Adaptation and Sensitivity Analysis of E. Coli Chemotaxis System

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Adaptation and sensitivity are essential properties for living organism to chase food sources. The chemotaxis system of Escherichia coli (E. coli) is one of the biological systems that behaves these two properties. Also, its molecular reaction and experiments are relatively well-studied. However, the mathematical relation between system parameters and these two properties are still needed. In this project, E. coli chemotaxis system is analyzed in the control-systems point of view.

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1. INTRODUCTION

Adaptation and sensitivity properties are essential for the living organism. Escherichia coli (E. coli), a kind of bacteria, can sense and track food sources by its chemotaxis system [1–4]. The moving of E. coli is a dynamic process, an E. coli cell stochastically changes its direction by tumbling [2]. Thus, E. coli can present chemotaxis feature by changing the tumbling frequency[2]. When the moving direction is toward a food source, E. coli lowers the tumbling frequency to keep approaching to a food source; on the other hand, when the moving direction is far from a food source, E. coli raises the tumbling frequency to stochastically change the current moving direction [2].

Why can E. coli present chemotaxis feature? and how does it accomplish this task? First, E. coli knows whether it is approaching a food source or not by sensing the ligand concentration, and the changes of concentration is correlated to the distance between E. coli and a food source. Second, E. coli processes the signal by CheR protein system (fig. 2), a cascade protein system that can differentiate the signal and also have properties similar to Kalman Filter [2]. Third, by sensing and processing ligand signal with CheR protein system, E. coli can adjust the tumbling frequency and eventually navigate to a food source (fig. 2).

Figure 1 shows the molecular details of E. coli chemotaxis pathway[2, 5]. After a receptor, which is composed of CheW and CheA protein, attaches to ligand, CheR will label this receptor with methyl group and initiate the signaling. Besides, CheB and CheZ protein are part of the negative feedback control, and CheY represents the output, which is the tumbling frequency (fig.1).

In this project, I focused on the parameter modulation, sensitivity, and adaptation, by both mathematical and simulated approaches. This project provides a control-systems point of view on E.coli chemotaxis system, which have potential application in bioengineering field.

2. METHODS

Definition of Sensitivity

Sensitivity represents the ability of biological system to sensing the changes of environmental signal. Let O_{peak} be the peak value of step response, O_1 be the initial value. The eq. 1 reveals the mathematical relation,

$$Sensitivity = \left| \frac{(O_{peak} - O_1)/O_1}{(I_2 - I_1)/I_1} \right| \tag{1}$$

Where I_1, I_2 respectively represent the values before and after transition of step begins (fig. 3).

Definition of Adaptation

Adaptation represents the ability of biological system to ignore the DC input signal. Let O_2 be the final value of step response.

$$Adaptation = \left| \frac{(O_2 - O_1)/O_1}{(I_2 - I_1)/I_1} \right|^{-1} \tag{2}$$

The reciprocal is applied to make positive relation between adaptation property and its value (fig. 3).

System Analysis

In this project, both mathematical derivation and SIMULINK (www.mathworks.com) are used to investigate the influences of parameter modulation on sensitivity and adaptation. There are several chemotaxis system models that can simulate the properties of adaptation and sensitivity, and a linear model with integral feedback [1] is discussed in this project (fig. 2 and fig. 4), the variables of the block diagram are selected as linear, small signal deviations of the averages of the several quantities away from their equilibrium values (fig. 2). First, the outputs of the

system are the activity of Che proteins and resulting motion in single x direction. The model is based on the following facts [1]:

- It is observed that when a ligand binds to a receptor, the reaction within pathway of Che proteins are simultaneous.
- When insertion of a concentration of attractants, the "activity" is measured by CheA drops quickly, then slowly recovers to exactly the same steady-state level. This property is called adaptation of activity.

  Parameters are displayed in table 1.

3. RESULTS

Transfer Function of Activity

According to the block diagram (fig. 4), the transfer function is derived as the eq. 3,

$$\begin{aligned} y &= \frac{kk_M}{s}(k_{CheR} - y) - R(s)k \\ &= -k\frac{sR(s) - k_{CheR}k_M}{s + k_1k_3} \\ &= \frac{-ks}{s + kk_M}R(s) + \frac{-kk_M}{s + kk_M}k_{CheR} \end{aligned} \tag{3}$$

The first part in eq. 3 reveals the response of this system is a high-pass filter, which means it filters out low frequency changes. Besides, the second part is related to the basal activity (also defined as final state in this project), which is equal to paramenter k_{CheR}.

