Reduction and Diffusion-Driven Instability Analysis In a Receptor-Based Model for Hydra Morphogenesis

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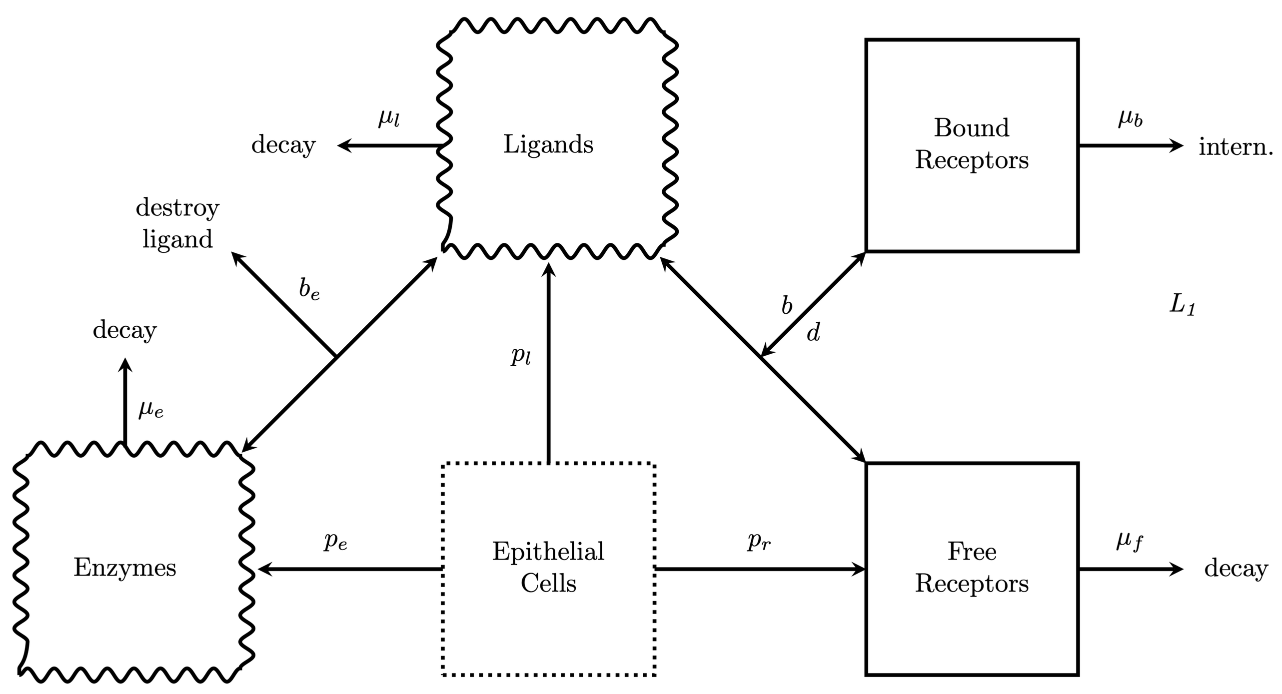
Abstract

How do complex structures emerge from an initially symmetric state? One mathematical approach, proposed by Alan Turing, involves studying reaction-diffusion equations. When given the right conditions, almost symmetrical initial datum to these equations can evolve into stable, spatially heterogeneous solutions known as Turing patterns. Such reaction-diffusion equations can be coupled to standard ODEs to model localized phenomena, opening the door to various new observable patterns - which are not necessarily Turing patterns - and a necessary condition for them to appear is diffusion-driven instability (DDI). We begin with a receptor-based model for Hydra morphogenesis [3], which we reduce by a quasi-static approximation before investigating the phenomenon of DDI in this new toy model.

