Spatial sensing in Dictyostelium: Switching Behavior

Pablo A. Iglesias[†] and Andre Levchenko[*]
[†]Electrical & Computer Engng, Johns Hopkins University
3400 N. Charles St. Baltimore, MD 21218
+1 (410) 516-6026, Fax +1 (410) 516-5566, pi@jhu.edu
[*]Biology Division, MS 156-29, Caltech
1200 E. California St., Pasadena, CA 91125
(626) 395-8542, andre@paradise.caltech.edu

1 Introduction

Many biological systems have the ability to sense the direction of external chemical sources and respond by polarizing and migrating toward chemoattractants or away from chemorepellants. This phenomenon, referred to as *chemotaxis*, is crucial for proper functioning of single cell organisms, such as bacteria and amoebae, as well as multi-cellular systems as complex as the immune and nervous systems. This property also appears to be important in such diverse processes as wound healing, tumor metastasis, immunity, angiogenesis and the development of the nervous system.

Unlike bacteria, which determine external spatial concentrations using a "temporal" sensing mechanism [1,2], larger eukaryotes can sense gradients while motionless, by subtracting concentration levels perceived by different parts of the cell [3] — a process known as *spatial sensing*.

To model this system accurately, several features of this sensing must be accounted for:

Perfect Adaptation A requirement for chemotaxis is the ability to adapt to different levels of external stimuli, so that it is the gradient in the concentration of signaling molecule rather than its average signal value that determines the response [3]. Chemotactic cells exhibiting adaptation respond to spatially homogeneous increases in external stimulus by transient activation of specific intracellular signaling pathways. In perfect adaptation the initial and final levels of the activation are the same. A general framework for achieving perfect

adaptation was presented in [4]. In particular, it was shown that that the robustness of perfect adaptation is the result of the system possessing the property of integral feedback control.

Spatial Sensing While eukaryotic cells such as *Dictyostelium* also demonstrate perfect adaptation to homogeneous changes in ligand concentration, they are able to polarize while motionless. A proposed mechanism for spatial sensing relies on achieving a balance between local *promotion* and global *inhibition* of activity. [3] These are in turn regulated by receptor occupancy. What determines the spatial gradient is the fact that promotion is regulated by the *local* concentration, whereas inhibition is regulation by the *global* concentration. A mathematical model was considered in [5] that accounts for perfect adaptation *and* spatial sensing by considering modifications at the receptor level.

Gain amplification While the model considered in [5] accounts for most of the behaviors observed in chemotactic *Dictyostelium* cells, it fails to show the large gains in sensitivity that are seen experimentally. In fact, it can be shown that the difference in activity between the front and rear of this model of the cell will always be *lower* than that of the external chemoattractant gradient. However, large gains over the external gradient have been measured experimentally, so that differences as low as 2% between the front and rear of the cell can polarize the cell and direct movement [3]. Mathematical models that account for this high amplification exist [6, 7], however, neither of these achieves its amplification at the same time as it achieves perfect adaptation.

One possible means of achieving both adaptation and large gains is to consider the model presented in [5] only as a *pre-processor* that determines cell polarity. This regulatory mechanism feeds into a secondary mechanism, exhibiting a saturating nonlinear response. In this paper we provide a mathematical model that can account for the large gain seen in the polarization of *Dictyostelium*.

2 Biological description

Signaling in the sensing system in *Dictyostelium* can be described as follows: activation of receptors by the ligand leads to activation of a G-protein, which, in turn activates the phosphoinositide 3 kinase (PI3K). This G-protein coupled system fits the general framework described in [5] that achieves both perfect adaptation and spatial sensing and for this reason will not be considered here. Instead, we treat the level of PI3K as the input to our amplification systems.

The signaling mechanism can be shown to produce a positive feedback loop as shown in Figure 1, which is a simplified model of the one presented in [8]. Receptor activation leads to increased levels of PI3K, which in turn converts phospatidylinositol (4,5)-biphosphate (PIP2) into phosphatidylinositol (PIP3). Concentration of PIP3 is usually measured experimentally and considered to be the signaling output. As shown in [8], activation of PIP3 leads to an increased production of the GTPase ARF6 which stimulates the production of the PIP2

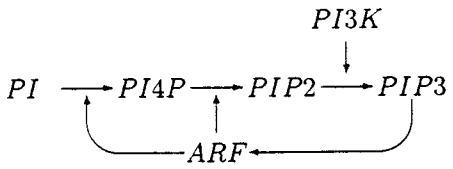

Figure 1: Regulation of PIP2 and PIP3 synthesis.

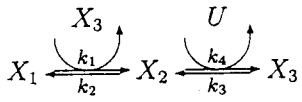

Figure 2: Simplified regulator mechanism for analysis.

precursor PI4P. ARF6 also provides positive feedback as it activates PI4P5 which synthesizes PIP2 from PI4P. Thus, production of PIP2 provides more substrate availability for PI3K. This positive feedback is a good candidate for the high-gain switching system that we seek in the sensing system in *Dictyostelium*.

2.1 Analysis

To analyse the system, we consider a simplified model, depicted in Figure 2. The molecule X_1 can be thought of as representing both PI and PI4P. This molecule in turn produces X_2 which represents PIP2. Finally, our activity level will be proportional to the concentration of the signaling molecule X_3. Production of X_3 is regulated by the external signal U. Note that the positive feedback is provided directly by this signal, as it activates production of X_2 from X_1.

