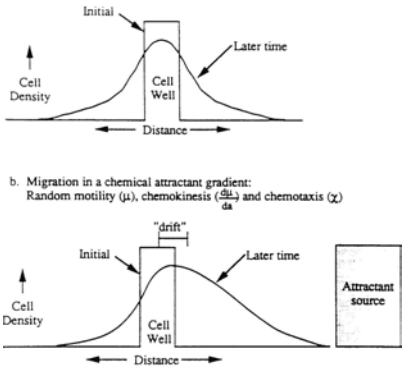
From Microscopic Parameters to Macroscopic Balances

(Expression for the Chemotactic Flux)

Random Motility and Chemotaxis



Macroscopic Flux (1)

$$\frac{\partial n^+}{\partial t}+\frac{\partial}{\partial x}(vn^+)=\lambda^- n^- -\lambda^+ n^+$$
$$\frac{\partial n^-}{\partial t}-\frac{\partial}{\partial x}(vn^-)=\lambda^+ n^+ -\lambda^- n^-$$

total cell density: $n \equiv n^+ + n^-$

flux: $j \equiv v(n^+ - n^-)$

steady state :

$$j_{eq}=\frac{-v^2\frac{\partial n}{\partial x}-nv\frac{\partial v}{\partial x}-vn(\lambda^+-\lambda^-)}{(\lambda^-+\lambda^+)}$$

Macroscopic Flux (2)

$T_p \equiv [\lambda^- + \lambda^+]^{-1}$ persistence time

$\mu \equiv T_p v^2$ random motility coefficient

$V_c \equiv T_p v(\lambda^- - \lambda^+)$ chemotactic velocity

$$j_{eq} = -\mu \frac{\partial n}{\partial x} + V_c n - T_p v n \frac{\partial v}{\partial x}$$

in phenomenological models

$j_{eq} = -\mu \frac{\partial n}{\partial x} + \underline{\alpha} n$

Three contributions to flux:

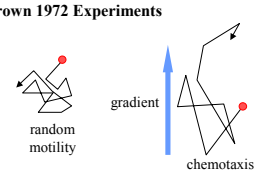
1. random motility
2. chemotaxis (right- and left- moving cells reverse differently)
3. chemokinesis (gradient in cell velocity)

To couple to external concentration field, combine with the experimentally determined dependencies of $\boldsymbol{\mu}$ *and* $\boldsymbol{T_p}$

Flux in a 1D Gradient (1)

Motivated by Berg & Brown 1972 Experiments

- runs & tumbles
- tumble duration is zero
- use velocity jump process in 1D
- motion in a gradient



$T_p = (\lambda^- + \lambda^+)^{-1}$

$\lambda^{+/-} = p_T^{+/-}(1-\psi)/2$

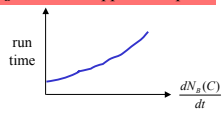
p_T: is the tumbling probability

ψ : "directional persistence"

probability of reversing after tumbling

receptor-mediated mechanism:

N_B – # of occupied receptors



Flux in a 1D Gradient (2)

$$\tau = \tau_0 e^{\sigma \frac{dN_b}{dt}}$$

relate to the frequency of tumbles

$$p_T^{+/-} = 1/\tau^{+/-} = p_0 e^{-\sigma \frac{dN_B}{dt}}$$

time derivative seen by the "bacterium"

$$\frac{dN_B}{dt} = \frac{\partial N_B}{\partial t} \pm v \frac{\partial N_B}{\partial x}$$

$$\lambda^+ + \lambda^- = (1-\psi)\cosh(\sigma v \frac{\partial N_b}{\partial x})$$

$$\lambda^+ - \lambda^- = p_0(1-\psi)\sinh(\sigma v \frac{\partial N_b}{\partial x})$$

$$\mu = \frac{v^2}{p_0(1-\psi)} \sec h(\sigma v \frac{\partial N_b}{\partial x})$$

$$V_c = v \tanh(\sigma v \frac{\partial N_b}{\partial x})$$

Flux in a 1D Gradient (3)

