Stability analysis of a bulk-surface model for membrane protein clustering

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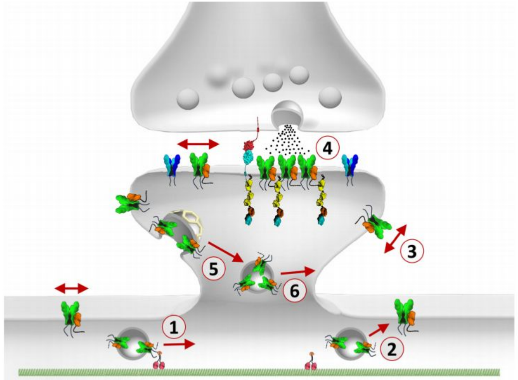
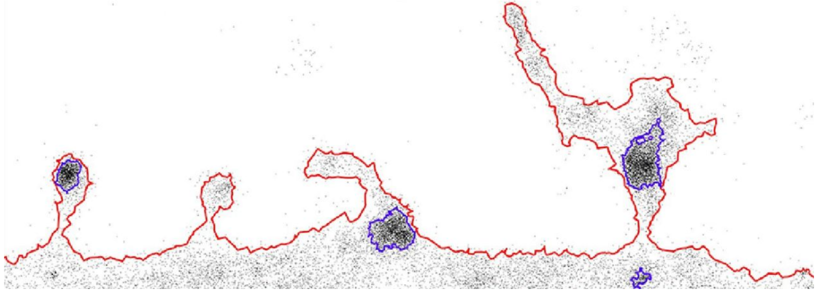
COLMEA 24/09/2020

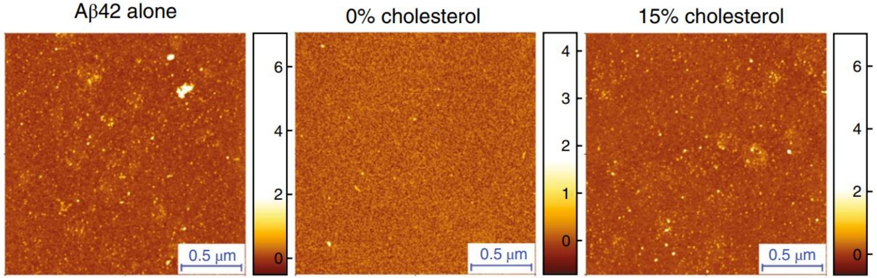
Introduction



AMPAR (D.Choquet, 2018)



FYN (Padmanabhan et at, 2019)



Amyloid - β (Habchi et al, 2018)

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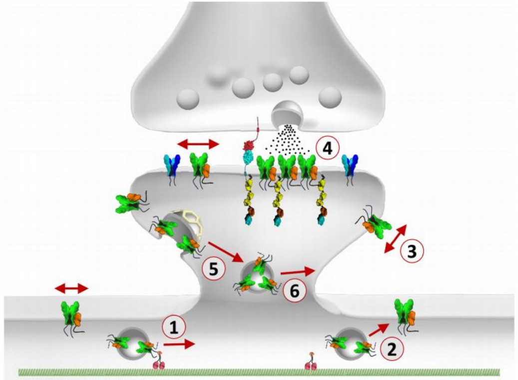

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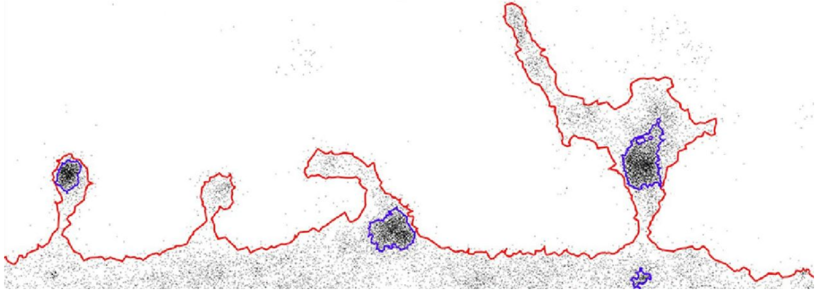

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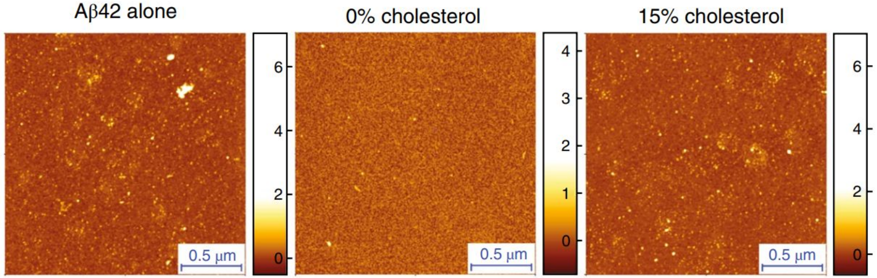

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- **Central Question: What spatial patterns can emerge on the plasma membrane *solely* through <u>protein-protein</u> interaction and <u>diffusion</u>?**

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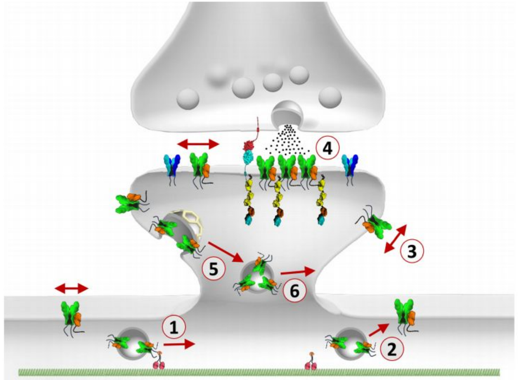

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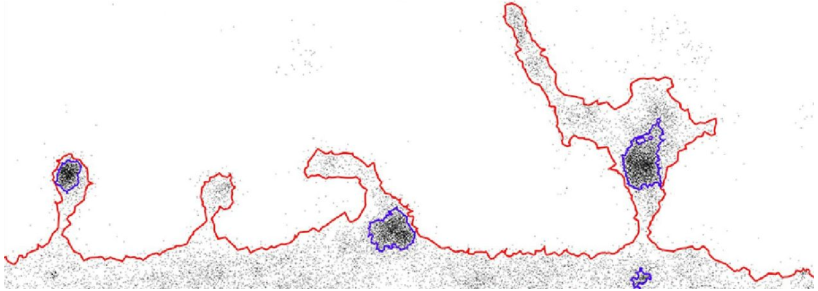

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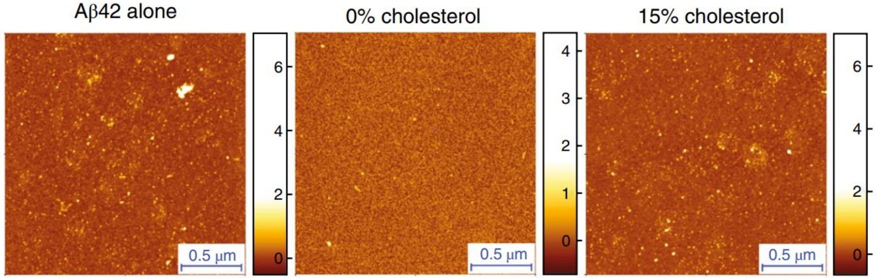
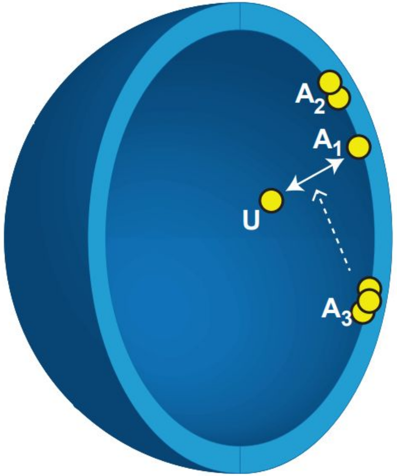


Amyloid - β (Habchi et al, 2018)

- **Central Question: What spatial patterns can emerge on the plasma membrane *solely* through <u>protein-protein</u> interaction and <u>diffusion</u>? What is the simplest mathematical model that exhibits heterogeneous protein distribution?**

Model Assumptions

- $\mathbf{U}$ volume component



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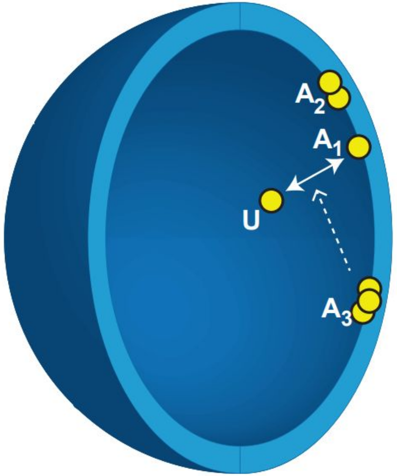
- $\mathbf{U}$ volume component
- $\mathbf{A}_j$ membrane oligomer of size j $\quad j = 1, 2, \cdots, N$



