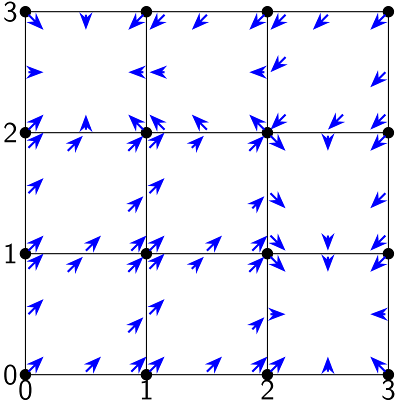


Rook Field

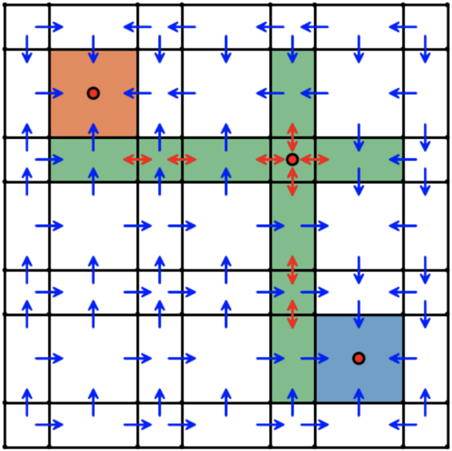


$\mathcal{F}_0 : \mathcal{X} \rightrightarrows \mathcal{X}$

$\mathcal{F}_1 : \mathcal{X} \rightrightarrows \mathcal{X}$



Rook Field

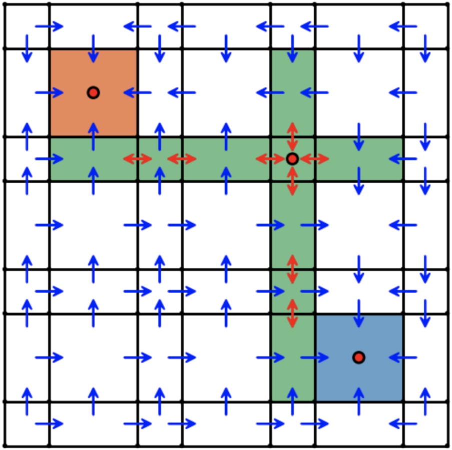


$\mathcal{F}_1 : \mathcal{X} \rightrightarrows \mathcal{X}$

Possible refinements of $\mathcal{F}_1$

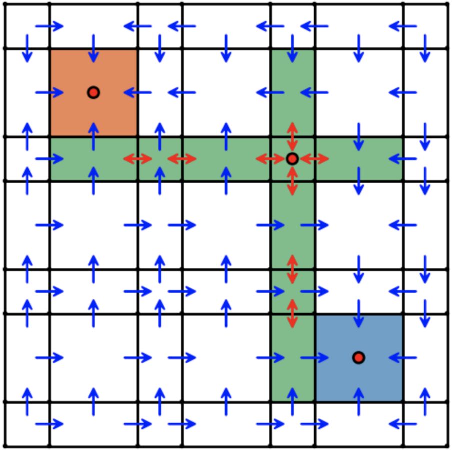
There are two types of "double-arrows" in $\mathcal{F}_1$:

- non-cyclic interactions
- cyclic interactions



$\mathcal{F}_1 : \mathcal{X} \rightrightarrows \mathcal{X}$

$\mathcal{F}_1$ vs $\mathcal{F}_2$



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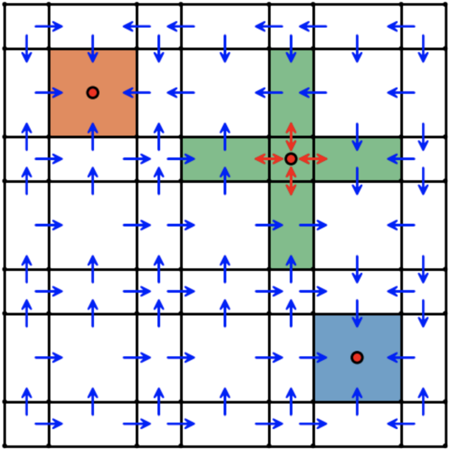

