Diffusive Cellular Relay Dynamics with Chemotaxis Effects

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In this work, we investigate the effect of chemotaxis (or the motion of cells along a concentration gradient) on diffusive cellular relay dynamics, which are prominent in the field of biology from neutrophil transmission to many other signaling pathways. We begin by discussing standard cellular relay models without chemotaxis and derive core principles regarding the critical behavior and motion of particles in these ansatz. We then elucidate the physics of chemotaxis, which is then applied to numerical simulations of cellular relay dynamics to demonstrate the change in behavior. Our results show that while chemotaxis impacts the fundamental cellular dynamics of the system, that overall critical behavior does not change significantly.

I. INTRODUCTION

Diffusive cellular relays are a critical area of study in the field of biophysics, which describe how cellular transmitters that diffuse down concentration gradients are able to trigger cellular signaling. Recent biological studies have suggested that these cellular signaling pathways have been implicated in everything from infant morphogenesis and cellular movement to immune response [1–3]. However, because of the complexity of the system, along with its dynamical nature, these diffusive cellular relays are difficult to analyze using traditional statistical mechanics techniques, requiring key simplifications that are biologically informed. Specifically, by modeling cells as signaling centers that integrate biological cues and participate in signaling pathways by emitting more signaling particles, existing work has shown that diffusive waves are observed with a constant asymptotic velocity v. These works either assume an excitable medium or assume that the medium is a fixed substrate of cells with fixed concentration, greatly simplifying the problem being addressed [3, 4]. However, this simplified model is already applicable to many problems like cell death and embryonic development [5, 6].

That being said, there is one key model where this fundamental assumption may not hold, the model of immune response. In immune response, since immune cells are not bound by the extracellular medium, instead traveling to the location of infection, which means that their concentration also changes with the concentration gradient. This behavior is known as chemotaxis, and in this paper, we study the effect of chemotaxis on these diffusive relays. Hence, in Section II, we present the classical model of diffusive relays, and in Section III, we provide a brief overview of chemotaxis. In Section IV, we integrate the two ideas, and in Section V, we present a simulation methodology and results.

II. CLASSICAL MODEL OF DIFFUSIVE RELAYS

Building off the work of Amir et al., the classical model of diffusive relays involves describing the system as a function of the concentration of the signaling molecule $c(\mathbf{r}, t)$, which abides by the equation

$$\frac{\partial c}{\partial t} = D\nabla^2 c + a\rho u[c - c_t] \tag{1}$$

where c_t is some threshold concentration and u is the classical step function. In this equation, the first $\nabla^2 c$ describes the diffusive motion of the signaling molecule down the concentration gradient, while the second term encodes an action potential like response–when the concentration at a given point exceeds the threshold c_t, the cells near that point start emitting at some rate a.

To analyze this equation, we use a wave-based ansatz, assuming that we can write $c(\mathbf{r}, t) = c_1(\mathbf{r} - \mathbf{v}t)$, where $\mathbf{v}$ is the spatial velocity. In this ansatz, we consider the 2-dimensional case, where we also assume that the extracellular medium is very thin, essentially creating a thin layer of cells.

In this case, defining a change of variables $r' = r - vt$, we find that we can rewrite $\frac{\partial c}{\partial t}$ as $-v\frac{\partial c}{\partial r'}$, where we assume that r is along the direction of a circularly propagating wavefront, centered at the origin (or where the relay begins from). Similarly,

$$\nabla^2 c = \left(\frac{\partial^2 c}{\partial r'^2} + \frac{\partial^2 c}{\partial y^2}\right) \tag{2}$$

where we consider y to be the direction perpendicular to the wavefront. In the case of the thin layer of cells, we note that there can be no variation in the wave with respect to height h, making the partial derivative of c with respect to y negligible. Hence, we can rewrite our original signaling equation as

$$-v\frac{\partial c}{\partial r'} = D\frac{\partial^2 c}{\partial r'^2} + \frac{a\rho}{h}u[c - c_t] \tag{3}$$

However, by the ansatz, we know that to trigger the diffusive wave in the first place, we must have $c(\mathbf{0}, 0) = c_t$,

so we can replace $u[c - c_t]$ with $u[-r']$, making the final differential equation

$$-v\frac{\partial c}{\partial r'} = D\frac{\partial^2 c}{\partial r'^2} + \frac{a\rho}{h}u[-r'] \tag{4}$$

To solve this differential equation, we divide it into two cases, the case with $r' > 0$ and the case with $r' < 0$. In the case with $r' > 0$, we have

$$\begin{aligned} -v\frac{\partial c}{\partial r'} &= D\frac{\partial^2 c}{\partial r'^2} \\ \implies c(r', t) &= c_1 e^{-vr'/D} + c_2 \end{aligned} \tag{5}$$

