Published in final edited form as:

SIAM J Appl Math. 2018 ; 78(3): 1712–1736. doi:10.1137/16M1108546.

INVESTIGATION OF A STRUCTURED FISHER'S EQUATION WITH APPLICATIONS IN BIOCHEMISTRY

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Abstract

Recent biological research has sought to understand how biochemical signaling pathways, such as the mitogen-activated protein kinase (MAPK) family, influence the migration of a population of cells during wound healing. Fisher's Equation has been used extensively to model experimental wound healing assays due to its simple nature and known traveling wave solutions. This partial differential equation with independent variables of time and space cannot account for the effects of biochemical activity on wound healing, however. To this end, we derive a structured Fisher's Equation with independent variables of time, space, and biochemical pathway activity level and prove the existence of a self-similar traveling wave solution to this equation. We exhibit that these methods also apply to a general structured reaction-diffusion equation and a chemotaxis equation. We also consider a more complicated model with different phenotypes based on MAPK activation and numerically investigate how various temporal patterns of biochemical activity can lead to increased and decreased rates of population migration.

Keywords

Stage-structure; Traveling Wave Solutions; Wound Healing; Biochemical Signaling Pathways

1. Introduction

Traveling wave solutions to partial differential equations (PDEs) are often used to study the collective migration of a population of cells during wound healing [4, 9, 27, 28, 30], tumorigenesis [26], and angiogenesis [39, 43]. R.A. Fisher introduced what is now referred to as Fisher's Equation in 1937 to model the advance of an advantageous gene in a population [14]. Since then, it has been used extensively in math biology literature to model the migration of a two-dimensional monolayer of cells during experimental wound healing assays [4, 21, 30].

Fisher's Equation is written as

$$u_t = Du_{xx} + \lambda u \left(1 - \frac{u}{K}\right) \quad (1)$$

with subscripts denoting differentiation with respect to that variable and $u = u(t, x)$ representing a population of cells over time t at spatial location x . The first term on the right hand side of (1) represents diffusion in space with rate of diffusion, D , and the second term represents logistic growth of the population with proliferation rate, λ , and carrying capacity, K . As shown in [35, § 11.2], (1) admits traveling wave solutions of the form

$$u(t, x) = U(z), z = x - ct$$

where c denotes the speed of the traveling wave solution and $U(z)$ denotes the traveling wave profile. Traveling wave solutions to (1) thus maintain a constant profile, $U(z)$, over time that moves leftward if $c < 0$ or rightward if $c > 0$ with speed $|c|$. It is also shown that (1) has a positive and monotonic profile for $|c| \geq 2\sqrt{D\lambda}$, which is biologically relevant when $u(t, x)$ denotes a population of cells. Kolmogoroff proved in 1937 that any solution to (1) with a compactly-supported initial condition will converge to a traveling wave solution with wavespeed $c = 2\sqrt{D\lambda}$ [25]. See [34, § 5.4] for a proof of this. There is also a wide literature on studies into extensions of Fisher's Equation, such as Fisher's Equation coupled with chemotaxis [2, 27], time-dependent rates of proliferation and diffusion [18], and space-dependent rates of diffusion [7].

Continuously-structured population models, or PDE models with independent variables to distinguish individuals by some continuously-varying properties, were first investigated via age-structured models in the early 20th century [32, 42]. The 1970s saw a revival in structured population modeling after the introduction of methods to investigate nonlinear structured population models [17], which led to our current understanding of semigroup theory for linear and nonlinear operators on Banach spaces [48]. Recent math biology studies have used structured equations in various contexts. Several studies have proved the existence of traveling wave solutions to structured population models [11, 12, 15, 45]. The authors of [10] developed a spatio-temporal structured framework to describe the molecular binding process for cell membranes and connected it with cell population dynamics to investigate several examples of cancer invasion. Another study used an independent variable representing subcellular β -catenin concentration to investigate how signaling mutations can cause intestinal crypts to invade healthy neighboring crypts [36]. An age-structured equation has also been used to describe demographic data for *Daphnia magna*, a species of water flea [41].

Recent biological research has focused on the influence of biochemical signaling pathways on the migration of a population of cells during wound healing. Particular emphasis has been placed on the mitogen-activated protein kinase (MAPK) signaling cascade, which elicits interesting patterns of activation and migration in response to different types of cytokines and growth factors in various cell lines [5, 31]. For example, experimental wounding assays of madine darby canine kidney cells (MDCKs) in [31] yielded a transient pulse of ERK 1/2 (a specific MAPK protein) activity in the cell sheet that only lasted for a few minutes. This pulse of activity was followed by a slow wave of activity that propagated from the wound margin to submarginal cells over the course of several hours. The second wave was determined to be crucial for regulating MDCK sheet migration. The authors of [31]

proposed that these fast and slow waves of ERK 1/2 activity could be caused by the production of reactive oxygen species (ROS) and epidermal growth factor (EGF), respectively. Similar experiments with fibroblasts also demonstrated this first transient wave of ERK 1/2 activity, but not the following slow wave. The authors of [5] found that human keratinocyte (HaCaT) cells exhibit ERK 1/2 activity primarily at the wound margin during similar experimental wound healing assays with a high density in response to treatment with transforming growth factor- β (TGF- β).

In this study, we detail an approach to investigate a continuously-structured extension of Fisher's Equation that is motivated by the above experimental observations. Previous structured population models (with the exception of [10]) have been restricted to traits that primarily increase over time, such as age or size, but our analysis allows for both activation and deactivation along the biochemical activity dimension.

In Section 2, we develop our structured population model and devote Section 3 to a review of relevant material from size-structured population models. We demonstrate the existence of self-similar traveling wave solutions to the model in Section 4. In Section 5, we study a more realistic version of our model where migration and proliferation of the population depend on MAPK activity levels. We derive two criteria for the cell population to activate and use numerical simulations to demonstrate that the cell population is most sensitive to parameter changes when only part of the cell population is activated. Some simulations also migrate furthest at the threshold between part of the population activating and all of the population activating. We make final conclusions and discuss future work in Section 6.

2. Model Development

We model a cell population during migrating into a wound, $u(t, x, m)$, by

$$u: [0, \infty) \times \mathbb{R}^n \times [m_0, m_1] \rightarrow \mathbb{R}$$

where t denotes time, x denotes spatial location, and m denotes activation along a biochemical signaling pathway with minimum and maximum levels m_0 and m_1 , respectively. As a first pass, we assume that any cells of the same MAPK activity level will activate identically over time in the same environment. This assumption allows us to model the activation distribution of the population over time deterministically by considering how cells of all possible MAPK activity levels activate and deactivate over time. We note that biochemical signaling is an inherently heterogeneous process, so our approach would benefit from a further investigation with stochastic differential equations. While cell migration is realistically a three-dimensional process, two-dimensional scratch assays are currently the most common experiments used to study cell migration during wound healing or cancer invasion [5, 19, 22]. For ease of analysis and numerical computation, we will use $n = 1$ here for one-dimensional migration. Note that one-dimensional equations have been used frequently to interpret two-dimensional scratch assays [4, 21, 33, 37], and the results here extend to two or three dimensions [20].

As discussed in [8], crucial aspects of a structured population model include the individual state, the environmental state, external forcing factors, and feedback functions. The *individual state* is a dimension used to distinguish between individuals of a population and is typically based on physiological properties such as age or size. As activation of biochemical signaling pathways influences cell migration through diffusive and proliferative properties of cells, we incorporate the biochemical activity dimension, m , as an individual state for our model.

The *environmental state* of a population is the external factors that influence individual behavior. Recall that external cytokines and growth factors, such as ROS, TGF- β , and EGF, influence activation of the MAPK signaling cascade and promote migration during wound healing. The cell population will not directly affect the level of external growth factor in this work, so an *external forcing factor* will be used to represent treatment with these chemicals here. The external chemical concentration at time t will be denoted by $s(t)$, and the activation response of cells to this chemical will be given by the function $f(s)$.

