Journal of the Egyptian Mathematical Society (2011) **19**, 52–56

Egyptian Mathematical Society

Journal of the Egyptian Mathematical Society

www.etms-eg.org
www.elsevier.com/locate/joems

ORIGINAL ARTICLE

Mathematical models of cell self-organization

Benoît Perthame

Univ. P. et M. Curie and CNRS, UMR 7598, Laboratoire Jacques-Louis, Lions, BC187, 4, place Jussieu, F75252 Paris cedex 05, France
Institut Universitaire de France and INRIA Paris-Rocquencourt, EPI BANG, France

Available online 7 December 2011

KEYWORDS

Cell movements;
Chemotaxis;
Kinetic equations;
Fokker–Planck equations

Abstract Various classes of Partial Differential Equations have shown to be successful in describing the self-organization of bacterial colonies, a topic also sometimes called socio-biology. For instance parabolic systems are standard; the classical Patlak–Keller–Segel system and Mimura's system are able to explain two elementary processes underlying qualitative behaviors of populations and complex patterns: oriented drift by chemoattraction and colony growth with local nutrient depletion.

More recently nonlinear hyperbolic and kinetic models also have been used to describe the phenomena at a smaller scale. We explain here some motivations for 'microscopic' descriptions, the mathematical difficulties arising in their analysis and how kinetic models can help in understanding the unity of these descriptions.

1. Introduction

Communities of cells can exhibit remarkable patterns which have attracted the attention of biologists and, with recent technology, has developed a new domain called 'socio-biology'. The organization of cells colonies result from highly complex but poorly understood interactions between cells and internal regulatory networks, which involve both chemical signaling and the effects of physical factors.

We present some classes of Partial Differential Equations which have been used and the reason of their success. We begin with the classical Patlak–Keller–Segel system and semilinear parabolic systems, as Mimura's system, that are able to explain two elementary processes underlying qualitative behaviors of populations and complex patterns: oriented drift by chemoattraction and colony growth with local nutrient depletion. We continue with the Hyperbolic Keller–Segel with Logistic Sensitivity (HKSLS) and finish with the kinetic models. This presentation is an extension of two previous presentations [42,33].

Although it is more realistic to work on bounded domains, we often write equations on the full space to simplify the settings. When set on a subset of $\mathbb{R}^d$, the equations are usually completed with zero flux boundary conditions which express the conservation of cells or chemical concentrations.

E-mail address: benoi.perthame@upmc.fr

1110-256X

Peer review under responsibility of Egyptian Mathematical Society.
doi:10.1016/j.joems.2011.09.005

Production and hosting by Elsevier

2. A nonlinear Fokker–Planck system for chemotaxis

The first model we wish to present is the famous nonlinear Fokker–Planck equation called the 'Patlak–Keller–Segel system' which has drawn an enormous mathematical literature ([26,27,36,12,22,32,41] and the references therein). In the absence of cell division, it is written as

$$\begin{cases} \frac{\partial}{\partial t}\rho(x,t) - d_\rho \Delta \rho(x,t) + \operatorname{div}[\rho(x,t)\chi \nabla S] = 0, \\ \tau \frac{\partial}{\partial t} S(x,t) - d_S \Delta S(x,t) + \alpha S(x,t) = \rho(x,t). \end{cases} \tag{1}$$

The system is set on $\mathbb{R}^2$ (because cells leave on a petri dish) and is completed with initial data that satisfy

$$\rho^0(x) \geqslant 0, \qquad \int_{\mathbb{R}^2} \rho^0(x)[1 + |x|^2 + |\ln \rho^0(x)|]\,\mathrm{d}x < \infty.$$

The parameter d_ρ represents the intensity of the basic brownian motion of cells, which density is denoted by $\rho(x,t)$. The drift term represents a directed movement towards the higher values of the signal $S(x,t)$ with a 'sensitivity' χ which may depend on ρ or S and represents the bias of the basic motion. Usually the signal is a chemical which is released by the cells themselves (see [36] for more detailed presentation of the biological processes). Then, the model parameters τ, d_ρ, α measure the molecular diffusion, degradation and release rates of this chemical; these coefficients may also be nonlinear, see [9] for instance. Because the cell division is neglected, we have

$$\int_{\mathbb{R}^2} \rho(x,t)\,\mathrm{d}x = M^0 := \int_{\mathbb{R}^2} \rho^0 \quad \forall t \geqslant 0.$$

Although very simple this system has led to a huge mathematical literature because it exhibits a concentration effect that it is easier to state in the full space $\mathbb{R}^2$.

