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Biased three-dimensional cell migration and collagen matrix modification

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ABSTRACT

Various tumours can be resected even for cure with complete removal. Surgical excision with a wide margin to ensure complete removal has therefore been suggested as the primary treatment for such lesions. The histological examination of the three-dimensional (3D) excision margins (*3D histology*) constitutes an important part of the quality control mechanisms in tumour surgery. Understanding histologically relevant properties of the constituents of the microenvironment in tumours and the circumferential portion of non-lesional tissue is therefore critical.

Accompanied by the increasing availability of high performance computers in recent decades, there has been a strong movement aiming at the development of mathematical models whose implementations allow *in silico* simulations of biological reaction networks. Due to its relevance in numerous biological and pathological processes, there have been various attempts to model biased migration of single cells. The model introduced in this paper plays a prominent role insofar as it covers the under-represented 3D case. Moreover, it is uniformly formulated for both two and three dimensions. The velocity of each cell is characterised by a generalised Langevin equation, a stochastic differential equation, where chemotaxis as well as contact guidance are considered to simulate selected aspects of interactions between carcinoma cell groups and fibroblast-like cells.

Algorithmic and numeric aspects of the developed equations are detailed in this paper and the results of the simulations are illustrated in different manners to emphasise specific features. A simple test scenario as well as a geometry based on segmentation data of a real histological slide has served for verification of the software. The resulting morphologies closely resemble that of desmoplastic stromal reaction readily identifiable in histological slides of infiltrating carcinoma, and the images can be interpreted in the context of *3D histology*.

1. Introduction

Complete removal of various solid tumour entities may help decrease recurrence and improve survival of oncological patients. Resection of a circumferential portion of non-lesional tissue may therefore be considered a standard surgical procedure in tumour surgery, and quality control algorithms include the histological examination of the three-dimensional (3D) excision margins (*3D histology*) [1]. Studying the reciprocal interactions between the tumour and the surrounding tissue in 3D therefore appears to be relevant. Various efforts have been made to learn more about the constituents of this microenvironment, for instance by using 3D cell culture systems [2,3]. The present study is addressing histologically relevant facets of this issue by the application of a systems biological approach.

As recently stated in [4], there exist only a few mathematical models that deal with three dimensions compared to the planar case, which focus on biased single-cell migration. Furthermore, the aforementioned article classifies and discusses the different approaches by detailing the particular pros and cons. What all these models which have been presented have in common is the integration of a certain stochastic influence which seems to be inevitable to describe single cell migration. Potential sources of this randomness are outlined in [5].

Unlike numerous 3D *in vitro* models [6–8], there is a lack of 3D *in silico* simulations in connective tissue research [9]. Computational models on both the cellular and tissue level, that capture real scenarios, are particularly lacking. In this paper, we develop an approach that bridges some of the aforementioned gaps. First of all, we state that the designed novel system of equations is a generalisation of a recently published paper limited to two spatial dimensions so far [10]. In the present publication, the corresponding equations are unified for the d-dimensional case, where either $d \in \{2,3\}$, i.e., a formal separation of plane and volume becomes obsolete.

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All biological processes and cell types in this study are interpreted as previously published [11–15]. We are describing migration (GO:0016477) properties of mesenchymal cells (EV:0200171) such as fibroblasts (EV:0200032) or myofibroblasts (EV:0200119). In this context it seems to be relevant that these cell types are producing collagen (GO:0005581) fibres, and exhibit both positive chemotaxis (GO:0006935) and contact guidance (GO:0009990). These cell types are henceforth referred to as *fibroblast-like cells* and (by major simplification) assumed to be the only cellular constituents in desmoplastic stromal reaction (DSR).

To obtain a mathematical model and corresponding algorithms, we are suggesting the use of a combination of the so called *force based dynamics* and the *persistent random walk* [4]. In this context, we characterise the velocity of a single cell by a generalised Langevin equation, which takes both chemotaxis and contact guidance into account. As the term *chemotaxis* denotes the preferred motion along a chemical gradient, taxis is considered *positive* if the migration occurs towards the source of the agent [16,17]. This agent is then referred to as *attractant*. Otherwise, the taxis is considered to be *negative* and the substance acts as *repellent*. Contact guidance is the bi-directional cell migration along physical structures, e.g., collagen fibre strands [18]. Fibroblast-like cells, which are in the focus of this paper, exhibit both positive chemotaxis [15] and contact guidance [13,14].

