Diffusive limits of stochastic velocity jump processes for biological agents

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Motivation

Bacterial (in vitro) dynamical patterns

- Bacterial colonies *in vitro* exhibit complex morphological aggregation patterns
- Hostile environmental conditions: low nutrient level, hard agar, presence of anti-biotics, etc.
- Adaptive survival strategies lead to complex spatio-temporal patterns.
- Complex self-organization: micro-level (cell-cell), macro-level (colony), chemical signalling, gene exchange, etc.

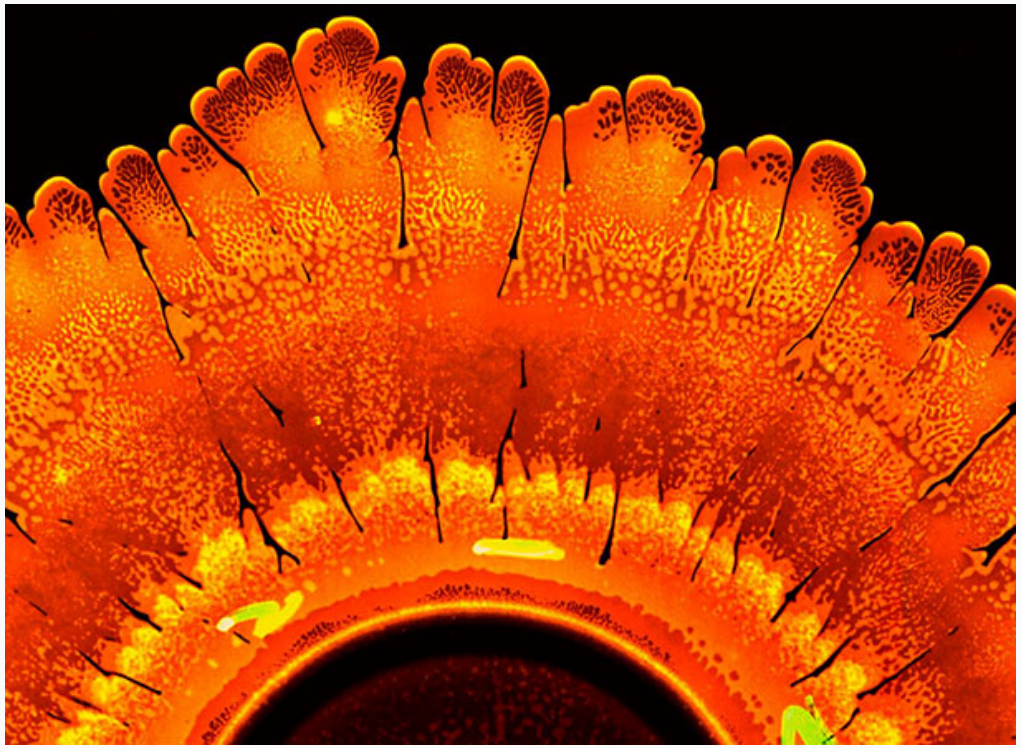
Examples: Paenbacillus dendritiformis

- Species discovered by E. Ben-Jacob (Univ. Tel-Aviv)
- Motile in hard substrates
- $\mathscr{T}$-morphotype: dentrite-type growth (*tip growth formation*), inherited and transferred by each single cell
- Intermediate hard agar, high levels of nutrient (peptone): the patterns are solid, compact colonies
- In stress conditions (low nutrient, presence of antibiotics): Complex pattern formation

Examples: Paenbacillus dendritiformis

Colony of *Paenbacillus dendritiformis*. Strain inoculated on 1.75% agar, 0.5 gl^{-1} concentration of peptone, presence of chloramphenicol. Courtesy: E. Ben-Jacob (Uni. de Tel-Aviv).

Examples: Paenbacillus dendritiformis

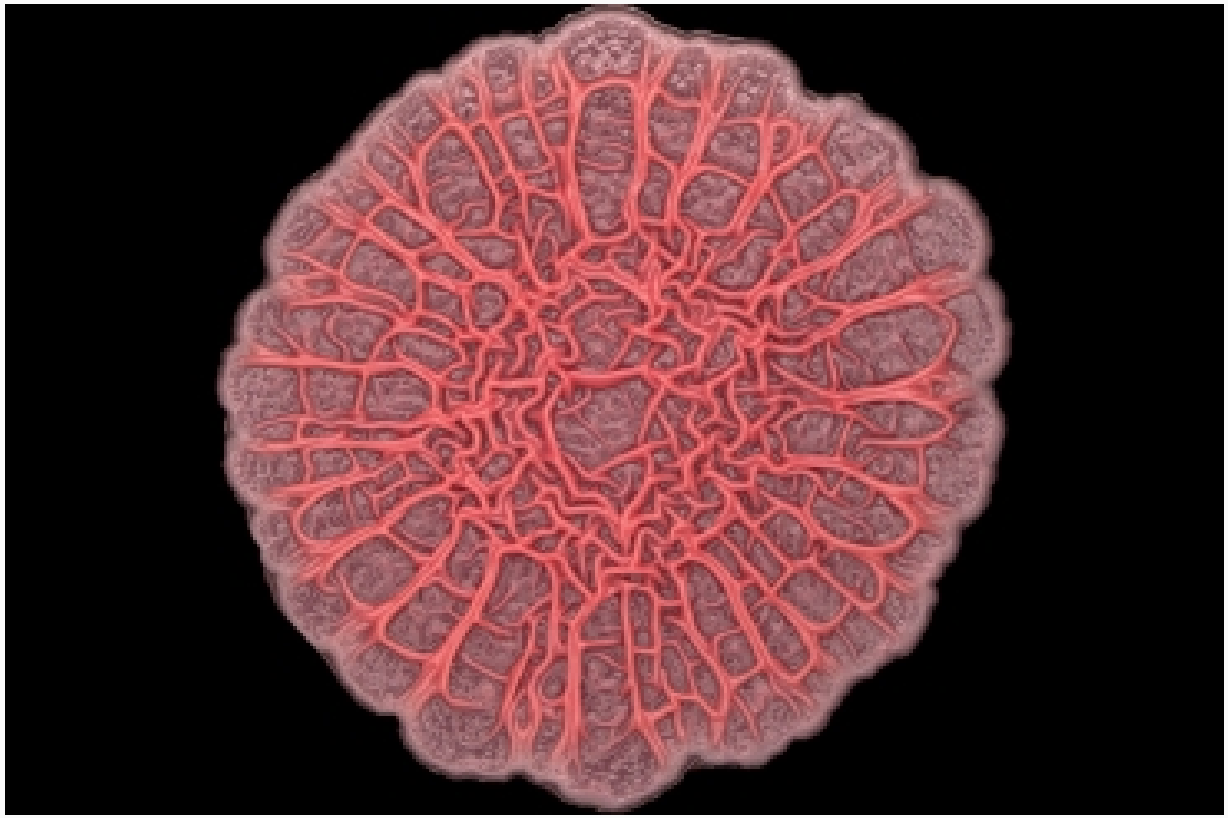


Colony of *Paenbacillus dendritiformis*. Strain inoculated on 1.75% agar, 12 gl^{-1} concentration of peptone. No antibiotics. Courtesy: E. Ben-Jacob (Uni. de Tel-Aviv).

Examples: Pseudomonas aeruginosa

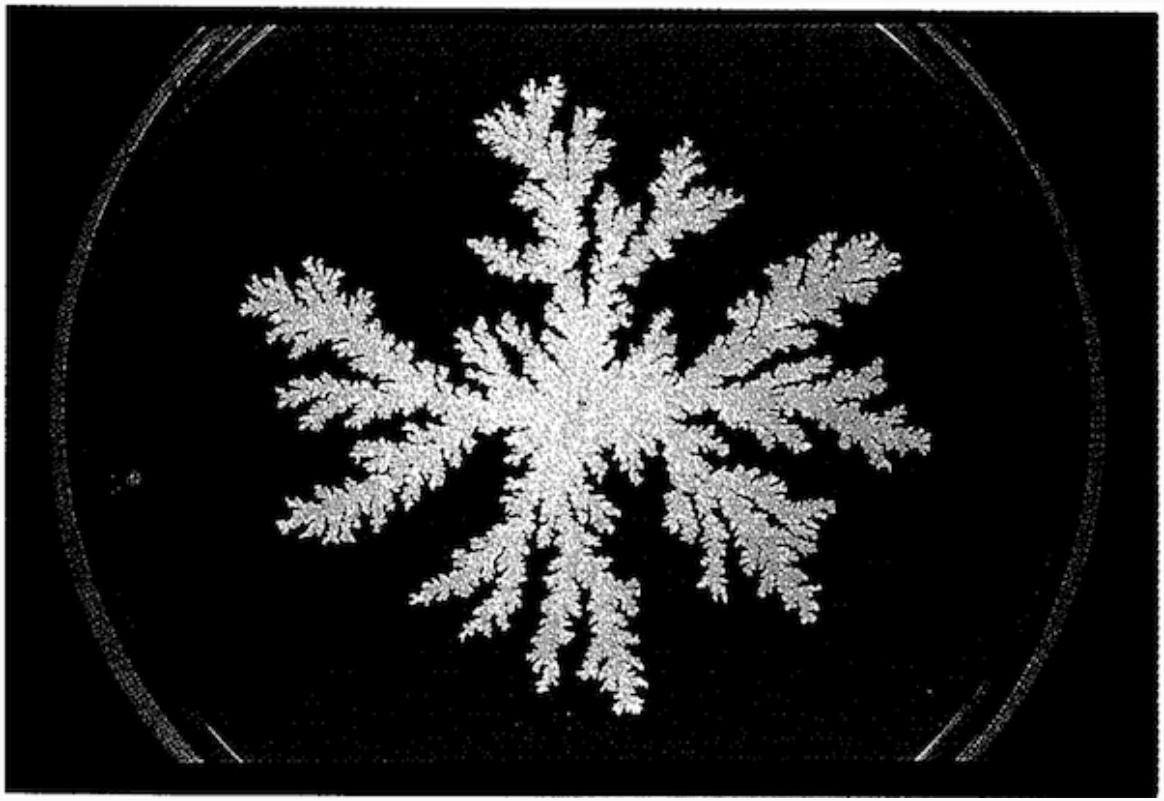
- *P. aeruginosa* pathogen, resistent to wide spectrum antibiotics; ubiquitious. Associated to serious illnesses.
- M. LeRoux (M.I.T.) disovered a mechanism to kill its competitors (other bacteria): secretion system type 6 (T6SS).
- Molecular syringe composed by proteins to inoculate toxins into neighboring cells.
- *P. aeruginosa* detect death of its kind and launch a counterattack.

Examples: Pseudomonas aeruginosa



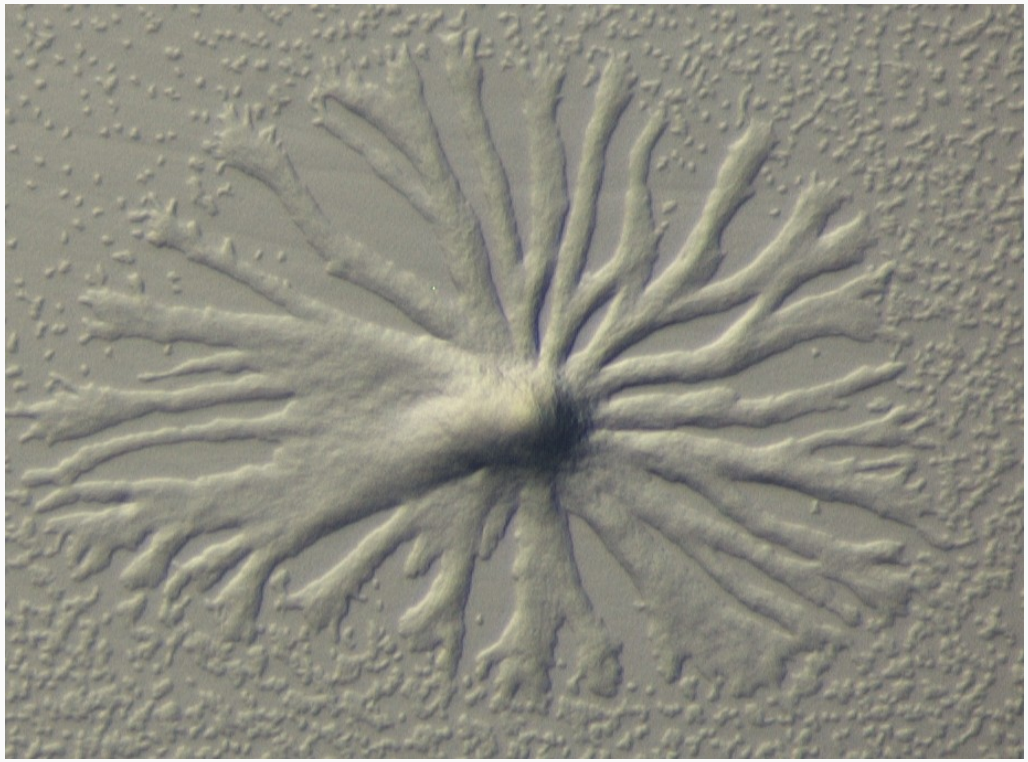
Colony of *Pseudomonas aeruginosa*. Strain inoculated on 3.75% agar. Cortesía: M. LeRoux (M.I.T.).