$\mathcal{F}_2 : \mathcal{X} \rightrightarrows \mathcal{X}$

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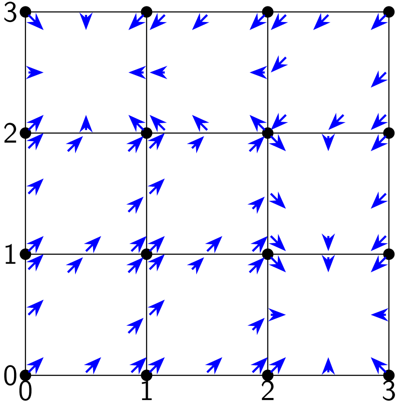
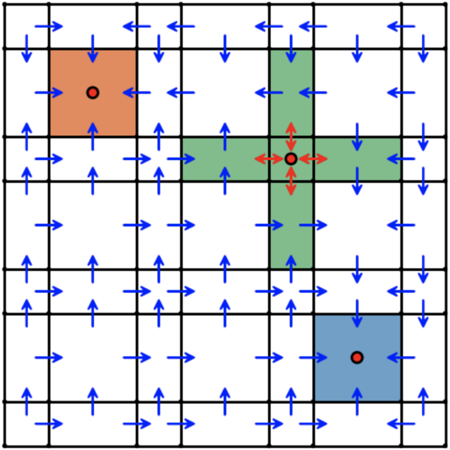
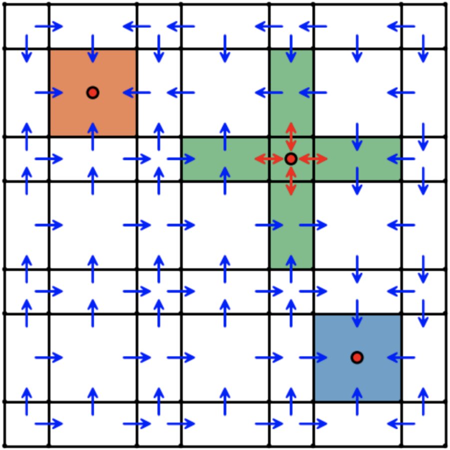


Rook Field



$\mathcal{F}_2 : \mathcal{X} \rightrightarrows \mathcal{X}$



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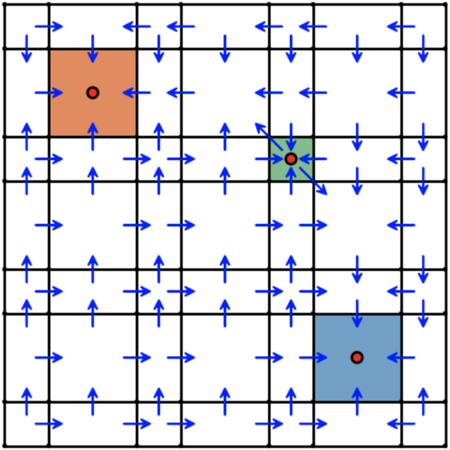
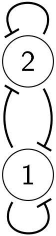
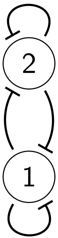


$\mathcal{F}_3 : \mathcal{X} \rightrightarrows \mathcal{X}$

Summary of Step 1



Regulatory Network



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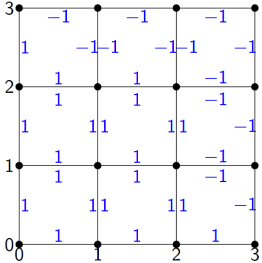
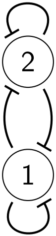
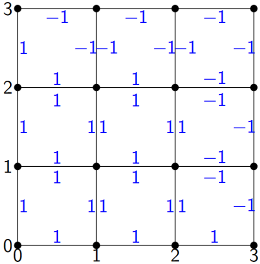


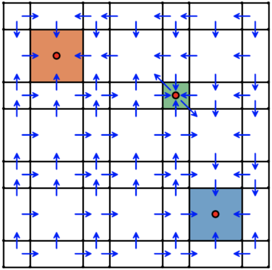
Wall labeling



Regulatory Network



Wall labeling



$\mathcal{F}_3 : \mathcal{X} \rightrightarrows \mathcal{X}$

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Forward invariant sets

Definition

Let $\mathcal{F}\colon \mathcal{X} \rightrightarrows \mathcal{X}$ be a multivalued map. A set $\mathcal{N} \subseteq \mathcal{X}$ is *forward invariant* under $\mathcal{F}$ if $\mathcal{F}(\mathcal{N}) \subseteq \mathcal{N}$.

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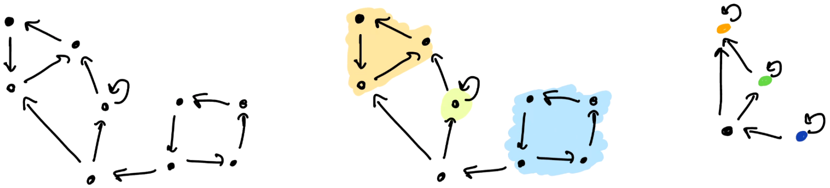
Theorem

The collection of forward invariant sets $\operatorname{Invset}^+(\mathcal{F})$ *is a distributive lattice under the operations of intersection* $\cap$ *and union* $\cup$.

