

Chemotaxis14.1 Glossary

Taxis: movement of an organism in response to a stimulus (light, temperature, food, electric, magnetic, chemical, e.g., pheromones, ...)

Directed locomotion: self-induced movement, so involves active forces, as opposed to random motion resulting from external forces, like collisions with other moving particles those resulting from

Transduction (of a signal): any process by which a biological cell converts one kind of signal or stimulus into another

Aggregation: self induced building <sup>up</sup> of a locally very high density of motile organisms, resulting from direct or indirect communication. Examples:

flocks of birds  
schools of fish  
herds of ungulates  
swarms of insects

But happens as well for single cell organisms, like

*E. coli*

*Dictyostelium discoideum* (slime mold)

"Dicty" for short

14.2 / Steps involved in directed locomotion resulting in aggregation :

- (i) detection and transduction of external signals  
(visual, chemical, mechanical, ...)
- (ii) integration of the external signals into an internal signal
- (iii) instigation and control of neural, biochemical, mechanical responses that generate a force leading to directed movement
- (iv) (often but not always) relay of the signal  
(relay : an act of passing something along from one person / group / station to another)

### Ways to move

- many single-celled organisms use flagella or cilia, driven by molecular motors, to "swim"

Example : run-and-tumble motion of *E. coli*

- eukaryotic cells use pseudopodia, driven by actin polymerization and depolymerization, to crawl or glide

### Kind of signals

- fish schools and flocks of birds involve alignment of individuals and hence, most likely, manage to behave as a super-individual via nearest-neighbour coordination mediated by visual information, so a form of direct communication

14.3 / - bacteria react to an external medium and, at the same time, may produce (or consume) that medium, so alter it, so a form of indirect communication via the environmental condition. Examples:

- E-coli can release a diffusible attractant
- myxobacteria glide on a slime trail and reinforce it by adding slime (reinforced random walk)
- while amoebae, the eucaryotic Dicty cells, release cyclic AMP when they starve

### Goals of directed locomotion:

- i) find food
- ii) avoid danger/poison
- iii) catch enemies (immune cells?)
- iv) find a mate (pheromones, insects)
- v) aggregate to form a stalk, and next spores, to disperse (Dicty), so to reproduce in a non-local manner

### Mathematical description of motion

- do we, like in statistical mechanics, include velocity as a component of the state of an individual?
- are changes in velocity described by jumps at certain points in time or as continuous in time, due to friction and other forces?
- are changes in position described by continuous movement or by jumps?

14.4

## 14.2 Plan

(Pattlak-)

14.3

### 1. Keller-Segel system

- a) phenomenological motivation
- b) stability analysis of steady states (initiation of pattern formation)
- c) formation of  $\delta$ 's (aggregation)

14.4

### 2. The simplest velocity jump process

- a) phenomenological motivation
- b) derivation of the telegraphers equation
- c) derivation of the diffusion equation

from  
micro  
to  
macro

### 14.5 3. A quite general balance law

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downloadable from [mi.uni-koeln.de/~dhorst/](http://mi.uni-koeln.de/~dhorst/)

D. Horstmann (2003, 2004) From 1970 until present. The

Keller-Segel model in chemotaxis and its consequences, I, II

Jahresbericht der DMV 105 (3) 103-165 and 106 (2) 51-69

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downloadable from [math.umn.edu/~othmer/](http://math.umn.edu/~othmer/)

H.G. Othmer, C. Xue (2013)

The mathematical analysis of biological aggregation and dispersal: progress, problems and perspectives

In: Dispersal, individual movement and spatial ecology: a mathematical perspective (M. Lewis, P. Maini & S. Petrovskii, eds.) Springer, pp. 79-127