Examples: Bacillus subtilis



Bacillis subtilis strain on 0.75% of agar substrate. Fractal growth due to low level of nutrient. Courtesy of: Fujikawa, Matsushita, J. Phys. Soc. Japan (1989).

Examples: Dictyostelium discoideum

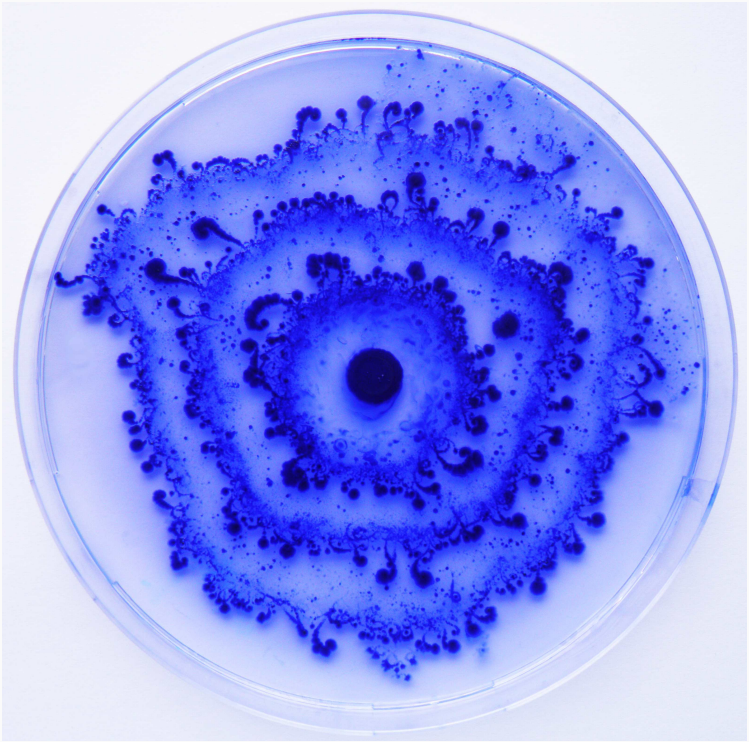


Dictyostelium discoideum strain on 0.8% agar substrate. Courtesy of: Freie Unversität Berlin.

Examples: Paenibacillus vortex and Escherichia coli

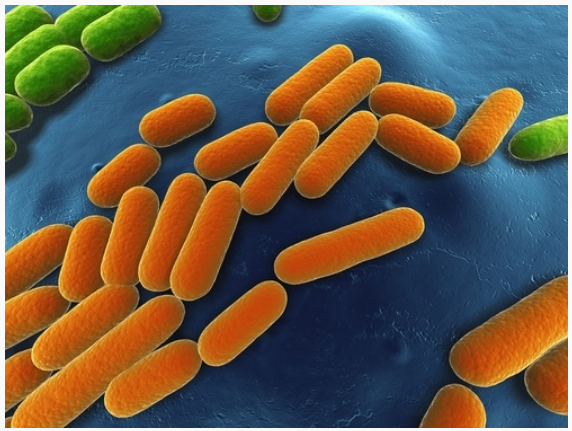
- *P. vortex*, highly active strain but sensitive to Ampicillin
- *E. coli* can degradate Ampicillin but it is immotile in high agar concentrations
- Two strains form a simbiotic colony: *E. coli* is transported by *P. vortex*; *E. coli* degrades the antibiotic

Examples: Paenibacillus vortex and Escherichia coli



Ring pattern of a mixed colony of *P. vortex* and *E. coli* on a 14 cm agar plate in the presence of Ampicillin. The rings represent different bacterial densities in alternating patterns of construction/expansion. Source: Finkelshtein et al. MBio, 6 (3), (2015).

Mathematical modeling: Bacillus subtilis



- Gram positive bacterium, rod-shaped, aerobe.
- Protective endospore (tolerate extreme environmental conditions)
- Very flagellated

In vitro experiments (cf. Ohgiwari et al., 1992)

- Strain of *B. subtilis* point inoculated in center of Petri dish
- Agar plate containing peptone as nutrient
- Average pore size of the agar smaller that size of bacteria, inducing two-dimensional growth on agar surface

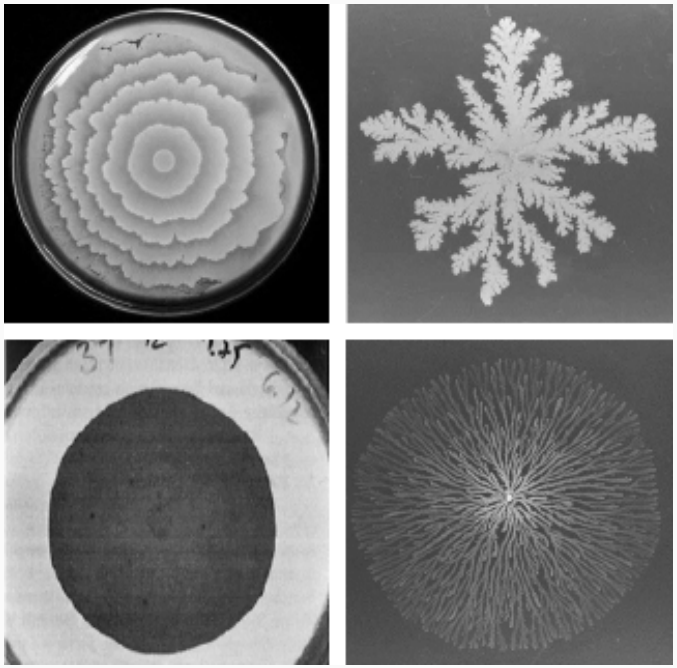
Observations

- Low nutrient, hard agar: Diffusion limited aggregation (DLA). Fractal patterns (**Matsuyama and Matsushita (1993); Ben-Jacob (1994)**). **(A)**
- Semi-solid agar, low nutrient: Dense branch morphology (DBM). Smooth colony envelope (**Ohgiwari et al. (1992)**). **(E)**
- Higher nutrient, soft agar: homogeneous colony, smooth boundary envelope. **(D)**
- Hard agar, high nutrient: envelope with fractal boundary. **(B)**
- Rings: transition from **(B)** to **(D)**.

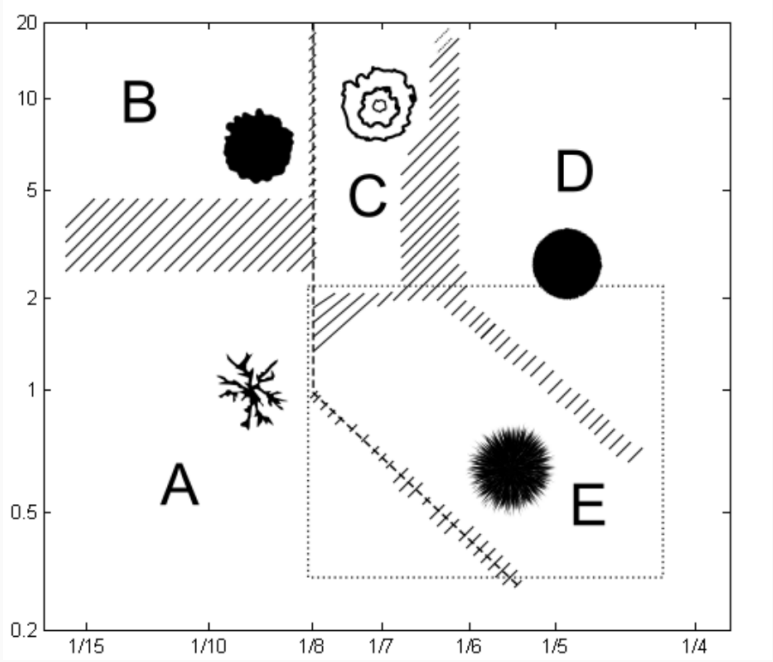
C_n - concentration of nutrient; C_a - agar concentration (softness $1/C_a$)

Morphological diagram

Rings (C) Fractal (A)



Disk (D) DBM (E)



C_n vs. $1/C_a$

How to model the dynamics?

- **Bacteria as discrete agents:** Model bacteria as discrete self-propelled particles. Move, interact with environment. Agents consume nutrients, multiply, sporulate and die. Suitable to track the internal state of bacteria.
- **Bacteria as a continuous density:** Describe the evolution of bacterial concentration. Other constituents (nutrients, signaling factors, etc.) are also densities.

Experimental observations

Ohgiwari et al. (1992)

- In the DBM regime: movement of bacteria inactive in the inner region with low nutrient levels; active at the periphery with high nutrient
- Cells become inactive again at the outermost front of bacterial colonies where cell density is apparently low

Kawasaki's model

Kawasaki et al. (1997): Non-linear PDE recation-cross-diffusion model

$$\begin{aligned} v_t &= D_v \Delta v - f(u,v) \\ u_t &= \nabla \cdot (D(u,v)\nabla u) + \theta f(u,v) \end{aligned} \tag{K}$$

v - nutrient and u - bacterial concentrations, $(x,y) \in \Omega \subset \mathbb{R}^2$, $t > 0$.
Diffusion coefficient: $D_v > 0$ constant.

$$D(u,v) = \sigma uv. \tag{1}$$

$0 < \sigma \sim 1/C_a$. Consumption rate: $f(u,v)$, $\theta > 0$ -conversion rate factor.
Kinetics:

$$f(u,v) = uv$$

Plus: no-flux boundary conditions + initial conditions.

Features:

- Conveys immotility when either *u or v* are low. Models high activity in the boundary only.
- Valid for the transition region **E** $\leftrightarrow$ **D**
- Complex dense morphology
- Rich mathematical structure (**Satnoianu, Maini and Sánchez-Garduño (2001); Sherratt (2010)**).

Chemotaxis

- Movement of an organism in response to a chemical stimulus
- It can be of attractive or repulsive nature (chemoattractant vs. chemorepellent)
- Ubiquituous in Nature: bacteria towards nutrients; endothelial cells towards angiogenic factors (tumor angiogenesis); fungal zoospores in the presence of metabolites or other chemorepellents (*biocontrol*)
- Macro and mesoscopic chemical phenomena: somatic cells, bacteria and other single-cell or multicellular organisms direct their movements according to certain chemicals

Experimental observations

E. Ben-Jacob's group (Univ. of Tel-Aviv):

- **Ben-Jacob et al. (1994)**: Experimental evidence of chemotaxis of *B. subtilis* towards amino acids (nutrients)
- **Golding et al. (1997)**: Role of chemotaxis in the formation of patterns; theoretical and experimental arguments
- **Ben-Jacob et al. (2000)**: Identified three types of chemotactic internal signalling:
  - (Repulsive - Long range) By starving bacteria in the center.
  - (Attractive - Short range) Bacteria in the front ask for help to metabolize waste.
  - **Nutrient chemotaxis:** Dominant signal. Attractive, short range.
- Proposed (**Ben-Jacob et al., 2000**), based on experiments, a relation bet. diffusion and chemotaxis (certain nutrient regimes).

Modelling chemotaxis

General form of chemotactic term of **Keller-Segel (1971)**-type: add a term of form $\mathrm{div} J_c$, where

$$J_c = \zeta(u, v)\chi(v)\nabla v$$

$\chi = \chi(v) \gtrless 0$ - chemotactic sensitivity function; $\zeta = \zeta(u, v)$ - bacterial response function to nutrient gradient.

