Mathematical Method of Bioengineering
Group Presentation

Keller-Segel Models for Chemotaxis

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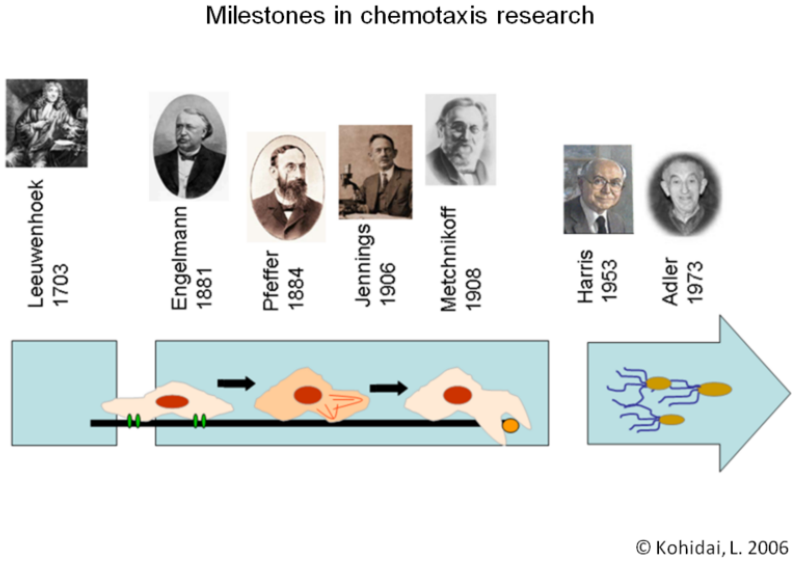
1. Motivation

For every creature in the world, their response toward internal and external signals plays an important role in survival. For animal, such movement can be finding the location for food or tracing for attractive mates. For cells in the body, this can be sperm cells are attracted to chemical substances released from the outer coating of the egg or fibroblasts into wounded regions to initiate healing.

Here, the directed movement of cells and organisms in response to chemical gradients, chemotaxis, has attracted significant interest due to its critical role in a wide range of biological phenomena.

The description of chemotaxis was first made by T W. Engelmann (1881) and W.F. Pfeffer (1884) in bacteria and H.S. Jennings (1906) in ciliates [1]. The significance of chemotaxis in biology and clinical pathology was widely accepted in the 1930s. The most fundamental definitions belonging to the phenomenon were also drafted by this time. The most important aspects in quality control of chemotaxis assays were described by H. Harris in the 1950s.



However, to talk about the modern chemotaxis that exists from the revolution of technology, we'd like to introduce the well-known model: Keller–Segel model(KS model). Theoretical and mathematical modeling of chemotaxis dates to the works of Patlak in the 1950s and Keller and Segel in the 1970s [2]. The general form of the model is:

$$u_t = \nabla(k_1(u,v)\nabla u - k_2(u,v)u\nabla v) + k_3(u,v)\,,$$

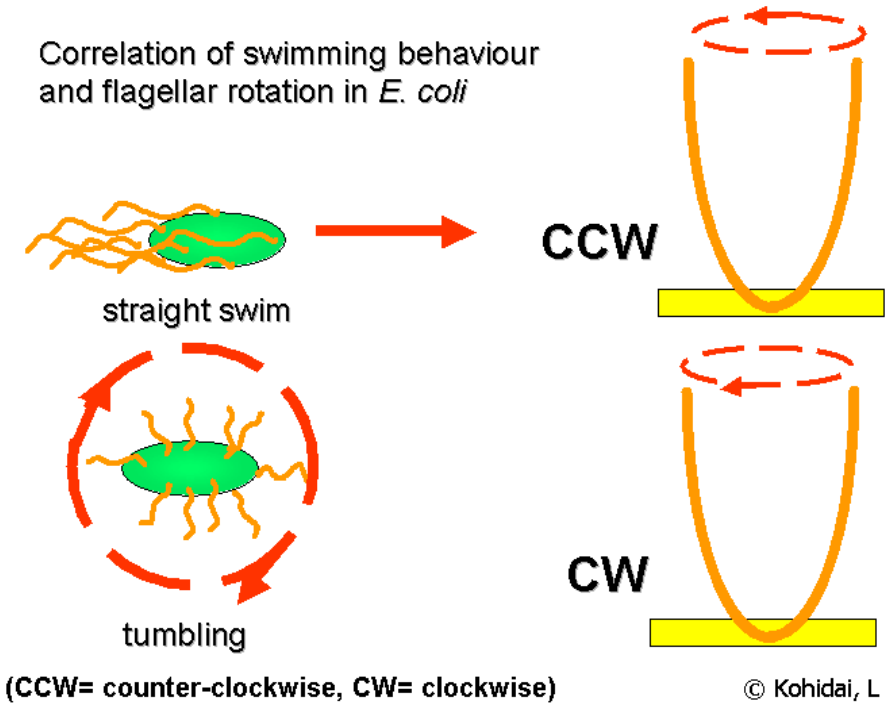
$$v_t = D_v\Delta v + k_4(u,v) - k_5(u,v)v,$$

It is a reduced form under quasi-steady-state assumptions on both of the models.

Here u denotes the cell density and v is the concentration of the chemical signal. K1 is the diffusivity of the cells, k2 is the chemotactic sensitivity, k3 describes the cell growth and death. In signal concentration model, k4 and k5 describe the production and degradation of the chemical signal. Note that cell migration is dependent on the gradient of the signal.

KS equation has been widely used for chemotaxis since its ability to capture key phenomena and intuitive nature. For example, *E. coli*, can be induced to form a variety of spatial patterns when provided a suitable environment, such reaction can be simulated by KS model. By utilizing KS equation, we can also understand whether chemotaxis may underpin embryonic pattern forming processes, such as the formation of the primitive streak, pigmentation patterning in snakes. We can also predict the tumor cell-induced angiogenesis, and macrophage invasion into tumor.

One famous example of chemotaxis is the movement of *E. coli*. *E. coli* has several flagella, which can rotate either counter-clockwise or clockwise rotation. Counter-clockwise rotation will move the bacteria in a straight line while clockwise rotation will only make bacteria tumbling in place. The movement of bacteria is actually looked like random walk with relatively straight swims since bacteria cannot go in a straight line for more than a few seconds due to rotational diffusion. Therefore it needs to repeatedly evaluate the chemical gradient to decide going straight or rotate [3].



2. Formulation of Classic Keller-Segel Model and Minimal Model

The classical Keller-Segel model (KS model) is composed by a set of equations. Equation (2.1) represents the cell density variation over time, and equation (2.2) represents the chemical attractant concentration variation over time [4].

$$u_t = \nabla \cdot (D_1 \nabla u - \chi u \nabla v) + f \tag{2.1}$$

$$v_t = D_2 \Delta v + g - h \tag{2.2}$$

Where u_t represent $\frac{\partial u}{\partial t}$, D_1 is the diffusion coefficient of cell, χ is the chemotactic sensitivity, v is the chemical attractant concentration, and function f regulates the cell die/divide, which controls the gross cell number in our observation. D_2 in equation (2.2) represents the diffusion coefficient of chemical attractant, function g regulates the production rate of chemical attractant, and function h regulates the degradation rate of chemical attractant.

Although the parameters in classical KS model are straight forward, it is very important to understand the formulation steps of classical KS model.

