کارگاه‌های آموزشی مرکز اطلاعات علمی

آموزش مهارت های کاربردی در تدوین و چاپ مقاله

اصول تنظیم قراردادها

مقاله نویسی علوم انسانی

THE NOISE PROBLEM IN CHEMOTAXIS

Nasrollah Rezaei-Ghaleh[1], Pouria Moshayedi

[1] PhD student, Institute of Biochemistry and Biophysics, University of Tehran, Enghelab Ave., P.O. Box: 13145-1384, Tehran, Iran.

nrezaeig@ibb.ut.ac.ir

Abstract

The chemotactic capability of some cells is infinitely useful for their survival. This capability is based upon mechanisms detecting concentration difference across the cell diameter. This signal (concentration gradient) decreases with the distance from the source. On the other hand, there is a noise caused by thermal motions of molecules infecting this signal. There is a threshold distance from the source beyond which the signal is weaker than noise and the cells lying there could not make a definite decision about the source direction. Probable mechanisms diminishing the noise and extending this distance threshold have been discussed in this article. It has also been argued that if the diffusion coefficient would be a function of concentration, it could cause different ways of Signal-to-Noise Ratio dependence on distance and imply interesting chemotactic behaviors of cell populations.

Keywords: Chemotaxis, Signal, Noise, Relay, Random walking.

Introduction

Many cells, when encountered with specific substances, have a capability to move toward (for chemo-attractants) or sometimes away from (for chemo-repellents) the source of those substances [1]. These cells traverse gradients of chemoeffectors by engaging in a biased random walk consisting of alternating periods of smooth runs and random tumbles. Detecting elevated levels of chemo-attractant decreases the probability of a tumble, thus propelling the cell in the favorable direction [2]. This infinitely useful phenomenon does not occur unless the cell possesses a mechanism to detect small differences in the concentration of chemo-attractant or chemo-repellent across its diameter. However, the thermal motion of molecules causes a noisy fluctuation in concentrations [3]. The cells far from the source observe too small concentration difference to discriminate it from this noise. As a result, it seems that only cells placing at distances below a threshold could detect the concentration difference and hence, move toward or away from the source and the cells beyond this threshold could not make a definite decision about source direction and remain wherever they place. The aim of this study is to investigate mechanisms to extend this distance threshold. Meanwhile, the impact of diffusion coefficient dependence on concentration has been discussed.

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Problem formulation

Consider a situation in which the source of, e.g. a chemo-attractant substance lies at origin and at $t=0$, it initiates to pour out the chemo-attractant substance with some constant rate, H. The concentration of this substance, C will be a function of place and time in general. Assuming the symmetry among different directions, C will be the same at all points placing on the same sphere around the source. Therefore, C will be a function of r, distance from source and time. In the steady state, $\partial C/\partial t$ is equal to zero and the rate with which chemo-attractant passes across the surface of any sphere around the source should be equal to H. It requires that [4]:

(1) $$4\pi r^2 D \, dC/dr = -H$$

in which D is the diffusion coefficient of medium and negative sign of H indicates that molecules move in the opposite direction of concentration gradient. The probable dependence of diffusion coefficient on concentration or distance is now ignored. Assuming C approaches zero when r approaches infinity, we will have:

(2) $$C_{(r)} = H / (4\pi Dr)$$

The chemotactic signal (S) is the gradient of concentration:

(3) $$S_{(r)} = - dC/dr = H / (4\pi Dr^2)$$

As $\partial S/\partial r < 0$, the cells farther from the source observe less pronounced signal. On the other hand, there is a noise due to thermal motion of molecules. This noise (N) is on the order of $C^{1/2}$ [5], or:

(4) $$N \approx (H / (4\pi Dr))^{1/2}$$

There are, of course, other sources of noise. For example, receptor molecules have not been distributed uniformly on the cell surface and hence, the chemo-attractant concentration observed really by the cell is a subject of another random noise [6]. However, these noises are independent of r and so, equally affecting the cells near and far from the source. As it is aimed to investigate how cells too far from the source have solved the noise problem, the mere noise considered here is the one caused by thermal motion of chemo-attractant molecules. In this way, the signal-to-noise ratio (SNR) will be on the order of:

(5) $$(H/(4\pi Dr^3))^{1/2}$$

and for every positive r, $\partial SNR / \partial r < 0$ and with r approaching infinity, SNR will tend to zero. The cells lying at places with SNR of less than unity become confused about the direction of source place and cannot make decision to which direction they should move [7]. Only cells within a limited region can detect source orientation and elicit proper behavior. This limitation may be severe especially when H is rather small or D is large. Do the cells have mechanisms to overcome this limitation? It is reasonable that cells would have developed such mechanisms through long time evolution and these creative cells should have had more chance to survive. If so, which mechanisms have been employed to solve this problem?