A *feedback function* included in our work will be the inhibition of individual cell proliferation in response to a confluent density. As proliferation is hindered by contact inhibition, we introduce a new variable,

$$w(t, x) := \int_{m_0}^{m_1} u(t, x, m) dm \quad (2)$$

to represent the population of cells at time t and spatial location x . Proliferation of the population will accordingly vanish as $w(t, x)$ approaches the carrying capacity, K .

Our model, which we term as a *structured Fisher's Equation*, is given by the PDE model

$$u_t + \underbrace{(f(s(t))g(m)u)_m}_{\text{activation}} = \underbrace{D(m)u_{xx}}_{\text{diffusion}} + \underbrace{\lambda(m)u \left(1 - \frac{w(t, x)}{K}\right)}_{\text{population growth}} \quad (3)$$

$$w(t, x) = \int_{m_0}^{m_1} u(t, x, m) dm$$

$$u(t = 0, x, m) = \phi_1(m)\phi_2(x)$$

$$u(t, x, m = m_1) = 0$$

$$w(t, -\infty) = K \quad w(t, x = +\infty) = 0$$

The function $g(m) \in C^1([m_0, m_1])$ denotes the rate of biochemical activation in the population, $s(t) \in L^\infty(\mathbb{R}^+)$ denotes the external chemical concentration in the population, $f(s) \in L^1_{loc}(0, \infty)$ denotes the activation response of cells to the level of signaling factor present, $D(m)$ and $\lambda(m)$ denote biochemically-dependent rates of cell diffusion and proliferation, and $\phi_1(m)\phi_2(x)$ denotes the initial condition of u . We assume a separable initial condition for simplicity. The spatial boundary conditions specify that the cell density has a confluent density at $x = -1$ and an empty wound space at $x = +1\infty$. We use a no flux boundary condition at $m = m_1$ so that cells cannot pass this boundary. In the remainder of this study, we will write $f(s(t))$ as $f(t)$ for simplicity, though we note that this function will differ between cell lines that respond differently to the same chemical during wound healing¹.

The solution space of (3), $\mathcal{D}$, is defined with inspiration from [48] and [47, § 1.1]. If we let Z denote the space of bounded and twice continuously differentiable functions on $\mathbb{R}$, then we define

$$\mathcal{D} := \{u(t, x, m) \mid \int_{m_0}^{m_1} u(t, x, m) dm \in Z\},$$

i.e., $u(t, x, m) \in \mathcal{D}$ if $w(t, x) \in Z$ for all $t > 0$. We note that $\int_{m_0}^{m_1} \phi(x, m)$ need only be bounded and piecewise continuous with a finite number of discontinuities [47]. If $\phi(x, m)$ is not sufficiently smooth in m , we obtain generalized solutions of (3) [48].

In Section 4, we will investigate (3) with constant rates of diffusion and proliferation (i.e., $D(m) = D$, $\lambda(m) = \lambda$) and $f(t) = 1$. By substituting

$$u^* = \frac{m_1 - m_0}{K} u, \quad t^* = \lambda t, f^*(t^*) = f(t^*/\lambda)$$

$$x^* = x\sqrt{\lambda/D}, \quad m^* = (m - m_0)/(m_1 - m_0),$$

$$g^*(m^*) = \frac{g(m^*(m_1 - m_0) + m_0)}{\lambda \cdot (m_1 - m_0)},$$

¹Note that an extension for modeling the dynamics governing $s(t)$ will be considered in a future study.

$$w^* = \int_0^1 u^*(t^*, x^*, m^*) dm^* \quad (4)$$

and dropping asterisks for simplicity, (3) can be non-dimensionalized to

$$u_t + \underbrace{(f(t)g(m)u)_m}_{\text{activation}} = \underbrace{u_{xx}}_{\text{diffusion}} + \underbrace{u(1 - \int_0^1 u(t, x, m) dm)}_{\text{population growth}} \quad (5)$$

$$w(t, x) = \int_0^1 u(t, x, m) dm$$

$$u(t = 0, x, m) = \phi_1(m)\phi_2(x)$$

$$u(t, x, m = 1) = 0$$

$$w(t, x = -\infty) = 1 \quad w(t, x = +\infty) = 0.$$

In Section 5, we will consider the full model (3) when the rates of cellular diffusion and proliferation are piece-wise constant functions of m and numerically investigate how different functions for $f(t)$ lead to increased and decreased levels of population migration. These rates of diffusion and proliferation are given by

$$D(m) := \begin{cases} D_1 & m \in M_{inact} \\ D_2 & m \in M_{act} \end{cases}, \lambda(m) := \begin{cases} \lambda_1 & m \in M_{inact} \\ \lambda_2 & m \in M_{act} \end{cases} \quad (6)$$

for $M_{inact} := [m_0, M_{crit})$ and $M_{act} := [m_{crit}, m_1]$. We can perform the same normalization as (4) but now use

$$x^* = x\sqrt{\lambda_1/D_1}, t^* = \lambda_1 t$$

$$f^*(t^*) = f(t^*/\lambda_1)$$

in which case (3) becomes

$$u_t + (f(t)g(m)u)_m = \tilde{D}(m)u_{xx} + \tilde{\lambda}(m)u\left(1 - \frac{w}{K}\right) \quad (7)$$

$$w = \int_{m_0}^{m_1} u(t, x, m) dm$$

$$u(t = 0, x, m) = \phi_1(m)\phi_2(x)$$

$$u(t, x, m = m_1) = 0$$

$$w(t, x = +\infty) = 0 \quad w(t, x = -\infty) = 1.$$

with

$$\tilde{D}(m) := \begin{cases} 1 & m \in M_{inact} \\ \bar{D} & m \in M_{act} \end{cases}, \tilde{\lambda}(m) := \begin{cases} 1 & m \in M_{inact} \\ \bar{\lambda} & m \in M_{act} \end{cases} \quad (8)$$

3. Background Material from Size-Structured Population Modeling

Before investigating the existence of traveling-wave solutions to (5), it is useful to review some key topics used to solve size-structured population models, as discussed in [48]. These topics will be useful in analyzing (3) in later sections. A reader who is familiar with using the method of characteristics to solve size-structured population models may briefly skim over this section to pick up on the notation used throughout our study.

As an example, we consider the size-structured model given by

$$u_t + (g(y)u)_y = Au \quad (9)$$

$$u(t = 0, y) = \phi(y)$$

where $u = u(t, y) : [0, \infty) \times [y_0, y_1] \rightarrow \mathbb{R}$ denotes the size distribution over y of a population at time t , y_0 and y_1 denote the minimum and maximum population sizes respectively, and $g(y) \in C^1([y, y_1])$ denotes the physical growth rate² of individuals of size y . In this section, we will work in the Banach space $\mathbb{X} = L^1([y, y_1] \rightarrow \mathbb{R})$ and assume $A \in$

$\mathcal{B}(\mathbb{X})$, the space of bounded and linear operators on $\mathbb{X}$. The method of characteristics will facilitate solving (9).

The goal of this section is to discuss techniques that can be used to solve (9) analytically, and provide an example problem to provide insight. In Section 3.1, we discuss the functions $\sigma(y; \underline{y})$ and $\sigma^{-1}(t; \underline{y})$, which will prove useful in solving (9). In Section 3.2, we discuss how to solve (9) along the characteristic curve $y = \sigma^{-1}(t; \underline{y})$. In Section 3.3, we discuss how to obtain the final solution form.

