Validating Models of Bacterial Chemotaxis by Simulating the Random Motility Coefficient

Zhiyu Wang†, MinJun Kim‡ and Gail Rosen†

***Abstract*— In order to characterize the random walk of *E. coli*, biologists have studied several parameters, such as the motility speed, run duration, and random motility coefficient. Previously, biologists indicated that the probability distributions of these parameters may vary depending on the presence or absence of a chemical gradient in the environment. For instance, in a gradient, the cell of *E. coli* exhibits a biased-random walk. Although it is suggested that the parameter distributions change from unbiased to biased conditions, there are contradicting reports of the actual distributions since they are usually derived from observations of cell movement. In this paper, we consider the problem conversely. We try hypotheses for the parameter distributions respectively for the unbiased and biased cases to simulate random walks. Then we can validate our chemotaxis model through the simulated random motility coefficient, under unbiased and biased environments.**

Keyword: *E. coli*; Chemotaxis; Random motility coefficient; Random walk;

I. INTRODUCTION OF *E. coli* AND CHEMOTAXIS

If we look at a single *E. coli*'s movement without chemical stimulus gradient through the microscope, we can observe two typical types of movements: run and tumble. The track of the *E. coli* movement can be seen as a series of runs and tumbles, shown in Fig. 1. The run is the smooth segment of the random walk. During runs, the cell keeps on a reasonable smooth track. During tumbles, the cell orients itself and selects a new direction to start another smooth run. It is the tumble that gives the cell a nearly random reorientation from which to begin the next run.[1]

Motility of *E. coli* is determined by the rotation mode of the flagellar filaments, each of which is driven by a reversible rotary motor located at the base of it. During a run, the flagella rotate in the counterclockwise direction (as viewed from the distal end) and form a coordinated bundle according to the flagellar left-handed helicity, and as a result form a nearly constant propulsion and drive the cell in a smooth track. On the contrary, during a tumble, because the clockwise rotation of the flagellum destabilizes the left-handed helicity and a series of sequenced ensued, for example a disruption of the coordinated bundle, each flagellum acting separately (each exerts force in a different direction), thus the sum of compulsion being random and causing the cell to move chaotically.[1][2][3][4][5]

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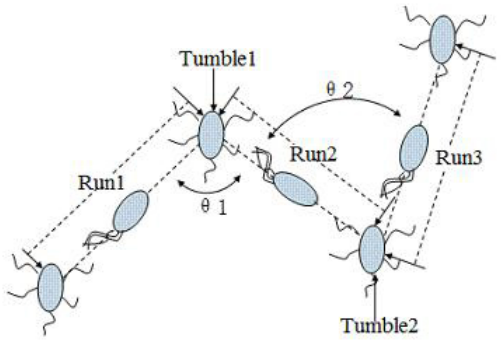

Fig. 1. Display of runs, tumbles and the respective parameters.

There are several parameters used to access the characteristics of the random walks of *E. coli* according to different cases. For example, in the case of accessing a single cell, motility can be interpreted in terms of its speed, tumbling frequency, the mean run duration, the turn angle between two successive runs and etc. Further, the dispersion of a population of cells in an isotropic medium can be described by two parameters: the random motility coefficient for the microscopic level and the diffusion coefficient for the macroscopic level.[1][2][6][7]

From the literature, we found that the probability distributions of these parameters are changed according to the presence or absence of a chemical gradient in the environment. Although the changes of the parameter exist, there are some disagreement of the actual distributions since they are usually derived from observations of the cell movement. In this paper, we develop hypotheses for the parameter distributions from the literature and use them to simulate unbiased and biased random walks. Then we can validate and compare our chemotaxis models by correlating the simulated random motility coefficient, under unbiased and biased environments.

The ultimate goal is to model chemotaxis and to detect changes in the motility coefficient. Such a model could be used conversely – to detect the state of E. coli by measuring the motility coefficient. A mathematical model of chemotaxis helps understanding of the mechanism and allows for engineering to improve the model or implement it in circuitry. For example, [8] implements a mathematical model emulating chemotactic receptor cooperation, in order to track a chemical source.

