

Towards Bacteria Inspired Stochastic Control Strategies for Microrobotic Swarm Intelligence

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(ABSTRACT)

Collective robotic behavior poses significant advantages over classical control methods such as system response and robustness. Biological cooperative communities have provided great insights for development of many control algorithms. Localized chemical signaling within bacterial communities is used for directed movement and dynamic density measurements. Both individual and population scale models have been created to adequately model community dynamics. These dynamics, including directed motion due to chemotaxis and density controlled functionality from quorum sensing, are modeled through an individual scale in a community scale environment. This modeling provides both a platform for analyzing the BacteriaBot engineered system as well as inspires decentralized stochastic control techniques for solving bacteria-like collaborative control problems.

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Chapter 1

Introduction

Swarm intelligence is a currently developing field with many algorithms that can be applied to achieve control solutions. The term was first introduced by Gerardo Beni in 1993 [1]. Swarm intelligence is defined by a system with many simple individuals which cannot complete a task individually but can collectively. This field develops systems which consist of many individuals which through acting collectively produce an emergent behavior that can complete complex tasks [2]. Developing collective control poses a significant obstacle for achieving a robust system behavior. Two main subsections for control involve a centralized or decentralized control scheme.

In order to adequately achieve a desired response, many parameters can be utilized. Principle parameters include the following: Proximity, Quality, Diverse Response, Stability, and Adaptability [3]. Proximity refers to an individual's ability to sense and react to local stimuli. The quality parameter refers to an individual's ability to rank the environment to a global known scale [4]. The diverse response refers to the ability of the systems response to be non-deterministic. This ideal stochastic response allows for multiple solutions to be found, and an optimal solution to be selected. The stability parameter refers to the system's ability to handle and smooth information to provide a controlled response to the environment. Adaptability suggests the system should be able to handle dynamic environments.

There are many existing algorithms for handling a form of swarm intelligence desired emergent behavior. The algorithms discussed in this thesis include: particle swarm optimization (PSO), ant colony optimization (ACO), honeybee optimization (HO), traveling salesman problem (TSP), pheromone tracking (PT), quorum sensing (QS), potential functions (PF), and flocking. Each individual algorithm contains a predictable emergent behavior that provides a solution to a task. The core tasks that these systems solve include: Scouting, Foraging, and Collective motion. All the algorithms involve mobile sensory platforms.

1.1 Control Methods

There are two main control methods for multi-robotic systems. These two methods are a centralized and a decentralized approach.

A centralized approach infers that all information for the system passes through a central location. This information center manipulates the information into commands for each individual agent for the system (figure 1.1a). This method provides excellent global information and avoids redundant processing. For applications such as networked sensing, this control method provides an advantage over the decentralized approach. As the number of agents within the system increases, the quantity of information to be processed and commands to output also increases. Often for a larger number of agents within a system, a centralized system is not plausible for real-time processing. Additionally, if the centralized control location becomes interrupted or faulty, the entire system becomes dysfunctional.

A decentralized approach distributes the information and control. Local collaboration is utilized to provide a collective effort for solving the system task. The range of this local communication is dependent upon the exact implementation of control system. Decentralized control provides parallel processing of local information (figure 1.1b). The major advantages of utilizing a decentralized control strategy include fault tolerance and the ease of scalability with large populations of agents. Due to the parallel processing of information, performance with large populations is not an issue with decentralized control methods.

Often times, a combination of both control methods are utilized. The control of the system is most often left to the individual agent (decentralized), where sensors and local interactions play a large role in decision making. The sensing and information gathering is often placed in a centralized location. This provides the benefit of collecting desired information as well as allowing for ease of scalability.

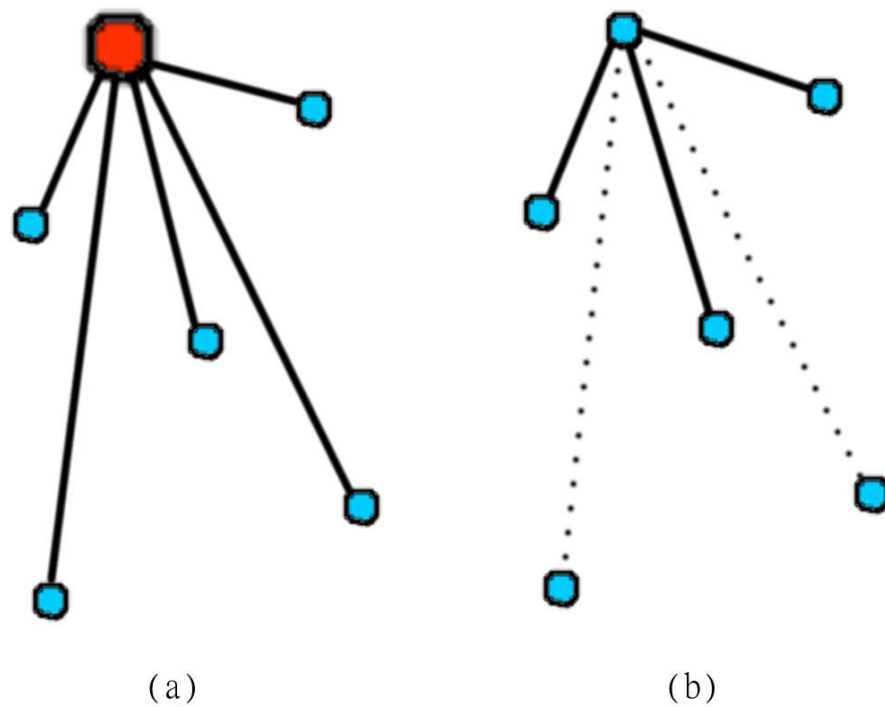


Figure 1.1: A visual comparison between the two primary control methods. (a) shows a centralized control scheme in which the central red dot signifies the central control location. (b) portrays a decentralized control scheme where the communication links are made between individual agents for local communication. Communication for a single agent is displayed with a solid line representing direct communication and a dotted line representing indirect communication.

1.2 Objective Tasks

The scouting task is the ability for a population to identify resource rich areas within an environment. Searching for resources is often a tedious task for an individual system to complete. The use of multiple agents expedites the searching process. Specific algorithms can provide solutions which attempt to optimize the searching for different criteria. These criteria can include time to identify resource rich positions, as well as time required to map an entire workspace. Often when an entire workspace must be mapped, a centralized system will be used. However when the criteria is simply to find a resource rich position, a decentralized system is more often used.

The foraging task involves the retrieval of various resources from an environment. This task can include functionality such as collective searching for resources, collective movement of resources, and path optimization for transportation of resources. The searching aspect is identical to the scouting task. However, some algorithms assume full knowledge of the workspace. Collective movement of resources involves multiple agents for the manipulation or transportation of resources. Often this aspect is solved by having multiple robots communicate locally to lift or manipulate environmental objects. Additionally, spacial constraints may make low level communication advantageous for cooperative systems [5]. The transportation of resources involves an optimization for the paths between a resource position and a deposit location, often called the hive. Transportation based foraging algorithms solve a dynamic problem for finding the lowest cost path between two or more points. This cost can be associated with multiple aspects of the system, including time required to transport resources or the length of the path required gather resources.

Collective motion tasks involve unifying movement patterns of multiple agents within a system. This movement pattern can pose solutions to grouping dynamics. Centralized control

for collective motion often provides a straight forward problem solution. However, move involved algorithms can produce complex dynamic emergent behavior with a decentralized control. This task's objective is to provide a control strategy in developing movement patterns for multiple individuals.

1.3 Existing Algorithms

The PSO algorithm is a decentralized neural network based interaction model. The idea is that local interactions in the form of a neural network can develop a desired system response. The bioinspiration for this algorithm is attributed to collective motion of animals, such as fish, birds, or mammals. The tasks that this algorithm can solve include both a scouting and a collective motion task, but implementations largely rely on the scouting task. The core algorithm involves knowing a previous best set of parameters [6]. This known best optimal set of parameters is sent through local communications. As the information propagates to other agents in the system, local maxima can swiftly be observed. This algorithm is often shown where the parameters include a quality based position in the solution space. The emergent behavior of the quality based position parameter develops a swift solution to a spatial problem. Additional quality information can be transmitted to provide insight into a solving a collective motion task. Equation 1.1 shows an example algorithm for an individual agent finding a spatial solution using local interactions and particle memory.

$$v_{t+1} = \omega v_t + \phi r(p - x_t) + \phi r(g - x_t) \quad (1.1)$$

where v is the particle's velocity, ϕ is a control parameter, r is a random number, p is the individual's optimal solution position, x is the particle's position, and g is the locally observed optimal solution position. The strength of this algorithm is in the response time of finding

the optimal solution. If the particles are initially uniformly distributed in the solution space, the optimal position can be found swiftly with fine tuned control parameters. However, as the number of agents increases and the range of the local interactions increase, the system loses efficiency due to the quantity of information that each individual has to process. The strength of this algorithm is that it both handles local maxima and discontinuities in the solution space elegantly.

The ACO algorithm is a path generation algorithm for minimizing the cost of movement. As the name suggests, the bioinspiration of this algorithm resides with ant colonies. The basis of this algorithm involves modifying the environment to label a path as being traveled. This environmental marker decays with time. The emergent behavior creates the highest concentrations of environmental markers along the path that is the shortest or most traveled [6, 7]. The longer the population has to interact with the environment, the more well defined the optimal path or paths will become. Again, the movement choices for an individual will contain some form of noise to allow for new paths to be detected. However, a balance between the probability to follow high concentrations of markers and picking a new direction must be fine tuned to produce a robust system response. This algorithm holds strengths in achieving optimal path planning in an unknown or dynamic environment. However, a disadvantage of this algorithm includes the high likelihood to fall into a local optimal solution instead of finding the global optimal solution.

The HO algorithm uses the basis of combinational searching to search an entire field for an optimal solution. This algorithm, as the name suggests, takes its bioinspiration from bees. With a desired solution for both scouting and foraging tasks, the HO algorithm can adequately and efficiently distribute networked sensors. This algorithm has two primary functions for the agents, being either a scouting agent or a harvesting agent. Until a good resource has been found, all agents take the role of a scouting agent. The scouting agents

attempt to maximize the distance between any other agents through making the desirable frequency of collisions with neighbors very low [3]. This effectively positions the agents far apart to decrease the likelihood of searching the same area twice. When a good resource has been found, a number of scouting agents switch to become harvesting agents. As a harvesting agent, they gather resources and transport them back to the hive. Upon depletion of the resource, the harvesters revert back to scouting agents. The emergent behavior that arises from this algorithm develops a dynamic response to harvesting resources. As the resources are placed or removed from the environment, the system response reacts.

