Pattern Formation and Synchronization in Biology

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Multicellular organisms rely on spatiotemporal phenomena. Modeling these phenomena informs science and enables the engineering of synthetic systems.

Diffusion-driven instability: 

Lateral inhibition: 

Credit: Kondo Lab (PNAS'07)
Credit: Salazar-Ciudad & Jernvall (PNAS'02)
Credit: Elowitz Lab (PLoS Comp Bio, 2011)
Outline:

1. Synchrony in reaction-diffusion systems
2. Pattern formation by diffusion-driven instability
3. Pattern formation by lateral inhibition
4. Synchronization of rotating helices
Synchrony in Reaction-Diffusion Systems

Let $x$ denote a vector of concentrations and consider the PDE

$$\frac{\partial x(t, \xi)}{\partial t} = f(x(t, \xi)) + D\nabla^2 x(t, \xi)$$

with spatial variable $\xi \in \Omega$ and zero-flux boundary condition.

Under what conditions do the solutions synchronize?

$$\left\| x(t, \xi) - \frac{1}{|\Omega|} \int_{\Omega} x(t, \xi) d\xi \right\|_{L^2(\Omega)} \to 0 \quad \text{as} \quad t \to \infty$$

No synchrony:

Synchrony:
Synchronization Criterion

Predict synchrony from the Jacobian matrix:

\[ J(x) = \frac{\partial f(x)}{\partial x} \]

and zero-flux eigenvalues of \(-\nabla^2\) on \(\Omega\):

\[ 0 = \lambda_0 \leq \lambda_1 \leq \lambda_2 \leq \cdots \]

If there exist \(P = P^T > 0\), \(\epsilon > 0\) and convex set \(\mathcal{X}\) such that

\[ P(J(x) - \lambda_1 D) + (J(x) - \lambda_1 D)^T P \leq -\epsilon I \quad \forall x \in \mathcal{X} \quad (1) \]

\[ PD + D^T P \geq 0 \quad (2) \]

then every classical solution \(x(t, \xi) \in \mathcal{X}\) synchronizes.

Same result for compartmental ODEs: \(-\nabla^2 \rightarrow\) Laplacian matrix
Verification with Linear Matrix Inequalities

Cover $J(\mathcal{X})$ with convex and conic hulls of constant matrices:

$$J(\mathcal{X}) \in \text{conv}\{Z_1, \cdots, Z_q\} + \text{cone}\{S_1, \cdots, S_m\}$$

$$\text{cone}\{S_1, \cdots, S_m\} = \{ \omega_1 S_1 + \cdots + \omega_m S_m \mid \omega_i \geq 0 \}$$

$$\text{conv}\{Z_1, \cdots, Z_q\} = \{ \theta_1 Z_1 + \cdots + \theta_q Z_q \mid \sum_i \theta_i = 1, \theta_i \geq 0 \}$$

A matrix $P$ satisfying

$$P(Z_k - \lambda_1 D) + (Z_k - \lambda_1 D)^T P < 0 \quad k = 1, \cdots, q$$

$$PS_k + S_k^T P \leq 0 \quad k = 1, \cdots, m$$

also satisfies (1) for some $\epsilon > 0$. 

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**Notice:** The image contains a diagram illustrating the convex and conic hulls of the matrices $S_1, \cdots, S_m$ and $Z_1, \cdots, Z_q$, with $J(\mathcal{X})$ highlighted.
Special Case: Linear Reaction-Diffusion Systems

\[
\frac{\partial x(t, \xi)}{\partial t} = Ax(t, \xi) + D\nabla^2 x(t, \xi) \quad \xi \in \Omega
\]

Decompose into ODEs:

\[
\dot{\sigma}_k(t) = (A - \lambda_k D)\sigma_k(t) \quad k = 0, 1, 2, \ldots
\]

using eigenfunctions of $\nabla^2$ as a basis: $x(t, \xi) = \sum_{k=0}^{\infty} \sigma_k(t) \phi_k(\xi)$

\[
\phi_0(\xi), \quad \phi_1(\xi), \quad \phi_2(\xi)
\]

Our synchrony condition implies stability of $A - \lambda_k D$, $k \geq 1$. 
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**Diffusion-Driven Instability (Alan Turing, 1952)**

Stable steady-state $x^*$ in reaction ODE:

$$\frac{dx(t)}{dt} = f(x(t)) \quad f(x^*) = 0$$

may be destabilized by diffusion in PDE:

$$\frac{\partial x(t, \xi)}{\partial t} = f(x(t, \xi)) + D \nabla^2 x(t, \xi)$$

**Example: activator-inhibitor system**

![Activator-inhibitor system](Image)

$$A = \left. \frac{\partial f(x)}{\partial x} \right|_{x=x^*} = \begin{bmatrix} + & - \\ + & - \end{bmatrix}$$

