IOP PUBLISHING NONLINEARITY

Nonlinearity **21** (2008) T283–T289 doi:10.1088/0951-7715/21/12/T04

OPEN PROBLEM

Partial differential equations and non-diffusive structures

A Stevens[1] **and J J L Velázquez**[2]

[1] Universität Heidelberg, Angewandte Mathematik und Bioquant, INF 267, D-69120 Heidelberg, Germany
[2] ICMAT (CSIC-UAM-UC3M-UCM), Facultad de Matemáticas, Universidad Complutense, Madrid 28040, Spain

E-mail: angela.stevens@uni-hd.de and velazque@mat.ucm.es

Received 15 September 2008, in final form 24 September 2008
Published 13 November 2008
Online at stacks.iop.org/Non/21/T283

Abstract
In this paper we give a short introduction to open problems and recent studies of classes of partial differential equations, which—in contrast to reaction–diffusion systems—describe phenomena with local interactions. Partial differential equations coupled with ordinary differential equations, models of transport type and hyperbolic systems are discussed with respect to their pattern forming behaviour.

Mathematics Subject Classification: 35K55, 45K05, 35L60, 35B10, 35B40, 82C70, 92C15, 92C17

1. Introduction

In the following we summarize some models of partial differential equations, which are characterized by the presence of at least one non-diffusible 'active agent'. We are interested in the pattern forming behaviour and the long time dynamics of such systems. From the applied point of view we will focus on biological examples and models here, although the mathematical questions we address also arise in other scientific contexts. From the mathematical point of view it turns out that the solutions of these models show peculiar patterns in comparison with mathematical models, where most agents in the system are assumed to diffuse. This latter type of systems and equations has been studied in mathematical biology in great detail, especially in the context of Turing type instabilities. The analysis of the 'more local' models requires different mathematical methods and techniques.

2. Reaction–diffusion equations coupled to ODEs

One example for a model of an interacting cell system whose continuous reaction–diffusion limit is given by a reaction–diffusion equation coupled to an ODE is the model for loss of

 © 2008 IOP Publishing Ltd and London Mathematical Society Printed in the UK

contact inhibition of malignant cells within a healthy tissue, proposed and analysed in [3, 17]. Two types of cells, malignant and healthy ones, move and divide on a two-dimensional lattice. The malignant cells, denoted by U, are supposed to be more motile and thus diffuse on the lattice much faster than the healthy cells, denoted by V. In the case of cell–cell contact the healthy cells are inhibited to grow, whereas the malignant cells can still grow in such a situation. Thus the malignant cells are able grow on top of other cells, i.e. the birth rate of U is assumed to be constant. The healthy V cells can only grow on empty sites. The death rate for all cells of type U and of type V increases with local overcrowding, since they are assumed to compete, e.g. for oxygen. In [3, 17] the following system of partial differential equations was rigorously derived for the macroscopic cell densities u, v by means of a hydrodynamic limit:

$$u_t = \Delta u + u(\beta - D(u) - D'(u)v),$$

$$v_t = v(\beta(1-v)\exp(-u) - D(u)).$$

Here $D(u) = \sum_{k=0}^{\infty} \gamma(k+1)\frac{u^k}{k!}\mathrm{e}^{-u}$ and γ relate to the death processes in the original interacting stochastic many particle models and β relates to the birth rate (cf [17]). The diffusion of the V cells vanishes in this limit.

An interesting question for this limiting system is, what are the qualitative dynamics of the populations of malignant and of healthy cells, i.e. under what conditions does one of the cell populations spread faster than the other within the heterogeneous tissue. A first result was given in [17]. Related questions were pursued in [8].

3. Drift–diffusion models coupled to an ODE

A by now classical drift–diffusion model, respectively, cross-diffusion model in mathematical biology is the Keller–Segel (KS) model for chemotaxis [14]. Cells exhibiting chemotaxis move towards regions of higher concentrations of an attractive chemical signal. Well-known examples are the chemotactic behaviour of *Escherichia coli* and of the slime mould amoebae *Dictyostelium discoideum*.

