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# Cooperative mechanism for improving the discriminating ability in the chemoreceptor neuron Binomial case

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**Abstract.** The discriminating ability (selectivity) of the chemoreceptor neuron is compared with that of its receptor proteins. The process of neuronal triggering is expected to be cooperative and threshold type in a sense that the neuron fires a spike if and only if the number of receptor proteins which are bound with odor molecules is above a definite threshold. The binomial distribution is utilized to estimate the firing probability if a definite odor is applied. It is established that a chemoreceptor neuron can have a much higher selectivity than its individual receptor proteins, provided that the chemical stimuli are presented at low concentrations. A possibility for the above mechanism to be valid in other sensory systems is discussed.

## 1 Introduction

The precision with which a living object is able to perceive information about the external world is an essential factor for its survival. Information is perceived through various sensors having distinct modalities. As discriminating ability or the selectivity of a sensor we mean its ability to distinguish stimuli of a definite modality with respect to their quality and intensity.[1]

The discriminating ability of an individual builds up along the pathway of neuronal processing of a sensory signal of a definite modality (Fitzpatrick et al. 1997). This can be illustrated by the improved selectivity of an individual organism compared to the discriminating ability measured for separate neurons at the initial part of the corresponding sensory tract (Bastian 1994).

At the same time, primary (receptor) neurons in a sensory tract must have an initial discriminating ability which is provided by means of specific physical mechanisms for each modality. For chemical senses, such as olfaction, a receptor neuron has a large number of receptor proteins on the part of its membrane exposed to the external medium. The receptor proteins are able to bind certain molecules presented in the medium (Shepherd 1992). The binding eventually results in opening of ion channels in the membrane, then in membrane depolarization. If the number of open channels is large enough to ensure threshold depolarization, the neuron fires a spike.

The discriminating ability of a chemoreceptor neuron depends on that of its receptor proteins. There are many types of receptor proteins designed for sensing different odors and distinct components of a single odor (Ressler et al. 1994). A given receptor protein may have more affinity to one odor, and less to another. This results in unequal probabilities $P_1$ and $P_2$ ($P_1 > P_2$) for binding odors $O_1$ and $O_2$, provided that the odors are presented at equal concentrations. The selectivity of the receptor protein with respect to $O_1$ and $O_2$ can be characterized by means of the following quotient

$$v = \frac{P_1}{P_2} \quad . \tag{1}$$

When an odor is presented at some concentration to the receptor neuron, it can generate spikes with a definite probability. One reason for the spiking process to be stochastic is the statistical physics of binding/releasing of odor molecules by receptor proteins. For small $P_1, (P_2)$, the process is Poissonian (van Drongelen et al. 1978; Lánský and Rospars 1993; Rospars et al. 1994) with intensity $\boldsymbol{P}_1(\boldsymbol{P}_2)$, which gives the probability of one spike per unit time.

The discriminating ability $\mu$ of the receptor neuron with respect to stimuli $O_1$ and $O_2$ could be characterized by means of the following quotient.

$$\mu = \frac{\boldsymbol{P}_1}{\boldsymbol{P}_2} \quad . \tag{2}$$

In this paper, we compare the selectivity of the receptor neuron with that of its receptor proteins. The above-

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[1] Corresponding characteristics are the selectivity and (differential) sensitivity

mentioned features of the chemoreceptor neuron, namely, the presence of a large population of identical receptor proteins, and the requirement to bind the threshold number of them in order to trigger the neuron, ensure validity of earlier described cooperative mechanism of improving selectivity in ensemble with the threshold (Vidybida 1988, 1991, 1995). The binomial case[2] of this mechanism allows the mathematical rigorous estimate of selectivity improvement without additional assumptions.

## 2 Statement of the problem

Let us consider a chemoreceptor neuron populated with $N$ identical receptor proteins. The proteins can bind odors $O_1$ and $O_2$. If $N_0 (N_0 \leq N)$ or more receptor proteins are bound, the neuron fires. The firing probability is determined in the stochastic processes of binding/releasing at a single receptor protein. The processes are generated by the following chemical reaction

$$O + R \underset{k_-}{\overset{k_+}{\rightleftharpoons}} OR \ , \tag{3}$$

where O is the odor molecule, $R$ is the receptor protein, and $k_+, k_-$ are the rate constants. Let an odor O be presented at a definite concentration, [O]. When chemical equilibrium is established, the probability for a single receptor protein to be bound can be calculated by means of the following relation

$$P = \frac{1}{1 + \frac{[O]_{1/2}}{[O]}} \ , \tag{4}$$

where $[O]_{1/2} = k_-/k_+$. Provided that the rate constants $k_+$ and $k_-$ differ for $O_1$ and $O_2$, Eq. (4) gives unequal values, $P_1$ and $P_2$. The unequalness means that the receptor protein can discriminate between the odors.

