Possible Stochastic Mechanism for Improving the Selectivity of Olfactory Projection Neurons

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A possible mechanism that provides increased selectivity of olfactory bulb projection neurons, as compared to that of the primary olfactory receptor neurons, has been proposed. The mechanism operates at low concentrations of the odor molecules, when the lateral inhibition mechanism becomes inefficient. The mechanism proposed is based on a threshold-type reaction to the stimuli received by a projection neuron from a few receptor neurons, the stochastic nature of these stimuli, and the existence of electrical leakage in the projection neurons. The mechanism operates at the level of the single individual projection neuron and does not require the involvement of other bulbar neurons.

Keywords: odors, olfactory bulb, olfactory receptor neurons, projection neurons, spike activity, selectivity, stochastic process.

INTRODUCTION

Primary reception of odors is provided by olfactory receptor neurons (ORNs). The ORNs are synaptically connected with mitral and tufted cells of the olfactory bulb. The latter cells, known as bulbar projection neurons (PNs), convey olfactory signals to upper brain structures (finally, to the olfactory cortex).

Communication between ORNs and PNs is of convergent nature: many ORNs synapse onto a single PN. The convergence degree depends on the animal species and can be fairly large [1]. This is one of the factors providing high sensitivity to odors [2-4].

It is known that the discriminating ability of PNs is better than that of ORNs [5, 6]. A general point of view is that the better selectivity of PN is due to the mechanism of lateral inhibition [5, 7, 8]. Such a mechanism has been well studied in the visual system, where it increases the contrast between domains of the visual field [9-11]. In the olfactory system, lateral inhibition is organized via granular cells, which are stimulated by mitral cells and inhibit other PNs [12, 13]. As a result, the system

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of PNs functions similarly to the "winner takes all" principle, and this can be the reason of PNs having better selectivity than ORNs.

In recent studies [14], it was realized that lateral inhibition in the olfactory bulb, unlike that in the retina, is organized nontopographically. Such a feature was discussed earlier [8]. If so, is lateral inhibition able to ensure the same "contrast enhancement" in olfaction as it does in vision? This question has been discussed [15], but a final answer to this question requires additional experimental studies.

Lateral inhibition of PNs happens due to the activity of inhibitory bulbar neurons. The recruitment of inhibitory neurons is necessary because there is a possibility of high odor concentrations, and such recruitment decreases with decreasing concentrations [5]. Therefore, the efficacy of lateral inhibition in improving the selectivity of PNs should decrease for low concentrations. Such a decrease has been observed [5].

In our paper, another mechanism for the selectivity gain in PNs is proposed. It is independent of lateral inhibition and could be very efficient at low odor concentrations. This mechanism can work for individual PNs without the involvement of other bulbar cells. The prerequisites of this mechanism are as follows:

(i) existence of a leakage in the PN membrane,

(ii) a threshold-type response of PNs to the respective stimuli, and

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(iii) the random nature of stimuli obtained by a PN from ORNs.

A similar mechanism is possible for both individual ORNs [17, 18] and "electronic nose" sensors based on adsorption-desorption of odors [19].

In this theoretical paper, a PN model is used, which has been proposed earlier [20]. The activity of a single ORN is described as a Poisson process. The communication between a set of a few ORNs and the corresponding PN is characterized by the convergence degree N and the minimal number of input spikes N_0 required for triggering that PN (firing threshold). For this system, the coefficient of selectivity gain g is defined, which shows how much the PN selectivity is improved, as compared to that of the ORN. The exact expression for g as a function of the system parameters has been found. The expression output is analyzed for different parameters. In particular, it is observed that, for physiologically relevant parameters, the PN selectivity can be several tens times better than that of ORNs due to the mechanism proposed.

METHODS

Neuronal Model with a Random Living Time of the Obtained Excitatory Impulses. A model of PN that was proposed earlier [20] has been used. In this model, an effect of the membrane leakage occurs during a random decay of individual input impulses. Before the decay, each impulse is stored unchanged, and it disappears at the decay moment. Thus, there is a finite set of possible values of depolarization. The random living time of a single obtained impulse is characterized by an exponential distribution. Therefore, the decay of total depolarization is exponential (as it should be), but the depolarization decreases by finite jumps with a height equal to the height of an input impulse. If the impulse height is small, as compared with the firing threshold, then this model describes the membrane leakage satisfactorily.

