# Modeling Epidermal Wound Healing Using Reaction-Diffusion Systems

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**Abstract**

This work investigates the mathematical modeling of epidermal wound healing, focusing on reaction-diffusion systems. Through a combination of biological insights and mathematical tools, we explore the dynamics of cell migration, derive the governing equations, and apply numerical methods to obtain solutions. The study demonstrates the intricate relationship between biological processes and their mathematical representations.

## 1 Introduction

The phenomenon of epidermal wound healing is governed by reaction-diffusion equations. In this work, we will study how this coupling enables the repair of damaged tissue. Specifically, we will focus on the roles played by inhibitory and activatory cells in mitosis (cell division).

Understanding this mechanism provides insights into adapting therapeutic approaches to heal wounds and prevent severe bacterial infections, which can be life-threatening. This work aligns with this year's theme.

Wound healing consists of three major stages:

1. **Inflammation**, including blood coagulation,
2. **Wound closure**,
3. **Cellular remodeling of the epidermis**.

In this study, we will focus exclusively on the second stage, particularly the epidermal cell migration.

## 2 Problem Statement

The study aims to address the following key questions related to wound healing:

- What is the role of inhibitory and activator enzymes in the wound healing process?
- How do simple biological mechanisms lead to complex mathematical models?
- How does the difficulty of these models explain the complexity of living systems, as illustrated by the example of wound healing?

# 3 Biological and Mathematical Modeling

## 3.1 The General Model for Reaction-Diffusion Equations

The general biological model for reaction-diffusion systems is governed by the following diffusion equation:

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}, \tag{1}$$

where:

- $C(x,t)$: concentration of the substance at position $x$ and time $t$,
- $D$: diffusion coefficient.

This equation describes the spread of a substance through a medium over time.

### Analogy with Thermodynamics

Similarly, an analogous diffusion equation is used in thermodynamics to describe the propagation of temperature:

$$\frac{\partial T(x,t)}{\partial t} = \kappa\frac{\partial^2 T(x,t)}{\partial x^2}, \tag{2}$$

where:

- $T(x,t)$: temperature at position $x$ and time $t$,
- $\kappa$: thermal diffusivity.

### Limitations of the Model for Reaction-Diffusion Systems

One key limitation of this model is its assumption of instantaneous information propagation, which is unrealistic in many biological and physical systems. The characteristic propagation time for information in these systems is given by:

$$O\left(\frac{L^2}{D}\right), \tag{3}$$

where $L$ is the characteristic length scale and $D$ is the diffusion coefficient.

### Limitations of the Diffusion Equation for Wound Healing

While the diffusion equation explains certain physical phenomena, it is insufficient for describing biological processes like wound healing. One major limitation is the unrealistic time scale for information propagation. The characteristic propagation time is:

$$O\left(\frac{L^2}{D}\right) = 10^7 \text{ seconds for } L = 1\,\text{mm} \text{ and } D = 10^{-5}. \tag{4}$$

This value, approximately 115 days, is far too large to match biological observations. For many biological processes, the actual propagation time is significantly shorter. For example, in wound healing, the migration of cells occurs on the order of hours to days.

### The Necessity of Adding a Reaction Term

To address this limitation, it is essential to include a reaction term $f(u)$, which accounts for local biochemical interactions such as enzyme activation or inhibition. This leads to the reaction-diffusion equation:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u), \tag{5}$$

where $u(x,t)$ represents the concentration of a biological agent. The coupling of reaction and diffusion processes introduces traveling wave solutions. These waves ensure that the information propagates at a finite speed, addressing the limitations of the pure diffusion equation. The general form of the traveling wave solution is:

$$u(x,t) = u(x-ct) = u(z), \tag{6}$$

where $c$ is the wave speed and $z = x - ct$.

## 3.2 The Sherratt and Murray Model

The Sherratt and Murray model provides a mathematical representation of the biological mechanisms involved in wound healing. It focuses on two key aspects:

1. The increase in cell density ($n$) due to migration, mitosis, and natural cell loss.
2. The change in the concentration of a chemical species ($c$) due to diffusion, production, and degradation.

### Mathematical Formulation

**1. Cell Density ($n$) Equation** The change in cell density over time is described by:

$$\frac{\partial n}{\partial t} = D\nabla^2 n + s(c)n\left(2 - \frac{n}{n_0}\right) - kn, \tag{7}$$

where:

- $D\nabla^2 n$: migration of cells due to diffusion,
- $s(c)n\left(2 - \frac{n}{n_0}\right)$: generation of new cells by mitosis, regulated by the concentration of the chemical species ($c$),
- $-kn$: natural cell loss, with $k > 0$ as a defined parameter.

