A 2-D Model of Dynamically Active Cells Coupled by Bulk Diffusion: Triggered Synchronous Oscillations and Quorum Sensing

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Active Cells Coupled by Spatial Diffusion

Formulate and analyze a 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.

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?
- 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 finite dimensional dynamics?
- 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?
Quorum Sensing Observations

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

- Collections of spatially segregated unicellular organisms such as yeast cells or bacteria coupled only through extracellular signalling molecules (autoinducers). 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. 72, (1998).

- Catalyst bead particles (BZ particles) interacting through a chemical diffusion field; Ref: Tinsley et al. “Dynamical Quorum Sensing... Collections of Excitable and Oscillatory Catalytic 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 absence of coupling by bulk diffusion, the cells are assumed to be in a quiescent state.

Our Contribution: Theoretical analysis of a PDE-ODE model with arbitrary intracellular kinetics in the limit where the cells have “small” radii.
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 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.


**Activator-Inhibitor RD Systems:** Are there any analogies between the PDE-ODE systems and the instabilities and bifurcations of localized spot patterns for RD systems in the semi-strong limit $\epsilon \to 0$ and $D = O(1)$? The GM model is

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

Rough Analogy: localized spot $\rightarrow$ “cell’; and inhibitor $u \rightarrow$ “bulk diffusion”.
A Coupled Cell Bulk-Diffusion Model: I

**Formulation:** of PDE-ODE coupled cell-bulk model in 2-D:

\[
\begin{align*}
    \mathcal{U}_T &= D_B \Delta \mathcal{X} \mathcal{U} - k_B \mathcal{U} , \quad \mathcal{X} \in \Omega \setminus \bigcup_{j=1}^{m} \Omega_j ; \\
    \partial_{n_x} \mathcal{U} &= 0 , \quad \mathcal{X} \in \partial \Omega , \\
    D_B \partial_{n_x} \mathcal{U} &= \beta_1 \mathcal{U} - \beta_2 \mu_j^1 , \quad \mathcal{X} \in \partial \Omega_j , \quad j = 1, \ldots, m .
\end{align*}
\]

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

Inside each cell there are \( n \) interacting species with mass vector \( \mu_j \equiv (\mu_j^1, \ldots, \mu_j^n)^T \) whose dynamics are governed by \( n \)-ODEs

\[
\frac{d\mu_j}{dT} = k_R \mu_c F_j (\mu_j / \mu_c) + e_1 \int_{\partial \Omega_j} (\beta_1 \mathcal{U} - \beta_2 \mu_j^1) \ dS_j , \quad j = 1, \ldots, m ,
\]

where \( e_1 \equiv (1, 0, \ldots, 0)^T \), and \( \mu_c \) is typical mass.

- Only \( \mu_j^1 \) 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 \( F_j(u_j) \) models the intracellular dynamics.
Coupled Cell Bulk-Diffusion Model: II

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.

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

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

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

$$\epsilon D \partial_n \epsilon_j U = d_1 U - d_2 u_1^j, \quad x \in \partial \Omega_{\epsilon_j}, \quad j = 1, \ldots, m.$$

Inside each of the $m$ cells there are $n$ interacting species $u_j = (u_1^j, \ldots, u_n^j)^T$, with intracellular dynamics

$$\frac{d u_j}{dt} = F_j(u_j) + \frac{e_1}{\epsilon \tau} \int_{\partial \Omega_{\epsilon_j}} (d_1 U - d_2 u_1^j) \, ds, \quad e_1 \equiv (1, 0, \ldots, 0)^T.$$

Remark: The time-scale is measured w. r. t intracellular reactions. The cells are disks of radius $\epsilon$ so that $\Omega_{\epsilon_j} \equiv \{x \mid |x - x_j| \leq \epsilon\}$ with $\epsilon \ll 1$.

Parameters: $d_j$ (permeabilities); $\tau$ (reaction time ratio); $D$ (diffusion length);

$$\tau \equiv \frac{k_R}{k_B}, \quad D \equiv \left(\frac{\sqrt{D_B/k_B}}{L}\right)^2, \quad \beta_1 \equiv (k_B L) \frac{d_1}{\epsilon}, \quad \beta_2 \equiv \left(\frac{k_B}{L}\right) \frac{d_2}{\epsilon}.$$
Coupled Cell Bulk-Diffusion Model: IV

Key Question: Can the effect of cell-bulk coupling induce or trigger oscillatory dynamics through a Hopf bifurcation that otherwise would not be present. Is the oscillation “coherent” in that we can observe synchronous in-phase temporal oscillations in the cells?

Mathematical Framework, Methodology, and Three Regimes for $D$:

- 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).

- $D = O(1)$; Effect of spatial distribution of cells is important (diffusion sensing).

- Simplify stability formulation when $D = O(\nu^{-1})$, where $\nu = -1 / \log \epsilon$. When $D = D_0/\nu$, there are stability thresholds due to Hopf bifurcations when $n \geq 2$. Both synchronous and asynchronous modes can occur.

