Asymptotic Analysis of a 2-D Quorum Sensing Model with Active Compartments Coupled with Bulk Diffusion

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General Theme

Formulate and analyze a 2-D model of dynamically active small “cells”, with arbitrary intracellular kinetics, that are coupled spatially by a linear bulk-diffusion field in a bounded 2-D domain. The formulation is a coupled PDE-ODE system, and exhibits quorum-sensing behavior, characterized by a collective behavior if the cell density is large enough.

Can we trigger synchronous temporal oscillations via a Hopf Bifurcation depending on the number (quorum-sensing) or locations (diffusion-sensing) of the small compartments?

Mathematically, for our PDE-ODE system the linearized problem around a steady-state is a Steklov-type nonself adjoint eigenvalue problem.

There are clear analogies between this class of models and activator-inhibitor systems.

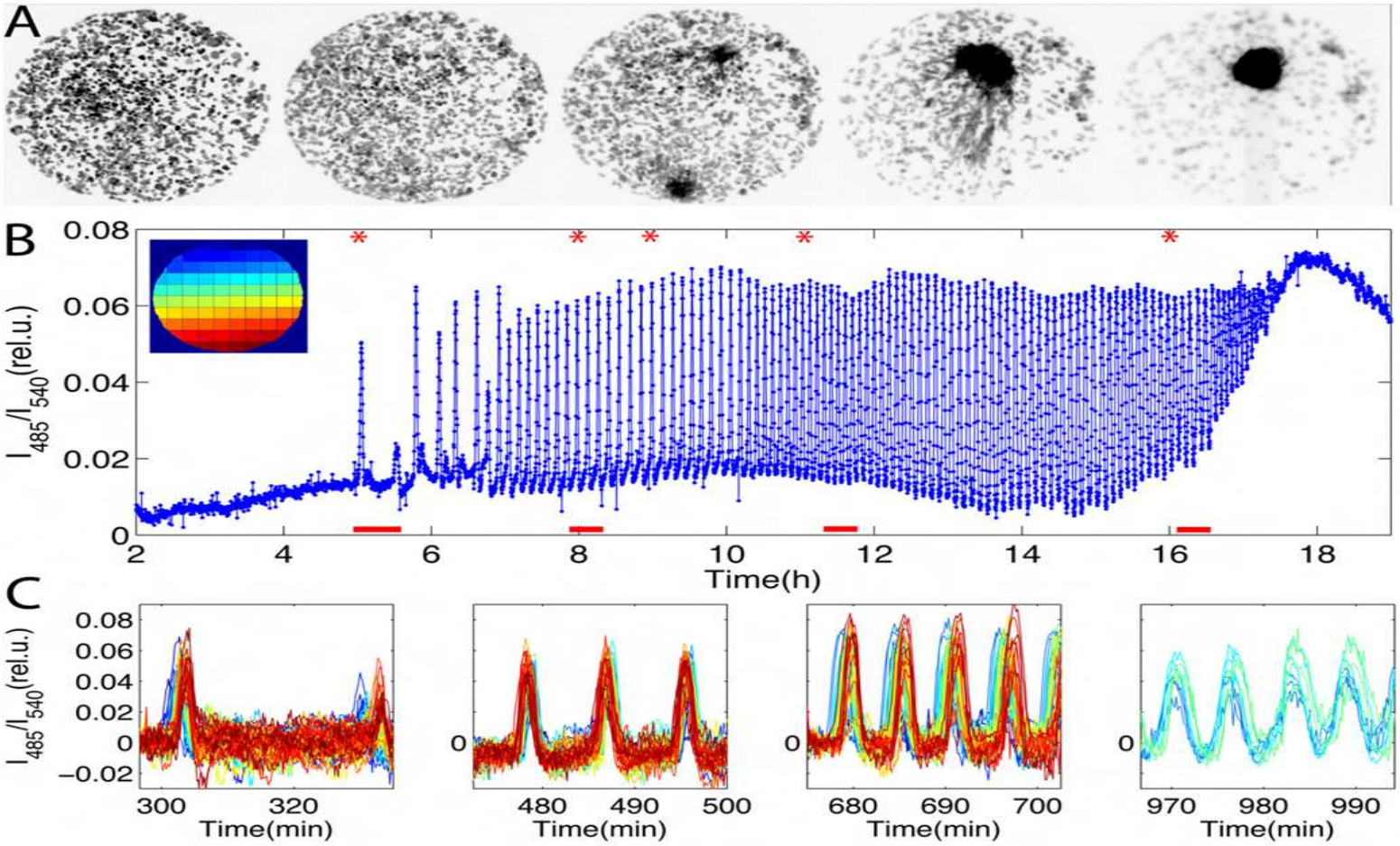
Dynamical Quorum Sensing in Nature

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 Colonies



Caption: The social amoebae *Dictyostelium discoideum* cells secrete cAMP into the medium which initiates aggregations when food becomes scarce, initiating a coordinated collective response. About 180 cells were confined to a 420μm-diameter area. Dark area in rightmost snapshot corresponds to final aggregation site of the population. **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 model for the coupled phases of the oscillators. Synchrony occurs between individual oscillators as the coupling strength 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; **Ref:** J. Muller, C. Kuttler, et al. "Cell-Cell Communication by Quorum Sensing and...", J. Math. Bio. **53** (2006), and J. Muller, H. Uecker, J. Math. Bio. **67** (2013). (steady-state analysis in 3-D, dynamics). This is our framework. With one intracellular dynamical component no oscillations were found in $\mathbb{R}^3$.

Our Contribution: Theoretical analysis of a PDE-ODE cell-bulk model in a bounded 2-D domain with bulk diffusion (PDE) coupled to arbitrary intracellular kinetics (ODE) with n components in the limit where m cells have "small" radii. Analysis of steady-state and spectral properties of the linearization to establish when oscillations can occur.

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

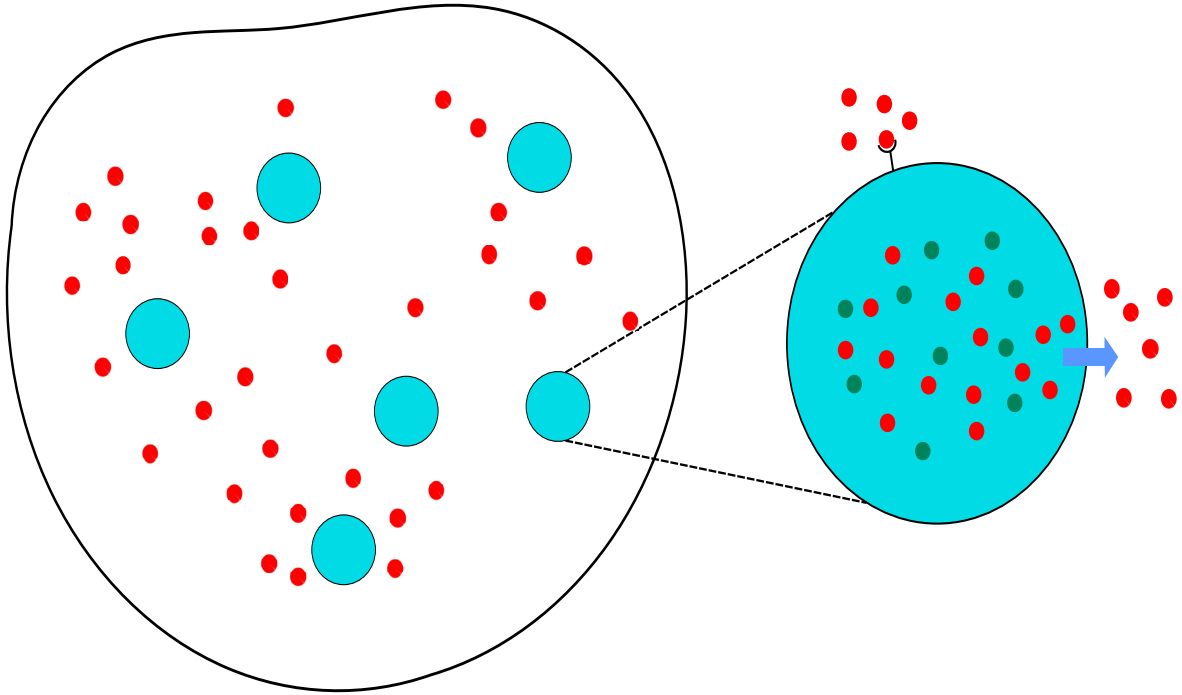
Specific Questions: Yes to all below

- 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).
- Are there wide parameter ranges where oscillations are synchronous?
- In the limit of large bulk-diffusivity, i.e. in a well-mixed system, can the PDE-ODE system be reduced to a finite dimensional dynamical system with global coupling?
- Can we exhibit quorum sensing behavior whereby a collective oscillation is triggered only if the number of cells exceeds a threshold? What parameters regulate this threshold?
- Can we exhibit diffusion sensing behavior whereby collective oscillations can be triggered only by clustering the cells more closely?
- Is there an analogy between the PDE-ODE bulk-cell system and the instabilities of spot patterns for activator-inhibitor RD systems:

$$v_t = \epsilon^2 \Delta v - v + \frac{v^2}{u}\,, \qquad \tau u_t = D\Delta u - u + \epsilon^{-2} v^2\,, \qquad \text{(GM Model)}\,.$$

For $\varepsilon \ll 1$: localized spot $\to$ "cell"; inhibitor $u \to$ "bulk diffusion".

