Mathematical Modelling of Epidermal Wound Healing

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1. INTRODUCTION

Reaction-diffusion systems are very commonly used in physical chemistry to study the concentrations and temperature distribution. These systems of equations undergo interconversions processes, that are controlled by rates and which spread with the corresponding diffusion coefficients. A typical reaction-diffusion system equation is of the form [1]:

$$u(x,t) = \frac{\partial u}{\partial t} = D\Delta u + f(u) \qquad (1)$$

where, u(x,t) is a state variable which describes the density/concentration of the substance or population at position x at time t. Δ denotes the Laplace operator, the first term on the right hand side is the diffusion term, with D being the diffusion coefficient and f(u) represents the smooth function that describes the process that changes the present (chemical reaction, birth, death).

When the smooth function f(u) is a simple logistic growth reaction term, then the equation is a non- linear reaction-diffusion equation also known as the Fisher -KPP (Kolmogorov-Petrovski-Puskinov) equation. This equation can be used to study the growth and genetics of population, cells. The generalized form of the Fisher equation is [1],

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru\left(1 - \frac{u}{K}\right) \qquad (2)$$

Where, D is the diffusion coefficient and r is the growth rate of species and K is the carrying capacity.

2. PROBLEM STATEMENT

Epidermis is a very thin outermost layer of the skin. As the epidermal wound occurs, the platelets and fibrin, a protein that is involved in clotting surround the wound and clot so that the wound does not bleed. Due to the biophysical and biochemical complexity of the process, it is not clearly understood. Mathematical modeling of the whole process, will not only help us increase our understanding of the wound healing process and timing, it will also provide biological insight of the process, which can be used to perform experiments mathematically that will have good medical implications.

Figure 1: Epidermal wound

Wound Healing process:

The whole process of wound healing occurs in 3 steps inflammation, wound closure and matrix remodeling in scar tissue.

Inflammation is the first step of the wound healing process, where the platelets release substances including, macrophages, phagocytes etc. that help to remove harmful substances from wound such as bacteria and prepare it to be healed.

Wound closure involves the epidermal migration which is the movement of epidermal cells to the wounded area. The epidermal cells undergo phenotypic alteration, causing them to move and rebuild and cover the wound, this process is known as Re-epithelization. The rate of epidermal cell migration is very slow at the

beginning, however once enough cells have migrated the mitotic activity increases to about 15 times faster rate.

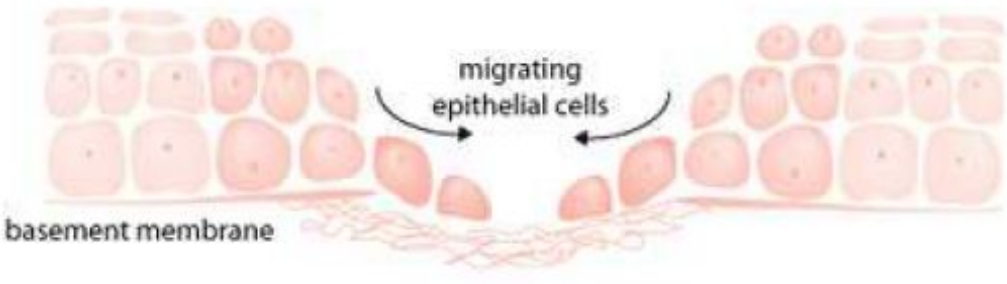

Figure 2: Wound closure through cell migration

The remodeling stage is to fix the disorganized healing that has happened during wound closure. The cells and proteins rearrange to align themselves to like the skin before the wound occurred.

The second step of wound healing has the maximum mathematical complexity, as there are several factors that affect the cell migration, including activators and inhibitors chemicals. Increased level of activator increased mitotic activity, while inhibitors inhibits mitosis.

The mathematical model to predict healing of the wound can be expressed in very simple terms as [1],

Rate of increase of cell density, n = cell migration + mitotic generation

This equation can be mathematically expressed as the Fisher-KPP equation with the appropriate parameters,

$$\frac{\partial n}{\partial t} = D\nabla.\left[\left(\frac{n}{n_0}\right)^p \nabla n\right] + sn\left(1 - \frac{n}{n_0}\right) \qquad (3)$$

Where, n is the cell density at time t, n_0 is the unwounded cell density, D is the diffusion and p are positive parameters that determine the cell migration, the mitotic growth is determined by the Verhulst logistic growth rate, with positive parameter s, as in the initial stage the cell density grows logistically until it reaches n_0, which is the carrying capacity of the cell.

When p=0, that is linear healing occurs, D is taken as the linear healing parameter, then equation (3) becomes a Fisher-KPP equation for linear wound healing

$$\frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} + sn(1-n) \tag{4}$$

with initial conditions n(x,0) = 0 inside the wound domain [0,1). The boundary conditions are n(1,t)=1 and n(0,t)=0, for all t.