Weak condensation graph



Definition

If P is a poset, the downsets of $p \in \mathrm{P}$ is given by $\mathrm{O}(p) = \{q \in \mathrm{P} \mid q \leq p\}$.

Proposition

$\mathrm{O}(\mathrm{SCC}(\mathcal{F}), \leq_{\bar{\mathcal{F}}}) \cong \mathrm{Invset}^{+}(\mathcal{F})$

Retrieving P

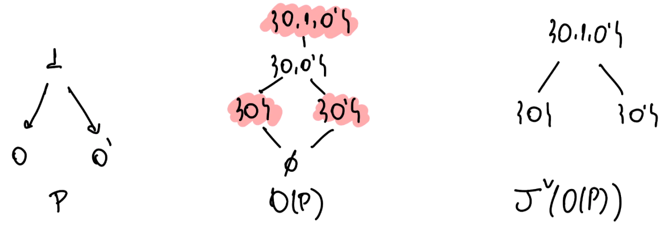
Definition (join-irreducible)

Let L be a finite distributive lattice. An element $a \in L$ is *join-irreducible* if it has an unique predecessor. The set of all join-irreducible is $\mathrm{J}^{\vee}(\mathrm{L})$.

Theorem (Birkhoff's representation theorem)

$\mathrm{L} \cong \mathrm{O}(\mathrm{J}^{\vee}(\mathrm{L}))$ *as lattices and* $\mathrm{P} \cong \mathrm{J}^{\vee}(\mathrm{O}(\mathrm{P}))$ *as posets.*

We refer to the isomorphism as λ.



Conley Complex: combinatorial setting

Given a P-grading, that is, $\pi : \mathcal{X}_b^{(N)} \to \mathsf{P}$, on the cubical complex $\mathcal{X}_b$, we can compute a P-graded chain complex on

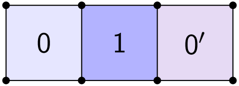
$$CH_*(p) \cong H_*(\lambda^{-1}(\mathsf{O}(p)), \lambda^{-1}(\mathsf{O}(p)^<); \mathbb{F}),$$

with boundary operator, called *connection matrix*,

$$\Delta\colon CH_*(p) \to \bigoplus_{q \prec p} CH_{*-1}(p).$$

Summary of Step 2

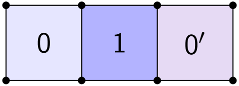
Example:



$$\begin{tikzcd} 1 \arrow[d] \arrow[dr] & \\ 0 & 0' \end{tikzcd}$$

Summary of Step 2

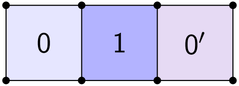
Example:



$$
\begin{tikzcd}
1 \arrow[d] \arrow[dr] & \\
0 & 0'
\end{tikzcd}
$$

$$CH_k(0;\mathbb{F}) \cong CH_k(0';\mathbb{F}) \cong \begin{cases} \mathbb{F} & \text{if } k = 0, \\ 0 & \text{otherwise.} \end{cases}$$

Example:



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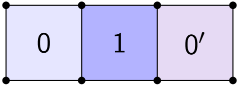
$$CH_k(1;\mathbb{F}) \cong H_k(\mathcal{X}_b, \lambda^{-1}(0) \cup \lambda^{-1}(0');\mathbb{F}) \cong \begin{cases} \mathbb{F} & \text{if } k = 1, \\ 0 & \text{otherwise.} \end{cases}$$

Summary of Step 2

Example:



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$$\Delta_1 \colon CH_1(1;\mathbb{F}) \to CH_0(0;\mathbb{F}) \oplus CH_0(0';\mathbb{F}),$$

takes the form $\left[\begin{smallmatrix} 1 \\ 1 \end{smallmatrix}\right]$

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Continuous dynamics

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A set $A \subset X$ is an *attractor* if there exists a compact set $K \subset X$ such that

$$A = \omega(K, \varphi) := \bigcap_{t \geq 0} \operatorname{cl}(\varphi((t, \infty), K)) \subset \operatorname{int}(K).$$

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Theorem (Kalies, Mischaikow, Vandervorst)

The set of all attractors of φ, $\mathsf{Att}(\varphi)$, *and the set of attracting blocks,* $\mathsf{ABlock}(\varphi)$ *are bounded distributive lattices, and*

$$\begin{aligned} \omega\colon \mathsf{ABlock}(\varphi) &\to \mathsf{Att}(\varphi) \\ K &\mapsto \omega(K) \end{aligned}$$

is a bounded lattice epimorphism.

