Structural causes of pattern formation and its breakdown

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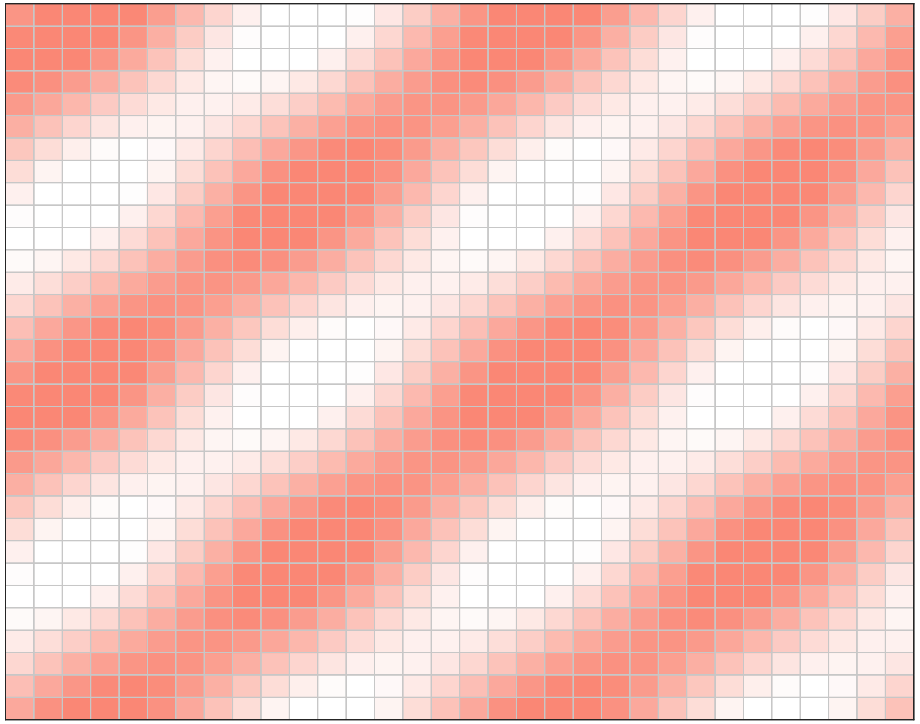
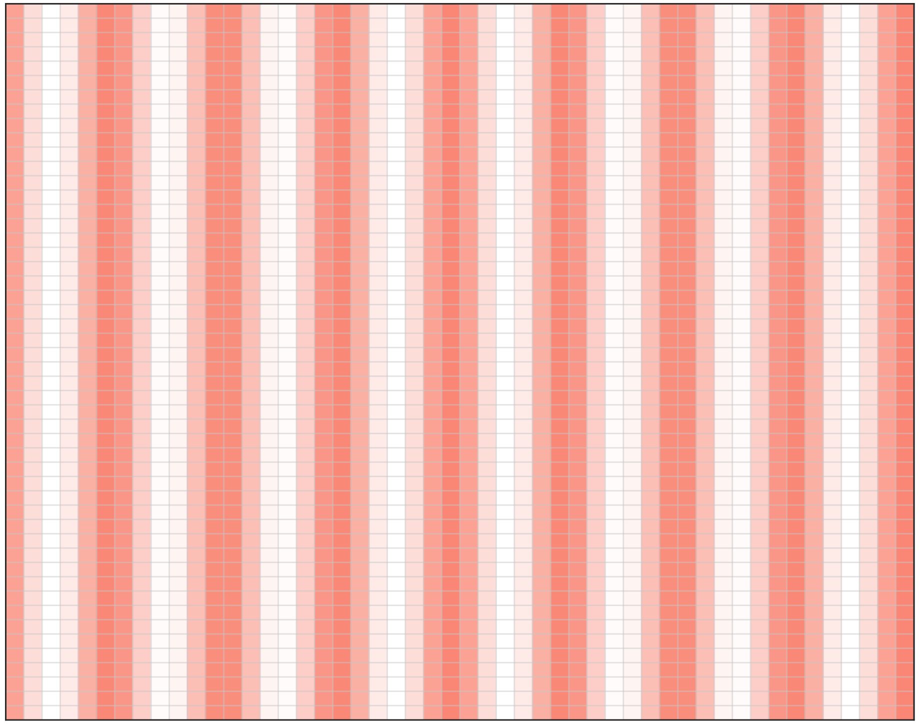
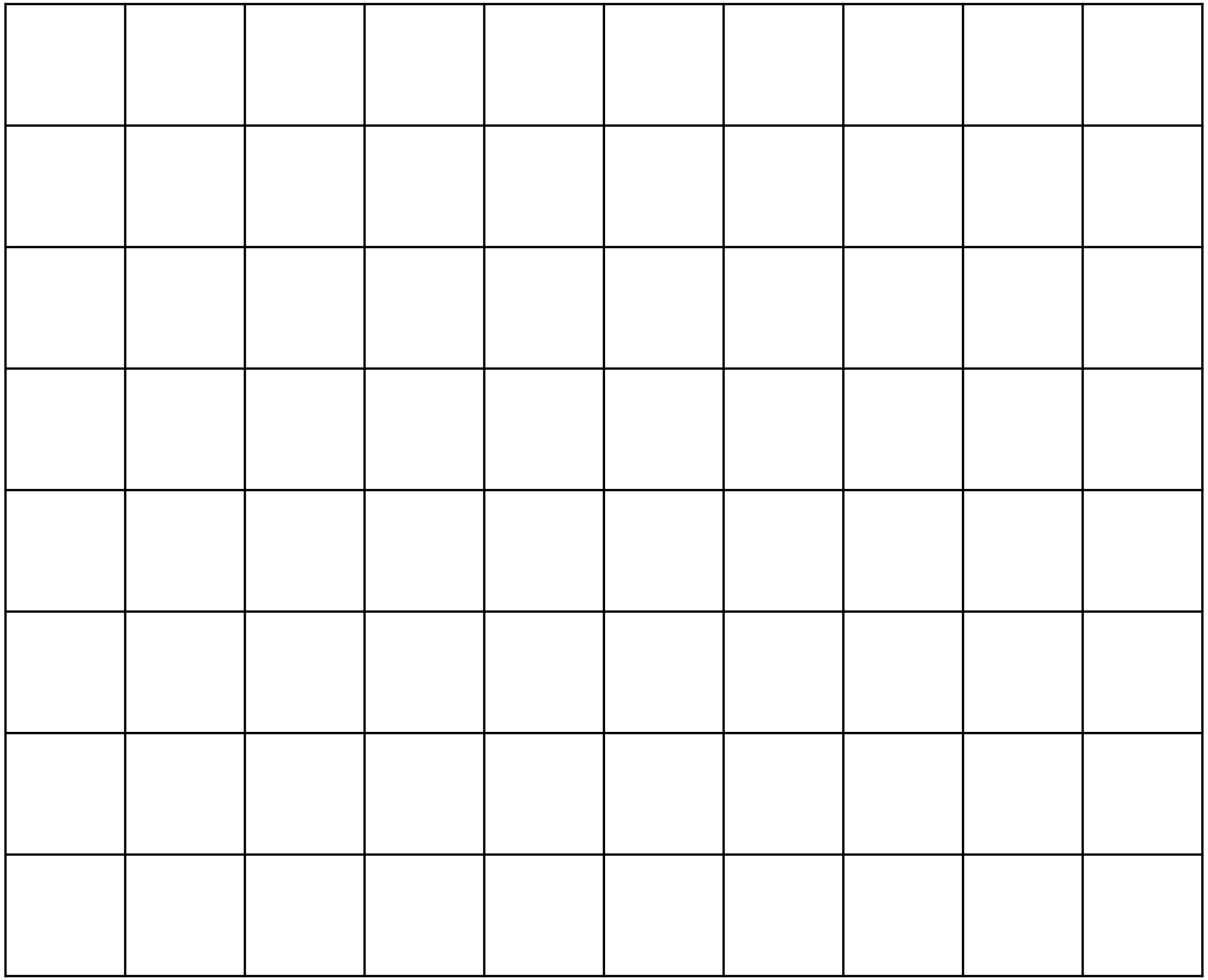




