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Travelling Waves in a Wound Healing Assay

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Abstract— Several authors have predicted that cell propagation in a number of biological contexts, for example, wound healing, tumour cell invasion, angiogenesis etc., occurs due to a constant speed travelling wave of invasion. The analyses of these models to arrive at this prediction is, in many cases, essentially an extension of the classical analysis of Fisher's equation. Here, we show that a very simple wound healing assay does indeed give rise to constant speed travelling waves. To our knowledge, this is the first verification of Fisher's equation in a medical context.

Keywords—Fisher's equation, Human peritoneal mesothelial cells, Invasion waves.

INTRODUCTION

Several authors have proposed that constant profile, constant speed travelling waves play an important role in a number of medical applications. For example, in epidermal wound healing, models have been proposed in which cells move and proliferate, sometimes in response to chemical signals, forming a wave which moves into the space to close the wound (see, for example, [1–3]). Mechanochemical models for dermal wound healing hypothesize that cells exert traction forces on extracellular matrix, setting up motion and guidance cues to which they respond as they invade the wound space and eventually close the wound [4,5].

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Tumour cancer cells are hypothesized to outcompete normal cells setting up waves of invasion [6], or to invade normal tissue by degrading extracellular matrix with proteases [7]. Angiogenesis, the process by which a tumour recruits endothelial cells and establishes its own vascular system, is thought to occur as a directed wave propagation of cells from the normal host vasculature to the tumour under the influence of tumour angiogenesis factors secreted by tumour cells (see, for example, [8]).

The above processes are modelled, in the main, by systems of coupled nonlinear partial-differential equations which describe the spatiotemoporal evolution of cells and signalling cues. Cells are assumed to diffuse (usually modelled by Fickian diffusion) and respond to various chemical signals via chemokinesis and/or chemotaxis, and to mechanical signals via haptotaxis (movement up adhesive gradients), and contact guidance. The models are solved using a mixture of analytical and numerical techniques and have been shown to exhibit constant profile constant speed travelling waves in cell density.

Although there is good evidence that such propagating travelling waves exist in ecology (see, for example, [9]), we are unaware of this being shown conclusively in the aforementioned medical applications.

In this paper, we consider a much simpler system and show that a wound healing assay does indeed appear to admit travelling waves of constant speed. Moreover, we show that the data is well fitted by Fisher's equation, a single reaction-diffusion equation that was initially proposed as a model for the spread of an advantageous gene in a population [10,11].

In the next section, we describe briefly the experimental set-up and results. Then, we consider the Fisher equation and compare its behaviour to the experimental results. Finally, we discuss the implications of this work.

WOUND HEALING ASSAY AND RESULTS

We refer the reader to the paper [12] for full experimental details. Briefly, human peritoneal mesothelial cells (HPMCs) were grown as monolayers on different substrates to confluence. Intracellular matrices used were collagen I, collagen IV, laminin, fibronectin, vitronectin, and hyaluronic acid. A 4 mm scrape wound was then made and the displaced cells were removed. The remaining cells were bathed in fresh culture medium and the position of the invading cell front was noted against a reference grid. Figure 1 shows the typically observed sharp front of cells invading the space left by the scrape.

The results for all substrates and all experiments were remarkably consistent. After a short period of time, the cell fronts progress with what appears to be a constant wavespeed (see Figure 2).

THE MODEL

We propose that the waves observed are Fisher waves. That is, we assume that the cell movement can be modelled by Fickian diffusion and that proliferation satisfies a logistic growth curve. Furthermore, we assume from the experimental set up that the process is occurring in one space dimension. Hence, the model is

$$\frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} + rn(N-n), \tag{1}$$

where $n(x,t)$ denotes cell number density at position x and time t, D is the diffusion coefficient (assumed constant), rN is linear growth rate of cells, and N is the carrying capacity.

