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Selectivity of chemoreceptor neuron

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Abstract

Discriminating ability (selectivity) of 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 can fire if and only if the number of its receptor proteins, which are bound with odor molecules, is above a definite threshold. Both deterministic and stochastic pictures are considered. The stochastic case is treated based on birth and death stochastic process and first passage technique. In both pictures, it is shown that a chemoreceptor neuron can have much a higher selectivity than its individual receptor proteins, provided the chemical stimuli are presented at low concentrations, and the threshold is high enough. This is in agreement with a preliminary estimate based on simplified probabilistic reasoning (Vidybida, A.K., 1999. Cooperative mechanism for improving the discriminating ability in the chemoreceptive neuron. Binomial case. Biol. Cybern. 81, 469–473). The mechanism of selectivity improvement is similar to that described before in cooperative chemical systems. A possibility for this mechanism to be valid at higher stages of processing of chemical signals, as well as in other sensory systems is discussed.

Keywords: Sensory systems; Selectivity; Cooperativity; Threshold; Olfaction; Chemoreception; Stochastic process

1. Introduction

In sensory systems, the discriminating ability increases while the sensory signal travels along the corresponding sensory pathways. Improving of discriminating ability at higher levels of processing of sensory signals has been found experimentally for vision (Norton et al., 1988; Smallman et al., 1996), hearing (de Vries, 1948; Price, 1978), electroreception (Bastian, 1994), olfaction (Kaissling, 1987; Duchamp-Viret and Duchamp, 1997).

All sensory systems have common structural and functional features. First, the systems have hierarchical structure, second, their functioning is of threshold type: a threshold must be exceeded for passing the signal from one stage to another in the hierarchy. When any noise is absent (deterministic situation), a single stage processing structure with adjustable reception threshold could ensure arbitrary high sensitivity, because the sensitivity is the same as the threshold height in this case. Two stage hierarchy with a modest selectivity at first stage and adjustable threshold at the second one could ensure arbitrary sharp selectivity in the whole system (Fig. 1). In the presence of internal noise the process of signal reception and

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processing becomes stochastic, and this imposes limits on otherwise unlimited improvement of informational quality by means of proper chosen thresholds.

In the chemoreceptor neuron, the chemical stimulus processing may be roughly described as a two stage process (Fig. 2). At first stage, the odor molecules are bound with and released by the receptor proteins (Margolis, 1987; Ressler et al., 1994), at the second stage, due to cooperative action of many bound receptor proteins, the neuron fires a spike. The receptor proteins have initial selectivity, and there is a threshold at the second stage. The purpose is to estimate a possible selectivity of chemoreceptor neuron as compared to selectivity of its receptor proteins. The deterministic case is considered based on idealized strength-duration dependence. In the stochastic case, the fluctuations in the binding-releasing statistics are taken into account based on standard techniques for birth and death processes.

The main conclusion of this paper is that the chemoreceptor neuron can have much better discriminating ability than its receptor proteins does, provided the stimuli are presented in low concentrations, and the total and threshold number of receptor proteins per single neuron are large enough.

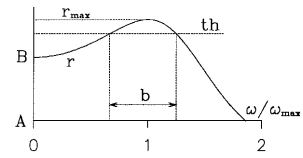

Fig. 1. Organization of sharp selectivity in a two level structure influenced by a set of stimuli parameterized with ω (e.g. microwaves). The curve r represents response level of primary structure; th is the threshold for channeling signal to the second structure; ω_{max} is the frequency of maximal response. Selectivity is defined as $S = 1/b$. S tends to infinity when th approaches the maximal response, r_{max} (from Vidybida, 1995).

If the stimulus O is applied at concentration $[O] = c$, in the stationary state, the mean fraction p of bound receptors due to Eq. (1) is given by the following expression:

$$p = 1/(1 + [O]_{1/2}/c), \tag{2}$$

where $[O]_{1/2} = k_-/k_+$. If another stimulus, O' with another rate constants, k'_+, k'_-, is applied at the same concentration, then Eq. (2) may give another value, p'.