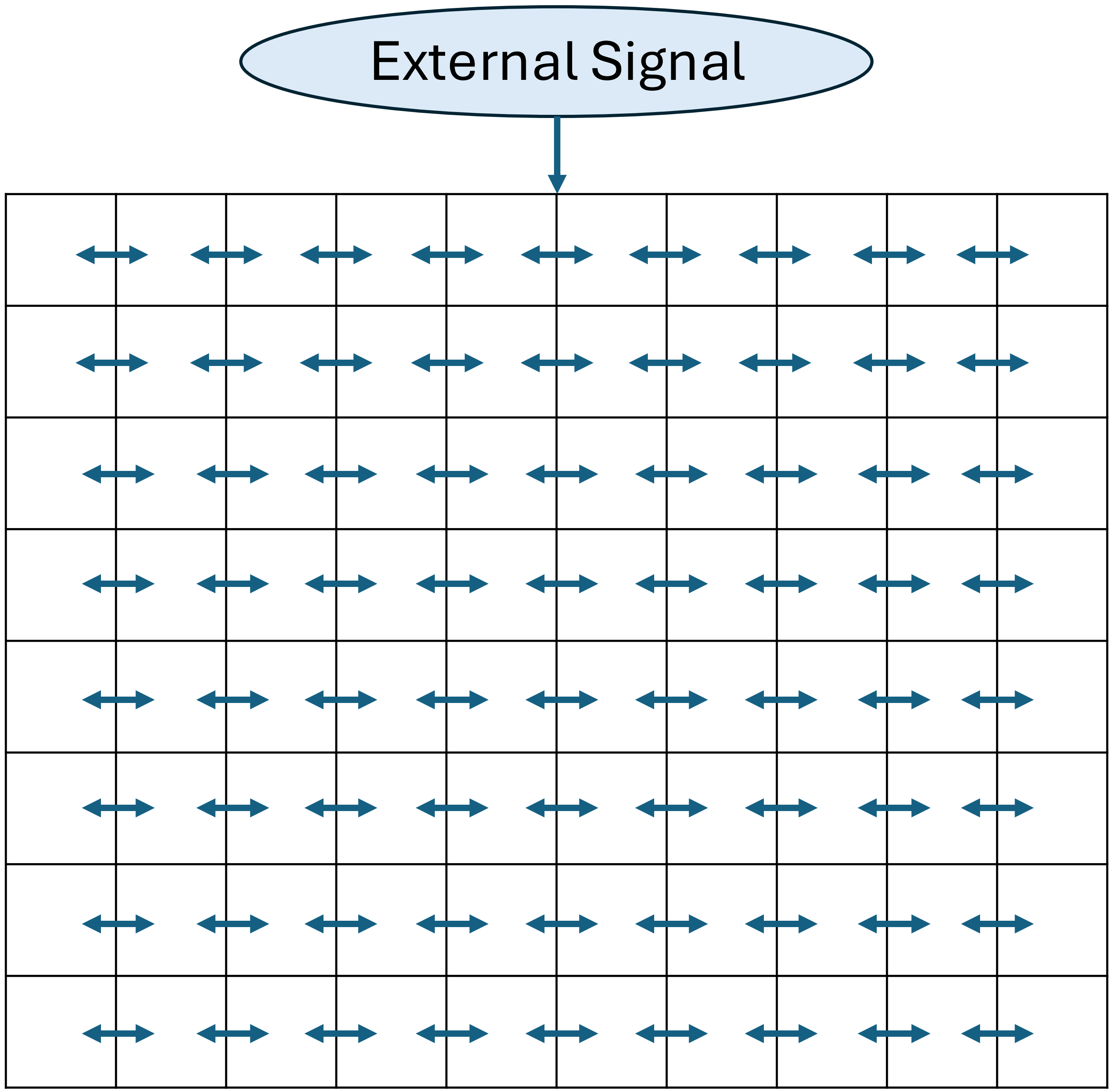
Biological background

1. There is a group of cells with the same developmental potential



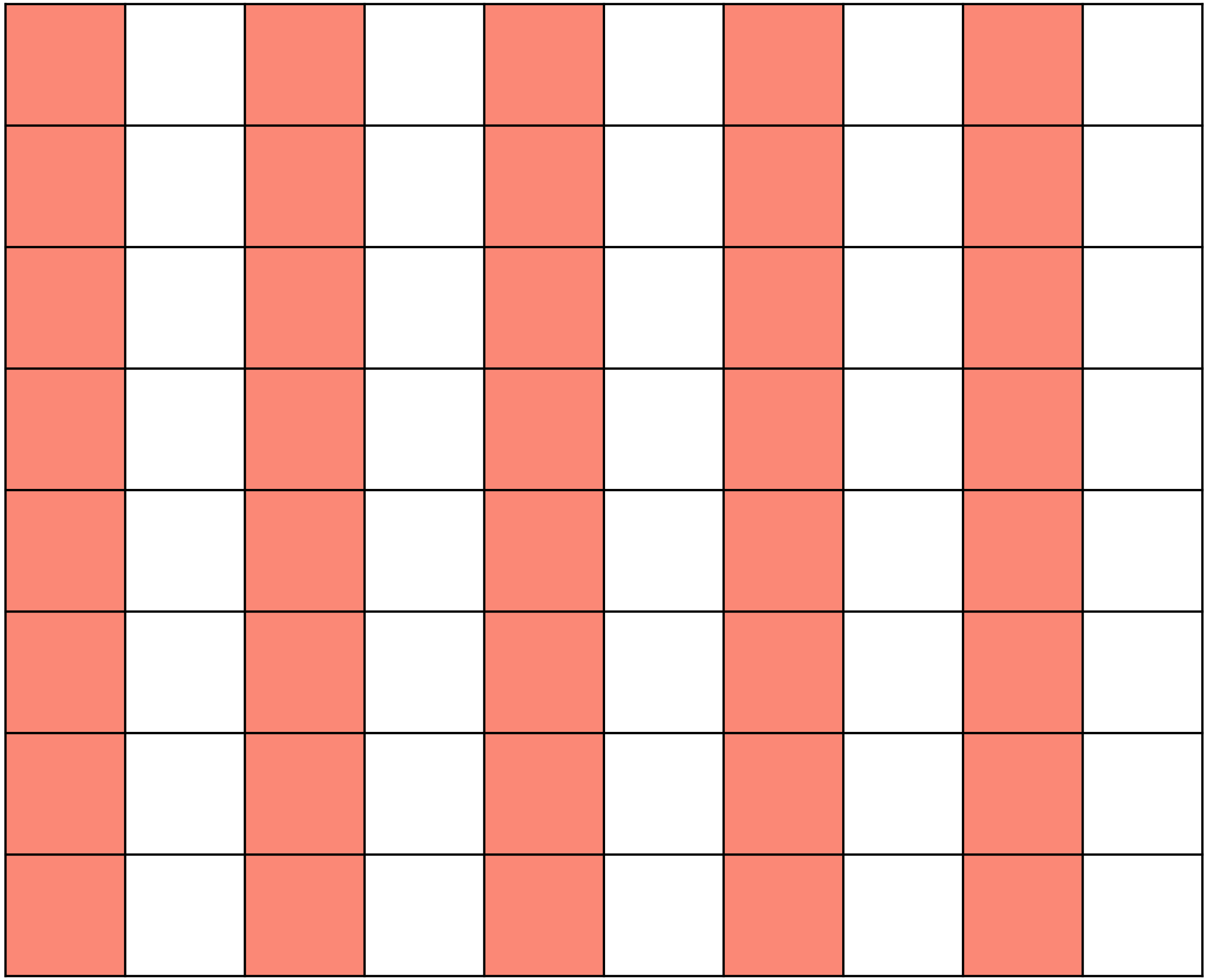
Biological background

1. There is a group of cells with the same developmental potential
2. An external signal prompts them to communicate



Biological background

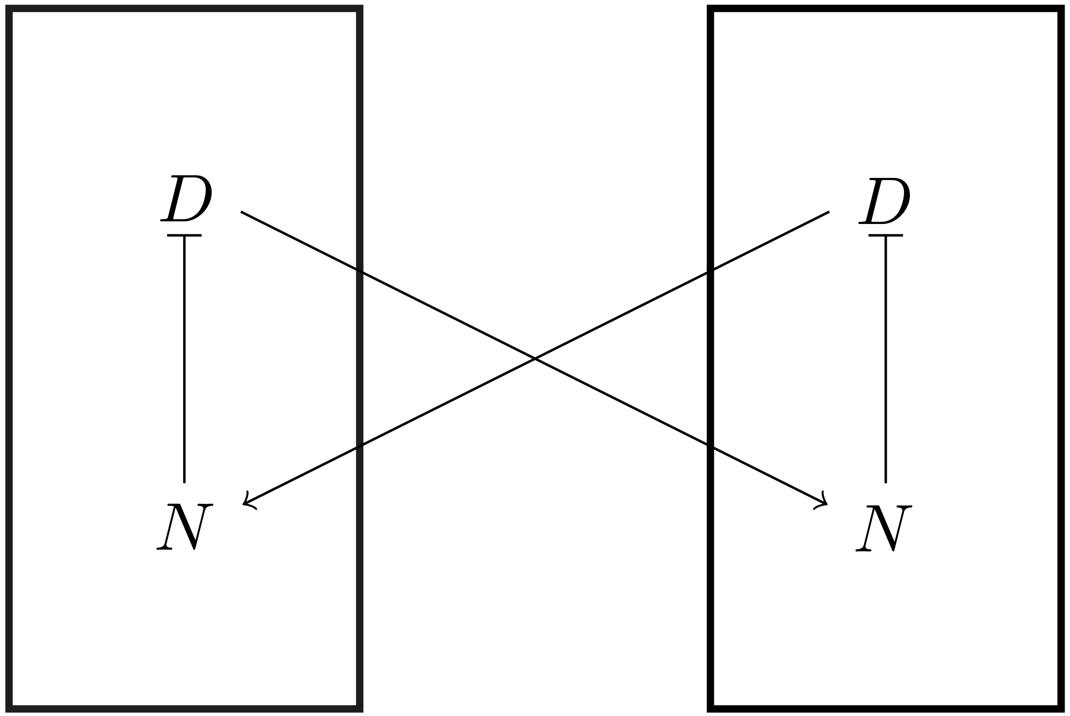
1. There is a group of cells with the same developmental potential
2. An external signal prompts them to communicate
3. A pattern of cell fates forms



Existing mathematical research

- Modeling *lateral inhibition*
  - Collier et al. (1996)

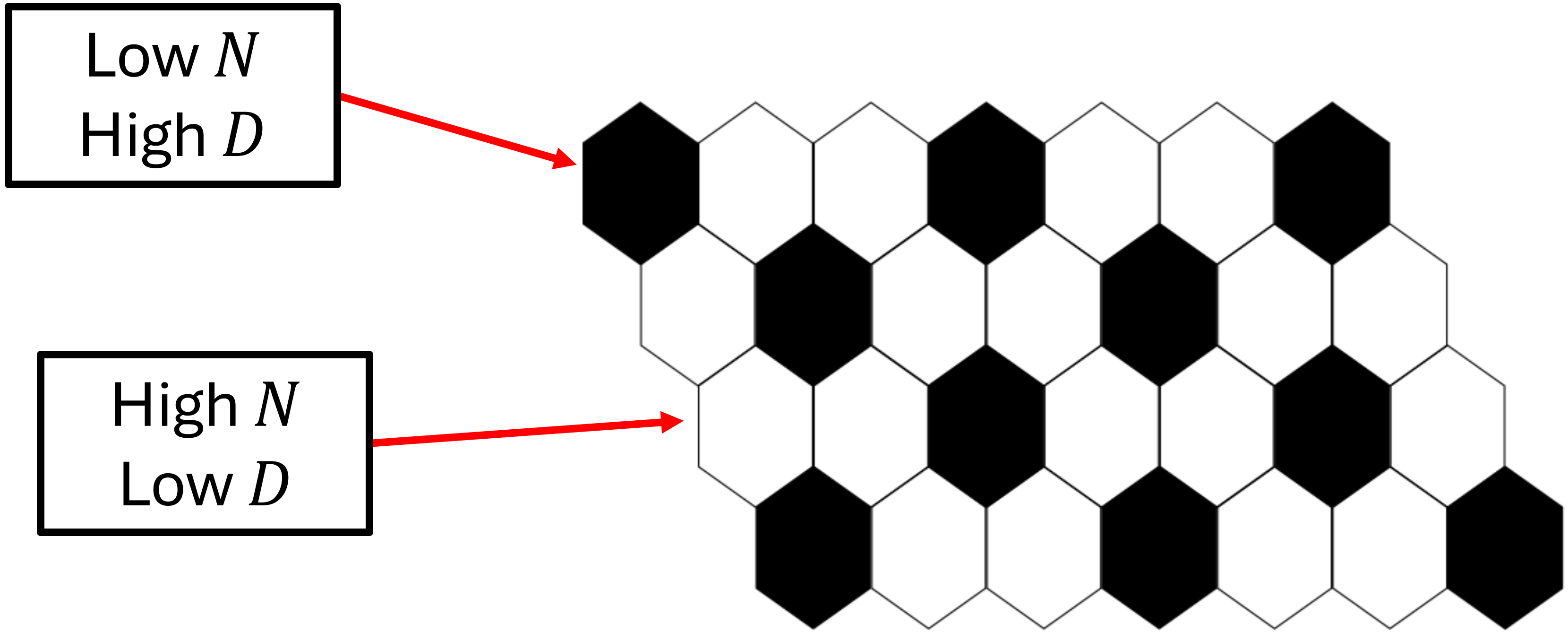
$$\frac{dN_i}{dt} = h(\overline{D_i}) - \mu N_i$$
$$\frac{dD_i}{dt} = g(N_i) - \rho D_i$$



- h and g are increasing and decreasing hill functions, respectively
- $\overline{D}_i$ is the average of D over the neighbors of the i^{th} cell

Existing mathematical research

