Topics in Localized Pattern Formation

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**Outline**

- **Topic I:** Berg-Purcell Problem Revisited. Determination of effective capacitance of a sphere with \( N \) small “traps” on the boundary. The homogenized limit and the mean first capture time. (**Lindsay, Bernoff**)

- **Topic II:** PDE/ODE Model of dynamically-active (ODE) small signalling compartments coupled by bulk-diffusion (PDE). Leads to the triggering of (synchronous) oscillations via a hopf bifurcation (**J. Gou, S. Iyaniwura**). Biologically: illustrates quorum and diffusion sensing behavior.

**Key Features:** Derivation and study of new discrete variational problems using from Green’s interaction matrices. Nonlinear matrix eigenvalue problems involving Green’s interaction matrices.
Topic I: Narrow Capture in 3-D

Caption: spherical target of radius $\varepsilon \ll 1$ centered at $x_0 \in \Omega$, with $N$ locally circular absorbing surface nanotrapns (nanopores) of radii $\sigma \ll \varepsilon$ modeled by homogeneous Dirichlet condition.

- A particle (protein etc.) undergoes Brownian walk ($dX_t = DdW_t$) until captured by one of the $N$ small absorbing surface nanotraps.
- Q1: How long on average does it take to get captured? (MFPT).
- Q2: What is the effect on the MFPT of the spatial distribution $\{x_1, \ldots, x_N\}$ of the surface nanotraps? (Capacitance).
Applications of Narrow Capture

**Nuclear Pores:** Genetic material enters nucleus via small pores.

Scaling: Nucleus $\approx 10\%$ of cell volume ($\varepsilon = 0.1$). Roughly, $N = 2000$ pores that occupy 2% of the surface area. (Eilenberg et al. Science 341(6146), 2013).

**Cell Signalling:** How long does it take an antigen to bind to a receptor on a T-cell to produce antibodies?
The MFPT PDE for Narrow Capture

The Mean First Passage Time (MFPT) $T$ satisfies

$$\Delta T = -\frac{1}{D}, \quad x \in \Omega \setminus \Omega_\varepsilon; \quad \partial_n T = 0, \quad x \in \partial \Omega,$$

$$T = 0, \quad x \in \partial \Omega_{\varepsilon a}; \quad \partial_n T = 0, \quad x \in \partial \Omega_{\varepsilon r},$$

where $\partial \Omega_{\varepsilon a}$ and $\partial \Omega_{\varepsilon r}$ are the absorbing and reflecting part of the surface of the small sphere $\Omega_\varepsilon$ within the 3-D cell $\Omega$.

- Calculate the averaged MFPT $\bar{T}$ for capture of a Brownian particle.
- $\bar{T}$ depends on the capacitance $C_0$ of the structured target (related to the Berg-Purcell problem, 1977). This is the inner or local problem.
- Derive new discrete optimization problems characterizing the optimal MFPT and determine how the fragmentation of the trap set affects $\bar{T}$.

Ref: [LBW2017] Lindsay, Bernoff, MJW, First Passage Statistics for the Capture of a Brownian Particle by a Structured Spherical Target with Multiple Surface Traps, SIAM Multiscale Mod. and Sim. 15(1), (2017), pp. 74–109.
Asymptotic Result for the Average MFPT

Using strong localized perturbation theory, for $\varepsilon \to 0$ the average MFPT is

$$\bar{T} \equiv \frac{1}{|\Omega \setminus \Omega_\varepsilon|} \int_{\Omega \setminus \Omega_\varepsilon} T \, dx = \frac{|\Omega|}{4\pi C_0 D_\varepsilon} \left[ 1 + 4\pi \varepsilon C_0 R(x_0) + \mathcal{O}(\varepsilon^2) \right] ,$$

where $R(x_0)$ is the regular part of the Neumann Green’s function for $\Omega$:

$$\Delta G = \frac{1}{|\Omega|} - \delta(x - x_0), \quad x \in \Omega; \quad \partial_n G = 0, \quad x \in \partial \Omega ,$$

$$G(x; x_0) = \frac{1}{4\pi|x - x_0|} + R(x_0), \quad \text{as} \quad x \to \xi; \quad \int_{\Omega} G \, dx = 0 .$$

