Oscillatory Dynamics for Active Membranes Coupled by Linear Bulk Diffusion

Michael J. Ward (UBC)

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Collaborators:, J. Gou (UBC-UMinn), Frederic Paquin-Lefebvre (UBC), Wayne Nagata (UBC), Yue-Xian Li (UBC)

Coupling Bulk Diffusion to Active Units

Theme: Coupling N distinct spatially distributed dynamically active but immobile "units" (catalyst particles, membranes, signalling compartments) via a passive bulk diffusion field (signalling molecule, chemical reagents, etc...), can lead to dynamically new behavior and a mechanism to trigger collective synchronous oscillations.

Mathematical Remarks:

- Synchronization here does not occur by coupling ODE's through nearest neighbour or network ODE coupling (Kuramoto's paradigm).
- Bulk diffusion can act effectively as a spatial delay mechanism.
- Linearized problems are non-self adjoint Steklov eigenvalue problems, that admit complex spectra.

Brief overview:

- 2-D quorum sensing models (Jia Gou's talk)
- 2-D bulk diffusion in a cylinder with two bulk species coupled to a dynamically active surface (Frederic Paquin-Lefebvre's talk)
- 1-D theory today

Multi-D: Quorum Sensing Observations

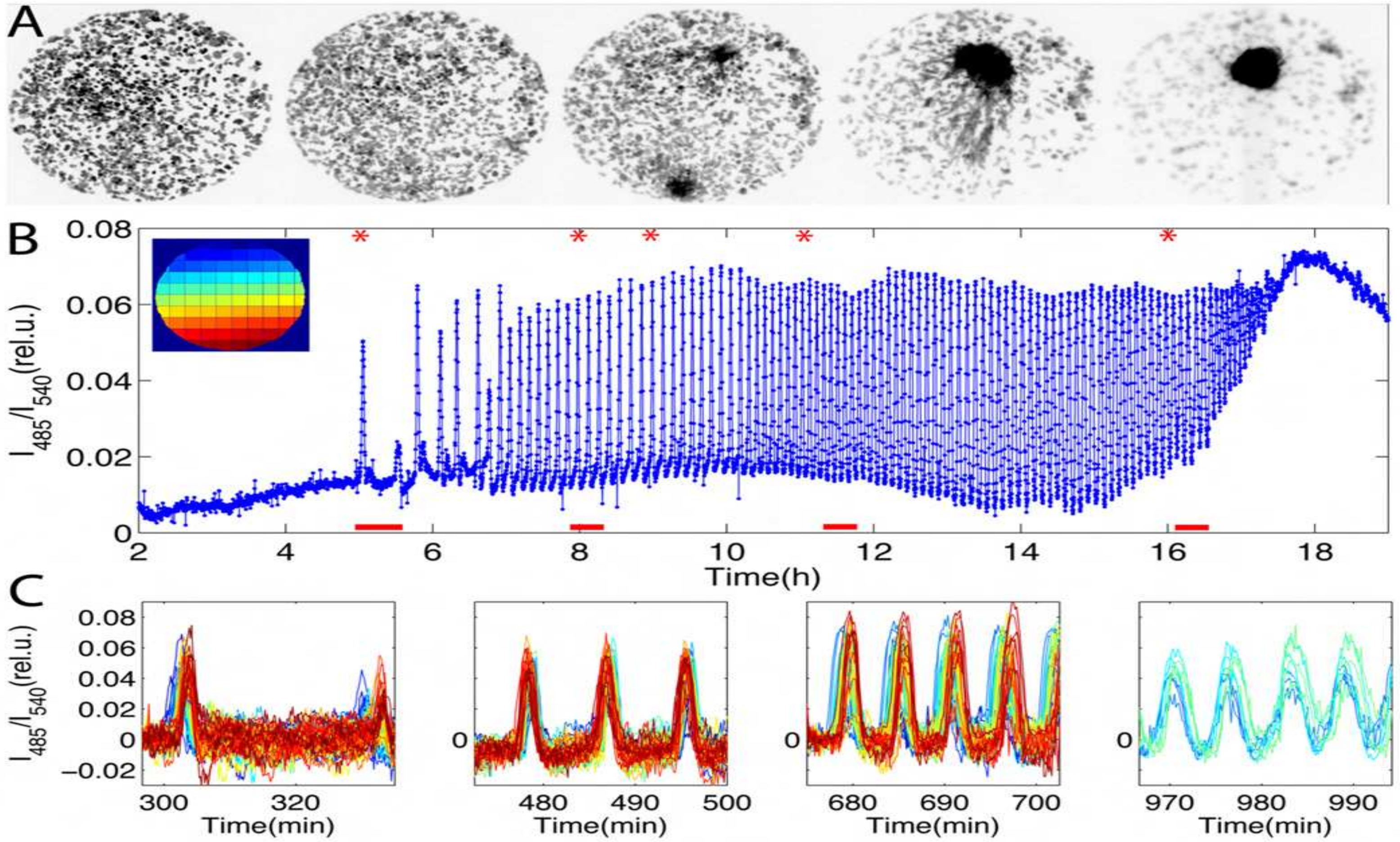
Collective oscillations in “cells” driven by intercellular chemical signalling.

