Journal of Theoretical Biology 394 (2016) 77–92

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Influences of Allee effects in the spreading of malignant tumours

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HIGHLIGHTS

- We introduce one of the first mathematical models of tumour invasion with growth thresholds.
- Only biologically relevant travelling wave fronts exist, opposing earlier models.
- Experimental observations in tumour spread are uncovered in our model.
- We show the relevance of incorporating the Allee effect in tumour spread.

ARTICLE INFO

Article history:
Received 23 April 2015
Received in revised form
10 November 2015
Accepted 30 December 2015
Available online 21 January 2016

Keywords:
Malignant tumour model
Allee effects
Travelling wave solutions
Geometric singular perturbation theory
Canard theory

ABSTRACT

A recent study by Korolev et al. [*Nat. Rev. Cancer*, 14:371–379, 2014] evidences that the Allee effect—in its strong form, the requirement of a minimum density for cell growth—is important in the spreading of cancerous tumours. We present one of the first mathematical models of tumour invasion that incorporates the Allee effect. Based on analysis of the existence of travelling wave solutions to this model, we argue that it is an improvement on previous models of its kind. We show that, with the strong Allee effect, the model admits biologically relevant travelling wave solutions, with well-defined edges. Furthermore, we uncover an experimentally observed biphasic relationship between the invasion speed of the tumour and the background extracellular matrix density.

1. Introduction

1.1. Allee effects and tumour growth

A recent article in *Nature Reviews Cancer*, (Korolev et al., 2014), has highlighted how a well-established concept in ecology—the Allee effect (Allee, 1938)—is also relevant to tumours but has yet to be incorporated into their modelling. In its strong form, the Allee effect refers to the observation that there is a population threshold below which a species has negative population growth, driving it to extinction. The weak form of the Allee effect describes a species that has small (but not negative) population growth at low populations (Courchamp et al., 2008). The ecological causes of Allee effects (which are observed within small populations) are multitudinous: the inability to find a mate; the negative impact on co-operative behaviours such as anti-predator vigilance; the increased sensitivity to demographic stochasticity; and, the lack of diversity in the extant gene pool (Courchamp et al., 1999; Keitt et al., 2001; Stephens and Sutherland, 1999). Evidence for the strong (Berger, 1990; Courchamp and MacDonald, 2001; Groom, 1998; Johnson et al., 2006; Lamont et al., 1993) and weak (Allee, 1938; Angulo et al., 2007; Davis et al., 2004; Tang et al., 2014; Taylor et al., 2004) Allee effects are plentiful across many taxa; additional reviews are available in Gregory et al. (2010); Kramer et al. (2009). Consequently, there is a proliferation of mathematical models of the Allee effect in ecology (e.g. Balasuriya, 2010; Balasuriya and Gottwald, 2010; Cushing, 2014; Hart and Aviles, 2014; Kribs-Zaleta and Mitchell, 2014; Lewis and Kareiva, 1993; Potapov and Rajakaruna, 2013; Yamamichi et al., 2014). While studies in ecology often worry about factors that might push a threatened species below the (strong) Allee threshold and thereby towards extinction (e.g. Sanderson et al., 2014), an intriguing possibility in cancer research is whether the Allee effect could be harnessed for controlling or negating the growth of cancerous cells (Korolev et al., 2014), consonant with recent experiments in bacteria (Smith et al., 2014).

While seldom stated, hints of the Allee effect are numerous in the cancer research literature. Firstly, at the most anecdotal level, a tumour is only deemed threatening if it is above a certain size, which is an

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http://dx.doi.org/10.1016/j.jtbi.2015.12.024
0022-5193/

implicit presumption of a strong Allee threshold. More concrete illustrations are available in clinical trials for papillary and follicular thyroid cancers (Machens et al., 2005), in which risk-of-spread versus initial tumour size figures indicate that the risk is effectively zero until a minimum primary tumour size is reached. Secondly, studies of tumour dormancy suggest the presence of mechanisms such as a restrictive apoptosis/proliferation equilibrium (a cell density at which natural cell death balances new cell production) or a minimum angiogenic potential requirement for blood vessel formation in the tumour (Ruppender et al., 2013). Such biological considerations translate to the inability of the tumour to grow unless a strong Allee threshold is reached. Thirdly, it has been shown experimentally that in the growth of blebs (spherical protrusions forming along the front boundary of tumours), there is a minimum surface tension below which the blebs cannot expand (Tinevez et al., 2009). Since this surface tension is governed by a variety of poorly understood factors such as available myosin (Tinevez et al., 2009), the existing microenvironment can be thought of as essentially imposing an Allee effect. Fourthly, Axelrod et al. (2006) and Pienta et al. (2008) provide evidence of the co-operation between nearby subclones in the early evolution of tumours through the production and exchange of growth factors. Since co-operation is adversely impacted at low populations, tumour cells must—as in ecological systems—encounter the Allee effect. Fifthly, deleterious mutations accumulate more in smaller tumours (Korolev et al., 2014), thereby driving the population to extinction with much higher probability than larger tumours. Sixthly—and at a much broader level—the very fact that cancers depend on genetic heterogeneity, mutations and subsequent evolution (Burrell et al., 2013; Greaves and Maley, 2012; Merlo et al., 2006), pinpoints the necessity of having a large enough gene pool for successful growth, that is, the requirement of an Allee effect.[1] For example, numerical results from a recent integral equation model that models the number of cells in clones with different mutation rates, indicate that there is a threshold genetic mutation rate below which the cancer cells suffer extinction (Amor and Solé, 2014). It is important to note that most evolutionary models of cancer (see the reviews by Merlo et al., 2006 and Michor et al., 2004) neglect the spatial structure, which is problematic given that tumours are clinically classified depending on their shape (Connolly et al., 2000). One way of incorporating genetic mutation information within a spatial spreading model is to treat the stochastic mutations as creating an effective strong Allee threshold.