Original model

Introduction: This model describes the time evolution of four chemical components (two diffusive, two non-diffusive) according to a classical reaction scheme. It originates from [3] and suggests a simple dynamics for limb regeneration in Hydra and admits a visual representation like follows:



Model Equations:

$$\begin{aligned}
&\partial_t r_f = -\mu_f r_f + m_1 \frac{r_b}{1+r_b} - b r_f \ell + d r_b && \text{in } \Omega\times(0,T), && r_f(\cdot,0) = r_f^0 && \text{in } \Omega,\\
&\partial_t r_b = -\mu_b r_b + b r_f \ell - d r_b && \text{in } \Omega\times(0,T), && r_b(\cdot,0) = r_b^0 && \text{in } \Omega,\\
&\partial_t \ell = d_1\Delta\ell - \mu_l \ell + m_2 \frac{r_b}{1+r_b} - b r_f \ell + d r_b - b_e \ell e && \text{in } \Omega\times(0,T), && \ell(\cdot,0) = \ell^0 && \text{in } \Omega,\\
&\partial_t e = d_2\Delta e - \mu_e e + m_3 \frac{r_b}{1+r_b} && \text{in } \Omega\times(0,T), && e(\cdot,0) = e^0 && \text{in } \Omega,\\
&\partial_\nu \ell = 0, \qquad \partial_\nu e = 0 && \text{on } \partial\Omega\times(0,T).
\end{aligned}$$

Domain: $\Omega = (0,L)$, where $L \in \mathbb{R}_{>0}$. We assume $L=1$ except stated otherwise.

Model reduction: quasi-static approximation and rescaling

Idea of the approximation:

- Goal is to simplify the analysis of chemical systems kinetics by assuming that some species are reaching their steady-state concentrations (much) faster than others.
- In practice, introduce a second time scale in the system $\tau = \varepsilon t$ and let $\varepsilon \to 0$
- Results in a differential-algebraic equation where, in most cases, one can explicitly solve the algebraic equation (otherwise, restriction of the differential equation to an algebraic manifold)

Singular limit:

Introduce $0 < \varepsilon \ll 1$, small parameter in the equation on $\partial_t r_b$. Let $\varepsilon \to 0$ and solve for r_b:

$$r_b(t,x) = \frac{b}{d+\mu_b} r_f(t,x)\ell(t,x), \qquad (t,x)\in\Omega\times(0,T).$$

Change of variable and parameter rescaling:

$$\text{new functions:}\quad u = \sqrt{\frac{b}{d+\mu_b}}r_f, \qquad v = \sqrt{\frac{b}{d+\mu_b}}\ell, \qquad w = \sqrt{\frac{b}{d+\mu_b}}e$$

$$\text{new parameters:}\quad \tilde m_1 = \sqrt{\frac{b}{d+\mu_b}}m_1, \quad \tilde m_2 = \sqrt{\frac{b}{d+\mu_b}}m_2, \quad \tilde m_3 = b_e m_3, \quad \tilde\mu_b = \sqrt{\frac{b}{d+\mu_b}}\mu_b$$

Reduced model equations:

$$\begin{aligned}
&\partial_t u = -\mu_f u + \tilde m_1 \frac{uv}{1+uv} - \tilde\mu_b uv && \text{in } \Omega\times(0,T), && u(\cdot,0) = u^0 && \text{in } \Omega,\\
&\partial_t v = d_1\Delta v - \mu_l \ell + \tilde m_2 \frac{uv}{1+uv} - \tilde\mu_b uv - vw && \text{in } \Omega\times(0,T), && v(\cdot,0) = v^0 && \text{in } \Omega,\\
&\partial_t w = d_2\Delta w - \mu_e w + \tilde m_3 \frac{uv}{1+uv} && \text{in } \Omega\times(0,T), && w(\cdot,0) = w^0 && \text{in } \Omega,\\
&\partial_\nu v = 0, \qquad \partial_\nu w = 0 && \text{on } \partial\Omega\times(0,T).
\end{aligned}$$

Notation: We drop the tilde $\tilde\square$ notation on parameters in the future. Moreover, we denote respectively by f, g, h, each reaction term for u, v, w and define the vector field $\boldsymbol{\phi} = (f,g,h)$. The quantity $\boldsymbol{X}$ denotes the vector (u,v,w).