Step Response

The step response is the condition that the food source suddenly drops in to the territory of E. coli cells. Therefore, the ligand signal is a step function, and the response is derived in eq. 4. Let $R(t) = u_0 1(t) \overset{Laplace}{\rightarrow} R(s) = \frac{u_0}{s}$,

$$y_{step}(s) = \frac{-k}{s + kk_M}u_0 + \frac{kk_M}{s + kk_M}k_{CheR} \tag{4}$$

$$\begin{aligned} y_{step}(t) &= -ku_0e^{-kk_Mt} + kk_Mk_{CheR}e^{-kk_Mt} \\ &= (kk_Mk_{CheR} - ku_0)e^{-kk_Mt} + k_{CheR} \end{aligned} \tag{5}$$

In eq. 5, both parts exponentially decay under time-constant kk_M, and latter term in eq. 5 represents the initial value $y(0^-)$.

Sensitivity Analysis

Because y(t) represents the frequency of tumbling, which is equal or greater than 0 (table 1). Therefore, eq. 5 must be satisfied under eq. 6

$$y(t_{peak}) = kk_Mk_{CheR} - ku_0 > -k_{CheR} \tag{6}$$

Therefore, the sensitivity under step response $r(t) = u_0 1(t)$ can be calculated by eq. 7,

$$\begin{aligned} Sensitivity &= \frac{(y(t_{step}) - k_{CheR})/k_{CheR}}{u_0} \\ &= \frac{kk_Mk_{CheR} - ku_0}{K_{CheR}u_0} \end{aligned} \tag{7}$$

In eq. 7, there is negative relation between sensitivity and u_0, the simulation (fig. 5) also shows there is optimized sensitivity under the constraint of eq. 6, and one of these combination is $k = 0.5; k_M = 2.0; k_{CheR} = 1$

Adaptation Analysis

According to eq. 3, the steady state of system in fig. 4 is equal to k_{CheR}. Therefore,

$$y_{step}(\infty) = k_{CheR} \tag{8}$$

$$\begin{aligned} Adaptation &= \frac{k_{CheR} - k_{CheR}}{u_0} \\ &= 0 \end{aligned} \tag{9}$$

This system possesses the property of perfect adaptation, which means the final state of step response is exactly equal to the initial state.

4. DISCUSSION

The transfer function of this chemotaxis system behaves like high-pass filter and the basal activity is controlled by k_{CheR}. When E. coli is approaching to a food source, the concentration of ligand will increase, and this system can receive the high-frequency signal and determine the tumbling frequency, which can prevent E. coli from swimming away from a food source (eq. 3).

Besides, the step response represents the condition that a suddenly change of ligand concentration, this condition can be experimentally implemented by adding glucose to the test tube which contains E. coli. According to the eq. 5, the response can first react to the step response and eventually return to the basal activity. Therefore, when a E. coli cell is not approaching to a food source, it will maintain its basal frequency of tumbling, which can probably navigate it the right direction. The simulation also confirms this phenomenon (fig. 5).

The sensitivity analysis implies that the u_0 of step response have negative correlation with sensitivity, and k, k_M can increase sensitivity. Sensitivity represent the ability of biological system to detecting changing signal. On the other hand, the adaptation analysis reveals that this system possesses perfect adaptation (eq. 9). The adaptation is the ability that biological system can return to the initial value after input stops changing.

These results implied the possibile modulation to optimize a biological system. By the aid of modern genetic technology, the structure and quantity of each protein in biological system can be modified for potential application. However, the biological system still obey the rules of control systems. When designing biological system, the concept of control systems in engineering can provide better strategy than trial-and-error.

5. CONCLUSION

First, The transfer function of the linear E. coli chemotaxis model have two terms that will exponentially decay with time-constant kk_M during the step response. Second, sensitivity and u_0 in step response has negative correlation. Third, the constraint of the parameters are derived in equation 6. And the last, this linear E. coli chemotaxis system possesses property of perfect adaptation, which means its final value is exactly equal to initial value after step response.