When L is a sublattice of ABlock that contains $\emptyset$ and X, $\mathsf{J}^{\vee}(\mathsf{L})$ is a Morse decomposition for φ.

Conley Complex: continuous setting

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Let $K_0, K_1 \in \mathrm{ABlock}(\varphi)$ and assume that $K_0 \subset K_1$.

Conley Complex: continuous setting

When L is a sublattice of ABlock that contains $\emptyset$ and X, $\mathsf{J}^{\vee}(\mathsf{L})$ is a Morse decomposition for φ.
Let $K_0, K_1 \in \mathrm{ABlock}(\varphi)$ and assume that $K_0 \subset K_1$.
The *(homological) Conley index* of $S = \mathrm{Inv}(K_1 \setminus K_0, \varphi)$ is

$$CH_*(S) := H_*(K_1, K_0; \mathbb{F}).$$

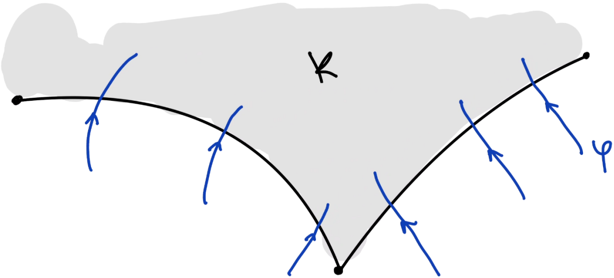
Theorem (Conley)

Let S be an isolated invariant set. If $CH_*(S) \neq 0$, then $S \neq \emptyset$.

From combinatorial dynamics to continuous dynamics

Theorem

If a geometric realization $|\cdot| : \mathcal{X}_b \to \mathbb{R}^N$ *satisfies certain transversality conditions with respect to the flow, then* $K = |\lambda^{-1}(p)|$ *is an attracting block for each* $p \in \mathrm{P}$ *and the Conley complex computed in Step 2 is the Conley complex of Step 3.*



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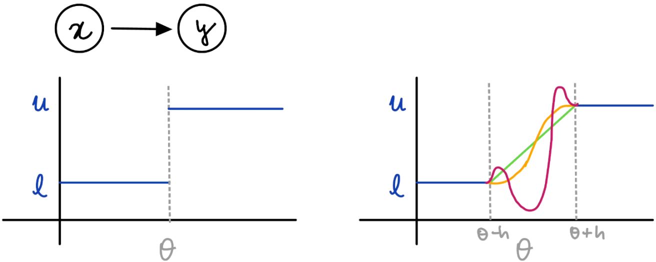
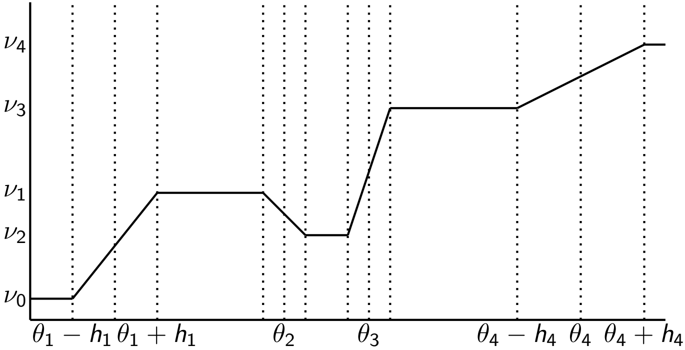


$$\dot{x}_n = -\gamma_n x_n + \dots$$

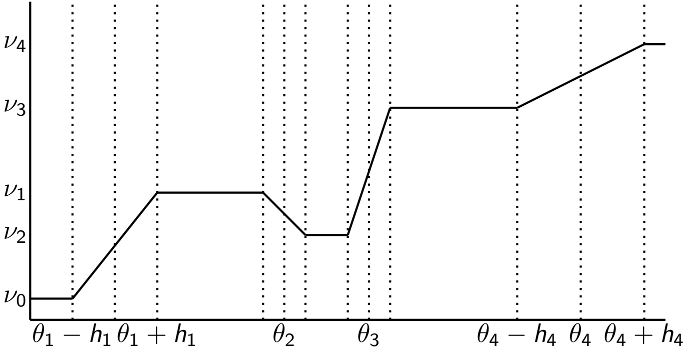
Ramp Systems

Let $\dot{x} = -\Gamma x + E(x; \nu, \theta, h)$ be a ramp system with fixed parameters.



