Frequency-dependent Chemotactic Target Selection

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Chemotaxis usually involves cellular motion towards an exogenous, often static, source of chemoattractant. We demonstrate an enhanced mechanism in which a single particle (the cell) releases a chemical that diffuses to fixed particles (targets) and signals the production of another chemical by the targets. This secondary chemical acts as the cell’s chemoattractant. To reach a single target, we describe optimal strategies that arise for the release of a fixed amount of probe chemical. In the presence of multiple targets, the one selected by the cell depends on the strength and, more interestingly, the frequency of probe chemical release. Although it involves one more step than standard chemotaxis, our simple chemical “pinging” mechanism can offer far greater flexibility in regulating target selection seen in a number of physical or biological realizations.

What is the best strategy an individual agent can take to select a specific target from many? A theoretical model of such targeting strategies is important in designing robotic communications [1], probing for natural resources, understanding antimicrobial defense mechanisms [2–4] and signaling among cells [5]. Although targets may be physically discerned through acoustical, optical, thermal, or chemical signals, at the cellular level, directed movement usually proceeds via the sensing of local chemical gradients [6, 7]. Chemotaxis is key for many organisms, including bacteria such as Myxococcus xanthus [8], Escherichia coli [9], and Dictyostelium discoideum [10].

In this Letter, we propose a new signaling mechanism in terms of gradient-guided cellular motion towards chemically responsive targets. Contrary to the study of standard chemotaxis where the cell moves along the chemical gradient of nutrients already present in the environment, we consider the following scenario. Initially, the cell sends out a chemical probe signal (species $a$), which diffuses to stationary targets. Upon contact, probe chemical $a$ induces the target to release a different chemical (species $b$) which then diffuses back to the cell. In response, the cell moves up the chemical gradient of the chemoattractant $b$. Classic chemotaxis models by Keller and Segel [11], and their extensions [12, 13] consider passive sources of a chemoattractant to which a cell responds. A schematic of our proposed “echotaxis” mechanism, a diffusive analogue of sonar, is shown in Fig. 1, where one cell and two targets are depicted. Here, we assume that chemoattractant $b$ is different from probe chemical $a$ (“paracrine” signaling) and that the cell uses only $b$ to guide its motion towards the target [14]. This mechanism may arise in the mating of yeast, where each sex of yeast emits a pheromone that up-regulates gene expression in the opposite sex [15]. The “paracrine” aspect of our model arises if production of the complementary pheromone is increased. An “autocrine” [16] mechanism (where $b = a$) is relevant to bacterial swarming and for-
where \( \mathbf{R}(t) \) is the position of the moving cell, \( \mathbf{R}_j \) are the fixed target positions, \( D_a, D_b \) the uniform probe and chemoattractant diffusivities, and \( \mu_a, \mu_b \) their uniform degradation rates. In Eq. 1, \( F(t) \) represents the time-dependent emission of probe chemical \( a \) by the cell at position \( \mathbf{R}(t) \), while in Eq. 2 the term \( \sum_j \delta(\mathbf{r} - \mathbf{R}_j)K_j[n_a(\mathbf{r}, t - \tau), t] \) represents the total production of \( b \) from \( a \) by all the targets \( j \), each at fixed position \( \mathbf{R}_j \). The functional \( K_j[n_a(\mathbf{R}_j, t - \tau), t] \) embodies all chemical steps in the production of chemoattractant \( b \) in response to contact with probe chemical \( a \). The production of chemoattractant \( b \) occurs with a delay \( \tau \), (the time taken for a single or multi-step reaction along the signaling pathway) after the targets are exposed to the probe \( a \) at a time \( t - \tau \) [5]. However, we will assume the simplest model for the conversion kernel \( K_j[n_a(\mathbf{R}_j, t - \tau), t] = k_jn_a(\mathbf{R}_j, t) \), representing instantaneous conversion of probe to chemoattractant with rate \( k_j \). Finally, Eq. 3 describes the motion of the cell in an effective time-dependent potential \( U[n_b(\mathbf{R}(t), t)] \) generated by the dynamics of the chemoattractant \( n_b(\mathbf{R}(t), t) \). Here, we assume the “force” on the cell is proportional to the local chemoattractant gradient \( \dot{r} = \dot{x} \propto n_b(\mathbf{r}, t) \). The response strength \( \gamma \) may contain a stochastic component due to low \( n_a, n_b \) concentrations or uncertainty in the signaling process. Nonetheless, we show that even in the ideal case of perfect signaling and constant \( \gamma \), novel target selection phenomena arise.