The probability of finding $N_0$ or more receptor proteins bound at the same time is given by the binomial distribution. We need to estimate the neuronal selectivity defined in Eq. (2), in terms of the selectivity of a single receptor protein defined in Eq. (1). In this task, we consider the values $N$, $N_0$, $P_1$ and $P_2$ as parameters, derivable from the neuron construction and conditions of odor presentation.

## 3 Mathematical estimates

In accordance with the statement of the problem, the probability $\boldsymbol{P}_1(\boldsymbol{P}_2)$ that the threshold $N_0$ will be achieved under stimulus $O_1$ ($O_2$) can be calculated based on the binomial distribution (Gnedenko 1969):

$$\boldsymbol{P}_i = \sum_{N_0 \leq k \leq N} C_N^k P_i^k (1 - P_i)^{N-k}, \quad i = 1, 2 \ . \tag{5}$$

The last expression can be evaluated based on various approximate formulae, such as the Poissonian distribution or the Moivre-Laplace formula.[3] Our purpose here is to find a rigorous estimate from below (a lower bound) for the ratio in Eq. (2). The above-mentioned approximate formulae would be useful for this purpose if applied together with an estimation of their precision. The precision (residual term) estimation must be uniform with respect to $N$ for all $N < \infty$ and for all $k \leq N$ to be useful here. It seems that the estimation of the residual term convenient for our calculations is not available.[4] Fortunately, the ratio of the expressions of type (5) can be estimated from below directly.

Let us rewrite Eq. (5) for $i = 1$ in the following form:

$$\boldsymbol{P}_1 = P_1^{N_0} \sum_{N_0 \leq k \leq N} C_N^k P_2^{k-N_0} (1 - P_2)^{N-k} L_k \ , \tag{6}$$

where

$$L_k = \left(\frac{P_1}{P_2}\right)^{k-N_0} \left(\frac{1 - P_1}{1 - P_2}\right)^{N-k} \ .$$

Let

$$0 < P_2 < P_1 < 1 \ . \tag{7}$$

In this case, $L_k$ has its smallest value for $k = N_0$:

$$L_{N_0} = \left(\frac{1 - P_1}{1 - P_2}\right)^{N-N_0} \ . \tag{8}$$

From Eqs. (6) and (8) we have for $\boldsymbol{P}_1$:

$$\boldsymbol{P}_1 > \frac{P_1^{N_0}}{P_2^{N_0}} \cdot \boldsymbol{P}_2 \cdot \left(\frac{1 - P_1}{1 - P_2}\right)^{N-N_0} \ . \tag{9}$$

Based on the definitions (1) and (2), let us rewrite Eq. (9) in the following form

$$\mu > v^{N_0} \cdot \left(\frac{1 - P_1}{1 - P_2}\right)^{N-N_0} \ . \tag{10}$$

In accordance with the inequality of Eq. (7), let us present $v = P_1/P_2$ in the following form

$$v = 1 + \epsilon, \quad \epsilon > 0 \ . \tag{11}$$

Equation (11) allows us to rewrite Eq. (10) as follows

$$\mu > (1 + \epsilon)^{N_0} \left(1 - \epsilon \frac{P_2}{1 - P_2}\right)^{N-N_0} \ ,$$

or

[2] The idea of considering the binomial case was suggested to the author by J. -P. Rospars (INRA, France).

[3] Both mentioned formulae require a definite relationships between $N, N_0$ and $P$ to be satisfied (Feller 1958, Ch. 6, p. 5, Ch. 7, p. 2 and 5). It is preferable not to base the estimate on any specific relation between $N, N_0$ and $P$ because these values can differ for different receptor neurons and odors.

[4] See, e.g. (Feller 1958, Ch. 6, p. 10, Ch. 7, p. 5).

$$\mu > \exp\left[N_0 \ln(1+\epsilon) + (N-N_0)\ln\left(1-\epsilon\frac{P_2}{1-P_2}\right)\right] \quad . \tag{12}$$

For further transformation of Eq. (12), Let us use the following inequality

$$\ln(1+x) \geq \frac{x}{1+x} \quad , \tag{13}$$

which is valid for every $x$ satisfying the following condition

$$x > -1 \quad . \tag{14}$$

From Eqs. (12) and (13) we have

$$\mu > \exp\left[N_0 \frac{\epsilon}{1+\epsilon} + (N-N_0)\frac{-\frac{\epsilon P_2}{1-P_2}}{1-\frac{\epsilon P_2}{1-P_2}}\right] \quad .$$

[The condition in Eq. (14) is valid due to Eq. (7)].

