# Active Cells and Active Boundaries:

# Analysis of a PDE/ODE model for Quorum and Diffusion Sensing in Biology

Michael J. Ward (UBC)

Shanghai Jiao Tong U.

Math Biology Summer School: July 2019

**Collaborators:**, J. Gou (UC Riverside); S. Iyaniwura (UBC);

# 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) in a bounded 2-D domain.

**Specific Questions:**

- Can one trigger oscillations in the small cells (Hopf bifurcation), that would otherwise not occur without the coupling via bulk diffusion?
- Can we exhibit quorum sensing behavior by which cells oscillate and synchronize their dynamics when the population reaches a threshold?
  - In terms of the number $m$ of cells per unit area, i.e. cell population density is $\rho = m/|\Omega|$.
  - What parameters regulate this threshold?
  - Usually studied from an ODE approach.
- Can we exhibit diffusion sensing behavior whereby cells oscillate and synchronize their dynamics based on:
  - cell spatial configuration (synchronization easier for clustered cells).
  - magnitude of diffusivity $D$ of extracellular chemical (autoinducer).
  - Requires a PDE-based model.

# Dynamical Quorum Sensing in Nature

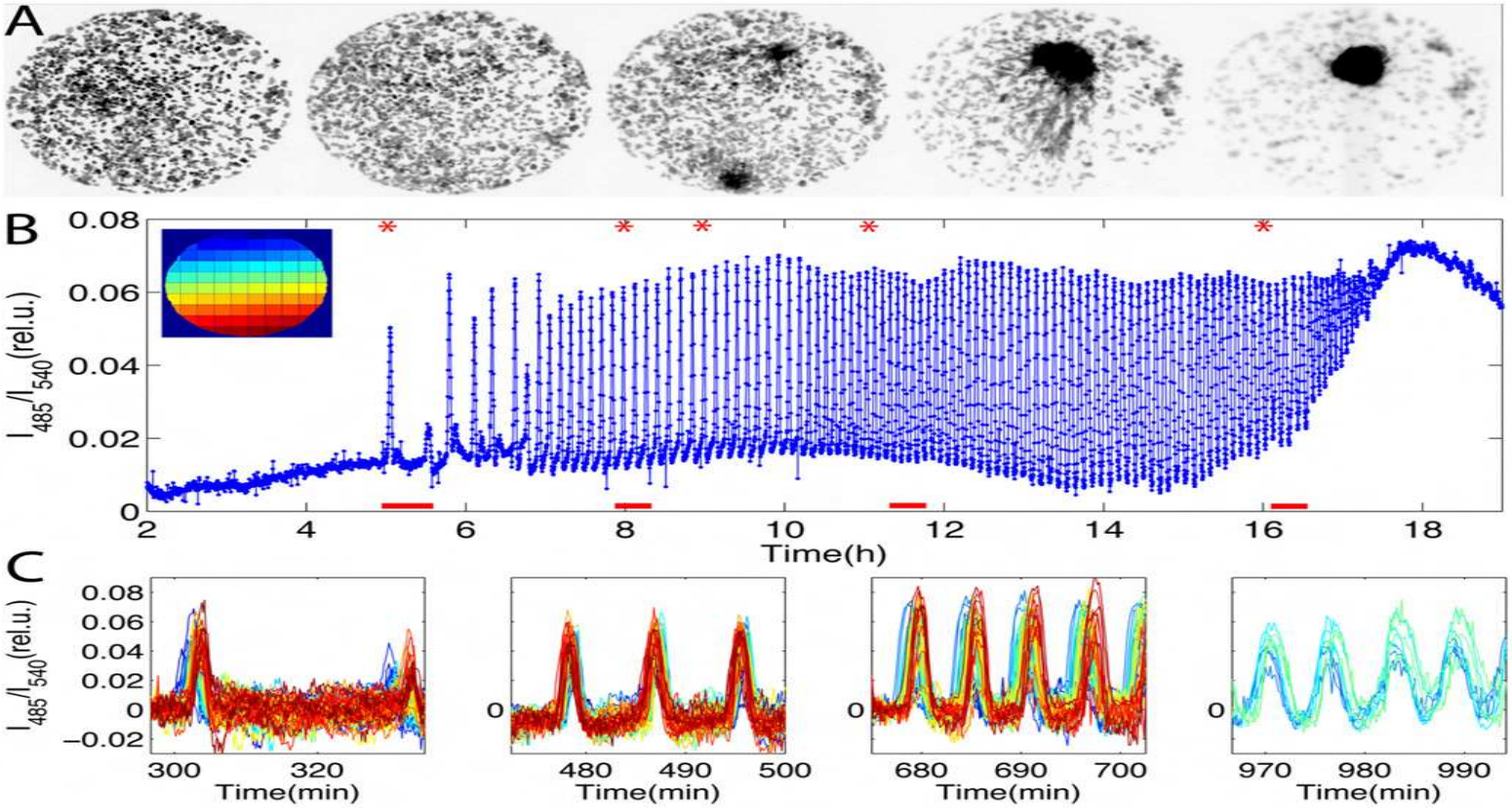
Collective behavior in “cells” driven by chemical signalling between them.

- Collections of spatially segregated unicellular (eukaryotic) organisms such as starving yeast cells (glycolysis) coupled only through extracellular signalling molecules (autoinducer 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. “Dynamical Quorum Sensing... Collections of Excitable and Oscillatory Cataytic Particles”, Physica D **239** (2010).

**Key Ingredient:** Need intracellular autocatalytic signal and an extracellular communication mechanism (bulk diffusion or autoinducer) that influences the autocatalytic growth. In the absence of coupling by bulk diffusion, the “cells” are in a quiescent state. Oscillations and ultimate sychronization occurs via a switchlike response to elevated levels of the autoinducer.

# Amoeba Colony (*Dictyostelium discoideum*)

- About 180 cells are confined into an area of 420 $\mu m$ in diameter (2-D).
- When resources are scarce, each cell secretes cAMP into the medium.
- Main Question: Is the oscillation an intrinsic property of the cells or does it only occur at the population level?




**Caption:** The cells secrete cAMP into the medium which first initiates a coordinated collective response. On longer time-scale cells aggregate. **Ref:** The Onset of Collective Behavior in Social Amoebae, T. Gregor et al. Science 2010

# Modeling Approaches

- **Large ODE system** of weakly coupled system of oscillators. Prototypical is the Kuramoto type-models for the coupled phases of the oscillators, of the form

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

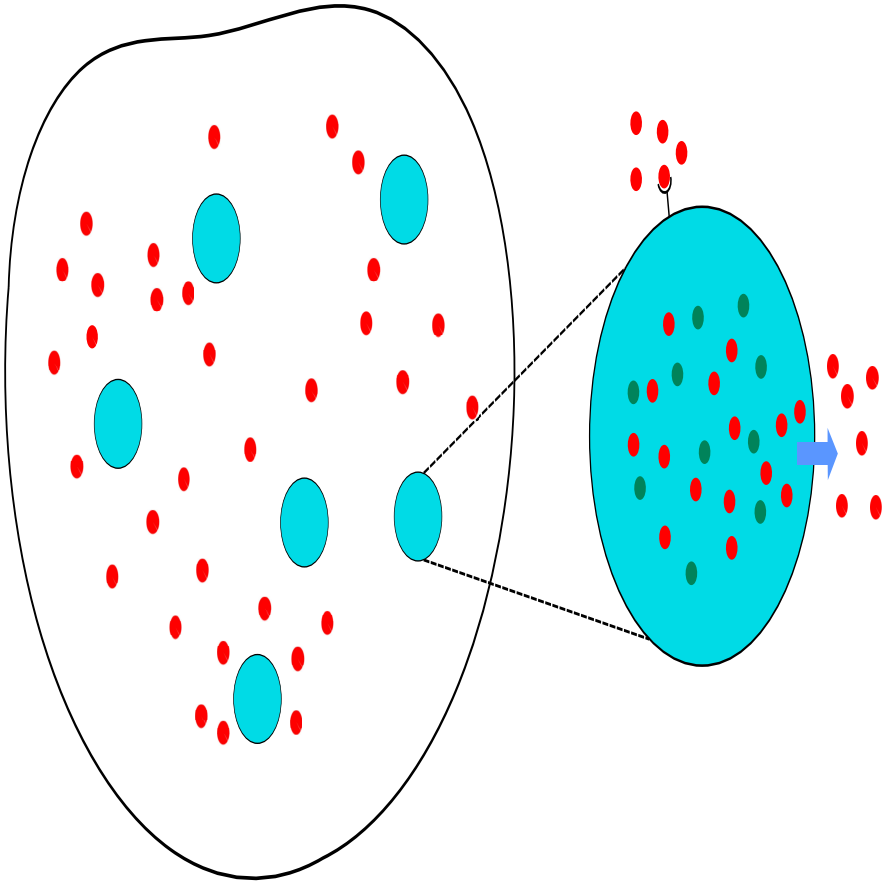
  Synchrony occurs between individual oscillators as the coupling strength $\sigma$ increases. (Vast literature, but not the mechanism here).

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

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

**Ref [GW]:** J. Gou, M.J. Ward, J. Nonlinear Sci., **26**(4), (2016), pp. 979–1029.

# Formulation of the 2-D Model: I



- The $m$ cells are circular and each contains $n$ chemicals $\mu_j = (\mu_{1j}, \ldots, \mu_{nj})^T$. When isolated they interact via ODE's $\mathbf{d}\mu_j/dt = \mathbf{F}_j(\mu_\mathbf{j})$.
- 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 $\Omega$. We assume that the permeability parameters are $\mathcal{O}(\epsilon^{-1})$.

**Parameters:** Bulk diffusivity $D_B$, bulk decay $k_B$, permeabilities, $\epsilon$, 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 $\sigma$ 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 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 $\mu_c$ is typical mass.

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

# 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 reactions. The dimensionless bifurcation parameters are: $d_{1j}$, $d_{2j}$ (permeabilities); $\tau$ (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

- Can one trigger oscillations in the small cells, via a Hopf bifurcation, that would otherwise not be present without the coupling via bulk diffusion? (i.e. each cell is a conditional oscillator). Intuition: Need reaction-time ratio $\tau$ in some interval $0 < \tau_- < \tau < \tau_+ < \infty$.
- Can we exhibit quorum sensing and diffusion sensing behavior?

**Three key regimes for $D$ with different behaviors:**

- $D = \mathcal{O}(1)$; Effect of spatial distribution of cells is a key factor whether oscillations are triggered or not (diffusion sensing behavior).
- $D = \mathcal{O}(\nu^{-1})$ with $\nu = -1/\log\epsilon$; HB thresholds can occur for both synchronous and asynchronous modes. Spatial location of cells not important to leading order.
- $D \gg \mathcal{O}(\nu^{-1})$; In this "well-mixed" regime, the PDE-ODE cell-bulk model reduces to a finite dimensional dynamical system with global coupling. Quorum sensing behavior observed.

**Mathematical Framework:** Use strong localized perturbation theory (SLPT) to construct steady-states, to formulate the linear stability problem, and to derive the limiting well mixed ODE system.

# 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* $\boldsymbol{u}^1 \equiv \left(u_1^1, \ldots, u_m^1\right)^T$*, where* $e_1 = (1, 0, \ldots, 0)^T$*:*

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

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 $\boldsymbol{F}_j$:

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

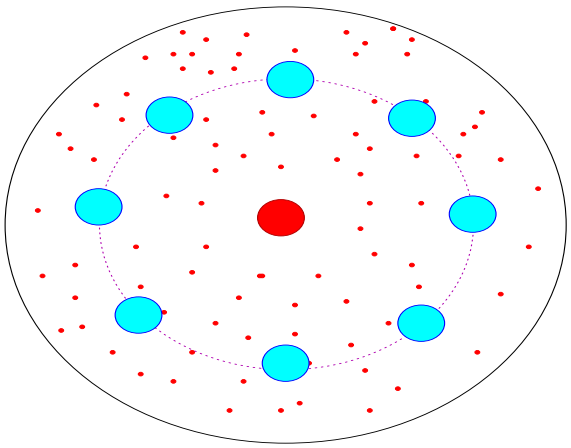
# Numerics for the GCEP

Linear stability analysis: Nonlinear matrix eigenvalue problem of the form

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

**Definition:** An unstable "mode" is a root $\lambda$ of $\mathcal{F}(\lambda)=\det\left(\mathcal{M}(\lambda)\right)=0$ in $\mathrm{Re}(\lambda)>0$. The number $N$ of unstable modes is the total number of such roots. The eigenvector $\boldsymbol{c}$ determines the amplitude and phase at each cell.

- Determine $N$ numerically from winding number computation of $\mathcal{F}(\lambda)$ over a large semi-circle in $\mathrm{Re}(\lambda)>0$. Gives a "stability map" in $(\tau,D)$ plane with $N=0$ (white), $N=2$ (grey), $N=4$ (blue), etc..
- Hopf bifurcation boundaries, $\lambda=i\lambda_I(D)$ and $\tau=\tau(D)$ can have folds in $D$. Compute with $\mathrm{Re}\mathcal{F}=0$ and $\mathrm{Im}\mathcal{F}=0$ using psuedo-arclength.



Tractable: Ring and Ring + Center Hole Pattern:

- Small identical cells inside unit disk, evenly spaced on a concentric ring of radius $r_0$.
- The center-cell can have different kinetics, or different permeabilities $d_1$ and $d_2$.
- Matrix spectrum $\mathcal{M}\boldsymbol{c}=\sigma\boldsymbol{c}$ available analytically.

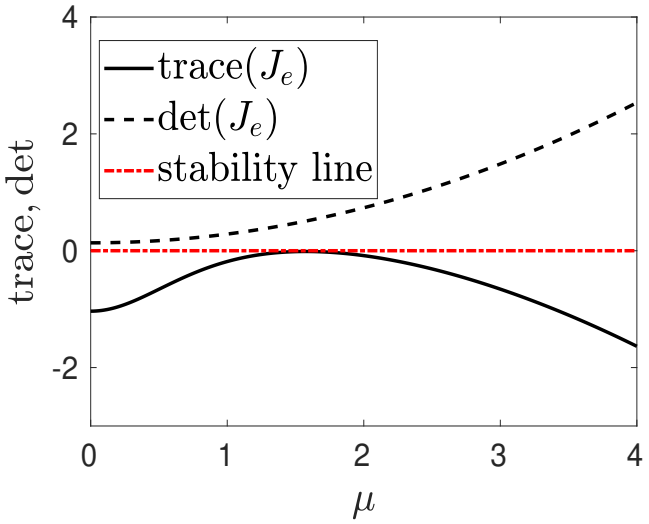
# Intracellular Selkov Reaction-Kinetics

**Selkov Kinetics:** Let $\boldsymbol{u} = (u_1, u_2)^T$ be intracellular dynamics given by Selkov model (used for modeling glycolysis oscillations):

$$F_1(u_1, u_2) = \alpha u_2 + u_2 u_1^2 - u_1\,, \quad F_2(u_1, u_2) = \epsilon_0 \left(\mu - (\alpha u_2 + u_2 u_1^2)\right)\,.$$

For an *isolated cell* $\exists$ a unique steady-state at $u_{1e} = \mu$, $u_{2e} = \mu/(\alpha + \mu^2)$. The determinant and trace of the Jacobian $J_e$ is

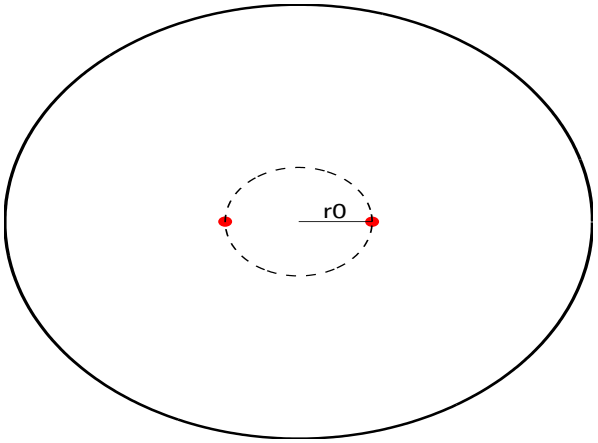
$$\text{trace}(J_e) = \frac{\left[\mu^2 - \alpha^2 - \epsilon_0(\alpha + \mu^2)^2\right]}{\alpha + \mu^2}\,, \quad \det(J_e) = \varepsilon_0(\alpha + \mu^2) > 0\,.$$




- **Fix Selkov parameters** as $\alpha = 0.9$, and $\epsilon_0 = 0.15$ and plot versus $\mu$.
- For $\mu = 2$ an isolated cell has a stable fixed point with no oscillations, but is near to stability threshold.

