

December 2nd, 2020

Exploring Bacterial Chemotaxis using an Agent-Based Model

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BIOL 309 - Mathematical Models in Biology

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Word Total: 1882

Summary

Bacteria's primary goals in life is to find nutrients, grow and divide. The strains that accomplish this the most effectively can quickly become dominant in their microbiome. Thus, there's a very strong selective pressure on bacteria to quickly find nutrients. Chemotaxis, the mechanism used to accomplish this, is already generally well understood by biologists. However, there are still subtleties behind how bacteria have mastered this problem left to be uncovered. Mathematical modeling can help us by simplifying the underlying system in order to reproduce it using software, where we can freely experiment with the system without the constraints of working with live organisms in a laboratory. By representing the molecular pathway with a system of ordinary differential equations, and simulating a colony of bacteria using an agent-based model, I was able to show chemotaxis happening in an artificial environment, albeit with some limitations.

Chemotaxis

Chemotaxis is the movement of an organism as a response to a chemical stimulus³. Bacteria exhibit this behavior towards many different chemicals; they are attracted to sources of nutrients, and avoid toxins. One problem unique to bacterial cells, due to their small size, is that the direction of a gradient cannot easily be determined between the front & back of the cell. The bacteria therefore needs a way to remember a past concentration, and compare it with the present, to determine if it's going in the right direction. It also needs to scan its environment to search for better nutrients. It accomplishes these goals through a process of "run & tumble", where the cell alternates between swimming straight in one direction (running), and randomizing its heading (tumbling). When the bacteria detects movement in a favorable direction, it decreases its tumbling frequency. This process is also called a *biased random walk*¹.

Bacteria are very sensitive to small changes in the nutrient gradient, and change their tumbling frequency quickly. This fast reaction happens over the span of milliseconds/seconds. Remarkably, the bacteria eventually returns to a stable state tumbling frequency after being exposed to a particular nutrient concentration for a long enough time, a phenomenon also called *perfect adaptation*². The adaptation is relatively slow, happening over the span of minutes.

On a molecular level, this entire system can be explained almost entirely by protein-protein interactions. The bacteria have transmembrane chemotaxis receptors, also called methyl-accepting chemotaxis proteins (MCP), that bind to extracellular ligands. The MCP receptors are coupled to a two-component regulatory system⁴ made up of CheA, the histidine protein

kinase, and CheY, the response regulator. Receptors in the active conformation increase phosphorylation of CheA, which in turn phosphorylate CheY. CheY-P then diffuses to the flagella, binding to them and increasing the likelihood of it rotating in a clockwise direction. Clockwise-turning flagella cause the cell to tumble. The binding of nutrients to the chemotaxis receptor lowers its affinity for the active conformation, consequently lowering the likelihood of a tumble. This phosphorylation cascade happens quickly⁶.

Methylation plays a key role in the adaptation process. Methylated MCP receptors are more active than unmethylated ones. Concomitant to the two-component regulatory system, active receptors increase phosphorylation of another enzyme, CheB. When activated, CheB demethylates the receptors. This process happens in equilibrium with CheR, which methylates the receptors at a relatively constant but slow rate. The methylation of the receptors over time eventually brings the tumbling frequency back to a steady state. This adaptation process happens slowly because methylation of the receptors is slower than a phosphorylation reaction⁶.

Mathematical Model

My model is inspired by the Barkai-Leibler model², as described in Uri Alon's textbook¹. Like his model, I've made the simplification that unmethylated receptors cannot phosphorylate CheY at all, and that the proportion of unmethylated receptors is much greater than the concentration of methylated receptors. However, unlike his model, I've included CheA and CheY in order to more completely represent the pathway. I've also included CheZ in the model, a phosphatase that dephosphorylates CheY. The entire system is summarized in **Figure 1**.