The TSP algorithm is a very common form of algorithm used in the manipulation aspect of foraging. This inspiration can be observed in some species of ants which require multiple individuals to manipulate the resource they are harvesting. Individually, a single agent cannot move the resource. However, multiple agents can move the resource. This proposes a probabilistic act of recruiting nearby agents to assist with an objective [4, 8]. There are two primary states for a simplistic TSP algorithm: the searching and assisting state. More complex algorithms can include additional states depending on the desired outcome. While in the searching state, it can follow any method to search for a resource. Once a resource is found, it can be transported back to the hive or it must recruit other individuals to assist in moving the resource. While in the assisting state, there is often a cost-benefit that the individual attempts to decide upon. This probabilistic decision can be based on a large quantity of parameters, including an individual's history of choices and current position as shown in equation 1.2.

$$p(a)_{i,j}^{t+1} = f(p_{max}^t, i, j) \quad (1.2)$$

where p is the probability of selecting the new state a , at positions i, j and time t . In some

cases, ACO can be viewed as a passive TSP algorithm which utilizes the cost probabilities from concentrations of ACO's markers [7]. There is a great cost for waiting and recruiting more agents to assist with the transportation. However if enough agents assist, the resulting transported resources could provide a benefit that outweighs the cost. The act of recruiting others to provide direct assistance for an objective is where the TSP becomes very useful.

PT algorithms are a more general case of the ACO. They employ time-based signals that are released into the environment for various reasons. Modifications of the decay rate can significantly alter the emergent behavior. This algorithm can provide solutions to any task, depending on the functionality that is presented with the signals. The specific use of the PT can range from controlling the spatial density to producing tracking patterns for paths most utilized. Slowly degrading signals combined with a repulsive reaction by agents will cause homogeneous distributions within an environment without the need for an individual to know a favorable distance. Fast degrading signals with an attraction cause the agents to shift towards higher densities.

QS algorithms are a form of passive TSP algorithm that functions based on the dynamic number density of agents in an area. As an observed density approaches various thresholds, certain functionality can be turned on or off. The inspiration for this type of algorithm comes from bacterial communities expressing luciferase at high densities. The biological inspiration utilizes methods similar to a PT algorithm, with the addition that the signal can diffuse in the environment. QS algorithms can also use external systems to determine the local densities of individuals in the population [9, 10]. This algorithm's strength is in maintaining a consistent response at specific densities. The major advantage of quorum sensing is that it allows for energy cost to complete a task to be minimized when multiple agents must be present [11]. The passive communication allows for agents not detecting the high density to become metabolically dormant while waiting for higher densities to be

achieved.

Potential functions are a close relative to both QS and HO. This algorithm utilizes information gathered through potential fields. These potential fields can be sensed either through an environment or determined through agent positions. In the case of agent positions, a desired density can be created through attractions and repulsions, as shown in equation 1.3 [12].

$$\dot{x}^i = -\nabla_{x^i} \rho(x^i) + \sum_{j=1, j \neq i}^M g(x^i - x^j) \quad (1.3)$$

where ρ is the attraction function for the field, g is the attraction function for agents, and x is the individual agent. While this equation portrays a deterministic model, stochastic models can also exist for creating a bias in movement.

The flocking algorithm involves mimicry of neighboring movements. Flocking algorithms are closely related to PT algorithms but are directed towards collective movement patterns rather than uniform density clustering. This can create complex emergent patterns in dynamic movement. By applying a vector of desired movement relative to the detected direction of immediate neighbors, various complex movement patterns emerge [13]. With the application of following a parallel trajectory, the flocking population will move in the same direction. If the trajectory is not parallel, torus and corkscrew motions can occur. Even more complex patterns can emerge if the vector varies over time. Additionally, a desired distance between neighbors and a relative position is desired. This creates a lattice of connections between individuals that can be defined as per the desired lattice structure.

1.4 Summary

The various algorithms presented here can be visually sorted for their solution to the tasks as shown in figure 1.2.

Although individual algorithms can achieve the desired response, it is often seen that multiple algorithms can be combined to further optimize the desired response. Newer algorithms, such as group search optimizer, takes advantageous aspects of PSO and ACO [14]. General algorithms pose an excellent starting point for designing control systems for specific applications. Additionally, the overarching algorithms have been inspired by biological systems significantly larger than bacteria. The remainder of this thesis discusses biological inspiration and dynamics of bacteria-based systems.

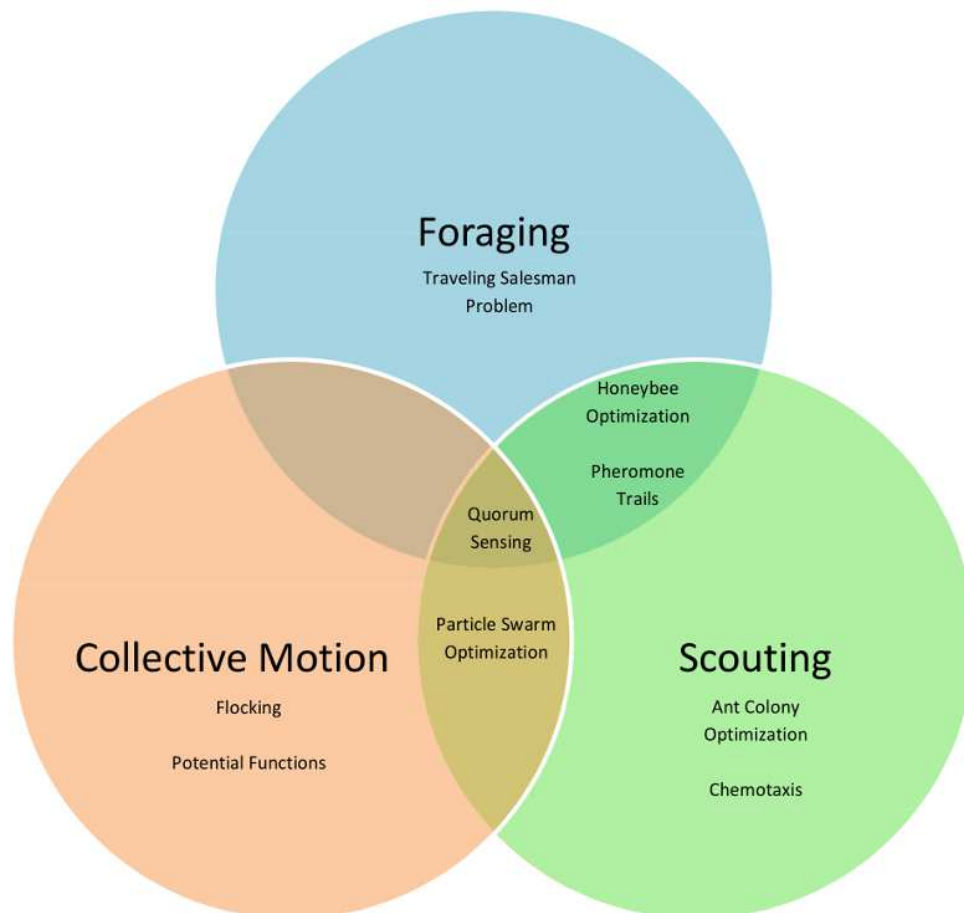


Figure 1.2: A visual summary of existing swarm intelligence algorithms sorted by the tasks they can complete.

Chapter 2

Computational Modeling of Bacteria Population Dynamics

Developing research fields for technology are including more bioinspiration. This increase in biologically inspired technology is a result of understanding the evolutionary purpose. Organism's main objective is to survive and prosper. In order to be prosperous, they must achieve a high biological fitness. This fitness is often influenced by the developmental stage of an individual's components. The greater the efficiency of these components, the more likely the organism is to survive into future generations. In engineering, we can observe the end result of these biological optimization processes and engineer solutions for tasks with similar requirements.

Bacteria possess simple and impressively efficient mechanisms for following chemical gradients and passive density measurements. These two main functions are described as chemotaxis and quorum sensing, respectively. Chemotaxis is a biological process in which organisms sense and respond to concentration gradients of select chemicals in order to achieve directed movement. Quorum sensing, in the biological perspective, is the ability to control specific functionality based on observed local population density. These two features of bacteria pose as significant inspirations for collective microrobotic behavior.

Many limitations exist with the ability to communicate information at the microscale. Current microrobotic system objectives include identifying chemical concentrations within a field. Currently, fluorescent signals are utilized to provide visual methods of observing desired chemicals[15]. Many limitations to this method include complexity of the fluorescent signals, low quality responses, and false positive detections. Efforts have been made to generate larger quality responses, but the physical limitations are difficult to overcome[16]. Additionally, control at this scale poses a significant barrier. When dealing with a large number of agents, a centralized control system becomes inefficient. Currently, there are centralized systems that can accurately manipulate objects in microenvironments [17, 18]. These systems that utilize magnetic fields are often limited in propulsion methods that dictate a

global pattern of movement[19, 20].

2.1 Bacteria Model

The modeling of bacteria include several main components. These components are motility, chemotaxis, quorum sensing, reproduction, and hydrodynamic interactions.

2.1.1 Motility

The motility model for this research adheres to a well researched organism, *Escherichia coli* (*E. coli*). This strain of bacteria is commonly used as the model organism for flagellated bacteria. Flagellated bacteria follow a motility pattern with two distinct states: movement in a single direction (run state), and reorientation (tumble state). While in a run state, the bacteria rotate all of its corkscrew-like flagella in the same direction. This causes the flagella to bundle and propel the bacteria in a single direction. During the tumble state, one or more of the flagella rotate in the opposite direction causing the bundle to disassemble. This creates no net force allowing the bacteria to rotate based on Brownian motion. The bacteria allocate a specific quantity of time to these states before switching to the other state. This behavior is described by a Poisson process. Poisson processes are mathematically described by an exponential distribution, as shown in equation 2.1.

$$f(t, \lambda_i) = \lambda_i e^{-\lambda_i t} \quad (2.1)$$

where λ_i is the mean value of the exponential distribution. Experimental observations provide the mean values. This value differs based upon the bacteria and the environment. With

standard isotropic motility media, *E. coli* has been observed to have the mean values of $\lambda_{run} = 0.9$ s and $\lambda_{tumble} = 0.1$ s [21].