Ben-Jacob's experimental observation (**Ben-Jacob et al. (2000)**): In semi-solid agar, low colony density,

$$|\zeta(u, v)| \propto uD_u. \qquad (*)$$

Example: if the diffusion coefficient is constant, $D > 0$, then we recover the classical Keller-Segel chemotactic flux, $J_c = \pm\chi u\nabla v$

Chemotactic model with non-linear cross diffusion

- **Leyva, Málaga, P, (2013)**. Model system in non-dimensional form:

$$
\begin{aligned}
v_t &= \Delta v - uv, \\
u_t &= \nabla \cdot (\sigma uv \nabla u) + uv - \chi_0 \nabla \cdot \left(\frac{\sigma v u^2}{(1+v)^2} \nabla v \right),
\end{aligned}
\tag{RDC}
$$

$(x, y) \in \Omega \subset \mathbb{R}^2,\ t \geq 0.$

- Non-linear degenerate cross-diffusion (Kawasaki):

$$D_u = \sigma uv,$$

- Chemotactic sensitivity: **Lapidus-Schiller (1976)** receptor's law (attractive),

$$\chi(v) = -\frac{\chi_0}{(1+v)^2}, \quad \chi_0 > 0.$$

Chemotactic model with non-linear cross diffusion (ii)

- Bacterial response function:

$$\zeta(u,v) = uD_u = \sigma u^2 v.$$

- No-flux boundary conditions:

$$\begin{aligned} (uv\nabla u - u^2 v\nabla v)\cdot\hat{\nu} &= 0, \\ \nabla v\cdot\hat{\nu} &= 0, \end{aligned} \qquad (x,y)\in\partial\Omega,\ \ t>0.$$

- Initial conditions:

$$u(x,y,0) = u_0(x,y), \quad v(x,y,0) = v_0(x,y), \qquad (x,y)\in\Omega.$$

Numerical simulations

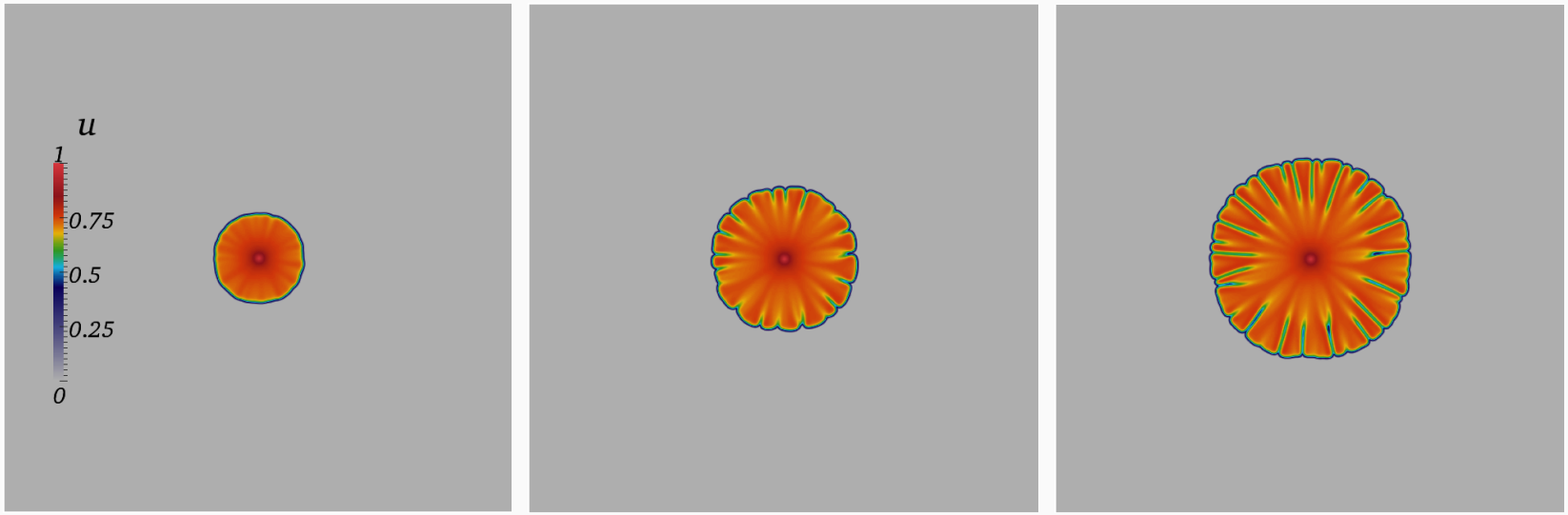
- Square domain $[0,1] \times [0,1]$. Grid of 2048×2048
- Finite difference, 2nd. order Runge-Kutta scheme
- Very small time steps to avoid instabilities (stiffness)
- Crudeness of the scheme compensated by parallel high performance computations with Graphic Processing Units (GPUs)
- Millions of steps in a few hours.
- NVIDIA Tesla© C2070 graphics card with 448 CUDA cores

- Initial conditions:

$$v(x,y,0) \equiv \overline{v}_0, \quad u(x,y,0) = 0.71\, e^{-(x^2+y^2)/6.25}, \text{ (Kawasaki)}$$

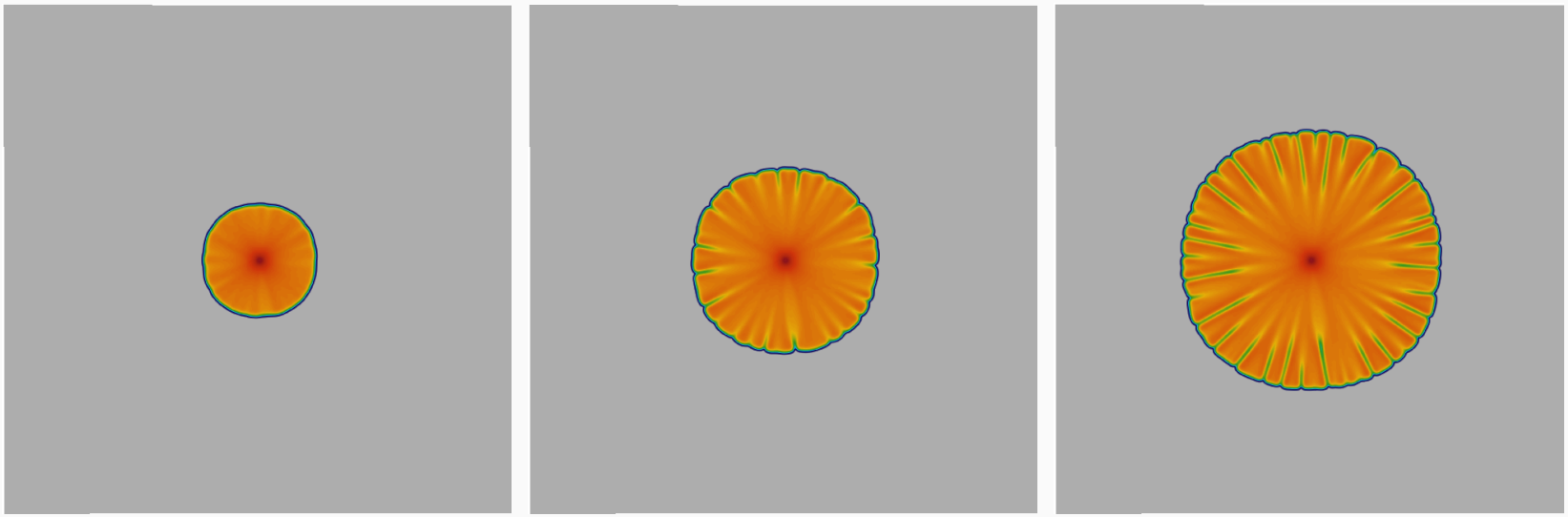
- Parameter values: $\sigma = 4.0$ (soft-medium agar); $\overline{v}_0 = 0.71$ (initial constant nutrient concentration); chemotactic signal $\chi_0 = 0, 2.5, 5.0$.

No chemotaxis: $\chi_0 = 0$



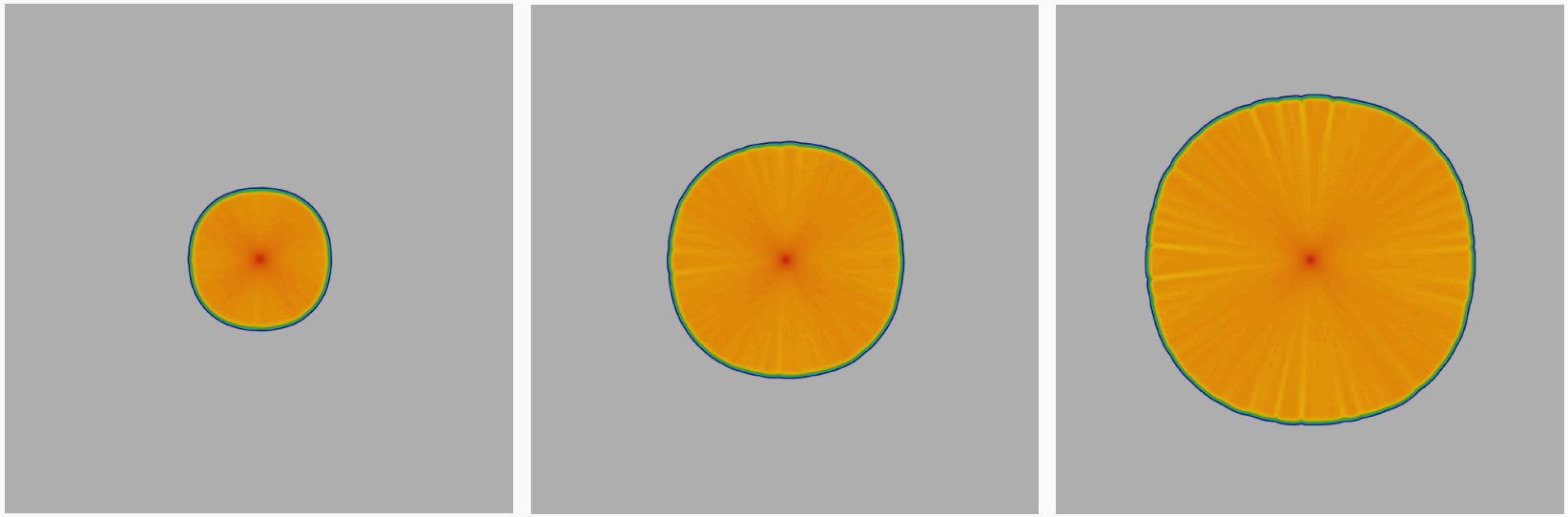
$t \sim 5\,\text{min.}$ $t \sim 10\,\text{min.}$ $t \sim 15\,\text{min.}$

$\chi_0 = 2.5$



$t \sim 5\,\text{min.}$ $t \sim 10\,\text{min.}$ $t \sim 15\,\text{min.}$

$\chi_0 = 5.0$



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Main results (i): Leyva, Málaga, P, (2013)

- Incorporation of a suitable chemotactic term to Kawasaki's nonlinear cross diffusion model, compatible with low-nutrient regime experimental observations (Ben-Jacob)
- High resolution numerical simulations confirm enhancement of the speed
- Numerical observation: In the low-nutrient, soft-agar regime: change in morphology, patterns become smoother (less branches) in the presence of chemotaxis
- Numerical estimation (one-d simulation) approximates well the asymptotic speed calculation
- Under the conservation law approximation, the front equation becomes a scalar reaction-diffusion equation with degenerate diffusion
- Asymptotics show that the speed of the envelope front increases with chemotaxis

Main results (ii): Butanda, Málaga, P, (2017)

- The change in morphology in the DBM regime can be explained and quantified
- Asymptotics: quantitative analysis shows that when the chemotactic sensitivity is increased, the eigenvalues of the linearized operator around the envelope front become "more stable"
- Energy estimates provide bounds for the eigenvalues of the linearized operator around the front. These bounds decrease as functions of the chemotactic sensitivity $\chi_0 \geq 0$, suggesting that, the patterns become more stable

Velocity-jump stochastic processes

Velocity-jump process

References:
Othmer, Dunbar, Alt (1988); Hillen and Othmer (200, 2002)

Features:

- Agents (particles, cells or microorganisms) make instantaneous jumps in velocity space rather than in physical space
- Probability distribution of time between turning events is exponential with mean $1/\lambda$ (mean run time)
- $V \subset \mathbb{R}^n$ subset of allowed velocities; symmetric with respect of the origin, compact set
- $T : V \times V \to \mathbb{R}$, $T(\boldsymbol{v}, \boldsymbol{v}')$ is the probability density of turning from velocity $\boldsymbol{v}'$ to velocity $\boldsymbol{v}$, if reorientation occurs

Forward Kolmogorov equation (i)

$p = p(x, t, \boldsymbol{v})$ probability density function, population of agents at time $t > 0$, position $x \in \Omega \subseteq \mathbb{R}^n$ with velocity $\boldsymbol{v} \in V$. $\Omega \subseteq \mathbb{R}^n$ open domain. The evolution of p is governed by the following transport or forward Kolmogorov equation:

$$\frac{\partial}{\partial t} p(x, t, \boldsymbol{v}) + \boldsymbol{v} \cdot \nabla_x p(x, t, \boldsymbol{v}) = -\lambda p(x, t, \boldsymbol{v}) + \lambda \int_V T(\boldsymbol{v}, \boldsymbol{v}') p(x, t, \boldsymbol{v}') \, d\boldsymbol{v}' + \mathscr{G},$$

$\mathscr{G}$ - reaction (production) term

Forward Kolmogorov equation (ii)

Interpretation:

- $\boldsymbol{v} \cdot \nabla_x p(x, t, \boldsymbol{v})$ - drift term, transport
- $-\lambda p$ - absorption term: agents leaving the "state" (x, v)
- $\lambda \int T p \, d\boldsymbol{v}'$ - agents jumping into the "state" (x, v) after a reorientation