3.1. The characteristic curves

For a fixed size $\underline{y} \in [y_0, y_1]$, the function

$$\sigma(y; \underline{y}) := \int_{\underline{y}}^y \frac{1}{g(y')} dy' \quad (10)$$

provides *the time it takes for an individual to grow from the fixed size $\underline{y}$ to arbitrary size y* . If $g(y)$ is positive and uniformly continuous on $[y_0, y_1]$, then $\sigma(y; \underline{y})$ is invertible [48]. We denote its inverse function, $\sigma^{-1}(t; \underline{y})$, as the *size curve*, which represents *the size of an individual over time that starts at size $\underline{y}$ at time $t = 0$* . For instance, if an individual has size $\underline{y}$ at $t = 0$, then that individual will have size $\sigma^{-1}(t_1; \underline{y})$ at time $t = t_1$. Some helpful properties of the growth curve are that $\sigma^{-1}(0; \underline{y}) = \underline{y}$ and

$$\frac{d}{dt} \sigma^{-1}(t; \underline{y}) = g(\sigma^{-1}(t; \underline{y})). \quad (11)$$

See Section A in the appendix for the derivation of (11).

As an example problem, consider $g(y) = (1 - y)/2$, $y_0 = 0$, $y_1 = 1$. Then we can compute

$$\sigma(y; \underline{y}) = 2 \log \left(\frac{1 - \underline{y}}{1 - y} \right)$$

$$\sigma^{-1}(t; \underline{y}) = 1 - (1 - \underline{y})e^{-t/2}.$$

We depict plots of $\sigma(y; \underline{y})$ in Figure 1(a) and $\sigma^{-1}(t; \underline{y})$ in Figure 1(b). Note that $\sigma(0.4; \underline{y} = 0) \approx 1$, so it takes an individual of size zero about 1 time unit to reach a size of 0.4. Conversely, $\sigma^{-1}(1; \underline{y} = 0) \approx 0.4$, so an individual that begins with a size of zero will be close to size 0.4 after 1 time unit. These computations are confirmed in Figure 1.

²Note that in this section, $g(y)$ denotes a growth rate with respect to size, y , whereas throughout the rest of our study, $g(m)$ denotes an activation rate with respect to biochemical activity, m .

3.2. Solving along $\sigma^{-1}(t, \underline{y})$

In order to solve (9) with the method of characteristics, we set $y = \sigma^{-1}(t, \underline{y})$ to define the variable $v(t, \underline{y})$ as

$$v(t, \underline{y}) := u(t, y = \sigma^{-1}(t, \underline{y})). \quad (12)$$

As shown in Section B of the appendix, substitution of (12) into (9) yields the characteristic equation

$$v_t = -g'(\sigma^{-1}(t, \underline{y}))v + Av, \quad (13)$$

where primes denote differentiation with respect to y . This characteristic equation has size $\underline{y}$ at time $t = 0$ and can be solved explicitly as³

$$v(t, \underline{y}) = \frac{g(\underline{y})}{g(\sigma^{-1}(t, \underline{y}))} e^{At} \phi(\underline{y}). \quad (14)$$

Returning to our example from Section 3.1, if we set $A = 0$, then we can compute the solution to (9) along $y = \sigma^{-1}(t, \underline{y})$ as

$$v(t, \underline{y}) = \frac{(1 - \underline{y})/2}{(1 - \underline{y})e^{-t/2}} \phi(\underline{y}) = e^{t/2} \phi(\underline{y}).$$

Some three-dimensional plots of $u(t, \underline{y})$ are depicted in Figure 1(c). We depict $\sigma^{-1}(t, \underline{y})$ in the (t, y) -plane below these curves to emphasize that we are solving (9) along the curves $y = \sigma^{-1}(t, \underline{y})$.

3.3. Final Solution Form

As (14) provides the solution to (9) along the arbitrary characteristic curve with initial size $\underline{y}$, we use it to solve the whole equation with the substitution $\underline{y} = \sigma^{-1}(-t, y)$, in which we find

$$u(t, y) = \begin{cases} \frac{g(\sigma^{-1}(-t, y))}{g(y)} e^{At} \phi(\sigma^{-1}(-t, y)) & \sigma^{-1}(t, y_0) \leq y \leq y_1 \\ 0 & y_0 \leq y < \sigma^{-1}(t, y_0). \end{cases} \quad (15)$$

If $\phi(y) \notin C^1(y_0, y_1)$, then (15) is viewed as a generalized solution to (9). Note that a piecewise form is needed for (15) because we do not begin with any individuals below the minimum size, y_0 , and thus the minimum possible size at time t is given by $\sigma^{-1}(t, y_0)$. If the

³To derive this, use separation of variables and with the help of (11) note that $\int_0^t g'(\sigma^{-1}(\tau, \underline{y})) d\tau = \ln[g(\sigma^{-1}(t, \underline{y}))/g(\underline{y})]$.

population is assumed to give birth to individuals of size y_0 over time, then the appropriate renewal equation representing population birth would replace the zero term in the piecewise function (see [3, § 9.5] for an example in size-structured populations and [15] for an example in age-structured populations).

Completing our example, we can compute the final solution to (9) when $g(y) = (1 - y)/2$ as

$$u(t, y) = \begin{cases} e^{t/2} \phi(1 - (1 - y)e^{t/2}) & 1 - e^{-t/2} \leq y \leq 1 \\ 0 & y < 1 - e^{-t/2} \end{cases}. \quad (16)$$

A contour of this solution is depicted in Figure 1(d). Note that the dashed line denotes $y = 1 - e^{-t}$, so $u(t, y) = 0$ for all points below this curve.

4. Existence of Traveling Wave Solutions to the Structured Fisher's Equation and Other Transport Equations

In this section, we aim to prove the existence of unique self-similar traveling wave solutions to (5), as summarized in Theorem 1. We do so with techniques described in the previous section.

Note that in this section, $g(m)$ is a function of biochemical activity level, and the characteristic curves, which will be given by

$$h(t; \underline{m}) := \sigma^{-1}(F(t; \underline{m})) \quad (17)$$

for $F(t) := \int_0^t f(t') dt'$, will compute *the activity level of an individual over time that starts at level $\underline{m}$ at time $t = 0$* . We will thus now refer to these as the *activation curves*.

We now state the main theorem:

Theorem 1

Equation (5) admits unique self-similar traveling wave solutions of the form

$$u(t, x, m) = \begin{cases} \frac{g(\sigma^{-1}(-F(t; m)))}{g(m)} W(z) \phi_1(\sigma^{-1}(-F(t; m))), & h(t; 0) \leq m < 1 \\ 0 & \text{otherwise} \end{cases}, \quad (18)$$

for $z = x - ct$, $c \geq 2$, $\phi(m) := \phi(x = -\infty, \underline{m})$, and $W(z)$ denoting the traveling wave profile to the classical Fisher's Equation.

In Section 3.3, we plot a numerical solution to (5) to demonstrate the equation's behavior and how it relates to (18). We prove Theorem 1 in Section 1. We then comment on how this

theorem can be extended to general reaction-diffusion and chemotaxis equations in Section 4.4.

4.1. Numerical Simulation of (5)

In Figure 2, we depict a numerical simulation of (5) with $f(t) = \beta e^{\gamma t}$, $g(m) = \alpha m(1 - m)$. Note that these terms will be explained in Section 5.4. For numerical implementation, we use a standard central difference scheme along the x -dimension, an upwind scheme with flux limiters (similar to those described in [46]) along the m dimension, and a Crank-Nicholson scheme to integrate along time. We discretized each independent variable of a uniform grid with step sizes of $\Delta x = 0.2$, $\Delta m = 0.00625$, $\Delta t = 10^{-3}$.

In each frame of Figure 2, the grayscale contour denotes the numerical simulation of $u(t, x, m)$ along x and m for $t = 0, 5$, or 10 . The blue profile under the contour is the result of numerical integration of $u(t, x, m)$ along the m dimension to depict $w(t, x)$. To the left of the contour in red, we plot the activation profile along m , $p(t, m)$, which has the exact form

$$p(t, m) = \begin{cases} \frac{g(\sigma^{-1}(-F(t, m)))}{g(m)} \phi_1(\sigma^{-1}(-F(t, m))) & h(t; m_0) \leq m \leq m_1 \\ 0 & m_0 \leq m < h(t; m_0). \end{cases} \quad (19)$$

Note that (19) is similar to (18) but is missing the $W(z)$ term.

