Quorum-Sensing and Diffusion-Mediated Communication for a Cell-Bulk ODE-PDE Model

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SIAM Dynamical Systems May 2021

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Active Cells Coupled by Diffusion

Formulate and analyze a model of (ODE) dynamically active small "cells", with arbitrary intracellular kinetics, that are coupled spatially by a linear bulk-diffusion field (PDE) "autoinducer" (AI) in a bounded 2-D domain Ω.
Collective behavior in "cells" due by diffusive chemical signalling

- Collections of unicellular (eukaryotic) organisms such as starving yeast cells (glycolysis) coupled only by extracellular signalling molecules (AI is Acetaldehyde). **Ref:** De Monte et al., PNAS **104**(47), (2007).
- Amoeba colonies (Dicty) in low nutrient enviroments, with cAMP organizing the aggregation of starving colonies; **Ref:** Nanjundiah, Bio. Chem. **72**, (1998), Gregor et al. Science, **328**, (2010).
- Catalyst bead particles (BZ particles) interacting through a chemical diffusion field; **Ref:** Tinsley, Showalter, et al. ".. Collections of Excitable and Oscillatory Cataytic Particles", Physica D **239** (2010).
- Bioluminescence for the marine bacterium *Vibrio fischeri* in tropical squids, and the human pathogen *Pseudomonas aeruginosa*, where an increase in the cell density leads to a sudden emergence of "collective" behavior (Bassler, Dockery-Keener). The AI in Gram-negative Proteobacteria is N-acylated L-homoserine lactones (AHLs).

QS and Diffusion-Induced Behavior

Quorum sensing: collective behavior triggered as the cell population exceeds a threshold. (Usually studied in the well-mixed limit)

Diffusion-Mediated Communication: collective behavior resulting from spatial effects from diffusive transport. (Spatial clustering of cells, shielding effects, spatially isolated cells, build-up of signalling gradient).

Two main types of QS systems:

- **Oscillatory:** emergence of intracellular oscillations as the cell density increases (i.e. glycolysis, social amoeba, catalyst bead particles).
  - In the absence of coupling by bulk diffusion, the "cells" are in a quiescent state. Oscillations and ultimate sychronization occurs via a switchlike response (Hopf bifurcation) to elevated AI levels.
- **Transitions:** between small and large amplitude bistable steady-states as the cell density increases (i.e. bioluminescence, *Pseudomonas aeruginosa*).
  - An increase in the number of cells, or the spatial clustering of cells, will lead to passage past a saddle-node point leading to a fast transition between bistable states.

Modeling Approaches

- **Oscillations: Large ODE system** of weakly coupled system of oscillators. Prototypical is the Kuramoto type-models of the form:

$$\frac{d\mathbf{x}_i}{dt} = \mathbf{F}(\mathbf{x}_i) + \sigma \sum_j C_{ij}\mathbf{H}(\mathbf{x}_j)\,,$$

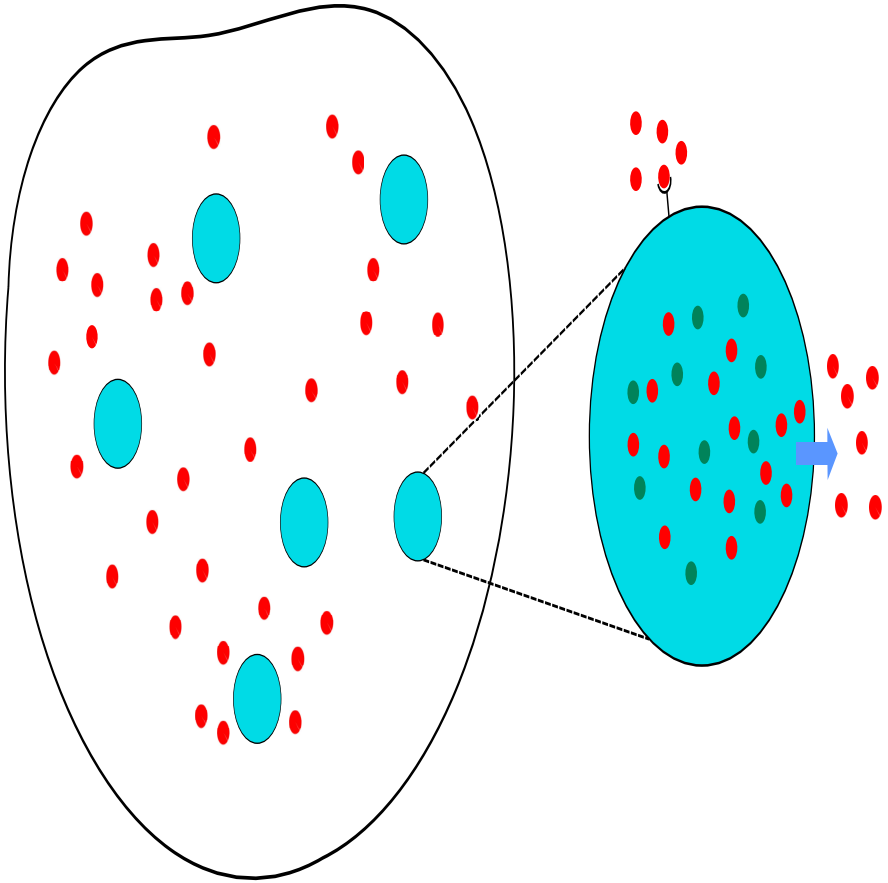
  Synchrony occurs between individual oscillators as the coupling strength σ increases. (Vast literature, but not the mechanism here).

- **Homogenization** approach of deriving reaction-diffusion systems through cell densities: Yields target and spiral wave patterns of cAMP in Dicty modeling (but phemenological).

- PDE-ODE agent-based models, but where diffusion is based on discrete Laplacian restricted to lattice sites.

- **More Recent:** PDE-ODE models coupling individual dynamically active "cells" through a bulk diffusion field. Our framework is related to:
  - **Ref:** J. Muller, C. Kuttler, et al. "Cell-Cell Communication by Quorum Sensing and...", J. Math. Bio. **53** (2006),
  - **Ref:** J. Muller, H. Uecker, J. Math. Bio. **67** (2013). (steady-state analysis in 3-D, dynamics).

Formulation of the 2-D Model: I



- The m cells are disks of radius σ and each contains n chemicals $\mu_j = (\mu_{1j}, \ldots, \mu_{nj})^T$. When isolated: interact via intracellular kinetics $\mathbf{d}\mu_j/dt = \mathbf{F}_j(\mu_\mathbf{j})$.
- A scalar bulk diffusion field (autoinducer) diffuses in the space between the cells via

$$\mathcal{U}_T = D_B \Delta_\mathbf{X} \mathcal{U} - k_B \mathcal{U} \, .$$

- There is an exchange across the cell membrane, regulated by permeability parameters, between the autoinducer and one intracellular species (Robin condition).

Scaling Limit: $\epsilon \equiv \sigma/L \ll 1$, where L is lengthscale for Ω. We assume that the permeability parameters are $\mathcal{O}(\epsilon^{-1})$.

Parameters: Bulk diffusivity D_B, bulk decay k_B, permeabilities, ϵ, and time-scale of intracellular reactions.

Formulation of the 2-D Model: II

Our PDE-ODE coupled cell-bulk model in 2-D with m cells is

$$\mathcal{U}_T = D_B \Delta_{\boldsymbol{X}} \mathcal{U} - k_B \mathcal{U}\,, \quad \boldsymbol{X} \in \Omega \backslash \cup_{j=1}^{m} \Omega_j\,; \quad \partial_{n_{\boldsymbol{X}}} \mathcal{U} = 0\,, \quad \boldsymbol{X} \in \partial\Omega\,,$$

$$D_B \partial_{n_{\boldsymbol{X}}} \mathcal{U} = \beta_{1j} \mathcal{U} - \beta_{2j} \mu_j^1\,, \qquad \boldsymbol{X} \in \partial\Omega_j\,, \quad j = 1, \ldots, m\,.$$

Each cell $\Omega_j \in \Omega$ is a disk of radius σ centered at some $\boldsymbol{X}_j \in \Omega$.

Inside each cell there are n interacting species with mass vector $\boldsymbol{\mu}_j \equiv (\mu_j^1, \ldots, \mu_j^n)^T$ whose dynamics are governed by n-ODEs, with (rank-one) coupling via integration of the diffusive flux over the j-th "cell"-membrane $\partial\Omega_j$:

$$\frac{d\boldsymbol{\mu}_j}{dT} = k_R \mu_c \boldsymbol{F}_j\left(\boldsymbol{\mu}_j/\mu_c\right) + \boldsymbol{e}_1 \int_{\partial\Omega_j} \left(\beta_{1j}\mathcal{U} - \beta_{2j}\mu_j^1\right) dS_j\,, \quad j = 1, \ldots, m\,,$$

where $\boldsymbol{e}_1 \equiv (1, 0, \ldots, 0)^T$, and μ_c is typical mass.

- Only one species μ_j^1 can cross the j-th cell membrane into the bulk.
- $k_R > 0$ is intracellular reaction rate; β_{1j}, β_{2j} are permeabilities.
- The dimensionless function $\boldsymbol{F}_j$ models the intracellular kinetics.

Formulation of the 2-D Model: III

Dimensionless Formulation: The concentration of signalling molecule $U(\boldsymbol{x},t)$ in the bulk satisfies the PDE:

$$\tau U_t = D\Delta U - U\,, \qquad \boldsymbol{x}\in\Omega\backslash\cup_{j=1}^m\Omega_{\epsilon_j}\,; \quad \partial_n U = 0\,, \quad \boldsymbol{x}\in\partial\Omega\,,$$

$$\epsilon D\partial_{n_j}U = d_{1j}U - d_{2j}u_j^1\,, \qquad \boldsymbol{x}\in\partial\Omega_{\epsilon_j}\,, \quad j=1,\ldots,m\,.$$

The cells are disks of radius $\epsilon \ll 1$ so that $\Omega_{\epsilon_j}\equiv\{\boldsymbol{x}\,|\,|\boldsymbol{x}-\boldsymbol{x}_j|\le\epsilon\}$.

