Foraging Strategies for *Dictyostelium discoideum*

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May 2010
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Abstract

The rate at which organisms are able to forage for food affects the rate at which they can grow, and thus foraging strategies are crucial for almost any organism. In the social amoeba *Dictyostelium discoideum* (Dicty), it is known that cell-cell communication plays an important role in aggregation of the cells, and thus we ask if it plays a similarly important role in foraging. In particular, we consider the role of repulsion in foraging: it has been observed that Dicty cells repel each other when in the unicellular state, but the role of this repulsion is not yet understood. Here, we use computer simulations to show that Dicty-Dicty repulsion improves foraging efficiency by allowing the cells to spread out more evenly and thus cover terrain more efficiently. Our results show that for a cooperative homogeneous population, repulsion leads to a significant increase in foraging efficiency; furthermore, an optimal repulsion strength for the population exists. We then show that if we introduce a cost to repulsion, non-repelling cheaters can invade such a homogeneous population. Under certain conditions, the cheaters will not take over entirely but rather enter into a stable coexistence with the repelling Dicty. In such a coexistence the repelling Dicty make up for the cost of repulsion by keeping other cells at a distance and thus obtaining more food than the non-repelling Dicty. This result suggests a possible explanation for the experimental result that *Polysphondylium*, another species of amoeba, is repelled by but does not repel Dicty or other *Polysphondylium* amoebae. In particular, our results suggest that the coexistence of *Dictyostelium* and *Polysphondylium* as repelling and non-repelling amoebae may have evolved together as a spatial mixture of amoebae, because the non-repelling strategy is advantageous only in the presence of repelling strains.
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1 Introduction

Understanding communication between cells is an important goal for biology today. For example, formation of multicellular organisms requires communication between cells during development; cancers in these organisms then may arise when cells ignore communication from other cells and reproduce indefinitely. The study of communication in single-celled organisms has also become increasingly important in recent years [1]. The study of quorum sensing networks in bacteria has revealed a complex communication network between cells [2, 3]. Understanding such communication networks allows us to begin understanding phenomena like bacterial biofilms—macroscopic films of bacteria that are often problematic in medicine—in which communication between individual cells is essential in the formation of a multicellular-like entity [4]. This thesis studies cellular communication in the unicellular amoeba *Dictyostelium discoideum* (Dicty). In particular, we provide evidence that the experimentally observed repulsion between Dicty cells can improve the efficiency at which the cells forage for food. Dicty is already a well-known and important example of cell-cell communication in that Dicty cells signal each other to start aggregating when they form a multicellular slug. While it is known that attraction between cells is important for Dicty aggregation into the multicellular state, we shown that repulsion may be important for foraging in the unicellular state.

1.1 *Dictyostelium* and repulsion

This paper considers Dicty as its model biological system. Dicty, a eukaryotic organism, is a type of cellular slime mold with two distinct stages in its life cycle: the unicellular and multicellular stage. In the unicellular or vegetative stage the Dicty cells exist as motile amoebae that reproduce asexually and forage for bacteria, which they eat by phagocytosis. The second part of the life cycle occurs when food is scarce, causing Dicty cells aggregate to form a multicellular motile slug. The slug cells differentiate into prespore and prestalk cells; eventually, the slug forms spores held up by the stalk. The stalk cells are non-viable and “sacrifice” themselves [5] so that the spore cells, elevated physically, might be better dispersed when they are carried to a new and presumably more food-rich environment. This thesis focuses on the vegetative state of the life cycle, during which the Dicty amoebae forage for bacteria. Little is known about how Dicty forage. However, communication is crucial for Dicty during aggregation; thus in this study we ask, is it likewise important for foraging?

**Dicty amoebas repel each other when in the vegetative state.** Dicty cells can respond to chemical signals through chemotaxis, and thus can communicate with other Dicty by secreting chemicals. Like other eukaryotic cells, the relatively large size of Dicty cells allows them to sense concentration differences across their own lengths and thus follow chemical gradients directly; in contrast, bacteria can only make temporal measurements of absolute concentrations due to their small size. Dicty cells are attracted to cyclic-AMP (cAMP) when aggregating [6]. They are also attracted to folate, a chemical that is presumed to let Dicty chemotact towards bacteria while feeding [7]. In addition to these two instances of positive (attractive) chemotaxis, negative (repulsive) chemotaxis has also been observed in Dicty. Repulsion between Dicty cells was first suggested by Samuel in 1961 [8] and confirmed by Keating and Bonner (KB) in 1977.
KB performed several experiments, such as placing two droplets of Dicty cells next to each other and noting that the cells spread apart away from each other, with hardly any cells occupying the space between the droplets. In 1979, experiments by Kakebeeke et al. [10] corroborated KB’s findings and also suggested that repulsion may have a role in foraging since production of the repellent stops as soon as feeding stops. However, the repellent is yet unidentified [11] and its role in foraging is still unproven. This thesis shows through simulations that repulsion indeed has a significant positive effect on foraging efficiency.

KB also note that while Dictyostelium cells repel each other, cells of the related species Polysphondylium violaceum do not. Furthermore, they showed that Polysphondylium cells are repelled by Dicty, but the converse is not true. It has been generally observed that different species of amoebae exhibit different levels of sensitivity to repellents [10]. These facts will be used to motivate the model that different cells have different repellent production rates and different sensitivities to repellent (see Sec. 2.1).

On short scales, Dicty move by extending random pseudopodia and responding to chemical gradients. Understanding foraging requires understanding how the cells move. Dicty move by extending out protrusions called pseudopodia. It has been shown that when chemotaxing by shallow gradients of cAMP, Dicty send out a number of randomly oriented pseudopodia with which they “smell” for attractant. They then retract those pseudopodia encountering less of the cAMP, thereby moving up the gradient [12]. Although it has not been proven, it is likely that Dicty chemotact by folic acid to bacteria in a similar manner. Even when not sensing chemical gradients, Dicty may have a sense of “touch”: if one pseudopod encounters a bacterium, the cell will be more likely to move in that direction than another [13]. Fig. 1a shows this effect in an experimental set up with low Dicty density (∼ 1 cell/ cm²) and high food density. Between the top image (t = 0 sec) and the second image (t = 10 sec), the Dicty cell sends out pseudopodia in both the upwards and downwards directions. The downwards direction contains two bacteria (top image, red circle), whereas the upwards direction does not. The next three images (t = 10-30 sec) show that the cell eventually chooses the downward direction (the red circle remains in the same position).

On long scales, Dicty move by a persistent random walk. Pseudopodia are small and describe how Dicty amoebae behave on short time scales (∼ 1 min). On longer time scales (∼ 10 min to a few hours), we require a more “zoomed out” description of Dicty motion. It has been shown that in the absence of any chemical signals Dicty cells perform a unique type of persistent random walk that does not fall into any of the classes usually considered in optimal foraging theory (Fig. 2d). This persistent random walk comes about by means of a short memory: the cells remember the direction of their last turn, and make their next turn away from it such that the overall zig-zag motion is fairly persistent [14]. Motion in the presence of attractants and/or repellents is likely to be more complicated. Fig. 1b shows the level of persistence in a sample walk in the presence of bacteria. Although the cell makes several turns, it continues in the same general direction for the two minutes shown in the figure. In fact, Dicty cells tend to move persistently for about 10 min in the absence of signals [14]. Thus we can think of the attraction to very nearby food particles using pseudopodia as a local effect and the persistence...
Figure 1: Images of a solitary Dicty cell foraging on an agar surface. (a) shows that the cell moves by sending out pseudopodia. The red circle in the top image encloses two food particles that presumably cause the cell to choose the downward direction. (b) The blue path (drawn by hand) shows that although the cell makes frequent local turns, its path is fairly persistent on longer scales up to several body lengths. (a) and (b) show the same cell, but note that $t = 0$ is not the same time in each. Images generously provided by Simon Nørrelykke, Princeton University (Princeton, NJ). Experimental details [Simon Nørrelykke, private communication]: Dicty are grown on *E. coli* and then harvested and plated on 1% agar at a density of $\sim 1$ cell/cm$^2$. After $\sim 100$ min *E. coli* from stationary phase are added to the surface. There are no nutrients available for the bacteria to grow so that the food remains stationary and constant until eaten by the Dicty.
as a global effect, both of which likely improve foraging efficiency (see Sec. 1.2 for further discussion). Our model attempts to capture only the more global affect of persistent motion; the specifics of how the Dicty move within the length scale of one cell length are neglected.

**Dicty as a model organism.** Dicty is a popular model organism for many reasons [15, 16]. Called “social amoebae,” Dicty interact with each other in very interesting ways: when starving, Dicty cells aggregate in beautiful spiral waves which are of great interest both mathematically and biologically. Furthermore, because Dicty has such a diverse life cycle, consisting of both unicellular and multicellular stages, studying Dicty has lead to insights in many different branches of biology from chemotaxis and aggregation dynamics to altruism and cheating. Dicty is also experimentally tractable: genetic variants are readily available as lab strains, and much is already known about their life cycle and how they respond to signals [16]. Studying model systems such as Dicty has been a very successful strategy in biology, since important structures and functions are conserved across evolutionary time and thus understanding of one organism can be generalizable to many others.

### 1.2 Optimal foraging theory

Optimal foraging theory is the study of how organisms can best search for food in their environment, and therefore its general principles are important in understanding Dicty foraging. Studies in this field typically label individuals as “searchers” (in our case, Dicty amoebae) and others as “prey” or “food” (bacteria). One then studies the best or optimal foraging strategy for the searchers to seek the prey in a certain environment. Foraging strategies are defined as different types of searches with simple parametrizations: for example, a simple random walk is one search strategy, and is represented with just one parameter, the diffusion coefficient. To find the “best” strategy we require a metric for success. The typical metric is the encounter rate of food particles, i.e., the rate at which the searcher encounters (and thus eats) the discrete food particles. Foraging theory can consider many variants to the general set-up outlined above: for example, foraging can be considered in one, two, or three dimensions; the food may be stationary or motile, and may be distributed in various manners such as in localized dense patches or uniformly across the environment; foraging may or may not be considered “destructive,” meaning that once food is eaten it may or may not regenerated. Because theoretical approaches are often intractable in such complex systems, simulation studies are very common in this field; see, for example, refs. [17, 18, 19, 20, 21].

**Persistence is important for foraging.** Although the standard metric for foraging success is the rate of encountering food, we can use a different intuition in the case that the food particles are stationary and uniformly distributed, as is the case of Dicty foraging experiments performed in the laboratory (i.e., Fig. 1). In such situations, the food encounter rate is simply a proxy for the amount of territory explored, because the uniform food distribution implies that the number of food particles encountered is simply proportional to the amount of territory explored. In the particular case of destructive foraging where food is not regenerated, the success is then measured by the amount of territory first covered by a given cell; re-explored
Figure 2: (A-C) An illustration of three types of commonly studied search strategies. (D) A numerical simulation of *Dictyostelium* motion using parameters generated from experimental data in the absence of chemical signals. Figure reproduced directly from [14].

territory is not counted in the total, because the food in that previously explored region will already have been depleted during the initial exploration by that or another cell.

Thinking about maximizing the territory explored helps us understand some important and relevant results in foraging theory, such as the need for persistent motion. Studies have shown that under conditions of sparse food distributions, a type of random walk called the Lévy walk is an effective search, outperforming a random walk search [19, 20]. A Lévy walk draws its angles randomly and its step sizes from an inverse power law distribution. The thick tail of power law the distribution (as compared to, for example, the Gaussian distribution) allows for occasional very long steps which bring the searcher into an entirely new region of unexplored territory. Fig. 2b shows a sample Lévy walk trajectory that illustrates this phenomenon. However, the Lévy walk is not always persistent enough: further studies have shown that under certain conditions the Lévy walks are outperformed by the simplest strategy, pure ballistic motion (moving in a straight line) [18]. This result stems from the same intuition that if the goal is to cover as much territory as possible, then given some finite radius for the searcher, every turn decreases the amount of new territory covered. Thus if there is no need to stay within a relatively confined area, ballistic motion is optimal. This result does not, however, imply that the best foraging strategy for Dicty would be to move ballistically and thus reach locations very far from their starting point. First, the food cannot be uniformly spread out for an arbitrarily large area because at some point the environment must change or a barrier be reached. Second, it may not be advantageous for the cells to spread arbitrarily far apart because if food becomes depleted and aggregation is initiated, those far away cells may not be able to sense the signal calling them to aggregate and thus may starve. Finally, even if a cell’s strategy is to move ballistically, physical limits such as rotational diffusion and the inability to

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To be precise, the probability density of the step size \( l \) is given by \( P(l) = l^{-\mu} \) with \( 1 < \mu \leq 3 \) and \( l \geq l_{\text{min}} \) for some \( l_{\text{min}} > 0 \) [19].
perfectly remember a direction limit the ability to move in a completely straight line. Thus, we do not investigate ballistic motion in this thesis.