- In the “well-mixed limit” $D \gg O(\nu^{-1})$, the coupled PDE-ODE cell-bulk model can be reduced to finite dimensional dynamics. Quorum sensing behavior observed.

Steady-States: Matched Asymptotics

In the outer region, the steady-state bulk diffusion field is

\[ U(x) = -2\pi \sum_{i=1}^{m} S_i G(x, x_i) . \]

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

\[ F_j(u_j) + \frac{2\pi D}{\tau} S_j e_1 = 0, \quad \left( 1 + \frac{D\nu}{d_1} \right) S + 2\pi \nu G S = -\frac{d_2}{d_1} \nu u^1 . \]

The entries of the \( m \times m \) Green’s interaction matrix \( G \) are

\[ (G)_{ii} = R_i, \quad (G)_{ij} = G(x_i; x_j) \equiv G_{ij}, \quad i \neq j, \]

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

\[ \Delta G - \varphi_0^2 G = -\delta(x - x_j), \quad x \in \Omega; \quad \partial_n G = 0, \quad x \in \partial \Omega. \]

\[ G(x; x_j) \sim -\frac{1}{2\pi} \log |x - x_j| + R_j + o(1), \quad \text{as} \quad x \to x_j . \]
Globally Coupled Eigenvalue Problem

For $\epsilon \to 0$, the perturbation to the bulk diffusion field satisfies

$$\eta(x) = -2\pi \sum_{i=1}^{m} c_i G_\lambda(x, x_i),$$

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

$$M c = 0, \quad M(\lambda) \equiv \left(1 + \frac{D\nu}{d_1}\right) I + \frac{2\pi\nu d_2}{d_1 \tau} DK(\lambda) + 2\pi\nu G_\lambda.$$

**Main Result:** discrete eigenvalues $\lambda$ must be roots of $\det M = 0$.

Here $G_\lambda$ is the Green's matrix formed from

$$\Delta G_\lambda - \varphi_\lambda^2 G_\lambda = -\delta(x - x_j), \quad x \in \Omega; \quad \partial_n G_\lambda = 0, \quad x \in \partial\Omega,$$

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

with $\varphi_\lambda \equiv D^{-1/2} \sqrt{1 + \tau \lambda}$. Also $K$ is the diagonal matrix defined in terms of the Jacobian $J_j \equiv F_{j,u}(u_e)$ of the intracellular kinetics $F_j$:

$$K_j = e_1^T (\lambda I - J_j)^{-1} e_1 = \frac{M_{j,11}(\lambda)}{\det(\lambda I - J_j)}.$$
The Distinguished Limit $D = D_0 / \nu$

Simplify: Assume identical intracellular dynamics: so $F_j = F$, $\forall j$:

- $G \sim D / |\Omega| + \mathcal{O}(1)$ and $G_\lambda \sim D / [(1 + \tau \lambda)|\Omega|] + \mathcal{O}(1)$ for $D \gg 1$.
- To leading order, the source strengths are independent of the locations of cells. No spatial information to leading order in $\nu$.

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 $\text{Re}(\lambda) > 0$. Here $J$ is the Jacobian of $F(u)$ 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 $\text{Re}(\lambda) > 0$ 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 $c = q_j$, where $q_j^T e = 0$ for $j = 2, \ldots, m$, where $e = (1, \ldots, 1)^T$. 

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Analogy with Localized Spot Patterns: I

Remark: Close analogy with spot stability analysis of Wei-Winter (2001) for the GM model in the “weakly coupled regime” $D = D_0/\nu$ with $D_0 = \mathcal{O}(1)$ in a bounded 2-D domain $\Omega$ with no flux conditions on $\partial\Omega$;

$$v_t = \epsilon^2 \Delta v - v + \frac{v^2}{u}, \quad \tau u_t = D\Delta u - u + \epsilon^{-2}v^2,$$

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 $\text{Re}(\lambda) > 0$ to the two NLEPs

$$C_{\pm}(\lambda) = \mathcal{F}(\lambda) \equiv \frac{\int_{0}^{\infty} \rho w (L_0 - \lambda)^{-1} w^2 \, d\rho}{\int_{0}^{\infty} \rho w^2 \, d\rho},$$

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

$$C_{-}(\lambda) \equiv \frac{(\mu + 1)}{2}, \quad \text{(asynchronous)},$$

$$C_{+}(\lambda) \equiv \frac{(\mu + 1)}{2} \left( \frac{1 + \tau \lambda}{1 + \mu + \tau \lambda} \right), \quad \text{(synchronous)}.$$
Analogy with Localized Spot Patterns: II

Main Result (Wei-Ward 2015): 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)

- **Quorum sensing oscillatory behavior occurs** for localized spot patterns in the $D = D_0/\nu$ regime.
- However, 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, $u$ 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

Remark: For $n = 1$ can prove no HB possible for any intracellular dynamics.