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6. FIGURES AND TABLES

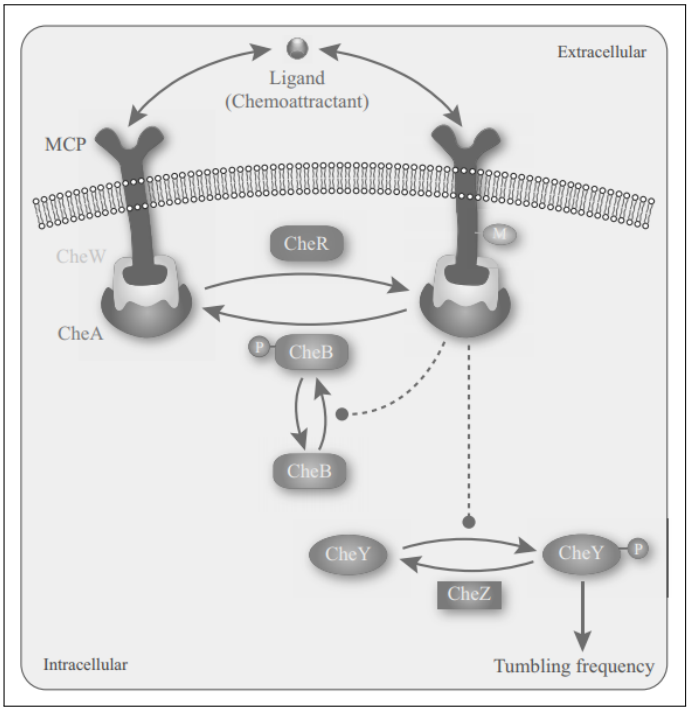

Fig. 1. Chemotaxis regulation in response to variations in the concentration of chemoattractant. (picture from [5])

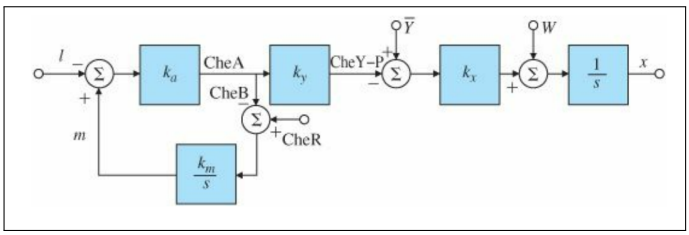

Fig. 2. Simplified block diagram of E. coli chemotaxis. l represents ligand, m the methylation, CheR the steadystate rate of methylation, and w the steady-state random walk motion (picture and discription from [1])

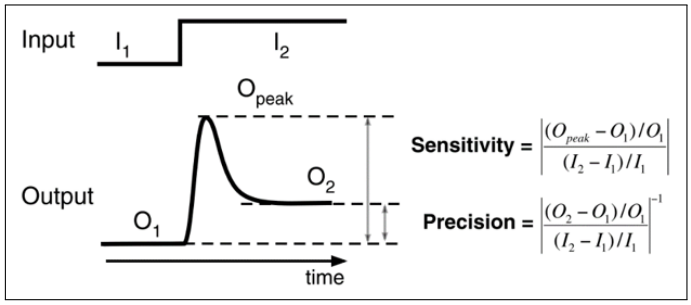

Fig. 3. Definition of sensitivity and precision. This definition is used to describe the regulation ability of biological system. (picture from [3])

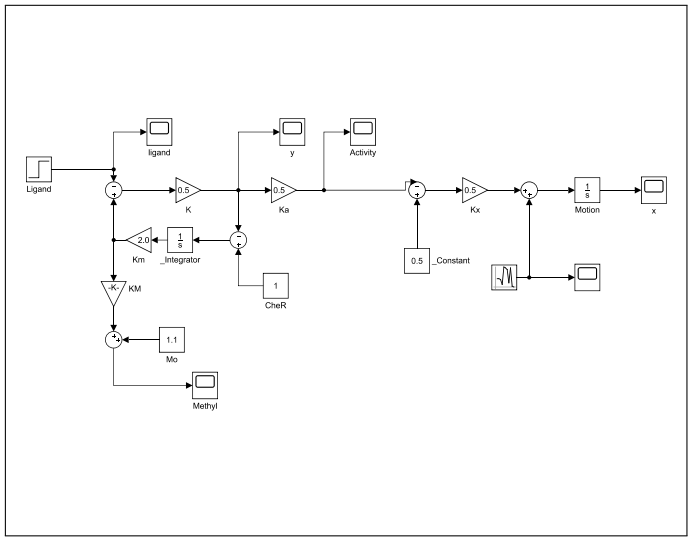

Fig. 4. A SIMULINK diagram of linearized E. coli chemotaxis system. Activity represents the tumbling frequency; x represents the position of E. coli ; CheR represents a kinase protein in chemotaxis pathway. This linearized biological system is based on [1]