A single receptor discriminates between O and O' if $p \neq p'$, or $[O]_{1/2} \neq [O']_{1/2}$. One expects for definiteness that $p > p'$, or equivalently

$$[\acute{O}]_{1/2} > [O]_{1/2}. \tag{3}$$

2. Methods

Having in mind the purpose to analyze selectivity in the context of threshold and binding-releasing statistics, the simplest possible model preserving that context was used. In this model, the binding-releasing of chemical stimulus by a single receptor protein takes place in accordance to the following chemical reaction:

$$O + R \underset{k_-}{\overset{k_+}{\rightleftharpoons}} OR, \tag{1}$$

where O is the stimulus molecule, R is the receptor protein, OR is the receptor protein occupied with chemical stimulus molecule. The receptor neuron in the model is reduced to a set of N identical receptor proteins incorporated in an excitable membrane (Fig. 2).

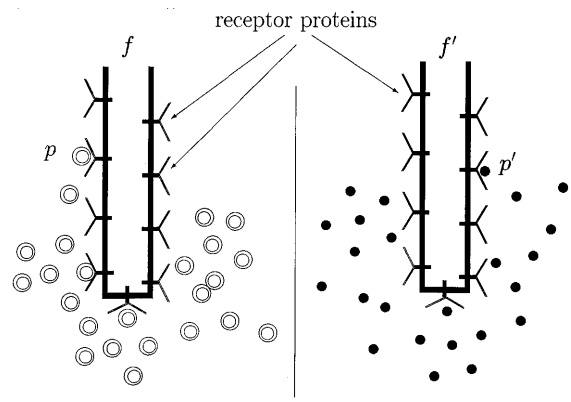

Fig. 2. Receptor protein and neuron selectivity. The odors are presented at equal concentrations. The binding probabilities p, p' as well as the firing rates f, f' are different due to differences in binding-releasing statistics for different odors.

The quality of discrimination can be expressed either as $\mu = p/p' > 1$, or $k = [O']_{1/2}/[O]_{1/2} > 1$.

The definition of discrimination at the neuronal level is given separately for deterministic and stochastic situation.

2.1. Deterministic situation

In this situation the reasoning is provided in terms of mean values, and statistical fluctuations are neglected. This could be approved for very large number N.

With each bound receptor OR an elementary depolarizing current i is associated. Thus, the total mean depolarizing current I due to application either O, or O' at concentration c will be

$$I = Npi, \quad I' = Np'i. \tag{4}$$

For describing the neuronal activity under stimulations (4) the idealized strength-duration relationship is used (Noble and Stein, 1966):

$$I = I_{\mathrm{Rh}}(1 - \mathrm{e}^{-t/\tau})^{-1}, \tag{5}$$

where t is the duration of current I, which is required for triggering (interspike interval); I_{Rh} is the rheobasic current — the greatest lower bound of currents which are able to trigger; τ is the membrane time constant. For the giant squid axon $I_{\mathrm{Rh}} = 2.241$ μA, $\tau = 2.856$ ms (Noble and Stein, 1966). The relationship (5) gives a threshold with respect to stimulating current: $I \to I_{\mathrm{Rh}} \Rightarrow t \to \infty$. The rheobasic current can be expressed in terms of threshold number, N_0 of bound receptor proteins, which is necessary for triggering: $N_0 = I_{\mathrm{Rh}}/i$. Eq. (5) can be rewritten in the following form:

$$Np = N_0(1 - \mathrm{e}^{-t/\tau})^{-1}, \tag{6}$$

where p is given by Eq. (2).

The neuronal selectivity v is expressed in terms of interspike intervals or firing frequencies as follows:

$$v = t'/t, \tag{7}$$

where t, t' are the interspike intervals under stimuli O, O', respectively, which are applied at equal concentrations.