This article is organised as follows. Subsequent to this introduction, we expound the mathematical model, where we briefly outline the concepts of [10], which serve as a basis for the stated generalisations. Section 3 addresses some issues of the numerical implementation, especially schemes for calculating discrete solutions for the corresponding continuous equations. Furthermore, the handling of inner and outer boundaries within the volume of interest (VOI) is discussed. The results are illustrated in Section 4, where we examine both a simple test scenario and a geometry based on real segmentation data. In conclusion, this manuscript ends with a discussion and an outlook on future research.

2. The model

First of all, we emphasise that the subsequently delineated model does formally not depend on the dimension $d \in \{2,3\}$. We simply obtain the two-dimensional (2D) case by setting the third component of each considered quantity $(\mathbf{f}, \nabla c, \mathbf{X}_t, \mathbf{V}_t)$ to zero and by restricting the weight functions w_i to $x_3 = 0$. For a better comprehension, we recapitulate in the following some of the main assumptions noted in [10]; a thorough mathematical derivation and analysis can be consulted therein. The crawling fibroblast-like cells are regarded as moving point objects in space, where cell $i \in \{1,\dots,M\}$ is characterised by its position $\mathbf{X}_t^{(i)} \in \mathbb{R}^d$ and its velocity $\mathbf{V}_t^{(i)} \in \mathbb{R}^d$ as functions of time t. In this study, the fibroblast-like cells react simultaneously on both external stimuli, chemotaxis and contact guidance whereby their particular influences are independently governed by corresponding proportionality factors. We model the temporal evolution of the cell variables by a stochastic differential equation (SDE) system,

$$d\begin{bmatrix}\mathbf{X}_t\\ \mathbf{V}_t\end{bmatrix} = \begin{bmatrix}\mathbf{0} & \mathbf{I}\\ \mathbf{0} & -\beta\mathbf{I}\end{bmatrix}\begin{bmatrix}\mathbf{X}_t\\ \mathbf{V}_t\end{bmatrix}dt + \begin{bmatrix}\mathbf{0}\\ \mathbf{T}_{\text{ext}}\end{bmatrix}dt + \begin{bmatrix}\mathbf{0}\\ \alpha\mathbf{I}\end{bmatrix}d\mathbf{W}_t, \tag{1}$$

where $\alpha, \beta > 0$. Furthermore, $\mathbf{I}$ is assumed to be the $d \times d$ unit matrix and $\mathbf{0}$ refers to a zero matrix of appropriate size. The stochastic influence is governed by the weighting of $\mathbf{W}_t$, which represents a vectorial standard Wiener process in $\mathbb{R}^d$.

The transposed gradient of the chemical attractant density c at point $\mathbf{x} \in \mathbb{R}^d$ acts as the directional bias in the case of chemotaxis, i.e., $\mathbf{g}(t,\mathbf{x}) = \nabla c^\top(t,\mathbf{x})$. The fibrous part of the extracellular matrix (ECM) is characterised as a vector field $\mathbf{f} = \mathbf{f}(t,\mathbf{x})$ which is both space- and time-dependent. The dynamics of $\mathbf{f}$ written in polar coordinates are described below. However, for contact guidance, we utilise the force $\mathbf{g}(t,\mathbf{x}) = \tilde{\mathbf{f}}(t,\mathbf{x})$ with (cf. [19])

$$\tilde{\mathbf{f}}(t,\mathbf{X}_t) = \begin{cases}\mathbf{f}(t,\mathbf{X}_t), & \text{if } \langle \mathbf{f}(t,\mathbf{X}_t), \mathbf{V}_t\rangle \geqslant 0\\ -\mathbf{f}(t,\mathbf{X}_t), & \text{else}\end{cases}.$$

This definition expresses the mathematical point of view that fibres have no orientation and that they exert a bi-directional impulse on cell velocity. Consequently, the cells are always deflected in an acute angle to the current velocity vector along $\tilde{\mathbf{f}}$.

