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Selectivity and Sensitivity Improvement in Co-operative Systems with a Threshold in the Presence of Noise

A. K. VIDYBIDA

Institute for Theoretical Physics, 252130, *Kiev* 130, *Ukraine, U.S.S.R.*

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High selectivity (specificity) and sensitivity to natural or artificial stimuli which are normally observed for biological systems can be realized in an ensemble composed of many co-operatively connected primary receptors. The co-operative interaction results in the formation of several stable states and a switching from one state to another is performed in a threshold manner. When any noise is absent the ensemble with a threshold can secure as high a selectivity and sensitivity as is desired. The presence of noise sets limits on the possible informational quality of a system because spontaneous switchings will occur. The question: What advantage as regards selectivity and sensitivity can a co-operative system with a threshold have is considered quantitatively as an example for a bistable chemical system. As a result it is established that a co-operative system may have much higher selectivity and sensitivity than its individual primary receptors.

Introduction

Systems with threshold-manner reactions are characteristic of biological objects. A system of voltage-dependent ion channels in an excitable neuronal membrane (Kostjuk, 1983), or the λ-phage repressor system (Ptashne, 1986), or the system of Ag-specific receptors on a lymphocyte surface (Kane *et al.*, 1989) are examples of such systems. A substantial role of such systems in keeping up homeostasis was mentioned by Ashby (1960). On the other hand, a system with a threshold may secure high specific (selective) and sensitive reactions to an applied stimulus, and also protection against an external noise, when compared with individual primary receptor characteristics. As a simple example they may serve an ensemble with an unstable threshold (Vidybida, 1988). The ensemble consists of a large number (N) of identical primary receptors, and any receptor has an active (switched on) and a non-active (switched off) state. Assume that some external stimulus characterized by a parameter ω can change the probability of finding a receptor in its active state. One may regard ω as a sound or electromagnetic signal frequency (Devjatkov, 1973); a spatial co-ordinate in a morphogenic field (Lewis *et al.*, 1977); a parameter that characterizes an antigenic determinant conformation (Paul, 1984); or a parameter which characterizes patterns to be recognized by a nervous system. We say that the primary receptor has a selectivity with respect to ω if the probability of finding a receptor in its active state depends on ω and has a maximum for some value $\omega = \omega_{max}$. The primary receptor response characteristic $\nu(\omega)$ is the probability normalized by unity at $\omega = \omega_{max}$ (see Fig. 1). The presence of threshold instability means that the ensemble will switch to its active state [e.g. a lymphocyte triggering

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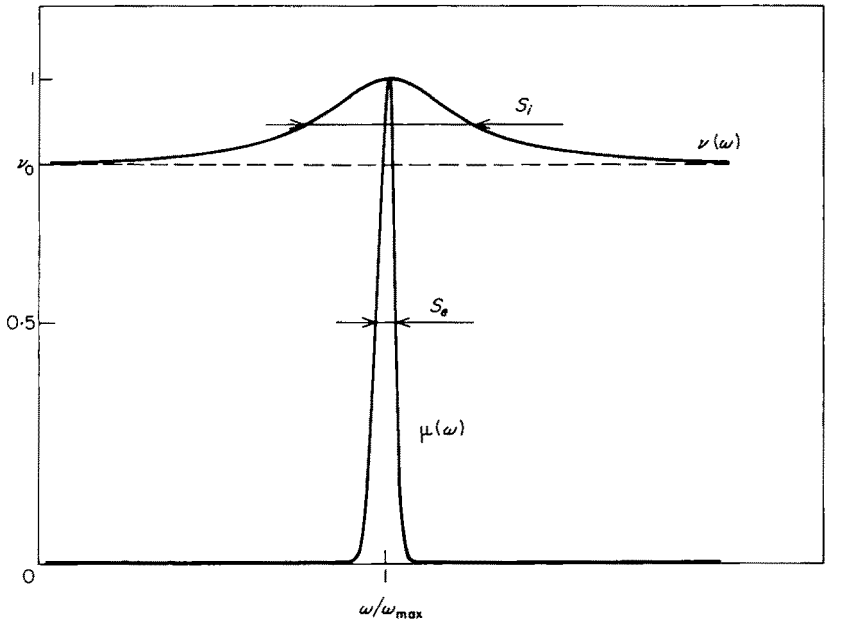