2.2. Stochastic situation

If numbers N, N_0 are not very large, the statistical fluctuations become essential. In this case the number of bound receptors at time t, $n(t)$ should be considered as realization of birth and death stochastic process described by a set of transition probabilities

$$p(n, t|n', t'), \quad t' \le t,$$
$$0 \le n \le N, \quad 0 \le n' \le N, \quad p(n, t|n', t) = \delta_{nn'}.$$

If one expected that during an infinitely small period of time only a single birth or death event may happen (ordinary process, Gnedenko, 1962) then the evolution of transition probabilities is given by the backward Master equation:

$$\frac{\partial p(n, t|n', t')}{\partial t} = r^-(n')(p(n, t|n', t') - p(n, t|n' - 1, t')) + r^+(n')(p(n, t|n', t') - p(n, t|n' + 1, t')), n, n' \in \{0, 1, \ldots, N\}, \tag{8}$$

where the infinitesimal transition probabilities $r^+(n)$, $r^-(n)$ are derived from Eq. (1): $r^+(n) = k_+(N - n)[O]$, $r^-(n) = k_- n$. The depolarizing current due to chemical stimulation, $I(t) = in(t)$, will be the fluctuating quantity which should be used as stimulating current in the Hodgkin and Huxley set of equations (Hodgkin and Huxley, 1952) in order to estimate mean firing rates f, f' under stimuli O, O'. The neuronal selectivity can be defined analogously to Eq. (7): $v = f/f'$. The straightforward treatment of this task would be numerical analysis similar to that made in (Vidybida, 1996) for another stochastic stimuli in the Hodgkin and Huxley set of equations. In this paper the numerical treatment is not applied. Instead, a limiting case is considered allowing one to obtain an analytical conclusion. Namely, expect that the triggering happens immediately after the number $n(t)$ of bound receptor proteins achieves the firing threshold N_0. In the framework of Hodgkin and Huxley equations, this condition might be satisfied if the membrane specific capacitance, C_{M} tends to zero. In this case the neuron will be engaged into next spike immediately after finishing the previous one provided $n(t)$ is still above the threshold.

Let one denote the mean time between two consecutive crossings the threshold N_0 by the $n(t)$ from above and below as W; the mean time between two consecutive crossings the threshold N_0 by the $n(t)$ from below and above as T; the spike duration (refractory time included) as t_0. Then the mean number of spikes, $\bar{n}_t$ during time t can be estimated as

$$\bar{n}_t = (t/t_0) \cdot (T/(T+W)), \tag{9}$$

and the mean firing frequency — as

$$f = \bar{n}_t/t = P_T/t_0, \tag{10}$$

where

$$P_T = T/(T+W) \tag{11}$$

is the probability to find at any moment of time $N_0 \le n(t) \le N$. The neuronal selectivity can be estimated as

$$v = f/f' = P_T/P'_T. \tag{12}$$

Actually, Eq. (9) gives underestimated number because the last spike in a series can finish after the moment when the threshold is crossed from above. This possibility to get one extra spike in a series can be ignored provided there are many spikes in the series:

$$T/t_0 \gg 1. \tag{13}$$

The times T, W can be calculated based on Eq. (8) by means of the standard mean waiting time (first passage) techniques[1]:

$$W = \sum_{0 \le l < N_0} B(N, l, p)/(N_0 k\_B(N, N_0, p)),$$

$$T = \sum_{N_0 \le l \le N} B(N, l, p)/(N_0 k\_B(N, N_0, p)), \tag{14}$$

where $B(N, l, p) = C_N^l p^l (1-p)^{N-l}$, and p is the probability to find any receptor protein bound with O, which is calculated in Eq. (2).

[1] The mathematical derivation of Eq. (14) is omitted due to space limitation.