**Group foraging.** The majority of literature on foraging theory considers the foraging of a single individual, and measures success by the rate at which the individual locates food. This paper deviates from this paradigm in that it considers group foraging: when the foraging of one individual is generalized to that of a population, are there any qualitatively different features? Some work has already been done to answer this question, particularly in the case of patchy food distributions. For example, Brown *et al.* [22] studied group foraging in insect-eating cliff swallows. They showed that since individuals can communicate with each other, group foraging is highly advantageous for the group because if one bird locates a swarm of insects it can signal its neighbors to join it. A possible objection to this argument is that it may not be beneficial for a selfish individual to alert other foragers to the existence of a patch of food [23]. Brown *et al.* address this objection by observing that individual birds have difficulty tracking swarms of insects for a long time, but with the help of others swarms can be tracked successfully and thus the individual can increase its own food intake by sharing with others. It is possible that Dicty behave in much the same way when they encounter large bacterial colonies, although the evolutionary advantage of alerting other Dicty may be due to genetic relatedness and not necessarily benefits to the individual as with the birds (see Sec. 1.3 for further explanation). In any case, when food is distributed uniformly as in our model, the concept of a “jackpot” of food does not apply and therefore there is no reason to attract other foragers to any one particular location. Thus one may argue that in the case of a uniform food distribution group foraging brings no advantages. We will show that this is not the case: if the cells communicate through repulsion, group foraging can in fact be advantageous even in the case of a uniform food distribution, because the cells will in general spread out more and cover more territory.

### 1.3 Evolution, cooperation, and cheating

When a Dicty produces repellent, it alerts nearby cells to its presence and thereby allows them to stay clear of regions in which food may already be depleted, or will soon be depleted, by the signaling cell. Thus when a Dicty repels, it is—in addition to helping itself—helping its neighbor. This section addresses the concept of altruism in nature in order to understand this kind of cooperative phenomenon in Dicty. To do so, we first discuss some facts about evolution and natural selection to understand why instances of altruism can exist in nature. We then introduce the field of game theory, a framework that allows us to describe mathematically situations of competing interests between individuals. The unification of these fields leads to the concept of the Evolutionarily Stable Strategy (ESS), a key idea in making predictions about the outcomes of evolution.

**Natural selection and competition, and altruism.** The theory of evolution is based on natural selection, an innately competitive theory commonly referred to as the survival of the fittest. Natural selection is the idea that those individuals who are most fit will reproduce more, and their frequency in the population will therefore increase. Individuals with unfavorable traits, on the other hand, will slowly die out. Because genetic mutations are constantly
creating new variants of different organisms, this theory does not lead to a steady state of just one homogeneous super-species, but rather a dynamic and diverse ecology if viewed over evolutionary time scales.

Competitiveness can be interpreted as selection of the fittest individuals. This is not, however, the complete or correct interpretation: natural selection occurs on genes, not individuals [24]. An example of this phenomenon is cannibalism in the garden spider. After courting male spiders, female spiders will sometimes cannibalize the male instead of eating them [25]. However, male spiders continue to seek females, despite the risk of being cannibalized. The individual male spider has no gain from taking this risk; its genes, on the other hand, stand to gain the chance of being propagated should mating occur. Thus spiders containing the gene(s) causing it to mate will be selected for and propagated throughout the population.

The concept of gene selection can help us understand one of the most intriguing and complex topics in evolutionary biology: altruism. If natural selection implies competition, why would altruism ever prevail? One response is that seemingly altruistic behavior may actually be beneficial to the individual, as in the case of the cliff swallows discussion in Sec. 1.2 that alert other swallows to the presence of insect swarms. However, altruism can exist even if the individual does not benefit. The explanation lies in the fact that since selection occurs at the level of genes, organisms with similar genes may behave altruistically towards one another. We know that individuals share a large proportion of their genetic material with their kin, such as parents, siblings, etc. If organisms can recognize their kin from unrelated individuals, a gene causing altruism towards kin could be beneficial to the gene, since it codes for altruism to other organisms likely to contain that same gene.2 Indeed, such phenomena are observed in nature: the spider Stegodyphus tentoriicola is known to forage more cooperatively with its kin than with unrelated spiders [27]. This is in fact just a different explanation for the brave male garden spiders discussed above: by attempting to mate, they are behaving altruistically towards their hypothetical and yet-unborn offspring. Thus thinking in this framework we can, somewhat disturbingly, account for phenomena like parents caring for their children.

Altruism is observed in Dicty and can be explained from these same principles. We first consider the well-studied phenomenon of stalk and spore formation. As mentioned in Sec. 1.1, when Dicty cells aggregate to form a slug and then differentiate into spore and stalk cells, only the spore cells are viable. If the cells were purely competitive, no cell would form part of the stalk because it conveys no advantage to the individual. The reason some cells contribute to the stalk is precisely because they are related: the genetic material in the stalk cells is propagated because much of it also exists in the genetically related viable spore cells. One can think of it another way: it does not seem surprising that the cells in our own bodies act cooperatively to allow us to function. And yet, our cells do not know that they are all part of one organism; instead, they cooperate because they all contain the same genes. If a group of identical Dicty cells is thought of as a multicellular organism even at the aggregation stage, cooperation becomes intuitive.

At this point it is possible to raise a subtle objection: even if some of the genes are shared

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2 In particular, altruism will take place only if the benefit/cost ratio is greater than \(1/r\) where \(r\) is the degree of relatedness of the organisms. For example, siblings have relatedness \(r = 1/2\) and thus altruism towards a sibling could only evolve if the benefit/cost ratio (where the benefit is to the sibling and the cost is to the individual) were greater than 2 [26].
between the stalk-forming and spore-forming cells, the particular gene that causes the cells to form the stalk evidently does not exist in the spore cells, and thus that gene is not propagating itself by behaving altruistically toward the spore-forming cells. The resolution to this difficulty is that the cells, initially indistinguishable or very closely related, differentiate randomly into prestalk and prespore cells [28]. Thus, it is not correct to think of a cell as either possessing or not possessing the stalk-forming gene. Instead, the genes of interest tell all cells to differentiate into a stalk cell with some probability, and differentiate into a spore cell otherwise. In this fashion cells can behave differently (i.e., by forming either stalk or spore cells) but can be genetically identical, and thus the selfish gene framework allows for the altruistic stalk-forming behavior. Repulsion during foraging may work much the same way: the fact that Dicty cells are highly related when they aggregate [28] implies that genetically related cells are spatially localized during the vegetative state. Thus, when a cell produces repellent it is benefiting not only itself but also genetically related cells in the vicinity.

**Game theory allows us to assess evolutionary stability.** We have argued that altruism can be explained through the idea of genetic relatedness between individuals, but until now have not argued for the stability any such situation. Here stability means that a population will persist over evolutionary time scales because mutants will not perform better than the existing cells. To address the issue of stability it is necessary to take a digression into the field of game theory. Game theory is the mathematical treatment of situations in which different individuals have different interests, and is applicable here because competition in nature is clearly such a situation. A short game theory primer is left to Appendix A, in which the concept of an Evolutionarily Stable Strategy (ESS) explained. A level of game theory covered by the primer is assumed for the remainder of this discussion. The key idea is that populations we observe in nature are those corresponding to ESS's, because non-ESS situations are unstable and thus only exist transiently.

The concept of ESS allows us to address issues of stability in general and in the case of Dicty. In case of stalk and spore formation described above, we have shown why some cells will form the stalk, but have not answered the following question: what is to prevent the spread of a mutation that causes the cell to become the stalk with a lower probability than the other cells? Such an individual that relies on the cooperation of others but does not contribute its fair share to the group is called a cheater. This question of cheaters has been studied extensively in the context of stalk and spore formation in Dicty (see, for example, refs. [29, 30, 31]). It is indeed the case that Dicty aggregations can contain cells of more than a single genotype [29], and thus the presence of a mutant cheater strain is not implausible. If one of the genotypes making up the slug is a cheater strain, it may be able to take advantage of the wild type (“altruistic”) clone, and indeed such cheaters do exist in nature [29]. The situation is complicated further because the presence of cheaters can cause the development of “anti-cheater” mutations, those that reduce the benefit of cheating [30, 32]. One example of such a mutation is a mutation that reduces the area over which cells aggregate. Since cells are constantly dividing, genetically identical cells tend to also be closer to each other in space. Thus if cells aggregate over a smaller area, a given slug is less likely to contain cells from more than one clone [30].

The above discussions of cheating in the well-studied stalk-spore system show that the so-
cial interactions in Dicty are extremely complex. For this reason, this thesis considers both the competitive and cooperative viewpoints when considering Dicty from an evolutionary perspective. We first consider cooperative strategies, and show that an optimal repulsion strength exists for a homogeneous (and thus cooperative) foraging Dicty population. We then consider the possibility of cheaters, and show that if there is an evolutionary cost to repulsion then cheaters not producing repellent can invade the population and take advantage of the repellent produced by others. Next we show that for each of a range of cost functions there exists an ESS containing a fixed proportion of repelling and non-repelling Dicty; i.e., such a population cannot be invaded by other cheating strains with any other repulsion strength. This coexistence of two Dicty types can be interpreted as cells that switch randomly between repelling and not repelling, or as two different species, one repelling and one not. Finally, we attempt to relate the two-species interpretation to KB’s results that Polysphondylium are repelled by—but do not repel—Dicty.
2 The model

This section discusses the model for Dicty foraging used in this study. The model is used for simulations of Dicty cells foraging in a two-dimensional square environment in order to probe the effects of Dicty-Dicty repulsion on foraging efficiency. Fig. 3 shows a visualization of a sample simulation performed in this study. In each simulation, \( N \) Dicty cells of length \( L \) are placed randomly in a finite square arena such that their density is given by \( 1/\delta^2 \), where \( \delta \) is the typical Dicty-Dicty spacing. The cells then forage for a fixed number of time steps, instantaneously eating any food particles they encounter. The food eaten by each cell is recorded and this number is used to represent the fitness of the cell. Particular details of the model, such as how repulsion is incorporated, are given below. Because the simulations require many parameters, a table of all parameters is given in Appendix C for convenient reference.

2.1 Instantaneous forces

Dicty move at constant speeds. In our model, the motion of the Dicty is described by computing a “force” on each Dicty at each time step. Note that these forces are not real forces, but rather serve to provide a common set of units with which the effects of repulsion, persistence, and noise can be combined. The forces are then added to yield a final force vector, such that the force on cell \( i \) is given by

\[
\mathbf{F}_\text{total}^{(i)} = \mathbf{F}_\text{persistence}^{(i)} + \sum_{j \neq i}^{N} \mathbf{F}_\text{repulsion}^{(j \rightarrow i)} + \mathbf{F}_\text{noise}^{(i)}
\]

After the total forces are computed, their magnitudes are discarded and each cell takes one step of unit length in the direction of its force vector. This means that all cells travel at an equal and constant speed of one unit per time step. This constant speed model is motivated by KB’s suggestion that chemical signals only cause Dicty cells to change orientation, not to change speed [9]. Furthermore, if magnitude of the force were taken into account, cells feeling a strong repulsion force would move more quickly and therefore eat more; in such a case, repulsion might seem beneficial for this reason only. In keeping the speed of motion constant, repulsion is only able to affect the direction of each cell’s motion, and thus if repulsion yields better foraging efficiencies we can conclude that it is because the Dicty followed less overlapping trajectories, not because they moved more quickly.

The following subsections will describe each of the three forces in some detail.

Persistence. The persistence term is motivated by the discussion in section 1.1 of Dicty’s persistent motion. We implement persistence as contributing a “memory” force to the total force, where the memory vector just points in the direction of the last step in the simulation. This implementation is motivated by the experimental result showing that when Dicty respond to chemoattractant they do not follow the direction of the gradient exactly, but rather follow a direction that is a combination of the external signal and some internal “memory” vector [33]. In our case, the memory is only one time step long for simplicity. Thus the persistence

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\(^3\)Note that the parameters used to generate the figure were chosen to best facilitate visualization; the main simulations are much larger (\( N = 2000 \) cells vs. \( N = 100 \) cells).
Figure 3: Six snapshots of a sample simulation that includes repulsion. The Dicty cells (red asterisks) eat the stationary bacteria (blue dots). The memory vectors (magenta arrows) point in the direction of the last step of the Dicty. Parameters: $N = 100$, $r_0 = 4$, $\delta = 8$, $P = 1.0$, $R = 0.5$, $S = 1.0$. Simulation used 250 time steps (times shown: 0, 50, 100, 150, 200, 250), periodic boundary conditions.
The persistence force $\overrightarrow{F}_{\text{persistence}}$ is proportional to the direction of the last step $\hat{\overrightarrow{F}}_{n-1} \equiv \frac{\overrightarrow{F}_{n-1}}{|\overrightarrow{F}_{n-1}|}$ with some proportionality constant $P$, which we call the persistence strength. Note that if persistence were the only force the cell would move in a straight line indefinitely.

**Repulsion.** The repulsion force acts between each pair of cells. The repulsion is due to a diffusive repellent molecule [9] which sets up a concentration gradients in the medium. Dicty cells can measure both absolute concentrations and concentration gradients: we suppose the cells use one or both of these methods to respond to the signals of other cells. Then, due to diffusion, the concentration profile decays with distance away from the source, and thus we pick a model in which force decreases with distance between the cells. In reality, the cells cannot repel each other instantaneously, because the repellent takes some finite time to diffuse the distance between cells. However, in this model we assume that the repulsion is instantaneous; i.e., that the force from cell $i$ on cell $j$ at time $t$ depends only on the distance between $i$ and $j$ at time $t$. Intuitively, we justify this by the fact that the particles diffuse much faster than the Dicty cells move. See Sec. 4.2 for a quantitative discussion.

