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Numerical Simulation of Bacterial Chemotaxis Based on Keller-Segel Model

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Abstract

Bacterial chemotaxis, which explains the movement of bacteria in response to chemical gradients, plays a critical role in various biological processes. This study presents a numerical simulation of bacterial chemotaxis in response to chemoattractant, using a mathematical model based on the classical Keller-Segel equations. The Keller-Segel model, a widely recognized mathematical representation of chemotactic behaviour, is utilized to describe the interactions between bacterial density and the concentration of the chemoattractant. Finite difference method is used to discretize the coupled partial differential equations of the Keller-Segel model. This approach allows for the efficient approximation of the spatial and temporal dynamics of the bacterial population and chemoattractant concentration. Through numerical experiments, we analyse the behaviour of the bacterial towards the chemoattractant. Additionally, we investigate the stability and convergence of the numerical scheme, ensuring the reliability of the simulation outcomes. This research provides valuable insights into the mechanisms underlying bacterial chemotaxis and offers a computational framework that can be extended to study other chemotactic systems.

Keywords: Chemotaxis; Keller-Segel; chemoattractant; Forward Difference Method

1 Introduction

Chemotaxis, a critical bacterial behaviour involving the sensing and response to chemical gradients [1], plays an important role in the navigation of bacterial movement. This process is facilitated through complex intracellular signalling pathways and receptor complexes positioned in the cell membrane. Cellular movement away from highly concentrated places is classified as diffusion. These receptor complexes can dynamically switch between active and inactive states in response to the presence of chemoattractant, guiding the bacteria towards favourable conditions. The activation of spatially specific cellular signal by chemoattractant causes cells to change direction and migrate towards the highest concentration of the chemoattractant [2].

The Keller-Segel model, a well-established mathematical framework, has been useful in explaining chemotactic movements. It is composed of linked partial differential equations that model the dynamics of chemoattractant concentration and cell density. However, the fundamental complexity of the Keller-Segel model, characterized by coupled nonlinear partial differential equations, complicates challenges for analytical solutions. Previous studies employing this framework have provided invaluable insights into the spatiotemporal dynamics of cellular behaviour in response to chemoattractant [3]. One significant application is in microbiology, where it has been useful in imitating the creation of elaborate spatial patterns in response to specific environmental conditions, as observed in phenomena such as E. coli behaviour [4].

Recognizing the limitations of the current Keller-Segel model, efforts have been devoted towards its remodelling to enhance its applicability and computational tractability. As part of this effort, the current research project concentrates on a minimalist approach to the Keller-Segel model. This includes converting the chemoattractant equation (v) into a one-dimensional diffusion equation, thus simplifying the model while preserving its key properties. This transformation is facilitated by employing the Forward Time Centered Space (FTCS) scheme, a numerical approach well-suited for solving partial differential equations.

Simultaneously, the movement of cells (*u*) is modelled using the finite difference method, employing a similar FTCS technique as utilized for the chemoattractant equation. This integrated approach enables for a thorough analysis of the spatiotemporal dynamics of cellular behaviour in response to chemoattractant. This study aims to minimal the Keller-Segel model, enhancing its computational efficiency and applicability to real-world scenarios. This report is conducted to address the challenges in modelling the movement of bacterial and chemotaxis using the Keller-Segel model by transforming the chemoattractant equation into a numerical approach involving one-dimensional diffusion and using the finite difference method to simulate bacterial movement, thereby providing a new framework for understanding the spatiotemporal dynamics of bacterial behaviour in response to chemoattractant.

2 Literature Review

2.1 Mathematical Approaches to Chemotaxis

Chemotaxis describes the movement of cells towards or away from chemical stimuli, an essential process in microbiology. For bacteria, chemotaxis allows them to locate nutrients and avoid harmful substances by moving along the chemical gradients. Chemotaxis responses in eukaryotic microorganisms are controlled by processes shared by all cells in the eukaryotic kingdom. These processes primarily include the regulation of microtubule- and/or microfilament-based cytoskeletal components [5]. For example, in the E. Coli, bacteria, the behaviour in chemotaxis is that they use their flagellar motors to swim towards or away from chemical gradients, and how stochastic fluctuations in the CheR protein affect their behaviour [6].