Coupled Cell Bulk-Diffusion Model: I



Caption: Schematic diagram showing the intracellular reactions and external bulk diffusion of the signal. The small blue shaded regions are the signalling compartments or "cells". The red dots are the signalling molecule undergoing passive bulk diffusion. There is an exchange across each cell membrane regulated by permittivity parameters β_j.

Scaling Limit: $\epsilon \equiv \sigma/L \ll 1$, where L is lengthscale for Ω. We assume that the permeabilities satisfy $\beta_j = O(\epsilon^{-1})$ for $j = 1, 2$.

A Coupled Cell Bulk-Diffusion Model: II

Formulation: of PDE-ODE coupled cell-bulk model in 2-D with m cells.

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

$$D_B \partial_{n_{\boldsymbol{X}}} \mathcal{U} = \beta_1 \mathcal{U} - \beta_2 \mu_j^1\,, \qquad \boldsymbol{X} \in \partial\Omega_j\,, \quad j = 1, \ldots, m\,.$$

Assume that signalling cells $\Omega_j \in \Omega$ are disks of a common radius σ centered at some $\boldsymbol{X}_j \in \Omega$. D_B is bulk diffusivity with bulk decay rate k_B.

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

$$\frac{d\boldsymbol{\mu}_j}{dT} = k_R \mu_c \boldsymbol{F}_j\left(\boldsymbol{\mu}_j/\mu_c\right) + \boldsymbol{e}_1 \int_{\partial\Omega_j} \left(\beta_1 \mathcal{U} - \beta_2 \mu_j^1\right)\, dS_j\,, \qquad j = 1, \ldots, m\,,$$

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

- Only μ_j^1 can cross the j-th cell membrane into the bulk.
- $k_R > 0$ is intracellular reaction rate; $\beta_1 > 0$, $\beta_2 > 0$ are permeabilities.
- The dimensionless function $\boldsymbol{F}_j(\boldsymbol{u}_j)$ models the intracellular dynamics.

Coupled Cell Bulk-Diffusion Model: III

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

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

$$\epsilon D\partial_{n_j}U = d_1 U - d_2 u_j^1\,, \qquad \boldsymbol{x}\in\partial\Omega_{\epsilon_j}\,, \quad j=1,\ldots,m\,.$$

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 $j=1,\ldots,m$,

$$\frac{d\boldsymbol{u}_j}{dt} = \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{\boldsymbol{e}_1}{\epsilon\tau}\int_{\partial\Omega_{\epsilon_j}}(d_1U - d_2u_j^1)\,ds\,, \qquad \boldsymbol{e}_1\equiv(1,0,\ldots,0)^T\,.$$

Remark: The time-scale is measured wrt intracellular reactions.

Parameters: d_j (permeabilities); τ (reaction time ratio); D (diffusion length);

$$\tau\equiv\frac{k_R}{k_B}\,, \quad D\equiv\left(\frac{\sqrt{D_B/k_B}}{L}\right)^2\,, \quad \beta_1\equiv(k_BL)\,\frac{d_1}{\epsilon}\,, \quad \beta_2\equiv\left(\frac{k_B}{L}\right)\frac{d_2}{\epsilon}\,.$$

Coupled Cell Bulk-Diffusion Model: IV

Qualitative: Cell-bulk coupling triggers oscillatory dynamics through a Hopf bifurcation that otherwise would not be present in individual cells. Need $0 < \tau_- < \tau < \tau_+ < \infty$. Synchronous oscillations commonly occur.

Mathematical Framework: Use strong localized perturbation theory to construct steady-state solutions to the coupled system and formulate the linear stability problem. **Online Notes:** LBJ winter school CityU HK (2010), (99 pages).

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.

Steady-States: Matched Asymptotics

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

$$U(\boldsymbol{x}) = -2\pi \sum_{i=1}^{m} S_i G(\boldsymbol{x}, \boldsymbol{x}_i)\,.$$

In terms of $\nu = -1/\log\epsilon$ *and a Green's matrix* $\mathcal{G}$*, we obtain a nonlinear algebraic system for the source strengths* $\boldsymbol{S} = (S_1, \ldots, S_m)^T$ *and* $\boldsymbol{u}^1 \equiv \left(u_1^1, \ldots, u_m^1\right)^T$*, where* $e_1 = (1, 0, \ldots, 0)^T$*, and* $j = 1, \ldots m$*;*

$$\boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{2\pi D}{\tau} S_j \boldsymbol{e}_1 = 0\,, \qquad \left(1 + \frac{D\nu}{d_1}\right)\boldsymbol{S} + 2\pi\nu\mathcal{G}\boldsymbol{S} = -\frac{d_2}{d_1}\nu\boldsymbol{u}^1\,.$$

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

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

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

where $\boldsymbol{c} = (c_1,\ldots,c_m)^T$ is a nullvector of the GCEP:

$$\mathcal{M}\boldsymbol{c} = \boldsymbol{0}\,, \qquad \mathcal{M}(\lambda) \equiv \left(1 + \frac{D\nu}{d_1}\right) I + \frac{2\pi\nu d_2}{d_1\tau} D\mathcal{K}(\lambda) + 2\pi\nu\mathcal{G}_\lambda\,.$$

The discrete eigenvalues λ of the linearization are roots of $\det \mathcal{M} = 0$.

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

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

The Distinguished Limit $D = D_0/\nu$

Simplify: 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 ν.

Result 1: The steady-state is linearly stable to synchronous perturbations iff

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

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.

Result 2: 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

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

Note: The $m-1$ asynchronous modes are $\boldsymbol{c} = \boldsymbol{q}_j$, where $\boldsymbol{q}_j^T\boldsymbol{e} = 0$ for $j = 2, \ldots, m$, and $\boldsymbol{e} = (1, \ldots, 1)^T$. The synchronous mode is $\boldsymbol{c} = \boldsymbol{e}$.

Analogy with Localized Spot Patterns: I

Remark: Close analogy with spot stability analysis of Wei-Winter (2001) for the 2-D GM model in the "weakly coupled regime" $D = D_0/\nu$, $D_0 = \mathcal{O}(1)$:

$$v_t = \epsilon^2 \Delta v - v + \frac{v^2}{u}\,, \qquad \tau u_t = D\Delta u - u + \epsilon^{-2} v^2\,, \quad \boldsymbol{x} \in \Omega\,.$$

For $\epsilon \to 0$, an m-spot steady-state solution is linearly stable on an $\mathcal{O}(1)$ time-scale iff there is no root in $\mathrm{Re}(\lambda) > 0$ to the two NLEPs

$$\mathcal{F}(\lambda) = \mathcal{C}_{\pm}(\lambda)\,, \qquad \mathcal{F}(\lambda) \equiv \frac{\int_0^\infty \rho w \left(L_0 - \lambda\right)^{-1} w^2\, d\rho}{\int_0^\infty \rho w^2\, d\rho}\,,$$

where $w(\rho)$ is the radially symmetric ground state of $\Delta_\rho w - w + w^2 = 0$, and $L_0\Phi \equiv \Delta_\rho \Phi - \Phi + 2w\Phi$. Here $\mu \equiv 2\pi m D_0/|\Omega|$ and

$$\mathcal{C}_-(\lambda) \equiv \frac{(\mu+1)}{2}\,, \quad \text{(async)}\,; \quad \mathcal{C}_+(\lambda) \equiv \frac{(\mu+1)}{2}\left(\frac{1+\tau\lambda}{1+\mu+\tau\lambda}\right)\,, \quad \text{(sync)}\,.$$

Note: $\mathcal{F}(\lambda)$ has a pole at $\lambda = \sigma_0 > 0$ with $L_0\Phi_0 = \sigma_0\Phi_0$, and has "similar" properties to $\frac{M_{11}}{\det(\lambda I - J)}$ for the coupled bulk-cell model.