Theorem 1 [3]. *Consider the case $\tau = \alpha = 0$, $d_\rho = d_S = 1$ and assume that the initial data satisfies $\rho^0(1 + |x|^2 + |\ln(\rho^0)|) \in L^1_+(\mathbb{R}^2)$. Then*

- *if $M^0 < \frac{8\pi}{\chi}$, there is a global weak solution to (1) and it behaves as the heat equation. For instance it converges to 0 as $t \to \infty$,*
- *if $M^0 > \frac{8\pi}{\chi}$, any weak solution blows-up in finite time. More precisely there is a T^* such that $\rho(t)$ becomes a singular measure as $t \to T^*$.*

For the critical mass, blow-up occurs in infinite time as a single Dirac mass [2]. Above the critical mass, at the blow-up time it is believed that, generically, the solution aggregates as one (or several) Dirac mass of weight $\frac{8\pi}{\chi}$ (see [17,46] and the references therein) but no rigorous proof is available. These results remain 'roughly' true in bounded domains, although more complicated statements are needed [1,24,38] because blow-up can occur on the boundary and thresholds as $\frac{4\pi}{\chi}$ occur. Higher dimension is also of interest, see [12,40] and the references therein. This blow-up phenomena for large initial data makes the success of the Keller–Segel system because many cells have tendency to aggregate in highly concentrated spots (see [36] for a general presentation).

3. Semilinear systems and dentritic patterns

The nutrient-based models also have a long history and are motivated by dentritic patterns of colonies of bacteria *Bacillus subtilis*. As described in [33], they are mostly formulated in terms of three quantities:

- the population density $u(x,t)$ of active cells. Under the effect of their flagella, active bacteria undergo a random movement resulting in a diffusion of intensity d_u, and they multiply according to the nutrient available locally;
- the nutrient concentration $v(x,t)$ diffuses and, because the nutrient is limited, it can diminish locally due to its consumption by multiplying cells;
- the population density of passive cells $w(x,t)$. For these cells the effect of their motion and multiplication is neglected. Active cells become passive according to some rules that differ from one model to the other, and do not move or multiply.

These ingredients lead to write general systems of the form of semilinear parabolic systems (where the last quantity w usually does not influence the first two)

$$\begin{cases} \frac{\partial}{\partial t} u(x,t) - d_u \Delta u(x,t) = u[vf(u,v) - g(u,v)], \\ \frac{\partial}{\partial t} v(x,t) - d_v \Delta v(x,t) = -uvf(u,v), \\ \frac{\partial}{\partial t} w(x,t) = ug(u,v). \end{cases} \tag{2}$$

These systems are particularly interested when $d_u \neq d_v$ and their analysis can be subtle. Several mathematical tools are due [44].

Such systems have been introduced to model chemical reactions, and the Gray–Scott system [19] is a simple and classical example which writes as

$$\begin{cases} \frac{\partial}{\partial t} u(x,t) - d_u \Delta u(x,t) = u[u^n v - \mu], \\ \frac{\partial}{\partial t} v(x,t) - d_v \Delta v(x,t) = -u^{n+1} v, \\ \frac{\partial}{\partial t} w(x,t) = \mu u(x,t). \end{cases} \tag{3}$$

Here $n \geqslant 0$ is an integer related to the mass action law for the molecules undergoing the chemical reaction and $\mu > 0$. Variations around this model can also be interpreted in terms of bacterial motion as proposed in Kessler and Levine [28], Golding et al. [30]; they replace the growth term $u^n v$ by $h(u)v$ where $h(\cdot)$ is a truncation function for small values of u and $h \approx 1$ for large values. The Gray–Scott model explains the instability that generates the digitation process. It is related to concentration effects of the equation on active cells; its solution u exhibits high values on the tip of the dendrite and move outwards where nutrients are low. These concentration points are traveling pulses that undergo secondary instabilities which explain their branching, see [29].