In the following analysis, we define dimensionless parameters by measuring length in units of the initial separation \( R_{\max} \) between the probe and its farthest target, and time in units of \( (R_{\max})^2/D_a \). In spatial dimension \( d \), the dimensionless equations are identical to Eqs. 1-3 except with \( D_a = 1 \), and the dimensionless quantities \( D, \mu_{a,b}, k_j, \gamma \), and \( F(t) \) defined by \( D_0/D_a, \mu_{a,b}R_{\max}^2/D_a, k_j/(D_aR_{\max}^d), \gamma/(D_aR_{\max}^d) \), and \( R_{\max}^dF(t)/D_a \), respectively.

The solutions to Eqs. 1 and 2 can be written in the form

\[
n_a(\mathbf{r}, t) = \int_0^t F(t')G_a(\mathbf{R}(t') - \mathbf{r}; t - t')dt',
\]

and

\[
n_b(\mathbf{r}, t) = \sum_j k_j \int_0^t G_b(\mathbf{r} - \mathbf{R}_j; t - t')n_a(\mathbf{R}_j; t')dt',
\]

where \( G_a(r; t) = (4\pi t)^{-d/2}e^{-r^2/4t}e^{-\mu_a t} \) and \( G_b(r; t) = (4\pi Dt)^{-d/2}e^{-r^2/4Dt}e^{-\mu_b t} \). Note that for \( d \leq 2 \), we must assume \( \mu_a, \mu_b > 0 \) if \( F(t \to \infty) > 0 \) in order for the chemical concentrations to remain bounded. Since bounds and analytic expressions for \( n_a(\mathbf{r}, t) \) and \( \mathbf{R}(t) \) can be found only in special cases (such as \( F(t) \propto \delta(t) \)), we numerically integrate Eqs. 1-3 on a fixed lattice using an implicit forward Euler scheme with size step \( \Delta x = 0.05 \) and time step \( \Delta t = 10^{-3} \lesssim (\Delta x)^2 \). The system boundary is chosen to be far enough away from the targets as to be irrelevant. We have also verified these results by comparing with those obtained from directly integrating Eqs. 4 and 5.

We first explore the qualitative behavior of the one-dimensional version of our model with initial condition \( n_a(x, 0) = n_b(x, 0) = X(0) = 0 \) and \( \gamma = 1 \). As a demonstration of the echotaxis mechanism, consider a cell moving towards a single target under different probe release protocols \( F(t) \). Different strategies of probe release qualitatively influence the ability of the cell to reach the target.

Fig. 2(a) shows the trajectories \( X(t) \) resulting from (i) a continuous release starting at \( t = 0 \), \( F(t) = \theta(t) \), (where \( \theta(t) \) is the Heaviside function), (ii) a single, instantaneous release of the probe, \( F(t) = \delta(t) \), and (iii) a periodic sequence of pulses, \( F(t) = \sum \delta(t - t_k) \). All “\( \delta \)-function” releases were approximated by releases of duration \( dt = 0.1 \). The cell starts to move only after a short delay during which some of the probe has reached the target, and the converted chemoattractant has diffused back to the cell. For a single impulse release of probe \( a \), the velocity of the cell towards the target is initially high but eventually goes to zero since the system runs out of the chemoattractant \( b \) once the single pulse of probe \( a \) has dissipated. Thus, for the single-pulse release in Fig. 2, the cell moves only part of the distance to the target. This can be circumvented by adding repeated \( \delta \)-function pulses, each one inducing the cell towards the target. The oscillations in \( X(t) \) correspond to minima and maxima in the gradient \( \partial_x n_a(x, t) \) of the chemoattractant \( b \) at the moving cell.