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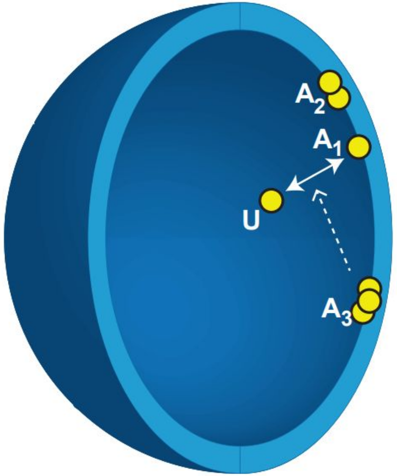

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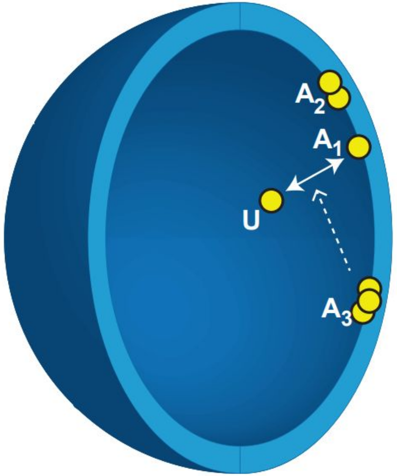

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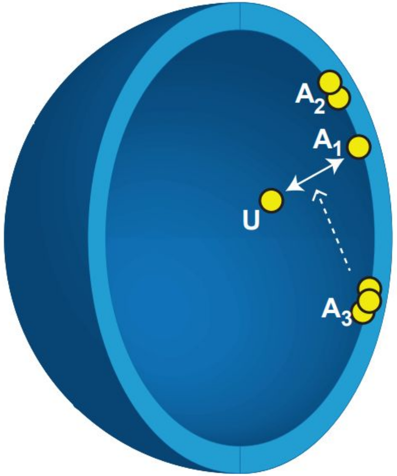

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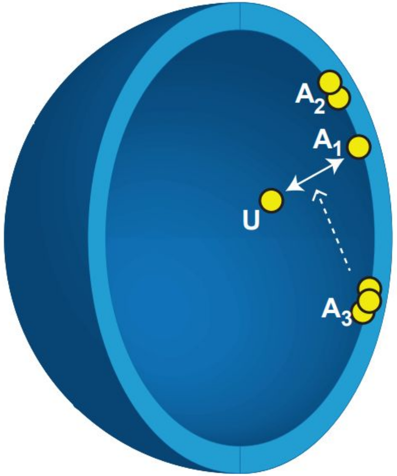
- Ω bounded region (cellular domain) with smooth boundary $\Gamma = \partial\Omega$
- Concentration variables: $u(x,t) : \Omega \times (0, \mathcal{T}] \to \mathbb{R}$ (mol/μm^3)

  $a_j(x,t) : \Gamma \times (0, \mathcal{T}] \to \mathbb{R}$ (mol/μm^2)

Governing Equations



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$$\partial_t u = D_u \nabla^2 u$$

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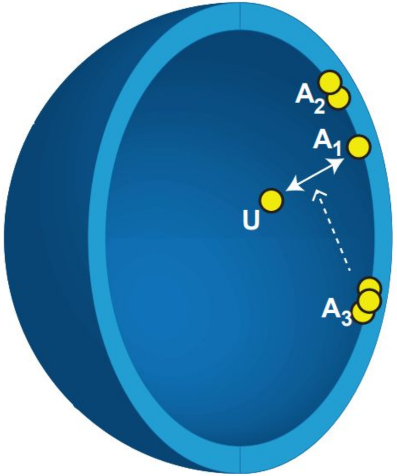

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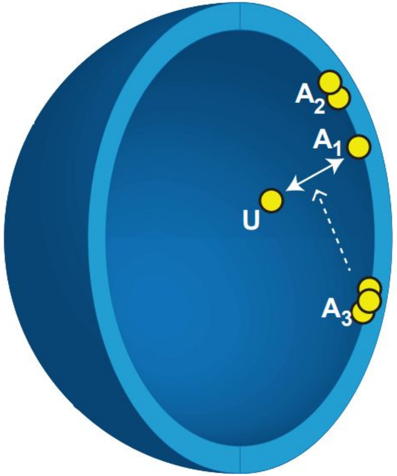
$$\partial_t u = D_u \nabla^2 u$$

$$-D_u (\mathbf{n} \cdot \nabla u) = f(u, a_1, a_N) \qquad (\mathbf{U} \xrightleftharpoons{f} \mathbf{A}_1)$$

$$\boxed{= (k_0 + k_b a_N) u - k_d a_1}$$

Governing Equations



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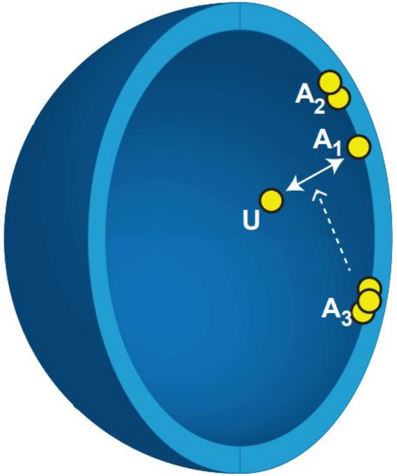
- On the Membrane:

boundary flux

$$\partial_t a_1 = D_1 \Delta a_1 + (k_0 + k_b a_N) u - k_d a_1$$

Governing Equations



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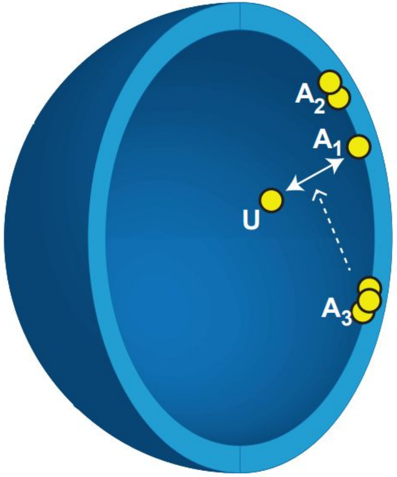
- On the Membrane:

boundary flux **dimerization**

$$\partial_t a_1 = D_1 \Delta a_1 + (k_0 + k_b a_N)u - k_d a_1 - 2k_m a_1^2 + 2k_2 a_2$$

Governing Equations



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boundary flux | dimerization | oligomerization

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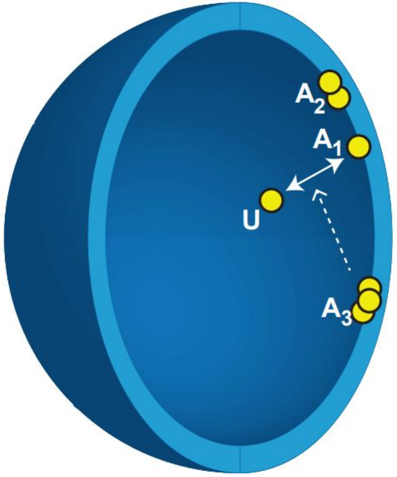

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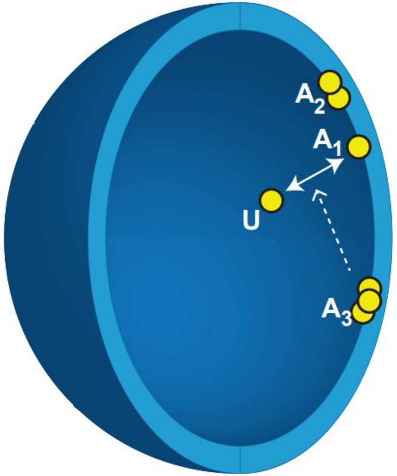
Governing Equations



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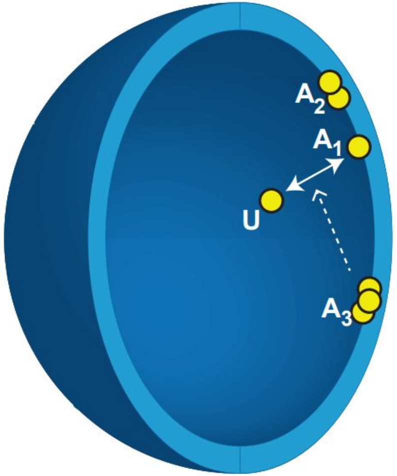

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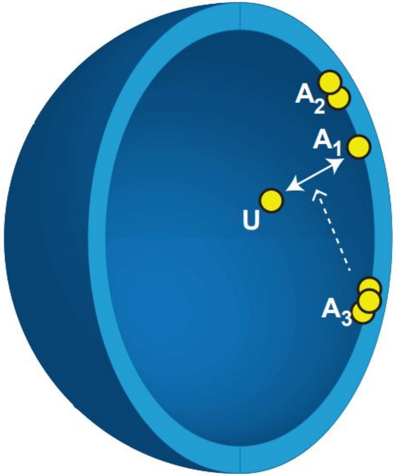