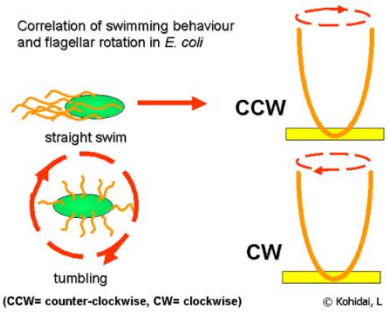


Figure 1: the movement of bacteria in straight and rotate

Mathematical modelling has been crucial in understanding chemotaxis. Various models have been developed to describe the spatial and temporal distribution of bacterial populations in response to chemical gradients. A study by [4], the use of partial differential equations to describe the spatial distribution of chemical gradients and bacterial populations, which provides insights into the mechanisms driving chemotaxis.

2.2 Keller-Segel Model

The Keller-Segel model, developed in 1970, is a foundational mathematical framework for describing chemotaxis [7]. Keller and Segel developed the Keller-Segel model to describe the aggregation of Dictyostelium discoideum, a form of slime mold, due to an appealing chemical component [8] It consists of coupled partial differential equations that model the dynamics of cell density and chemoattractant concentration. The classical Keller-Segel model is given by:

$$u_t = \nabla \cdot (k_1(u,v) \cdot \nabla u - k_2(u,v) \cdot u \cdot \nabla v) + k_3(u,v)$$
$$v_t = D_v \nabla^2 v + k_4(u,v) - k_5(u,v)$$

where *u* is Cell density, *v* is concentration of chemoattractant, D_v is chemoattractant diffusion, $k_1(u,v)$ is Cell diffusivity, $k_2(u,v)$ is chemotactic sensitivity, $k_3(u,v)$ is cell growth and death, $k_4(u,v)$ is chemoattractant production, and $k_5(u,v)$ is chemoattractant synthesis and degradation[9]. The model has been used to investigate a variety biological process, such as bacterial chemotaxis, embryonic development, and tumor growth. For example, this Keller-Segel model help to clarify the behaviour of biological tissues at various scales, ranging from the microscopic level of individual cells to the microscopic level of entire organisms [8].

2.3 Numerical Approach in Chemotaxis Modelling

To address the challenges posed by the Keller-Segel model, numerical method such as finite difference methods are used. These methods facilitate the simulation of chemotactic behaviour by discretizing the equations and enabling their solution on a computational grid. In the preceding paper, for example they describe numerical techniques and modelling of bacterial movement in response to chemoattractant [10]. The study compares the chemotaxis effectiveness of two populations of E. Coli bacteria, one with constant CheR concentration and the other with changing CheR concentration, using a two-dimensional numerical simulation. Simultaneously, the movement of cells is modelled using the finite difference method, implying a similar FTCS technique as utilized for the chemoattractant equation. This integrated approach enables a comprehensive investigation of the spatiotemporal dynamics of cellular behaviour in response to chemoattractant. Based on a review of previous research, an innovative approach to the Keller-Segel model has been developed, with the goal of streamlining the existing system of two partial differential equations. This includes changing one equation into a one-dimensional equation, where x represents the distance from the source, and solving both equations using the numerical finite difference method. To test this strategy, it must be used with documented data and conditions from earlier studies on bacterial chemotaxis. MATLAB was the primary computational tool used to create 2D visualizations of the spatiotemporal dynamics of chemoattractant distribution and bacterial cell movement under various conditions.