Capacitance Problem: “exterior” problem in potential theory. $C_0$ satisfies

$$\Delta v = 0, \quad y \in \mathbb{R}^3 \setminus \Omega_0 ; \quad v = 0, \quad y \in \Gamma_a, \quad \partial_n v = 0, \quad y \in \Gamma_r ,$$

$$\lim_{R \to \infty} \int_{\partial \Omega_R} \partial_n v \, ds = -4\pi; \quad v \sim -\frac{1}{C_0} + \frac{1}{|y|} + \mathcal{O}(|y|^{-2}), \quad |y| \to \infty .$$
Capacitance $C_0$ of Structured Target

The inner problem for the capacitance $C_0$ is equivalent to finding the probability $w(y)$ that a particle is captured starting at $y \in \mathbb{R}^3 \setminus \Omega_0$:

$$
\Delta w = 0, \quad y \in \mathbb{R}^3 \setminus \Omega_0 \text{ (outside unit ball)}
$$

$$
w = 1, \quad y \in \Gamma_a \text{ (absorbing pores)}
$$

$$
\partial_n w = 0, \quad y \in \Gamma_r \text{ (reflecting surface)}
$$

$$
w \sim \frac{C_0}{|y|} + O\left(\frac{1}{|y|^2}\right), \quad \text{as } |y| \to \infty.
$$

Remarks:

- $C_0 = 1$ if entire surface is absorbing.
- The diffusive flux $J$ into the sphere is

$$
J = D \int_{\Gamma_a} \partial_n w \, dS = 4\pi D C_0.
$$

- The sub-inner problem near a pore is the classic electrified disk problem.
Berg-Purcell Problem: I

This is the Berg-Purcell (BP) problem (Physics of Chemoception, Biophysics, 20(2), (1977)) \( \approx 1500 \) citations)

BP assumed
- \( N \gg 1 \) disjoint equidistributed small pores.
- common pore radius \( \sigma \ll 1 \).
- dilute fraction limit, i.e. \( f \equiv N\sigma^2/(4\pi) \ll 1 \).

Using a “physically-inspired” derivation, BP postulated that

\[
C_{0bp} = \frac{N\sigma}{N\sigma + \pi}, \quad J_{bp} = 4\pi D \frac{N\sigma}{N\sigma + \pi} = 4DN\sigma + \mathcal{O}(\sigma^2).
\]

Suggests that \( J \) is proportional to the total pore perimeter when \( \sigma \ll 1 \).

Our Goal: Calculate \( C_0 \), and the flux \( J \), systematically for a collection of disjoint pores centered at \( \{y_1, \ldots, y_N\} \) over the surface. Study the effect of the location of the pores and fragmentation. For equidistributed pores derive the BP result and the asymptotic corrections to it.
Berg-Purcell Problem: II

BP analysis revisited by Shoup-Szabo (Biophysical J. 1982). Replace trap set by effective trapping parameter \( k \), so that for a sphere of radius \( R \)

\[
\Delta u = 0, \quad r \geq R; \quad Du_r = ku, \quad r = R.
\]

Then, the flux \( J = \int_\Omega Du_r r \big|_{r=R} \) into the sphere is \( J = 4\pi DC \), where

\[
u = 1 - \frac{C}{r}, \quad \text{with} \quad \frac{1}{C} = \frac{1}{R} + \frac{D}{kR^2}.
\]

Now estimate \( k \): On an infinite plane with a single trap of radius \( a \)

\[
J_{\text{disk}} = \int_{\text{disk}} Du_z |_{z=0} d\mathbf{x} = 2\pi D c_{\text{disk}}, \quad c_{\text{disk}} = \frac{2a}{\pi}.
\]

Thus \( J_{\text{disk}} = k_{\text{disk}} = 4aD \). Now estimate

\[
k \approx k_{\text{disk}} \left( \frac{N}{4\pi R^2} \right) = \frac{4D}{\pi R \sigma} f, \quad \text{where} \quad f \equiv \frac{N\pi\sigma^2}{4\pi}
\]

and \( \sigma \equiv a/R \). Finally, this yields the BP capacitance and BP flux

\[
\frac{1}{C_{\text{bp}}} = \frac{1}{R} \left( \frac{\pi}{N\sigma} + 1 \right), \quad J_{\text{bp}} = 4\pi DR \left( \frac{N\sigma}{N\sigma + \pi} \right).
\]
Main Result for $C_0$ and flux $J$: I