The exact form of the repulsion in this model is an exponential,

$$|\overrightarrow{F}_{\text{repulsion}}| = R \exp\left(-\frac{r_{ij}}{r_0}\right)$$

where $R$ is the repulsion strength, $r_{ij}$ is the distance between cells $i$ and $j$, and $r_0$ is the repulsion length scale. The exponential function was chosen because its length scale and overall amplitude can be tuned as separate parameters (unlike, for example, $\overrightarrow{F} = \frac{A}{r^2}$, which only has one parameter). It is important to control these two quantities separately because we would like to fix the length scale to a sensible value and then adjust the strength independently based on how much repellent the cell is producing. The exponential was also chosen because it is close to the concentration profile of a diffusing molecule from a fixed point source. See Sec. 4.1 for a more complete discussion.

**Noise.** The noise term is implemented by adding independent zero-mean Gaussian terms to the $x$- and $y$-components of the force. Because only the direction of the force is used, we have an extra normalization constant among the three forces and thus can set the magnitude of the noise to unity without loss of generality. Therefore the variances of the two Gaussians are set to half, such that the variance of the noise vector is one. The resulting noise vector has a uniformly distributed angle and a magnitude that follows the $\chi^2$ distribution with mean one. The fact that the noise magnitude follows the $\chi^2$ distribution is not significant; it is simply a convenient choice to use a Gaussian in each direction.

With each of the three forces defined, we can now rewrite Eq. 1 more explicitly:

$$\overrightarrow{F}^{(i)} = P\overrightarrow{F}_{n-1}^{(i)} + \sum_{j \neq i}^{N} R_j \hat{r}_{ji} \exp\left(-\frac{r_{ij}}{r_0}\right) + \left( \begin{array}{c} \mathcal{N}(0, \frac{1}{2}) \\ \mathcal{N}(0, \frac{1}{2}) \end{array} \right)$$

where $\mathcal{N}(0, \frac{1}{2})$ is a Gaussian random variable with mean zero and variance one half and $\hat{r}_{ji} \equiv \frac{\vec{r}_{ji} - \vec{r}_{ij}}{|\vec{r}_{ji} - \vec{r}_{ij}|}$, the unit vector in the direction pointing from cell $j$ to cell $i$.

The fact that the angle is uniformly distributed when the $x$- and $y$-components are independent identical Gaussians can be seen by noting that the joint density, $P(x, y) = P(x)P(y) = \frac{1}{\sqrt{\pi}} \exp(-x^2) \frac{1}{\sqrt{\pi}} \exp(-y^2) = \frac{1}{4} \exp(-(x^2 + y^2)) = \frac{1}{4} \exp(-r^2)$ is independent of $\theta$. 

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15
The repulsion strength $R_j$ in Eq. 2 represents the amount of repellent produced by cell $j$. In this study, we would generally like to vary this parameter and analyse the results. However, in addition to adjusting repellent production, Dicty might also be able to adjust their sensitivity to the repellent produced by other cells (see Sec. 3.4). In this case, Eq. 2 becomes

$$
\vec{F}(i) = P \hat{F}_{n-1}^{(i)} + S_i \sum_{j \neq i}^N R_j \hat{r}_{ji} \exp(-r_{ij}/r_0) + \left( \frac{\mathcal{N}(0, \frac{1}{2})}{\mathcal{N}(0, \frac{1}{2})} \right) \nn
$$

where $S_i$ is the repellent sensitivity of cell $i$. The overall strength of repulsion in this equation is now $S_i R_j$, the product of the sensitivity of cell $i$ and the production of cell $j$.

### 2.2 Units

The simulations presented here use arbitrary units because it is not possible to make exact correspondences with real units given several unknowns in the system (e.g., the diffusion dynamics of the repellent, the response curve of Dicty to different levels of repellent, etc.). However, we may still sketch approximately the length and time scales associated with the simulations. In the simulations the cells have a length of 1 unit, and thus each unit represents, very approximately, the length of a cell or 10$\mu$m. Since the velocity is set to 1 unit per time step, the time scale should be about 2 min per time step to match the realistic velocity of about 5 $\mu$m/min. Then an entire simulation, generally about 500 time steps long, represents about 1000 min or 10-20 hours. Indeed, when performing experiments, movies of longer than 10-20 hours are not feasible because the bacteria begin to divide by extracting trace amounts of the nutrients from the agar [13].

### 2.3 Other assumptions

**Destructive foraging.** In this model I consider only “destructive foraging,” meaning that the food is not regenerated after it is eaten. This choice is experimentally motivated: we would eventually like to compare our results to experimental data such as that shown in Fig. 1. In this laboratory set-up, the food is not regenerated after it is eaten by a Dicty cell because the bacteria do not divide on the time scales of the experiments.

**Periodic boundary conditions.** The simulations presented in this study use a two-dimensional square arena with periodic boundary conditions. Using a two-dimensional area is again experimentally motivated. The choice of boundary conditions is prevalent in the foraging theory literature (see, for example, refs. [19, 20]), and is also a sensible choice here. Furthermore, it was verified that the basic results presented here are reproducible with hard boundary conditions (data not shown). The results produced by simulations with periodic and hard boundary conditions deviate mainly in uninteresting parameter regimes: for example, at extremely large repulsion strengths, the Dicty cells form a square lattice instead of a triangular lattice when hard instead of periodic boundary conditions are used.
Food particles are placed on a square lattice. Our simulations are intended to measure the amount of food eaten by the Dicty given a uniform food distribution. Any additional noise introduced by randomly placing the food in the arena is not of interest; rather, we are just interested in the amount of territory explored by the cells. Thus in the simulations food particles are placed on a lattice of size equal to $L$, the size of the Dicty cell. Then the amount of food eaten by a Dicty cell is just the number of lattice squares that were first visited by that cell. This method is computationally much more tractable than placing the food particles randomly and off-lattice.

Cell division is neglected. In all simulations the number of cells $N$ stays constant throughout; neither cell division nor cell death is considered. The above section (2.2) discusses the approximate timescales of the simulations to be about 10-20 hours. However, when provided with sufficient food, the Dicty divide approximately every 4 hours [13], meaning that we would expect several rounds of division on the time scales of our simulations. We do not include division because the main goal of this thesis is to understand the benefits of repulsion in that it causes foraging cells to spread out more; including cell division would complicate the model in a way not directly relevant to the goal. Furthermore, incorporating cell division would likely only increase the benefits conferred by repulsion, because immediately after division the two daughter cells are located right next to each other and should spread out as soon as possible to cover more territory.

Attraction to food is neglected. Dicty are not attracted to food in the simulations. This choice was motivated by considering the effects of including an attraction force similar in nature to repulsion; i.e., an exponential or some other decaying function. Because the food is uniformly distributed and not sparse, the effect of including this force would have the following effect: a Dicty cell that comes sufficiently near to a food particle would quickly “fall into” the potential well around that food particle and eat it very shortly after. Thus the result of including attraction would be to effectively increase the size of the Dicty cell (and introduce some small delay in eating). We are not interested in such rescalings of the parameters. Therefore, in the case of uniform food distributions, attraction to food is an additional parameter that is unlikely to alter the basic results of this study. It is important to note, however, that attraction to food might play an important role in the case of non-uniform food distributions where Dicty might be attracted to large patches of food from a far distance away.

2.4 Cost functions

Sec. 1.1 introduced the experimental result that certain other species of amoebae do not produce repellent, or at least are not repelled by Dicty. This fact raises the possibility that cells of these other species are cheaters, taking advantage of the repellent produced by the Dicty. For example, if only one such cheater existed in the population, it would be surrounded by repelling cells, and although other cells are effectively unaware of its presence, it is aware of them and can avoid them. Thus this cell may have a fitness almost equal to the Dicty cells without paying the evolutionary cost of producing a repellent.
To assess this possibility of cheaters in a quantitative manner we must introduce a cost of repulsion into the model. The cost function clearly must be monotonically increasing. We will use the linear cost function $C(R) \propto R$ in this study, and we take $C(0) = 0$ for convenience, such that we think of producing no repellent as having zero cost. We can justify this choice by noting that we will not consider large values of repulsion (most values are of order unity or smaller) and thus a linear approximation will not deviate very much from the true value. Furthermore, we have no information on the true functional form of the cost, and thus a simple function should be chosen to avoid artifacts arising from special properties of the cost function.

Note that in some simulations we allow $R$ to take on negative values. In these cases, the cost function must also be defined for $R < 0$. In such cases we use the modified cost function $C(R) \propto |R|$ so that producing attractant and repellent are equally costly for the cell.
3 Results

3.1 Preliminary investigations

The effects of repulsion are visible in the distance correlation function. We first measure the Dicty-Dicty distance correlation function in order to determine the effects of repulsion on the typical Dicty-Dicty distance in the simulation arena. The correlation function is defined as the histogram of Dicty-Dicty distances, normalized so that for a random distribution of points it should be flat and equal to one. The red line in Fig. 4 shows that non-repelling Dicty indeed distribute themselves randomly in the arena. The blue line in Fig. 4 shows that for a nonzero repulsion strength the distance correlation functions exhibits a sharp dip at small distances, meaning that repulsion is indeed having an effect on the distribution of Dicty in the arena. In particular, Dicty are less likely to be found at positions close to each other when $R > 0$. Furthermore, as expected, the width of the dip is approximately equal to the repulsion length scale, which is set to $r_0 = 4$ in the figure.

Repulsion length scale $r_0$ should be on the order of the typical Dicty-Dicty spacing, $\delta$. Initial investigations of the parameter space were performed in order to search for the interesting parameter regime in this system. Because the length scale $r_0$ of the repulsion force is set by physical constants such as the diffusion coefficient and degradation rate of the repellent molecule, it was kept as a fixed parameter and the repulsion strength $R$ was instead varied. To determine at which value to fix $r_0$, we performed some preliminary simulations and found that when the length scale $r_0$ was too small or too large compared to the typical Dicty-Dicty distance $\delta$, changing the repulsion strength $R$ did not have a strong effect on foraging because repulsion was either negligible or saturating. Therefore, to explore the effects of changing $R$, the repulsion length scale $r_0$ was set to be on the same order as the typical Dicty-Dicty distance $\delta$. In particular, $r_0 = \frac{1}{2} \delta$ was used in the simulations presented here.

Persistence strength $P$ should be on the order of the noise strength, which is set to unity. As discussed in Sec. 1.2, persistence is important in foraging because a forager undergoing purely diffusive random walk re-covers a significant amount of territory many times. The persistence strength $P$ controls the persistence of the Dicty motion in the simulations. Because the strength of the persistence “force” is an abstract quantity, the persistence lengths of the trajectories were computed numerically using the method outlined in Sec. B.2. Fig. 5a shows both the numerical persistence length and the food eaten as a function of $P$. (Note that in this figure and all that follow in thesis, the units of food eaten are normalized as the fraction of all food particles eaten, such that after an infinite number of time steps the food eaten should saturate at one). Because the repulsion strength $R$ is set to zero in this case, the persistence force is competing only with the noise, which has unit variance. Thus for $P \ll 1$ the noise dominates and for $P \gg 1$ persistence dominates. The figure shows that at large $P$ the food eaten begins to saturate to the maximum efficiency and that further increases in $P$ do not increase foraging efficiency.\footnote{The reason for this saturation is that the Dicty begin to eat the maximum possible amount in the simulation. In 500 time steps, moving at one unit per time step, the Dicty can eat at most 500 food particles each, or $2000 \times 500 = 10^6$ in total. The total number of food particles in this simulation is about $8 \times 10^5$, so the Dicty could eat almost all of them in 500 steps. Therefore, $P$ should be on the order of unity in this case.}

It is important to note that because of the periodic boundary
Figure 4: Normalized Dicty-Dicty distance correlation function for non-repelling (red) and repelling (blue) cells. The blue curve shows a drop at low distances due to the repulsion. Parameters: $N = 1000$, $r_0 = 4$, $\delta = 8$, $P = 1.0$, $R = 0.0$, $0.5$, $S = 1.0$. Simulation used 500 time steps, periodic boundary conditions.

Conditions, increasing the persistence arbitrarily is always advantageous; however, we are not interested in exploring this regime for the biological reasons outlined in Sec. 1.2. Instead, as with the choice of $r_0$, we seek a non-extreme value such that it will not obscure the effect of repulsion on foraging. The green curve and the unit variance of the noise suggest that $P \approx 1.0$ is a good choice. The value $P = 1.0$ is also consistent with the known persistence length in real units. The persistence length of Dicty motion in the absence of signals is known to be on the order of 50 $\mu m$, or about 5 cell lengths [14]. Because the simulations here use a cell size of $L = 1$, the persistence length should be set to about 5 units (see Sec. 2.2 for a discussion on units). Fig. 5b (a subset of Fig. 5a, blue curve) shows that at $P = 1.0$ the numerical persistence length is very close to the desired value of 5 units. Thus the value of $P = 1.0$ was used in the following simulations presented here.

3.2 Fitness landscapes

Repulsion improves foraging efficiency in a homogeneous population. In a homogeneous population, repulsion does indeed improve foraging results, following our intuition that if cells repel each other they are less likely to crowd an area and consequently will cover more territory. Fig. 6a shows the group fitness as a function of the group repulsion strength. The reason that the fitness drops rapidly at high repulsion strengths is that when the cells repel too strongly they freeze up into a solid-like lattice and thus cover very little territory: they move only through small fluctuations around their lattice positions. At very low repulsion strengths the cells do not repel each other effectively and thus are susceptible to bunching up and foraging ineffectively. This effect is further worsened in the case of Dicty-Dicty attraction ($R < 0$), as the cells bunch up and a large amount of territory is covered redundantly by many cells.
Figure 5: Numerical persistence length and food eaten vs. $R$.