Rather than a limitation of growth for small values of u as in the Kessler and Levine model, Mimura et al. [34,35] proposed a limitation on the transition rate to the passive state for large values of u or v. The choice of the reaction terms f and g in the general system (2) is then given by

$$\begin{cases} \frac{\partial}{\partial t} u(x,t) - d_u \Delta u(x,t) = u\left[v - \frac{\mu}{(a+u)(b+v)}\right], \\ \frac{\partial}{\partial t} v(x,t) - d_v \Delta v(x,t) = -uv, \\ \frac{\partial}{\partial t} w(x,t) = \frac{\mu u}{(a+u)(b+v)}. \end{cases} \tag{4}$$

Even though the underlying pattern formation mechanism is very similar, the resulting dendritic patterns differ from those obtained with the Gray–Scott model and are more realistic.

As we will see it in Section 4, another possible way to generate branching patterns uses only forces, e.g. chemoattrac-

tants and chemorepellents, as it was done in Section 2 for chemotaxis.

4. Hyperbolic Keller–Segel equations

Hyperbolic model have been proposed to improve the Keller–Segel system (1) because of biological observations as wave propagations. A very rich model has been proposed by [15] which includes control mechanisms within cells that prevent overcrowding. Volume filling and quorum sensing are such well-known effects which both lead to saturating nonlinearities [23,21,40]. This lead [15] to consider the Hyperbolic Keller–Segel system Logistic Sensitivity

$$\begin{cases} \frac{\partial}{\partial t}\rho(x,t) + \operatorname{div}[\rho(x,t)(1-\rho(x,t))\nabla S] = 0, \quad t \geqslant 0, x \in \mathbb{R}^d, \\ -\Delta S(x,t) + S(x,t) = \rho(x,t), \end{cases} \tag{5}$$

together with an initial data satisfying

$$0 \leqslant \rho^0(x) \leqslant 1, \quad \rho^0 \in L^1(\mathbb{R}^d).$$

This system has the capability to generate a very interesting multiscale dynamics (in particular when a small diffusion term is added) which was investigated in [8,15]. Patches where $\rho(x,t) \approx 1$, $S(x,t) \approx 1$ are obtained quickly that correspond to steady shock waves from 0 to 1 but which evolve when the diffusion is not exactly zero and this generates an elaborate geometrical motion.

The mathematical analysis of system (5) is very interesting and differs from the case of a multidimensional scalar conservation law ($S fixed), except in one dimension where BV estimates are possible and give existence as for standard conservation laws [13,45]. But in higher dimension all the usual methods for scalar conservations fail to apply. The BV estimates do not seem to hold true (even though they are not disproved either), neither L^1 contraction principle. Regularizing effects, as produced by the kinetic formulation [31], cannot hold true for system (5) in higher dimension because the flux points essentially in the direction of $S and the non-degeneracy condition cannot be met in this case because it expresses that variations of the unknown generate the full space. These are the difficulties in proving the

Theorem 2. [14]*The system (5) admits a weak solution* $\rho \in L^\infty(\mathbb{R}^+ \times \mathbb{R}^d)$, $S \in L^\infty(\mathbb{R}^+; W^{2,q}(\mathbb{R}^d))$ *for* $1 \leqslant q < \infty$, *satisfying* $0 \leqslant \rho(x,t) \leqslant 1$, $0 \leqslant S(x,t) \leqslant 1$, *and all the following entropy inequalities, for* η *convex (in the weak sense and with initial data* $\eta(\rho_0)$*)*

$$\frac{\partial}{\partial t}\eta(\rho) + \operatorname{div}(\nabla S\, Q(\rho)) + (\rho - S)[Q - g\eta'](\rho) \leqslant 0, \tag{6}$$

with $Q'(\rho) = \eta'(\rho)\rho(1-\rho)$.