Inside each cell there are n interacting species $\boldsymbol{u}_j=(u_j^1,\ldots,u_j^n)^T$, with intracellular dynamics for each $j=1,\ldots,m$,

$$\frac{d\boldsymbol{u}_j}{dt} = \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{\boldsymbol{e}_1}{\epsilon\tau}\int_{\partial\Omega_{\epsilon_j}}(d_{1j}U - d_{2j}u_j^1)\,ds\,, \qquad \boldsymbol{e}_1\equiv(1,0,\ldots,0)^T\,.$$

Remark: The time-scale is measured wrt intracellular kinetics. The dimensionless bifurcation parameters are: d_{1j}, d_{2j} (permeabilities); τ (reaction-time ratio); D (effective diffusivity);

$$\tau\equiv\frac{k_R}{k_B}\,, \quad D\equiv\left(\frac{\sqrt{D_B/k_B}}{L}\right)^2\,, \quad \beta_{1j}\equiv(k_BL)\,\frac{d_{1j}}{\epsilon}\,, \quad \beta_{2j}\equiv\left(\frac{k_B}{L}\right)\frac{d_{2j}}{\epsilon}\,.$$

Theoretical Framework

Depending on intracellular kinetics F_j:

- **Oscillations:** Intracellular kinetics are a conditional oscillator: Quiescent when uncoupled from the bulk. Bulk coupling triggers a Hopf bifurcation for the entire collection of cells. (Sel'kov kinetics).
- **Transitions:** Intracellular kinetics have a saddle-node structure and bistable states when uncoupled from bulk. Bulk-coupling induces an effective bifurcation parameter, depending on the number of cells and other bulk parameters, that can sweep past fold points.

Two key regimes for D with different behaviors:

- $D = \mathcal{O}(1)$; Effect of spatial distribution of cells is a key factor whether either intracellular oscillations or saddle-node transitions occur.
- $D = \mathcal{O}(\nu^{-1})$ with $\nu = -1/\log\epsilon$; PDE-ODE system can be reduced to a limiting ODE system where there is a weak effect of cell locations.
  - $D \to \infty$; The classic "well-mixed" regime: Obtain an ODE system with global coupling and no spatial effects. (QS behavior).

Mathematical Framework: Use strong localized perturbation theory to construct steady-states, to analyze the linear stability problem. Derive the reduced ODE system for $D = \mathcal{O}(\nu^{-1})$. Compare with FlexPDE numerics.

Steady-States: Matched Asymptotics

Main Result (Steady-State): *In the outer region, the ss bulk diffusion field is*

$$U(\boldsymbol{x}) = -2\pi \sum_{i=1}^{m} S_i G(\boldsymbol{x}, \boldsymbol{x}_i)\,, \quad \text{where} \quad \boldsymbol{S} \equiv (S_1, \ldots, S_m)^T .$$

In terms of $\nu = -1/\log\epsilon$ *and a Green's matrix* $\mathcal{G}$*, we obtain a nonlinear algebraic system for* $\boldsymbol{S}$ *and* $\boldsymbol{u}^1 \equiv (u_1^1, \ldots, u_m^1)^T$*, where* $e_1 = (1, 0, \ldots, 0)^T$*:*

$$(\mathcal{H} + 2\pi\nu\mathcal{G})\,\boldsymbol{S} = -\nu\mathcal{W}\boldsymbol{u}^1\,; \quad \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{2\pi D}{\tau} S_j \boldsymbol{e}_1 = 0\,, \quad j = 1, \ldots, m\,.$$

Here $\mathcal{W} \equiv \text{diag}\left(\frac{d_{21}}{d_{11}}, \ldots, \frac{d_{2m}}{d_{1m}}\right)$ *and* $\mathcal{H} \equiv \text{diag}\left(\left(1 + \frac{\nu D}{d_{11}}\right), \ldots, \left(1 + \frac{\nu D}{d_{1m}}\right)\right)$.

In this ss formulation, the entries of the $m \times m$ Green's matrix $\mathcal{G}$ are

$$(\mathcal{G})_{ii} = R_i\,, \qquad (\mathcal{G})_{ij} = G(\boldsymbol{x}_i; \boldsymbol{x}_j)\,, \quad i \neq j\,,$$

where, with $\varphi_0 \equiv 1/\sqrt{D}$, $G(\boldsymbol{x}; \boldsymbol{x}_j)$ is the reduced-wave G-function:

$$\Delta G - \varphi_0^2 G = -\delta(\boldsymbol{x} - \boldsymbol{x}_j)\,, \quad \boldsymbol{x} \in \Omega\,; \qquad \partial_n G = 0\,, \quad \boldsymbol{x} \in \partial\Omega\,.$$

$$G(\boldsymbol{x}; \boldsymbol{x}_j) \sim -\frac{1}{2\pi}\log|\boldsymbol{x} - \boldsymbol{x}_j| + R_j + o(1)\,, \qquad \text{as} \quad \boldsymbol{x} \to \boldsymbol{x}_j\,.$$

Globally Coupled Eigenvalue Problem (GCEP)

Linear Stability: *For $\epsilon \to 0$, the perturbed bulk diffusion field satisfies*

$$u(\boldsymbol{x},t) = U(\boldsymbol{x}) + e^{\lambda t}\eta(\boldsymbol{x})\,, \qquad \eta(\boldsymbol{x}) = -2\pi \sum_{i=1}^{m} c_i G_\lambda(\boldsymbol{x},\boldsymbol{x}_i)\,.$$

Inside the j-th cell we have $\boldsymbol{u}_j = \boldsymbol{u}_{ej} + 2\pi D\tau^{-1} c_j e^{\lambda t}(\lambda I - J_j)^{-1}\boldsymbol{e}_1$. Here $\boldsymbol{c} = (c_1,\ldots,c_m)^T$ is a nullvector of the GCEP:

$$\mathcal{M}\boldsymbol{c} = \boldsymbol{0}\,, \qquad \mathcal{M}(\lambda) \equiv 2\pi\nu\mathcal{G}_\lambda + \mathcal{H} + \nu\frac{2\pi D}{\tau}\mathcal{W}\mathcal{K}(\lambda)\,.$$

In this GCEP, $\mathcal{G}_\lambda$ is the Green's matrix formed from

$$\Delta G_\lambda - \varphi_\lambda^2 G_\lambda = -\delta(\boldsymbol{x}-\boldsymbol{x}_j), \quad \boldsymbol{x}\in\Omega\,; \qquad \partial_n G_\lambda = 0\,, \quad \boldsymbol{x}\in\partial\Omega\,,$$

$$G_\lambda(\boldsymbol{x};\boldsymbol{x}_j) \sim -\frac{1}{2\pi}\log|\boldsymbol{x}-\boldsymbol{x}_j| + R_{\lambda,j} + o(1)\,, \qquad \text{as} \quad \boldsymbol{x}\to\boldsymbol{x}_j\,,$$

with $\varphi_\lambda \equiv D^{-1/2}\sqrt{1+\tau\lambda}$. Here $\mathcal{K}$ is the diagonal matrix defined in terms of the Jacobian $J_j \equiv \boldsymbol{F}_{j,\boldsymbol{u}}(\boldsymbol{u}_{ej})$ of the intracellular kinetics $\boldsymbol{F}_j$:

$$\mathcal{K}_j = \boldsymbol{e}_1{}^T(\lambda I - J_j)^{-1}\boldsymbol{e}_1 = \frac{M_{j,11}(\lambda)}{\det(\lambda I - J_j)}\,, \quad \text{where} \quad e_1 = (1,0,\ldots,0)^T\,.$$

Properties of the The GCEP: I

For $\varepsilon \to 0$, the discrete eigenvalues λ of the linearization of the PDE-ODE system around the steady-state satisfy

$$\Lambda(\mathcal{M}) \equiv \{\lambda \,|\, \det \mathcal{M}(\lambda) = 0\}\,.$$

Proposition: *For $\varepsilon \to 0$, a steady-state solution is linearly stable when for all $\lambda \in \Lambda(\mathcal{M})$ we have Re$(\lambda) < 0$. Moreover, if $\mathcal{S}_e$ and $\boldsymbol{u}_{ej}$ for $j = 1, \ldots, m$ is a non-degenerate solution to the nonlinear algebraic system (NAS), for which J_j is non-singular, then $\lambda = 0$ is not a root of det$\mathcal{M}(\lambda) = 0$.*

- If the NAS has a unique branch of solutions as a parameter is varied, then stability cannot be lost through a zero-eigenvalue crossing. Instead, look for Hopf bifurcations with $\lambda = i\lambda_I$.
- The GCEP matrix $\mathcal{M}$ is symmetric but non-Hermitian when $\lambda = i\lambda_I$.
- If there is a saddle-node bifurcation for the NAS, then $\lambda = 0$ is a root of the GCEP.
- For $\nu \ll 1$, saddle-node points associated with steady-states of the intracellular kinetics are $\mathcal{O}(\nu)$ close to those of the coupled system.

Properties of the The GCEP: II

In terms of the eigenvector $\boldsymbol{c} = (c_1, \ldots, c_m)^T$ of the GCEP $\mathcal{M}\boldsymbol{c} = 0$:

$$\varepsilon \partial_n U|_{\partial\Omega_{\varepsilon_j}} \sim S_j + \sum_{\lambda\in\Lambda(\mathcal{M})} c_j e^{\lambda t}\,, \quad u_j^1 \sim u_{ej}^1 + \frac{2\pi D}{\tau} \sum_{\lambda\in\Lambda(\mathcal{M})} (\mathcal{K}\boldsymbol{c})_j\, e^{\lambda t}\,,$$

for $j = 1, \ldots, m$. When intracellular oscillations occur, the complex-valued vector $\mathcal{K}\boldsymbol{c}$ provides their relative magnitude and phases near onset.

Numerics for the GCEP: Nonlinear matrix eigenvalue problem of the form

$$\mathcal{M}(\lambda; \tau, D)\boldsymbol{c} = \mathbf{0}\,.$$

An unstable "mode" is a root λ of $\mathcal{F}(\lambda) = \det(\mathcal{M}(\lambda)) = 0$ in $\mathrm{Re}(\lambda) > 0$. The number N of unstable modes is the total number of such roots.

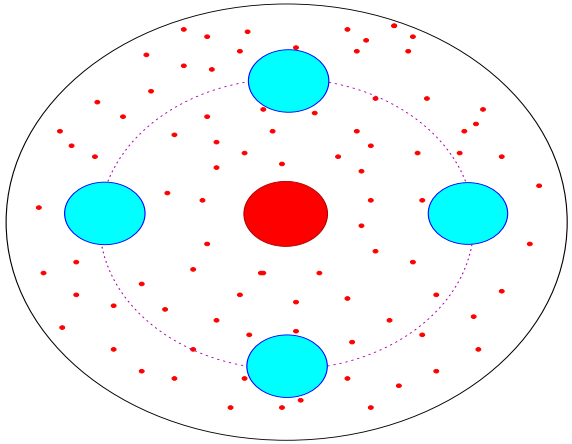
- Compute N from winding number computation of $\mathcal{F}(\lambda)$ over a large semi-circle in $\mathrm{Re}(\lambda) > 0$. Gives a "stability map" in (τ, D) plane.
- Hopf bifurcation boundaries, $\lambda = i\lambda_I(D)$ and $\tau = \tau(D)$ can have folds in D. Compute with $Re\mathcal{F} = 0$ and $Im\mathcal{F} = 0$ using psuedo-arclength continuation.
- Challenging to treat if m is large.

