# On the Mathematical Modeling of Epidermal Wound Healing

**Jesse Kreger**

OCCIDENTAL COLLEGE

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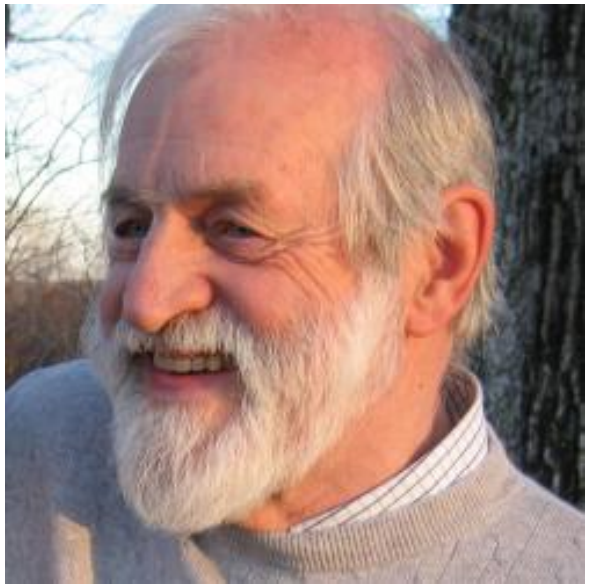
# Purpose of Talk

- The purpose of this talk is to present various mathematical models of epidermal wound healing, beginning with the pioneering work done in the field by Jonathan Sherratt and James Murray (1990)

http://www.macs.hw.ac.uk/jas/



https://www.maths.ox.ac.uk/people/james.murray

# Purpose of Talk

- Mathematical models of epidermal wound healing:
  - Have increased in mathematical/biological complexity over time
  - Give us insight into a complex biological reaction
  - Are excellent examples of complex systems of coupled nonlinear partial differential equations

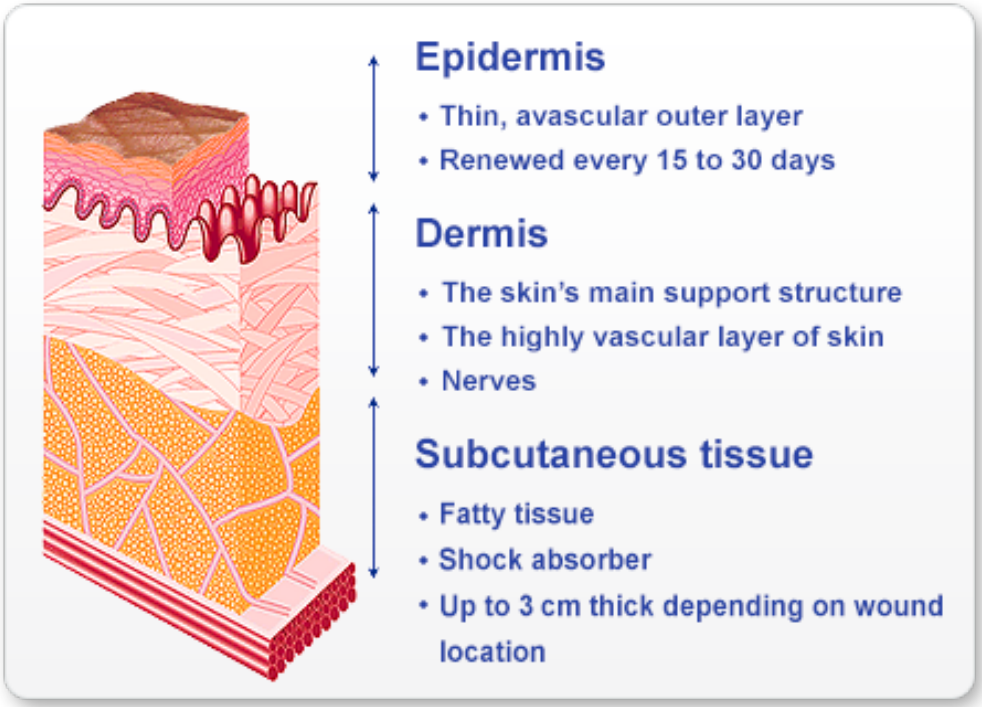
# Purpose of Talk

- Mathematical models of epidermal wound healing:
  - Have increased in mathematical/biological complexity over time
  - Give us insight into a complex biological reaction
  - Are excellent examples of complex systems of coupled nonlinear partial differential equations
- Coupled nonlinear partial differential equations are **HARD** to solve!

# Outline

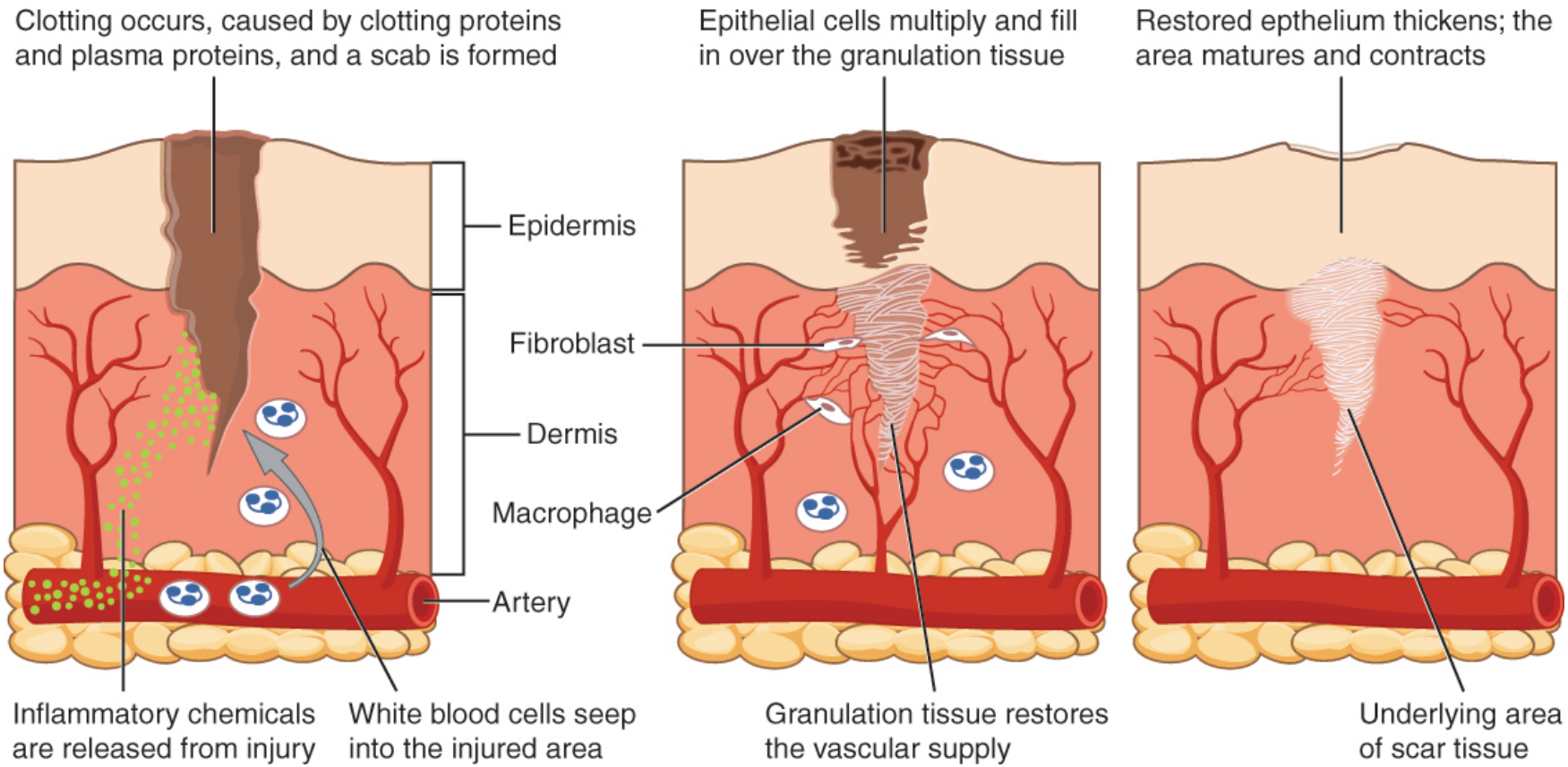
# What is an Epidermal Wound?

