



The Speed of Corneal Epithelial Wound Healing

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Abstract—We propose a reaction-diffusion model of the mechanisms involved in the healing of corneal surface wounds. The model focuses on the stimulus for increased mitotic and migratory activity, specifically the role of epidermal growth factor. We determine an analytic approximation for the speed of travelling wave solutions of the model and verify the result numerically. The predicted speed compares very well with experimentally measured healing rates.

Keywords—Travelling waves, Epidermal growth factor, Reaction diffusion, Mitosis migration.

1. MODEL EQUATIONS

Cell migration and proliferation are central to the healing of wounds in the corneal epithelium [1]. Biological evidence suggests that both processes are regulated by epidermal growth factor (EGF), which is secreted by the cells themselves. Here, we propose a reaction-diffusion model to investigate the relative importance of the stimulatory effects of EGF on migration and cell division. The unwounded levels of cell density and EGF concentration and the time scale used in the nondimensionalization process are determined directly from experimental data [2-4]. The governing nondimensional equations are:

$$\frac{\partial n}{\partial t} = \overbrace{\nabla \cdot (D_n(c)\nabla n)}^{\text{Cell Migration}} + \overbrace{s(c)n(2-n)}^{\text{Mitotic Generation}} - \underbrace{n}_{\text{Natural Loss}} \tag{1}$$

$$\frac{\partial c}{\partial t} = \underbrace{D_c \nabla^2 c}_{\text{Diffusion}} + \underbrace{f(n)}_{\text{Production by Cells}} - \underbrace{\frac{\mu n c}{(\hat{c} + c)}}_{\text{Decay of Active EGF}} - \delta c \tag{2}$$

where $n(\underline{r}, t)$ and $c(\underline{r}, t)$ denote cell density and EGF concentration, respectively, at position \underline{r} and time t , $D_n(c) = \alpha c + \beta$, and $D_c, \mu, \delta, \alpha, \beta$ and \hat{c} are all positive constants. These can all be estimated from experimental data. We determine D_c theoretically using the Stokes-Einstein relation [5] and predict values for μ and \hat{c} using a simple model for receptor-chemical interaction on the cell surface [6-9]. *In vitro* data specifically determines δ [10] and the values of α and β can be estimated by matching model solutions with wound healing data [6,11,12]. Throughout the paper, we use the biologically realistic parameter set, found in this way and given in Figure 1.

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We consider the problem in one space dimension and investigate the behaviour of travelling wave solutions to these equations which move from a region where the cell density and EGF concentration are at their unwounded levels, $n = c = 1$ (as $x \rightarrow -\infty$), into a region of no cell density, $n = 0$, with the EGF concentration at its wounded level, $c = f(0)/\delta$ (as $x \rightarrow +\infty$).

2. ANALYSIS

We model EGF production by a constant source term due to the tear film and an additional term to account for chemical released by the exposed underlying tissue within the wound, which is rapidly degraded by cells at the wound edge [13,14]. Hence, we take $f(n) = A + B(n)$, where

$$B(n) = \begin{cases} \sigma, & \text{if } n < 0.2, \\ \sigma(2 - 5n), & \text{if } 0.2 \leq n \leq 0.4, \\ 0, & \text{if } n > 0.4, \end{cases}$$

and A and σ are positive constants [6]. In this scheme, it is the rapidity of the degradation that results in the experimentally observed increase in cell proliferation and motility in a band of cells at the wound edge. Numerical solutions of the model (Figure 1) suggest that the system evolves to travelling waves of constant speed and shape in n and c . The speed of these travelling waves ($\approx 64 \mu\text{m h}^{-1}$) compares very favourably with the healing rate of actual corneal wounds ($\approx 60 \mu\text{m h}^{-1}$) for sufficiently large values of σ [6] and is robust to any small change in parameters. Moreover, by reducing the effects of mitotic generation and migration, numerical simulations show that wounds can heal in the virtual absence of either mitosis or migration but with a much slower rate of healing than is predicted experimentally. This emphasizes the importance of both processes for effective wound healing.