- Suspensions of yeast cells coupled only through extracellular signalling molecules (aceteldehyde as autoinducers) showing glycolytic oscillations. **Ref:** De Monte et al., PNAS **104**(47), (2007).
- Amoeba colonies (Dicty) in low nutrient environments, with cAMP ultimately organizing the aggregation of starving colonies; **Ref:** Nanjundiah, Biophysics Chem. (1998). Gregor et al. Science, (2010).
- Catalyst bead particles (BZ particles) interacting through a chemical diffusion field; **Ref:** K. 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) that influences the autocatalytic growth. In the absense of coupling by bulk diffusion, the cells are assumed to be in a quiescent state.

Contribution (Gou-MJW): Theoretical analysis of a 2-D PDE-ODE model with arbitrary intracellular kinetics in the limit where the cells have “small” radii.

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, Gregor, Thomas, et al. Science 2010

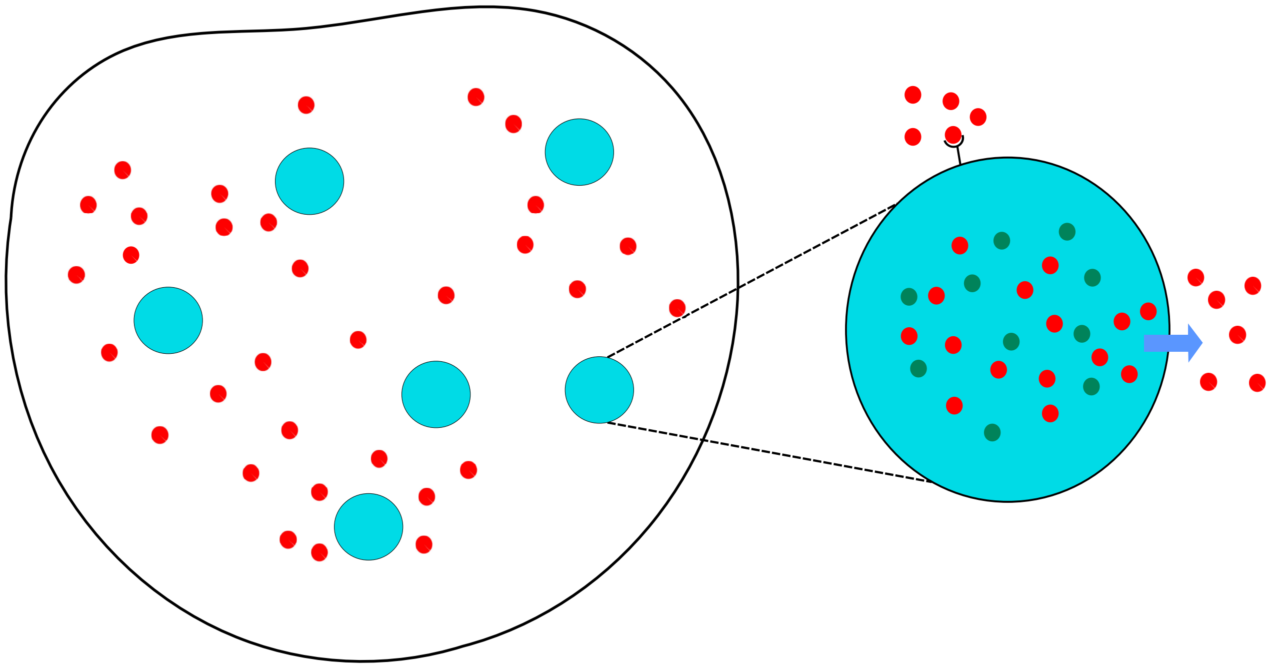
Modeling Approaches

- **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..)
- **Homogenization** approach of deriving RD systems through cell densities: Can predict target and spiral wave patterns of cAMP in Dicty modeling.
- **More Recent (Multiscale):** 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). (steady-state analysis in 3-D). This is our framework.

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.

Ref: J. Gou, M.J. Ward, J. Nonlinear Science, online first, April 2016 (51 pages).

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.

Active Cells Coupled by Spatial Diffusion

Specific Questions:

- 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 these 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?

Go see: Jia Gou's talk tomorrow afternoon

Membrane-Bound Turing Patterns

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

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

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)).