(a) Persistence length and food eaten vs. persistence strength, $P$ in the case of no repulsion. (a) When $P \approx 1$, the food eaten increases drastically for increasing $P$ because the persistence begins to overtake the noise; when $P$ is large, increasing $P$ does not affect foraging efficiency. Numerical persistence length increases with $P$ as it should. (b) A persistence strength of $P = 1.0$ yields a numerical persistence length of $\sim 5$. Parameters: $N = 2000$, $r_0 = 10$, $\delta = 20$, $R = 0$. Simulation used 500 time steps, periodic boundary conditions; results are averaged over $n = 5, 15$ trials for (a) and (b) respectively.

Note that as $R$ increases in Fig. 6, the numerically calculated diffusion coefficient of the cells decreases monotonically (data not shown). This indicates that repulsion is not actually speeding up the cells, but rather guiding them to explore unexplored territory.

The clear optimum in Fig. 6a (black dashed line) suggests that in a situation of complete cooperation, the cells should operate with a repulsion strength of $R_{\text{global}} \approx 0.50$, or about half the strength of the persistence and noise forces. When cells repel at $R = R_{\text{global}}$ the food eaten is $\sim 7\%$ larger than if $R = 0$ (from Fig. 6a). If such an advantage corresponds approximately with a $7\%$ increase in growth rate, the advantage is enormous: in the case of exponential growth, after 500 generations a strain growing $7\%$ faster will outnumber the slower-growing strain by a factor of $10^{10}$.

**Optimum persists for correctly chosen cost functions.** When a cost is introduced, the global optimum shown in Fig. 6 must shift, and if the cost is too large then the optimum will no longer be present. Fig. 6b shows the result when a cost of $C(R) = 0.1|R|$ is introduced. The repulsion optimum shifts to $R_{\text{global}} \approx 0.15$. However, Fig. 6c shows that when the cost is increased to $C(R) = 0.4|R|$ the optimum shifts to $R = 0$; the best strategy in this case in not to repel, because even repelling a small amount is not worth the large marginal cost.

**Cheaters can invade a homogeneous population.** Next, we assess whether or not cheaters can invade a population repelling at the optimal repulsion strength (with no cost) of $R = R_{\text{global}} \approx 0.50$. We first consider the case where the cheaters constitute a very small fraction of the total population; this case represents the situation in which one cell mutates to become a cheater, and then either thrives or dies out depending on whether or not the mutation is
Figure 6: Global fitness of a Dicty population as a function of global repulsion strength for different cost functions, where the fitness equals the fraction of food eaten by the Dicty population. (a) Without a cost, a clear optimum exists at 0.5. (b) With a small cost, the optimum shifts but is still nonzero. (c) For a large cost, the optimum is at $R = 0$; it is never beneficial to repel. Parameters: $N = 2000$, $r_0 = 10$, $\delta = 20$, $P = 1.0$, $S = 1.0$. Simulation used 500 time steps, periodic boundary conditions; results are averaged over $n = 20$ trials.
Figure 7: Fitness of two Dicty populations as a function of global repulsion strength of the cheater. The green line represents fitness of the “normal” cells which are repelling at the global optimum $R \approx 0.50$. The blue line represents the fitness of the cheaters whose repulsion strength is given by the $x$-axis value. The fitness is measured by considering the mean food eaten by cells of each type, normalized so that a score of 1.0 indicates a given type has eaten its share of the food. The total fitness (dashed black line) is then simply the fraction of total food eaten. Parameters: $N = 1950\text{normal} + 50\text{cheater} = 2000$, $r_0 = 10$, $\delta = 20$, $P = 1.0$, $R_{\text{normal}} = 0.50$, $S = 1.0$. Simulation used 500 time steps, periodic boundary conditions; results are averaged over $n = 20$ trials.
advantageous. Figure 7 shows the performance of different cheaters (with no cost) when the cheaters make up 2.5% of the total population of cells. As expected, when cheaters do not repel they eat less because nearby cells are not aware of them. The green and blue two lines cross at $R = R_{\text{global}} \approx 0.50$ because at that point we have a homogeneous population; the cheaters and normal cells are identical. When $R_{\text{cheater}} > R_{\text{global}}$ the cheaters do better than the normal cells because in this plot we do not consider the cost of repulsion, and therefore they keep the normal cells out of their way at no cost. Of course, if the cost exists but is small, the super-repelling cheaters still may have an advantage. If the cost is large, on the other hand, the non-repelling cheaters (or any cheaters with $R < R_{\text{global}}$) may dominate. Thus for almost any cost function cheaters can invade a homogeneous population repelling at the global optimum, and the type of cheaters that invade depends on the cost. Note that the total fitness (dashed black line) decreases monotonically with increasing $R_{\text{cheater}}$ for $R_{\text{cheater}} > R_{\text{global}}$ because the benefit to the small number of cheaters does not outweigh the loss to the rest of the population.

Although invasion is interesting, the most biologically relevant situations are stable equilibria. Based on the discussion above it seems possible that the cost function could be tuned such that the cheaters and the normal cells have the same fitness and can coexist. But the cost is cannot be tuned: the expense of producing and secreting a repellent molecule is fixed by biological realities. In this case, is coexistence of two repulsion types still possible? In fact it is. The resolution comes from the fact that Figure 7 was produced with a fixed proportion of cheaters, namely 2.5%. Consider the situation in which the cost is high so that the non-repelling cheaters are at the advantage and invade. Once they become a more substantial fraction of the population, will they still have the advantage? The next subsection considers exactly this case, and shows that as invasion of a population proceeds, the advantage of the invading party continually decreases until a stable equilibrium is reached.

**Cheaters benefit more when their frequency is lower.** Figure 7 shows the fitness of cheaters when they exist as a low proportion of the population. What happens as the frequency of cheaters increases? Intuitively, we expect the benefit of cheaters to be reduced, since when the population reaches 100% cheaters it is now operating homogeneously at some repulsion strength which is not the global optimum. We now focus on the case of non-repelling ($R = 0$) cheaters who gain an advantage by avoiding the cost of producing repellent. Fig. 8a shows a plot of fitness vs. $\alpha$, the proportion of non-repelling cheaters in the population. As expected, the fitness of the cheaters decreases with increasing $\alpha$, although it eventually starts to increase for $\alpha$ close to one. The intuition for the latter effect comes from the fact that the cheaters and non-cheaters are competing for a depletable, scarce resource. When cheaters are few, their fitness is low simply because by lacking repulsion they cannot forage as effectively as the normal cells. However, when $\alpha$ is large the cheaters are hindered not only by the fact that they cannot repel and thus forage more slowly, but also by the fact that the repelling normal cells forage faster and are able to steal a proportion of the food that should belong to the cheaters. At large $\alpha$ the normal cells are too few for the repellent they provide to significantly help the cheaters in foraging; they only detract from the fitness of the non-repellers by stealing food. Therefore,
(a) Without a cost, non-repelling cheaters always do worse than Dicty repelling at the global optimum \( R_{\text{global}} \).

(b) When a cost of \( C(R) = 0.1R \) is applied, the fitness curves of the cheaters and normal Dicty cross at approximately \( \alpha = 0.625 \), or 62.5% cheaters.

Figure 8: Fitness of non-repelling cheaters (blue), non-cheaters (green) and the total population (black, dashed) as the fraction of cheaters, \( \alpha \), is varied from 0 to 1. Parameters: \( N = 2000 \), \( r_0 = 10 \), \( \delta = 20 \), \( P = 1.0 \), \( R_{\text{normal}} = 0.50 \), \( R_{\text{cheater}} = 0 \), \( S = 1.0 \). Simulation used 500 time steps, periodic boundary conditions; results are averaged over \( n = 50 \) trials.
when \( \alpha \) approaches unity and the competitors disappear, the cheaters’ fitness increases slightly. This intuition of competition does not apply to the total fitness, which decreases monotonically as \( \alpha \) increases. In other words, the best case for the group is all cells repelling, and the more cells not repelling, the lower the group fitness. This effect is an artifact of the fact that repulsion cost is not included in the plot. Once a cost is added (Fig. 8b), the total fitness no longer decreases monotonically.

Introduction of a cost can lead to stable coexistence. Appendix section A.4 explains that an Evolutionarily Stable Strategy (ESS) requires the fitness of all individuals in the population to be equal. This means that if there is no cost to repulsion as in Fig. 8a, the two species could not coexist as they will never have the same fitness. To illustrate that coexistence is possible once a cost is considered, we introduce an arbitrary (but illustrative) cost function \( C = 0.1R \) such that the fitness of the normal cells is reduced but the fitness of the non-repelling cheaters is unaffected. The result (Fig. 8b) shows that if an appropriate cost is introduced, the two fitness curves can cross and thus there exists a proportion of cheaters (in this case \( \alpha^* \approx 0.625 \)) for which the fitnesses of the two species are equal.

This result shows that there is a situation for which the two types of cells have equal fitness. We now show that such a steady-state is stable. To see this, consider small deviations \( \alpha = \alpha^* + \Delta \alpha \). When \( \Delta \alpha \) is positive such that \( \alpha > \alpha^* \) then the fitness of the normal cells is larger (in the figure, the green line is above the blue line) so that the normal cells will then outperform the cheaters and \( \alpha \) will be pressured back to the steady-state value \( \alpha^* \). Likewise, when \( \Delta \alpha \) is negative such that \( \alpha < \alpha^* \) then the fitness of the cheaters is larger such that \( \alpha \) will again tend back to \( \alpha^* \). Thus the equilibrium is stable; if \( \alpha = \alpha^* \) the proportions of the two types will stay constant. The repulsion strategies of these Dicty is an ESS.

Note that the total fitness (black dashed line) is not largest at \( \alpha = \alpha^* \), meaning that the ESS is not a global optimum. This is a general property of game-theoretic situations: when all individuals act rationally in their best interests, the interests of the group are not best served.\(^6\)

Oscillations are not possible with only two types of Dicty. The above discussion shows that for the cost function \( C(R) = 0.1R \), when the fraction of cheaters is \( \alpha = \alpha^* \approx 0.625 \) then the fitnesses of the two types of cells are equal, and thus they can coexist. We then showed that the equilibrium is stable. It is important to notice, furthermore, that this stable equilibrium will be reached regardless of the initial condition on \( \alpha \); i.e., in a population consisting only of \( R = 0 \) and \( R = 0.5 \) Dicty, if one of the two types becomes present in an infinitesimally small fraction, it will grow until the proportions are equal to \( \alpha = \alpha^* \). The reason for this is that \( \alpha \) is the only dynamical variable in this evolutionary system, and any dynamical system with only one variable cannot exhibit oscillations. In this case only one fixed point exists, and it was shown to be a sink. Thus for any initial values of \( \alpha \) the system will tend to that sink at \( \alpha^* \).

\(^6\)Another interesting fact about that total fitness is that it does not peak at \( \alpha = 0 \) because the normal cells are repelling at the global optimum as determined when the cost is zero, not the global optimum when \( C(R) > 0 \) is in this plot.
3.3 *In silico* evolution

The results presented above indicate that non-repelling Dicty and repelling Dicty may be able to form a stable coexistence. However, the stability analysis presented thus far only considers deviations in the proportions $\alpha$ of the two types; it does not consider the possibility of invasion by Dicty with any other repulsion strengths. In this section we consider this possibility using evolution simulations in which different types of Dicty compete for food, and then reproduce proportionally to their fitness before the next generation begins. The approach is fundamentally different from that in the previous section: instead of exploring the parameter space and inferring the stable situation by finding the fitness maximum, we instead let the population evolve *in silico* to determine if those supposedly stable populations are indeed robust to invasion.

Evolution simulations are consistent with predictions made by fitness landscapes.

To validate the method of evolution simulations we first confirm the results presented in the above section and in Fig. 8. Using the same parameters, we perform an evolution simulation with the types considered above ($R = 0$ and $R = 0.5$). In this simulation, the two types reach the proportions of 62.5%/32.5% predicted by the results in Fig. 8b (data not shown; this effect is illustrated in Fig. 9). We then consider robustness to invasion by introducing three additional types ($R = 0.25, 1, 5$) that could potentially invade the population. Note that our previous nomenclature of “normal” and “cheater” cells is no longer applicable as we now consider many different types of cells; from this point forward, each type will simply be labeled by its repulsion strength $R$. Fig. 9 shows the results of an evolution simulation with these five types. The population of $N = 2000$ Dicty cells starts with equal proportions of the five types ($R = 0, 0.25, 0.5, 1, 5$), and after each generation the proportions are readjusted to reflect the variation in fitness across the different types. Figure 9a shows that the three types $R = 0.25, 1, 5$ become extinct and only the two types predicted to coexist ($R = 0$ and $R = 0.5$) remain. Furthermore, the proportions asymptotically approach the expected 62.5% of $R = 0$ cells predicted by the fitness landscape arguments presented in the above section (the cost function used the same as in the above case for this reason, namely $C(R) = 0.1R$).