3. Results

3.1. Deterministic situation

For stimuli O, O', let one introduce the threshold concentrations:

$$[O]_0 = [O]_{1/2} p_0/(1-p_0), \qquad [O']_0 = [O']_{1/2} p_0/(1-p_0),$$

where $p_0 = N_0/N$.

$$[O']_0 > [O]_0, \tag{15}$$

due to Eq. (3). In this case, for perfect discrimination between O and O' it is enough to apply each stimulus at concentration which satisfies the following condition

$$[O]_0 < c < [O']_0,$$

and which exists due to Eq. (15). In this condition the stimulus O' will not be able to cause triggering, whereas O will cause spiking with some frequency. If the stimuli are applied at concentration $c > [O']_0$ then interspike intervals t, t' will differ, $t' > t$. The intervals can be compared based on Eq. (6):

$$v = t'/t = \ln(p'/(p'-p_0))/\ln(p/(p-p_0)).$$

Due to Eq. (3) $p' < p$ for all concentrations c. If

$$c \to [O']_0, \tag{16}$$

then $p' \to p_0$, and $t' \to \infty$, as well as

$$p \to p_0(1+\varepsilon), \tag{17}$$

where

$$\varepsilon = (k-1)(1-p_0)/(1+p_0(k-1)) > 0. \tag{18}$$

Therefore, at cond. (16) $p - p_0 \ge \varepsilon p_0 > 0$ which ensures finite interspike interval for O.

In particular, the concentration $c = [O']_0$ can be chosen. In this case O' will not trigger whereas O will trigger with finite frequency. The numerical value of this frequency is important, because very rare spikes do not represent practical interest. Inversely, if a frequency, say 1 Hz, is considered as practically suitable, how close could p and $p' = p_0$ be? The estimate can be found based on Eq. (6) and numerical value $\tau \sim 3$ ms, which is mentioned above. From Eq. (6) one has

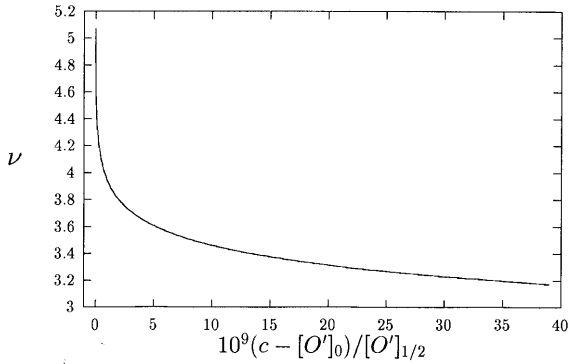

Fig. 3. Dependence of selectivity on concentration at which both stimuli are applied. Here $[O']_{1/2}/[O]_{1/2} = 1.01$, $N_0/N = 0.1$. The interspike interval t for O is ~ 14.2 ms for all concentrations presented in the x-axis.

$$t = \tau \ln(p/(p - p_0)). \tag{19}$$

Substituting Eq. (17) into Eq. (19) one has: $1000 = 3 \ln(1 + 1/\varepsilon)$, and further

$$\varepsilon \sim 10^{-100}. \tag{20}$$

In terms of $[O]_{1/2}$, $[O']_{1/2}$ one has from Eq. (18):

$$k = \varepsilon + 1 - p_0(\varepsilon + 1)/(1 - p_0(\varepsilon + 1)) \approx 1 + \varepsilon \sim 1 + 10^{-100}. \tag{21}$$

Thus, in deterministic picture, selectivity could be extremely precise, provided the concentrations of stimuli are maintained with similar precision (Fig. 3). The same configuration could be used for measuring very small differences in concentration of a single odor, if such small differences would be meaningful (see Section 4).

3.2. Stochastic situation

In accordance with Eq. (12), the selectivity of the whole neuron can be estimated as follows. Denote $\varepsilon = p/p' - 1 > 0$. For the probability P'_T to find $n(t) \geq N_0$ if the stimulus O' is applied one has from Eq. (11), Eq. (14)

$$P'_T = \frac{T'}{T' + W'} = \sum_{N_0 \leq k \leq N} C_N^k p'^k (1 - p')^{N-k} < \left(\frac{p'}{p}\right)^{N_0} \left(\frac{1 - p'}{1 - p}\right)^{N - N_0} P_T.$$