On the other hand, in the case with $r' < 0$, we have

$$\begin{aligned} -v\frac{\partial c}{\partial r'} &= D\frac{\partial^2 c}{\partial r'^2} + \frac{a\rho}{h} \\ \implies c(r', t) &= c_3 e^{-vr'/D} + c_4 - c_5\frac{a\rho r'}{hv} \end{aligned} \tag{6}$$

To analyze these results, we work with the boundary conditions. At $r' = -\infty$, the cells have been emitting for time $\frac{-r'}{v}$, with each of these cells emitting at a density of $\frac{a\rho}{h}$. This means that at the asymptotic limit, $c_5 = 1$. On top of that, since we have demonstrated that the amount of signaling molecule can grow at most linearly, we must have that $c_3 = 0$ so that the concentration does not explode at $r' = -\infty$. To match derivatives, we find that

$$\frac{\partial c}{\partial r'} = \begin{cases} \frac{-c_1 v}{D} e^{-vr'/D} & r' > 0 \\ \frac{-c_3 v}{D} e^{-vr'/D} - \frac{c_5 a\rho}{hv} & r' < 0 \end{cases} \tag{7}$$

At $r' = 0$, since $c_3 = 0$ and $c_5 = 1$, $\frac{a\rho}{hv} = \frac{c_1 v}{D}$, meaning that $c_1 = \frac{a\rho D}{hv^2}$. Choosing c_2 and c_4 to set c to 0 at $r' = \infty$, as the wave has not yet reached that location, we find that we can generally write

$$c(r') = \begin{cases} \frac{a\rho D}{hv^2} e^{-vr'/D} & r' > 0 \\ \frac{a\rho D}{hv^2} - \frac{a\rho}{hv} r' & r' < 0 \end{cases} \tag{8}$$

Hence, we can thus relate the velocity of the wave v to the critical concentration $c_t = c(0)$ and find that

$$v = \sqrt{\frac{a\rho D}{hc_t}} \tag{9}$$

which is an overall asymptotic result relating the wave propagtion to the concentration threshold present[3].

III. CLASSICAL MODEL OF CHEMOTAXIS

This section provides a brief mathematical overview of the physics of chemotaxis in a simple diffusive concentration gradient. In the setting of chemotaxis, opposite to signaling molecules, which diffuse **down** a concentration gradient, the cells instead diffuse **up** the concentration gradient, attempting to travel to the source of the signal. However, since there are a much smaller number of cells relative to signaling molecules, the cells themselves cannot be typically modeled as a continuous distribution, instead modeled as concrete particles undergoing Brownian motion. These particles are taken to undergo the simplest model of Brownian motion – "run and tumble" – where particles "run" forward by some random amount before stochastically reorienting themselves.

To justify the use of a continuum model for these chemotaxis molecules, we analyze a simple model of Brownian motion in one dimension as discussed by Keller and Segel in 1970 [7]. Instead of considering the direct collisions between cells as the cause for Brownian motion, instead consider the collisions between cells and their corresponding signaling molecules as the cause for the Brownian motion. Hence, consider some varying concentration $c(x)$ of the signaling molecule across the one dimensional plane. In general, assume that the number of collisions between the concentration molecules and a given cell is $f(c(x))$. Overall, the only dependency for the frequency of collisions is the signaling molecule density.

Then, writing the density of cells as $\rho(x)$, the step size taken as Δ, and the location of cellular receptors as an offset y from the center of the cell, we can write that the net flux of cells is

$$\begin{aligned} J(x) = &\int_{x-\Delta}^{x} \rho(x') f(c(x' + y)) dx' \\ &- \int_{x}^{x+\Delta} \rho(x') f(c(x' - y)) dx' \end{aligned} \tag{10}$$

since the receptors on the right side of the cells induce hops to the left and the receptors on the left side of the cell induce a hop to the left. To generalize this result, we approximate the integrals, keeping only lowest order terms in the step size Δ, meaning that we estimate

$$\begin{aligned} J(x) &= \Delta^2 \\ &\left[-f(c(x))\frac{\partial \rho}{\partial x} + \rho(x)\frac{\partial c}{\partial x}\frac{\partial f(c)}{\partial x}\left(\frac{2y}{\Delta} - 1\right)\right] \end{aligned} \tag{11}$$