In Figure 2, we observe that the cell population initially activates because $f(t) > 0$, so the cell population moves up the m -dimension, as observed at $t = 5$. $f(t)$ soon becomes negative, in which case the cell population will begin to deactivate and move down the m -dimension, which is observed at $t = 10$. If we continued plotting $u(t, x, m)$ at later time points, we would observe the whole contour approaching $m = 0$ as the population continues to deactivate. Meanwhile, along the spatial domain we see the cell population moving to the right at a constant speed, as we would expect from the $W(z)$ term from (18). Note that there is numerical error in this simulation due to numerical diffusion along the m dimension, which is unavoidable but can be decreased with finer values of Δm during computation.

4.2. Proof of Theorem 1

Proof—After taking the time derivative of $w(t, x)$, which was defined in (2), we can rewrite (5) as a system of two coupled PDEs⁴:

$$u_t + (f(t)g(m)u)_m = u_{xx} + u(1 - w)$$

$$w_t = w_{xx} + w(1 - w). \quad (20)$$

⁴Note that either $g(m_0) = 0$ or $u(t, m = m_0, x) = 0$ for $t > 0$, so that the activation term drops out when integrating over m for w .

We next set up the characteristic equation for u by setting $m = h(t, \underline{m})$ for a fixed value of $\underline{m}$, which gives

$$v(t, x; \underline{m}) := u(t, x, m = h(t; \underline{m})). \quad (21)$$

Substituting (21) into (20) provides our characteristic equation

$$v_t = v_{xx} + v[1 - w - f(t)g'(h(t; \underline{m}))]$$

$$w_t = w_{xx} + w(1 - w), \quad (22)$$

a time-dependent system of two coupled PDEs in time and space. Note that the bottom equation for (22) is Fisher's Equation, which has positive monotonic traveling wave solutions for any speed $c \geq 2$ (see [35, § 11.2]).

We next aim to derive traveling wave solutions to (22). From our knowledge of size-structured population models from Section 3, we intuit the ansatz of a self-similar traveling wave solution, which we write as

$$v(t, x; \underline{m}) = \frac{g(\underline{m})}{h(t; \underline{m})} V(z), z = x - ct \quad (23)$$

$$w(t, x) = W(z).$$

In this ansatz, $V(z)$ will define a traveling wave profile for v and $\frac{g(\underline{m})}{h(t; \underline{m})}$ will provide the height of the function over time. With the aid of the chain rule, we observe that:

$$v_t(t, x; \underline{m}) = -\frac{f(t)g'(h(t; \underline{m}))g(\underline{m})}{g(h(t; \underline{m}))}V - c\frac{g(\underline{m})}{g(h(t; \underline{m}))}V_z$$

$$v_{xx}(t, x; \underline{m}) = \frac{g(\underline{m})}{h(t; \underline{m})}V_{zz},$$

where subscripts denote differentiation with respect to t , x , or z and primes denote differentiation with respect to m . Substituting (23) into (22) reduces it to the autonomous system

$$-cV_z = V_{zz} + V(1 - W)$$

$$-cW_z = W_{zz} + W(1 - W). \quad (24)$$

The existence of a traveling wave solution can now be proven by showing the existence of bounded solutions to (24) with the properties

$$(V, V_z, W, W_z)(-\infty) = (\phi_1(\underline{m}), 0, 1, 0), (V, V_z, W, W_z)(\infty) = (0, 0, 0, 0). \quad (25)$$

We note that the equations for W are independent of V and are the system of differential equations that yield the traveling wave profile for Fisher's equation [35]. We thus have that $W(-\infty) = 1, W_z(-\infty) = W(\infty) = W_z(\infty) = 0$ are already satisfied for $c \geq 2$. For a fixed value of c , call this solution W_c . We then observe by substitution that $\phi_1(\underline{m})W_c$ satisfies the equations for V . We now have that (18) is a solution to (5).

We now show that $(\phi_1(\underline{m})W_c(z), W_c(z))^T$ is the unique solution (for c fixed) of (24) and (25) as follows. Let V, W be solutions to (24). We can then multiply the first equation of (24) by W and the second by V and subtract the two solutions to find

$$-cV_zW + cVW_z = V_{zz}W - VW_{zz} = (V_zW - VW_z)_z.$$

The above gives that

$$V_zW - VW_z = ke^{-cz}$$

and boundedness of V, V_z, W , and W_z ensures that $k = 0$. Because $W > 0$, we find that

$$\left(\frac{V}{W}\right)_z = 0,$$

which suggests that

$$V = \phi_1(\underline{m})W$$

is the unique solution to the upper portion of (24).

4.3

4.4. Note on the generality of results

We have focused on Fisher's Equation in this work due to its applicability to the math biology literature and cell migration in particular. The methods provided in Section 1 for the existence of a unique self-similar traveling wave solution are also applicable for a wide variety of structured transport equations, including reaction-diffusion and chemotaxis

equations. For example, consider the nondimensionalized structured reaction-diffusion equation given by

$$u_t + (f(t)g(m)u)_m = u_{xx} + uR(w) \quad (26)$$

$$w_t = w_{xx} + wR(w). \quad (27)$$

We have the following corollary:

Corollary 2—Suppose $R(w) \in C^1(\mathbb{R})$ has a single value, $w_l > 0$, such that $R(w_l) = 0$ or two values, $0 < w_l^1 < w_l^2$, such that $R(w_l^1) = R(w_l^2) = 0$ and $d_w(wR(w)) > 0$ at $w = w_l^1$. Then (26) will have the unique self-similar traveling wave solution given by

$$u(t, x, m) = \begin{cases} \frac{g(\sigma^{-1}(-F(t), m))}{g(m)} W_c(z) \phi(\sigma^{-1}(-F(t), m)), & h(t; 0) \leq m < 1 \\ 0 & \text{otherwise} \end{cases} \quad (28)$$

where $W_c(z)$ is a traveling wave solution with speed c for (27).

Proof: Note that the given conditions for $R(w)$ are sufficient for the existence of a traveling wave solution for $w(t, x)$, which we will write as $W_c(z)$ [13, § 4.4]. The speed of this solution, c , will depend on the form of $R(w)$ and possibly the initial condition for $w(t, x)$.

We may then assume the characteristic equation $v(t, x; \underline{m}) := u(t, x, m = h(t, \underline{m}))$ takes the form

$$v(t, x; \underline{m}) = \frac{g(\underline{m})}{h(t, \underline{m})} V(z)$$

and $w(t, x) = W(z)$. This yields the autonomous system of ordinary differential equations

$$-cV_z = V_{zz} + VR(W)$$

$$-cW_z = W_{zz} + WR(W),$$

from which we observe that $V = \phi_1(\underline{m}) W_c$ and $W = W_c$ will provide a solution to this system. The proof of uniqueness of this solution is identical to the proof of uniqueness of the solution for (24). This proves the existence of unique self-similar traveling wave solutions to structured reaction diffusion equation given by (26).

Note that the form of the reaction-diffusion equation given in (27) is general and well studied. If R is given by $R(w) = a(w-1)(\alpha-w)$ for constants $a > 0$ and $\alpha \in (0, 1)$, then (27) represents the bistable equation. A traveling wave solution then exists for a unique speed, c , which we will write as $W_c(z)$ [24]. Corollary 1 now guarantees that (26) will have the unique self-similar traveling wave solution given by (28).

