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Cite as: AIP Conference Proceedings **2293**, 020006 (2020); https://doi.org/10.1063/5.0026549
Published Online: 25 November 2020

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Abstract. Two examples of recent research in which collective cell movement plays an important role are reviewed. In the first example, the phenomenon of cranial neural crest cell migration, it will be shown how a very simple hybrid agent-based model has been used in an interdisciplinary collaboration to yield novel biological insights. In the second example, the classical model for angiogenesis will be revisited and a new partial differential equation model derived for this phenomenon.

INTRODUCTION

Collective cell migration is a recurrent theme in biology – in normal development, cells migrate long distances collectively, either in sheets or as individuals; in wound healing cells move to repair and regenerate structures; in disease, such as cancer, cells move to form new blood vessels (the process of angiogenesis, which also occurs in wound healing) and also to invade organs, leading to often fatal secondary tumours. Understanding such collective behaviour is still an open problem. Here, this phenomenon is considered in the context of two different areas – normal development and angiogenesis – and recent key findings are reviewed.

CRANIAL NEURAL CREST

The neural crest is a transient embryonic structure in vertebrates that gives rise to most of the peripheral nervous system and several non-neural cell types (for example, muscle cells in the cardiovascular system, pigment cells, *etc.*). There are four neural crests – cranial, trunk, vagal and sacral (enteric nervous system) and cardiac. Neural crest is an excellent paradigm for studying multiscale cell-cell local and non-local interactions as it is more experimentally amenable than many other systems, so that mathematical modelling predictions can be tested in the laboratory [1]. Cranial neural crest cells are of particular interest as they are very similar in behaviour to highly aggressive cancers, such as melanoma and neuroblastoma.

Cranial neural crest cells (NC cells) emerge from the neural tube and have to travel along a domain that is growing (to a length of about one millimetre) on a timescale of about a day. Clearly, random diffusion can not be a realistic mechanism for this to happen, so cells must be directed in some way. It is known that the overlying ectoderm produces the growth factor VEGF (vascular endothelial growth factor) which is a chemoattractant consumed by NCs. It is therefore tempting to hypothesize that a cell-induced gradient in this chemoattractant is used by cells to successfully migrate along the domain. This hypothesis was tested in chick by [2], where the domain was approximated as a growing two-dimensional flat rectangle. The VEGF dynamics were represented by a reaction-diffusion equation, suitably modified for a growing domain, while the NC cells were modelled as discrete agents that stochastically sampled their environment, consumed VEGF and moved up the resultant VEGF gradients. It was shown that the dynamics resulted in only a few cells successfully invading the domain, contrary to experimental observations. These simulations disproved the simple hypothesis but led to the suggestion that cells along the stream may have different responses, with cells at the back ("followers") responding to an (unspecified) signal generated by those at the front ("leaders"), while those at the front responded to the chemoattractant. This hypothesis was validated experimentally in [2].

International Conference of Numerical Analysis and Applied Mathematics ICNAAM 2019
AIP Conf. Proc. 2293, 020006-1–020006-3; https://doi.org/10.1063/5.0026549
Published by AIP Publishing. 978-0-7354-4025-8/$30.00

The model was further tested by predicting the outcome of various implantation experiments, which led to the hypothesis that cell behaviour was not fixed, but could be altered by the environment. These ideas were validated in further experimental studies in which the model successfully predicted the outcome of applying a source of VEGF to the stream [3] and manipulating the number of leader cells [4]. The model showed some simulations in which there was the possibility that leaders "escaped" and might not be able to signal followers. In [5] it was shown that the gene DAN is expressed at the entrance to the domain and it slows down the leading cells (the authors also showed that it had the same effect on certain highly aggressive cancer cells).