We omit the calculation details as they are mostly algebra and are not physically insightful. This final form of the equation allows for the reduction of the flux into two key terms, a diffusive term, and a chemotactic term. The first term in the expression for the flux $J(x)$ can be rewritten as

$$-\mu\frac{\partial \rho}{\partial x} \tag{12}$$

which is an explicitly diffusive term with $\mu = \Delta^2 f(c(x))$, where $f(c(x))$ can be seen as the inverse of

the timestep between each jump of size Δ. The second term in the expression can be rewritten as

$$\chi = \Delta^2 \left(\frac{2y}{\Delta} - 1\right) \frac{\partial f(c)}{\partial x}$$
$$\chi\rho(x)\frac{\partial c}{\partial x} \tag{13}$$

where the cells hence either diffuse up or down the concentration gradient of the signaling molecule depending on the size of χ. Specifically, Keller and Segel find through a complex analysis, that we omit for the sake of brevity, that a reasonable $f(c)$ is [7]

$$\frac{\partial f(c)}{\partial x} = kk'V\left(\frac{cV}{N}\right)^N e^{N-cV}(2\pi N)^{-1/2} \tag{14}$$

where N is the threshold of the receptor and k, k' are experimentally derived arguments that determine the frequencies of jumps. We note that with this equation for χ, χ is positive as long as $\left(\frac{2y}{\Delta} - 1\right)$ is positive, which means that the size of the cell must be larger than the step size used. For small molecules, like the signaling molecules, this is not true, which is why we observe diffusion down the concentration gradient. However, for larger cells like neutrophils, which are on the order of 10 microns in size, the size of the cell is far larger than the step size taken in Brownian motion, meaning that overall motion is up the concentration gradient [7].

IV. INTEGRATION OF CHEMOTAXIS INTO THE DIFFUSIVE RELAY MODEL

To integrate chemotaxis into the diffusive relay, the formula for the concentration gradient remains the same at

$$\frac{\partial c}{\partial t} = D\nabla^2 c + a\rho u[c - c_t] \tag{15}$$

Instead of having a separate complex diffusion based differential equation for the density of cells, we instead use a simplified model using the fact that the concentration gradient is approximately linear in the signaling molecule as found by Amir et al. [3]. Hence, we make the simplifying assumption that the cells perform chemotaxis towards the origin of the signal at a constant velocity v_c, defined by the constant concentration gradient and triggered by the same action potential as the wave of the signaling molecules (so that we do not see unnecessary movement before the wave arrives), making the equation

$$\frac{\partial \rho}{\partial t} = v_c(\nabla \cdot \rho)u[c - c_t] \tag{16}$$

We note that we can find a number of interesting observations from this equation alone. Over time t, the layer at radius r thus moves to radius $r - v_c t$, increasing the density at radius r by a factor of $\frac{r+v_c t}{r} = 1 + \frac{v_c t}{r}$. We note that this does not affect asymptotic behavior at all for, as the time taken after reaching r is much smaller than r itself for large values of r, meaning that the effects of chemotaxis should only be seen at small r [3].

V. SIMULATION

For simulation, we adopt the philosophy presented by Amir et al. and modify it slightly to incorporate chemotaxis. Amir et al. utilize Green's functions to numerically integrate the propagation of the cellular signaling wavefront, and provide such code in a Mathematica notebook [3]. We adapt the Mathematica notebook to also scale density by a factor of $1 + \frac{v_c \delta t}{r}$ as described in the above section, where δt is specifically measured as

$$\delta t = t - t_{wave} \tag{17}$$

where t_{wave} is the time when the waveform reaches that coordinate.

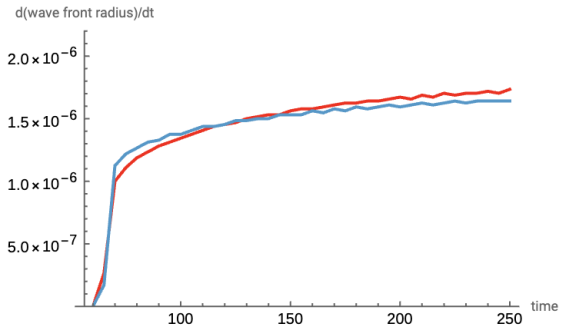

FIG. 1. Two different wavefront spread speeds, where red is the non-chemotaxis model and blue is the chemotaxis model.

We find that in this simulation as shown in Figure 1, that the non-chemotaxis model shown in red has its initial wavefront spread slower. This is because with the effect of chemotaxis, the movement near the initial wavefront triggers more emission of the signaling molecule due to a sharper concentration gradient, leading to faster immediate response. However, the overall response spreads slightly slower because the addition of a $1 + \frac{v_c t}{r}$ term in the numerator of the density also has a corresponding normalizing term to conserve overall number density. This small normalizing term makes the overall propagation smaller, as when cells clump towards the source of the signal, it takes longer for signaling molecules to reach the frontier, similar to the Doppler effect.