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linearization about u*

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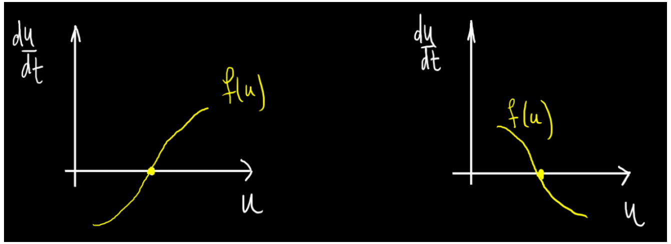

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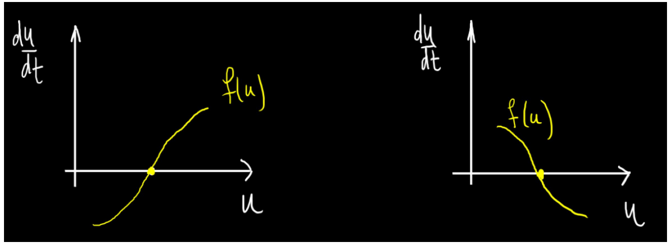

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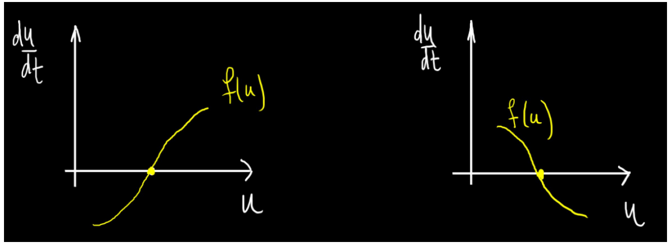

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(Hartman & Grobman)

$$\frac{d\,\delta\mathbf{u}}{dt} = \mathcal{J}(\mathbf{u}^*)\,\delta\mathbf{u}$$

$$\mathcal{J}(\mathbf{u}^*) = \begin{bmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_1}{\partial u_2} & \cdots & \frac{\partial f_1}{\partial u_N} \\ \frac{\partial f_2}{\partial u_1} & \frac{\partial f_2}{\partial u_2} & \cdots & \frac{\partial f_2}{\partial u_N} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_N}{\partial u_1} & \frac{\partial f_N}{\partial u_2} & \cdots & \frac{\partial f_N}{\partial u_N} \end{bmatrix}_{|\mathbf{u}=\mathbf{u}^*}$$

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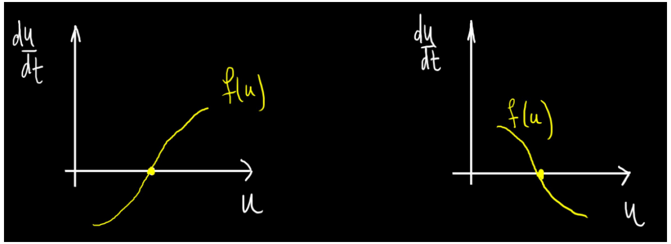

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linearization about u*

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(Hartman & Grobman)

$$\frac{d\delta\mathbf{u}}{dt} = \mathcal{J}(\mathbf{u}^*)\,\delta\mathbf{u} \qquad \max(\Re(\lambda)) \begin{cases} > 0 & \text{unstable} \\ < 0 & \text{locally stable} \end{cases}$$

$$\mathcal{J}(\mathbf{u}^*) = \begin{bmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_1}{\partial u_2} & \cdots & \frac{\partial f_1}{\partial u_N} \\ \frac{\partial f_2}{\partial u_1} & \frac{\partial f_2}{\partial u_2} & \cdots & \frac{\partial f_2}{\partial u_N} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_N}{\partial u_1} & \frac{\partial f_N}{\partial u_2} & \cdots & \frac{\partial f_N}{\partial u_N} \end{bmatrix}_{|\mathbf{u}=\mathbf{u}^*}$$

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- Reaction-diffusion systems

$$\frac{\partial u}{\partial t} = \underbrace{D_u \nabla^2 u}_{\text{diffusion}} + \underbrace{f_1(u, v)}_{\text{reaction}}$$

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$$\frac{\partial u}{\partial t} = \nabla^2 u + \gamma f_1(u,v)$$

$$\frac{\partial v}{\partial t} = d\nabla^2 v + \gamma f_2(u,v) \qquad d = \frac{D_v}{D_u}$$

Non-dimensional form

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diffusion reaction

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Non-dimensional form

Steady-states

$$\nabla^2 u + \gamma f_1(u,v) = 0$$

$$d\nabla^2 v + \gamma f_2(u,v) = 0$$

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Non-dimensional form

Steady-states

$$\nabla^2 u + \gamma f_1(u,v) = 0$$

$$d\nabla^2 v + \gamma f_2(u,v) = 0$$

$$u^*, v^* \in \mathbb{R} \quad \text{s.t}$$

$$f_1(u^*, v^*) = 0, \quad f_2(u^*, v^*) = 0$$

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- Reaction-diffusion systems

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Non-dimensional form

Steady-states

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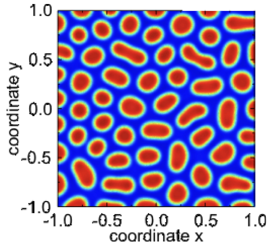
Revision: Local Stability Analysis



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Turing Instability if

→ locally stable (ODE system)

→ Linearly unstable

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Jacobian matrix
of the ODE system

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Look for solutions in the form

$$\mathbf{w} = \sum_{l=0}^{\infty} \mathcal{A}_l(t)\omega_l \quad \text{where} \quad \nabla^2 \omega_l = -\eta_l \omega_l \quad \text{and} \quad 0 = \eta_0 < \eta_1 \le \eta_2 \le ...$$

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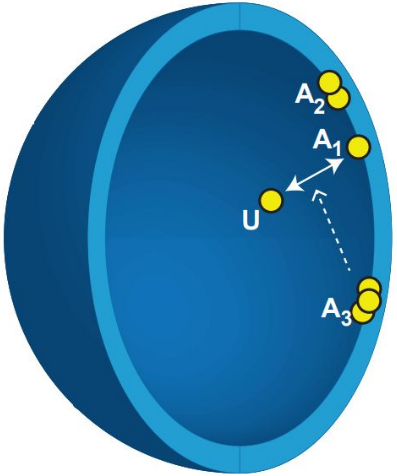
$$h(l) := \underbrace{\max(\Re(\lambda(\eta_l)))}_{\text{Dispersion relation}} \begin{cases} > 0 & \text{unstable} \\ < 0 & \text{locally stable} \end{cases}$$

Governing Equations



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$$(\mathbf{U} \overset{f}{\rightleftharpoons} \mathbf{A}_1)$$

- On the Membrane:

boundary flux | dimerization | oligomerization

$$\partial_t a_1 = D_1 \Delta a_1 + (k_0 + k_b a_N) u - k_d a_1 - 2k_m a_1^2 + 2k_2 a_2 - k_g a_1 \left(\sum_{l=2}^{N-1} a_l \right) + \sum_{j=3}^{N} k_j a_j$$

$$\partial_t a_2 = D_2 \Delta a_1 + k_m a_1^2 - k_g a_1 a_2 - k_2 a_2 + k_3 a_3$$

$$\partial_t a_j = D_j \Delta a_j + k_g a_1 a_{j-1} - k_g a_1 a_j - k_j a_j + k_{j+1} a_{j+1}, \quad j = 3, \ldots, N-1$$

$$\partial_t a_N = D_N \Delta a_N + k_g a_1 a_{N-1} - k_N a_N$$

Model Reduction

- Mass conservation: $M(t) := \int_\Omega u(x,t)dx + \sum_{j=1}^{N} \left\{ j \cdot \int_\Gamma a_j(x,t)ds \right\}$

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- Reduced surface system:

$$\partial_t a_1 = \Delta a_1 + \gamma \left\{ (k_0 + k_b a_N) \mathcal{U}[a_1, a_2, ..., a_N] - a_1 - 2k_m a_1^2 + 2k_2 a_2 - k_g a_1 \left(\sum_{l=2}^{N-1} a_j \right) + \sum_{j=3}^{N} k_j a_j \right\},$$

$$\partial_t a_2 = d_2 \Delta a_2 + \gamma \left(k_m a_1^2 - k_2 a_2 - k_g a_1 a_2 + k_2 a_3 \right),$$

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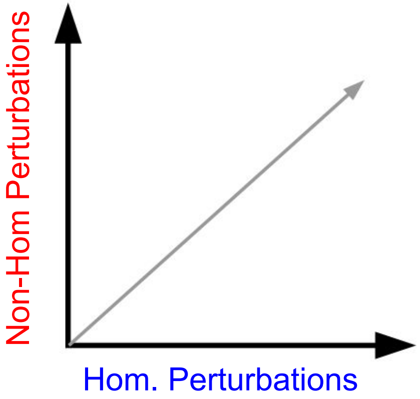
Stability Analysis