Mathematically, the model can be formulated as follows. The resting state of a neuron is characterized by zero depolarization, V = 0. When obtaining an input impulse, the depolarization advances by h, the height of the input impulse. The h is analogous to the EPSP amplitude. Between the moments of obtaining two consecutive impulses, the depolarization does not change, V(t) = const, if no decay happens. Therefore, at any time moment, the depolarization takes a value from the discrete set, $V \in \{0, h, 2h, 3h, ...\}$. The neuron is characterized by a firing threshold V_0 ; if depolarization is greater than V_0 , then the neuron generates an output spike and appears in its resting state. The triggering condition formulated in terms of V_0 can be reformulated in terms of the minimal number N_0 of input spikes capable of triggering:

$$N_0 = [V_0/h] + 1,$$

where brackets [x] denote the integer part of x.

Until now, the model described corresponds to the model known as a "perfect integrator" [21]. It has been additionally expected [20] that any impulse obtained by the neuron has a random living time. The living time is exponentially distributed with the constant μ . This means that any impulse may disappear during a small interval, [t; t + dt], with the probability μdt . If the neuron keeps k excitatory impulses at moment t, the depolarization is equal to V(t) = kh. Let us believe that stimulation is absent after t. During a short interval, [t; t + dt], any of the k impulses can decay/disappear. Let us expect that the impulses decay independently. Then the probability that depolarization decreases by h during dt is $k\mu dt$. Thus, at the end of the interval [t; t + dt], the depolarization is equal to V(t + dt) = (k - 1)hwith the probability $k\mu dt$, and to V(t + dt) = khwith the probability $1 - k\mu dt$. Averaging over many realizations, we obtain the mean value of depolarization:

$$V(t + dt) = (k - 1)hk\mu \, dt + kh(1 - k\mu \, dt) = = kh(1 - \mu \, dt) \approx V(t)e^{-\mu \, dt}.$$

It is clear from the latter considerations that, on average, the depolarization decreases exponentially, as it should be for electrical leakage, and the constant μ has a physical meaning of the inverse membrane relaxation time, $\mu = 1/\tau$. This model could be named, according to its authors, as the KKPT model.

A Projection Neuron that is Stimulated by Many ORNs. The communication scheme between ORNs and a PN is shown in Fig. 1. It is not necessary to take into consideration additional cells, in particular the granular ones, and additional dendrites possibly ending in other glomeruli or nearby, for investigating of how the randomness, threshold, and leakage influence the PN selectivity.



F i g. 1. Scheme of communication between ORNs and a PN. Up to several thousands ORNs [22] (the concrete number depends on the animal species) can converge through a single glomerulus onto a single PN. All those ORNs express the same receptor protein.

Let N denote the number of ORNs converging onto a single PN. When stimulated with an olfactory stimulus (odor), each ORN generates a random train of spikes contributing to the compound stimulus applied to the PN. Taking into account the specificities of primary odor reception through the receptor proteins, it is natural to consider the ORN output series as a Poisson stream with the intensity λ_{in} , where the subscript "in" indicates that the spike train represents an input to the PN from a single ORN. The integral input effect coming to the PN will be a Poisson stream with the intensity $\lambda_{int} = N \lambda_{int}$.

Selectivity Definition. In order to compare the selectivity of an individual ORN with that of the PN, it is necessary to formulate an exact quantitative definition of those selectivities. In order to give such a definition, let us consider a situation where an ORN is exposed in two separate experiments to two different olfactory stimuli, O and O', having same odor concentration. This will result in spiking of the ORN with the intensities λ_{in} and λ'_{in} , respectively. Let us assume that the odor O' possesses a stronger affinity to the ORN receptor proteins than O does. Then, $\lambda'_{in} > \lambda_{in}$, and

$$\lambda_{in}' = \lambda_{in} + \Delta \lambda_{in},$$

where $\Delta \lambda_{in} > 0$. The selectivity (or discriminating ability) S between stimuli O and O' affecting the ORN can be defined as the following quotient:

$$s = \frac{\Delta \lambda_{in}}{\lambda_{in}}.$$
 (1)

ORNs of this type converge on the PN, and the latter will generate more output spikes per time unit for the action of odor O':

$$\lambda_o' = \lambda_o + \Delta \lambda_o$$

The PN ability S to discriminate between O and O' can be defined in a similar manner:

$$S = \frac{\Delta \lambda_o}{\lambda_o}.$$
 (2)

The selectivity gain g can now be defined as follows:

$$g = \frac{S}{s}.$$

Taking into account expressions (1) and (2), the latter can be represented as a derivative:

$$g = \frac{\lambda_{in}}{\lambda_o} \frac{d\lambda_o}{d\lambda_{in}},\tag{3}$$

where g can be called the coefficient of selectivity gain. The selectivity improvement takes place if g > 1.