For the experimental set up, the initial conditions would be of Heaviside type. However, we actually take as our starting point the first measurement, which is after 9.5 hours. At this stage, the initial condition will be a "smoothed" Heaviside. However, the exact profile of the initial condition is not as important as the observation that it has compact support. Under these

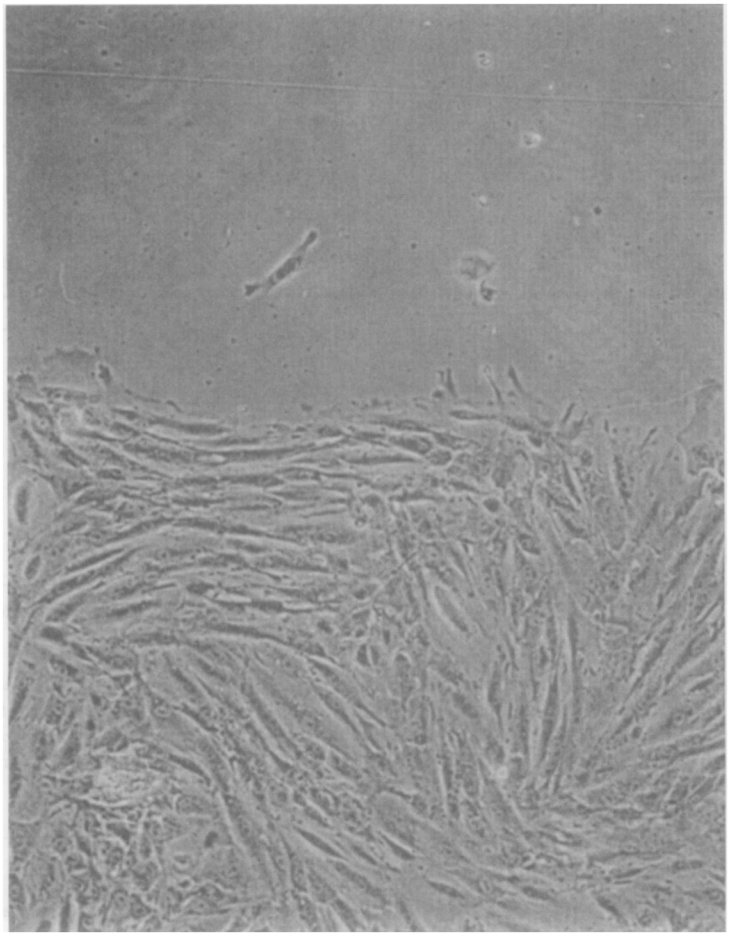

Figure 1. A typical human peritoneal mesothelial cell front ten hours after wounding.

conditions, it is well known that the model exhibits a constant profile travelling wave moving with constant speed (see, for example, [13] for references)

$$v = 2\sqrt{rND}. \tag{2}$$

Thus, we see that this travelling wave solution has a nontrivial set of initial conditions for which it is asymptotically attracting. Figure 3 illustrates a typical plot of front distance from origin with time, together with a least-squares fit assuming a front moving with constant speed. As can be seen, the actual wave initially moves at a speed greater than that of the fit, then it moves more slowly, then the speed increases almost monotonically to the asymptotic wavespeed. In all the experiments we analysed, the wavefront initially moves at a speed greater than the speed predicted from the least-squares fit. Then, the speed decreases below that of the fitted speed. After this, in some cases, we see a monotonic increase to the fitted speed, in other cases we see a slight overshoot (as in Figure 3) before it eventually settles down. Figure 4 illustrates this more clearly. Note that the prediction from the Fisher equation is that initially the wavespeed will be greater than the asymptotically predicted wavespeed, then the speed will decrease and approach the asymptotic wavespeed from below [14]. This is very close to the behaviour that we observe experimentally.

To make a quantitative comparison between the predicted wavespeed and the actual wavespeed, we need to know the cell doubling time and diffusion coefficient. Unfortunately, these quantities were not measured in the original experiments. However, we know that typical cell doubling times