For simulation purposes, both the position and bearing of the bacterial agent must be recorded as a function of time. Additionally, a timer must be created for each movement state of the bacteria. When this timer reaches 0, a new timer is created as the state is switched. During the run state, the bacterium moves in a straight line at a constant speed. During the tumble state, the bacterium changes its bearing based upon rotational diffusion. Due to the nature of the tumble, a new direction is sampled from a normal distribution with a mean of 90 degrees and a standard deviation of 39 degrees [21].

2.1.2 Chemotaxis

When bacteria are within a chemically anisotropic environment, the random walking motion exhibits a bias. The bacteria sense chemical gradients within the environment and determine if a given direction is favorable or unfavorable. The bias in the random walk is created through modification of the mean value for run times [21]. This, however, is limited to the biological resolution of sensing a chemical signal. This resolution has been observed to be 3 nM for the detection of L-aspartate in *E. coli* [22].

When a favorable gradient is detected, the mean of the run time increases. The specific quantity of increased run time mean depend upon both the slope of the gradient detected as well as the absolute concentration of the chemicals [21]. As the run time increases, a bacterial population will exhibit a bias distribution in a chemotactic field. This increase in run time used in this simulation has a mean value of $\lambda_{run} = 1.3$ s. A bias random walk provides a robust solution in finding both local and absolute maxima for a scouting task.

2.1.3 Quorum Sensing

The quorum sensing function for bacteria includes a function that is activated when a specific number density of individuals has been reached. This involves a passive communication between individuals in a population. Bacteria in a quorum sensing network create, release, and sense signaling molecules in the environment. Once a threshold has been sensed for these molecules, specific genetic functionality can either be expressed or suppressed. A well researched model organism for quorum sensing is *Vibrio fischeri* (*V. fischeri*). These bacteria utilize quorum sensing to express bioluminescence at high cell densities. The production of the signaling molecules follow a positive feedback loop, based on the sensed concentration of signaling molecules present. This feedback loop is shown in equation 2.2, a hill function.

$$A_t = (A_1 + A_2 \frac{Q^n}{Q^n + Q_0^n}) \quad (2.2)$$

where A_t is the total generation rate, A_1 is the constant generation rate, A_2 is the increased generation rate, n is the hill coefficient, Q is the measured concentration, and Q_0 is the threshold at which the production rate significantly increases to an up regulated state ($A_1 + A_2$). Once a higher threshold, Q_t , has been reached, the additional functionality becomes active. For this biological system, a hill coefficient of 2.5 is used [23]. A smaller hill coefficient will produce a more gradual response to increased concentrations, while a larger hill coefficient will produce a sharper response.

The signaling molecules undergo a spatiotemporally changing concentration. This concentration can be modeled by three main components: generation, mass transport, and degradation. The generation is modeled by a specific quantity of molecules released into the environment at a given position and time. As time elapses, mass transport will occur and relocate the concentrations of the molecules towards a homogenous mixture in the field.

Finally, degradation causes the molecule concentrations to decrease over time. The mass transport and degradation components can be observed in a modified mass transport equation, as shown in equation 2.3.

$$\frac{\partial Q}{\partial t} = D \frac{\partial^2 Q}{\partial x_i^2} - u_i \frac{\partial Q}{\partial x_i} - dQ \quad (2.3)$$

where Q is the concentration of signaling molecules, u_i is the velocity of the fluid field, D is the diffusion coefficient of the signaling molecules, and d is the degradation of signaling molecules. Both advection and diffusion influence the mass transportation of the signaling molecules, however, diffusion is orders of magnitudes stronger due to the weak advective flow around moving bacteria.

Due to the computational expensiveness of solving equation 2.3, a numerical method known as the Alternating Direction Implicit (ADI) is used [24]. A solution can be calculated with order 1 operations, with the only influence being the resolution of elements in the mesh. Selection of this mesh size is important to allow a good resolution for the bacteria to sense chemicals as well as maintaining a reasonable computation time. The stability criteria for solving this differential equation follows the form of equation 2.4.

$$\frac{D \cdot t}{\left(\frac{X_f}{X_m}\right)^2} \leq \frac{1}{2} \quad (2.4)$$

where D is the diffusion coefficient, t is the timestep, X_f is the field size, and X_m is the mesh size.

The use of a mesh dictates the use of assumptions. These assumptions include what value the mesh element represents as well as providing a sensory value for the bacteria. Each mesh element represents the average cubic micron concentration of signaling molecules. In

order to achieve a greater resolution for sensing, a linear interpolation function is used to interpolate the concentration values between four mesh nodes.

2.1.4 Reproduction

Bacteria have the capability to reproduce by dividing, through binary fission. This process is largely influenced by the media that the bacteria moves through. With nutrient rich media, the bacteria flourish and reproduce rapidly. Conversely, nutrient deficient media causes the bacteria to reproduce at a much slower rate [25]. The process in which this simulation handles reproduction is by describing the time it will take for an individual bacteria to divide with a Poisson process. This Poisson process again uses the same exponential distribution, as outlined in equation 2.1, with a mean of the desired media's reproductive rate. When the timer of the bacteria ends, the bacteria divides. This produces 2 bacteria at the same position which can now independently interact with the environment as desired. The doubling time used in this work is 1.62 per hour [25].

2.1.5 Hydrodynamic Interactions

At high densities, the bacterial movement is also affected by hydrodynamic interactions between neighboring bacteria. This form of interaction can be modeled with a force dipole which results in changes in direction and position of interacting bacteria. These interactions largely depend upon the geometry of the bacteria and the distance between two interacting bacteria. It can be shown that for *E. coli*, the range of these interactions require a volume fraction of at least 5-10% or distances of less than $3\ \mu\text{m}$ [26]. Within the simulation, each bacterial agent produces a dipole force which causes neighboring bacteria to shift their locations. This force dipole can be expressed through a simultaneous change in position and

orientation as shown in equations 2.5, 2.6 and 2.7 [26].

$$u(r) = \frac{lF}{8\pi\nu|r|^2} [3(\hat{r} \cdot d')^2 - 1] \hat{r} \quad (2.5)$$

$$\dot{x} = V_0 d + u \quad (2.6)$$

$$\dot{d} = \frac{1}{2}\omega \times d + \Gamma d \cdot E \cdot (I - dd) \quad (2.7)$$

where u is advective flow from the force dipole, l is the distance between the dipoles, ν is the viscosity of the fluid, $\hat{r}$ is the distance between interacting bacteria, d' is movement direction, x is the position, V_0 is the velocity, d is the direction, ω is the vorticity, Γ is geometric factors, F is the dipole force, E is the strain rate tensor, and I is the identity matrix. Due to the nature of the advective flow around a bacteria, closely packed populations will tend to align and move faster in groups [27, 28].

2.2 Model Parameters

This simulation holds many variables which are important for adequately representing a real system. A list of the parameters can be seen in table 2.1.

2.3 Experimental Validation

2.3.1 Chemotaxis Validation

In order to validate the chemotactic movement model, an analysis of the resulting distributions is made. Experimentally, linear gradients of chemoattractants are often used to

Table 2.1: Parameters used in the simulation. Individual values can be readily changed to simulate different environments, modified responses, and synthetic systems.

Var	Value	Description	Unit
λ_r	0.9 [21]	Average run time	s
λ'_r	1.3	Chemotactic run time average	s
λ_t	0.1 [21]	Average tumble time	s
λ'_t	0.1 [21]	Chemotactic tumble time average	s
v	20 [21]	Average speed of bacteria	$\frac{\mu m}{s}$
θ	5.93 [21]	Tumble rate	$\frac{rad}{s}$
t_s	0.01	Timestep	s
X_f	5000	Field side size	μm
X_m	1000	Mesh size	<i>elements</i>
β	1.68 [25]	Reproductive doubling time	$\frac{1}{hr}$
A_1	0.552 [29]	Constant signaling molecule generation rate	$\frac{molecules}{s}$
A_2	5.52 [29]	Upregulated signaling molecule generation rate	$\frac{molecules}{s}$
d	10.8 [29]	Abiotic degradation of signaling molecule	$\frac{Percent}{hr}$
Q_0	1.00 [23]	Upregulation value for QS	$\frac{molecules}{\mu m^3}$
Q_t	15.06 [29]	Threshold for QS activation	$\frac{molecules}{\mu m^3}$
C_t	3×10^{-9} [22]	Chemotactic detection threshold	M
C_g	1×10^{-4}	Chemotactic gradient	$\frac{M}{mm}$

analyze the resulting distribution of bacteria. These linear gradients are often constructed using rectangular channels of a constant depth. A diffusion based method of creating a linear gradient is achieved through a 3 channel microfluidic device with the center channel acting as the experimental testing area, as shown in figure 2.1 [30].

The two side channels provide a steady flow of the chemoattractant and a buffer with concentrations depending upon the desired gradient. A linear time invariant gradient for the concentration of desired chemicals, in this case a chemoattractant, is established across the width of the channel. When bacteria interact with a chemo-attractant gradient, bacteria exhibit a bias random walk which produces a bias distribution. A prominent method of analyzing the distribution of bacteria is to use a chemotactic partitioning coefficient (CPC) as shown in its discrete form in equation 2.8.