Output Intensity. It is clear from definition (3) that, in order to determine g, one has to find λ_o as a function of λ_{in} . Instead of the output intensity λ_o , it is possible to use the mean output inter-spike interval T_o . Then

$$\lambda_o = \frac{1}{T_o}.\tag{4}$$

In order to find T_o , let us consider the PN as a system with N_0 possible states labeled with numbers $k = 0, 1, 2, ..., N_0 - 1$. A state with number k corresponds to the situation when the PN contains k input impulses (see Fig. 2).

Systems of this type are known in the theory of stochastic processes as those with a drain at the right end. A theory has been developed, which gives the mean triggering waiting time for a system of this kind in terms of the transition rates and other parameters. One could use, e.g., equation (1.69) in [23]. The straightforward application of this equation with the transition rates specified in Fig. 2 results in the following expression for T_c :

$$T_o = \frac{1}{\lambda_{tot}} \sum_{0 \le l \le N_0 - 1} \sum_{0 \le k \le l} \frac{l!}{k!} \left(\frac{\mu}{\lambda_{tot}}\right)^{l-k}.$$
 (5)

$$\bigcirc \xrightarrow{\lambda_{tot}} (1) \xrightarrow{$$

F i g. 2. Different states of excitation of the PN. The interstate transition rates are specified near the arrows. If in state number $N_0 - 1$ the PN obtains one more impulse, it generates a spike and then appears in its resting state.

RESULTS

Selectivity. After elementary transformations, one obtains the following expression instead of (5):

$$T_o = \frac{1}{\lambda_{tot}} \sum_{0 \le j \le N_0 - 1} \left(\frac{\mu}{\lambda_{tot}}\right)^j \frac{1}{j+1} \frac{N_0!}{(N_0 - 1 - j)!}.$$
 (6)

An expression for the selectivity (3), with expression (4) taken into account, can be rewritten as follows:

$$g = -\frac{\lambda_{in}}{T_o} \, \frac{d \, T_o}{d \, \lambda_{in}} \, .$$

Substituting here the expression for T_o from (6), one, after transformations, gets the following:

$$g = 1 + \frac{\sum_{j=0}^{N_0 - 1} \frac{j}{j+1} \left(\frac{\mu}{N\lambda_{in}}\right)^j \frac{1}{(N_0 - j - 1)!}}{\sum_{j=0}^{N_0 - 1} \frac{1}{j+1} \left(\frac{\mu}{N\lambda_{in}}\right)^j \frac{1}{(N_0 - j - 1)!}} .$$
 (7)

This expression, seemingly cumbersome, is amenable to the exact analysis. In the subsequent section, numerical estimates will be given. Here, it is possible to formulate some limiting conclusions.

If a secondary neuron generates an output spike in response to each input impulse coming from the primary unit, then $N_0 = 1$. In this case, each of the two sums in (7) is reduced to a single term with j = 0, which gives no selectivity gain:

$$N_0 = 1 \quad \Rightarrow \quad q = 1.$$

If more than one input impulse is required for triggering, then $N_0 > 1$, and (7) can be presented as follows:

$$g = 1 + \frac{\sum_{j=1}^{N_0 - 1} \frac{j}{j+1} \left(\frac{\mu}{N\lambda_{in}}\right)^j \frac{1}{(N_0 - j - 1)!}}{\frac{1}{(N_0 - 1)!} + \sum_{j=1}^{N_0 - 1} \frac{1}{j+1} \left(\frac{\mu}{N\lambda_{in}}\right)^j \frac{1}{(N_0 - j - 1)!}}$$
(8)

Consider the perfect integrator case, $(\mu = 0)$. In this case, there is no leakage, and, as can be seen from (8), there is no selectivity gain:

$$\mu = 0 \quad \Rightarrow \quad g = 1.$$

Similarly, there is no selectivity gain for the case of very intense stimulation:

$$\lambda_{in} \to \infty \quad \Rightarrow \quad q \approx 1.$$

If the stimulation is very weak, $(\lambda_{in} \rightarrow 0)$, the right side of Eq. (8) turns into N_0 . Thus, the selectivity gain equals the threshold height measured in units of the amplitude of input impulses:

$$\lambda_{in} \to 0 \quad \Rightarrow \quad g \approx N_0.$$

The latter example should be taken with caution, since output spikes at a very weak stimulation will arrive too rarely to exert a physiological effect.