Thus, for v^{-1} one has

$$v^{-1} < \left(\frac{p'}{p}\right)^{N_0} \left(\frac{1 - p'}{1 - p}\right)^{N - N_0} = \exp\left(N_0 \ln \frac{p'}{p} + (N - N_0) \ln \frac{1 - p'}{1 - p}\right) < \exp\left(-N \ln(1 + \varepsilon) \frac{p_0 - p}{1 - p}\right),$$

where $p_0 = N_0/N$. This gives for v

$$v > \exp(N \ln(1 + \varepsilon)(p_0 - p)/(1 - p)), \tag{22}$$

or finally[2]

$$v > \mu^{N(p_0 - p)/(1 - p)}. \tag{23}$$

From Eqs. (22) and (23) it can be concluded that the selectivity of the chemoreceptor neuron as a whole could be very high for modest selectivity in a single receptor protein, provided the stimuli O, O' are presented at concentration c, which is subthreshold:

$$N_0/N > p = 1/(1 + [O]_{1/2}/c) \Leftrightarrow c < [O]_{1/2} N_0/(N - N_0). \tag{24}$$

Some examples are given in the Table 1. The course of selectivity and mean firing frequency when stimuli concentration changes is given in Fig. 4.

As regards the condition (13), it could be satisfied for relatively slow reactions (1). Situation is illustrated in Fig. 5.

4. Discussion

In this paper a selectivity of model chemoreceptor neuron is compared with that of receptor proteins incorporated in its membrane. Based on realistic structural and functional features of the neuron, it was concluded that the selectivity of neuron as a whole can be significantly improved. These features are: (i) two-level hierarchy of signal

[2] This estimate is similar to Eq. (14) in (Vidybida, 1995), where selectivity is estimated for a cooperative chemical system.

Table 1
Numerical examples of improved selectivity[a]

N	N_0	$[O]/[O]_{1/2}$	k	μ	ν	f (Hz)
5000	2000	0.61	1.05	1.031	1355.9	0.59
5000	2000	0.6	1.005	1.0031	1.97	0.074
5000	200	0.033	1.05	1.05	9.22	1.52
5000	20	0.0016	1.1	1.1	3.41	0.26
200	20	0.004	1.1	1.1	3.25	0.39

[a] The firing rate f for the O is calculated as P_T/t_0.

reception; (ii) a threshold for channeling signal from the first level to the second one.[3] The threshold concept is double-bounded with the concept of cooperativity. Indeed, there is a cooperativity behind the firing threshold, because the threshold emerges due to cooperation between voltage-dependent sodium channels. On the other hand, there is a cooperativity in front of the threshold, because due to it the elementary inputs must cooperate in order to trigger further stages of information processing. Therefore, the mechanism of selectivity improvement described in this paper is treated, as well as similar mechanisms in triggering states in bistable chemical system (Vidybida, 1995), in triggering degranulation in cytolytic T-lymphocyte (Vidybida, 1991), in improving temporal discrimination during synaptic integration (Vidybida, 1996) as cooperative mechanisms.

The selectivity of chemoreceptor neuron is treated in deterministic and stochastic paradigm. In both paradigms the summation of elementary depolarizing currents generated by bound receptor proteins is treated as first stage of signal reception. The spike triggering is considered as the second stage. The first stage selectivity, which is expressed in terms of compound stimulating current or receptor potential (Kaissling, 1977), should be the same as that of single receptor protein expressed in terms of binding probability with odor. In both paradigms the selectivity is improved at the second stage. In the deterministic paradigm all fluctuations are ignored, and neuronal response to chemical stimulus is estimated based on idealized strength-duration curve. This curve possesses a threshold for triggering, and this makes possible to improve discriminating ability enormously (Eqs. (20) and (21)). The small concentration differences evaluated in Eqs. (20) and (21) fall far beyond the meaningful limits for concentration definition. Indeed, concentration in a volume V is subjected to fluctuations, which are proportional to $1/\sqrt{N}$, where N is the mean number of molecules in V (Kittel, 1959). In case of chemoreceptor neuron a space in the vicinity of, e.g. olfactory cuticle can be taken as V. This volume cannot contain more than $\sim 10^{18}$ molecules. Therefore, in Eqs. (20) and (21) only $\varepsilon \geq 10^{-9}$ does make sense. The much smaller numbers displayed in Eqs. (20) and (21) simply demonstrate that without taking into account the

