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A Toy Model for the Evolution of Directed Motility

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a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Nonequilibrium systems dissipate energy and hence break time reversal symmetry. As a result, a polarization vector in such systems is allowed to couple to the system's velocity vector. Thus, one expects that, generically, a polarized nonequilibrium system would exhibit directed motion along the polarization direction. However, the coupling between the polarization and the motion may be very weak. Here we conduct a computational experiment with a model of a 1-d gas of active agents (motors) in an enclosure (cell) with polarized mechanical properties to demonstrate that (1) generic values of the parameters of the system, indeed, result in a weak directed motion, and (2) a biological evolution-inspired genetic algorithm can strongly amplify the polarization-velocity coupling in relatively few generations. This toy model suggests that directed motility (e.g., chemotaxis) may be present generically in the context of living cells, and evolution may only need to amplify the taxis speed instead of performing a much harder task of evolving the taxis from scratch.

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Chapter 1

Introduction

1.1 The evolution of cell motility

It is hard to imagine life without motion. From an evolutionary standpoint, the necessity for cellular motility is quite obvious: cells must traverse environments with nonuniform nutrient distributions while also avoiding predators. In multicellular organisms, cell motility is also essential for complex biological processes such as collective immune response and tissue repair, as well as pathological phenomena like cancer metastasis. Biologists have long studied the various mechanisms cells use to traverse their natural habitats and the evolutionary origins of such processes.

One notable class of motility machineries are bacterial flagella, long rotating filaments paired with a stator and motor used to generate thrust. These marvelous structures are composed of over 20 different proteins assembled in a temporally and spatially precise manner and allow a bacterium to swim distances of about 60 cell lengths at a time [1, 2]. Swimming eukaryotes also make use of flagella, and there is even strong agreement that the evolutionary origin of the flagellum traces back to a single ancestor of all eukaryotes [3]. Archaea use a functionally similar rotary device, the archaellum, to achieve motility [3]. However, the subunits of archaella and flagella are distinct and both use different energy sources, indicating separate evolutionary ancestry [4]. Another type of motility, cell crawling, can be achieved by various different independent mechanisms and the scientific community does not have a consensus with regard to its origins [3]. For the most part, the question of the evolutionary origins of cellular motility remains a mystery in biology [3, 5]. How could motility, such as that provided by the elaborate structure of the bacterial flagellum, have been evolved via natural selection? Some argue this could not have been the case. As in the complex hardware of a wristwatch, proponents of creationism argue that removing any component from the intricate bacterial motor of *E. coli* causes the entire system to fail, making it impossible for such a device to be attained through the incremental modifications of natural selection [6]. This claim is known as irreducible complexity and it has served as the poster-child argument for advocates of intelligent design since the 1990s.

Biologists have refuted irreducible complexity with various arguments and evidence. For instance, while chemotaxis provides an obvious evolutionary advantage to cells, it has been shown that mere random, undirected motility, is also advantageous for survival and is preferable to the absence of any motility at all [7]. This suggests an avenue of natural selection where cells can evolve random motility before moving on to developing more complicated, directed mechanisms. Furthermore, all three domains of life — bacteria, archaea, and eukarya — have evolved a plethora of different mechanisms for motility, a clear demonstration of convergent evolution [4]. This indicates that motility is much more robust than advocates of intelligent design suggest. There have also been attempts to describe pathways by which Darwinian evolution can create complex multi-part systems [8]. Recent work has also demonstrated the rapid evolution of ion processes and modularity in the *E. coli* flagellum [9]. Overall, biologists have created a large body of work that dismisses irreducible complexity. As physicists, we would like to offer a different perspective.