Two particularly interesting limiting cases of the KS model exist. First, the case where the diffusion of the chemotactic species is much slower than the diffusion of the chemo-attractant. In suitable non-dimensional units the model then reduces to a parabolic–elliptic system:

$$u_t = \Delta u - \nabla(u\nabla v), \qquad x \in \Omega \in \mathbb{R}^N, \quad t > 0, \tag{1}$$

$$0 = \Delta v + u - c \qquad x \in \Omega, \quad t > 0. \tag{2}$$

Here $u = u(t,x)$ denotes the concentration of the chemotactic organism and $v = v(t,x)$ denotes the concentration of the chemo-attractant. This system is usually stated with zero-flux boundary conditions for a bounded domain Ω and initial data $u(0,x) = u_0(x)$. A compatibility condition which allows to solve (2) with zero-flux conditions is given by $c = \frac{1}{|\Omega|}\int_\Omega u_0\,\mathrm{d}x$.

The mathematical properties of system (1) and (2) have been studied extensively, in particular steady states and conditions for initial data which ensure the global existence of solutions or blow-up in finite time. The number of papers on the KS model and related systems is rather large by now. A summary of the results on this topic in published papers and preprints until 2002 can be found in [9, 10].

So far a second interesting limiting case for the KS type of models has been studied much less. Instead of a diffusible chemo-attractant a kind of non-diffusible attractive memory is

assumed to be given:

$$u_t = \Delta u - \nabla(u \nabla g(z)), \qquad x \in \Omega \subset \mathbb{R}^N, \quad t > 0, \tag{3}$$

$$z_t = f(u, z). \tag{4}$$

For specific positive g and negative f chemotactic travelling bands were already discussed in [15], see also [11] and further references therein. In [23] and [2] the existence of global solutions for such models was proved.

Mathematically the situation becomes more involved for positive f. A specific example for system (3) and (4) with $g(z) = \theta \log(z)$ for $\theta > 0$ and $f(u, z) = u$ was introduced in [18, 24]. The idea for this model originated from a self-attracting reinforced random walk of a single particle, the derivation of conditions for recurrence and transience and the biological phenomenon of slime trail following and aggregation of myxobacteria (cf the review paper [19] for reinforced random walks and the book [4] for the self-organization of myxobacteria).

The PDE model (3) and (4) cannot provide an accurate description of the dynamics of the self-attracting reinforced random walk of a single particle in any nontrivial continuum limit. However, it seems likely that for a many particle model this PDE–ODE system results as a limit under suitable conditions on the number of particles and the law of reinforcement. Nevertheless, the rigorous derivation of (3) and (4) starting from a stochastic many particle system has not been obtained so far. In case equation (4) also allows diffusion, a rigorous derivation of the system from a moderately interacting stochastic many particle system has been obtained in [25].

For $f(u, z) = u \cdot z$ and $g(z) = \log(z)$ blow-up in finite time in one space dimension for specific initial data was proved in [16]. These functions give rise to a much stronger tendency for blow-up of solutions than the case $f(u, z) = u$ and $g(z) = \theta \log(z)$ for any $\theta > 0$. Therefore, the asymptotic behaviour of the solutions of (3) and (4) for $f(u, z) = u$ and $g(z) = \theta \log(z)$ for different space dimensions has recently been studied in [26] in more detail. Results include blow-up in finite time, blow-up in infinite time and convergence of solutions to zero in a self-similar way. Most of these solutions exhibit involved asymptotics, which require a careful analysis of several boundary layers. As a general rule *larger* values of θ and *smaller* values of the spatial dimension N yield a stronger tendency for blow-up. As a consequence, many critical parameter values occur for which the solutions change their asymptotic behaviour.

The asymptotics given in [26] do not yield blow-up for $\theta < 1$ in any space dimension. Given the form of equation (3) one can expect an increasing strength of the chemotactic attraction for increasing θ. The dependence of the behaviour of (3) and (4) on the space dimension N is not so obvious and requires a more detailed analysis than what is shown so far in [26]. An intuitive explanation for the dependence of blow-up on the spatial dimension is as follows: for smaller dimensions the motion of a Brownian particle covers space more densely than for larger dimensions. As a consequence, the modification of the environment (given by v) is smaller for larger dimensions and therefore the tendency for blow-up is weaker. Blow-up results from steepening gradients in the attractive environment v. In the case of a diffusing chemical environment v the result is different. Then the tendency for blow-up of solutions is stronger in larger dimensions.

