Multiscale Analysis in Biology

Some successes and open problems

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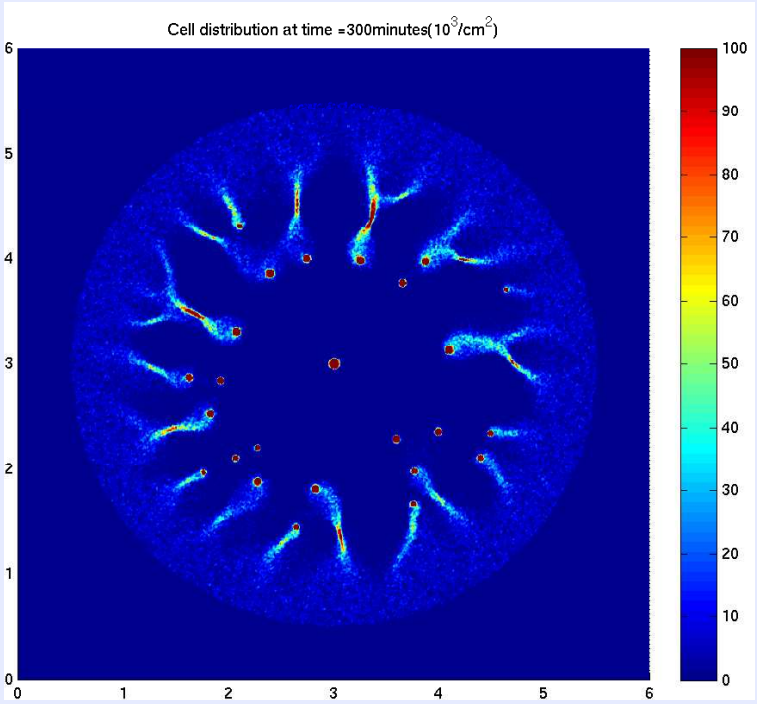
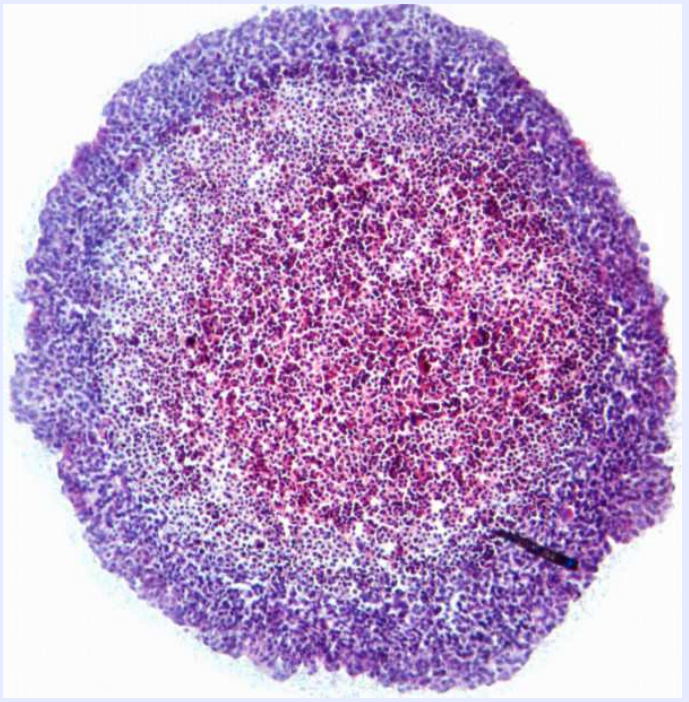


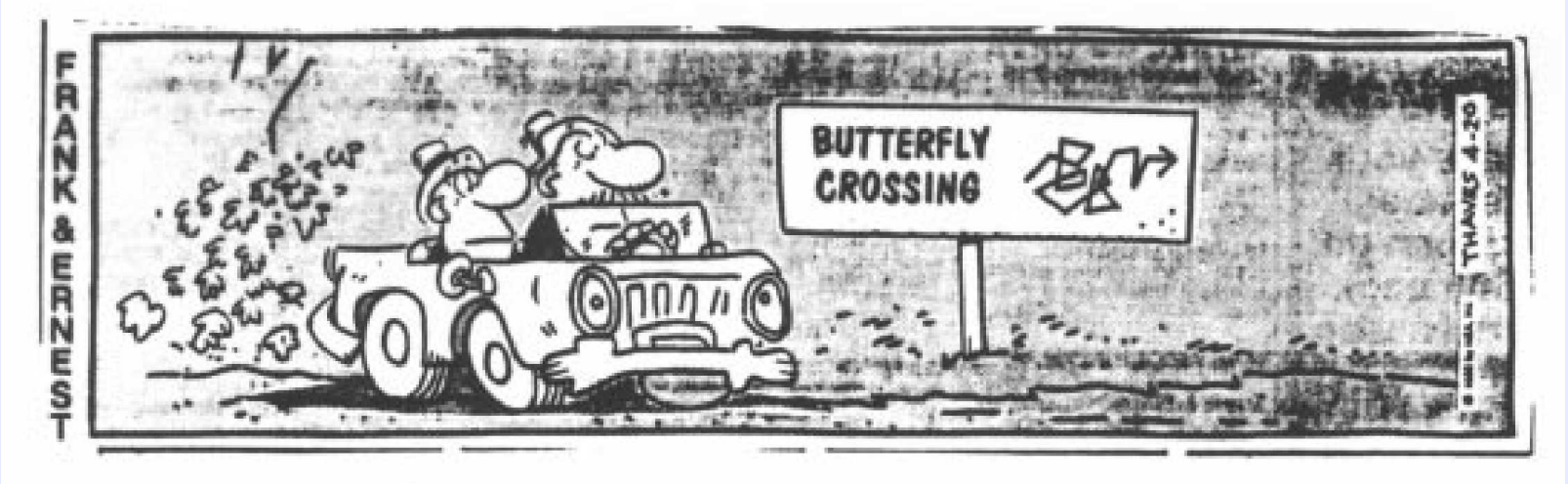


Why understanding motility is important ...

Movement is an essential component of both normal and pathogenic behavior at the cell, organismic and population level

- Early development – we start as a single cell but ultimately have 250 cell types correctly located in the adult and this involves movement at both the single cell and tissue level
- The immune system – e.g., neutrophils respond to bacterial invasion
- Wound healing – some cells move into a wound to fight infection, others to close the wound
- Angiogenesis – this is the process of forming new blood vessels
- Metastasis in cancer – invasion of new sites by active migration and passive transport in the circulatory system
- Organism/population level – searching for food, mates, flocking for predator avoidance or migration, avoidance of toxic substances ...

The basic problem and terminology .....



Taxis: A behavioral response in which a motile cell or organism alters its direction of motion in response to an external stimulus, without changing its speed or turning rate.

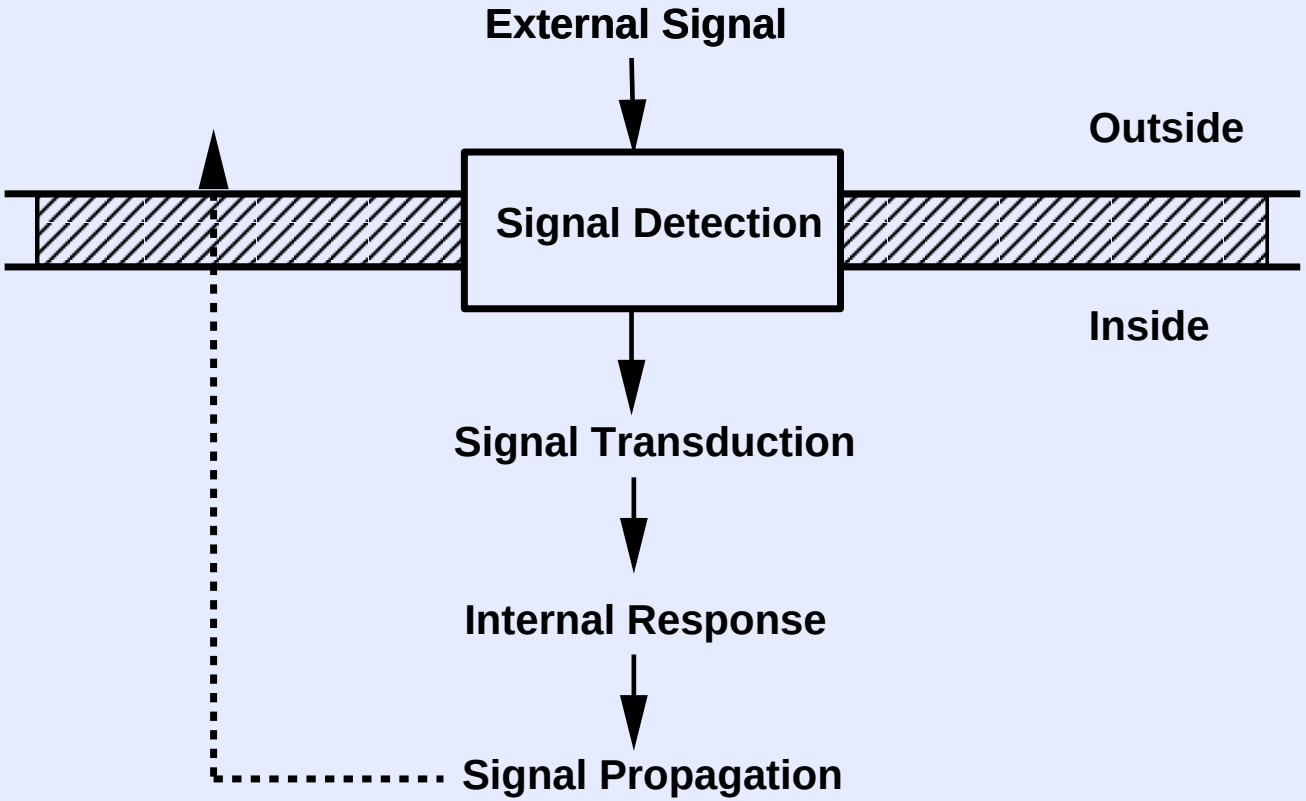
Examples: Chemotaxis, geotaxis, aerotaxis, haptotaxis, ...

Kinesis: A behavioral response in which a motile cell or organism changes its rate of locomotion or turning in response to the intensity, but not the direction, of an external stimulus.

In many systems the external stimulus is a scalar field, but stresses can play a role.

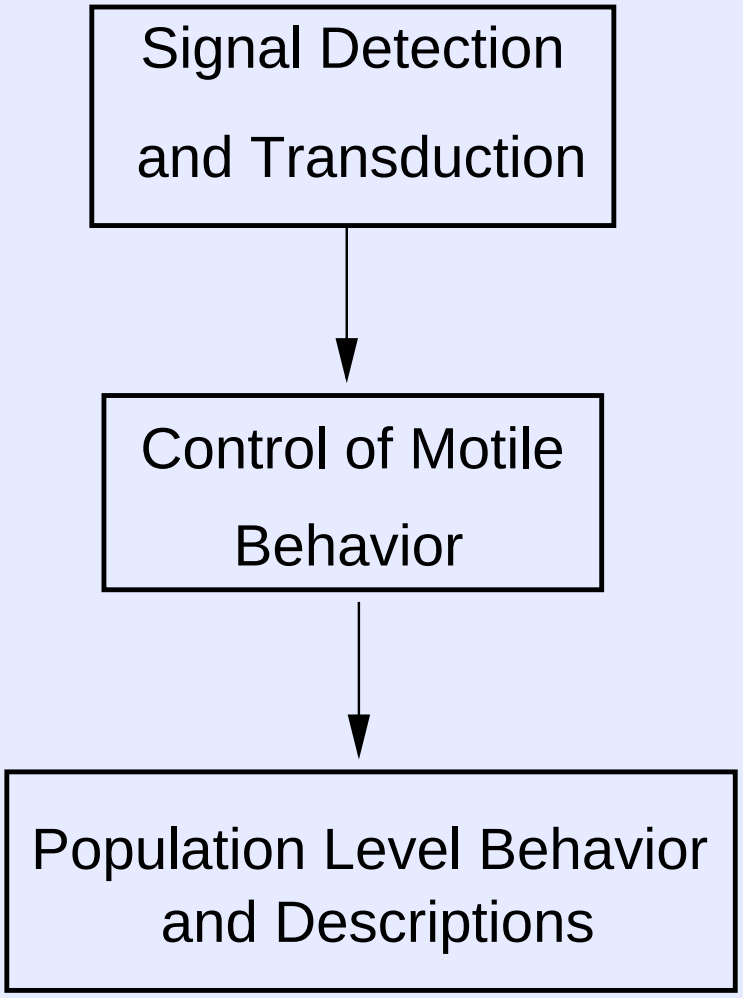
The basic processes at the individual level

- A signal of some sort
- Transduction of the signal into ‘information’ that can affect movement

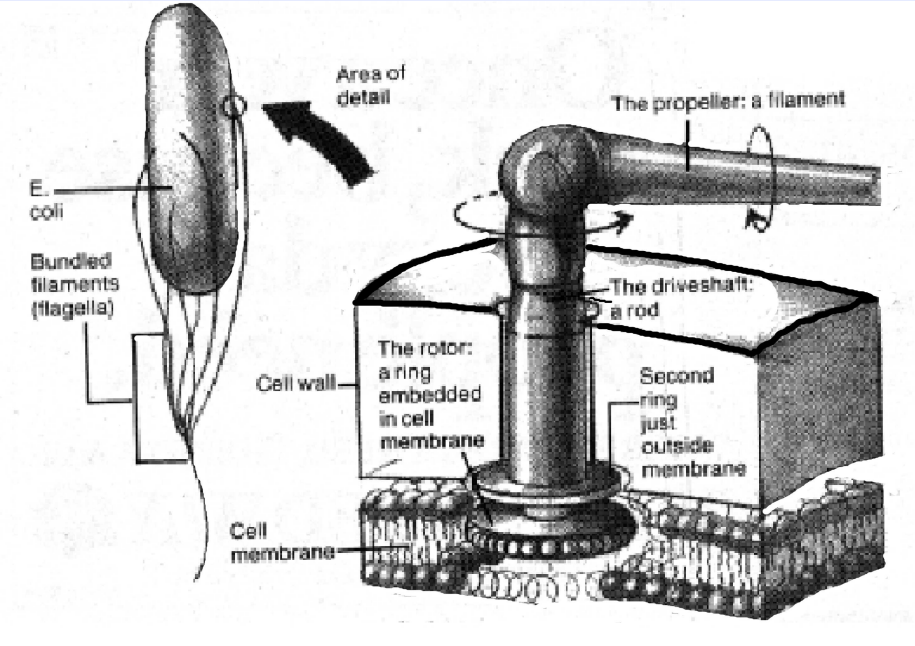


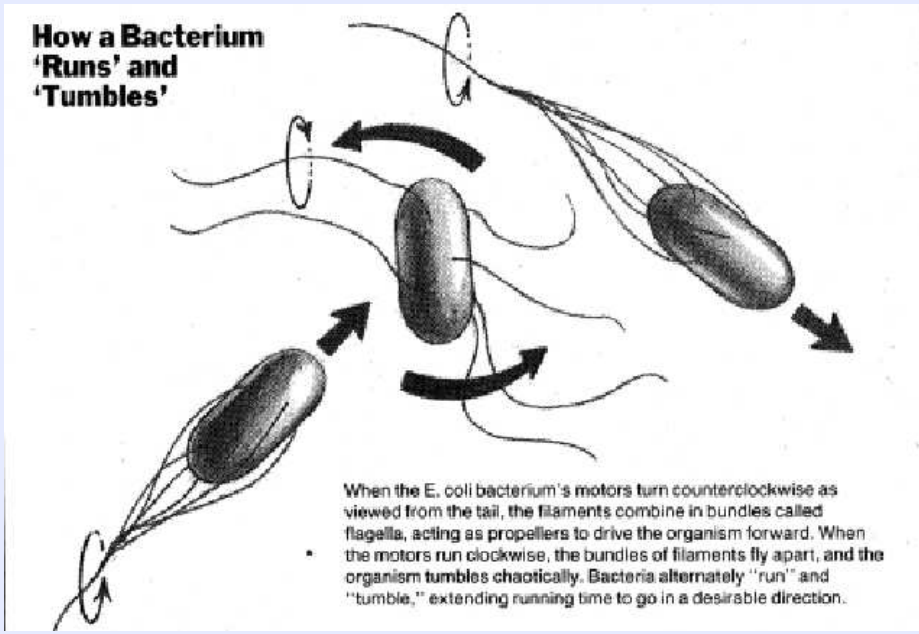
- Movement – which of course involves mechanics