14.5

14.3 The Patlak-Keller-Segel system

If the flux has both a component  $-d\nabla u$  (describing random motion by Fick's Law) and a component

$$\chi(s)\nabla s u$$

describing deterministic motion with a velocity (so both speed and direction) determined by the concentration  $s$  of a chemical and the gradient of that concentration, we have as a balance law

$$(14.1) \quad \frac{\partial u}{\partial t} = \nabla \cdot (d\nabla u - \chi(s)\nabla s u) = \nabla \cdot (d\nabla u - (\chi(s)\nabla s)u)$$

Ignoring the <sup>(important)</sup> issue of how exactly simple organisms should be able to "measure" the gradient of  $s$ , the idea is that the direction of movement is determined by the direction of the gradient of  $s$  (if  $s$  is something positive, then in the direction of increasing  $s$ , while if  $s$  is something that is to be avoided, in the direction of decreasing  $s$ ) but that the speed depends on absolute values of  $s$  as well, via the so-called chemotactic sensitivity  $\chi(s)$ . So this allows for the incorporation of adaptation: if  $s$  is already very high, a further increase may be <sup>of</sup> far less importance than when it is at moderate or low levels. To (14.1) we now add

$$(14.2) \quad \frac{\partial s}{\partial t} = \Delta s + u - s$$

14.6/ where we have put the constant in front of  $s$  equal to  $-1$  by a scaling of time, the constant in front of  $u$  equal to  $+1$  by a scaling of  $u$  and the diffusion constant equal to  $1$  by a scaling of the spatial variable  $x$ . So the chemical  $s$  is produced by the organisms that are described by the density  $u$ , it degrades and it diffuses. So together (14.1) - (14.2) describe the movement of organisms that communicate with each other via a feedback loop involving the "environmental" variable  $s$ . Let's assume that  $s$  attracts, i.e.,

$\chi(s) > 0$ . So the organisms move towards higher values of  $s$ . At the same time they produce  $s$ . Even though  $s$  diffuses away from the positions where it is produced, we expect the concentration to be relatively high where a lot is produced, i.e., where there are many organisms?

Question: does the combination of directed locomotion and production of the signal lead to aggregation?

A related, but much simpler question is: are uniform steady states of (14.1) - (14.2) unstable?

Note that, in a bounded domain with no flux boundary conditions, we have

$$\int_{\Omega} u = \text{constant}$$

where the constant is set by the initial condition (we only model redistribution over  $\Omega$ , there is neither creation nor destruction). This observation motivates us to now investigate whether or not pattern formation is initiated if we perturb the "uniform/

14.7/ "flat/constant in space" steady state

We now specialise to one-dimensional space

$$u(t,x) = \bar{u}, \quad s(t,x) = \bar{u}$$

with  $\bar{u}$  a parameter measuring how many organisms exist. Introducing  $U$  and  $S$  via

$$u(t,x) = \bar{u} + U(t,x), \quad s(t,x) = \bar{u} + S(t,x)$$

and linearizing the equations we obtain the system

$$\frac{\partial U}{\partial t} = d \frac{\partial^2 U}{\partial x^2} - \lambda(\bar{u}) \bar{u} \frac{\partial^2 S}{\partial x^2}$$

$$(14.3) \quad \frac{\partial S}{\partial t} = \frac{\partial^2 S}{\partial x^2} + U - S$$

and next by the separation-of-variables Ansatz

$$\begin{pmatrix} U \\ S \end{pmatrix} (t,x) = e^{\lambda t} \cos \sqrt{\mu} x \begin{pmatrix} U_0 \\ S_0 \end{pmatrix}, \quad \mu > 0,$$

the eigenvalue problem

$$(14.4) \quad \begin{aligned} \lambda U_0 &= -\mu d U_0 + \lambda(\bar{u}) \bar{u} \mu S_0 \\ \lambda S_0 &= -\mu S_0 + U_0 - S_0 \end{aligned}$$

leading to

$$\det \begin{pmatrix} \lambda + \mu d & -\lambda(\bar{u}) \bar{u} \mu \\ -1 & \lambda + \mu + 1 \end{pmatrix} = 0$$

i.e.