Ramp Systems

Let $\dot{x} = -\Gamma x + E(x; \nu, \theta, h)$ be a ramp system with fixed parameters.



Remark: To go from Ramp Systems to Wall Labelings, it is enough to evaluate the vector field at $\theta \pm h$.

Validating $\mathcal{F}_1$

If h satisfies

$$\theta_{m_k,n,j_k} + h_{m_k,n,j_k} < \theta_{m_{k+1},n,j_{k+1}} - h_{m_{k+1},n,j_{k+1}}, \tag{1}$$

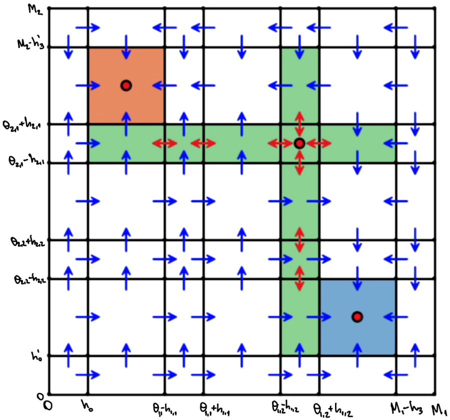
$$\frac{E_n(D_{\mathbf{v}})}{\gamma_n} \notin \left[\theta_{m_{k_n},n,j_{k_n}}, \theta_{m_{k_n},n,j_{k_n}} + h_{m_{k_n},n,j_{k_n}}\right), \tag{2}$$

and

$$\frac{E_n(D_{\mathbf{v}})}{\gamma_n} \notin \left(\theta_{m_{k_n+1},n,j_{k_n+1}} - h_{m_{k_n+1},n,j_{k_n+1}}, \theta_{m_{k_n+1},n,j_{k_n+1}}\right], \tag{3}$$

then there is a geometrization where the flow is transverse.

Geometric realization for $\mathcal{F}_1$



Validating $\mathcal{F}_2$: sneak peek

It involves the construction of a perturbed surface and the following type of analytical bounds

(i) Outer transversality:

$$2h_{n_o,n_g,j_{k_{n_g}}} < \frac{L_{n_g}}{U_{n_o}} \frac{\mathrm{length}(\xi')}{2}. \tag{4}$$

(ii) Inner transversality:

$$2h_{n_o,n_g,j_{k_{n_g}}} < \frac{L_{n_g}}{U_{n_o}} 2h_{o_\xi(n_o),n_o,j_{k_{n_o}}}. \tag{5}$$

where L_n, U_n are lower/upper values that depend on the parameters.

Validating $\mathcal{F}_3$

Theorem

If $\dot{x} = -\Gamma x + E(x; \nu, \theta, h)$, *then, in some rectangular region,*

- $\dot{x}_n = -\gamma_n x_n + f_n(x_{\sigma^{-1}(n)})$ *is a monotone cyclic feedback system.*
- *There is an unique equilibrium whose eigenvalues of the linearization satisfy*

$$\chi(\lambda) = \prod(-\gamma_n - \lambda) - \frac{(-1)^k \delta C(\nu)}{\prod h_{\sigma(n),n}}$$

Validating $\mathcal{F}_3$

Theorem

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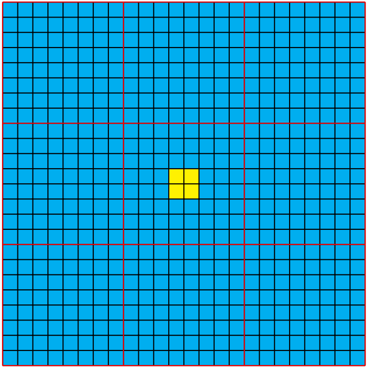
$$\chi(\lambda) = \prod(-\gamma_n - \lambda) - \frac{(-1)^k \delta C(\nu)}{\prod h_{\sigma(n),n}}$$

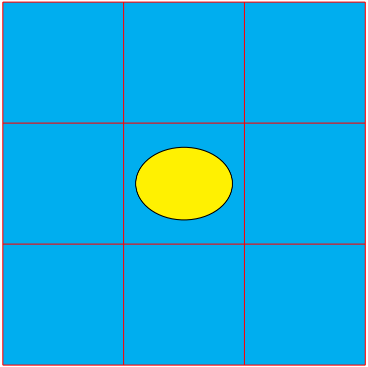
Tranversality is obtained in two flavors, either by

1. level-sets of Lyapunov functions,
2. or similar arguments to $\mathcal{F}_2$ (outer/inner transversality).