3. Methodology and Results

3.1. Laplacian and Euler's Method

Analytical methods become complex when it comes to solving PDEs in higher dimensions. Our approach is to find the laplacian of the 2nd order PDE to solve the system of equations for wound healing . [2]

$$\frac{\partial^2 n}{\partial x^2} = \nabla^2 \mathrm{n} \tag{5}$$

Now substituting this in equation(4), we have,

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n + sn(1-n) \tag{6}$$

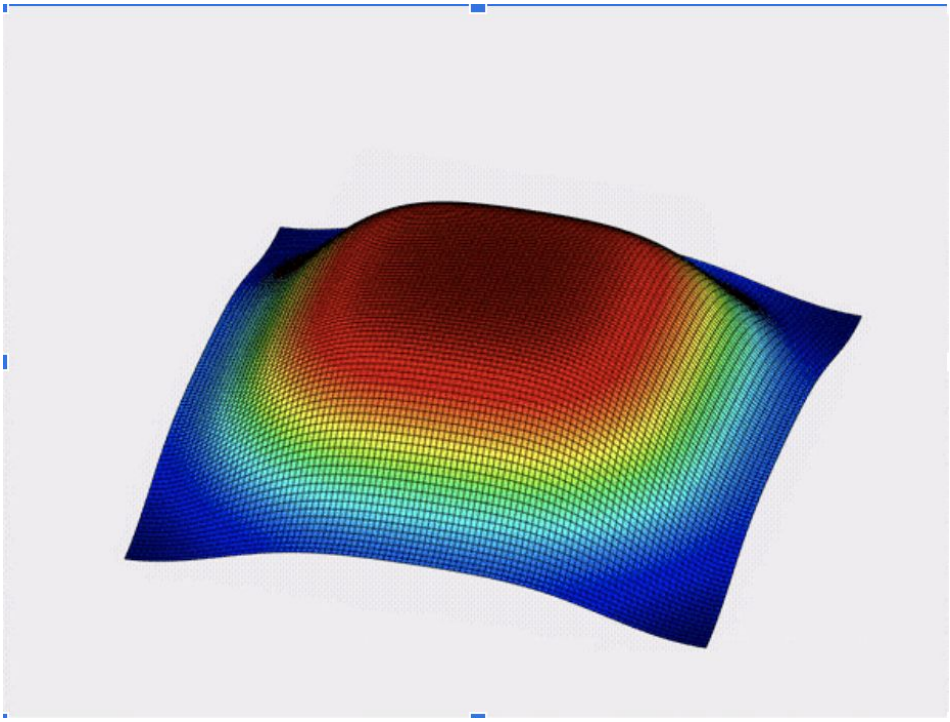

Figure 3: Plot of the solutions of PDE

For a non-zero 's' from equation (6), we observe the expanding wave grows with amplitude near one which explains the constant growth of epidermal cells until the wound is healed.

Advection, defined as the process of transfer of substance through can be implemented to our current model to understand the dynamic system. By implementation of Advective flow terms, we can describe the directed motion of cells during the wound healing process. This also explains the motion of cells towards the higher levels of substrate [2]

The model including the advection term can be written as

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n + sn(1-n) + \nabla \mathrm{n}$$

where $\nabla \mathrm{n} \rightarrow$ gradient of n = $\frac{\partial n}{\partial x}$ is the vector field

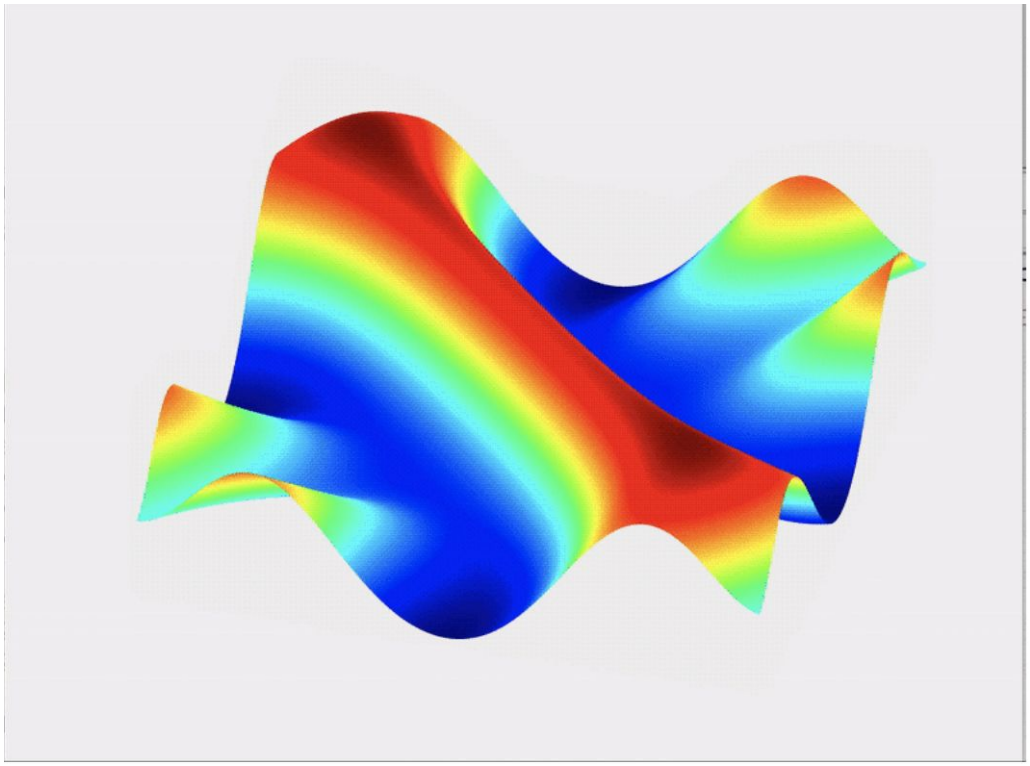

Figure 4: Plot of the solution of PDE with added advection velocity

When we include advection, we observe a central saddle in the graph behaviour of the model.