The same method could also be applied to a structured chemotaxis equation given by

$$u_t + (f(t)g(m)u)_m = -(us_x)_x + \alpha u(1-w) \quad (29)$$

$$w_t = -(ws_x)_x + \alpha w(1-w) \quad (30)$$

$$s_t = bs(1-s) - ws.$$

Here, $u = u(t, x, m)$ now denotes a cell density simultaneously activating along the biochemical pathway, m , and migrating up the gradient of some chemoattractant $s = s(t, x)$, and $w(t, x) = \int u(t, x, m) dm$ denotes the cell density in time and space. Conditions for the existence of smooth- and discontinuous-fronted traveling wave solutions for (30), denoted as $W_c(z)$, are provided in [38]. From the same proof methods detailed above, our results now also guarantee the existence of a unique self-similar traveling wave solution to (29) when $W_c(z)$ has infinite support.

5. Structured Fisher's Equation with MAPK-dependent Phenotype

We now study a version of Fisher's Equation where cellular migration and proliferation depend on biochemical activity, m , as described by (7). Various cell lines have reduced rates of proliferation and increased migration in response to MAPK activation [5, 6, 31], so we let m denote activity along the MAPK signaling cascade in this section. We consider a model with two subpopulations: one with a high rate of diffusion in response to MAPK activation and the other with a high rate of proliferation when MAPK levels are low. MAPK activation will depend on an external forcing factor to represent the presence of an extracellular signaling chemical, such as ROS, TGF- β , or EGF. While the method of characteristics is not applicable to spatial activation patterning here due to the parabolic nature of (3) in space, we can investigate temporal patterns of activation and deactivation. *We will exhibit simple scenarios that give rise to three ubiquitous patterns of biochemical activity: 1.) a sustained wave of activation, 2.) a single pulse of activation, and 3.) periodic pulses of activation.*

Before describing these examples, we first introduce some tools to facilitate our study of (7). We will detail some activation criteria in Section 5.2, and discuss numerical issues and the derivation of a time-dependent averaged Fisher's Equation in Section 5.3 before illustrating the different activation patterns and their effects on migration in Section 5.4.

5.1. Model Description

Recall that the biochemically-dependent structured Fisher's Equation is given by (7). Given some $m_{crit} \in (0, 1)$, we define two subsets of $[0, 1]$ as $M_{inact} := [0, m_{crit})$, $M_{act} := [m_{crit}, 1]$, and the rates of diffusion and proliferation by (8) for $\bar{D} > 1$ and $\bar{\lambda} < 1$. Hence for $m \in M_{inact}$ the population is termed as *inactive* and primarily proliferates whereas for $m \in M_{act}$ the population is termed as *active* and primarily diffuses.

We let $\text{supp}(\phi_1(m)) = [\underline{m}_{\min}, \underline{m}_{\max}]$ for $\underline{m}_{\max} < m_{crit}$ and assume that $\int_0^1 \phi_1(m) dm = 1$ so $\phi_1(m)$ represents a probability density function for the initial distribution of cells in m . We accordingly denote

$$\Phi_1(m) := \begin{cases} 0 & m \leq 0 \\ \int_0^m \phi_1(m') dm' & 0 < m \leq 1 \\ 1 & 1 < m \end{cases}$$

as the cumulative distribution function for $\phi_1(m)$.

5.2. Activation Criteria

To facilitate future numerical simulations, we will derive a condition for a cell population with an initial condition contained in M_{inact} to enter M_{act} . Note that to do so, we can ask when the characteristic curve for the maximum level of initial support will reach the threshold value, m_{crit} . This implies that the solution will enter the active population if $h(t; \underline{m}_{\max}) > m_{crit}$ which is analogous to

$$F(t) > \sigma(m_{crit}; \underline{m}_{\max}) \quad (31)$$

for some values of t . By standard calculus arguments, (31) will occur if

$$F(t_{\max}) > \sigma(m_{crit}; \underline{m}_{\max}) \quad (32)$$

where the maximum for $F(t)$ occurs at $t = t_{\max}$. We denote (32) as the *activation criterion* for (7). By the same argument, for the entire population to enter M_{act} at some point, then we can derive the *entire activation criterion* as

$$F(t_{\max}) > \sigma(m_{crit}; \underline{m}_{\min}). \quad (33)$$

5.3. Numerical Simulation Issues and Derivation of an Averaged time-dependent Fisher's Equation

We depict the $u = 1$ isocline for a numerical simulation of (7) in Figure 3 with $g(m) = \alpha m(1 - m)$, $f(t) = \beta \sin(\gamma t)$, $\alpha = 1/2$, $\beta = 1$, and $\gamma = 1.615$. These terms will be explained in

Example 3 below. The numerical scheme is the same as that described in Section 4.1, except $m = 0.025$ here. From (32), we see that this simulation should not enter the active population with an initial condition of $\phi_1(m) = {}^{10/3}I_{[.05,0.35]}(m)$, where $I_M(m)$ denotes an indicator function with support for $m \in M$. In Figure 3, however, we observe that the numerical simulation does enter the active population, which causes a significant portion of the population to incorrectly diffuse into the wound at a high rate.

Numerical simulations of advection-driven processes have been described as an “embarrassingly difficult” task, and one such problem is the presence of numerical diffusion [29, 46]. Numerical diffusion along the m -dimension is hard to avoid and here causes a portion of the cell population to enter the active population in situations where it should not. Numerical diffusion can be reduced with a finer grid, but this can lead to excessively long computation times. With the aid of the activation curves given by (17), however, we can track progression of cells in the m -dimension analytically and avoid the problems caused by numerical diffusion completely.

To avoid the problems caused by numerical diffusion, we derive a time-dependent Fisher’s Equation for $w(t, x)$ in the appendix that represents the average behavior along m with time-dependent diffusion and proliferation terms. This equation is given by

$$w_t = D(t)w_{xx} + \lambda(t)w(1 - w), \quad (34)$$

$$w(t = 0, x) = \phi_2(x)$$

$$w(t, x = -\infty) = 1 \quad w(t, x = \infty) = 0$$

where

$$D(t) = \bar{D} + (1 - \bar{D})\Phi_1(\psi(t))$$

$$\lambda(t) = \bar{\lambda} + (1 - \bar{\lambda})\Phi_1(\psi(t))$$

for $\psi(t) = \sigma^{-1}(-R(t); m_{crit})$ denoting the threshold value in $\underline{m}$ that separates the active and inactive regions.

5.4. Three biologically-motivated examples

We next consider three examples of (7) that pertain to common patterns of biochemical activity during wound healing. We will use numerical simulations of (34) to investigate how different patterns of activation and deactivation over time affect the averaged cell population profile. We will also investigate how the profile changes when crossing the activation and

entire activation thresholds derived in (32) and (33). In each example, we fix $m_{crit} = 0.5$, $\bar{D} = 100$, $\bar{\lambda} = 1/100$, $\phi_1(m) = {}^{10/3}I_{[.05,0.25]}(m)$, $\phi_2(x) = I_{(-\infty,5]}(x)$ and $g(m) = \alpha m(1 - m)$, and use a different terms for $f(t)$ to mimic different biological situations. The choice for $g(m)$ ensures that the distribution along m stays between $m = 0$ and $m = 1$. The method of lines is used to compute (34), with a standard central difference discretization scheme in space and MATLAB's ode45 command is used for time integration.

Example 1: Single Sustained MAPK activation wave: $f(t) = 1$ —In this example, we consider a case where we observe the entire cell population approach a level of $m = 1$ over time. Such a scenario may represent the sustained wave of ERK 1/2 activity observed in MDCK cells from [31]. We use $f(t) = 1$ to observe this behavior. We provide the functions for $\sigma(m; \underline{m})$, $h(t; \underline{m})$, and $\psi(t)$ that result from this choice of terms in the appendix.

In Figure 4, we plot (19) to depict an example activation profile, $p(t, m)$, over time to show the activation behavior of the population. As expected, we observe all of $p(t, m)$ converging to $m = 1$. We include some specific plots of the activation curves, $h(t; \underline{m})$, for this example.