Sign structure allows $A - \lambda D$ to be unstable even if $A$ is stable.
Instability of $A_0$ implies $A - \lambda D$ unstable for large $\lambda d$
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Lateral Inhibition

Common in multicellular organisms, e.g., Delta-Notch system in metazoans:

Ligand in one cell inhibits production of ligand in adjacent cells. This competition generates fine-grained patterns:

Goal: Determine when and what kind of patterns emerge.
Challenge: Large scale and nonlinear dynamical model, e.g.,

\[
\begin{align*}
\dot{N}_i &= \beta - \gamma N_i - kN_i \langle D_j \rangle_i \\
\dot{D}_i &= g(S_i) - \gamma D_i - kD_i \langle N_j \rangle_i \\
\dot{S}_i &= -\gamma S_i + kN_i \langle D_j \rangle_i
\end{align*}
\]

Idea: Expose system as an interconnection of cells by defining input and output

\[
u_i = \begin{bmatrix} \langle N_j \rangle_i \\ \langle D_j \rangle_i \end{bmatrix} \quad y_i = \begin{bmatrix} N_i \\ D_i \end{bmatrix}
\]

\[
u = \begin{bmatrix} u(1) \\ u(2) \end{bmatrix}
\]

\[
\begin{align*}
\dot{N} &= \beta - \gamma N - kNu(2) \\
\dot{D} &= g(S) - \gamma D - kDu(1) \\
\dot{S} &= -\gamma S + kNu(2)
\end{align*}
\]

\[
y = \begin{bmatrix} N \\ D \end{bmatrix}
\]
Interconnection:

Subsystems: Monotone (Hirsch; Angeli, Sontag) with opposite input and output orders \(\Rightarrow\) decreasing steady-state I/O map:

\[ T(u) \]

The fixed point of this map defines a homogeneous steady-state.

Homogeneous steady state unstable if \( \lambda_{\min}(P)|T'(u^*)| < -1 \)
Pattern Templates from Graph Partitioning

A partition of the vertex set into classes \( O_1, \ldots, O_r \) is equitable if the weighted adjacency matrix satisfies

\[
\sum_{v \in O_j} p_{uv} = \overline{p}_{ij} \quad \forall u \in O_i.
\]

Look for steady-states with identical values in the same class:

\[
P \begin{bmatrix} u_1 \\ \vdots \\ u_N \end{bmatrix} = P \begin{bmatrix} T(u_1) \\ \vdots \\ T(u_N) \end{bmatrix}
\]

\[
\begin{bmatrix} w_1 \\ \vdots \\ w_r \end{bmatrix} = \overline{P} \begin{bmatrix} T(w_1) \\ \vdots \\ T(w_r) \end{bmatrix}
\]
Which Partitions Admit Patterns?

Define reduced graph with vertices $\overline{V} = \{O_1, \ldots, O_r\}$ and edges
$\overline{E} = \{(O_i, O_j) : i \neq j, \overline{p}_{ij} \neq 0 \text{ or } \overline{p}_{ji} \neq 0\}$

If the reduced graph is bipartite and $\lambda_{\min}(\overline{P})|T'(u^*)| < -1$
then a steady-state pattern obeying the partition exists.

$|T'(u^*)| > 1$
$|T'(u^*)| > 2$
$|T'(u^*)| > \sec(\pi/N)$
A synthetic lateral inhibition system currently being developed:

Main idea in a caricature:
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Synchronisation of Rotating Helices

Symbiotic spirochetes on surface exhibit traveling waves, providing thrust. Can hydrodynamics explain these waves?

Can we mimic this property in bacteria propelled robots?

Credit: Sidney Tamm
Low Reynolds # simulation model revealing translational and rotational effects on synchronization

Transverse translation

Transverse rotation

Low Reynolds # simulation model revealing translational and rotational effects on synchronization
Conclusions

Multicellular organisms rely on spatiotemporal phenomena.

Modeling these phenomena informs science and enables the engineering of synthetic systems.
Publications mentioned in the talk:

**Arcak** “Certifying spatially uniform behavior in reaction-diffusion PDE and compartmental ODE systems” – *Automatica*, 2011

**Hsia, Huang, Holtz, Arcak, Maharbiz** “A feedback quenched oscillator produces Turing patterning with one diffuser” – *PLOS Comp. Bio.*, 2012

**Ferreira and Arcak** “A graph partitioning approach to predicting patterns in lateral inhibition systems” – *SIAM J. Applied Dynamical Systems*, 2013

**Tu, Arcak, Maharbiz** “Decoupling translational and rotational effects on the phase synchronization of rotating helices” – *Physical Review E*, 2015

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