Analogy with Localized Spot Patterns: II

Main Result (Wei-Ward 2016): *For $\mu > 1$, i.e. if $m > m_c = |\Omega|/(2\pi D_0)$, then $\exists$ a unique HB threshold $\tau = \tau_H > 0$ for the synchronous mode, with linear stability iff $0 \leq \tau < \tau_H$. We have $\tau_H \to +\infty$ as $m \to m_c^+$. No HB for $\tau = \mathcal{O}(1)$ when $m < m_c$.*

Remarks: (Localized Spot Patterns)

- This suggests that Quorum sensing synchronized oscillatory behavior occurs for localized spot patterns in the $D = D_0/\nu$ regime when m exceeds a threshold.
- However, QS is not realized, as all asynchronous modes are linearly unstable for any $\tau \geq 0$ iff $m > m_c$.
- Short-range autocatalytic activation of v (i.e. v^2 term), and long range inhibition from u (i.e. bulk diffusion). Since $\epsilon^{-2} v^2 \sim \sum_{j=1}^m S_j \delta(x - x_j)$, in the outer region, away from the localized spots, the inhibitor field u satisfies

$$\tau u_t = D\Delta u - u + \sum_{j=1}^m S_j \delta(x - x_j)\,.$$

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, λ satisfies the cubic

$$\mathcal{H}(\lambda) \equiv \lambda^3 + \lambda^2 p_1 + \lambda p_2 + p_3 = 0\,,$$

where $p_1 \equiv \tau^{-1}(\gamma + \zeta) - \mathrm{tr}(J)$, while p_2 and p_3 are

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

where γ and ζ are defined in terms of the area $|\Omega|$ of Ω, the number m of cells, and D_0 (with $D = D_0/\nu$) by

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

Hopf Bifurcation criterion: By Routh-Hurwitz any HB must satisfy

$$p_1 > 0\,, \qquad p_3 > 0\,, \qquad p_1 p_2 = p_3\,.$$

The Distinguished Limit $D = D_0/\nu$: III

Asynchronous Mode: When $n = 2$, λ satisfies the quadratic

$$\lambda^2 - \lambda q_1 + q_2 = 0\,,$$

where

$$q_1 \equiv \mathrm{tr}(J) - \frac{\gamma}{\tau}\,, \qquad q_2 \equiv \det(J) - \frac{\gamma}{\tau} G^e_{u_2}\,.$$

For a Hopf bifurcation to occur, we require that $q_1 = 0$ and $q_2 > 0$.

Illustrate Theory with Sel'kov Kinetics

Let $\boldsymbol{u} = (u_1, u_2)^T$ be intracellular dynamics given by Sel'kov model (used for modeling glycolysis oscillations):

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

Fix parameters as: $\mu = 2$, $\alpha = 0.9$, and $\epsilon_0 = 0.15$. **Fix area as:** $|\Omega| = \pi$.

Remark: With these Sel'kov parameters, the uncoupled dynamics has a stable fixed point, and there is a unique steady-state solution to the coupled PDE-ODE system.

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

Goal: Derive and analyze a reduced finite-dimensional dynamical system characterizing the cell-bulk interations from PDE-ODE system.

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

$$U_0' = -\frac{1}{\tau}U_0 - \frac{2\pi}{|\Omega|\tau}\sum_{j=1}^{m}\left(d_1 U_0 - d_2 u_j^1\right) ,$$

$$\boldsymbol{u}_j' = \boldsymbol{F}_j(\boldsymbol{u}_j) + \frac{2\pi}{\tau}\left[d_1 U_0 - d_2 u_j^1\right]\boldsymbol{e}_1 , \qquad j = 1, \ldots, m ,$$

where $\boldsymbol{e}_1 = (1, 0, \ldots, 0)^T$. Large system of ODEs with weak but global coupling when $0 < d_1 << 1$ and $0 < d_2 \ll 1$, or when $\tau \gg 1$.

If we assume that the cells are identical, and look for $\boldsymbol{u}_j = \boldsymbol{u}$, $\forall j$, then the bulk concentration $U_0(t)$ and (common) intraceullar dynamics $\boldsymbol{u}$ satisfy

$$U_0' = -\frac{1}{\tau}\left(1 + \frac{2\pi m d_1}{|\Omega|}\right)U_0 + \frac{2\pi d_2 m}{\tau|\Omega|}u_1 ,$$

$$\boldsymbol{u}' = \boldsymbol{F}(\boldsymbol{u}) + \frac{2\pi}{\tau}\left[d_1 U_0 - d_2 u_1\right]\boldsymbol{e}_1 .$$

Remark: $|\Omega|/m$ is a key parameter.(Effective area per cell)

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

Ex: Selkov with $d_1 = 0.8$, $d_2 = 0.2$. Global Bif. Plot of Periodic Solns.