1.2 A physical perspective: generic motility

By abstracting away the details of biology and viewing cells as any other system in statistical physics, we argue that motility can naturally arise in living matter as a consequence of some simple physical observations. If we consider an arbitrary statistical system in equilibrium, any given trajectory in phase space is just as probable as its time-reversed trajectory. Therefore, no motion can be observed in the thermodynamic limit,

$$\langle \mathbf{v} \rangle = \left\langle \frac{d\mathbf{x}}{dt} \right\rangle = \left\langle \frac{d\mathbf{x}}{d(-t)} \right\rangle = 0. \tag{1.1}$$

However, for non-equilibrium systems, this is no longer true — the production of entropy breaks time-reversal symmetry. Thus, spontaneous motion is permitted for a nonequilibrium system. If a nonequilibrium system additionally breaks spatial inversion symmetry, one expects generically for the velocity vector to be coupled to the asymmetry vector. In the spirit of Landau, the most general way to express the velocity vector $\mathbf{v}$ of a system is a function of all other quantities of the system that could produce a vector that also respects the symmetries of the Hamiltonian. Thus, unless there exists a symmetry to prohibit the coupling between velocity and a polarization vector $\mathbf{p}$, we expect

$$\mathbf{v} \propto \mathbf{p}. \tag{1.2}$$

This simple, yet powerful, fact has been studied extensively both in experimental settings and analytic calculations. Indeed, it has been demonstrated analytically that an asymmetric passive gear immersed in a bacterial bath should experience spontaneous rotational motion [10], results which have also been confirmed experimentally [11]. Furthermore, analytic calculations have shown coupling between the velocity and polarization vectors for a system of passive asymmetric dumbbells submerged in a nonequilibrium bath [12]. Similar calculations and experiments have been done for various other systems and geometries [13, 14]. All of these serve as examples of how structurally asymmetric nonequilibrium systems can rectify random fluctuations, coupling their velocity to a polarization vector and thus achieving spontaneous motion. Why should cells be any different?

1.3 Evolution and generic motility

Living cells are constantly consuming energy: they are inherently nonequilibrium systems. Additionally, in the presence of chemical gradients, electrical fields, or mechanical stimuli, cells have the ability to polarize their structure [15]. Establishing such polarization and thus determining the front and back of the cell has been observed to be a prerequisite for cell motility [16, 17]. Thus, given the symmetry arguments in Sec. 1.2, one might expect for motility to have always been present in living cells. However, while nonequilibrium and structural asymmetry seem to comprise a minimum set of ingredients required for motility, the symmetry arguments outlined above do not provide a way to predict the strength of said motility. It may be that generic motility present in cells is too weak to be measurable, let alone useful for cellular function. It remains to be determined whether strong motility could naturally arise in a nonequilibrium asymmetric system through the amplification of the generically-present $\mathbf{v}-\mathbf{p}$ coupling via a random process such as evolution. The aim of this thesis is to answer this question with computational experiments.

Chapter 2

Methods

Motivated by biology and the symmetry arguments of 1.2, we wish to create a minimal model for the evolution of directed motility in a nonequilibrium asymmetric system. We take a computational approach, using the rigid-body physics simulation library, PyMunk [18], and design a toy system that fulfills the requirements for motility. We then present a genetic algorithm that plays the role of natural selection, used to evolve a large population of toy systems.

2.1 A minimal system capable of motility

2.1.1 System overview

The two ingredients needed for motility are 1) time-reversal symmetry breaking and 2) structural polarization. With this in mind, we designed the one-dimensional model depicted in Fig. 1. It consists of a box with two outer walls and two inner walls. There are springs at each side, each with a differing spring constant k_1 and k_2. Each spring connects an outer wall to its corresponding inner wall. Each spring has a rest length ℓ. The outer walls of the box are themselves connected by a spring with spring constant $K \gg k_1, k_2$ and rest length $L \gg \ell$. The interior of the box is filled with a dilute gas of N_m active motors. The motors do not collide with each other. The entire system, motors and walls, are subject to a viscous drag force, quantified by a parameter β which ranges from zero to one. For every second in simulation, a body loses $1 - \beta$ percent of its velocity. The total mass of the walls M is much greater than the mass of an individual motor m.