**Main Result:** For $\sigma \to 0$, [LBW2017] derived that

$$
\frac{1}{C_0} = \frac{\pi}{N\sigma} \left[ 1 + \frac{\sigma}{\pi} \left( \log \left( 2e^{-3/2}\sigma \right) + \frac{4}{N} \mathcal{H}(y_1, \ldots, y_N) \right) + O(\sigma^2 \log \sigma) \right],
$$

$$
J = 4DN\sigma \left[ 1 + \frac{\sigma}{\pi} \log(2\sigma) + \frac{\sigma}{\pi} \left( -\frac{3}{2} + \frac{2}{N} \mathcal{H}(y_1, \ldots, y_N) \right) + \cdots \right]^{-1}.
$$

The interpore interaction energy $\mathcal{H}$, subject to $|y_j| = 1 \ \forall \ j$, is

$$
\mathcal{H}(y_1, \ldots, y_N) \equiv \sum_{j=1}^{N} \sum_{k=j+1}^{N} g(|y_j - y_k|); \quad g(\mu) \equiv \frac{1}{\mu} + \frac{1}{2} \log \mu - \frac{1}{2} \log(2+\mu).
$$

Here $y_j$ for $j = 1, \ldots, N$ are the nanopore centers with $|y_j| = 1$.

**Remarks:**

- Flux $J$ minimized when $\mathcal{H}$ minimized
- $g(\mu)$ is monotone decreasing, positive, and convex.
- Indicates that optimal configuration should be (roughly) equidistributed.
Main Result for $C_0$ and flux $J$: II

Here $g(|y_j - y_k|) = 2\pi G_s(y_j; y_k)$, $G_s$ is the surface-Neumann G-function

$$G_s(y_j; y_k) = \frac{1}{2\pi} \left[ \frac{1}{|y_j - y_k|} - \frac{1}{2} \log \left( \frac{1 - y_j \cdot y_k + |y_j - y_k|}{|y_j| - y_j \cdot y_k} \right) \right].$$

Key steps in singular perturbation analysis for $C_0$:

- Asymptotic expansion of global (outer) solution and local (inner) solutions near each pore (using tangential-normal coordinates).
- The surface $G_s$-function has a subdominant logarithmic singularity on the boundary (related to surface diffusion). This fact requires adding “logarithmic switchback terms in $\sigma$” in the outer expansion.
- The leading-order local solution is the tangent plane approximation and yields electrified disk problem in a half-space, with (local) capacitance $c_j = 2\sigma / \pi$.
- **Key:** Need corrections to the tangent plane approximation in the inner region near the pore. This higher order term in the inner expansion satisfies a Poisson-type problem, with monopole far-field behavior.
- Asymptotic matching and solvability conditions yield $1/C_0$. 

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Asymptotics versus Numerics (Small N)

Asymptotic Results: For $\sigma \to 0$

\[
J = 4D\sigma \left[ 1 + \frac{\sigma}{\pi} \left( \log(2\sigma) - \frac{3}{2} \right) - \frac{\sigma^2}{\pi^2} \left( \frac{\pi^2 + 21}{36} \right) + \cdots \right], \quad (N = 1),
\]

\[
J = 4DN\sigma \left[ 1 + \frac{\sigma}{\pi} \log(2\sigma) + \frac{\sigma}{\pi} \left( -\frac{3}{2} + \frac{2}{N} \mathcal{H}(y_1, \ldots, y_N) \right) + \cdots \right]^{-1}, \quad (N > 1).
\]

Numerics: Compare with full numerics from multipole theory based on integral equations [Bernoff, Lindsay]. Vertices at Platonic Solids.