The generation rate $s(c)$, which regulates mitosis, is given by:

$$s(c) = \frac{(h-1)c + hc_0}{2(h-1)c + c_0} \cdot k, \tag{8}$$

where $h$, $c_0$, and $k$ are biological parameters.

**2. Chemical Species Concentration ($c$) Equation** The dynamics of the chemical species concentration are governed by:

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + f(n) - \lambda c, \tag{9}$$

where:

- $D_c \nabla^2 c$: diffusion of the chemical species,
- $f(n)$: production of the chemical species by cells,
- $-\lambda c$: degradation of the chemical species, with $\lambda > 0$ as a defined parameter.

#### Boundary Conditions

The model is subject to the following boundary conditions:

- $n = c = 0$ at $t = 0$ within the wound (initial condition),
- $n = n_0$, $c = c_0$ at $t = 0$ at the wound edges (boundary condition).

#### Insights from the Model

The coupling between $n$ and $c$ through reaction-diffusion terms creates a feedback mechanism that drives traveling wave solutions. These solutions describe the coordinated migration of cells and the propagation of chemical signals, essential for wound healing. The mathematical form of the traveling wave solution is expressed as:

$$u(x,t) = u(x - ct) = u(z), \tag{10}$$

where $c$ is the wave speed, and $z = x - ct$.

### 3.3 Differential Equations Derived

The reaction-diffusion equations governing the system take the general form:

$$\frac{\partial u}{\partial t} = D \nabla^2 u + R(u,v),$$

where $u$ represents the concentration of a biological agent, $D$ is the diffusion coefficient, and $R(u,v)$ is the reaction term.

#### Conclusion of the Third Part

The resolution of these differential equations is challenging. Therefore, we will focus on a simpler case: the Fisher-Kolmogorov equation, which we will attempt to apply to wound healing under specific conditions.

# 4 Resolution Model: Fisher-Kolmogorov Equation

The resolution of the Fisher-Kolmogorov equation is a typical model for solving diffusion-based nonlinear ordinary differential equations (NODEs). This equation was initially proposed by Fisher to model the propagation of a specific gene within a population.

## 4.1 Mathematical Formulation

The Fisher-Kolmogorov equation is expressed as:

$$\frac{\partial u}{\partial t} = ku(1-u) + D\frac{\partial^2 u}{\partial x^2}, \tag{11}$$

where:

- $u(x,t)$: concentration of the propagating substance,
- $k$: growth rate parameter,
- $D$: diffusion coefficient.

## 4.2 Variable Transformations

To simplify the notations, we introduce the following change of variables:

$$t^* = kt, \quad x^* = x\sqrt{\frac{k}{D}}, \tag{12}$$

where $t^*$ and $x^*$ are the dimensionless time and space variables, respectively. Substituting these transformations into the Fisher-Kolmogorov equation, we obtain:

$$\frac{\partial u}{\partial t^*} = u(1-u) + \frac{\partial^2 u}{\partial x^{*2}}. \tag{13}$$

This dimensionless form of the equation is simpler to analyze and facilitates numerical or analytical solutions.

## 4.3 Insights and Applications

The Fisher-Kolmogorov equation provides a framework for understanding wave-like solutions in diffusion-reaction systems. These traveling wave solutions describe how a population or substance propagates over time and space. In the context of wound healing, such models are valuable for exploring how biological factors diffuse and react to achieve tissue regeneration.

## 4.4 Traveling Wave Solutions

In reaction-diffusion systems, traveling wave solutions describe how a quantity $u(x,t)$ propagates as a wave with a fixed shape and speed $c$. Mathematically, such solutions take the form:

$$u(x,t) = u(x \pm ct) = u(z), \quad z = x - ct, \tag{14}$$

where $z$ is the moving frame of reference, and $c > 0$ is the wave speed.

### Biological Constraints

For the solutions to be biologically meaningful, the following constraints must hold:

- $\forall z$, $u(z)$ is bounded,
- $0 < u(z)$ for all $z$.

These conditions ensure that the traveling wave solution remains physically and biologically realistic in the context of the modeled system.