> **Theorem:** Let C_u, C_v, C_w be positive constants satisfying
>
> $$C_u \geq \frac{m_1}{\min(\mu_f,\mu_b)}, \qquad C_v \geq \frac{m_2}{\min(\mu_l,\mu_b,1)}, \qquad C_w \geq \frac{m_3}{\mu_e},$$
>
> then the region $\Sigma := [0,C_u]\times[0,C_v]\times[0,C_w]$ is an invariant rectangle of the system, providing uniform global estimates on $u(t,x), v(t,x), w(t,x)$ for any $\boldsymbol{X}^{\boldsymbol{0}} \in \Sigma$ and all $t>0$, $x\in\Omega$.

Diffusion-driven instability and Turing patterns

We are interested in pattern formation linked to destabilization of a spatially homogeneous state.

Diffusion-driven instability (DDI):

- DDI is a bifurcation leading to a loss of stability of a constant steady state.
- The steady state is asymptotically stable as a solution of the kinetic system, i.e. $d_1 = d_2 = 0$.
- The steady state is unstable in the system with diffusion.

Turing Patterns:

- Turing patterns are continuous patterns which arise due to DDI of a constant steady state.
- They are formed around the constant steady state (close-to-equilibrium patterns).

Far-from-equilibrium patterns:

- This is another type of patterns which exhibit singularities.
  - Patterns with jump-discontinuity (arise in systems with multiple constant stationary solutions).
  - Spike patterns (arise e.g. due to diffusion-driven unbounded growth). [1]

Steady states & a necessary and sufficient condition for DDI

Steady states:

- There exists (up to) four steady states given by the relation

$$\bar{\boldsymbol{X}}_0 = \Big(0,0,0\Big), \qquad \bar{\boldsymbol{X}} = \left(\frac{m_1}{\mu_f+\mu_b V} - \frac{1}{V}, \quad V, \quad \frac{m_3}{\mu_e}\left(1 - \frac{\mu_f+\mu_b V}{m_1 V}\right)\right),$$

  where V is one of the (up to) three roots of a polynomial of degree three such that $V > \mu_f/(m_1-\mu_b)$.
- Multiple cases are identified for the sign and amount of roots (V) of this polynomial:

$$(-), \quad (+), \quad (-,-), \quad (-,+), \quad (+,+), \quad (-,-,-), \quad (-,-,+), \quad (-,+,+), \quad (+,+,+)$$

- We show there is only one scenario occurring: $(-,+,+)$. This yields three nonnegative steady states: $\bar{\boldsymbol{X}}_0, \bar{\boldsymbol{X}}_{\boldsymbol{u}}, \bar{\boldsymbol{X}}$, of type (stable, unstable, stable), which is ideal for observing jump-discontinuity patterns.

DDI in the model:

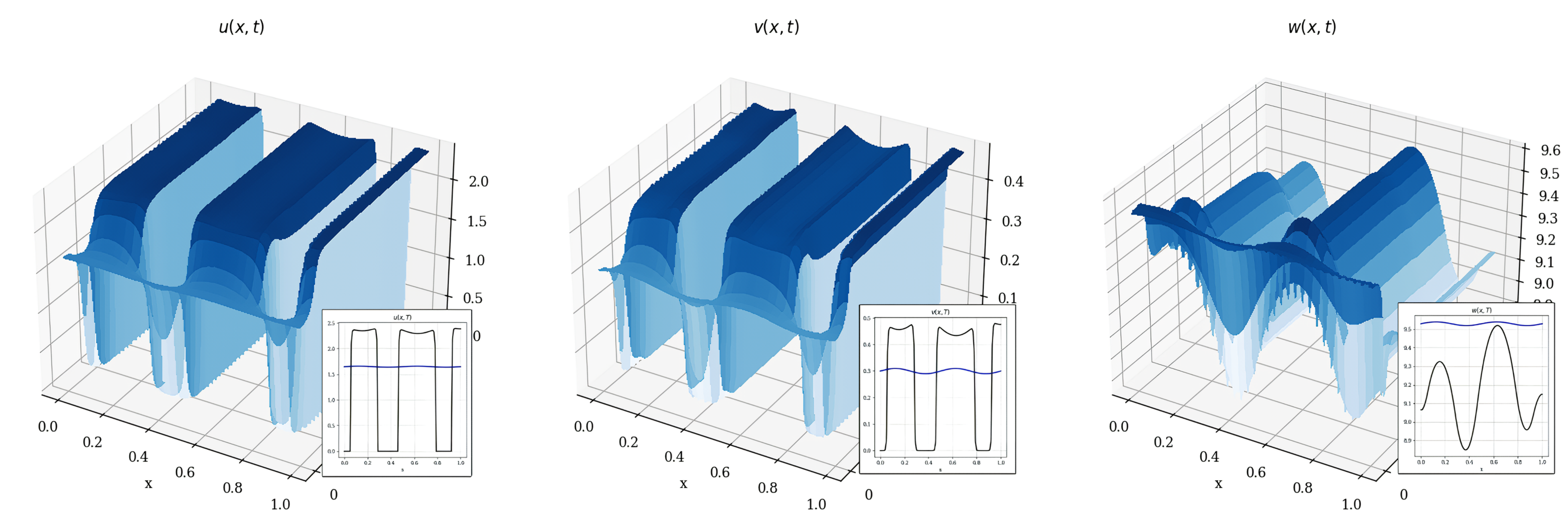
- $\bar{\boldsymbol{X}}_0$, cannot exhibit DDI since it is unconditionally asymptotically stable.
- $\bar{\boldsymbol{X}}_{\boldsymbol{u}}$ cannot exhibit DDI since it is unstable.
- $\bar{\boldsymbol{X}}$ can exhibit DDI (see theorem below), and we identify two cases:
  - $d_1 \geq 0$ sufficiently small and $d_2 > 0$, fixed.
  - $d_1 > 0$, fixed and $d_2 \geq 0$, sufficiently large (either with conditions or unconditionally if L large)

> **Theorem:** Let $\bar{\boldsymbol{X}}$ be a constant, non-zero, positive steady state of the system. Then, $\bar{\boldsymbol{X}}$ can exhibit DDI if and only if
>
> $$\det\left[\nabla_{u,v}\begin{pmatrix} f\\ g\end{pmatrix}(\bar{\boldsymbol{X}})\right] < 0$$

- For a fixed domain $\Omega = (0,L)$, the smallness condition on d_1 is given by

$$d_1 < \frac{L^2}{\pi^2 \nabla_u f(\bar{\boldsymbol{X}})} \det\left[\nabla_{u,v}\begin{pmatrix} f\\ g\end{pmatrix}(\bar{\boldsymbol{X}})\right].$$

Simulations:



Parameters:

$$\mu_f = 0.87, \quad \mu_b = 0.68, \quad \mu_l = 0.05, \quad \mu_e = 0.60, \quad m_1 = 5.36, \quad m_2 = 9.68, \quad m_3 = 17.27,$$
$$d_1 = 0.0001, \qquad d_2 = 0.1.$$

For culture: A well-known condition for DDI is $\nabla_u f(\bar{\boldsymbol{X}}) > 0$, also called *autocatalysis condition*. Unfortunately, all the patterns induced by that condition are unstable and thus impossible to observe in practice. Such case does not occur in our model.

Conclusion and open problems

- We have precise conditions for DDI but DDI is not sufficient for Turing patterns.
- So far we only proved existence of Turing patterns numerically with simulations
  - How do we recognize Turing patterns and distinguish them from other patterns in simulations?
  - How can we prove the existence of Turing patterns analytically?

References

[1] Steffen Härting and Anna Marciniak-Czochra. Spike patterns in a reaction-diffusion-ode model with Turing instability. *arXiv*, March 2013.

[2] Chris Kowall, Anna Marciniak-Czochra, and Finn Münnich. Stability results for bounded stationary solutions of reaction-diffusion-ODE systems, 2022.

[3] Anna Marciniak-Czochra. *Developmental models with cell surface receptor densities defining morphological position.* PhD thesis, Universität Heidelberg, 2004.

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