The components in an integrated description



*E. coli*as a model system

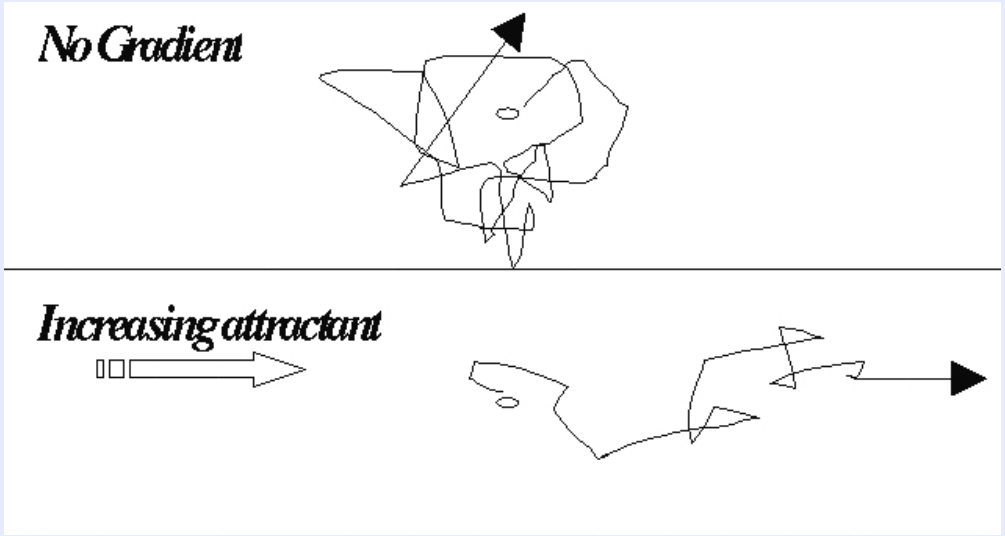




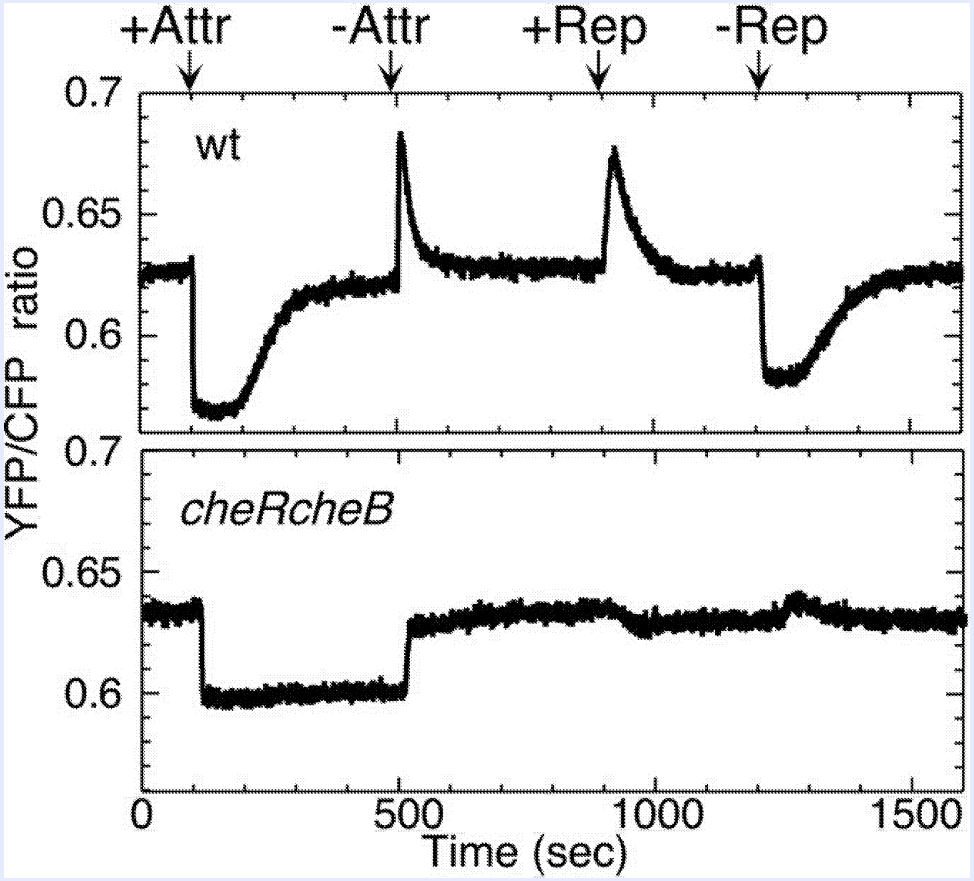
Counterclockwise rotation (CCW): 'runs'

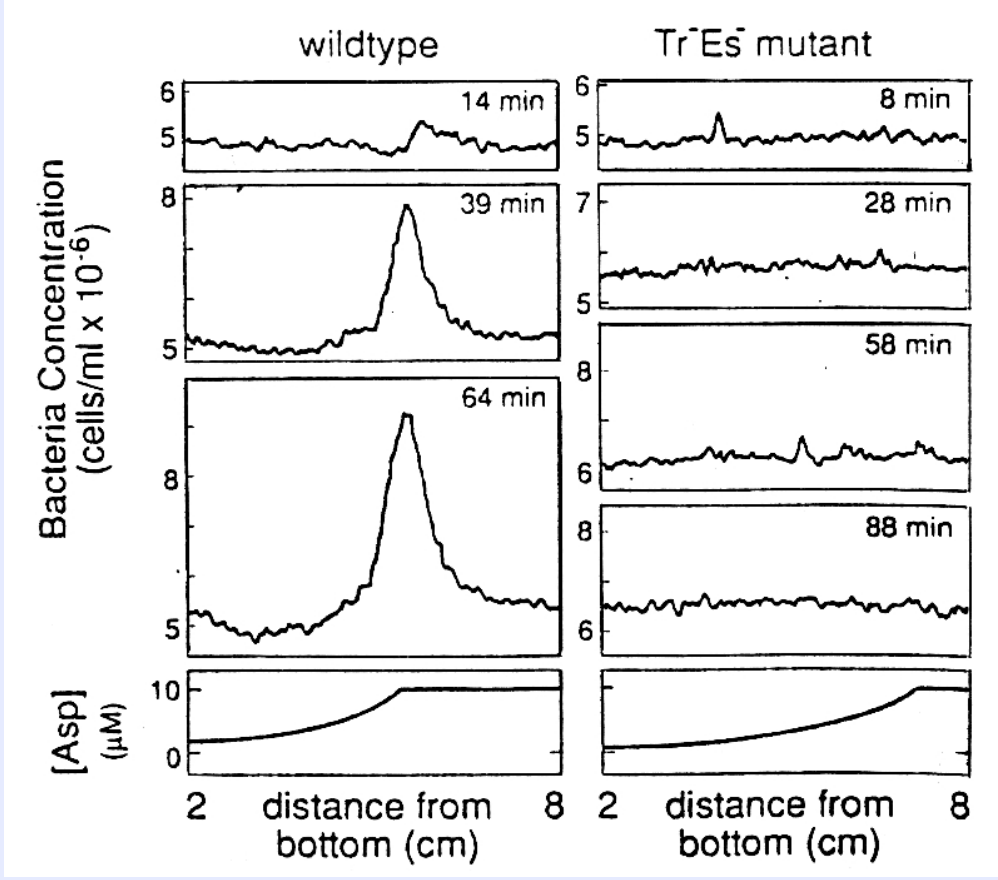
Clockwise rotation (CW) : 'tumbles'

Bias: Probability of CCW *i.e.,* probability of running



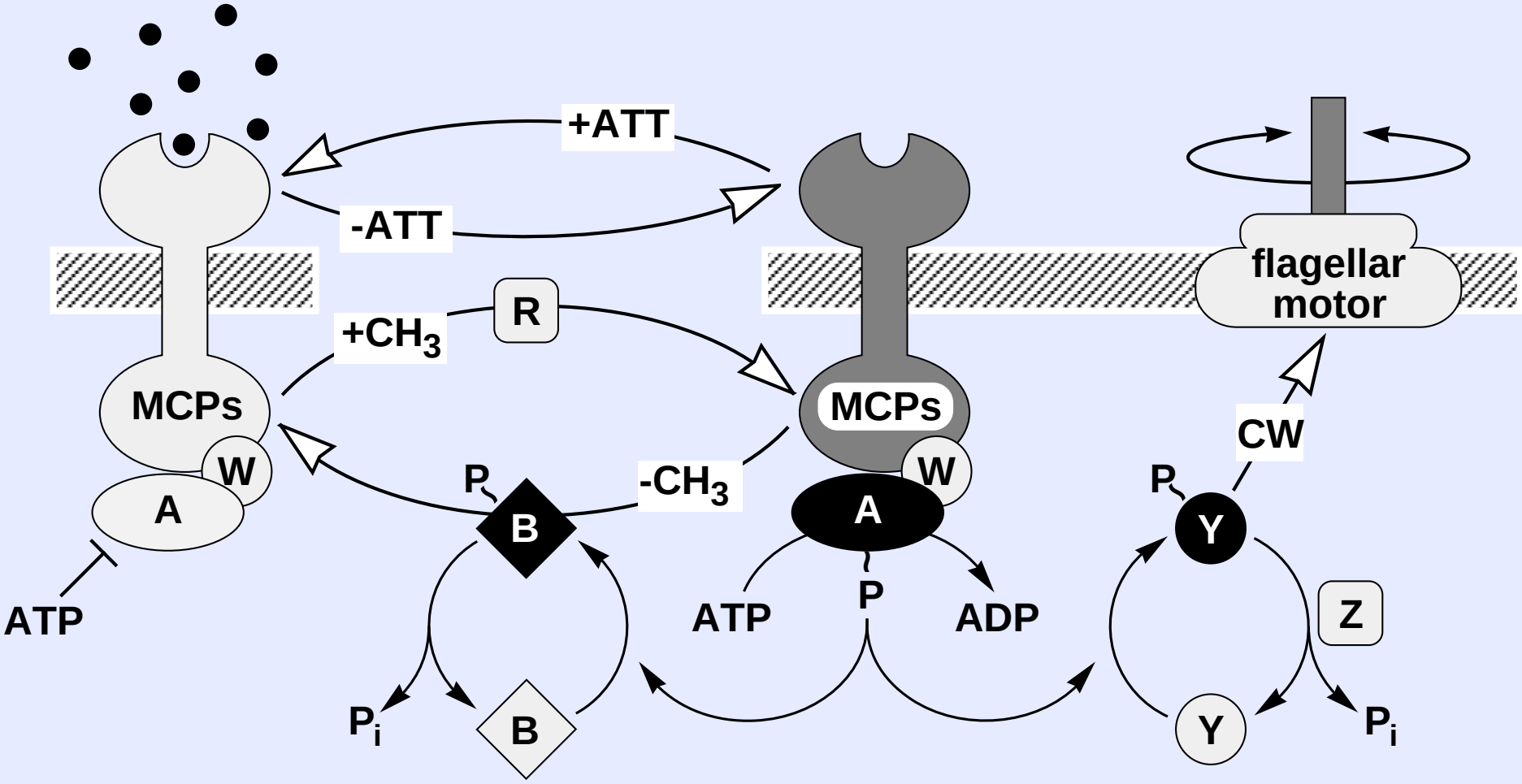
E. coli also adapt to constant stimuli





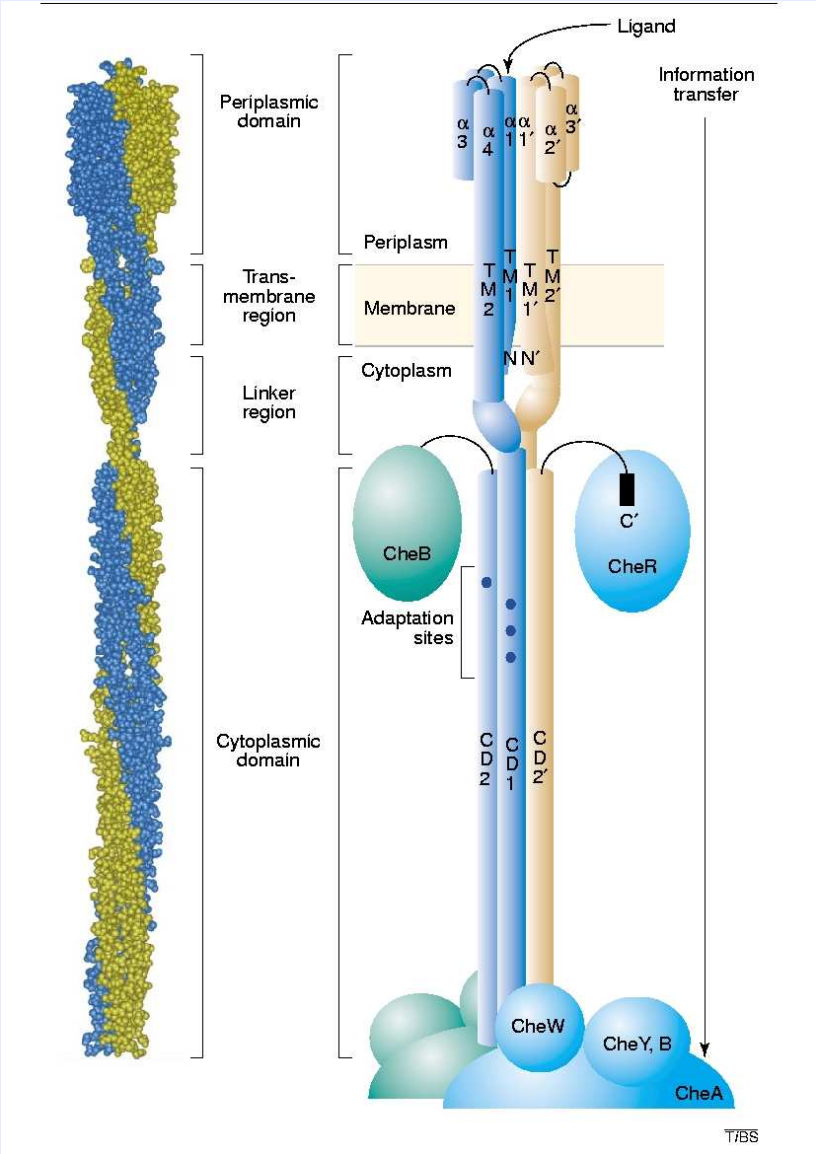
Clearly adaptation is essential for aggregation! This is probably also the case for *P. mirabilis* , but is not the case for amoeboid cells; they can aggregate in steady gradients without adaptation, but not in periodic waves of attractant.

