A self-consistent cell flux expression for simultaneous chemotaxis and contact guidance in tissues

1. Introduction

Blood and tissue cells modify their movement in response to a large number of external cues. Two such responses that are well established from in vitro studies are chemotaxis, a directed movement up a concentration gradient of a soluble stimulus, and contact guidance, a bi-directional movement along aligned fibers of the extracellular matrix [17, 9, 8, 4]. Competition between these cues has received little study in vitro [18] but almost certainly occurs in vivo. Of particular interest to this work are the cases where fiber alignment occurs dynamically due to macroscopic deformation of the tissue, as can occur in morphogenesis and wound contraction, for example.

We have developed a continuum mechanical model that relates tissue deformation to fibril alignment and consequent contact guidance, termed the anisotropic...
biphasic theory (ABT), developed for tissue-equivalents [3]. The ABT has been applied to understand the role of fibroblast contact guidance in wound contraction [14]. However, as suggested above, wound contraction typically involves chemotaxis as well as contact guidance, because of chemotactic factors generated from an inflammatory response occurring in the wound site. Thus, to understand the consequences of simultaneous chemotaxis and contact guidance of fibroblasts in wound contraction (or of blood and tissue cells in almost any physiological process involving tissue contraction), the ABT needs to be modified to account for chemotaxis as well as contact guidance. Rather than extend the ABT by heuristically writing a flux expression that accounts for both responses [10–12], we chose to derive a self-consistent expression based on an underlying stochastic model for cell movement that has been developed and applied separately for chemotaxis [6] and contact guidance [5].

We first summarize the ABT and then the stochastic cell movement model, and then extend the latter for simultaneous chemotaxis and contact guidance by a two-parameter perturbation analysis in terms of the two associated cues, a chemotactic factor gradient and aligned tissue fibers. We present results from analysis of the first-order perturbation, which includes the cell flux expression heuristically proposed by others but reveals paradoxical results. We examine the cell flux expression for contact guidance in the ABT in light of these results. We then present second-order perturbation results that resolve the paradoxical results at first-order.

1.1. The anisotropic biphasic theory of tissue mechanics

The ABT accounts for the intrinsic biphasic nature of tissues, that is, a fiber network surrounded by an interstitial fluid, via volume-averaged mass and momentum conservation equations. More relevant to this work, the ABT also accounts for fiber alignment, modeled by a tensor $\Omega_f$, due to inhomogeneous network deformation (i.e. anisotropic strain) and for cell alignment, modeled by a tensor $\Omega_c$, in response to fiber alignment. (this key assumption has been recently validated [2, 7].) Cell alignment results in anisotropic migration and traction. Because the spatial distribution of cell traction drives the deformation and hence the mechanical interplay, there is also an account for the distribution of cells, or cell concentration $c(r,t)$, with a species conservation equation.

A simple power law that has been proposed to relate $\Omega_c$ to $\Omega_f$ is

$$\Omega_c = \frac{3}{tr(\Omega_f)^\kappa}(\Omega_f)^\kappa$$

where $\kappa$ measures contact guidance sensitivity. For example, $\kappa > 1$ implies the cells align to a greater extent than the surrounding fibers. The cell conservation equation was written as

$$\partial_t c(r,t) = \partial_r^T \mathcal{D}_0 \Omega_c \partial_r c(r,t)$$

so that the assumed cell flux expression $J$ that modeled contact guidance was anisotropic diffusion of the form

$$J = -\mathcal{D}_0 \Omega_c \nabla c$$