- Computer simulations of the model for a choice of constants



- Patterns form through a **bifurcation** as external signal varies
- Coarse-grained patterns are observed when there is **long-range signaling** or **additional chemical signaling** (lateral stabilization)
  - Vasilopoulos and Painter (2016), Hadjivasiliou et al. (2016), de Back et al. (2013)

Model-independent predictions of pattern formation

We can predict patterns without assuming reaction rates

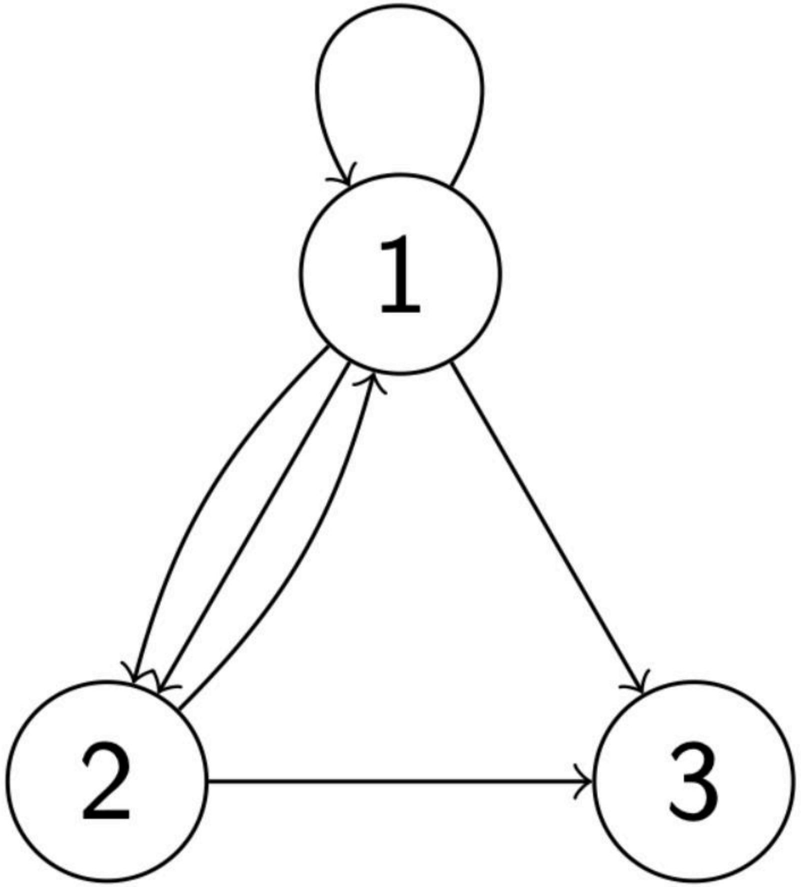
Model-independent analysis

- The cell-communication network is a **regular network**

Any **admissible ODE** has the form:

$$\frac{d\boldsymbol{x}_1}{dt} = f(\boldsymbol{x_1}, \overline{\boldsymbol{x_1}, \boldsymbol{x_2}}, \lambda)$$
$$\frac{d\boldsymbol{x}_2}{dt} = f(\boldsymbol{x_2}, \overline{\boldsymbol{x_1}, \boldsymbol{x_1}}, \lambda)$$
$$\frac{d\boldsymbol{x}_3}{dt} = f(\boldsymbol{x_3}, \overline{\boldsymbol{x_1}, \boldsymbol{x_2}}, \lambda)$$