II. PARAMETERS FOR *E. coli* MOTILITY

Speed, v, is defined as the cell's linear velocity during a run or a tumble. During the run, we could consider the speed as a constant for the reason that all of the filaments rotate in the same directions, and the total propulsion could be seen as a constant.

$$v_{run} \approx constant \tag{1}$$

During the tumble, the *E. coli*'s speed first tends to abruptly decrease and then it takes longer to recover from tumble and reach its original speed. All of these changes are regulated by the rotation mode of the flagellar filaments, the helicity of the flagellar filaments. [7][9] According to [7], the speed under unbiased environment is 24.1±6.8 μm/s. Fig. 2 shows the simulation of movement speed during a series of runs and tumbles and Fig. 3 shows the record of real speed.

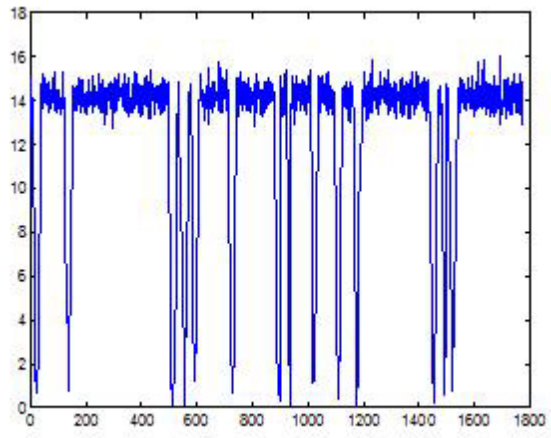

Fig. 2. Simulation of the motility speed during 15 runs and 14 tumbles. The run speed is stimulated as a normal distribution $\mathcal{N}(\mu$=14.2,σ=0.5).The tumble speed is stimulated as two stages, the decreasing branch and the increasing branch, during each of which speed change is a half-normal (one-sided) distribution $\mathcal{N}(\mu$=0,σ=0.5).

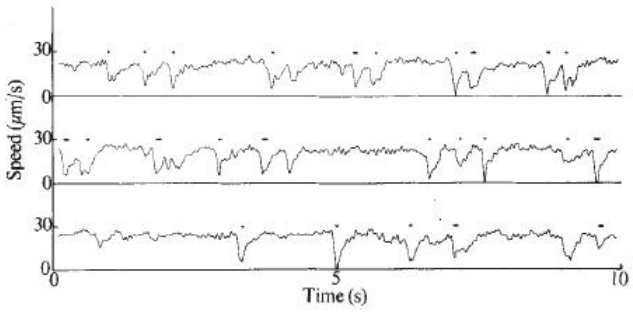

Fig. 3. The real speed of *E. coli*. Tumbles occurred during the intervals shown by the bars. There are 26 runs and tumbles.[1]

Run Duration, T_{run}, is defined as the time between tumbles. The total number of tumbles occurring up to time t is a Poisson process which causes the distribution of run duration to be exponential,with short intervals more likely.[1][7]

$$P(T_{run} = t) = \lambda_r e^{-\lambda_r t} \tag{2}$$

According to [7], the run duration under unbiased environment is 0.84±0.71 s.

Run Distance, D_{run}, is defined as the displacement between two continuous tumbles. Because the speed during run is nearly a constant, we can approximately say that D_{run}=v_{run}*T_{run} and D_{run} and T_{run} have nearly the same distribution type.

$$P(D_{run} = l) = \lambda_d e^{-\lambda_d l} \tag{3}$$

The distances of successive runs are not correlated. [1] [9]

Tumbling Frequency, f, the frequency of tumbles in unit time, is related to run duration. Now we usually consider the tumbling response to be the result of a Poisson process.[9] According to [7], the tumbling frequency under unbiased environment is 1.37/s.