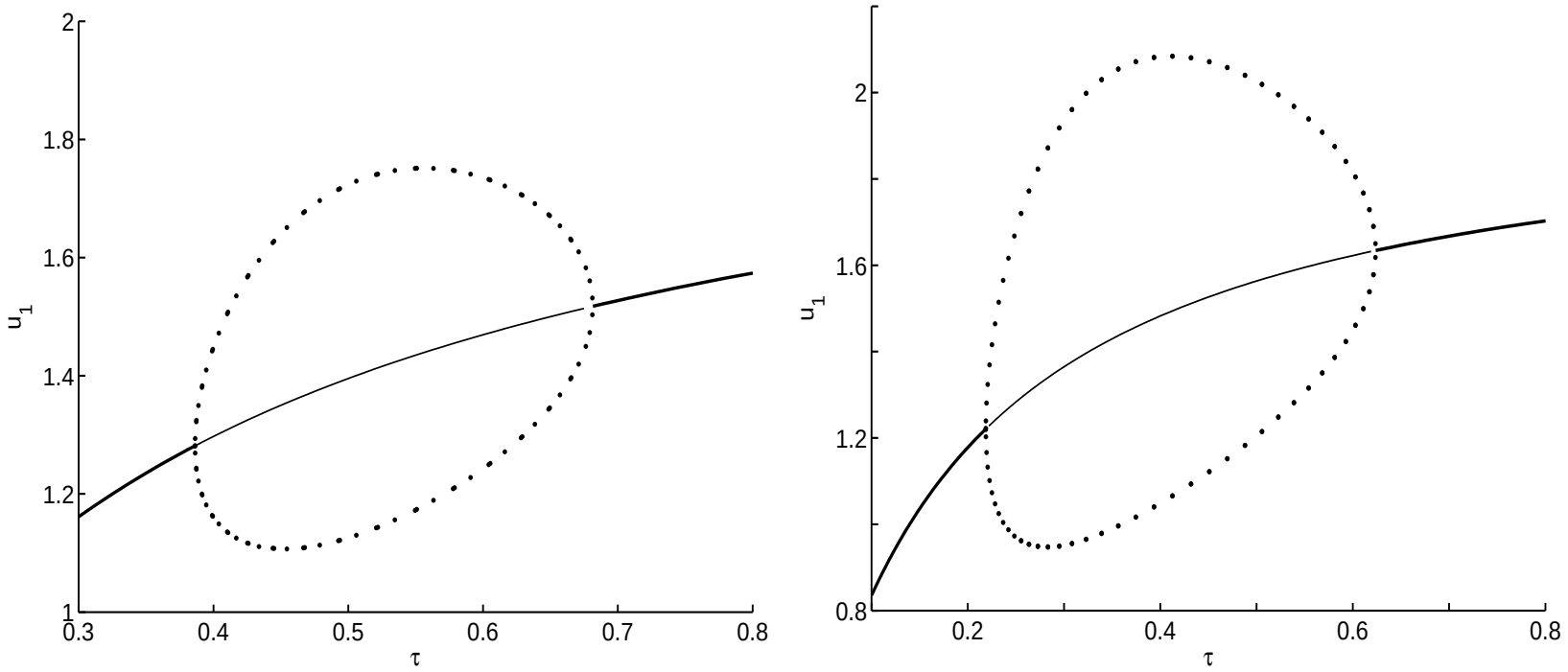


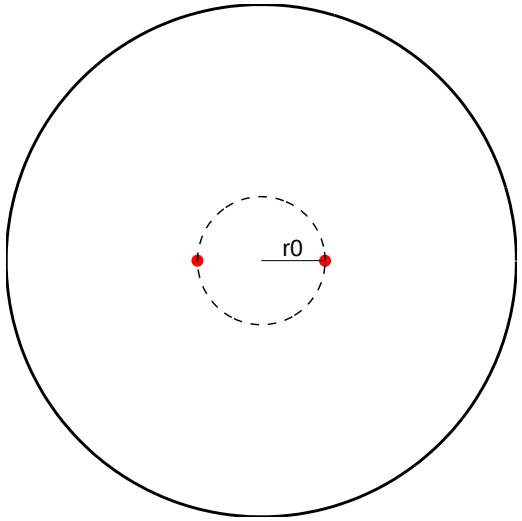
Figure: Global bifurcation diagram of u_{1e} versus τ for the Sel'kov model as computed using XPPAUT from the limiting ODE dynamics. Left panel: $m = 3$ (HB points at $\tau_{H-} = 0.3863$ and $\tau_{H+} = 0.6815$). Right panel: $m = 5$ (HB points at $\tau_{H-} = 0.2187$ and $\tau_{H+} = 0.6238$).

Key: Stable synchronous oscilations occur in some τ interval. Limiting well-mixed ODE dynamics is independent of cell locations and D.

$D = \mathcal{O}(1)$: Small Cells on a Ring: I

When $D = \mathcal{O}(1)$, linear stability properties depend on both D and the spatial configuration of cells.

Simplest (analytically tractable) example: Put m small cells inside the unit disk evenly spaced on a concentric ring of radius r_0. Assume identical kinetics.



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

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

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

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

$D = \mathcal{O}(1)$: Small Cells on a Ring: II

Remarks on Simplification: For m cells on a concentric ring, then:

- This pattern has a steady-state with $S_j = S_c$ for all $j = 1, \ldots, m$.
- Entries in $\mathcal{G}_\lambda$ readily calculated in terms of sums of modified Bessel functions of complex argument.
- $\mathcal{G}_\lambda$ and $\mathcal{G}$ are symmetric, cyclic matrices. Hence $\boldsymbol{v}_1 = (1, \ldots, 1)^T$ (synchronous mode). Matrix spectrum of $\mathcal{G}_\lambda$ readily calculated (mode degeneracy occurs).

Numerical Computations of the GCEP:

- Use Sel'kov dynamics with parameters specified previously. For the unit disk $|\Omega| = \pi$.
- HB boundaries: set $\lambda = i\lambda_I$ and fix D, r_0, and we take $\epsilon = 0.05$. Compute roots using Newton iteration for $\lambda_I > 0$ and $\tau_H > 0$ for each $j = 1, \ldots, m$.
- Use winding number principle of complex analysis to check where $\mathrm{Re}(\lambda) > 0$ in open regions of the τ versus D plane.

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

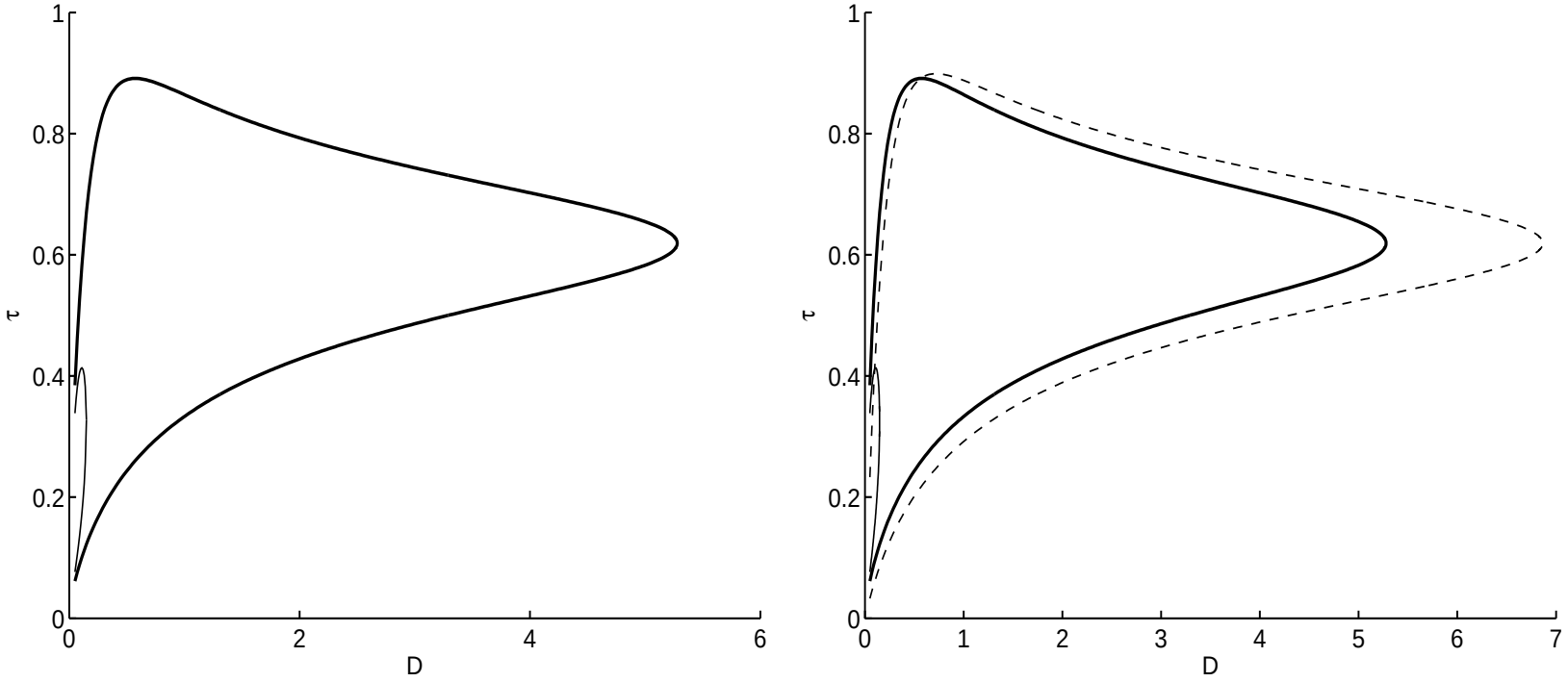


Figure: Left: HB boundaries for $m = 2$ and $r_0 = 0.25$. Heavy solid is synchronous mode and solid is asynchronous mode. Instability only within the lobes. Right: same plot but dashed curve is from $D = D_0/\nu$ theory.

Remarks:

- $D = D_0/\nu$ theory only moderately good to predict bounded instability lobe for synchronous mode.
- Asynchronous instability lobe exists only for D small.