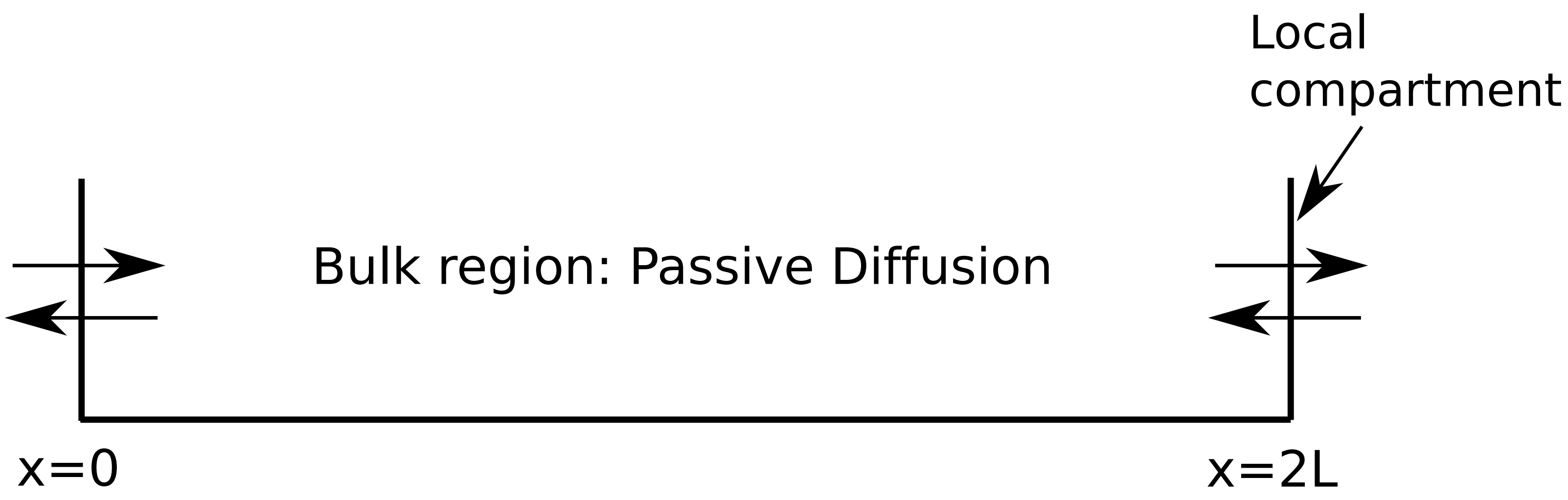
Go to talk of F. Paquin-Lefebvre for HB stability analysis with $N = 2$.

Go to talk of C. MacDonald for new numerical methodologies to compute coupled bulk-surface PDEs.

Today: One-Dimensional Theory

Mathematical Model:

- There is one local compartment (cell) located at each boundary of the domain $[0, 2L]$.
- There are N dynamically interacting substances within each compartment, but only one substance can be secreted into the buk $0 < x < 2L$.
- The signaling substance diffuses and is degraded in the bulk. It regulates its own secretion on the boundaries.



1-D Theory: General Model

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

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

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

$$G_1(a,b) = \kappa_1(a - b)\,, \qquad \mathcal{P}(a,b) = a - b\,.$$

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 ϕ 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:

$\phi_x(L) = 0 \,,$ Even: In-Phase Synchronization

$\phi(L) = 0 \,,$ Odd: Anti-Phase Synchronization

Linear Stability Analysis

For both cases, the eigenvalue λ 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.

Spectral Theory: One-ODE and $L \to \infty$

Suppose the "cell" dynamics has a single component, and define

$$F\left(C(0,t),u\right) \equiv \mathcal{F}(u) + \beta \mathcal{P}\left(C(0,t),u\right) \, .$$

For the infinite-line problem where $L \to \infty$, λ satisfies

$$\sqrt{1+\tau\lambda} = \frac{c + a\lambda}{b+\lambda} \, ,$$

Here a, b, and c, are defined by

$$a \equiv -\frac{G_c^e}{\sqrt{D}} \, , \qquad b \equiv -F_u^e \, , \qquad c \equiv \frac{1}{\sqrt{D}} \left[G_c^e F_u^e - G_u^e F_c^e \right] \, .$$

Rigorous Spectral Results:

- Case 1: Assume $b > 0$ and $1 < a < c/b$. If $c/b > 3a + 2\sqrt{2}(a^2-1)^{1/2}$, there exist two HB points $\tau = \tau_{\pm}$.
- Case 2: If $ab - c < 0$, no HB occur.
- Case 3: Assume $b > 0$ and $c/b < a < 1$, there is no HB.
- Case 4: Assume $b > 0$ and $c/b < 1 < a$, HB exists at some $\tau = \tau_H$.

Note: $ab - c < 0$ leads to $G_u^e F_c^e / \sqrt{D} < 0$, etc.

Spectral Theory: One-ODE and $L \to \infty$

$$\tau C_t = D C_{xx} - C\,, \quad x > 0\,; \qquad D C_x\big|_{x=0} = G(C(0,t),u)\,,$$
$$C \to 0 \quad \text{as} \quad x \to \infty\,,$$
$$\frac{du}{dt} = F(C(0,t),u) \equiv \mathcal{F}(u) + \sigma G(C(0,t),u)\,,$$

for some $\sigma > 0$. Let $C_e(x)$ and u_e denote the steady-state, and N be the number of unstable eigenvalues of the linearization.

Theorem 1: (HB with Linear Coupling Impossible) Consider linear coupling $G(C(0,t),u) \equiv \kappa\left[C(0,t) - u\right]$. Then, for any $\tau > 0$, $N = 0$ when $\mathcal{F}'(u_e) < \mathcal{F}_{\text{Lth}}$, and $N = 1$ when $\mathcal{F}'(u_e) > \mathcal{F}_{\text{Lth}} \equiv \sigma\kappa / \left[1 + \kappa/\sqrt{D}\right] > 0$.