Turn Angle, θ, is the angle between two consecutive runs. After each tumble, the *E. coli* will start a new run, but the direction of the new run is chosen nearly at random. If under an unbiased environment, the angle θ is selected at random, and we could assume its distribution to be a uniform distribution between 0 and π.

$$P(\theta = a) = \mathcal{U}(0, \pi) \tag{4}$$

In this situation, the mean of θ is $1/2\pi$ and the mean of $cos\theta$ is 0. If θ is concentrated around 0, the mean of $cos\theta$ is about 1, which means a high degree of the persistence of the direction of two successive runs. On the other hand, if θ is concentrated around π, the mean of $cos\theta$ is about -1 and this means a low degree of the persistence of the direction of two successive.[1][7][9]

Between the biased and unbiased environment, there is no great difference for the two types of movement. The only difference is the distributions of the two types of movement. In the positive stimulation, that is, an increasing chemoattractant gradient or a decreasing chemorepellent gradient, *E. coli* decreases the probability of clockwise rotation and, therefore, the probability of tumbles. On the contrary, in the negative stimulation, that is, a decreasing chemoattractant gradient or an increasing chemorepellent gradient, the probability of clockwise rotation increases and, therefore, the probability of tumbles increases. Table I shows us the distributions under biased and unbiased environments.[2][10]

Individual-cell's swimming behavior was thoroughly quantified by Berg and Brown using a three-dimensional tracking microscope to track *E. coli* AW405 cells in an isotropic solution and in the presence of aspartate and serine gradients. Lovely and Dahlquist made the important step of relating the individual-cell observations of Berg and Brown to macroscopic cell transport parameters. From the swimming speeds ($\mathbf{V}$), run durations (τ), and turn angles ($\mathbf{\Theta}$), we can compute the motility coefficient (μ_0):

$$\mathbf{V} = [v_1, v_2, \ldots, v_n] \tag{5}$$

$$\tau = [\tau_1, \tau_2, \ldots, \tau_n] \tag{6}$$

$$\mathbf{\Theta} = [\theta_1, \theta_2, \ldots, \theta_n] \tag{7}$$

$$\mu_0 = \frac{E^2[\mathbf{V}] * E[\tau]}{3 * (1 - E[cos\mathbf{\Theta}])} \tag{8}$$

TABLE I

DISTRIBUTION OF PARAMETERS UNDER BIASED AND UNBIASED ENVIRONMENT FOUND IN THE LITERATURES

	Unbiased	Biased
Speed, ($\mu m/s$) v	μ=24.1μm/s,σ=6.8μm/s, approximately constant during run[7][11]	exact values not in literature, approximately constant during run[11]
Run Duration (s), T_{run}	Exponential Distribution, $\mathcal{E}(\lambda$=1/0.84) [1][7]	Exponential Distribution, expected to have a longer mean but no number*[2]
Run Distance (μm), D_{run}	Exponential Distribution, $v_{run} * T_{run}$	Exponential Distribution*, $v_{run} * T_{run}$
Tumble Frequency (tumbles/s), f	Poisson Distribution, $\mathcal{P}(\lambda$=1.37)[1][7][11]	Poisson Distribution, expected to have a larger mean but no value reported in literature [1][11]
Turn Angle (radians), θ	Hypothesized Uniform, $\mathcal{U}(0,\pi)$ [1]	Hypothesized Uniform–unknown [1]

*The distributions are different with the direction of run along or against the chemical stimulus gradient. When the cell is moving along the increasing chemoattractor gradient or against the decreasing chemorepellent gradient, the exponential distribution has a larger-valued mean than that when the cell is moving against the increasing chemoattractor gradient or along the decreasing chemorepellent gradient.