Now consider the case where the cell contains a fixed amount of probe chemical \( a \). How does the cell’s probe chemical release protocol affect its trajectory toward the target? Suppose the release occurs in a single pulse whose
duration $T$ and amplitude $F_0 = F(t \leq T)$ may vary such that the total amount $F_0 T$ of chemical released is constant. Fig. 2(b) shows that for the parameters used, large magnitude, short duration releases allow the cell to only make it approximately three-quarters of the way to the target. Although in these cases the velocity can reach a high value, the cell may still not reach the target before all chemical signals have dissipated. For lower intensity, but longer duration releases, the cell is more able to reach the target. Qualitatively, this can be understood by noting that a single $\delta$-function release gives a lower bound on the distance traveled. If the probe is released more slowly, the cell moves slightly closer to the target, amplifying the effect of the probe chemical that is released a short time later because this aliquot can reach the cell quicker, and the chemical has less time to decay. However, if probe is released too slowly, the time required for the cell to reach the probe may be large. We find that the release protocol that gives the fastest arrival at the target, conditioned on reaching the target, is typically one in which the time the cell takes to reach the target, and the duration of the chemical release, are nearly equal. In this example, we find the shortest arrival time arises when $F_0 \approx 5$ and $T \approx 4$.

We now illustrate the mechanism of target selection among multiple targets. First consider the one-dimensional case with a cell and two targets. The farther target (at $X_1 = 1$) is assigned a probe-to-chemoattractant conversion rate $k_1 = 1$, while the closer target at $X_2 = -0.25$ has a smaller conversion rate $k_2 = 0.5$. Fig. 3(a) shows that the when release of probe chemical is in the form of a Heaviside function, target selection can be controlled by probe release rate. For the parameters chosen, if $F(t) = 0.1 \times \theta(t)$, the far target is chosen. As the amplitude of release is increased beyond approximately 0.235, the near target is selected by our chemotactic mechanism. When the release rate is large, the cell is initially pulled strongly towards the near target. Because the distance to the far target increases substantially before the signal from this target reaches the cell, the signal strength diminishes and is insufficient to pull the cell back towards the far target. When the probe release rate is small, the cell is unable to move much towards the near target before the stronger signal from the far target reaches the cell, and the cell ultimately goes to the far target.

Target selection can depend not only on probe release intensity, but also on probe release frequency. Fig. 3(b) illustrates target selection when the probe chemical is released either as a Heaviside function or as a series of pulses. For the parameters chosen, the constant release $F(t) = \theta(t)$ results in the cell arriving at the near target. For pulsed release with period $P = 3, 7$, the cell initially moves towards, and depending on the pulse intensity, may arrive at the near target before eventually being pulled to the farther, stronger target. If the release frequency is increased even further, (period $P = 0.2$, red dotted curve), the trajectories will again arrive at the closer, weaker target. Since the underlying processes are dissipative, at very high frequencies, the cell cannot respond fast enough to distinguish the pulses and a rapid succession of pulses is equivalent to an effective-amplitude, constant emission.

The choice of target can be physically understood in terms of a particle undergoing motion in a time-varying potential field. Once the probe chemical is released and diffuses to the targets, the initially flat potential develops minima at the targets. The target ultimately selected corresponds to the minimum reached by the initially metastable cell.

A more quantitative understanding of the selection phenomenon can be found in the small $\gamma$ limit, where the cell does not move much under the influence of a single probe pulse (such as the trajectory corresponding to $F(t) = 0.14 \times \sum_i \delta(t - 7i)$ in Fig. 3(b)). Upon substituting Eq. 4 into Eq. 5 and considering the resulting equation for the instantaneous velocity (in $d = 1$), $\dot{X}(t) = \gamma \lim_{s \to -\infty} X(t) F_0 \sum_j k_j \int_0^t \partial_x G_0(x - X_j; t - t') G_a(X(0) - X_j; t') dt'$. If the cell does not move appreciably under the influence of a single probe pulse, we can approximate $\dot{X}(t)$ by setting $x \approx X(t = 0)$ in the integrand. Upon Laplace transforming the above equation and taking the limit $s \to 0$ we get the asymptotic distance traveled by the cell $X_\infty \propto F_0 \sum_j k_j \exp \left[ - \left( \sqrt{\mu_a/D_a} + \sqrt{\mu_b/D_b} \right) |X_j| \right]$ as a result.