$D = \mathcal{O}(1)$: HB Boundaries $m = 3$

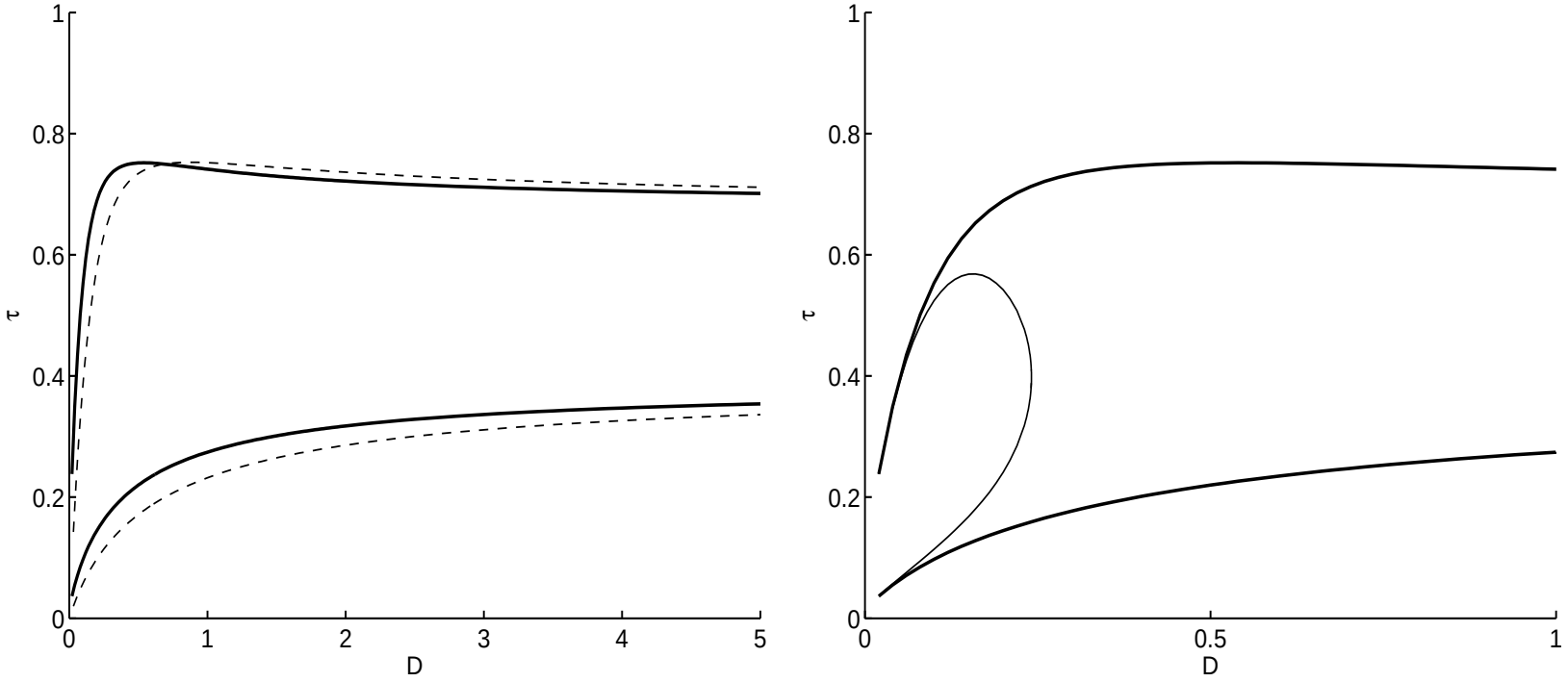


Figure: Left: HB boundaries for $m = 3$ and $r_0 = 0.50$. Heavy solid is synchronous mode and dashed is $D = D_0/\nu$ theory. Region is now unbounded. Right: (zoom near origin) Heavy solid is synchronous mode, and solid is asynchronous mode.

- $D = D_0/\nu$ theory very good for predicting unbounded instability lobe for synchronous mode.
- Horizontal asymptotes are the upper and lower thresholds for τ_H computed from well-mixed regime.
- Asynchronous instability lobe exists only for D small.

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

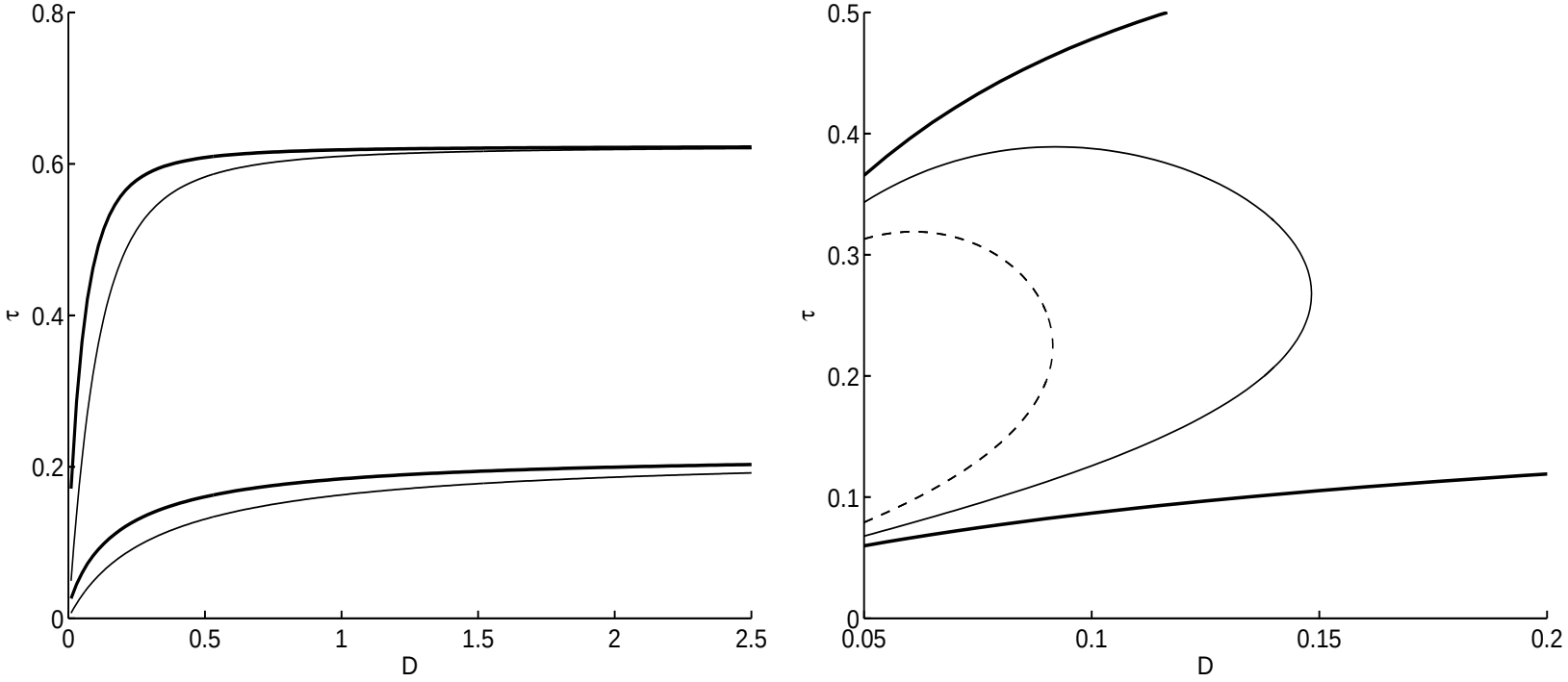


Figure: Left: HB boundaries for $m = 5$ and $r_0 = 0.50$. Heavy solid is synchronous mode and solid is $D = D_0/\nu$ theory. Region is unbounded. Right: (zoom near origin) Heavy solid is synchronous mode, while solid and dashed are the two asynchronous modes.

- $D = D_0/\nu$ theory again very good.
- Horizontal asymptotes are HB values of τ from well-mixed regime.
- Two asynchronous instability lobes exist near the origin.

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

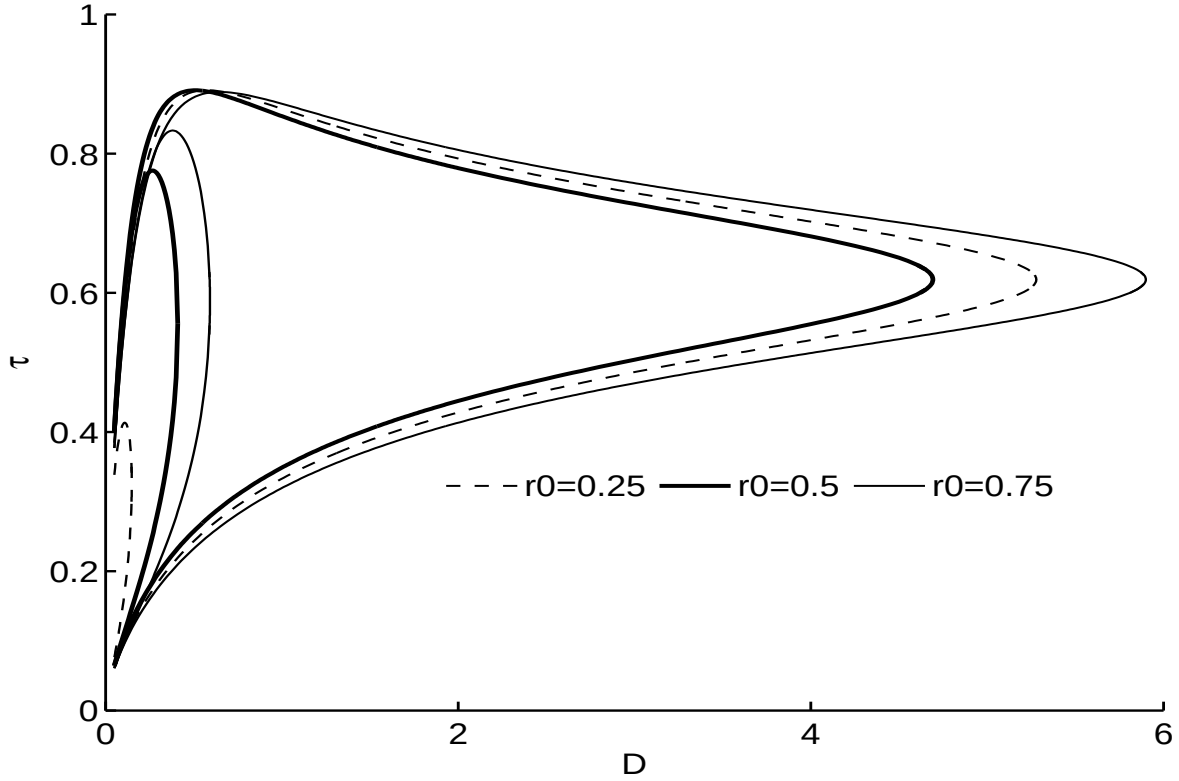


Figure: Let $m = 2$ and vary r_0: HB boundaries for the synchronous mode (larger lobes) and the asynchronous mode (smaller lobes).