TABLE II

PARAMETERS FOR SIMULATION OF RANDOM WALK UNDER UNBIASED ENVIRONMENT

Run distance	$\mathcal{E}(\lambda$=1/0.5)
Turn angle	1/2Sinθ $\theta\in[0,\pi]$
Direction of turn angle	Bernoulli(up=1/2,down=1/2)

In an isotropic solution (microscopic level), the random motility coefficient describes population-scale random motility where $E[]$ is the expected value, which is computed by the mean. At macroscopic level, the random motility coefficient is the operational equivalent of a diffusion coefficient.[9][12][13]

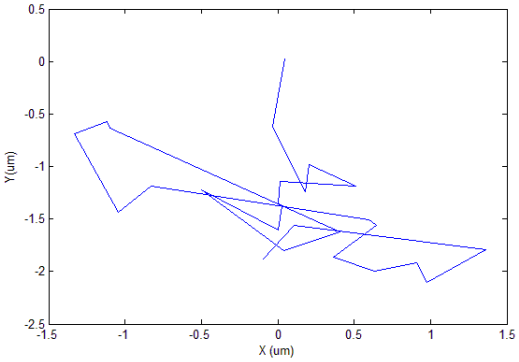

Fig. 4. Simulation of the random walks for *E. coli* under unbiased environment. There are 26 runs and tumbles in this figure and the angle between two successive runs follows the 1/2Sinθ distributions with θ between 0 and π. The starting point is (0,0).

Fig. 5. Z-axis picture from three stereo plots of a track of one cell of *E. coli* strain AW405 (wild type for chemotaxis) viewed along the x, y and z axes. The cell was tracked in Adler's motility medium at 49.78k for 29.5 seconds, and the x, y and z outputs were sampled 12.6 times per second. There are 26 runs and tumbles.[1]

III. SIMULATION FOR UNBIASED AND BIASED CASES

In this simulation, we only use several parameters, because some parameters are highly related, for example run duration and tumble frequency. The selected values have no physical meaning, for we only want to see the tendency.

A. Simulation of the unbiased random walks

The run distance is exponentially distributed. The turn angle θ follows a uniform distribution between 0 and π (azimuthally symmetric about the initial direction). When the cell selects an azimuthal angle, the decision of whether it is upwards or downwards depends on a Bernoulli random variable with the probability for upwards 1/2 and the probability for downwards also 1/2. Table II shows the parameters for the simulation and Fig. 4 shows the simulation result, compared with the real track of *E. coli* random walk in Fig. 5.

B. Simulation of the biased random walk

In the species like *E. coli*, there will be a tendency of positive stimulation (an increasing chemoattractant gradient or a decreasing chemorepellent gradient) decreasing the probability of clockwise rotation and, therefore, the probability of tumbles. On the other hand, a tendency for the negative stimulation (a decreasing chemoattractant gradient or an increasing chemorepellent gradient) increasing this probability. We could conclude that in this situation the runs in the "right" direction are prolonged, and the runs in the "wrong" direction are shortened. The outcome is a random walk of the bacterial cell, biased towards the chemoattractant or away from the chemorepellent. [2]

The run distance is exponentially distributed, but one is for the "right" track with a larger-valved mean $\frac{1}{\lambda}$ and the other is for the "wrong" track with a smaller-valued mean $\frac{1}{\lambda}$. The turn angle follows the specific distributions with θ between 0 and π (azimuthally symmetric to the initial direction). When the cell selects an azimuthal angle, the decision of whether it is upwards or downwards depends on a Bernoulli random variable with the probability for upwards 1/2 and the probability for downwards also 1/2. The run distance distribution depends on the direction of the *E. coli* on the "right" or "wrong" track (the cumulative angle of turn angle). Table III shows the parameters for the

TABLE III

PARAMETERS FOR SIMULATION OF RANDOM WALK UNDER BIASED ENVIRONMENT

Run distance along the stimulus gradient	$\mathcal{E}(\lambda=1/0.6)$
Run distance against the stimulus gradient	$\mathcal{E}(\lambda=1/0.4)$
Turn angle	1/2Sinθ θ∈[0,π]
Direction of turn angle	Bernoulli(up=1/2,down=1/2)

simulation and Fig. III-B shows the simulation result.