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Marginal density (zero-velocity moment)

$$\rho(x, t) = \int_V p(x, t, \boldsymbol{v}) \, d\boldsymbol{v}.$$

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The derivation of the transport equation from first principles was derived by **Stroock (1974).**

Experimental observations

- Bacteria alternate two basic modes of motion:
  - run, simple linear motion with constant speed
  - tumble, reorientation of the cell; it spins around
- Duration of a tumble $\ll$ duration of a run
- Speed of bacterium does not change from run to run
- Speed distribution of change in direction between the run preceding a tumble and the one following is approximately the same from tumble to tumble
- parameter that changes: duration of runs

Stochastic model

Assumptions:

- the duration of a tumble is negligible: there is a direction of a bacterium at a given instant
- the motion is Markovian in the state space: $(x, \boldsymbol{v}) \in \Omega \times V$; $V = s\mathbb{S}^{n-1}$, s - speed
- the direction (or velocity) is a Poisson-type process on V with intensity $\lambda > 0$ (turning frequency or turning rate)
- In general $\lambda : [0, +\infty) \times \Omega \times V \to [0, +\infty)$, so that the conditional probability that a tumble has not occurred bet. t_0 and t given that at time t_0 the bacterium was at $x \in \Omega$ with velocity $\boldsymbol{v}$ is

$$\exp\left[-\int_{t_0}^{t} \lambda(\xi, x + \xi\boldsymbol{v}, \boldsymbol{v})\, d\xi\right]$$

Exponentially distributed times with parameter λ

Stochastic process (i)

- two-step process, both described by discontinuous jumps and continuous motion
- state space: $(x, \boldsymbol{v}) \in \Omega \times V$; $V = s\mathbb{S}^{n-1}$, s - speed
- process is piecewise deterministic with flow

$$f = \boldsymbol{v} = s\theta = \frac{dx}{dt}, \qquad \theta \in \mathbb{S}^{n-1}$$

- transition probability: $T(\boldsymbol{v}, \boldsymbol{v}')$, probability density of turning from velocity $\boldsymbol{v}$ to $\boldsymbol{v}'$ during a tumble
- We call this process Φ_c ("chemotactic")

Stochastic process (ii)

It can be shown that:

- Φ_c is a piecewise deterministic time-homogeneous stochastic process with the strong Markov property (**Jacobsen (2006)**, Theorem 7.5.1) with flow $f = \boldsymbol{v} = s\theta$ and

$$L := f \cdot \nabla_x, \qquad L^* = -\nabla_x \cdot f$$

- there exists an invariant probability measure for Φ_c (**Meyn, Tweedie (2009)**, Theorem 3.1)

$$P((x, \boldsymbol{v}), \{x\} \times B) = \int_B T_x(\boldsymbol{v}', \boldsymbol{v}) \nu(d\boldsymbol{v}')$$

for $B \subset V$. Weak Feller process if mapping

$$(x, \boldsymbol{v}) \mapsto \int_B T_x(\boldsymbol{v}', \boldsymbol{v}) g(x, \boldsymbol{v}') \nu(d\boldsymbol{v}')$$

is bounded and continuous for g same. Thm. 3.1: Weak Feller process and bounded in prob. on average $\Rightarrow$ there exists a prob. measure

Stochastic process (iii)

- Φ_c is a semi-martingale with the strong Markov property (**Jacobsen (2006)**, Theorem 4.7.1). Ito's formula with $h \in C^2$,

$$h(\Phi_t) = h(\Phi_0) + \int_0^t (Lh)(\Phi_s)\, ds + \sum_{0<\tau_k \le t} (h(\Phi_{\tau_k}) - h(\Phi_{\tau_k}^-))$$

  τ_k - time of the k-th jump

- take expectation of Ito's formula to obtain a generalized Dynkin formula (**Øksendal (2000)**, section 7.4)

$$(\mu_t - \mu_0)h = \int_0^t \mu_s(Lh)\, ds + \int_0^t \lambda(Q - I)\, ds,$$

  where μ_t - law of Φ_t, $\lambda(\Phi_t)$ jump intensity rate at Φ_t, Q is associated operator of the probability transition kernel

$$Q(y, \{x\} \times B) = \int T_x(\boldsymbol{v}', \boldsymbol{v})\nu(d\boldsymbol{v}'), \quad y = (x, \boldsymbol{v}), B \subset V.$$

Stochastic process (iv)

- upon differentiation

$$\mu_t' = L^* \mu_t + \lambda (Q^* - I)$$

- this implies (**Bect (2010)**, Theorem 13) that the probability function $p = p(x, \boldsymbol{v}, t)$ (prob. density that the process is at state $(x, \boldsymbol{v})$ at time t) satisfies

$$\frac{\partial p}{\partial t} = L^* p - \lambda p + Q^*(\lambda p)$$

- since $f = \boldsymbol{v}$ does not depend on x we obtain the forward Kolmogorov (transport) equation for p

$$\frac{\partial p}{\partial t} + \boldsymbol{v} \cdot \nabla_x p = -\lambda p + \int_V \lambda \, T_x(\boldsymbol{v}, \boldsymbol{v}') p(x, t, \boldsymbol{v}') \, \nu(d\boldsymbol{v}')$$

Diffusive limits: the method of Hillen and Othmer

Method of Hillen and Othmer

Hillen and Othmer (2000, 2002): Method to obtain a mean-field limiting system for first moments based on regular outer (or Hilbert) expansions on p (asymptotic method from kinetic theory).

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Assumptions:

- $V \subset \mathbb{R}^n$ is assumed to be symmetric with respect to the origin (that is, $\boldsymbol{v} \in V \Rightarrow -\boldsymbol{v} \in V$) and compact.
- For fixed $(x,t) \in \Omega \times (0,+\infty)$ we regard

$$\mathscr{T} p(\boldsymbol{v}) := \int_V T(\boldsymbol{v},\boldsymbol{v}') p(x,t,\boldsymbol{v}')\, d\boldsymbol{v}',$$

  as an integral operator in $L^2(V)$
- $\mathscr{K} := \{f \in L^2(V) : f \geq 0\}$.

Assumptions on T

- The turning kernel is supposed to satisfy:

$$T(\boldsymbol{v},\boldsymbol{v}') \geq 0 \text{ for all } (\boldsymbol{v},\boldsymbol{v}') \in V \times V;\ \int_V T(\boldsymbol{v},\boldsymbol{v}')\, d\boldsymbol{v} = 1, \text{ for all } \boldsymbol{v}' \in V, \text{ and } \int_V \int_V T(\boldsymbol{v},\boldsymbol{v}')^2\, d\boldsymbol{v}\, d\boldsymbol{v}' < +\infty. \tag{T_1}$$

There exist functions u_0, ϕ, ψ in $\mathscr{K}$ satisfying $u_0 \not\equiv 0$, $\phi, \psi \neq 0$ a.e., such that

$$u_0(\boldsymbol{v})\phi(\boldsymbol{v}') \leq T(\boldsymbol{v},\boldsymbol{v}') \leq u_0(\boldsymbol{v})\psi(\boldsymbol{v}'), \tag{T_2}$$

for all $(\boldsymbol{v},\boldsymbol{v}') \in V \times V$.

$$\|\mathscr{T}\|_{\langle 1\rangle^\perp \to \langle 1\rangle^\perp} < 1, \text{ where } \langle 1\rangle^\perp \subset L^2(V) \text{ is the orthogonal complement of constants in } L^2(V). \tag{T_3}$$

$$\int_V T(\boldsymbol{v},\boldsymbol{v}')\, d\boldsymbol{v}' = 1, \text{ for all } \boldsymbol{v} \in V. \tag{T_4}$$

The turning operator

For every given $\lambda > 0$, constant in $\boldsymbol{v} \in V$, the turning operator, $\mathscr{L} : L^2(V) \to L^2(V)$, is defined as

$$\mathscr{L}p(\boldsymbol{v}) := -\lambda p(\boldsymbol{v}) + \lambda \mathscr{T} p(\boldsymbol{v}) = -\lambda p(\boldsymbol{v}) + \lambda \int_V T(\boldsymbol{v}, \boldsymbol{v}') p(\boldsymbol{v}')\, d\boldsymbol{v}'.$$

Properties of the turning operator

Theorem (Hillen and Othmer, 2000, 2002)

Under (T_1) - (T_4)*:*

(a) $\mu = 0$ *is a simple eigenvalue of* $\mathscr{L} : L^2(V) \to L^2(V)$ *with eigenfunction* $f(\boldsymbol{v}) \equiv 1$.

(b) *For all* $g \in \langle 1 \rangle^\perp$, $\langle g, \mathscr{L} g \rangle_{L^2} = \int_V g \mathscr{L} g \, d\boldsymbol{v} \leq -\mu_2 \|g\|^2_{L^2(V)}$, *where* $\mu_2 = \lambda(1 - \|\mathscr{T}\|_{\langle 1 \rangle^\perp \to \langle 1 \rangle^\perp})$.

(c) *All non-zero eigenvalues* μ *of* $\mathscr{L}$ *satisfy the estimate* $-2\lambda < Re\mu \leq -\mu_2 < 0$, *and to within scalar multiples there is no other positive eigenfunction.*

(d) $\mathscr{L}$ *restricted to* $\langle 1 \rangle^\perp \subset L^2(V)$ *has a linear pseudo-inverse* $\mathscr{F}$ *with norm*

$$\|\mathscr{F}\|_{\langle 1 \rangle^\perp \to \langle 1 \rangle^\perp} \leq \frac{1}{\mu_2}.$$

Parabolic scaling

Fundamental assumption: There exists a small parameter $\varepsilon > 0$ such that the scaling

$$\tau = \varepsilon^2 t, \quad \xi = \varepsilon x,$$

satisfies

$$\tau, \xi = O(1), \quad \text{as } \varepsilon \to 0^+.$$

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satisfies

$$\tau, \xi = O(1), \quad \text{as } \varepsilon \to 0^+.$$

- **E. coli**: characteristic speed, $s \approx 10$ μm/sec.; mean run time of $1/\lambda \approx 1$ sec. (cf. **Othmer, Xue, 2013**).
- **B. subtilis**: charac. speed $s \approx 1$ μm/sec. (cf. **Hillesdon et al., 1995**); average run time of $1/\lambda \approx 1$ sec. (cf. **Ito et al., 2005**)
- Typical experimental scales $L = 1$ mm. (length), $T = 10^4$ sec. (time) $\Rightarrow \varepsilon = 10^{-2}$ (*E. coli*); $\varepsilon = 10^{-1}$ (*B. subtilis*).

Outer or Hilbert expansion

Kolmogorov equation in rescaled coordinates (ξ, τ) (without kinetic term):

$$\varepsilon^2 \frac{\partial}{\partial \tau} p(\xi, \tau, \boldsymbol{v}) + \varepsilon \boldsymbol{v} \cdot \nabla_\xi p(\xi, \tau, \boldsymbol{v}) = -\lambda p(\xi, \tau, \boldsymbol{v}) + \int_V \lambda T(\boldsymbol{v}, \boldsymbol{v}') p(\xi, \tau, \boldsymbol{v}') \, d\boldsymbol{v}',$$

where $(\xi, \tau) \in \widetilde{\Omega} \times (0, +\infty)$, $\widetilde{\Omega} := \varepsilon\Omega = \{\varepsilon x : x \in \Omega\}$, $\boldsymbol{v} \in V$.

Hilbert regular expansion: the population density underlies a regular perturbation expansion of the form

$$p(\xi, \tau, \boldsymbol{v}) = p_0(\xi, \tau, \boldsymbol{v}) + \varepsilon p_1(\xi, \tau, \boldsymbol{v}) + \varepsilon^2 p_2(\xi, \tau, \boldsymbol{v}) + O(\varepsilon^3).$$

Marginal density independent of $\varepsilon > 0$; thus, we assume

$$\int_V p_j(\xi, \tau, \boldsymbol{v}) \, d\boldsymbol{v} = 0,$$

for all $j \geq 1$ and all (ξ, τ).