3 Methodology

3.1 Mathematical Formulation

The existing current Keller-Segel model is still too complicated to solve and simulate the cell behaviour. Some more assumption needs to be made to simplify the model. Thus, this study come up with minimal model of Keller-Segel model. The necessity assumption is as follow; (i) Individual cells undergo a combination of random motion and chemotaxis towards chemical attractant. (ii) Cell neither die or divide. (iii) The attractant is produced at constant rate. (iv) The degradation rate of attractant is also in the constant rate and (v) The attractant diffuses passively over the field. Hence, the minimal model of Keller-Segel model can be built as:

$$v_t = D_2 \cdot \nabla^2 v \tag{3.1}$$

$$u_t = D_1 \cdot \nabla^2 u - \mathcal{X} \cdot \nabla \cdot (u \cdot \nabla v) \tag{3.2}$$

where, D_1, D_2 *and* $\mathcal{X}$ be positive constants.

The equations can be solved numerically by using FTCS scheme, for the chemoattractant equation (3.1), it can be discretized as:

$$\frac{v_i^{n+1} - v_i^n}{\Delta t} = D_2 \frac{v_{i+1}^n - 2v_i^n + v_{i-1}^n}{\Delta x^2} \tag{3.3}$$

Then, the equation (3.3) can be simplified as:

$$v_i^{n+1} = v_i^n + \frac{D_2 \cdot \Delta t}{\Delta x^2}[v_{i+1}^n - 2v_i^n + v_{i-1}^n] \tag{3.4}$$

For the movement of cells equation (3.2), it also can be discretized as:

$$\frac{u_i^{n+1} - u_i^n}{\Delta t} = D_1 \frac{u_{i+1}^n - 2u_i^n + u_{i-1}^n}{\Delta x^2} - \mathcal{X}\left[\left(\frac{u_{i+1}^n - u_{i-1}^n}{2\Delta x}\right)\left(\frac{v_{i+1}^n - v_{i-1}^n}{2\Delta x}\right) + u_i^n\left(\frac{v_{i+1}^n - 2v_i^n + u_{i-1}^n}{\Delta x^2}\right)\right] \tag{3.5}$$

Then, the equation (3.5) can be simplified as:

$$u_i^{n+1} = u_i^n + D_1 \cdot r(u_{i+1}^n - 2u_i^n + u_{i-1}^n) - \mathcal{X} \cdot \frac{r}{4}[(u_{i+1}^n - u_{i-1}^n)(v_{i+1}^n - v_{i-1}^n)] + \mathcal{X} \cdot r[u_i^n \cdot (v_{i+1}^n - 2v_i^n + v_{i-1}^n)] \tag{3.6}$$

where $r = \frac{\Delta t}{\Delta x^2}$, i = discrete point for space, n = discrete point for time, Δt = time step size and Δx = space step size.

3.2 Von Neumann Stability Analysis

The stability for the new minimal model of Keller-Segel need to be analysed. Because the scheme is one for a partial differential equation, different method is utilized for their stability analysis. The method which will be employing is the von Neumann stability analysis. To assess the stability of numerical scheme applied to the minimal model of Keller-Segel, the well-established von Neumann method will be used in this study. Given the complexity of the cell density equation (*u*), this study will initially simplify the analysis by considering the heat equation as a representative as the equation can be symbolized with chemoattractant equation, (*v*). The heat equation in one-dimensional after discretised by using FTCS scheme is given by:

$$\frac{u_i^{n+1}-u_i^n}{\Delta t} = \alpha \frac{u_{i+1}^n - 2u_i^n + u_{i-1}^n}{\Delta x^2}.$$

where u_i^n represents the temperature at spatial point *i* and time step *n, Δt* is the time step size and *Δx* is the spatial step size. After substitute with error equation, then simplified the equation and use the amplification factor, G, the equation become:

$$|e^{\alpha \Delta t}| = \left|1 - \frac{4\alpha \Delta t}{\Delta x^2}\left(\frac{sin^2(k_m \Delta x)}{2}\right)\right| \leq 1$$