Due to the hyperbolic character of equation (4) the asymptotics of the solutions of (3) and (4) depend very sensitively on the initial data in some cases. The strongest dependences occur for $N = 1, \theta = 1$. This has been rigorously proved in [13]. Also the concentration of mass to a Dirac mass in infinite time has been shown for the case $N = 1, 1 < \theta < 3$.

It would be interesting to obtain rigorous proofs for various other asymptotic results derived in [26] and to understand them in a more general context.

4. Models of transport type

Models of transport type are extensively studied in the context of age and stage structured population dynamics, especially in epidemiology. Usually the dynamics of a distribution function $f = f(t, x, \theta)$ is described with respect to time, space and a set of internal variables or age/stage parameters θ. These variables can include magnitudes such as cell orientation or shape, the state within the cell cycle, age with respect to a disease state and magnitudes for internal cell states, such as chemical concentrations. Depending on the setting, f can be understood as a cell density or a probability distribution. Examples are given in [27] and [20]. Further classical references are cited in these books.

An example for a transport model analysed in mathematical biology is

$$(\partial_t f + v(\theta) \cdot \nabla_x f)(t, x, \theta) = \int_{[-1,1]} [K(\hat{\theta}, \theta; f) f(t, x, \hat{\theta}) - K(\theta, \hat{\theta}; f) f(t, x, \theta)] \, \mathrm{d}\hat{\theta}. \tag{5}$$

The left-hand side of this equation describes cell motion with speed $v(\theta)$, which may depend on the set of internal variables θ. The right-hand side describes the transition between different cell states. More generally derivatives with respect to θ could also be included and further dependences considered. Equations such as (5) have been used to study reorientation of cells due to interaction with themselves and with external cues. In the context of chemotaxis (cf [1]) the kernel K depends on an external attractive chemical signal instead of (or additionally to) f itself. For alignment of small stiff filaments and elongated cells equation (5) was discussed in [5] and [7], but cell motion in space was omitted.

The fact that the changes in the internal variables take place locally, i.e. in regions of a size which is smaller than the characteristic length scale used to define the distribution $f(t, x, v)$, justifies the discussion of equation (5) together with the other type of models presented in this paper.

4.1. Pattern formation in transport models with internal variables

An interesting feature of models of type (5) is that they can generate patterns with a characteristic wavelength. This is well known for reaction–diffusion systems and was discovered in the classical work by Turing [28]. The existence of pattern forming instabilities for (5) has been proved in [21] for a discrete set of state variables. The linearization of equations of type (5) can exhibit periodic oscillations with a characteristic wavelength, if at least three state variables are present. It has also been proved that the formation of nontrivial patterns is possible with at least four internal variables, if the resulting system is symmetric under reflections. The basic model in this case is

$$\begin{aligned}
(u_1)_t + \alpha(u_1)_x &= S_2(u_1, u_2, v_1, v_2) - T_1(u_1, u_2, v_1, v_2),\\
(u_2)_t + \beta(u_2)_x &= T_1(u_1, u_2, v_1, v_2) - T_2(u_1, u_2, v_1, v_2),\\
(v_1)_t - \alpha(v_1)_x &= T_2(u_1, u_2, v_1, v_2) - S_1(u_1, u_2, v_1, v_2),\\
(v_2)_t - \beta(v_2)_x &= S_1(u_1, u_2, v_1, v_2) - S_2(u_1, u_2, v_1, v_2).
\end{aligned}$$

Under suitable conditions on α, β, T_1, T_2 and S_1, S_2 the solutions of the linearized system show patterns with a defined wavelength.

These results can be interpreted in analogy to Turing's results. Nontrivial patterns are possible in reaction–diffusion systems only if they are complex enough. Linear systems with

one diffusing chemical cannot generate patterns, but—as Turing proved—this is possible if at least two different chemicals with different diffusion coefficients are involved. In the case of systems of type (5) the patterns are generated by a nontrivial coupling of the cell motility with the dynamics of the internal cell variables.