It is possible to prove that the derivative with respect to λ_{in} of the right side of (7) is negative. Thus, *9* decreases with increasing λ_{in} . Therefore, in all other cases (namely, with $N_0 > 1$, $\mu > 0$, and with moderate stimulation applied), the selectivity gain will be within the limits: $1 < g < N_0$, and a certain selectivity improvement will be observed. Numerical examples are given below.

Numerical Examples. In order to present numerical examples, we should choose values for the quantities appearing in Eq. (8). Experimental data for figuring all required quantities for a single species are absent. Therefore, approximate estimates and analogies should be used. The quantities used for calculations are given in Table 1. The EPSP amplitude h produced in the PN by a single spike coming from an ORN is not reported. This value is required to determine the PN triggering threshold in h units: $N_0 \approx V_0/h$. Therefore, the h value for hippocampal CA1 pyramidal neurons can be used. The actual amplitude for the PN may be substantially lower due to mutual dendrite shunting through the gap junctions [6, 24]. The electrical leakage rate (the decay rate of input impulses mentioned above) is calculated as $\mu = \tau^{-1} = 0.0111$ msec⁻¹. The convergence degree is taken as N = 5000 [1] for all cases. The resulting selectivity gain g and the corresponding output rate λ_{a} are given in Table 2.

The dependence of the necessary quantities on the stimulus intensity and the threshold height is shown in Figs. 3 and 4.

T a b l e 1. Experimental Values for the Parameters; Sources are Indicated in Brackets

Parameters	Characteristics			
Threshold	height	ORN spike	PN membrane	
Depolarization	EPSP amplitude	Frequency	relaxation time,	
V_0 , mV	h, μV	λ_{in} , msec ⁻¹	τ, msec	
Limits				
5-12 [13, 25]	30-665;	10 ⁻³ [26]	90 [27]	
	the mean is			
	131 [28]			
		200-1		

T a b l e 2. Results of Numerical Calculations; λ_o and \mathcal{G} Are Calculated Using Eqs. (4) and (7), Respectively; N_0 Is Chosen in Accordance with the Data of Table 1

Threshold N_0	Output frequency λ_o , sec ⁻¹	g
300	10.3	1.78
400	5.3	3.15
500	0.67	30.3



F i g. 3. Dependences of $\mathcal{G}(1)$ and $\lambda_o(2)$, sec⁻¹, on the λ_{in} , sec⁻¹, for the threshold $N_0 = 300$; N = 5000, and $\tau = 90$ msec; \mathcal{G} is dimensionless.



F i g. 4. Dependences of $\mathcal{G}(1)$ and $\lambda_o(2)$, sec⁻¹, on the threshold N_0 for $\lambda_{in} = 0.5 \text{sec}^{-1}$.

DISCUSSION

A higher selectivity of the secondary olfactory sensory neurons, as compared to the primary ones, has been discussed many times [4, 5, 16, 29, 30]. Lateral inhibition has been proposed as a sole mechanism explaining the higher selectivity of PNs [5, 7, 12]. This mechanism seems to be inefficient at low odor concentrations [5].

In our paper, a different mechanism has been proposed, which is based exclusively on the stochastic nature of the stimuli received by PNs, on the threshold-type reaction to the above stimuli, and on the electrical leakage through the PN membrane. This mechanism does not depend on lateral inhibition and is capable of functioning at low odor concentrations. A coefficient of the selectivity gain, g, is defined in order to get the quantitative description. Possible values of g for physiologically real parameters are obtained. The coefficient of selectivity gain is characterized by the following. There is no selectivity gain if the secondary neuron is triggered by each single input impulse (g = 1). This is, however, not the case for PNs. The selectivity gain increases with increasing triggering threshold (N_0). Also, there is no gain if the electrical leakage is absent. Similar situation takes place if input stimulation is very intense, when, despite the leakage, every set of N_0 input impulses triggers the secondary neuron. For a very low intensity of input stimulation (low odor concentration), 9 approaches its maximal value ($g \approx N_0$). Under moderate odor concentrations, $1 < g < N_0$. For the parameters taken from a physiological range, the mechanism proposed can provide several tens of times higher selectivity of a secondary neuron, as compared to that of the primary ones.