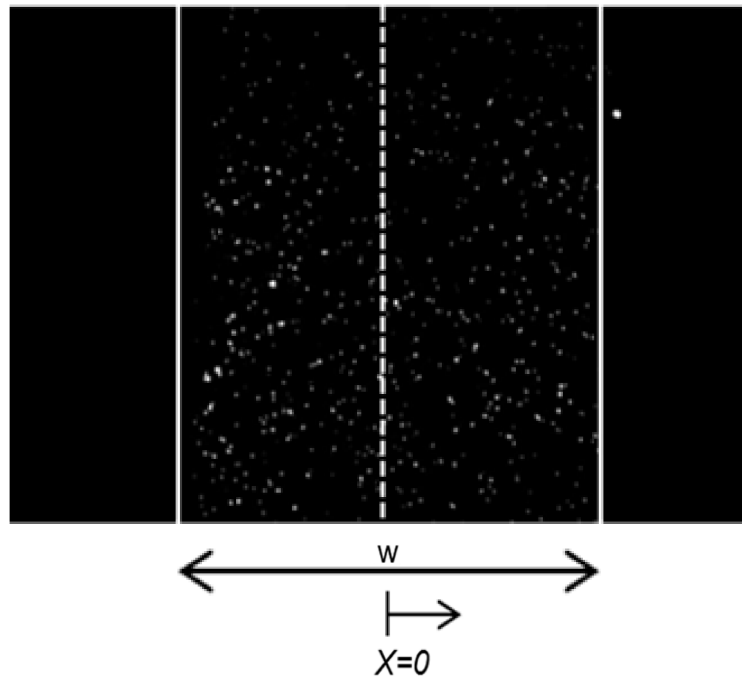


Figure 2.1: An example chemotactic gradient channel where w is the width of the channel and the dotted line represents the center of the channel is where $x = 0$. Experimentally, bacteria are transformed to express green fluorescent protein (GFP) to facilitate detection of their distribution.

$$CPC = \frac{1}{N} \left(\sum_{i=1}^N \left(x_i > \frac{w}{2} \right) - \sum_{i=1}^N \left(x_i < \frac{w}{2} \right) \right) \quad (2.8)$$

where N is the number of agents, x_i is the position of an agent, and w is the width of the channel. Having a positive number infers the agents moved along the gradient. The CPC value can range between -1 and 1, inferring complete repulsion or attraction. The simulation setup for this analysis involves placing a single bacteria in the center of the field with random orientation. The bacteria is allowed to interact, sense, and move within the environment for 10 minutes. The resulting position is recorded for analysis. This process was repeated for 50,000 instances. The resulting discrete CPC of the 50,000 bacteria was 0.6104. This suggests that there exists a bias as expected in favor of the chemoattractant. The resulting positions of a fraction of the bacteria is visualized in figure 2.2.

An additional 50,000 bacteria were simulated without a chemotactic gradient. The resulting distribution produced a CPC value -0.0268, which suggests there is negligible bias observed without a chemotactic gradient. The small negative number is an artifact of the stochastic nature of the movement model, where the number approaches 0 as the number of simulations approaches infinity. CPC values on the order of 0.6 have been experimentally observed for chemoattractant gradients of $1 \times 10^{-4} \frac{M}{mm}$ [30].

2.3.2 Quorum Sensing Validation

The quorum sensing aspect of the simulation relates to multiple aspects of cellular interactions. The type of environment largely dictates the form in which bacteria will produce and detect the signaling molecules. With nutrient-rich environments, bacteria will flourish producing a high cell density in less time than in a nutrient-deficient environment. Two important factors for achieving a valid quorum sensing model are verifying both time and cell

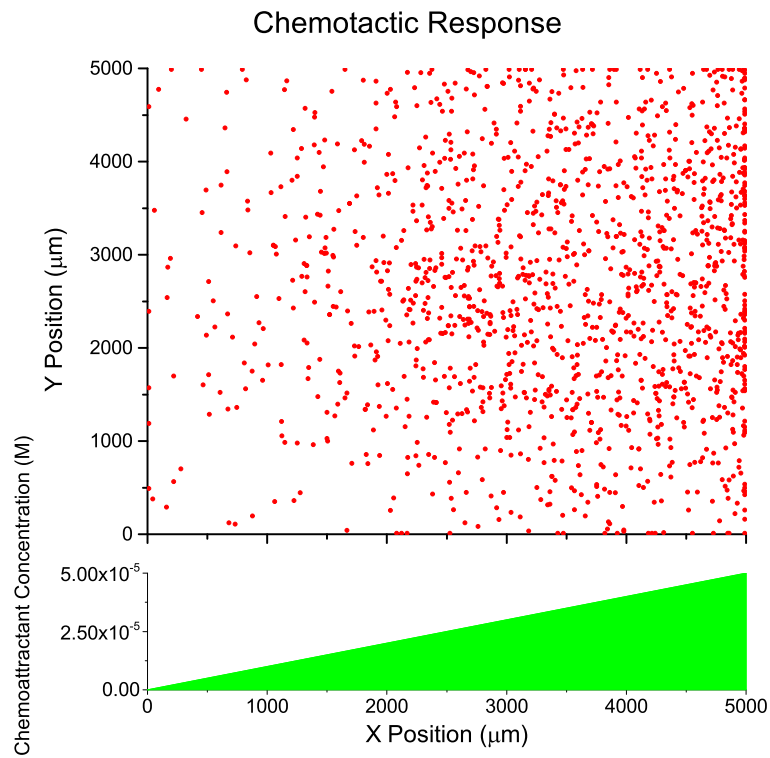


Figure 2.2: Resulting positions of 1,500 bacteria after 10 minutes of random walking. There is a larger concentration of bacteria on the right side, where the chemoattractant concentration is larger.

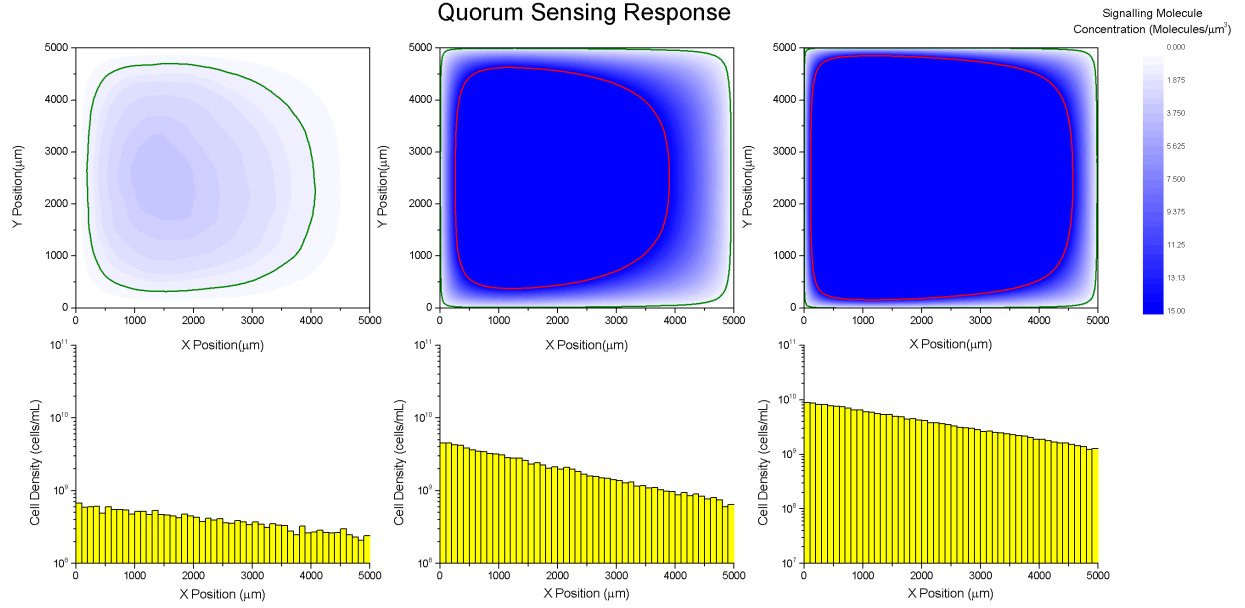


Figure 2.3: Quorum sensing signaling molecule concentration field for three different cell densities gradients. The green line binds the area in which the up regulation threshold has been reached for quorum sensing molecule production. The red line binds the area in which quorum sensing functionality has been turned on.

density. Given enough time in an enclosed environment, a single bacteria can achieve quorum sensing functionality. In effort to constrain some of the variables, the simulation setup for this validation is to have gradients of cell densities of immobile bacteria create signaling molecules over an hour of time. Three different gradients were selected, with varying cell densities between 10^8 and $10^{10} \frac{\text{cells}}{\text{mL}}$. The observed cell densities for the production network used in this simulation has been reported to be between 10^9 to $10^{10} \frac{\text{cells}}{\text{mL}}$ [29]. After an hour of simulated time, figure 2.3 shows the resulting signaling molecule fields for the given cell densities. As expected, the cell density gradient below the experimentally observed density did not achieve quorum sensing. The cell densities above the threshold achieve quorum sensing for the majority of the area. There are edges of the field which do not achieve quorum sensing despite the cell density, but this is likely due to the local observed cell density at the edge causing a delay in increased signaling molecule production rate.

2.4 Simulation Capabilities

Although the individual validations show that the simulation provides realistic results comparable to experimental data, the real power in this simulation environment is predicting environments which are more difficult to experimentally test. Both chemotactic and quorum sensing functionality can be tested with greater complexity than what is permitted in experimental setup.

2.4.1 Computational Modeling of the Chemotaxis Response in a Complex Environment

Chemical gradients can naturally occur in various forms. In experimental setups, they are limited by the form of flow and diffusion based models. Flow based models utilize moving fluid to generate a gradient. These gradients are limited to achieving different concentrations in a single axis, usually producing a linear gradient in a single direction. Diffusion based models utilize static point sources, which can be used individually or in an array. This simulation environment can achieve any chemotactic gradient field that can be described by a function. This function can be written to vary spatially and temporally. As an example of this capability, a two point chemotactic gradient field was produced to observe the bacterial bias movement. Figure 2.4 shows the resulting positions of the bacterial agents.