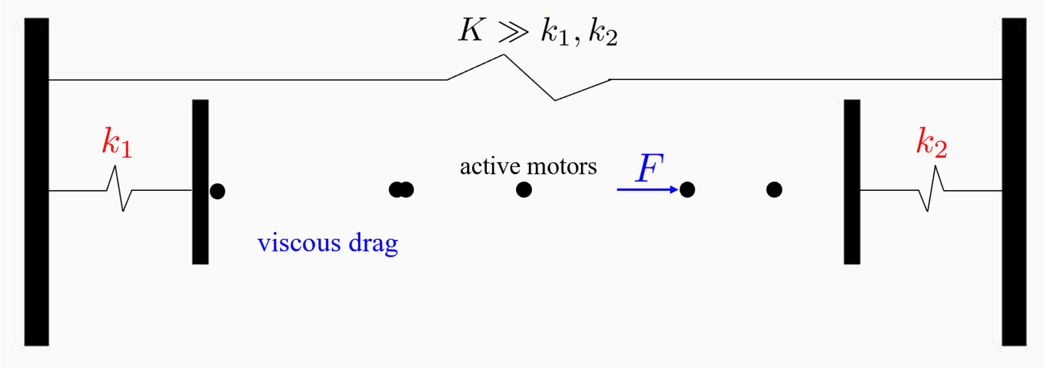

Figure 1: A minimal system that can achieve motility. The differing spring constants are responsible for the structural asymmetry. The active motors and viscous drag force fulfill the requirement of nonequilibrium. This system should exhibit generic $\mathbf{v} - \mathbf{p}$ coupling.

2.1.2 Motor details

Each motor i is driven by a force $F_i = f_i + \eta$ where $f_i \sim \mathcal{N}(f_0, \sigma_f^2)$ is a constant and η is thermal noise $\eta \sim \mathcal{N}(0, \sigma^2)$. Motors do not collide with each other and can only interact with one another by coming into contact with an inner wall at the same time. When a motor encounters an interior wall, it experiences a perfectly inellastic collision and pushes against the wall with

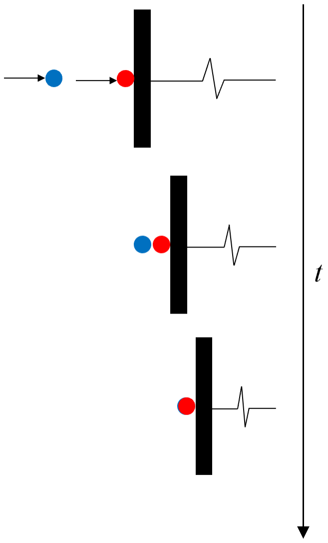

Figure 2: Motors tend to cluster when colliding with a spring at the same time. The “forget” parameter p_s prevents this.

a constant force. It continues to transfer energy to the box until the spring force overcomes the motor force. At this point, the motor force F switches direction to $-F$, causing the motor to turn around. Each motor has a constant probability to spontaneously switch direction at each time step, parametrized by p_s. Without this behavior, motors will tend to cluster into groups via the mechanism depicted in Fig. 2. Eventually, two groups of motors would be left, effectively reducing the complexity of our system and leading to uninteresting, predictable collisions between motors and the inner walls.

2.2 A genetic algorithm

Genetic algorithms are a wide class of optimization methods inspired by the biological phenomenon of natural selection. They consist of the steps in Fig. 3:

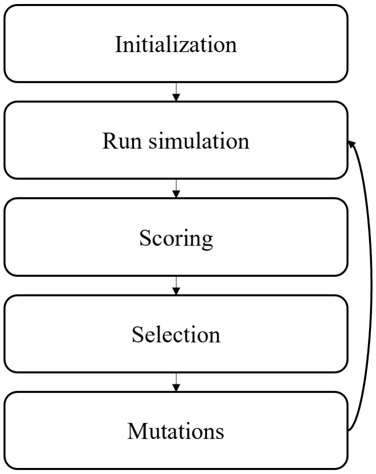

Figure 3: The general structure of a genetic algorithm. One loop through this computational graph is equivalent to one generation of simulation.