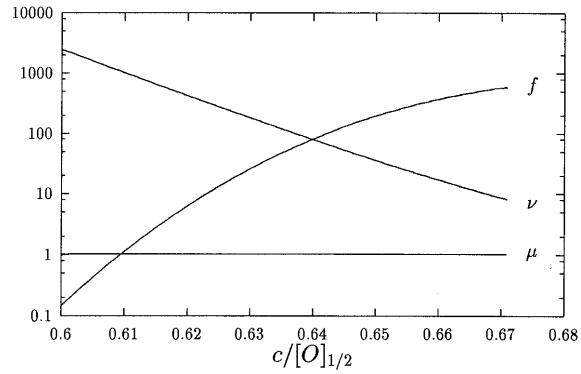

Fig. 4. Dependence of selectivity and firing frequency on concentration at which both stimuli are applied. Here $[O]_0 = 0.67[O]_{1/2}$, $k = 1.05$, $N = 5000$, $N_0 = 2000$, f is calculated in accordance to Eq. (10) with $t_0 = 1$ ms.

[3] The same features are characteristic at the stage when signal passes from receptor neurons to secondary neurons (van Drongelen et al., 1978; Kaissling, 1987; Rospars and Fort, 1994). In this case, N is the total number of primary neuronal terminals converging at a single secondary neuron, and N_0 is the number of synaptic inputs necessary to trigger the secondary cell.

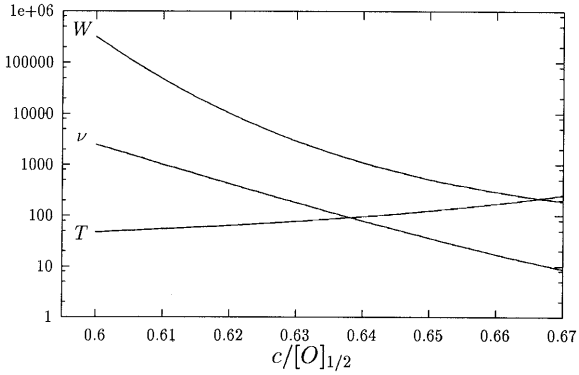

Fig. 5. Mean times, T, W between consecutive crossings of the threshold vs. concentration. Here $k_{-} = 0.1\ s^{-1}$, $N = 5000$, $N_0 = 2000$, T and W are in ms.

stochastic nature of odor reception unrealistically a good estimate can be obtained.

In the stochastic paradigm the binding-releasing process (1) is treated as birth and death process producing internal noise, which prevents from unlimited selectivity improvement mentioned in Fig. 1. The triggering is expected to happen immediately when the number of bound receptors reaches the firing threshold. This might bring the firing rate independent of the stimulus intensity in deterministic paradigm, where the intensity must be just superthreshold (Fig. 3). In the stochastic paradigm, the selectivity improvement takes place only at subthreshold stimulation. In this case the triggering happens due to superthreshold fluctuations, probability of which depends on the stimulus intensity. Therefore a kind of stimulus-reaction relationship is preserved (Fig. 4).

The route to spiking, which is considered here is 'one threshold crossing — many spikes' (Eq. (13)). This requires relatively slow processes in reaction (1) (Fig. 5). Another route, 'many threshold crossings — single spike' is possible as well. It is not clear which one takes place in reality. The receptor neuron construction, which is adopted here (Fig. 2), is simplified, but it seems that the second messenger stage can be introduced with preserving conclusions of this paper. The numerical data used for calculation (Table 1) are partially taken from experiment (N), and partially chosen deliberately (N_0, μ), because required experimental data are not available.[4] Therefore, it is not clear, what the above cooperative mechanism, if present in real olfactory or taste system, might serve for: to obtain a sharply selective neuron starting from modestly selective proteins (first row in the Table 1), or to obtain a reasonably selective neuron starting from proteins with poor selectivity (second row in the Table 1). Finally it could be mentioned that the same mechanism might be effective at the first relay point after the receptor neuron, because both the structural and functional features necessary for its operation are presented there. In this connection, it is interesting that in frogs, decreasing of odor concentration leads to more pronounced selectivity improvement in bulbar neurons as compared with selectivity of the receptor neurons (Duchamp-Viret et al., 1990, p. 260), which is in concordance with conclusions of this mechanism (Fig. 4, Eq. (24)).