3.2. Using MATLAB PDE solver

The fisher equation given in (4) is solved through MATLAB PDE solver. We assume the positive parameter, s to be equal to 1. To solve the system of PDE, 3 functions were defined for initial condition (ic), boundary conditions (bcfun) and the pde equations(pde). Using PDE solver these functions were implemented to find the numerical solution and the following plot was obtained.

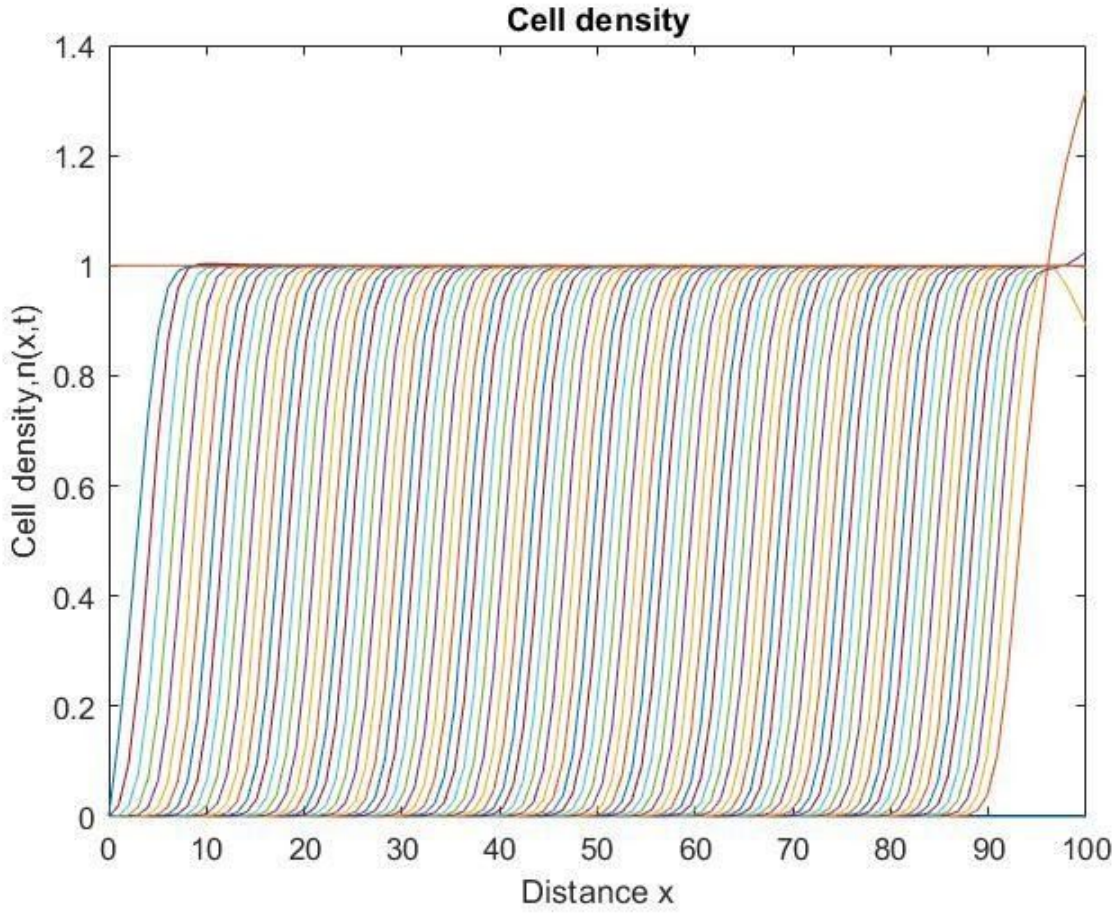

Figure 5: Numerical solution from MATLAB pde solver

We can see that there is a constant growth of cells until it reaches 1 which implies that the wound is healed.

4. Summary

Fisher's equation has been most popular in terms of modeling gene population and cell growth[6]. It has been proven by experimental methods to be most efficient in understanding modeling complex real time dynamic systems. Wound healing can be juxtaposed with cell growth to observe how it compares with this system and thereby implementing in this project. Fisher's equation was thus used to model the system biology of it. By implementing 2 methodologies, we were able to understand the process of wound healing. Using these models, we can perform mathematical experiments and observe the implications on them medically.

Work distribution: Both team mates Harshita Govindaraju (hg293) and Sumana Ramanathan (sr1423) contributed equally in all parts of the project.

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5. References

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