Left: One pore: log-log plot of relative error. Leading-order (solid), three-term (dotted), four-term (dashed). Right: Comparison of rescaled flux $J/(4\sigma)$ versus $\sigma$ when pores are centered at vertices of platonic solids. Marked points are full numerics.
Clustering and Fragmenting the Pore Set

Left: $N = 20$ equally-spaced nanopores (centers shown only) clustered in the polar region $\theta \in (0, \frac{\pi}{3})$ with total absorbing fraction $f = 0.05$. Blue pore: is the equivalent area as a single nanopore. Nanopore radius is $\sigma = 2 \sqrt{f/N}$. Right: optimal dodecahedron pattern.

$$\frac{1}{C_0} \approx 5.41 \text{ (single Pore)}; \quad \frac{1}{C_0} \approx 2.79 \text{ (clustered)}; \quad \frac{1}{C_0} \approx 1.98 \text{ (optimal)}.$$

Conclude I: subdividing a single nanopore into 20 smaller, but clustered, nanopores of same total area roughly halves the MFPT to the target.

Conclude II: The MFPT for 20 optimally distributed pores is significantly smaller than for 20 clustered pores.
Discrete Energy: Equidistributed Points

Find global minimum $\mathcal{H}_{\text{min}}$ of $\mathcal{H}$ when $N \gg 1$

$$\mathcal{H} = \sum_j \sum_{k \neq j} g(|y_j - y_k|), \quad \text{where} \quad g(\mu) \equiv \frac{1}{\mu} + \frac{1}{2} \log \left( \frac{\mu}{2 + \mu} \right).$$

- What is asymptotics of $\mathcal{H}_{\text{min}}$ as $N \to \infty$?
- For large $N$, many local minima, so finding global min is difficult.
- Cannot tile a spherical surface with hexagons (must have defects).
- Related to classic Fekete point problems of minimizing pure Coulombic energies on the sphere (Smale’s 7th problem).

Three Coverings of $N = 800$ points

Uniform Random

Not Great

Equispaced in $(\theta, \phi)$

Better

Fibonacci Spirals

Best (so far...)
Scaling Law: Equidistributed Points

Formal Large \( N \) Limit: For \( N \) large and “equidistributed points”, we have

\[
H_{\text{min}} \sim \frac{N^2}{4} - d_1 N^{3/2} + \frac{N}{8} \log N \\
+ d_2 N + d_3 N^{1/2} + \cdots,
\]

with \( d_1 = 1/2 \), \( d_2 = 1/8 \) and \( d_3 = 1/4 \). Better to use \( d_1 = 0.55230 \) for “pure” Coulombic interactions [Saff].

Main Result (Scaling Law): For \( N \gg 1 \), but small pore surface area fraction \( f = \mathcal{O}(\sigma^2 \log \sigma) \) and with equidistributed pores, the optimal \( C_0 \) and \( J \) are

\[
\frac{1}{C_0} \sim 1 + \frac{\pi \sigma}{4f} \left( 1 - \frac{8d_1}{\pi} \sqrt{f} + \frac{\sigma}{\pi} \log \left( \beta \sqrt{f} \right) + \frac{2d_3 \sigma^2}{\pi \sqrt{f}} \right), \quad \beta \equiv 4e^{-3/2} e^{4d_2},
\]

\[
J \sim 4\pi D \left[ 1 + \frac{\pi \sigma}{4f} \left( 1 - \frac{8d_1}{\pi} \sqrt{f} + \frac{\sigma}{\pi} \log \left( \beta \sqrt{f} \right) + \frac{2d_3 \sigma^2}{\pi \sqrt{f}} \right) \right]^{-1}.
\]

BP Result is the leading-order term. Our analysis yields correction terms for the sphere. Most notable is the \( \sqrt{f} \) term, where \( f \equiv N \sigma^2 / 4 \).
Fragmentation Effects

Effect of Fragmentation: fix pore fraction $f$, increase $N$, and obtain $\sigma$ from $f = N \pi \sigma^2/[4\pi]$. Locate pores centered at spiral Fibonacci points.

Caption: 1001 Nanopores at vertices of the spiral Fibonacci points.

Caption: From top to bottom: $f = \{0.02, 0.05, 0.1, 0.15\}$ For $N = 2000$, $f = 0.02$, full numerics gives $C_{0n}^{-1} = 1.1985$ and $C_{0}^{-1} = 1.2028$ (scaling law).