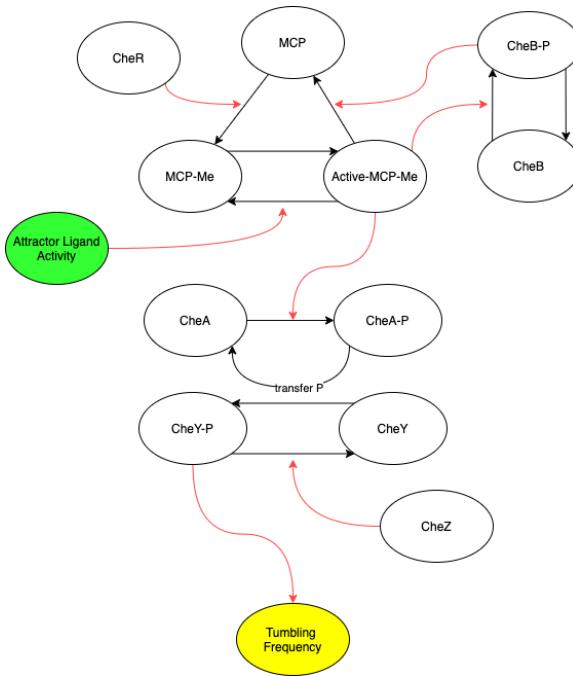


Figure 1: Diagram showing transitions (black) and interactions (red) between the different components in the system. The attractor ligand activity (green) is the input of the system, while the tumbling frequency (yellow) is the output. MCP represents the entire receptor complex, and MCP-Me represents the methylated form of the complex.

The interactions between the components can be modeled as a system of first-order ordinary differential equations (ODE). For reference, a legend of the different variables in the system are given below:

Variable	Description
A	Quantity of phosphorylated CheA proteins (CheA-P)
A_{max}	Total quantity of CheA proteins
γ	Quantity of phosphorylated CheY proteins (CheY-P)
γ_{max}	Total quantity of CheY proteins
B	Quantity of phosphorylated CheB proteins (CheB-P)
B_{max}	Total quantity of CheB proteins
M_{me}	Quantity of inactive methylated MCP receptors

M_{me}^*	Quantity of active methylated MCP receptors
C	Amount of attractor ligand activity
All α values are constants of proportionality, while the K values are Michaelis constants.	

Below are the 5 equations governing the system:

$$\frac{dA}{dt} = \alpha_A M_{Me}^* \frac{(A_{max} - A)}{K_A + (A_{max} - A)} - \alpha_Y A (Y_{max} - Y) \quad (1)$$

The phosphorylation of CheA is influenced by the level of active methylated MCP (M_{me}^*), using a Michaelis-Menten (MM) equation with unphosphorylated CheA as the substrate ($A_{max} - A$). For simplicity, I'm assuming the rate of transfer of phosphoryl from CheA-P to CheY is proportional to the product of the concentration of both reactants, A and $Y_{max} - Y$.

$$\frac{dY}{dt} = \alpha_Y A (Y_{max} - Y) - \alpha_Z \frac{Y}{K_Z + Y} \quad (2)$$

The phosphorylation of CheY is a direct result of the transfer from A , making the first term in (2) the same as the last term in (1). The dephosphorylation of CheY is caused by CheZ, simply modelled using a constant term (α_Z) since I assume the quantity of active CheZ does not vary. The dephosphorylation follows MM kinetics.

$$\frac{dB}{dt} = \alpha_B M_{Me}^* \frac{(B_{max} - B)}{K_B + (B_{max} - B)} - \alpha_{B'} B \quad (3)$$

The phosphorylation of CheB is influenced by the level of active methylated MCP (M_{me}^*), using a MM equation with unphosphorylated CheB as the substrate ($B_{max} - B$). I assume the rate of dephosphorylation of CheB is proportional to its own quantity.

$$\frac{dM_{me}}{dt} = \alpha_1 C M_{me}^* - \alpha_2 M_{me} + \alpha_R \quad (4)$$

$$\frac{dM_{me}^*}{dt} = \alpha_2 M_{me} - \alpha_1 C M_{me}^* - \alpha_M B \frac{M_{me}^*}{K_C + M_{me}^*} \quad (5)$$

For simplicity, since the quantity of unmethylated MCP receptor is assumed to be much greater than the quantity of the methylated forms, I omit it from the system of equations. The

dynamic equilibrium between the active (M_{me}^*) and inactive (M_{me}) forms of the methylated MCP receptor is controlled using two different proportionality constants α_1 and α_2 , and influenced by the level of attractant ligand (C). The methylation of MCP into M_{me} is assumed to happen at a constant rate (α_R) since unmethylated MCP at saturation. The demethylation of M_{me}^* is influenced by B and follows MM kinetics.

Solutions to System

Using Euler's method, solutions for the differential equations were computed and plotted using a computer program.

The maximum proteins levels were all arbitrarily set to 1. The constants involving a protein changing conformation were set relatively high ($\alpha_1 = \alpha_2 = 100$), the constants involving methylation were set low ($\alpha_M = 1$, $\alpha_R = 0.1$), and the constants involving phosphorylation reactions were intermediate ($\alpha_A = \alpha_Y = \alpha_Z = \alpha_B = \alpha_{B'} = 10$). These were chosen as thus to represent the relative orders of magnitude of the rates within a biological system. All the Michaelis constants were set to 0.5.