Theorem 2: Suppose that $G_c^e > 0$, $G_u^e > 0$, and define $\mathcal{F}_{\text{th}} \equiv -\frac{\sigma G_u^e}{1+G_c^e/\sqrt{D}} < 0$. We have

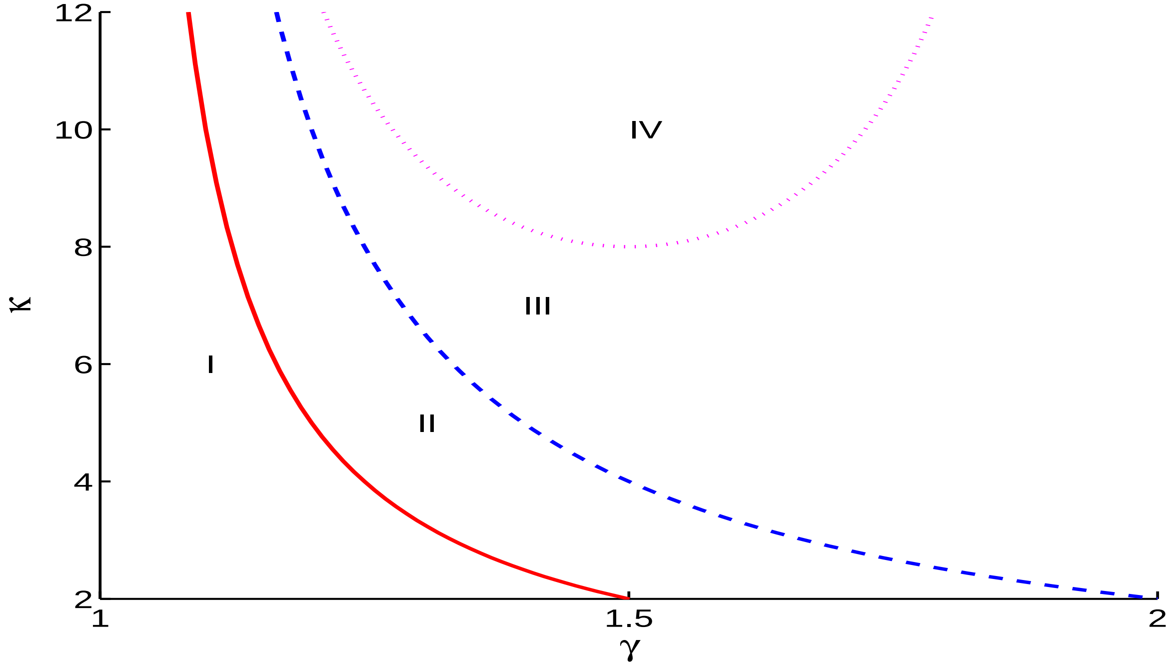
- $\mathcal{F}'(u_e) > \mathcal{F}_{\text{th}}\,, \quad \to \quad N = 1 \;\; \forall \tau > 0\,,$
- $-\sigma G_u^e < \mathcal{F}'(u_e) < \mathcal{F}_{\text{th}}\,, \quad \to \quad N = 2$ or $N = 0$ for $\tau > \tau_H$ or $\tau < \tau_H\,,$
- $\mathcal{F}'(u_e) < -\sigma G_u^e\,, \quad \to \quad N = 0 \;\; \forall \tau > 0\,.$

Example: An Explicitly Solvable Model I

Consider the sigmoidal-shaped coupling function:

$$G(C(0,t),u) = \kappa \frac{C(0,t)-u}{1+\beta(C(0,t)-u)^2}\,, \quad F(C(0,t),u) = \gamma C(0,t) - u\,.$$