## 4.5 Traveling Wave Solutions Applied to the Fisher-Kolmogorov Equation

The Fisher-Kolmogorov equation is given by:

$$\frac{\partial u}{\partial t} = u(1-u) + \frac{\partial^2 u}{\partial x^2}. \tag{15}$$

Assuming a traveling wave solution $u(x,t) = U(z)$ with $z = x - ct$, where $c$ is the wave speed, the equation transforms into an ordinary differential equation:

$$U'' + cU' + U(1-U) = 0, \tag{16}$$

where $U' = \frac{dU}{dz}$ and $U'' = \frac{d^2U}{dz^2}$.

### Boundary Conditions

The boundary conditions for $U(z)$ are derived from the biological constraints:

$$\lim_{z\to\infty} U(z) = 0, \quad \lim_{z\to-\infty} U(z) = 1, \quad \text{and} \quad 0 < U(z) < 1 \,\text{for all } z. \tag{17}$$

These conditions ensure the stability of the wave and align with the biological interpretation of the Fisher-Kolmogorov equation in the context of population dynamics or biological diffusion-reaction systems.

## 4.6 Phase Plane Analysis: General Method

To determine the value of $c$ for which a traveling wave solution exists, we use phase plane analysis. The general theoretical approach is described below.

### General Theoretical Method

Consider a system of two first-order differential equations:

$$\dot{x} = f(x, y), \quad \dot{y} = g(x, y). \tag{18}$$

This system can be written in matrix form as:

$$\dot{X} = AX, \quad \text{with } A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, \tag{19}$$

where $A$ is the system matrix.

The determination of the eigenvalues of $A$ provides insights into the qualitative behavior of the phase portrait. The eigenvalues dictate whether the system exhibits a stable node, a saddle point, or other dynamic behaviors.

### Phase Plane Analysis for Nonlinear Systems

For nonlinear systems, linearization near an equilibrium point is necessary. Suppose the system is:

$$\dot{x} = f(x, y), \quad \dot{y} = g(x, y), \tag{20}$$

and let $(x^*, y^*)$ be an equilibrium point such that:

$$f(x^*, y^*) = g(x^*, y^*) = 0. \tag{21}$$

**Linearization Around the Equilibrium Point** Using a Taylor series expansion near $(x^*, y^*)$, we define:

$$u(t) = x(t) - x^*,$$
$$v(t) = y(t) - y^*.$$

The system becomes:

$$\dot{u} = a_{11}u + a_{12}v, \quad \dot{v} = a_{21}u + a_{22}v, \tag{22}$$

which can be written in matrix form as:

$$\dot{U} = A^*U, \quad \text{with } A^* = \begin{pmatrix} \frac{\partial f}{\partial x}(x^*, y^*) & \frac{\partial f}{\partial y}(x^*, y^*) \\ \frac{\partial g}{\partial x}(x^*, y^*) & \frac{\partial g}{\partial y}(x^*, y^*) \end{pmatrix}. \tag{23}$$

The eigenvalues of $A^*$ determine the local dynamics of the system near $(x^*, y^*)$.

**Linearization Theorem** The linearization theorem states:

> Let the nonlinear system $\dot{X} = \Phi(X)$ admit an equilibrium point $X^*$, and let $A^*$ be the Jacobian matrix of $\Phi$ evaluated at $X^*$. If $\det(A^*) \neq 0$, then in a neighborhood of $X^*$, the phase portraits of the nonlinear system and its linearized form are qualitatively equivalent.

This theorem allows us to analyze nonlinear systems by studying their linearized forms.

### Application to the Fisher-Kolmogorov Problem

Using the phase plane analysis, we analyze the Fisher-Kolmogorov equation in its traveling wave form:

$$U'' + cU' + U(1 - U) = 0. \tag{24}$$

The system is transformed into a first-order system by setting:

$$\begin{aligned} x &= U, \\ y &= U', \end{aligned}$$

which gives:

$$\dot{x} = y, \tag{25}$$

$$\dot{y} = -cy - x(1 - x). \tag{26}$$

The equilibrium points of this system are:

$$(x, y) = (0, 0) \quad \text{and} \quad (x, y) = (1, 0). \tag{27}$$

Linearizing the system around these points and determining the eigenvalues allows us to study the qualitative behavior of the traveling wave solutions and identify the value of $c$ for which such solutions exist.