ANGIOGENESIS

The process by which the body regenerates new blood vessels is termed *angiogenesis*, and typically occurs as a natural response in wound healing – tissue devoid of oxygen emits signals that cause cells to break away from blood vessels and move towards the source of the signal, generating new vasculature. This process has been modelled in a number of different contexts and has been likened to a "snail-trail" (see, for example, [6, 7, 8]). A simple version of this model takes the form [9]:

$$\frac{\partial N}{\partial t} = D\frac{\partial^2 N}{\partial x^2} - \chi\frac{\partial}{\partial x}(N\frac{\partial c}{\partial x}) + \lambda Nc - \beta_e NE - \beta_n N^2, \tag{1}$$

$$\frac{\partial E}{\partial t} = \frac{1}{h}|D\frac{\partial N}{\partial x} - \chi N\frac{\partial c}{\partial x}|. \tag{2}$$

Formulated in one-dimension, here, $N(x,t)$ and $E(x,t)$ are the densities of the so-called *tip* cells (that respond to the chemical signal $c(x,t)$) and *stalk* cells (that "follow" the tips), respectively, where x is the distance measured from the blood vessel from which the tips are leaving and t is time. The parameters $D, \chi, \lambda, \beta_e, \beta_n, h$ are all positive constants. The first two terms on the RHS of the N equation model diffusion and chemotaxis, while the three kinetic terms model, respectively, the formation of more tips (branching) as an increasing function of chemoattractant concentration, tip annihilation via a tip-stalk interaction, or tip-tip interaction, leading to the formation of a loop. It is assumed that the flux of the tip cells initiates proliferation of the stalk cells, hence the term on the RHS of the second equation, where h is a scaling factor. Typically, there would be a further reaction-diffusion equation for c but here we assume that c is prescribed. For fuller details (including initial and boundary conditions) see the above references. The above system has been studied in detail and shown to exhibit a travelling pulse in N, followed by a travelling wave in E. In the context of tumour angiogenesis, it is known that tumour cells produce VEGF, which plays the role of the chemoattractant c and this is how a tumour becomes vascularised and gains more nutrient, allowing it to grow and eventually metastasize. In that context, the model was extended to two spatial dimensions and discretised, to produce one of the first models of tumour angiogenesis [10].

The above model is derived in a phenomenological way from an hypothesised set of rules. A systematic derivation starting from a discrete system and then taking the continuum limit was carried out recently in [11, 12] and it was found, surprisingly, not to lead to the traditional model, but to a new model:

$$\frac{\partial N}{\partial t} = (1 - a_n N - a_e E)[D\frac{\partial^2 N}{\partial x^2} - \chi\frac{\partial}{\partial x}(N\frac{\partial c}{\partial x})] + \lambda Nc - (\mu a_e NE + a_n N^2), \tag{3}$$

$$\frac{\partial E}{\partial t} = \mu N + a_n N[\mu N + D\frac{\partial^2 N}{\partial x^2} - \chi\frac{\partial}{\partial x}(N\frac{\partial c}{\partial x})]. \tag{4}$$

Here, $N(x,t)$ and $E(x,t)$ are normalised tip and stalk densities, respectively and a_n, a_e and μ are parameters (see the original paper for full details).

A further surprise is that this model, which looks quite different from the original snail-trail model, was shown to yield very similiar (almost identical) behaviour to the original model, for the range of parameters investigated. Presently, we are in the process of examining why this is the case (in prep.).

DISCUSSION

Collective migration of individuals is a common phenomenon occurring in ecology, epidemiology, biology and medicine. We have focused on two very different examples in which the individuals are cells, but have seen that

there are many shared properties. The individuals do not all behave in the same way – some are informed (so-called "leader cells" in cranial neural crest, "tip cells" in angiogenesis) responding to external guidance cues and, in turn, signalling to others (the "follower cells" in cranial neural crest, "stalk cells" in angiogenesis). We have shown two ways in which these processes can be modelled – via hybrid agent-based models, or using the more traditional partial differential equation approach. We have shown how such models can lead to the discovery of new biology as well as leading to new mathematical challenges. A further challenge in this field in general is to see if we can use a mathematical approach to determine the "hallmarks of collective movement", namely, can we find what are the key mechanisms necessary to generate robust collective movement, and can we map these onto biological processes and determine how different systems (for example, cells, animals, humans, *etc.*) generate these mechanisms?

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