- Common ailment that is often caused by a scrape or burn
- Epidermis is injured but the dermis and flesh beneath the wound are not harmed
- Mathematical modeling can provide insight into biological responses




http://www.urgomedical.com/understanding-together-2/skin-and-wound-healing/

# Biology of Epidermal Wound Healing




http://philschatz.com/anatomy-book/contents/m46058.html

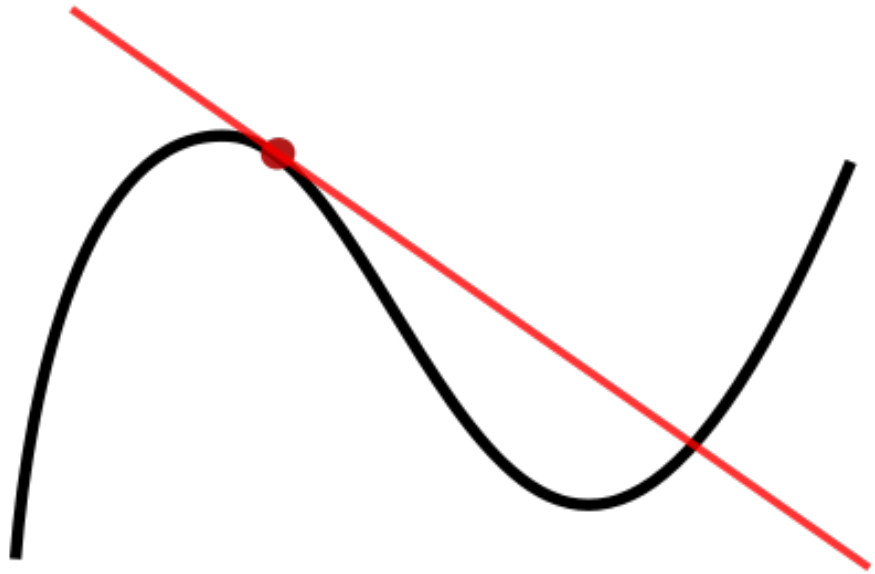
# What is a mathematical model?

- Description of a system in terms of mathematical ideas/language
- Use themes and structure of system to produce quantifiable results
- **Provide insight into how the system operates**

1. State real world problem
2. Convert problem into mathematical equations
3. Solve/perform analysis on equations
4. Interpret results

# Differential Equation Review

- A differential equation is an equation containing **derivatives**
- Ordinary differential equations contain *ordinary* derivatives
- Partial differential equations contain *partial* derivatives



# The Logistic Equation

- The logistic equation is a model of population growth first proposed by Pierre Verhulst in 1840s
- It is given by

$$\frac{dP(t)}{dt} = rP\left(1 - \frac{P}{K}\right)$$

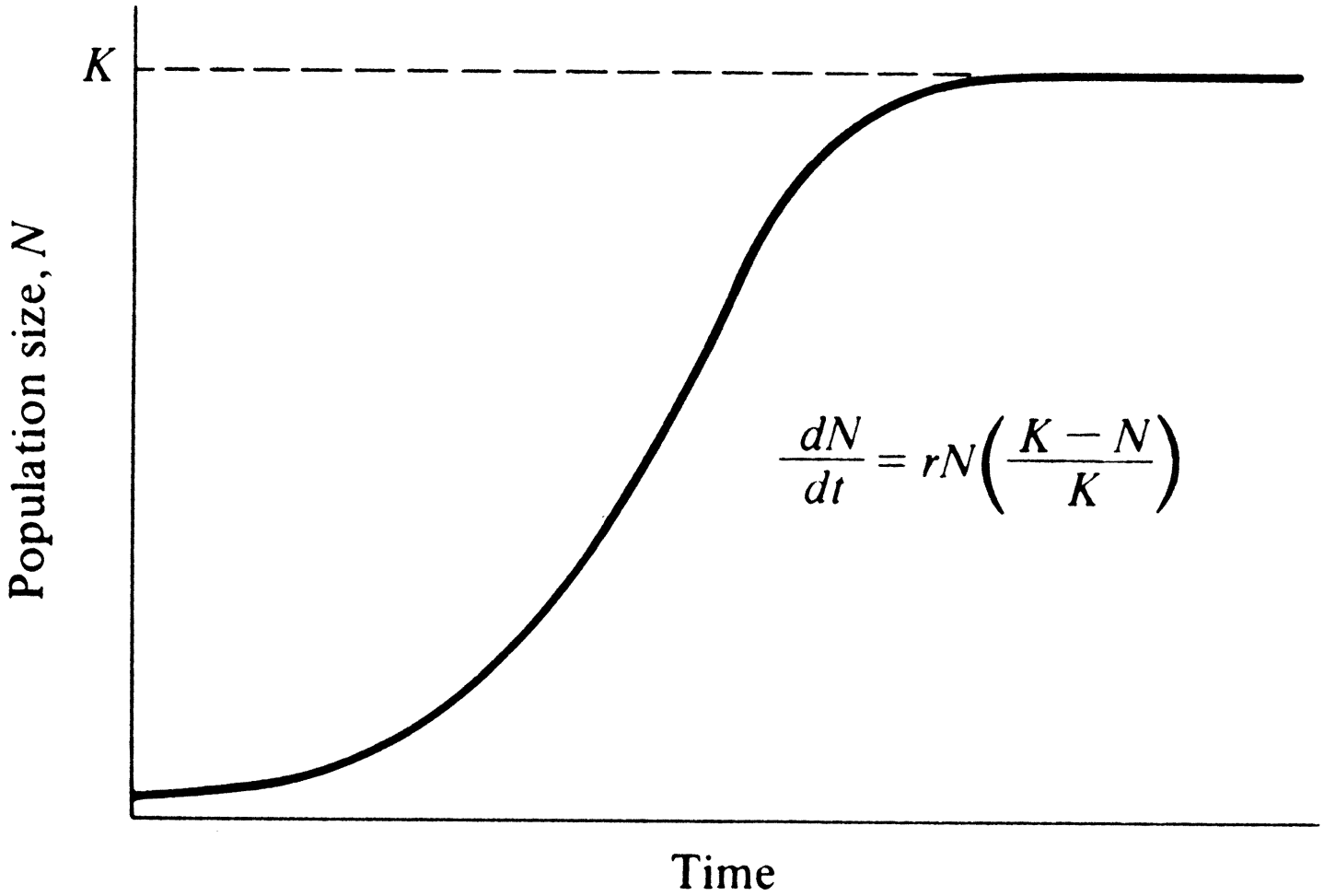
where $K$ is the carrying capacity and $r$ is the rate of population growth

- Bernoulli differential equation $\Longrightarrow$ directly solvable

$$P(t) = \frac{KP_0e^{rt}}{K + P_0(e^{rt} - 1)}$$

where $P_0$ is the initial population

# Solutions to the Logistic Equation

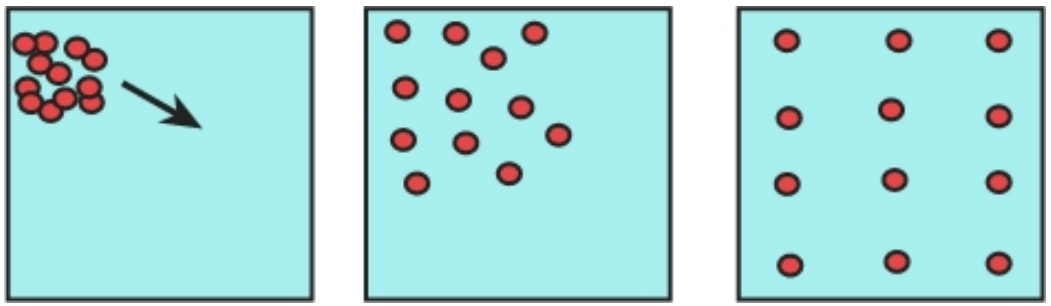



http://www.zo.utexas.edu/courses/Thoc/PopGrowth.html

# Diffusion Equation

- The Fickian diffusion equation models the dynamics of cells undergoing **diffusion** (net movement of molecules from a region of high concentration to a region of low concentration)
- It is given by