We start deriving the classical KS model from a very basic assumption by letting an arbitrary surface S enclosing a volume V [5]. According to the general conservation equation, the rate of change of the amount of material u in V equals to the rate of flux of u across S out of V plus the u created/disappeared in V. Thus

$$\frac{\partial}{\partial t}\int_V u dv = -\int_S \Phi \cdot n ds + \int_V f dv \tag{2.3}$$

where Φ is the flux of material u and f is the source term of u. According to the Divergence theorem

$$\int_S \Phi \cdot n ds = \int_V \nabla \cdot \Phi dv \tag{2.4}$$

and since the function of the cell density u is continuous, and the volume V is arbitrary, the integrand must be zero. Thus, the equation can be rewritten as

$$\int_V (u_t + \nabla \cdot \Phi - f) dv = 0 \tag{2.5}$$

where we rewrite $\frac{\partial u}{\partial t}$ into u_t. We then simplified the equation into

$$u_t = \nabla \cdot (D \nabla u) + f \tag{2.6}$$

This equation holds for a general flux transport Φ whether by diffusion or by some other processes.

Since the flux in our chemotaxic model is contribute by to two different terms, which are cell diffusion flux and chemotaxis flux.

$$\Phi_{total} = \Phi_{diff} + \Phi_{chemo} \tag{2.7}$$

Where we consider Fick's law as the process of cell diffusion flux.

$$\Phi_{diff} = -D\nabla u \tag{2.8}$$

And the chemotaxis flux,

$$\Phi_{chemo} = \chi u \nabla v \tag{2.9}$$

where χ is chemotactic coefficient. The analysis of χ in various forms has been carried out by different researchers.

Now, plug in the Φ_{total} into equation (2.6) yields

$$u_t = \nabla \cdot D_1 \nabla u - \nabla \cdot \chi u(u,v) \nabla v + f(u,v) \tag{2.10}$$

the cell density part of the classical KS model. By repeating the same process above, for one chemical attractant, we yield the chemical attractant concentration part of the classical KS model.

$$v_t = \nabla \cdot D_2 \nabla v + g(u,v) - h(u,v) \tag{2.11}$$

Yet, the classical KS model is still too complicated for us to solve and to simulate the cell behavior. Some more assumption needs to be made to simplify our model. Thus, we come up with Minimal Model of classical KS model. The necessity assumptions are as follow,

- Individual cells undergo a combination of random motion and chemotaxis towards chemical attractant.
- Cell neither die nor divide.
- The attractant is produced at constant rate.
- The degradation rate of attractant is linearly dependent on its concentration.
- The attractant diffuses passively over the field.

Using these assumptions, the cell proliferation/death term f(u,v) of equation (2.10) is now 0, the term g(u,v) in the equation (2.11) is now only the function of u, and the term h(u,v) in the equation (2.11) is now only the function of v. Taking D_1, D_2, and χ also be positive constant, thus the parabolic quasi-linear equation of minimal model of KS model can be noted as

$$u_t = \nabla \cdot (D_1 \nabla u - \chi u \nabla v) \tag{2.12}$$

$$v_t = \nabla^2 D_2 v + g(u) - h(v) \tag{2.13}$$

3. Analyzation of Keller-Segel Minimal Model

$$u_t = \nabla(D_1 \nabla u - \chi u \nabla v) \tag{3.1}$$

$$v_t = D_2 \nabla^2 v + au - bv \tag{3.2}$$

As shown in equation (3.1) and (3.2), this is a set of coupled non-linear PDEs, so they can't be solved analytically. However, we can simplify this model to study some other properties of the KS model.

Homogeneous Steady States

Homogeneous steady state of a PDE model means that the solution is constant in both space and time. So the Ut and Vt must satisfy:

$$u(x,t) = u1,\ v(x,t) = v1$$

$$\frac{\partial u1}{\partial t} = \frac{\partial v1}{\partial t} = 0$$

$$\frac{\partial u1}{\partial x} = \frac{\partial u1}{\partial x} = 0$$

$$\Rightarrow\ au1 = bv1$$

This means that attractant rate must be exactly balanced by the decay rate.