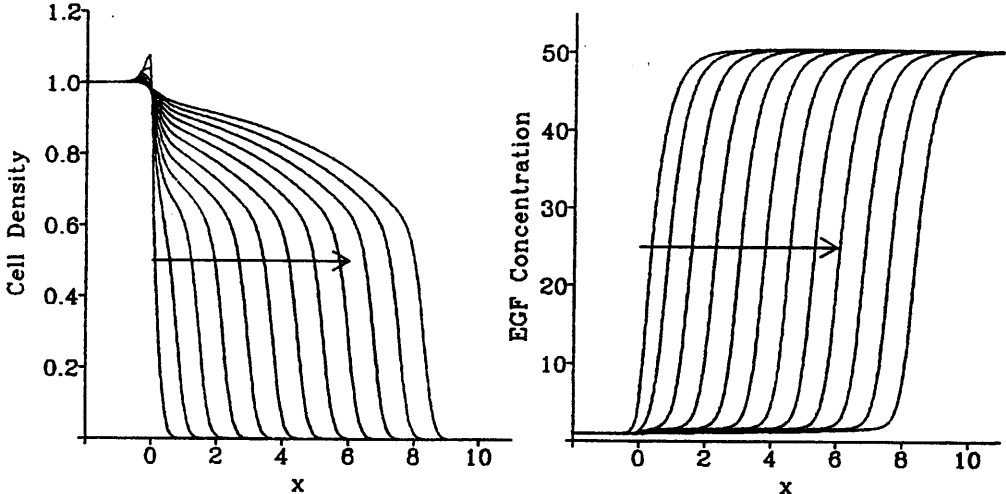


Figure 1. Numerical solutions of the model equations (1), showing cell density and EGF concentration as functions of space at equal time intervals. The parameter values are: $\alpha = 0.01$, $\beta = 0.1$, $D_c = 25$, $\mu = 13786$, $\hat{c} = 3$, $\delta = 110$, $s(c) = 0.915c + 0.0851$, $A = 560$ and $\sigma = 4000$. The form of the solutions is a front of cells moving into the wound, with an associated wave of EGF. The initial conditions are $n = c = 0$ for $x \geq 0$ and $n = c = 1$ for $x < 0$ and the dimensionless time intervals are $1/12$. The equations were solved numerically using the method of lines and Gear's Method.

In the single Fisher reaction-diffusion equation [15], travelling wave solutions can be investigated by introducing the coordinate, $z = x - at$, where a is the speed in the positive x direction. This transforms the parabolic partial differential equation to a second order system of ordinary differential equations. It is well known that the value of the parameter a at which the eigenvalues at the trivial steady state change from complex (stable spiral) to real (stable node) determines the speed of the travelling waves which result from initial conditions with compact support. By

analogy, we investigate the dependence of the wave speed on the model parameters by considering the eigenvalues of the *fourth* order system of travelling wave ordinary differential equations at the wounded and unwounded steady states. For general parameter values, the eigenvalues cannot be determined analytically. However, it is straightforward to calculate the eigenvalues and eigenvectors of the Jacobian matrix numerically. Furthermore, by varying the parameter a and using a bisection method, we can show that the only change in eigenvalues from complex to real occurs at a dimensional wave speed of $68.4 \mu\text{m h}^{-1}$, which is very close to the wave speed observed in numerical solutions of the partial differential equations. This suggests that this change may determine the observed wave speed.

By estimating $\frac{d(\log n)}{dx}$ for large x , we evaluate numerically the rate at which the wave of the partial differential equation approaches the wounded steady state and verify that the trajectory corresponding to the travelling wave solution does indeed approach the equilibrium point along the eigenvector corresponding to the eigenvalue which bifurcates at $a = 68.4 \mu\text{m h}^{-1}$ (Figure 2). At this point, there is a change from oscillatory (complex eigenvalues) to monotone (real) convergence, and the former would result in negative cell densities which is biologically implausible. Although the figures illustrate results for only a single set of parameter values, the method is valid for a wide range of parameter domains.