This computational result suggests that even more complex chemical gradient fields can be tested. With these fields tested, an expected distribution model can be generated. The robust and simple movement model of bacteria can adequately identify and follow gradient fields with no global communication. With higher number densities found at concentration maxima that can be predicted, a quorum sensing response at specific thresholds provides

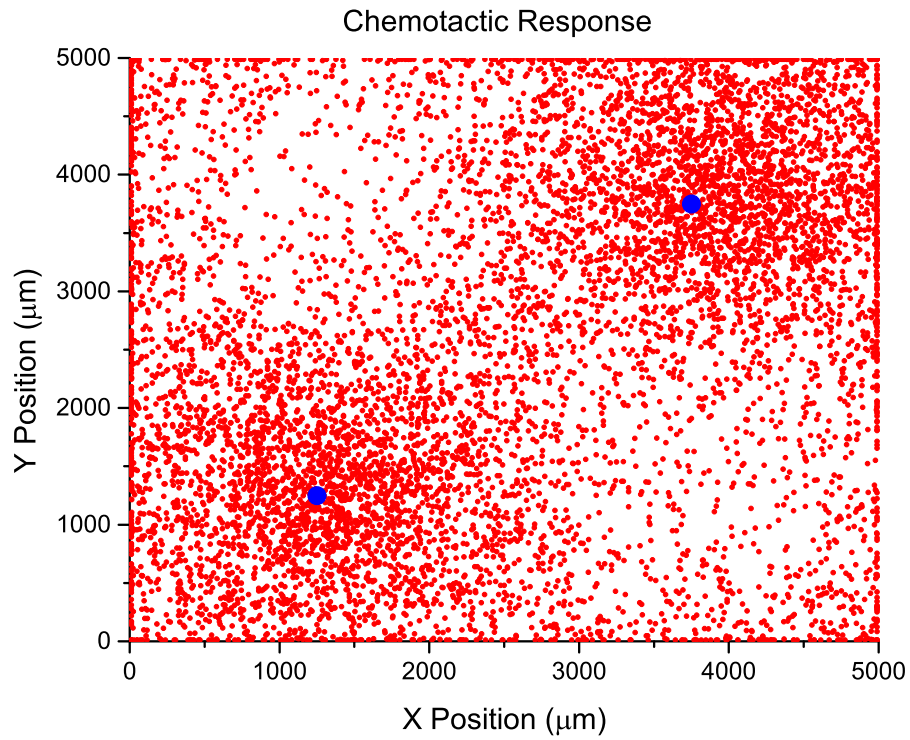


Figure 2.4: A two chemoattractant source response. The point source locations are at the blue circles and independently follow a radial gradient. The final positions, after an hour of simulated time, are plotted.

meaningful results.

2.4.2 Quorum Sensing Response Demonstration for Biosensing Applications

Similar to the gradient of cell densities in a static environment, a dynamic environment can also be modeled. Using chemotaxis as the method of creating a bias in the distribution, a quorum sensing response can be output from the simulation environment. As shown in figure 2.5, the chemotaxis has allowed for the migration of bacteria towards the origin.

The quorum sensing field is developing a greater concentration close to the origin allowing the bacteria only in this area to begin up regulation. Despite the uniform starting conditions, the quorum sensing molecule concentrations exhibit a distinct gradient that mimics the known chemical gradient. In addition to utilizing the chemotactic gradient to create a dynamic environment in which a quorum sensing network can react spatially, applying various thresholds to the quorum sensing functionality can provide a benchmark for desired system response. As shown in figure 2.6, the exact threshold applied after a given quantity of time can have a great influence on the response areas. The chemotactic source has been identified, but if too small of a threshold is applied, false positives may be observable.

2.5 Conclusion

The computational bacterial model presented here can handle many aspects of natural bacterial interactions. These include the random walk motion, chemotactic bias to random walk, quorum sensing communication network, reproduction model, and hydrodynamic interactions. The movement adheres to the biological stochastic model. Quorum sensing reacts to

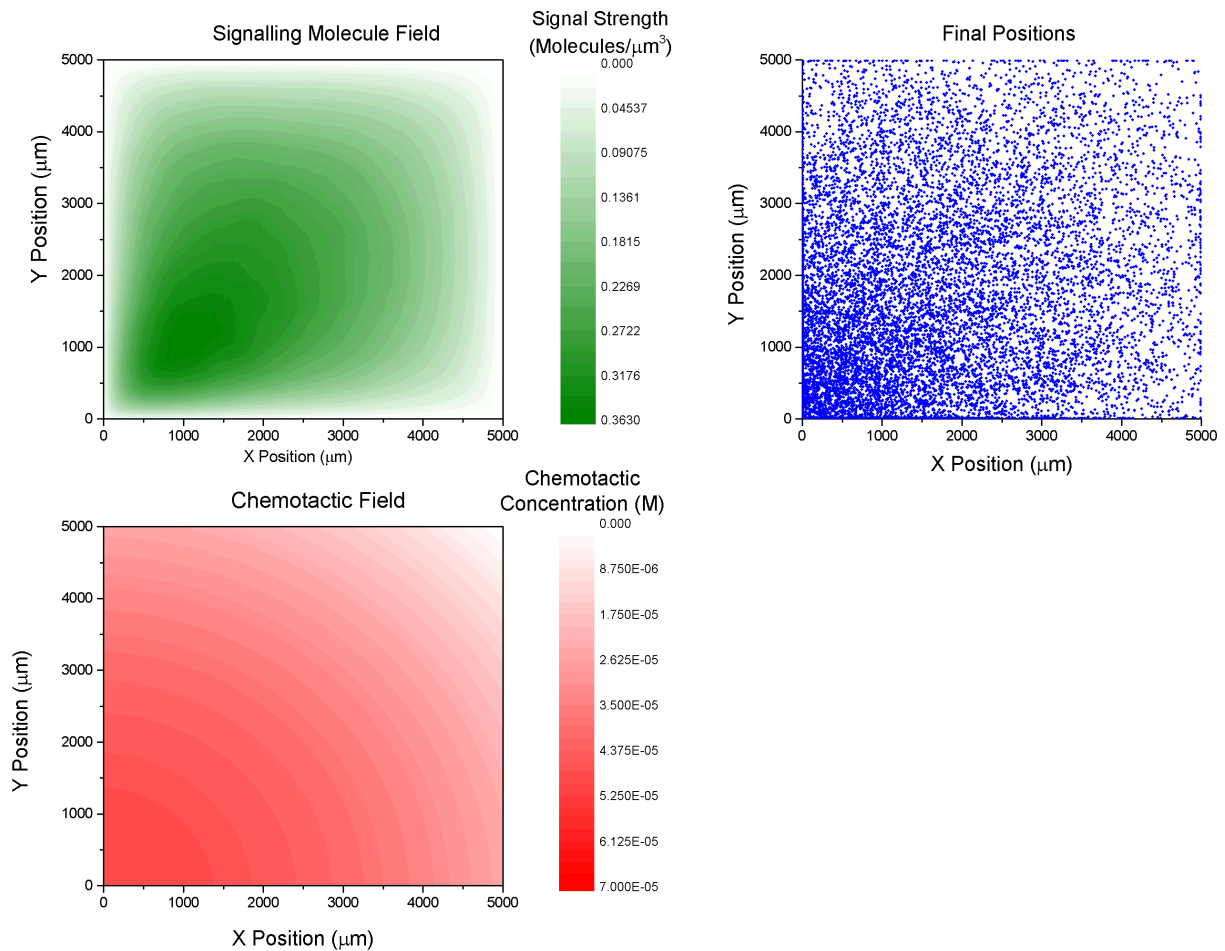


Figure 2.5: A simulation of 10,000 bacteria with a radial chemotactic gradient towards the origin. The starting positions for bacteria were uniformly distributed across the entire field. The resulting distribution and signaling molecule concentration field after 1000 s is shown.

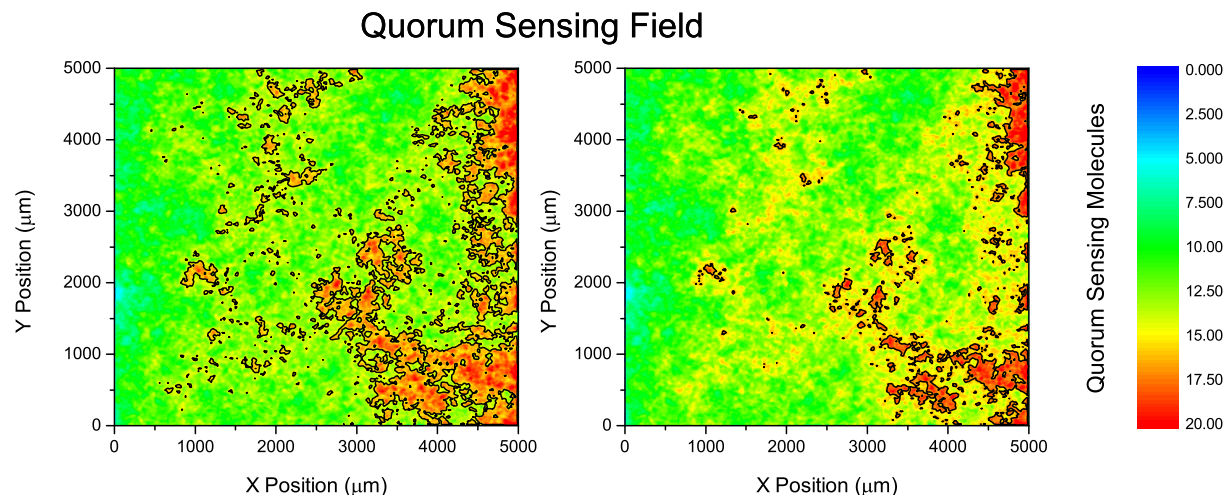


Figure 2.6: A comparison of two different thresholds applied to a quorum sensing network. Both images represent the same quorum sensing field after 1 hour of simulated time and uniform initial conditions for 2,500 bacteria exposed to a linear chemotactic gradient increasing from left to right. Black boundaries in the left image bound the areas for a concentration above $15 \frac{\text{molecules}}{\mu\text{m}^3}$, while in the right image they bound the areas for more than $16 \frac{\text{molecules}}{\mu\text{m}^3}$.

the localized densities in the same ways observed experimentally in the literature. Reproduction can adequately model the population growth for long simulations. Hydrodynamic interactions are taken into account between individual bacteria, which become important at high cell densities. This experimentally validated computational platform can be used as a predictive tool for the design of bacteria based engineered systems, such as distributed networks of mobile biosensors.

Chapter 3

Computational Modeling of BacteriaBot Population Dynamics

As a further development of the bacteria inspired motion towards an engineered system, a method of transportation for micro scale particles can include bacterial propelled microparticles. The use of bacteria as component for an engineered system at the micrometer scale is a novel solution to the actuation and powering grand challenges for micro/nano-robotics [31]. In the engineered system of bacterial propelled microparticles, the bacteria harvest chemical energy from the environment and resolve the requirements of propulsion mechanism, and sensing capabilities [32, 33]. Prospective applications of this engineered system include distributed networked sensors, microassembly, and localized drug delivery [34, 35, 36]. This chapter describes the development of a model to describe population scale dynamics and emergent behavior of bacteria propelled micro particles (BacteriaBots).