**Remark:** When coupled to the other cells there is a new (but unique) steady-state and the PDE-ODE coupling can trigger oscillations via a HB.

# $D = \mathcal{O}(1)$: Ring Patterns




Analytically Tractable Example:

- $m$ small cells inside the unit disk, evenly spaced on a concentric ring of radius $r_0$.
- Assume identical kinetics and permeabilities, so that $\boldsymbol{F}_j = \boldsymbol{F}$, $d_{1j} = d_1$, and $d_{2j} = d_2$.

**Spectral Problem (from GCEP):** *Must find the roots* $\lambda$ *to* $\mathcal{B}_j(\lambda) = 0$, *where*

$$\mathcal{B}_j(\lambda) \equiv \omega_{\lambda,j} + \frac{1}{2\pi\nu}\left(1 + \frac{D\nu}{d_1}\right) + \left(\frac{d_2 D}{d_1 \tau}\right)\frac{M_{11}}{\det(\lambda I - J)}\,, \qquad j = 1, \ldots, m\,.$$

*Here* $\omega_{\lambda,j}$ *are the eigenvalues of the* $\lambda$*-dependent Green's matrix* $\mathcal{G}_\lambda$*:*

$$\mathcal{G}_\lambda \boldsymbol{v}_j = \omega_{\lambda,j}\boldsymbol{v}_j\,, \qquad j = 1, \ldots, m\,,$$

- $\exists$ a steady-state with $S_j = S_c$ for all $j = 1, \ldots, m$.
- $\mathcal{G}_\lambda$ and $\mathcal{G}$ are symmetric, cyclic matrices. Hence $\boldsymbol{v}_1 = (1, \ldots, 1)^T$ (synchronous mode).
- For the unit disk, the Green's matrix $\mathcal{G}_\lambda$ is given analytically in terms of an infinite series of modified Bessel functions of complex argument.

# $D = \mathcal{O}(1)$: Ring Patterns: II

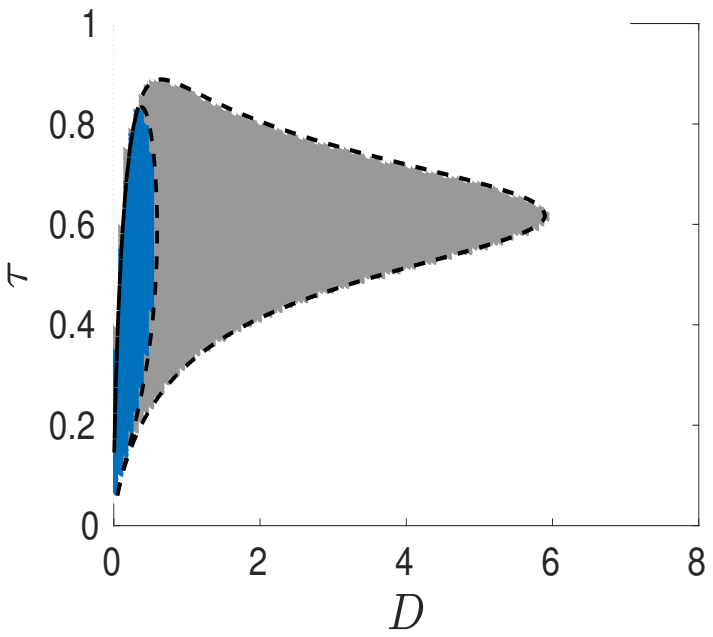
**Linear Stability Computations (Theory):**

- **Phase Diagram:** Compute Hopf Bifurcation (HB) boundaries in the $\tau$ versus $D$ plane for each $j = 1, \ldots, m$ by setting $\lambda = i\lambda_I$. Fix $r_0$, $\epsilon = 0.05$, $d_1 = 0.8$, and $d_2 = 0.2$.
- **Winding Number** computations used to check where $\mathrm{Re}(\lambda) > 0$ in open regions of the $\tau$ versus $D$ plane.
- **Cyclic Symmetric Matrices:**: Matrix spectrum of $\mathcal{G}_\lambda$ readily calculated. Note: $\boldsymbol{v}_1 = \boldsymbol{e} \equiv (1, \ldots, 1)^T$ (synchronous mode), while $\boldsymbol{e}^T \boldsymbol{v}_j = 0$ for $j = 2, \ldots, m$ are the asynchronous modes. However, mode degeneracy occurs due to cyclicity and symmetry of $\mathcal{G}_\lambda$. In particular, if $m = 5$, there are exactly two asynchronous branches.

**Qualitative Questions:** What is the effect of:

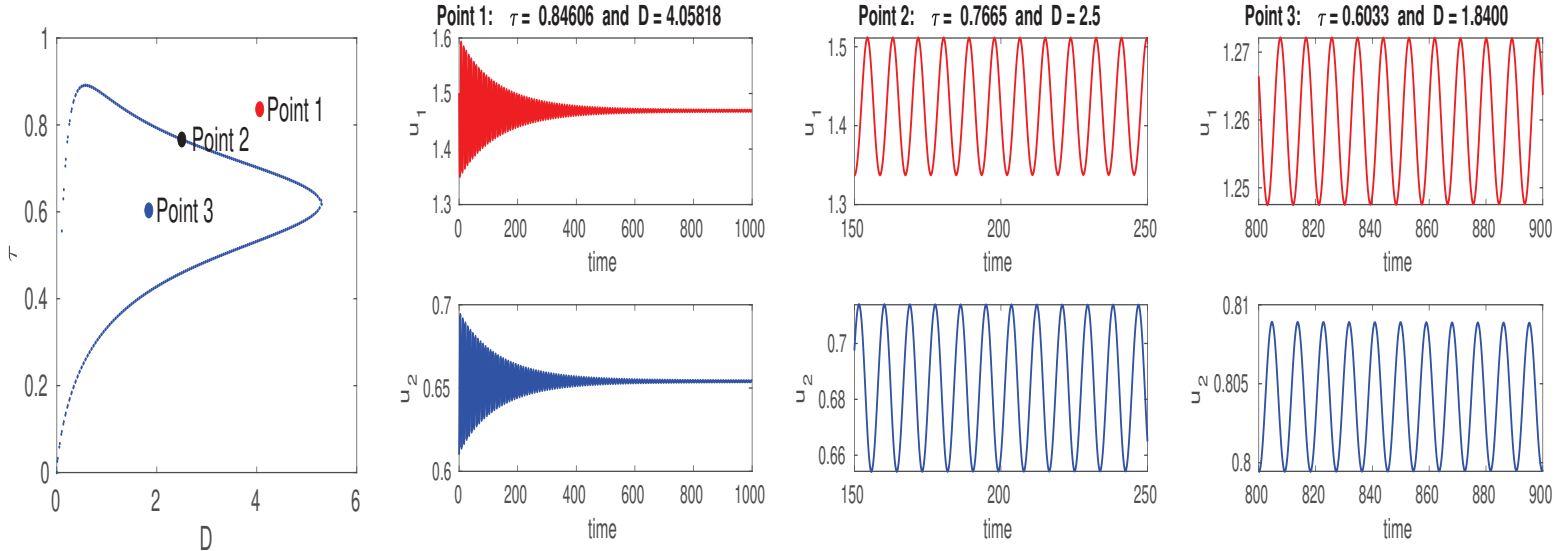
- cell clustering (i.e. smaller $r_0$?)
- the cell permeabilities $d_1$ and $d_2$?
- the number $m$ of cells?
- small changes in the intracellular kinetics?

# $D = \mathcal{O}(1)$: HB Boundaries: $m = 2$ Cells

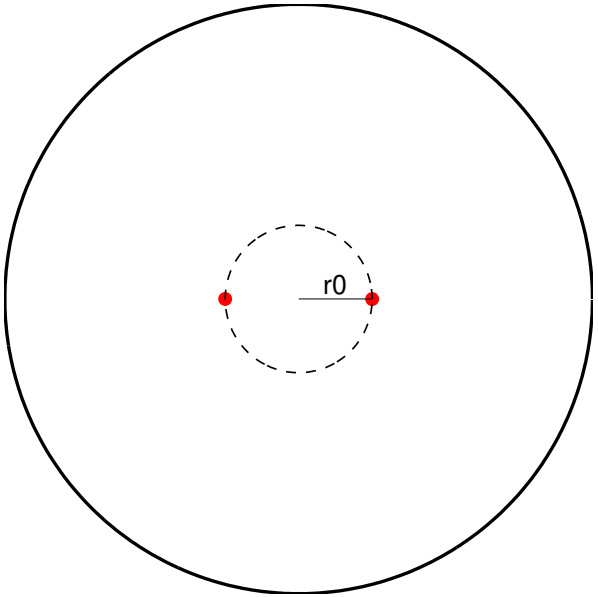


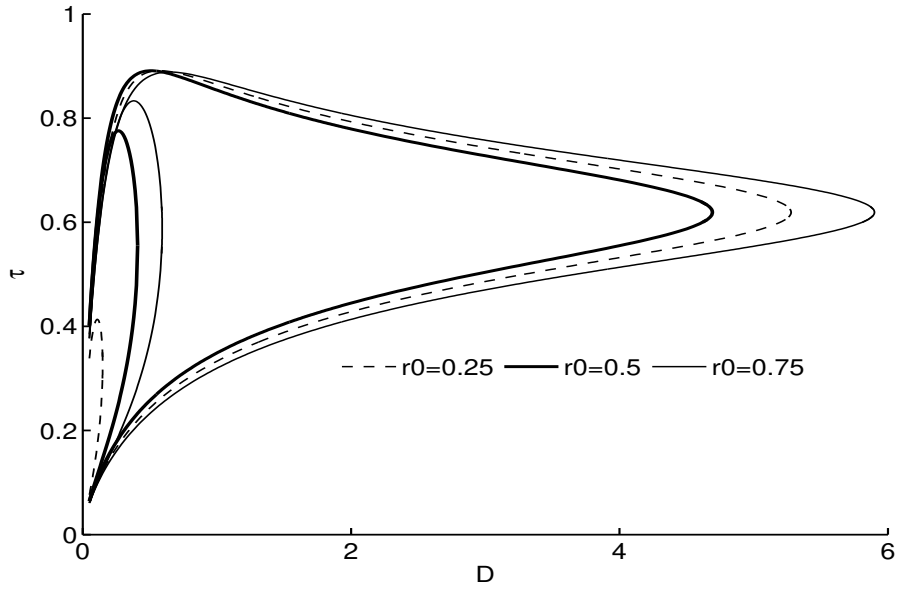

- HB boundaries $\tau$ vs. $D$ for $m = 2$ and $r_0 = 0.75$.
- Synchronous and asynchronous HB boundaries (heavy dashed).
- $N = 2$ (grey) and $N = 4$ (blue). (winding-number results)
- Asynchronous lobe exists only for $D$ small.
- Predicts no oscillations for $D \gg 1$.

Numerical Validation: FlexPDE for a similar map with $r_0 = 0.25$



# $D = \mathcal{O}(1)$: Diffusion Sensing Behavior



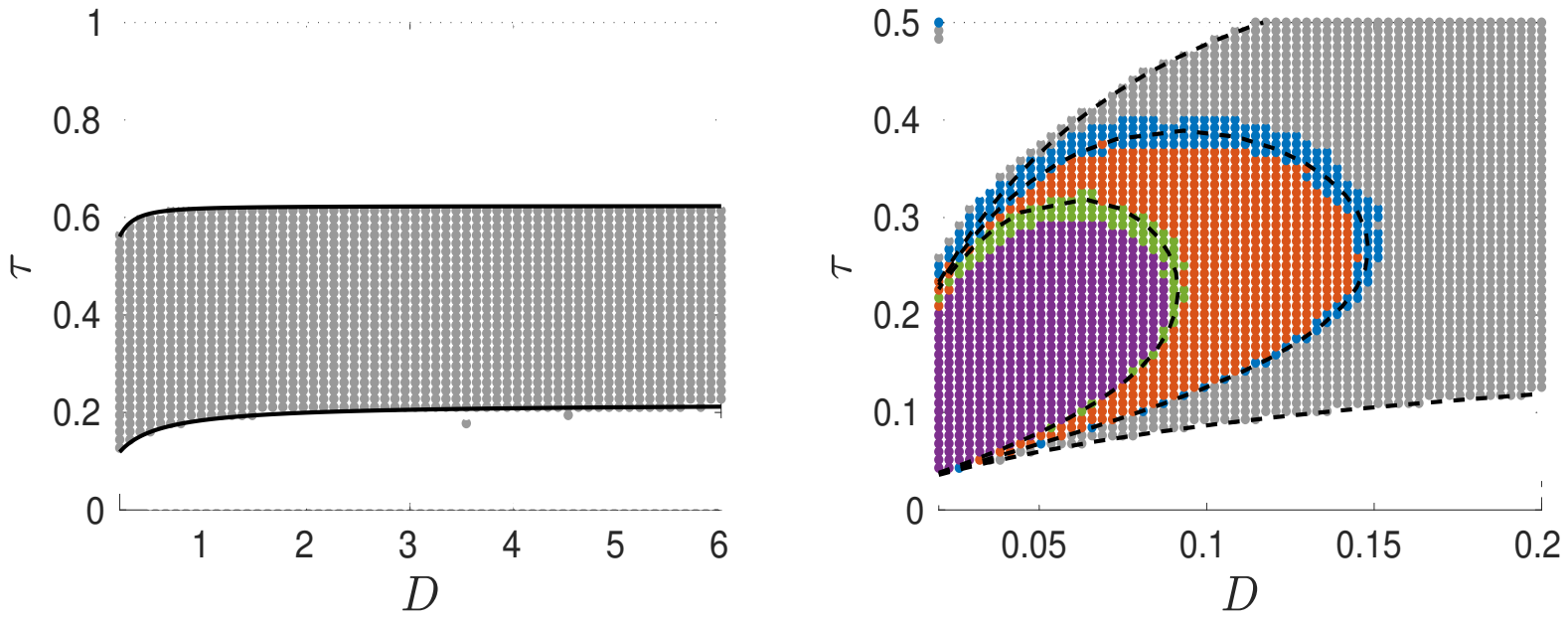




**Caption:** Let $m = 2$ and vary $r_0$: HB boundaries in $\tau$ versus $D$ for the synchronous mode (larger lobes) and the asynchronous mode (small lobes for $D$ small).