Formally, the force term $\mathbf{T}_{\text{ext}}$ is identical for both modes of taxis, i.e.

$$\mathbf{T}_{ext} = \mathbf{T}_{\text{ext}}(\mathbf{V}_t, \mathbf{g}(t,\mathbf{X}_t)) = \frac{\kappa}{2}\left(1 - \frac{1}{2}\frac{\langle \mathbf{g}, \mathbf{V}_t\rangle}{\|\mathbf{g}\|(\|\mathbf{V}_t\| + \varepsilon)}\right)\mathbf{g}, \tag{2}$$

where, as mentioned above, $\mathbf{g}$ is either equal to $\nabla c^\top$ or to $\tilde{\mathbf{f}}$ evaluated at $(t,\mathbf{X}_t)$. We assume that fibre modification is solely mediated by migrating fibroblast-like cells. As detailed in [19], we interpret the Euclidean norm $r(t,\mathbf{x}) = \|\mathbf{f}(t,\mathbf{x})\|$ as the mean density and the normalised vector $\boldsymbol{\omega}(t,\mathbf{x}) = \mathbf{f}(t,\mathbf{x})/\|\mathbf{f}(t,\mathbf{x})\|$ as the mean direction of the fibrous material, i.e., we consider the polar coordinate representation of $\mathbf{f}$:

$$\mathbf{f} = r\boldsymbol{\omega}, \quad r \in \mathbb{R}^+, \quad \boldsymbol{\omega} \in \mathcal{S}^{d-1}. \tag{3}$$

For the moment, we suppose $(t,\mathbf{x})$ to be fixed and define

$$r(s) = \|\mathbf{f}(t+s,\mathbf{x})\| \quad \text{and} \quad \boldsymbol{\omega}(s) = \frac{\mathbf{f}(t+s,\mathbf{x})}{\|\mathbf{f}(t+s,\mathbf{x})\|}$$

as functions of an infinitesimal time increment $s \geqslant 0$. With regard to a numerical implementation, s will assume the role of the time step size Δt within the iterative scheme. However, the temporal evolution of the density is then modelled by the ordinary differential equation (ODE) [19]

$$\frac{dr}{ds}(s) = (p_f - d_f r(s))\sum_{i=1}^{M} w_i(\mathbf{x}), \tag{4}$$

where production rate p_f and decay rate d_f are positive constants. These dynamics of the scalar-valued densities according to (4) are identical when compared with the planar case in [10]. In contrast, an analogous adaptation cannot be accomplished for the fibre orientation since the direction is described by two angles, the azimuth and the polar angle, and fibre orientation proceeds in planes of varying orientations.

The value $w_i(\mathbf{x}) \in [0,1]$ in (4) reflects the local influence that fibroblast-like cell i exerts on the ECM at point $\mathbf{x}$. In this paper, the representation of the weight functions $w_i = w_i(\mathbf{x})$ varies from the previous 2D versions (see [19,10]). Whereas the 3D adaptation of (1) may be considered straightforward, this is not the case for the weight functions. Thus, their characterisation is a central point in this study and it will be subsequently presented in detail.

We assume fibroblast-like cells to be producing new fibres, whose directions are associated with the tangents of the smoothed and time-lagged versions $\tilde{\mathbf{X}}_{t-\tau}^{(i)}$ of the their fluctuating cell trajectory $\mathbf{X}_t^{(i)}$ [10]. As a consequence, the mean fibre orientation $\boldsymbol{\omega}$ is rotated in the direction of $\tilde{\mathbf{X}}_{t-\tau}^{(i)}$. If several cells affect the ECM at a certain point $\mathbf{x}$, then $\boldsymbol{\omega}(0) \neq \mathbf{0}$ is turned towards the *weighted cumulative velocity vector* [10]

$$\overline{\mathbf{V}}\left(t,\mathbf{x},\boldsymbol{\omega}(0),\mathbf{S}_v\left(\tilde{\mathbf{V}}_{t-\tau}^{(i_1)},\tilde{\mathbf{V}}_{t-\tau}^{(i_2)}\right)\right) = \operatorname{sgn}\left(\left\langle \boldsymbol{\omega}(0), \mathbf{S}_v\left(\tilde{\mathbf{V}}_{t-\tau}^{(i_1)},\tilde{\mathbf{V}}_{t-\tau}^{(i_2)}\right)\right\rangle\right) \times \mathbf{S}_v\left(\tilde{\mathbf{V}}_{t-\tau}^{(i_1)},\tilde{\mathbf{V}}_{t-\tau}^{(i_2)}\right), \tag{5}$$

where we modified the sign function in such a way that $\operatorname{sgn}(0) = 1$. Furthermore, vector

$$\mathbf{S}_v(\mathbf{V}^{(1)},\mathbf{V}^{(2)}) = w_1\mathbf{V}^{(1)} + \operatorname{sgn}(\langle \mathbf{V}^{(1)},\mathbf{V}^{(2)}\rangle)w_2\mathbf{V}^{(2)} \tag{6}$$