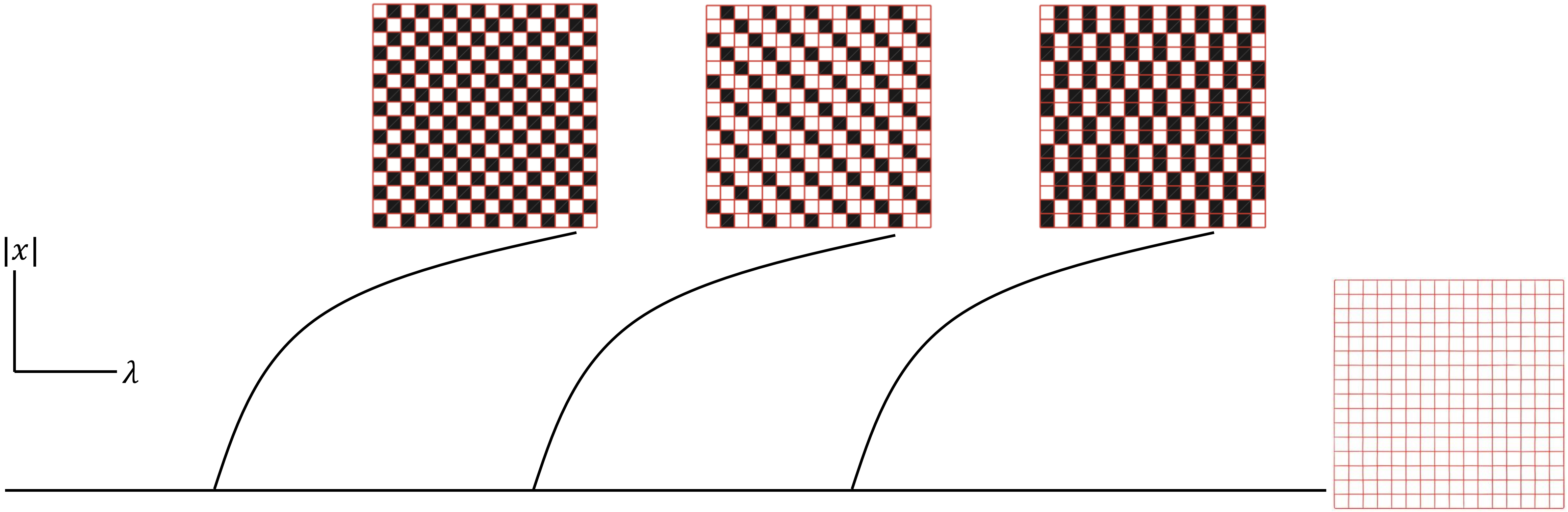
for $\boldsymbol{x_i} \in \mathbb{R}^s$ (*node space*) and some smooth function f that is symmetric in its second and third arguments



- Network structure restricts possible solutions

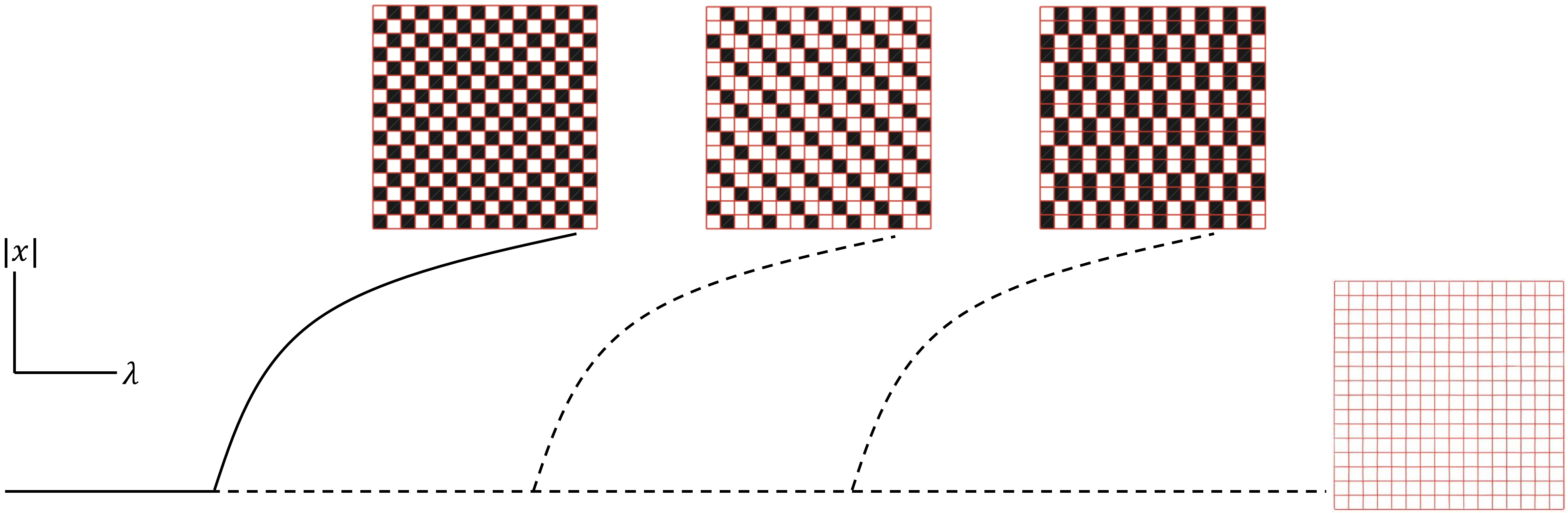
Bifurcating patterns in regular networks

- Bifurcations in admissible ODEs lead to patterns
  - Wang and Golubitsky (2004)