Stability Analysis

If the homogeneous steady state is stable to small perturbations in the absence of diffusion but unstable to small spatial perturbations when diffusion is present, the system exhibits Turing instability. The main process driving the spatially inhomogeneous instability is diffusion.

In determining the necessary and sufficient conditions for diffusion-driven instability of the steady state, we look at the spatially inhomogeneous perturbations and then explore whether the perturbations are amplified or attenuated.

If amplification occurs, then a situation close to the spatially uniform steady state will destabilize, leading to some new state in which spatial variations predominate, and even there could possibly exist oscillating solutions. This process is supposed to happen by chaning the parameters D1,D2, χ, and a.

We perform the stability analysis in one dimension. Introduce the variables u' and v' by the definitions

$$u(x,t) = u1 + u'(x,t)$$
$$v(x,t) = v1 + v'(x,t)$$

Plug u' into equation (3.1) , we get

$$\frac{\partial u'}{\partial t} = D_1 \frac{\partial^2 u'}{\partial x^2} - \chi \left((u1 + u') \frac{\partial^2 v'}{\partial x^2} + \frac{\partial u'}{\partial x} \frac{\partial v'}{\partial x} \right)$$

This is still non-linear equation. So we assume u' and v' are very mall.

$u' \frac{\partial^2 v'}{\partial x^2}, \frac{\partial u'}{\partial x} \frac{\partial v'}{\partial x}$ are smaller compared to other parts of the equation and can be neglected. Then we get:

$$\frac{\partial u'}{\partial t} = D_1 \frac{\partial^2 u'}{\partial x^2} - \chi u1 \frac{\partial^2 v'}{\partial x^2} \qquad (3)$$

Similarly, plug v' into (2), we get

$$\frac{\partial v'}{\partial t} = D_2 \frac{\partial^2 v'}{\partial x^2} + au' - bv' \qquad (4)$$

The boundary conditions are

$\frac{\partial u'}{\partial x} = 0$ at x=0 and x=L

$\frac{\partial v'}{\partial x} = 0$ at v=0 and v=L

Linearize u' and v' into a vector

$$\text{y=} \begin{pmatrix} u - u1 \\ v - v1 \end{pmatrix}$$

Plug into equation (3) and (4)

$y_t = A\nabla^2 y + By$ (7) Where A=$\begin{pmatrix} D_1 & -\chi u1 \\ 0 & D_2 \end{pmatrix}$ B=$\begin{pmatrix} 0 & 0 \\ a & -b \end{pmatrix}$

Define $\mathbf{Y}$(x) as time-independent solution of spatial eigenvalue

$$\nabla^2 \boldsymbol{Y} + k^2 \boldsymbol{Y} = 0$$

We can know the solution of Y is in the form:

$$\boldsymbol{Y} \propto \cos\left(\frac{\pi n x}{L}\right)$$

So the full solution should be in the form:

$$y(\boldsymbol{x},t)=\sum_{k} C_k e^{\lambda t}\, Y_k(x)$$

Plug this form into (7), we get

$$\lambda Y_k = BY_k - k^2 \mathrm{A} Y_k \qquad (8)$$

To solve the eigenvalue λ

$$\begin{vmatrix} \lambda + k^2 D_1 & -k\chi u1 \\ -a & \lambda + b + k^2 D_2 \end{vmatrix} = 0$$

$$\lambda^2 + q\lambda + \mathrm{r} = 0$$

$$\text{Where } q = k^2(D_1 + D_2) + b$$

$$r = k^2[D_1(D_2 k^2 + B) - \chi u1 a]$$

So different values of D_1, D_2, χ will determine the stability of this system.