- Asynchronous lobe is smallest when $r_0 = 0.25$ (i.e. for closely-spaced cells). Implies that $D$ has to be only increased a bit before asynchronous oscillations are impossible.
- If $r_0 = 0.75$ the two cells are rather close to their images across the boundary of the disk (Neumann BC).
- Diffusion sensing: If $D = 5$ and $\tau = 0.6$, we are outside instability lobe for $r_0 = 0.5$ but within the lobes for $r_0 = 0.25$ and $r_0 = 0.75$. Thus a more clustered configuration will trigger oscillations for the same $D$.

# $D = \mathcal{O}(1)$: HB Boundaries $m = 5$

HB boundaries: $m = 5$ cells and $r_0 = 0.5$.(Right is zoom of left)

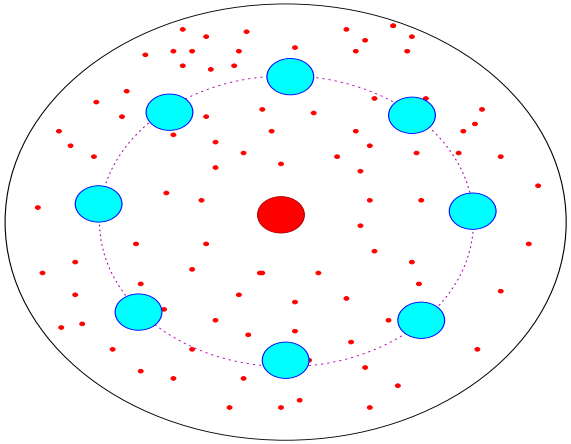



- $N = 2$ (grey), $N = 6$ (red), $N = 10$ (cyan).
- Asynchronous lobes: only for $D$ small. Two such lobes when $m = 5$.
- Instability lobe for synchronous mode is now unbounded (left figure).

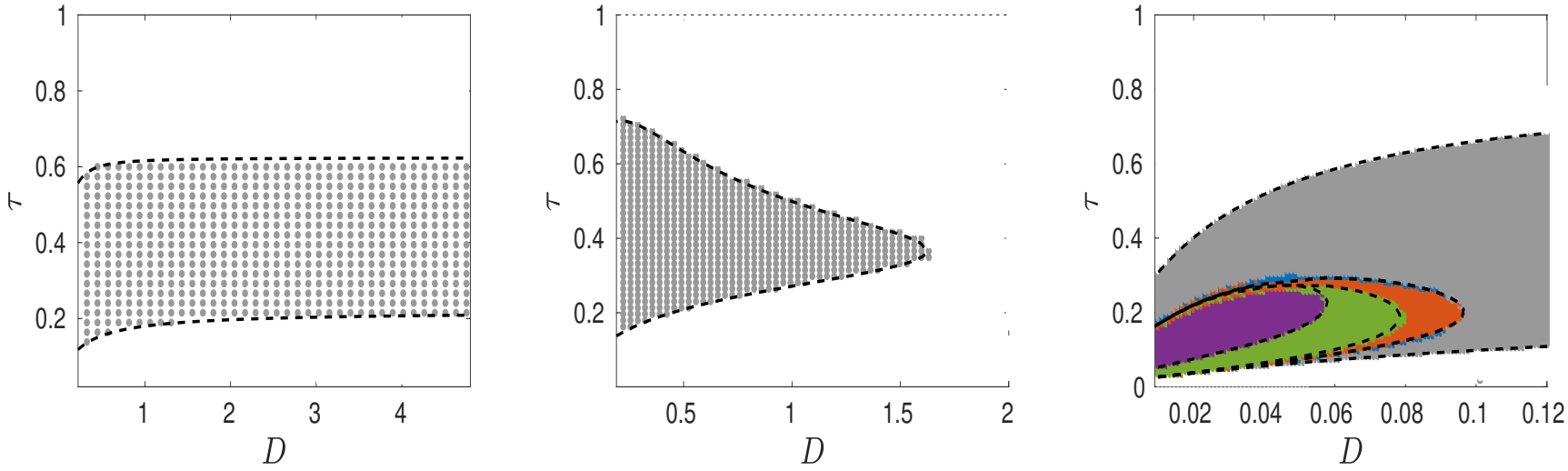
**Implication:** The unbounded lobe for the synchronous mode indicates that for the well-mixed limit $D \to \infty$ a Hopf bifurcation for the steady-state will occur when $\tau = \tau_{\pm}$ (horizontal asymptotes), and that an oscillatory instability occurs for $\tau_- < \tau < \tau_+$.

# Ring + Center Pattern: Role of Permeability

Consider $m = 5$ with a defective cell at the center of the disk with different permeabilities than four identical cells on a ring of radius $r_0 = 0.75$.



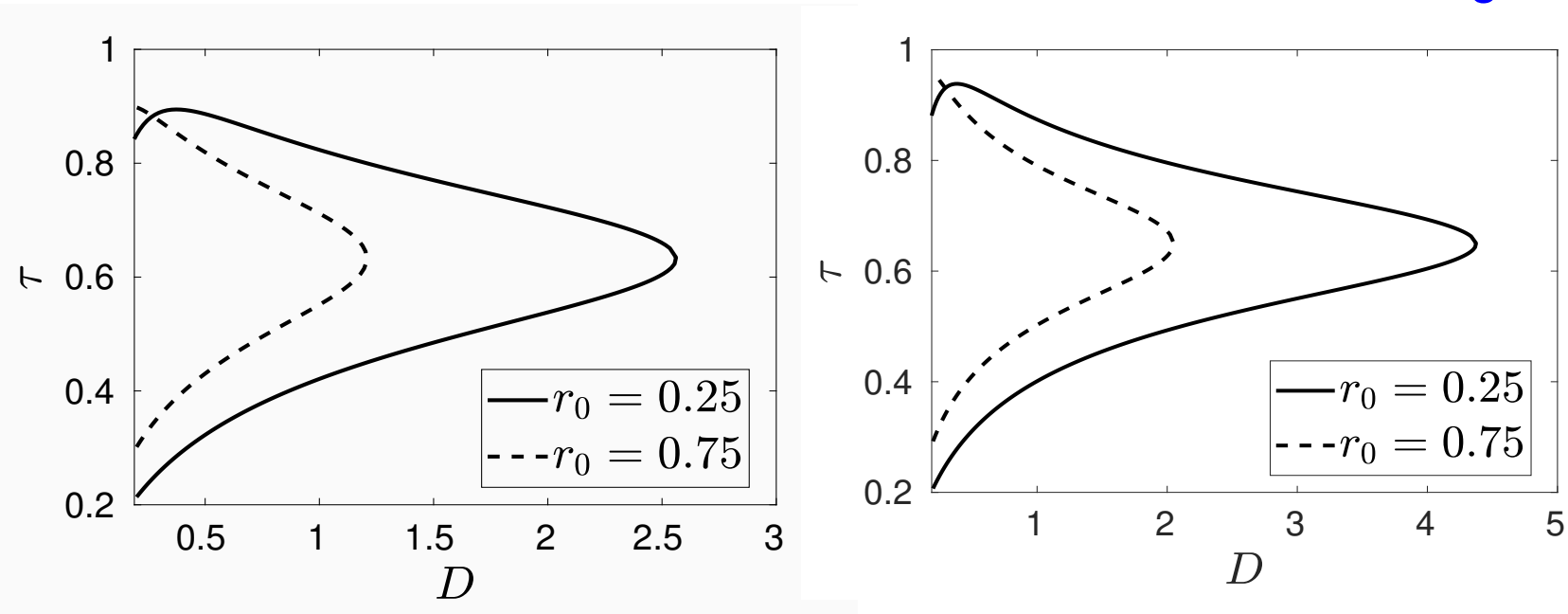
- **Ring Cells:** $d_1 = 0.8$, $d_2 = 0.2$ (identical kinetics)
- **Center Cell: Case I:** $d_1 = 0.8$, $d_2 = 0.2$. **Case II (Defective):** $d_1 = 0.4$, $d_2 = 0.2$.
- $\mathcal{M}$ is a $5\times5$ symmetric matrix with a $4\times4$ cyclic block with the fifth row being $(b, b, b, b, r)$.




**Caption:** Left: **Case I:** all identical. Middle: **Case II:** center defective. Right: Zoom for small $D$ with $N = 0$ (white), $N = 2$ (grey), $N = 4$ (blue), $N = 6$ (red), $N = 8$ (green), $N = 10$ (cyan).

# Ring + Center Pattern: A Triggering Center Cell

Consider $m = 5$ with a defective cell at the center of the disk that has a different intracellular kinetic (Selkov) parameter closer to stability threshold of an isolated cell than the four identical cells on the ring.




**Caption:** Lobes of instability for the synchronous mode $\boldsymbol{c} = (1, 1, 1, \xi)$: Left: all identical cells $d_1 = 0.3$, $d_2 = 0.2$, $\alpha = 0.9$. Right: center-cell has $\alpha = 0.86$.

- Small change in intracellular kinetics can have large effect on region in $\tau$ versus $D$ parameter space where oscillations occur.
- With more clustering $(r_0 = 0.25)$, one can have a larger bulk diffusivity $D$ before autoinducer wanders too far from cells to trigger collective behavior.

# The Distinguished Limit $D = D_0/\nu$

**Simplification:** Assume identical intracellular dynamics: so $\boldsymbol{F}_j = \boldsymbol{F}$, $\forall j$:

- $G \sim D/|\Omega| + \mathcal{O}(1)$ and $G_\lambda \sim D/\left[(1+\tau\lambda)|\Omega|\right] + \mathcal{O}(1)$ for $D \gg 1$.
- To leading order, the source strengths are independent of the locations of cells. No spatial information to leading order in $\nu = -1/\log\epsilon$.
- The GCEP becomes: $(\sigma_1 I + \sigma_2 E)\boldsymbol{c} = 0$ for some $\sigma_j(\lambda)$, where $E = \boldsymbol{e}\boldsymbol{e}^T$ and $\boldsymbol{e} = (1,..,1)^T$. Thus, $\exists\ m-1$ asynchronous modes $\boldsymbol{c} = \boldsymbol{q}_j$, with $\boldsymbol{q}_j^T\boldsymbol{e} = 0$ for $j = 2,\ldots,m$. The synchronous mode is $\boldsymbol{c} = \boldsymbol{e}$.

**Lemma:** Steady-state is linearly stable to synchronous perturbations iff

$$\frac{M_{11}(\lambda)}{\det(\lambda I - J)} = -\frac{\tau}{2\pi d_2}\left(\frac{\kappa_1\tau\lambda + \kappa_2}{\tau\lambda + 1}\right); \quad \kappa_1 \equiv \frac{d_1}{D_0} + 1\,, \quad \kappa_2 \equiv \kappa_1 + 2\pi d_1\frac{m}{|\Omega|}\,,$$

has no eigenvalue in $\mathrm{Re}(\lambda) > 0$. Here $J$ is the Jacobian of $\boldsymbol{F}(\boldsymbol{u})$ at the leading-order steady-state for $D = \mathcal{O}(\nu^{-1})$. $M_{11}(\lambda)$ is the $(1,1)$ cofactor.

**Lemma:** For $m \geq 2$, the steady-state is linearly stable to the asynchronous or competition modes iff no eigenvalue in $\mathrm{Re}(\lambda) > 0$ for

$$\frac{M_{11}}{\det(\lambda I - J)} = -\frac{\tau}{2\pi d_2}\left(\frac{d_1}{D_0} + 1\right).$$

# The Distinguished Limit $D = D_0/\nu$: II

**Lemma:** *For $n = 1$ then no HB is possible for any intracellular dynamics $F$.*

Next, let $n = 2$, so that there are two intracellular species $(u_1, u_2)^T$:

**Synchronous Mode:** Then, $\lambda$ satisfies the cubic

$$\mathcal{H}(\lambda) \equiv \lambda^3 + \lambda^2 p_1 + \lambda p_2 + p_3 = 0\,; \qquad p_1 \equiv \tau^{-1}(\gamma + \zeta) - \mathrm{tr}(J)\,,$$

$$p_2 \equiv \det(J) - \frac{\gamma}{\tau} G^e_{u_2} + \frac{1}{\tau}\left(\frac{\gamma}{\tau} - \zeta \mathrm{tr}(J)\right), \quad p_3 \equiv \frac{1}{\tau}\left(\zeta \det(J) - \frac{\gamma}{\tau} G^e_{u_2}\right).$$

Here $\gamma$ and $\zeta$ are defined in terms of the effective "cell density" $m/|\Omega|$ by

$$\gamma \equiv \frac{2\pi d_2 D_0}{d_1 + D_0} > 0\,, \qquad \zeta \equiv 1 + \frac{2\pi d_1 D_0}{(d_1 + D_0)} \frac{m}{|\Omega|} > 1\,.$$

HB criterion: By Routh-Hurwitz we must have $p_1 > 0$, $p_3 > 0$, $p_1 p_2 = p_3$.

**Asynchronous Mode:** When $n = 2$, $\lambda$ satisfies the quadratic

$$\lambda^2 - \lambda q_1 + q_2 = 0\,; \quad \text{where} \quad q_1 \equiv \mathrm{tr}(J) - \frac{\gamma}{\tau}\,, \quad q_2 \equiv \det(J) - \frac{\gamma}{\tau} G^e_{u_2}\,.$$

HB criterion: we must have $q_1 = 0$ and $q_2 > 0$.

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

**Goal:** Derive and analyze a reduced finite-dimensional dynamical system characterizing the cell-bulk interations from PDE-ODE system for $D \to \infty$.