Simple Ligand/receptor Equilibrium

$$N_B = \frac{N_{total} c}{K_D + c} \Rightarrow \frac{dN_B}{dc} = \frac{N_T K_d}{(K_d + c)^2}$$

$$\mu = \frac{v^2}{p_0(1-\psi)}[\cosh(\sigma v \frac{\partial c}{\partial x}\frac{dN_B}{dc})]^{-1}$$

$$V_c = v \tanh(\sigma v \frac{\partial c}{\partial x}\frac{dN_B}{dc})$$

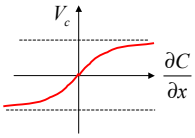
chemotactic coefficient, χ

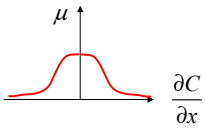
small gradients:

$$\mu = \frac{v^2}{p_0(1-\psi)}, \qquad V_c = \sigma v^2 \frac{dN_B}{dc}\frac{\partial c}{\partial x}$$

If the model is correct: macroscopic flux can be estimated from data on binding and microscopic parameters for cell migration

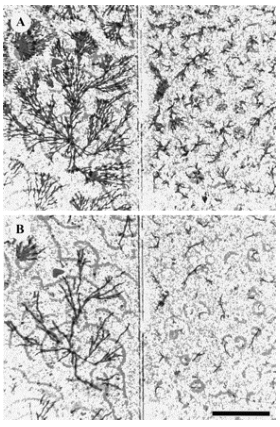
Flux in a 1D Gradient (4): Analysis





1. Random motility coefficient increases with temporal gradient
2. Random motility coefficient is a decreasing function of spatial gradient: at large gradients all cells swim in one direction
3. Chemotactic velocity has a limiting value: the population can not move faster than the maximal cell speed

Cell density + diffusing signal



"Chemotactic Wave Paradox"

Observation

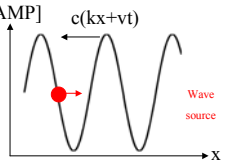
aggregation to the source of chemical wave
pulse of cAMP is nearly symmetric
Devreotes & Tomchik, *Science* 212, 443-6, 1981

Simple-model:

symmetric chemotactic velocity
no net directed motion

Worse: cells stay longer in the negative gradient region

Prediction: cells move away from the wave source



What is the problem?

Experiment: Cells move only in the wave front and not in the back => chemotactic response can not be determined by the concentration gradient alone

$$\chi = \chi(\alpha)$$

chemotactic sensitivity

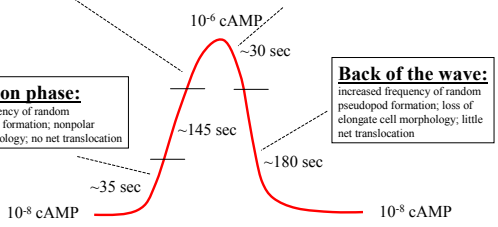
Model: Soll, Wessels, Sylwester, 1993

Translocation phase:
Rapid & persistent translocation; suppressed lateral pseudopods formation; elongate shape

Peak of the wave:
suppression of pseudopod formation and cellular translocation; freeze in cell morphology

Decision phase:
high frequency of random pseudopod formation; nonpolar cell morphology; no net translocation

Back of the wave:
increased frequency of random pseudopod formation; loss of elongate cell morphology; little net translocation



Chemotaxis-driven Linear Instability (1)

Keller & Segel, 1971: cells migrate in a self-imposed field of chemoattractant

$$\frac{\partial n}{\partial t} = -\frac{\partial}{\partial x}\left(-\mu\frac{\partial n}{\partial x} + \chi n\frac{\partial c}{\partial x}\right), \quad \left.\frac{\partial n}{\partial x}\right|_{0,L} = 0$$
$$\frac{\partial c}{\partial t} = -\frac{\partial}{\partial x}\left(-D\frac{\partial c}{\partial x}\right) + fn - kc, \quad \left.\frac{\partial c}{\partial x}\right|_{0,L} = 0$$

$$s.s.: \bar{n} = N/L, \bar{c} = \bar{n}f/k$$
$$n(x,t) = \bar{n} + n'(x,t)$$
$$c(x,t) = \bar{c} + c'(x,t)$$

Linearized equations:

$$\frac{\partial n'}{\partial t} = \mu\frac{\partial^2 n'}{\partial x^2} - \chi\bar{n}\frac{\partial^2 c'}{\partial x^2}$$
$$\frac{\partial c'}{\partial t} = D\frac{\partial^2 c'}{\partial x^2} + fn' - kc'$$

Solution:

$$\begin{pmatrix} n'(x,t) \\ c'(x,t) \end{pmatrix} = \sum_{i=1}^{\infty}\begin{pmatrix} A_i \\ B_i \end{pmatrix}\cos(q_i x)\exp(\lambda_i t)$$

why $i \neq 0$?