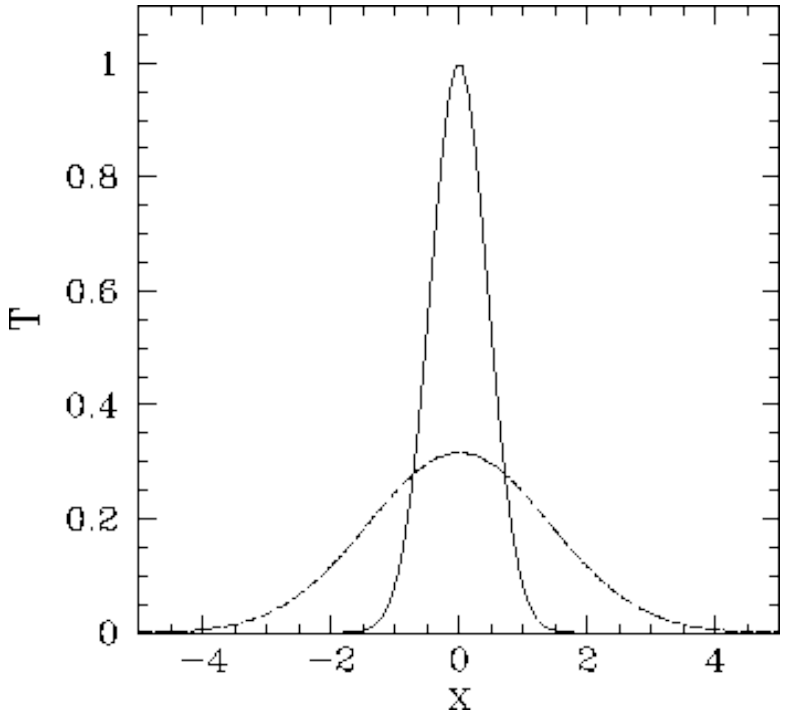
$$\begin{aligned}\frac{\partial n}{\partial t} &= D\nabla^2 n(\vec{x},t)\\ &= D\left(\frac{\partial^2 n}{\partial x_1^2}+\frac{\partial^2 n}{\partial x_2^2}+\cdots\right)\end{aligned}$$



http://www.biologycorner.com/bio1/notes_diffusion.html

# Solutions to Diffusion Equation

- Analytic solution methods exist for simple initial/boundary conditions and geometries
- Numerical techniques exist for more complicated initial/boundary conditions and geometries




http://farside.ph.utexas.edu/teaching/329/lectures/node78.html

# Single Reaction-Diffusion PDE Model

- Pioneering work done by Sherratt and Murray (1990)
- Convention that wound declared 'healed' when surface reaches 80% of original cell density
- Model assumptions
  - Surface of wound contains no epidermal cells
  - Wound heals as epidermal cells diffuse toward the wound

$$\boxed{\text{rate of change of cell density, } n(\vec{x},t)} = \boxed{\text{cell migration}} + \boxed{\text{mitotic generation}}$$

# Single Reaction-Diffusion PDE Model

- rate of change of cell density, $n$ = $\dfrac{\partial n}{\partial t}$
- cell migration = $D\nabla\left[\left(\dfrac{n}{n_0}\right)^p \nabla n\right]$ (**nonlinear** Fickian diffusion)
- mitotic generation = $sn\left(1 - \left(\dfrac{n}{n_0}\right)\right)$ (logistic growth)
- Thus the governing equation for the model is

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

with initial condition $n(x, 0) = 0$ for $x \in \Omega$ (where $\Omega$ is the wounded area) and boundary condition $n(x, t) = n_0$ for $x \in \partial\Omega$

# The Linear Diffusion Case

- In the linear diffusion case, we set $p = 0$

$$\begin{aligned}\frac{\partial n}{\partial t} &= D\nabla \cdot \left[\left(\frac{n}{n_0}\right)^0 \cdot \nabla n\right] + sn\left(1 - \left(\frac{n}{n_0}\right)\right) \\ &= D\nabla \cdot \left(\nabla n\right) + sn\left(1 - \left(\frac{n}{n_0}\right)\right) \\ &= D\nabla^2 n + sn\left(1 - \left(\frac{n}{n_0}\right)\right) \end{aligned} \tag{2}$$

- We can then scale out (non-dimensionalize) $s$ and $n_0$ such that $s, n_0 = 1$
- This leaves us with

$$\frac{\partial n}{\partial t} = D\nabla^2 n + n\left(1 - n\right) \tag{3}$$

with initial condition $n(x, 0) = 0$ for $x \in \Omega$ and boundary condition $n(x, t) = 1$ for $x \in \partial\Omega$

# Fisher-Kolmogorov Equation

- The Fisher-Kolmogorov equation has known **traveling wave** solutions
  - A traveling wave is a wave front that propagates through a medium with constant speed
  - Traveling wave solutions represent a front of epidermal cells diffusing into the wound

# Numerical Solutions to Fisher-Kolmogorov Equation

- Start with 1-D Fisher-Kolmogorov equation

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

- Discretize in space and time

$$\frac{n_i^{j+1} - n_i^j}{\Delta t} = D\frac{1}{(\Delta x)^2}\left(n_{i-1}^j - 2n_i^j + n_{i+1}^j\right) + n_i^j(1-n_i^j) \tag{5}$$

- Solve for next time step

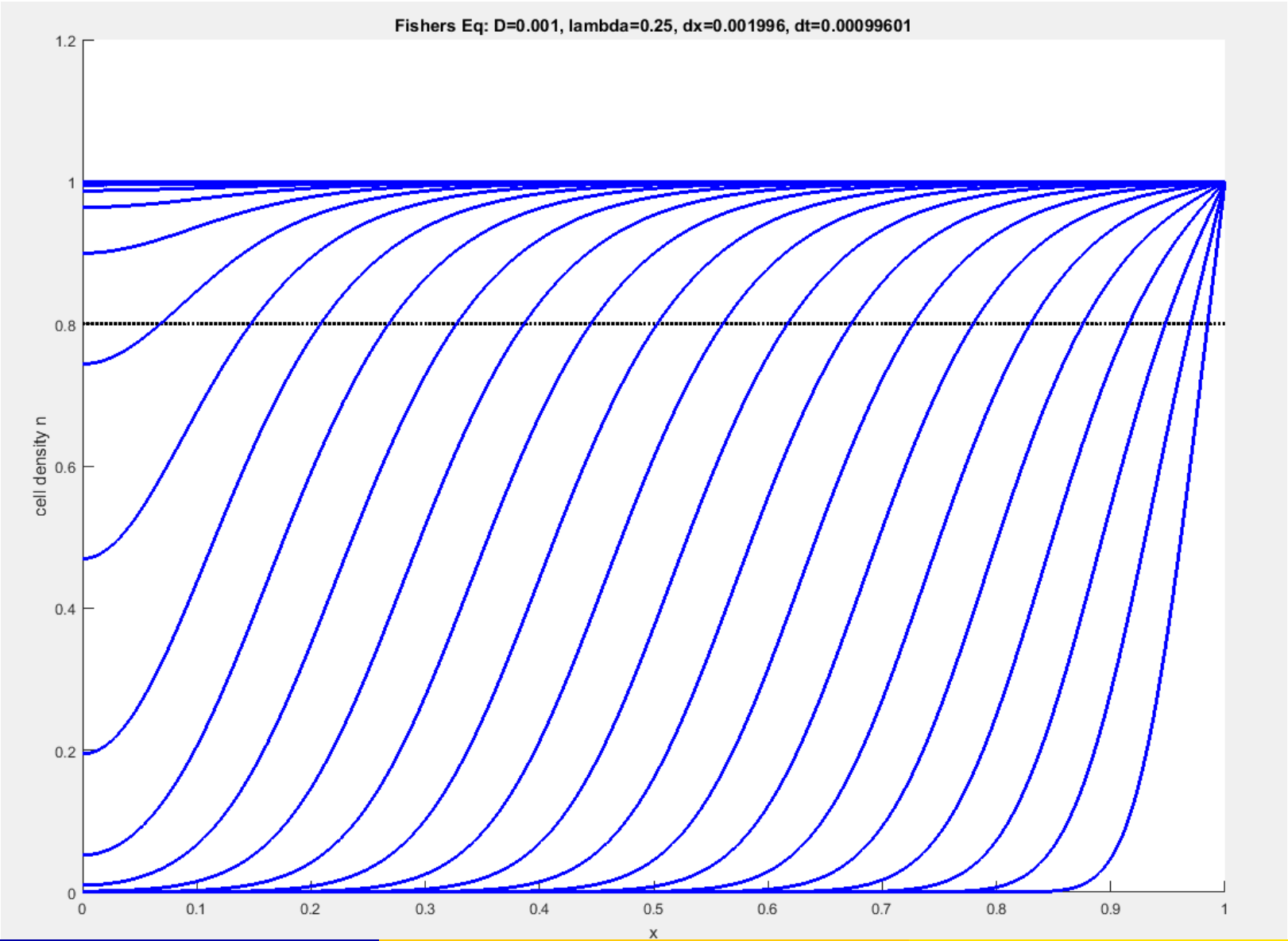
$$n_i^{j+1} = D\frac{\Delta t}{(\Delta x)^2}\left(n_{i-1}^j - 2n_i^j + n_{i+1}^j\right) + \Delta t n_i^j(1-n_i^j) + n_i^j \tag{6}$$