Proposal: peturbed turning rate, unperturbed turning kernel

Perturbations of **Schnitzer (1993)** type: first order perturbation of a certain turning frequency λ_0 *independent of* $\boldsymbol{v}$, together with an unperturbed turning kernel T_0 that depends only on $(\boldsymbol{v}, \boldsymbol{v}') \in V \times V$:

$$T = T_0(\boldsymbol{v}, \boldsymbol{v}'),$$
$$\lambda(\boldsymbol{v}) = \lambda_0 + \varepsilon\lambda_1(\boldsymbol{v}).$$

Turning operator:

$$\mathscr{L}_0 p(\boldsymbol{v}) := -\lambda_0 p(\boldsymbol{v}) + \lambda_0 \int_V T_0(\boldsymbol{v}, \boldsymbol{v}') p(\boldsymbol{v}')\, d\boldsymbol{v}', \qquad \mathscr{L}_0 : L^2(V) \to L^2(V).$$

Interior parabolic limit

Proposition (interior parabolic limit with perturbed turning rate; P, 2018)

Under the above assumptions, if $p = p(\xi, \tau, \boldsymbol{v})$ is a solution to the scaled transport equation, where the turning kernel admits a first order perturbation of the form $\lambda = \lambda_0 + \varepsilon\lambda_1(\boldsymbol{v})$ (with λ_0 independent of $\boldsymbol{v}$), then the leading order term p_0 of a regular Hilbert expansion $p = p_0 + \varepsilon p_1 + \varepsilon^2 p_2 + O(\varepsilon^3)$ satisfies

$$p_0(\xi, \tau, \boldsymbol{v}) = \bar{p}_0(\xi, \tau), \qquad \rho(\xi, \tau) = \int_V p(\xi, \tau, \boldsymbol{v})\, d\boldsymbol{v} = |V|\bar{p}_0(\xi, \tau),$$

where $\bar{p}_0 = \bar{p}_0(\xi, \tau)$ is a solution to the parabolic limit equation

$$\frac{\partial \bar{p}_0}{\partial \tau} = div_\xi\left(\mathbb{D}\nabla_\xi \bar{p}_0\right) - div_\xi\left(\bar{p}_0 \boldsymbol{w}_c\right),$$

for $\xi \in \widetilde{\Omega}_\delta := \{\xi \in \widetilde{\Omega} : dist(\xi, \partial\Omega) \geq \delta > 0\} \subset \widetilde{\Omega} = \varepsilon\Omega$, with some $\delta > 0$ (away from the boundary), and $\tau > 0$.

The diffusion tensor $\mathbb{D} \in \mathbb{R}^{n\times n}$ *and the chemotactic velocity* $\boldsymbol{w}_c \in \mathbb{R}^n$ *are given by*

$$\mathbb{D} = -\frac{1}{|V|}\int_V \boldsymbol{v} \otimes (\mathscr{F}_0 \boldsymbol{v})\, d\boldsymbol{v},$$

and

$$\boldsymbol{w}_c = -\frac{1}{|V|}\int_V \boldsymbol{v}\mathscr{F}_0\big(\bar{\lambda}_1(\boldsymbol{v}) - \lambda_1(\boldsymbol{v})\big)\, d\boldsymbol{v},$$

respectively, where

$$\bar{\lambda}_1(\boldsymbol{v}) = \int_V \lambda_1(\boldsymbol{v}')\, T_0(\boldsymbol{v}, \boldsymbol{v}')\, d\boldsymbol{v}',$$

is the average bias. Here $\mathscr{F}_0$ *denotes the pseudo-inverse of the operator* $\mathscr{L}_0$ *restricted to the subspace* $\langle 1\rangle^\perp \subset L^2(V)$.

Proof sketch (i)

- Substitute Hilbert expansion and collect powers of ε. At order $O(1)$,

$$0 = \lambda_0 p_0(\xi,\tau,\boldsymbol{v}) + \lambda_0 \int_V T_0(\boldsymbol{v},\boldsymbol{v}') p_0(\xi,\tau,\boldsymbol{v}')\, d\boldsymbol{v}' =: \mathscr{L}_0 p_0(\xi,\tau,\boldsymbol{v}).$$

  yielding $p_0(\xi,\tau,\boldsymbol{v}) = \bar{p}_0(\xi,\tau) = |V|^{-1}\rho(\xi,\tau)$. $\mathscr{L}_0$ has pseudo-inverse $\mathscr{F}_0$ on $\langle 1\rangle^{\perp}$.

- This implies

$$\int_V \boldsymbol{v}\cdot\nabla_\xi \bar{p}_0(\xi,\tau)\, d\boldsymbol{v} = 0$$

  (V is a symmetric set).

- Collecting powers of $O(\varepsilon)$, $O(\varepsilon^2)$, we obtain a hierarchy of equations for p_1, p_2, whose solvability conditions yield the interior parabolic limit for $\overline{p}_0$

Proof sketch (ii)

- Equation at order $O(\varepsilon)$:

$$\mathscr{L}_0 p_1 = \boldsymbol{v} \cdot \nabla_\xi \bar{p}_0 + \lambda_1(\boldsymbol{v})\bar{p}_0 - \int_V \lambda_1(\boldsymbol{v}')\, T_0(\boldsymbol{v}, \boldsymbol{v}')\bar{p}_0\, d\boldsymbol{v}'$$

- Solvability condition: $\mu = 0$ is a simple eigenvalue of $\mathscr{L}_0^*$ with a unique positive eigenfunction $g(\boldsymbol{v}) \equiv 1 \in L^2(V)$; therefore,

$$\langle 1, \mathscr{L}_0 p_1 \rangle_{L^2(V)} = \langle \mathscr{L}_0^* 1\,, p_1 \rangle_{L^2(V)} = 0,$$

  as $\mathscr{L}_0$ is singular, yielding

$$0 = \int_V \lambda_1(\boldsymbol{v})\bar{p}_0(\xi, \tau)\, d\boldsymbol{v} - \int_V \int_V \lambda_1(\boldsymbol{v}')\, T_0(\boldsymbol{v}, \boldsymbol{v}')\bar{p}_0(\xi, \tau) d\boldsymbol{v}\, d\boldsymbol{v}'$$

  trivially satisfied because of (T_1).

Proof sketch (iii)

- We can define a pseudo-inverse of $\mathscr{L}_0$ on $\langle 1 \rangle^\perp \subset L^2(V)$: $\mathscr{F}_0 = (\mathscr{L}_{0|\langle 1 \rangle^\perp})^{-1}$. Thus,

$$p_1(\xi, \tau, \boldsymbol{v}) = \mathscr{F}_0\big(\mathscr{R}_1(\bar{p}_0(\xi, \tau))\big),$$

where

$$\mathscr{R}_1 p(\boldsymbol{v}) := \boldsymbol{v} \cdot \nabla_\xi p(\boldsymbol{v}) + \lambda_1(\boldsymbol{v}) p(\boldsymbol{v}) - \int_V \lambda_1(\boldsymbol{v}') T_0(\boldsymbol{v}, \boldsymbol{v}') p(\boldsymbol{v}')\, d\boldsymbol{v}'$$

- Equation at order $O(\varepsilon^2)$:

$$\begin{aligned}\mathscr{L}_0 p_2 &= \frac{\partial}{\partial \tau}\bar{p}_0 + \boldsymbol{v} \cdot \nabla_\xi p_1 + \lambda_1(\boldsymbol{v}) p_1 - \int_V \lambda_1(\boldsymbol{v}') T_0(\boldsymbol{v}, \boldsymbol{v}') p_1(\xi, \tau, \boldsymbol{v}')\, d\boldsymbol{v}' \\ &= \frac{\partial}{\partial \tau}\bar{p}_0 + \mathscr{R}_1\big(p_1(\xi, \tau, \boldsymbol{v})\big).\end{aligned}$$

Proof sketch (iv)

- Solvability condition ($L^2(V)$ product of RHS with $\mathrm{span}\{1\} \subset L^2(V)$):

$$0 = \int_V \left[\frac{\partial}{\partial \tau} \bar{p}_0(\xi, \tau) + \mathscr{R}_1\left(\mathscr{F}_0\left(\mathscr{R}_1(\bar{p}_0(\xi, \tau))\right)\right) \right] d\boldsymbol{v}$$

- Define the average bias as

$$\bar{\lambda}_1(\boldsymbol{v}) := \int_V \lambda_1(\boldsymbol{v}') T_0(\boldsymbol{v}, \boldsymbol{v}') \, d\boldsymbol{v}'$$

(average bias, over all incoming velocities, of the turning rate to $\boldsymbol{v}$). Thus,

$$p_1(\xi, \tau, \boldsymbol{v}) = \mathscr{F}_0\left(\boldsymbol{v} \cdot \nabla_\xi \bar{p}_0(\xi, \tau)\right) + \mathscr{F}_0\left((\lambda_1(\boldsymbol{v}) - \bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0(\xi, \tau)\right)$$

- Do the math:

$$\int_V \boldsymbol{v} \cdot \nabla_\xi p_1(\xi, \tau, \boldsymbol{v}) \, d\boldsymbol{v} = \int_V \boldsymbol{v} \cdot \nabla_\xi \left(\mathscr{F}_0\left(\boldsymbol{v} \cdot \nabla_\xi \bar{p}_0(\xi, \tau)\right) \right) d\boldsymbol{v} + \\ + \int_V \boldsymbol{v} \cdot \nabla_\xi \left(\mathscr{F}_0\left((\lambda_1(\boldsymbol{v}) - \bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0(\xi, \tau)\right) \right) d\boldsymbol{v}.$$

Proof sketch (v)

$$\int_V \boldsymbol{v}\cdot\nabla_\xi\Big(\mathscr{F}_0\big(\boldsymbol{v}\cdot\nabla_\xi\bar{p}_0(\xi,\tau)\big)\Big)\,d\boldsymbol{v} = \int_V \mathrm{div}_\xi\Big([\boldsymbol{v}\otimes(\mathscr{F}_0\boldsymbol{v})]\nabla_\xi\bar{p}_0\Big)\,d\boldsymbol{v}$$
$$= -\mathrm{div}_\xi\big(|V|\mathbb{D}\nabla_\xi\bar{p}_0(\xi,\tau)\big),$$

Identity: $\int_V \boldsymbol{v}\cdot\nabla_\xi\big(\beta\,\bar{p}_0\big)\,d\boldsymbol{v} = \mathrm{div}_\xi\Big(\bar{p}_0\int_V\beta\,\boldsymbol{v}\,d\boldsymbol{v}\Big)$, for any scalar $\beta=\beta(\xi,\tau,\boldsymbol{v})$; thus,

$$\int_V \boldsymbol{v}\cdot\nabla_\xi\Big(\mathscr{F}_0\big((\lambda_1(\boldsymbol{v},\hat{S})-\bar{\lambda}_1(\boldsymbol{v},\hat{S}))\bar{p}_0(\xi,\tau)\big)\Big)\,d\boldsymbol{v} = \mathrm{div}_\xi\big(|V|\bar{p}_0(\xi,\tau)\boldsymbol{w}_c\big)$$

Proof sketch (v)

$$\int_V \boldsymbol{v}\cdot\nabla_\xi\Big(\mathscr{F}_0\big(\boldsymbol{v}\cdot\nabla_\xi\bar{p}_0(\xi,\tau)\big)\Big)\,d\boldsymbol{v} = \int_V \mathrm{div}_\xi\Big([\boldsymbol{v}\otimes(\mathscr{F}_0\boldsymbol{v})]\nabla_\xi\bar{p}_0\Big)\,d\boldsymbol{v}$$
$$= -\mathrm{div}_\xi\big(|V|\mathbb{D}\nabla_\xi\bar{p}_0(\xi,\tau)\big),$$

Identity: $\int_V \boldsymbol{v}\cdot\nabla_\xi\big(\beta\bar{p}_0\big)\,d\boldsymbol{v} = \mathrm{div}_\xi\Big(\bar{p}_0\int_V\beta\,\boldsymbol{v}\,d\boldsymbol{v}\Big)$, for any scalar $\beta=\beta(\xi,\tau,\boldsymbol{v})$; thus,

$$\int_V \boldsymbol{v}\cdot\nabla_\xi\Big(\mathscr{F}_0\big((\lambda_1(\boldsymbol{v},\hat{S})-\bar{\lambda}_1(\boldsymbol{v},\hat{S}))\bar{p}_0(\xi,\tau)\big)\Big)\,d\boldsymbol{v} = \mathrm{div}_\xi\big(|V|\bar{p}_0(\xi,\tau)\boldsymbol{w}_c\big)$$

where

$$\mathbb{D} = -\frac{1}{|V|}\int_V \boldsymbol{v}\otimes(\mathscr{F}_0\boldsymbol{v})\,d\boldsymbol{v},\quad \boldsymbol{w}_c = -\frac{1}{|V|}\int_V \boldsymbol{v}\mathscr{F}_0\big(\bar{\lambda}_1(\boldsymbol{v})-\lambda_1(\boldsymbol{v})\big)\,d\boldsymbol{v},$$

are the diffusion tensor and chemotactic velocity.