Our proof in [14] is based on the kinetic formulation on the function $f(t,y,\xi) = \mathbf{1}_{\xi < u(t,y)}$. It is equivalent to write all the entropy inequalities (6) with a help of variable ξ

$$\begin{cases} \frac{\partial f}{\partial t} + (\xi - S)g(\xi)\frac{\partial f}{\partial \xi} + g'(\xi)\nabla_y S \cdot \nabla_y f = \frac{\partial m}{\partial \xi}, \\ m(t,y,\xi) \geqslant 0 \ \text{ a bounded measure on } [0,T] \times \mathbb{R}^d \times \mathbb{R}, \ \ \forall T > 0, \\ f(0,y,\xi) = \mathbf{1}_{\xi < \rho_0(y)}, \\ -\Delta S + S = \rho := \int_0^\infty f(t,y,\xi)\,\mathrm{d}\xi \ \text{ in } \mathbb{R}^d. \end{cases} \tag{7}$$

Including long range repellent and short range attraction, the model becomes

$$\begin{cases} \partial_t n + \operatorname{div}[n(1-n)\nabla c - n\nabla S] = 0, \\ -D_c \Delta c + c = \alpha_c n, \\ \partial_t S - D_S \Delta S + \tau_S S = \alpha_S n. \end{cases} \tag{8}$$

It has been proposed and studied in [10,43]. Its interest is to generate branching instabilities which makes it an alternative to the nutrient models of Section 3 for dentritic patterns formation.

5. Kinetic equations

Both hyperbolic and parabolic models describe the macroscopic cell colony. They can be derived from descriptions at the individual scale just as in the classical of fluid dynamics derived from the boltzmann equation.

For cells, the use of kinetic models was motivated by the observation that *Escherichia coli* (but this is true for *B. subtilis* mentioned in Section 3) move by a sequence of jumps (of order of 1 second) and tumbles which are much faster. This motivated Othmer, Dunbar and Alt [39] to propose a kinetic model in the 1980s. The subject has been renewed recently after the work [20,11,18].

The unknown is now the density $f(t,x,v)$ of cells moving with velocity v. Once adimensionalized, the model reads

$$\begin{cases} \partial_t f + v \cdot \nabla_x f = \int_V (T[S](v',v)f' - T[S](v,v')f)\,\mathrm{d}v', \\ -\Delta S + S = \rho(x,t) := \int_V f(t,x,v)\,\mathrm{d}v, \\ f(0,x,v) = f^0(x,v), \end{cases} \tag{9}$$

where $f' = f(t,x,v')$, V is the range of possible velocities of cells during the jump (usually it is a ball or a sphere). The most interesting and original aspect of this model is the tumbling kernel $T[S](v',v)$ which gives the rate of change from velocity v' to velocity v depending on the chemoattractant (signal) $S(x,t)$.

For example one can choose

$$T[S](v',v) = k_- S(x - \varepsilon v') + k_+ S(x + \varepsilon v), \tag{10}$$

a way to say that the tumbling rate increases when the signal S increases and that the cells react with a short delay ε (due to the progressive saturation of receptors which triggers the tumbling). The memory effect plays a fundamental role in the existence theory [11,7] because they allow for the use of the dispersive aspect of kinetic equations. The method has proved to be also successful for tumbling kernels depending on the gradient of S, see [25,7]. One of the most remarkable result is possible blow-up [6], for example

$$T[S](v',v) = \chi(v \cdot \nabla S(x))_+, \tag{11}$$

Another class of tumbling kernels has also been proposed after the observation that bacteria increase the duration of their jump when chemoattractant concentration increases (along their trajectory). The tumbling kernel (see [25,16,5]) is written

$$T[S](v',v) = \psi\left(\frac{\partial S}{\partial t} + v' \cdot \nabla S(x)\right), \tag{12}$$

with $\psi(\cdot)$ a decreasing function indicating that cells indeed have tendency to make longer jumps when they feel higher chemoattractant along their trajectory. The modeling interest of this

kernel is that the drift-diffusion limit contains more biophysics; it is written

$$\begin{cases} \frac{\partial}{\partial t}\rho(x,t) - d_\rho \Delta\rho(x,t) + \mathrm{div}[U_S \rho(x,t)] = 0, \\ U_S(x,t) = A\int_V \frac{v_1}{\psi\left(\frac{\partial S}{\partial t} + v_1|\nabla S|\right)}\, \mathrm{d}v \frac{\nabla S}{|\nabla S|}, \end{cases} \tag{13}$$

and $S(x,t)$ is still given by a parabolic or elliptic equation as in Section 2.

For this type of model, pulse waves exist is a wide range of conditions see [4]. This is in opposition to the standard Keller–Segel model (1) for which traveling waves exist only with birth/death terms, see [37] and the references therein.

References

[1] P. Biler, Global solutions to some parabolic-elliptic systems of chemotaxis, Adv. Math. Sci. Appl. 9 (1999) 347–359.