Properties of the The GCEP: III

Remark: Nonlinear matrix eigenvalue problems and available solution strategies usually restriced to Hermitian case, or where $\mathcal{M}(\lambda)$ is a polynomial or rational function of λ or where λ enters as low rank. (N. Higham, V.Mehrmann). Not our situation.

Simplest Cases to Consider:

- A concentric ring pattern of identical cells in the disk: (Cyclic matrix).
- A concentric ring with center-cell pattern in the disk, with identical ring cells and a defective center cell: ($m-1$ dimensional Cyclic sub-block).
- Reduction of the GCEP for the $D = D_0/\nu$ regime, where only one matrix eigenvalue σ of $\mathcal{M}\boldsymbol{c} = \sigma\boldsymbol{c}$ can cross through zero.
- For the unit disk, we have explicit formulae for the Green's matrices.



The Distinguished Limit $D = D_0/\nu$

For $D = D_0/\nu \gg 1$, the Green's matrix satisfies

$$\mathcal{G}_\lambda = \frac{D_0}{\nu|\Omega|(1+\tau\lambda)} + \mathcal{G}_0 + \mathcal{O}(\nu)\,, \qquad \nu \equiv -1/\log\varepsilon\,,$$

where $\mathcal{G}_0$ is the Neumann G-matrix for $\Delta G = |\Omega|^{-1} - \delta(x-\xi)$.
To solve $\det(\mathcal{M}(\lambda)) = 0$, we use this approximation for $\mathcal{G}_\lambda$ and matrix perturbation theory to get the eigenvalues σ_k of $\mathcal{M}\boldsymbol{c} = \sigma\boldsymbol{c}$ to $\mathcal{O}(\nu^2)$.

Proposition: *Suppose that $\lambda = \lambda^\star$ is a root of $\mathcal{Q}_s(\lambda) = 0$, where*

$$\mathcal{Q}_s(\lambda) \equiv 1 + \frac{\gamma}{m}\boldsymbol{e}^T\boldsymbol{v}_1 + 2\pi\nu\left(\frac{\boldsymbol{v}_1^T\,\mathcal{G}_0\,\boldsymbol{v}_1}{\boldsymbol{e}^T\,\boldsymbol{v}_1}\right) \quad \text{with} \quad \boldsymbol{v}_1^T \equiv (1/b_1, \ldots, 1/b_m)\,,$$

and

$$\gamma \equiv \frac{2\pi m D_0}{(1+\tau\lambda)|\Omega|}\,, \quad b_j \equiv \frac{(d_{1j}+D_0)}{d_{1j}}\left[1 + \frac{\eta_j}{\tau}K_j\right], \quad \eta_j \equiv \frac{2\pi d_{2j} D_0}{d_{1j}+D_0}\,.$$

Suppose that $\mathrm{tr}(J_j) \neq \eta_j/\tau$. Then, $\det\mathcal{M}(\lambda^\star) = 0$ to $\mathcal{O}(\nu^2)$ and the corresponding (unnormalized) eigenvector $\boldsymbol{c}$ of the GCEP is $\boldsymbol{c} = \boldsymbol{v}_1$ at $\lambda = \lambda^\star$. HB boundaries in the τ versus D_0 parameter plane satisfy

$$\mathrm{Re}\,[\mathcal{Q}_s(i\lambda_I)] = 0\,, \qquad \text{and} \qquad \mathrm{Im}\,[\mathcal{Q}_s(i\lambda_I)] = 0\,.$$

ODE System for the $D = D_0/\nu$ Regime

Proposition: *Let* $\varepsilon \to 0$ *and assume that* $D = D_0/\nu \gg 1$ *where* $D_0 = \mathcal{O}(1)$ *and* $\nu = -1/\log\varepsilon \ll 1$. *Then, the PDE-ODE system reduces to the following* $nm+1$ *dimensional ODE-DAE system for* $\overline{U} \approx |\Omega|^{-1}\int_\Omega U\,d\boldsymbol{x}$ *and the intracellular species:*

$$\frac{\mathrm{d}\overline{U}}{\mathrm{d}t} = -\frac{1}{\tau}\overline{U} - \frac{2\pi D_0}{\tau|\Omega|}\boldsymbol{e}^T\boldsymbol{b}\,; \qquad \frac{\mathrm{d}\boldsymbol{u}_j}{\mathrm{d}t} = \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{2\pi D_0\boldsymbol{e}_1}{\tau}b_j\,, \quad j = 1,\ldots,m\,,$$

where $\boldsymbol{e} \equiv (1,\ldots,1)^T$, $\boldsymbol{e}_1 \equiv (1,0,\ldots,0)^T$. *Here* $\boldsymbol{b} \equiv (b_1,\ldots,b_m)^T$ *is the solution to the linear system*

$$\big(I + D_0P_1 + 2\pi\nu\,\mathcal{G}_0\big)\boldsymbol{b} = \overline{U}\,\boldsymbol{e} - P_2\,\boldsymbol{u}^1\,,$$

where $\boldsymbol{u}^1 \equiv (u_1^1,\ldots,u_m^1)^T$, $P_1 \equiv \mathit{diag}\Big(\frac{1}{d_{11}},\ldots,\frac{1}{d_{1m}}\Big)$ *and* $P_2 \equiv \mathit{diag}\Big(\frac{d_{21}}{d_{11}},\ldots,\frac{d_{2m}}{d_{1m}}\Big)$, *while* $\mathcal{G}_0$ *is the Neumann Green's matrix.*

Remarks: ODE system is not the classic one for the well-mixed regime. It depends on D_0 and the spatial configuration $\{\boldsymbol{x}_1,\ldots,\boldsymbol{x}_m\}$ of cells via $\mathcal{G}_0$.

The Well-Mixed Regime $D \gg \mathcal{O}(\nu^{-1})$

Well-Mixed ODEs: For $D \to \infty$ the PDE-ODE model reduces to $u(x,t) \sim U_0(t)$, where

$$U_0' = -\frac{1}{\tau} U_0 - \frac{2\pi\rho}{m\tau} \sum_{j=1}^{m} \left[d_{1,j} U_0 - d_{2,j} u_j^1 \right] ,$$

$$\boldsymbol{u}_j' = \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{2\pi}{\tau} \left[d_{1,j} U_0 - d_{2,j} u_j^1 \right] \boldsymbol{e}_1 , \qquad j = 1, \ldots, m .$$

Here $\boldsymbol{e}_1 = (1, 0, \ldots, 0)^T$, and ρ is the effective cell density defined by

$$\rho \equiv \frac{m}{|\Omega|} .$$

For $m \gg 1$, this is a large system of ODEs with global coupling.

Remarks:

- For Sel'kov kinetics and identical cells, can establish oscillatory instability on $\tau_{H-} < \tau < \tau_{H+}$ when $m > m_c$ (QS threshold).
- Kuramato order parameter can be used to study onset of synchronization for heterogeneous cells.

(I) Switch-like Onset of Oscillations

Let $\boldsymbol{u} = (u_1, u_2)^T$ be intracellular dynamics given by Sel'kov kinetics:

$$F_{1j}(u_1, u_2) = \alpha_j u_2 + u_2 u_1^2 - u_1\,, \quad F_{2j}(u_1, u_2) = \epsilon_0 \left(\mu_j - (\alpha_j u_2 + u_2 u_1^2)\right)\,.$$

For an *isolated cell* $\exists$ a unique steady-state for which

$$\text{trace}(J_{ej}) = \frac{\left[\mu_j^2 - \alpha_j^2 - \epsilon_0(\alpha_j + \mu_j^2)^2\right]}{\alpha + \mu_j^2}\,, \quad \det(J_{ej}) = \epsilon_0(\alpha_j + \mu_j^2) > 0\,.$$

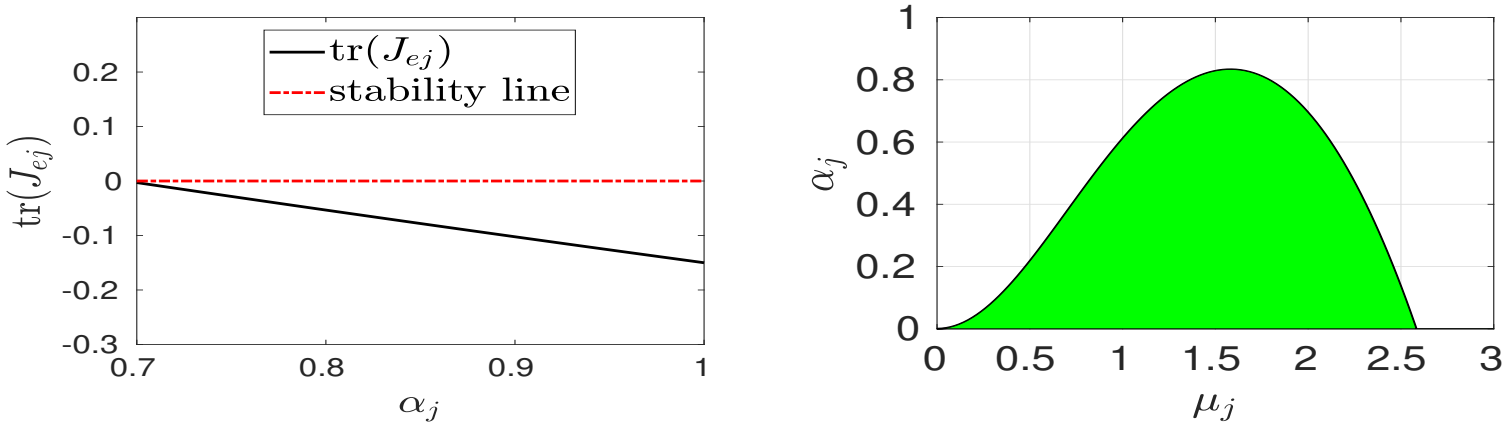


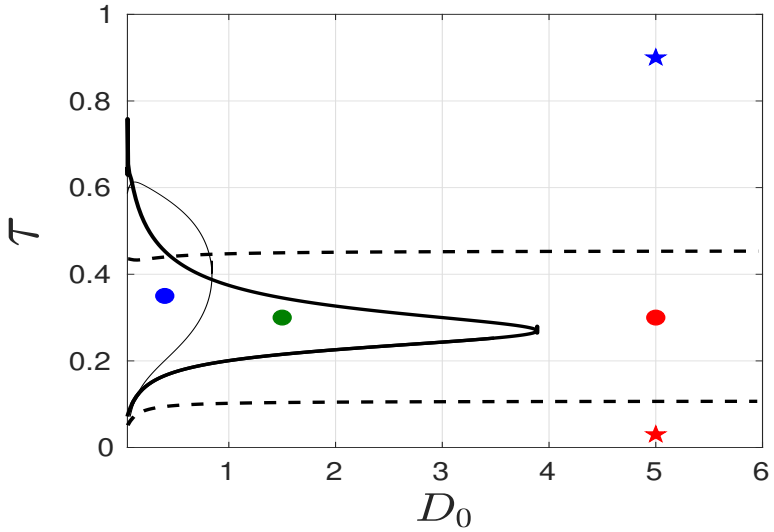
Figure 1: Left: trace(J_{ej}) versus α_j for $\mu_j = 2$ and $\varepsilon_0 = 0.15$. Right panel: instability region.