**An asymptotic analysis** yields that in the bulk that $u(x,t) \sim U_0(t)$, where

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

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

where $\boldsymbol{e}_1 = (1, 0, \ldots, 0)^T$. Here $\rho$ is the effective cell density and

$$\rho \equiv \frac{m}{|\Omega|} , \qquad \kappa_{1,j} \equiv 2\pi d_{1,j} , \qquad \kappa_{2,j} \equiv 2\pi d_{2,j} .$$

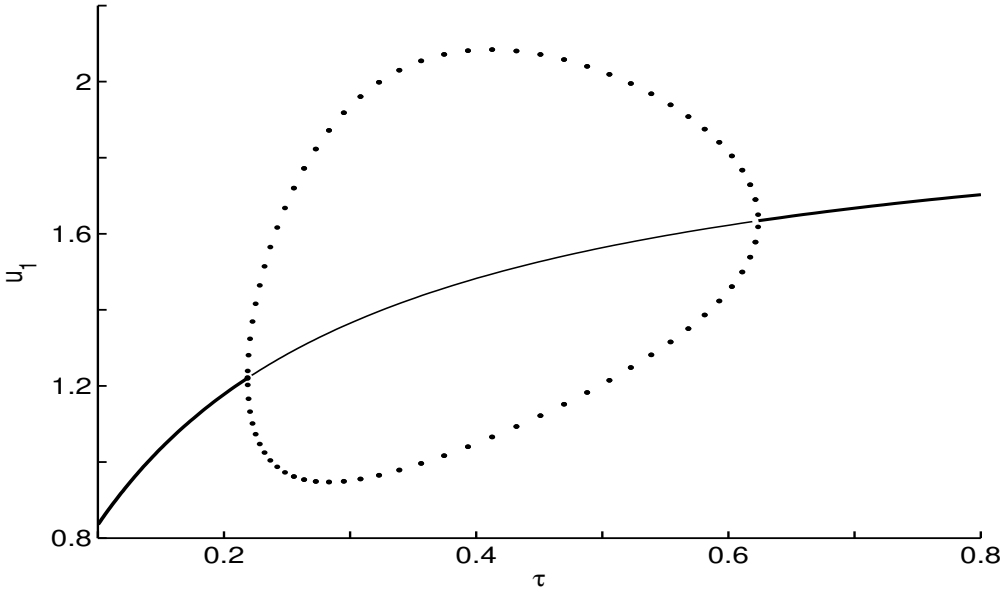
Large system of ODEs with weak but global coupling when $0 < d_{1j} << 1$ and $0 < d_{2j} \ll 1$, or when $\tau \gg 1$.

**Identical Cells:** Look for $\boldsymbol{u}_j = \boldsymbol{u}$ , $\forall j$. We get

$$U_0' = -\frac{1}{\tau} \left( 1 + \kappa_1 \rho \right) U_0 + \rho \frac{\kappa_2}{\tau} u_1 , \qquad \boldsymbol{u}' = \boldsymbol{F}(\boldsymbol{u}) + \frac{1}{\tau} \left[ \kappa_1 U_0 - \kappa_2 u_1 \right] \boldsymbol{e}_1 .$$

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

Selkov with $d_1 = 0.8$, $d_2 = 0.2$ and $|\Omega| = \pi$. Global Bifurcation Study.




Caption: Global solution branches $u_{1e}$ versus $\tau$ for $m = 5$ cells: Heavy (thin) solid is stable (unstable) steady-steady. Dots indicate stable periodic solution branch. HB points at $\tau_{H-} = 0.2187$ and $\tau_{H+} = 0.6238$.

**Key:** Stable synchronous oscillations occur in some $\tau$ interval. Limiting well-mixed ODE dynamics is independent of cell locations and $D$.

**Quorum sensing** (Qualitative): Collective behavior of "cells" in response to changes in their population size. There is a threshold number $m_c$ of cells or a critical cell density $\rho$ that is needed to initiate a collective behavior.

**Quorum sensing** (Math): For what range of $m$, do the well-mixed ODEs have a stable periodic solution on $\tau_{H-} < \tau < \tau_{H+}$ with HB points at $\tau_{H\pm}$?

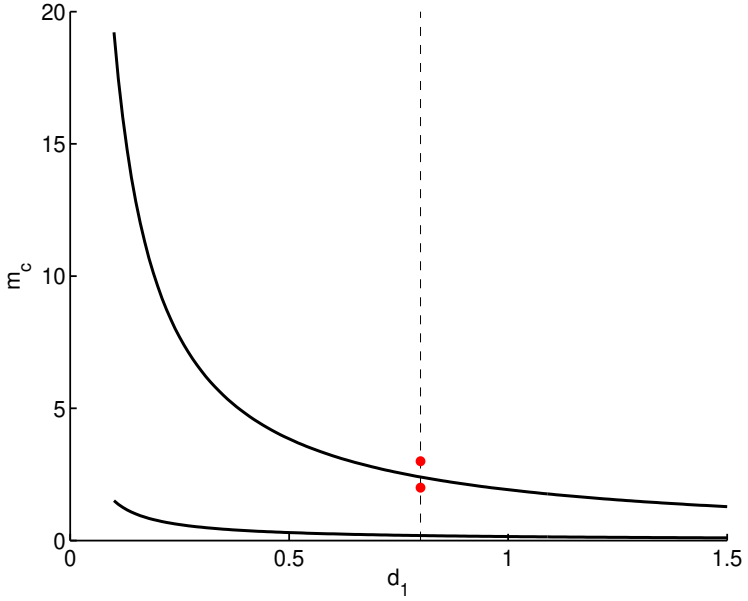
# Quorum Sensing Behavior

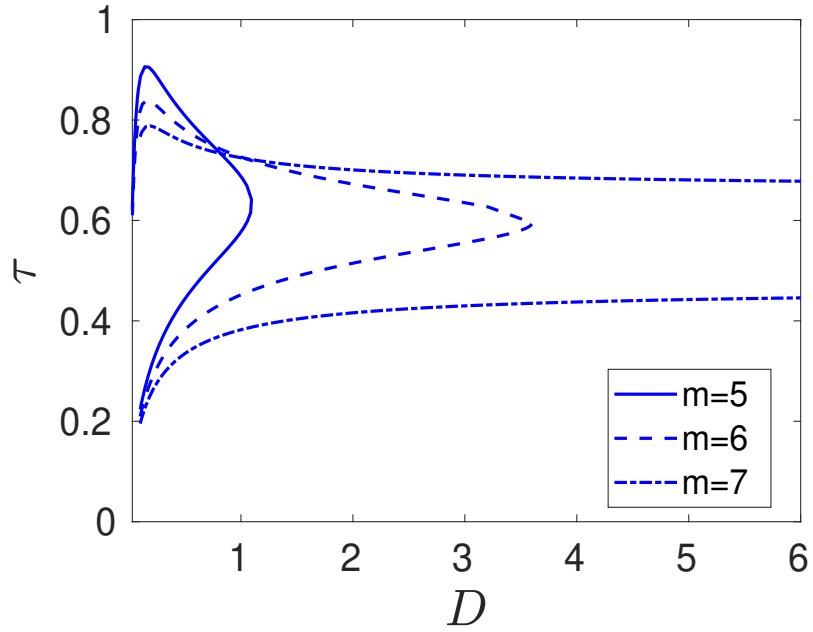
What parameters control control QS behavior? We will study QS behavior as the permeability $d_1$ is varied and $d_2 = 0.2$: Recall:

$$\partial_{n_j} U = d_1 U - d_2 u_j^1 \,, \qquad \text{on} \quad \partial\Omega_{\varepsilon_j} \,, \quad j = 1, \ldots, m \,.$$

**Remark:** Equivalent to finding the range of $m$ for which the instability lobe for the synchronous mode is unbounded in the $\tau$ versus $D$ plane.

Left: Quorum threshold $m_c$ vs. $d_1$ from ODEs. Right: $\tau$ vs. $D$ for $d_1 = 0.3$, $r_0 = 0.5$.




Key: $m_c$ sensitive to small changes in $d_1$

$d_1 = 0.8\,, m_c = 3\,;$ $d_1 = 0.3\,, m_c = 7\,;$ $d_1 = 0.2\,, m_c = 12\,;$ $d_1 = 0.1\,, m_c = 19\,.$

# Large Cell Populations: Synchronization I

In the well-mixed limit $D \to \infty$, the PDE-ODE system reduces to

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

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

where $\rho = m/|\Omega|$ is the "cell density" $\kappa_{1,j} \equiv 2\pi d_{1,j}$ and $\kappa_{2,j} \equiv 2\pi d_{2,j}$.

**Non-Identical Cells:** We take $\tau = 0.5$, and fix common permeability parameters $d_{1j} = 0.8$ and $d_{2j} = 0.2 \ \forall j$. The intracellular kinetics $\boldsymbol{F}_j$ are not identical. Selkov parameters $\varepsilon_0 = 0.15$ and $\mu = 2$ are fixed for each cell, but $\alpha$ can vary from cell to cell. Isolated cells are not oscillatory.

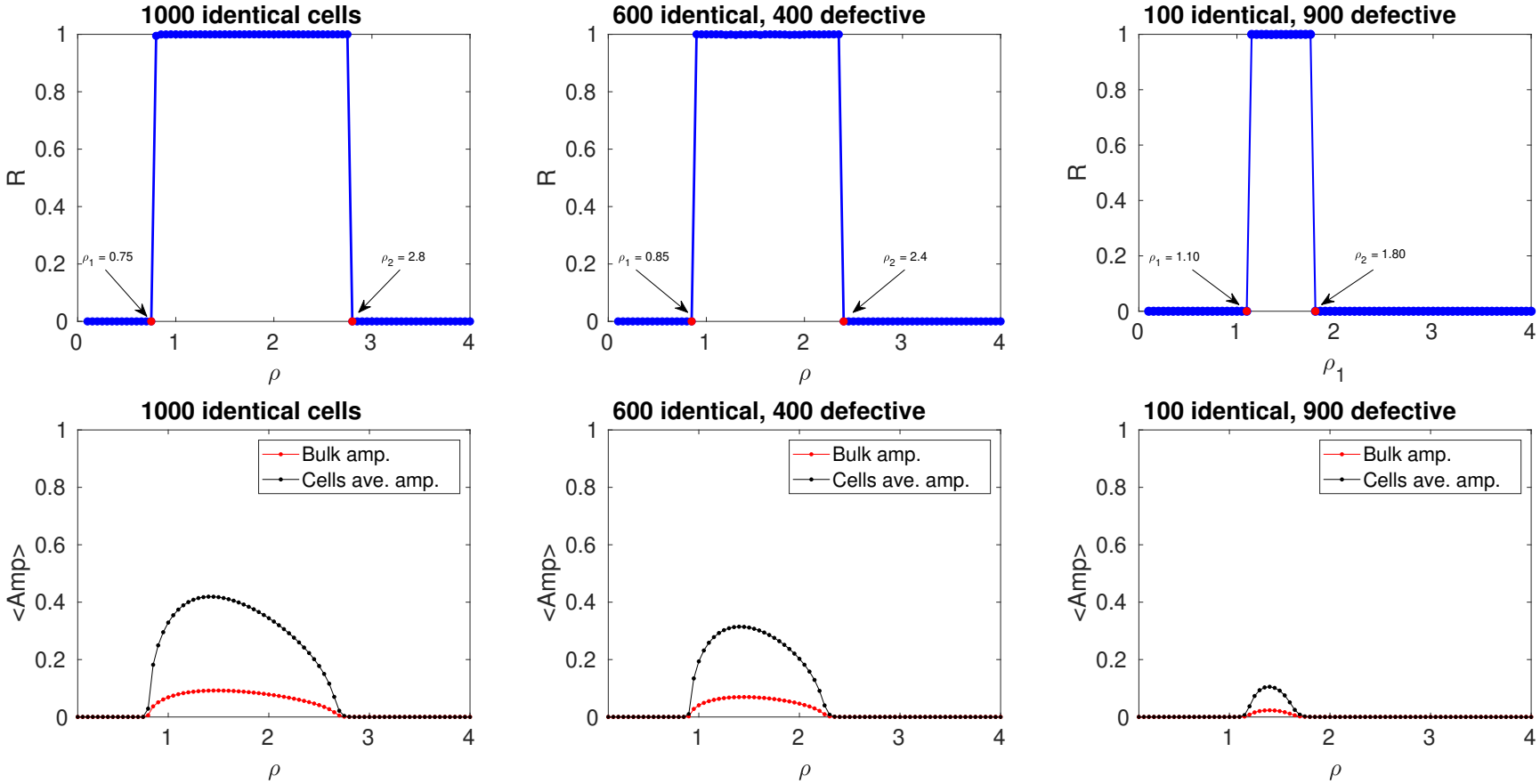
**Kuramoto order parameter:** (measures the degree of oscillator phase synchrony):

$$R = \left\langle \left| N^{-1} \sum_{j=1}^{N} \exp[i\theta_j(t)] - \left\langle N^{-1} \sum_{j=1}^{N} \exp[i\theta_j(t)] \right\rangle \right| \right\rangle , \quad 0 \le R \le 1 .$$

$R = 1$ (Perfect phase synchrony); $R = 0$ (No phase coherence);

# Large Cell Populations: Synchronization II

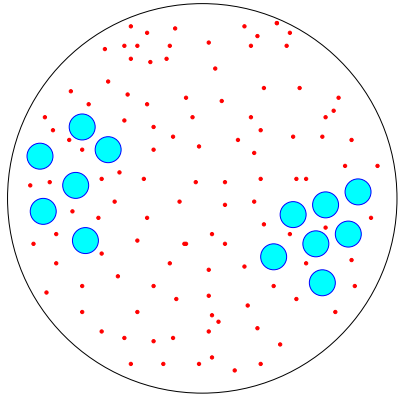
Computations of order parameter $R$ with respect to $\rho$. Iyaniwura (UBC)




- Identical cells: $\alpha = 0.9$. "Defective" cells: $\alpha$ is random in $0.921 \leq \alpha \leq 0.952$.
- Population density $\rho$ plays a dual role of triggering and quenching oscillations
- Interval of $\rho$ where synchrony occurs decreases as the number of defective cells increases.

# Cell-Bulk Model: Further Directions

Let $D = \mathcal{O}(1)$. Consider $m$ "randomly" placed cells in a disk. Can we observe clusters of oscillating and non-oscillating cells? (i.e. "chimera"-type states.)



- How do we solve the spectral problem in arbitrary domains? (fast multipole methods for $G$ and $G_\lambda$)
- Numerics for the GCEP for large numbers of cells.
- What if the steady-state solution is not unique (hysteresis) or if intracellular dynamics has a time-delay?
- Intracellular dynamics to model a specific biological system (LuxIR circuit in *Vibrio fischeri*).
- Derive a RD system in the homogenized limit of $m \gg 1$ but $m\epsilon^2 \ll 1$.
- Two bulk-diffusing (autoinducer) species.
- PDE-ODE Model in 3-D. (interactions are, in general, much weaker owing to $1/r$ decay of Green's function).

# PDE-ODE Cell-Bulk Model in 3-D

The dimensionless bulk concentration $U(\mathbf{x},t)$ satisfies

$$\frac{\partial U}{\partial t} = D\,\Delta U - \kappa\, U, \quad \mathbf{x}\in\Omega\setminus\cup_{j=1}^{m}\Omega_{\varepsilon_j}\,; \quad \partial_n U = 0, \quad \mathbf{x}\in\partial\Omega\,,$$

$$\varepsilon D\,\partial_n U = d_{1,j}\,U - \frac{d_{2,j}}{\varepsilon}u_j^1\,, \quad \mathbf{x}\in\partial\Omega_{\varepsilon_j}\,, \quad j=1,\ldots,m,$$

which is coupled to the dimensionless intracellular dynamics for the $j^{\text{th}}$ cell

$$\frac{d\boldsymbol{u}_j}{dt} = \boldsymbol{F}_j\left(\boldsymbol{u}_j\right) + \boldsymbol{e}_1\int_{\partial\Omega_{\varepsilon_j}}\left(\frac{d_{1,j}}{\varepsilon}U - \frac{d_{2,j}}{\varepsilon^2}u_j^1\right)dS\,, \quad j=1,2,\ldots,m,$$

where $\boldsymbol{u}_j = (u_j^1,\ldots,u_j^n)^T$, $\boldsymbol{e}_1\equiv(1,0,...,0)^T$, and $d_{2,j}=\mathcal{O}(1)$.