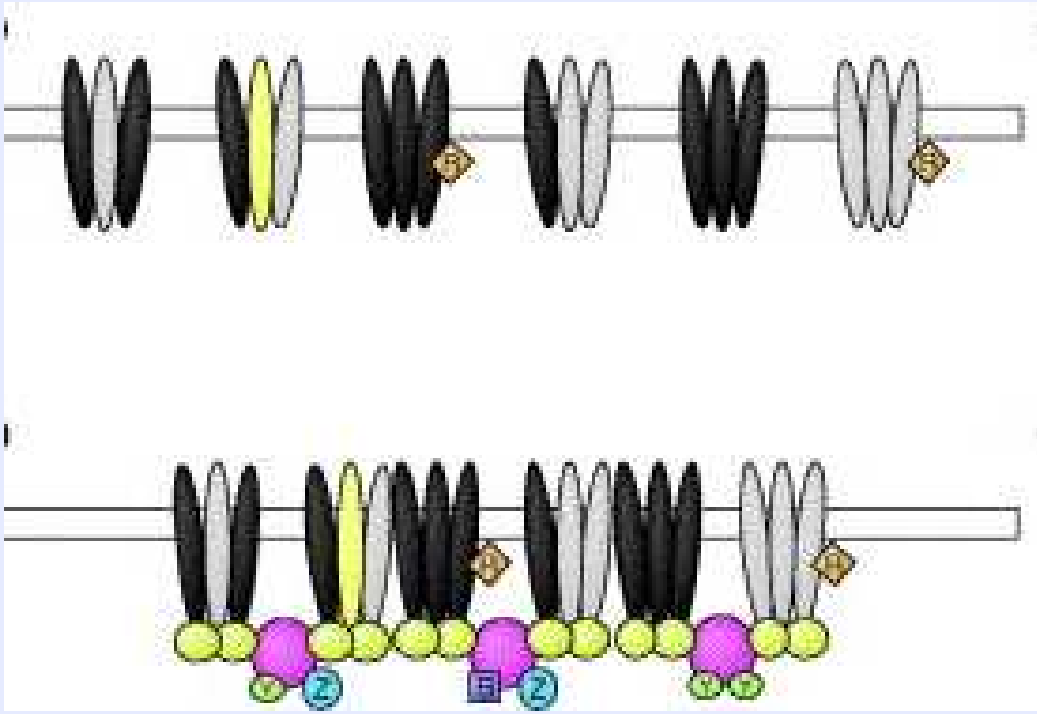
Signal transduction in *E. coli*



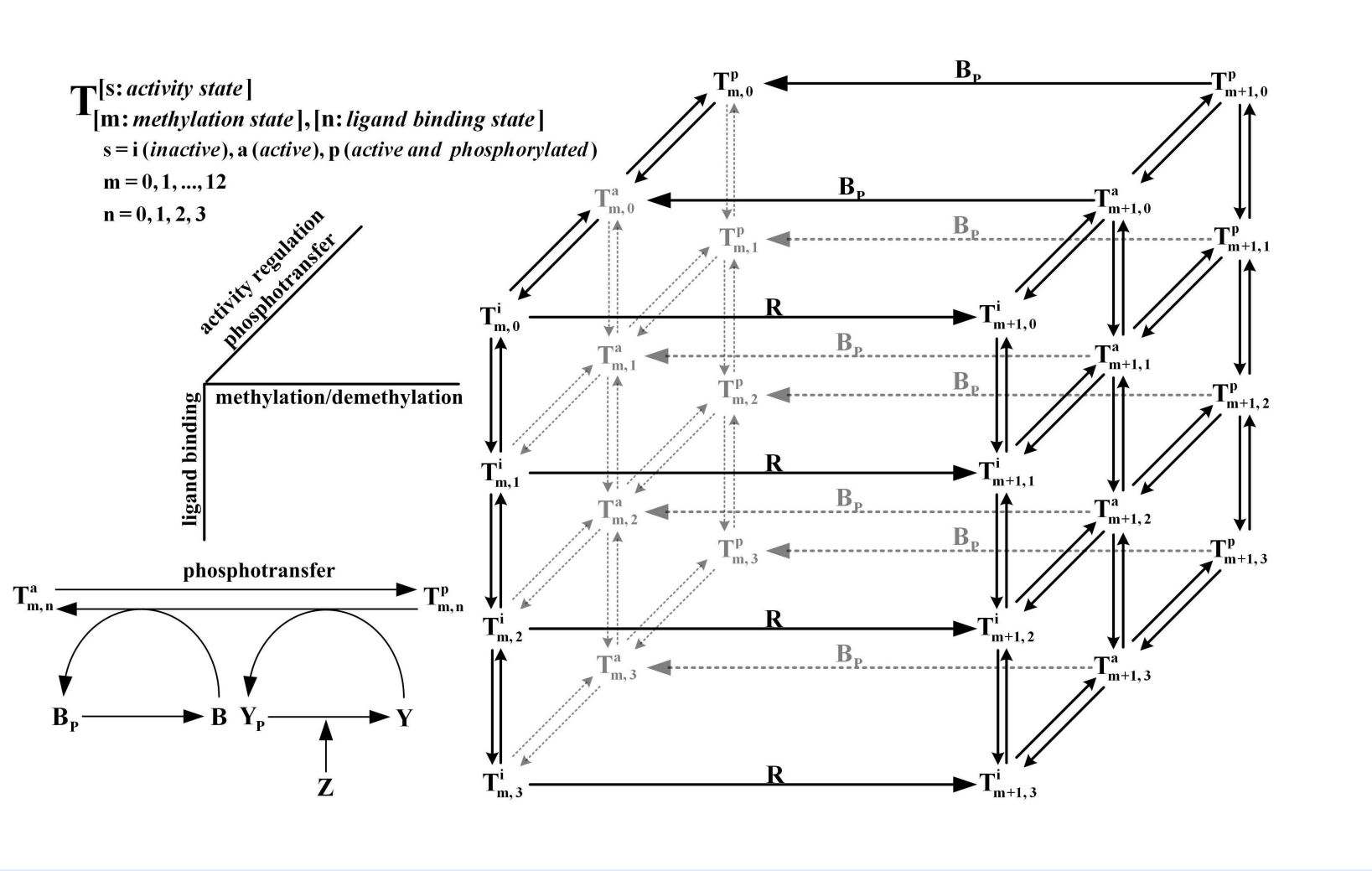
P. Spiro, et al., A model of excitation and adaptation in bacterial chemotaxis, PNAS, 94, 7263-7268, (1997).

The Tar receptor





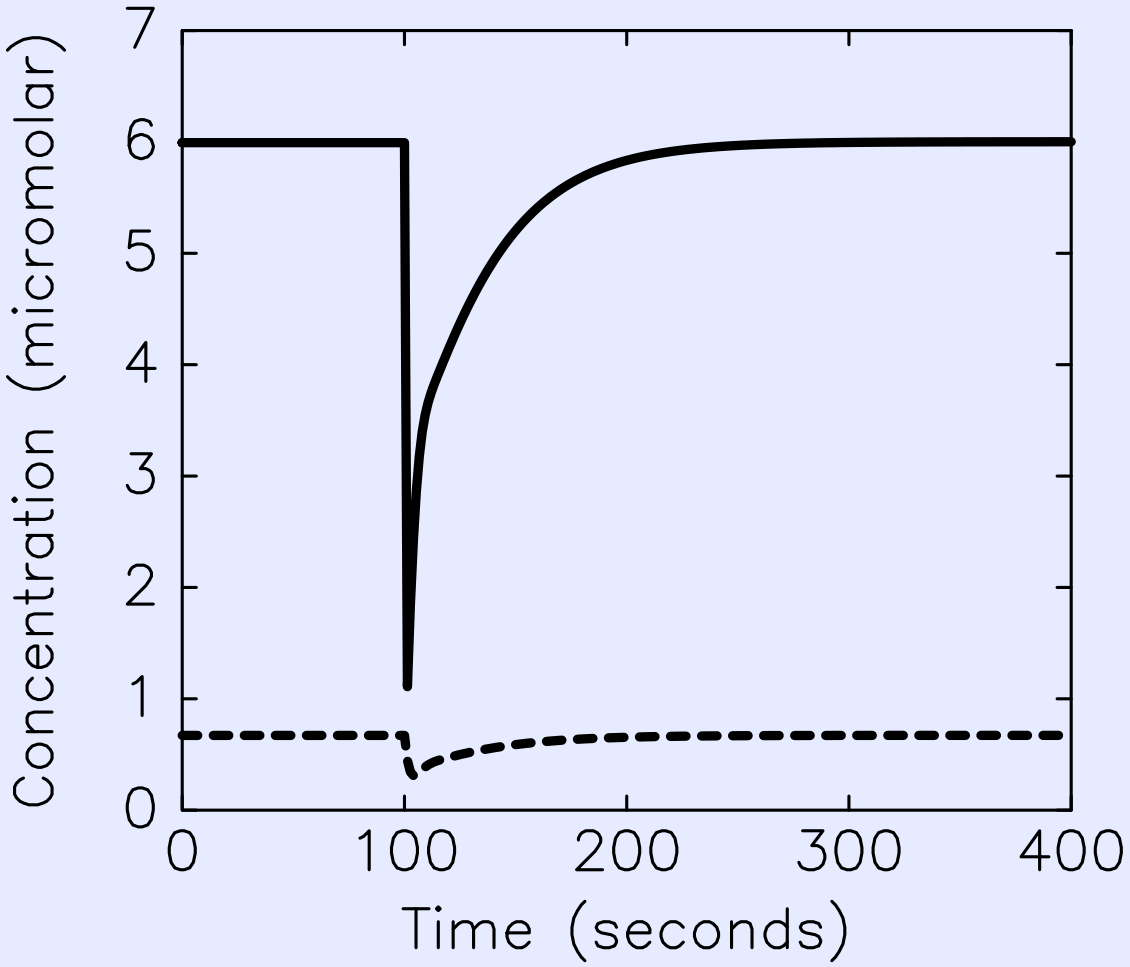
The underlying network



There are 158 variables, but on a relevant time scale this can be reduced to 16, and with some approximation, to 4.

Xiangrong Xin and Hans G. Othmer A 'trimer of dimers'- based model for the chemotactic signal transduction network in bacterial chemotaxis, Bull Math Biol (2012).

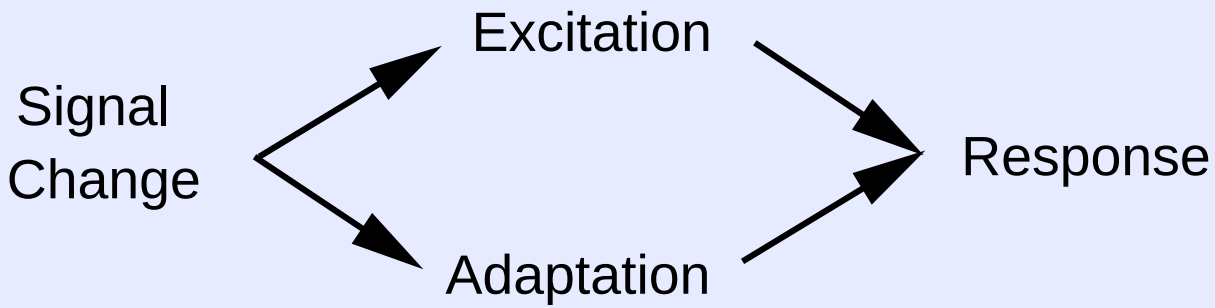
Simple response from a complex network



Even though the network is very complicated, the input-output behavior is very simple! This may be a common (and highly adaptive) phenomenon in signal transduction networks.

The big question is how to extract this from the full model!

A cartoon model for internal dynamics



$$\frac{dy_1}{d\tau} = \frac{g(S(\tau)) - (y_1 + y_2)}{\tau_E}, \qquad \frac{dy_2}{d\tau} = \frac{g(S(\tau)) - y_2}{\tau_A}, \qquad Response = h(y_1)$$

If $\tau_E << \tau_A$, then for $\tau >> \tau_E$, y_1 relaxes to $y_1 \sim \tau_A \dot{y}_2$. In a steady linear gradient of attractant

$$\frac{dS}{dt} = v \cdot \nabla S,$$

and $u \equiv \dot{y}_2$ is given by

$$u(T) = e^{-T/\tau_A} u(0) \pm \Omega f(T)$$

$$\Omega \equiv |v| S' \qquad f(T) = (1 - e^{-T/\tau_A})$$

Now we can see why adaptation is essential ..

For steps of fixed length we can write

$$u_n \equiv u(nT) = \lambda_0 u_{n-1} \pm \lambda_1$$

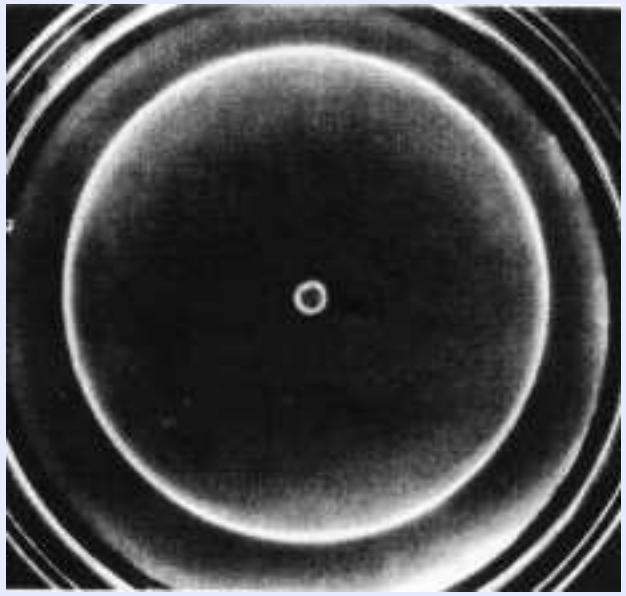
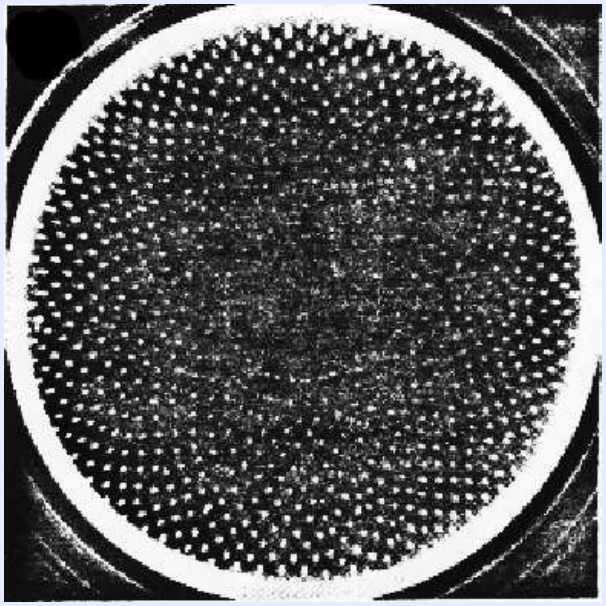
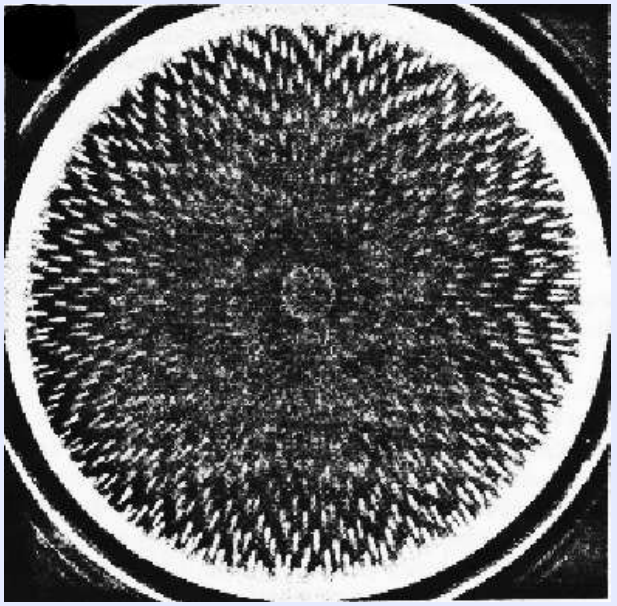
$$u_n = \lambda_0^n u_0 + \lambda_1 \left[\pm\lambda_0^{n-1} \pm \lambda_0^{n-2} + \cdots \pm \lambda_0\right]$$

Consider two realizations, right-left and left-right:

$$\begin{aligned} u^-(2T) &= e^{-T/\tau_A} u^+(T) - \Omega f(T) \\ &= e^{-2T/\tau_A} u(0) - \Omega f^2(T) \end{aligned}$$

$$\begin{aligned} u^+(2T) &= e^{-T/\tau_A} u^-(T) + \Omega f(T) \\ &= e^{-2T/\tau_A} u(0) + \Omega f^2(T). \end{aligned}$$

Pattern formation in *E. coli*

Basic experimental facts

- Cells are chemotactic towards aspartate; asp$^-$ cells do not aggregate
- Cells still use the ‘run-and-tumble’ strategy
- Cells can become nonmotile, which leads to stable spots
- Succinate is the primary carbon source
- Cells produce and secrete aspartate via the TCA cycle, but when starved they consume it
- Cells double every 2 hours

E. O. Budrene and H. C. Berg, Dynamics of formation of symmetrical patterns by chemotactic bacteria, Nature, 376, 49–53 (1995).