$$(14.5) \quad \lambda^2 + (\mu(d+1) + 1) \lambda + \mu(d(\mu+1) - \lambda(\bar{u}) \bar{u}) = 0$$

14.8 / with solutions

$$\lambda_{\pm} = \frac{-B \pm \sqrt{B^2 - 4C}}{2}$$

where

$$B = (\mu(d+1) + 1) > 0$$

$$C = \mu (d/(\mu+1) - \chi(\bar{u})\bar{u})$$

Observation 1 If  $\text{Im } \lambda \neq 0$  then  $\text{Re } \lambda < 0$

Observation 2 If  $\lambda_{\pm}$  are real then  $\lambda_- < 0$  and

$$\lambda_+ > 0 \iff C < 0$$

Conclusion the uniform steady state is unstable  
iff  $C < 0$ , i.e.,

$$d(\mu^2 + 1) < \chi(\bar{u})\bar{u}$$

Interpretation initiation of pattern formation is promoted by

- high  $\bar{u}$ , i.e., high initial concentration of the organism (assuming  $u \mapsto \chi(u)u$  is increasing)
  - high  $\chi$ , i.e., high chemotactic sensitivity
  - low  $d$ , low random mobility of the organism
- and, if you recall the scaling of  $u$  and time
- high rate of  $s$  production
  - low degradation rate of  $s$



14.9 / Also note that it is easier to destabilize the lower modes, i.e., small  $\mu$  (recall  $\mu = \frac{4\pi}{L}$  on an interval of length  $L$ ; therefore we can also say that long intervals or small diffusion coefficient for  $s$  promote instability)

Overall conclusion The feedback loop

signal production  
move towards stronger signal

may lead to growing peaks provided the "equalizing" influence of diffusion is not too strong.

But what happens when pattern formation is initiated?  
What is the asymptotic behaviour for large  $t$ ?

Probably the website ~~hcm.bonn~~ [hcm.uni-bonn.de/people/profile/juan-j-velazquez/](http://hcm.uni-bonn.de/people/profile/juan-j-velazquez/) of Juan J.L. Velázquez is the easiest/best entry to literature about the following

- since  $\int_{\Omega} u = \text{constant}$  we never have blow-up in the  $L_1$ -norm and, also,  $\int_{\Omega} s \rightarrow \int_{\Omega} u$  as  $t \rightarrow \infty$

- in one-dimensional space, solutions stay bounded
- in two-dimensional space and for  $\int_{\Omega} u$  large enough (in fact  $\frac{8\pi}{\lambda}$  for a ball), a Dirac may form in finite time
- in three-dimensional space Dirac's may form in infinite time

14.10

- there are some ways to extend the model and describe the movement and, possibly, merging of Dirac's after they have been formed

Conclusion in two-dimensional space the model can account for aggregation in one spot, for  $\chi$  constant,

Remarkably one can for an interval, and with no-flux boundary conditions, study steady states by way of phase plane analysis, see R. Schaaf, Global solution branches of two point boundary value problems, Springer LNIM 1458, 1990. One first integrates the equation for  $u$ :

$$d \frac{\partial u}{\partial x} - \chi u \frac{\partial s}{\partial x} = \text{constant}$$

and by the boundary conditions the constant has to be zero and hence

$$u(x) = \lambda e^{\frac{\chi}{d} s(x)}$$

with  $\lambda$  a parameter corresponding, somewhat indirectly, to  $\int_{\Omega} u$ . If we substitute this expression for  $u$  in the equation for  $s$  we obtain