The levels of attractant (orange lines in Figure 2 & 3) were arbitrarily modulated to simulate environmental conditions a bacteria might be subject to. As expected, the level of CheY-P (Y) respond to an abrupt change in the attractant level by quickly decreasing (or increasing), and then slowly coming back to a steady state (Figure 2).

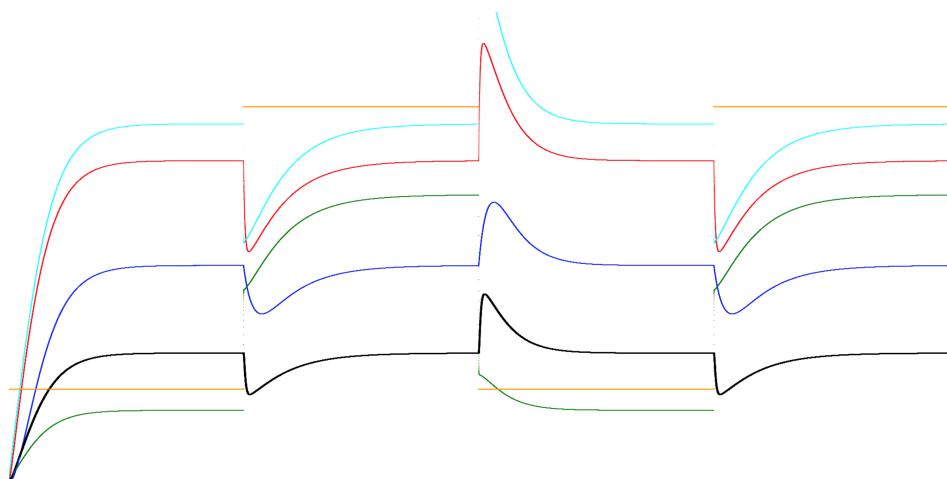


Figure 2: Y = black, C = orange, A = red, B = blue, M_{me} = green, M_{me}^* = cyan

When attractant is increasing, Y decreases to a lower level, corresponding to a lower tumbling frequency. Likewise, if the attractant is decreasing, Y increases to a higher level. When the attractant level returns to a constant value, Y returns to its steady state, characteristic of perfect adaptation (Figure 3).

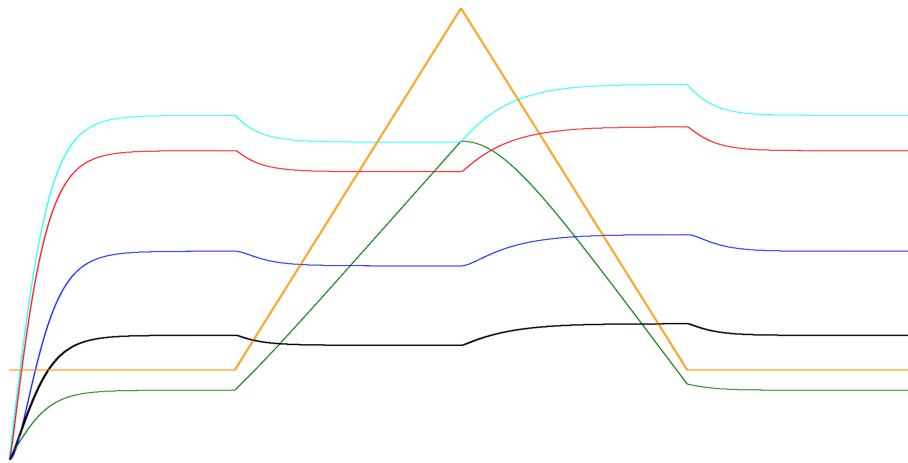


Figure 3: Y = black, C = orange, A = red, B = blue, M_{me} = green, M_{me}^* = cyan

Agent-based Bacteria Model

In order to understand if the behaviour of the system on a molecular level is sufficient to explain chemotaxis on a physical level, I developed an agent-based model computer program.

An attractant gradient was put in the middle of the artificial environment, going from a value of 0 (lowest concentration) near the edges to 1 (highest concentration) in the center. Each bacteria in the simulation has its own set of proteins levels, which are updated every turn using the local attractant level as input, and using the system of differential equations to changes its protein levels in consequence. The bacteria also alternate between a state of tumbling, where they turn at a constant rate for a random number of turns, and a state of running, where they swim straight. A bacteria in the running state has a probability of switching to a tumble state as a function of the level of CheY-P (Y) in the bacteria.