Numerical Solution

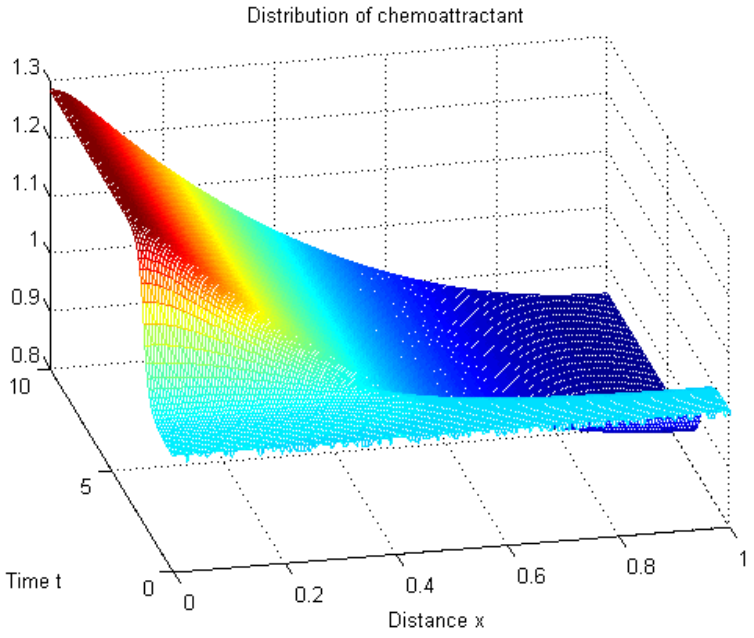
The equations can be solved numerically. The solution is:

$$\frac{u_i^{n+1} - u_i^n}{\Delta t} = D\frac{u_{i-1}^{n-1} - 2u_i^{n-1} + u_{i+1}^{n-1}}{\Delta x^2} - \chi\left(\frac{u_{i+1}^{n-1} - u_{i-1}^{n-1}}{2\Delta x}\frac{v_{i+1}^{n-1} - v_{i-1}^{n-1}}{2\Delta x}\right.$$

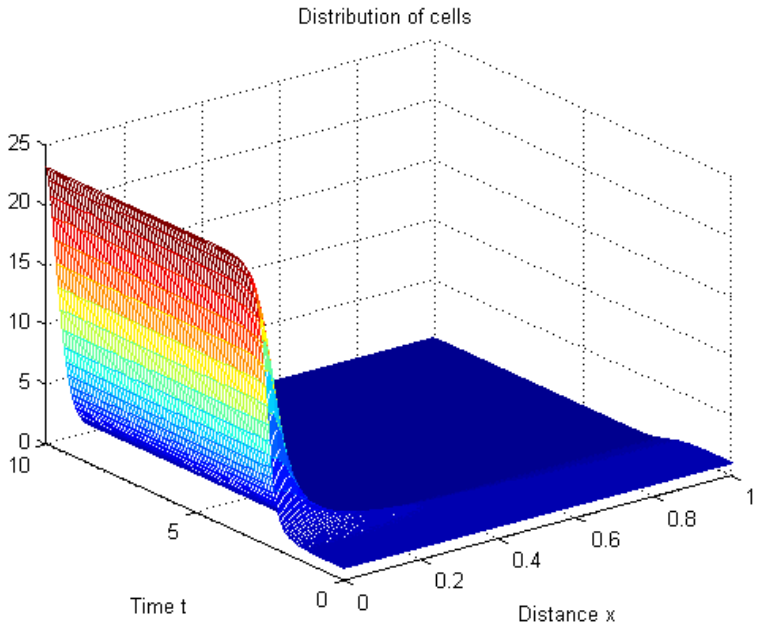
$$\left. + \mathrm{u}\frac{v_{i-1}^{n-1} - 2v_i^{n-1} + v_{i+1}^{n-1}}{\Delta x^2}\right)$$

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

Where i indicates distance and n indicates time.



This is our matlab result.D_1=0.1, D_2=1, Initial condition: u(x,0)=1, 1 v(x,0)=$1+0.1e^{-10x^2}$ With zero flux boundary condition.



We can see that migrations of cells are influenced by distribution of external chemical signals. Cells tend to move to the places with higher concentrations of chemoattractant.