with $0 \leq x \leq 1$ and $t \geq 0$

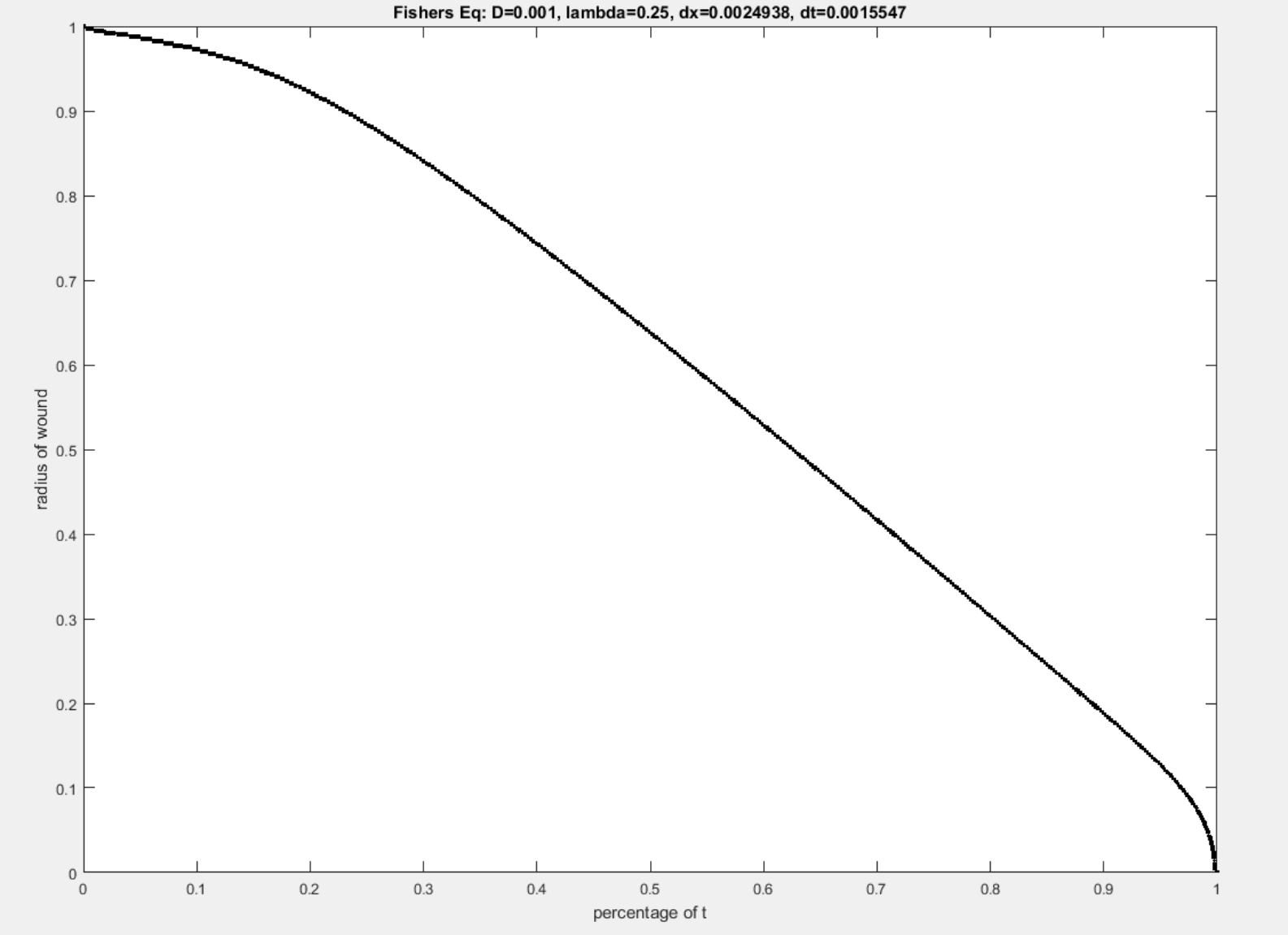
- We can now use a Forward Euler marching scheme to compute solution curves at each successive time step $(\mathcal{O}(\Delta t) + \mathcal{O}(\Delta x)^2)$

$$D\frac{\Delta t}{(\Delta x)^2} \leq \frac{1}{2} \tag{7}$$

# Numerical Solutions to Fisher-Kolmogorov Equation



# Time versus Wound Radius Plot



# The Nonlinear Diffusion Case

- Recall that we were originally interested in the equation

$$\frac{\partial n}{\partial t} = D\nabla \cdot \left[\left(\frac{n}{n_0}\right)^p \cdot \nabla n\right] + sn\left(1 - \left(\frac{n}{n_0}\right)\right) \tag{8}$$

- Sherratt and Murray were interested in the case when $p = 4$, so we have

$$\frac{\partial n}{\partial t} = D\nabla \cdot \left[\left(\frac{n}{n_0}\right)^4 \cdot \nabla n\right] + sn\left(1 - \left(\frac{n}{n_0}\right)\right) \tag{9}$$

  with initial condition $n(x, 0) = 0$ for $x \in \Omega$ and boundary condition $n(x, t) = n_0$ for $x \in \partial\Omega$

- This is a nonlinear partial differential equation $\Longrightarrow$ hard to analyze

# The Nonlinear Diffusion Case

- Non-dimensionalizing the equation we have

$$\frac{\partial n}{\partial t} = D\nabla \cdot \Big[n^p \cdot \nabla n\Big] + n\Big(1 - n\Big) \tag{10}$$

with initial condition $n(x, 0) = 0$ for $x \in \Omega$ and boundary condition $n(x, t) = 1$ for $x \in \partial\Omega$

# Numerical Solutions to the Nonlinear Diffusion Case

- Discretize in time and space

$$\begin{aligned}\frac{n_i^{j+1}-n_i^j}{\Delta t} &= D\frac{1}{\Delta x}\left[\left(n^p\frac{\partial n}{\partial x}\right)^j_{i+1/2}-\left(n^p\frac{\partial n}{\partial x}\right)^j_{i-1/2}\right]+n_i^j(1-n_i^j)\\ &= D\frac{1}{\Delta x}\left((n^j_{i+1/2})^p\frac{n_{i+1}^j-n_i^j}{\Delta x}-(n^j_{i-1/2})^p\frac{n_i^j-n_{i-1}^j}{\Delta x}\right)+n_i^j(1-n_i^j)\\ &= D\frac{1}{(\Delta x)^2}\left[\left(\frac{n_{i+1}^j+n_i^j}{2}\right)^p(n_{i+1}^j-n_i^j)-\left(\frac{n_i^j+n_{i-1}^j}{2}\right)^p(n_i^j-n_{i-1}^j)\right]\\ &+ n_i^j(1-n_i^j)\end{aligned} \tag{11}$$