One should note that although this result was foreshadowed by the fitness landscape studies such as that shown in Fig. 8b, the result shown here in Fig. 9a is more meaningful for several reasons. First, Fig. 8b shows that with the right proportions the two types $R = 0$ and $R = 0.5$ can coexist, but it makes no statements about other possible coexistences involving other types. One could imagine that the evolution simulation found another local minimum involving some or all of the other three types. However, this does not happen regardless of initial conditions (see the next subsection, Fig. 10). Second, even if no other stable point exists, the coexistence of the $R = 0$ and $R = 0.5$ types may have also been stable with certain nonzero proportions of the other types. The evolution simulation is able to sample the space of different proportions $\alpha$ (in this case a four-dimensional vector, since we have five types) until steady-state is reached. From the figure we see that the coexistence only involves the original two types.

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7 Refer to Sections B.3-B.5 for a discussion of the numerical methods in these evolution simulations.

8 The $x$-axis of the plot is shown in a log scale to show interesting effects are short times and also to show clearly that all types start from an equal share (i.e., one fifth) of the total population.
Figure 9: An evolution simulation with Dicty types of five different repulsion strength values, \( R = 0, 0.25, 0.5, 1, 5 \). Only \( R = 0 \) and \( R = 0.5 \) survive, and with expected proportions. Parameters: \( N = 2000, r_0 = 10, \delta = 20, P = 1.0, S = 1.0, C(R) = 0.1R \). Each simulation used 500 time steps, periodic boundary conditions. Evolution repeats for 600 generations.
A very interesting feature in Fig. 9a is that the red (proportion of $R = 0.5$ cells) and green (proportion of $R = 0.25$ cells) cross after about 30 generations. This effect indicates that at the start of the simulation, when the population consisted of many different types, the fitness of the cells was mainly dictated by the differences in costs, such that the proportions were “sorted” by $R$. Later, only after the $R = 5$ and $R = 1$ types became extinct\(^9\), does the true nature of the $R = 0, 0.25, 0.5$ competition emerge such that the $R = 0.5$ type does better than the $R = 0.25$ type despite the higher repulsion cost.

Fig. 9b shows the fitness of the five types as the evolution simulation proceeds. The figure confirms that the fitnesses were simply sorted by $R$ at the start of the simulation. The inset shows that after the extinction of the $R = 5$ and $R = 1$ types, the $R = 0.25$ fitness indeed becomes lower than the fitnesses of $R = 0$ and $R = 0.5$ types, which are approximately equal to each other as expected. This crossing-over effect is very interesting and would be an interesting subject of further investigation.

The dashed black line in Figure 9b shows the cooperative fitness: if all cells were to repel at the global optimum for a homogeneous population with cost $C(R) = 0.1R$ (which is $R \approx 0.15$; see Fig. 6b), they would have the fitness as indicated (Fig. 6b). This line shows us that the competitive outcome arrived at in the simulation is less favorable to the group than the the cooperative outcome. This expected result is called the “tragedy of the commons” in game theory.

**Evolution simulations are robust to changes in initial conditions.** The results shown in Fig. 9 use an equal proportions of the five types as the initial condition. It is important to check that the results are not simply artifacts of the initial conditions, but rather occur robustly. Fig. 10 shows the same experiment repeated 10 times with randomly selected initial conditions, all plotted on the same axes. In each case the types $R = 0.25, 1, 5$ reach extinction and the types $R = 0, 0.5$ coexist with the same proportions. Not surprisingly, however, the time to reach steady state depends on the initial conditions, and also varies from trial to trial due to the inherent randomness in the system.

**Mutation-based evolution simulations yield consistent results.** The above simulations start with some fixed set of $R$-values and, as evolution proceeds, the proportions of the different types change. We now present results from a more general type of simulation in which the set of possible $R$-values are not fixed in advance but rather can be explored during the simulation. In particular, we let the population start homogeneously with all cells having $R = 0$, and we now allow $R$ to take on any real number. After each generation, the cells performing better are more likely to produce offspring and thus some multiply while others die out (the specific algorithm used to update the population between generations is called the roulette wheel algorithm; details are left to Sec. B.4). Some noise is then added to the $R$-values and the next generation proceeds. The added noise is crucial because it allows for new $R$-values to be explored during

\(^9\)Note that immediately before extinction of the $R = 0.25$ and $R = 0.5$ types the fitness (Fig. 9b) becomes very noisy. This happens because right before extinction there is only one (or very few) cells of that type, and thus there is no averaging effect to produce a smooth curve.
Figure 10: The result shown in Fig. 9 is robust to initial conditions, as shown here by repeating the simulation with 10 different sets of initial conditions. In each case only the $R = 0$ and $R = 0.5$ strains survive, although the time to extinction for the other three types depends on the initial conditions and some randomness. Parameters (same as in Fig. 9): $N = 2000$, $r_0 = 10$, $\delta = 20$, $P = 1.0$, $S = 1.0$, $C(R) = 0.1R$. Each simulation used 500 time steps, periodic boundary conditions. Evolution repeats for 600 generations. Initial conditions for each of the types $i$ are given by $n_i = \frac{Z_i^2 + 0.5}{\sum_i(Z_i^2 + 0.5)}$ where the $Z_i$ are independent normally distributed random variables with mean zero and unit variance.
Figure 11: The distribution of $R$-values (y-axis) vs. evolution generations (x-axis) in an evolution simulation. These results are consistent with the stable coexistence shown in Fig. 9. Parameters: $N = 2000$, $r_0 = 10$, $\delta = 20$, $P = 1.0$, $S = 1.0$. Each simulation used 500 time steps, periodic boundary conditions. Evolution repeats for 5000 generations. Evolution parameters: $\sigma = 0.01$, $\nu = 0.001$, $\gamma = 20$, $\epsilon = 0.001$. See Sec. B.5 for a description of these evolution parameters. Cost function: $C(R) = 0.082|R|$. 

The simulation; without it, each generation would only contain the same set of $R$-values as the previous generation, but with updated proportions according to the relative fitnesses.

Fig. 11 shows the result of such a simulation. The y-axis represents the relative frequency of the different $R$-values, so that each column of the images sums to one. The distribution then evolves towards the right. (Note that the cost function used in this simulation differs slightly from that used earlier because branching occurs more reliably with a slightly smaller cost). The figure shows that a homogeneous population of non-repelling Dicty evolve into two distinct populations, one with $R \approx 0$ (non-repelling) and one with $R > 0$ (repelling). The eventual repulsion strength of the repelling types depends on the particulars of the simulation such as the cost function. However, in all simulations that involve branching of this sort, one branch always remains at $R \approx 0$ (other simulations not shown). The reason that $R = 0$ represents a “special” value is that the cost function $C(R) \propto |R|$ has a minimum at $R = 0$. The assumption that a cost is associated with producing both repellent and attractant is biologically reasonable; thus, we can state with some generality that such branching evolutions are likely to produce one non-repelling type.

The results presented here are consistent with those presented above (Figs. 9, 10) that show a coexistence between a repelling and non-repelling type. However, the results presented by the continuous-$R$ simulations show not only that certain pre-chosen types die out, but in fact that cells of any repulsion strength $R \approx 0$ or $R \approx 0.6$ will not emerge. We now possess evidence that repulsion may have evolved in amoebas due to foraging benefits, and that during the evolutionary process the repelling cells may have been mixed spatially with non-repelling cells such that two the types entered into a stable coexistence.
3.4 Varying the repellent sensitivity, $S$

In this section we extend our model so that repellent sensitivity $S$ can be adjusted in addition to the repellent production strength $R$. As we have seen, Dicty with $R > 0$ can do well both in the absence and presence of non-repelling Dicty. In the discussion of Fig. 8 we observed that the repelling cells in fact steal a portion of the food “belonging” to the non-repellers by keeping them out of the way and thus eating more. In such cases, it is possible that the non-repelling Dicty would be better off by ignoring the repellent and competing for the food in the vicinity of the repelling cells. In other words, in some cases Dicty may wish to ignore the repulsion of others, if those others are producing reckless amounts of repellent. In other cases the opposite might be true: it may be beneficial to be more sensitive to repellent than other cells, if for example most cells in the vicinity repel very weakly. This phenomenon motivates an extension of our model where the repellent sensitivity $S$ can now be varied.

Fig. 12 shows the result of an evolution simulation allowing both $R$ and $S$ to vary. In this simulation the cost of sensing repellent is set to zero so that we can observe the dynamics of $S$ in the simplest way. The reason a cost is not needed is that $S$ will not increase indefinitely even without a cost: being overly sensitive to repellent causes the repulsion force to dominate the persistence force (see Eq. 3), and an overly sensitive cell will therefore perform a less persistent walk. We have shown (Fig. 5) that persistence is important for foraging, and thus these cells that sacrifice persistence will sacrifice foraging efficiency. This phenomenon explains why it is not advantageous to increase $S$ arbitrarily, even when no cost is introduced.

Fig. 12 shows that branching occurs both in $R$ (Fig. 12a) and $S$ (Fig. 12b). Furthermore, from Fig. 12c we can associate the branches in Figs. 12a and 12b. In particular, we see in Fig. 12c that the non-repelling type ($R \approx 0$) evolves to be more sensitive to repellent ($S \approx 4$) than the repelling type ($R \approx 0.5$, $S \approx 2$). One reason why sensitivity is valuable in this simulation is that the $R \approx 0$ group is not fixed exactly at $R = 0$, and thus there are many cells repelling very weakly. To detect the signals from these weakly repelling cells requires a high sensitivity to repellent. This effect is especially important for those cells producing very little or no repellent, because these cells are in the most danger of bumping into other cells while foraging. Therefore these weakly repelling cells develop more repellent sensitivity than the strongly repelling cells. Similarly, the repelling cells are already able to keep others away, and thus it is not as important for them to be very sensitive to repellent. These cells then evolve to a lower value ($S \approx 2$) so as not to significantly decrease persistence.

Biologically speaking, there is of course a cost to sensing repellent just as there is one to producing it. The result presented here is one of many possible combinations of cost functions and other parameters, but it illustrates a key idea: that even if repellent sensitivity can be tuned by evolution, stable coexistences can still result, and thus our results can still explain the variance across species observed by KB.

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10When incorporating sensitivity in the model, we use the update rules given by Eq. 3 instead of Eq. 2.
Figure 12: An evolution simulation allowing both (a) $R$ and (b) $S$ to vary. A branching occurs in both cases, at approximately the same time ($t \approx 800$ generations). (c) shows the two-dimensional distribution over $R$ and $S$ at the end of the simulation: in particular, those cells with $R \approx 0.5$ develop less sensitivity than those with $R \approx 0$. Parameters: $N = 2000, r_0 = 10, \delta = 20, P = 1.0$. Each simulation used 500 time steps, periodic boundary conditions. Evolution repeats for 5000 generations. Evolution parameters: $\sigma_R = \sigma_S = 0.03, \nu_R = \nu_S = 0.001, \gamma = 30, \epsilon = 0.001$. Cost functions: $C_R(R) = 0.0995|R|$, $C_S(S) = 0$. 

(a) Evolution of $R$.  

(b) Evolution of $S$.  

(c) The distribution of $R$ and $S$ and the final time, $t = 5000$. 
4 Theoretical considerations

4.1 Concentration gradient from a point source

Section 2.1 describes the model of the repulsion force as exponentially decaying in the distance \( r \) between two Dicty. This section considers the validity of this assumption by deriving the true concentration gradient of a repellent molecule, assuming it is produced by the cell at a constant rate \( \Gamma \) and degraded with some first order rate constant \( k \). In order to solve for the steady state concentration gradient, we take the cell with diameter \( L \) to be at origin, and therefore we can assume rotational symmetry of the gradient. We can solve the diffusion equation in two dimensions assuming a boundary conditions that the repellent is produced at a constant rate \( \Gamma \) at \( r = L/2 \) and that the repellent concentration decays to zero as \( r \to \infty \). We begin with the diffusion equation:

\[
\frac{\partial c}{\partial t} = D \nabla^2 c
\]

If we assume that the proteins are also degraded at some rate \( k \), then the equation becomes

\[
\frac{\partial c}{\partial t} = D \nabla^2 c - kc
\]

The rotationally invariant form in two dimensions is

\[
\frac{\partial c}{\partial t} = D \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right) - kc
\]

At steady state, we set \( \frac{\partial c}{\partial t} = 0 \), except for the boundary condition \( \frac{\partial c(0,t)}{\partial r} = \Gamma \)

\[
0 = \frac{d^2 c}{dr^2} + \frac{1}{r} \frac{dc}{dr} - \frac{k}{D} c
\]

We first translate this differential equation into dimensionless units with the transformation

\[
x = \sqrt{\frac{k}{D} r}
\]

such that the equation becomes

\[
0 = \frac{d^2 c}{dx^2} + \frac{1}{x} \frac{dc}{dx} - c
\]

We can then multiply through by \( x^2 \) to arrive at the modified Bessel equation:

\[
0 = x^2 \frac{d^2 c}{dx^2} + x \frac{dc}{dx} - x^2 c
\]

The solution is a modified Bessel function, and because of our boundary condition that \( c(r) \) decays to zero as \( r \to \infty \) we pick as our solution the modified Bessel function of the second
kind, $K_0(x)$, such that $c(r) = c_0 K_0 \left( \frac{r}{2D} \right)$. This function has asymptotic forms

$$K_0(x) \simeq \begin{cases} 
- \ln \frac{x}{2} - \gamma & \text{for } x \ll 1 \\
\sqrt{\frac{x}{2\pi}} \exp(-x/2) & \text{for } x \gg 1
\end{cases}$$

where $\gamma \approx 0.577$ is Euler’s constant.