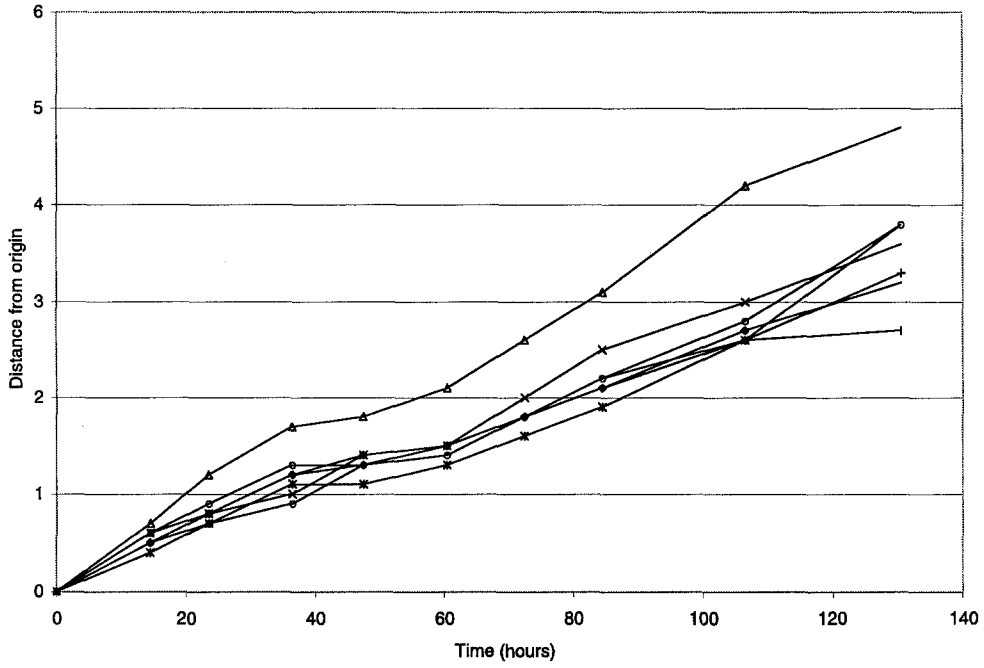

Figure 2. Typical plots from experimental data for the position of the invading cell front (taking the origin as the position at 9.5 hours and measuring time from that point) over different substrates. Distance units are 0.25 mm: control ($\diamond$), collagen I ($\circ$), collagen IV ($\triangle$), laminin ($\times$), fibronectin ($*$), vitronectin ($\bullet$), hyaluranic acid ($+$).

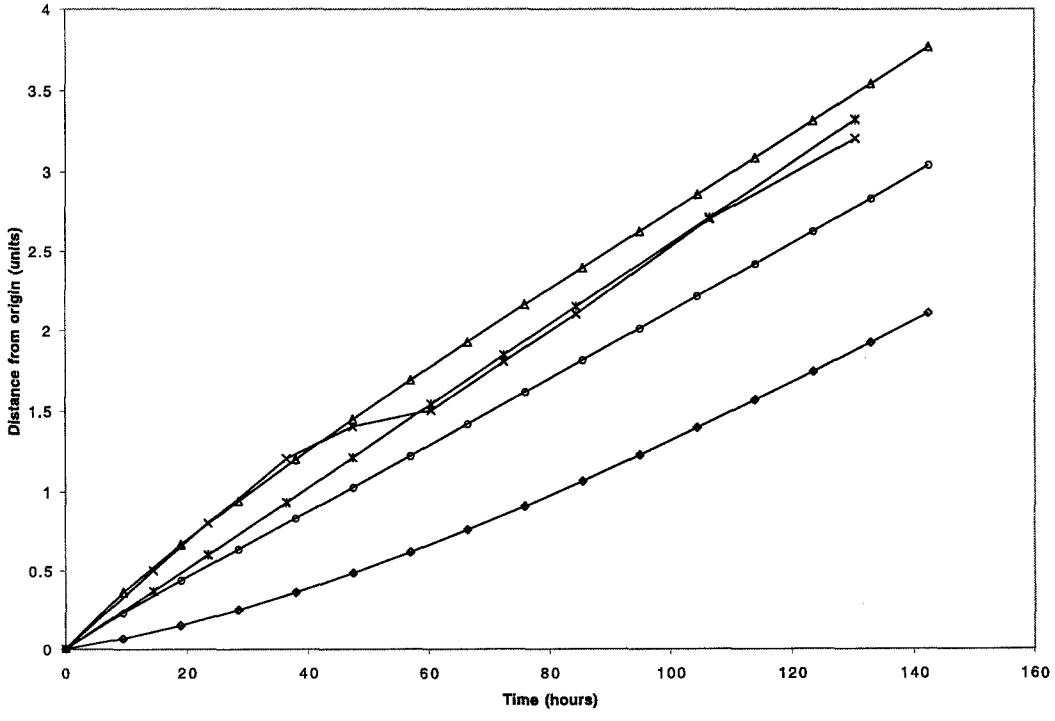

Figure 3. A least-squares straight-line fit to a typical data set. Also plotted are the positions of the computed wavefront assuming different threshold values defining the front: experimental data ($\times$), least-squares fit ($*$), $u = 0.5$ ($\diamond$), $u = 0.1$ ($\circ$), $u = 0.01$ ($\triangle$).