3.1 Introduction to the BacteriaBot System

In order to model the BacteriaBot system, the bacteria model adheres to all the previous models described in chapter 2, with an added constraint of being tethered to a particle. Multiple bacteria simultaneously attempt to propel the particle, causing the motion to be in the direction of a net force. As shown in figure 3.1, there are a number of bacteria attached to the particle at different locations to form the engineered system.

Additionally, the individual bacteria propulsion force relies upon the direction of the flagellar bundle. Previous work from our lab has shown an experimentally validated computational model for a single BacteriaBot which takes into account each bacterium state and direction of force vector [37]. Taking all these factors into account can be done, at a significant computational expense. In the alternative approach presented here, an experimentally derived statistical system is created. This model forms the basis for the computational modeling of emergent behavior of the BacteriaBot system.

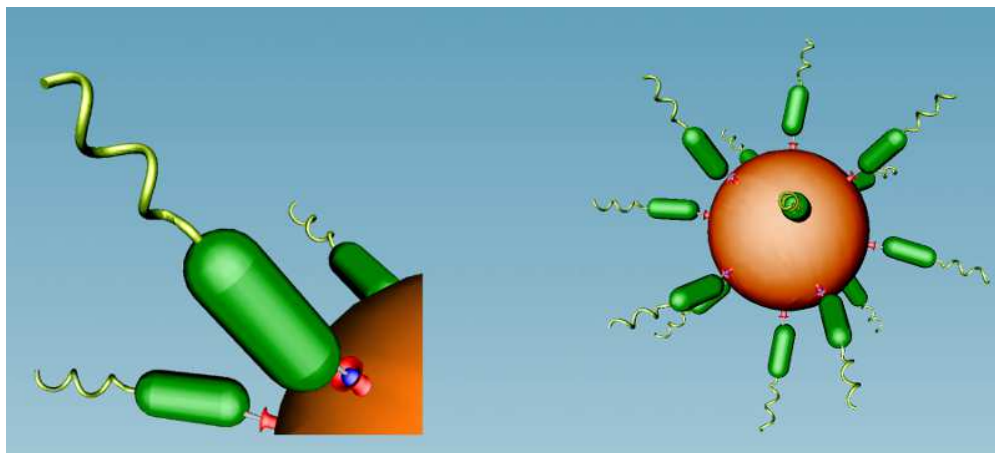


Figure 3.1: CAD representation of the BacteriaBot engineered system. The orange represents the engineered particle (e.g. drug-laden particle) and the green represents the bacteria. The red and blue signify a possible attachment method (e.g. biotin-streptavidin conjugate) for attaching the bacteria to the microparticle.

3.2 Statistical Modeling of BacteriaBot Motility

The movement model follows the same principle as the bacteria model in isotropic and chemotactic environment response. The isotropic model and chemotactic model take data from experimental observations conducted by a fellow labmate and Ph.D. student Ali Sahari. In these experiments, BacteriaBots comprising of bacteria attached to 6 μm diameter spherical particles were used. These BacteriaBots were placed into either an isotropic environment or a chemotactic environment and then were observed via optical microscopy and their motion was recorded at 10 frame rates per second.

3.2.1 Isotropic Environment

The movement of a BacteriaBot significantly differs from the movement of an individual bacterium. Bacteria have an inherent switch of states from running to tumbling. BacteriaBots do not, as it is very unlikely that all the attached bacteria are on the same movement

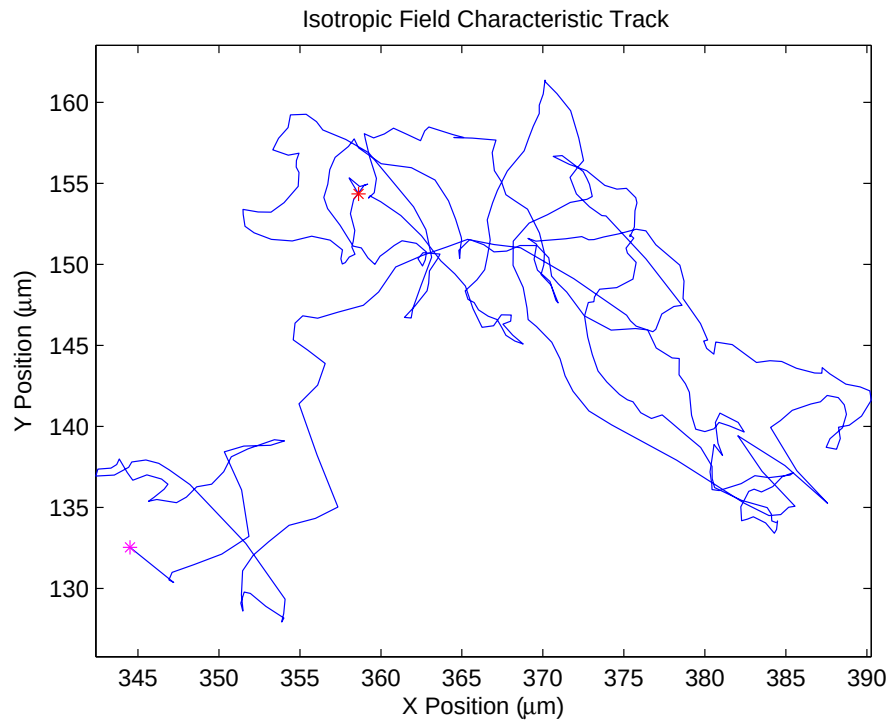


Figure 3.2: A representative track of a single $6\mu\text{m}$ spherical particle propelled by bacteria. The red asterisk represents the starting position while the magenta asterisk represents the final position.

state. Therefore, a model must be created from observation of the movement and estimation of parameters. Due to the nature of the simulation environment, two key factors are the direction and magnitude of displacement in a given timestep for the individual. These can be directly measured by tracking the movement path in a video. An example track of a BacteriaBot moving in an isotropic environment can be seen in figure 3.2

Additional important information is how these values change in time. The final observed parameters from the particle tracking include speed (v), change in speed (a), change in direction (ω), and rate of change in direction (α). Speed is calculated by the magnitude of the change in position between two adjacent frames. The change in speed is calculated by comparing two adjacent speeds. Change in direction is calculated by comparing the angle

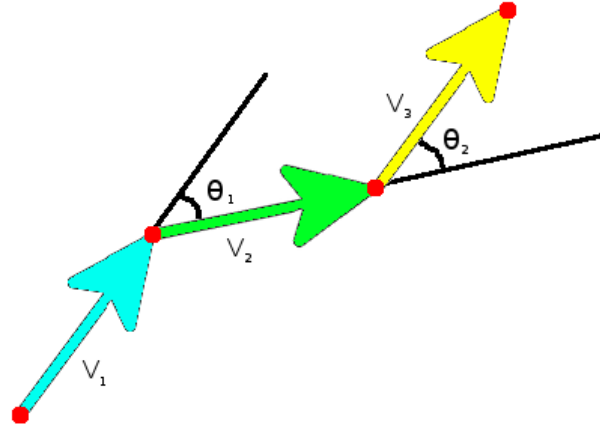


Figure 3.3: The four tracking parameters of speed (v), change in speed (a), change in direction (ω), and rate of change in direction (α) are created by comparing a maximum of 4 adjacent frames. Each frame produces a single red point. By comparing adjacent frames, a displacement vector can be created. From these points, various parameters can be extracted for the movement model.

change between two adjacent velocity vectors. Finally, the rate of change in direction is the result from comparing adjacent changes in direction. For a visual representation of these values, refer to figure 3.3 and supporting equations 3.1 and 3.2.

$$a = v_2 - v_1 \quad (3.1)$$

$$\alpha = \omega_2 - \omega_1 \quad (3.2)$$

Once these parameters are extracted from the experimental recordings, a statistical model is created to match the distribution of values.

The proposed statistic model for the observed patterns in the four parameters is a time auto-correlated gamma distribution for speed and a uniform distribution for change in direction. These were determined by observing the frequency of occurrences in the recorded parameters,

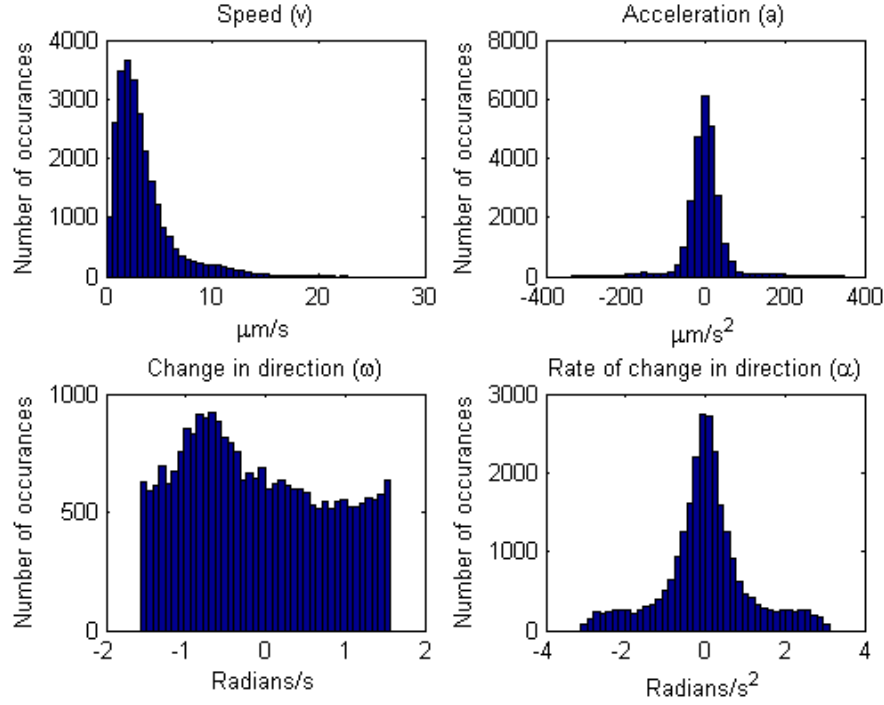


Figure 3.4: A histogram of the various parameters observed through analysis of the isotropic environment trajectories of BacteriaBots. The v histogram exhibits a gamma distribution and ω exhibits a uniform distribution. The a and α histograms exhibit a normal distribution with a mean of 0.

as shown in figure 3.4. As seen in both the a and α histograms, there is a mean of zero. This suggests that there exists a time auto-correlation for the distribution. Additionally, the shape of the v and ω histograms suggest their respective distributions.