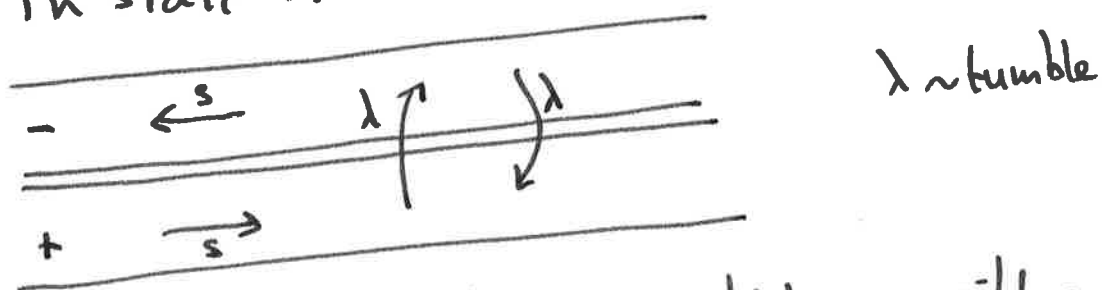
$$0 = \frac{\partial^2 s}{\partial x^2} + \lambda e^{\frac{\chi}{d} s} - s$$

which can be studied along the lines of lectures: b. pdf.

Question how do we choose  $\chi$ ? Is it possible to incorporate a more mechanistic description of what is going on within individual organisms in the specification of  $\chi$ ?

## 14.4 A caricature and its various limits

On a line, a particle can only move in two directions. So if the speed is fixed, it is characterized by a binary variable and we shall use the labels  $+$  for moving to the right (if we picture the line like \_\_\_\_\_) and  $-$  for moving to the left. Let  $s$  now denote the speed and let  $u^\pm(t, x)$  denote the density at time  $t$  and position  $x$  of, respectively, particles in state  $+$  and particles in state  $-$ .



One should "picture" the line as a highway with a separate lane for each type of particle (so no collisions!). But now we introduce something that is completely forbidden on a highway: particles may jump from one lane to another. This means that, in our idealized description, they instantaneously change direction while keeping the same speed. If we assume that jumps occur according to a Poisson process with intensity  $\lambda$ , we find that  $u^\pm$  satisfy the following system of first order linear PDE

$$(14.6) \quad \begin{aligned} \frac{\partial u^+}{\partial t} + s \frac{\partial u^+}{\partial x} &= -\lambda u^+ + \lambda u^- \\ \frac{\partial u^-}{\partial t} - s \frac{\partial u^-}{\partial x} &= +\lambda u^+ - \lambda u^- \end{aligned}$$

14.12 / Now introduce

density  $u(t, x) = u^+(t, x) + u^-(t, x)$  (14.7)

flux  $j(t, x) = s(u^+(t, x) - u^-(t, x))$

then indeed

$$(14.8) \quad \frac{\partial u}{\partial t} + \frac{\partial j}{\partial x} = 0$$

as one can see by adding the two equations in (14.6).  
We now perform a little computation

$$\begin{aligned} \frac{\partial j}{\partial t} &= s \left( \frac{\partial u^+}{\partial t} - \frac{\partial u^-}{\partial t} \right) = -s^2 \frac{\partial u^+}{\partial x} - s^2 \frac{\partial u^-}{\partial x} - \lambda s u^+ + \lambda s u^- \\ &= -s^2 \frac{\partial u}{\partial x} - 2\lambda j \end{aligned}$$

and hence

$$\frac{\partial^2 j}{\partial x \partial t} = -s^2 \frac{\partial^2 u}{\partial x^2} - 2\lambda \frac{\partial j}{\partial x} \stackrel{(14.8)}{=} -s^2 \frac{\partial^2 u}{\partial x^2} + 2\lambda \frac{\partial u}{\partial t}$$

while if we differentiate (14.8) with respect to  $t$  we get

$$\frac{\partial^2 u}{\partial t^2} + \frac{\partial^2 j}{\partial t \partial x} = 0$$

so combining the last two lines we find

$$(14.9) \quad \frac{\partial^2 u}{\partial t^2} + 2\lambda \frac{\partial u}{\partial t} = s^2 \frac{\partial^2 u}{\partial x^2}$$

and that involves only the density  $u$

an equation that is known as the telegrapher's equation.