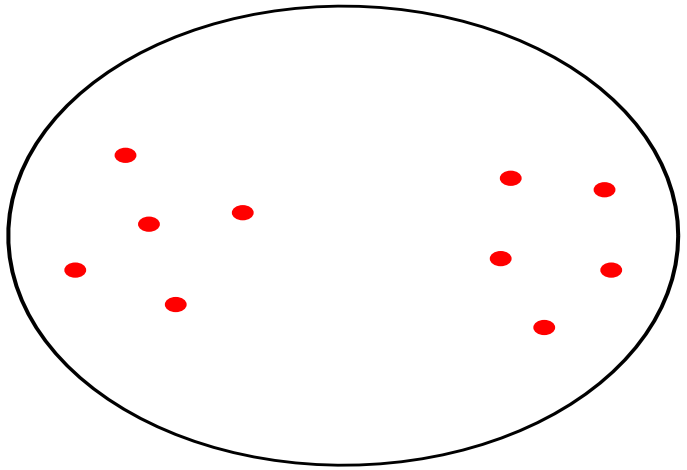
Baseline set: $\alpha_j = 0.9$, $\mu = 2$ and $\epsilon_0 = 0.15$, close to stability threshold of an isolated cell. For Sel'kov, the NAS always has a unique steady-state. Hence, instabilities can only occur via HB points.

Example: $m = 10$ cells: Two Clusters

Baseline Set: $d_2 = 0.2$, $\alpha = 0.9$, $\mu = 2$, $\epsilon_0 = 0.15$, and cell radius $\varepsilon = 0.05$.

Question: what is the effect of varying the influx permeability rate d_1 into the cells from the bulk medium when $D = D_0/\nu$?.

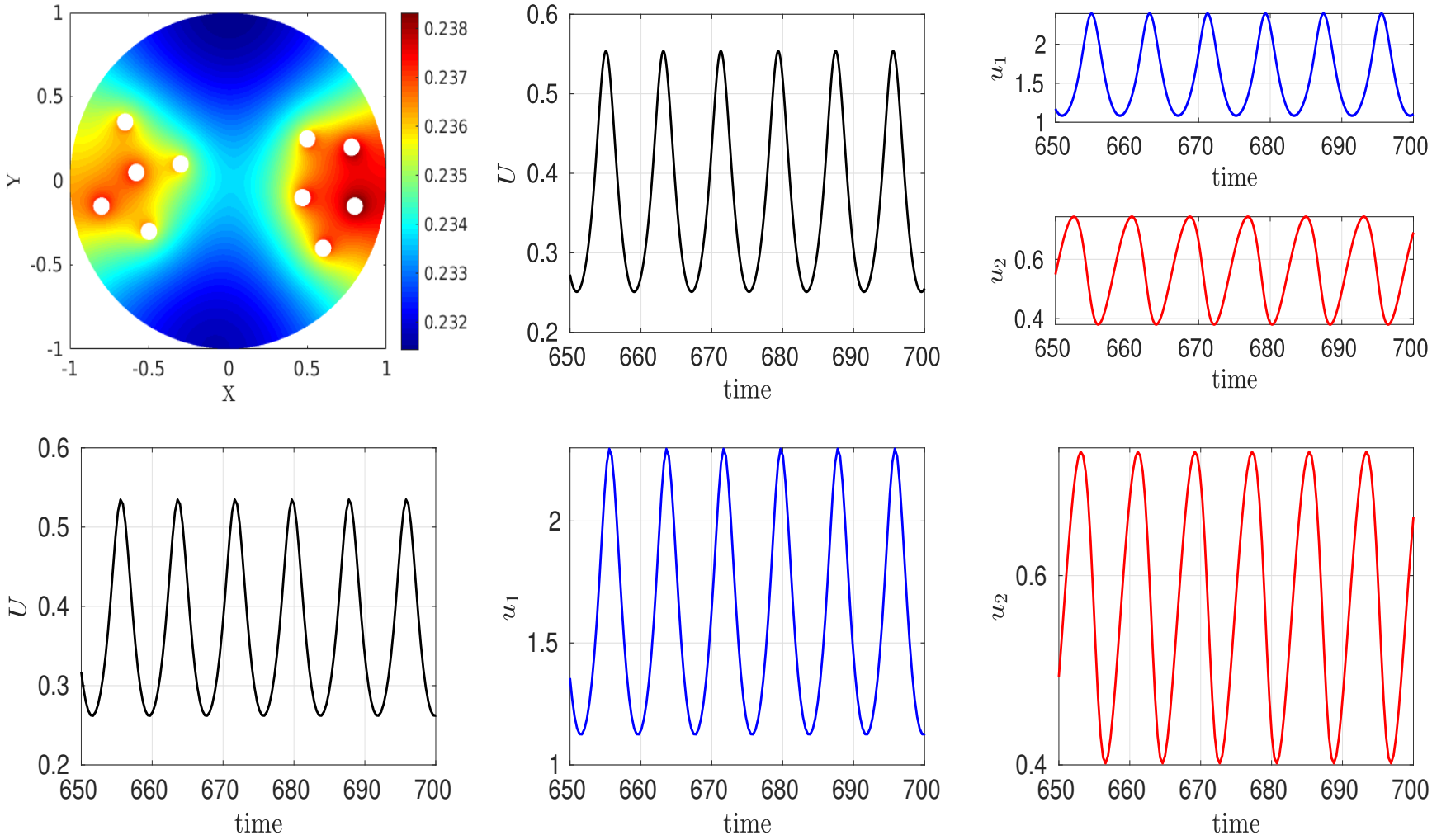




Caption: HB boundaries in the τ versus D_0 plane for $m = 10$ cells with two groups/clusters of cells. Dashed curve: identical cells with $d_1 = 0.8$. Thin solid: $d_1 = 0.8$ for the first group and $d_1 = 0.4$ for second group. Heavy solid: non-identical cells with d_1 uniformly in $0.4 \leq d_1 \leq 0.8$. FlexPDE simulations given below at indicated points.

Observe: Oscillations predicted within the lobes. HB boundaries depend sensitively on d_1.

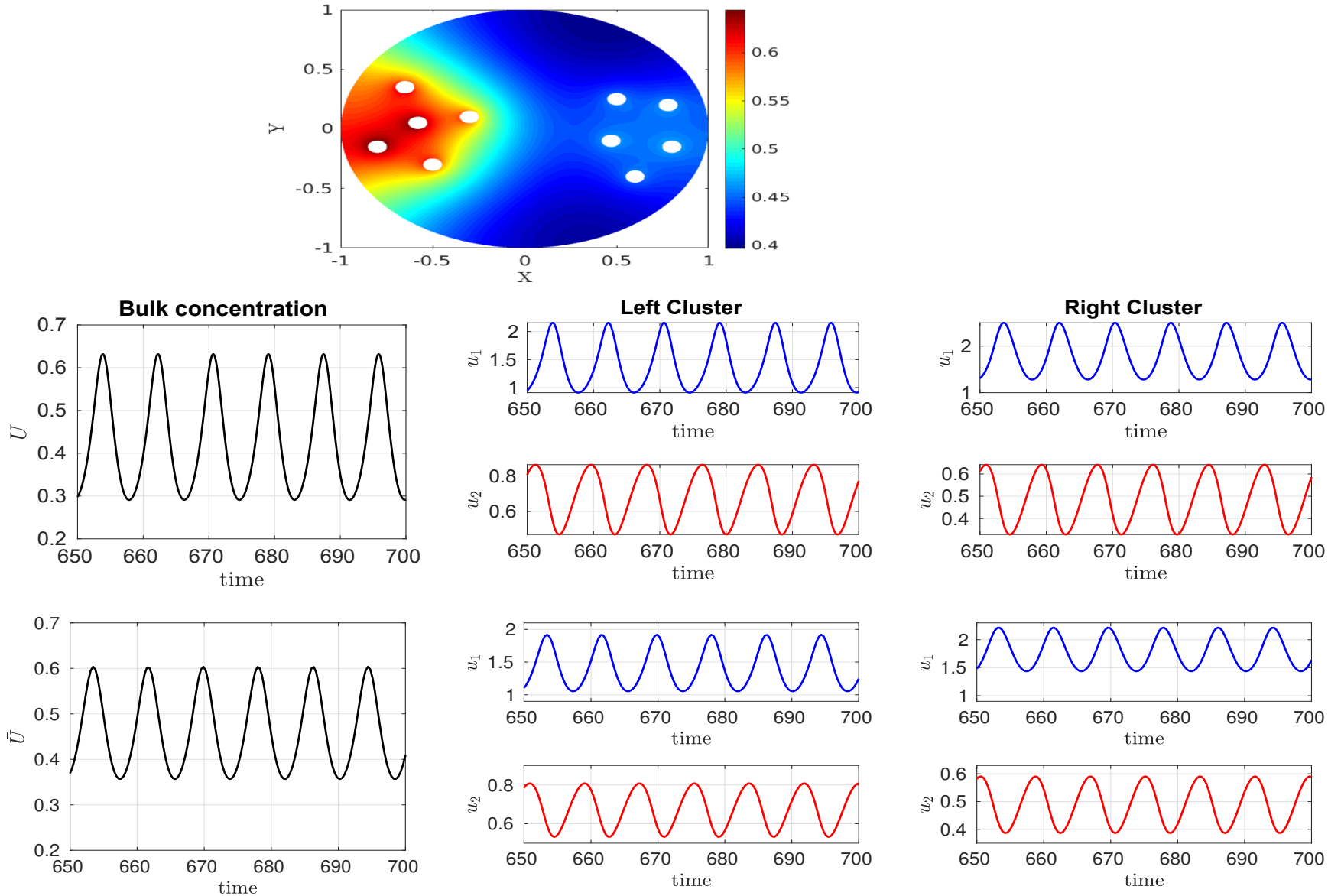
Two Identical Clusters: Red Dot



Caption: Top row: FlexPDE results at $(D_0, \tau) = (5.0, 0.3)$ with identical influx rates $d_{1j} = 0.8$ for $j = 1, \ldots, m$. Lower row: $\bar{U}$, u_1, and u_2, as computed from the ODEs.