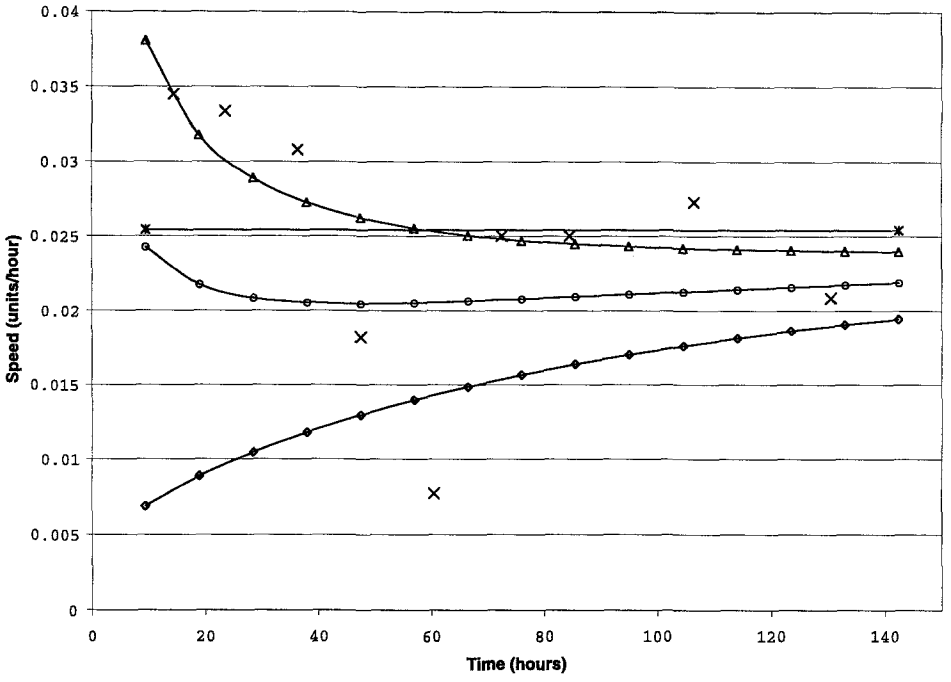

Figure 4. Velocity plots corresponding to Figure 3. Velocity estimates from the experimental data (×), least squares fit (*), $u = 0.5$ (◇), $u = 0.1$ (○), $u = 0.01$ (△).

range between one and seven days (see Table 1 in [15]), and typical diffusion coefficients are of the order of $10^{-6}\,\mathrm{mm}^2 s^{-1}$. So, assuming a cell doubling time of five days and a diffusion coefficient of say $10^{-6}\,\mathrm{mm}^2 s^{-1}$, we predict a wavespeed of $9.1 \times 10^{-3}\,\mathrm{mmhr}^{-1}$, which compares well with the actual measured wavespeeds that lie within the range $5.4 \times 10^{-3}\,\mathrm{mmhr}^{-1}$—$9.4 \times 10^{-3}\,\mathrm{mmhr}^{-1}$ calculated from the data (variation arising due to different patients and different substrates).

CONCLUSIONS

Several authors have predicted constant speed travelling waves for various biological processes. This prediction has been based on models that are, essentially, extensions of the basic Fisher equation in which cell movement is affected by mechanochemical cues and cell division is affected by chemical signals. In this paper, we have considered a very simple wound healing migration assay and have shown that it exhibits constant speed travelling waves with a speed consistent with that predicted by Fisher's equation. Moreover, we have shown that the way in which the wavespeed approaches this asymptotic wavespeed is very close to that predicted by the model. To our knowledge, this is the first verification of Fisher's equation in a medical context.

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