**Near Well-Mixed Limit:** An interesting limit where there is $\mathcal{O}(1)$ interaction between the cells is when

- $D=\mathcal{O}(\varepsilon^{-1})$, $\kappa=\mathcal{O}(1)$, $d_{1,j}=\frac{\widetilde{d}_{1,j}}{\varepsilon}$, where $\widetilde{d}_{1,j}=\mathcal{O}(1)$ .
- In this regime, Quorum and Diffusing sensing can be studied through a common limiting system.

# ODE System in Near Well-Mixed Limit

In this limit, the PDE-ODE system reduces to

$$U_0' = -\kappa\, U_0 + \frac{4\pi}{|\Omega|}\sum_{j=1}^{m}(p_{2,j}\, v_j^1 - p_{1,j}\, U_0) - \frac{16\pi^2\varepsilon}{|\Omega|}\sum_{j=1}^{m} p_{1,j}\,(\mathcal{G}\,\boldsymbol{c})_j + \dots\,,$$

$$\frac{d\boldsymbol{v}_j}{dt} = \boldsymbol{F}_j\,(\boldsymbol{v}_j) + 4\pi\boldsymbol{e}_1(p_{1,j}U_0 - p_{2,j}v_j^1) + 16\varepsilon\pi^2\,\boldsymbol{e}_1\,p_{1,j}(\mathcal{G}\,\boldsymbol{c})_j + \dots\,,\quad j = 1,\dots,m\,,$$

where $\boldsymbol{c} = (c_1,\dots,c_m)^T$, $\mathcal{G}$ is Neumann Green's matrix in 3-D and

$$p_{1,j} \equiv \frac{D_0\,\widetilde{d}_{1,j}}{\widetilde{d}_{1,j} + D_0}\,,\quad p_{2,j} \equiv \frac{D_0\,d_{2,j}}{\widetilde{d}_{1,j} + D_0}\,,\quad c_j \equiv \frac{d_{2,j}v_j^1 - \widetilde{d}_{1,j}U_0}{\widetilde{d}_{1,j} + D_0}\,,\quad j = 1,\dots,m\,.$$

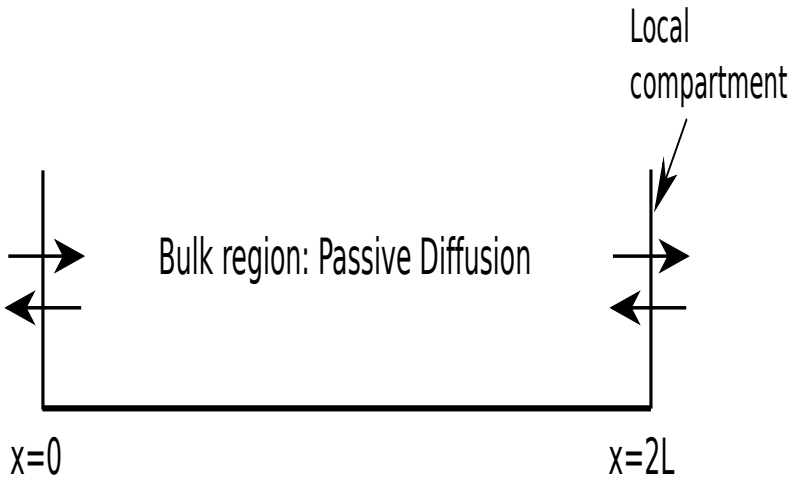
- For $D_0 \to 0$, then $p_{1,j} \to 0$ and $p_{2,j} \to 0$ (no cell-cell communication).
- For $D_0 \to \infty$ (well-mixed), then $p_{1,j} \to \widetilde{d}_{i,j}$, $p_{2,j} \to d_{2,j}$, and $c_j \to 0$ (maximal cell-cell communication, but cell configuration insignificant).
- For $D_0 = \mathcal{O}(1)$ dependence on cell configuration and shape of confining domain $\Omega$ is at $\mathcal{O}(\varepsilon)$ term through Neumann G-matrix $\mathcal{G}$.
- ODE system: reveals both quorum sensing and diffusion sensing behavior.

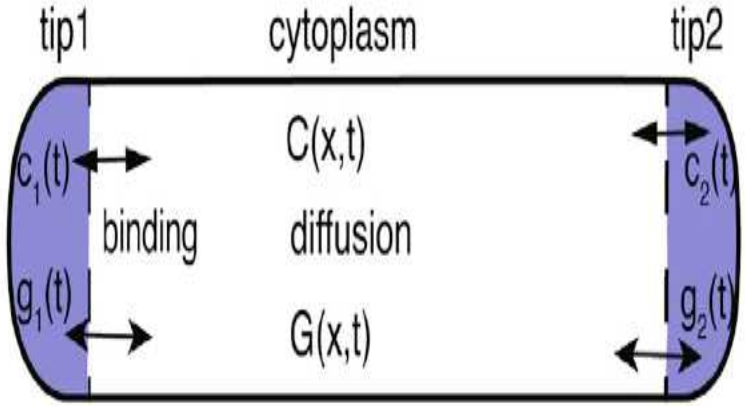
# Thanks For Your Attention!

# Topic II: 1-D PDE-ODE Bulk-Cell Model

**Mathematical Model:**

- One compartment (cell) at each endpoint of the domain $[0, 2L]$.
- $N$ dynamically interacting substances within each cell, but only one substance can be secreted into the bulk $0 < x < 2L$.
- The signaling substance diffuses and is degraded in the bulk.
- Distinct from "quasi-static" models where compartments yield nonlinear flux-type boundary conditions. (Glass et al, Othmer, Riecke).




**Ref [GLNW]:** J. Gou, Y. X. Li, W. Nagata, M. J. Ward, *Synchronized Oscillatory Dynamics for a 1-D Model of Membrane Kinetics Coupled by Linear Bulk Diffusion*, SIADS, **14**(4), (2015), pp. 2096–2137.

# 1-D Theory: General Model

The bulk diffusion field $C(x,t)$ for the signalling molecule satisfies

$$\tau C_t = DC_{xx} - C\,, \qquad t>0\,, \quad 0<x<2L\,,$$
$$DC_x(0,t) = G(C(0,t),u_1(t))\,, \qquad -DC_x(2L,t) = G(C(2L,t),v_1(t))\,.$$

Inside each compartment, there are $N$ species that can interact, and that their dynamics are described by $N$-ODE's of

$$\frac{d\boldsymbol{u}}{dt} = \boldsymbol{\mathcal{F}}(\boldsymbol{u}) + \beta\mathcal{P}(C(0,t),u_1)\boldsymbol{e_1}\,, \qquad \frac{d\boldsymbol{v}}{dt} = \boldsymbol{\mathcal{F}}(\boldsymbol{v}) + \beta\mathcal{P}(C(2L,t),v_1)\boldsymbol{e_1}\,.$$

where $\boldsymbol{u} = (u_1,u_2,...,u_N)^T$ and $\boldsymbol{e}_1 = (1,0,...,0)^T$. Thus, only one component can diffuse into the bulk.

**Special Case:** Linear coupling is a special case

$$G(a,b) = \kappa_1(a-b)\,, \qquad \mathcal{P}(a,b) = a-b\,.$$

**Conditional Oscillator:** When $\beta = 0$, we assume that the isolated ODE system has a linearly stable steady state. With coupling to the bulk the steady-state is modified, and can trigger oscillations through a HB.

# Steady State and Linear Stability

Assuming identical compartments, the symmetric steady-state solution satisfies a nonlinear algebraic system

$$-C_e^0 \tanh(\omega_0 L) = \omega_0 G(C_e^0, u_{1e}), \quad \boldsymbol{\mathcal{F}}(\boldsymbol{u}) + \beta \mathcal{P}(C(0,t), u_1)\boldsymbol{e_1} = 0.$$

To study its linear stability, we introduce

$$C(x,t) = C_e(x) + e^{\lambda t}\eta(x), \quad \boldsymbol{u} = \boldsymbol{u}_e + e^{\lambda t}\boldsymbol{\phi}.$$

Upon linearizing, we obtain a Steklov-type spectral problem for $\phi$ and $\eta(x)$ on $0 < x < L$:

$$D\eta_{xx} - (1+\tau\lambda)\eta = 0, \qquad 0 < x < L; \qquad D\eta_x(0) = G_c^e \eta_0 + G_{u_1}^e \phi_1,$$
$$J_e\boldsymbol{\phi} + \beta(\mathcal{P}_c^e \eta_0 + \mathcal{P}_{u_1}^e \phi_1)\boldsymbol{e}_1 = \lambda\boldsymbol{\phi}.$$

For the boundary condition of $\eta(x)$ at the midline $x = L$, we have two possibilities:

$$\phi_x(L) = 0, \qquad \text{Even: In-Phase Synchronization}$$
$$\phi(L) = 0, \qquad \text{Odd: Anti-Phase Synchronization}$$

# Linear Stability Analysis

For both cases, the eigenvalue $\lambda$ are roots of $\mathcal{G}(\lambda) = 0$, where

$$\mathcal{G}(\lambda) = 1 - p_{\pm}(\lambda) \frac{M_{11}(\lambda)}{\det\left(J_e - \lambda I\right)} ,$$

- $J_e = (\frac{\partial F_i}{\partial u_j})_{ij}$ is the Jacobian matrix of the uncoupled ODE system evaluated at the new steady-state
- $M_{11}$ is the cofactor of the element $a_{1,1}$ of the matrix $J_e - \lambda I$.
- $p_{\pm}(\lambda)$, determined by the bulk diffusion field, is

$$p_{+}(\lambda) \equiv \beta \left( \frac{G^e_{u_1} \mathcal{P}^e_c - \mathcal{P}^e_{u_1} G^e_c - \mathcal{P}^e_{u_1} D\Omega_\lambda \tanh(\Omega_\lambda L)}{G^e_c + D\Omega_\lambda \tanh(\Omega_\lambda L)} \right) , \quad \text{(In-phase)}$$

$$p_{-}(\lambda) \equiv \beta \left( \frac{G^e_{u_1} \mathcal{P}^e_c - \mathcal{P}^e_{u_1} G^e_c - \mathcal{P}^e_{u_1} D\Omega_\lambda \coth(\Omega_\lambda L)}{G^e_c + D\Omega_\lambda \coth(\Omega_\lambda L)} \right) , \quad \text{(Anti-phase)} ,$$

where we take the principal value of $\varphi_\lambda = \sqrt{\frac{1+\tau\lambda}{D}}$.

# Theoretical Framework for Analysis

**Linearized Analysis:**

- Find HB points for in-phase and anti-phase modes.
- Use winding number criterion of complex analysis for information on linear stability, to get phase diagrams.
- Rigorous spectral results for one-ODE and $L \to \infty$.

**Global Bifurcation Analysis:** Track global branches of in-phase and anti-phase periodic solutions branches emanating from HB points. Method of lines for Bulk Diffusion and XPPAUT. Identify secondary bifurcations such as Hopf-Hopf points, Torus bifurcations, etc.

**Full Numerical Simulations** of the PDE-ODE to verify bifurcation studies.

**Weakly Nonlinear Analysis:**

- Determine whether HB points are sub or supercritical.
- **Key Challenge:** Derive amplitude equations with Steklov structure.

# Selkov Compartmental Dynamics: I

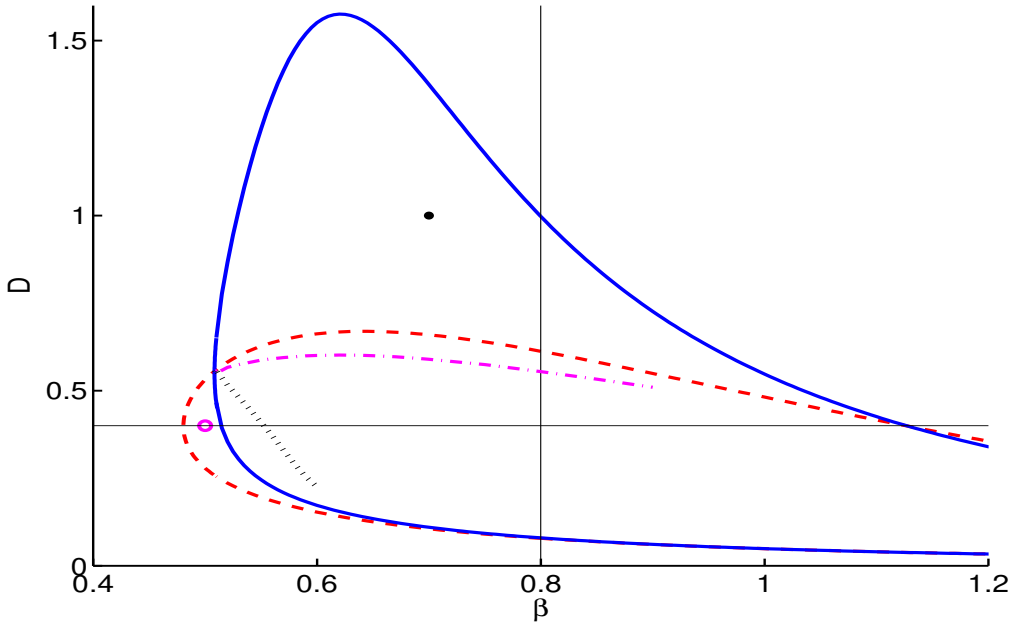
Suppose $\boldsymbol{u}(t) = (V(t), W(t))$, and that there is linear coupling $G = \kappa(V(t) - C(0,t))$. Choose Selkov membrane dynamics

$$\frac{dV}{dt} = f(V,W) + \beta(C(0,t) - V)\,, \qquad f(V,W) \equiv \alpha W + WV^2 - V\,,$$

$$\frac{dW}{dt} = g(V,W) = \epsilon_0(\mu - (\alpha W + WV^2))\,.$$

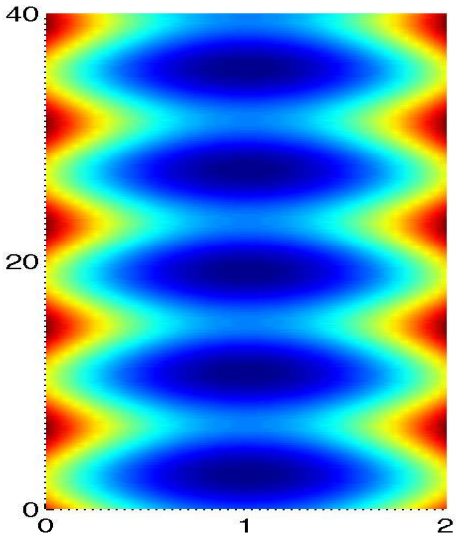
We fix the Selkov parameters $\mu = 2$, $\alpha = 0.9$ and $\epsilon_0 = 0.15$.