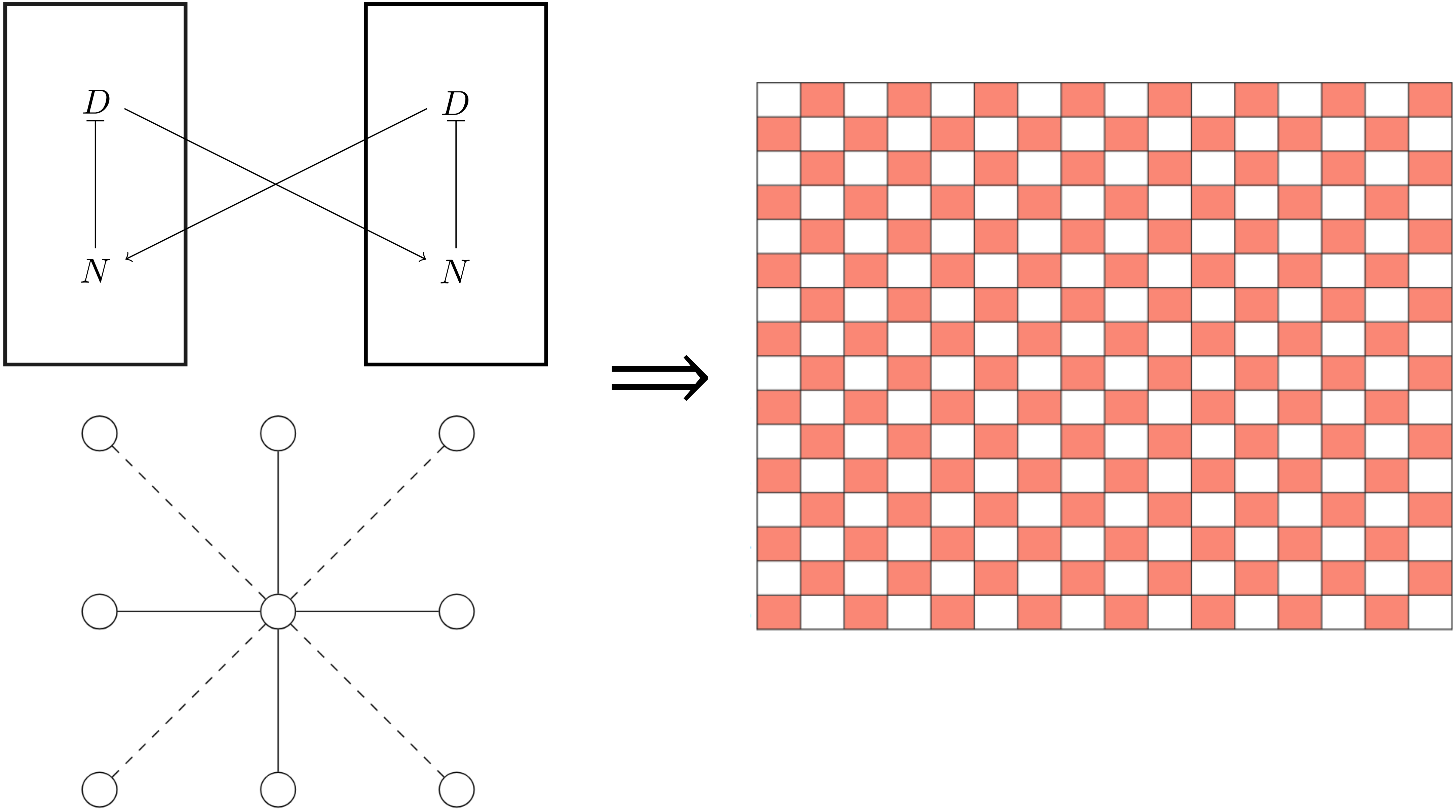


Bifurcating patterns in regular networks

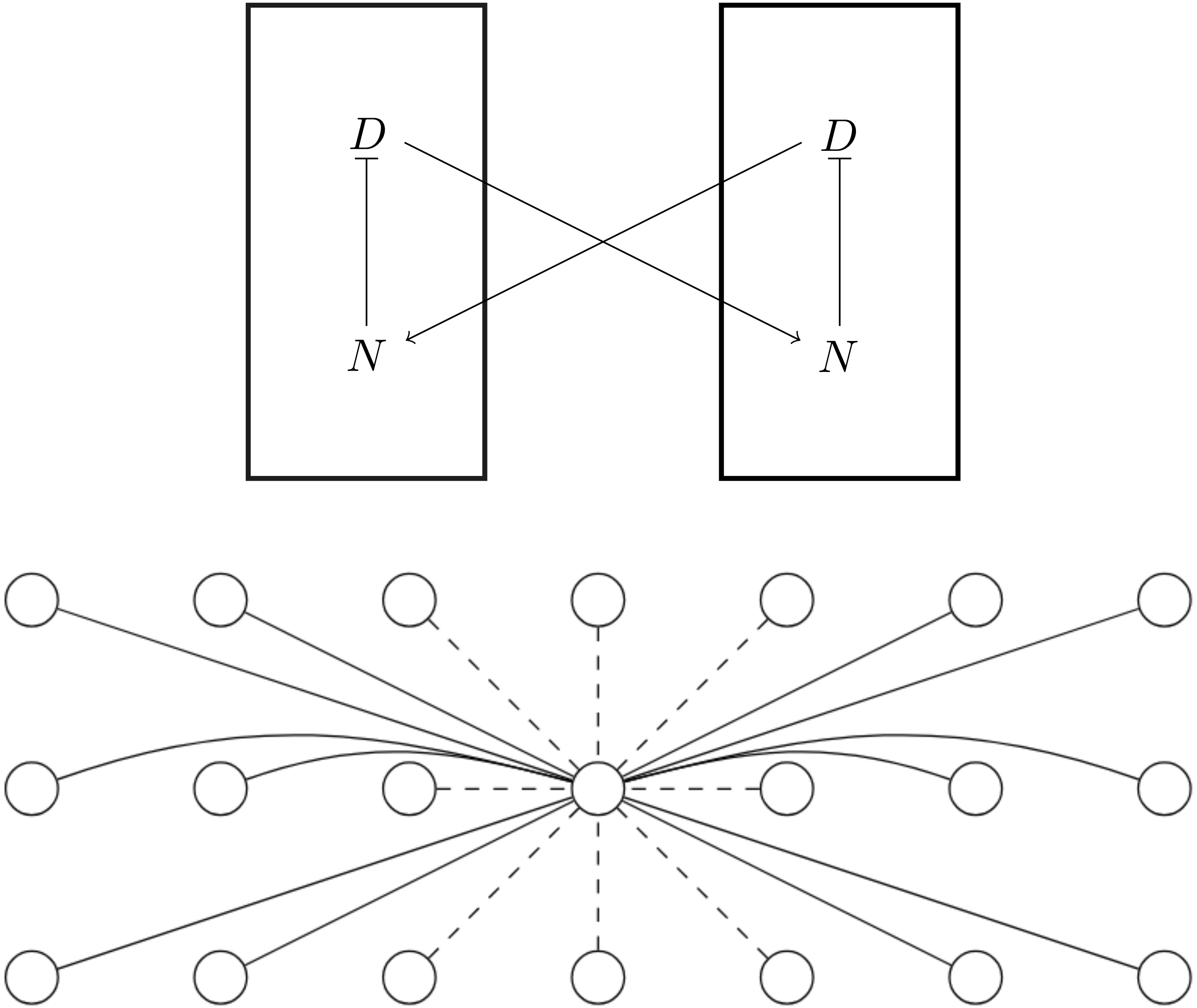
- Bifurcations in admissible ODEs lead to patterns
  - Wang and Golubitsky (2004)
- Only the first bifurcation is stable
- What properties of the system determine the first bifurcation?



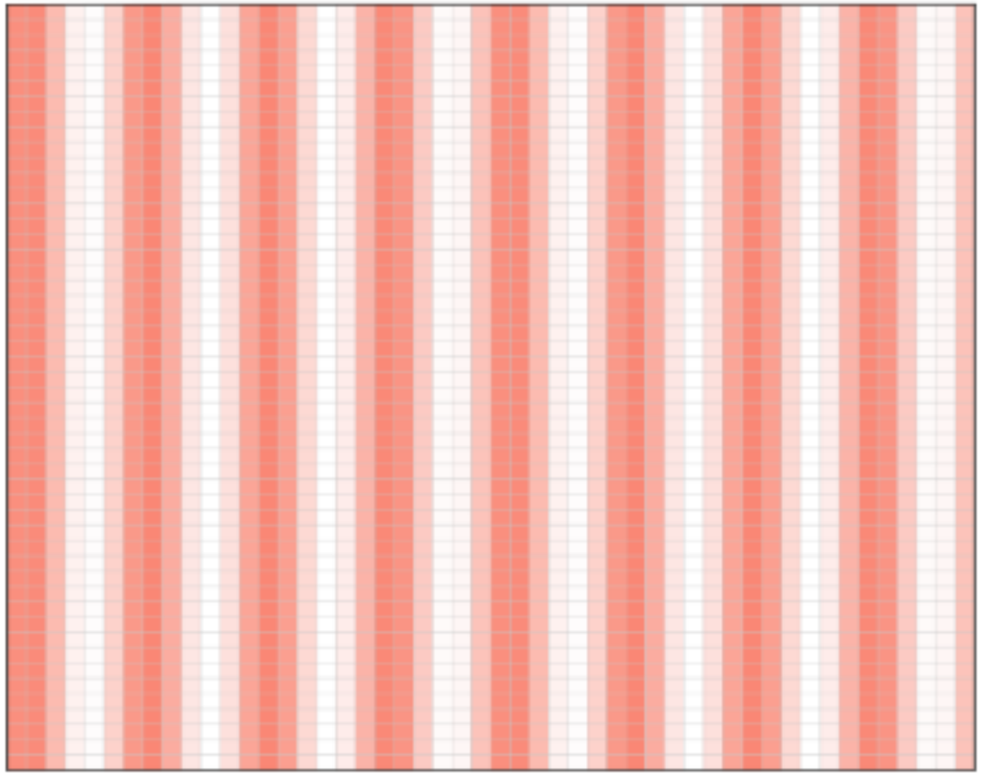
Chemical signaling selects the first bifurcation