[2] A. Blanchet, J. Carrillo, N. Masmoudi, Infinite time aggregation for the critical Patlak–Keller–Segel model in $\mathbb{R}^2$, Comm. Pure Appl. Math. 61 (10) (2008) 1449–1481.

[3] A. Blanchet, J. Dolbeault, B. Perthame, Two dimensional Keller–Segel model in $\mathbb{R}^2$: optimal critical mass and qualitative properties of the solution, Electron. J. Diff. Eqns. 2006 (44) (2006) 1–32.

[4] N. Bournaveas, A. Burguin, V. Calvez, B. Perthame, J. Saragosti, P. Silberzan, Mathematical description of bacterial traveling pulses. Plos Comp. Biol., in press.

[5] N. Bournaveas, V. Calvez, Global existence for the kinetic chemotaxis model without pointwise memory effects, and including internal variables, Kinet. Relat. Models 1 (2008) 29–48.

[6] N. Bournaveas, V. Calvez, Critical mass phenomenon for a chemotaxis kinetic model with spherically symmetric initial data, Annales de l'Institut Henri Poincaré (C) Non Linear Analysis 26 (5) (2009) 1871–1895.

[7] N. Bournaveas, V. Calvez, S.Gutierrezet B. Perthame, Global existence for a kinetic model of chemotaxis via dispersion and Strichartz estimates, Comm. PDE 33 (1) (2008) 79–95.

[8] M. Burger, Y. Dolak, C. Schmeiser, Asymptotic analysis of an advection-dominated chemotaxis model in multiple spatial dimensions, Commun. Math. Sci. 6 (1) (2008) 1–28.

[9] V. Calvez, J.A. Carrillo, Volume effects in the Keller–Segel model: energy estimates preventing blow-up, J. Math. Pure Appl. 9 (86) (2006) 155–175.

[10] F. Cerretti, B. Perthame, C. Schmeiser, M. Tang, N. Vauchelet, Waves for an hyperbolic Keller–Segel model and branching instabilities. Report INRIA-0049089 (2010). To appear in M3AS.

[11] F.A.C.C. Chalub, P.A. Markowich, B. Perthame, C. Schmeiser, Kinetic models for chemotaxis and their drift-diffusion limits, Monatsh. Math. 142 (2004) 123–141.

[12] L. Corrias, B. Perthame, H. Zaag, Global solutions of some chemotaxis and angiogenesis systems in high space dimensions, Milano J. Math. 72 (2004) 1–29.

[13] C.M. Dafermos, Hyperbolic Conservation Laws in Continuum Physics, second ed., Springer-Verlag, Berlin, 2005.

[14] A.L. Dalibard, B. Perthame, Existence of solutions of the hyperbolic Keller–Segel model, Trans. AMS 361 (5) (2009) 2319–2335.

[15] Y. Dolak, C. Schmeiser, The Keller–Segel model with logistic sensitivity function and small diffusivity, SIAM J. Appl. Math. 66 (2005) 286–308.

[16] Y. Dolak, C. Schmeiser, Kinetic models for chemota xis:hyrodynamics limits and spatio-temporal mechanisms, J. Math. Biol. 51 (2005) 595–615.

[17] J. Dolbeault, C. Schmeiser, The two-dimensional Keller–Segel model after blow-up, Discr. Cont. Dyn. Syst. 25 (2009) 109–121.

[18] R. Erban, H.G. Othmer, Taxis equations for amoeboid cells, J. Math. Biol. 54 (2007) 847–885.

[19] P. Gray, S.K. Scott, Autocatalytic reactions in the isothermal continuous stirred tank reactor: isolas and other forms of multistability, Chem. Eng. Sci. 38 (1) (1983) 29–43.

[20] T. Hillen, H.G. Othmer, The diffusion limit of transport equations derived from velocity-jump processes, SIAM J. Appl. Math. 61 (3) (2000) 751–775.

[21] T. Hillen, K.J. Painter, Volume-filling and quorum-sensing in models for chemosensitive movement, Canad. Appl. Math. Quart. 10 (4) (2002) 501–543.

[22] T. Hillen, K.J. Painter, A user's guide to PDE models for chemotaxis, J. Math. Biol. 58 (2009) 183–217.