scoring, selection, and mutation. Since our goal is to demonstrate that our system can evolve directed motility via random fluctuations in system parameters, we use a genetic algorithm rather than a different optimization scheme. We are not interested in the precise $\mathbf{a}^*$ that globally optimizes model performance, nor the best initialization scheme, nor hyperparameter optimization. We are interested in determining if the model can evolve to an appreciable amount of motility without fine tuning.

2.2.1 Initialization

We initialize a population of $N = 100$ systems (Fig. 1) each with no polarization $k_1 = k_2$. We use a damping coefficient of $\beta = 0.4$. This value of β puts us in the overdamped, low Reynolds number regime, while also keeping simulation times reasonable. It is also convenient for calculations as $-\log \beta \approx 1$. Each system is filled with a dilute gas of motors with density $\rho = N_m/L = 0.02$.

Each motor is initialized to be much weaker than the springs with a mean force of $f_0/k_1\ell = f_0/k_2\ell = 10^{-3}$ and coefficient of variation $CV = \sigma_f/f_0 = 0.2$. The thermal noise is $\sigma/f_0 = 0.1$. Since the springs connecting the inner to outer walls play a role analogous to a cell membrane, we use the biologically inspired value $\ell/L = 0.02$. The "forget" parameter of each motor is $p_s = 0.01$ for each simulation second. This was empirically observed to be enough to prevent motors from clustering in the time scale of a complete simulation run. Simulations were carried out with $\Delta t = 0.01$ seconds for a total duration of 1000 simulation seconds. The duration of one simulation is of the time scale of about 50 motor-wall collisions.

Each member of the population is described by a genome, or parameter vector

$$\mathbf{a} = (k_1, k_2, N_m, \mathbf{p}_s) \qquad \mathbf{p}_s \in [0,1]^{N_m}, \tag{2.1}$$

which consists of the two spring constants k_1, k_2, the number of motors N_m, and the "forget" probabilities for each motor $\mathbf{p}_s$.

2.2.2 Scoring

Since any random, undirected motility has been determined to be evolutionarily advantageous [7], we use the velocity v of a system to determine its fitness. The velocity of such a system is a random variable $v = v(\mathbf{a})$. Computationally, v is the function that runs a PyMunk simulation of a system with parameter vector $\mathbf{a}$.

2.2.3 Selection

In the selection step, we weigh each system i according to its velocity v^i. The probability of a genome $\mathbf{a}^i$ to advance to the next population is the canonical distribution

$$p(\mathbf{a}^i) = \frac{e^{sv^i}}{\sum e^{sv^i}} \tag{2.2}$$

where s is a hyperparameter of the genetic algorithm that determines the selection strength, and in turn, convergence rate. We do not perform hyperparameter optimization. A new population of N genomes is drawn from this distribution.

2.2.4 Mutation

A mutation function μ introduces slight random perturbations to each genome $\mathbf{a}^i$ in a new population,

$$\mu(\mathbf{a}^i) = \mathbf{a}^{i'} \quad \text{with} \quad \left\langle \mu(\mathbf{a}^i) \right\rangle = \mathbf{a}^i. \tag{2.3}$$

We ran two experiments with mutation functions

$$\mu_1 = \begin{cases} k_1' \sim \mathcal{N}(k_1, 0.01k_1) \\ k_2' \sim \mathcal{N}(k_2, 0.01k_2) \\ N_m' = N_m \end{cases} \tag{2.4}$$

and

$$\mu_2 = \begin{cases} k_1' \sim \mathcal{N}(k_1, 0.01k_1) \\ k_2' \sim \mathcal{N}(k_2, 0.01k_2) \\ N_m' = N_m + n_i \text{ where } n_i = -1, 0, 1 \text{ with equal probability,} \end{cases} \tag{2.5}$$

respectively.