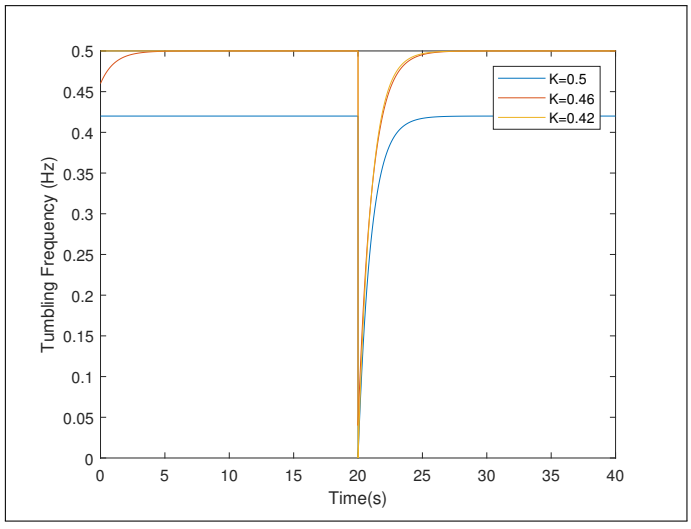

Fig. 5. Step responses of activity under different values of k in table 1

Table 1. Parameters in linear chemotaxis system[1].

Parameters	Biological Meaning	Domain
k	forward amplification	$k \geq 0$
k_m	feedback amplification	$k_m \geq 0$
K_{CheR}	the concentration of methylase	$K_{CheR} \geq 0$
Activity	the frequency of templing	$Activity \geq 0$

Adaptation and Sensitivity Analysis of Linearized E. coli Chemotaxis System

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Problem Setup:

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Why can E. coli present chemotaxis feature? and how does it accomplish this task? First, E. coli knows whether it is approaching a food source or not by sensing the ligand concentration, and the changes of concentration is correlated to the distance between E. coli and a food source. Second, E. coli processes the signal by CheR protein system, a cascade protein system that can differentiate the signal and also have properties similar to Kalman Filter[4]. Third, by sensing and processing ligand signal with CheR protein system, E. coli can adjust the tumbling frequency and eventually navigate to a food source.

Problem Statement:

In this project, I intend to investigate the effect of parameter modulation on E. coli chemotaxis system which possesses properties of sensitivity and adaptation (Fig. 1B). Also, I intend to use the linearized chemotaxis model of E. coli based on [1] (Fig. 1A) to investigate the following properties:

(1) Sensitivity and parameter modulation (Fig. 1A)
The sensitivity is the ratio of the peak value and initial steady state value after and before the stimulation (Fig. 1B). The sensitivity represents the ability of biological system to sensing the changes of input signal[2].

(2) Adaptation and parameter modulation (Fig. 1A).
The adaptation is the ratio of final value and initial value in step response, which represents the ability of biological system to adapting to environment[2].

(3) The K and Km in Fig. 1A are referred to the biochemical pathway, which can be modulated by molecular modification, their values can affect the system on regulation properties. Besides, the performance of regulation is measured according to the definition (1), (2).

(4) To extend this system to a 2D problem (moving in the plane field), and measure the performance of each chemotaxis systems. I divided this problem into several steps:
   i. Model the stochastic process of tumbling
   ii. Model the concentration of food (ligand) in the plane field.
   iii. Calculate the performance of each biological system.

Materials and Methods:

The linearized chemotaxis model is constructed by Matlab SIMULINK. In this model, the input is the concentration of ligand (food), the output is the activity (frequency) of tumbling, and x is the location of E. coli on a line(Fig. 1A). This system possesses perfect sensitivity and adaptation under the specific combination of K and Km (Fig. 1B).

To deal with problem (1) , (2) and (3), I intend to use the concept of the root locus method, which is a classic method that relates parameter modulation to stability. In this project, K and Km are changeable values of this system. Therefore, I plan to solve the mathematical relation between parameter modulation and the regulation properties- sensitivity and adaptation.

Although E. coli mostly tracking food sources in 3D field, while extending this model to 2D can still make this model more practical. In order to simulate the tracking process, I made several assumptions:

(1) Tumbling is a Poisson process with mean value λ.