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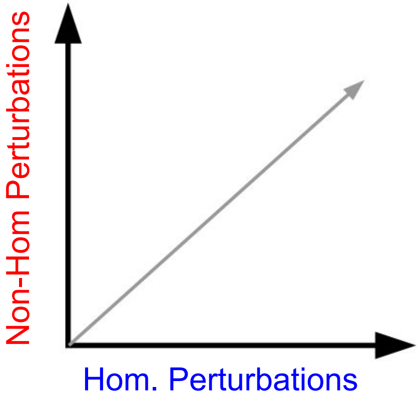

$$a_j = a_j^* + \delta_j(t)$$

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Stability Analysis

$$a_{s,j} = a_j^* + s\,\varphi_j(x,t)$$

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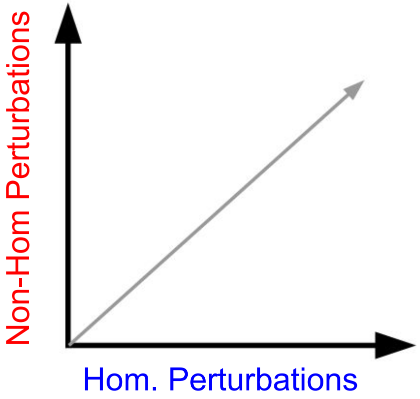

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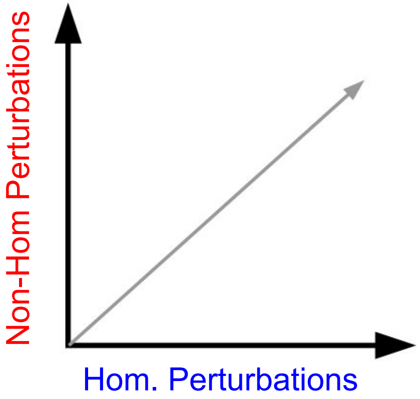

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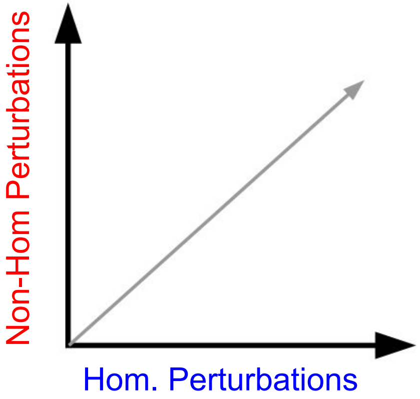

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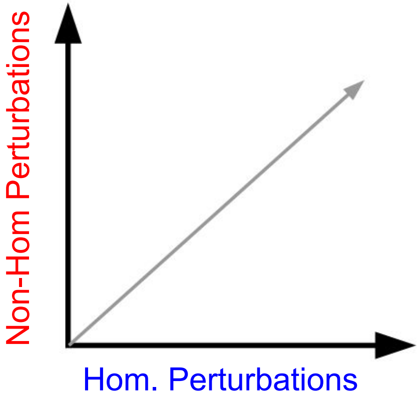

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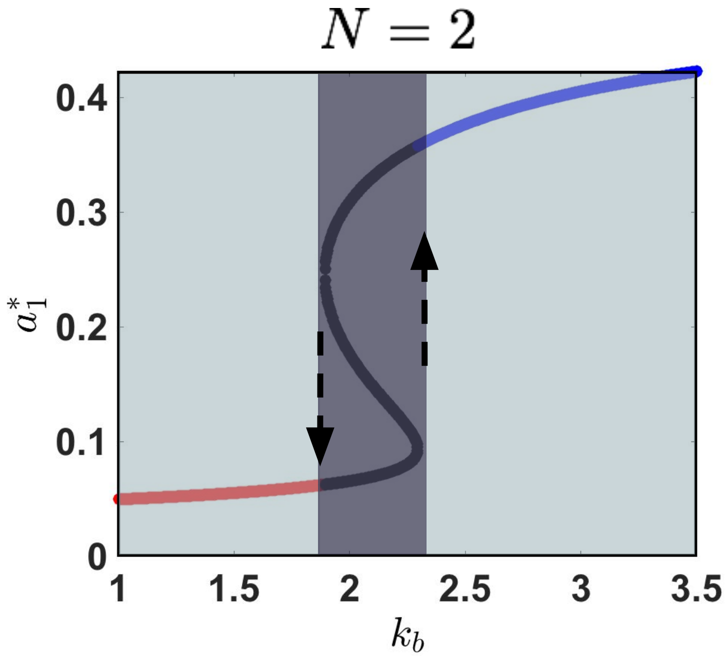
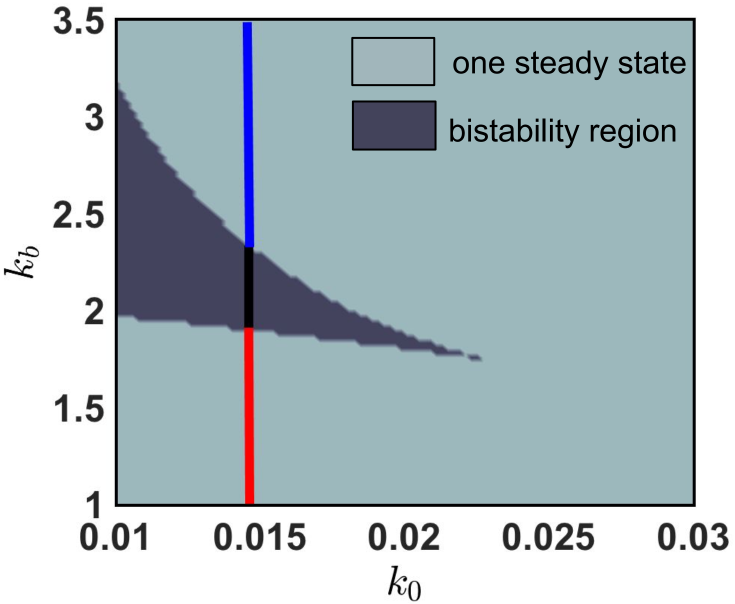
Theorem: Assume kb *small*. Then there is a unique steady state and no-diffusion driven instabilities $k_b \le \frac{2}{\mathcal{M}_0} \min\left\{ k_0 |\Gamma|, \frac{d_2 \eta_i |\Omega|}{\gamma} \right\}$

Homogeneous Perturbations and Bistability



(Feedback rate)

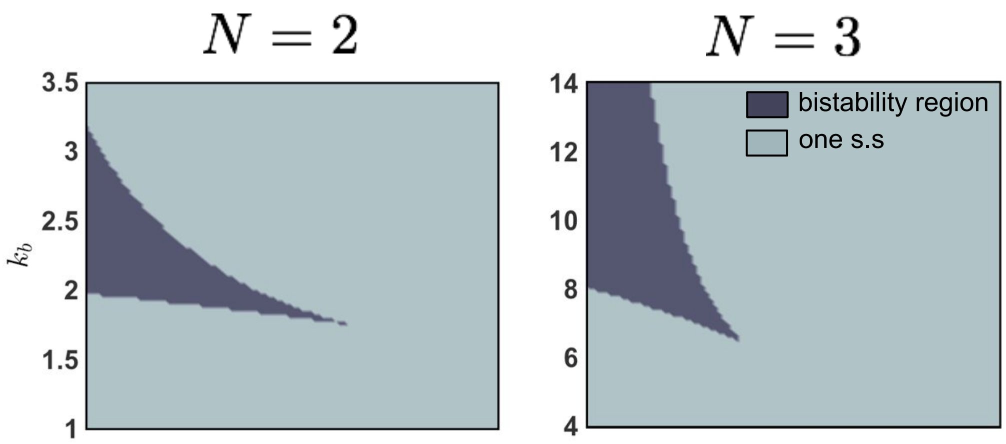


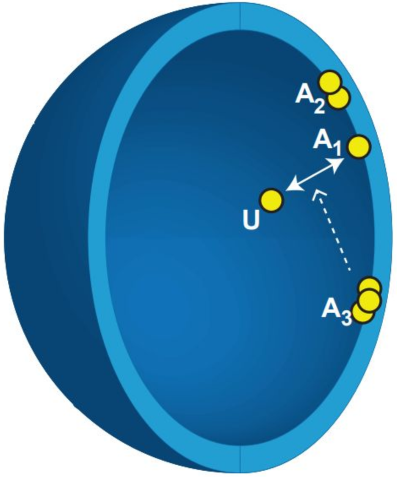
(Feedback rate)

(basal rate of monomer influx)