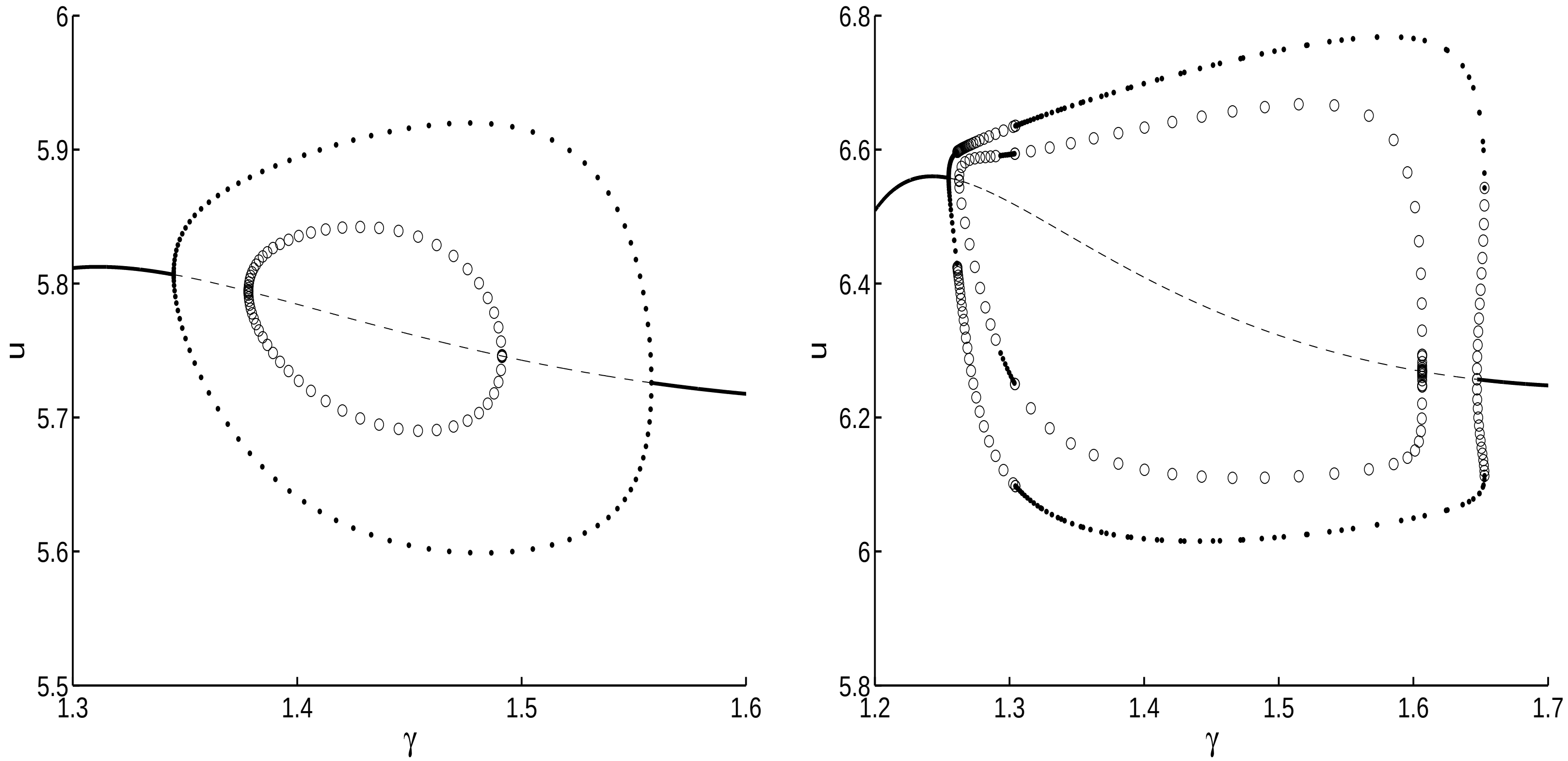
for which $a = -[2-\kappa(\gamma-1)]/\kappa(\gamma-1)^2$, $b=1$, and $c=(1-\gamma)a$.



Caption: Phase diagram in the κ versus γ plane for the infinite-line problem when $D=1$. Region I: no steady-state. Region II and III: steady-state is stable $\forall \tau > 0$. Region IV: there is a unique HB $\tau = \tau_H$. We have stability if $0 < \tau < \tau_H$, instability if $\tau > \tau_H$.

Example: An Explicitly Solvable Model II

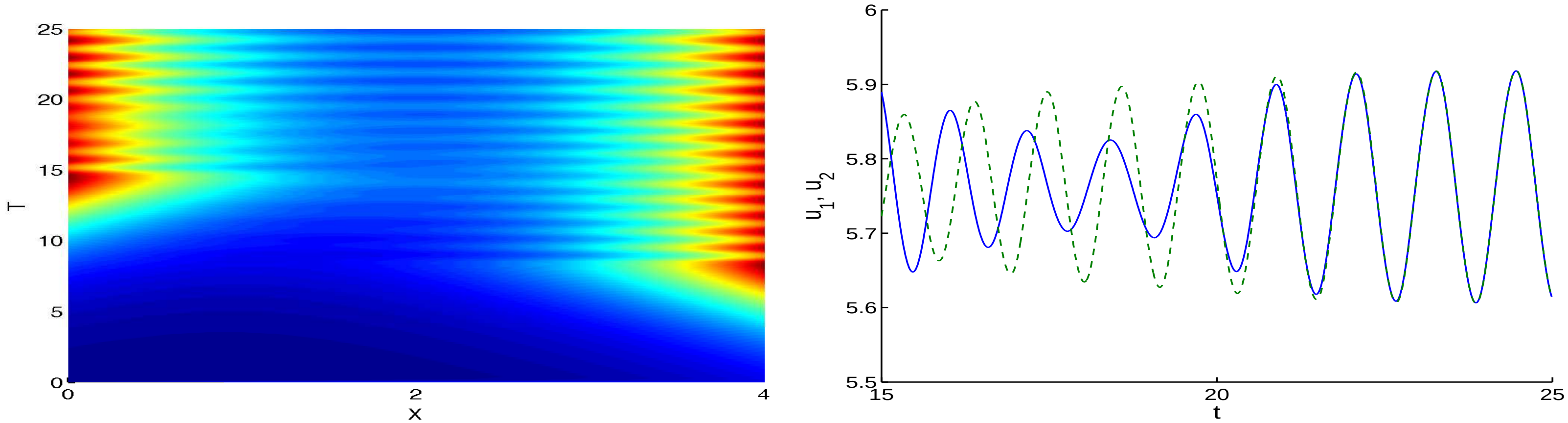
Now consider the finite domain problem with $L = 2$ and $D = 1$. Plot global bifurcation diagrams of periodic solutions.