Conclusion: Fragmentation effects are significant until $N$ becomes large.
Compare full numerics with the asymptotic scaling law

\[ J \sim 4\pi D \left[ 1 + \frac{\pi \sigma}{4f} \left( 1 - \frac{8d_1 \sqrt{f}}{\pi} + \frac{\sigma}{\pi} \log \left( \beta \sqrt{f} \right) + \frac{2d_3 \sigma^2}{\pi \sqrt{f}} \right) \right]^{-1}. \]

Fix 2\% pore coverage \( (f = 0.02) \) and choose spiral Fibonacci points.

\[ \begin{array}{|c|c|}
\hline
N & \mathcal{E}_{rel} \\
\hline
51 & 1.02\% \\
101 & 0.90\% \\
201 & 0.76\% \\
501 & 0.58\% \\
1001 & 0.37\% \\
2001 & 0.34\% \\
\hline
\end{array} \]

Caption: \( f = 0.02 \) (2\% pore coverage). Scaling law accurately predicts the flux to the target for the biological parameters \( f = 0.02 \) and \( N = 2001 \).
Effective Robin Condition: Leakage $\kappa_h$

Consider the planar case with $\sigma$ pore radius and $f$ coverage. Previous empirical laws (Berezhkovskii 2013) for a hexagonal arrangement

$$\kappa = \frac{4Df}{\pi\sigma} \chi(f), \quad \chi(f) = \frac{1 + 1.37\sqrt{f} - 2.59f^2}{(1 - f)^2},$$

Our homogenized Robin condition: use scaling law for $C_0$ and find $\kappa_h$ from

$$\Delta v_h = 0, \quad |y| > 1; \quad \partial_n v_h + \kappa_h v_h = 0, \quad |y| = 1; \quad v_h(y) \sim \frac{1}{|y|} - \frac{1}{C_0}, \quad |y| \to \infty.$$ 

For the unit sphere, and in terms of $d_1, d_2, d_3$ and $\beta \equiv 4e^{-3/2}e^{4d_2}$, we get

$$\kappa_h \sim \frac{4Df}{\pi\sigma} \left[ 1 - \frac{8d_1}{\pi} \sqrt{f} + \frac{\sigma}{\pi} \log \left( \beta \sqrt{f} \right) + \frac{2d_3\sigma^2}{\pi\sqrt{f}} \right]^{-1} \approx \frac{4Df}{\pi\sigma} \left[ 1 + 1.41\sqrt{f} + \cdots \right].$$
Further Directions

- Rigorus results for the large $N$ behavior of $\mathcal{H}$.
- Not just MFPT, but full time-dependent probability density.
- Potential theoretic methods (fast) to compute capacitance (L. Greengard, J. Kaye, preprint archive)
- Derive an explicit formula for the capacitance of a bumpy sphere containing $N$ nanopores
  - Local analysis near a pore is possible, but no explicit globally-defined surface Neumann Green’s function.
  - Needed for asymptotics: computation of surface Neumann Green’s function and its local behavior near the singularity.
- Full numerical computations based on integral equations challenging.
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).


**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 synchronization 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 oscillator phases:

\[
\frac{dx_i}{dt} = F(x_i) + \sigma \sum_j C_{ij} H(x_j),
\]

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:


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
  \[ \frac{d\mu_j}{dt} = F_j(\mu_j). \]

- 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

\[
U_T = D_B \Delta_X U - k_B U, \quad X \in \Omega \setminus \bigcup_{j=1}^{m} \Omega_j; \quad \partial_n \cdot U = 0, \quad X \in \partial \Omega,
\]

\[
D_B \partial_n \cdot U = \beta_{1j} U - \beta_{2j} \mu_{1j}^1, \quad X \in \partial \Omega_j, \quad j = 1, \ldots, m.
\]

Each cell \( \Omega_j \in \Omega \) is a disk of radius \( \sigma \) centered at some \( X_j \in \Omega \).