3.2.2 Chemotactic Environment

The second experimentally-derived statistical model generated is for a chemotactic environment. The same four parameters are extracted from the BacteriaBot trajectories. However, an additional step takes place before determining what aspects of the track is desirable for the model. When the BacteriaBot is moving in the direction of the known gradient, it is a

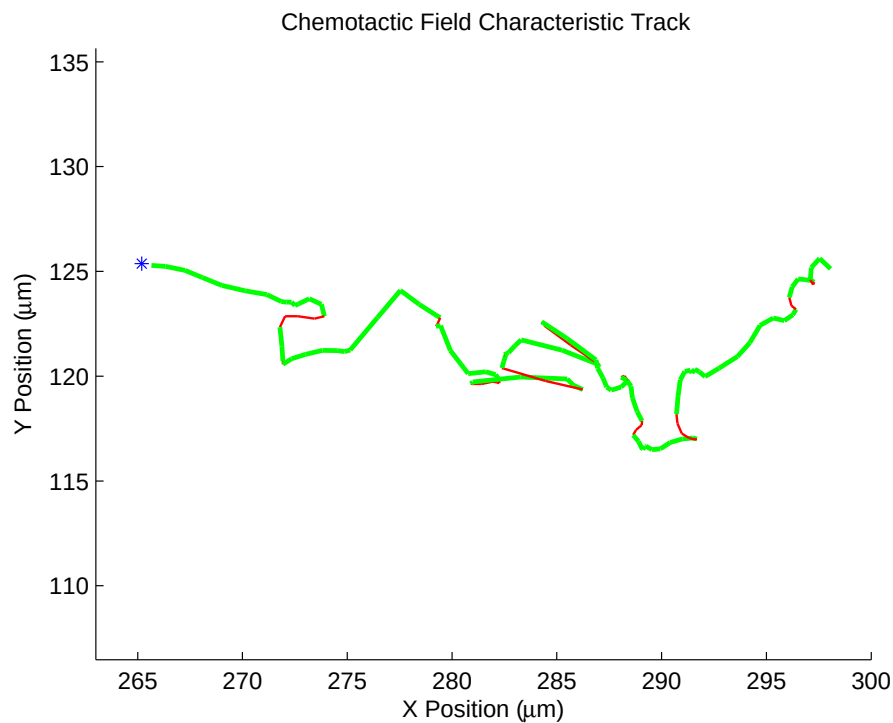


Figure 3.5: The chemotactic track is divided into two portions. The known chemotactic gradient exists along the x axis with larger x values correlating to stronger concentrations. The blue asterisk marks the starting position. The thick green lines represent the data used for the chemotactic model, while the thin red line segments show the remaining tracked paths.

good assumption that the bacteria attached to the sphere are sensing a favorable gradient. When they are moving against the gradient, it is not a good assumption that the bacteria are sensing a favorable gradient. Therefore, the tracks from the moving spheres are divided into two different datasets. Each vector in the track trajectory is compared for a difference between chemoattractant observed by bacteria. If this vector achieves an observed difference greater than the $3 \times 10^{-9}M$, the vector is placed into a chemoattractant dataset. If the vector is not greater than the detection threshold, it is added to the isotropic environment dataset. Figure 3.5 depicts a pictorial representation of this separation of data.

These tracks were passed through the analysis code to identify the frequency of occurrence

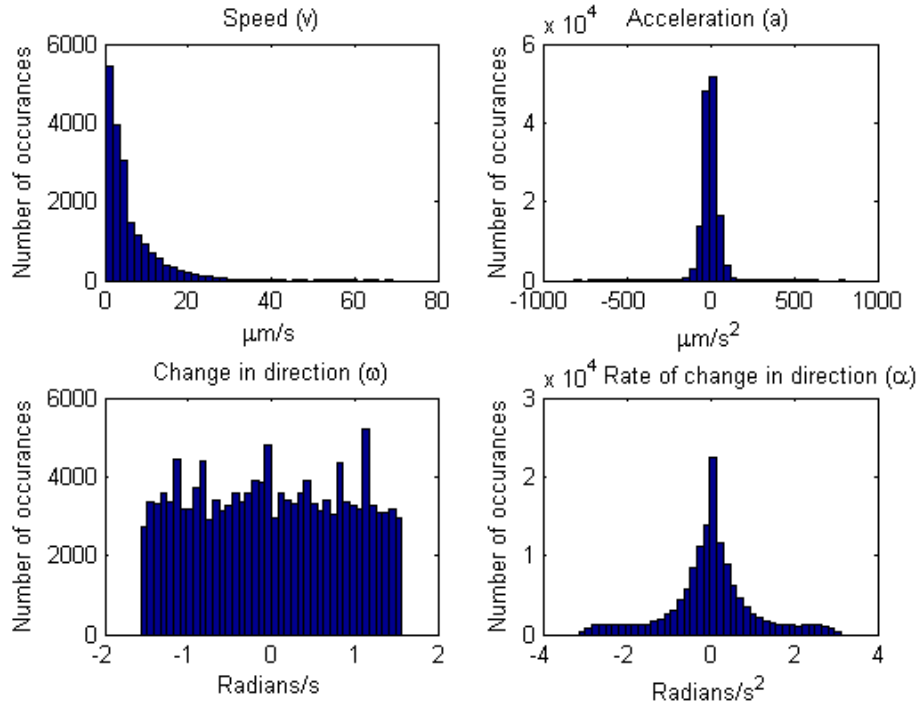


Figure 3.6: A histogram of the various parameters observed through analysis of the chemotactic environment tracks. The v histogram exhibits an exponential distribution and ω exhibits a uniform distribution. The a and α histograms exhibit a normal distribution with a mean of 0.

for the four parameters of speed (v), change in speed (a), change in direction (ω), and rate of change in direction (α). A very similar outcome for the shapes of the histograms can be observed in figure 3.6.

Although the v histogram appears to achieve an exponential distribution, this can still be described by a gamma distribution by finely tuning the parameters. The mean of the speed for the chemotactic environment shows an increase of 31% in comparison to the isotropic environment. This can be explained by having a higher probability of bacteria applying their force to the particle to generate a larger net force. The remainder of the parameters show no difference in distribution between an isotropic environment and a chemoattractant environment.

3.3 Reproductive, Quorum Sensing, and Hydrodynamic Interaction Models

The primary difference between the bacteria model and the BacteriaBot model is the movement. However, the other models must be modified slightly to fit a realistic response for BacteriaBots. A slight modification of the reproductive, quorum sensing, and hydrodynamic interaction models must incur for accurate representation of the system.

First, the reproductive model does not change in the frequency of divisions on a single bacteria level. However, since the BacteriaBots have multiple bacterium attached to it, it will occur more frequently. A list of reproductive timers is allocated to each BacteriaBot allowing for each individual bacterium to react as it normally would, if it was not attached to the particle. When a division occurs, the bacteria can either stay attached to the particle or detach. Through experimental observations, the reproducing bacteria split into two with one of the bacteria remaining attached to the particle and the other detaching. The simulation environment handles this phenomena by leaving one bacterium attached and releasing the second bacterium into the environment.

Second, the quorum sensing model must be modified to handle the BacteriaBots. To expand the existing computational platform, the BacteriaBots act as though there is a uniform distribution of bacteria along the outer edge of the sphere. With this distribution, the individual bacterium can function independently as describe in the bacteria model. However as the entire particle makes a decision, the particle may exhibit partial responses. To handle this, a majority of the bacteria must express a specific condition in order to assume the entire BacteriaBot expresses that condition. In other words, more than half of the bacteria must express quorum sensing in order to state that the BacteriaBot is expressing quorum sensing. In the future, this can be validated experimentally and the computational model

parameters can be adjusted accordingly.

Finally, the hydrodynamic interactions must be modified. Due to the difference in size, geometry, and scale for the hydrodynamic interactions, the same model may not be applicable. Instead, a flow field is developed for each time instance based upon the movement direction of the BacteriaBots. This flow field is based on the hydrodynamic induced drag of a sphere. At high densities, the BacteriaBots can collide. This is not taken into account, and invalidates BacteriaBot simulation models that occur at high densities. At lower densities, it is assumed that the BacteriaBots can pass nearby each other with little interactions. This assumption is experimentally verified.

3.4 Experimental Validation

The movement models were created to best represent the statistical models that they were generated to represent. Due to the methods of defining the statistical model, it would be expected that a dataset from the models match the distributions of modeled set. Figure 3.7 shows the a new data set generated by the statistical model for an isotropic environment. The model-generated dataset for the isotropic environment includes 2000 trajectories at a length of 500 vectors. The generated histograms closely matches the original data from the isotropic environment.