The models discussed in [21] are motivated by the peculiar counter migrating periodic wave-like patterns—or ripples—in cultures of myxobacteria (cf [4]). After alignment these bacteria move in a nearly one-dimensional manner, basically in two directions, and reverse upon contact after the exchange of a signal. It was proved in [21] that models with 'reasonable' functional dependences can reproduce the experimentally described ripples, if they contain three internal cell states for the cells moving in the same of the two possible directions, which means overall six equations for the full system. This result indicates that a minimal amount of complexity is required for such a system with local interaction to create the requested patterns. Of course more research is needed to clarify if and how the observed biological phenomenon relates to the models suggestions, i.e. what could be the mechanics of the different cell states. An additional test for the model is the experimental observation that the wavelength of the periodic pattern increases and finally disappears, if a specific type of mutants is added to the culture, namely, bacteria which are unable to submit the signal for reversal to their neighbours which are in direct contact with themselves. The suggested model together with the natural extension for the mutant population perfectly reflects this qualitative feature mathematically (cf [21]).

In [21] mathematical methods have been developed to study classes of equations of type (5) which generate patterns. A more systematic classification of such models is still open to do. It would also be interesting to study analogous effects for nonlinear problems. The analysis of pattern formation for nonlinear systems has been done for reaction–diffusion systems. Such results are lacking so far for nonlinear versions of the equations discussed in [21]. This seems interesting to analyse from the mathematical point of view.

4.2. Alignment in transport models

Models of type (5) were also discussed in [5] to study alignment of small, stiff filaments or elongated bacteria, namely

$$\partial_t f(t,\theta) = \int_{[-1,1]} [K(\hat{\theta},\theta;f) f(t,\hat{\theta}) - K(\theta,\hat{\theta};f) f(t,\theta)]\,\mathrm{d}\hat{\theta} \tag{6}$$

with

$$K(\theta,\hat{\theta};f) = \int_{[-1,1]} G_\sigma(\hat{\theta} - M_w(\theta)) f(t,w)\,\mathrm{d}w,$$

where G_σ is the standard periodic Gaussian

$$G_\sigma(u) = (4\pi\sigma)^{-1/2} \sum_{m\in\mathbb{Z}} \exp(-(u+2m)^2/(4\sigma)), \tag{7}$$

$M_w(\theta) = \theta + V(w-\theta)$ is the optimal reorientation due to interaction of bundles of filaments with those of orientation w, and V is the orientational angle. Here $\sigma = 0$ is a limiting case, where G_σ is the Dirac mass. Uniform convergence of solutions for $\sigma \to 0$ was established in [6].

In [5] and [7] involved bifurcation results for steady state solutions of (6) were obtained. In [12] and [22] the full equation was rigorously analysed. In [12] the model for deterministic

alignment mechanisms, namely, $\sigma = 0$, was studied. It was rigorously proved that for a specific class of initial data the solutions of the equation do align the filament bundles along two opposite directions. Nevertheless, the amount of mass aligning for each of the opposite directions turned out to be arbitrary. This is due to the deterministic character of the model. In [22] it was proved that in the presence of stochastic effects on the alignment mechanism, namely, $\sigma > 0$, mass selection results and only two values for the ratio between the masses aligning in opposite directions are possible. Either identical masses are aligned in the two directions, or most of the mass is concentrated in only one direction. Which of the two cases occurs depends on the specific form of the interaction given by V, as discussed in [22].

The results in [12] and [22] are basically local results and have been derived either for specific initial distributions or under suitable smallness conditions for the intensity of the stochasticity, the strength of the interactions for alignment, and others. It would be interesting to clarify the necessity of these restrictions.

The analysis in [5, 7, 12, 22] is restricted to spatially homogeneous situations. How additional spatial dependences do affect the system is largely open.