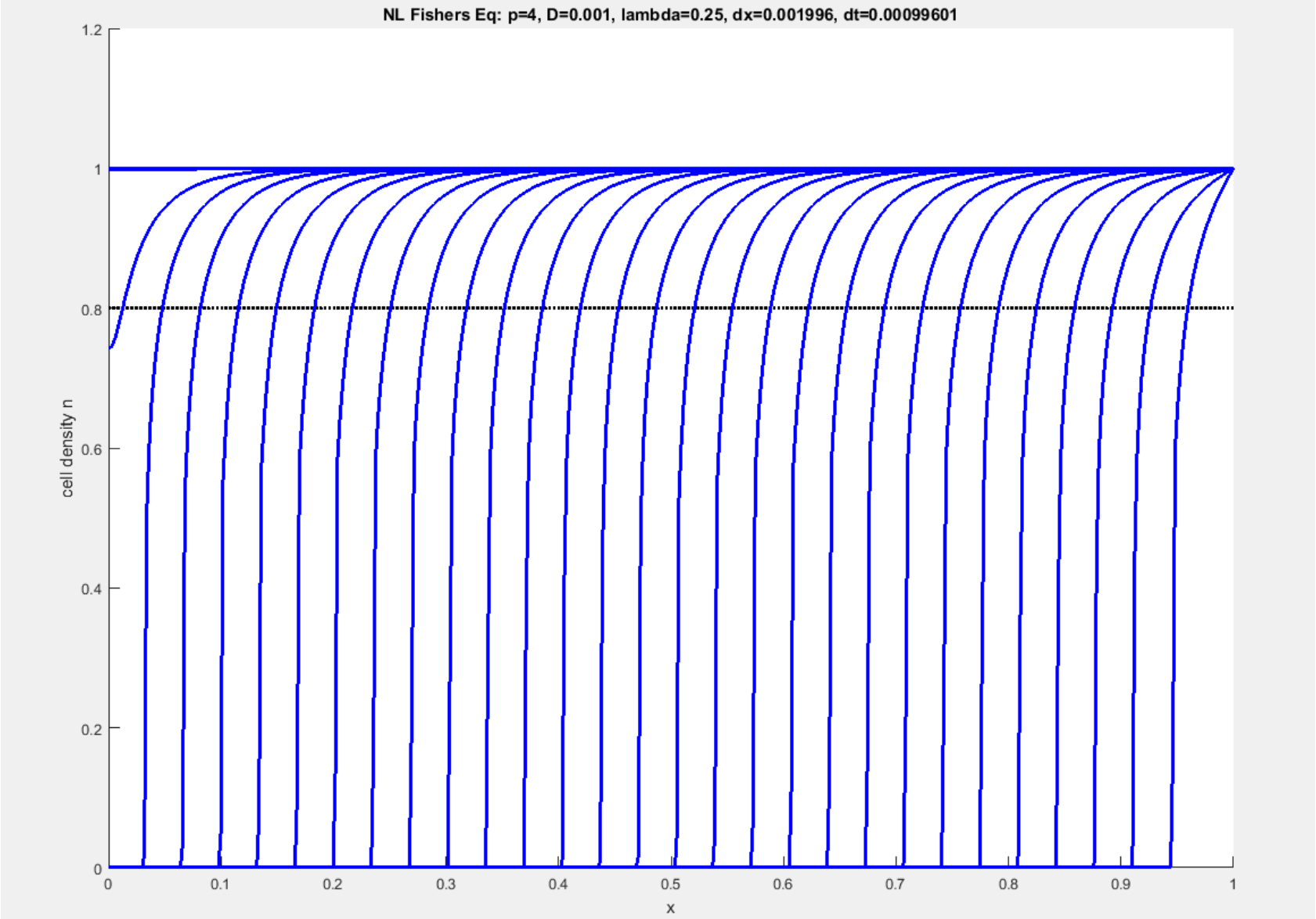
- Solve for $n_i^{j+1}$

$$\begin{aligned}n_i^{j+1} &= D\frac{\Delta t}{(\Delta x)^2}\left[\left(\frac{n_{i+1}^j+n_i^j}{2}\right)^p(n_{i+1}^j-n_i^j)-\left(\frac{n_i^j+n_{i-1}^j}{2}\right)^p(n_i^j-n_{i-1}^j)\right]\\ &+ (\Delta t)n_i^j(1-n_i^j)+n_i^j\end{aligned} \tag{12}$$

- We can now use a Forward Euler marching scheme to compute solution curves at each successive time step $(\mathcal{O}(\Delta t)+\mathcal{O}(\Delta x)^2)$

$$D\frac{\Delta t}{(\Delta x)^2}\leq\frac{1}{2} \tag{13}$$

# Numerical Solutions to the Nonlinear Diffusion Case



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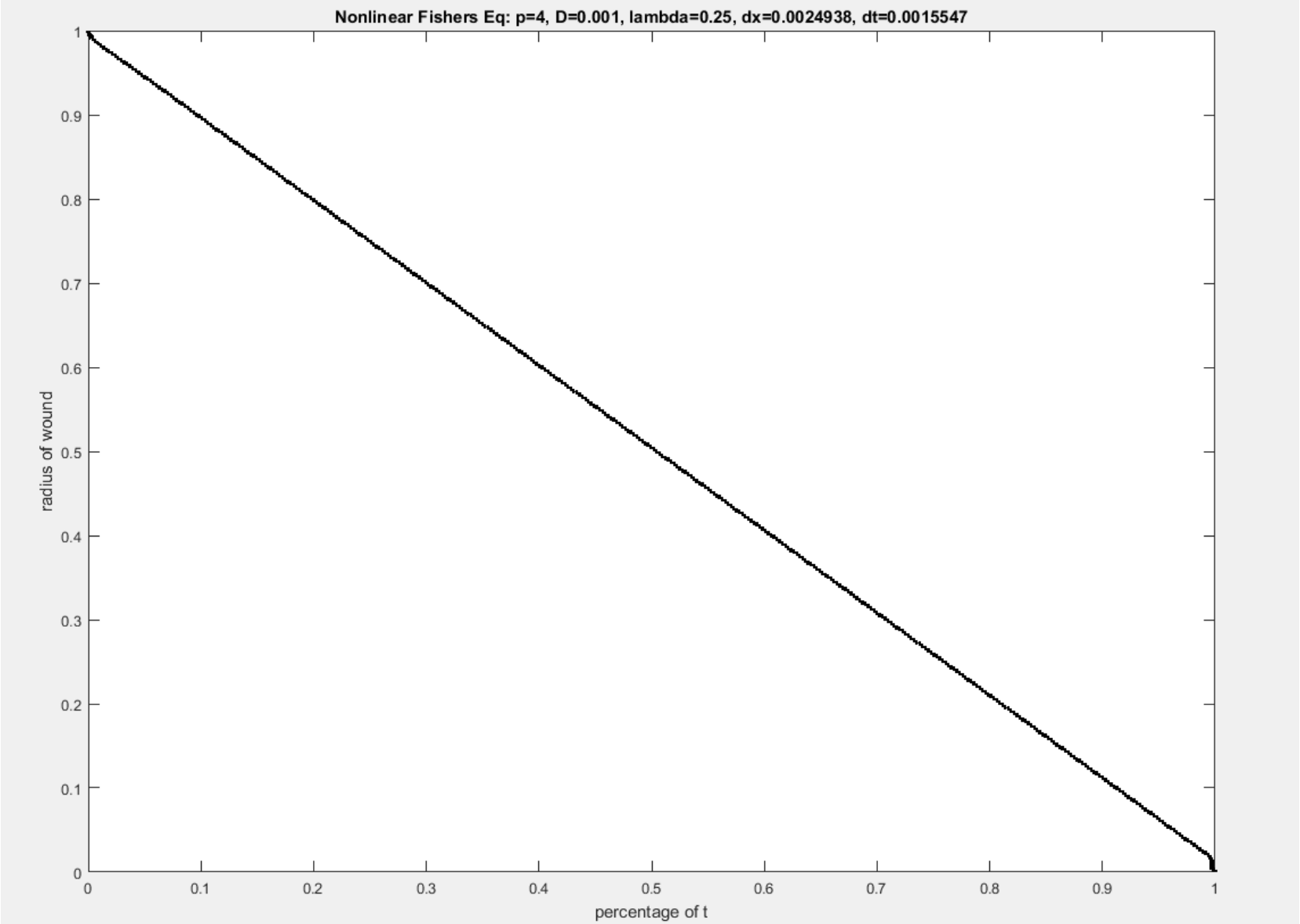


# Drawbacks to the Single PDE Model

- The single reaction-diffusion PDE model:
  - Not an ideal fit to experimental data
  - Speed of wave fronts were slightly off
  - Lacked characteristic ‘lag then linear phase’
- But all is not lost, as this led to improvements in the model

# An Improved Model

- Because of the pitfalls of the previous model, Sherratt and Murray became convinced of the need for a biochemical regulatory mechanism (1991)
- This mechanism includes both a mitosis activating chemical and a mitosis inhibiting chemical

| | | | | | | |
|---|---|---|---|---|---|---|
| rate of change of cell density, $n(\vec{x}, t)$ | = | cell migration | + | mitotic generation | − | natural loss |
| rate of change of chemical concentration, $c(\vec{x}, t)$ | = | diffusion of $c$ | + | production of $c$ | − | decay of chemical |

# Cell Density Equation

- cell migration $= D\nabla^2 n$
- natural loss $= kn$, where $k$ is a positive constant
- mitotic generation $= s(c) \cdot n \cdot \left(2 - \frac{n}{n_0}\right)$, where $s(c)$ is a function of chemical concentration
  - For activator, $s(c) = k \cdot \frac{2c_m(h-\beta)c}{c_m^2 + c^2} + \beta$
  - For inhibitor, $s(c) = \frac{(h-1)c + hc_0}{2(h-1)c + c_0} \cdot k$
  - $\beta = \frac{c_0^2 + c_m^2 - 2hc_0c_m}{(c_0 - c_m)^2}$
  - $h$ is a constant that corresponds to the max of $s(c)$
  - $k$ is the coefficient of natural loss
  - $c_m$ is a constant parameter that corresponds to the maximum level of chemical activation of mitosis, $c_0$ is the initial chemical concentration
  - Note that $s(c_0) = k$ which makes mitotic generation - natural loss logistic in the unwounded state

# Chemical Concentration Equation

- diffusion of $c$ = $D_c \nabla^2 c$
- decay of active chemical = $\lambda c$ where $\lambda$ is a positive constant
- production of $c$ by cells = $f(n)$
  - For activator, $f(n) = \lambda c_0 \cdot \frac{n}{n_0} \cdot \left( \frac{n_0^2 + \alpha^2}{n^2 + \alpha^2} \right)$
  - For inhibitor, $f(n) = \frac{\lambda c_0}{n_0} \cdot n$
  - With no cells there will be no production of $c$ and thus $f(0) = 0$
  - in the unwounded condition there is no chemical in the first place, and thus $f(n_0) = \lambda c_0$ to cancel out the decay of the active chemical term

# An Improved Model

- Full model given by

$$\frac{\partial n}{\partial t} = D\nabla^2 n + s(c)\cdot n\cdot\left(2-\frac{n}{n_0}\right) - kn \tag{14}$$

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + f(n) - \lambda c \tag{15}$$

with initial conditions $n(x,0) = 0, c(x,0) = 0$ for $x \in \Omega$ and boundary conditions $n(x,t) = n_0,\ c(x,t) = c_0$ for $x \in \partial\Omega$