2.2.5 An edge case

One might suspect that the genetic algorithm will drive the population to 1) evolve a large polarization and 2) evolve to have small spring constants. This way, the motors are able to transfer more energy to the rest of the box. What should happen when a spring constant becomes so small that a single motor can push an internal wall a whole distance ℓ? At this point, the inner wall will touch the outer wall and the motor will never turn around, continuing to transfer energy to the box for eternity. This is not good. Thus, we have to amend our selection function Eq. 2.2. One fix is to simply restrict the values of k the algorithm is allowed to mutate to. We avoid this approach as it limits the parameter space and is not compatible with a system where the number of motors can change, as in μ_2. A different simple fix is to just make $p(\mathbf{a}^i)$ extremely small if at any point an outer and inner wall come into contact, regardess of what $v(\mathbf{a}^i)$ comes out to be. This is the approach we take here. One could argue that this is not a valid selection rule, as it is discrete and dichotomous. A system either experiences this penalty or not. Perhaps a better way to deal with this issue is to implement a continuous penalty function $f(r)$ that depends on the distance between the inner and outer walls r. We believe that this complication is not necessary to achieve the goals of this thesis, so we stick with our simpler, discrete selection function.

2.3 Limitations

While the goal of this paper is not the study of a particular system, but rather a demonstration of what can be achieved with a minimal model, we acknowledge that there are various limitations to our system and genetic algorithm. For example, we do not consider any coupling between the system of Fig. 1 and its environment — we did state earlier that cells often polarize their structure due to external stimuli. However, here we assume that k_1 and k_2 do not vary with time and that there is nothing outside of the box. Furthermore, the motors are swimming in the same medium that the rest of the box structure is embeded in. Thus, the unobstructed movement of motors in the interior of the system does not transfer any momentum to the rest of the box. In reality, the movement of a motor inside a cell would cause the rest of the cell to recoil back slightly, due to transfer of momentum through the medium. These are complications we do not consider here. Furthermore, the mutation function μ_2 allows populations to increase the number of motors without bound. This is clearly not possible in real systems as they are constrained by energy budgets.

Chapter 3

Results and Discussion

3.1 Sanity check

First, we observe that when there is no polarization, a population of $N = 500$ systems performs an unbiased random walk[1], shown in Fig. 4. As predicted by the arguments in Sec. 1.2 and Eq. 1.2, a lack of polarization results in no rectification of the motor forces.

3.2 Convergence to motility

If we turn on the genetic algorithm, thus allowing the spring constants to become asymmetric, $N = 100$ populations initialized with no polarization equilibrate to a non-negligible directed motility for both μ_1 and μ_2 (Fig. 5). We use distance per motor collision to quantify velocity. This takes into account the motor gas density ρ that is allowed to fluctuate across generations when

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[1] All quantities with dimensions of length presented in this chapter are in units of the system length L.