References

[1] Alt W 1981 Singular perturbation of differential integral equations describing biased random walks *J. Reine Angew. Math.* **322** 15–41

[2] Corrias L, Perthame B and Zaag H 2004 Global solutions of some chemotaxis and angiogenesis systems in high space dimensions *Milan J. Math.* **72** 1–28

[3] De Masi A, Luckhaus S and Presutti E 2007 Two scales hydrodynamic limit for a model of malignant tumour cells *Ann. Inst. H. Poincaré Probab. Statist.* **43** 257–97

[4] Dworkin M and Kaiser D (ed) 1993 *Myxobacteria II* (American Society for Microbiology Press)

[5] Geigant E 1999 Nichtlineare Integro-Differential-Gleichungen zur Modellierung interaktiver Musterbildungsprozesse auf $\mathbb{S}^1$ *PhD Thesis* Bonn University *Bonner Mathematische Schriften* vol 323 (Bonn University)

[6] Geigant E 2000 Stability analysis of a peak solution of an orientational aggregation model *EQUADIFF 99: Proc. Int. Conf. on Differential Equation (Berlin)* vol 2 (Singapore: World Scientific) pp 1210–16

[7] Geigant E and Stoll M 2003 Bifurcation analysis of an orientational aggregation model *J. Math. Biol.* **46** 537–63

[8] Heinze S and Schweitzer B 2005 Creeping fronts in degenerate reaction–diffusion systems *Nonlinearity* **18** 2455–76

[9] Horstmann D 2003 From 1970 until present: the Keller–Segel model in chemotaxis and its consequences: I *Jahresber. Deutsch. Math.-Verein.* **105** 103–65

[10] Horstmann D 2004 From 1970 until present: the Keller–Segel model in chemotaxis and its consequences: II *Jahresber. Deutsch. Math.-Verein.* **106** 51–69

[11] Horstmann D and Stevens A 2004 A constructive approach to travelling waves in chemotaxis *J. Nonlinear Sci.* **14** 1–25

[12] Kang K, Perthame B, Stevens A and Velázquez J J L 2008–2009 An integro-differential equation model for alignment and orientational aggregation *J. Diff. Eqns* at press

[13] Kang K, Stevens A and Velázquez J J L 2008 Qualitative behaviour of a Keller–Segel model with non-diffusive memory *Max-Planck-Institute for Mathematics in the Sciences, Leipzig, Germany*, *Preprint* 35 *Commun. Partial Diff. Eqns* submitted

[14] Keller E F and Segel L A 1970 Initiation of slime mold aggregation viewed as an instability *J. Theor. Biol.* **26** 399–415

[15] Keller E F and Segel L A 1971 Travelling bands of chemotactic bacteria: a theoretical analysis *J. Theor. Biol.* **30** 235–48

[16] Levine H and Sleeman B 1997 A system of reaction diffusion equations arising in the theory of reinforced random walks *SIAM J. Appl. Math.* **57** 683–730

[17] Luckhaus S and Triolo L 2004 The continuum reaction–diffusion limit of a stochastic cellular growth model *Rend. Mat. Ac. Lincei* s.9 **15** 215–23

[18] Othmer H G and Stevens A 1997 Aggregation, blow-up and collapse. The ABC's of taxis in reinforced random walks *SIAM J. Appl. Math.* **57** 1044-81

[19] Pemantle R 2007 A survey of random processes with reinforcement *Probab. Surv.* **4** 1–79

[20] Perthame B 2007 *Transport Equations in Biology, Frontiers in Mathematics* (Basle: Birkhäuser)
[21] Primi I, Stevens A, Velázquez J J L Pattern forming instabilities driven by non-diffusive interaction *Preprint*
[22] Primi I, Stevens A and Velázquez J J L 2007 Mass-selection in alignment models with non-deterministic effects *Max-Planck-Institute for Mathematics in the Sciences, Leipzig, Germany*, *Preprint* 34 *Commun. Partial Diff. Eqns* submitted
[23] Rascle M 1979 Sur une équation intégro-différentielle non linéaire issue de la biologie *J. Diff. Eqns* **32** 420–53
[24] Stevens A 1995 Trail following and aggregation of myxobacteria *J. Biol. Syst.* **3** 1059–68
[25] Stevens A 2000 The derivation of chemotaxis equations as limit dynamics of moderately interacting stochastic many-particle systems *SIAM J. Appl. Math.* **61** 183–212
[26] Stevens A and Velázquez J J L Asymptotics study of a partial differential equation system motivated by reinforced random walks *Preprint*
[27] Thieme H 2003 *Mathematics in Population Biology* (*Princeton Series in Theoretical and Computational Biology*) (Princeton: Princeton University Press)
[28] Turing A 1952 The chemical basis of morphogenesis *Phil. Trans. R. Soc.* B **237** 37–72