To understand the typical values of $x = \sqrt{\frac{r}{2D}}$ we need to be able to estimate $D$ and $k$. To estimate the diffusion coefficient of the repellent we must assume some properties of the molecule. Let us take it to be a spherical particle with the typical size of a protein molecule, about 4nm, such that it has a radius of $r = 2$nm. If we assume a temperature of about 300K and a viscosity of water, then we compute the diffusion coefficient through the Einstein relation:

$$D = \frac{k_BT}{\gamma} = \frac{k_BT}{6\pi\eta r} = \frac{4 \times 10^{-21} \text{J}}{6\pi(0.1 \text{cP})(2 \text{nm})} \approx 100 \mu\text{m}^2/\text{s}$$

Although we can estimate $D$, the decay constant $k$ of the repellent molecule in unknown since the identity of the molecule is unknown. We do know, however, that the length $\sqrt{\frac{D}{k}}$ is the relevant scale of the Bessel function decay. We can therefore associate our repulsion length scale $r_0$ with this quantity: since our repulsion force decays with length scale $r_0$, these two quantities $r_0$ and $\sqrt{\frac{D}{k}}$ describe the same thing. Making this association, we can re-write the asymptotic forms of the concentration profile in terms of $r$ and $r_0$:

$$c(r) \approx \begin{cases} 
- \ln \frac{r}{2r_0} - \gamma & \text{for } r < r_0 \\
\sqrt{\frac{4\pi}{2\pi}} \exp(-r/2r_0) & \text{for } r > r_0
\end{cases}$$

(4)

Note that $K_0(r)$ diverges as $r \to 0$, meaning that the concentration profile diverges at the origin. This mathematical result does not prevent us from proceeding because we are in fact not interested in the behavior at or very near to the origin. Indeed, the cell has a finite radius $L/2 \approx 5 \mu\text{m}$, meaning that we are only interested in the solution where $r \geq L/2$, which does not diverge.

We can now use Eq. 4 to help justify our choice of the exponentially decaying repulsion force described in Section 2.1. If we assume the repulsion “force” (see Sec. 2.1) is proportional to the gradient (a similar assumption is made in, for example, ref. [34]), then our assumption that the force is exponential translates into an assumption that the concentration gradient, and thus the concentration profile itself, follows an exponential decay. Fig. 13 shows the Bessel function theoretically derived here compared with the simple exponential decay assumed in the model. We see that the two functions deviate significantly for small $x$, but that they both follow the same general shape and decay exponentially in a similar manner for large $x$. Of course, an exact match between the Bessel solution and our model is not necessarily the goal: because the dynamics of the repellent are likely much more complex than that which we discuss here, we instead would like to pick the simplest function that decays and captures the general behavior of the system. Indeed, the concentration gradients may not only be caused by diffusion and degradation, but perhaps also by enzymes secreted by the cells that degrade the repellent, thus causing much more complex concentration profiles. If such enzymes are secreted
Figure 13: The modified Bessel function of the second kind $K_0(x)$ (blue) compared with a simple exponential decay $e^{-x}$ (purple). The two functions deviate significantly for small $x$ because the Bessel function diverges at zero, but the two functions follow a similar decay for larger values of $x$.

by the cell, they would be more concentrated nearer to the cell (i.e., $r \approx L/2$) and then the true concentration would be lower than the Bessel solution for small $r$, as is our exponential model (Fig. 13). In short, the simple exponential approximation is a reasonable choice for this model given that the model does not attempt to mimic the true concentration profiles with quantitative precision.

Finding the production rate $\Gamma$. In the above calculation we assumed as a boundary condition that the cell produces repellent at some constant rate $\Gamma$, but did not specify the rate. To complete the picture of the 2D diffusion model, we now estimate this analytically. Fick’s first law of diffusion tells us that the flux (which has units of concentration per length per time in two dimensions) of repellent is given by

$$J = -D \nabla c$$
$$= -D \frac{\partial c}{\partial r} \hat{r}$$

in the radially symmetric case. We are interested in the outward flux at the cell boundary $r = L/2$, since this can be related to the repellent production by the cell. Since $L \ll r_0$ (in our simulations $L/r_0 \approx 0.1$), we can use the small $r$ approximation in Eq. 4,

$$c(r) = c_0 \left( -\ln \frac{r}{2r_0} - \gamma \right)$$
$$\frac{\partial c}{\partial r} = -\frac{c_0}{r} \hat{r}$$

when $r \ll r_0$. Then the flux is given by

$$J = D \frac{c_0}{r} \hat{r}$$
Figure 14: If a Dicty cell moves quickly compared to the diffusion time scales of the repellent, it feels its own gradient, leading to more persistent motion.

To compute the rate of repellent production $\Gamma$ we then integrate along the circumference of the cell

$$\Gamma = \int_C J(r = L/2, \theta) \cdot \hat{n} ds$$

where $C$ is the circular curve around the cell, $\hat{n}$ is the normal vector and $ds$ is the scalar differential following the curve $C$. Because $C$ is a circle around the origin, in this case $\hat{n} = \hat{r}$. Then,

$$\Gamma = \int_C \frac{Dc_0}{L/2} (\hat{r} \cdot \hat{r}) ds = 2\pi (L/2) \frac{Dc_0}{L/2} \Gamma = 2\pi Dc_0$$

(5)

The quantity $\Gamma$ has units $[\mu m^2/s][\text{particles}/\mu m^2] = [\text{particles/s}]$ and thus is a rate of repellent production as expected. Note that since we are using the asymptotic limit of $r \ll r_0$, the degradation rate $k$ does not appear in this expression. In general, this quantity should depend on $k$, since the when the degradation rate is higher one must supply more particles at the source.

We now have a complete picture of our simple model. If the repellent is identified it would be interesting to estimate these parameters and ask if the above production rate is plausible given the machinery available to the cell.


4.2 Self-repulsion

The model presented here considers how a given Dicty cell is repelled by all other cells in the vicinity, but does not consider how the cell responds to its own repellent. As discussed above, the realistic picture of repulsion is that each cell emits some repellent molecule which then forms a concentration gradient centered at the cell. Consider a Dicty cell moving very quickly, so that the concentration gradient of the repellent molecule has not yet changed on the time scale of the moving Dicty. The cell will then be at a position where there is a concentration gradient due to its own repellent. There is no reason to believe that a Dicty cell can differentiate its own repellent from that of another cell center. Thus the effect of self-repulsion is to increase persistence, because the gradient seen by the cell is one which causes it to continue moving in its original direction. See Figure 14 for an illustration of this effect.

If most of the repellent gradient felt by a cell were its own gradient, then our repulsion model would not be interesting as the model would mainly describe persistent motion due to one’s own gradient; the cell-cell communication would be unimportant. Therefore, we would like to show that the main source of concentration gradient sensed by a Dicty is from repellent produced by other cells, not by itself. The intuitive justification for this fact is that the concentration gradients change quickly on the timescales of the motion of a cell, so that by the time a cell moves the gradient has already reached a new steady-state and thus it does not feel its own gradient significantly.

We estimate the effect of self repulsion by considering the ratio of timescales of the gradient and the Dicty. In particular, we compare the times it takes a change in the gradient to propagate a distance $r$ and compare it with the time it takes a Dicty to move the same distance $r$. The speed of Dicty is known to be about $0.1 \mu m/s$; thus, we know the time it takes a Dicty to move a fixed distance $r$ from the origin: $\tau_{\text{dicty}} = r/v$. We would like to understand the corresponding timescale for the concentration profile to change over a distance $r$. We estimate this by considering the result of removing the source altogether at $t = 0$ and estimating the time it takes for the concentration gradient to feel this change at some distance $r$ from the origin. We accomplish this with a simple dimensional argument. The parameters of interest are the length $r$, the diffusion coefficient $D$, and the degradation rate $k$. The timescale $\tau_{\text{gradient}}$ should be increasing with $r$ since the disturbance takes longer to propagate farther from the origin. It must be decreasing with $k$ and $D$, because these numbers represent rates at which the concentration changes. Given these criteria, the unique combination the yields a time scale is

$$\tau_{\text{gradient}} \propto \frac{r}{\sqrt{kD}}$$

where we have used $r_0 \equiv \sqrt{\frac{D}{k}}$ as above. Then the ratio of the timescales is given by

$$\frac{\tau_{\text{gradient}}}{\tau_{\text{dicty}}} = \frac{r_0 v}{D} \approx \frac{(100 \mu m)(0.1 \mu m/s)}{100 \mu m/s} = 0.1$$

This simple dimensional argument indicates that the timescales of the gradient are likely shorter than the timescales of the moving Dicty. Of course, a dimensional argument is not rigorous and leaves out an undetermined prefactor. It may be possible to estimate this prefactor by
analysis of the diffusion equation, either numerically or analytically. However, estimating a more precise prefactor will not necessarily lead to conclusive results: the above ratio depends on $r_0$ (or, alternatively, $k$), an unknown length that is very difficult for us to estimate and whose value may fall within a range of several orders of magnitude. Thus we leave it as future work to improve this calculation should experimental data become available. See ref. [34] for an in-depth discussion of self-repulsion.
5 Discussion

The results presented here indicate that repulsion improves foraging efficiency in *Dictyostelium*. Furthermore, in silico evolution simulations show that if repulsion has an evolutionary cost in the correct range, an evolutionary branching process exists in which some Dicty evolve to produce repellent whereas others do not. This result may explain the existence of variability among cellular slime molds with respect to the production of, and sensitivity to, chemical repellents.

5.1 Implications and speculations

Speciation vs. switching: two interpretations. Our results suggest that two types of cells with different repulsion strengths can coexist. From a game theory standpoint, this means that when they exist in the correct proportions, cells with these two repulsion strengths have the same fitness. As discussed in Sec. A.3, we can interpret this fact either as (i) there being two different species with the two different repulsion strengths, or as (ii) that each single individual is switching between two different repulsion strengths.\(^{11}\) Thus, our results point either to one species switching between different repulsion strengths, or to two different species of amoebae which repel different amounts. Experiments are required to differentiate between these cases. KB's [9] findings show that while Dicty cells repel each other, *Polysphondylium* cells do not. Furthermore, KB found that while *Polysphondylium* cells are repelled by Dicty, the converse is not true. This is very suggestive of situation (i), a coexistence of two types, \(R_1 = 0\) and \(R_2 > 0\) where \(R_2\) depends on the cost function. Thus KB's results provide a possible explanation for interpretation (i). Although there is no direct experimental evidence for (ii), it remains an interesting possibility.

Selective cheating: do cells know when to cheat? Our results show that in a population of repelling Dicty, if one Dicty does not produce repellent its fitness may be higher than the others (Fig. 8b) because the non-repelling individual can still sense the repelling individuals and stay clear of them. One possible interpretation of this data is that different species repel each other, but when they come in contact with another species they turn off their repulsion mechanism and start to take advantage of the repelling species. This is a possible extension of interpretation (ii) above. Such a scheme would require the kin recognition: the amoebae would have to know whether or not the surrounding amoebae were related. If the different species use different repellent molecules, then kin recognition could be accomplished by sensing which of the repellents are present. Note that the discrete switching strategy described here can easily be generalized into a continuous strategy: a species senses the relative concentrations (or gradients) of different repellents and thus "computes" the relative abundance of related vs. unrelated amoebae. Based on this quantity the amoeba produces a corresponding amount of repellent, this being an increasing function of the number of kin in the vicinity.

Consequences of spreading out. Sec. 1.3 raises the idea that if cells aggregate over a smaller area, the aggregate slug is less likely to contain non-identical strains and thus the

\(^{11}\)This is called a “mixed strategy” in game theory.
aggregate is less susceptible to cheaters. This logic points to a disadvantage of repulsion, since repulsion causes cells to spread farther apart. Spreading out is disadvantageous not only because of cheaters, but also because if cells are much too spread out aggregation might not be possible at all. How can we reconcile these problems with the repulsion strategy presented here? One resolution comes from the cell divisions neglected by our model: even if cells are spreading out, they are constantly dividing and thus their density will not decrease indefinitely except in cases of extreme repulsion. Another resolution is that we have only considered the perspective of cooperative repelling Dicty. The previous paragraph discusses the possibility of switching cells that can take advantage of the repulsion of other cell types. These switching types may in fact want to spread out so that they can more easily invade the territory of repulsive cell types.

5.2 Future work

Attraction to bacteria and non-uniform food distributions. As discussed in Sec. 1.1, Dicty cells are thought to chemotact towards bacteria via folic acid; furthermore, either by this mechanism or another, it has been observed that when a Dicty cell encounters a colony of bacteria it is able to stay and feed on the colony until it is depleted [13]. Incorporating these attraction mechanisms into the model could prove interesting. The zoomed in picture of a Dicty extending pseudopodia and following bacteria (as in Fig. 1a) might be too detailed to incorporate this type of simulation study, but a long-range attraction to bacteria may be important. Such an attraction, when implemented, appeared to have little qualitative effect on the results (data not shown). The reason for this lack of effect is that our simulations use uniform and dense food distributions, and as such the attraction from many randomly located food particles tends to cancel out except at small distances: when the Dicty comes very close to a food particles, the attraction from that bacterium dominates and the Dicty is “sucked in” to the potential well and eats it. Then the attractive force acts simply to increase the effective size of the bacteria, or, conversely, the effective size of the Dicty cells. This leads to a higher foraging rate but no quantitative difference in the results.