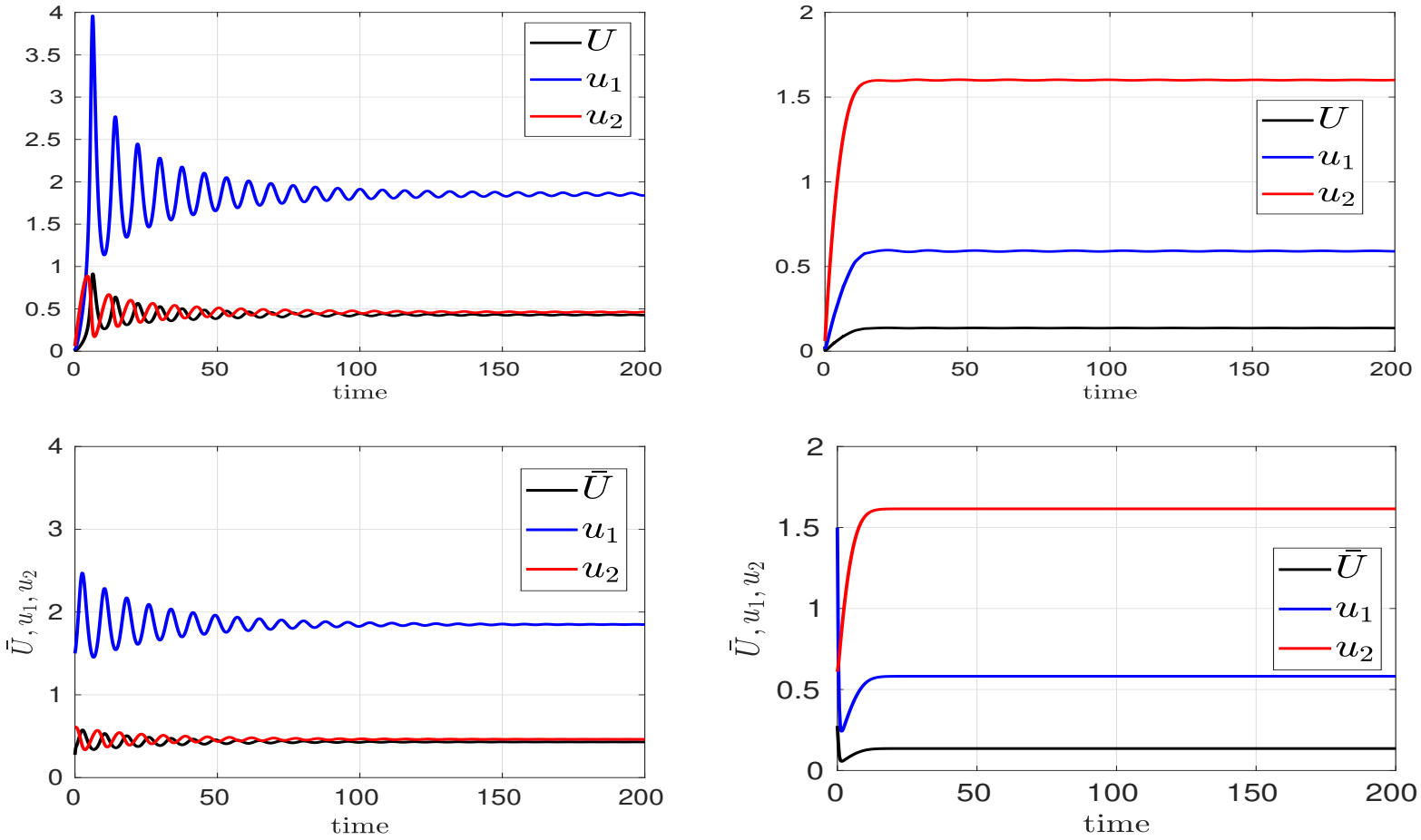
Observe: Nearly synchronized intracellular oscillations.

Two Distinct Clusters: Blue Dot



Caption: Top/ middle rows: FlexPDE results at $(D_0, \tau) = (0.4, 0.35)$. Cells in the left and right clusters have $d_1 = 0.4$ and $d_1 = 0.8$, resp. Lower row: $\bar{U}$, u_1, and u_2, from the ODEs.

Two Identical Clusters: Red/Blue Stars

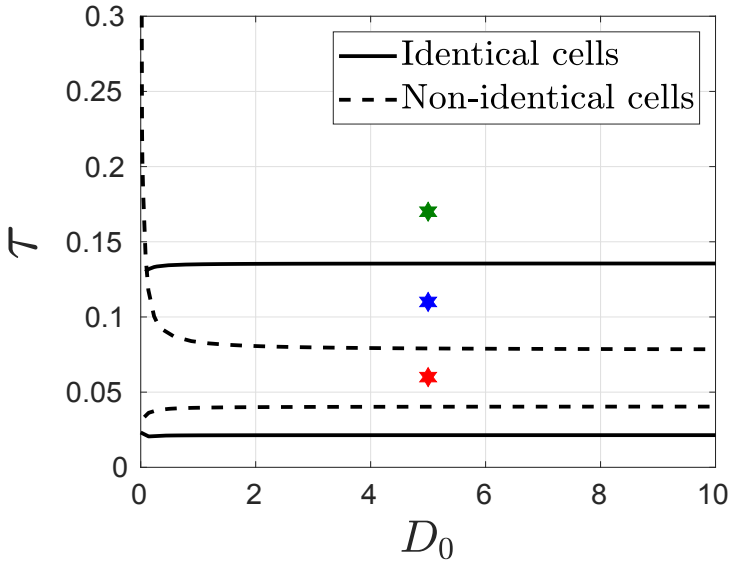


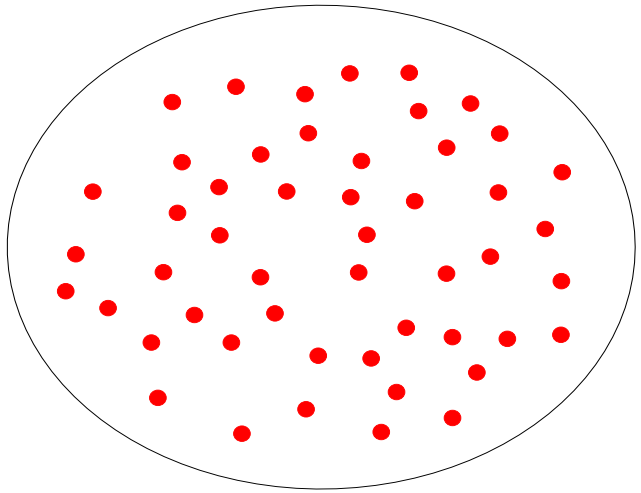
Caption: Top Row: FlexPDE results at the blue star with $(D_0, \tau) = (5.0, 0.9)$ (left panel) and at the red star with $(D_0, \tau) = (5.0, 0.03)$ (right panel). Identical influx rates $d_1 = 0.8$ for all cells. Lower row: $\bar{U}$, u_1, and u_2, from the ODE system.

Observe: oscillatory versus monotonic approach to the steady-state.

Larger m for $D = \mathcal{O}(\nu^{-1})$: I

We uniformly distribute $m = 50$ cells in the unit disk.





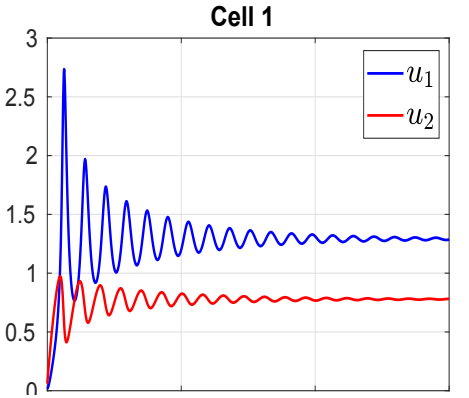
Caption: Left: HB boundaries in the (D_0, τ) plane for $m = 50$ randomly placed cells in the unit disk.

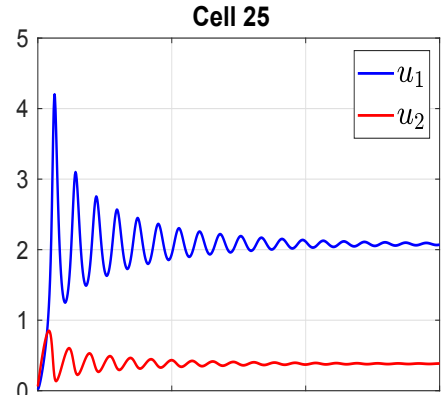
- **Heavy solid curves: identical cells with $d_1 = 0.8$.**
- **Dashed curves: Each cell has an influx parameter d_1 uniformly distributed on $0.4 < d_1 < 0.8$.**

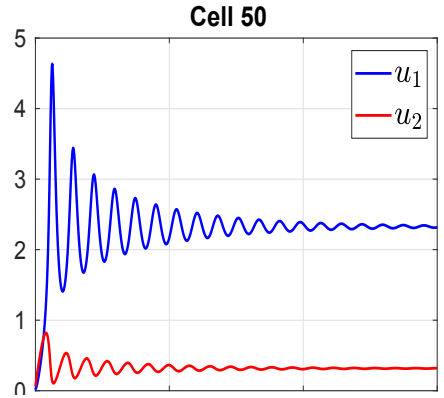
Right: spatial pattern of $m = 50$ cells. Parameters: $d_2 = 0.2$, $\varepsilon = 0.02$, $\alpha = 0.9$, $\mu = 2$, $\epsilon_0 = 0.15$.