Note that the density changes along these curves by the height function $\frac{g(\sigma^{-1}(-F(t, m)))}{g(m)}$, which is equivalent to the height function of the self-similar traveling wave ansatz made in (23).

In Figure 5(a), we depict a numerical simulation of $u(t, x)$ over time using (34). The Regions denoted as “P” and “D” denote when the population is primarily proliferating ($\Phi_1(\psi(t)) > 1/2$) or diffusing ($\Phi_1(\psi(t)) < 1/2$) over time. The profile maintains a high cell density but limited migration into the wound during the proliferative phase and then migrates into the wound quickly during the diffusive phase but can not maintain a high cell density throughout the population. In Figure 5(b), we investigate how the numerical simulation profile of $u(t = 40, x)$ changes as α varies from $\alpha = 0$ to $\alpha = 0.2$. In the region denoted “No activation”, the entire population is still in the inactive population at $t = 40$ and thus does not progress far into the wound or change with α . The population is split between the active and inactive populations at $t = 40$ for simulations in the region denoted “Activation.” The profiles here are very sensitive to increasing values of α , as they migrate further into the wound while maintaining a high density near $x = 0$. Simulations from the region denoted as “Entire Activation” are entirely in the active population by $t = 40$. As α increases, these simulations do not migrate much further into the wound but do have decreasing densities at $x = 0$. These results suggest that a combination of proliferation and diffusion must be used to maximize population migration while maintaining a high cellular density behind the population front. The optimal combination for a far-moving front with a confluent density appears to occur at the entire activation threshold.

Example 2: Single pulse of MAPK activation: $f(t) = \beta e^{\gamma t} - 1$ —We now detail an example that exhibits a pulse of activation in the m dimension, which may represent the transient wave of ERK 1/2 activation observed in MDCK cells in [31]. The authors of [40] proposed that this wave may be caused by the rapid production of ROS in response to the wound, followed by its quick decay or consumption by cells. We now let $f(t) = \beta e^{\gamma t} - 1$. This forcing function arises if ROS is present but decaying exponentially over time and

modeled by $s(t) = \beta e^{\gamma t}$, $\beta > 0$, $\gamma < 0$ and cells activate linearly in response to the presence of ROS but have a baseline level of deactivation, which may be given by $f(s) = s - 1$. We provide the functions for $\sigma(m; \underline{m})$, $h(t, \underline{m})$, and $\psi(t)$ that result from this choice of terms in the appendix, as well as the activation criteria.

In Figure 6, we use (19) to depict the activation profile, $p(t, m)$, over time to show the activation behavior of the population. We also include some specific plots of the activation curves, $h(t, \underline{m})$, which show a pulse of MAPK activity in the population that starts decreasing around $t = 5$. Note that $h(t, 0.35)$ crosses the $m = m_{crit}$ line but $h(t, 0.05)$ does not, so (32) is satisfied for this parameter set (the population becomes activated) but (33) is not (the entire population does not become activated).

In Figure 7(a), we depict a numerical simulation of (34) for this example. The population quickly transitions to a diffusing stage due to the pulse of MAPK activation and shows the smaller densities (u approximately less than 0.2) migrating into the wound rapidly while the density behind the population front drops. As the pulse of MAPK activation ends and the population transitions back to a proliferating phenotype, the population restores a high density behind the cell front and begins to develop a traveling wave profile, as suggested by the parallel contour lines. In Figure 7(b), we investigate how the numerical solution profile for $u(t = 30, x)$ changes as β varies from $\beta = 2$ to $\beta = 9$ while keeping all other parameters fixed. We observe that the profile is the same for all inactive simulations as (32) is not satisfied. As β increases past the activation threshold, the profile shows increased rates of migration into the wound. After passing the entire activation threshold (33), the profile continues to migrate further as β increases, but appears less sensitive to β . This increased migration is likely due to the population spending more time in the active population for larger values of β . Note that for all simulations shown, the pulse of MAPK activation has finished by $t = 30$.

Example 3: Periodic pulses of MAPK activation: $f(t) = \beta \sin(2\pi t/\gamma)$ —As a last example, we exhibit a scenario with periodic waves of activity. Such behavior was observed in some of the experiments performed in [49], in which cell cultures of the HaCaT cell line were periodically treated with TGF- β to investigate how periodic treatment with TGF- β affects activation of the SMAD pathway (the canonical pathway for TGF- β , which also influences cell proliferation and migration). We let $f(t) = \beta \sin(2\pi t/\gamma)$, $\beta, \gamma > 0$, which occurs if the concentration of TGF- β over time is given by $s(t) = 1 + \sin(2\pi t/\gamma)$, and cells activate linearly in response to s and have a baseline rate of deactivation, given by $f(s) = \beta(s - 1)$. Note that $f(t)$ has frequency γ . We provide the functions for $\sigma(m; \underline{m})$, $h(t, \underline{m})$, and $\psi(t)$ that result from this choice of terms in the appendix, as well as the activation criteria.

In Figure 8, we use (19) to depict the activation profile, $p(t, m)$, over time to show the activation behavior of the population. We also include some specific plots of the activation curves $h(t, \underline{m})$, which demonstrate periodic waves of activation along m . Note that $h(t, 0.05)$ crosses the $m = m_{crit}$ line, so (33) is satisfied, and the entire population becomes activated at some points during the simulation.

In Figure 9(a), we depict a numerical simulation of (34) for this example. The population phenotype has a period of 4π , and we see that the lower densities migrate into the wound most during the diffusive stages, whereas all densities appear to migrate into the wound at similar speeds during the proliferative stages. In Figure 9(b), we investigate how the profile for $w(t=40, x)$ changes as γ varies between $\gamma=0$ and $\gamma=37$ while keeping all other parameters fixed. All “No Activation” profiles appear the same because (32) is not satisfied. As γ increases past this threshold, more of the population becomes activated during the simulation, culminating in a maximum propagation of the population at the entire activation threshold given by (33). As increases above this threshold, the population tends to migrate less far, although the population does migrate far for γ near 33. In the “Entire Activation” Region, the population appears to spend too much time in the active population and diffuses excessively with limited proliferation. These simulations lead to shallow profiles that do not migrate far into the wound.

6. Discussion and Future work

We investigate a structured Fisher’s Equation that incorporates an added dimension for biochemical activity that influences population migration and proliferation. The method of characteristics proves to be a useful way to track the progression along the population activity dimension over time. We prove the existence of a unique self-similar traveling wave solution to the equation when diffusion and proliferation do not depend on MAPK activity. The height function of the self-similar traveling wave ansatz along characteristic curves is demonstrated in Figures 4, 6, and 8. These methods are also applicable to structured reaction-diffusion and chemotaxis equations.

Activation of the MAPK signaling cascade is known to influence collective migration during wound healing through cellular migration and proliferation properties. For this reason, we also consider a structured PDE model in which the rates of cellular diffusion and proliferation depend on the levels of MAPK activation in the population. We derive two activation criteria for the model to establish conditions under which the population will become activated during simulations. As numerical simulations of the structured equation are prone to error via numerical diffusion, we derive a time-dependent PDE equation in time and space to represent the average population behavior along the biochemical activity dimension. Using this time-dependent equation, we exhibit three simple examples that demonstrate biologically relevant activation patterns and their effects on population migration: a sustained wave of activity, a pulse of activity, and periodic pulses of activity. We find that the population tends to migrate farthest while maintaining a high cell density at the entire activation threshold value, given by (33), for the sustained wave and periodic pulse patterns of activation. The single pulse case continues migrating further into the wound after passing the entire activation threshold but appears less sensitive after doing so.