Geometric realization for $N = 2$

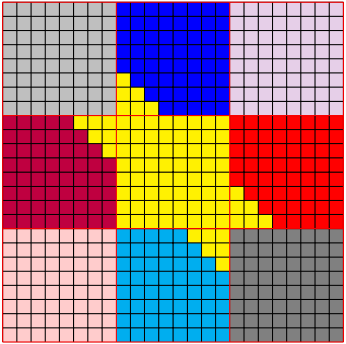


(a) $\mathcal{X}_{\mathrm{J}}$ with π_3-grading for $\delta_{o_\xi} = -1$.

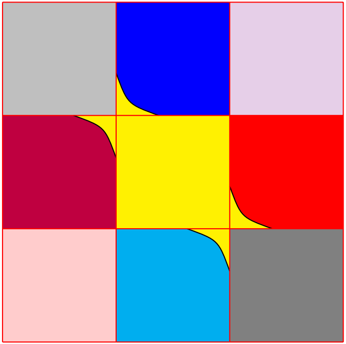


(b) Geometrization of $\mathcal{X}_{\mathrm{J}}$ for $\delta_{o_\xi} = -1$.

Geometric realization for $N = 2$



(a) $\mathcal{X}_{\mathrm{J}}$ with π_3-grading for $\delta_{o_\xi} = 1$.



(b) Geometrization of $\mathcal{X}_{\mathrm{J}}$ for $\delta_{o_\xi} = 1$.

DSGRN

The software Dynamic Signature of Gene Regulatory Networks provides **all** possible wall-labelings associated to a GRN.[1]

[1] up to a certain number of in and out edges.

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DSGRN

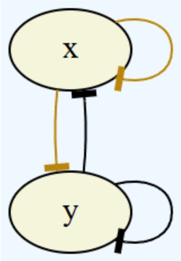
The software Dynamic Signature of Gene Regulatory Networks provides **all** possible wall-labelings associated to a GRN.[1]

This is possible by discretizing the whole parameter space into a finite collection of semi-algebraic sets.

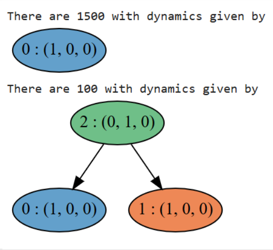
Given any region, our computation provides a complete description of its dynamics in terms of Conley Index Theory for sufficiently small h.

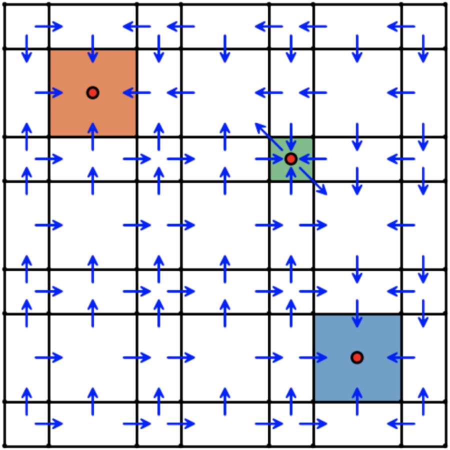
[1] up to a certain number of in and out edges.

2D dimensional example: 1,600 parameter regions



Regulatory Network

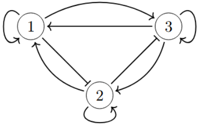




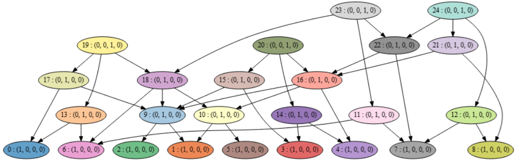
3D dimensional example

$$\dot{x}_1 = -\gamma_1 x_1 + r_{1,1}(x_1) + r_{1,2}(x_2) + r_{1,3}(x_3)$$
$$\dot{x}_2 = -\gamma_2 x_2 + r_{2,1}(x_1)\left(r_{2,2}(x_2) + r_{2,3}(x_3)\right)$$
$$\dot{x}_3 = -\gamma_3 x_3 + r_{3,2}(x_2)\left(r_{3,1}(x_1) + r_{3,3}(x_3)\right),$$

