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Comment

The spatial patterning potential of nonlinear diffusion Comment on "Phase separation driven by density-dependent movement: A novel mechanism for ecological patterns" by Quan-Xing Liu et al.

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Spatial pattern formation is ubiquitous in biology, with examples ranging from animal coat markings to skeletal patterns in the limb. A fundamental question in biology is, how do these patterns arise? In 1952, the mathematician Alan Turing proposed a quite novel model for this. He showed that a system of reacting and diffusing chemicals could amplify small spatial fluctuations about an initial spatially uniform steady state, to give rise to spatially heterogeneous patterns [1]. He termed these chemicals "morphogens" and hypothesised that they served as pre-patterns for cells, whose differentiation fate would be determined based on the concentration of morphogen they experienced. Counter-intuitively, it is diffusion that drives this patterning process. Later on, this idea was more fully explored by Gierer and Meinhardt [2], who couched the mechanism in terms of "short-range activation, long-range inhibition". While the theory remains controversial in biology, there are many examples of putative Turing morphogens (see, for example [3,4]) and the patterning process has been shown to occur in chemistry [5,6].

Liu et al. [7] propose that in ecology, movement, instead of playing a dissipative role when modelled as diffusion in the Turing approach, could actually play an active role in patterning. They propose the Cahn–Hilliard modelling framework [8], a single equation of 4th order in spatial components, as a possible mechanism for segregation in animals. This model was first developed in the context of phase separation in a binary alloy and proposes that a free energy, whose variational derivative (the chemical potential) is given by the particular form $f(N) - \kappa\nabla^2 N$ where N is concentration and κ a positive parameter, is minimised. This leads to the process of phase separation where, essentially, N separates out spatially into regions that correspond to the zeros of $f(N)$ that are potential wells of the free energy.

Phase field methods have been applied to model patterns that can be delineated by a threshold value of a single scalar field. The Cahn–Hilliard equation, which is central to the paper by Liu et al., governs initial and boundary

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value problems of phase segregation phenomena. While the non-convex free energy function underlying this class of methods has a clear physical meaning for phase segregation of solids and fluids, its use to represent patterns in tissues rests on more abstract foundations. This lack of physical interpretation notwithstanding, non-convex "free energy" functions have been defined and complemented by gradient energy terms to describe the evolution of scalar patterns in two- and three-dimensional tissues. Examples include the dynamics of growth and possible break up of a tumour as a model for transition towards malignancy [9–12]. In this group of models a threshold value of a scalar field demarcates points in the domain to lie within or outside the tumour, and its evolution is governed by the Cahn–Hilliard equation. Other authors have extended this treatment with another scalar field to describe the growth of a capillary network that develops around a tumour during the process of angiogenesis [13–15]. The choice of free energy functions underlies the diversity of three-dimensional patterns whose evolution can be represented by this framework. It is common, especially in some of the preceding applications to tumour dynamics, to couple phase field treatments with equations that govern mass transport and reactions of nutrients, signalling molecules and growth factors.

In [16] a single generalised Cahn–Hilliard equation is proposed to describe cell fronts invading an open wound. While in this example the Cahn–Hilliard term arises due to interaction energy considerations between cells, Liu et al. [7] argue that this can be generalised in the context of ecology to be a nonlinear diffusion term, arising due to density-dependent diffusion. They indicate, for example, that the well-known Patlak–Keller–Segel [17,18] chemotaxis model can also be viewed in the context of a nonlinear diffusion, if one uses the chemoattractant concentration as a proxy for cell density. They present a number of ecological examples (mussel beds, ants, elk) where animals form groups and point out that in these cases movement is density-dependent. They propose these case studies as motivation for more detailed study of density-dependent movement models.

Such models are becoming more prevalent in the literature. For example, the typical diffusion models used for cell density are derived under the assumptions that cells are point particles. However, as soon as one relaxes that assumption and allows for volume exclusion, the diffusion term becomes highly nonlinear and different modelling assumptions on how cells interact locally become encoded in the form of the nonlinearity of the diffusion term for the global (population-level) behaviour of the tissue [19]. An open question is, what functional forms of nonlinear diffusion give results that are similar so that the details of the local behaviour do not matter at the global level? Moreover, in biology, and indeed, ecology, individuals of the same type cluster and this calls into question the mean-field approximation under which most reaction/interaction terms are derived. For example, it was shown in [20] that a reaction–diffusion model for cell spreading in a wound healing assay which accounts for spatial correlation and volume exclusion can give significantly different predictions for parameter values to those from a model based on mean-field dynamics.

Density-dependent diffusion has been proposed as a way to model barriers to cell movement. For example, in [21] it is proposed that in certain scenarios cancer cells can only invade normal tissue once the latter's density is reduced to below its carrying capacity. This model predicts a novel travelling wave behaviour in which there are acellular gaps between the invading cancer cell front and the retreating normal cell front. The authors show that this prediction is borne out experimentally.

There is a long history of computational models proposed to describe the movement of cells in epithelial sheets and an important open question is which modelling approach should be used for which application and could results be due to model framework and not the underlying biology? To tackle these problems requires a comparison of these models, which is challenging as there is no common framework to facilitate a precise comparison. However, there have been efforts to derive continuum approximations to some of these models. In [22] it was shown that the cellular Potts model [23] of collective cell motion can be approximated by a diffusion equation with nonlinear diffusion term of the form $\frac{1+N^2}{(1-N)^2}$ where N is cell density, scaled appropriately, while in [24] it was shown that the cell-centre model [25] reduces, in a simple one-dimensional case, to a nonlinear diffusion equation with diffusion term $\frac{1}{N^2}$. An open question remains as to whether it is possible to derive such approximations in more complicated situations to allow a fuller comparison of models.

In conclusion, it is clear that throughout biology, medicine and ecology nonlinear diffusion plays an important role in spatial organisation. It is also clear that there are many open mathematical questions that must be addressed to allow for a rigorous underpinning theory for these models and analysis and also to enable us to determine in concise ways how different assumptions, leading to different forms of nonlinearity, impact model predictions.

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