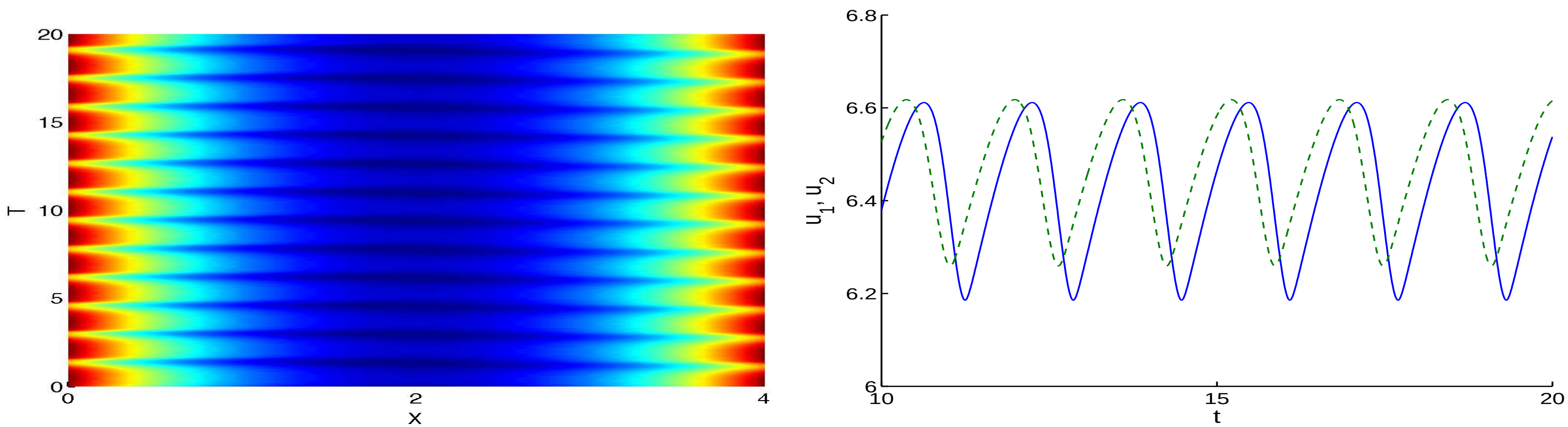
Caption: Global bifurcation diagrams for $\tau = 0.1$, $\beta = 1$, with respect to γ for $\kappa = 9$ (left) and $\kappa = 12$ (right). Two HB points, and the synchronized periodic branch is stable for $\kappa = 9$ and mostly stable for $\kappa = 12$, but has subcritical bifurcation in right figure.

Example: An Explicitly Solvable Model III

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



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.

Weakly Nonlinear Theory for a HB: I

Consider a one-ODE model in a finite domain $[0, L]$. Goal: predict whether HB is sub or super-critical for the in-phase (synchronous) mode.

$$\frac{\tau}{D} C_t = C_{xx} - \frac{1}{D} C \,, \quad 0 < x < L \,,$$
$$D C_x(0,t) = G(C(0,t), u) \,, \qquad C_x(L,t) = 0 \,,$$
$$\frac{du}{dt} = F(C(0,t), u) \,.$$

Suppose $\exists$ a HB for in-phase mode when $D = D_0$ and that $\lambda = i\lambda_I$.

Methodology:

- Detune D as $D = D_0 + \epsilon^2 D_1 + ...$, and expand $C = C_e + \sum_{k=1}^{3} \epsilon^k C_k + ...$, $u = u_e + \sum_{k=1}^{3} \epsilon^k u_k + ...$ where $C_k = C_k(x,t,T)$ and $u_k = u_k(t,T)$ and $T = \epsilon^2 t$.
- For the linearized problem write:

$$C_1(x,t,T) = A(T) e^{i\lambda_I t} \eta_0(x) + \text{c.c.} \,, \qquad u_1(t,T) = A(T) e^{i\lambda_I t} \phi_0 + \text{c.c.} \,,$$

Derive amplitude equation for $A(T)$ using multi-scale expansion.

Weakly Nonlinear Theory for a HB: II

- Define the extended operator $\mathcal{L}$ (B. Friedman 1964)

$$\mathcal{L}\begin{pmatrix} u(x) \\ u_1 \end{pmatrix} = \begin{pmatrix} \frac{D_0}{\tau} u''(x) - \frac{1}{\tau} u(x) \\ F_c^e u(0) + F_u^e u_1 , \end{pmatrix} .$$