$\nu_{1,1,1} = 1.01$	$\nu_{1,1,2} = 4.0$	$\nu_{1,2,1} = 1.0$	$\nu_{1,2,2} = 4.0$	$\nu_{1,3,1} = 1.0$	$\nu_{1,3,2} = 2.0$
$\nu_{2,1,1} = 0.875$	$\nu_{2,1,2} = 0.797$	$\nu_{2,2,1} = 0.22$	$\nu_{2,2,2} = 0.875$	$\nu_{2,3,1} = 0.44$	$\nu_{2,3,2} = 0.875$
$\nu_{3,1,1} = 0.76$	$\nu_{3,1,2} = 1.0$	$\nu_{3,2,1} = 1.0$	$\nu_{3,2,2} = 0.85$	$\nu_{3,3,1} = 0.5$	$\nu_{3,3,2} = 1.0$
$\theta_{1,1} = 6.5$	$\theta_{1,2} = 1.497$	$\theta_{1,3} = 1.87$	$\theta_{2,1} = 8.0$	$\theta_{2,2} = 1.0$	$\theta_{2,3} = 1.16$
$\theta_{3,1} = 3.5$	$\theta_{3,2} = 1.46$	$\theta_{3,3} = 1.61$	$\gamma_1 = \gamma_2 = 1$	$\gamma_3 = 1.2$	$h_{i,j} = 0.1$



Network



parameter node $52,718,681,992$

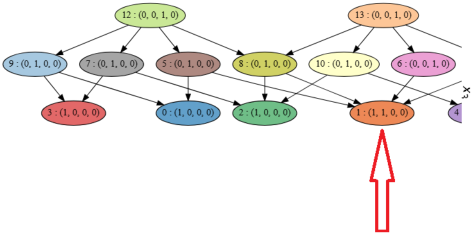
3D dimensional example

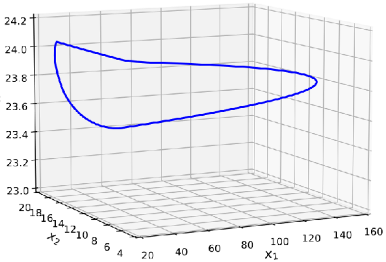
$$\dot{x}_1 = -\gamma_1 x_1 + r_{1,1}(x_1) r_{1,2}(x_2) r_{1,3}(x_3)$$

$$\dot{x}_2 = -\gamma_2 x_2 + r_{2,1}(x_1) r_{2,2}(x_2)$$

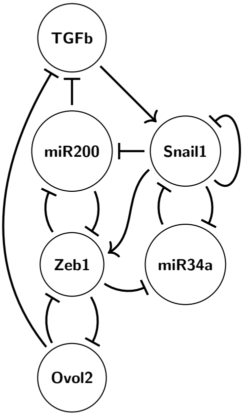
$$\dot{x}_3 = -\gamma_3 x_3 + r_{3,2}(x_2) r_{3,3}(x_3),$$

$\nu_{1,1,1} = 1.80$	$\nu_{1,1,2} = 8.56$	$\nu_{1,2,1} = 13.07$	$\nu_{1,2,2} = 3.25$	$\nu_{1,3,1} = 20.10$	$\nu_{1,3,2} = 1.07$
$\nu_{2,1,1} = 2.44$	$\nu_{2,1,2} = 0.84$	$\nu_{2,2,1} = 0.16$	$\nu_{2,2,2} = 6.10$	$\nu_{3,2,1} = 2.39$	$\nu_{3,2,2} = 1.36$
$\nu_{3,3,1} = 0.05$	$\nu_{3,3,2} = 5.03$	$\theta_{1,1} = 27.17$	$\theta_{1,2} = 2.26$	$\theta_{1,3} = 11.73$	$\theta_{2,1} = 39.10$
$\theta_{2,2} = 1.25$	$\theta_{3,2} = 10.47$	$\theta_{3,3} = 6.70$	$\gamma_1 = 1$	$\gamma_2 = \gamma_3 = 0.5$	$h_{i,j} = 0.5$





6D dimensional example



Regulatory network for reversible epithelial-to-mesenchymal transition as proposed by T. Hong, K. Watanabe, C.H. Ta, A. Villarreal-Ponce, Q. Nie, and X. Dai, An ovol2-zeb1 mutual inhibitory circuit governs epithelial-mesenchymal transitions, PLOS Comput. Biol. 11 (2015)

58 dim parameter space

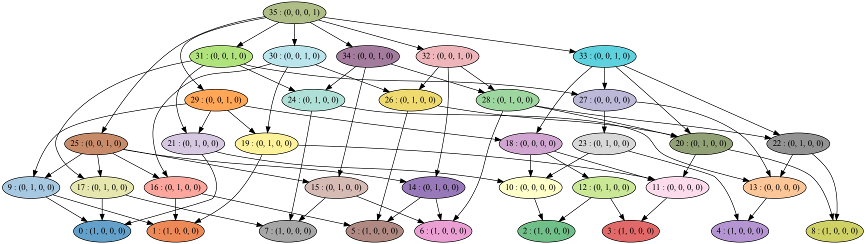


Figure: Morse graph for the map $\mathcal{F}_3$ generated by the parameter node $52,717,613,010$.