If we put  $\frac{s^2}{2\lambda} = d$  and let  $\lambda, s \rightarrow \infty$  while keeping  $d$  constant we obtain, formally, our old friend

$$(14.10) \quad \frac{\partial u}{\partial t} = d \frac{\partial^2 u}{\partial x^2}$$

14.13

14.5 A quite general balance law

In classical mechanics, a particle is characterized by its mass, position and velocity. Newton's Second Law tells us how a force  $F$  changes the velocity  $v$  (acceleration, deceleration, change of direction) in a continuous manner. If we put the mass equal to 1, but allow also for jumps of the velocity, we obtain <sup>as</sup> the balance law the transport equation  $p(t, x, v)$

$$(14.11) \quad \frac{\partial p}{\partial t} + \nabla_x \cdot v p + \nabla_v \cdot F p = -\lambda p + \lambda \int T(\cdot, v') p(t, x, v') dv'$$

where  $p$  is, in the spirit of statistical mechanics, the density of a large number of particles,  $v$  denotes velocity, jumps occur according to a Poisson process with rate  $\lambda$  and  $T$  is the velocity redistribution kernel in the sense that

$$\int_{\omega} T(v, v') dv$$

is the probability that the new velocity belongs to  $\omega$ , given that the old velocity was  $v'$  and a jump is happening.

But note that i) Avogadro's number is really big and that a population of Dicty cells consists of far less individuals ii) we ignore collisions, so (14.11) doesn't have a Boltzmann type collision operator at the right hand side but a linear redistribution operator iii) since  $v$  is now an independent variable, we may write  $v \cdot \nabla_x p$  instead of  $\nabla_x \cdot v p$  iv) if the force depends only on position and not on velocity, we may likewise replace  $\nabla_v \cdot F p$  by  $F \cdot \nabla_v p$ ; however, friction does involve velocity

14.14 v) the description (14.11) ignores mechanical cell-cell interactions, but we can incorporate indirect interactions via an environmental variable  $s$  by allowing  $F$ ,  $\lambda$  and  $T$  to depend on  $s$ , while incorporating in the equation for  $s$  a production term proportional to  $p$ .

However, biological organisms differ from each other in many ways, not just in their mass. Which of these differences matter, depends on the context, on the questions being asked. See LNinBiomath68.pdf in the Bibliography for many examples as well as some general theory. We can incorporate these ideas in the present bookkeeping framework by introducing

$i$ -state  $y$

where  $i$  now stands for "internal", since the individual state is the triple  $(x, v, y)$ , and

$$f = f(x, v, y, s)$$

such that, for an individual with state  $(x, v, y)$  experiencing environmental condition  $s$  we have

$$\frac{dy}{dt} = f(x, v, y, s)$$

All we have to do next is to add a term

$$\nabla_y \cdot fp$$

to the left hand side of (14.11).

14.15 The general idea of deriving macroscopic equations from microscopic (or mesoscopic) descriptions, is to reduce (14.11) to a diffusion equation (so that, in the end, only the easily observable characteristic "position" remains) by a suitable limit procedure. The advantage of this complicated exercise is that, hopefully, the coefficients in the resulting diffusion equation contain "traces" of our sub-models for change of velocity and i-state, so carry an interpretation that helps to deduce insights from an analysis of the diffusion equation. We refer to the Othmer-Xue paper (and the references given there) mentioned on page 14.4 for technical elaboration. The procedure is based on the "parabolic" scaling

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

and the limit  $\varepsilon \rightarrow 0$ . The last section of Othmer-Xue, called "Macroscopic descriptions of eukaryotic cell movement", provides examples of how this approach yields both insights and questions (like: does a cell "judge" the environmental condition by temporal sensing along its path through space or by spatial sensing across its own body?)