- Nonlinear coupled system of partial differential equations

# Non-Dimensionalizing the Model

- Length scale $L$
- Cell cycle timescale $1/k$
- We use the scales given below

$$n^* = \frac{n}{n_0},\ c^* = \frac{c}{c_0},\ x^* = \frac{x}{L},\ t^* = kt,\ D^* = \frac{D}{(kL^2)},$$

$$\lambda^* = \frac{\lambda}{k},\ c_m^* = \frac{c_m}{c_0},\ \alpha^* = \frac{\alpha}{n_0},\ D_c^* = \frac{D_c}{(kL^2)}$$

# Non-Dimensionalizing the Model

- Dropping the $^*$ for simplicity we have

$$\frac{\partial n}{\partial t} = D\nabla^2 n + s(c)\cdot n\cdot(2-n) - n \tag{16}$$

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + \lambda f(n) - \lambda c \tag{17}$$

with initial conditions $n(x,0) = 0, c(x,0) = 0$ for $x \in \Omega$ and boundary conditions $n(x,t) = 1,\ c(x,t) = 1$ for $x \in \partial\Omega$

# Numerical Solutions

- Using the method of lines we have

$$n_i^{j+1} = D\frac{\Delta t}{(\Delta x)^2}\left(n_{i-1}^j - 2n_i^j + n_{i+1}^j\right) + \Delta t \cdot s(c_i^j) \cdot n_i^j \cdot (2 - n_i^j) + n_i^j \quad (18)$$

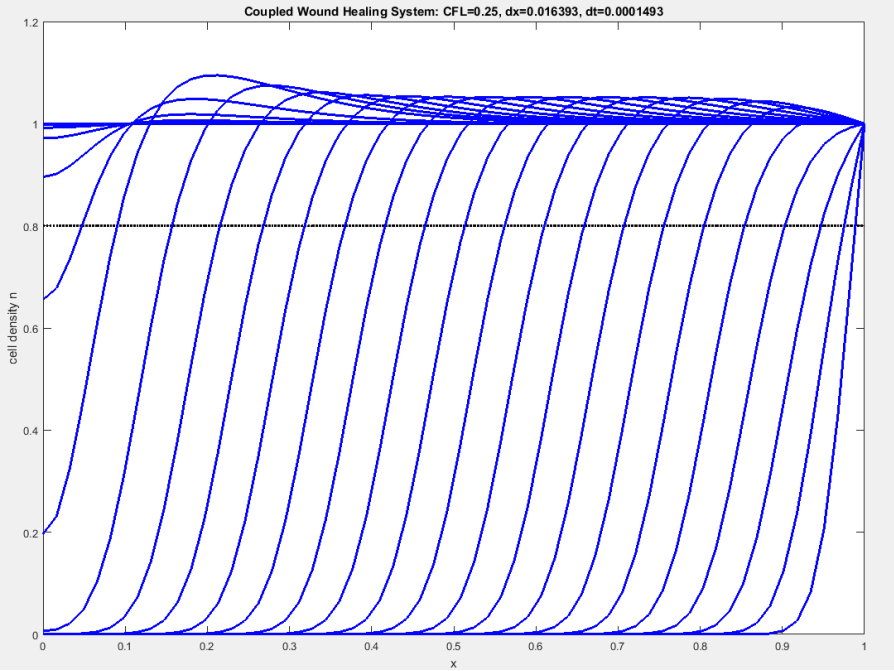
$$c_i^{j+1} = D_c\frac{\Delta t}{(\Delta x)^2}\left(c_{i-1}^j - 2c_i^j + c_{i+1}^j\right) + \Delta t\left(\lambda f(n_i^{j+1}) - \lambda c_i^j\right) + c_i^j \quad (19)$$

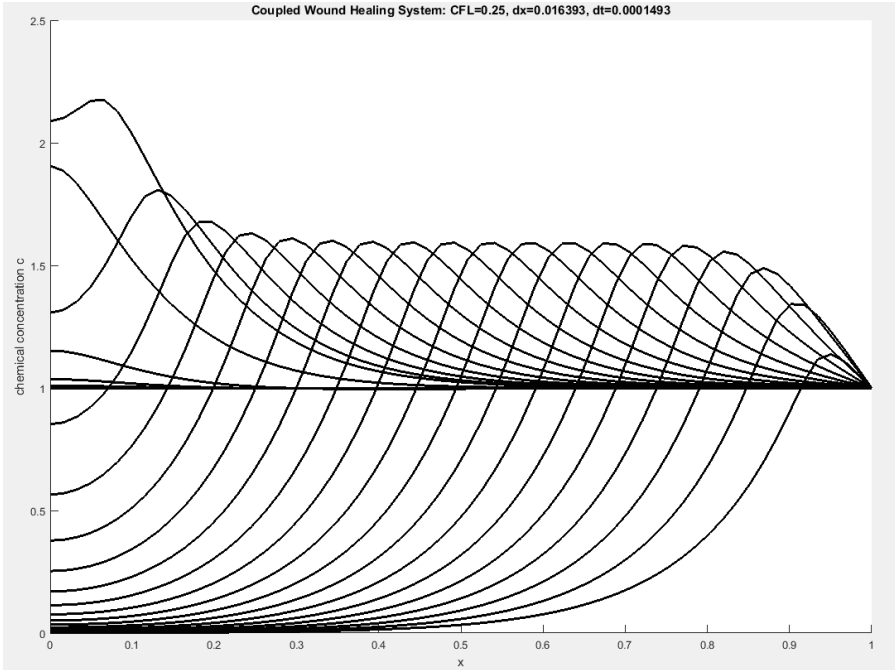
- We can now use a Forward Euler marching scheme to compute solution curves at each successive time step
  - This numerical scheme will converge if both CFL conditions are satisfied

$$D\frac{\Delta t}{(\Delta x)^2} \leq \frac{1}{2} \quad (20)$$

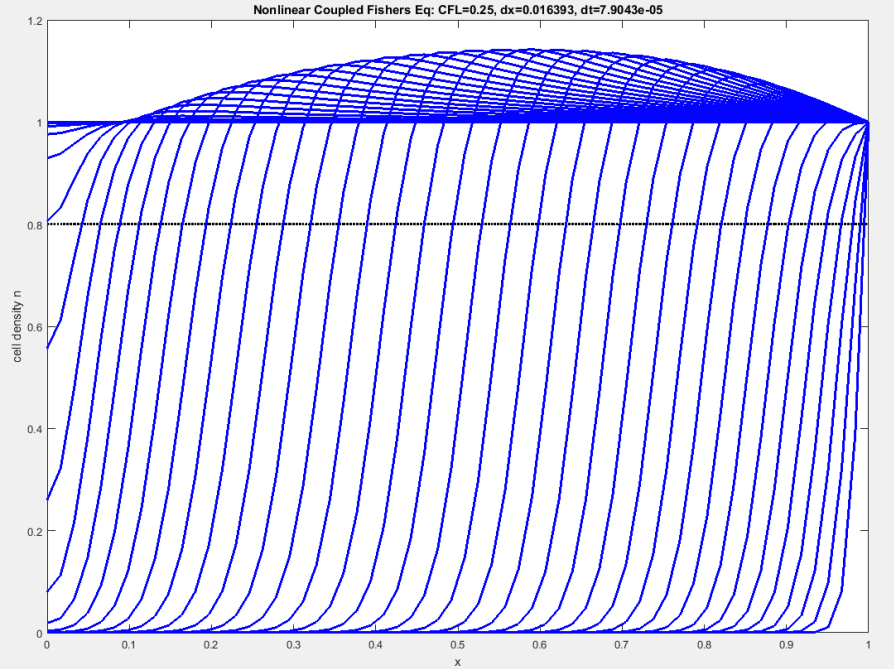
$$D_c\frac{\Delta t}{(\Delta x)^2} \leq \frac{1}{2} \quad (21)$$

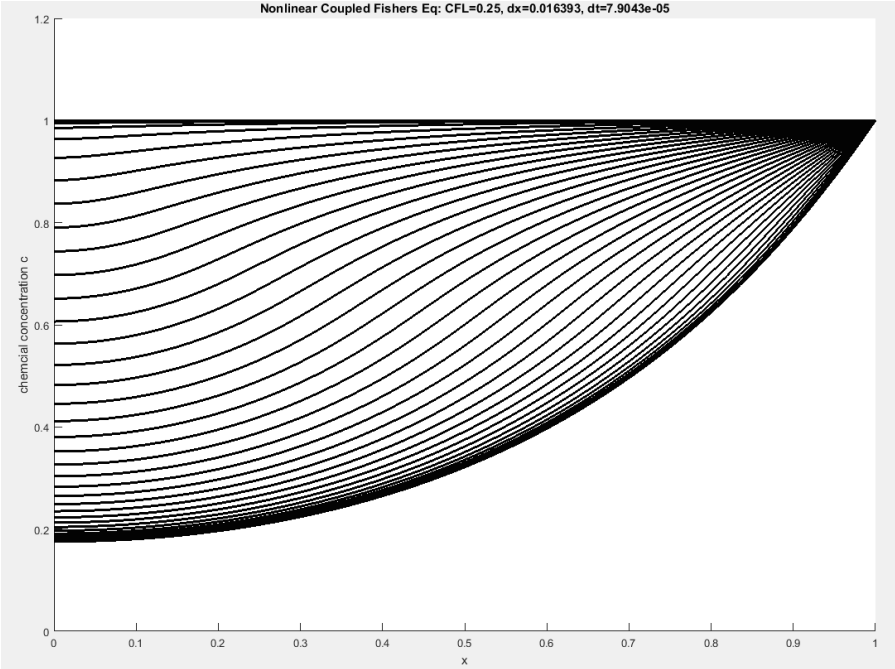
# Numerical Solutions (Activator Case)