Coarse-grained patterns from long-range signals

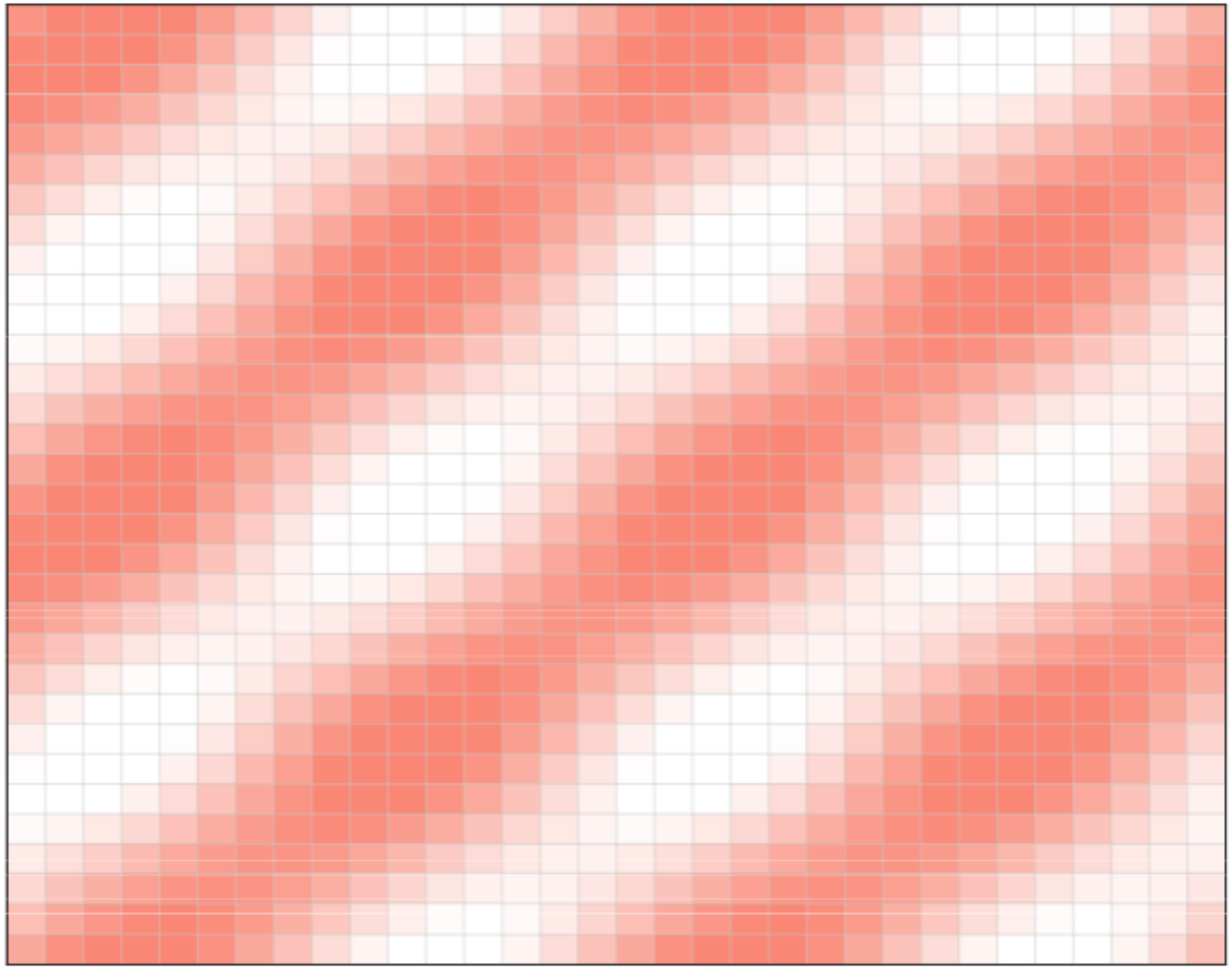


$\Rightarrow$

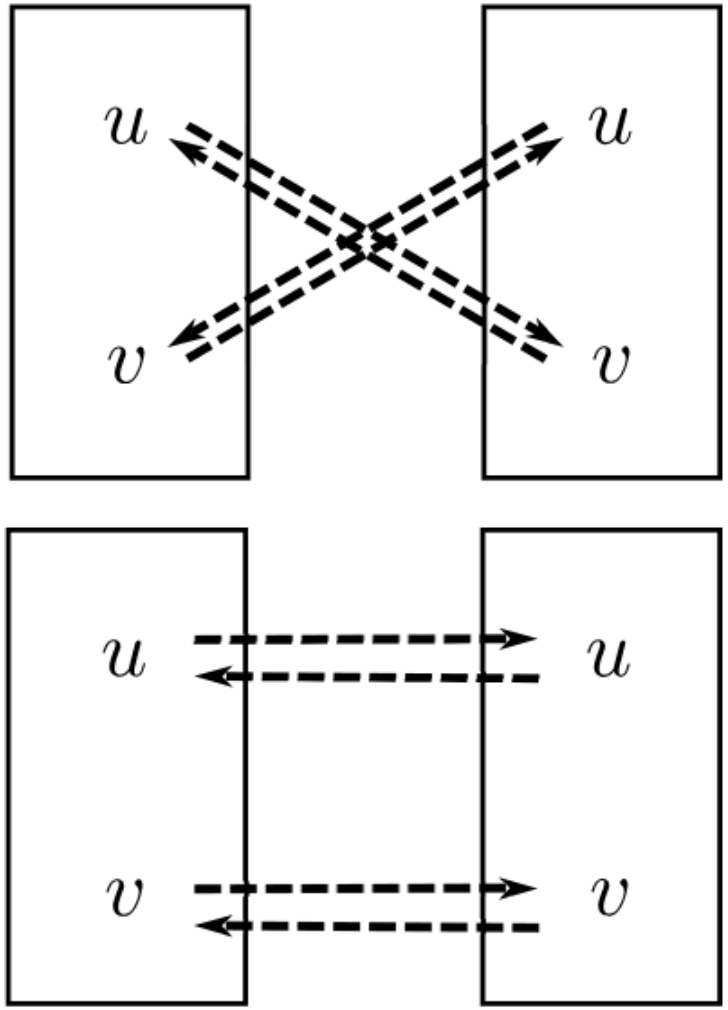


Coarse-grained patterns require additional signals

Observed Pattern



Necessary chemical interactions



Can we generalize this idea beyond Notch signaling?

Chemical signaling dynamics

$$\frac{d\boldsymbol{x}_1}{dt} = f(\boldsymbol{x_1}, \overline{\boldsymbol{x_1}, \boldsymbol{x_2}}, \lambda)$$

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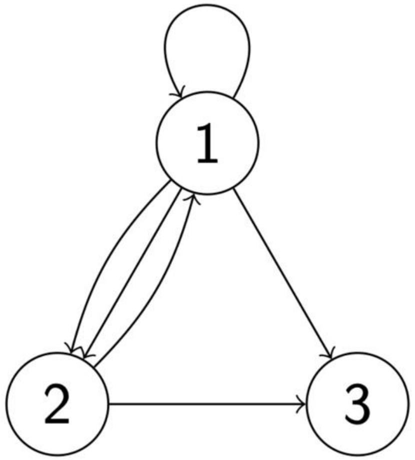
Cell-communication dynamics



Let $f := f(u, \overline{v, w})$

Internal dynamics

$$Q = D_u f$$

Coupled dynamics

$$R = D_v f$$

Adjacency matrix

$$A = \begin{pmatrix} 1 & 1 & 0 \\ 2 & 0 & 0 \\ 1 & 1 & 0 \end{pmatrix}$$

When evaluating the Jacobian J at a synchronous equilibrium,

$$J = \begin{pmatrix} Q + R & R & 0 \\ 2R & Q & 0 \\ R & R & Q \end{pmatrix} = \begin{pmatrix} Q & 0 & 0 \\ 0 & Q & 0 \\ 0 & 0 & Q \end{pmatrix} + \begin{pmatrix} R & R & 0 \\ 2R & 0 & 0 \\ R & R & 0 \end{pmatrix} = Q \otimes I + R \otimes A$$

Bifurcating pattern depends on cell communication and chemical signaling

Theorem (Golubitsky and Lauterbach, 2009): The critical eigenvalues of J evaluated at a synchronous steady-state are the union of the eigenvalues of

Cell-level dynamics

$$Q + \mu_i R$$

Global cell-communication

where Q, R are the internal and coupled dynamics and μ_i is an eigenvalue of A. The eigenvectors are $u \otimes v_i$ where u is an eigenvector of $Q + \mu_i R$ and (μ_i, v_i) is an eigenvalue-eigenvector pair of A

Bifurcating Pattern

Criteria for different patterns with 2 chemicals

- Suppose the adjacency matrix A has real eigenvalues $\mu_1 < \cdots < \mu_k$ with algebraic multiplicities $\alpha_1, \ldots, \alpha_k$
- Let $\det(R) = 0$
- Take $B = \mathrm{tr}(Q)\mathrm{tr}(R) - \mathrm{tr}(QR)$