Proof sketch (vi)

- The solvability condition reads:

$$
\begin{aligned}
0 = |V|\frac{\partial}{\partial\tau}\bar{p}_0 - \mathrm{div}_\xi\left(|V|\mathbb{D}\nabla_\xi\bar{p}_0\right) + \mathrm{div}_\xi\left(|V|\bar{p}_0\boldsymbol{w}_c\right) + \\
+ \int_V \lambda_1(\boldsymbol{v})\mathscr{F}_0\Big(\boldsymbol{v}\cdot\nabla_\xi\bar{p}_0 + (\lambda_1(\boldsymbol{v}) - \bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0\Big)\,d\boldsymbol{v} + \\
- \int_V\int_V \lambda_1(\boldsymbol{v}')T_0(\boldsymbol{v},\boldsymbol{v}')\mathscr{F}_0\Big(\boldsymbol{v}'\cdot\nabla_\xi\bar{p}_0 + (\lambda_1(\boldsymbol{v}') - \bar{\lambda}_1(\boldsymbol{v}'))\bar{p}_0\Big)\,d\boldsymbol{v}'\,d\boldsymbol{v}
\end{aligned}
$$

But the last two integrals cancel each other because of (T_1). Result:

$$
\frac{\partial\bar{p}_0}{\partial\tau} = \mathrm{div}_\xi\left(\mathbb{D}\nabla_\xi\bar{p}_0\right) - \mathrm{div}_\xi\left(\bar{p}_0\boldsymbol{w}_c\right).
$$

Boundary conditions

Boundary conditions of the limiting equation for ρ depend on boundary conditions of the transport equation. In this case, the latter depend only on the no normal mass flux nature of the former.

Boundary conditions

Boundary conditions of the limiting equation for ρ depend on boundary conditions of the transport equation. In this case, the latter depend only on the no normal mass flux nature of the former.

$\Omega \subset \mathbb{R}^n$, bounded domain with piecewise smooth oriented boundary. For each $\xi \in \partial\widetilde{\Omega} = \varepsilon\Omega$, $\hat{v}(\xi)$ is the normal unit vector. Boundary of the phase space:

$$\partial\widetilde{\Omega} \times V = \Gamma_+ \cup \Gamma_- \cup \Gamma_0,$$

$$\Gamma_\pm := \{(\xi, \boldsymbol{v}) \in \partial\widetilde{\Omega} \times V : \pm \boldsymbol{v} \cdot \hat{v}(\xi) > 0\}, \quad \Gamma_0 := \{(\xi, \boldsymbol{v}) \in \partial\widetilde{\Omega} \times V : \boldsymbol{v} \cdot \hat{v}(\xi) = 0\}.$$

Assume Γ_0 is of zero measure with respect to $d\gamma_\xi d\boldsymbol{v}$, where $d\gamma_\xi$ is the Lebesgue measure on $\partial\widetilde{\Omega}$

Traces

Trace spaces:

$$L^p_\pm := L^p(\Gamma_\pm; |\boldsymbol{v}\cdot\hat{\nu}(\xi)| d\gamma_\xi d\boldsymbol{v}\}, \quad 1 \le p < +\infty.$$

$p_{|\Gamma_\pm} \in L^p_\pm$ denotes the trace of $p \in W^{1,p}(\widetilde{\Omega}\times V)$ on $\Gamma_\pm$, for fixed $\tau > 0$. Assume enough regularity so that the traces are well defined. If p is smooth enough, then

$$p_{|\partial\widetilde{\Omega}\times V}(\xi,\tau,\boldsymbol{v}) = \lim_{\substack{\widetilde{\xi}\in\widetilde{\Omega}\\ \widetilde{\xi}\to\xi}} p(\widetilde{\xi},\tau,\boldsymbol{v}), \qquad \text{for each } \xi \in \partial\widetilde{\Omega}$$

If for each $\xi \in \partial\widetilde{\Omega}$,

$$V^\pm := \{\boldsymbol{v} \in V : \pm\boldsymbol{v}\cdot\hat{\nu}(\xi) > 0\},$$

then we may as well define

$$p_{|\partial\widetilde{\Omega}\times V}(\xi,\tau,\boldsymbol{v}) =: \begin{cases} p_{|\Gamma_+}(\xi,\tau,\boldsymbol{v}), & \text{if } \boldsymbol{v}\in V^+,\\ p_{|\Gamma_-}(\xi,\tau,\boldsymbol{v}), & \text{if } \boldsymbol{v}\in V^-. \end{cases}$$

The biological no-flux condition

General form of boundary conditions for the transport equation:

$$p_{|\Gamma_-}(\xi, \tau, \boldsymbol{v}) = (\mathscr{B} p_{|\Gamma_+})(\xi, \boldsymbol{v}, \tau), \quad (\xi, \boldsymbol{v}) \in \Gamma_-, \tau > 0,$$

incoming flux of cells, $p_{|\Gamma_-}$, is related to the outgoing one, $p_{|\Gamma_+}$, through a linear bounded operator $\mathscr{B} : L^p_+ \to L^p_-$.

The biological no-flux condition

General form of boundary conditions for the transport equation:

$$p_{|\Gamma_-}(\xi,\tau,\boldsymbol{v}) = (\mathscr{B}p_{|\Gamma_+})(\xi,\boldsymbol{v},\tau), \quad (\xi,\boldsymbol{v}) \in \Gamma_-, \tau > 0,$$

incoming flux of cells, $p_{|\Gamma_-}$, is related to the outgoing one, $p_{|\Gamma_+}$, through a linear bounded operator $\mathscr{B} : L^p_+ \to L^p_-$.

The boundary operator satisfies the biological no-flux condition condition if

$$\int_V p(\xi,\tau,\boldsymbol{v})\,(\boldsymbol{v}\cdot\hat{\nu}(\xi))\,d\boldsymbol{v} = 0, \quad \xi \in \partial\widetilde{\Omega},\ \tau > 0. \qquad \text{(BFC)}$$

$p = p(\xi,\tau,\boldsymbol{v}) = p_{|\Gamma_+}(\xi,\tau,\boldsymbol{v}) + (\mathscr{B}p_{|\Gamma_+})(\xi,\tau,\boldsymbol{v})$ is the trace of the solution to the transport equation $p = p(\xi,\tau,\boldsymbol{v})$ on $\partial\widetilde{\Omega}\times V$ for each fixed $\tau > 0$. No agents (cells or particles) move across the boundary.

Regular reflection boundary operator

Definition (Palczewski, 1992)

$\mathscr{B} \in \mathscr{L}(L^p_+, L^p_-)$ is a regular reflection boundary operator if there exists a C^1-piecewise mapping $\mathscr{V} : \Gamma_- \to \mathbb{R}^n$ satisfying:

(a) If $(\xi, \boldsymbol{v}) \in \Gamma_-$ then $(\xi, \mathscr{V}(\xi, \boldsymbol{v})) \in \Gamma_+$.

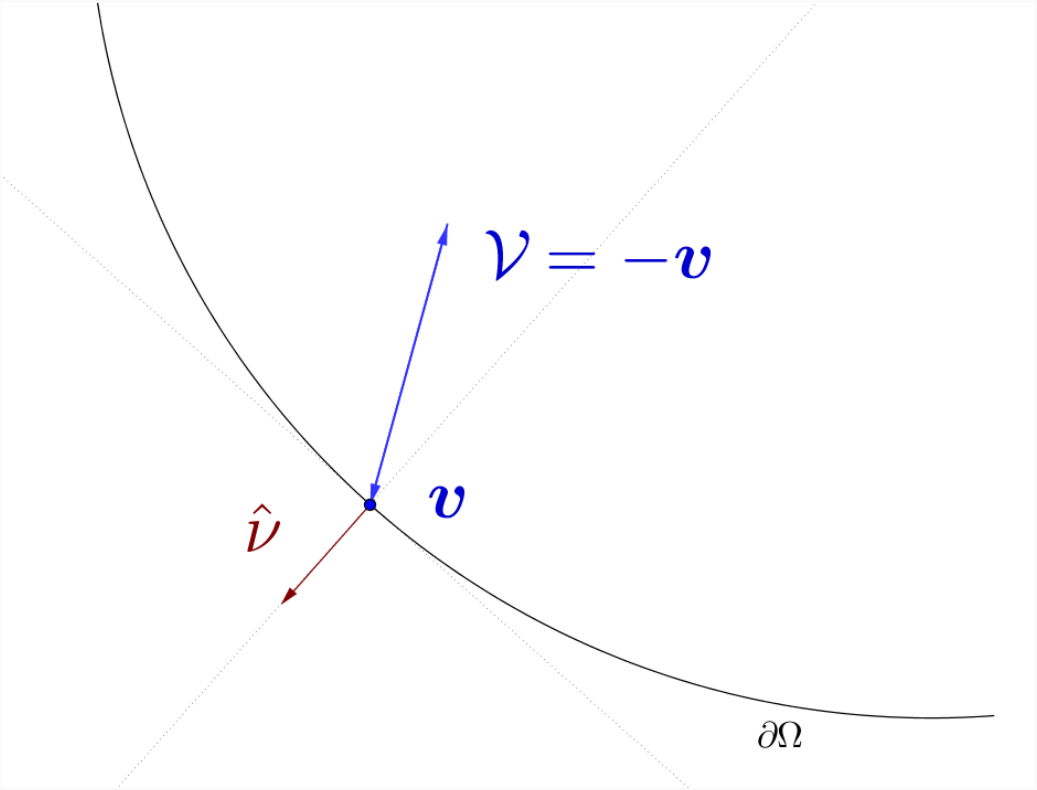
(b) $(\mathscr{B}p)(\xi, \boldsymbol{v}) = p(\xi, \mathscr{V}(\xi, \boldsymbol{v}))$, for all $(\xi, \boldsymbol{v}) \in \Gamma_-$, $p \in L^p_+$.

(c) $|\mathscr{V}(\xi, \boldsymbol{v})| = |\boldsymbol{v}|$ for any $(\xi, \boldsymbol{v}) \in \Gamma_-$.

(d) $|\hat{\nu}(\xi) \cdot \boldsymbol{v}| = |\hat{\nu}(\xi) \cdot \mathscr{V}(\xi, \boldsymbol{v})| |\det \partial \mathscr{V} / \partial \boldsymbol{v}|$, for all $(\xi, \boldsymbol{v}) \in \Gamma_-$.

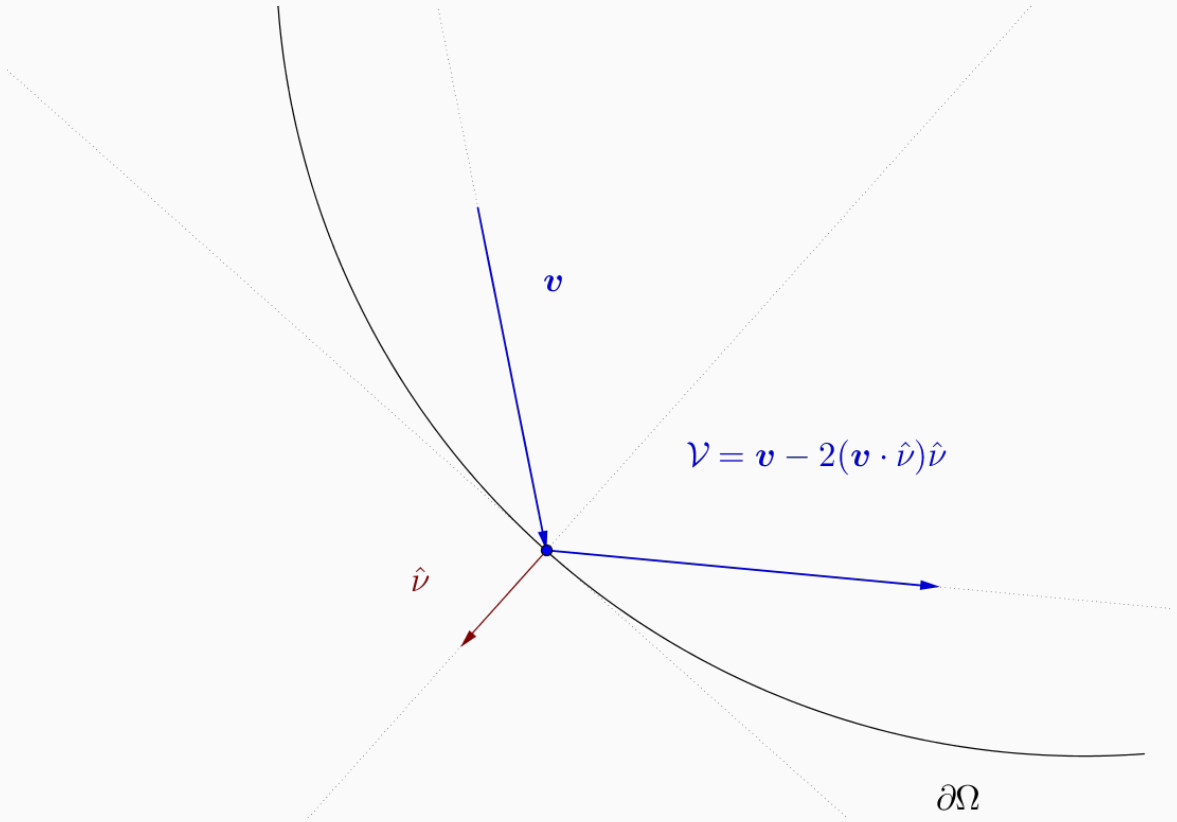
(e) $\mathscr{V}(\xi, \beta \boldsymbol{v}) = \beta \mathscr{V}(\xi, \boldsymbol{v})$ for any $\beta > 0$, $(\xi, \boldsymbol{v}) \in \Gamma_-$.