- Define the inner product of $U \equiv (u(x),\ u_1)^T$ and $V \equiv (v(x),\ v_1)^T$ by

$$\langle U, V \rangle \equiv \int_0^L u(x) \overline{v}(x)\, dx + u_1 \overline{v}_1 \,,$$

on the subspace where

$$u_x(L) = 0 \,, \qquad D_0 u_x(0) = G_c^e u(0) + G_u^e u_1 \,.$$

- We have $\langle \mathcal{L}U, V \rangle = \langle U, \mathcal{L}^\star V \rangle$, in terms of the adjoint $\mathcal{L}^\star$ defined by

$$\mathcal{L}^\star V \equiv \begin{pmatrix} \frac{D_0}{\tau} v''(x) - \frac{1}{\tau} v(x) \\ F_u^e v_1 - G_u^e v(0)/\tau \end{pmatrix} .$$

where V is a two-component vector satisfying the adjoint BC

$$v_x(L) = 0 \,, \qquad D_0 v_x(0) = G_c^e v(0) - \tau F_c^e v_1 \,.$$

Weakly Nonlinear Theory for a HB: III

- If $\mathcal{L}U = i\lambda_I U$, then $\mathcal{L}^\star V = -i\lambda_I V$.
- At order 3 we have

$$C_3(x,t,T) = \mathcal{C}_4 + \mathcal{C}_3 e^{i\lambda_I t} + \mathcal{C}_2 e^{2i\lambda_I t} + \mathcal{C}_1 e^{3i\lambda_I t} + \text{c.c.}\,,$$

$$u_3(t,T) = U_4 + U_3 e^{i\lambda_I t} + U_2 e^{2i\lambda_I t} + U_2 e^{3i\lambda_I t} + \text{c.c.}\,,$$

where $\mathcal{C}_k = \mathcal{C}_k(x,T)$ and $U_k = U_k(T)$ and

$$\mathcal{L}\begin{pmatrix} \mathcal{C}_3 \\ U_3 \end{pmatrix} - i\lambda_I \begin{pmatrix} \mathcal{C}_3 \\ U_3 \end{pmatrix} = \begin{pmatrix} \mathcal{R}_1 \\ A'\phi_0 - \mathcal{R}_3 \end{pmatrix}, \qquad 0 < x < L\,,$$

where $\mathcal{C}_3(x)$ satisfies the inhomogeneous BC

$$\mathcal{C}_{3x}(L) = 0\,, \qquad D_0 \mathcal{C}_{3x}\big|_{x=0} - [G_c^e \mathcal{C}_3(0) + G_u^e U_3] = \mathcal{R}_2\,.$$

- Here $\mathcal{R}_1$ depends on A', while $\mathcal{R}_2$ and $\mathcal{R}_3$ are linear combinations of A and $A^2|A|$.
- Imposing a solvability condition with an adjoint, we get the amplitude equation $A' = D_1 b_1 A + b_2 A^2|A|$.

Weakly Nonlinear Theory for a HB: IV

- Writing $A = re^{i\theta}$ yields

$$r' = r(c_{11} + c_{21}r^2)\,, \qquad \theta' = c_{12} + c_{22}r^2.$$

The nontrivial fixed point $r_o = \sqrt{-\frac{c_{11}}{c_{21}}}$ correponds to periodic solution

$$\begin{pmatrix} C(x,t,T) \\ u(t,T) \end{pmatrix} \sim \begin{pmatrix} C_e(x) \\ u_e \end{pmatrix} + \epsilon \left[r_e e^{i(\lambda_I + \epsilon^2 \tilde{\theta})t} \begin{pmatrix} \eta_0(x) \\ \phi_0 \end{pmatrix} + \text{c.c.} \right] .$$

- Can infer sub or supercritical HB in terms of coefficients.
- If $b_{1R} > 0$, the symmetric s-s solution $(C_e(x),\, u_e)$ is linearly stable if $D_1 < 0$ and is unstable if $D_1 > 0$. An unstable branch of periodic solutions $\exists$ for $D_1 < 0$ if $b_{2R} > 0$ (subcritical Hopf). If $b_{2R} < 0$, $\exists$ a stable periodic solution branch in the region $D_1 > 0$ (supercritical Hopf).

Remarks: Similar approach can be extended to more ODEs, two bulk diffusing species (membrane-bulk coupling problem in 2-D).