Are cell-based computational models feasible?

- For a single bacterium certainly ! We have one ...
- What about for spatial patterns?

  Consider the Budrene-Berg experiments, and suppose we innoculate with 1000 cells in a spot. Cells divide every two hours, so after 3 days we have

  $$10^3 \cdot 2^{36} \quad \sim \quad \times 10^{15} \text{ cells}$$

  Suppose we also need 10 internal variables for each cell.

  Thus .....

  A Monte Carlo simulation of the stochastic process may be feasible for the first few division cycles, but certainly not later !!

- We need a higher-level description .....

The phenomenological approach to chemotaxis

Let $\Omega \subset R^n$ be compact with smooth boundary, let n be the 'particle' density, and let v be the 'attractant' density.

$$\begin{aligned} n_t &= \nabla \cdot (\nabla n - n \nabla \Phi(v)) \\ &= \nabla \cdot (\nabla n - n \chi \nabla v) \\ v_t &= D \Delta v + f(n, v) \\ & n_n = v_n = 0 \end{aligned}$$

Chemotactic Sensitivity: $\chi \equiv \Phi_v(n, v, x, \dots)$

Chemotactic Velocity: $\mathbf{u}_c = \nabla \Phi = \chi \nabla v$

Fundamental question: Given a microscopic model of individual cells, how does one obtain the chemotactic sensitivity ?

The transport equation for a velocity-jump process

The transport equation in the absence of internal dynamics and signals

$$\frac{\partial}{\partial t}p(x,v,t) + v \cdot \nabla p(x,v,t) = -\lambda_0 p(x,v,t) + \lambda_0 \int_V T(v,v')p(x,v',t)dv' \quad (1)$$

$$= -\lambda_0 p(x,v,t) + \mathcal{T}p(x,v,t) \equiv \mathcal{L}p(x,v,t) \quad (2)$$

G. C Papanicolaou – Asymptotic analysis of transport processes, Bull. AMS, 81, 330-392 (1975).

- Identify the correct time and space scalings for the parabolic limit so that there are new time and space scales for which $\tau = \epsilon^2 t \qquad \xi = \epsilon x$
- Analyze the spectral properties of the turning operator $\mathcal{L}$
- Construct the outer solution:

$$p(\xi,\tau,v) = \sum_{k=0}^{\infty} \epsilon^k p_k(\xi,\tau,v)$$

The time and space scales for bacteria

We estimate a diffusion time scale as

$$\tau_{DIFF} \sim \frac{L^2}{D} = \frac{L^2 \lambda}{s^2}.$$

We can also define a characteristic drift time as

$$\tau_{DRIFT} = \frac{L}{s},$$

and we assume that the space scale L is such that the time scales are related as follows:

$$\tau_{RUN} \equiv \lambda^{-1} \ll \tau_{DRIFT} \ll \tau_{DIFF}. \tag{3}$$

For example, a characteristic speed for bacteria such as *E. coli* is $10 - 20\mu/\mathrm{sec}$, and $\lambda^{-1} \sim \mathcal{O}(1)$ second. On a length scale of 1 mm, $\tau_{DRIFT} \sim 50 - 100\,\mathrm{seconds}$ and $\tau_{DIFF} \sim 2500 - 10^4\,\mathrm{seconds}$. Therefore we have $\tau_{RUN} \sim \mathcal{O}(1)$ on the dimensional scale, and

$$\begin{aligned} \tau_{DRIFT} &\sim O(1/\epsilon), \\ \tau_{DIFF} &\sim O(1/\epsilon^2), \end{aligned}$$

Some technical hypotheses on $\mathcal{T}$

(T1) $T(v,v') \geq 0, \quad \int_V T(v,v')dv = 1, \quad$ and $\quad \int_V \int_V T^2(v,v')dv'dv < \infty$.

(T2) *There are functions u_0, ϕ, and $\psi \in \mathcal{K}$ with the properties that $u_0 \not\equiv 0$ and ϕ and ψ vanish at most on a set of Lebesgue measure zero, and such that for all $(v,v') \in V \times V$*

$$u_0(v)\phi(v') \leq \ T(v',v) \ \leq u_0(v)\psi(v').$$

(T3) $\|\mathcal{T}\|_{\langle 1 \rangle^\perp} < 1$, where $\langle 1 \rangle^\perp$ is the orthogonal complement in $L^2(V)$ of the span of 1.

(T4) $\int_V T(v,v')dv' = 1$

The effect of all these conditions is to make $\mathcal{L}_0$ a Perron-Froebenius operator, so that we can prove the following.

Theorem

Define $\mu_2 \equiv \lambda_0 \left(1 - \|\mathcal{T}\|_{\langle 1 \rangle^\perp}\right)$

Assume **(T1)-(T4)**; then

1. 0 is a simple eigenvalue of $\mathcal{L}_0$ and the corresponding eigenfunction is $\phi(v) \equiv 1$.

2. All nonzero eigenvalues satisfy $-2\lambda_0 <$ Re $\mu \leq -\mu_2 < 0$, and to within scalar multiples there is no other positive eigenfunction.

3. There is a decomposition $L^2(V) = \langle 1 \rangle \oplus \langle 1 \rangle^\perp$.

4. $\|\mathcal{L}_0\|_{\mathbf{L}(L^2(V), L^2(V))} \leq 2\lambda_0$.

5. $\mathcal{L}_0$ restricted to $\langle 1 \rangle^\perp \subset L^2(V)$ has an inverse $\mathcal{F}_0$ with norm

$$\|\mathcal{F}_0\|_{\mathbf{L}(\langle 1 \rangle^\perp, \langle 1 \rangle^\perp)} \leq \frac{1}{\mu_2}.$$

The rest is easy!

$$\frac{\partial p(x,v,t)}{\partial t} + v \cdot \nabla p(x,v,t) = -\lambda_0 p(x,v,t) + \lambda_0 \int_V T(v,v') p(t,x,v') dv'$$

$$\tau = \epsilon^2 t \qquad \xi = \epsilon x, \qquad p = p_0 + \epsilon p_1 + \epsilon^2 p_2 + \epsilon^n \cdots$$

$$\begin{aligned}
\epsilon^0 : \qquad & \mathcal{L}_0 p_0 &\equiv\ & -\lambda_0 p_0 + \lambda_0 \int_V T(\mathbf{v},\mathbf{v}') p_0 dv' = 0 \\
\epsilon^1 : \qquad & \mathcal{L}_0 p_1 &=\ & v \cdot \nabla p_0 \\
\epsilon^2 : \qquad & \mathcal{L}_0 p_2 &=\ & \frac{\partial p_0}{\partial \tau} + v \cdot \nabla p_1
\end{aligned}$$

$$\mathcal{L}_0 p_1 = v \cdot \nabla p_0 : \qquad \int_V (v \cdot \nabla p_0) dv = 0,$$

$$\boxed{p_1 = \mathcal{F}_0 \left(v \cdot \nabla p_0 \right)}$$

$$\mathcal{L}_0 p_2 = \frac{\partial p_0}{\partial \tau} + v \cdot \nabla p_1 : \qquad \int_V \left[\frac{\partial p_0}{\partial \tau} + v \cdot \nabla \left(\mathcal{F}_0 \left(v \cdot \nabla p_0 \right) \right) \right] dv = 0$$

$$\frac{\partial n_0}{\partial \tau} = \nabla \cdot \left(D \nabla n_0 \right)$$

Diffusion tensor:

$$D \equiv \frac{1}{\omega} \int_V v \mathcal{F}_0 v dv$$

If $T(\mathbf{v}, \mathbf{v}') = 1/\omega$, $\omega = |V|$ i.e. the redistribution is uniform, then

$$D = \frac{1}{\omega} \int_V \frac{vv}{\lambda_0} dv = \frac{s^2}{\lambda_0 n} I$$

General results

One can

- *prove in general that the diffusion tensor is positive definite*
- *derive necessary and sufficient conditions for* $D = \delta I$
- *derive error estimates for the diffusion approximation*
- add bias in the turning kernel to obtain the classical chemotaxis equation

1. Thomas Hillen and H. G. Othmer, SIAM JAM, 61, 751-775, (2000).
2. H. G. Othmer and T. Hillen, SIAM JAM, 62, 1222-1250, (2002).

The jump process with internal states and forces

Suppose that the internal variables $y \subset R^m$ involved in signal transduction evolve according the equations

$$\frac{dy}{dt} = f(y, S)$$

where S is the external signal. Inclusion of internal state variables y and external forces F in the jump process leads to the following transport equation.

$$\frac{\partial}{\partial t}p(x, v, y, t) + \ v \cdot \nabla_x p(x, v, y, t) + \ \nabla_v \cdot (Fp(x, v, y, t))$$

$$+\nabla_y \cdot (f_i(y, S)p(x, v, y, t)) = -\lambda(y)p(x, v, y, t) + \lambda(y) \int_V T_0(v, v', y)p(x, v', y2, t)dv'$$

The micro to macro step via moments

Assumptions

- Assume that excitation is fast, and define $z_2 = y_2 - S(x)$.
- Scale time and space as before

Then we have to solve

$$\begin{aligned} \epsilon^2 \frac{\partial p}{\partial t} \quad &+ \quad \epsilon \nabla_x \cdot (vp) + \frac{\partial}{\partial z_2} \left(-\frac{z_2}{t_a} - G'(S) \left(\epsilon \nabla S \cdot v + \epsilon^2 \frac{\partial S}{\partial t} \right) p \right) \\ &= \quad (\lambda_0 + a_1 z_2 + a_2 z_2^2 + \cdots) \left(-p + \int_V T(v, v') p(v') \, dv' \right) \end{aligned}$$

Moments

Define internal state moments as follows.

$$M_j = \int z_2^j \, p \, dz_2 \quad \forall \, j = 0, 1, 2, 3, \ldots, \qquad M = (M_0, M_1, M_2, \ldots)^t.$$

$$\epsilon^2 \frac{\partial}{\partial t} \mathbf{\Lambda M} + \epsilon \mathbf{v} \cdot \nabla_x \mathbf{\Lambda M} = \epsilon^2 \mathbf{B M} + \epsilon \mathbf{C M} + \mathbf{D M}.$$

Here

$$\mathbf{B} = -G'(S) \frac{\partial S}{\partial t} \mathbf{J}^t, \qquad \mathbf{C} = -G'(S)(\nabla S \cdot \mathbf{v}) \mathbf{J}^t,$$

and

$$\mathbf{D} = -\frac{1}{t_a} \text{diag}\,\{0, 1, 1, \ldots\} + \mathcal{L} \mathbf{\Lambda} (\lambda_0 \mathbf{I} + a_1 \mathbf{J} + a_2 \mathbf{J}^2 + \cdots),$$

where $\mathcal{L}$ is the turning operator, $\mathbf{\Lambda} : l^\infty(L^2(V)) \to l^\infty(L^2(V))$ is a diagonal scaling operator $\mathbf{\Lambda} = \text{diag}\left\{1, 1, \frac{1}{2}, \frac{1}{3}, \cdots\right\}$, and $\mathbf{J} : l^\infty(L^2(V)) \to l^\infty(L^2(V))$ is the shift operator.

The asymptotic analysis

Write $\mathbf{M}$ as an expansion in powers of ϵ as

$$\mathbf{M} = \mathbf{M}^0 + \epsilon \mathbf{M}^1 + \epsilon^2 \mathbf{M}^2 + \cdots$$

Define:

$$D_n = -\frac{1}{|V|\lambda_0} \int_V v \otimes \mathcal{B}v \, dv$$

and

$$\chi(S) = -\frac{a_1 t_a}{|V|\lambda_0} G'(S) \int_V v \otimes (t_a \lambda_0 \mathcal{L} - 1)^{-1} v dv,$$

For unbiased re-orientation

$$T(v, v') = \frac{1}{|V|}.$$

and

$$D_n = \frac{s^2}{N\lambda_0} I, \qquad \chi(S) = G'(S) \frac{a_1 s^2 t_a}{N\lambda_0 (1 + t_a \lambda_0)}.$$

The classical chemotaxis equation

$$\frac{\partial n}{\partial t} = \nabla_x \cdot \left(\frac{s^2}{N\lambda_0} \nabla_x n - G'(S) \frac{a_1 s^2 t_a}{N\lambda_0(1 + t_a\lambda_0)} n \nabla_x S \right).$$

If we include finite excitation time and directional persistence we obtain

$$\chi(S) = \frac{a_1 t_a}{|V|\lambda_0} G'(S) \int_V v \otimes (t_e\lambda_0\mathcal{A} - 1)^{-1} (t_a\lambda_0\mathcal{A} - 1)^{-1} v dv,$$

and this reduces to

$$\chi(S) = \frac{a_1 s^2 t_a G'(S)}{N\lambda_0(1 + (1-\psi_d)t_a\lambda_0)(1 + (1-\psi_d)t_e\lambda_0)}.$$

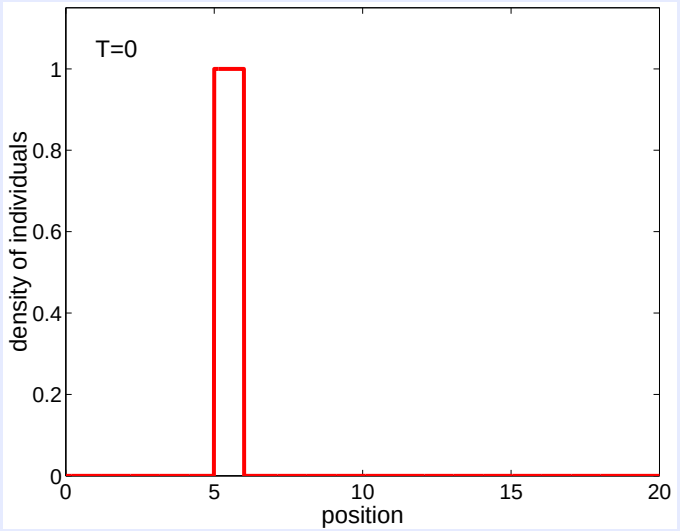
Thus

$$\frac{\partial}{\partial t} n = \nabla \cdot \left(\frac{s^2}{N(1-\psi_d)\lambda_0} \nabla n - \frac{a_1 s^2 t_a G'(S)}{N\lambda_0(1 + (1-\psi_d)t_a\lambda_0)(1 + (1-\psi_d)t_e\lambda_0)} n \nabla S \right)$$

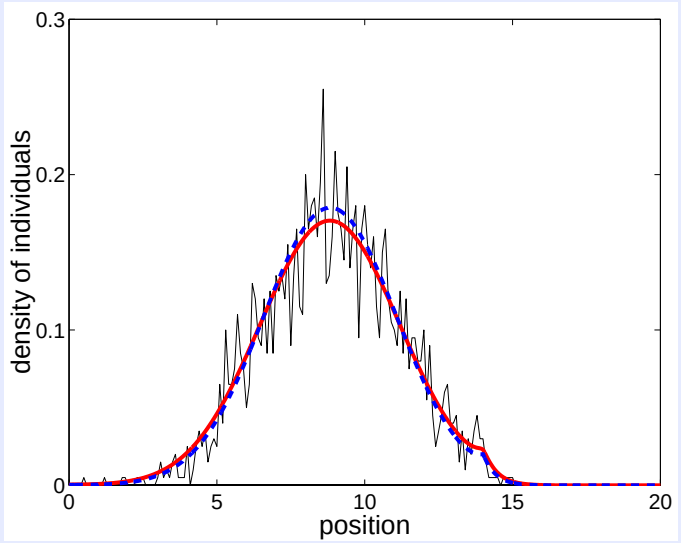
C. Xue and H. G. Othmer Multiscale models of taxis-driven patterning in bacterial populations, SIAM JAM, 70, 1, 133-167, (2009).