Example 1: Bounce back reflection boundary condition



$\mathscr{V}(\xi, \boldsymbol{v}) = -\boldsymbol{v}, \ (\xi, \boldsymbol{v}) \in \Gamma_-$. An agent (particle or cell) hits the boundary and bounces back with the same velocity but with opposite direction

Example 2: Specular reflection boundary condition



$\mathscr{V}(\xi, \boldsymbol{v}) = \boldsymbol{v} - 2(\boldsymbol{v} \cdot \hat{\nu}(\xi))\hat{\nu}(\xi)$, $(\xi, \boldsymbol{v}) \in \Gamma_-$. An agent bounces back making the same angle with respect to the tangent to the boundary

Non-local (in velocity) boundary conditions

Definition

$\mathscr{K} \in \mathscr{L}(L^2_+, L^2_-)$ is a (non-local in velocity) diffusive boundary operator if for all $(\xi, \boldsymbol{v}) \in \Gamma_-$,

$$(\mathscr{K} p_{|\Gamma_+})(\xi, \tau, \boldsymbol{v}) = \int_{V^+} h(\xi, \boldsymbol{v}, \boldsymbol{v}') p_{|\Gamma_+}(\xi, \tau, \boldsymbol{v}') \, |\boldsymbol{v}' \cdot \hat{\nu}(\xi)| \, d\boldsymbol{v}'$$

where $h = h(\xi, \boldsymbol{v}, \boldsymbol{v}') \geq 0$ is a measurable function called the Gaussian equilibrium and normalized such that

$$\int_{V^-} h(\xi, \boldsymbol{v}, \boldsymbol{v}') \, |\boldsymbol{v} \cdot \hat{\nu}(\xi)| \, d\boldsymbol{v} = 1.$$

A linear combination of a regular reflection with a diffusive boundary operator is called a Maxwell-type boundary operator, $\mathscr{H} \in \mathscr{L}(L^2_+, L^2_-)$, where $\mathscr{H} = \alpha(\xi)\mathscr{R} + (1 - \alpha(\xi))\mathscr{K}$ for some $\alpha(\cdot) \in L^\infty(\partial\widetilde{\Omega})$, $0 \leq \alpha \leq 1$. $\mathscr{K}$ is called the diffusive part of $\mathscr{H}$ and $\mathscr{R}$ is a reflection.

Maxwell-type boundary operators have no normal flux

Lemma

Any Maxwell-type boundary operator satisfies the biological no-flux condition.

Proof: Follows from straightforward calculations.

No flux boundary conditions in the parabolic limit

Proposition (P, 2018)

Under the assumptions above, let us suppose that $\partial\Omega$ is piecewise smooth, that the regular Hilbert expansion of the solution to the transport equation is smooth enough, and that the kinetic boundary conditions imposed on p satisfy the no normal mass flux across the boundary condition. Then the leading term $\rho(\xi,\tau) = |V|\bar{p}_0(\xi,\tau)$ of the Hilbert expansion satisfies the following no normal flux boundary condition at $\partial\widetilde{\Omega}$,

$$\Big(\mathbb{D}\nabla_\xi \rho(\xi,\tau) - \rho(\xi,\tau)\boldsymbol{w}_c\Big)\cdot\hat{\nu}(\xi) = 0, \qquad \xi \in \partial\widetilde{\Omega},\ \tau > 0,$$

whereupon the diffusion tensor $\mathbb{D}$ and the chemotactic velocity $\boldsymbol{w}_c$ are defined as before.

Note: The no normal mass flux condition could be satisfied by other boundary conditions that could include, for instance, boundary operators of Maxwell type (reflection and diffusion effects are combined), or non-local boundary conditions (see **Beals and Protopopescu, 1987**; **Lods, 2005**).

Proof sketch (i)

- Substituting the Hilbert expansion, the no normal mass flux condition is

$$\int_V \big(p_0(\xi,\tau,\boldsymbol{v})+\varepsilon p_1(\xi,\tau,\boldsymbol{v})+O(\varepsilon^2)\big)(\boldsymbol{v}\cdot\hat{\nu}(\xi))\,d\boldsymbol{v}=0, \qquad \xi\in\partial\widetilde{\Omega},\,\tau>0.$$

  and independent of $\varepsilon>0$. Thus, w.l.o.g.,

$$\int_V p_j(\xi,\tau,\boldsymbol{v})(\boldsymbol{v}\cdot\hat{\nu}(\xi))\,d\boldsymbol{v}=0, \quad \forall j\geq 0,\,\xi\in\partial\widetilde{\Omega},\,\tau>0$$

- The condition for $j=0$ is trivially satisfied,

$$\int_V p_0(\xi,\tau,\boldsymbol{v})(\boldsymbol{v}\cdot\hat{\nu}(\xi))\,d\boldsymbol{v}=\bar{p}_0(\xi,\tau)\Big(\int_V \boldsymbol{v}\,d\boldsymbol{v}\Big)\cdot\hat{\nu}(\xi)=0,$$

  p_0 is independent of $\boldsymbol{v}$ and V is symmetric.
- The condition for $j=1$ reads

$$\int_V \Big(\mathscr{F}_0\big(\boldsymbol{v}\cdot\nabla_\xi\bar{p}_0(\xi,\tau)\big)+\mathscr{F}_0\big((\lambda_1(\boldsymbol{v})-\bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0(\xi,\tau)\big)\Big)(\boldsymbol{v}\cdot\hat{\nu}(\xi))\,d\boldsymbol{v}=0.$$

Proof sketch (ii)

- We can show that

$$\begin{aligned}\int_V \mathscr{F}_0\big((\boldsymbol{v}\cdot\nabla_\xi \bar{p}_0)\big)(\boldsymbol{v}\cdot\hat{v}(\xi))\,d\boldsymbol{v} &= \int_V \Big(\boldsymbol{v}(\mathscr{F}_0\boldsymbol{v})^\top \nabla_\xi \bar{p}_0\Big)\cdot\hat{v}(\xi)\,d\boldsymbol{v}\\ &= \left[\Big(\int_V \boldsymbol{v}(\mathscr{F}_0\boldsymbol{v})^\top\,d\boldsymbol{v}\Big)\nabla_\xi \bar{p}_0\right]\cdot\hat{v}(\xi)\\ &= -|V|\big(\mathbb{D}\nabla_\xi \bar{p}_0\big)\cdot\hat{v}(\xi).\end{aligned}$$

- Also,

$$\begin{aligned}&\int_V \mathscr{F}_0\big((\lambda_1(\boldsymbol{v})-\bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0\big)(\boldsymbol{v}\cdot\hat{v}(\xi))\,d\boldsymbol{v}\\ &\quad= \Big(\int_V \mathscr{F}_0(\lambda_1(\boldsymbol{v})-\bar{\lambda}_1(\boldsymbol{v}))\,\boldsymbol{v}\,d\boldsymbol{v}\Big)\cdot\hat{v}(\xi)\bar{p}_0\\ &\quad= |V|(\boldsymbol{w}_c\cdot\hat{v}(\xi))\bar{p}_0.\end{aligned}$$

Proof sketch (ii)

- We can show that

$$\begin{aligned}\int_V \mathscr{F}_0\big((\boldsymbol{v}\cdot\nabla_\xi \bar{p}_0)\big)(\boldsymbol{v}\cdot\hat{v}(\xi))\,d\boldsymbol{v} &= \int_V \Big(\boldsymbol{v}(\mathscr{F}_0\boldsymbol{v})^\top \nabla_\xi \bar{p}_0\Big)\cdot\hat{v}(\xi)\,d\boldsymbol{v}\\ &= \left[\Big(\int_V \boldsymbol{v}(\mathscr{F}_0\boldsymbol{v})^\top\,d\boldsymbol{v}\Big)\nabla_\xi \bar{p}_0\right]\cdot\hat{v}(\xi)\\ &= -|V|\big(\mathbb{D}\nabla_\xi \bar{p}_0\big)\cdot\hat{v}(\xi).\end{aligned}$$

- Also,

$$\begin{aligned}&\int_V \mathscr{F}_0\big((\lambda_1(\boldsymbol{v})-\bar{\lambda}_1(\boldsymbol{v}))\bar{p}_0\big)(\boldsymbol{v}\cdot\hat{v}(\xi))\,d\boldsymbol{v}\\ &\quad= \Big(\int_V \mathscr{F}_0(\lambda_1(\boldsymbol{v})-\bar{\lambda}_1(\boldsymbol{v}))\,\boldsymbol{v}\,d\boldsymbol{v}\Big)\cdot\hat{v}(\xi)\bar{p}_0\\ &\quad= |V|(\boldsymbol{w}_c\cdot\hat{v}(\xi))\bar{p}_0.\end{aligned}$$

- This yields the result.

Modeling density-dependent cross-diffusion

Choice of the turning kernel and velocity space

Modeling: $S = S(\xi, \tau)$ concentration of a chemical signal (chemoattractant). The perturbed turning frequency λ_0 might be a function of (ξ, τ) through $S = S(\xi, \tau)$ or the density $\rho = \rho(\xi, \tau)$, but constant in $\boldsymbol{v}$. λ_1 may depend on $\boldsymbol{v}$ and on $S, \nabla S$ etc. Notation: $\lambda_1 = \lambda_1(\boldsymbol{v}, \hat{S})$.

- Turning kernel: unperturbed (in ε) from a uniform reorientation in velocity space,

$$T = T_0(\boldsymbol{v}, \boldsymbol{v}') := \frac{1}{|V|};$$

  satisfies (T_1) - (T_4)

- Choice of V: Uniform distribution of velocities in all directions with constant magnitude $s > 0$,

$$V := s\mathbb{S}^{n-1} := \{s\boldsymbol{v} : |\boldsymbol{v}| = 1, \boldsymbol{v} \in \mathbb{R}^n\}.$$

Choice of the turning frequency

- Experimental observations: tumbling time is low when the concentration of the chemoattractant is low for *B. Subtilis* (cf. **Menolascina et al., 2017**)
- To model aggregation, λ must be a decreasing function of ρ (**Othmer et al., 1988**; **Méndez, et al., 2012**).
- First order perturbation of Schnitzer (1993) type:

$$\begin{aligned}\lambda(\boldsymbol{v},\hat{S}) &= \lambda_0(\xi,\tau)+\varepsilon\lambda_1(\boldsymbol{v},\hat{S}) \\ &:= \frac{\mu_0}{\rho(\xi,\tau)S(\xi,\tau)}+\varepsilon\kappa(S(\xi,\tau))\left(\boldsymbol{v}\cdot\nabla_\xi S(\xi,\tau)\right)\end{aligned}$$

$\mu_0 > 0$ is a constant with units of square moles over time ($[M]^2/[T]$). $\kappa = \kappa(S)$ is a scalar function with units $1/[M]$.

Resulting diffusion tensor

The pseudo-inverse, $\mathscr{F}_0 : \langle 1 \rangle^\perp \subset L^2(V) \to L^2(V)$ reduces to multiplication by $-\lambda_0^{-1}$. Therefore, the diffusion tensor is

$$\mathbb{D} = -\frac{1}{|V|} \int_V \boldsymbol{v} \otimes (\mathscr{F}_0 \boldsymbol{v})\, d\boldsymbol{v} = \frac{\lambda_0^{-1}}{|V|} \int_V \boldsymbol{v} \otimes \boldsymbol{v}\, d\boldsymbol{v}.$$

Since $|V| = s^{n-1}|\mathbb{S}^{n-1}| =: s^{n-1}\omega_n$ and

$$\int_V \boldsymbol{v} \otimes \boldsymbol{v}\, d\boldsymbol{v} = \int_{\mathbb{S}^{n-1}} s^2 \eta \otimes \eta s^{n-1}\, dS_\eta = s^{n+1} \frac{\omega_n}{n} \mathbb{I}_n,$$

then $\mathbb{D} = (\lambda_0 s^2/n)\mathbb{I}_n$, that is,

$$\mathbb{D} = (\lambda_0 s^2/n)\mathbb{I}_n = \left(\frac{s^2}{\mu_0 n}\right) \rho S\, \mathbb{I}_n.$$

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Observation: The scalar quantity $D(\rho, S) := \left(\frac{s^2}{\mu_0 n}\right)\rho S$ has units of square length over time ($[L]^2/[T]$), effective diffusion coefficient. The parameter $\sigma = s^2/\mu_0 n$ measures the hardness of the agar: hard medium means s is low, and the turning frequency per unit mass μ_0 should be large; lower values of σ indicate harder substrates.