[4] Actually, N_0 is estimated for pheromone as 1 (Kaissling, 1987). This case is treated as separate, which is not considered here. For ordinary odors, experimental data (Duchamp-Viret and Duchamp, 1997) suggest $N_0 \gg 1$. The same is valid for the secondary cells (Duchamp-Viret et al., 1990). This same mechanism might be used for developing of artificial sensors where the relation $N_0 \gg 1$ could be ensured by construction.

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References

Bastian, J., 1994. Electrosensory organisms. Phys. Today 47 (2), 30–37.

van Drongelen, W., Holley, A., Døving, K.B., 1978. Convergence in the olfactory system: quantitative aspects of odour sensitivity. J. Theor. Biol. 71, 39–48.

Duchamp-Viret, P., Duchamp, A., 1997. Odor processing in the frog olfactory system. Prog. Neurobiol. 53, 561–602.

Duchamp-Viret, P., Duchamp, A., Sicard, G., 1990. Olfactory discrimination over a wide concentration range. Comparison of receptor cell and bulb neuron abilities. Brain Res. 517, 256–262.

Gnedenko, B.V., 1962. The Theory of Probability. Chelsea, New York.

Hodgkin, A.L., Huxley, A.F., 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117, 500–544.

Kaissling, K.-E., 1987. In: Colbow, K. (Ed.), R.H. Wright Lectures on Insect Olfaction. Simon Fraser University, Burnaby, B.C., Canada, p. 190 S.

Kittel, C., 1959. Elementary Statistical Physics. Chapman, London, p. 278.

Kaissling, K.-E., 1977. Structure of odor molecules and multiple activities of receptor cells. In: Le Magnen, J., Mac Leod, P. (Eds.), Olfaction and Taste IV. London, Paris, pp. 9–16.

Margolis, F.L., 1987. Olfactory receptor neurons: specific gene expression and a hypothetical model for stimulus receptors. Discuss. Neurosci. 4 (3), 47–52.

Noble, D., Stein, R.B., 1966. The threshold conditions for initiation of action potentials by exitable cells. J. Physiol. 187, 129–162.

Norton, T.T., Casagrande, V.A., Irvin, G.E., Sesma, M.A., Petry, H.M., 1988. Contrast-sensitivity function of W-, X-, and Y-like relay cells in the lateral geniculate nucleus of bush baby. J. Neurophysiol. 59, 1639–1656.

Price, G.R., 1978. Action potentials in the cat at low sound intensities: thresholds, latencies, and rates of charge. J. Acoust. Soc. Am. 64, 1400–1405.

Ressler, K.J., Sullivan, S.L., Buck, L.B., 1994. Information coding in the olfactory system: evidence for a stereotyped and highly organized epitope map in the olfactory bulb. Cell 79, 1245–1255.

Rospars, J.-P., Fort, J.-C., 1994. Coding of odour quality: roles of convergence and inhibition. Network Comput. Neural Syst. 5, 121–145.

Smallman, H.S., MacLeod, D.I.A., He, S., Kentridge, R.W., 1996. Fine grain of the neural representation of human spatial vision. J. Neurosci. 16 (5), 1848–1855.

Vidybida, A.K., 1991. Selectivity and sensitivity improvement in co-operative system with a threshold in the presence of thermal noise. J. Theor. Biol. 152, 159–164.

Vidybida, A.K., 1995. Estimation of possible selectivity and sensitivity of a cooperative system to low-intensive microwave radiation. Phys. A 221, 30–40.

Vidybida, A.K., 1996. Neuron as time coherence discriminator. Biol. Cybern. 74, 539–544.

de Vries, H., 1948. Brownian movement and hearing. Physica 14, 48–60.