ODE-DAE Results for Non-Identical Cells

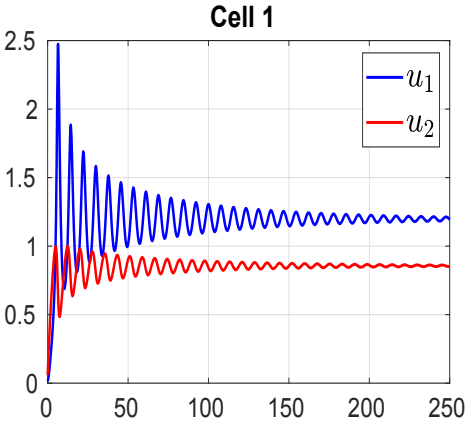
Simulations at indicated points in phase diagram

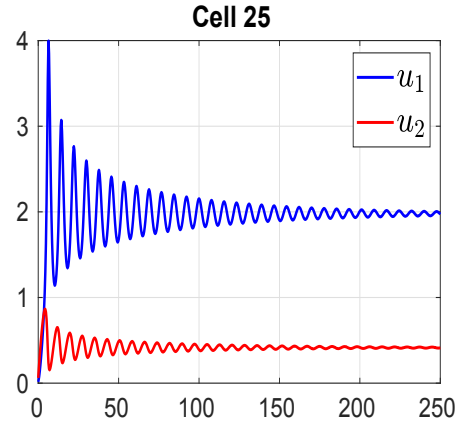


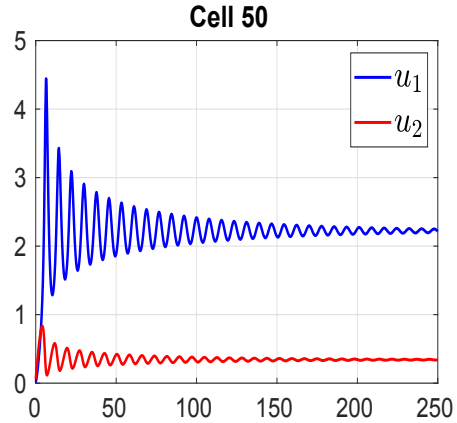




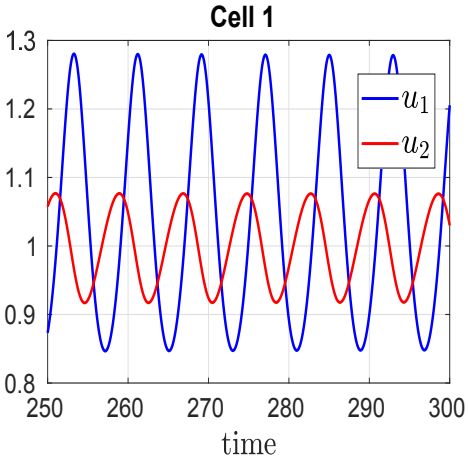
Green Point

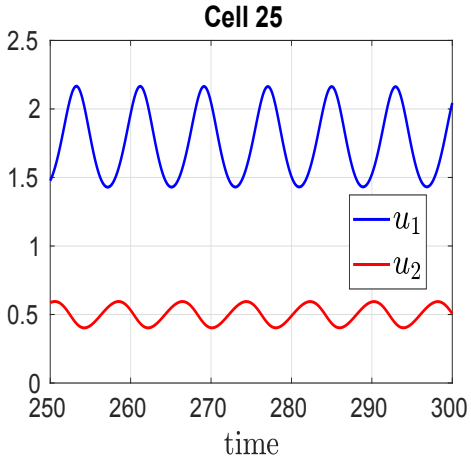


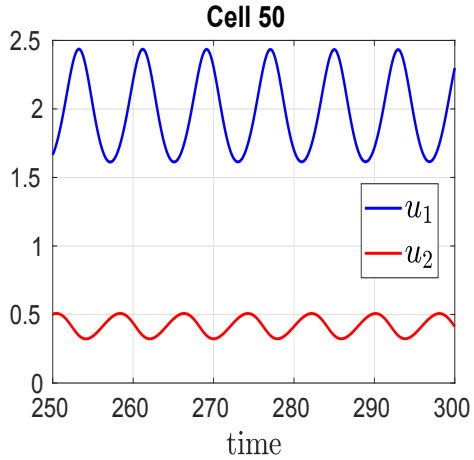




Blue Point

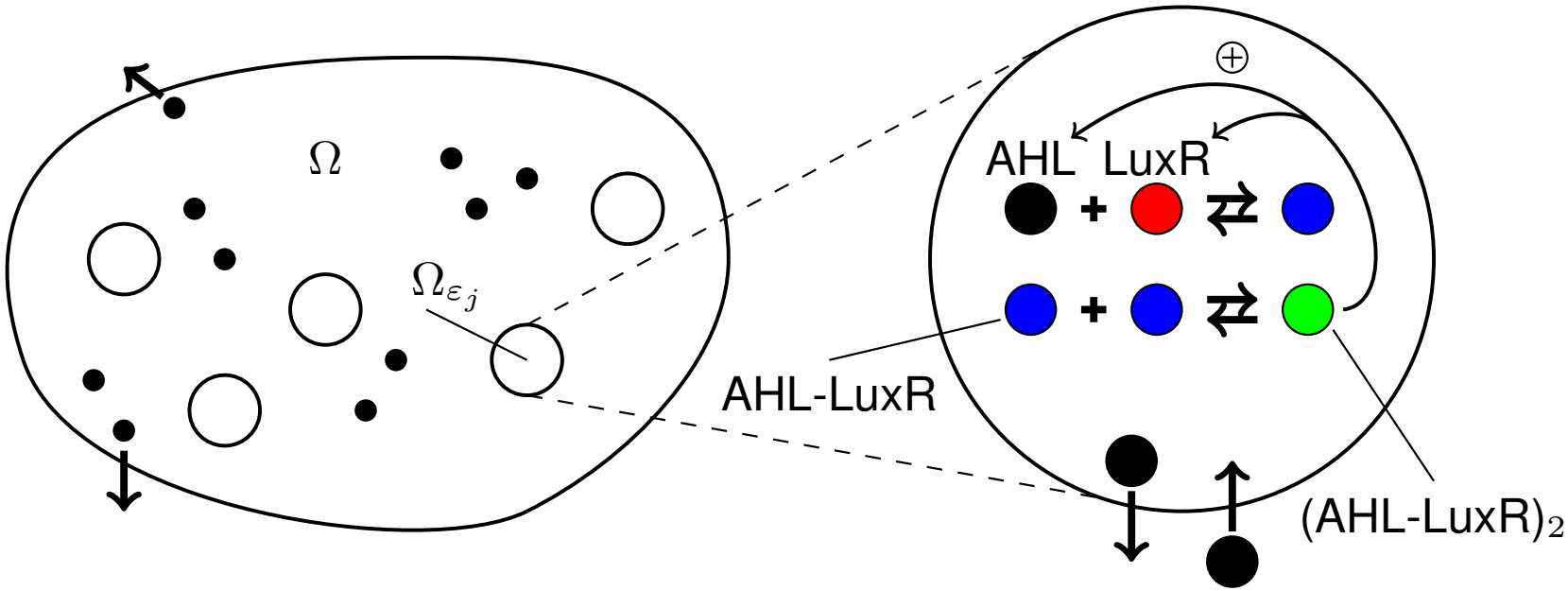






Red Point

(II) Quorum-Sensing Induced Transitions



The Lux-intracellular kinetics $\boldsymbol{F}_j \in \mathbb{R}^4$ in dimensionless form are (Ref. Melke et al„ PloS Comp. Bio. **6**(6), (2010))

$$\frac{\mathrm{d}u_{1j}}{\mathrm{d}t} = c + \frac{\kappa_{1A} u_{4j}}{\kappa_{DA} + u_{4j}} - \kappa_{2A} u_{1j} - u_{1j} u_{2j} + \kappa_5 u_{3j} + \varepsilon^{-1} \int_{\partial\Omega_{\varepsilon_j}} (d_{1j} U - d_{2j} u_{1j})\, ds\,,$$

$$\frac{\mathrm{d}u_{2j}}{\mathrm{d}t} = 1 + \frac{\kappa_{1R} u_{4j}}{\kappa_{DR} + u_{4j}} - \kappa_{2R} u_{2j} - u_{1j} u_{2j} + \kappa_5 u_{3j}\,,$$

$$\frac{\mathrm{d}u_{3j}}{\mathrm{d}t} = u_{1j} u_{2j} - \kappa_5 u_{3j} - 2\kappa_3 {u_{3j}}^2 + 2\kappa_4 u_{4j}\,, \qquad \frac{\mathrm{d}u_{4j}}{\mathrm{d}t} = \kappa_3 {u_{3j}}^2 - \kappa_4 u_{4j}\,.$$

Here u_{1j}, u_{2j}, u_{3j}, and u_{4j} are the dimensionless concentrations of AI, LuxR, LuxR-AHL, and $(LuxR\text{-}AHL)_2$, respectively.

Saddle-Node Structure: No Bulk Coupling

Steady-states of bulk-decoupled Lux system are determined by roots of the quintic $q(u_{3e}) = 0$:

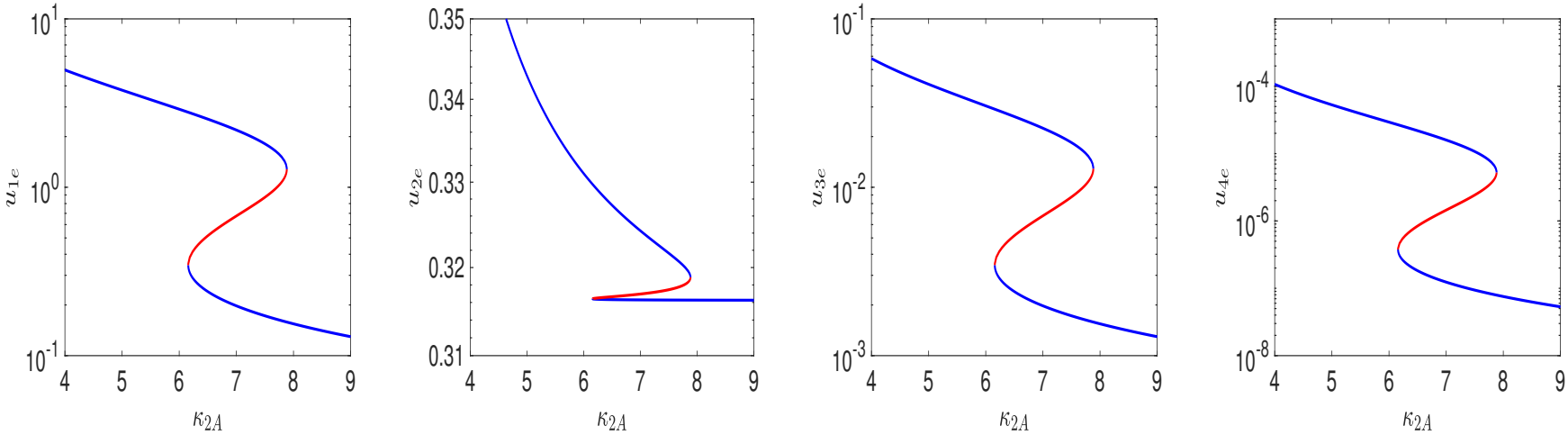
$$q(u_{3e}) \equiv \frac{1}{\kappa_{2A}\kappa_{2R}\kappa_5}\left(c + \frac{\kappa_{1A}u_{3e}^2}{\kappa_A + u_{3e}^2}\right)\left(1 + \frac{\kappa_{1R}u_{3e}^2}{\kappa_R + u_{3e}^2}\right) - u_{3e}\,,$$

where $\kappa_A \equiv \kappa_{DA}\dfrac{\kappa_4}{\kappa_3}\,, \quad \kappa_R \equiv \kappa_{DR}\dfrac{\kappa_4}{\kappa_3}\,.$