Problem solution

A simple route to diminish noise is the time-integration of infected signal. This process eliminates noise and achieves much more pure signal [3]. The enzymatic reactions in the signaling pathway related to chemotaxis apply such time-integration and improve the SNR. The occurrence of several enzymatic reactions in the signaling pathway applies successive time-integration and enhances SNR considerably. Mechanisms lengthening the time duration over which integration occurs also improve SNR. However, noise is reduced only as the square root of time through this process [5]. In addition, the process of time integration occurs at the expense of time resolution. For example, if this duration is too long, Brownian random rotations occur during this period and hence, the received signal no longer contains any information on the source orientation. Another method of noise elimination is space-summation [3]. This

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may occur through convergence from membrane receptors to intracellular target sites. However, noise is again reduced only as the square root of size [5]. The extension of space along which space-summation occurs diminishes space resolution and this is obviously too expensive for chemotaxis. Then, it is only applicable at small scale, between adjacent membrane receptors and intracellular target sites in the vicinity of the membrane. Another method to make relatively far cells move toward the source is a simple co-operation between cells (a relay phenomenon). If a cell near enough to detect source direction secretes another specific substance, it can play the role of secondary source. In this condition, the cell too far from the primary source may be near enough to secondary source to detect its direction, move toward it and arrive in a new position in which it will be able to recognize correct direction of primary source. As another mechanism to overcome the noise problem, the cell receiving chemo-attractant but not recognizing the source direction may initiate random walking around and hence, provide the chance for itself to enter region where it is possible to find the source direction.

Discussion

Four above-mentioned methods, time-integration, space-summation, relay and random walking can increase the distance threshold for chemotaxis to occur far beyond which obtained from the theory.

The existence of any noise-diminishing mechanism can be examined experimentally. Setting a source with specific H and a medium with specific D, if a cell is able to detect source direction even when it resides beyond a threshold distance calculated theoretically, it is concluded that some mechanisms should have diminished the noise. Also, if the chemotactic behavior of individual cell differs from cells in populations, it may be due to some relay mechanisms. On the other hand, if the fourth mechanism (random walking) exists, it is expected that, when the source initiates to pour out the substance, cells too far from the source are stimulated to move around randomly and more of them (compared to conditions when the source pours out no substance) are found in places even farther from the source.

The point that SNR decreases continuously when the cell moves away from the source indicates an important difference between chemo-attraction and chemo-repelling phenomena. The cell moving toward chemo-attractant source experiences a continuously amplifying signal while the cell moving away from the chemo-repellent source observes a continuously damping signal. Therefore, a slight displacement of cell toward the chemo-attractant source causes the cell to observe stronger SNR and moves more in the same direction. On the other hand, when a slight displacement of cell away from the chemo-repellent source occurs, the cell experiences weaker SNR and hence, weaker repulsion from the source. This difference may explain why chemo-attraction is more simply and commonly observed than chemo-repelling.

Another point is that the diffusion coefficient of the medium (D) may not be really a constant but instead, if the cells could modify D according to chemo-attractant concentration, it would be a function of C (and hence, r). As a result, SNR would be a function of r different from that obtained above. This can help to diminish the noise problem. For example, if the cells could decrease D when encountered to chemo-attractant, this causes a greater concentration gradient established in any distance from the source and so, enhances SNR. Therefore, the cells already observing low SNR now receive greater SNR and can detect the source orientation.

On the other hand, diverse dependences of D on C can cause surprising ways of SNR dependence on r and imply interesting

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chemotactic behaviors of cell populations. For example, SNR may have one or more maxima in the vicinity of source and then uniformly decline with increase of *r*. If there is one maximum, the cell farther than the maximum point away from source but near enough to detect proper SNR moves toward the source and reaches the maximum point. It continues to move toward the source until it arrives in a new place where the SNR it receives declines again below a threshold value. Then, it resides there and no longer moves toward the source. As a result, it is expected that whenever the source initiates to pour out a chemo-attractant substance, chemotactic cells move toward it and finally accumulate at a specific distance from the source. If the cell would need the chemo-attractant but too high concentration of the chemo-attractant would be noxious for the cell, such a phenomenon could be enormously useful for the cell survival. Meanwhile, if there are more than one SNR maximum points and the SNR between these points declines below a threshold value, it is expected that chemotactic cells accumulate at more than one layers around the source. This may be beneficial regarding the population density problem.

Conclusion

There are at least four major mechanisms (time-integration, space-summation, relay and random walk) for chemotactic cells to challenge the noise problem. The idea presented at this article simply explains why chemo-attraction is more commonly observed than chemo-repelling. If the diffusion coefficient depends on the chemo-effector concentration, it causes different ways of SNR dependence on distance from the source and hence, implies novel chemotactic behaviors.

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