# Numerical Solutions (Inhibitor Case)



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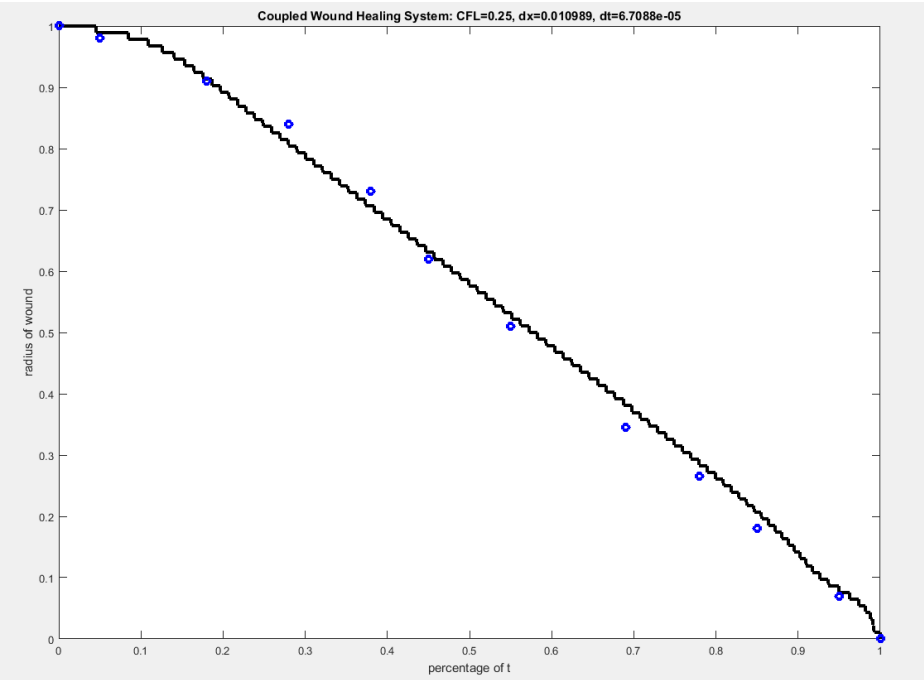
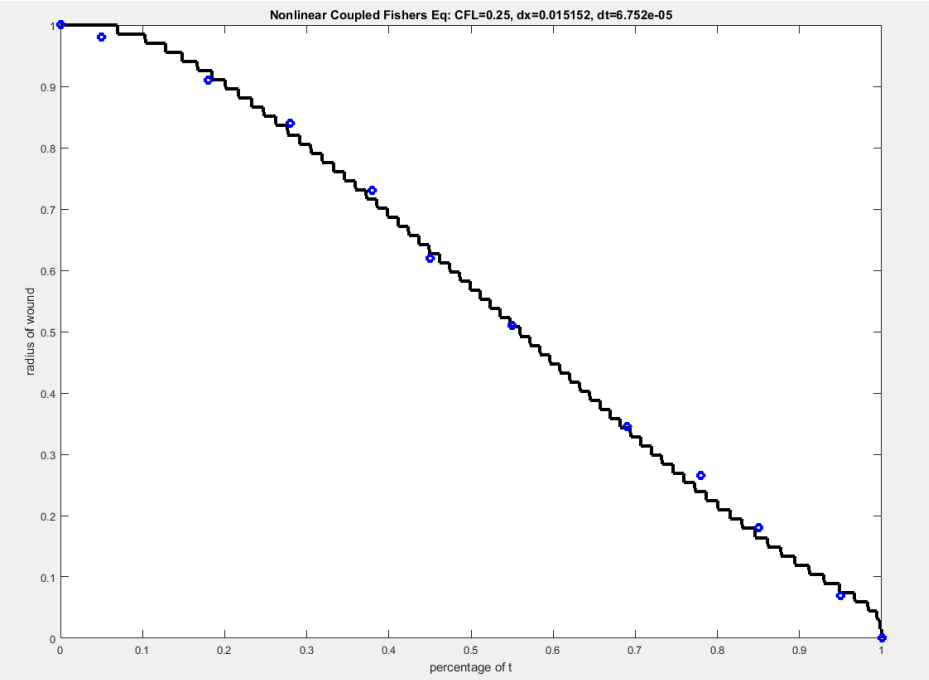


# Nova Computational Modeling Software

# Nova Computational Modeling Software Fun ☺

# Simplifying the PDE Model

- Characteristic variable transformation $z = x + at$ where $a$ is the traveling wave speed
  - $n(x,t) = N(z)$
  - $c(x,t) = C(z)$

$$\frac{\partial n(x,t)}{\partial t} = \frac{dN(z)}{dz} \cdot \frac{\partial z(x,t)}{\partial t} = N' \cdot a = aN' \tag{22}$$

$$D\nabla^2 n = D\frac{\partial^2 n}{\partial x^2} = D\frac{d^2 N(z)}{dz^2} \cdot \frac{\partial z(x,t)}{\partial x} = DN'' \tag{23}$$

$$D_c\nabla^2 c = D_c\frac{\partial^2 c}{\partial x^2} = D_c\frac{d^2 C(z)}{dz^2} \cdot \frac{\partial z(x,t)}{\partial x} = D_c C'' \tag{24}$$

# Reduction to ODE

- By plugging the respective derivatives in, the model becomes a coupled system of ordinary differential equations given by

$$aN' = DN'' + s(C) \cdot N \cdot (2 - N) - N \tag{25}$$

$$aC' = D_c C'' + \lambda f(N) - \lambda C \tag{26}$$

with biologically appropriate conditions of
$N(-\infty) = C(-\infty) = 0,\ N(\infty) = C(\infty) = 1$, and
$N'(\pm\infty) = C'(\pm\infty) = 0$

- Here we also make the simplification to a linearized $s(C) = \gamma C + 1 - \gamma$ where $\gamma = \dfrac{2(h-1)}{c_m - 2}$

# Simplification of $\lambda \to \infty$

- This simplification represents the chemical concentration kinetics coming to a state of equilibrium
- As $\lambda \to \infty$, the terms not containing a $\lambda$ in the chemical PDE become negligible

$$\begin{aligned} 0 &= -aC' + D_c C'' + \lambda f(N) - \lambda C \\ &= 0 + 0 + \lambda f(N) - \lambda C \\ &= \lambda(f(N) - C) \end{aligned}$$

- As $\lambda \neq 0$, this implies that $f(N) = C(z)$
- By rearranging terms we get the single ODE given by

$$N'' = \frac{aN'}{D} - \frac{s(f(N)) \cdot N \cdot (2 - N) - N}{D} \tag{27}$$

with boundary conditions $N(\infty) = 1,\ N(-\infty) = 0,\ N'(\pm\infty) = 0$

# Asymptotic Stability Analysis

- Converting the system to two first order ODEs we have

$$N' = M \tag{28}$$

$$M' = \frac{aM - s(f(N)) \cdot N \cdot (2 - N) + N}{D} \tag{29}$$

with equilibrium values are $(N, M) = (0, 0)$ and $(N, M) = (1, 0)$

- Then the Jacobian is given by

$$J(N, M) = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial M} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial M} \end{bmatrix}$$

# Traveling Wave Solutions for Simplified System

- Converting the system to two first order ODEs we have that

$$J(0,0) = \begin{bmatrix} 0 & 1 \\ \dfrac{-[2s(0)-1]}{D} & \dfrac{a}{D} \end{bmatrix}$$

$$\Lambda = \frac{1}{2}\Big[\frac{a}{D} \pm \sqrt{\Big(\frac{a}{D}\Big)^2 - 4\Big(\frac{2s(0)-1}{D}\Big)}\Big]$$

- The bifurcation value is

$$a^* = 2\sqrt{\Big(D(2(s(0)-1)\Big)} = 2\sqrt{\Big(D(2(1-\gamma)-1)\Big)} = 2\sqrt{D(1-2\gamma)}$$

- For $a > a^*$ we have an unstable node which allows for traveling wave solutions and thus this simplified ODE system has traveling wave solutions