Earlier, a concept has been proposed that the convergent nature of communication between ORNs and PN also might improve the PN selectivity [3]. To my knowledge, no physical mechanism for such improvement has been proposed. The mechanism proposed in this paper also is not based on the convergence principle. Indeed, as can be seen from Eqs. (7) and (8), the degree of convergence N is used only for calculation of the intensity of compound stimulation from the set of ORNs, $\lambda_{tot} = N \lambda_{in}$. The same value of λ_{tot} can be ensured either by a large number of low-activity ORNs or by a small number of high-active units. In both cases, the same selectivity gain will be obtained provided that other parameters are the same. Here, it should be mentioned that spontaneous activity of ORNs has been excluded from consideration. This activity can worsen the detection of weak olfactory stimuli [31]. At the same time, due to the high degree of convergence, uncorrelated spontaneous noise can be averaged out [3, 8]. Therefore, the convergence may indirectly play some role in the mechanism proposed.

To finish our discussion on ORN spontaneous activity, it should be mentioned that this activity can be rather low [26, 32], while the time required for odor perception can be quite short [33] (actually, much shorter than the mean interspike interval in spontaneous activity). Thus, it may happen that the influence of spontaneous activity is minimal during the odor perception time.

An interesting feature to discuss is the dependence of selectivity on the odor concentration. With increase in concentration, the ORN spiking frequency λ_{in} increases as well. In this case, the proposed mechanism predicts a decrease in the PN selectivity. This is in accordance with some experimental observations [26]. In other experiments, it was observed that the selectivity increased with increase in odor concentration [16], or it was independent of the concentration [29]. This contradiction could be resolved if the odor concentration applied by Tan et al. [26] was lower than that in other studies [4, 16]. Indeed, a progressive recruitment of bulbar neurons with increasing the odor concentration was also observed in the latter experiments. In this process, the number of active inhibitory neurons grows faster than that of excitatory ones [5, 32]. This is a prerequisite for lateral inhibition. At higher concentrations, the latter could be more efficient in improving the PN selectivity. This explains the selectivity increase with increasing odor concentrations observed by Duchamp-Viret et al. [16]. At the lowest concentrations, the proportion of inhibitory neurons among all active units in the olfactory bulb is considerably lower than at high concentrations, or inhibitory activity is absent at all [5]. In this case, lateral inhibition does not work, whereas the mechanism discussed here predicts a selectivity improvement with decreasing concentrations.

It should be mentioned that the possible mechanism for the selectivity gain proposed here is based on theoretical analyses of a considerably simplified pattern. In particular, the model used to describe a projection neuron corresponds to the widely used leaky integrate-and-fire model only "on average." This model was proposed earlier [20]. It has been used here because it is possible to obtain exact mathematical expressions characterizing stochastic triggering process when using this model. Such a model can be a suitable approximation of the leaky integrateand-fire model when the height (amplitude) of an individual EPSP is rather small.

Further, a processing of input spikes might happen at the level of the dendritic tree [34, 35]. This fact can be taken into account in the current approach, but it requires a sizable extension, and this can be done in further publications. Another simplification is that individual ORNs are considered to be identical, whereas they can differ from each other in their sensitivity and response rate [36].

Additionally, when estimating ORN activity (firing rate λ_{in}), one should take into account that communication from an ORN to the PN can be inhibited presynaptically [37]. This may result in decreasing the ORN effective activity and/or corresponding increase of the firing threshold N_0 . This might improve the effect of increasing the selectivity gain.

Further, the axon from a single ORN evidently arborizes and forms several synapses [38]. This might increase the ORN effective activity and cause a corresponding decrease of the firing threshold N_0 expressed in terms of the number of ORN spikes, with a negative effect on the selectivity gain.

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This is a theoretical study, and it was not related to experiments on animals or tests on humans.

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