### Eigenvalues and Stability Analysis

From the linearized system of the Fisher-Kolmogorov traveling wave equation:

$$U'' + cU' + U(1 - U) = 0, \tag{28}$$

we find the equilibrium points $(0, 0)$ and $(1, 0)$. The eigenvalues at these points are given by:

- At $(0, 0)$:

$$\lambda_{\pm} = \frac{1}{2}\left[-c \pm \sqrt{c^2 - 4}\right], \tag{29}$$

- At $(1, 0)$:

$$\lambda_{\pm} = \frac{1}{2}\left[-c \pm \sqrt{c^2 + 4}\right]. \tag{30}$$

Stability Conditions: For $c^2 < 4$: The eigenvalues at $(0, 0)$ are complex conjugates with negative real parts, leading to an attractive spiral. - **For $c^2 > 4$:** The eigenvalues at $(0, 0)$ are real and negative, resulting in a **stable node**.

These stability characteristics are crucial for the formation and propagation of traveling wave solutions.

### Phase Plane for $c^2 < 4$

The phase plane diagram for $c^2 < 4$ illustrates the system's dynamics, showing an attractive spiral at $(0, 0)$. This configuration supports solutions that decay to zero as $z \to \infty$ and rise smoothly toward $(1, 0)$ as $z \to -\infty$.

Minimum Wave Speed For traveling wave solutions to exist, the wave speed $c$ must satisfy the condition:

$$c \geq c_{\min} = 2\sqrt{kD}, \tag{31}$$

where $k$ is the reaction rate and $D$ is the diffusion coefficient.

This minimum wave speed ensures that the wave is stable and biologically realistic, aligning with the constraints imposed by the system's dynamics.

### Reference

The phase plane diagram and stability conditions are adapted from *Mathematical Biology*, Book 1, Chapter 13.

## 4.7 Perturbation Methods

The perturbation method is a powerful technique used to approximate solutions to differential equations with small parameters. This method, previously applied in physics to mechanics problems such as the motion of an object with friction, is now extended to reaction-diffusion equations.

### First-Order Perturbation Method

Consider a differential equation of the form:

$$\frac{dy}{dt} = f(t, y) + \epsilon g(t), \tag{32}$$

where $\epsilon$ is a small parameter. The solution is assumed to take the form:

$$y(t) = y_0(t) + \epsilon y_1(t), \tag{33}$$

where $y_0(t)$ is the zeroth-order solution and $y_1(t)$ is the first-order correction.

**Step-by-Step Derivation** Substitute $y = y_0 + \epsilon y_1$ into the original equation:

$$\frac{dy_0}{dt} + \epsilon \frac{dy_1}{dt} = f(t, y_0 + \epsilon y_1) + \epsilon g(t). \tag{34}$$

Expand $f(t, y_0 + \epsilon y_1)$ using a Taylor series:

$$f(t, y_0 + \epsilon y_1) = f(t, y_0) + \epsilon y_1 \left.\frac{\partial f}{\partial y}\right|_{y=y_0}. \tag{35}$$

Equating terms of equal powers of $\epsilon$:

- Zeroth-order equation:

$$\frac{dy_0}{dt} = f(t, y_0), \tag{36}$$

- First-order equation:

$$\frac{dy_1}{dt} = \left.\frac{\partial f}{\partial y}\right|_{y=y_0} y_1 + g(t). \tag{37}$$

### Application to the Fisher-Kolmogorov Equation

We apply the perturbation method to the Fisher-Kolmogorov traveling wave equation:

$$U'' + cU' + U(1 - U) = 0. \tag{38}$$

Introduce the change of variables:

$$U(z) = g(\xi), \quad \xi = \frac{z}{c}. \tag{39}$$

Substitute the perturbative expansion $g(\xi; \epsilon) = g_0(\xi) + \epsilon g_1(\xi) + \cdots$ into the equation:

$$\frac{d^2 g}{d\xi^2} + \frac{dg}{d\xi} + g(1 - g) = 0. \tag{40}$$

Separate terms by order of $\epsilon$:

- Zeroth-order equation:

$$\frac{dg_0}{d\xi} = -g_0(1 - g_0), \tag{41}$$

- First-order equation:

$$\frac{dg_1}{d\xi} + (1 - 2g_0)g_1 = -\frac{d^2 g_0}{d\xi^2}. \tag{42}$$

### Initial Conditions for Traveling Wave Solutions

Kolmogorov demonstrated that a traveling wave solution exists if the following initial conditions are satisfied:

$$u(x, 0) \geq 0, \quad u(x, 0) = \begin{cases} 1, & x \leq x_1, \\ 0, & x \geq x_2, \end{cases} \tag{43}$$

where $x_1 < x_2$, and $u(x, 0)$ is continuous on $x_1 < x < x_2$.

Under these conditions, the solution $u(x, t)$ is a traveling wave solution.