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

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

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

where $p_1, p_2,$ and $p_3$, are defined by

$$p_1 \equiv \frac{(\gamma + \zeta)}{\tau} - \text{tr}(J), \quad p_2 \equiv \det(J) - \frac{\gamma}{\tau} G_{u_2}^e + \frac{1}{\tau} \left( \frac{\gamma}{\tau} - \zeta \text{tr}(J) \right),$$

$$p_3 \equiv \frac{1}{\tau} \left( \zeta \det(J) - \frac{\gamma}{\tau} G_{u_2}^e \right),$$

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

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

**Hopf Bifurcations:** By Routh-Hurwitz criterion, any HB must satisfy

$$p_1 > 0, \quad p_3 > 0, \quad p_1 p_2 = p_3.$$
The Distinguished Limit $D = D_0/\nu$: III

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

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

where

$$q_1 \equiv \text{tr}(J) - \frac{\gamma}{\tau}, \quad q_2 \equiv \text{det}(J) - \frac{\gamma}{\tau} G_{u_2}^e.$$

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

**Example: Sel’kov Kinetics**

Let $u = (u_1, u_2)^T$ be intracellular dynamics given by Sel’kov model (used for modeling glycolisis 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.
The Well-Mixed Regime $D \gg O(\nu^{-1})$: I

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

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

$$U_0' = -\frac{1}{\tau} U_0 - \frac{2\pi}{|\Omega|} \sum_{j=1}^{m} (d_1 U_0 - d_2 u_1^j) \ ,$$

$$u_j' = F_j(u_j) + \frac{2\pi}{\tau} \left[ d_1 U_0 - d_2 u_1^j \right] e_1 , \quad j = 1, \ldots, m ,$$

where $e_1 = (1, 0, \ldots, 0)^T$. Large system of ODEs with weak coupling when $0 < d_1 \ll 1$ and $0 < d_2 \ll 1$, or when $\tau \gg 1$.

If we assume that the cells are identical, and look for $u_j = u$, $\forall j$, then the bulk concentration $U_0(t)$ and intracellular dynamics $u$ satisfy

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

$$u' = F(u) + \frac{2\pi}{\tau} \left[ d_1 U_0 - d_2 u_1 \right] e_1 .$$

**Remark:** $|\Omega|/m$ is a key parameter. (Effective area per cell)
The Well-Mixed Regime \( D \gg O(\nu^{-1}) \): II

Consider Selkov dynamics with \( d_1 = 0.8, d_2 = 0.2 \).

Figure: Global bifurcation diagram of \( u_{1e} \) versus \( \tau \) 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 oscillations occur in some \( \tau \) interval. Limiting well-mixed ODE dynamics is independent of cell locations and \( D \).
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.

**Linear Stability Formulation (GCEP):** Must find the roots \( \lambda \) to \( F_j(\lambda) = 0 \), where

\[
F_j(\lambda) \equiv \omega_{\lambda,j} + \frac{1}{2\pi\nu} \left( 1 + \frac{D\nu}{d_1} \right) + \left( \frac{d_2D}{d_1\tau} \right) \frac{M_{11}}{\det(\lambda I - J)}, \quad j = 1, \ldots, m.
\]

Here \( \omega_{\lambda,j} \) are the eigenvalues of the \( \lambda \)-dependent Green’s matrix \( G_\lambda \):

\[
G_\lambda v_j = \omega_{\lambda,j} v_j, \quad j = 1, \ldots, m,
\]
Remarks on Simplification: For $m$ cells on a concentric ring

- This pattern has a steady-state with $S_j = S_c$ for all $j = 1, \ldots, m$.
- Entries in $G_\lambda$ readily calculated in terms of sums of modified Bessel functions of complex argument.
- $G_\lambda$ and $G$ are symmetric, cyclic matrices. Hence $v_1 = (1, \ldots, 1)^T$ (synchronous mode). Matrix spectrum of $G_\lambda$ readily calculated (mode degeneracy occurs).

Computations:

- 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 $\text{Re}(\lambda) > 0$ in the $\tau$ versus $D$ plane.
\[ D = \mathcal{O}(1): \text{HB Boundaries } m = 2 \]

**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 $\tau_H$ 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 $\tau$ 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?

Key: In other words, find the range of $m$ for which the instability lobe for the synchronous mode is unbounded in the $\tau$ versus $D$ plane.
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 $m_c = 19$. 
Outlook and References

Further Directions: Let $D = \mathcal{O}(1)$. Consider “random” spatial configuration of cells in 2-D domain.

- **Q1:** How do we solve the GCEP? (fast multipole methods for $G$ and $G_\lambda$)
- **Q2:** Can we observe clusters of oscillating and non-oscillating cells?
- **Q3:** Analyze effect of a defector cell that triggers oscillations in the others. (discrete “target” patterns?)
- **Q4:** Large time dynamics in terms of time-dependent Green’s function? (distributed delay equation).

References


Ref: Available at [http://www.math.ubc.ca/~ward/prepr.html](http://www.math.ubc.ca/~ward/prepr.html)