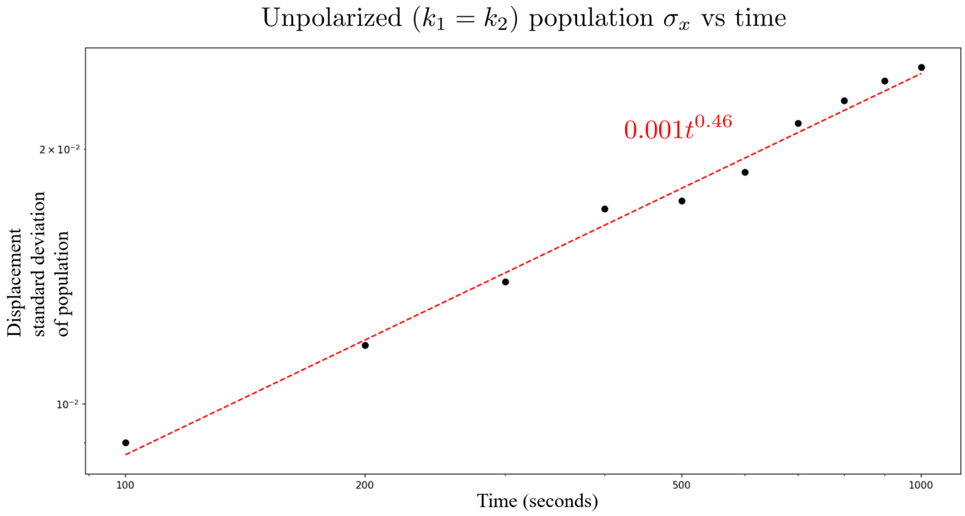

Figure 4: (log-log) The relationship between displacement and time is $x \sim t^{1/2}$, indicating that a nonpolarized ensemble of systems exhibits diffusion.

using μ_2. For instance, in the μ_2 experiments, the average number of motors per generation increases throughout the entire 350 epochs, yet, the distance per collision settles around generation 150. This form of measurement also gives a notion of how efficient the motors are at transferring energy to the rest of the system[2]. Changing the hyperparameter s changes the rate of convergence. Recall that we did not perform optimization to tune s.

Were our populations able to evolve strong motility? Let us estimate the maximum theretical distance per collision our system could have achieved. A typical motor traversing the interior of its box while undergoing a viscous drag

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[2] The y-axis contains a factor of 10^{-5} because everything is being divided by $L = 1000$ for our system as well as by the total number of collisions, which at initialization are about $\sim 50L\rho_0 = 1000$.

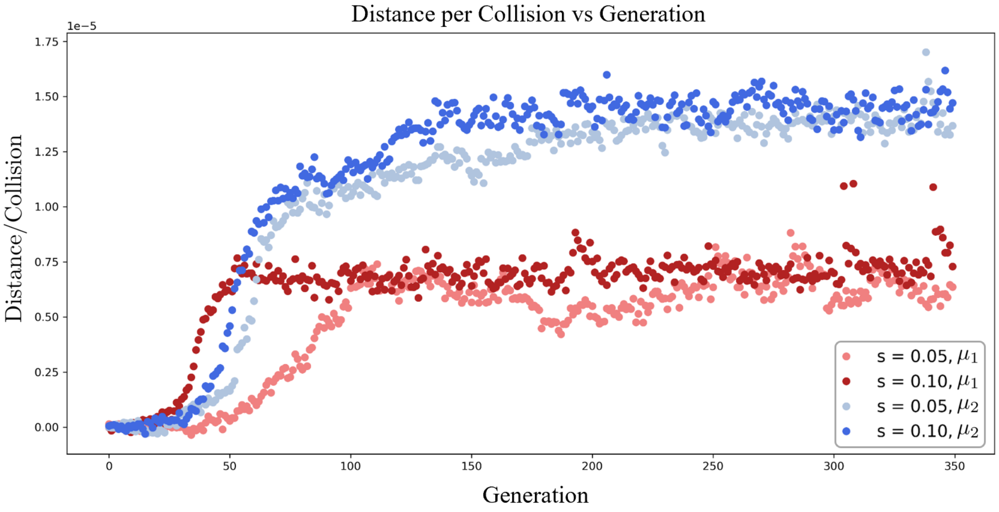

Figure 5: The evolution of four populations across 350 generations. Each population is initialized with zero polarization $k_1 = k_2$. All populations reach a steady state after about 150 generations.

force $-\gamma v$ will obey the equation of motion

$$m\dot{v} = f_0 - \gamma v \implies v_{\text{term}} = \frac{f_0}{\gamma}, \tag{3.1}$$

where m is the mass of the motor. To relate this to the β parameter in our model, we use the definition of β from Sec. 2.1.1 and finite difference to find

$$\begin{cases} v(t + \Delta t) = \beta v(t) \\ v(t + \Delta t) = (1 - \gamma \Delta t/m) v(t) \end{cases} \tag{3.2}$$

$$\implies \gamma = m \frac{1 - \beta^{\Delta t}}{\Delta t} \longrightarrow -m \log \beta. \tag{3.3}$$