The exact comparison between the model and experiments can be further observed through the means of the two dataset. For the isotropic environment, the experimental velocity observed was $6.8 \pm 5.4 \frac{\mu m}{s}$. The model produced a velocity of $6.8 \pm 5.0 \frac{\mu m}{s}$. Similarly, the acceleration resulted in $0.0 \pm 49.5 \frac{\mu m}{s^2}$ and $0.0 \pm 49.5 \frac{\mu m}{s^2}$ for the experiment and model respectively. The time series autocorrelation enforces the model's acceleration mean and standard deviation to be identical to the experimental observations while the gamma distribution sam-

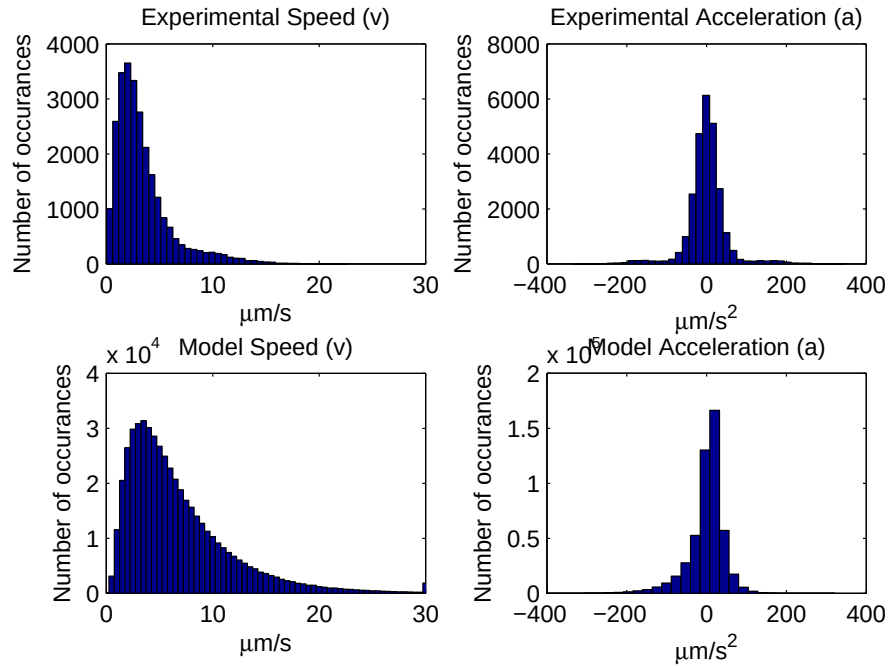


Figure 3.7: A comparison between the isotropic movement model and the isotropic experimental data.

ple provides a good sampling for the exact velocity values. It is important to note that there is a decrease in the standard deviation for the velocity due to the time autocorrelation. The decrease in acceleration mean is likely due to a small sample for the model. The chemotactic model produced a similar trend for the decrease in mean velocity.

Additionally, the chemotactic model should create a bias in the distribution. Figure 3.8 shows a resulting distribution from utilizing the BacteriaBot model in a linear gradient field.

This bias can again be described with the CPC measurement as described in the previous chapter. After 5 minutes of movement, the CPC value obtained from experiment was 0.42 ± 0.10 [38]. Comparatively, the computational model with 10,000 BacteriaBots produced a CPC value of 0.38. This value lies within the standard deviation of the experiments.

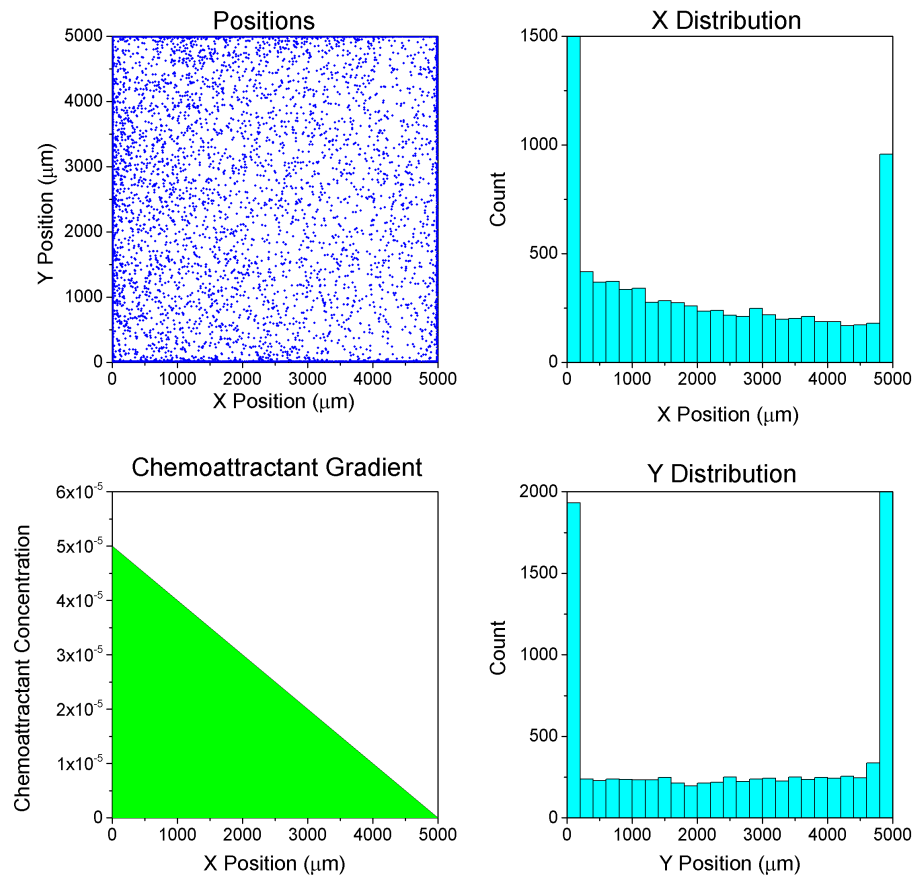


Figure 3.8: The resulting distribution of 10,000 BacteriaBots after 1 hour of simulation time. There are a significant quantity of BacteriaBots that crowd near the edges of the simulation domain. This characteristic was also observed experimentally, with the data omitted after becoming poorly mobile near the boundaries.

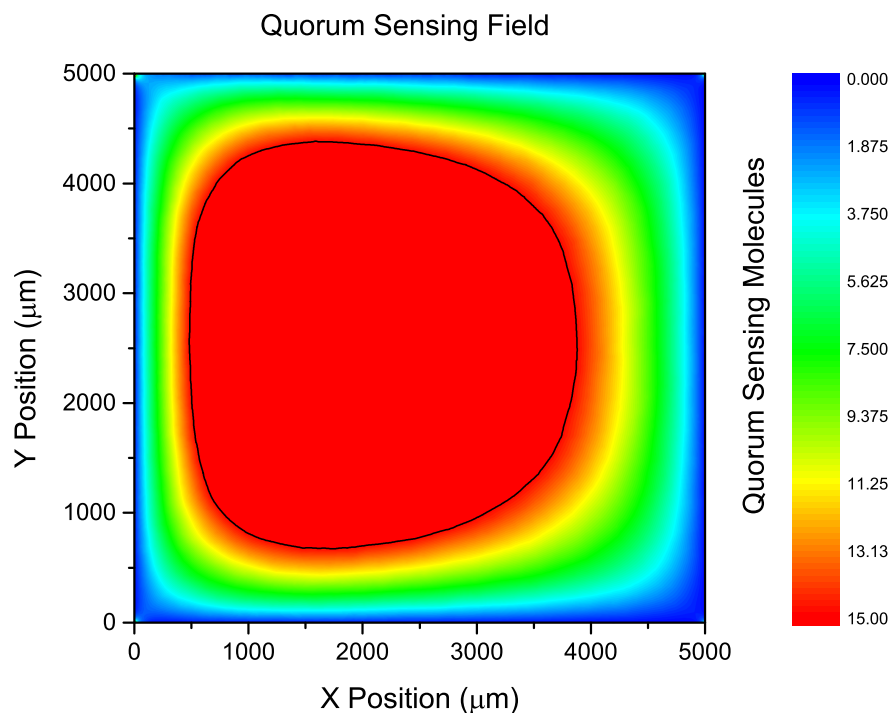


Figure 3.9: The distribution of quorum sensing molecules after 1 hour of simulated time. The field initialization consisted of 10,000 BacteriaBots with a linear chemotactic gradient located along the x-axis (reducing from left to right).

3.5 System Capabilities

Although the movement pattern matches the experimentally observed distributions, the real capability of this system can be seen when quorum sensing is added and observed. Additionally, more complex fields can also be introduced to the movement system to determine how it will react. Similar to the bacteria model, varying quorum sensing thresholds and chemotactic fields can be tested. Additionally, observations of the quorum sensing response as a function of the bacteria and BacteriaBot interactions pose interesting results. Figure 3.9 shows the quorum sensing molecule distribution produced by bacteria, due to reproduction, and BacteriaBots interacting in the same environment.

3.6 Conclusion

The BacteriaBot model can adequately represent the movement patterns as well as the quorum sensing network of a BacteriaBot population at low densities. The distribution of BacteriaBots can be predicted for new environments of desired applications for the engineered system. A time series auto-correlation gamma distribution for velocity and a time series auto-correlation normal distribution for changes in direction adequately represents the movement of BacteriaBots in both isotropic and chemotactic environments. The previous models of reproduction and quorum sensing for bacteria can be slightly modified to fit realistic responses for the BacteriaBot system.

Chapter 4

Summary and Future Work

In order to adequately model population scale interactions of bacteria, one must include individual models for isotropic motility, chemotactic motility, quorum sensing, reproduction, and hydrodynamic interactions. Motility is modeled using a Poisson process which switches between a run and tumble state. Quorum sensing creates a communication network between local bacteria to determine localized number densities. Combining the individual stochastic models, emergent behavior can be predicted through careful selection of system parameters.

BacteriaBot's movement can be modeled through statistical means. Depending on the environment, the BacteriaBot will follow a time auto-correlated gamma distribution for speed and a time auto-correlated uniform distribution for change in direction. With this model, complex interactions can be observed on a population scale. It is important to accurately model the system reaction to engineer systems to create desired responses. With these proven models, BacteriaBots can be modeled in dynamic environments to provide an expected response for the real system.

Additional directions for this simulation environment include the addition of the collision dynamics for the spherical particles and creating more complex fields for a population of agents to interact with. The complex fields could represent intended applications for the system, such as a porous tumor environment for bacterial agents to deliver drug nanoparticles. Additionally, a more generic movement model could be implemented for BacteriaBots. Currently, the simulation environment contains the model for a single particle size. Different particle sizes will likely react with a different movement model. Finally, only three major parameters were observed for methods of system modeling. These three methods include the modification of the starting population, time until the observed response, and the chemotactic field. There are many other parameters that could be potentially controlled for a fully synthetic system which pose as important future research directions. Additionally, feedback controllers could be developed and simulated within the environment to control

the response. Modifications such as achieving different movement speeds dependent upon the quorum sensing molecules sensed could pose as a potential direction for controlling the modeled system.

This study presents models to adequately describe the input-output relationships between system inputs and outputs. The system inputs observed in this study include population size, time delays for the system to develop a response, and a dynamic chemotactic field. The system outputs observed in this study include resulting distribution of agents within the system and activation of the quorum sensing functionality. Results from this simulation environment can adequately model the response of a population as validated by complementary experimental work as well as predict the response of an untested population [30, 38].

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