For non-uniform food distributions, however, these effects may play an important role. Firstly, to analyze the case of non-uniform food distributions, some adjustments to the model would have to made. One important adjustment would be to relax the assumption that eating is instantaneous, since a Dicty cell takes several hours to eat an entire colony . Preliminary experimental data indicates that while this feeding on a colony occurs, other Dicty may be attracted to the feeding ground [13]. This may be an “intentional” effect, i.e., some genes in the Dicty intentionally case the attraction. This could happen if the attraction is evolutionarily beneficial to the genes of the feeding individual, since highly related Dicty will be attracted to the feeding ground. Such an effect might be possible because the cells in a localized area tend to be genetically identical. However, such an explanation is not robust to cheaters that do not attract other Dicty to food-rich regions. Thus we should also seek some selfish motivation for attracting others, as in the case of the foraging cliff swallows described in Sec. 1.2 that were able to better track insect swarms once more foragers arrived. Perhaps, for example, it is biologically advantageous to eat the colony of bacteria as quickly as possible, and thus signaling others to join is important. Another possibility is that this effect is “unintentional”, i.e., genes of the Dicty have no control over the the attraction. In such a case it is possible that the
attraction have no benefit to the individual. A possible explanation is a “messy eating” theory: that the feeding process produces a by-product that attracts other Dicty. It is reasonable to suppose that, if such a by-product exists and can diffuse freely, Dicty would evolve to chemotact towards it.

In any of these cases, the attraction would need to be stronger than the repulsion so as to overcome it. After the food is depleted, the repulsion would again dominate, which would help to effectively spread out the concentrated group of Dicty. Measuring the way in which Dicty disperse after a bacterial colony is depleted is another way that one could measure the possibility of repulsion.

**Evolution simulations with group fitness.** The evolution simulations presented here are competitive in nature; each individual has its own fitness and reproduces accordingly. However, as discussed in Section 1.3, the nature of Dicty is neither entirely competitive nor entirely cooperative. Thus, it would be interesting to perform evolution simulations in a more cooperative framework. Section 5.1 discusses the two interpretations of the stable coexistence of Dicty with different repulsion strengths: one in which multiple species exist, and another in which Dicty of the same species switch their repulsion mechanisms during their lifetimes. By mixing these two interpretations we can imagine a situation in which Dicty of two species are competing, and each one can actively switch its repulsion mechanism, presumably in different manners. In this case we cannot label the different types of Dicty just by their repulsion strength: we must separately take note of which species they belong to. Then one can ask if a stable coexistence between these two species exists, or if one takes over the other. Evolution simulations can be performed by computing the fitness of each individual not just by its own foraging rate, but also by incorporating a contribution set by the fitness of its entire species. A simple implementation could compute the fitness as the sum of the individual fitness and the group fitness weighted by some tunable parameter representing the relative importance of group fitness to the individual.

**Self-avoiding walks.** It has been observed that when foraging in regions of high food density, Dicty perform a self-avoiding random walk on long timescales [13]. Such a strategy prevent Dicty from retracing over already explored paths, and thus serves to improve foraging efficiency. One explanation for this phenomenon is that the cells lay down a track of slime which contains a repellent chemical, and thus they tend to avoid previously explored areas. However, this is not the only possible explanation: an attraction to food may be enough to explain this phenomenon, because if Dicty are attracted to food they are effectively repelled by areas without food, i.e., those paths they have already explored. It would be interesting to study these dynamics both through simulation and theoretical polymer-physics analyses. Furthermore, if a repulsive track is lain down by the Dicty, it would be an extremely challenging but interesting task to purify the repellent both in the repulsive slime and in the diffusive repellent considered in this thesis, and to ask if they are the same molecule.

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12 See refs. [35, 36] for a discussion of the evolution of cooperation with simulation techniques.
Data and correlation functions. Figure 4 shows that when repulsion is turned on, a corresponding dip appears for low distances in the Dicty-Dicty distance correlation function. It would be interesting to analyze data of Dicty motion tracks in order to identify whether or not such a dip in the correlation function actually exists in real foraging data. Such an experiment would not only provide further corroboration for the discovery of Dicty repulsion, but would also yield access to more quantitative information about the nature of the repellent. For example, the shape and size of the dip in correlation function could help us understand the effective range of the repulsion. This would be a good way to measure repulsion just from watching Dicty forage; identification of the particular repellent molecule is not needed.

Identifying the repellent. The existence of a repellent molecule was discovered by KB in 1977 [9] and has since been confirmed by other experiments [10]. However, in more than 30 years since this discovery the identity of the repellent molecule remains unknown. Finding this repellent is a crucial step in understanding the system as it would facilitate many further experiments. For example, we might ask if a given Dicty repels a constant amount or if it switches between different repulsion strengths as suggested in Section 5.1. Identification of the repellent would also allow for experimental verification of the simulations performed here, for example by attempting to genetically knock out the repellent and examining the effect on foraging efficiency.

Adaptive dynamics theory. Our simulations results show a branching process which causes a coexistence of two different $R$-values. To accompany these simulations, one would like to find a theoretical explanation for this phenomenon. The field of adaptive dynamics contains the appropriate tool set for this type of problem. Adaptive dynamics combines the concept of frequency dependence from game theory with the tools of population dynamics [37]. Frequency dependence is the phenomenon that the fitness of a mutant depends on its frequency in the population; it is essentially that effect illustrated in Fig. 8. Population dynamics is the mathematical modelling of inheritance of traits in a population. In particular, adaptive dynamics combines these concepts to mathematically determine whether or not a mutant can invade a population previously in equilibrium. To do so one must parametrize the different cell types with a real number; in this case, the repulsion strength $R$ is the natural parametrization (although one could extend the model to include the repellent sensitivity $S$ as well). A review of adaptive dynamics can be found in ref. [37].

A repulsion strength continuum? The above discussions demonstrate the possibility of a coexistence between two types of Dicty. Apart from considering coexistence of discrete types, we can also ask if a continuum of $R$-values is possible. In particular, for a given cost function, can a continuum of $R$-values represent an ESS? First, let us consider the case of only two types as in Fig. 8. In this case, we picked an arbitrary cost $C = 0.1R$ to go from Fig. 8a to Fig. 8b and found the two curves to cross at one point. This would have been the case for any linear cost function within a reasonable range (cost functions with strong nonlinearities might lead to several crossings). The intuition here is that once a cost is added we can choose one parameter (the proportion of cheaters $\alpha$) in order to solve one equation (the crossing of the two curves).
Let us now consider the case of three types. The fitnesses are now functions of two variables: namely the two parameters $\alpha$ and $\beta$ representing the relative frequencies of the three types. To find an ESS with the three types we require the three fitness landscapes to cross at a single point: thus, we must solve two equations in two parameters, $\alpha$ and $\beta$. Again, this may be possible for well-behaved fitness functions. Clearly, this concept generalizes: with $n$ discrete types, an ESS may exist as the solution to $n - 1$ equations in $n - 1$ variables. As $n \to \infty$, the set of $n$ discrete types becomes a continuum of repulsion strengths.

Although a continuum of repulsion strengths may be possible in theory, the results of Fig. 11 indicate that such a continuum may not constitute an ESS for realistic fitness functions in the Dicty foraging system. It would be an interesting direction of future work to analytically understand the necessary conditions on the fitness landscapes such that a repulsion continuum ESS might be possible.

5.3 Conclusion

In 1977 Keating and Bonner discovered repulsion by *Dictyostelium* when in the vegetative amoeba state. Since then, it has been suggested that repulsion may play a role in foraging, but neither the identity of the repellent nor its function have been determined. This thesis demonstrates that repulsion improves foraging efficiency for simulated foraging amoebae, and thus suggests that it would be beneficial for Dicty to have evolved a repulsion mechanism. Our results also shows that although repulsion is beneficial, non-repelling cheaters can invade the population and a stable coexistence between the two types is possible. This result may explain KB’s experimental result that while *Polysphondylium* cells are repelled by Dicty, the converse is not true. Finally, our results are not limited to Dicty and illustrate an interesting phenomenon in foraging theory generally: that even in cases of uniform food distributions, communication between foragers can confer benefits to the population.

Acknowledgements

I would like to thank my advisor Ned Wingreen for enthusiasm and support from start to finish. I feel very fortunate to have worked on this project with such a great advisor. Thanks also to Iain Couzin for helpful comments and the use of the GPU computing cluster; to Colin Torney for help with CUDA programming and using the computing cluster; to Thomas Gregor for serving as my second reader; to Joonas Govenius for UNIX hacksors; and to all members of the Wingreen and Couzin labs for listening to my presentations and providing feedback.
A Game Theory primer

A.1 Definition of a strategy

To begin the discussion of game theory we must define the concept of a strategy. A strategy is the set of rules of a player decides to follow before the game begins, and is in general contingent on the moves of the other player. For example, a strategy for how to play a game of chess would contain one’s move in every possible contingency of the game (this is, of course, much too complicated for anyone to every write down). Thus, when the strategies of both game are determined, the entire game is predetermined. Of course when actually playing chess it does not seem as if the game is predetermined. This is because in reality an entire strategy is much too complex for sometime to decide in advance, and thus a player “decides” what to do each move. Thus what we refer to as a “strategy” in chess is not the same as the precise definition of strategy we use to in discussion of game theory.

A.2 The Prisoner’s Dilemma and Nash Equilibria (NE)

The Prisoner’s dilemma is one of the most famous games in game theory. The associated story as as follows: two criminals are caught by the police and asked to implicate the other. If both keep quiet then there is insufficient evidence to give them a long sentence, and therefore both receive only a short sentence (say, one year). If only one talks, however, he is let free in exchange for the information and the other is given a long sentence (ten years). If both talk then they both receive a medium sentence (seven years; they are forgiven three out of the ten years for giving information). Such a game can be represented by a “payoff matrix” as follows:

<table>
<thead>
<tr>
<th></th>
<th>player 2 keeps quiet</th>
<th>player 2 talks</th>
</tr>
</thead>
<tbody>
<tr>
<td>player 1 keeps quiet</td>
<td>-1, -1</td>
<td>-10, 0</td>
</tr>
<tr>
<td>player 1 talks</td>
<td>0, -10</td>
<td>-7, -7</td>
</tr>
</tbody>
</table>

The numbers in the payoff matrix shows the payoff (“utility” in economics terms; “fitness” in biological terms) to each player in each of the four cases (the format is that the payoff to player 1 is listed first in each box). Because higher payoffs are preferred, the payoffs in this case are given by \(-1 \times \) the number of years in prison.

The basic tragedy of game theory lies in the fact that if both players behave rationally, then they will both talk. The intuition is the following: consider the game from player 1’s perspective. If player 2 keeps quiet, then player 1 is better off talking so that he is let free instead of serving one year. If player 2 talks, then player 1 is also better off talking, because is sentence is then seven years instead of ten. Thus, regardless of the action of player 2, player 1 is better off talking. The same logic of course also applies to player 2, and thus both will talk. This situation is called a Nash Equilibrium (NE). A NE is defined as a set of strategies under which no player would have been better off by playing differently. Note that the NE of the Prisoner’s Dilemma is the situation with the lowest total fitness (-7 + -7 = -14).

Mixed strategies. Thus far we have discussed strategies as deterministic entities, such as a strategy describing each move in a game of chess that depends only on the previous moves. However, one could also envision a case where one’s strategy involved randomization. Continuing with the example of chess, it seems unreasonable that randomizing could help one win a
game. Likewise, in the case of the Prisoner’s Dilemma it is clear that talking is the best option, and randomization could only hurt. Thus we move to a new example, the game of pennies. In this game, each of two players has a penny and places it on the table as either heads or tails. If both players play the same move, player 1 wins. Otherwise, player 2 wins. The payoff matrix looks like this:

<table>
<thead>
<tr>
<th></th>
<th>heads</th>
<th>tails</th>
</tr>
</thead>
<tbody>
<tr>
<td>heads</td>
<td>1, -1</td>
<td>-1, 1</td>
</tr>
<tr>
<td>tails</td>
<td>-1, 1</td>
<td>1, -1</td>
</tr>
</tbody>
</table>

In this game, if player 1 suspects that player 2 will play heads, he will also play heads, and so forth. Imagine, for example, a case in which the strategy of both players is to play heads. This is not a NE because player 2 can do better by playing tails. But if player 2 played tails, we would also not have a NE because then player 1 would want to play tails. In fact, if one player has any prior information as to the move of the other player, then he will play accordingly, and then the other player will play accordingly, and so on. This chain of reasoning indicates that if any play has information as to the other players intentions, a NE is not possible, because the original player will “regret” letting that information be known. Then the only way to construct an equilibrium is in such a way that both players have no information about what the other player will play. This means that both players must randomize with probability one half, i.e., both players should just flip the coin.

It is in this explanation that the above definition of a strategy becomes crucial. Even if both players are planning on playing heads, one can argue that player 2 has no information that player 1 is going to play heads, and thus will only regret afterwards his decision to play heads. This is the wrong framework in which to think about Nash Equilibria. Instead, we can turn to another definition of a NE as a situation in which no player has any regrets about his move after the game is resolved. This framework is exactly the one we need to understand evolutionary biology, because evolution is an infinitely repeated game, and players will always be “correcting their mistakes” until an equilibrium is reached.