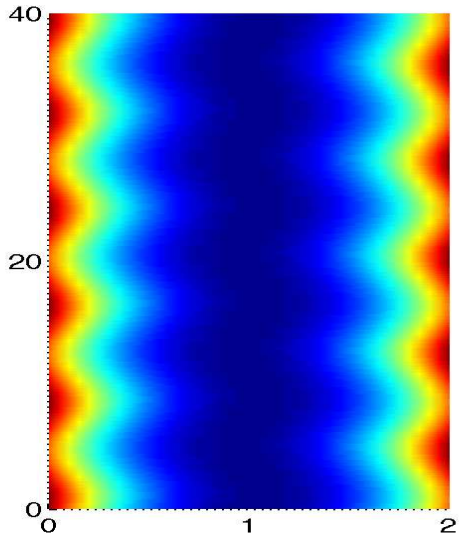
Linear stability phase diagram in $D$ vs $\beta$ plane for $\kappa = k = L = 1$.



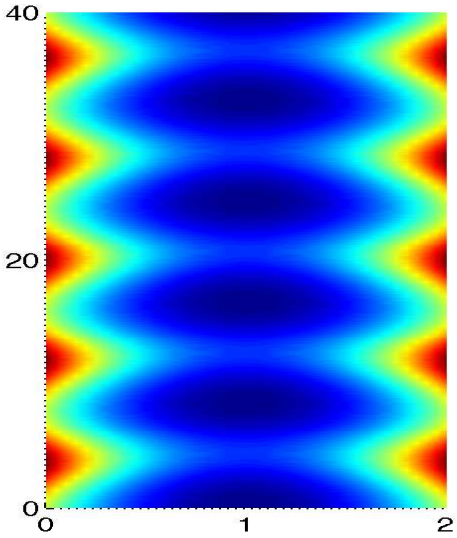

**Caption:** In-phase and anti-phase oscillations occur within the open loops bounded by the blue solid and red dashed curves. Above the faint-hashed curve, the in-phase periodic solution is stable; below the magenta dot-dashed curve the anti-phase periodic solution is stable.

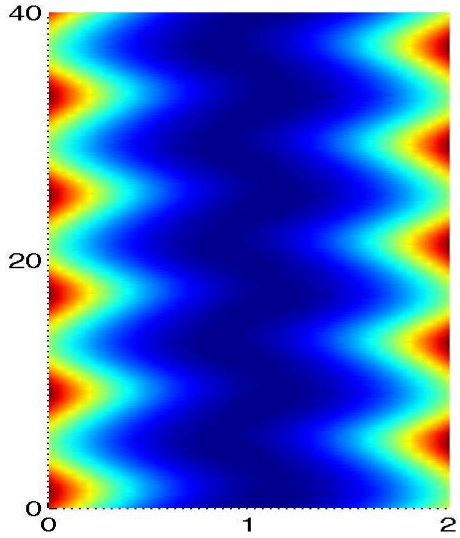
# Selkov Compartmental Dynamics: II




Full numerics for $C(x,t)$ confirming the theory at the blue and red dots in the phase diagram. Left: (blue dot) is in-phase. Right: (red dot) anti-phase.

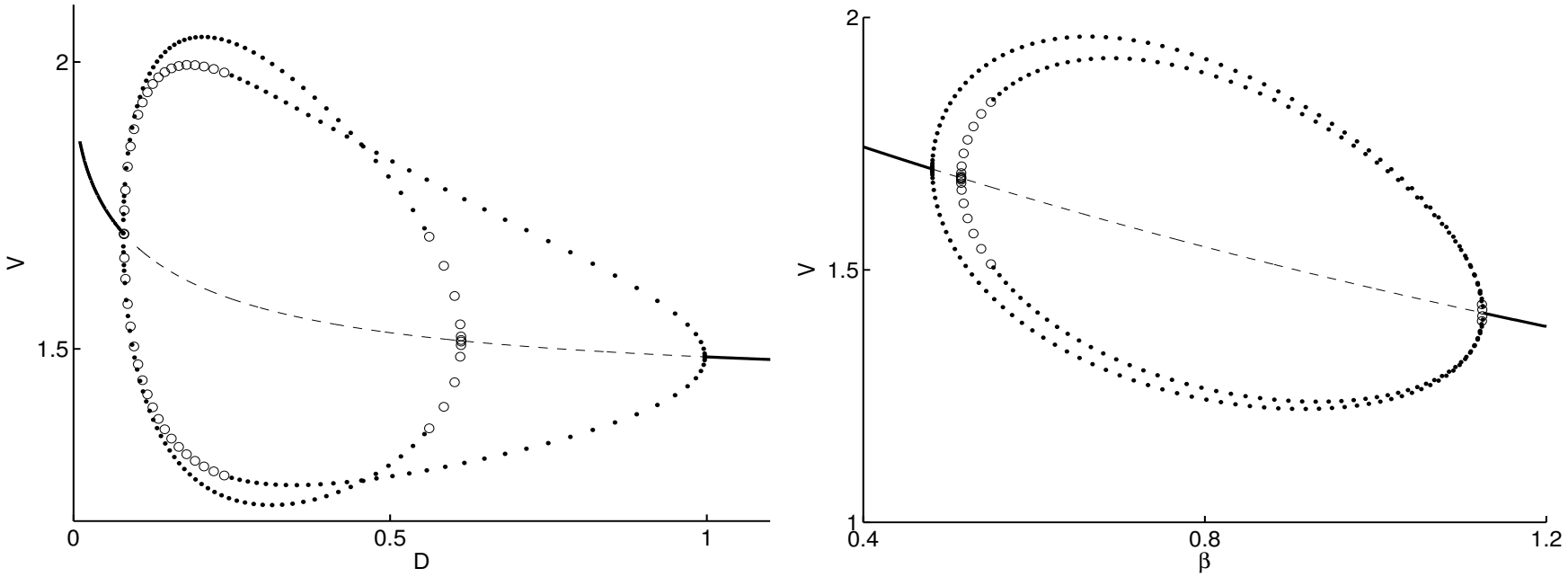



Full numerics for $D = 0.4$ and $\beta = 0.8$, showing different long-time results, either in-phase or anti-phase, depending on the initial conditions. Parameter values are within both in-phase and anti-phase loops.

# Selkov Compartmental Dynamics: III

**Global Bifurcation Study:** slices through linear stability phase diagram




**Caption:** Bifurcation diagram of $V$ for slices through linear stability phase diagram. Left: $V$ versus $D$ for $\beta = 0.8$ (vertical slice). Right: $V$ versus $\beta$ for $D = 0.4$ (horizontal slice). The solid (dashed) lines are linearly stable (unstable) branches of steady-states. Closed loops are branches of in-phase and anti-phase periodic solutions, with solid (open) circles indicating stable (unstable) periodic solutions. Left: bifurcating branch near $D = 1$ is the in-phase synchronous branch. Right: the outer loop is the anti-phase branch. Torus bifurcations occur where the periodic solution branches lose stability.

# Modeling and References

**Biological "Realistic" Models:**

- Simplified version of the GnRH neuron hormone model from (Li-Khadra, 2008) where $C(x,t)$ is the GnRH concentration in the bulk medium.
- Cell-cell signaling in Dictyostelium (Goldbeter 1990), where $C(x,t)$ is the concentration of the cAMP in the bulk region, and $u$ is the total fraction of cAMP receptor in the active state on the two membranes.

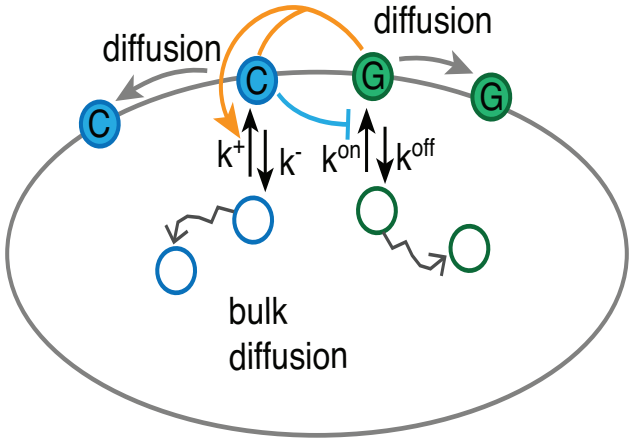
**Ref [GLNW]:** J. Gou, Y. X. Li, W. Nagata, M. J. Ward, *Synchronized Oscillatory Dynamics for a 1-D Model of Membrane Kinetics Coupled by Linear Bulk Diffusion*, SIADS, **14**(4), (2015), pp. 2096–2137.

**Ref [G]:** J. Gou et al. *A Theory of Synchrony by Coupling Through a Diffusive Chemical Signal*, Physica D, **339**, (2017), pp. 1–17.

**Ref [GW]:** J. Gou, M. J. Ward, *Oscillatory Dynamics for a Coupled Membrane-Bulk Diffusion Model with Fitzhugh-Nagumo Kinetics*, SIAP, **76**(2), (2016), pp. 776-804.

# Topic III: Bulk-Surface RD Systems

Coupling passive diffusion in a bulk domain with a reaction-diffusion process on the domain boundary through a Robin boundary condition.




- H. Levine *Membrane Bound Turing Patterns*, Phys. Rev. E. (2005). Turing patterns occur even with equal diffusivities.
- A. Madzvamuse et al, Proc. Roy. Soc. A, (2015). General Turing stability analysis of spatially uniform state.
- Modeling: A. Madzvamuse et al, *A coupled bulk-surface model for cell polarization*, J. Theo. Bio. (2019). Giese, Frey et al: various models of *protein pattern formation*.

**Our Focus:** For a class of coupled bulk-surface RD model in a disk, develop a weakly nonlinear theory for pattern formation near bifurcation points. Derive and analyze amplitude equations for Hopf, Turing, Turing-Hopf instabilities. Thesis work of Paquin-Lefebvre (UBC)

# Coupled Membrane-Bulk System I

Dimensionless Formulation: Let $\Omega = \{\mathbf{x} \in \mathbb{R}^2 \mid ||\mathbf{x}| < R\}$. In the bulk, we assume passive diffusion

$$\frac{\partial U}{\partial t} = D_u \Delta U - \sigma_u U\,, \quad \frac{\partial V}{\partial t} = D_v \Delta V - \sigma_v V\,, \quad \mathbf{x} \in \Omega\,, \quad t > 0\,,$$

coupled to the surface with the Robin boundary condition

$$D_u \left.\frac{\partial U}{\partial r}\right|_{r=R} = K_u \left(u - U|_{r=R}\right)\,, \qquad D_v \left.\frac{\partial V}{\partial r}\right|_{r=R} = K_v \left(v - V|_{r=R}\right)\,.$$

This 2-D bulk problem is coupled to a nonlinear 1-D RD system on the boundary (membrane) of the circular disk

$$\frac{\partial u}{\partial t} = \frac{d_u}{R^2}\frac{\partial^2 u}{\partial \theta^2} - K_u \left(u - U|_{r=R}\right) + f(u,v)\,,$$
$$\frac{\partial v}{\partial t} = \frac{d_v}{R^2}\frac{\partial^2 v}{\partial \theta^2} - K_v \left(v - V|_{r=R}\right) + g(u,v)\,.$$

**Ref:** [PNW] F. Paquin-Lefebvre, W. Nagata, M. J. Ward, *Pattern Formation and Oscillatory Dynamics in a 2-D Coupled Bulk-Surface Reaction Diffusion System*, to appear, SIADS, (2019), (48 pages).

# Coupled Membrane-Bulk System II

**Outline of Analysis:**

- Construct radially symmetric steady-state solution $\mathbf{u}_e(r)$, and linearize introducing $\mathbf{u} = \mathbf{u}_e + e^{\lambda t + in\theta}\mathbf{\Phi}$. Derive the eigenvalue relation. Linearization is not around a spatially uniform state.
- Plot marginal stability curves for Hopf $n = 0$ and Turing $n = 1$ branches. The bifurcation parameters are taken as $D_v$ and $K_v$, and we consider any such two-parameter path crossing a marginal stability boundary.
- Key step: formulate appropriate adjoint of linearized operator, inner product, orthogonality relation, and solvability condition.
- Multi-scale expansion in order to derive normal form amplitude equations for Hopf, Turing, and Turing-Hopf instabilities. Central is to derive explicit "computable" formulae for the coefficients for arbitrary $f$ and $g$.

# Membrane-Bulk: WNA (Technical I)

$$\dot{W} = \mathbf{F}(W) = \begin{pmatrix} D_u \Delta U - \sigma_u U \\ D_v \Delta V - \sigma_v V \\ \frac{d_u}{R^2} u_{\theta\theta} - K_u \left(u - U\right) + f(u,v) \\ \frac{d_v}{R^2} v_{\theta\theta} - K_v \left(v - V\right) + g(u,v) \end{pmatrix}$$

for functions satisfying

$$W \in \mathcal{W} \equiv \left\{ \begin{pmatrix} U(r,\theta) \\ V(r,\theta) \\ u(\theta) \\ v(\theta) \end{pmatrix} \middle| \begin{array}{l} D_u \partial_r U|_{r=R} = K_u \left(u - U|_{r=R}\right) \\ D_v \partial_r V|_{r=R} = K_v \left(v - V|_{r=R}\right) \end{array} \right\} .$$

For a radially symm. base-state $W_e(r) \in \mathcal{W}$, let $\tilde{W} = W - W_e$. Expand

$$\dot{\tilde{W}} = \mathcal{L}\tilde{W} + \mathcal{B}(\tilde{W},\tilde{W}) + \mathcal{C}(\tilde{W},\tilde{W},\tilde{W}) + \dots ,$$

where $\mathcal{L}\tilde{W}$ is the linearized operator with eigenfunctions $\mathcal{L}\mathbf{\Phi}_n = \lambda \mathbf{\Phi}_n$,

$$\mathcal{L}(\tilde{W}) = \begin{pmatrix} D_u \Delta \tilde{U} - \sigma_u \tilde{U} \\ D_v \Delta \tilde{V} - \sigma_v \tilde{V} \\ \frac{d_u}{R^2} \tilde{u}_{\theta\theta} - K_u \left(\tilde{u} - \tilde{U}\right) + f_u^e \tilde{u} + f_v^e \tilde{v} \\ \frac{d_v}{R^2} \tilde{v}_{\theta\theta} - K_v \left(\tilde{v} - \tilde{V}\right) + g_u^e \tilde{u} + g_v^e \tilde{v} \end{pmatrix} , \quad \text{where} \quad \mathbf{\Phi}_n = \begin{pmatrix} \tilde{W}_1(r) e_1^T \phi_n \\ \tilde{W}_2(r) e_2^T \phi_n \\ \phi_n \end{pmatrix} e^{in\theta} .$$

# Membrane-Bulk: WNA (Technical II)

Stability Threshold: Re$(\lambda_{max}(n,\mu_0)) = 0$ for $n = 0, 1, 2, \ldots$ and $\mu_0 \equiv (K_v, D_v)^T$. Derive the adjoint $\mathcal{L}^\star(W^\star)$ and introduce inner product

$$\langle W^\star, W\rangle = \int_0^{2\pi}\int_0^R \left[\overline{U^\star}U + \overline{V^\star}V\right] r dr d\theta + \int_{\partial\Omega}\left[\overline{u^\star}u + \overline{v^\star}v\right] d\sigma\,,$$

where $W \equiv (U, V, u, v)^T$ and $W^\star \equiv (U^\star, V^\star, u^\star, v^\star)^T$.