A natural next step for this analysis is to use a structured population model of this sort in combination with biological data to thoroughly investigate the effects of MAPK activation and deactivation on cell migration and proliferation during wound healing. Previous mathematical models have focused on either collective migration during wound healing assays in response to EGF treatment (while neglecting the MAPK signaling cascade) [23,

37] or MAPK propagation during wound healing assays (while neglecting cell migration) [40]. To the best of our knowledge, no mathematical models have been able to reliably couple signal propagation and its effect on cell migration during wound healing. The examples detailed in this work intentionally used the simplest terms possible as a means to focus on the underlying mathematical aspects. With a separate in-depth study into the biochemistry underlying the MAPK signaling cascade and its relation with various cytokines or growth factors, more complicated and biologically relevant terms for $g(m)$, $f(s)$, and $s(t)$ can be determined to help elucidate the effects of MAPK activation on cell migration during wound healing.

As various pathways become activated and cross-talk during wound healing to influence migration [16], future studies could also investigate a population structured along multiple signaling pathways, $u(t, x, \vec{m})$ for the vector $\vec{m} = (m_1, m_2, \dots, m_n)^T$. Because the cell population also produces cytokines and growth factors for paracrine and autocrine signaling during wound healing, these models would also benefit from variables representing ROS, TGF- β , EGF, etc.

While the main motivation for this study is epidermal wound healing, there are potential applications in other areas of biology. Fisher's equation has also been used to study population dynamics in ecology and epidemiology [1, 20, 44]. Our framework could be extended to a case where an environmental effect, such as seasonal forcing, impacts species migration or susceptibility of individuals to disease. The results presented here may thus aid in a plethora of mathematical biology studies.

Acknowledgments

Funding: This work is supported in part by the Interdisciplinary Quantitative Biology (IQ Biology) program at the BioFrontiers Institute, University of Colorado, Boulder, which is supported by NSF IGERT grant number 1144807. This work is also supported in part by the Joint NSF/NIH Mathematical Biology Initiative Program via grant NIGMS-R01GM126559.

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Appendix

Appendix A. Properties of $\sigma^{-1}(t, y)$

If we assume that g is positive and uniformly continuous, then $\sigma^{-1}(t, y)$ exists and satisfies the following:

$$\frac{d}{dt}\sigma^{-1}(t; \underline{y}) = g(\sigma^{-1}(t; \underline{y})), \sigma^{-1}(0; \underline{y}) = \underline{y}. \quad (35)$$

To derive (35), see that

$$\begin{aligned} y(t) &= \sigma^{-1}(t; \underline{y}) \\ \Rightarrow \sigma(y(t); \underline{y}) &= t \\ \Rightarrow \frac{d}{dt}(\sigma(y(t); \underline{y})) &= \frac{d}{dy}\sigma(y(t); \underline{y}) \frac{dy}{dt} = 1 \\ \Rightarrow \frac{1}{g(y(t))} \frac{dy}{dt} &= 1 \\ \Rightarrow \frac{dy}{dt} &= g(y(t)) \\ \Rightarrow \frac{d}{dt}\sigma^{-1}(t; \underline{y}) &= g(\sigma^{-1}(t; \underline{y})). \end{aligned}$$

and for the initial condition,

$$\begin{aligned} \sigma(\underline{y}, \underline{y}) &= 0 \\ \Rightarrow \sigma^{-1}(0, \underline{y}) &= \underline{y}. \end{aligned}$$

Appendix B. Derivation of (13)

In (12), we defined

$$v(t; \underline{y}) := u(t, y = \sigma^{-1}(t; \underline{y})).$$

Taking the derivative of $v(t; \underline{y})$ with respect to time, we find with the aid of the chain rule:

$$\begin{aligned} \frac{d}{dt}v(t; \underline{y}) &= \frac{\partial}{\partial t}u(t, y = \sigma^{-1}(t; \underline{y})) + \frac{\partial}{\partial y}u(t, y = \sigma^{-1}(t; \underline{y})) \cdot \frac{d}{dt}\sigma^{-1}(t; \underline{y}) = -\frac{\partial}{\partial y}\left[g(\sigma^{-1}(t; \underline{y}))u(t, y = \sigma^{-1}(t; \underline{y}))\right] \\ &+ Au(t, y = \sigma^{-1}(t; \underline{y})) + g(\sigma^{-1}(t; \underline{y}))\frac{\partial}{\partial y}u(t, y = \sigma^{-1}(t; \underline{y})) = -g'(\sigma^{-1}(t; \underline{y}))v(t; \underline{y}) + Av(t; \underline{y}). \end{aligned}$$

Appendix C. Derivation of the time-dependent Fisher's Equation

To investigate the averaged cell population behavior along m over time, we integrate (7) over m to find

$$w_t(t, x) = (D_1 w_{xx} + \lambda_1 w(1 - w))I_{[M_{inact}]}(m) + (D_2 w_{xx} + \lambda_2 w(1 - w))I_{[M_{act}]}(m). \quad (36)$$

An explicit form for (36) thus requires determining how much of the population is in the active and inactive populations over time. This is determined with the activation curves by calculating

$$h(t; \underline{m}) < m_{crit} \Leftrightarrow F(t) < \sigma(m_{crit}; \underline{m}) \Leftrightarrow \underline{m} < \sigma^{-1}(-F(t); m_{crit}) =: \psi(t). \quad (37)$$

Thus, $\underline{m} = \sigma^{-1}(-F(t); m)$ maps the distribution along m at time t back to the initial distribution, $\phi_1(\underline{m})$, and $\psi(t)$ denotes the threshold value in $\underline{m}$ between the active and inactive populations over time. $\Phi_1(\psi(t))$ thus denotes the portion of the population in the inactive population, and $1 - \Phi_1(\psi(t))$ denotes the portion in the active population over time.

We thus derive a nonautonomous PDE for w , which we will term the *averaged nonautonomous Fisher's Equation*, as:

$$w_t = D(t)w_{xx} + \lambda(t)w(1 - w),$$

$$w(t = 0, x) = \phi_2(x)$$

$$w(t, w = -\infty) = 1 \quad w(t, w = \infty) = 0$$

where

$$D(t) = D_2 + (D_1 - D_2)\Phi_1(\psi(t))$$

$$\lambda(t) = \lambda_2 + (\lambda_1 - \lambda_2)\Phi_1(\psi(t)).$$

Appendix D. Activation terms and criteria from Section 5

Recall that in each example, we set $m_{crit} = 0.5$, $D_1 = 0.01$, $D_2 = 1$, $\lambda_1 = .25$, $\lambda_2 = 0.0025$, $\phi_1(m) = {}^{10}/_3 I_{[.05, 0.25]}(m)$, $\phi_2(x) = I_{(-\infty, 5]}(x)$ and $g(m) = \alpha m(1 - m)$.

D.1. Example 1

Using (10), (37), and $f(t) = 1$, we compute

$$\sigma(m; \underline{m}) = \frac{1}{\alpha} \log \left(\frac{m}{1-m} \frac{1-m}{\underline{m}} \right); \underline{m}, m \in (0, 1)$$

$$h(t; \underline{m}) = \sigma^{-1}(t; \underline{m}) = \underline{m} \left((1 - \underline{m}) e^{-\alpha t} + \underline{m} \right)^{-1}$$

$$\psi(t) = (1 + e^{\alpha t})^{-1}$$

These functions demonstrate that the distribution along m is always activating along m but never reaches the $m = 1$ line, as $\sigma(m; \underline{m}) \rightarrow \infty$ as $m \rightarrow 1^-$ for any $\underline{m} \in (0, 1)$. The entire population (excluding $\underline{m} = 0$) approaches $m = 1$ asymptotically, however, as $\lim_{t \rightarrow \infty} \sigma^{-1}(t; \underline{m}) = 1$.