Parameter regions of Instability

Hom.
Perturbations

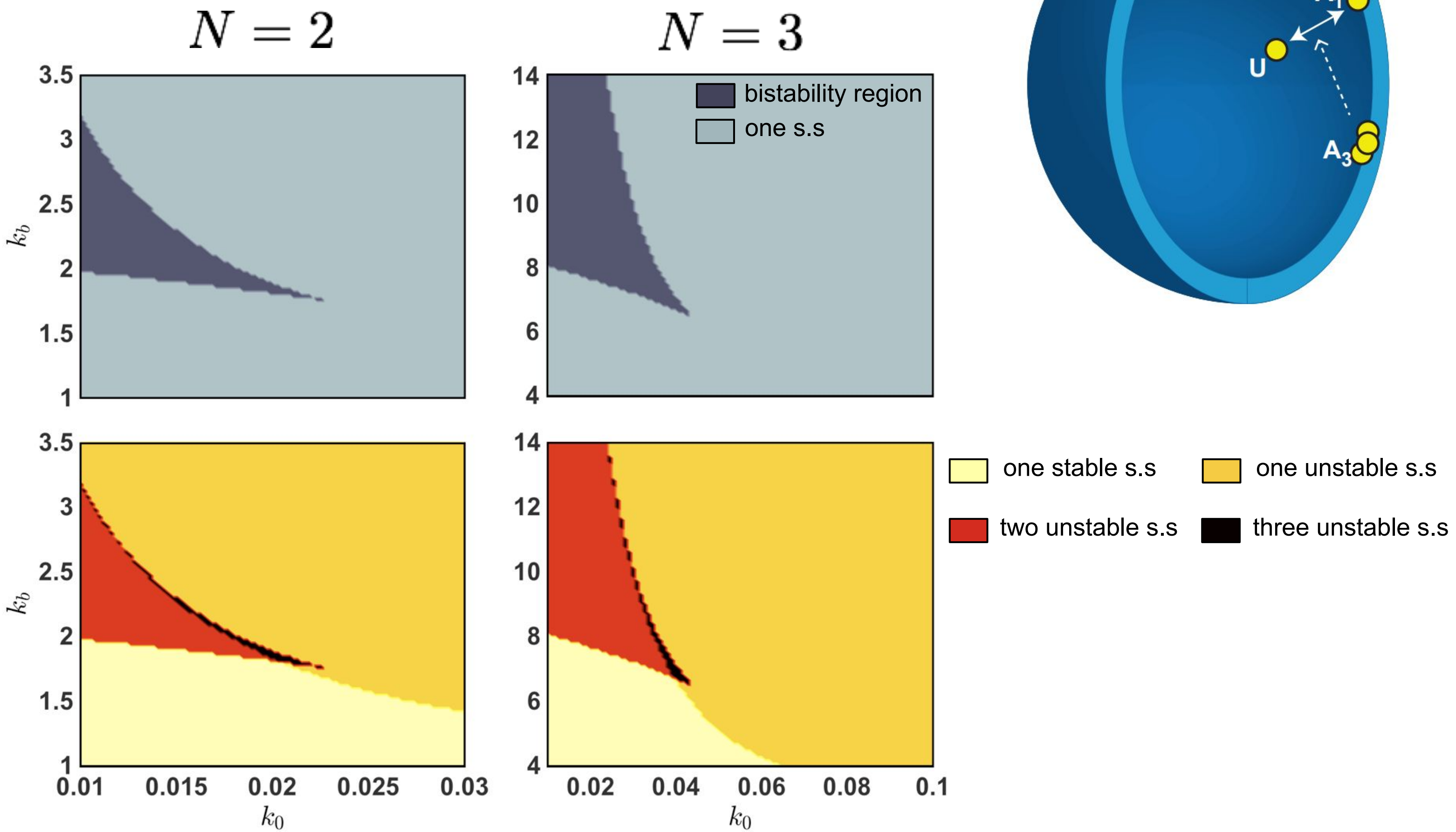




Parameter regions of Instability

Hom.
Perturbations

Non-Hom
Perturbations



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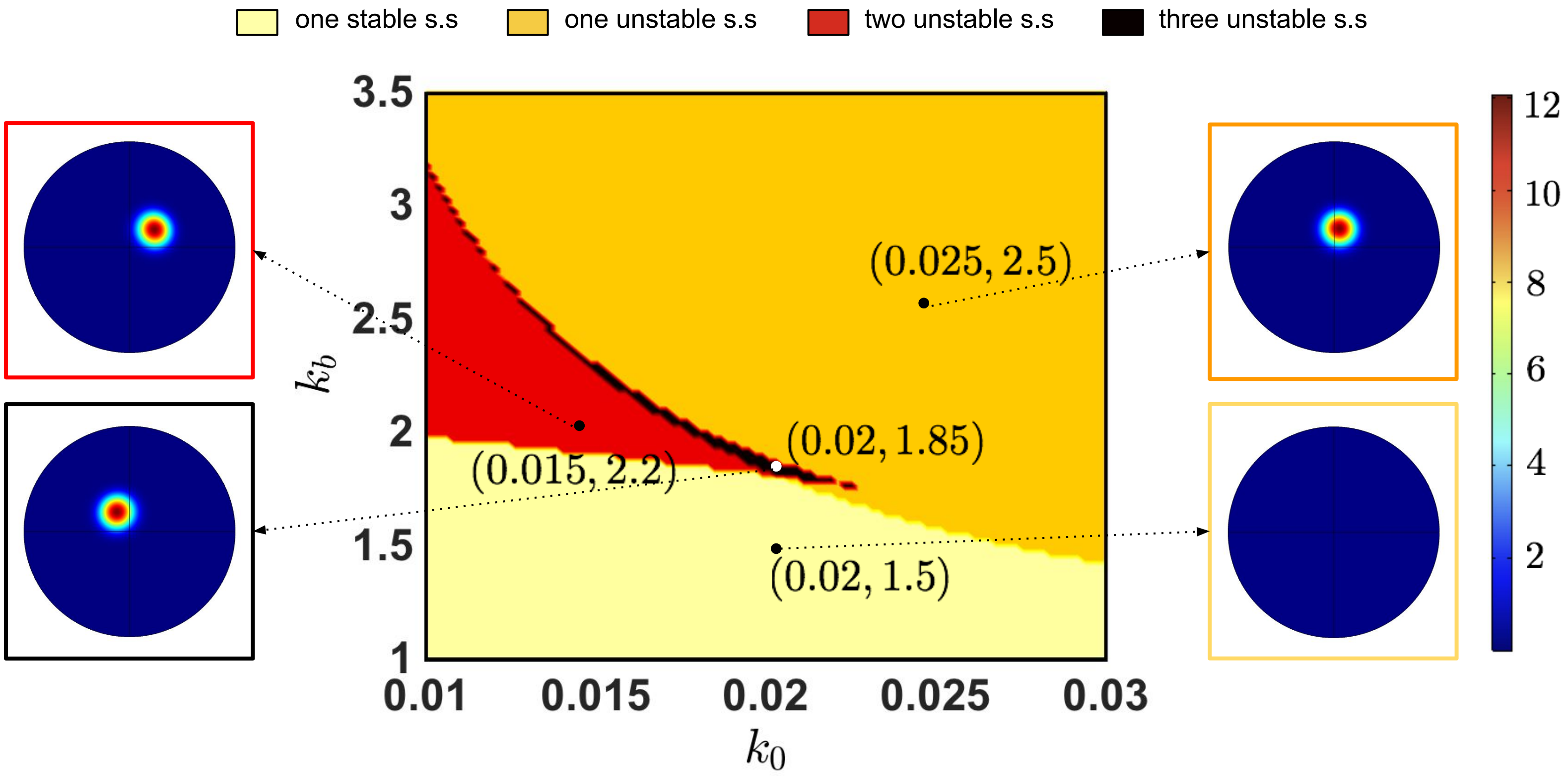
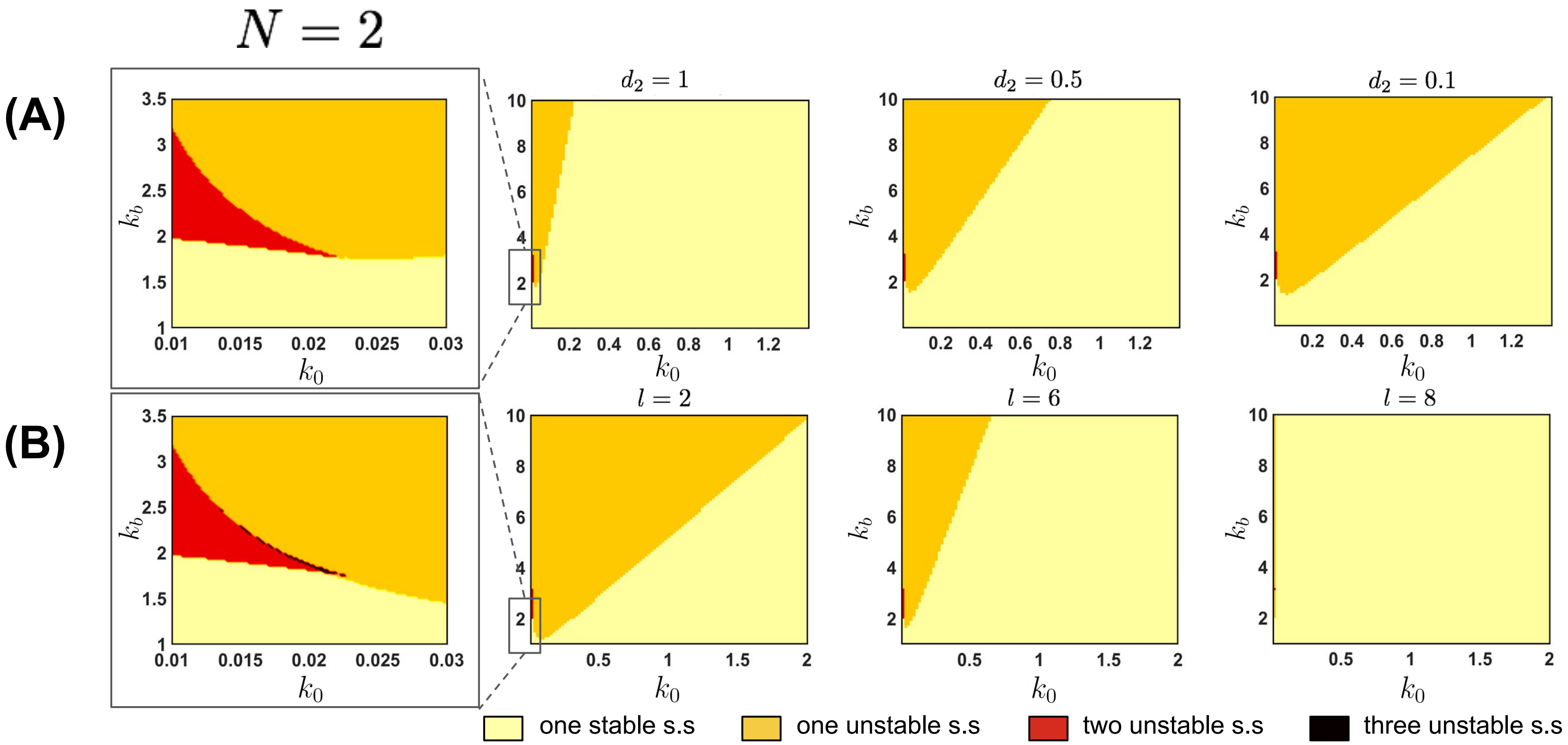
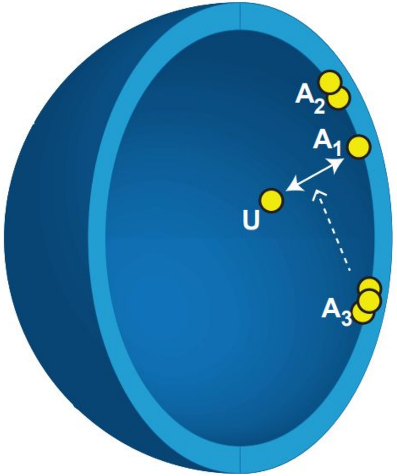