Pairing this with Eq. 3.1,

$$\langle v_{\text{term}} \rangle = -\frac{f_0}{m \log \beta}. \tag{3.4}$$

An overestimate for the maximum theoretical distance per collision can be approximated by considering an elastic collision between a motor and a wall containing all the mass of the box M. The solution to Eq. 3.1 has time scale

$$\tau = \frac{m}{\gamma} = -\frac{1}{\log \beta} \tag{3.5}$$

Therefore, the maximum distance per collision is

$$v_{\max}\tau \approx -\frac{m}{M}\frac{\langle v_{\mathrm{term}} \rangle}{\log \beta}. \tag{3.6}$$

For our choices of parameters, $v_{\max}\tau \approx 3 \times 10^{-4}$. This indicates that without fine tuning, the μ_2 populations were able to converge to at least 5% the maximum theoretical velocity. The μ_1 populations converged to at least 2% the maximum theoretical velocity.

3.3 Coupling between v and p

The arguments of Sec. 1.2 also predict polarization and velocity to be strongly correlated. This is what we observe in Fig. 6.

There is a clear qualitative difference between the behavior of the μ_1 and μ_2 experiments. In particular, the curving behavior of the μ_2 experiments are an artifact of the issues described in Sec. 2.2.5. The explanation is as follows: as the motor gas density increases, which μ_2 allows, it becomes more likely for multiple motors to collide with an inner wall at the same time. The forces of each motor are additive. As the motors work together, both motors can push for a larger distance before the spring force overcomes the joint motor force. For large enough ρ, there are enough motors to push the inner wall a distance ℓ and we encounter the selectivity rule described in Sec. 2.2.5. Namely, if enough motors collide with an inner wall at once and are able to push the wall up against the outer wall, that particular system will effectively be killed off. Thus, the μ_2 experiments avoid extremely large polarizations to avoid this

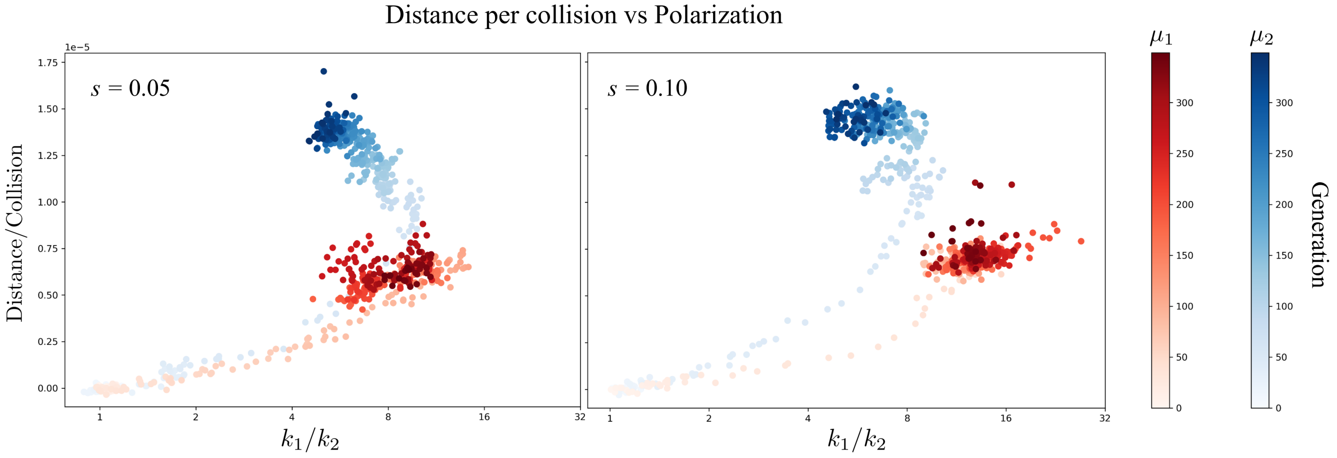

Figure 6: The correlation between distance per collision and polarization, quantified by k_1/k_2. Notice the curving of the μ_2 experiment.