Numerical results

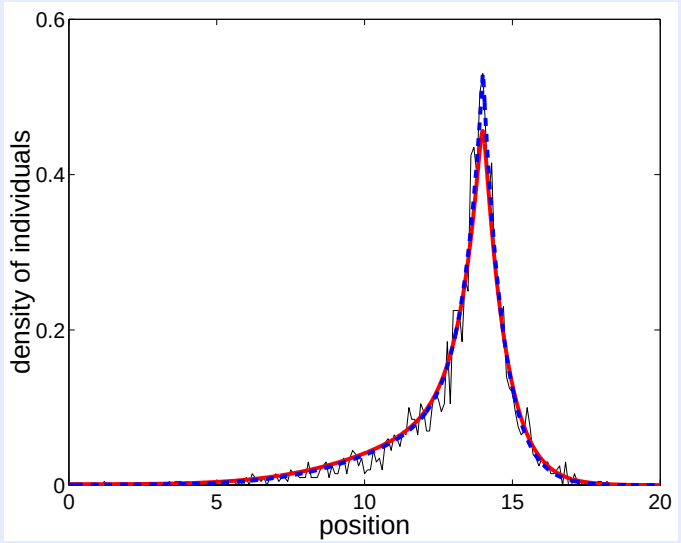
T=0



T=500



T=1500



black: stochastic simulation of the velocity jump process

red: macroscopic moment equations (and hyperbolic chemotaxis equation)

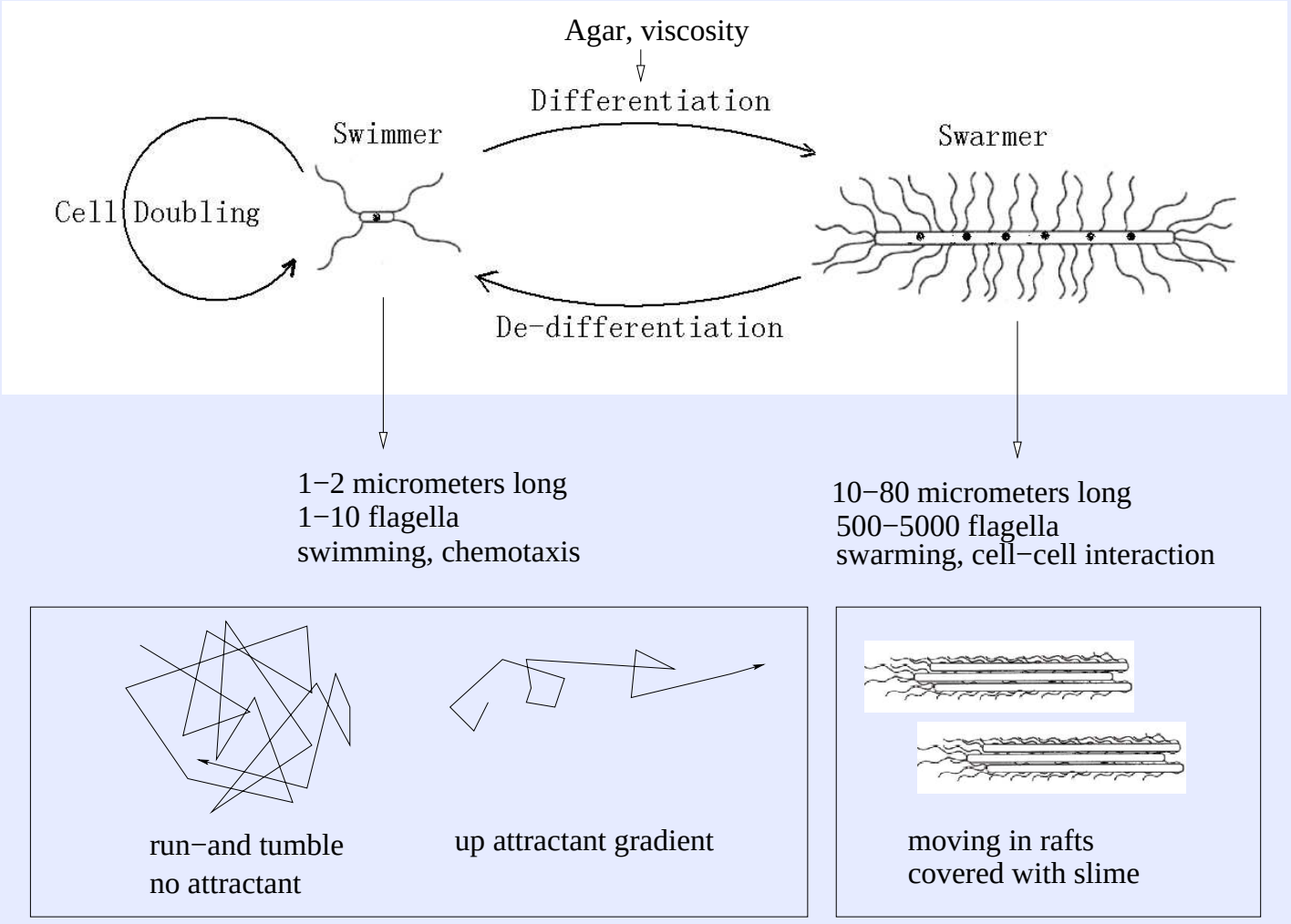
blue: classical chemotaxis equation

R. Erban and H. G. Othmer, SIAM JAM, 65, 361-391 , (2004).

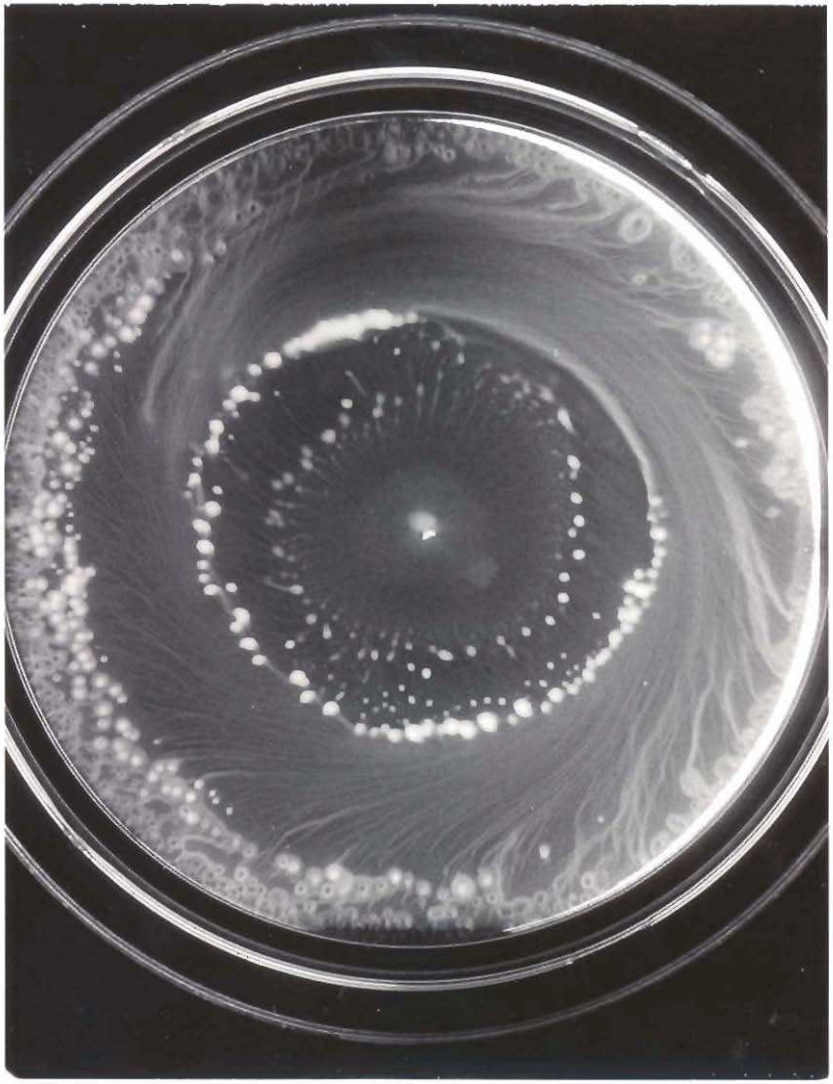
R. Erban and H. G. Othmer, Multiscale Modeling and Simulation, 3, 362-394, (2005).

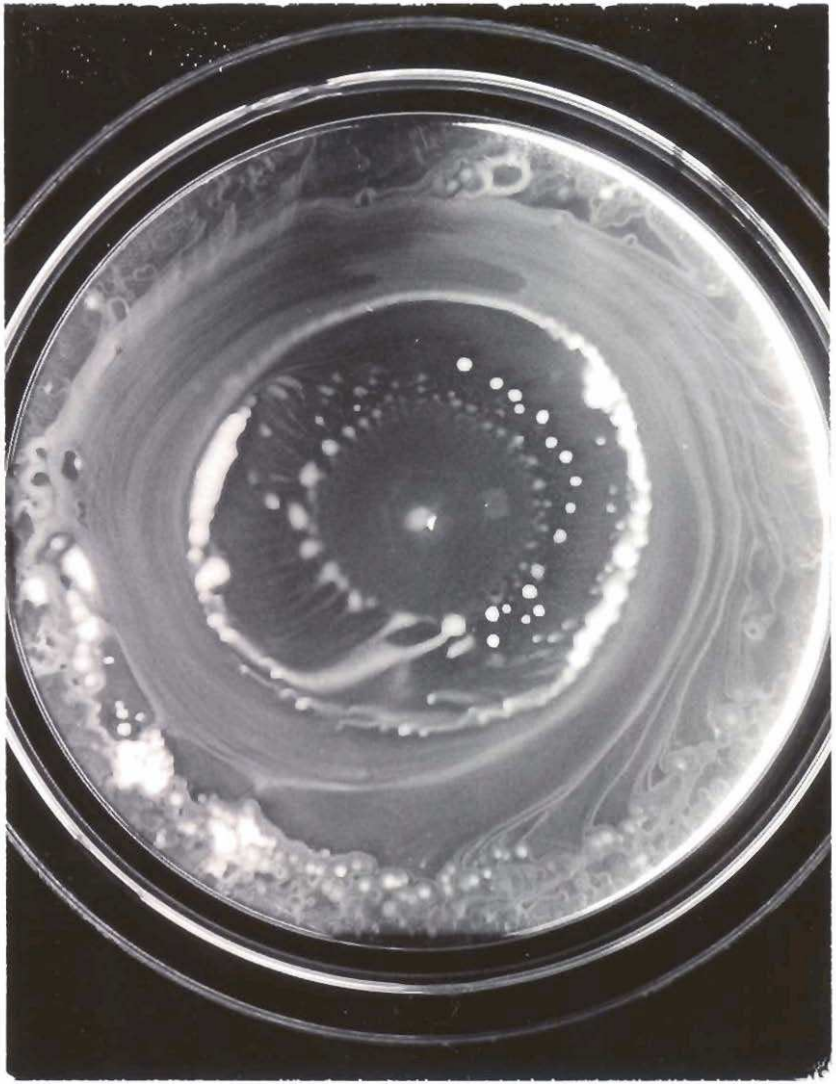
Basic facts about *Proteus mirabilis*

- In liquid medium, *P. mirabilis* cells are predominantly swimmers.
- When inoculated on hard surfaces, swimmers differentiate into swarmers.



New experimental results on patterning in the core

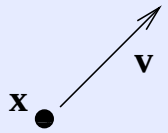




Photos courtesy of Elena Budrene

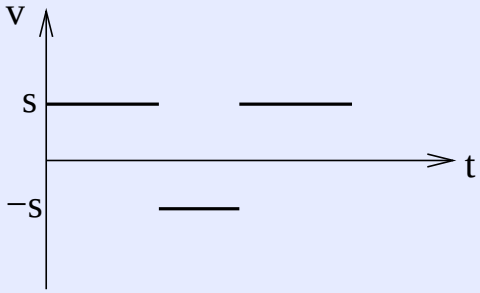
The hybrid cell-based model

- The movement of each cell is modeled by a velocity jump process.

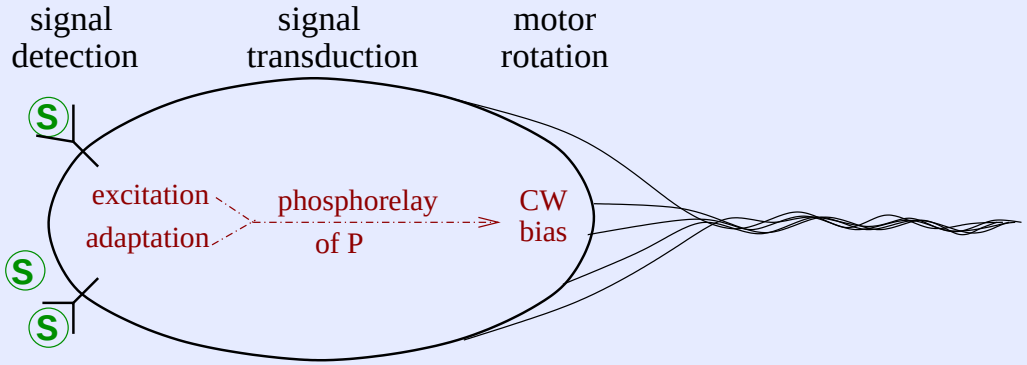


$\mathbf{x}$: position

$\mathbf{v}$: velocity



- The turning rate is determined by a simplified single cell signal transduction model.



$$\frac{dy_1}{dt} = \frac{G(c(\mathbf{x},t)) - (y_1 + y_2)}{t_e} \tag{4}$$

$$\frac{dy_2}{dt} = \frac{G(c(\mathbf{x},t)) - y_2}{t_a}$$

$$\lambda = \lambda_0 (1 - \frac{y_1}{\gamma_0 + |y_1|}) \tag{5}$$

- A cell divides into two daughter cells every 2 hours.
- The attractant and nutrient concentrations are governed by

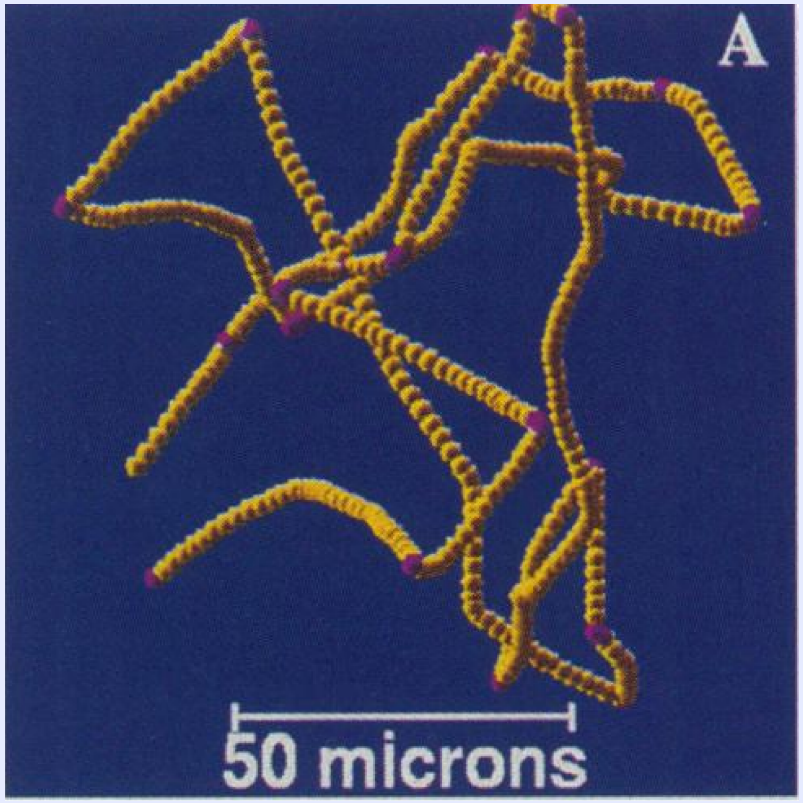
$$\frac{\partial c}{\partial t} = D_c \triangle c + \text{ secretion by cells } - \text{ degradation}$$
$$\frac{\partial f}{\partial t} = D_f \triangle c - \text{ uptake by cells}$$