Inside each cell there are \( n \) interacting species with mass vector \( \mu_j \equiv (\mu_{1j}, \ldots, \mu_{nj})^T \) whose dynamics are governed by \( n \)-ODEs, with (rank-one) coupling via integration over the \( j \)-th “cell”-membrane \( \partial \Omega_j \):

\[
\frac{d\mu_j}{dT} = k_R \mu_c F_j (\mu_j / \mu_c) + e_1 \int_{\partial \Omega_j} (\beta_{1j} U - \beta_{2j} \mu_{1j}^1) \, dS_j, \quad j = 1, \ldots, m,
\]

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

- Only one species \( \mu_{1j}^1 \) 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 \( F_j(u_j) \) models the intracellular dynamics.
Formulation of the 2-D Model: III

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

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

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

The cells are disks of radius $\epsilon \ll 1$ so that $\Omega_{\epsilon_j} \equiv \{ x \mid |x - x_j| \leq \epsilon \}$.

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

$$\frac{d u_j}{dt} = F_j(u_j) + \frac{e_1}{\epsilon \tau} \int_{\partial \Omega_{\epsilon_j}} (d_{1j} U - d_{2j} u_j^1) \, ds , \quad e_1 \equiv (1, 0, \ldots, 0)^T .$$

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);

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

Two key regimes for $D$ with different behaviors:

- $D = O(1)$; Effect of spatial distribution of cells is a key factor whether oscillations are triggered or not (diffusion sensing behavior).
- $D \gg O(\nu^{-1})$; 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.
Main Result (Steady-State): In the outer region, the ss bulk diffusion field is

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

In terms of \( \nu = -1/\log \epsilon \) and a Green's matrix \( G \), we obtain a nonlinear algebraic system for \( S \) and \( u^1 \equiv (u^1_1, \ldots, u^1_m)^T \), where \( e_1 = (1, 0, \ldots, 0)^T \):

\[
F_j(u_j) + \frac{2\pi D}{\tau} S_j e_1 = 0, \quad (\mathcal{H} + 2\pi \nu G) S = -\nu \mathcal{W} u^1, \quad j = 1, \ldots, m.
\]

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 \( G \) are

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

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 (GCEP)

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

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

Inside the $j$-th cell we have $u_j = u_{ej} + 2\pi D \tau^{-1} c_j e^{\lambda t} (\lambda I - J_j)^{-1} e_1$. Here $c = (c_1, \ldots, c_m)^T$ is a nullvector of the GCEP:

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

In this GCEP, $G_\lambda$ is the Green’s matrix formed from

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

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

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

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

Linear stability analysis: Nonlinear matrix eigenvalue problem of the form

\[ \mathcal{M}(\lambda; \tau, D)c = 0. \]

Definition: An unstable “mode” is a root \( \lambda \) of \( \mathcal{F}(\lambda) = \det(\mathcal{M}(\lambda)) = 0 \) in \( \text{Re}(\lambda) > 0 \). The number \( N \) of unstable modes is the total number of such roots. The eigenvector \( c \) 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 \( \text{Re}(\lambda) > 0 \). 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 \( \text{Re}\mathcal{F} = 0 \) and \( \text{Im}\mathcal{F} = 0 \) 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 \( \mathcal{M}c = \sigma c \) available analytically.
**Intracellular Selkov Reaction-Kinetics**

**Selkov Kinetics:** Let \( u = (u_1, u_2)^T \) 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

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

- **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 \( F_j = F \), \( d_{1j} = d_1 \), and \( d_{2j} = d_2 \).

Spectral Problem (from GCEP): Must find the roots \( \lambda \) to \( B_j(\lambda) = 0 \), where

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

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

\[
G_\lambda v_j = \omega_{\lambda,j} v_j , \quad j = 1, \ldots, m ,
\]

- \( \exists \) a steady-state with \( S_j = S_c \) for all \( j = 1, \ldots, m \).
- \( G_\lambda \) and \( G \) are symmetric, cyclic matrices. Hence \( v_1 = (1, \ldots, 1)^T \) (synchronous mode).
- For the unit disk, the Green's matrix \( G_\lambda \) 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 $\text{Re}(\lambda) > 0$ in open regions of the $\tau$ versus $D$ plane.

- **Cyclic Symmetric Matrices:** Matrix spectrum of $G_\lambda$ readily calculated. Note: $v_1 = e \equiv (1, \ldots, 1)^T$ (synchronous mode), while $e^Tv_j = 0$ for $j = 2, \ldots, m$ are the asynchronous modes. However, mode degeneracy occurs due to cyclicity and symmetry of $G_\lambda$. 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 $r_0 = 0.25$
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 $D$. 