Then, after split to two parts, and assuming the $sin^2(k_m \Delta x)$ just a function, then this condition only hold if:

$$\frac{\alpha \Delta t}{\Delta x^2} \leq \frac{1}{2}$$

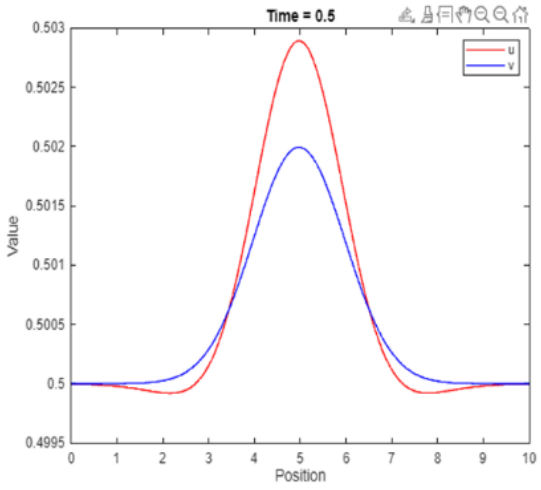
Hence, the ratio between the step size of time and the step size of space must not exceed $\frac{1}{2\alpha}$. In summary, the FTCS scheme is stable for the heat equation when step sizes are small enough to satisfy the requirement for stability. In this study, the minimal Keller-Segel model without advection terms will be looked, which means it will only have 2nd order differentiations in addition to non-differentiated terms.

4 Results and Discussion

The choice of parameter values plays a crucial role in accurately capturing the biological phenomena under investigation, and thus, optimizing these settings is essential for obtaining meaningful insights from simulations of Keller-Segel model. This study approach involves examining the sensitivity of the Keller-Segel model to change in each parameter, allowing the study to pinpoint the most influential factors driving chemotactic behaviour. For the minimal model Keller-Segel that will used in this study, the equation (3.4) and (3.6) will be involved with these parameters setting values: $\mathcal{X} = 4.02,\ D_1 = 2,\ D_2 = 1,\ L = 10,$ and $t = 0.5, 0.8, 1.0, 5.0$ while $\mathcal{X}$ is chemotactic sensitivity, D_1 is cell diffusivity, D_2 is chemoattractant diffusion, L is length of domain and t is total simulation time. The values for the space step and the time step size used were $\Delta x = 0.05\ and\ \Delta t = 1 \div 42000$, giving a step ratio of 1:210, which should be sufficiently small that the stability criterion is met for diffusion. Then, the number of spatial points is $N_x = L/\Delta x$ and number of time steps is $N_t = t/\Delta t$.

According to equations (3.4) and equation (3.6), the initial conditions for density cell (*u*) and concentration of chemoattractant (*v*) are set to have a value of 0.5 throughout the simulation domain, except for a single point at the centre, $x = \frac{N_x}{2}$ where there are set to 0.6. For the boundary condition, this study used Neumann boundary conditions for density cells and concentration of chemoattractant. This means that the derivative of *u* and *v* with respect to *x* evaluated at the first grid point, (x_1) and the last grid point, (x_N) is equal to zero.