λ is a real number, and λ>0

(2) When E. coli is not tumbling, it moves with constant speed direction Vec and speed rate V.

i. Vec is a normal vector with [length, θ] = [1, θ_t].

ii. V represents the speed rate

(3) During the tumbling process, E. coli changes θ of speed direction Vec with Gaussian distribution (u=0, σ).

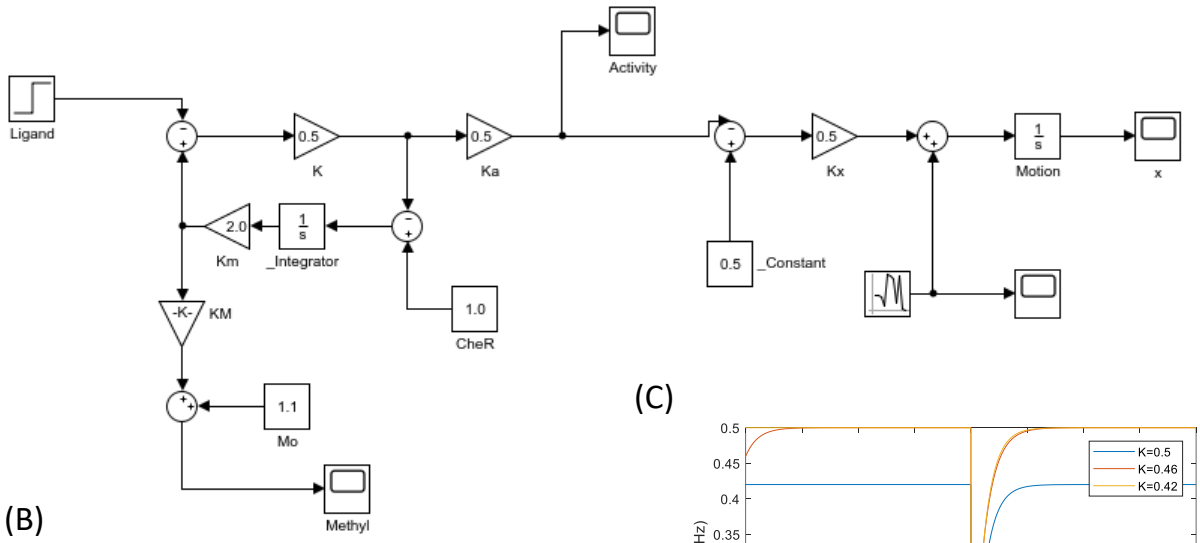
Finally, these assumptions are the fundamental for E. coli moving simulation in the plane field.

Preliminary Results and Discussion:

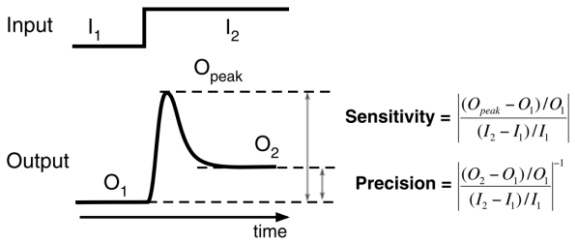
(1) The linearized chemotaxis system of E. coli is constructed based on Matlab SIMULINK, and it possesses the same properties of the one in [1].

(2) When Km = 2, sensitivity under different K values are plotted in Fig. 1C.

(A)



(B)



(C)

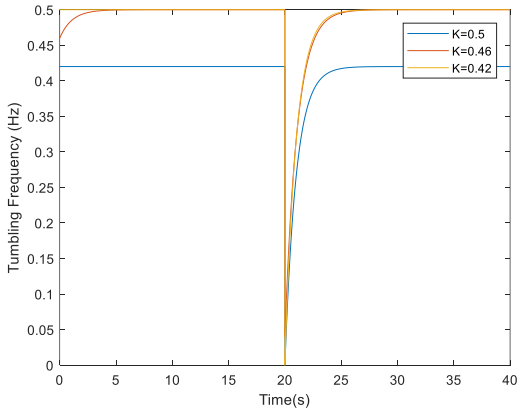


Fig. 1. (A) A SIMULINK diagram of linearized E. coli chemotaxis system. Activity represents the tumbling frequency; x represents the position of E. coli ; CheR represents a kinase protein in chemotaxis pathway. This linearized biological system is based on [1] (B) Definition of sensitivity and precision. This definition is used to describe the regulation ability of biological system. (picture from [2])(C) Step responses of activity under different values of K.

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