The differential equations describing this system are

$$\frac{d[X_1]}{dt} = -k_1[X_1][X_3] + k_2[X_2] \tag{1}$$

$$\frac{d[X_3]}{dt} = -k_3[X_3] + k_4[X_2][U_{ss}] \tag{2}$$

Moreover, conservation requires that

$$[X_1] + [X_2] + [X_3] = [X_T]$$

For our analysis, we will consider constant values of external signal, and first look for possible equlibria. We will then linearize the equations about this equibrium to determine stability of the system.

It is possible to show that

$$[X_{1ss}] = [X_T], \quad [X_{2ss}] = 0, \quad [X_{3ss}] = 0 \tag{3}$$

is *always* a solution of (1-2). A second solution exists. However, as we are only interested in non-negative solutions, this solution will be inadmissible in certain

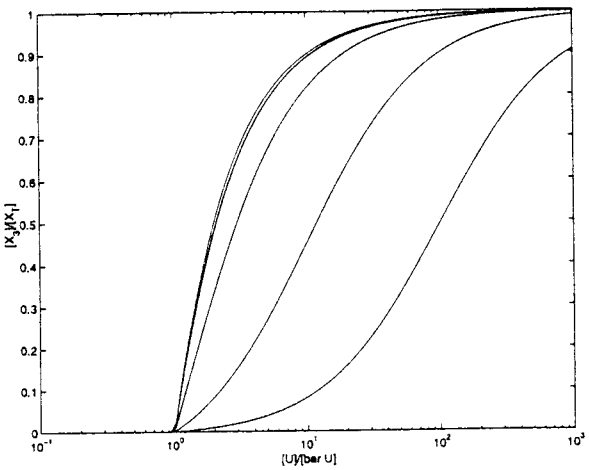

Figure 3: Dependence of activity on input concentration. Shown is the concentration of $[X_{3ss}]/[X_T]$ as a function of the ratio between $[U_{ss}]/[U_{th}]$. The steepness of the curve depends on the parameter $\alpha = k_1[X_T]/k_2$. Shown are curves for values of $\alpha = 0.01$, (steepest) 0.1, 1.0, 10 and 100.

cases. We can show that this will depend on whether the concentration level of the external signal $[U_{ss}]$ is above or below the threshold:

$$[U_{th}] = \frac{k_2 k_3}{k_1 k_4 [X_T]}$$

Case 1: $[U_{ss}] \leq [U_{th}]$

In this case, the second solution is negative and thus does not represent a physical condition. If follows that, if we consider the level of $[X_3]$ as our activity level, we can consider the system as being "off."

Case 2: $[U_{ss}] > [U_{th}]$

In this case, we have two possible non-negative solutions, (3), and a second solution with concentrations concentrations:

$$\frac{[X_{1ss}]}{[X_T]} = \frac{[U_{th}]}{[U_{ss}]}, \quad \frac{[X_{2ss}]}{[X_T]} = \frac{1 - [U_{th}]/[U_{ss}]}{1 + k_4/k_3[U_{ss}]}, \quad \text{and} \quad \frac{[X_{3ss}]}{[X_T]} = \frac{[U_{ss}] - [U_{th}]}{[U_{ss}] + k_3/k_4} \quad (4)$$

The dependence of activity ($[X_{3ss}]$) on the input concentration is shown in Figure 3.

2.2 Local stability analysis

We now consider the local stability properties of these two equilibria by linearizing (1) and (2). In particular, let

$$[X_1] = [X_{1ss}] + x_1, \quad [X_3] = [X_{3ss}] + x_3, \quad [X_2] = [X_T] - [X_1] - [X_3]$$

Then, the homogeneous linear differential equation describing the system has the second-order characteristic polynomial

$$s^2 + \underbrace{(k_2 + k_3 + k_1[X_{3ss}] + k_4[U_{ss}])}_{\alpha_1} s + \underbrace{(k_2k_3 + k_1k_4[U_{ss}]([X_{3ss}] - [X_{1ss}]))}_{\alpha_0}$$

which is stable provided the coefficients α_0 and α_1 are positive. It is clear that this can only fail if $\alpha_0 \leq 0$.

For the first equilibrium point, i.e. $[X_{1ss}] = [X_T]$, $[X_{2ss}] = [X_{3ss}] = 0$,

$$\alpha_0 = k_2k_4 - k_1k_3[U_{ss}][X_T] = k_2k_4\,(1 - [U_{ss}]/[U_{th}]) \tag{5}$$

Thus, the same threshold value for the input concentration $[U_{ss}]$ that determines the number of possible equilibria also determines whether the system is stable. In particular, if only one equilibrium exists, it is stable. If two equilibria exist, this equilibrium is unstable.

We now look at the second equilibrium (4). It can be shown that, in this case,

$$\alpha_0 = k_1k_4[X_T][U_{ss}] - k_2k_3 = k_2k_3\,([U_{ss}]/[U_{th}] - 1)$$

Since this equilibrium only appears when $[U_{ss}] > [U_{th}]$, it is always stable.

It follows that the system described by Figure 2 shows a "switching" behaviour, in that whenever the external concentration is below the threshold value, the system exhibits zero activity — as measured by the concentration of X_3. This activity level rises rapidly as the external signal level increases eventually saturating.

3 Conclusions

In this paper we have demonstrated that positive feedback exhibited by the PIP2-PIP3 cascade found in *Dictyostelium* provides a high-gain saturating nonlinearity. Together with the G-protein based adaptation mechanism considered in [5] we can account for perfect adaptation, high gain spatial sensing observed in this cell.

Acknowledgments

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