To visually communicate the result of the numerical simulation of chemotaxis by Keller-Segel model, graphical representations were constructed by using MATLAB, depicting the fluctuations in *u* and *v* over different time intervals. These plots, featuring red lines for cell density and blue lines for chemoattractant concentration.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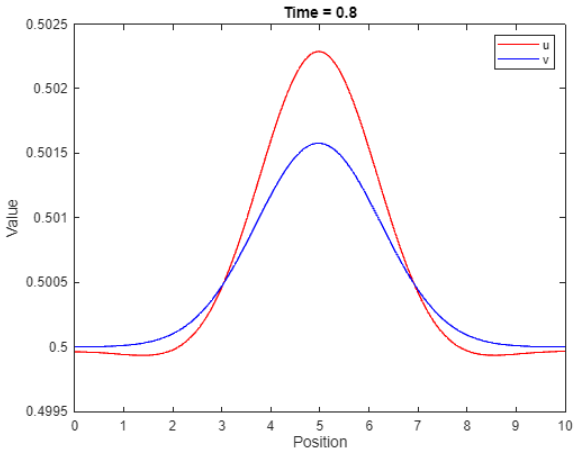
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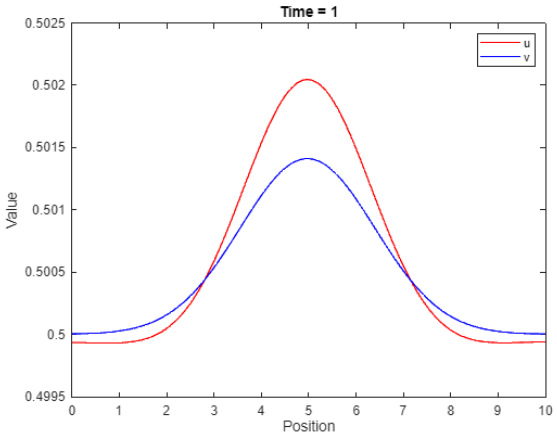
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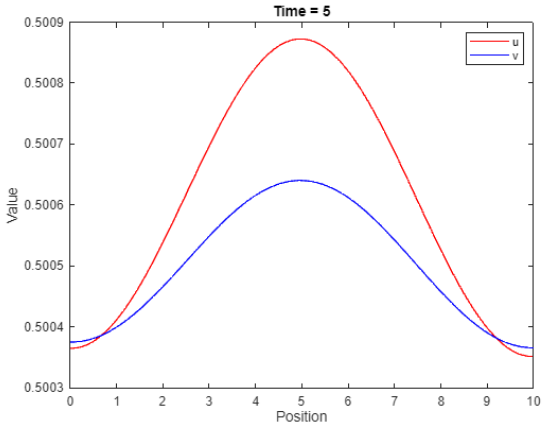
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0 1 2 3 4 5 6 7 8 9 10

Figure 2: A simulation of spatiotemporal distribution of cell density (red lines) and concentration of chemoattractant (blue lines) at distinct time points (specifically, *t*=0.5, 0.8,1,0 and 5.0).

These Figure 2 simulates the initial cell and chemoattractant concentrations, shows as high values at the domain's centre. This initial situation simulates biological circumstances in which cells are discharged from a concentrated source, such as a wound site or an infection point, and are surrounded by a high concentration of chemoattractant generated by the tissue. As time progresses, the position of cells and chemoattractant changes. The reduction in the values of cell density and chemoattractant concentration indicates that both elements are moving away from their initial concentration point. Concentration gradients drive this diffusion process, in which cells move from low to high concentrations of chemoattractant, led by chemical signals. Simultaneously, the chemoattractant diffuses away from its source, gradually reducing concentration gradients. Cells detect and move along the concentration gradient of the chemoattractant, migrating from areas of lower concentration to areas of higher concentration, a process known as chemotaxis. Over time, the chemoattractant diffuses away from its source, reducing the overall concentration gradient. As the chemoattractant spreads out, the concentration gradients become less steep, leading to a slower migration of cells. The interaction between cell density and chemoattractant concentration is dynamic, as cells move towards the chemoattractant, they can alter the local concentration, further influencing their movement. Eventually, an equilibrium state may be reached where the distribution of cells and chemoattractant becomes more uniform, with reduced directional movement of cells. This process is crucial in biological scenarios such as wound healing, where cells need to move towards the site of injury in response to chemoattractant signals.

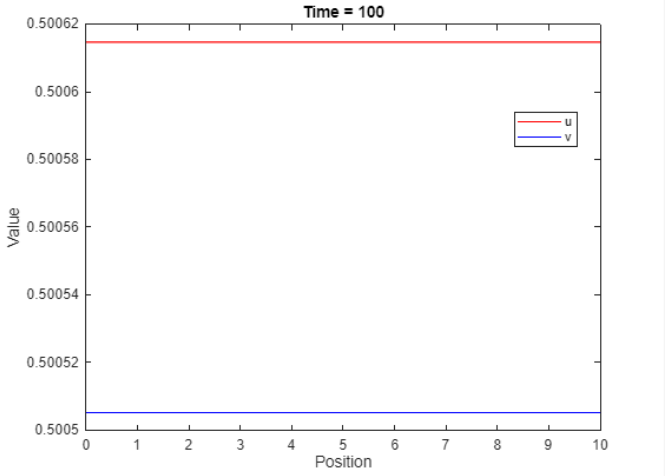

Figure 3: A simulation of the decreasing in the values of cell density and concentration chemoattractant over time.