If we assume constant rates,

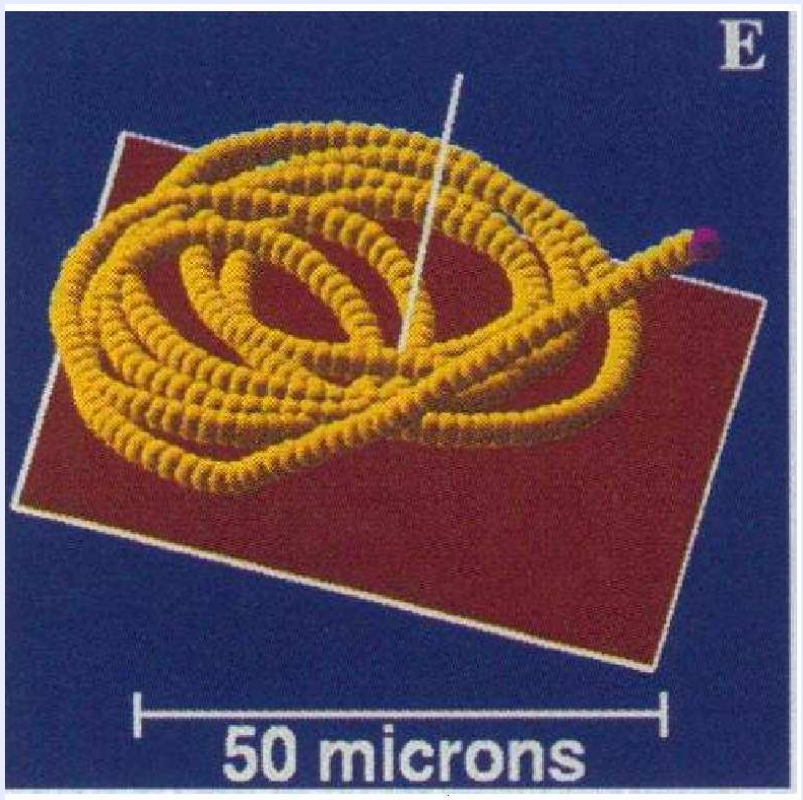
$$\frac{\partial c}{\partial t} = D_c \triangle c + \gamma \sum_{n=1}^{N} \delta(\mathbf{x} - \mathbf{x}^i) - \mu c \quad \text{in } D^2 \times \mathbb{R}^+$$
$$\frac{\partial f}{\partial t} = D_f \triangle c - k \sum_{n=1}^{N} \delta(\mathbf{x} - \mathbf{x}^i)) \quad \text{in } D^2 \times \mathbb{R}^+$$
$$+ \quad \text{Neumann BC: } \frac{\partial c}{\partial n} = \frac{\partial f}{\partial n} = 0 \quad \text{in } \partial D^2 \times \mathbb{R}^+$$

- The model was originally developed for *E. coli*, where it predicts very well the network and ring formation.

Cell tracks: the effect of the boundary



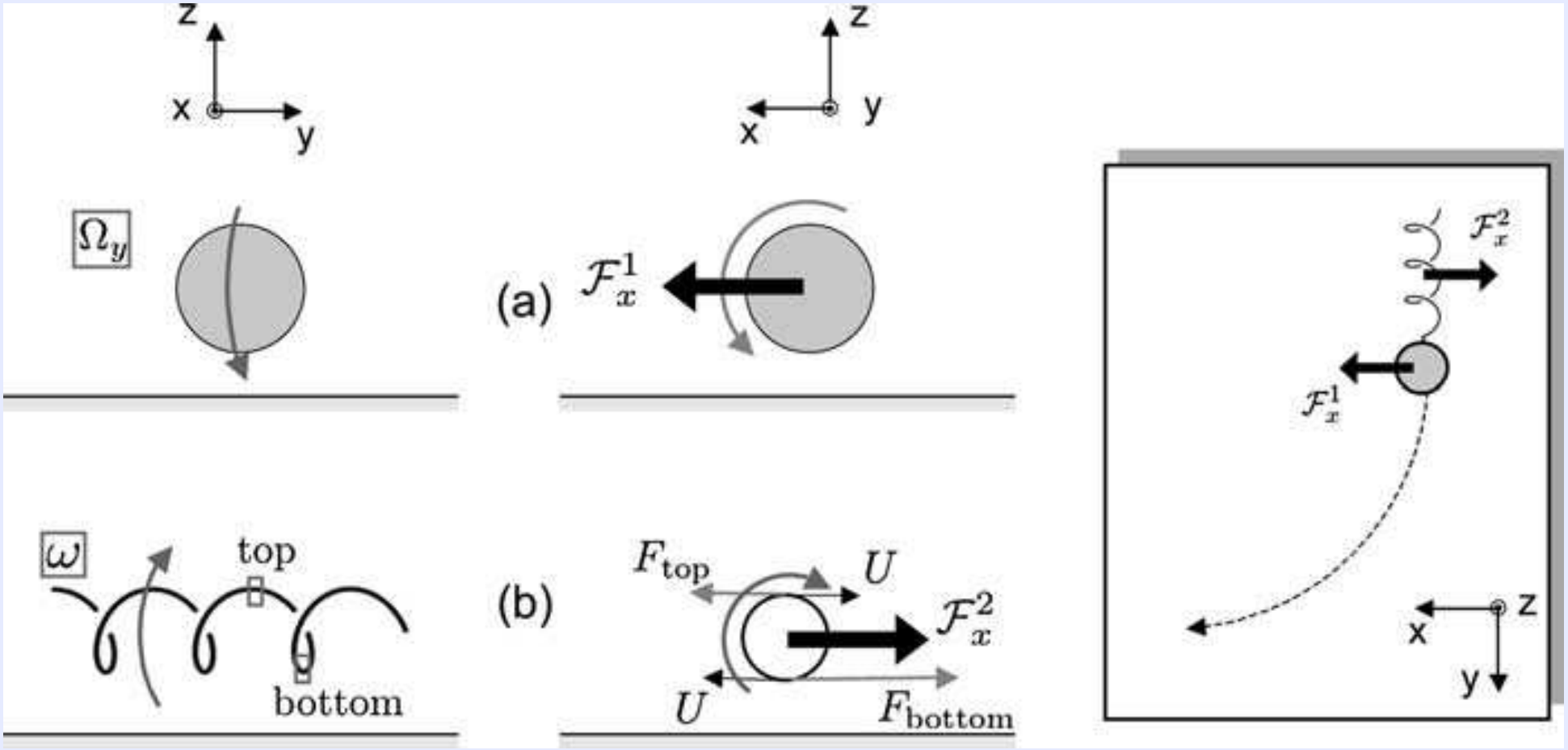
A track far from the surface



A track near the surface

Frymier *et. al.*, Three-dimensional tracking of motile bacteria near a solid planar surface, PNAS, 92, 1995

The physical picture



E. Lauga *et. al.*, Swimming in circles: Motion of bacteria near solid boundaries, Biophy. J., 2006

The mechanics

- Cell body length $1 - 2\mu m \approx 10^{-6} m$
  Cell "run" speed $10 \sim 30\mu m/s \approx 10^{-5} m/s$
  If we use viscosity of water $\nu \approx 10^{-6} m^2/s$ at 20^o C

$$Re = \frac{UL}{\nu} \approx 10^{-5} = 0.00001$$

  and so one can use the Stokes approximation .

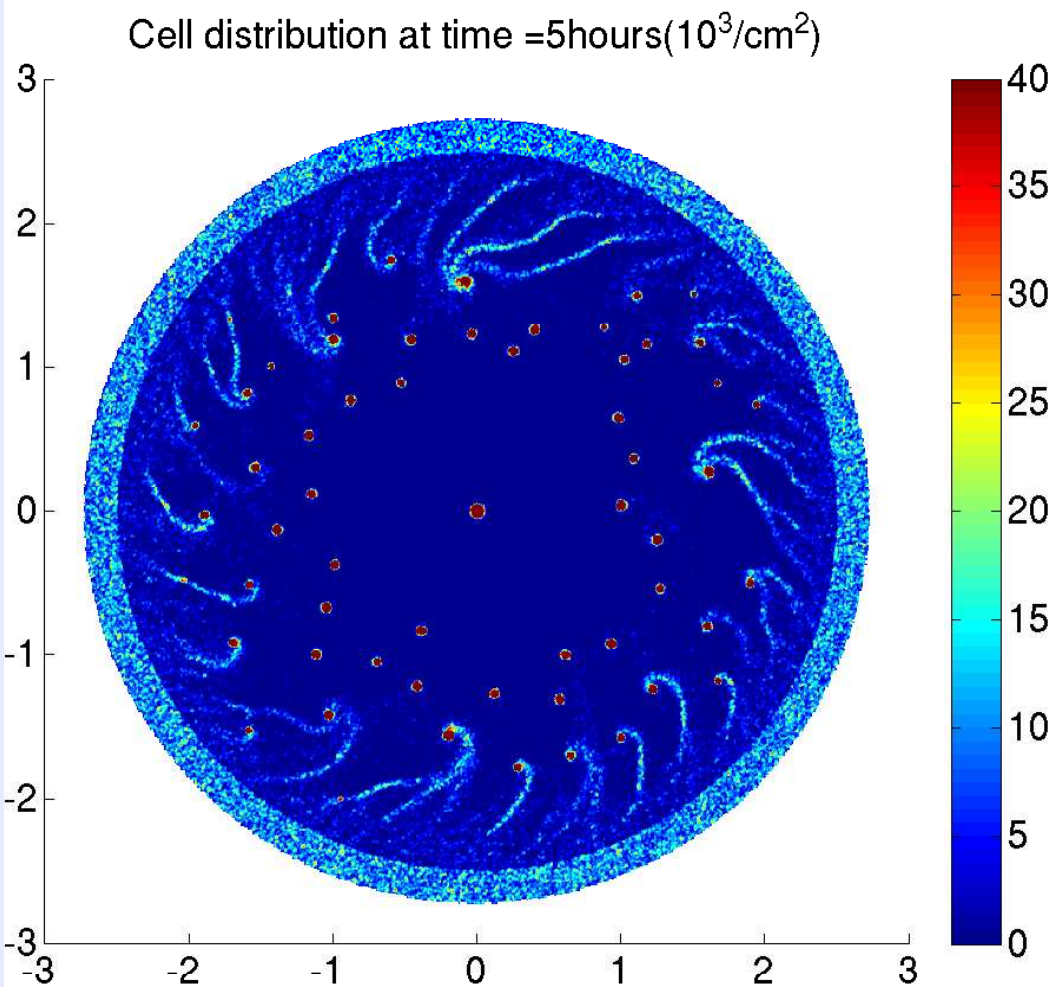
- Theoretically, one can solve for the velocity field and calculate the torque and force acting on each cell, but the system is complicated to solve.

- We simplify all this by assuming cells are well separated, and incorporate a constant bias to the right in the cell velocity:

$$\frac{d\mathbf{v}_i}{dt} = \varepsilon_b \frac{\mathbf{v_i}}{|\mathbf{v}_i|} \times \mathbf{n}$$

  where is the upward normal to the plane.

Comparison with experimental results



Swimming near a surface leads to ..

If the torque on a cell is given by $F = \omega_0 v \times \nu$, then

$$\frac{\partial}{\partial t} n = D_n \Delta n - \nabla \cdot \left[G'(S) n \left(\chi_0 \nabla S + \beta_0 (\nabla S)^{\perp} \right) \right],$$

where

$$D_n = \frac{s^2}{2\lambda_0(1-\psi_d) + \frac{2\omega_0^2}{\lambda_0(1-\psi_d)}},$$

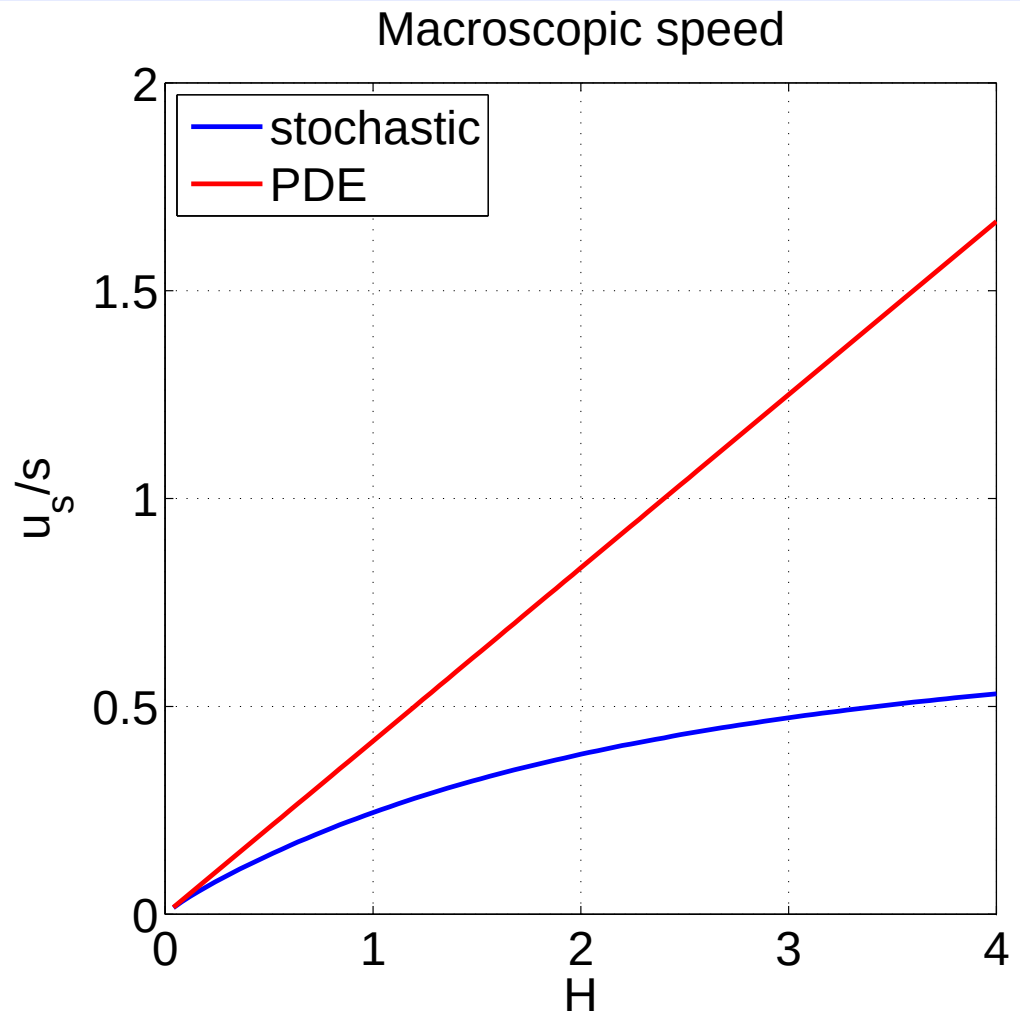
$$\chi_0 = \frac{a_1 s^2 (1-\psi_d)[\lambda_0(1-\psi_d)(\lambda_0(1-\psi_d) + \frac{1}{t_a}) - \omega_0^2]}{2((\lambda_0(1-\psi_d) + \frac{1}{t_a})^2 + \omega_0^2)(\lambda_0^2(1-\psi_d)^2 + \omega_0^2)},$$

$$\beta_0 = \frac{\omega_0 a_1 s^2 (1-\psi_d)(2\lambda_0(1-\psi_d) + \frac{1}{t_a})}{2((\lambda_0(1-\psi_d) + \frac{1}{t_a})^2 + \omega_0^2)(\lambda_0^2(1-\psi_d)^2 + \omega_0^2)},$$

and

$$\nabla S = \begin{pmatrix} \frac{\partial S}{\partial x_1} \\ \frac{\partial S}{\partial x_2} \end{pmatrix}, \quad (\nabla S)^{\perp} = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \nabla S.$$

Problems with large gradients



C. Xue, E. Budrene and H. G. Othmer, Radial and spiral stream formation in Proteus mirabilis colonies, PLoS Comp Biol, 7, 1-11, (2011).

Some insight into why it doesn't work ..