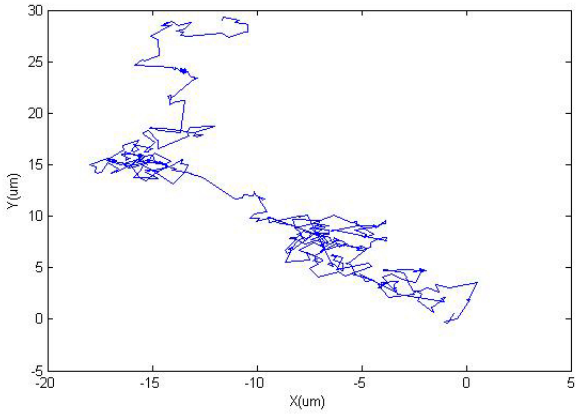

Fig. 6. Simulation of the random walks for *E. coli* under biased environment. There are 500 runs in this figure and the angle between two successive runs follows the 1/2Sinθ distributions with θ between 0 and π. There is an increasing positive stimulus concentration along the positive direction of y axis. The starting point is (0,0).

C. Simulation of the random motility coefficient of E. coli under unbiased and biased environment

The run duration is exponentially distributed. Because the speed during run stage in the unbiased walk can be assumed as a constant, the run time interval is also exponential distribution. The motility speed during the runs follows the normal distribution with a relatively small standard deviation; during the tumble, the change of motility speed follows the uniform distribution. The turn angle follows the 1/2Sinθ distributions with θ between 0 and π (azimuthally symmetric about the initial direction).

Simulation steps for the unbiased case are: (1) use exponential distribution to generate a random number for the run duration; (2) sample the speed for the run duration and use normal distribution to generate a series of random numbers for the run speed; (3) use 1/2Sin distribution to generate a random number for the turn angle; (4) repeat steps (1)(2)(3); (5) calculate the random motility coefficient. The only difference between the unbiased and biased cases is the exponential distribution: when the direction of the *E.coli* movement is on the the "right" or "wrong" track, the distributions are different and depends on the turn angle. Table IV shows the parameters for the simulation and Fig. III-C shows the simulation result under unbiased case. Table

TABLE IV

PARAMETERS FOR SIMULATION OF THE RANDOM MOTILITY COEFFICIENT UNDER UNBIASED ENVIRONMENT. $\mathcal{N}$ IS A NORMAL DISTRIBUTION, $\mathcal{E}$ IS AN EXPONENTIAL DISTRIBUTION, AND [A,B] IS A UNIFORM DISTRIBUTION.

Run speed	$\mathcal{N}(\mu=14.2,\sigma=0.5)$
Run duration	$\mathcal{E}(\lambda=1/10)$
Tumble speed change	one-sided $\mathcal{N}(\mu=0,\sigma=0.5)$
Turn angle	1/2Sinθ θ∈[0,π]

TABLE V

PARAMETERS FOR SIMULATION OF THE RANDOM MOTILITY COEFFICIENT UNDER BIASED ENVIRONMENT

Run speed	$\mathcal{N}(\mu=14.2,\sigma=0.5)$
Run duration along chemoattractor gradient	$\mathcal{E}(\lambda=1/15)$
Run duration against chemoattractor gradient	$\mathcal{E}(\lambda=1/7.5)$
Tumble speed change	one-sided $\mathcal{N}(\mu=0,\sigma=0.5)$
Turn angle	1/2Sinθ θ∈[0,π]
Direction of turn angle	Bernoulli(up=1/2,down=1/2)

V and Fig. III-C show the biased case. We use a chi-square goodness-of-fit test to find the best distribution of these two cases. The log-likelihood of the data to a normal distribution is performed, and it is found that for the unbiased case, a Lognormal distribution has the lowest log-likelihood score (Eq. 9) and for the biased case the lowest score is a Gamma distribution (Eq. 10).

$$P(x=a)=\frac{1}{a\sigma\sqrt{2\pi}}e^{\frac{-(ln(a)-\mu)^2}{2\sigma^2}} \tag{9}$$

$$P(x=a)=\frac{1}{\beta^{\alpha}\Gamma(\alpha)}a^{\alpha-1}*e^{a/\beta} \tag{10}$$