Figure 3 suggests that the system is approaching a steady state after a several times. In the Keller-Segel model, this steady state shows a balance between cell and chemoattractant diffusion, as well as consumption and production rates. At this steady state, the concentrations of cells and chemoattractant are uniformly distributed across the domain, indicating a condition of dynamic equilibrium. However, it is important to consider that maintaining real steady state in biological systems can be difficult due to a variety of factors such as cell growth, chemoattractant degradation, and external perturbations. As a result, what we see in Figure 2 may reflect a quasi-steady state, in which the system appears to reach a stable distribution within the observed time but continues to experience dynamic changes beyond that.

The Keller-Segel model also can indicates the difference results of both density cells and chemoattractant concentration based on the values parameter of chemotactic sensitivity.

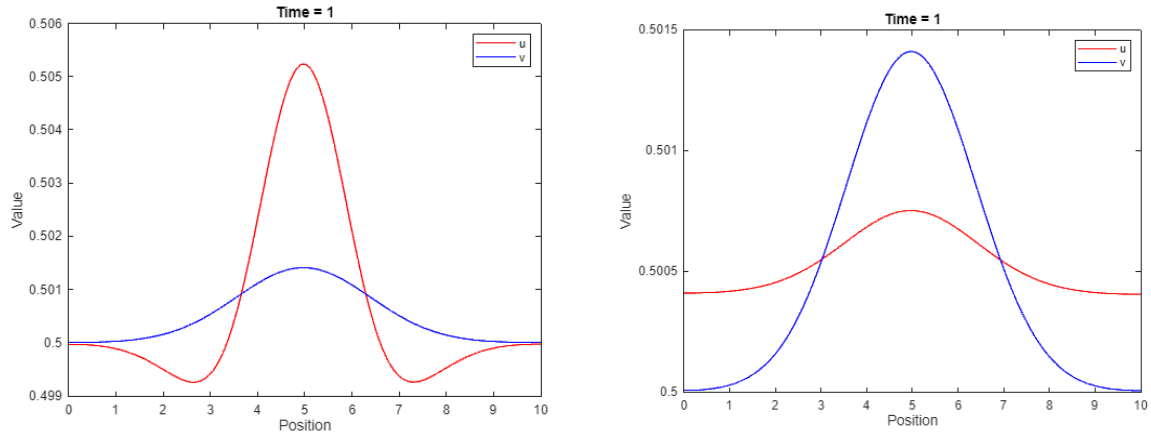

Figure 4: A representation of the dynamical of cell density and chemoattractant concentration. From left, the chemotactic sensitivity, $D_1 = 0.5$ and the chemotactic sensitivity, $D_1 = 10$.

Notably, in the figure 4, When the chemotactic sensitivity is reduced, the distant peak between (*u*) and (*v*) becomes more prominent, indicating that cells are less attracted to the chemical signal. This implies that with lower sensitivity values, cells respond less to the chemical gradient, resulting in a larger separation between the cell density and chemical concentration peaks. On the other hand, increasing chemotactic sensitivity causes the peak of (*v*) to become larger than that of (*u*). This means that at higher sensitivity levels, cells are more strongly attracted to the chemical signal, causing them to gather more closely near the chemical source. As a result, the chemical concentration peak becomes more conspicuous, outweighing the cell density peak. In biological situations, such findings are consistent with the expected behaviour of cells responding to chemoattractant gradients. Cells normally migrate towards higher concentrations of chemoattractant, led by chemical cues that direct them to areas of injury or infection. Thus, the model's representation of increased chemotactic response at higher sensitivities and decreased response at lower sensitivities reflects fundamental biological processes. This qualitative comparison with shown biological phenomena strengthens the model's validity by proving its capacity to simulate genuine cellular behaviours under a variety of chemotactic scenarios.