Recall the internal dynamics

$$\begin{aligned}\frac{dz_1}{dt} &= \frac{-z_1 - z_2}{t_e} \\ \frac{dz_2}{dt} &= -\frac{z_2}{t_a} - G'(S(x(t),t))\left(\nabla S \cdot \mathbf{v} + \frac{\partial S}{\partial t}\right)\end{aligned}$$

and the chemotactic velocity

$$\left[\frac{a_1 s}{N\lambda_0(1+(1-\psi_d)t_a\lambda_0)(1+(1-\psi_d)t_e\lambda_0)}\right] s t_a G'(S)\nabla S$$

Thus if the Lagrangian derivative of the signal is too large the internal state cannot adapt rapidly enough. In principal one simply has to retain higher moments, as the following show.

But there is a phenomenological 'solution' to this ..

A phenomenological fix ..

$$S + R \underset{k^-}{\overset{k^+}{\rightleftarrows}} \overline{SR}$$

The evolution equation for the bound receptor density is

$$\frac{d}{dt}\overline{SR} = k^+ S \cdot R_0 - (k^+ S + k^-)\overline{SR} \tag{6}$$

The input G can be taken as proportional to the fraction of receptors occupied

$$G(S) = G_0(\frac{S}{K_D + S}) \tag{7}$$

where $K_D = k^-/k^+$. We have to compare the time scales

$$\tau_{sig} \equiv \frac{S}{s|\nabla S|} \quad \tau_{rec} \equiv \frac{1}{k^+ S + k^-}$$

and if $\tau_{sig} < \tau_{rec}$ then the equilibration assumption is not valid since the receptors cannot process the signal.

A phenomenological fix ..

Define the rates of change

$$\frac{\delta S}{\delta t}_{(sig)} =\equiv \frac{s|\nabla S|}{S}$$

and

$$\frac{\delta S}{\delta t}_{(rec)} \equiv \frac{S}{k^+ S + k^-}$$

A more ‘correct ’ Lagrangian derivative of the signal, which appears in the analysis using the cartoon model, is

$$min\{s\nabla S, (k^+ S + k^-)S\} \tag{8}$$

Of course the *min* function in (**??**) is difficult to handle analytically, so an alternate form that captures the essential properties is

$$\frac{1}{\frac{1}{\Omega} + \frac{1}{s\nabla S}} = \frac{s\Omega\nabla S}{\Omega + s\nabla S}$$

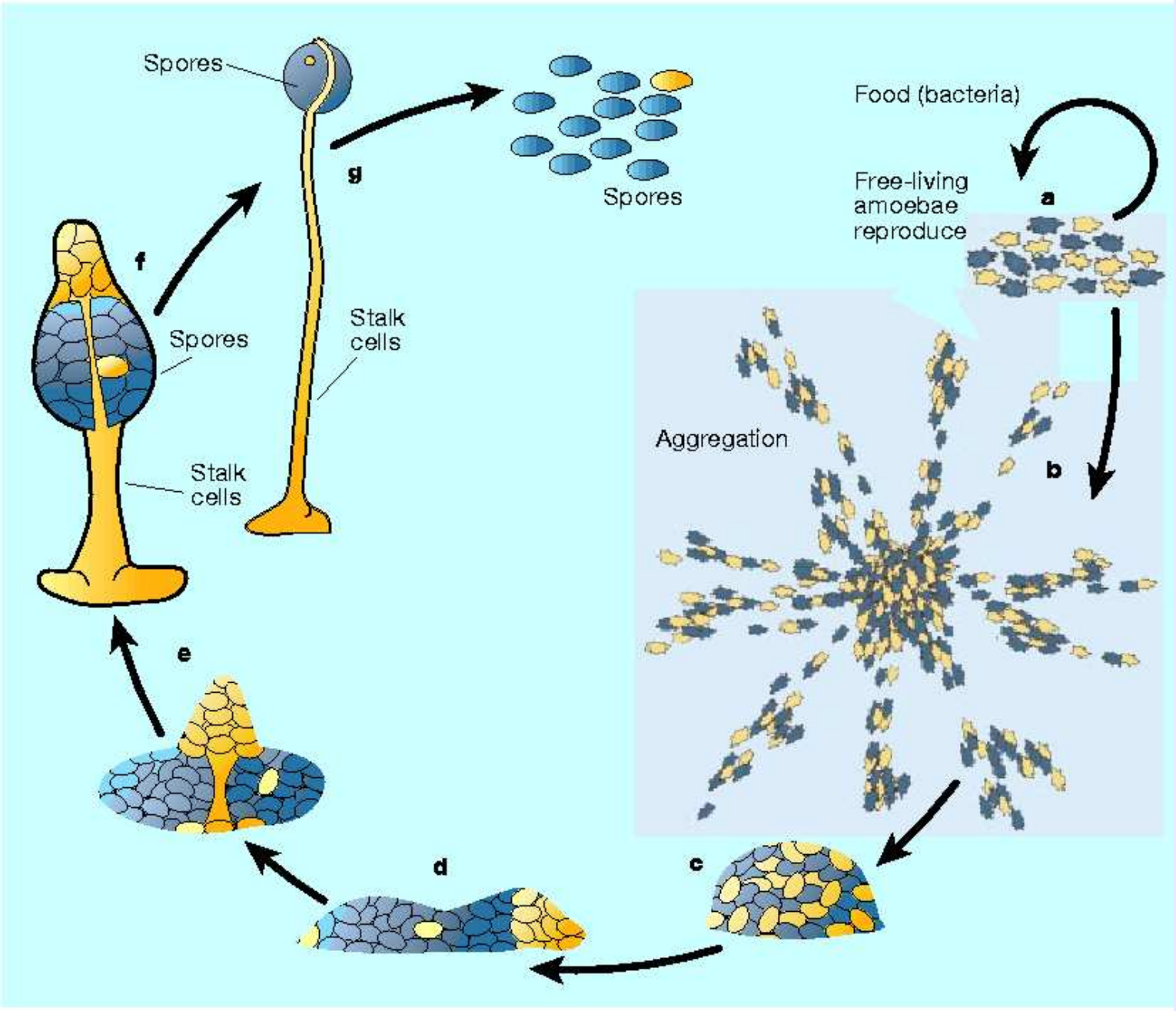
wherein

$$\Omega \equiv (k^+ S + k^-)S.$$

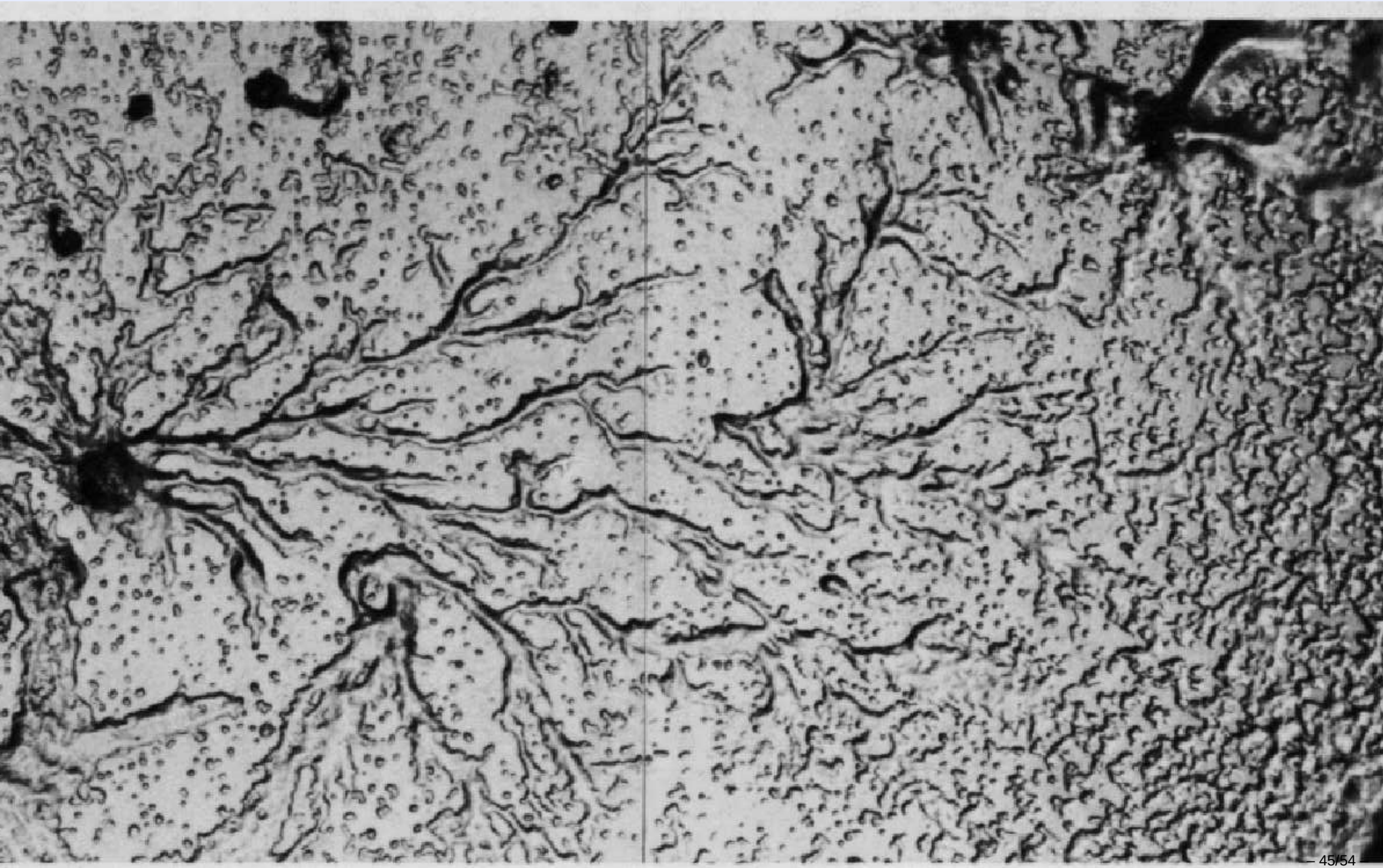
The amoeboid problem –

– crawling is harder than swimming!

The life cycle of *Dictyostelium discoideum*



Aggregation patterns

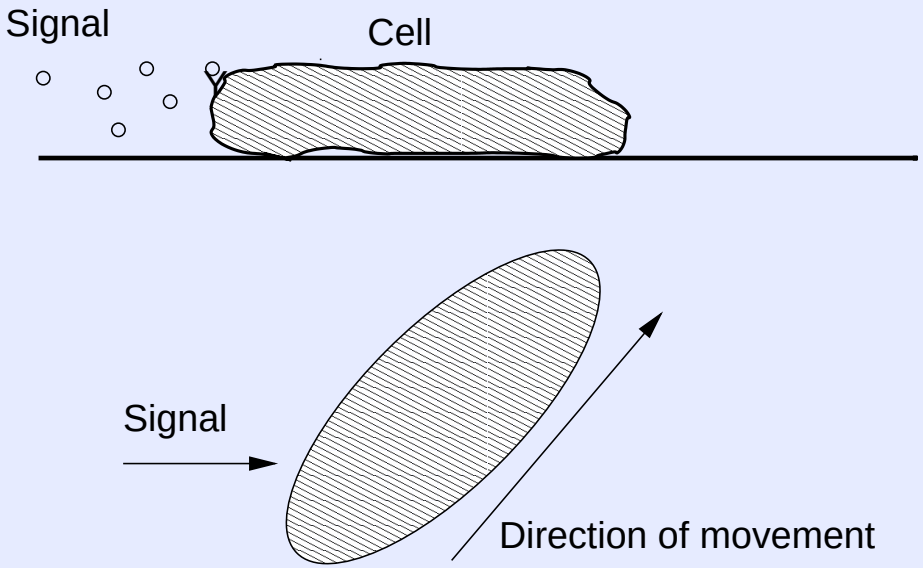


How do we model and analyze these behaviors, and what do we learn from that process?

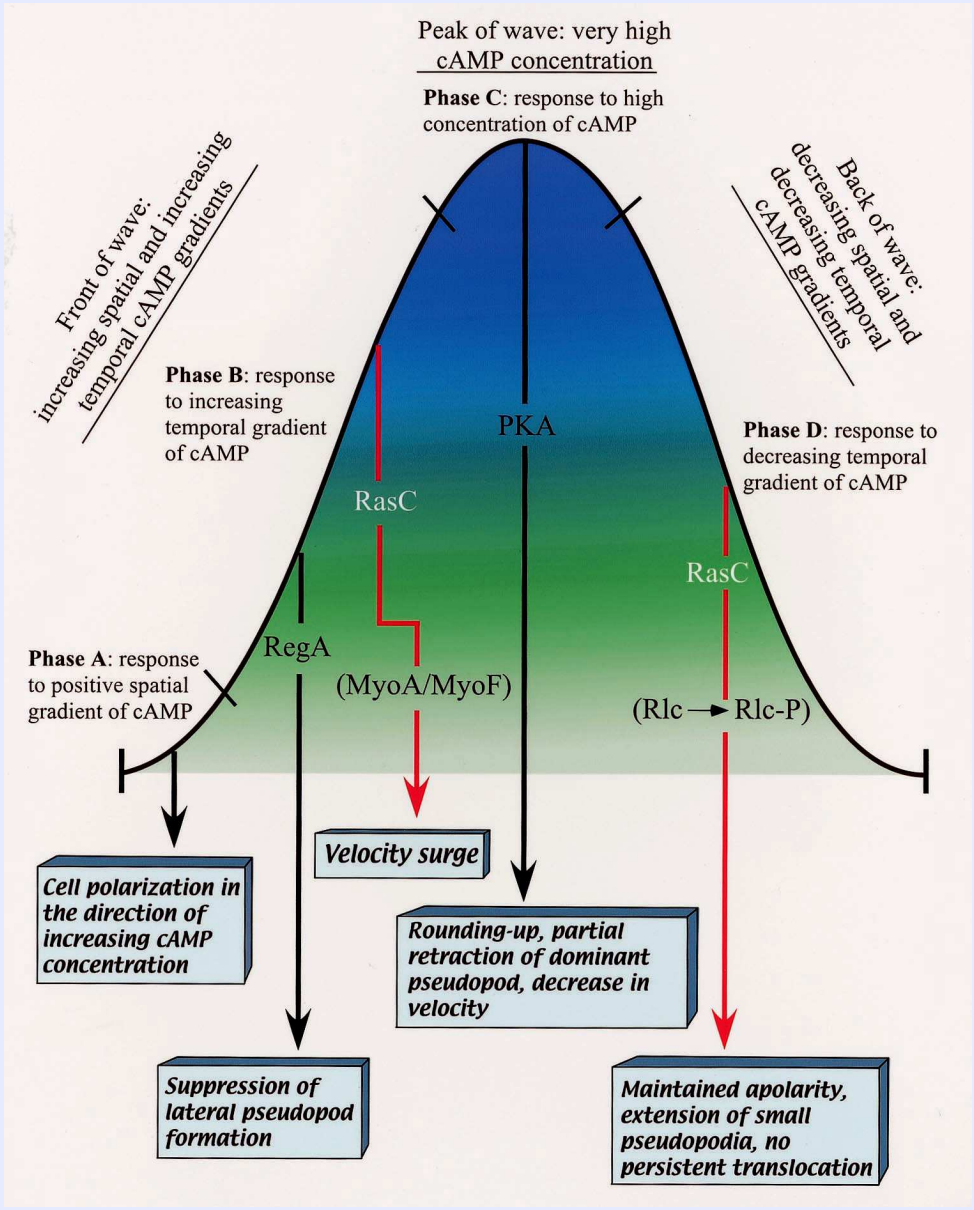
What cellular-level processes are involved in producing the population-level aggregation patterns, or in other words, what must a cell do to have a chance of passing on its genes?

- Some cells (or small groups of cells) must become pacemakers
- A cell must detect the external signal cyclic adenosine 3',5'-monophospahte (cAMP)
- It must choose a direction in which to move
- Cells must amplify and relay the signal, and adapt to the ambient signal
- They must move for an appropriate length of time
- Eventually a cell interacts with its neighbors and moves collectively, first in pairs, then in streams, ..
- Slightly later it has to 'decide' what type of cell to become in the final fruiting body. This is a collective decision reached by the community (absent cheaters!).
- The entire aggregate has to stop migrating and erect the fruiting body

Orientation and movement in a wave



In an aggregation wave ...