4. Modeling the chemotaxis of E. coli

The migration of E. coli can be directed by chemical gradients created by aspartate. Here, we look at the migration of E. coli cells, taking into consideration the randomness of their movement as well as empirical data. The movement of the E. coli can be modeled by the statement [6]:

$$Tumbling \begin{cases} yes\ if\ 1 > \dfrac{c(t)}{c(t-1)} \\ yes\ if\ \dfrac{X}{100} * \dfrac{c(t)}{c(t-1)} < rand \\ no\ otherwise \end{cases}$$

E. coli check the current chemoattractant concentration roughly every second [7]. If the concentration of aspartate has decreased since the last time the concentration was checked, the cell will tumble. But if the concentration has increased, the cell will compare the ratio of current concentration over previous concentration multiplied by a factor X/100, where X is some percentage to a random number between 0 and 1. If this second condition is met, the cell will also tumble. This makes it possible for the cell to tumble despite travelling up the concentration gradient. Additionally, due to the ratio of concentrations, a cell experiencing a greater jump in concentration will be less likely to tumble.

The diffusion of the chemoattractant can be modeled by one-dimensional diffusion, where x is the distance from the source:

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}$$

The concentration of the chemoattractant is zero everywhere to begin with:

$$IC: C(x,0) = 0$$

And the concentration at the source will be held constant while the concentration at an infinite distance from the source will remain zero.

$$BC1: C(0,t) = C_0$$

$$BC2: C(\infty,t) = 0$$

By applying a Laplace transform to the diffusion equation, we obtain:

$$sC(x,s) - C(x,0) = D\frac{\partial^2 C(x,t)}{\partial x^2}$$

With the initial condition, this can be reduced to:

$$D\frac{\partial^2 C(x,t)}{\partial x^2} - sC(x,s) = 0$$

This is now a simple ODE with solution of the form:

$$C(x,s) = k_1 e^{\sqrt{\frac{s}{D}}x} + k_2 e^{-\sqrt{\frac{s}{D}}x}$$

The boundary conditions must be transformed into the s domain and are applied to the above equation to obtain the values of k_1 and k_2:

$$BC2: L\{C(\infty,t)\} = 0 \rightarrow k_1 = 0$$

$$BC1: L\{C(0,t)\} = \frac{C_0}{s} = k_2$$

Therefore, the diffusion equation in the s domain is:

$$C(x,s) = \frac{C_0}{s} e^{-\sqrt{\frac{s}{D}}x}$$

Transforming back to the time domain, we obtain the final equation describing the diffusion of the aspartate:

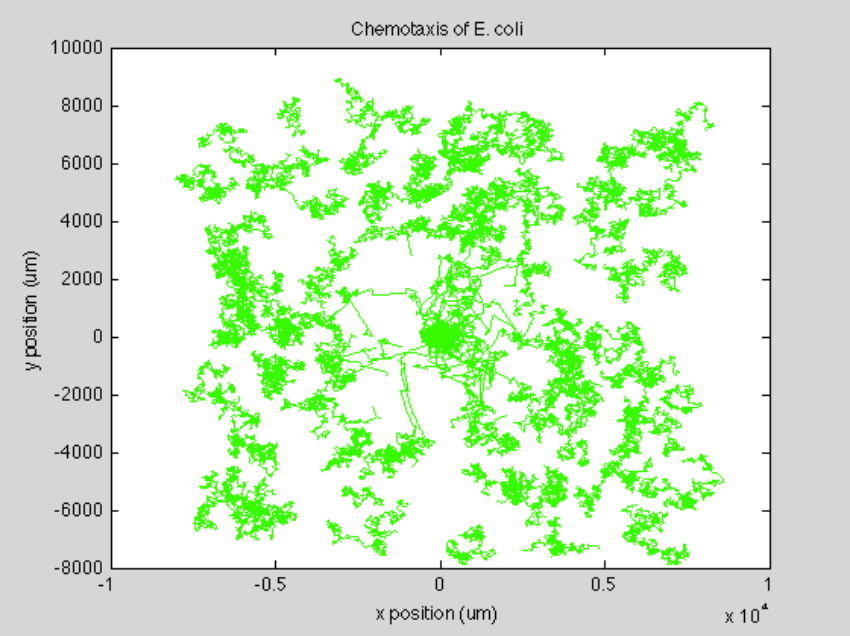
$$C(x,t) = C_0\, erfc\left(\frac{x}{2\sqrt{Dt}}\right)$$