58 dim parameter space and 4,429,771,960,320 parameter regions.

Parameter node $1,739,757,491,101$

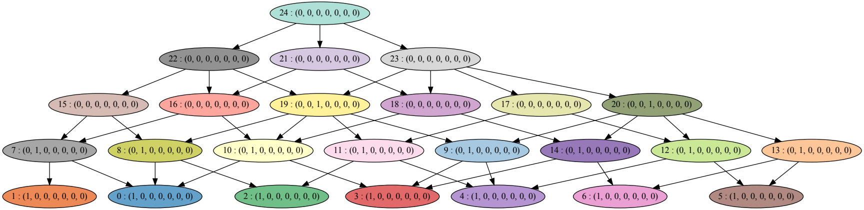


Figure: Morse graph for the map $\mathcal{F}_2$ generated by the parameter node $1,739,757,491,101$ of the parameter graph of the network in Figure 43.

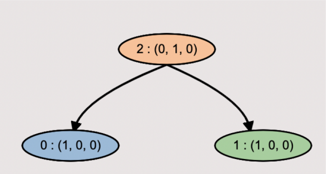
In this example there are 17 equilibria, all identified by the morse sets.

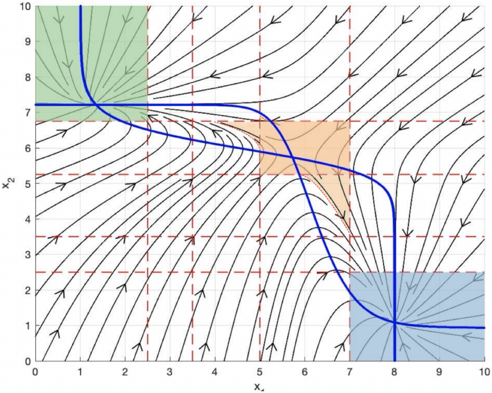
Hill functions

$$\begin{aligned}\dot{x}_1 &= -\gamma_1 x_1 + H^-_{1,1}(x_1)H^-_{1,2}(x_2)\\ \dot{x}_2 &= -\gamma_2 x_2 + H^-_{2,1}(x_1)H^-_{2,2}(x_2),\end{aligned}$$

$$H^-_{i,j}(x) = \nu_{i,j,2} + (\nu_{i,j,1} - \nu_{i,j,2})\frac{\theta_{i,j}^{s_{i,j}}}{x^{s_{i,j}} + \theta_{i,j}^{s_{i,j}}},$$

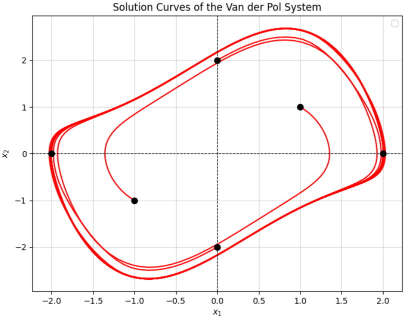
$$\begin{aligned}&\nu_{1,1,1} = 1.8662,\ \nu_{1,1,2} = 1.1061,\ \theta_{1,1} = 0.6927\\ &\nu_{1,2,1} = 1.1705,\ \nu_{1,2,2} = 0.2608,\ \theta_{1,2} = 1.9914\\ &\nu_{2,1,1} = 2.8064,\ \nu_{2,1,2} = 0.1614,\ \theta_{2,1} = 1.1436\\ &\nu_{2,2,1} = 0.7340,\ \nu_{2,2,2} = 0.6581,\ \theta_{2,2} = 0.4310\\ &\gamma_1 = 0.8147,\ \gamma_2 = 0.9058,\ s_{i,j} = 20.\end{aligned}$$

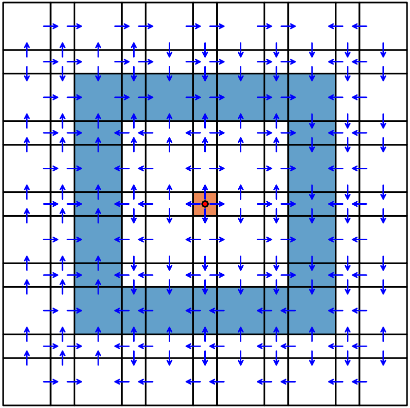




$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = -x_1 + (1 - x_1^2)x_2$$

$$\dot{x}_1 = -\gamma_1 x_1 + r_{1,1}(x_1) + r_{1,2}(x_2)$$
$$\dot{x}_2 = -\gamma_2 x_2 + r_{2,1}(x_1) + r_{2,2}(x_2)$$





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Questions

Thank you for your attention!
Questions?