- Asynchronous lobe is smallest when $r_0 = 0.25$.
- $D = D_0/\nu$ theory curves would overlap.
- Clear effect of 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 $r_0 = 0.75$.

Quorum Sensing Behavior I

Quorum sensing (Qualitative): collective behavior of "cells" in response to changes in their population size. There is a threshold number m_c of cells that are needed to initiate a collective behavior.

Quorum sensing (Mathematical): For what range of m, does there exist $\tau_{H\pm} > 0$ such that the well-mixed ODE dynamics is unstable on $\tau_{H-} < \tau < \tau_{H+}$ with HB points at $\tau_{H\pm}$? What parameters control this behavior?

We will study QS behavior as the permeability d_1 is varied: Recall:

$$\partial_{n_j} U = d_1 U - d_2 u_j^1$$

on the boundary of each cell.

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

Quorum Sensing Behavior II

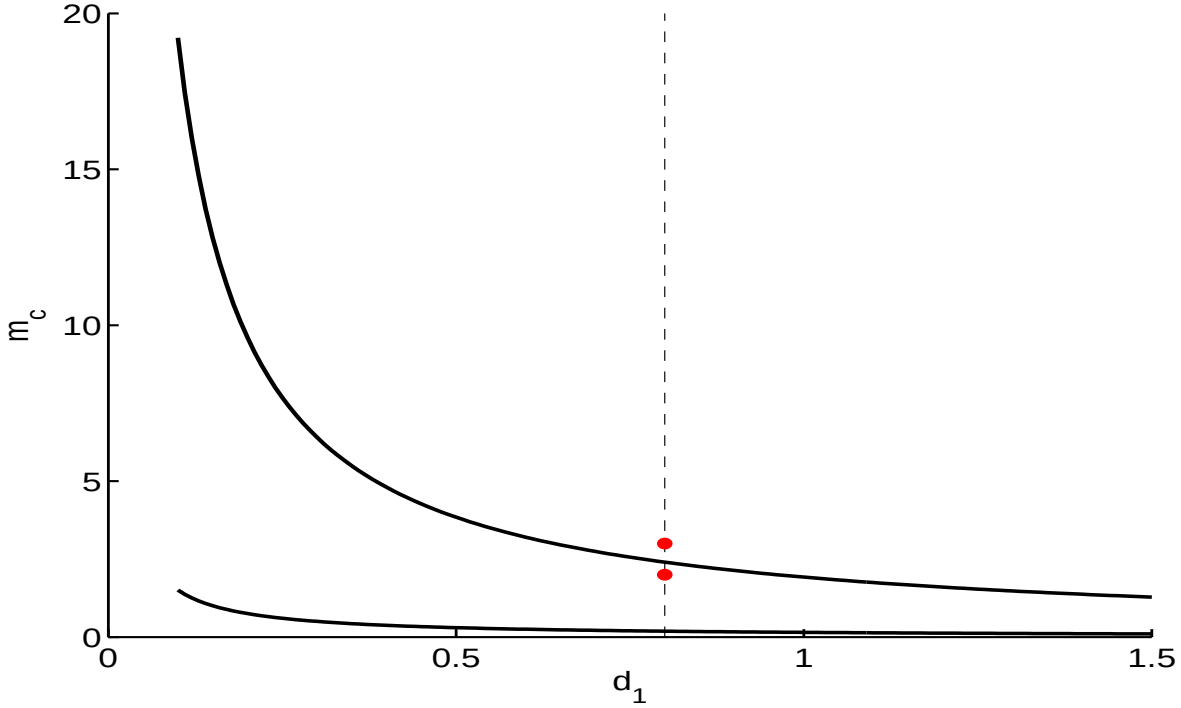


Figure: Quorum sensing threshold m_c (upper curve) in the well-mixed regime versus d_1 when $d_2 = 0.2$.

Key Point: Small changes in permeability d_1 significantly alters m_c.

- When $d_1 = 0.8$, then $m_c = 2.4$, i.e. $m_c = 3$.
- When $d_1 = 0.5$, then $m_c = 4$.
- When $d_1 = 0.2$, then $m_c = 12$.
- When $d_1 = 0.1$, then $m_c = 19$.

Some Specific Further Questions

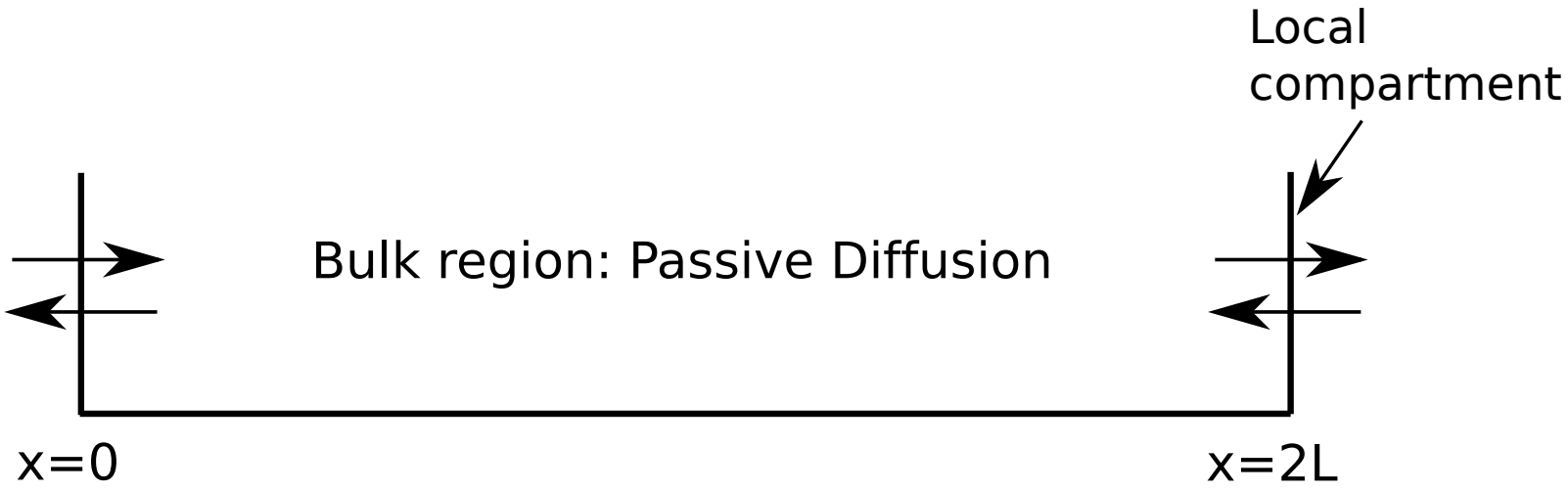
Let $D = \mathcal{O}(1)$. Consider m "randomly" placed cells in a 2-D domain.