FIG. 1. An individual primary receptor $[\nu(\omega)]$ and a co-operative ensemble $[\mu(\omega)]$ response characteristics. ν_0 is an idividual receptor noise (background) level—the (normed) probability to be switched on without an external stimulus. In the case of CTL $\nu_0 \simeq 0$; in the model reaction (4) $\nu_0 = \varkappa_2/(\varkappa_1+\varkappa_2)/[\varkappa_2(\omega_{max})/(\varkappa_1+\varkappa_2(\omega_{max}))]$, where $\varkappa_1, \varkappa_2$ are the rate constant values without external stimulus.

(Kane *et al.*, 1989)] if and only if the number of primary receptors which are in their own active state exceeds some threshold number $N_0 \leq N$. So, the ensemble response characteristic $\mu(\omega)$ may be estimated approximately based on a probability multiplication rule:

$$\mu(\omega) = [\nu(\omega)]^{N_0}.$$

If the response characteristic $\nu(\omega)$ has a maximum for some value $\omega = \omega_{max}$ then it may be characterized by the half-width S_i. The $\mu(\omega)$ half-width S_e is then estimated as

$$S_e = S_i/\sqrt{N_0}. \tag{1}$$

For example, it follows from (Kane *et al.*, 1989) that the triggering of cytolytic T lymphocyte (CTL) may occur if alloantigen is binded with not less than ~40 000 of its surface receptors. Here $N_0 \sim 40\,000$, and so the CTL recognition (and triggering) will be ~200 times more specific (selective) than the corresponding alloantigen recognition by a receptor. It follows from (1) and Fig. 1 that the higher the threshold level the more selective is the ensemble response. On the other hand, it is desirable that the threshold level is near the systems background level (without stimulus) activity to secure high sensitivity. But if the background and threshold levels are close to each other the spontaneous (caused by an interval noise) switchings will

frequently occur: the level of fluctuations increases near a threshold (Ma, 1986). Thus, to answer what advantage as regards selectivity and sensitivity a system may have with a threshold a quantitative consideration is needed. As an example of such a system in which a noise level together with threshold and background levels arise naturally, as inherent features, we consider a model bistable chemical system which is an extension of the Shlögl model (Shlögl, 1971) to a noisy case:

$$\left.\begin{aligned} A+2X &\underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} 3X \qquad (2)\\ B+X &\underset{k_2^+}{\overset{k_2^-}{\rightleftharpoons}} C^* \qquad (3)\\ C^* &\underset{\varkappa_2(\omega)}{\overset{\varkappa_1}{\rightleftharpoons}} C^{\#}, \qquad (4) \end{aligned}\right\} \text{ the Shlögl model}$$

where $A = \text{const}$, $B = \text{const}$, $C = C^* + C^{\#} = \text{const}$, and C^* and $C^{\#}$ may be understood as active and non-active conformations of the same molecule C regarded as a primary receptor. We do not specify a concrete stimulus able to shift the reaction (4) balance. In particular it may be an external electromagnetic field with frequency ω which can change (Ivlev & Mel'nikov, 1986) one of the rate constants $\varkappa_1, \varkappa_2$. The (thermal) noise appears in the model (2–4) by taking into account the probabilistic nature of the rate constants. We suppose that the reactions in (4) are much faster than any reaction in (2) or (3). This implys some simplifications as regards the corresponding dynamical system dimension as well as an adequate noise consideration. As a result the dynamics of the system are described by the Langevine equation (Gardiner, 1985)

$$dX/dt = -k_1^- X^3 + k_1^+ AX^2 - k_2^- BX + k_2^+ C^* + \sqrt{2D}\xi(t), \qquad (5)$$

with a white noise as a source of noise: $\langle \xi(t)\xi(t+\tau)\rangle = \delta(\tau)$. Equation (5) with the noise excluded describes a bistable system with two stable rest states characterized by X_1, X_3 $(X_1 < X_3)$ concentrations (Shlögl, 1971), and if the C^* concentration exceeds some threshold value the system will switch from the X_1 to X_3 state. To determine the "diffusion coefficient" D we take into account that it is adequate to describe the system using concentration values at a single point, as eqn (5) does, if and only if the spatial homogeneity is secured. So, the volume where the reactions (2–4) proceed must be small enough to avoid the nucleation processes (when two stable concentrations coexist in the same volume). The maximum among such volumes is called a coherent volume. Its characteristic size L depends on the efficiency of mixing. Suppose mixing is caused by thermal diffusion only then we have the following estimation for L