Stability Analysis: Numerical predictions



Governing Equations



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boundary flux — dimerization

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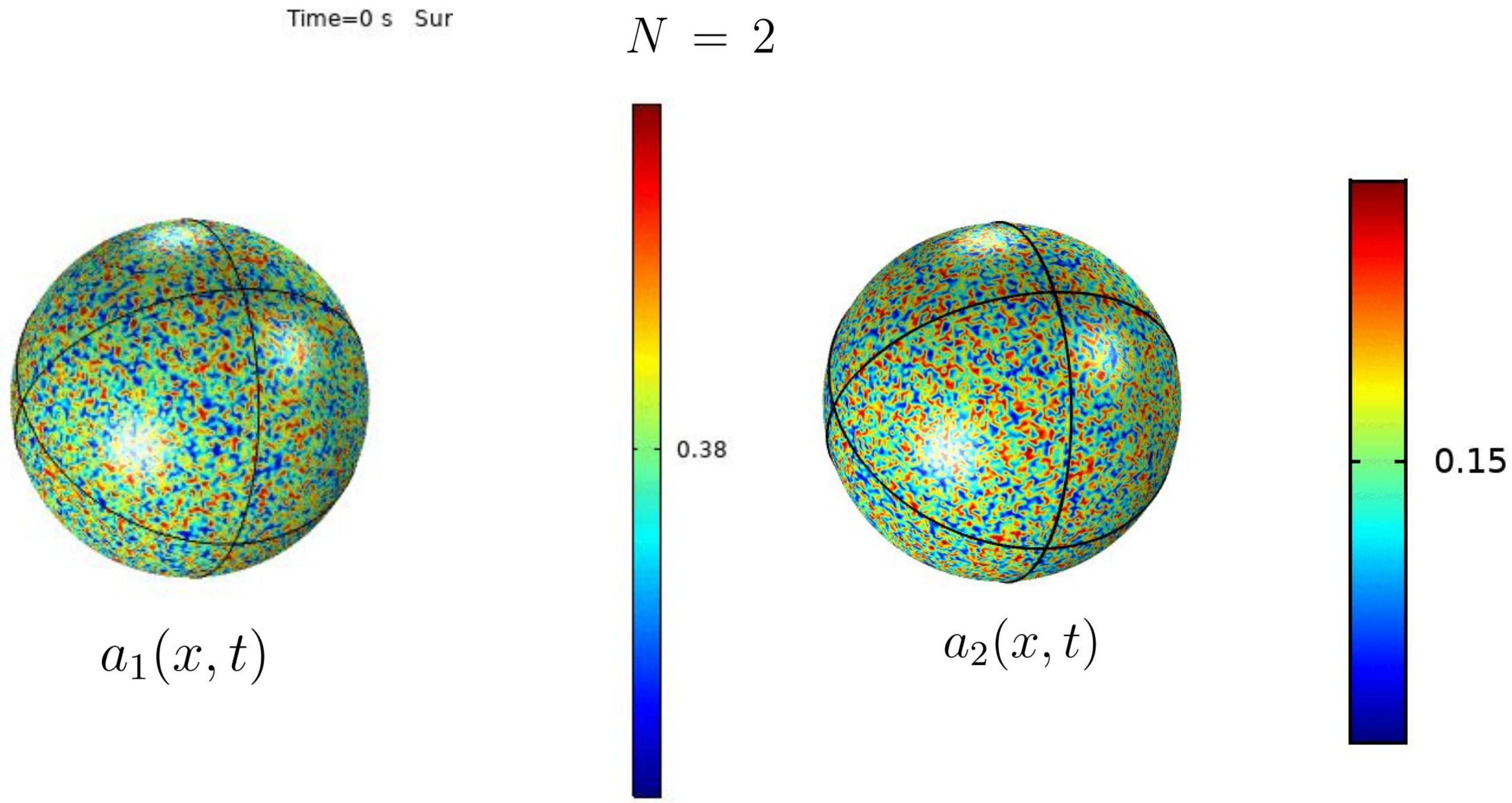