Criteria for different patterns with 2 chemicals

- Suppose the adjacency matrix A has real eigenvalues $\mu_1 < \cdots < \mu_k$ with algebraic multiplicities $\alpha_1, \ldots, \alpha_k$ (symmetric adjacency matrices are common)
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- Let $\det(R) = 0$ (sparsity of intercellular chemical signaling)
- Take $B = \mathrm{tr}(Q)\mathrm{tr}(R) - \mathrm{tr}(QR)$
- Then there are four possible generic bifurcations

Pattern given by eigenvector associated with μ_1

Critical Pattern Space	Number of Critical Eigenvalues	Determinant Condition	Trace Condition
P^{μ_1}	α_1 (real)	$B > 0$	NDG
P^{μ_1}	$2\alpha_1$ (imag.)	NDG	$\mathrm{tr}(R) < 0$
$P^{\mu_k} = \mathrm{span}\{\vec{1}_n\}$	1 (real)	$B < 0$	NDG
$P^{\mu_k} = \mathrm{span}\{\vec{1}_n\}$	2 (imag.)	NDG	$\mathrm{tr}(R) > 0$

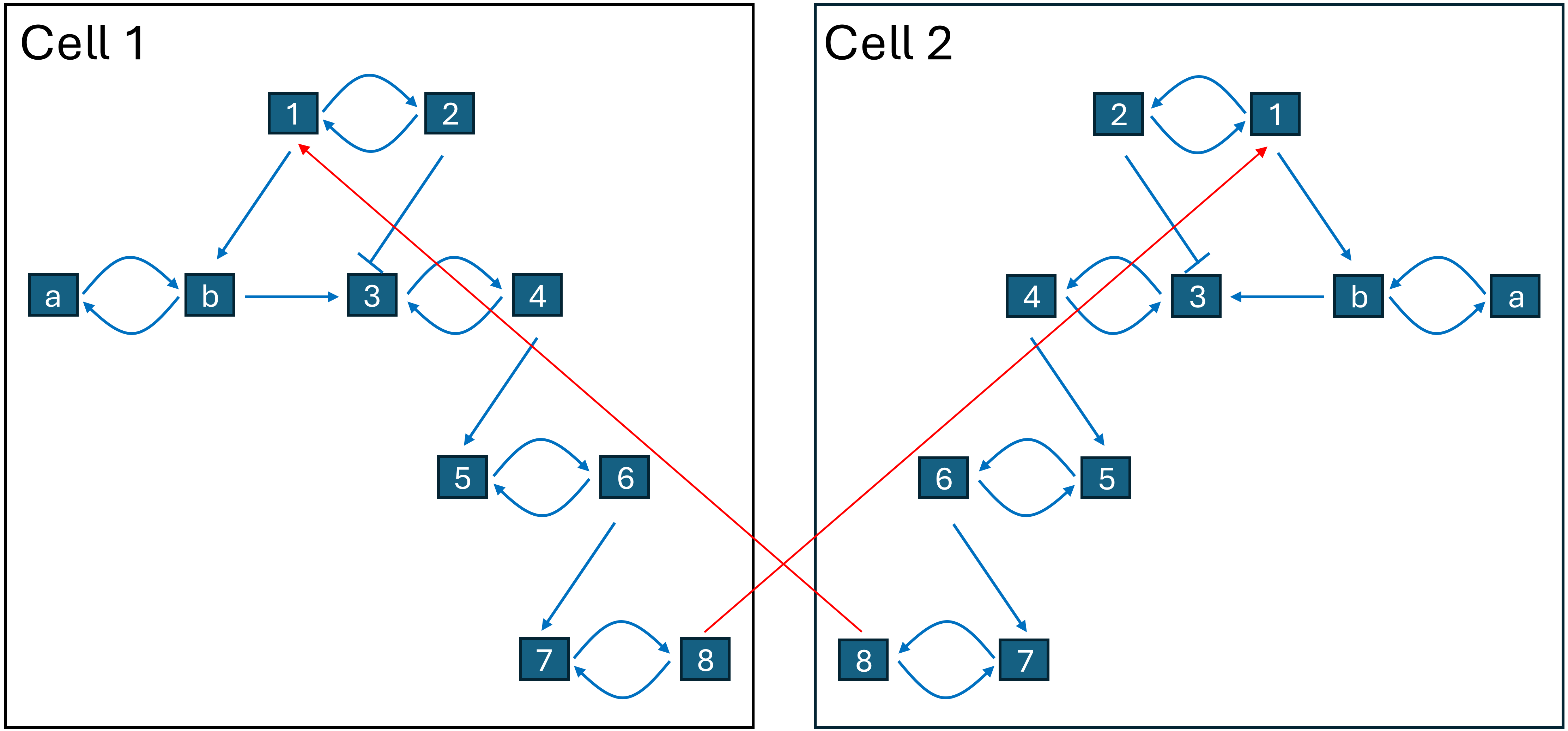
No pattern forms

By removing unnecessary assumptions, we can perform a more complete analysis of pattern formation

- We can more readily:
  1. Predict molecular causes of pattern breakdown
  2. Infer information about necessary chemical interactions