**Fredholm Alternative Lemma:** Let $\lambda_c$ denote the critical eigenvalue at a given bifurcation point $\mu_0 = (K_v^c, D_v^c)$. Then,

$$\mathcal{L}(\mu_0;\mathbf{\Phi}_n) = \lambda_c\mathbf{\Phi}_n\,,\quad \mathcal{L}^\star(\mu_0;\mathbf{\Phi}_n^\star) = \overline{\lambda_c}\mathbf{\Phi}_n^\star\,,\quad \lambda_c \equiv \begin{cases} i\lambda_I & n=0 \\ 0 & n\neq 0\end{cases}.$$

Consider the inhomogeneous problem

$$\lambda_c X - \mathcal{L}(\mu_0;X) = \mathcal{F} \quad \text{with} \quad \left[\partial_r\begin{pmatrix}D_u x_1\\ D_v x_2\end{pmatrix}\Big|_{r=R} - \begin{pmatrix}K_u(x_3 - x_1|_{r=R})\\ K_v(x_4 - x_2|_{r=R})\end{pmatrix}\right] = \begin{pmatrix}\xi(\theta)\\ \eta(\theta)\end{pmatrix},$$

where $X \equiv (x_1(r,\theta), x_2(r,\theta), x_3(\theta), x_4(\theta))^T$.A necessary condition for a solution is

$$\langle\mathbf{\Phi}_n^\star, \mathcal{F}\rangle + \int_{\partial\Omega}\overline{U_n^\star}\xi\, d\sigma + \int_{\partial\Omega}\overline{V_n^\star}\eta\, d\sigma = 0\,.$$

# Membrane-Bulk: Normal Forms

Two-parameter sweep across linear stability boundary $(K_v^c, D_v^c)^T$:

$$\mu = (K_v^c, D_v^c)^T + \varepsilon^2 \mu_1 \, .$$

The weakly nonlinear theory (WNA) yields Normal Forms:

$$\frac{dA_0}{d\tau} = g_{1000}^T \mu_1 A_0 + g_{2100} |A_0|^2 A_0 \, , \quad \text{(Hopf)} \, ,$$
$$\frac{dA_n}{d\tau} = g_{0010}^T \mu_1 A_n + g_{0021} |A_n|^2 A_n \, , \quad \text{(Pitchfork)} \, .$$

and the codimension-two Turing-Hopf:

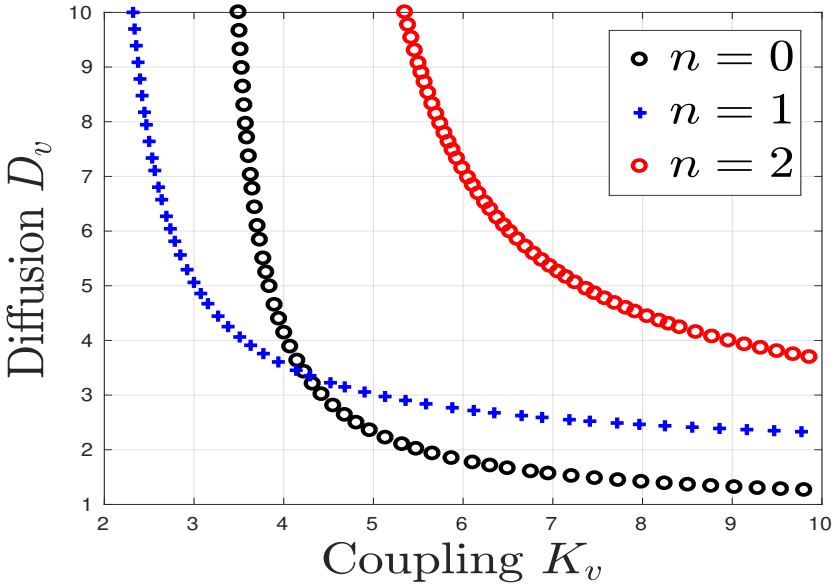
$$\frac{dA_0}{d\tau} = g_{1000}^T \mu_1 A_0 + g_{2100} |A_0|^2 A_0 + g_{1011} |A_n|^2 A_0 \, ,$$
$$\frac{dA_n}{d\tau} = g_{0010}^T \mu_1 A_n + g_{0021} |A_n|^2 A_n + g_{1110} |A_0|^2 A_n \, .$$

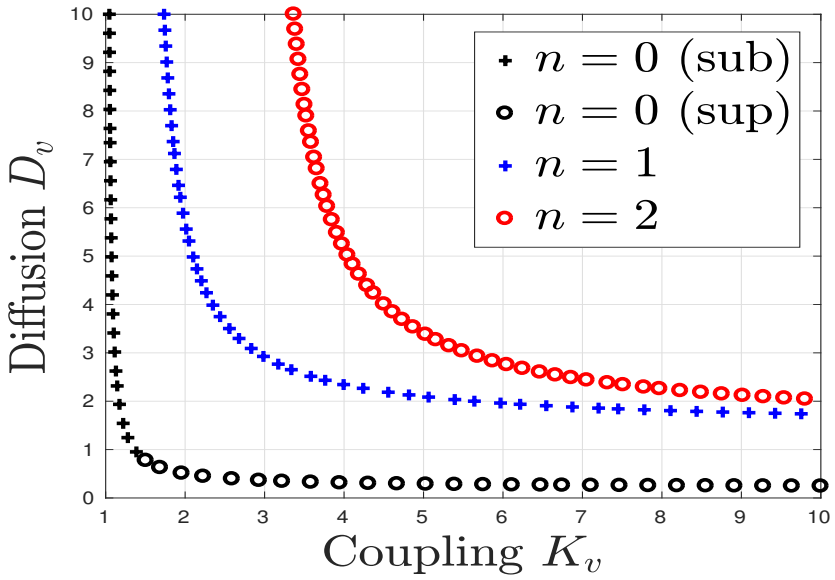
WNA provides explicit formulae for all the coefficients in the normal form.

Example: Consider Brusselator membrane kinetics

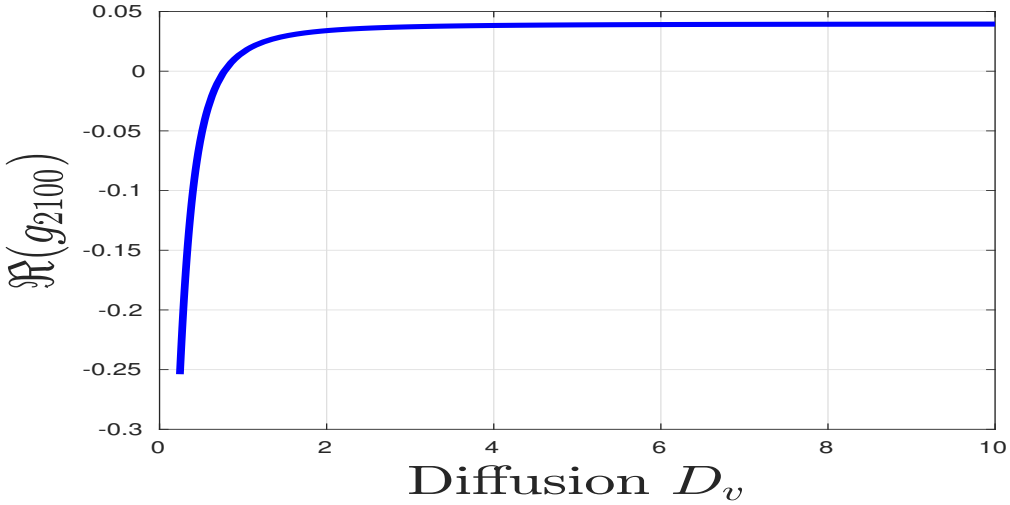
$$f(u,v) = a - (b+1)u + u^2 v \, , \quad g(u,v) = bu - u^2 v \, ; \quad a > 0 \, , \quad 0 < b < a^2 + 1 \, .$$

# Membrane-Bulk: Linear Stability, WNA



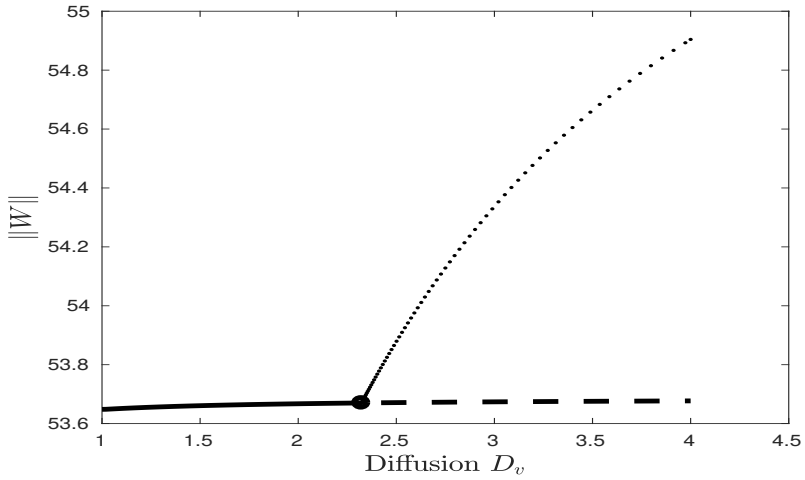



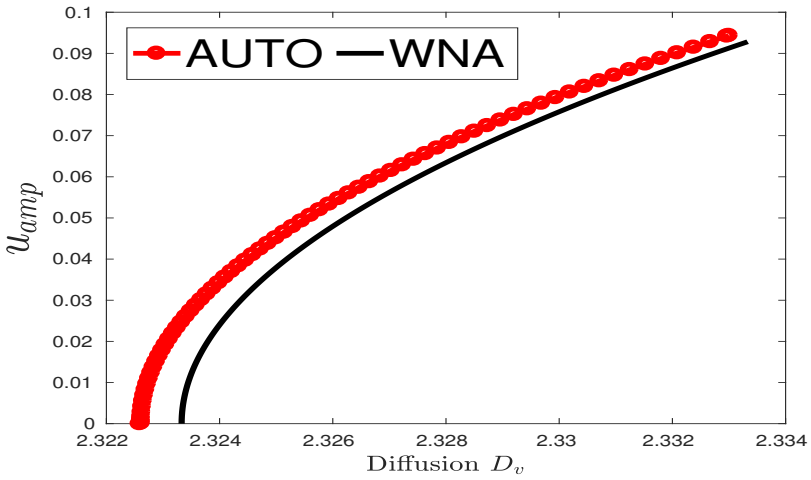

**Caption:** Linear stability phase diagram in $(K_v, D_v)$ plane with $R = 1$, $D_u = 1$ $\sigma_u = \sigma_v = 0.01$, $K_u = 0.1$, $d_u = d_v = 0.5$, $a = 3$ and $b = 7.5$ (left) and $b = 8.7$ (right). Right: "o" indicates supercritical and "+" indicates subcritical.



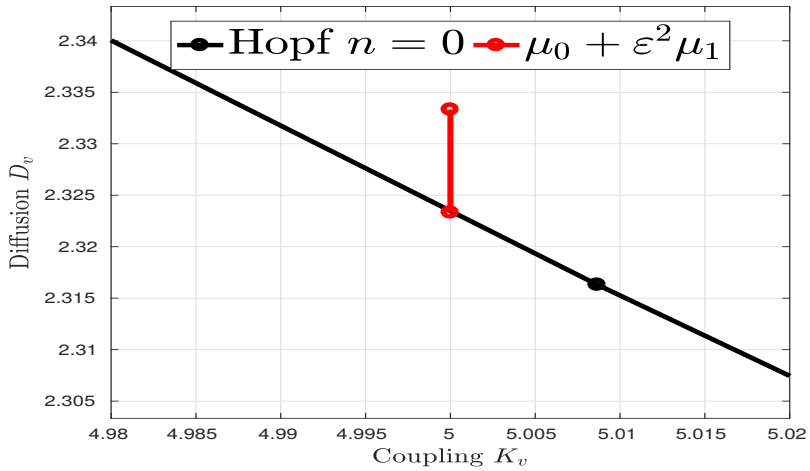

**Caption:** Transition from a super to sub-critical Hopf bifurcation. Plot of the normal form coefficient Re$(g_{2100})$ along Hopf stability curve for $b = 8.7$.

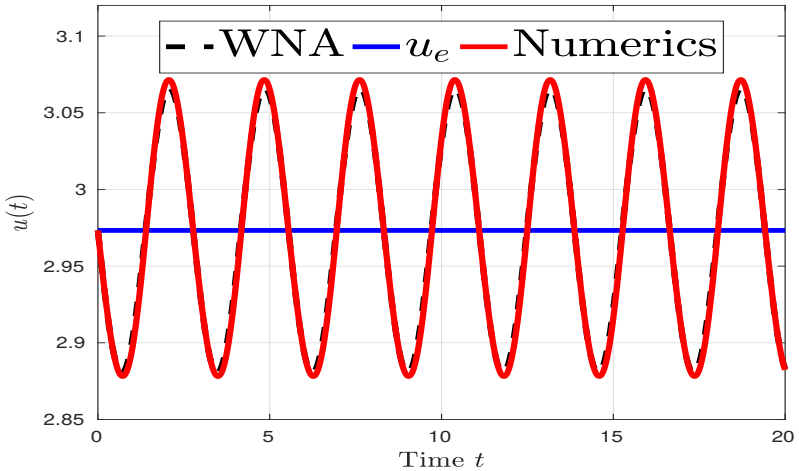
# Membrane-Bulk: Supercritical Hopf



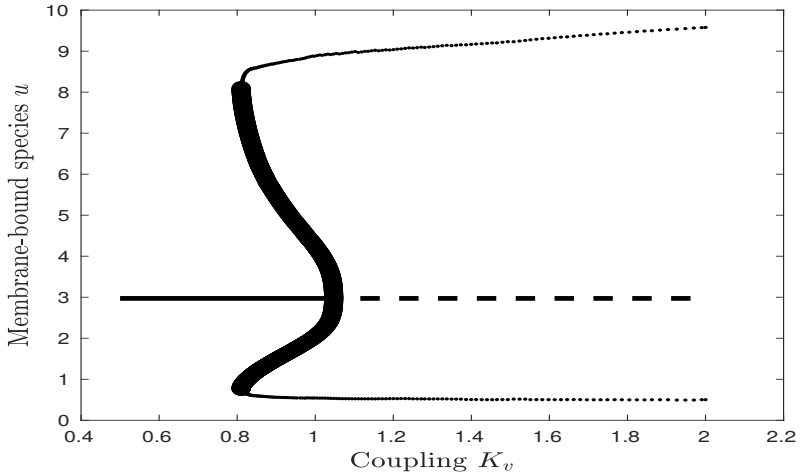

**Caption:** Supercritical Hopf: $b = 7.5$ and $K_v = 5$. Left: global periodic solution branches (AUTO). Right: local branching: weakly nonlinear vs. AUTO