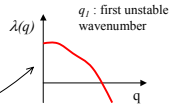
Linear instability of uniform state: $\lambda_i > 0$

Keller-Segel (2)

For every wavenumber q : $\begin{bmatrix} \lambda+\mu q^2 & -\chi\bar{n}q^2 \\ -f & \lambda+Dq^2+k \end{bmatrix}\begin{pmatrix} A \\ B \end{pmatrix}=\begin{pmatrix} 0 \\ 0 \end{pmatrix}$

Nontrivial solutions $(A\neq 0, B\neq 0)$ when $\det(M)\neq 0$

$\lambda_{1,2}$ satisfy $(\lambda+\mu q^2)(\lambda+Dq^2+k)-\chi\bar{n}q^2 f=0$



q_1 : first unstable wavenumber

Condition for instability : $\mu(Dq^2+k)<\chi\bar{n}f$

Using the B.C. : $\mu\left[\frac{D(\pi i)^2}{L^2}+k\right]<\chi\bar{n}f$

Interpretation :
1) small μ, D, k, i
2) large L
3) large $\chi, \bar{n}, f$

This is just linear analysis ...

Keller-Segel (3)

- Instability is promoted by

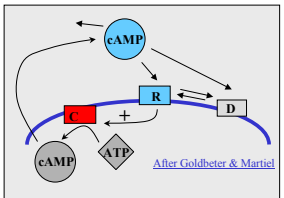
  low random motility & chemoattractant degradation
  high chemotactic sensitivity, secretion rate, cell density

- Problems

  no saturating effect: $\lim_{t\to\infty} n(x,t)=\delta(x)$
  instability does not appear to involve linear mechanism
  mechanism is more complicated

References:
1. E.F. Keller and L.A. Segel, J. theor. Biol. (26), 399-415, 1970
2. T. Hillen and K. Painter, Adv. Appl. Math. (26), 280-315, 2001

cAMP Network: Cartoon

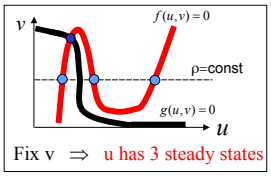


After Goldbeter & Martiel

Variables:
v – fraction of receptors in the active state
u – extracellular cAMP

$\frac{\partial u}{\partial t}=\Delta u+\frac{1}{\varepsilon}f(u,v)$ - "fast" & diffusing

$\frac{\partial v}{\partial t}=g(u,v)$ - "slow" & localized



Fix v $\Rightarrow$ u has 3 steady states

Other examples: Ca induced calcium release
Growth factor-induced growth factor release

JL Martiel, A. Goldbeter, "A model based on receptor desensitization for cAMP signaling in Dictyostelium cells", Biophys.J. , 52, 807, 1987

Reaction, Diffusion, Chemotaxis

Cell density

Diffusing messenger (cAMP)

cell state

$$\frac{\partial n}{\partial t} = \nabla \cdot (\mu \nabla n - \chi(v) n \nabla u)$$

$$\frac{\partial u}{\partial t} = \lambda[\phi(n) f_1(u,v) - (\phi(n) + \delta) f_2(u)] + \nabla^2 u$$

$$\frac{\partial v}{\partial t} = -g_1(u)v + g_2(u)(1-v).$$

$$\chi(v) = \chi_0 \frac{v^m}{N^m + v^m}, \; m > 1.$$

Chemotactic coefficient is a function of internal state of the cell

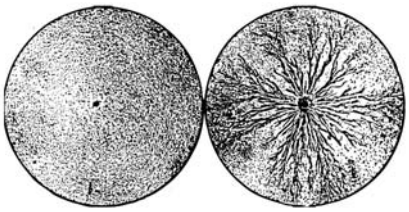
Reaction, Diffusion, Chemotaxis: *continuum model*