$$kL^2/(2D_X) \leqslant 1, \qquad (6)$$

where D_X is the molecular diffusion coefficient for the X-type molecule and k is the rate of the fastest process in (2) and (3). If we consider the reactions in the coherent volume V_C the stochastic term in (5) arises from fluctuations $n(t)$ of the

mean number N^* of C^*-type molecules in V_C expressed in terms of C^*-concentration fluctuations. As it follows from the probabilistic nature of eqn (4) $n(t)$ is normally distributed and has a correlation function $\langle n(t)n(t+\tau)\rangle = N^*\varkappa_1 \exp(-\gamma|\tau|)/\gamma$, where $\gamma = \varkappa_1 + \varkappa_2$. As the processes in (4) are much faster when compared to (2) and (3) we may consider a non-correlated stochastic process $A\xi(t)$ instead of the short-correlated process $n(t)$, where A should be chosen to equalize both spectral densities for the zeroth harmonic. When expressed in terms of $k_2^+C^*$, this gives:

$$\frac{k_2^+C^*}{N^*}\, n(t) \to \left(\frac{2k_2^{+2}C^{*2}\varkappa_1}{N^*\gamma^2}\right)^{1/2} \xi(t),$$

and so

$$D = \frac{k_2^{+2}C^{*2}\varkappa_1}{N^*\gamma^2}. \tag{7}$$

If T denotes the temperature; η is the solvent viscosity; r is the molecule radius; α is the volume fraction of C-type molecules then there follows from eqn (6) $[D_X = k_BT/(6\pi r\eta)]$

$$N^* = \alpha \frac{\varkappa_2}{\gamma}\left(\frac{k_BT}{3\pi}\right)^{1.5} \frac{1}{r^{4.5}\eta^{1.5}k^{1.5}}. \tag{8}$$

For water as a solvent at $T = 310$ K, with $r = 1{\cdot}5$ Å, $\alpha = 0{\cdot}05$, $\varkappa_1/\varkappa_2 \sim 1$, $k \sim 1\ \text{sec}^{-1}$, eqn (8) gives $N^* \sim 10^{15}$,

It is known that for a bistable system with noise the switching from one state to another occurs from time to time. The characteristic of this process is the mean waiting times $T_{1\to 3}$ or $T_{3\to 1}$ for a first switching (Gardiner, 1985). What we are interested in is a changeover of $T_{1\to 3}$ when ω, and so C^* changes. The changeover for various ω values is described by the co-operative response characteristic $\mu(\omega)$:

$$\mu(\omega) \equiv \frac{T_{1\to 3}[C^* + \Delta C^*(\omega_{\max})]}{T_{1\to 3}[C^* + \Delta C^*(\omega)]}.$$

We also introduce the response characteristic of an individual primary receptor

$$\nu(\omega) \equiv [C^* + \Delta C^*(\omega)]/[C^* + \Delta C^*(\omega_{\max})].$$

The following relation between two response characteristics is established, provided $\Delta C^*(\omega_{\max})/C^*$ is small enough (see Appendix A)

$$\mu(\omega) = [\nu(\omega)]^P, \tag{9}$$

where $P = N^*\gamma/k_2^+$.

The exponent P may be referred to as the degree of co-operativity of the response, which may be very large. For example if the above assumptions regarding the coherent volume are fulfilled then $P \gg 10^{15}$. From eqn (9) and Fig. 1 we see that if $\nu(\omega)$ has a broad maximum and P is big enough, then $\mu(\omega)$ will have a very sharp maximum, i.e. high selectivity with respect to ω. The effect is measured by a half-width contraction:

$$S_i/S_e = \sqrt{P.(1-\nu_0)},$$

where ν_0 is the background (noise) level of an individual primary receptor (see Fig. 1).