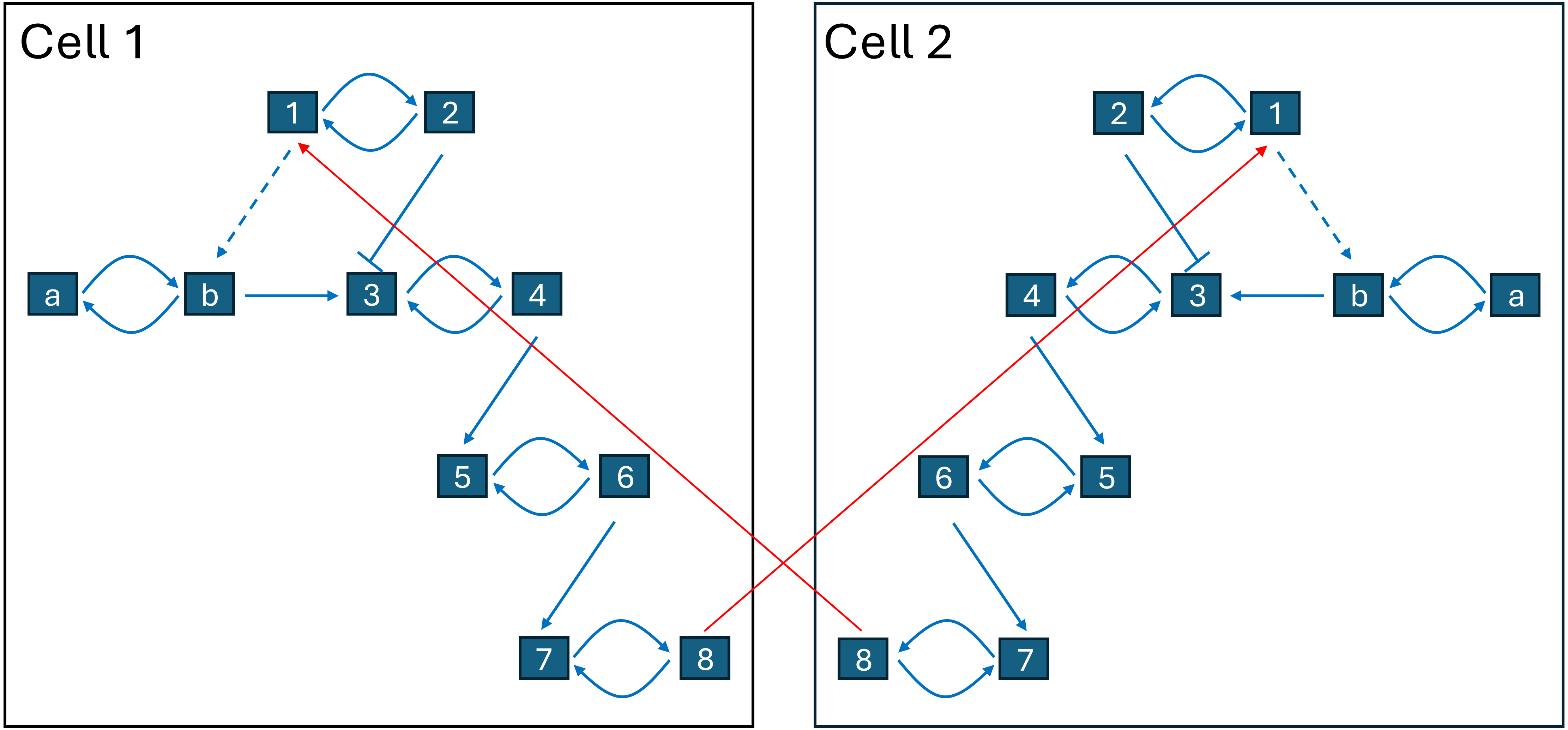
Inferring causes of pattern breakdown

- Suppose the following signaling results in a pattern

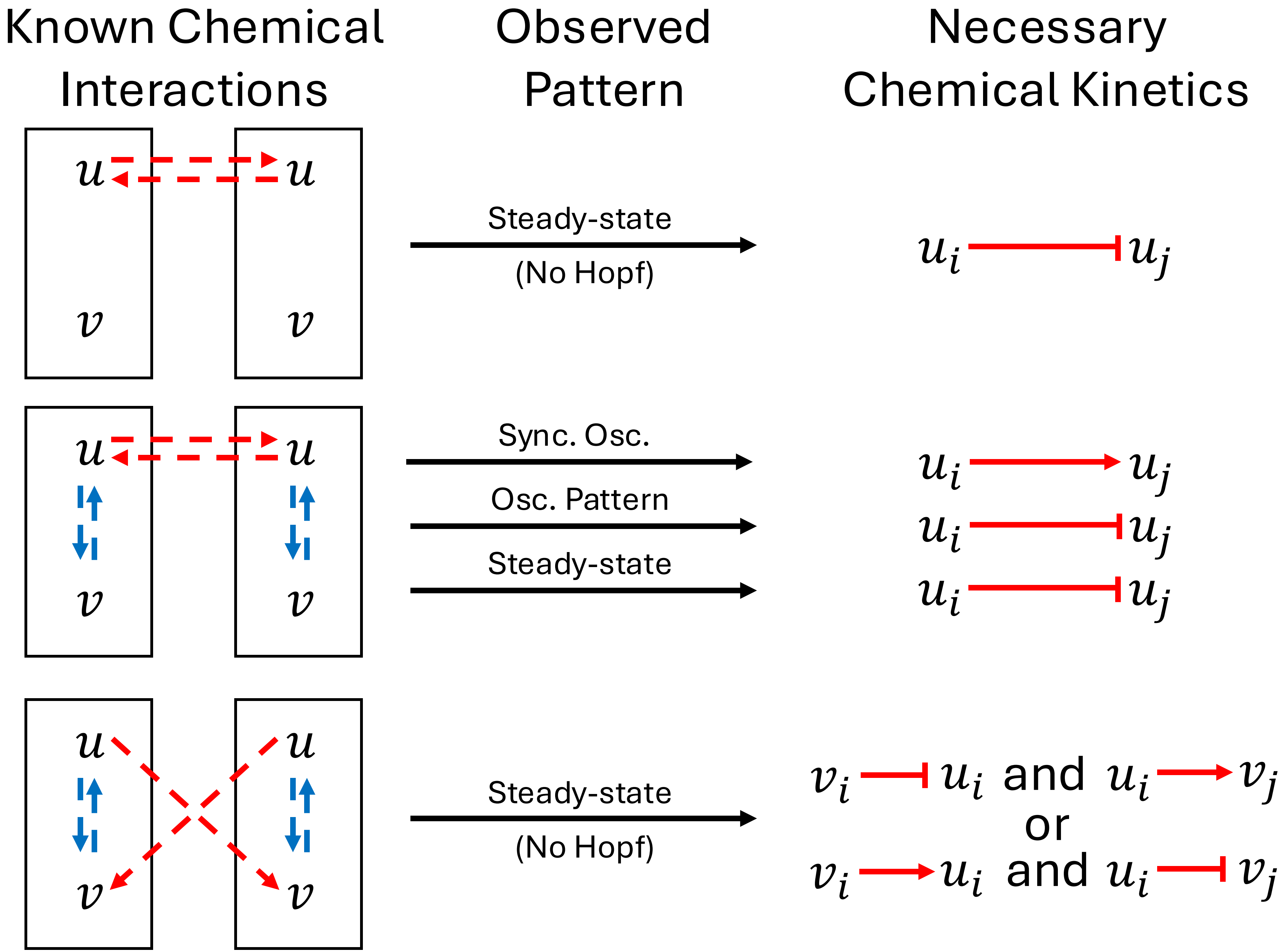


Inferring causes of pattern breakdown

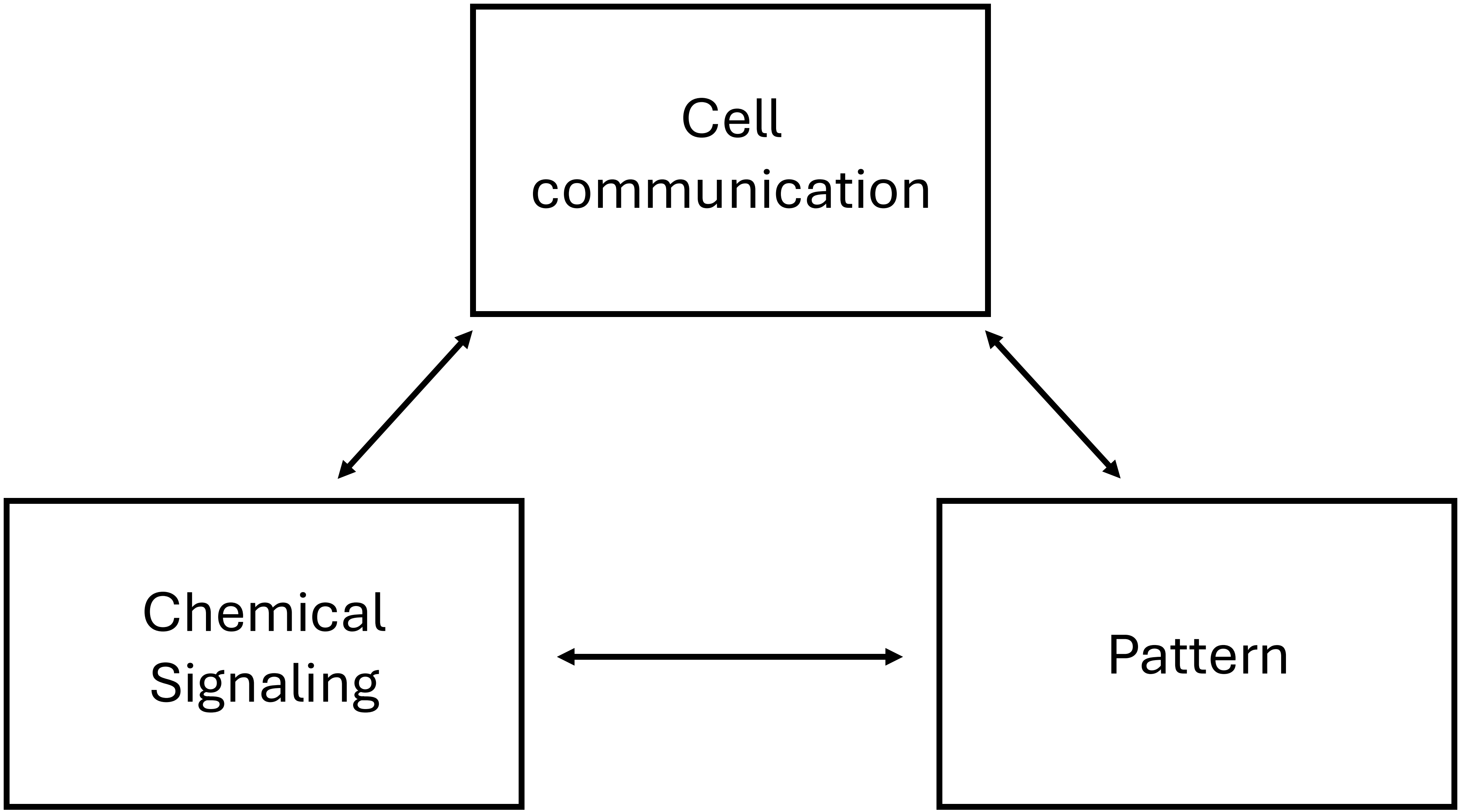
- Making the dotted arrow small will break the pattern



Inferring chemical signaling from partial information



If you have two, you can learn about the other



Conclusions

- By using a model independent approach, we can predict cellular patterns with minimal assumptions
- Stripping away assumptions allows us to develop criteria for pattern formation
  - The criteria allow us to infer molecular causes of pattern breakdown and infer unknown chemical kinetics

Future work

- Generalize the theory to incorporate general chemical signaling networks
- Incorporate small perturbations to the network structure

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