$D = \mathcal{O}(1)$: Diffusion Sensing Behavior
**$D = \mathcal{O}(1)$: 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 $\tau_- < \tau < \tau_+$. 
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): $d_1 = 0.4$, $d_2 = 0.2$.
- $M$ is a $5 \times 5$ symmetric matrix with a $4 \times 4$ 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 $c = (1, 1, 1, \xi)$: 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 Well-Mixed Regime $D \gg \mathcal{O}(\nu^{-1})$: I

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

$$
U_0' = -\frac{1}{\tau} U_0 - \frac{\rho}{\tau} \left( \frac{1}{m} \sum_{j=1}^{m} [\kappa_{1,j} U_0 - \kappa_{2,j} u_1^j] \right),
$$

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

where $e_1 = (1, 0, \ldots, 0)^T$. Here $\rho$ is the effective cell density and

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

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 $u_j = u, \forall j$. We get

$$
U_0' = -\frac{1}{\tau} (1 + \kappa_1 \rho) U_0 + \rho \frac{\kappa_2}{\tau} u_1,
\quad u' = F(u) + \frac{1}{\tau} [\kappa_1 U_0 - \kappa_2 u_1] e_1.
$$
The Well-Mixed Regime $D \gg O(\nu^{-1})$: 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 QS behavior? We will study QS behavior as the permeability $d_1$ is varied and $d_2 = 0.2$: Recall:

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

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

$$
U_0' = -\frac{1}{\tau} U_0 - \frac{\rho}{m\tau} \sum_{j=1}^{m} \left[ \kappa_{1,j} U_0 - \kappa_{2,j} u_1^1 \right],
$$

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

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 $d_{1,j} = 0.8$ and $d_{2,j} = 0.2$ $\forall j$. The intracellular kinetics $F_j$ 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):

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

$R = 1$ (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 $U(x, t)$ satisfies

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

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

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

$$\frac{d u_j}{dt} = F_j (u_j) + e_1 \int_{\partial \Omega_{\epsilon_j}} \left( \frac{d_{1,j}}{\epsilon} U - \frac{d_{2,j}}{\epsilon^2} u_j^1 \right) dS, \quad j = 1, 2, \ldots, m,$$

where $u_j = (u_j^1, \ldots, u_j^n)^T$, $e_1 \equiv (1, 0, \ldots, 0)^T$, and $d_{2,j} = O(1)$.

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

- $D = O(\epsilon^{-1})$, $\kappa = O(1)$, $d_{1,j} = \frac{\tilde{d}_{1,j}}{\epsilon}$, where $\tilde{d}_{1,j} = O(1)$.
- 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

\[ U'_0 = -\kappa U_0 + \frac{4\pi}{|\Omega|} \sum_{j=1}^{m} (p_{2,j} v^1_j - p_{1,j} U_0) - \frac{16\pi^2 \varepsilon}{|\Omega|} \sum_{j=1}^{m} p_{1,j} (G \mathbf{c})_j + \ldots, \]

\[ \frac{dv_j}{dt} = F_j (v_j) + 4\pi e_1 (p_{1,j} U_0 - p_{2,j} v^1_j) + 16\varepsilon \pi^2 e_1 p_{1,j} (G \mathbf{c})_j + \ldots, \quad j = 1, \ldots, m, \]

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

\[ p_{1,j} \equiv \frac{D_0 \tilde{d}_{1,j}}{\tilde{d}_{1,j} + D_0}, \quad p_{2,j} \equiv \frac{D_0 d_{2,j}}{\tilde{d}_{1,j} + D_0}, \quad c_j \equiv \frac{d_{2,j} v^1_j - \tilde{d}_{1,j} U_0}{\tilde{d}_{1,j} + D_0}, \quad j = 1, \ldots, m. \]

- 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 \( p_{1,j} \to \tilde{d}_{1,j} \), \( p_{2,j} \to d_{2,j} \), and \( c_j \to 0 \) (maximal cell-cell communication, but cell configuration insignificant).
- For \( D_0 = O(1) \) dependence on cell configuration and shape of confining domain \( \Omega \) is at \( O(\varepsilon) \) term through Neumann G-matrix \( G \).
- ODE system: reveals both quorum sensing and diffusion sensing behavior.