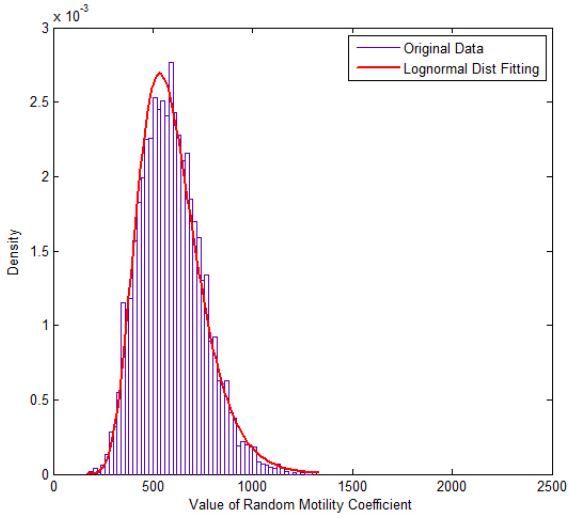

Fig. 7. Distribution of the simulated random motility coefficient under unbiased case and its curve fitting. There are 5000 periods during each of which there are 20 runs and 19 tumbles. For the data, Mean:599, Std:164. Lognormal parameter estimates: μ=6.3629, σ=0.2677.

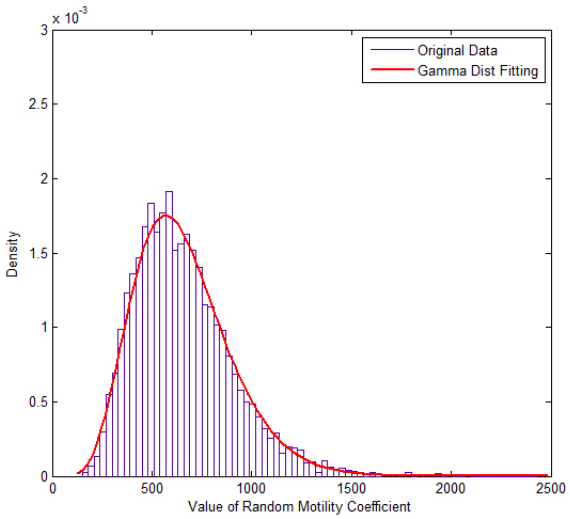

Fig. 8. Distribution of the simulated random motility coefficient under biased case and its curve fitting. There are 5000 periods, during each of which there are 20 runs and 20 tumbles. The Mean is 658 and the Std is 239. They indicate that the motility coefficient is slightly higher and has a higher variance than the unbiased walk distribution. While the mean increase is not as significant as we expected, we did expect such a heavier tail since the motility will have some significant increases. Gamma parameter estimates: α=7.5713, β=86.8551.

IV. CONCLUSIONS AND DISCUSSION

A. Discussion

Due to the lack of references about the parameters' distributions under biased case, we assume they were similar to the unbiased – the only difference being the change in a few statistical properties. This makes it difficult to detect if a cell is in an unbiased/biased state. Although interestingly, such a trend will increase the mean and make the distribution tails heavier. In the future, we will verify our parameters via *E. coli* experiments and experimentally determine the distributions through quantitative experiments. We will also experimentally verify the random motility coefficient under the biased and unbiased cases. It is hoped that through cell motility, the presence of a stimulus can be detected.

B. Conclusions

In this paper, we surveyed the *E. Coli* literature for cell swimming speed, run duration, run distance, tumble frequency, and turn angles in unbiased and biased random walks. As a preliminary step, we simulate the cell speed in an unbiased scenario and compare the simulation to experimental measurements. We then searched the literature for parameters concerning the distribution models for unbiased and biased walks. It was found that the parameters are pretty-well characterized for the unbiased case, but are unknown for the biased case. The random motility coefficient is then examined, and a model is built. We assume very similar distributions for the parameters except that the run distance will change as a function of the cell going along or against the stimulus gradient. This change increases the mean and variance of the motility coefficient, and such an increase indicates that the cell is in a biased state. Such parameters should be verified experimentally, and the model can be improved so that the biased or unbiased state of the cell can be inferred from the motility and/or speed, run distance, and tumble angle parameters.

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