FIG. 3. *Two examples of the aggregation patterns produced by the model of Höfer et al. [11]. (From [10], with permission.). The computational scheme is based on an ADI splitting for diffusion, first-order explicit upwinding for the chemotaxis terms, and an explicit Euler step for the reaction terms. The results shown are at t = 80 minutes (left) and t= 140 minutes (right).*

Simple model captures the phenomenology

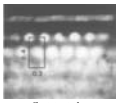
Experiments (1)

(cell density)



time

Linear Transport + Nonlinear Chemistry



Castets et al,
PRL, 64, 2953 (1990)

"… a mathematical model of the growing embryo will be described. This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge"

1. Diffusion can have a destabilizing effect
2. Nonlinear chemistry can generate patterns
3. These mechanisms operate in development

A.M. Turing, "The Chemical Basis of Morphogenesis", Phil. Trans. Roy. Soc. B 237 (1952)

Diffusive Instability: The Model

$$\frac{\partial C_1}{\partial t} = D_1 \frac{\partial^2 C_1}{\partial x^2} + R_1(C_1, C_2); \quad \left.\frac{\partial C_1}{\partial x}\right|_{0,L} = 0$$
$$\frac{\partial C_2}{\partial t} = D_2 \frac{\partial^2 C_2}{\partial x^2} + R_2(C_1, C_2); \quad \left.\frac{\partial C_2}{\partial x}\right|_{0,L} = 0$$

uniform s.s.:

$R_1(\bar{C}_1, \bar{C}_2) = 0, \quad R_2(\bar{C}_1, \bar{C}_2) = 0$

perturbations:

$C_1'(x,t) = C_1(x,t) - \bar{C}_1$

$C_2'(x,t) = C_2(x,t) - \bar{C}_2$

Linearize around uniform steady state

$$\frac{\partial C_1'}{\partial t} = D_1 \frac{\partial^2 C_1'}{\partial x^2} + a_{11} C_1' + a_{12} C_2'$$
$$\frac{\partial C_2'}{\partial t} = D_2 \frac{\partial^2 C_2'}{\partial x^2} + a_{21} C_1' + a_{22} C_2'$$

$$a_{ij} \equiv \left.\frac{\partial R_i}{\partial C_j}\right|_{\bar{C}_1, \bar{C}_2}$$

Only "chemistry"

L.A. Segel and J.L. Jackson, "Dissipative Structure: An Explanation and an Ecological Example", J. theor. Biol., 1972, 37, 545-559

Diffusive Instability: Linear Analysis

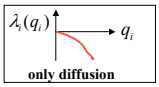
Linear dynamics: $\begin{pmatrix} C_1'(x,t) \\ C_2'(x,t) \end{pmatrix} = \sum_{i=0}^{\infty} \begin{pmatrix} A_i \\ B_i \end{pmatrix} \cos(q_i x) \exp(\lambda_i t)$

Stability: $\lambda_i < 0 \ \forall i$

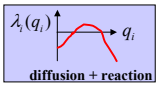
$(\lambda_i - a_{11} + D_1 q_i^2)(\lambda_i - a_{22} + D_{22} q_i^2) - a_{12} a_{21} = 0$

uniform perturbations decay when

1. $a_{11} + a_{22} < 0$
2. $a_{11} a_{22} - a_{12} a_{21} > 0$



only diffusion



diffusion + reaction

Can nonuniform perturbations grow under these conditions?

Diffusive Instability: Conditions

Necessary and sufficient conditions

1. $a_{11} + a_{22} < 0$
2. $a_{11}a_{22} - a_{12}a_{21} > 0$

uniform SS is stable (only chemistry)

3. $a_{11}D_2 + a_{22}D_1 > 0$

chemistry + transport

Possible Jacobians:

$\begin{bmatrix} + & - \\ + & - \end{bmatrix}$ → activator/inhibitor system

$\begin{bmatrix} + & + \\ - & - \end{bmatrix}$

What does this mean?