Time=0 s Sur
$N = 2$
0.38
0.15
$a_1(x,t)$
$a_2(x,t)$

Parameter regions of Instability

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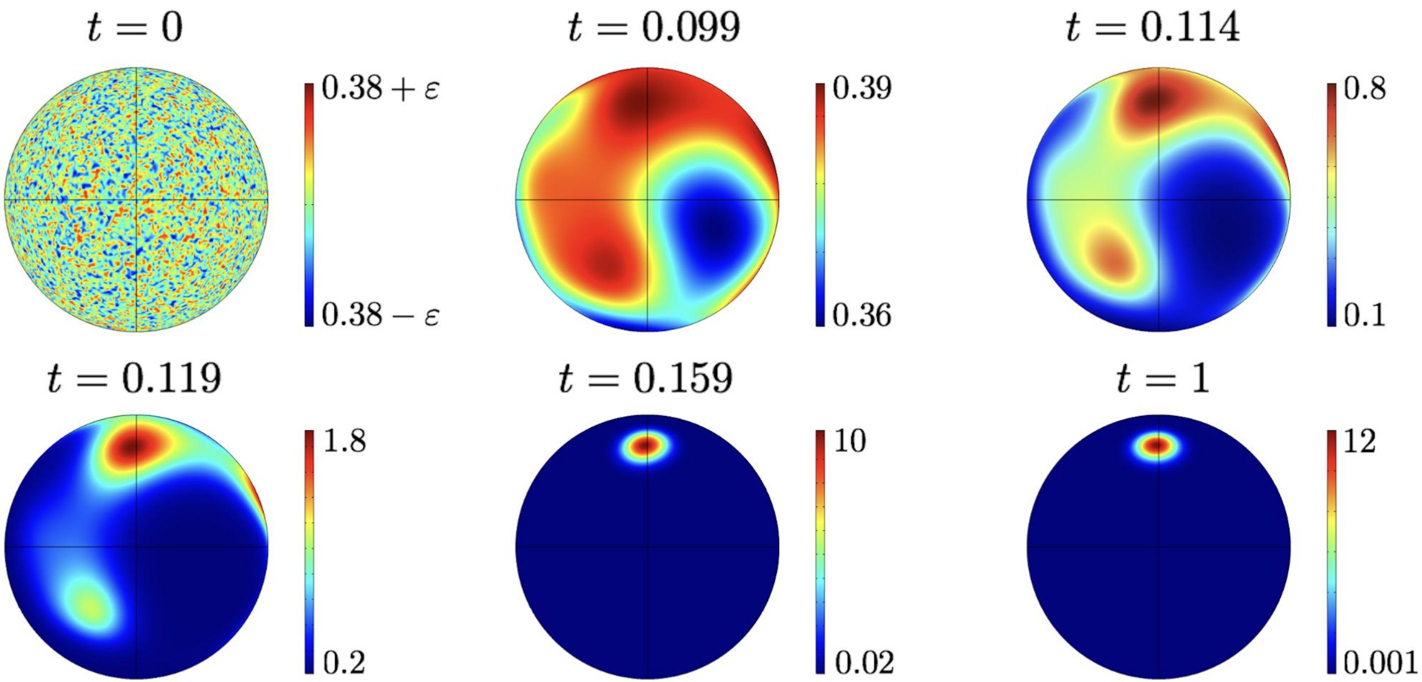
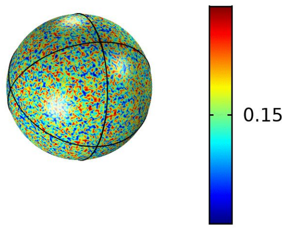
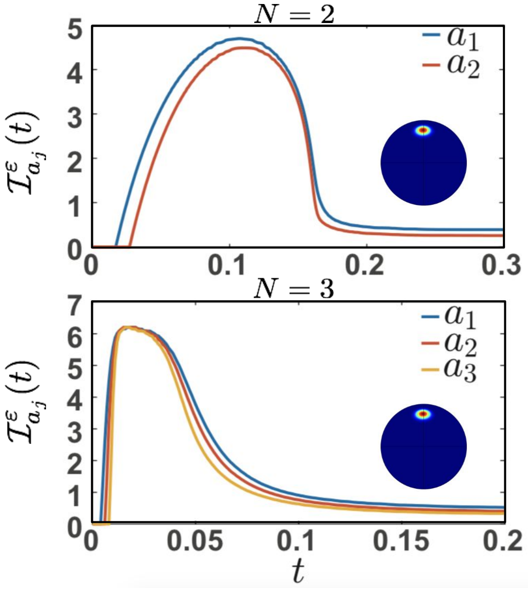
$$= (k_0 + k_b a_N)u - k_d a_1$$

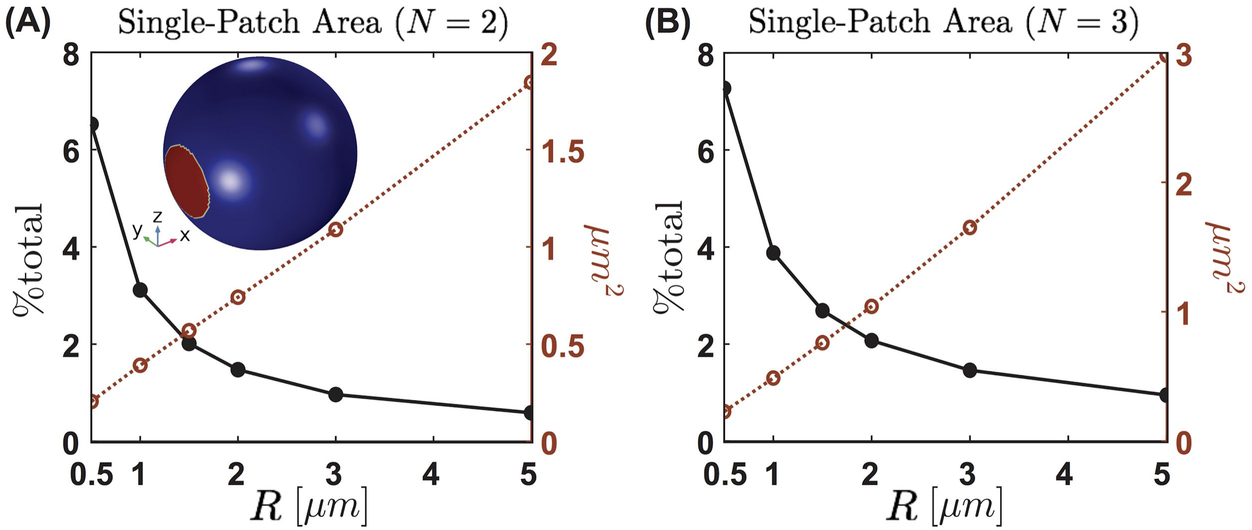


Analysis of the patch area



$$\mathcal{I}_j^{\varepsilon}(t) = \int_{\Gamma} \mathbb{1}_{\{a_j(x,t) > \langle a_j \rangle(t) + \varepsilon\}} ds$$





Conclusions

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- Under homogeneous perturbations, bistability is promoted by a combination of mass conservation and positive feedback.

- Feedback rate (kb) must be strong enough to promote a diffusion driven instability. If the rate is low, then the system converges back to the spatially homogeneous steady-state (theorem for N=2, conjecture for N>2)

Conclusions

- Bulk-surface model for protein aggregation with a positive feedback exhibits a spatial heterogeneous single-patch steady-states.

- Under homogeneous perturbations, bistability is promoted by a combination of mass conservation and positive feedback.

- Feedback rate (kb) must be strong enough to promote a diffusion driven instability. If the rate is low, then the system converges back to the spatially homogeneous steady-state (theorem for N=2, conjecture for N>2)

- The single-patch steady-states consistently appears for a range of parameter regions of instability. A rich gets richer mechanism seems to explain that fact.

References

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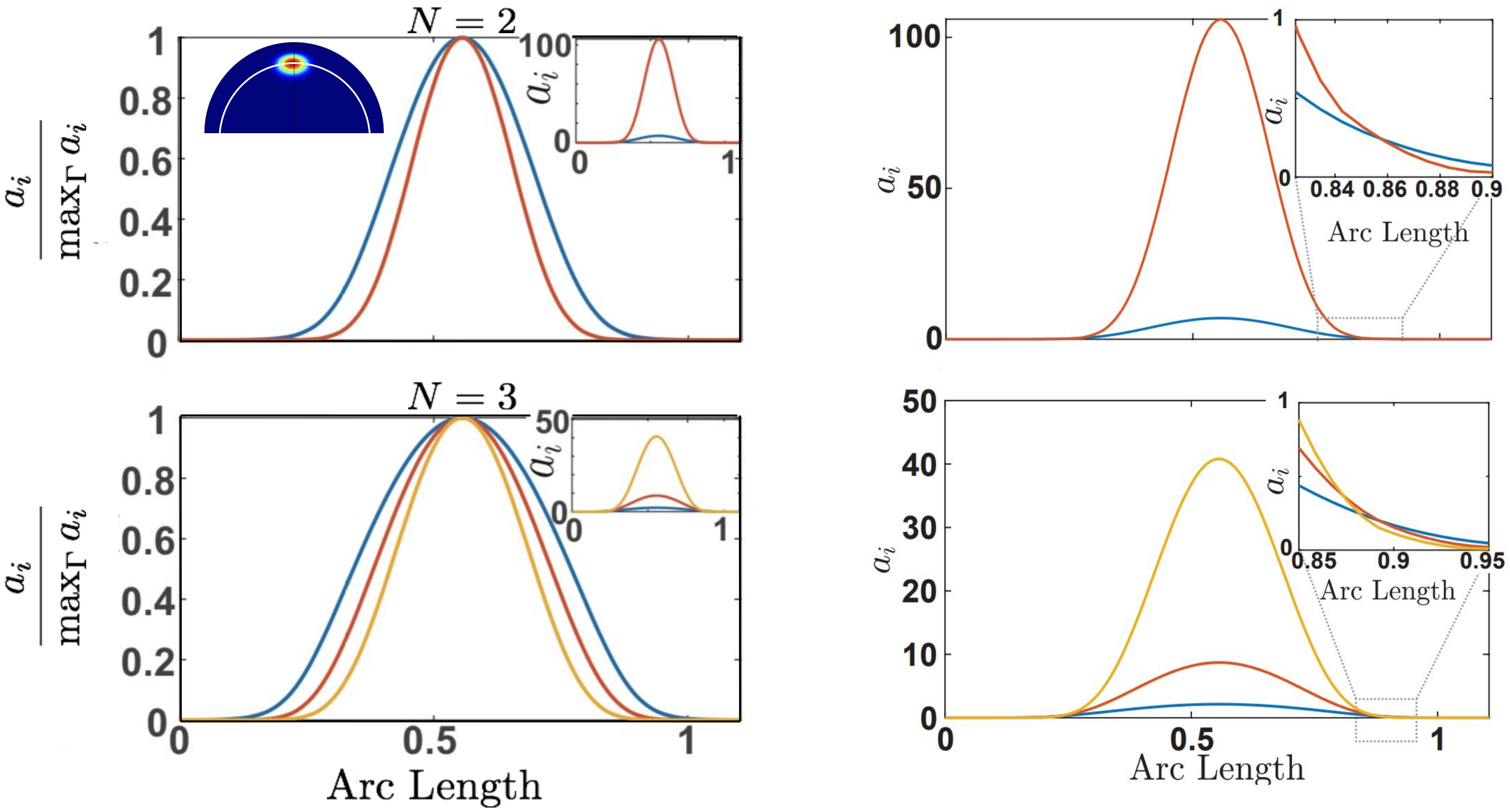
Backup slides