Resulting chemotactic term (i)

The average bias vanishes,

$$\overline{\lambda_1}(\boldsymbol{v}) = \int_V \lambda_1(\boldsymbol{v}')\, T_0(\boldsymbol{v}, \boldsymbol{v}')\, d\boldsymbol{v}' = \frac{1}{|V|} \int_V \kappa(S)(\boldsymbol{v}' \cdot \nabla_\xi S)\, d\boldsymbol{v}'$$
$$= \frac{\kappa(S)}{|V|} \left(\int_V \boldsymbol{v}\, d\boldsymbol{v} \right) \cdot \nabla_\xi S = 0,$$

thus,

$$\boldsymbol{w}_c = \frac{1}{|V|} \int_V \boldsymbol{v} \mathscr{F}_0\big(\lambda_1(\boldsymbol{v}, \hat{S})\big)\, d\boldsymbol{v} = -\frac{\lambda_0^{-1}}{|V|} \int_V \boldsymbol{v} \kappa(S)(\boldsymbol{v} \cdot \nabla_\xi S)\, d\boldsymbol{v} = -\mathbb{X} \nabla_\xi S,$$

where

$$\mathbb{X} := \frac{\kappa(S)}{\lambda_0 |V|} \int_V \boldsymbol{v}\boldsymbol{v}^\top\, d\boldsymbol{v} = \frac{\kappa(S)}{\lambda_0 |V|} \int_V \boldsymbol{v} \otimes \boldsymbol{v}\, d\boldsymbol{v},$$

is the chemotactic sensitivity tensor.

Resulting chemotactic term (ii)

The chemotactic velocity is:

$$\boldsymbol{w}_c = -\left(\frac{s^2}{\mu_0 n}\right) \kappa(S) \rho S \nabla_\xi S.$$

Resulting chemotactic term (ii)

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$$\boldsymbol{w}_c = -\left(\frac{s^2}{\mu_0 n}\right)\kappa(S)\rho S\nabla_\xi S.$$

Diffusion and chemotaxis terms are related: model underlies the experimental observation by Ben-Jacob: the chemotactic flux is

$$\mathbf{J}_c := \left(\frac{s^2}{\lambda_0 n}\right)\kappa(S)\rho^2 S\nabla S,$$

then $\mathbf{J}_c = \zeta(\rho, S)\kappa(S)\nabla S$, where the "bacterial response" function ζ satisfies

$$\zeta(\rho, S) = \left(\frac{s^2}{\lambda_0 n}\right)\rho^2 S = \rho D(\rho, S).$$

Choice of the chemotactic sensitivity function

Receptor law (**Lapidus-Schiller, 1976**):

$$\kappa(S) = \frac{\chi_0 K_d}{(K_d + S)^2},$$

where $\chi_0 > 0$ is a dimensionless constant measuring the strength of the chemotaxis, and $K_d > 0$ is the receptor-ligand binding dissociation constant. K_d has nutrient concentration units $[M]$, it has a unique value, determined experimentally. Meaning: for very high concentrations of the chemical signal, the chemotactic response of bacteria vanishes due to saturation of the receptors.

Resulting equation

Upon substitution:

Mean-field equation for the marginal density $\rho = |V|\bar{p}_0$:

$$\frac{\partial \rho}{\partial \tau} = \mathrm{div}_\xi \left(\left(\frac{s^2}{\mu_0 n} \right) \rho \, S \, \nabla_\xi \rho \right) - \mathrm{div}_\xi \left(\left(\frac{s^2}{\mu_0 n} \right) \rho^2 \, S \, \frac{\chi_0 K_d}{(K_d + S)^2} \nabla_\xi S \right)$$

for $\xi \in \widetilde{\Omega}$, $\tau > 0$.

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for $\xi \in \widetilde{\Omega}$, $\tau > 0$.

Boundary conditions:

$$\left(\rho S \nabla_\xi \rho - \frac{\chi_0}{K_d} \rho^2 S \nabla_\xi S \right) \cdot \hat{\nu}(\xi) = 0, \qquad \xi \in \partial\widetilde{\Omega}, \; \tau > 0.$$

Adding a reaction term (i)

- Main observation: the "velocity jump" process is Markovian, the probability that agents reach the position x at time t does not depend on previous times, $t - T$, with $T > 0$. (There is no history dependence.) It is legitimate to add production/consumption terms.
- Let $\widetilde{\mathscr{G}}(p, S) =$ consumption rate of the nutrient by the bacteria; then the growth rate of bacteria is $\theta\widetilde{\mathscr{G}}(p, S)$, where $\theta > 0$ is a (dimensionless) conversion constant. Choice: Michaelis-Menten rule,

$$\widetilde{\mathscr{G}}(p, S) = \frac{kpS}{1 + \gamma S},$$

$k > 0$ is the intrinsic consumption rate, and $\gamma > 0$ is a saturation constant (k/γ is the maximum consumption rate by one single cell.) This function can be approximated by

$$\widetilde{\mathscr{G}}(p, S) = kpS,$$

valid for low nutrient concentrations.

Adding a reaction term (ii)

- Important assumption: the number of directional changes outnumber the birth events. Thus, the pure movement "velocity jump" process occurs on a much faster scale than the production events due to kinetics. Since $t =$ fast time variable, $\tau =$ slow time scale, then the pure kinetics are governed by an equation of the form $p_\tau = \widetilde{\mathscr{G}}(p, S)$, that is, $p_t = \varepsilon^2 \widetilde{\mathscr{G}}(p, S)$. Hence we define,

$$\mathscr{G}(p, S) := \varepsilon^2 \widetilde{\mathscr{G}}(p, S) = \varepsilon^2 kpS.$$

The resulting scaled "velocity jump" process equation with reaction term reads

$$\varepsilon^2 \frac{\partial}{\partial \tau} p(\xi, \tau, \boldsymbol{v}) + \varepsilon \boldsymbol{v} \cdot \nabla_\xi p(\xi, \tau, \boldsymbol{v})$$
$$= -\lambda p(\xi, \tau, \boldsymbol{v}) + \int_V \lambda T(\boldsymbol{v}, \boldsymbol{v}') p(\xi, \tau, \boldsymbol{v}')\, d\boldsymbol{v}' + \varepsilon^2 kp(\xi, \tau, \boldsymbol{v}) S(\xi, \tau).$$

Adding a reaction term (iii)

- The kinetic term appears at order $O(\varepsilon^2)$, the procedure gets unaffected up to order two. The resulting mean field equation is

$$\frac{\partial \rho}{\partial \tau} = \mathrm{div}_\xi \left(\left(\frac{s^2}{\mu_0 n} \right) \rho \, S \, \nabla_\xi \rho \right) - \mathrm{div}_\xi \left(\left(\frac{s^2}{\mu_0 n} \right) \rho^2 \, S \, \frac{\chi_0 K_d}{(K_d + S)^2} \nabla_\xi S \right) + k\theta\rho S.$$

Equation for the chemical signal

The dynamics of the chemical (nutrient) concentration $S = S(\xi, \tau)$ is governed by a standard reaction-diffusion equation (diffusive limit of a stochastic positional jump process)

$$\frac{\partial S}{\partial \tau} = D_S \Delta_\xi S - k\rho S, \quad \xi \in \widetilde{\Omega},\ \tau > 0,$$

subject to Neumann (no-flux) boundary conditions

$$\nabla_\xi S \cdot \hat{\nu}(\xi) = 0, \qquad \xi \in \partial\widetilde{\Omega},\ \tau > 0.$$

$D_S > 0$ is the diffusion constant associated to the nutrient concentration and $-k\rho S$ is the consumption rate of the nutrient by the bacteria.

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Initial conditions:

$$\rho(\xi, 0) = \rho_0(\xi), \quad S(\xi, 0) = S_0(\xi), \quad \xi \in \widetilde{\Omega},$$

being ρ_0, S_0, known functions.

Non-dimensionalization

Scaled, dimensionless quantities:

$$x := \left(\frac{\theta K_d k}{D_S}\right)^{1/2} \xi, \quad t := \theta k K_d \tau, \quad v := \frac{S}{K_d}, \quad u := \frac{\rho}{\theta K_d}, \quad \sigma_0 = \left(\frac{\theta K_d^2}{D_S}\right) \sigma$$

Resulting equations:

$$\begin{aligned} u_t &= \sigma_0 \nabla \cdot (uv \nabla u) - \sigma_0 \chi_0 \nabla \cdot (u^2 v \nabla v) + uv, \\ v_t &= \Delta v - uv, \end{aligned} \qquad x \in \Omega,\ t > 0,$$

$$\begin{aligned} (uv\nabla u - \chi_0 u^2 v \nabla v) \cdot \hat{\nu} &= 0, \\ \nabla v \cdot \hat{\nu} &= 0, \end{aligned} \qquad x \in \partial\Omega,\ t > 0,$$

$$u(x,0) = u_0(x), \quad v(x,0) = v_0(x), \qquad x \in \Omega,$$

where now Ω denotes the rescaled bounded, open domain in the new non-dimensional variables.

Kinetic derivation of cross-diffusion chemotactic model

Theorem (P, 2018)

Let $\Omega \subset \mathbb{R}^n$ be an open, bounded domain, with piecewise smooth boundary $\partial\Omega$. Then the above system of equations, constitute the formal diffusive limit when $\varepsilon \to 0^+$ of the solutions to a velocity jump process governed by a transport equation for a non-dimensional agent distribution $q = q(x, t, \boldsymbol{v})$, of the form

$$\varepsilon^2 q_t + \varepsilon \boldsymbol{v} \cdot \nabla q = -\lambda q + \int_V \lambda\, T_0(\boldsymbol{v}, \boldsymbol{v}') q \, d\boldsymbol{v}' + \varepsilon^2 q v,$$

and a reaction diffusion equation

$$v_t = \Delta v - uv,$$

for the (non-dimensional) chemical signal concentration $v = v(x, t)$, where

$$u(x, t) = \int_V q(x, y, \boldsymbol{v})\, d\boldsymbol{v},$$

is the zero velocity moment or marginal density.

Kinetic derivation of cross-diffusion chemotactic model

Theorem (continued)

Here $\overline{V} = \widetilde{s}\mathbb{S}^{n-1} := \{\widetilde{s}\,\boldsymbol{v} : |\boldsymbol{v}| = 1, \boldsymbol{v} \in \mathbb{R}^n\}$ *is the uniform set of non-dimensional velocities, the turning kernel and turning frequency admit asymptotic expansions of the form*

$$T_0(\boldsymbol{v}, \boldsymbol{v}') = \frac{1}{|\overline{V}|}, \qquad \lambda = \frac{1}{u(x,t)v(x,t)} + \varepsilon\chi_0(\boldsymbol{v}\cdot\nabla v),$$

and subject to boundary conditions of no normal mass flux type for q *satisfying*

$$\int_{\overline{V}} q(x,t,\boldsymbol{v})(\boldsymbol{v}\cdot\hat{\nu}(x))\,d\boldsymbol{v} = 0, \qquad x \in \partial\Omega,\, t > 0,$$

together with Neumann boundary conditions for the chemical concentration

$$\nabla v \cdot \hat{\nu}(x) = 0, \qquad x \in \partial\Omega,\, t > 0.$$

Kinetic derivation of cross-diffusion chemotactic model

Theorem (continued)

Here $\varepsilon > 0$ is a dimensionless small parameter associated to the "velocity jump" process in the diffusion regime. The limiting process is taken in the following sense: if q admits a formal Hilbert expansion of the form $q = q_0 + \varepsilon q_1 + O(\varepsilon^2)$ for $0 < \varepsilon \ll 1$ small, then the leading order term or marginal density $u = |\overline{V}| q_0$ and the concentration v satisfy the limiting system of mean-field equations, where $v_0(x) := v(x,0)$ denotes the initial nutrient concentration, and

$$u_0(x) := u(x,0) = \int_{\overline{V}} q(x,0,\boldsymbol{v})\, d\boldsymbol{v},$$

is the initial distribution of agents for all possible velocities.

Kinetic derivation of cross-diffusion chemotactic model

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Reference: P, J. Math. Biol. (2018), to appear. arXiv:1711.03015

Conclusions

- Formal macroscopic limit (parabolic regime) of a stochastic "velocity jump" process in order to arrive at system with a doubly degenerate cross-diffusion term and a nutrient taxis drift term.
- Both fluxes (the diffusive and the chemotactic) are density-dependent, degenerate, and related to each other.
- Derivation makes precise the microscopic interpretation of the phenomenological bacterial response function introduced by Ben-Jacob.
- Helpful to understand the interplay of the microscopic description of both diffusion and taxis.
- Incorporates microscopic parameters into the modeling process.
- The bacterium *B. subtilis* is used as a prototype, but the method and results apply in more generality.

Thanks!