In terms of these roots u_{3e},

$$u_{4e} = \frac{\kappa_3}{\kappa_4}u_{3e}^2\,, \quad u_{1e} = \frac{1}{\kappa_{2A}}\left[c + \frac{\kappa_{1A}u_{3e}^2}{\kappa_{DA}\frac{\kappa_4}{\kappa_3} + u_{3e}^2}\right]\,, \quad u_{2e} = \frac{1}{\kappa_{2R}}\left[1 + \frac{\kappa_{1R}u_{3e}^2}{\kappa_{DR}\frac{\kappa_4}{\kappa_3} + u_{3e}^2}\right]\,.$$

With the bifurcation parameter κ_{2A}, we observe a bistable structure



$D = \mathcal{O}(1)$: QS Up-Regulated Transition: I

Proposition: *For $\nu \to 0$, the NAS of the full cell-buk coupled problem has a solution branch with $\mathbf{S} = \nu \mathbf{S}_0 \mathbf{e} + \mathcal{O}(\nu^2)$ where $\nu = -1/\log \varepsilon$, on which we have m scalar nonlinear algebraic problems $q_j(u_{3j}; m) = 0$:*

$$q_j(u_{3j}; m) \equiv \frac{1}{\kappa_j(m)\kappa_{2R}\kappa_5} \left(c + \frac{\kappa_{1A} u_{3j}^2}{\kappa_A + u_{3j}^2} \right) \left(1 + \frac{\kappa_{1R} u_{3j}^2}{\kappa_R + u_{3j}^2} \right) - u_{3j}.$$

The effective bifurcation parameter, $\kappa_j(m)$, depending on the cell index j, the population m, and cell locations through the Green's matrix is

$$\kappa_j(m) \equiv \kappa_{2A} + \frac{2\pi D \nu d_2/d_1}{1 + \nu \frac{D}{d_1} + 2\pi\nu \left(\mathcal{G}\mathbf{e}\right)_j}, \qquad \mathbf{e} \equiv (1, \ldots, 1)^T,$$

where $\mathcal{G}$ is the Green's matrix for the reduced-wave operator while $(\mathcal{G}\mathbf{e})_j$ denotes the j^{th} component of $\mathcal{G}\mathbf{e}$. In terms of the roots of $q_j = 0$,

$$u_{1j} = \frac{1}{\kappa_{2A}} \left(c + 2\pi D S_j + \frac{\kappa_{1A} u_{3j}^2}{\kappa_A + u_{3j}^2} \right), \quad u_{2j} = \frac{1}{\kappa_{2R}} \left(1 + \frac{\kappa_{1R} u_{3j}^2}{\kappa_R + u_{3j}^2} \right), \quad u_{4j} = \frac{\kappa_3}{\kappa_4} u_{3j}^2,$$

$$S_{0j} = -\frac{\nu d_2}{d_1 \kappa_{2A}} \left(c + \frac{\kappa_{1A} u_{3j}^2}{\kappa_A + u_{3j}^2} \right) \left(1 + \nu \frac{D}{d_1} + \frac{2\pi d_2 D \nu}{d_1 \kappa_{2A}} + 2\pi\nu \left(\mathcal{G}\mathbf{e}\right)_j \right)^{-1}.$$

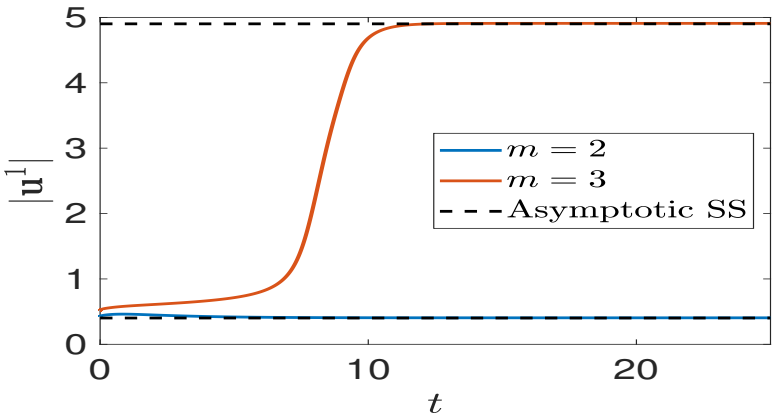
$D = \mathcal{O}(1)$: QS Up-Regulated Transition: II

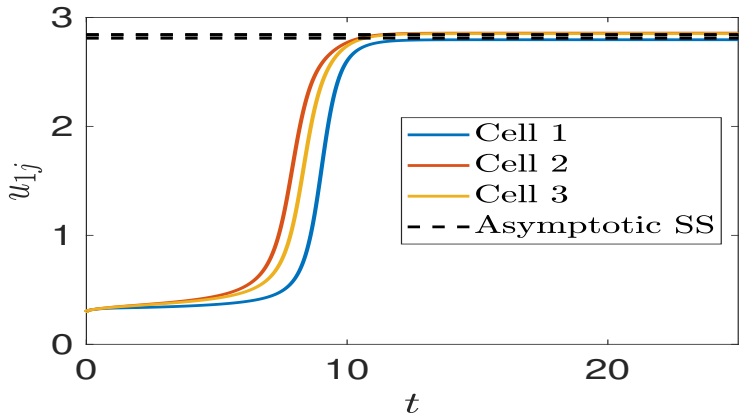
The lower saddle-node point for roots of $q = 0$ occurs at $\kappa_j = \kappa_c \approx 6.16$.
The effective parameters $\kappa_j(m)$ are

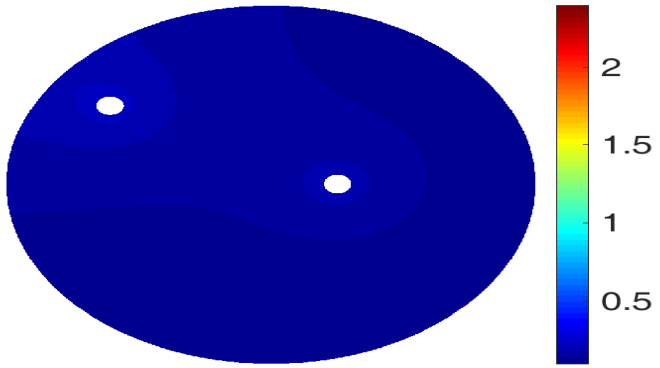
$$\kappa_1(2) \approx 6.30\,, \quad \kappa_2(2) \approx 6.21\,; \qquad \kappa_1(3) \approx 6.13\,, \quad \kappa_2(3) \approx 6.09\,, \quad \kappa_3(3) \approx 6.09\,.$$

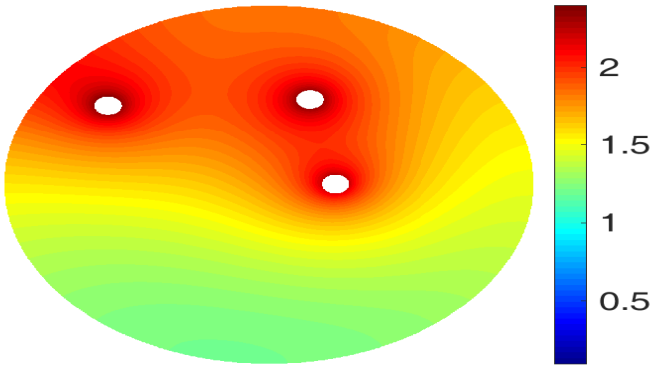
Since $\kappa_j(2) > \kappa_c$ and $\kappa_j(3) < \kappa_c$ for all $j = 1, \ldots, m$, the asymptotic theory predicts that the critical population for a QS transition is $m = 3$.

Param: $D = \tau = 1$, $\varepsilon = .05$, $d_1 = d_2 = .5$, $\boldsymbol{x}_1 = (.25, 0)^T$, $\boldsymbol{x}_2 = 0.75e^{4\pi i/5}$, $\boldsymbol{x}_3 = .5e^{2\pi i/5}$.