Conclusion

Chemotaxis is a fundamental biological process that affects phenomena such as immune response, wound healing, and microbial infection. Keller-Segel model is the central for understanding the behaviour of chemotaxis as it is a theoretical framework that can integrate principles of diffusion and chemotactic cell migration. Through this model, this study helps to gain insights into spatiotemporal dynamics of cell density and chemical concentration gradients and unravelling the interplay between migration and chemical signalling. By using the minimal model of Keller-Segel, this study simulates the diffusion-driven processes where cell density and chemoattractant concentration spread from initial high-concentration points, highlighted the dynamic nature of chemotactic responds. Despite challenges in achieving a true steady state due to various biological factors, the model effectively demonstrates how chemotactic sensitivity influences the spatial patterns crucial for cell migration.

In future research, more research is needed to improve the understanding of chemotaxis and its applications. The combination of experimental validation and computational simulation can close the gap between theory and observation. Multiscale techniques, exploring disturbing effects, and clinical applications also can help the theory and practice to enhance the understanding deeper of chemotaxis.

References

[1] Murray, J. D. (2002). *Mathematical biology. I*, volume 17 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, New York, third edition. An introduction.

[2] Wang, F. (2009) "The Signaling Mechanisms Underlying Cell Polarity and Chemotaxis." *Cold Spring Harbor Perspectives in Biology*, vol. 1, no. 4, 2 Sept. 2009, pp. a002980–a002980, https://doi.org/10.1101/cshperspect.a002980

[3] Hazelbauer, Gerald L. (2012) "Bacterial Chemotaxis: The Early Years of Molecular Studies." *Annual Review of Microbiology*, vol. 66, no. 1, 13 Oct. 2012, pp. 285–303, https://doi.org/10.1146/annurev-micro-092611-150120

[4] Tindall, M. J., et al. (2008) "Overview of Mathematical Approaches Used to Model Bacterial Chemotaxis II: Bacterial Populations." *Bulletin of Mathematical Biology*, vol. 70, no. 6, 19 July 2008, pp. 1570–1607, https://doi.org/10.1007/s11538-008-9322-5

[5] Stock, J. B., and M. D. Baker. (2009) "Chemotaxis." *ScienceDirect*, Academic Press, 1 Jan. 2009, www.sciencedirect.com/science/article/pii/B9780123739445000687

[6] Matthäus, F., et al. (2009) "E. Coli Super diffusion and Chemotaxis—Search Strategy, Precision, and Motility." *Biophysical Journal*, vol. 97, no. 4, Aug. 2009, pp. 946–957, https://doi.org/10.1016/j.bpj.2009.04.065

[7] Horstmann, D. (2003). From 1970 until present: the Keller-Segel model in chemotaxis and its consequences. i. Jahresber. Deutsch. Math. - Verein., 105(1):103–165

[8] Horstmann, Dirk, and Michael Winkler. (2005) "Boundedness vs. Blow-up in a Chemotaxis System." *Journal of Differential Equations*, vol. 215, no. 1, Aug. 2005, pp. 52–107, https://doi.org/10.1016/j.jde.2004.10.022

[9] Hillen, Thomas, and Kathleen M Painter (2009). "Global Existence for a Parabolic Chemotaxis Model with Prevention of Overcrowding." *Advances in Applied Mathematics*, vol. 26, no. 4, 1 May 2001, pp. 280–301,https://doi.org/10.1006/aama.2001.0721

[10] Kollmann, Markus, et al. (2005) "Design Principles of a Bacterial Signaling Network." *Nature*, vol. 438, no. 7067, 24 Nov. 2005, pp. 504–507, https://doi.org/10.1038/nature04228