- **Q1:** How do we solve the GCEP (spectral problem) in arbitrary domains? (fast multipole methods for G and G_λ)
- **Q2:** Can we observe clusters of oscillating and non-oscillating cells? (i.e. "chimera" type states.)
- **Q3:** Analyze effect of a defector cell with different cell properties than its neighbours that triggers oscillations in the others. Can we get discrete "target-type" patterns or discrete spiral-wave patterns?
- **Q4:** Large time dynamics in terms of time-dependent Green's function? (distributed delay equation).
- **Q5:** Analyze coupled bulk-cell model when the intracellular kinetics has a time-delay (gene expression delays). With only one intracellular ODE we can now get oscillations.
- **Q6:** What if the steady-state solution is not unique (hysteresis)?
- **Q7:** Derive a RD system in the homogenized limit of $m \gg 1$ but $m\epsilon^2 \ll 1$.
- **Q8:** Need numerical approach to solve the PDE-ODE system.

Perspective: Related PDE-ODE Models

1-D Model: $0 < x < 2L$ **(bulk) coupled to "compartments" at** $x = 0, 2L$**:**

- There is one local compartment (cell) located at each boundary.
- There are N dynamically interacting substances within each compartment, but only one substance can be secreted into the bulk.
- The signaling substance diffuses and is degraded in the bulk. It regulates its own secretion on the boundaries.



Remark: A related class of models are "quasi-static" ones where the compartments are not dynamically active but instead there are nonlinear flux-type boundary conditions. (Glass et al, Othmer, Riecke).

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

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

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

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

Conditional Oscillator: When $\gamma = 0$, 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.

Analysis of PDE-ODE model

Goal: Construct symmetric steady-state solution $C_e(x)$ with $C_e'(L) = 0$, and formulate the linear stability problem with Steklov structure using $C = C_e + e^{\lambda t}\eta(x)$ and $\boldsymbol{u} = \boldsymbol{u}_e + e^{\lambda t}\boldsymbol{\phi}$ yielding

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

Key: Consider anti-phase (-) ($\eta(L) = 0$) and in-phase (+) $\eta_x(L) = 0$ modes.

Spectral Problem: Discrete eigenvalues λ are roots of $\mathcal{G}_\pm(\lambda) = 0$, where

$$\mathcal{G}_\pm(\lambda) \equiv 1 - p_\pm(\lambda)\frac{M_{11}(\lambda)}{\det\,(J_e - \lambda I)}\,; \quad M_{11}(\lambda)\ \ (1,1)\ \text{cofactor of}\ (J_e - \lambda I)^{-1}\,.$$

where $p_\pm(\lambda)$ with $\Omega_\lambda \equiv \sqrt{D^{-1}(1+\tau\lambda)}$ are

$$p_+(\lambda) \equiv \gamma\left(\frac{G_{u_1}^e\mathcal{P}_c^e - \mathcal{P}_{u_1}^e G_c^e - \mathcal{P}_{u_1}^e D\Omega_\lambda\tanh(\Omega_\lambda L)}{G_c^e + D\Omega_\lambda\tanh(\Omega_\lambda L)}\right)\,,$$
$$p_-(\lambda) \equiv \gamma\left(\frac{G_{u_1}^e\mathcal{P}_c^e - \mathcal{P}_{u_1}^e G_c^e - \mathcal{P}_{u_1}^e D\Omega_\lambda\coth(\Omega_\lambda L)}{G_c^e + D\Omega_\lambda\coth(\Omega_\lambda L)}\right)\,.$$

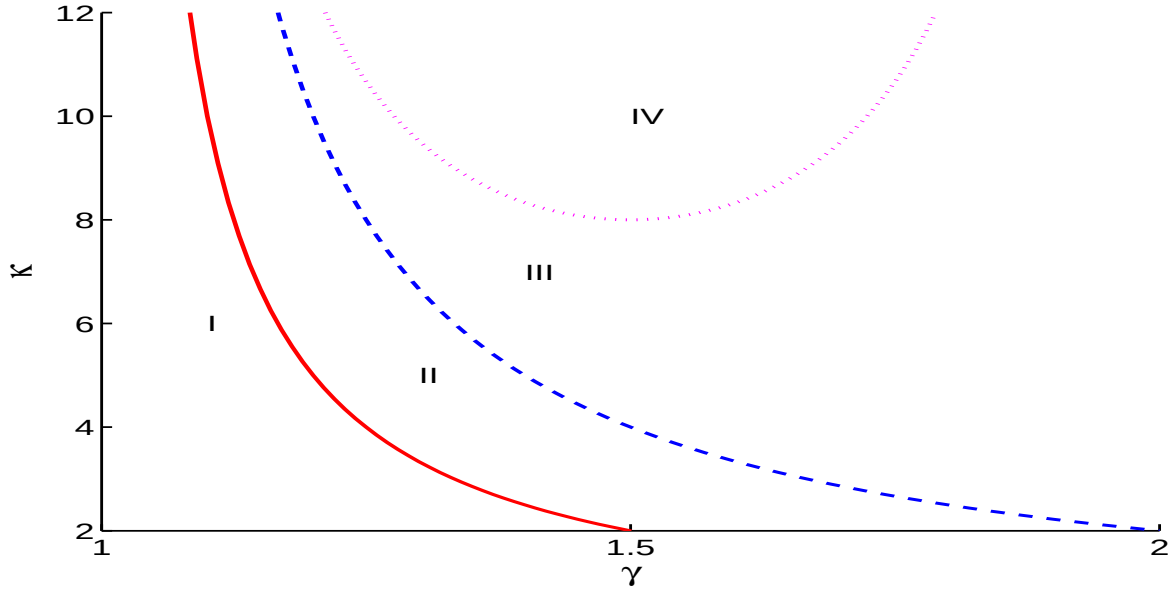
Simple Example with One Species: I

Analysis: Identify HB points for in-phase and anti-phase modes and then compute global branches of periodic solutions using AUTO. For $N = 1$, can derive a normal form ODE for predicting sub- or supercritical HB.

Simple Example: Let $N = 1$ and consider

$$G(C(0,t),u) = \kappa \frac{C(0,t) - u}{1 + (C(0,t) - u)^2}\,, \qquad \frac{du}{dt} = \gamma C(0,t) - u\,.$$

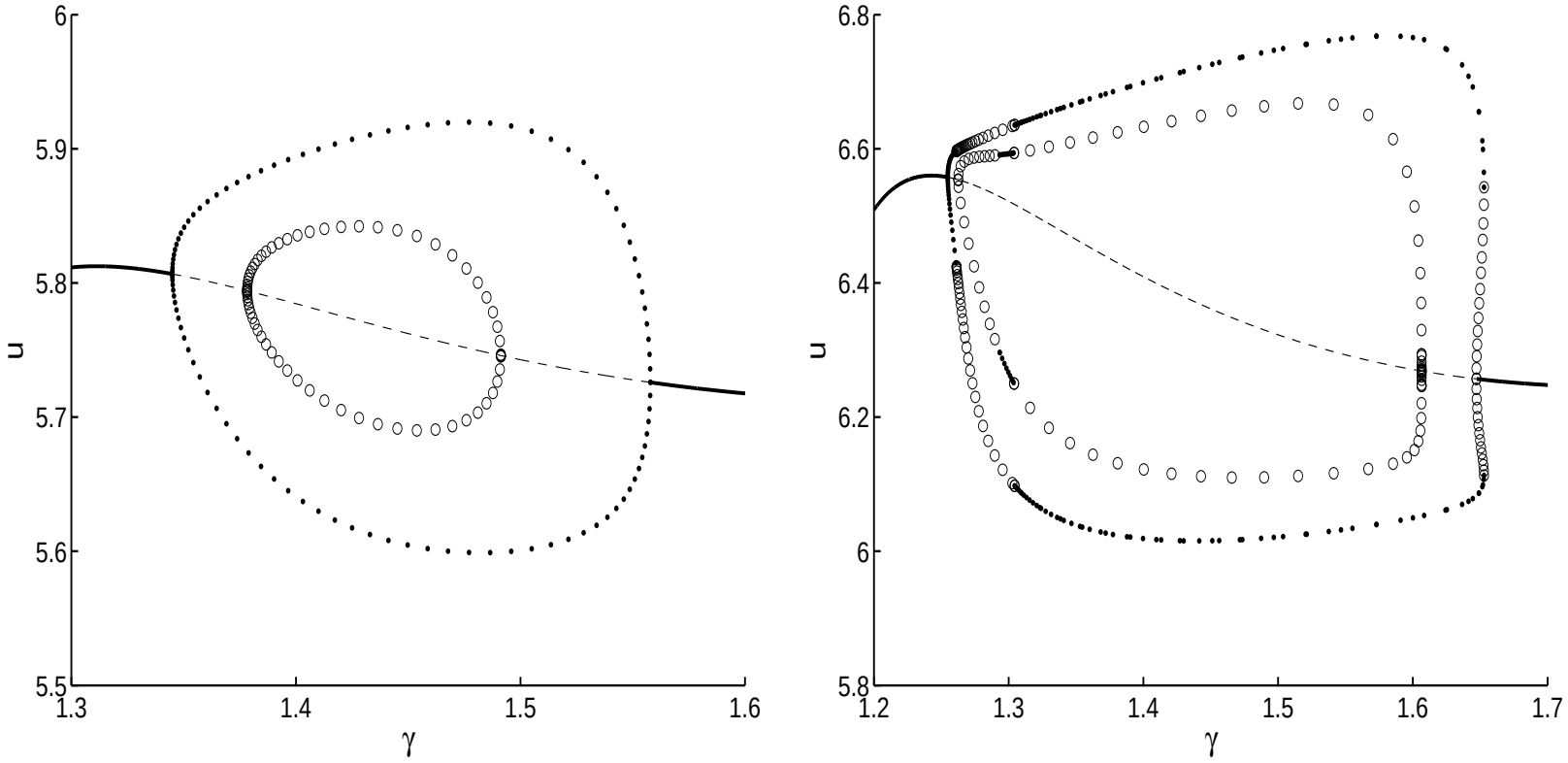
Theory: yields a κ vs. γ Phase Diagram showing where a HB can occur.