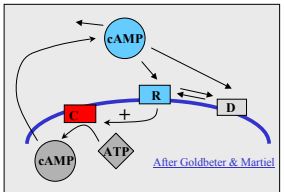
1. One substance is an "inhibitor" (pick 2)
2. The other one is an "activator" (1)
3. Range of activator is less than the range of inhibitor

$$\frac{D_1}{a_{11}} < \frac{D_2}{|a_{22}|}$$

More species and dimensions:

1) Satnoianu RA, Menzinger M, Maini PK. "Turing instabilities in general systems". J Math Biol. 2000, 41, 493
2) De Wit A, "Spatial patterns and spatiotemporal dynamics in chemical systems" Adv. Chem. Phys., (109), 435, 1999

cAMP Network: Cartoon



After Goldbeter & Martiel

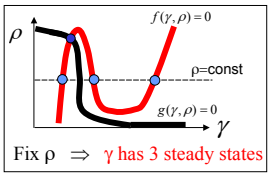
Variables:

ρ – fraction of receptors in the active state

γ – extracellular cAMP

$\frac{\partial \gamma}{\partial t} = \Delta\gamma + \frac{1}{\varepsilon} f(\gamma, \rho)$ - "fast" & diffusing

$\frac{\partial \gamma}{\partial t} = g(\gamma, \rho)$ - "slow" & localized

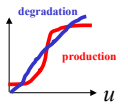


Fix ρ ⇒ γ has 3 steady states

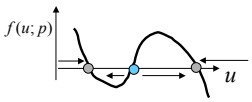
Other examples: Ca induced calcium release
Growth factor-induced growth factor release

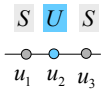
JL Martiel, A. Goldbeter, "A model based on receptor desensitization for cAMP signaling in Dictyostelium cells", Biophys.J. , 52, 807, 1987

Positive Feedback Alone: Bistability



Two stable steady states

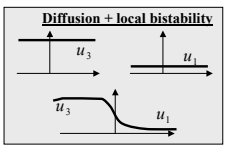




$\frac{du}{dt} = f(u;p) \equiv P(u;p) - R(u;p)$

balance of production & degradation

$\frac{\partial u}{\partial t} = f(u;p) + D\frac{\partial^2 u}{\partial x^2}$ - with diffusion



Nonuniform transitions between uniform steady states

AS Mikhailov, "Foundations of Synergetics-I", Springer, 1994

Bistable Media: Propagating Fronts

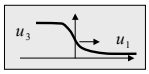
$$\frac{\partial u}{\partial t} = f(u;p) + D\frac{\partial^2 u}{\partial x^2}$$

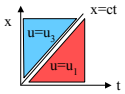
Look for self-similar solutions:

wave propagating to the right

$u(x,t) = u(x-ct); \xi \equiv x - ct$

$\lim_{\xi\to-\infty} u(\xi) = u_3;\ \lim_{\xi\to+\infty} u(\xi) = u_1$





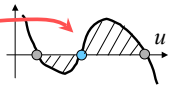
Both the propagation speed (c) and its profile are uniquely determined by the properties of the medium : all fronts in a bistable medium have the same profile, independently of initial conditions

Change variables:

$-cu_\xi = f(u) + Du_{\xi\xi}$

What determines the direction and speed of propagation?

$$\int_{-\infty}^{+\infty} \left(-cu_\xi = f(u) + Du_{\xi\xi}\right) u_\xi \Rightarrow c = \frac{\int_{u_1}^{u_3} f(u;p)du}{\int_{-\infty}^{+\infty} (\frac{du}{d\xi})^2 d\xi}$$



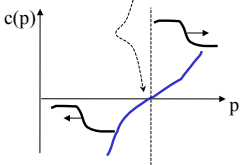
AS Mikhailov, "Foundations of Synergetics-I", Springer, 1994

Bistable Media: Front Speed

Front stationarity ($c = 0$) is determined by kinetics alone:

$$\int_{u_1}^{u_3} f(u;p)\,du = 0$$

The front is stationarity only for a single parameter value:



Expressions for speed are available only for 2 cases:

$$f(u) = -k(u-u_1)(u-u_2)(u-u_3) \Rightarrow c = \frac{1}{2}\sqrt{kD}(u_1+u_3-u_2)$$

$$f(u) = k[(u_1-u)+(u_3-u_1)H(u-u_2)] \Rightarrow c = \frac{\sqrt{kD}(u_1+u_3-u_2)}{\sqrt{(u_2-u_1)(u_3-u_2)}}$$

AS Mikhailov, "Foundations of Synergetics-I", Springer, 1994