The system sensitivity is estimated by the $T_{1\to3}$ changeover corresponding to a small deviation ΔC^* of a concentration C^*. When the "diffusion coefficient" changeover is neglected, and $T_{1\to3}$ is changed because of the deformation of the "potential" in the Fokker–Planck equation (Gardiner, 1985) which corresponds to eqn (5) we have the following expression

$$\frac{T_{1\to3}(C^*)}{T_{1\to3}(C^*+\Delta C^*)} = \exp\left(\tfrac{2}{3}N^* \cdot \frac{\gamma}{k_2^+} \cdot \frac{\Delta C^*}{C^*}\right).$$

Thus, the dynamical pattern of a system may be changed very dramatically by a minute concentration change provided the coherent volume and as a result are N^* large enough.

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APPENDIX

Let $F(X)$ denote the deterministic part of the right-hand side of eqn (5). We introduce a "potential" $U(X)$ using the following expression

$$U(X) = -\int^X F(Y)\,\mathrm{d}Y.$$

The "potential" has two minima at points X_1 and X_3 and one maximum at point X_2. The maximum is supposed to be pronounced, so the inequalities

$$[U(X_2) - U(X_1)]/D \gg 1,$$

$$[U(X_2) - U(X_3)]/D \gg 1$$

are satisfied. The inequalities make it possible to apply the Arrhenius approximation for the mean waiting time for the first switching:

$$T_{1\to3} = \frac{2\pi}{|U''(X_1)\,U''(X_2)|^2} \exp\,(U_{1,2}/D), \tag{A.1}$$

where $U_{1,2} = U(X_2) - U(X_1)$. Our purpose is to estimate how much $T_{1\to 3}$ changes when C^* gets a small positive increment ΔC^*. The ΔC^* is thought to be small enough, so that the following inequalities hold

$$\frac{\Delta C^*}{C^*} \ll 1, \qquad k_2^+ \Delta C^* \ll -F(X_0), \tag{A.2}$$

where X_0 is the minimum point of $F(X)$. We also assume the inflection point of $F(X)$s graph to be above the X-axis. Then it follows from (A.2) that

$$k_2^+ \Delta C^* \ll (X_2 - X_1)|F'(X_i)|, \qquad i = 1, 2. \tag{A.3}$$

The rest points X_i get deviations ΔX_i which can be estimated in the ΔC^*s first-order:

$$\Delta X_i = -k_2^+ \Delta C^* / F'(X_i). \tag{A.4}$$

It follows from eqn (A.4) and inequality (A.3) that

$$|\Delta X_i| \ll X_2 - X_1.$$

This inequality allows us to neglect the change in the pre-exponential term in eqn (A.1). The change in the exponent in (A.1) is due to the change in $U_{1,2}$:

$$U_{1,2} \to U_{1,2} + (X_1 - X_2) k_2^+ \Delta C^*, \tag{A.5}$$

and in D:

$$D \to D + D \cdot (1 - 2\varkappa_2/\varkappa_1)\, \Delta C^*/C^*.$$

The expressions are valid up to the first-order of ΔC^*. If

$$2\varkappa_2/\varkappa_1 \leq 1 \tag{A.6}$$

the deviation of the "diffusion" coefficient has an effect of the same sign as does $\Delta U_{1,2}$ [see (A.5)]. We neglect this part of the effect to make the final expressions more demonstrative. Thus, using (A.5), we have

$$\frac{T_{1\to 3}(C^*)}{T_{1\to 3}(C^* + \Delta C^*)} \approx \exp\left(\tfrac{3}{2} N^* \frac{\gamma}{k_2^+} \cdot \frac{\Delta C^*}{C^*}\right). \tag{A.7}$$

In the last transformation, we assume for definiteness, that in (A.6) an equality takes place and that

$$(X_2 - X_1)/C^* \sim 1.$$

Using eqn (A.7) with $\Delta C^*(\omega)$ and $\Delta C^*(\omega_{\max})$ substituted for ΔC^*, we have, up to the first-order of $\Delta C^*/C^*$,

$$\mu(\omega) = \left[\exp\left(\frac{\Delta C^*(\omega)}{C^*} - \frac{\Delta C^*(\omega_{\max})}{C^*}\right)\right]^P \approx [\nu(\omega)]^P.$$