Caption: Phase diagram for infinite-line problem when $D = 1$. Region I: no s.s.. Region II and III: s.s. is stable $\forall \tau > 0$. Region IV: a unique HB $\tau = \tau_H$, with stability iff $0 \leq \tau < \tau_H$.

Simple Example with One Species: II

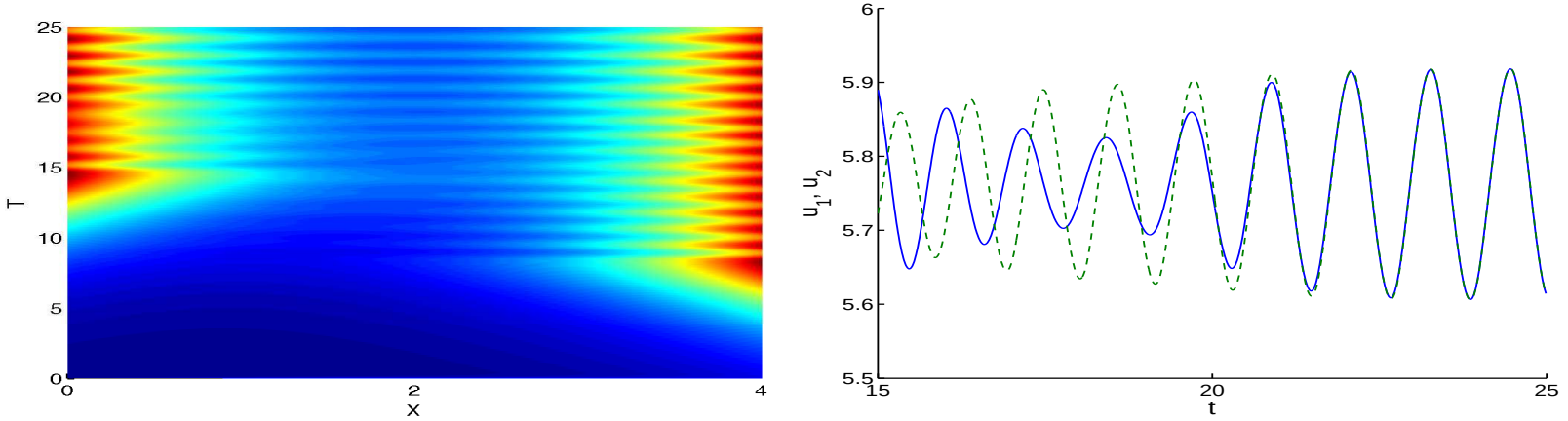
Now consider the finite domain problem with $L = 2$ and $D = 1$. Compute global bifurcation diagrams of periodic solutions (AUTO: Doedel).



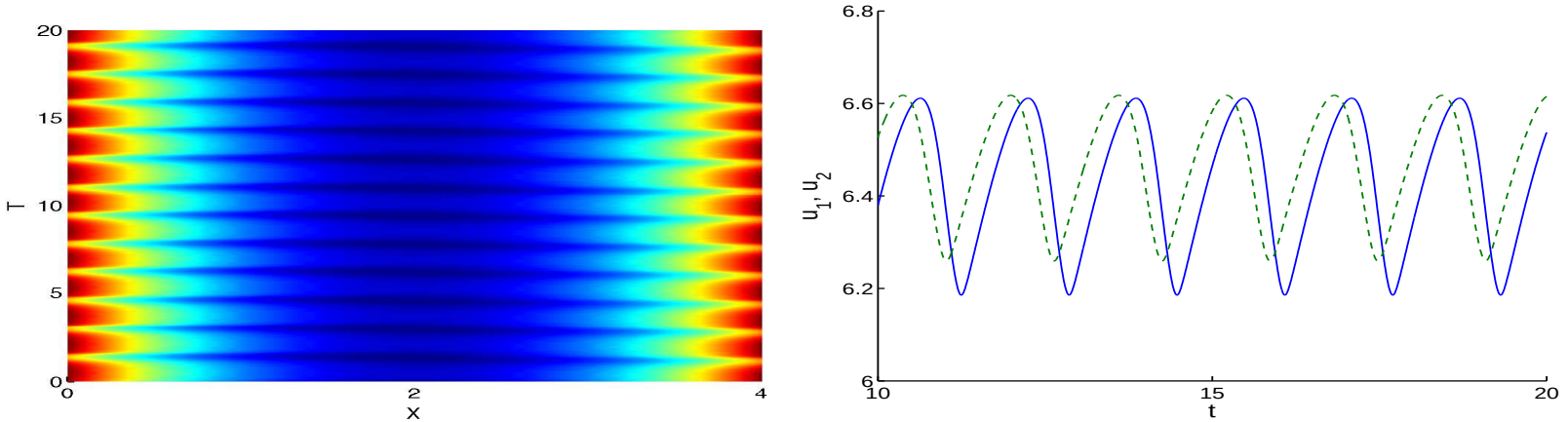
Caption: Global bifurcation diagrams for $\tau = 0.1$, $\sigma = 1$, with respect to γ for $\kappa = 9$ (left) and $\kappa = 12$ (right). Two HB points, and the synchronized periodic branch is stable for $\kappa = 9$ and mostly stable for $\kappa = 12$, but has subcritical bifurcation in right figure.

Simple Example with One Species: III

Full numerics: finite domain with $L = 2$, $D = 1$, $\tau = 0.1$, and $\sigma = 1$.



Caption: Full numerics for $\kappa = 9$ and $\gamma = 1.45$, with $C(x, 0) = 1$, with $u_1(0) = 0.04$ and $u_2(0) = 0.5$. Theory predicts that only the synchronous mode is stable. This is confirmed.



Caption: Full numerics for $\kappa = 10.5$ and $\gamma = 1.28$. Theory predicts that synchronous and anti-phase periodic solutions are both linearly unstable. We observe phase-locking behavior.

Membrane-Bound Turing Patterns

Let Ω be the unit ball in N-D with $N = 2, 3$. Suppose in the bulk Ω that there are 2 species

$$u_t = D_u \Delta u - \sigma_u u \,, \qquad v_t = D_v \Delta v - \sigma_v v \,,$$

and that the nonlinear chemical reactions are localized to $\partial\Omega$

$$\frac{du_m}{dt} = -r_d u_m + r_a u|_{\partial\Omega} + f(u_m, v_m) \,,$$
$$\frac{dv_m}{dt} = -p_d v_m + p_a v|_{\partial\Omega} + g(u_m, v_m) \,,$$

with linear coupling conditions on $\partial\Omega$

$$D_u \partial_n u = r_d u_m - r_a u \,, \qquad D_v \partial_n v = p_d v_m - p_a v \,.$$

Key: Can get spatial patterning even in $D_u = D_v$ (Levine-Rappel, Phys. Rev. E. **72**(2005)). Mathematical theory: group of M. Roger.

In progress: In 2-D can perform a normal form analysis of any HB point exploiting the structure of the Steklov linearization to predict sub or super-criticality (with F. Paquin-Lefebvre (UBC) and W. Nagata (UBC)).

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