FIG. 3: Amplitude and frequency dependent target selection. (a) Amplitude-dependent target selection showing a transition from selecting the further, stronger, target to selecting the weaker, nearer target for a Heaviside release protocol. The transition occurs at amplitude $F_0 \approx 0.235$. (b) Frequency dependent target selection, showing a weaker nearer target being selected for constant chemical release $F(t) = \theta(t)$ and very high frequency pulsed release $F(t) = 0.2 \sum \delta(t - 0.2 \bar{t})$, and a further stronger target being selected for pulsed release at intermediate frequencies (corresponding to periods $P = 3, 7$). These trajectories may first arrive at the nearer target depending upon probe chemical release amplitude. The target strengths are $k_1 = 1$, $k_2 = 0.5$, while $\mu_a = \mu_b = 0.1$ and $D = \gamma = 1$. The initial separation between the cell and the targets are $R_1 = 1$ and $R_2 = 0.25$ respectively.
of one single probe pulse. If $X_{\infty} < 0$, the next probe pulse will be released when the cell is closer to the left target, and the cell will eventually incrementally move leftward. If $X_{\infty} > 0$, the cell will ultimately arrive at the right target. Therefore, $X_{\infty} = 0$ defines an approximate boundary for selection between two targets in $d = 1$.

Generalizing the phenomenon to $d$ dimensions, we expect that for each release sequence $F(t)$, there will be at least one $d - 1$ dimensional surface that separates trajectories that evolve to different targets starting from a given initial position on the $d$ dimensional manifold. Figure 4 shows trajectories of cells searching and selecting between two targets in $d = 2$. The separatrix for $F(t) = \theta(t)$ is indicated by the dashed curve that divides the space such that trajectories originating from the right/left of this line are led to the stronger/weaker target respectively. We then start the cell within regions where one target is clearly selected when the probe chemical is released with $F(t) = \theta(t)$, but with either a diminished released rate or with pulsed release, such that the average rate of chemical released per unit time is 1. As in the $d = 1$ case we find that for Heaviside function release, a larger release rate favors the weaker, closer target, while a smaller release rate favors the stronger, farther target (dashed curve). In one dimension we found that slow pulsed release favored the far, strong target over the near, weak target. In contrast, for $d = 2$, we find that slow pulsed release favors the near target (solid black curve). This may be understood as follows, in $d = 1$, pulsed release causes the cell to quickly go towards the near target, but a subsequent wave of chemotactant from the far target caused the cell to ultimately select the far target. In two dimensions, the radial divergence in the concentration fields causes the signal from the far target to be insufficiently strong to pull the cell from the weaker target.

Numerous variants of our basic model, such as mobile targets that sense probe chemical, stochastic effects, and delays in the signaling processes can be straightforwardly investigated. Another example, is “autocrine” signaling, relevant to bacterial aggregation, where the probe is identical to the chemotactant ($a = b$). In this case, we expect that targeting will persist, but be suppressed due to the attraction to the cell’s own probe chemical. However, it has been shown in two-dimensions that when stochastic effects and chemical decay are included, cells do not localize but can remain diffusive [12].

In conclusion, we have proposed a new mechanism of chemotaxis by which signaling agents can select between potential targets by controlling the amount of, and frequency at which probe chemical is released. Since our moving source problem is intrinsically nonlinear, we employed numerical calculations to provide evidence of a critical target-switching release amplitude, as well as a window of pinging frequencies within which a cell chooses a target different from that chosen at, zero, very low, or very high frequencies. This effect arises from a nonlinear interplay between diffusion, decay, and chemotactant production. Our numerical experiments have shown that target selection is observed over a wide range of system parameters, and is dependent particularly on pinging frequency. An in-depth analysis of such models and the parameters within which that provide qualitatively different behaviors could address the evolutionary questions that decide which organisms will adopt these richer strategies of chemotaxis and why.

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