Stability Analysis: Numerical Integration



Stability analysis

$$\partial_t a_1 = \Delta a_1 + \gamma \left\{ \frac{(k_0 + k_b a_2)}{|\Omega|} \left[\mathcal{M}_0 - \int_\Gamma (a_1 + 2a_2)\, ds \right] - a_1 - 2k_m a_1^2 + 2k_2 a_2 \right\}$$

$$\partial_t a_2 = d_2 \Delta a_2 + \gamma \left\{ k_m a_1^2 - k_2 a_2 \right\}$$

- Theorem: $k_b \leq \frac{2}{\mathcal{M}_0} \min \left\{ k_0 |\Gamma|, \frac{d_2 \eta_i |\Omega|}{\gamma} \right\}$ $\Rightarrow$ 1) Unique steady-state 2) No diffusion-driven instability

Steady-state analysis

$$\frac{\partial a_1}{\partial t} = \Delta a_1 + \gamma \mathcal{F}_1(a_1, a_2 \ldots, a_N) \qquad \frac{\partial a_j}{\partial t} = d_j \Delta a_j + \gamma \mathcal{F}_j(a_1, a_2 \ldots, a_N), \;\; j = 2, \ldots, N$$

- Spatially Homogeneous Steady-states: $\mathbf{a}^* = (a_1^*, a_2^*, a_3^*, \ldots, a_N^*)$ s.t $\mathcal{F}_j(\mathbf{a}^*) = 0$

$$\mathcal{F}_j(\mathbf{a}^*) = 0 \longrightarrow a_j^* = C_j (a_1^*)^j$$

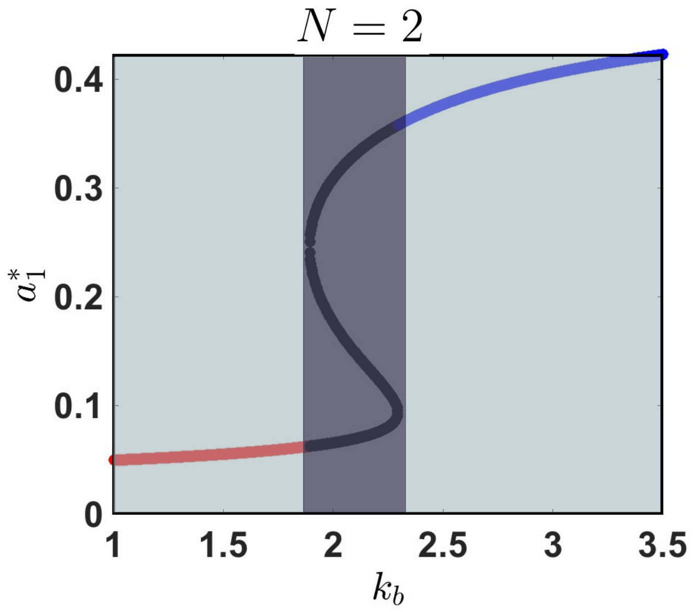
$$\mathcal{F}_1(\mathbf{a}^*) = 0 \longrightarrow \mathcal{P}_N(a_1^*) = 0$$

$$\mathcal{P}_N(a_1^*) = -k_0 \mathcal{M}_0 + (|\Omega| + k_0|\Gamma|)\, a_1^* + k_0|\Gamma| \left[\sum_{j=2}^{N-1} j C_j (a_1^*)^j\right]$$

$$+ \boxed{C_N\, (k_0|\Gamma|N - \mathcal{M}_0 k_b)\, (a_1^*)^N} + k_b|\Gamma| C_N \left[\sum_{j=1}^{N} j C_j (a_1^*)^{N+j}\right]$$

≥ 0 ➡ 1 steady-state

< 0 ➡ ???



Stability Analysis: Overview

$$\partial_t a_1 = \Delta a_1 + \gamma \left\{ (k_0 + k_b a_N)\mathcal{U}[a_1, a_2, ..., a_N] - a_1 - 2k_m a_1^2 + 2k_2 a_2 - k_g a_1 \left(\sum_{l=2}^{N-1} a_j \right) + \sum_{j=3}^{N} k_j a_j \right\},$$

$$\partial_t a_2 = d_2 \Delta a_2 + \gamma \left(k_m a_1^2 - k_2 a_2 - k_g a_1 a_2 + k_2 a_3 \right),$$

$$\partial_t a_j = d_j \Delta a_j + \gamma \left(k_g a_1 a_{j-1} - k_j a_j - k_g a_1 a_j + k_{j+1} a_{j+1} \right), \quad j = 3, \ldots, N$$

$$\partial_t a_N = d_N \Delta a_N + \gamma \left(k_g a_1 a_{N-1} - k_N a_N \right)$$

$$\mathcal{U}[a_1, a_2, ..., a_N](t) := \frac{1}{|\Omega|} \left[M_0 - \sum_{j=1}^{N} \left\{ j \cdot \int_\Gamma a_j ds \right\} \right]$$

- Homogeneous Perturbations:

$$a_j = a_j^* + \delta_j(t) \longrightarrow \frac{da_j}{dt} = \gamma \mathcal{F}_j(a_1, a_2 \ldots, a_N) \longrightarrow \mathcal{J}[\mathbf{a}^*] = \gamma \left[\frac{\partial \mathcal{F}_j^*}{\partial a_i} \right]_{1 \le i,j \le N}$$

- Arbitrary Perturbations:

$$a_{s,j} = a_j^* + s\, \varphi_j(x,t) \longrightarrow \left. \frac{d}{ds} \right|_{s=0} \mathcal{U}[\mathbf{a}_s] = -\sum_{j=1}^{N} \int_\Gamma \varphi_j ds = 0$$

$$\int_\Gamma \varphi_j ds = 0$$

Different linearization!!!

Stability Analysis: Overview (cont.)

- In vector notation, $\partial_t \Phi = \mathbf{D} \Delta \Phi + \tilde{\mathcal{J}}(\mathbf{a}^*)\Phi$, $\mathbf{D}_{jj} = d_j$
- $-\Delta \omega_l = \eta_l \omega_l$ Eigenmodes where $0 = \eta_0 < \eta_1 \leq \eta_2 \leq \ldots$
- $\Phi = \mathcal{A}_0\, \omega_0 + \sum_{l \in \mathbb{N}} \mathcal{A}_i\, \omega_l(x)$ ⟶ $\frac{d\mathcal{A}_l}{dt} = \left[-\eta_l \mathbf{D} + \gamma \tilde{\mathcal{J}}(\mathbf{a}^*)\right] \mathcal{A}_l$

  $l = 0, 1, 2, \ldots$
- Dispersion relation $h(l) := \max\left(\mathrm{Re}(\lambda(\eta_l))\right) > 0$ ⟶ Diffusion-driven Instability

Our model: properties and reduction

- Mass conservation: $M(t) := \int_\Omega u(x,t)dx + \sum_{j=1}^{N} \left\{ j \cdot \int_\Gamma a_j(x,t)ds \right\}$ const.
- Non-local functional:
  $D_u \to \infty \quad u(x,0) = u_0$ ⟶ $$\mathcal{U}[a_1, a_2, ..., a_N](t) := \frac{1}{|\Omega|}\left[M_0 - \sum_{j=1}^{N}\left\{ j \cdot \int_\Gamma a_j ds \right\}\right]$$
- Non-dimensional reduced system:

$$\partial_t a_1 = \Delta a_1 + \gamma\left\{ (k_0 + k_b a_N)\mathcal{U}[a_1, a_2, ..., a_N] - a_1 - 2k_m a_1^2 + 2k_2 a_2 - k_g a_1 \left(\sum_{l=2}^{N-1} a_j\right) + \sum_{j=3}^{N} k_j a_j \right\},$$

$$\partial_t a_2 = d_2 \Delta a_2 + \gamma\left(k_m a_1^2 - k_2 a_2 - k_g a_1 a_2 + k_2 a_3\right),$$

$$\partial_t a_j = d_j \Delta a_j + \gamma\left(k_g a_1 a_{j-1} - k_j a_j - k_g a_1 a_j + k_{j+1} a_{j+1}\right), \quad j = 3, \ldots, N$$

$$\partial_t a_N = d_N \Delta a_N + \gamma\left(k_g a_1 a_{N-1} - k_N a_N\right)$$

$$\gamma = \frac{k_d R^2}{D_1}$$