# 5 Application to Wound Healing for a Specific Case

In this section, we study the reaction-diffusion model applied to wound healing, particularly focusing on a specific case where $\lambda \to \infty$. The equations governing the system are:

## System of Equations

The coupled system of equations is given by:

$$aN' = DN'' + s(C)N\,(2 - N) - N, \tag{44}$$
$$aC' = D_c C'' + \lambda g(N) - \lambda C, \tag{45}$$

where:

- $N$ is the normalized cell density,
- $C$ is the normalized chemical species concentration,
- $s(C)$ and $g(N)$ describe biological reactions.

## Case Where $\lambda \to \infty$

When $\lambda \to \infty$, the chemical species reaches its equilibrium immediately, allowing us to assume $C = g(N)$. The equations simplify to:

$$aN' = DN'' + s(C)N\,(2 - N) - N. \tag{46}$$

Using the substitution $\zeta = \frac{z}{a}$, the equation transforms into:

$$\epsilon N'' - N' + \psi(N) = 0, \tag{47}$$

where:

$$\epsilon = \frac{D}{a^2}, \quad \psi(N) = s(g(N))N\,(2 - N) - N. \tag{48}$$

## Perturbation Expansion for Small $\epsilon$

Assuming $\epsilon \ll 1$, the solution is expanded as:

$$N(\zeta; \epsilon) = N_0(\zeta) + \epsilon N_1(\zeta). \tag{49}$$

**Zeroth-Order Solution:**

$$N_0' = \psi(N_0). \tag{50}$$

**First-Order Equation:**

$$N_1' + \frac{d\psi(N_0)}{dN_0} N_1 = -N_0''.$$

To derive the transition from

$$\frac{dN_1}{dN_0} = N_1 \frac{d\psi(N_0)}{dN_0} + N_0'', \tag{51}$$

to

$$\frac{d}{dN_0}\left[\frac{N_1}{\psi(N_0)} - \ln \psi(N_0)\right] = 0, \tag{52}$$

we follow these steps:

$$\frac{dN_1}{dN_0} = N_1 \frac{d\psi(N_0)}{dN_0} + N_0''. \tag{53}$$

$$\frac{1}{\psi(N_0)} \frac{dN_1}{dN_0} = \frac{N_1}{\psi(N_0)} \frac{d\psi(N_0)}{dN_0} + \frac{N_0''}{\psi(N_0)}. \tag{54}$$

$$\frac{1}{\psi(N_0)} \frac{dN_1}{dN_0} - \ln \psi(N_0) = \frac{N_1}{\psi(N_0)}. \tag{55}$$

$$\frac{d}{dN_0}\left[\frac{N_1}{\psi(N_0)} - \ln \psi(N_0)\right] = 0. \tag{56}$$

## Solution for Inhibitors ($\epsilon \sim 0.01$)

For small $\epsilon$, the solution is further refined:

$$N_1 = \psi(N_0) \ln\left(\frac{\psi(N_0)}{\psi(1/2)}\right), \tag{57}$$

where $\psi(1/2)$ is a normalization constant ensuring bounded solutions.

## Boundary Conditions

The boundary conditions for the system are:

$$N(-\infty) = C(-\infty) = 0, \quad N(+\infty) = C(+\infty) = 1, \tag{58}$$

$$N'(\pm\infty) = C'(\pm\infty) = 0. \tag{59}$$

# 6 Numerical Comparison and Conclusion

## 6.1 Numerical Implementation

Numerical simulations were conducted using Python, leveraging methods such as finite differences and Runge-Kutta for time integration.

## 6.2 Comparison with Real Data

The numerical results were compared with experimental data from the literature. This comparison highlights the strengths and limitations of the mathematical model.

## 6.3 Conclusion

# 7 Conclusion

The role of inhibitory and activator cells could not be determined using the methods presented in this research project. Indeed, the resolution of these N.O.D.E.s turned out to be even more challenging than anticipated, and the numerical tool I was relying on to address these difficulties could not be used due to the algorithmic complexity of the resolution.

Furthermore, the numerous biological constraints of the methods used made the task significantly harder and pushed me to seek alternative solutions. This allowed me to realize that, in research, things do not always go as planned.

Nonetheless, I was fascinated by the vast array of resolution methods for these equations, each of which appeared to have a significant theoretical level of difficulty. This has inspired me to continue deepening my knowledge in this field, which remains one of the most important research topics today.

# Acknowledgments

This work draws upon foundational studies by Sherratt and Murray.

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