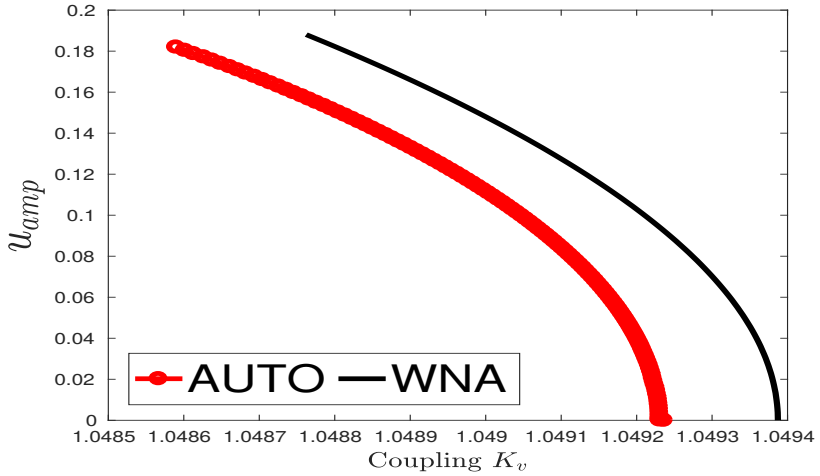


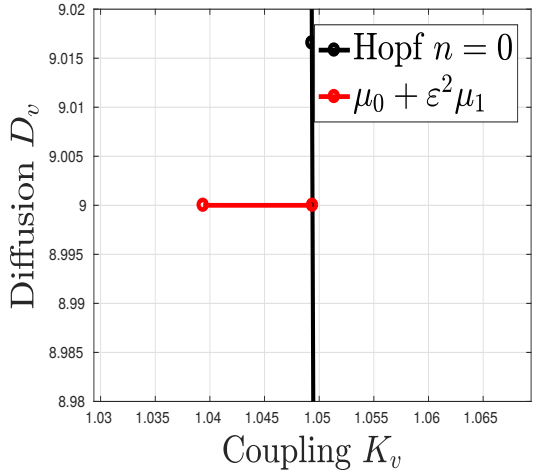

**Caption:** Left: parameter path $\mu = (K_v, D_v) = (5, 2.32)^T + \varepsilon^2 (0, 1)^T$, $\varepsilon = 0.1$. Right: weakly nonlinear vs. full numerics for membrane oscillations.

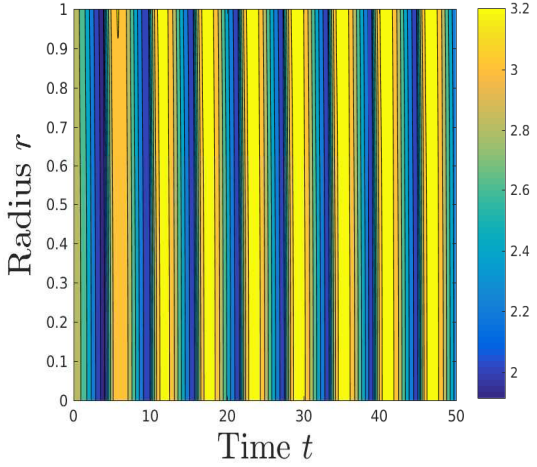
# Membrane-Bulk: Subcritical Hopf

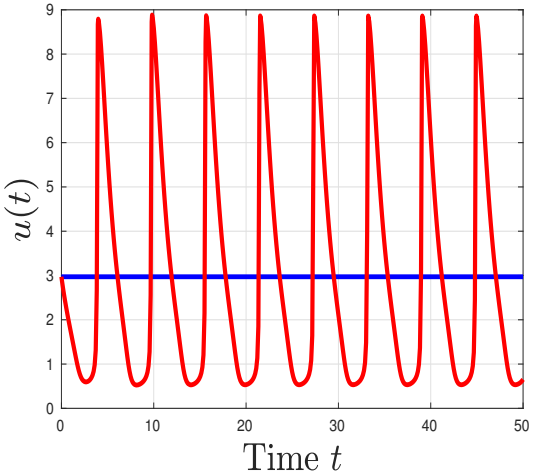



**Caption:** Subcritical Hopf: $b = 8.7$ and $D_v = 9$. Left: global periodic solution branches (AUTO). Right: local branching: weakly nonlinear vs. AUTO

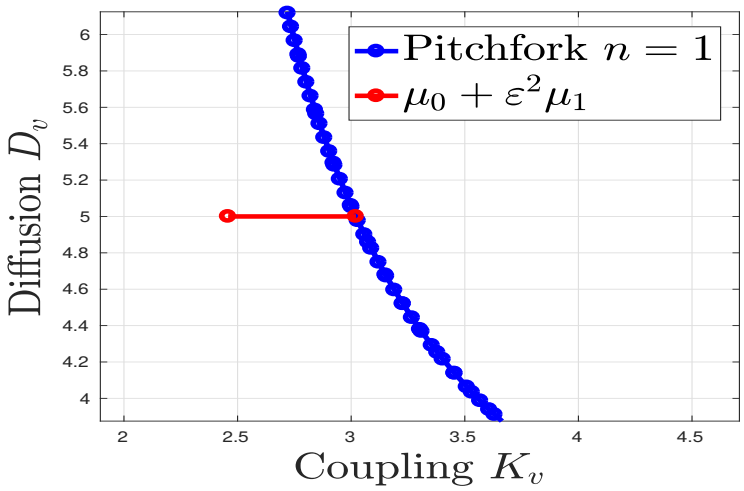


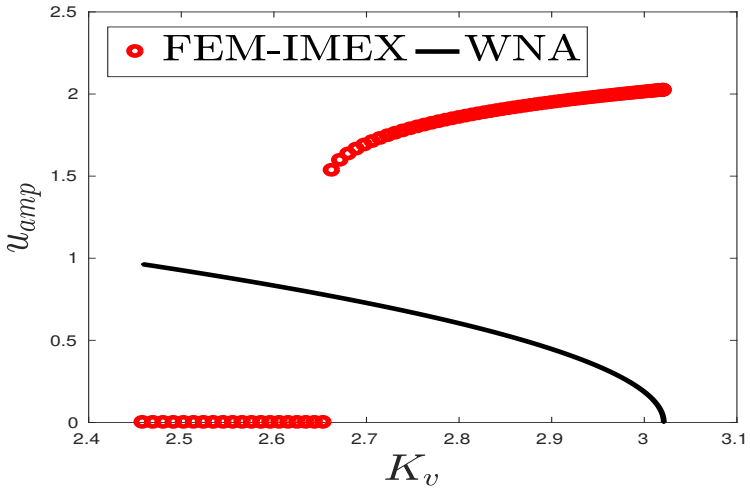



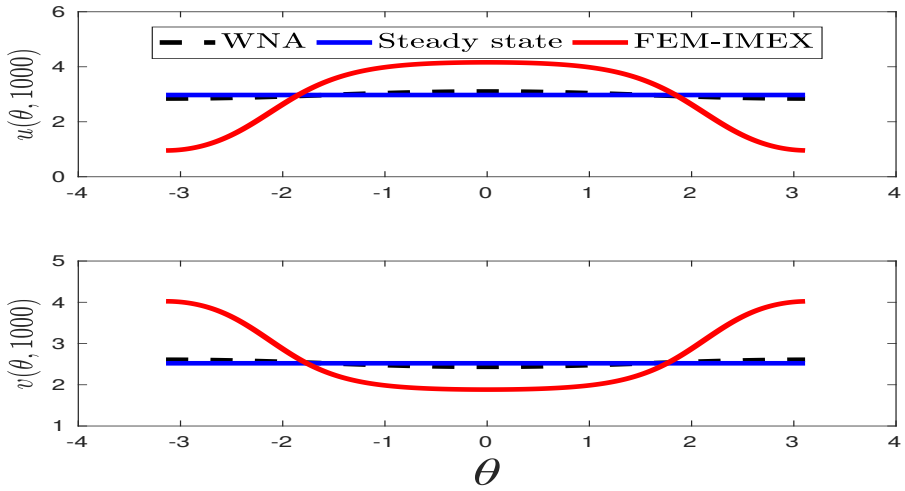

**Caption:** Left: parameter path with $D_v = 9$ and $\varepsilon = 0.1$. Middle: $U(r, t)$ for bulk. Right: relaxation oscillations for membrane oscillations.

# Membrane-Bulk: Subcritical Pitchfork



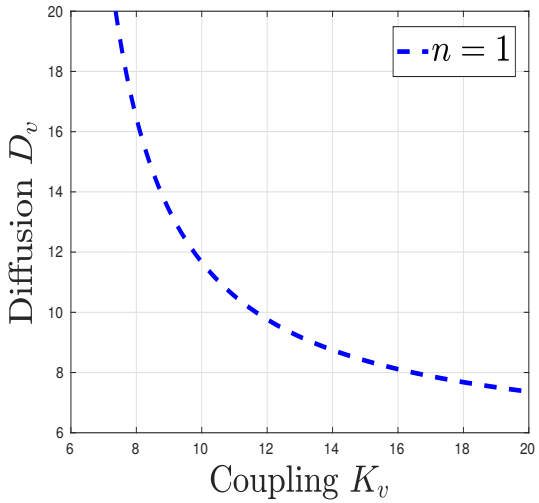



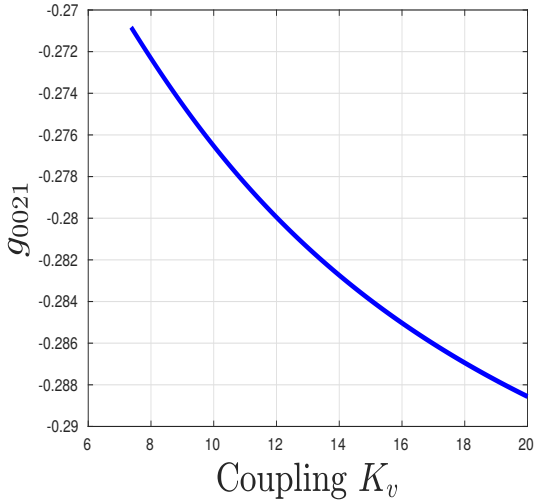

Left: parameter path with $D_v = 5$, $b = 7.5$, and $\varepsilon = 0.075$. Right: WNA approx (solid), stable branches by time-stepping to steady state in full numerics.

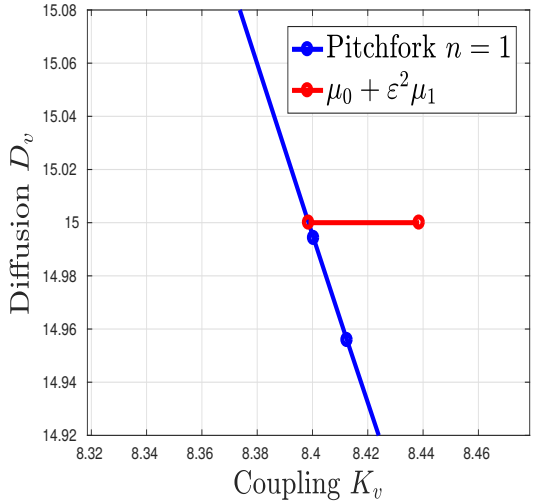



Stable membrane pattern at $t = 1000$ (red curve) as evolved from the unstable branch near a subcritical pitchfork.

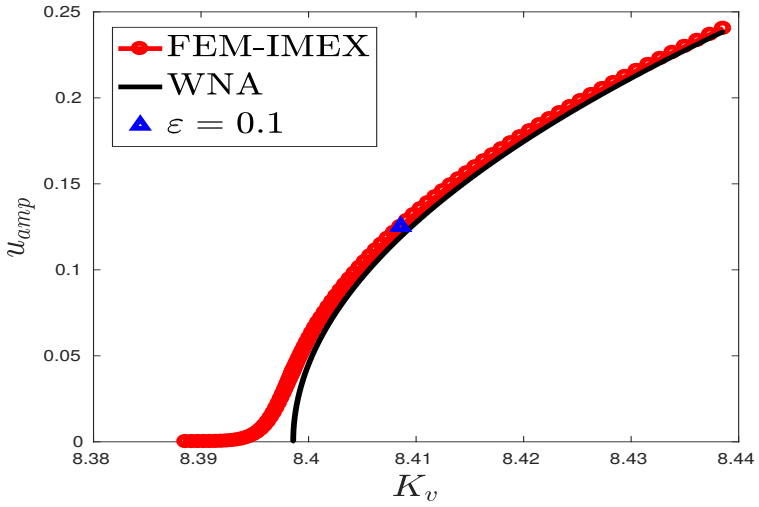
# Membrane-Bulk: Supercritical Pitchfork

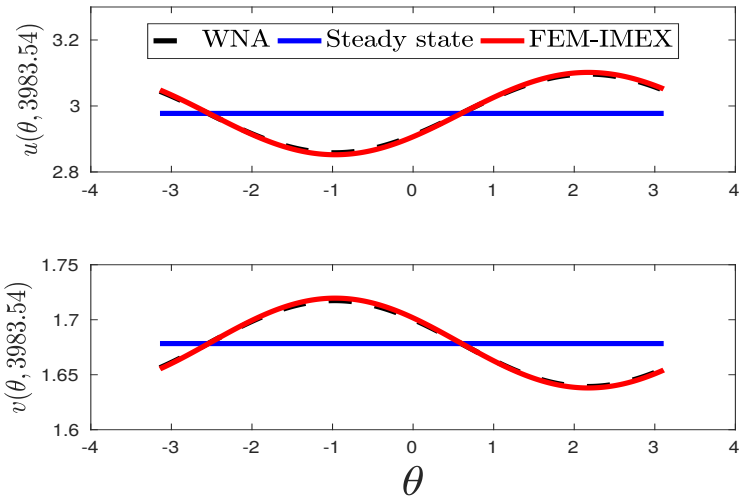



Same parameters except now $b = 5$ and $d_u = d_v = 1.0$. Pitchfork is now supercritical




Left: bifurcation diagram (AUTO) versus WNA. Right: stable Turing pattern.

# Further Directions

- **1-D Periodic Chains:** "active units" on a ring coupled by bulk diffusion. The synchronous mode has the best stability properties.
- **1-D Non-Identical Compartments:** Eigenfunctions no longer of in-phase and anti-phase type. New behavior: oscillations can exist in only one compartment, with the other being essentially quiescent.
- **1-D Theory:** Numerical global bifurcation study. Follow Torus (secondary) bifurcation branches.
- **Membrane-bulk RD systems:** coupling 3-D passive bulk diffusion to an RD process on the surface (modeling, linear and weakly nonlinear stability theory).
- **Localized membrane-bound RD patterns** obtained from coupling to bulk-diffusion. Thesis work of Daniel Gomez (UBC). (Movie)

Thanks For Your Attention!