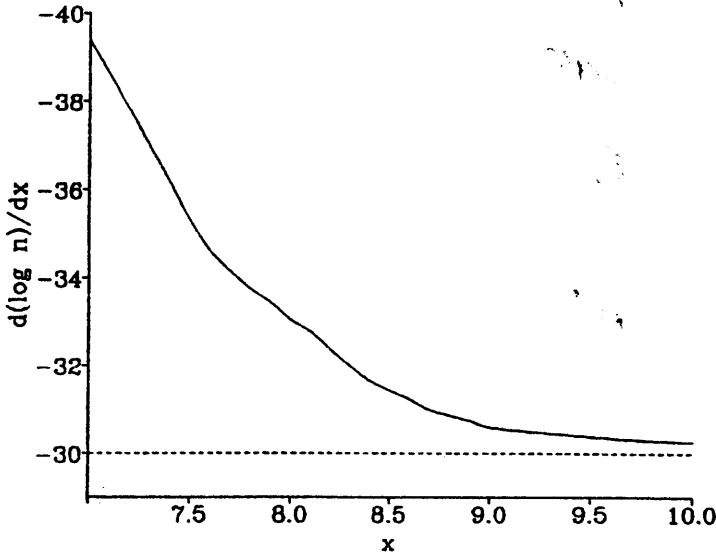


Figure 2. The change in $\frac{d(\log n)}{dx}$ with space for waves illustrated in Figure 1. Under the assumption that $n \sim n_0 e^{\lambda x}$ as $x \rightarrow \infty$, this function should tend to λ . Here $\lambda = -30$, which is the real part of the eigenvalue that changes character at the critical wave speed, $a = 68.4 \mu\text{m h}^{-1}$. This verifies the approach of the conjectured trajectory corresponding to the travelling wave solution. The irregular appearance of the curve is a true reflection of the approach and does not indicate any numerical inaccuracy. The parameter values and method of numerical solutions are as in Figure 1.

For biologically realistic parameter values, $\beta \ll D_c$ and $\beta \ll A + \sigma$. This enables us to determine an approximate solution of the quartic equation for the eigenvalues λ , and hence, derive an analytical expression for the wave speed. Crucially, the coefficients of λ^3 and λ are small compared with the coefficients of λ^4 and λ^2 , and setting these coefficients to zero gives a quadratic equation in λ^2 , whose roots are independent of wave speed. Substituting these roots into the quartic and looking for a change of the nonconstant roots from complex to real, we determine a critical wave speed

$$a_{crit} = \frac{2}{\beta + D_c} \sqrt{\beta D_c \left(2D_c s \left(\frac{A + \sigma}{\delta} \right) - D_c - \delta \beta \right)}.$$

The analytically determined wave speed is $68.3 \mu\text{m h}^{-1}$ which compares extremely well with the numerically evaluated wave speed $68.4 \mu\text{m h}^{-1}$. An important biological implication of this result

is that the rate of healing of corneal epithelial wounds can be increased by increasing the cell diffusion coefficient or the secretion rate of EGF. However, increasing the chemical diffusion coefficient does not have a significant effect. In a future publication [6], we will discuss the modification of this analytical expression for the wave speed to predict healing times when EGF is applied topically to the wound.

3. DISCUSSION

Previous models have been proposed for general epidermal wound healing [7–9,11,12]. Here, we present a model for corneal epithelial wound healing, which has particular clinical significance for keratectomy operations. We have considered the effect of epidermal growth factor, a protein whose receptor is expressed abundantly on epithelial cells [16]. Experimental measurements show that the healing rate of a normal corneal wound is approximately $60 \mu\text{m h}^{-1}$ [17] and, in this paper, we have compared this healing rate with numerically simulated and analytically determined wave speeds for biologically realistic model parameters.

We have assumed that there is a source of chemical at the centre of the wound, in addition to the constant supply from the tear film. Experience with scalar reaction diffusion equations [15] leads us to look for a change in the type of eigenvalues at the leading steady state in the travelling wave ordinary differential equations as the wave speed, a , increases. To our knowledge, this method of determining the wave speed has only been used previously in systems of reaction diffusion equations, such as predator prey models, in which all the kinetic terms are per capita [18]. For such models, there are no diagonal terms in the linearized system, resulting in a simple factorization of the eigenvalue equation. The numerically evaluated 'bifurcation' wave speed and the analytical expression for the speed in terms of the model parameters agree closely with the experimentally determined speed. The results of our simple model suggest that serum-derived factors can alone account for the overall features of the healing process.

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