We also analyze the shape of the final concentration of the signaling molecules in both cases. We find that as in Figure 2, the concentration of the chemotaxis model far away from the source of the signal is slightly lower than that of the non-chemotaxis model, as some of the

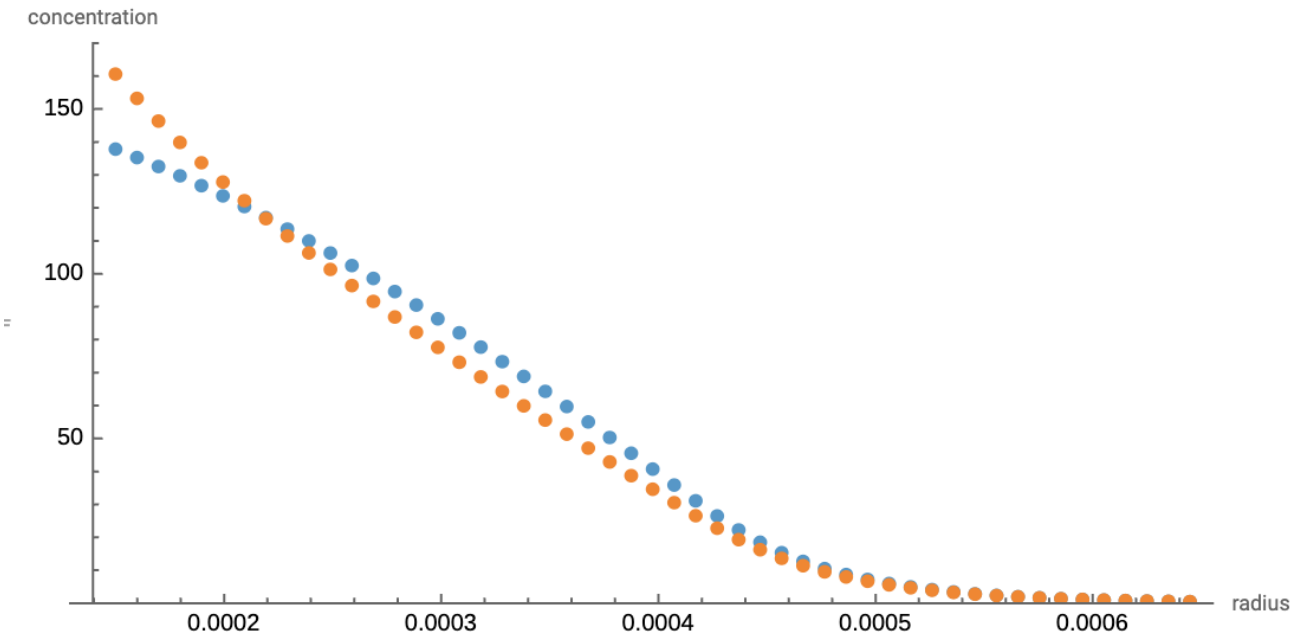

FIG. 2. Two different concentration landscapes, where blue is the non-chemotaxis model and orange is the chemotaxis model.

cells and hence signaling molecules have moved closer to the source of the signal. However, near the signal, where the density of cells has moved, the concentration of the signaling molecules are far higher than the non-chemotaxis model. This makes sense as the cells have moved closer to the source of the signal and thus emit signaling molecules closer to the source of the signal.

Hence, this simulation verifies the overall intuition from Section IV that chemotaxis should not impact asymptotic dynamics and only change dynamics at small dimensions.

VI. CONCLUSION

Hence, in this paper, we have provided a summary of existing frameworks for diffusive cell relays, explaining existing asymptotic bounds for the spread of cellular signaling wavefronts. We have also elucidated the seminal model of cellular movement along concentration gradients, proving a summary of the Keller-Segel model for chemotaxis. Using these two models, we integrated a simple toy model of chemotaxis into the simulation framework for diffusive cell relays proposed by Amir et al. [3]. We find that while asymptotic behavior does not change significantly, chemotaxis causees the strength of cellular signaling to increase significantly near the source of the interaction, possibly indicating the origin of effects critical to our immune response. Future work would likely seek to extend this model of chemotaxis by extending it to the full Keller-Segel model by proposing a new method to efficiently solve the coupled system of differential equations, which would further elucidate the real-world nature of this cellular diffusion effect.

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