The result of the pennies game is enlightening for several reasons. First, it shows us that in some situations the only stable situations are ones in which some or all players randomize. (At the risk of belaboring the point: it is not the strategies themselves that are random; rather, the strategies are determined \textit{a priori} and just encode for randomization in some or all cases). Second, it brings to light the key criterion for random or “mixed” strategies: for a player to randomize between two or more options, he must be indifferent to all such options. In the case of the pennies game, this is clear: given that player 1 is randomizing with probabilities 0.5, player 2 is indifferent between playing heads or tails because in each case his expected payoff is 0. If, given the strategy of player 1, player 2 were to prefer tails to heads, even slightly, then it would not be equilibrium behavior for him to ever play heads, since he could have done better (on average) by playing tails with probability one.

Note that when considering mixed strategies we must always consider the expected payoff, not the payoffs of particular realizations of the game. For example, if both players randomize in the game of pennies then one player will lose and thus he will regret randomizing instead of just playing the opposite strategy. This “regret” is not meaningful, because \textit{before} knowing the outcome of the randomization the player could not have picked a better strategy than...
randomization. We see that the expected payoff is zero for each player, and this cannot be improved upon in this symmetric zero-sum game.

A.3 Evolutionarily Stable Strategies (ESS)

As mentioned above, evolution can be thought of as a repeated game: in each generation, every individual competes with its strategy (namely, its genes). At the end, some individuals perform better than others and the situation repeats. The populations that we observe in nature are those that are stable and persist for many generations. Evolution is, of course, noisy and thus complete stability over infinite time is not feasible. This is partly because the environment itself (i.e., the terms of the game, or the entries of the payoff matrix) changes slowly with time due to external factors like climate changes on Earth. However, it is still of interest to look for strategies that are robust to small changes in the genetic material because these strategies will persist for long enough time scales for us to observe them.

To discuss stability of evolution we introduce the concept of an Evolutionarily Stable Strategy (ESS). One can think of an ESS as a more specific case of the NE: an ESS occurs when all individuals in a population cannot do better by changing strategies. The phrase “changing strategies” means two things. First, an individual could change its behavior and thus play a different strategy. Second, an individual could mutate and become a slightly different individual in the next generation. Note that from the purely mathematical perspective the difference between these two scenarios is not important: in either case, an ESS is simply a type of NE.

The above discussion lends itself to a game theoretical definition of evolution that brings useful intuition: evolution is a stochastic optimization algorithm that samples the parameter space of all possible individuals until it reaches an ESS.

A.4 A repulsion ESS in Dictyostelium

To make this discussion more concrete, let us now return to the subject of this thesis, repulsion in Dictyostelium. For simplicity, let us consider the case where only the repulsion strength $R$ is varied. In this case, the strategy of a Dicty cell is parametrized by a single real number $R$. Then an ESS is a situation in which no Dicty could, by changing its value of $R$, do better. A key property of any ESS is that all Dicty must have the same fitness. To see this, let us imagine a case where our ESS consists of a mixture of two types of Dicty, those that repel at $R_1$ and those that repel at $R_2$. Imagine further that the fitness of the cells repelling at $R_1$ is higher than the fitness of those cells repelling at $R_2$. Then, every cell repelling at $R_2$ will regret not instead repelling at $R_1$, and evolution will eventually cause these cells to change their repulsion strength to $R_1$. This this situation is clearly not an equilibrium, and thus we have shown that in any ESS all individuals must have the same fitness. Note that we have encountered this concept before: in the case of mixed strategies, the payoffs of all strategies must also be the same (see above). Indeed, this connection further illustrates the duality between the two pictures of this situation: one in which different types of individuals represent different species (ESS view), and one in which different types represent the fact that individual cells are switching strategies within their lifetime (mixed strategy view). In either picture, every individual must have the same fitness.
B Computational methods

B.1 Simulation code

The simulation code for this project was written partly in the CUDA programming language for NVIDIA GPU processors, and partly in MATLAB. In particular, the individual simulations were performed on the GPU cluster, with the update at each timestep constituting a parallel process so that the positions of $\sim 256$ Dicty could be updated simultaneously, thus reducing the computational burden of computing $N^2$ pairwise distances at each time step. The evolution simulations were run from a MATLAB client, such that the after each GPU simulation the MATLAB client would compute fitnesses and update the population distribution (i.e., the values of $R$ and/or $S$ for each cell) accordingly. All code is available upon request.

B.2 Computation of physical quantities: diffusion coefficient, distance correlation function, and persistence length

Simulation data was used to compute physical properties of the Dicty foraging system. This section discusses the details of computing each of these properties.

The effective diffusion coefficient $D_{\text{eff}}$ is computed by first smoothed with running average filter of width 5 time steps. Then, the diffusion coefficient is computed for each cell at each time by the formula

$$D_{\text{eff}}(t) = \frac{\left| \vec{r}(t) - \vec{r}(t - \Delta t) \right|^2}{\Delta t}$$

The diffusion coefficients are then averaged over all times $t \in (\Delta t, t_{\text{max}})$ for each cell. Because the velocity of a Dicty is fixed at unity in our simulations, the diffusion coefficient as above is normalized so that a random walk gives $D_{\text{eff}} = 1$.

The distance correlation function is a normalized histogram of pairwise distances between Dicty cells. For random distribution of points, the distances from one point to others is simply proportional to the area element $rdrd\theta$ and thus grows linearly with $r$ as the area element grows. Then for a randomly distributed population we expect the distance correlation to increase linearly as $r$ increases. To normalize this effect we divide the histograms by the Jacobian $2\pi rdr$. The histograms are also normalized by the Dicty density per unit area so that a uniform distribution gives a correlation function of one. When computing the correlation function the boundary effects are problematic: although after normalization the correlation function should be flat, in practice it drops for larger $r$ because there are no Dicty outside the boundaries of the arena. To overcome this problem the area is first copied into a $3 \times 3$ tiling and then the correlation function is computed from the middle arena. Edge effects are thus removed.

The persistence length $\lambda_p$ is computed as the distance traveled by a Dicty before its angle correlation drops to one half. To be precise, we find the time that solves

$$\cos(\Delta \theta_{t_{1/2}} - \Delta \theta_{1}) = \frac{1}{2}$$
where $\Delta \theta \equiv \theta_t - \theta_{t-1}$ and the compute the distance traveled in that time

$$
\lambda_p = |\vec{r}(t_{1/2}) - \vec{r}(0)|
$$

The persistence length is then averaged over all cells to give the final result.

### B.3 A basic genetic selection algorithm

In order to perform the evolution simulations we must choose a genetic selection algorithm, i.e., an algorithm defining how the population is updated at every generation of the evolution simulation. Here we first consider algorithms for the evolution simulations where each individual is given a distinct type $i$ from a set of types $I$. The most basic algorithm is based on the idea that the rate of reproduction is proportional to fitness [38]. Thus, at the end of a generation we would like to let the organisms reproduce proportionally to their fitness. We would further like to keep the population size fixed for simplicity and computational tractability. Thus, we let all populations reproduce proportionally to their fitness and then normalize, so that if $n_t^{(i)}$ is the number of type $i$ individuals at generation $t$, $f_t^{(i)}$ is the fitness of type $i$ individuals at generation $t$, and $N = \sum_i n_t^{(i)}$ is the total number of individuals, then $n_{t+1}^{(i)}$ is given by

$$
n_{t+1}^{(i)} = \frac{f_t^{(i)} n_t^{(i)}}{\sum_i f_t^{(i)} n_t^{(i)}} N
$$

This update rule is used in the simulations discussed in Section 3.3.

### B.4 The roulette wheel algorithm

The deterministic algorithm mentioned above does not capture the randomness inherent in evolutionary processes. Indeed, such an algorithm limits the end result of the simulation to be nothing more that a redistribution of the frequency of types $i$. To introduce randomness into the simulation, we parametrize the types $i$ and add a small amount noise to these values at each time step. In this study, the parameters of interest are the repellent production $R$ and sensitivity $S$. Then instead of considering the population as a mixture of different discrete types $i$ we consider a continuum in our parameter space. This framework leads to a difficulty, however. If the population contains a set of organisms whose types are represented by a continuous parameter, then it does not make sense to discuss the frequency of a particular type in the population: indeed, each individual is unique in general. Thus the concept of allowing an organism to reproduce proportional to its fitness becomes inappropriate, and a new algorithm is necessary.

The roulette wheel algorithm addresses exactly this issue. This algorithm was conceived of by De Jong in 1975 [38] and an implementation was discussed by Goldberg in 1989 [39]. The idea of the algorithm is that at each generation, a hypothetical “roulette wheel” is divided up into $N$ section where $N$ is the number of individuals, the size of each section being proportional to the fitness at the last generation. The new population (before adding noise) of $N$ individuals is then arrived at by “spinning the roulette wheel” $N$ times, i.e., drawing a random type with the associated probabilities (i.e., $p_t^{(i)} = \frac{f_t^{(i)}}{\sum_i f_t^{(i)}}$) $N$ times with replacement. The mean outcome
of this algorithm is that each type reproduces proportionally to its fitness, but randomness is also introduced. After the draws from the roulette wheel, a small amount of noise is added to the parameters of the new types. In this study I used Gaussian noise with mean zero.

The roulette wheel algorithm is, of course, not the only possible genetic selection algorithm. Other algorithms include stochastic remainder selection, stochastic universal selection, truncation sampling, and tournament selection (reviewed in ref. [40]).

### B.5 Learning rates and fitnesses

In the above discussions I have assumed that reproduction varies linearly with fitness, where fitness was implicitly defined as the amount of food eaten by a Dicty in one simulation. However, the differences in the amounts of food eaten by different types of Dicty are extremely small and thus using the food eaten as the fitness directly results in slow convergence of the evolution algorithms. To overcome this difficulty, I consider the fitness as a steeper function of the food eaten. In particular, the simulations in this study use

\[ f = \exp(\gamma F) \]  

where \( \gamma = \gamma_0(1 + \epsilon t) \) (7)

Here \( F \) is the food eaten as computed directly from the individual foraging simulations, \( \gamma \) is the “learning rate” or “gain” and \( f \) is the resulting fitness used in the updated rules discussed above.\(^{13}\) When the learning rate \( \gamma \) is large, small differences in the amount of food eaten by different types of Dicty will be amplified into very large fitness differences and thus the evolution (or, in machine learning parlance, “learning”) will proceed quickly. When the \( \gamma \) is small, on the other hand, small differences in the amount of food eaten will result in only correspondingly small differences in the fitness such that evolution will proceed slowly (indeed, note that for small \( \gamma \), \( f \approx 1 + \gamma F \)). Equation 7 shows that \( \gamma \) starts from \( \gamma_0 \) at \( t = 0 \) and decreases with time. This trick allows evolution to proceed very rapidly at first, but then slow down as the population approaches equilibrium. However, this slowdown in not drastic: we use \( 0 \leq \epsilon \ll 1 \) with typical values of \( \epsilon \approx 1/1000 \). In fact, in practice it is not always necessary to set \( \epsilon \neq 0 \) because as the population approaches equilibrium the differences in raw fitnesses \( F \) decreases as well, such that the evolution slows down without any explicit “intervention”.

The same method is used for the noise \( \sigma \) used in the algorithm described in Sec. B.4. In particular, the noise \( \sigma \) has an associated decay parameter \( \nu \) such that the noise at a given generation is given by \( \sigma = \sigma_0(1 + \nu t) \) with \( 0 \leq \nu \ll 1 \). In the case where \( R \) and \( S \) are both varies each has its own parameters: \( \sigma_R, \nu_R, \sigma_S, \) and \( \nu_S \).

\(^{13}\)The concept of a learning rate comes from optimization theory; indeed, evolution and optimization are very closely related fields since evolution can be seen as a complex method for optimizing fitness with constraints (see, for example, ref. [41]).
C Table of simulation parameters

The table below summarizes the key parameters used in the simulation experiments, and may be a useful reference for the reader.

<table>
<thead>
<tr>
<th>symbol</th>
<th>meaning</th>
<th>typical value</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>persistence strength</td>
<td>1.0</td>
<td>“force”</td>
</tr>
<tr>
<td>R</td>
<td>repellent production</td>
<td>0-5</td>
<td>“force”</td>
</tr>
<tr>
<td>S</td>
<td>repellent sensitivity</td>
<td>0-5</td>
<td>“force”</td>
</tr>
<tr>
<td>r₀</td>
<td>repulsion length scale</td>
<td>10</td>
<td>length</td>
</tr>
<tr>
<td>δ</td>
<td>Dicty-Dicty spacing</td>
<td>20</td>
<td>length</td>
</tr>
<tr>
<td>L</td>
<td>Dicty diameter</td>
<td>1</td>
<td>length</td>
</tr>
<tr>
<td>N</td>
<td>number of cells</td>
<td>2000</td>
<td>(none)</td>
</tr>
<tr>
<td>C(R)</td>
<td>cost of repelling others</td>
<td>0.1R</td>
<td>fitness</td>
</tr>
<tr>
<td>C(S)</td>
<td>cost of smelling others</td>
<td>0.1S</td>
<td>fitness</td>
</tr>
</tbody>
</table>

Note that the arena size and Dicty density are not given as a parameter. This is because these parameters are fixed by the typical Dicty-Dicty spacing δ and the number of cells N. In particular, the side lengths of the square arena and the density are given by \(\sqrt{N\delta^2}\) and \(\frac{1}{\delta^2}\) respectively.
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