[23] T. Hillen, K.J. Painter, C. Schmeiser, Global existence for chemotaxis with finite sampling radius, Discrete Contin. Dyn. Syst. Ser. B 7 (1) (2007) 125–144.

[24] D. Horstmann, From 1970 until present: the Keller–Segel model in chemotaxis and its consequences I, Jahresber. Deutsch. Math.-Verein 105 (2003) 103–165.

[25] H.J. Hwang, K. Kang, A. Stevens, Global solutions of nonlinear transport equations for chemosensitive movement, SIAM J. Math. Anal. 36 (4) (2005) 1177–1199.

[26] E.F. Keller, L.A. Segel, Model for chemotaxis, J. Theor. Biol. 30 (1971) 225–234.

[27] E.F. Keller, L.A. Segel, Traveling bands of chemotactic bacteria: a theoretical analysis, J. Theor. Biol. 30 (1971) 235–248.

[28] D.A. Kessler, H. Levine, Fluctuation induced diffusive instabilities, Nature 394 (1998) 556–558.

[29] T. Kolokolnikov, M.J. Ward, J. Wei, The existence and stability of spike equilibria in the one-dimensional Gray–Scott model: the pulse-splitting regime, Physica D 202 (2005) 258–293.

[30] I. Golding, Y. Kozlovsky, I. Cohen, E. Ben-Jacob, Studies of bacterial branching growth using reaction–diffusion models for colonial development, Phys. A 260 (1998) 510–554.

[31] P.L. Lions, B. Perthame, E. Tadmor, Kinetic formulation of scalar conservation laws, J. AMS 7 (1) (1994) 169–191.

[32] P.K. Maini, Applications of mathematical modelling to biological pattern formation, In Coherent structures in complex systems (Sitges, 2000), Lecture Notes in Phys. 567 (2001) 205–217.

[33] A. Marrocco, H. Henry, I.B. Holland, M. Plapp, S.J. Séror, B. Perthame, Models of self-organizing bacterial communuities and comparisons with experimental observations, Math. Model. Nat. Phenom. Mathematical Modelling of Natural Phenomena 5 (1) (2010) 148–162.

[34] M. Matsushita, J. Wakita, H. Itoh, I. Rafols, T. Matsuyama, H. Sagaguchi, M. Mimura, Interface growth and and pattern formation in bacterial colonie, Physica A 249 (1998) 517–524.

[35] M. Mimura, H. Sakaguchi, M. Matsushita, Reaction diffusion modelling of bacterial colony patterns, Physica A 282 (2000) 283–303.

[36] J.D. Murray, Mathematical biology, Second edition., Springer, 2002.

[37] G. Nadin, B. Perthame, L. Ryzhik, Traveling waves for the Keller–Segel system with Fisher birth terms. Interfaces Free Bound., in press

[38] T. Nagai, Blow-up of radially symmetric solutions to a chemotaxis system, Adv. Math. Appl. Sci. 5 (1995) 581–601.

[39] H.G. Othmer, S.R. Dunbar, W. Alt, Models of dispersal in biological systems, J. Math. Biol. 26 (3) (1988) 263–298.

[40] B. Perthame, Mathematical tools for kinetic equations, Bull. Amer. Math. Soc. (N.S.) 41 (2) (2004) 205–244.

[41] B. Perthame, Transport equations in Biology (LN Series Frontiers in Mathematics), Birkhauser, 2007.

[42] B. Perthame, Why hyperbolic and kinetic models for cell populations self organization?, in: E. Tadmor, J.-G. Liu, A.E. Tzavaras (Eds.), Hyperbolic Problems: Theory, Numerics and Applications. AMS 2009.

[43] B. Perthame, C. Schmeiser, M. Tang, N. Vauchelet, Traveling plateaus for a hyperbolic Keller–Segel system with logistic sensitivity; existence and branching instabilities. Work in preparation.
[44] M. Pierre, Weak solutions and supersolutions in L^1 for reaction-diffusion systems, J. Evol. Equ 3 (1) (2003) 153–168.
[45] D. Serre, Systems of Conservation Laws, Cambridge University Press, Cambridge, 2000.
[46] J.J.L. Velázquez, Point dynamics in a singular limit of the Keller–Segel model. I. motion of the concentration regions, SIAM J. Appl. Math. 64 (2004) 1198–1223.