# Cooperative Reaction Diffusion Systems

- Chinese mathematical biologists Haiyan Wang and Shilang Wu demonstrated existence of traveling wave solutions for the full system
- Consider the reaction-diffusion partial differential equation system

$$\frac{\partial A}{\partial t} = d_1 \nabla^2 A + g_1(A, B) \tag{30}$$

$$\frac{\partial B}{\partial t} = d_2 \nabla^2 B + g_2(A, B) \tag{31}$$

where $g_1$ and $g_2$ are differentiable functions of $A$ and $B$. We call the system **cooperative** if

$$\frac{\partial g_1}{\partial B} \geq 0 \tag{32}$$

$$\frac{\partial g_2}{\partial A} \geq 0 \tag{33}$$

- In the epidermal wound healing system $\frac{\partial g_2}{\partial c} = \lambda f(n) \not\geq 0$ for $n > \alpha$

# Bounding the System

- Wang and Wu define an upper and lower bound cooperative system given by

$$\frac{\partial n}{\partial t} = D\nabla^2 n + s(c)\cdot n\cdot(2-n) - n \tag{34}$$

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + \lambda f^{\pm}(n) - \lambda c \tag{35}$$

where

$$f^{+}(n) = \begin{cases} f(n) & , \ 0 \le n \le \alpha \\ f(\alpha) & , \ n \ge \alpha \end{cases}$$

and

$$f^{-}(n) = \begin{cases} f(n) & , \ 0 \le n \le f_0 \\ f(f_0) & , \ n > f_0 \end{cases}$$

- Through further analysis we can apply Wang and Wu's previous results on cooperative reaction-diffusion systems to the wound healing model

# Traveling Wave Solutions to Full Model

## Theorem

*Let $D, D_c$ be positive constants and let $\gamma \in (0, \frac{1}{2}),\ \alpha \in (0,1),$*

$$\frac{D_c}{D} < 2 + \frac{\lambda}{1-2\gamma},$$

*and*

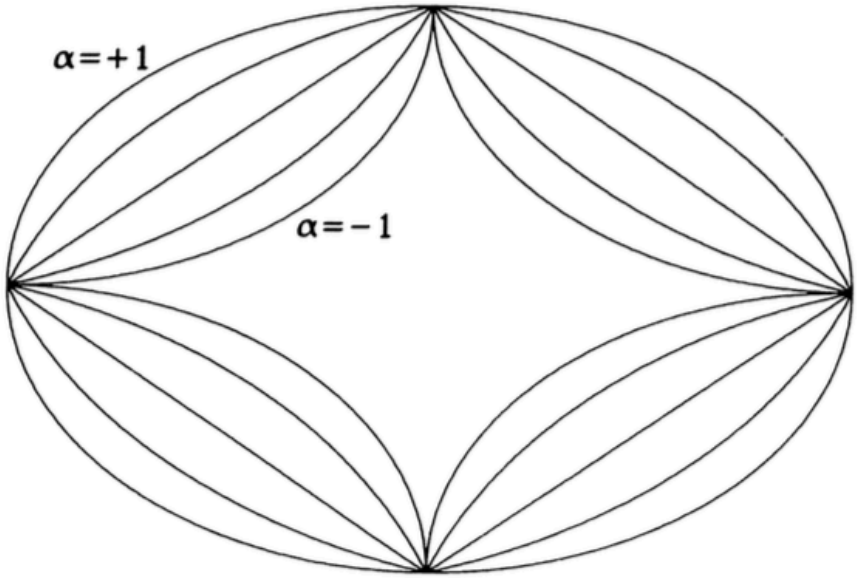
$$\frac{2\gamma f'(0)}{1-\gamma} \leq \begin{cases} 1 + \dfrac{1-2\gamma}{\lambda} & , D \geq D_c \\ \left(2 - \dfrac{D_c}{D}\right)\dfrac{1-2\gamma}{\lambda} + 1 & , D \leq D_c \end{cases}$$

*Then the Sherratt/Murray epidermal wound healing system admits a physically relevant traveling wave solution for $a > a^*$ and does not admit a physically relevant traveling wave solution for $a < a^*$ where the minimum wave speed $a^*$ is given by*

$$a^* = 2\sqrt{(1-2\gamma)D}.$$

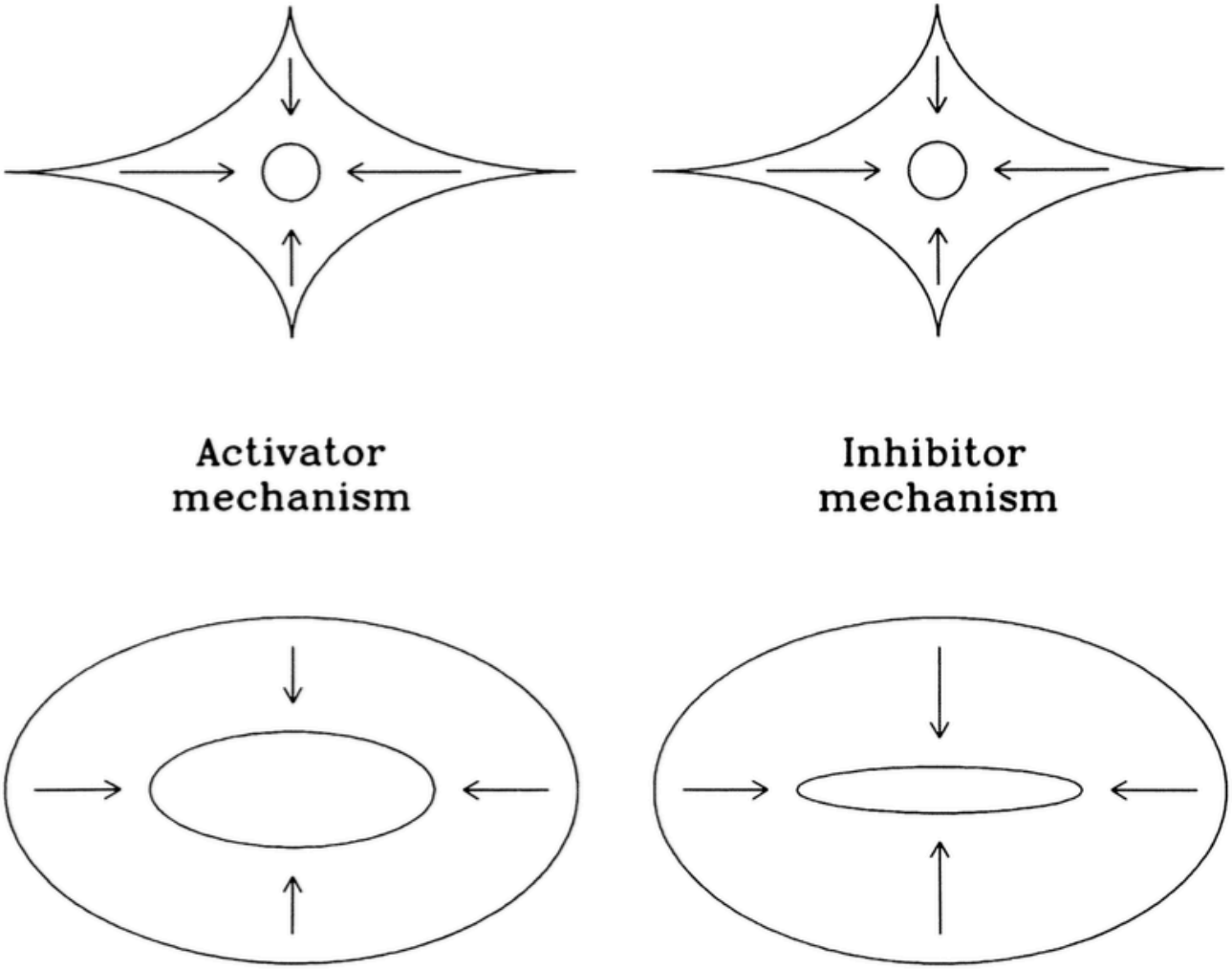
# Clinical Implications: Varying Wound Geometry

$$f_{shape}(x;\alpha) = \frac{1}{2}\left(1+\frac{1}{\alpha}\right) - \text{sign}(\alpha)\left[\frac{1}{2}\left(1+\frac{1}{\alpha^2}\right) - \left(x+\frac{1}{2\alpha}-\frac{1}{2}\right)^2\right]^{-1/2} \quad (36)$$




- $\alpha = -1$ implies the wound shape is a cusp
- $-1 < \alpha < 0$ implies the wound shape is a cusped diamond
- $\alpha = 0$ implies the wound shape is a diamond
- $0 < \alpha < 1$ implies the wound shape is more ovate
- $\alpha = 1$ implies the wound shape is an ellipse

# Geometry of Epidermal Wound Healing



# Nova Demonstration of Geometry

# Topical Addition Slide?

# Conclusion

- Mathematical models of epidermal wound healing:
  - Have increased in mathematical/biological complexity over time
  - Give us insight into a complex biological reaction
  - Are excellent examples of complex systems of coupled nonlinear partial differential equations
- Traveling wave solutions to the full coupled system given by Sherratt and Murray exist
- Opportunity for future mathematical and biological research

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