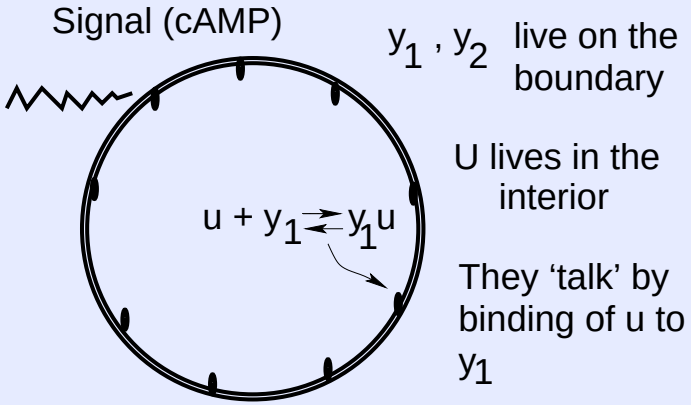


AND ... A cell also stimulates itself when it signals!

Some basic questions concerning direction sensing and polarization

- What is the source of the sensitivity and amplification (cells can respond to differences as small as 2% front-to-back and produce a much larger –estimated to be six-fold– intracellular gradient)?
- What is the role of actin polymerization in the amplification and the ‘imprinting’ of directionality?
- What are the long-term morphological changes that characterize polarization?
- How do we model these processes at a microscopic level? Are stochastic effects negligible, important, dominant ..? Note that forces and the motile machinery that generates them are crucial here.
- Can we embed the microscopic processes/models in useful macroscopic equations?

A spatially-distributed cartoon model



$$\frac{dy_1}{d\tau} = \frac{S(\tau) - (y_1 + y_2)}{\tau_e} - k^+ y_1 u + k^- y_{\bar{1}} u$$

$$\frac{dy_2}{d\tau} = \frac{S(\tau) - y_2}{\tau_a}$$

$$\frac{\partial u}{\partial \tau} = \Delta u \qquad \text{in } \Omega$$

$$-D\frac{\partial u}{\partial n} = k^+ y_1 u - k^- y_{\bar{1}} u \qquad \text{on } \partial\Omega$$

How does one define a transport equation when the internal state lives in a Banach space?

Signal transduction for orientation ..

$$\frac{\partial y_1}{\partial t}(\theta,t) = \frac{S(\theta,t) - y_1(\theta,t) - y_2(\theta,t)}{t_e}$$
$$\frac{\partial y_2}{\partial t}(\theta,t) = \frac{S(\theta,t) - y_2(\theta,t)}{t_a}$$

Let $x = (x_1, x_2)$ be the centroid position and write

$$S(\theta,t) = S\big(x_1 + R_0\cos\theta, x_2 + R_0\sin\theta, t\big)$$

$$S(\theta,t) \sim S(x) + R_0\cos\theta\frac{\partial S}{\partial x_1}(x) + R_0\sin\theta\frac{\partial S}{\partial x_2}(x)$$

$$\begin{pmatrix} p_0(x,t) \\ q_0(x,t) \\ q_1(x,t) \\ q_2(x,t) \end{pmatrix} = \int_0^{2\pi} \begin{pmatrix} y_1 \\ y_2 \\ y_2 cos\theta \\ y_2 sin\theta \end{pmatrix} d\theta$$

Moving cells ..

$$\begin{aligned}
\frac{dq_0}{dt} &= \frac{2\pi S(x) - q_0}{t_a} \\
\frac{dq_1}{dt} &= \frac{R_0\pi\frac{\partial S}{\partial x_1}(x) - q_1}{t_a} \\
\frac{dq_2}{dt} &= \frac{R_0\pi\frac{\partial S}{\partial x_2}(x) - q_2}{t_a} \\
\frac{dp_0}{dt} &= 2\pi\frac{\partial S}{\partial x_1}(x)v_1 + 2\pi\frac{\partial S}{\partial x_2}(x)v_2 + 2\pi\frac{\partial S}{\partial t}(x) - \frac{p_0}{t_a}
\end{aligned}$$

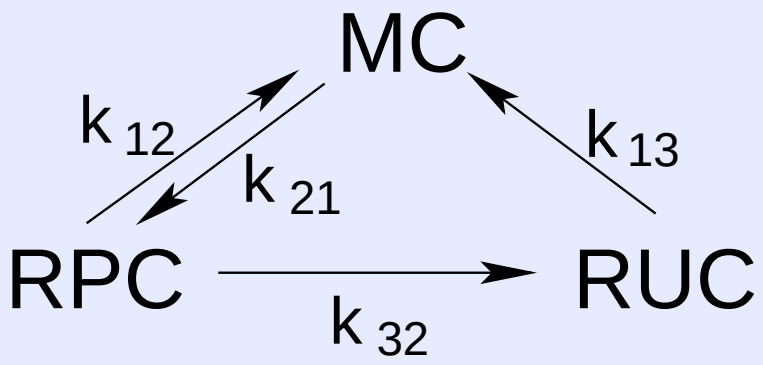
Newton's Law

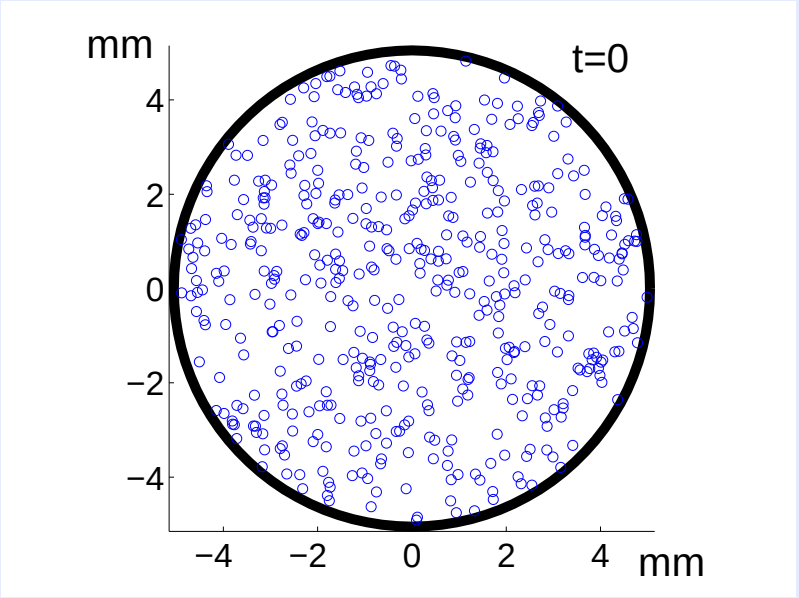
$$\frac{dx_1}{dt} = v_1 \qquad \frac{dx_2}{dt} = v_2.$$

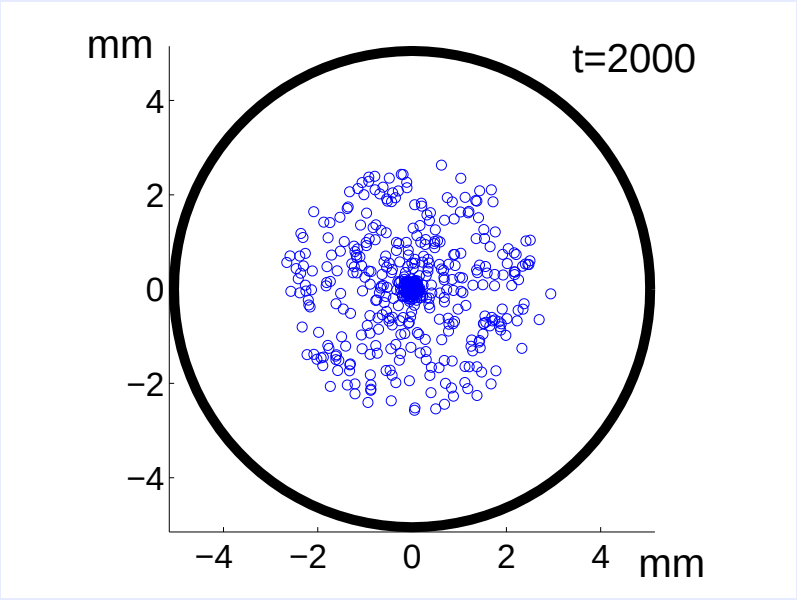
$$\frac{dv_1}{dt} = \frac{\gamma q_1 - v_1}{t_d} \qquad \frac{dv_2}{dt} = \frac{\gamma q_2 - v_2}{t_d}$$

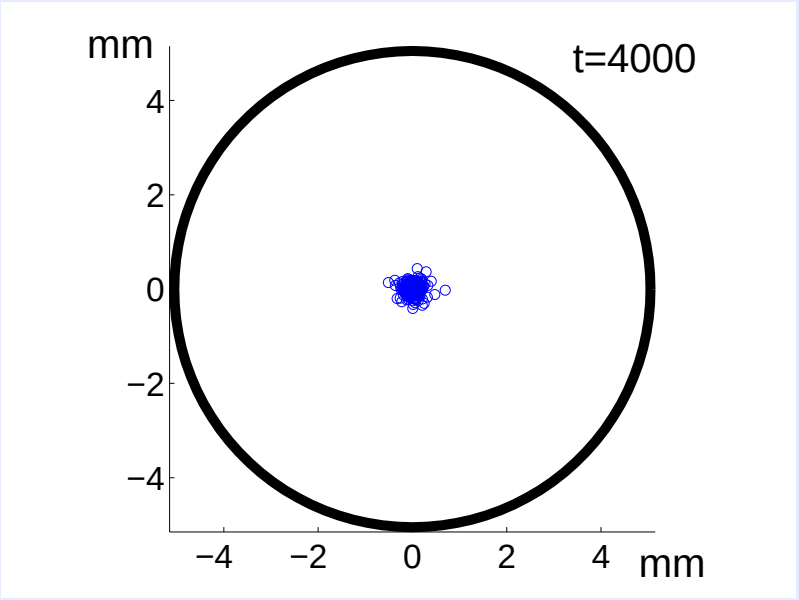
This suffices for a steady gradient, but doesn't solve the back-of-the-wave problem.

For that we introduce resting states...



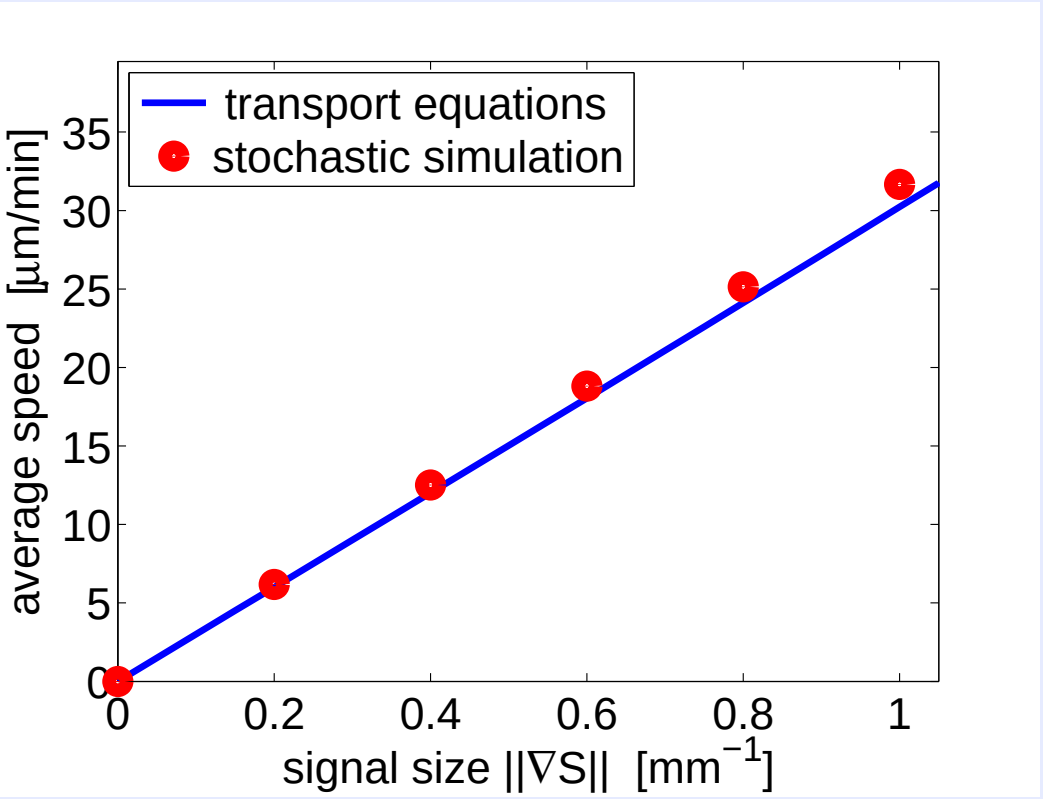


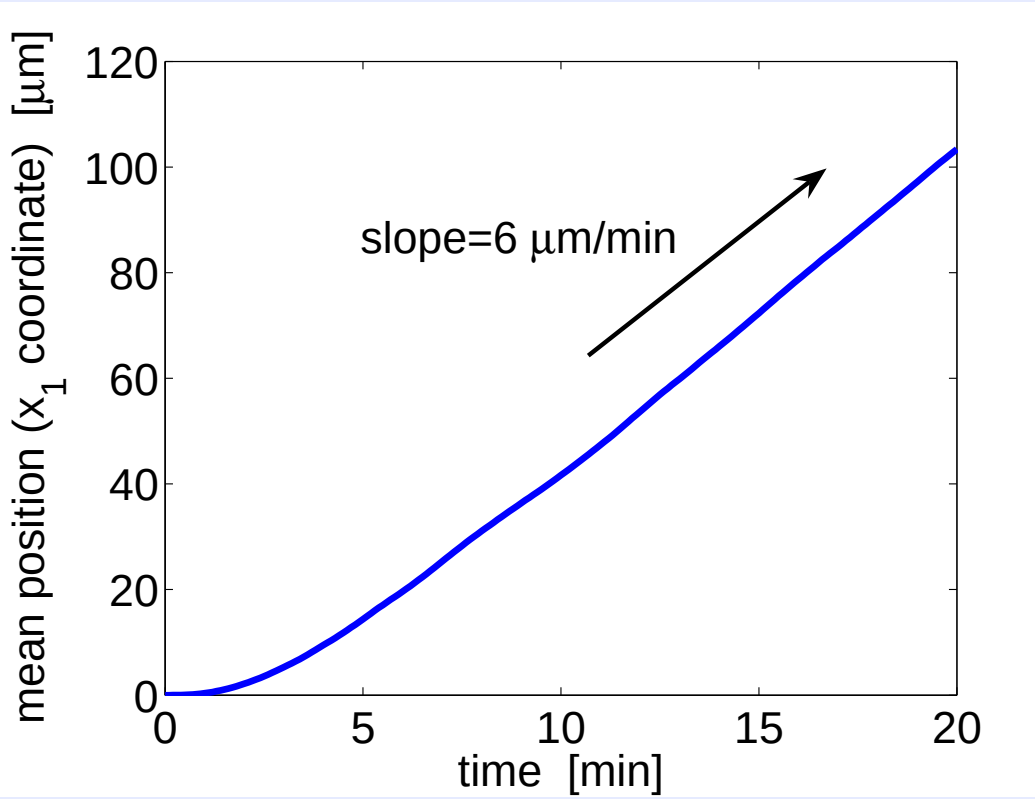




This solves the back of the wave problem.

Comparison of predictions





Radek Erban and Hans G. Othmer Taxis equations for amoeboid cells, J. Math. Biol., 54, 847-885, (2007).

Conclusions ..

- For simple systems such as bacteria one can derive PKS equations from the transport equation with internal state variables, and thereby derive the chemotactic sensitivity in terms of characteristics of the microscopic motion.

- For amoeboid cells such as Dd, its harder to obtain reduced equations, but the moment equations reflect the population-level behavior well.

- Whether PKS can be obtained from the transport equations is still open ...