selectivity rule. Notice that the red μ_1 experiments do not display such an artifact. We can further confirm this explanation by looking at the evolution of the average of the spring constants. As ρ increases in the μ_2 experiments, the average of the spring constants must also increase.

3.4 Conclusions

Our computational experiments have demonstrated that it is, in fact, possible to evolve appreciable directed motility in a generic system without fine tuning as long as the system meets the minimum requirements for generic motility. These requirements are 1) nonequilibrium and 2) structural asymmetry, features of many biological systems, such as cells. Thus, it seems plausible that evolution could have picked up on the weak generic motility found in these systems and amplified it via natural selection.

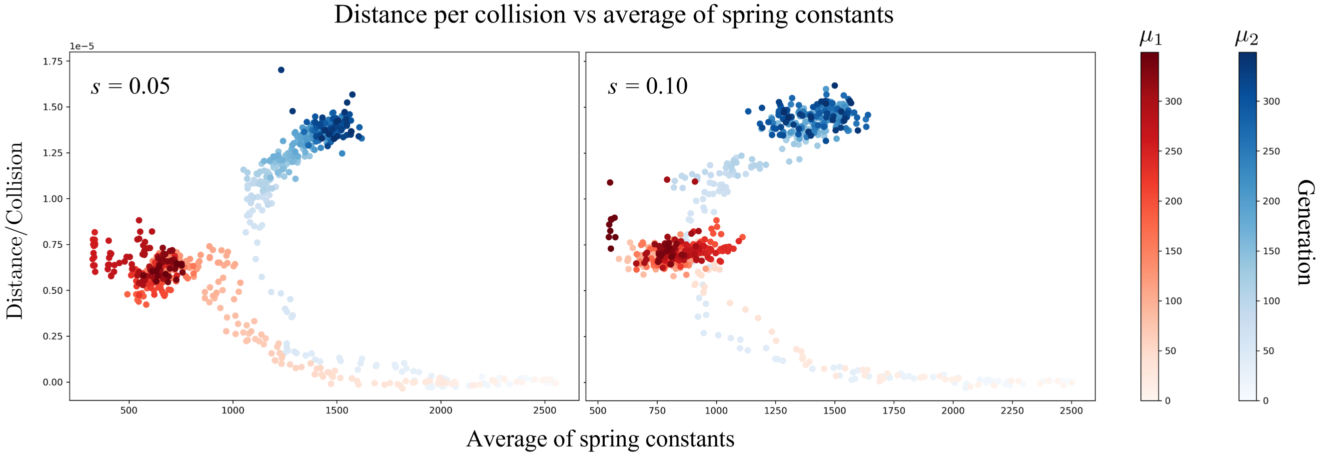

Figure 7: Correlation between distance per collision and the average of the spring constants. The average spring constant reduces across generations in all cases. This is to be expected, as this makes it easier for motors to transfer energy to the rest of the system.

3.5 Future directions

One of the most obvious improvements that can be made to our current model is to place energy constraints on μ. Unlike μ_2, which can mutate a system to have a much larger number of motors than what it started with, an energy-constrained μ would force a population to face a trade-off. Is it more advantageous to have few, strong motors, or a large quantity of weak motors? The complexity of the motors should also be increased in order to expand the parameter space and strengthen our arguments about the generic character of motility. If the convergent evolution we see in cellular motility is to offer any intuition, it should be the case that in a large parameter space, there exist multiple adequate local optima for our genetic algorithm to find.

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