The system was modeled with the following biological parameters:

- $D_{asp} = 8.0 \times 10^{-10}\ m^2/s$ [8]
- $v_{avg} = 27\ \mu m/s$ [4]
- $C_0 = 6938\ mol/m^3$
- $d_{E.coli} = 2\ \mu m$
- $X = 60$
- Minimum detectable concentration of aspartate $= 10^{-8}$ M [9]

V_{avg} describes the average speed of the bacteria. C_0, the concentration of aspartate at the source, is given the value of the saturation point of aspartate in water. The diameter of the E. coli is two microns. And X, the variable scaling the probability of tumbling while travelling up the chemical gradient, is 60. Additionally, the cells cannot detect the presence of aspartate below a concentration of 10^{-8} M.

By applying the relationships and variable mentioned, the paths taken by E.coli cells can be seen in the figure below. It is clear that the cells migrate towards position (0,0), which is the source of the chemoattractant. The cells further from the center continue to tumble because the concentration of the chemoattractant does not reach a high enough value for them to recognize it. Additionally, it is apparent that cells travelling up the chemical gradient do not simply take a direct path to the center, but still experience tumbling to some degree.



4. Conclusion

According to our analysis of chemotaxis simulation via KS model, we come up with three main conclusions:

- Under certain conditions KS model applied well:
  1. Values of D1, D2, B, and n must be small.
  2. Values of L, x, A, and u must be large.
- KS model is a combination of Fourier's law, Fick's law, random walk approaches, and stochastic processes.
- Able to simulate the time variant cell behavior and the formation of steady state.

5. Future Works

We would like to extend out discussion of multi-chemical species combines within one simulation equation; time delay between signal detection and response; cell collisions with we ignore in our simulation; and add in the cell division and death ratio to our system. Also, the reality of any specific biological system are actually a combination of different KS models, one or two models is simply not enough. Furthermore, we would like to extend our model to 3D.

6. Acknowledgement

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7. Reference

1. http://en.wikipedia.org/wiki/Chemotaxis

2. Horstmann, D.: From 1970 until present: the Keller–Segel model in chemotaxis and its consequences I. Jahresberichte DMV 105(3), 103–165 (2003)

3. http://en.wikipedia.org/wiki/File:ChtxCCW_CW.png

4. Evelyn F. Keller, Lee A. Segel. “Initiation of Slime Mold Aggregation Viewed as Instability”. *J. theor. Biol.* (1970) 26, 399-4 15

5. T. Hillen · K. J. Painter. “A user’s guide to PDE models for chemotaxis”. *J. Math. Biol.* (2009) 58:183–217

6. Betney, Russel et al. “Pico Plumber.” *University of Aberdeen*, 2009.

7. Segall, Jeffrey et al. “Temporal comparisons in bacterial chemotaxis”. *USA Biophysics*, 1986: 8987-8991.

8. Polson, Alfred. “On The Diffusion Constants of the Amino-Acids”. Institute of Physical Chemistry, *The University of Upsala, Sweden*. 20 August 1937.

9. Maeda, Kayo et al. “Effect of Temperature on Motility and Chemotaxis of Escherichia coli”. *J. Bacteriology*, 1976: 1039-1046.

10. Adler, Julius. “Chemotaxis in Bacteria”. *Annu. Rev. Biochem*, 1975: 341-356.