Let us rewrite the last estimate in the form

$$\mu > \exp\left[N \cdot \left(1-\frac{1}{v}\right) \cdot \frac{q-P_1}{1-P_1}\right] \quad , \tag{15}$$

where

$$q = \frac{N_0}{N} \quad .$$

The estimate in Eq. (15) is a direct consequence of the statement of the problem in Eqs. (1), (2), (5) and (7) without additional assumptions. Its domain of validity is as follows[5]:

$$\begin{cases} 0 < N_0 \leq N \\ 0 < P_2 < P_1 < 1 \end{cases} \quad . \tag{16}$$

We are interested in the situation when $\mu$ increases with increasing $N$. In accordance with (15), this will be the case provided $q > P_1$, or

$$N_0 > NP_1 \quad . \tag{17}$$

This inequality means that the threshold number of bound receptor proteins, which is necessary to trigger the neuron, must be greater than the mean number of bound proteins if the stimulus $O_1$ is presented.

In order to illustrate the effectiveness of the mechanism for improving selectivity, numerical calculations have been made for $\mu$ as a function of $P_1$ based on Eqs. (2) and (5), and low binding for $\mu$ in accordance with Eq. (15), for numerical values presented in Table 1

The curves obtained are displayed in Fig. 1. Note that all values in Table 1 together with all values of $P_1$ represented in Fig. 1 reside in the domain of validity of estimate (15), defined in (16). The same is valid for Fig. 2.

[5] {, logical "and".

**Table 1.** Parameters used for numerical examples and graphical illustrations

| | $N$ | $N_0$ | $v$ |
|---|---|---|---|
| 1 | 200 | 50 | 1.2 |
| 2 | 400 | 100 | 1.2 |
| 3 | 600 | 150 | 1.2 |

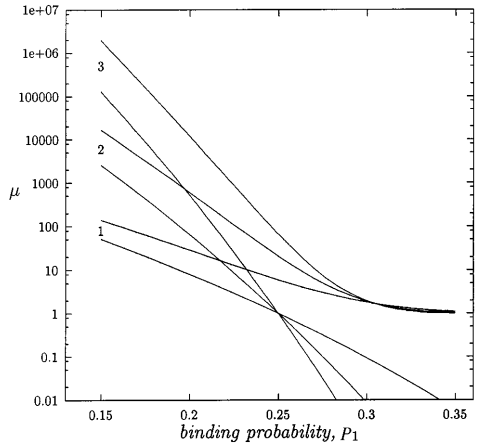


**Fig. 1.** Comparison of the neuronal selectivity with the estimate obtained [in Eq. (15)]. The curve pairs 1–3 correspond to rows 1–3 in Table 1. In each pair, the *upper curve* is calculated by means of exact formulae (2) and (5), and the *lower curve* represents the right-hand side in Eq. (15)

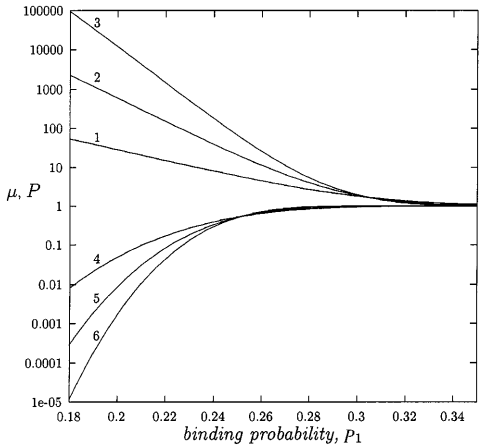


**Fig. 2.** Comparison of the ensemble selectivity with the probability, $P$, of attaining the threshold. The curve pairs (1,4), (2,5) and (3,6) correspond to rows 1–3 in Table 1. Curves 4–6 are calculated by means of (5) for $i = 1$; curves 1–3 are the same as in Fig. 1

## 4 Conclusions and discussion

In this paper, we compare the selectivity of a chemoreceptor neuron with that of receptor proteins incorporated into its membrane. As a working model for estimates, we consider the probabilistic one, where the number of receptor proteins bound with odor at any moment is given by the binomial law. A more realistic approach should be based on the birth-death stochastic

process, in accordance with (3), as has been done for another system (Vidybida 1991). We consider a simplified mechanism for triggering; the spike is generated immediately at the moment when the threshold is attained, and it has zero duration. A more realistic model should include the membrane charging-discharging processes and a finite spike duration, as well as the refractory time.

The final estimate (15) for selectivity in the ensemble in terms of selectivity of its individual receptor molecules is mathematically rigorous. Its dependence on the total number of identical receptor subunits, $N$, is similar to that found before in another cooperative systems (Vidybida 1988, 1991, 1995) based on approximate estimates.

In Fig. 2, the selectivity as a function of $P_1$ is shown together with the firing probability for the more effective stimulus $O_1$. From Fig. 2, we can conclude that the effect of selectivity improvement is better displayed at low intensities.