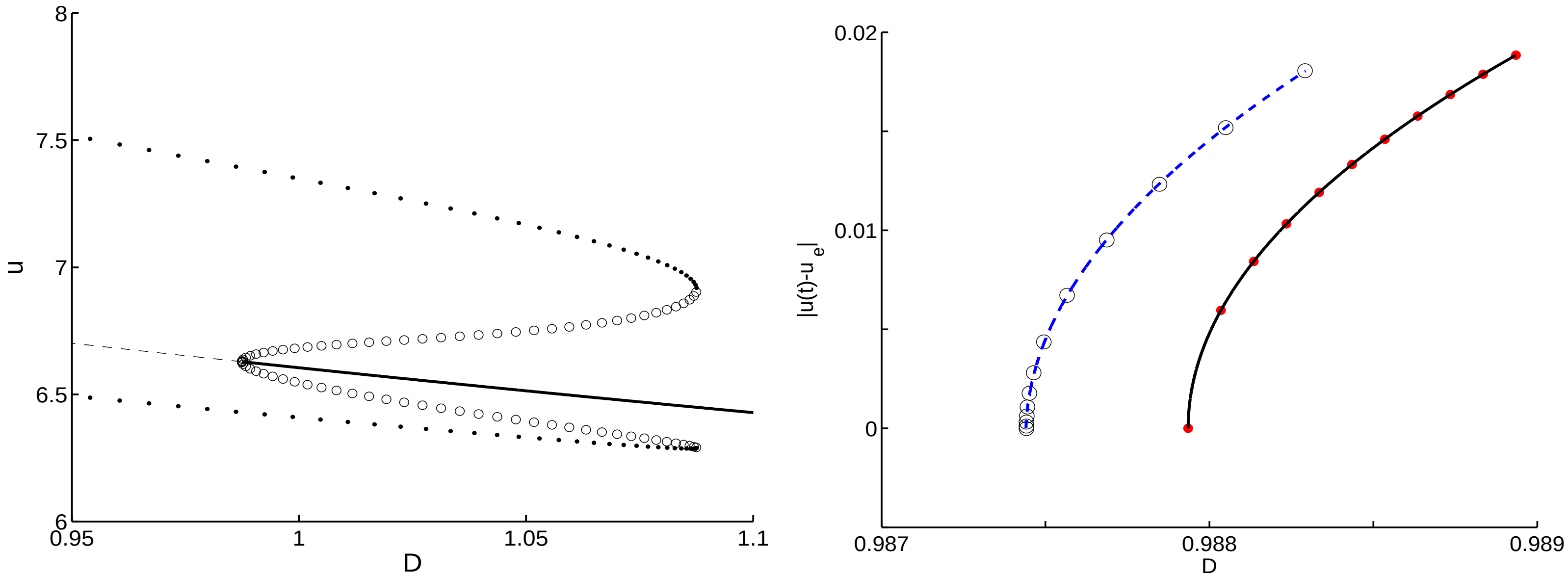
Weakly Nonlinear Theory for a HB: V

Consider our explicitly solvable model with

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

Set $\tau = 0.1$, $L = 5$, $\beta = 1$, $\kappa = 12$, and $\gamma = 1.7$.

Upshot: Weakly nonlinear theory predicts the subcritical behavior

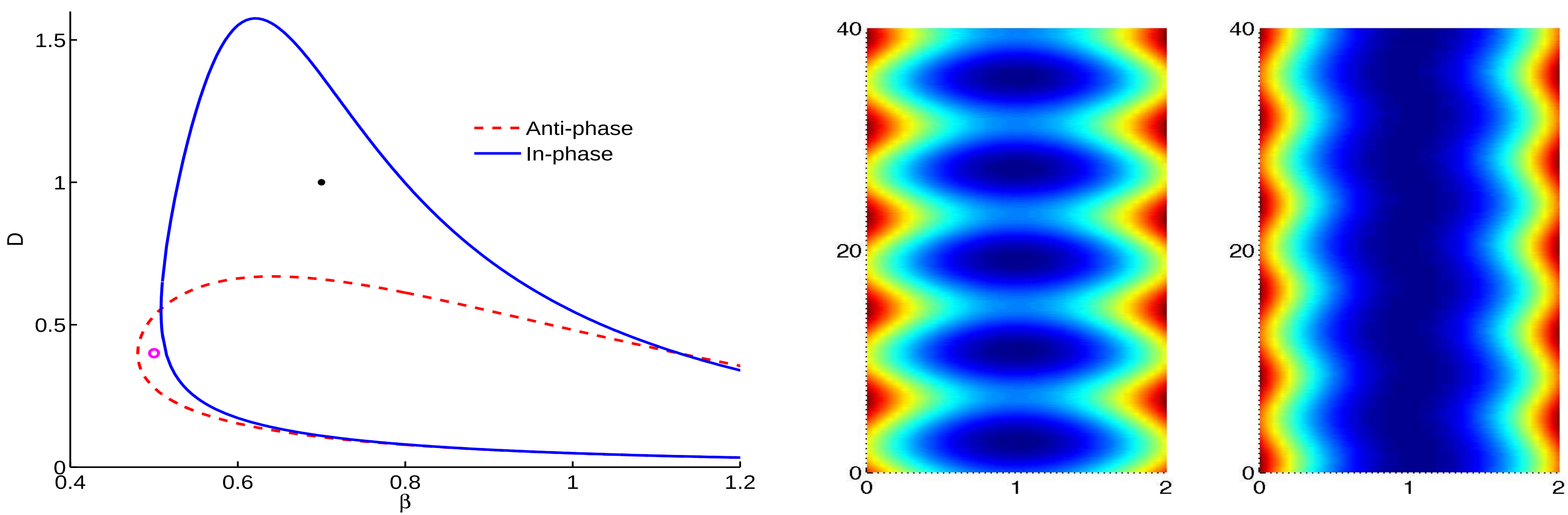


Caption: Left: Bifurcation diagram wrt D showing a subcritical HB. Right: Comparison of bifurcation diagrams obtained from full numerics and from weakly nonlinear analysis. The y-axis shows $|u(t) - u_e|$.

2-ODE Compartmental Dynamics

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

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



Caption: Left: Phase diagram in D vs β plane. Right: full numerics for $C(x,t)$ confirming the theory. (left: blue dot) is in-phase, (right: red dot) anti-phase.

Extensions and Perspectives

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.

Extensions of Methodology:

- **1-D Periodic Chains:** of "active units" coupled by bulk diffusion. The synchronous mode has the best stability properties.
- **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.

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