$D = D_0/\nu \gg 1$: QS Transitions: I

QS Transitions: For the large D regime, $D = D_0/\nu$ with $\nu \equiv -1/\log\varepsilon$, then for a ring pattern of m cells in the disk we have

$$\kappa_{\text{eff}}(m) \equiv \kappa_{2A} + \frac{2\pi D_0 d_2/d_1}{1 + \frac{D_0}{d_1} + 2\pi\nu g_1(m)},$$

where $\mathcal{G}\mathbf{e} = g_1\mathbf{e}$, and

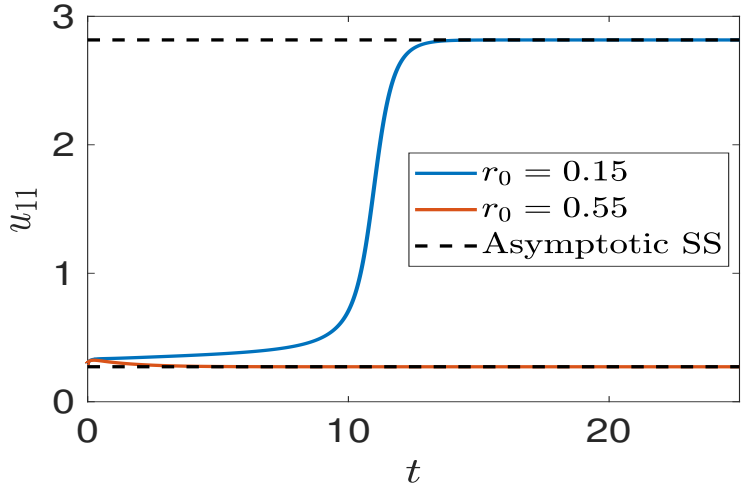
$$g_1(m) = \frac{mD_0}{\nu|\Omega|} + \frac{1}{2\pi}\left(-m\log\left(mr_0^{m-1}\right) - \log\left(1 - r_0^{2m}\right) + mr_0^2 - \frac{3m}{4}\right).$$

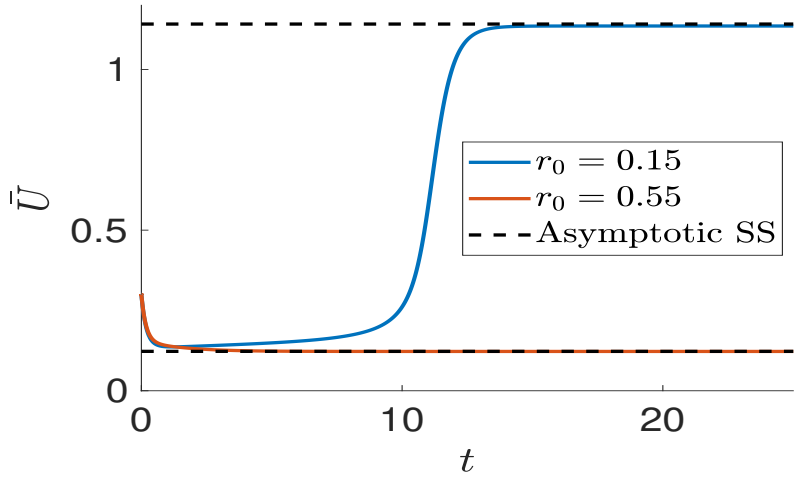
Observe that the $\mathcal{O}(1)$ term depends on the ring radius r_0. When m increases so that $\kappa_{\text{eff}}(m) < \kappa_c \approx 6.16$, we predict a QS transition.

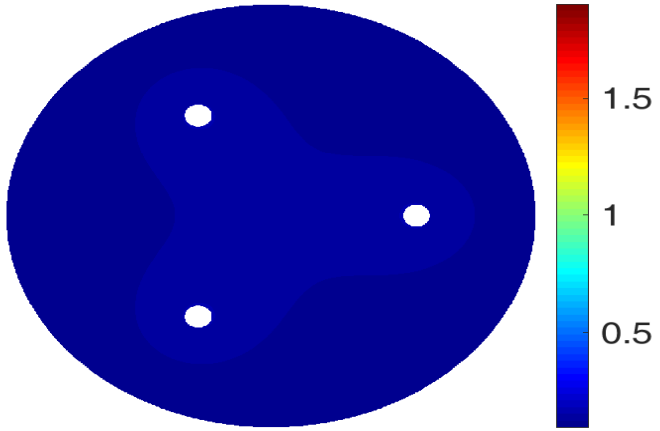
ODE-DAE Dynamics: For $D = D_0/\nu$, we have a ODE-DAE dynamical system that includes the effect of cell locations at $\mathcal{O}(\nu)$. Time-dependent QS transitions can be observed dynamically.

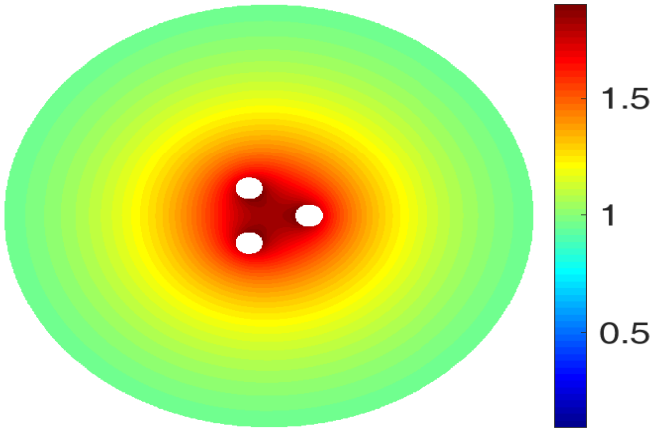
$D = D_0/\nu \gg 1$: QS Transitions: II

Cell Clustering can Trigger QS Transition to an up-regulated state.
Parameters: $D_0 = \tau = 1$, $\varepsilon = 0.05$, $d_1 = d_2 = 0.5$, $m = 3$, and ring radii $r_0 = 0.15$ (clustered) or $r_0 = 0.55$ (segregated).



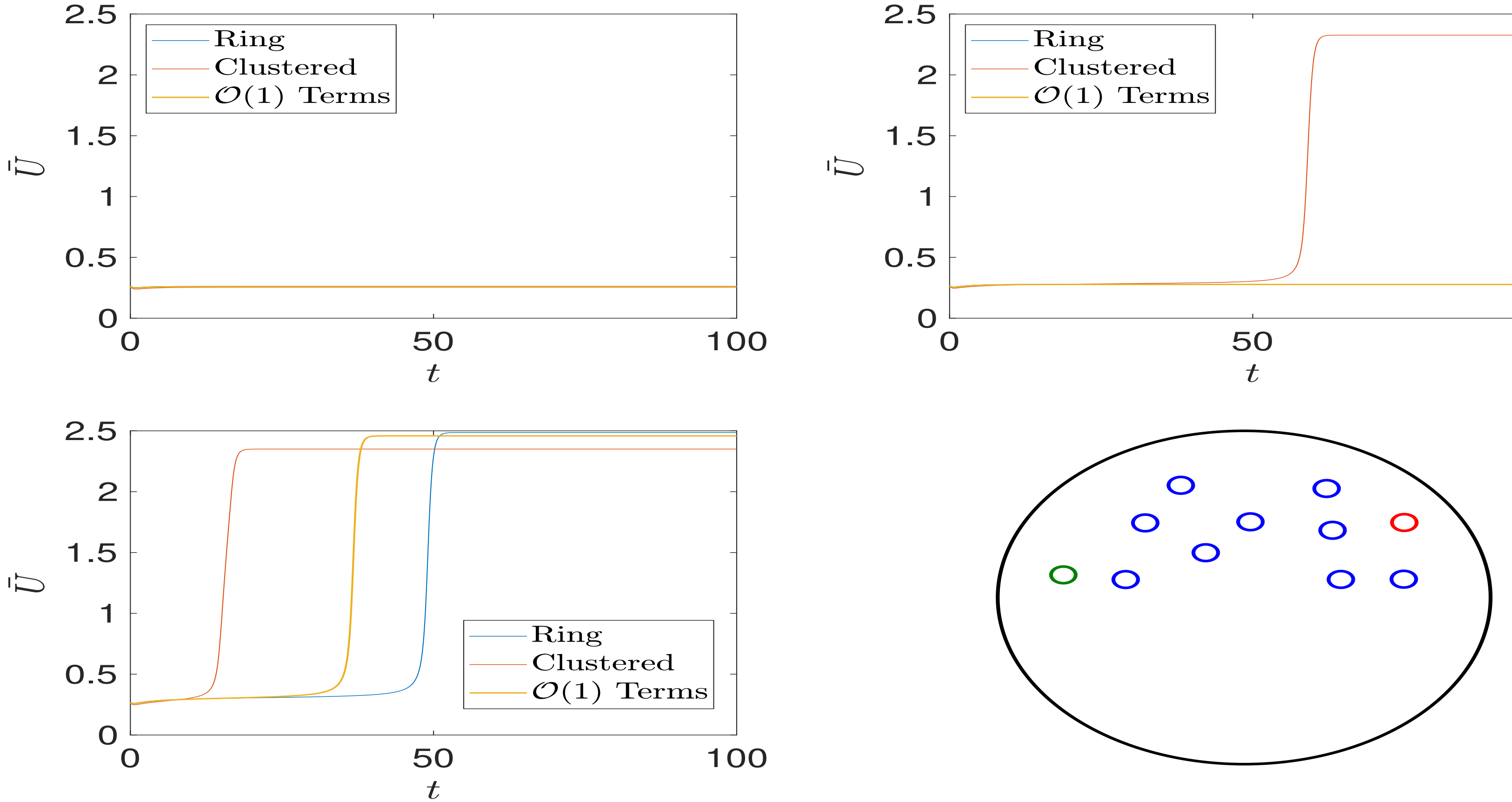






$D = D_0/\nu \gg 1$: QS Transitions: Larger m

Small m was used to confirm asymptotic theory with FlexPDE simulations.
Asymptotic theory is easy to apply for much larger m.



Caption: ODE-DAE results for Average bulk $\bar{U}$ in the top left, top right, and bottom left panels for 9, 10, and 11 cells, respectively. Weakly clustered patterns in bottom right, with green and red disks being the respective 10^{th} and 11^{th} cells. The ring pattern achieves a quorum at 11 cells, while the weakly clustered pattern has a quorum at 10 cells.

Perspectives and Extensions

- Rigourous: Well-posedness? Long-time attractors of PDE-ODE dynamics?
- Intracellular oscillatory dynamics with biologically realistic kinetics and measured permeabilities for a specific biological system (glycolysis).
- PDE-ODE Model in 3-D bounded domains. Interactions are, in general, much weaker owing to $1/r$ decay of Green's function.
- Two-bulk diffusing species with equal bulk diffusivities: Turing-type symmetry breaking bifurcations induced by membrane permeabilities? (Rauch and Millonas, 2004), (Rappel and Levine (2005).
- Numerical challenge: rootfinding on $\det\mathcal{M}(\lambda) = 0$ from the GCEP for large numbers of cells when $D = \mathcal{O}(1)$. Need reliable numerical algorithms for large-scale nonlinear matrix eigenvalue problems.
- Include models of cell motion where the cell centers slowly migrate in response to signalling gradients.
- Provides alternative framework for other agent-based models with discrete diffusion restricted to lattice sites.

References: Cell-Bulk Coupling

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- S. Iyaniwura, J. Gou, M. J. Ward, *Synchronous Oscillations for a Coupled Cell-Bulk PDE-ODE Model with Localized Cells on* $\mathbb{R}^2$, to appear, J. Eng. Math., (2020), (24 pages).

Thanks For Your Attention!