From the final expression (15), for chemoreceptor neurons, the mechanism for selectivity improvement can be effective provided that relation (17) is satisfied for the total and threshold numbers of receptor proteins and the binding probability for a single receptor protein. The probability depends on the odor concentration in accordance with Eq. (4). Thus, the neuron can be more selective than its receptor proteins provided that the odor is presented at low concentration, when the mean number of bound receptor proteins is below the firing threshold, $N_0$. In this situation, binding of the threshold number of receptor proteins and firing may occur due to statistical fluctuations, and is impossible in the deterministic picture. This suggests the fundamental statistical nature of the mechanism considered. In order for the mechanism to be valid, the stimuli concentrations must ensure that the mean number of occupied receptor proteins is just subthreshold. Thus, in this model, with $N_0$ fixed, the selectivity can be improved only for a narrow range of concentrations. In contrast, for real neurons, the adaptation mechanisms are characteristic (Krylov and Makovsky 1978; Softky and Koch 1993; Koch 1997). Introducing adaptation into this model might ensure the improved discriminating ability over a wider range of concentrations.

In connection with what is stated above, a natural question arises. If odor is presented at low concentration, the threshold binding and firing of the receptor neuron may be quite improbable. Can this improbable event be significant for information processing in the nervous system? To find an answer, we can use the data represented in Fig. 2. For example, for $P_1 = 0.2$, curve 1 in Fig. 2 gives a value for $\mu$ of 10–100, and curve 4 gives the probability of reaching the threshold of 0.1–0.01, which is quite probable. Looking for higher improvement of selectivity, we must consider lower values for $P_1$ (and higher values for $N_0$, $N$), and obtain fairly low probabilities of firing for a single neuron. Those quite improbable firings of individual receptor neurons may still be significant for information processing. Indeed, for the nervous system, the mean firing frequency (MFF) is significant. The MFF can be rather high even for an improbable event, provided the sampling rate (SR, the number of trials per unit time) is high.

The framework of this paper was not intended to introduce the sampling rate concept, because time-dependent phenomena are ignored (see above). The SR depends on the rate constants characterizing transients at a single receptor molecule during binding/releasing of odor [$k_\pm$ in Eq. (3)], and transients in the cell during firing/refraction. The latter limit SR which is inherent to a single neuron to a value of about 1 kHz because for a single successful trial (spike) at least 1 ms has to be spent. Based on this SR, we can conclude that the above-mentioned value of the firing probability can ensure a MFF for a single receptor neuron of 10–100 Hz.

In order to assess the significance of less probable triggerings of a separate chemoreceptor neuron, we should take into account that there are many identical receptor neurons of a definite type in the periphery of the chemosensory tract.[6] Estimating here their number to be 1000–2000, we can introduce the effective SR, which characterizes the rate of receiving signals from a pool of identical receptor neurons by a single glomerulus. Taking into account that the neurons from the pool converge onto 1 or 2 glomeruli (Ressler et al. 1994), this SR can be about $10^6$ Hz (the SR of 1 kHz at the level of a single neuron is taken into account).[7]

The cooperative and threshold-type mechanisms for signal processing are typical for the nervous system. For olfaction, for example, a secondary neuron can be triggered only by the cooperative action of many receptor neurons terminated onto it. (Duchamp-Viret et al. 1989). Therefore, the improved discriminating ability of the secondary neurons as compared to that of receptor neurons, which has been observed experimentally (Duchamp and Sicard 1984; Duchamp-Viret et al. 1989) could be explained based on the mechanism discussed here.

It should also be mentioned that a similar improvement of the discriminating ability along the sensory tract, which is observed for visual (Lindblom and Westheimer 1993; He et al. 1995) and auditory (Fitzpatrick et al. 1997; Eggermont and Epping 1987) systems, could be explained based on the mechanism discussed in this paper.

Finally, it is appropriate to notice that application of the above consideration to the olfactory system of a concrete living object is not straightforward. First of all, the numbers specified in Table 1 are rather illustrative. The real values for $N$ and $N_0$ vary from species to species and may be different for different odors in the same species

[6] In the mouse, for example the total number of receptor neurons in the olfactory epithelium is $4–8 \times 10^6$, and a single odorant receptor-type protein is expressed in 5000–10000 receptor neurons (Ressler et al. 1994).

[7] See also the Discussion in Innocenti et al. (1994), where it is explained how the axonal arborization pattern can affect properties of signal transmission and improve the effective SR.

(Kaissling, Max-Planck-Institut fuer Verhaltenphysiologie Seewiesen, Germany, personal communication, 1998). Also, the transduction mechanism includes the second messenger stage, the integration and adaptation (decay of the inward current for prolonged stimuli), as has been found for salamander olfactory receptor neurons (Firestein et al. 1990). These features will be incorporated in the above consideration in further papers.

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