I chose to set the probability of tumbling according to a logistic function in order to make it bound between 1 and 0, and be able to easily adjust its sensitivity to the input. In the simulation, the steady state of Y is first computed, and stored in a variable as Y_{ss} , which is then treated as a constant for the remainder of the simulation. The logistic function was

shifted to the right, and its steepness increased, in order to fix the steady state tumbling frequency at around $f \approx \frac{1}{100}$, or approximately once every 100 turns. The relationship is as described in Equation 6 and shown Figure 4.

$$P(\text{tumble}) = \frac{1}{1 + e^{-45(Y - Y_{ss} - 0.1)}} \quad (6)$$

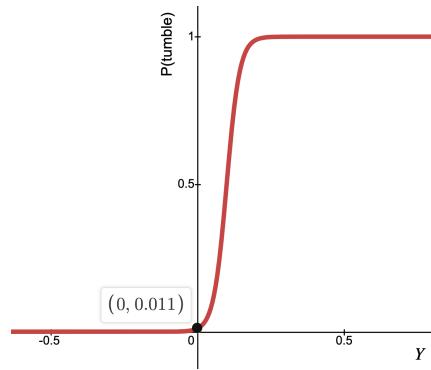


Figure 4: Function of $P(\text{tumble})$ over Y

Using the simulation, we can observe the behaviour of one single bacteria, and its levels of Y . It exhibits both sensitivity to the local level of attractant, as well as perfect adaptability (Figure 5).

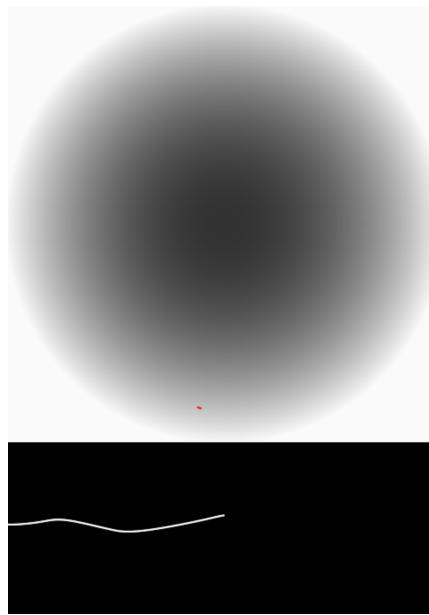


Figure 5: A single bacteria (red dot on bottom of canvas), and a plot of the levels of Y over time (under canvas). Link: <https://michelcarroll.github.io/chemotaxis/single-bacteria-simulation.html>

Increasing the number of concurrent bacterial agents, we can see the average behaviour of a colony of bacteria. After enough time has passed, the bacteria tend to accumulate in the center of the canvas where the nutrient concentration is highest (Figure 6).

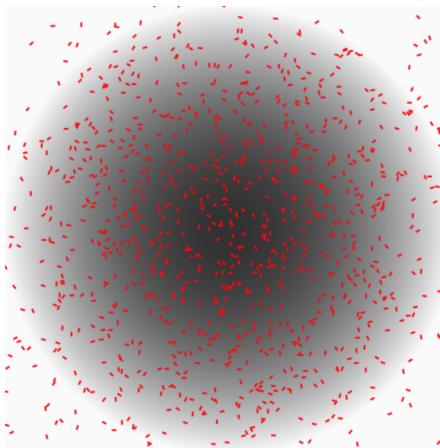


Figure 6: Simulation with $n = 1000$ bacteria after a minute of runtime. Link: <https://michelcarroll.github.io/chemotaxis/colony-simulation.html>

Conclusion & Model Limitations

While my model is adequate for showing perfect adaptation of bacteria with respect to chemotaxis, it isn't sufficient in explaining how bacteria can be sensitive to small changes in attractant. As shown in the colony simulation, the bacteria don't strongly discriminate between the regions of low concentration and high concentration. In real bacterial colonies, the bacteria would likely be more optimal, and eventually congregate in the region of highest attractant concentration. Further experimentation should be done to explore if the lack of sensitivity is due to my choice of constants, or if the structure of the model intrinsically isn't able to represent a more sensitive system.

My attempt at representing the tumbling frequency as a function of phosphorylated CheY resulted in a fair demonstration of chemotaxis in the bacteria agents. However, the choice of a logistic function and the parameters I chose for it to calculate the tumbling frequency have no obvious biological basis. More investigation into the literature should be done to learn how phosphorylated CheY proteins bind the flagella complex, and how they quantitatively impact its rotation. Based on those findings, a more biologically sound model should be designed to better represent the relationship between γ and the tumbling frequency.

In a real bacterial colony, bacteria may be exchanging chemical signals such as pheromones to help peers find a chemical source⁵. This wasn't taken into consideration in my model, but may be playing a big part in how efficiently a colony as whole can survive in an environment with a heterogenous nutrient distribution.

Project code can be found at:

<https://github.com/MichelCarroll/bacterial-chemotaxis-model/archive/master.zip>

References

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