D.2. Example 2

For $f(t) = \beta e^{\gamma t} - 1$, we compute

$$\sigma(m; \underline{m}) = \frac{1}{\alpha} \log \left(\frac{m}{1-m} \frac{1-m}{\underline{m}} \right); \underline{m}, m \in (0, 1)$$

$$h(t; \underline{m}) = \underline{m} \left(\underline{m} + (1 - \underline{m}) \exp \left[at - \frac{\alpha \beta}{\gamma} (\exp(\gamma t) - 1) \right] \right)^{-1}$$

$$\psi(t) = \left(1 + \exp \left[-at + \frac{\alpha \beta}{\gamma} (\exp(\gamma t) - 1) \right] \right)^{-1}.$$

Using (32), we determine our activation criterion for this example as

$$\frac{1 - \beta + \log \beta}{\gamma} > \frac{1}{\alpha} \log \left(\frac{m_{crit}}{1 - m_{crit}} \frac{1 - \underline{m}_{max}}{\underline{m}_{max}} \right).$$

If we fix $\gamma = -1$, $\alpha = 1$, $m_{crit} = 0.5$, $\underline{m}_{max} = 0.35$, and $\underline{m}_{min} = 0.05$, we find that the above inequality is satisfied for β approximately greater than 2.55. This may represent a scenario in which we know the decay rate of the ROS through γ , the activation rate of the MAPK signaling cascade through α , the MAPK activation distribution before ROS release with $\underline{m}_{min}$ and $\underline{m}_{max}$, and the activation threshold with m_{crit} . The values of β denote the concentration of released ROS, which should be at least 2.55 to see the population activate. We similarly find that the entire population will activate at some time for $\beta > 5.68$.

D.3. Example 3

For $f(t) = \beta \sin(\gamma t)$, we compute

$$\sigma(m; \underline{m}) = \frac{1}{\alpha} \log \left(\frac{m}{1-m} \frac{1-m}{\underline{m}} \right); \underline{m}, m \in (0, 1)$$

$$h(t; \underline{m}) = \underline{m} \left(\underline{m} + (1 - \underline{m}) \exp \left[\frac{\alpha \beta}{\gamma} (\cos(\gamma t) - 1) \right] \right)^{-1}$$

$$\psi(t) = \left(1 + \exp \left[\frac{\alpha \beta}{\gamma} (1 - \cos(\gamma t)) \right] \right)^{-1}.$$

The activation criterion (32) can be solved as

$$\frac{2\beta}{\gamma} > \frac{1}{\alpha} \log \left(\frac{m_{crit}}{1 - m_{crit}} \frac{1 - \underline{m}_{max}}{\underline{m}_{max}} \right).$$

We thus calculate that if we fix $\beta = 1$, $\alpha = 1/2$, $\underline{m}_{max} = 0.35$, $\underline{m}_{min} = 0.05$, and $m_{crit} = 0.5$, then the activation criterion (32) is satisfied for $\gamma < 1.615$ and the entire activation criterion (33) is satisfied for $\gamma < 0.34$. These estimates would tell us how frequently signaling factor treatment is needed to see different patterns of activation in the population.

Fig. 1. Solving (9) analytically for $g(y) = (1 - y)/2$, $A = 0$, and $\phi(y) = e^{-(y-0.1)^2/16}$. (a) Plots of $t = \sigma(y; \underline{y})$ for $\underline{y} = 0, 0.2, 0.4$, and 0.6 . (b) Plots of $y = \sigma^{-1}(t; \underline{y})$ for $\underline{y} = 0, 0.2, 0.4$, and 0.6 . (c) Plots of $v(t; \underline{y})$ for $\underline{y} = 0, 0.2, 0.4, 0.6$. The curves in the (t, y) -plane denote $y = \sigma^{-1}(t; \underline{y})$. (d) Log-scale plot of $u(t, y)$. The dashed line denotes the minimum level of support over time.

Fig. 2.

Solutions to (5) with $f(t) = \beta e^{\gamma t} - 1$, $g(m) = \alpha m(1 - m)$ at $t = 0, 5$, and 10 for $\alpha = 1$, $\beta = 3$, $\gamma = -1/4$. In each frame, the grayscale contour depicts the numerical simulation of $u(t, x, m)$ along, the red profile is a plot of $p(t, m)$ to denote the activation profile at time t , and the blue profile is the result of numerical integration of $u(t, x, m)$ along the m dimension to depict $w(t, x)$.

Fig. 3.

Two views of the isocline for $u = 1$ from a numerical simulation of (7) with $g(m) = \alpha m(1 - m)$ and $f(t) = \beta \sin(\gamma t)$ for $\alpha = 0.5$, $\beta = 1$, $\gamma = 1.615$, $\bar{D} = 100$, $\bar{\lambda} = 1/100$, and an initial condition of $\phi_1(m) = {}^{10/3}I_{[.05, 0.35]}(m)$ and $\phi_2(x) = I_{[x, 5]}(x)$. The numerical scheme is discussed in Section 5.3 and the step sizes used are $m = 1/80$, $x = 1/5$, $t = 10^{-3}$. From (32), the simulation should not cross the $m = m_{crit}$ plane, which is given by the red plane. We see in frame (a) that the simulation does cross the $m = m_{crit}$ plane due to numerical diffusion, which causes the high rate of diffusion along x seen in frame (b).

Fig. 4.

The analytical solution for the activation profile, $p(t, m)$, for Example 1 for $\alpha = 0.5$, and $\phi_1(m) = I_{(0.05, 0.35)}(m)$. The solid black curves denote $h(t, \underline{m})$ for $\underline{m} = 0.05, 0.15$, and 0.35 and the dashed line denotes $m = m_{crit}$. Note that a log scale is used along p for visual ease.

Fig. 5.

Numerical simulations of the averaged time-dependent Fisher's equation for Example 1. In (a), we depict a simulation of $w(t, x)$ over time for $\alpha = 0.05$. The letters "P" and "D" denote when the population is primarily proliferating or diffusing, respectively. In (b), we depict how the profile for $w(t = 40, x)$ changes for various values of α . The descriptions "No Activation", "Activation", and "Entire Activation" denote values of α for which the population is entirely in the inactive population, split between the active and inactive populations, or entirely in the active population at $t = 40$, respectively.

Fig. 6.

The analytical solution for the activation profile, $p(t, m)$, for Example 2 for $\alpha = 0.5$, $\beta = 3$, $\gamma = -1/4$ and $\phi_1(m) = I_{(0.05, 0.35)}(m)$. The solid black curves denote $h(t, \underline{m})$ for $\underline{m} = 0.05, 0.15$, and 0.35 and the dashed line denotes $m = m_{crit}$. Note that a log scale is used along p for visual ease.

Fig. 7.

Numerical simulations of the averaged time-dependent Fisher's equation for Example 2. In (a), we depict a simulation of $w(t, x)$ over time for $\alpha = 1$, $\beta = 8$, $\gamma = -1$. Regions denoted with a "P" or "D" denote when the population is primarily proliferating or diffusing, respectively. In (b), we depict how the profile for $w(t = 30, x)$ changes for various values of β . The descriptions "No activation", "Activation", and "Entire Activation" denote values of β for which the population is entirely in the inactive population, split between the active and inactive populations, or entirely in the active population at $t = t_{\max}$.

Fig. 8.

The analytical solution for the activation profile, $p(t, m)$, for Example 3 for $\alpha = 1/2$, $\beta = 4$, $\gamma = 1$ and $\phi_1(m) = I_{(0.05, 0.35)}(m)$. The solid black curves denote $h(t, \underline{m})$ for $\underline{m} = 0.05, 0.15$, and 0.35 and the dashed line denotes $m = m_{crit}$. Note that a log scale is used along p for visual ease.

Fig. 9.

Numerical simulations of the averaged time-dependent Fisher's equation for Example 3. In (a), we depict a simulation of $w(t, x)$ over time for $\alpha = 0.5$, $\beta = 1$, and $\gamma = 4\pi$. Regions denoted with a "P" or "D" denote when the population is primarily proliferating or diffusing, respectively. In (b), we depict $w(t = 40, x)$ for various values of γ . The descriptions "No activation", "Activation", and "Entire Activation" denote values of γ for which the population is entirely in the inactive population, split between the active and inactive populations, or entirely in the active population at $t = t_{\max}$.