There are a variety of tumour growth models which examine the roles of additional effects such as acidity (Gatenby and Gawlinski, 1996; McGillen et al., 2014; Bertuzzi et al., 2010), adhesion (Chaplain et al., 2011; Gerisch and Chaplain, 2008; Sherratt et al., 2009), non-local interactions (Szymanska et al., 2009; Gerisch and Chaplain, 2008), cell plasticity in proliferation versus migration (Gao et al., 2005; Hatzikirou et al., 2012; Tektonidis et al., 2011; Martínez-González et al., 2012), in a range of tumour types. Most models fall into two classes: those which simulate a network of cells (Tektonidis et al., 2011; Hatzikirou et al., 2012), and those which rely of continuum modelling (e.g. Chaplain et al., 2011; McGillen et al., 2014; Szymanska et al., 2009; Gatenby and Gawlinski, 1996; Sherratt et al., 2009; Martínez-González et al., 2012), although some models that make a connection between the two exist, (e.g. Painter and Hillen, 2013; Bellomo et al., 2010; Engwer et al., 2015). Very recently, a spatio-temporal tumour cell growth model incorporating micro-environmental influences has been studied. That analysis reveals an Allee effect depending on the cell motility versus local cell density, (Böttger et al., 2015).

[1] This is stating that genetic diversity produces an implicit Allee effect, different from studies on the impact of a *separately imposed* Allee effect on genetic diversity (Wittman et al., 2014a,b).

1.2. A new model for malignant tumour invasion

In light of this emergent viewpoint on the relevance of the Allee effect in cancers, we offer in this paper, one of the first cancer spreading model that explicitly includes the Allee effect. Specifically, we examine how the inclusion of the Allee effect changes conclusions in comparison to the commonly used logistic growth model. For our comparison – the first of its kind – we choose to examine a model of a malignant, solid tumour invading through the extracellular matrix (ECM) via hapto- or chemotaxis, as opposed to the more complex, metastatic dissemination regime (Wells et al., 2013). In particular, our analysis applies to the spread of tumours in which hapto- or chemotaxis is the dominant mechanism of cell migration, such as melanoma (Marchant et al., 2000; Perumpanani and Byrne, 1999). We focus on the behaviour of the tumours on a long time scale; we do not analyse the transient dynamics.

We assume that an invasive tumour front can be modelled, mathematically, by a travelling wave solution (TWS) with constant speed c. TWSs correspond to stationary solutions in an appropriately moving frame and are defined on a one-dimensional, unbounded spatial domain. While this choice of domain is a simplification of the geometry of tumour invasion, it is a reasonable approximation, while still yielding a model that is amenable to mathematical analysis.

We build on a model of malignant tumour invasion derived in Perumpanani et al. (1999) and subsequently studied in Harley et al. (2014a); Marchant et al. (2000). In these articles, a logistic growth term is used to model the growth of the cancer cells (see Section 1.4); Allee effects are neglected. Here, we replace this logistic growth term with an Allee growth term and study the existence of TWSs of the following dimensionless model for malignant tumour invasion (see Section 2 for the derivation):

$$\begin{aligned}\frac{\partial u}{\partial t} &= \overbrace{-u^2 w}^{\text{proteolysis}} + \overbrace{\varepsilon\beta\frac{\partial^2 u}{\partial x^2}}^{\text{diffusion}},\\ \frac{\partial w}{\partial t} &= \underbrace{f(u,w)}_{\text{growth}} - \underbrace{\frac{\partial}{\partial x}\left(\frac{\partial u}{\partial x}w\right)}_{\text{hapto-/chemotaxis}} + \underbrace{\varepsilon\frac{\partial^2 w}{\partial x^2}}_{\text{diffusion}},\end{aligned} \tag{1}$$

with

$$f(u,w) = f_{\text{Allee}}(w;\alpha) := w(1-w)(w-\alpha), \quad |\alpha| < 1. \tag{2}$$

The dependent variables $u \geq 0$ and $w \geq 0$ represent the dimensionless ECM and cancer cell densities, respectively. The independent variables $t > 0$ and $x \in \mathbb{R}$ represent time and one-dimensional space, respectively. Both species are assumed to diffuse slowly, which is modelled by the small parameter ε: $0 \leq \varepsilon \ll 1$. We further assume that the ECM diffuses more slowly than the cancer cells: $0 \leq \beta \leq 1$ and β independent of ε. Observe that our analysis is also able to capture the situation of the ECM not diffusing, i.e. $\beta = 0$. The observed migration of the cancer cells up the gradient of ECM is modelled by the hapto- or chemotaxis term. As the cancer cells migrate they break down the ECM; this is modelled by the proteolysis term. The cubic function describing the growth of the cancer cells, (2), models the Allee effect, with different values of α corresponding to different strengths. Consistent with the definition in Section 1.1, the Allee effect modelled by (2) describes the following.

A positive α models the strong Allee effect. Since the carrying capacity of the cancer cell density has been scaled to one in (2), we require $\alpha < 1$. The strong Allee effect imposes a growth threshold on the tumour, whereby the cancer cell population only increases (at a given location) if $\alpha < w < 1$, since otherwise $f_{\text{Allee}} \leq 0$. See also Fig. 1. In the context of tumour invasion, $\alpha \gtrapprox 0$ is the most appropriate representation of the strong Allee effect as it is unlikely that a large threshold value (relative to the carrying capacity) is needed for the proliferation of cancer cells.