Trade-off between sensitivity and selectivity in systems with convergence

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Abstract. It was observed before that in neuronal systems with convergence, a possible amplification can be as large as the degree of convergence. This is in the case when a single impulse from the converging inputs is enough to trigger the secondary neuron. On the other hand, if a number of impulses are required for triggering, a gain in discriminating ability may be obtained along with decrease in sensitivity. We discuss this trade-off in terms of concrete estimates using olfactory sensory neuron and the set of its receptor proteins as an example of system with convergence.

INTRODUCTION

In a neural system, a convergent organization of inter-neuronal connections is a typical pattern. E.g., the degree of convergence observed for rat hippocampal pyramidal cells is about 12 000, [1]. In the olfactory system of mouse, see Fig. 1, about 5 000 olfactory receptor neurons (ORN) send their output spikes to a single mitral cell, [2]. Our purpose is to figure out what role the convergence may have in forming sensitivity and selectivity in a sensory system. For this purpose we use olfactory system as an example.

PROBABILISTIC DESCRIPTION

Real neurons are noisy [4]. This has a consequence for a sensory system under weak stimulation. Namely, if a stimulus has low level, the response to it becomes probabilistic. The dose-response dependence becomes probabilistic as well: the higher is the dose, the higher is the response probability, [5, 6]. The sensitivity is considered to be higher when the same stimulus evokes a response (output spike) with higher probability.
SENSITIVITY GAIN DUE TO CONVERGENCE

It was observed, [7], that threshold stimulus able to evoke a response at the level of whole animal can be 10-100 times lower than that at the level of ORN. This might be due to convergence in the olfactory sensory pathways. At the stage of ORN-mitral cell communication, the explanation has been proposed by W. van Drongelen et. al., [5, 6]. Namely, if under a certain stimulation (odor concentration) an ORN output activity can be modeled as Poisson stochastic process with intensity $\lambda$, then compound input of $N$ ORN outputs into a single mitral cell can be modeled as Poisson process of intensity $N\lambda$. The probability that a single ORN emits a spike during time interval $T$ is $P_{\text{ORN}} = 1 - e^{-\lambda T} \approx \lambda T$. The latter approximation is valid for a short enough $T$. Expect that a single input spike is able to trigger the secondary neuron. Then the probability that the secondary neuron emits a spike during $T$ is $P_m = 1 - e^{-N\lambda T} \approx N\lambda T$. In this case we have sensitivity gain equal to $N\lambda T = N$. Actually, a real mitral cell requires more than a single input impulse for triggering. Denote the required for triggering number of input impulses as $N_0$. It can be proven that the mitral cell output rate $R_m$ in this case satisfies the following estimate:

$$R_m \leq \frac{N}{N_0} \frac{\lambda}{N}.$$  

The equality holds here if the mitral cell is modeled as perfect integrator. The corresponding sensitivity gain $G_n$ is as follows:

$$G_n = \frac{R_m}{\lambda} \leq \frac{N}{N_0}.$$  

(1)

SELECTIVITY GAIN INSIDE THE OLFACTORY RECEPTOR NEURON

The olfactory system has the remarkable capacity to discriminate among a wide range of odor molecules. This begins with the ORN, which performs the task of converting information contained in the odor molecules into information contained in membrane signals and neural space, [8]. Discriminating ability of ORN starts to build up already at the level of individual receptor proteins. The primary act of odor perception happens when odor molecule physically contacts with a receptor protein integrated in the ORN’s membrane. During this contact, the molecule can be bound to the receptor with some probability $p$. The probability $p$ depends on the chemical nature of the molecule, which determines its affinity to a given receptor. It is namely due to this dependence that an ORN is able to discriminate between different odors.

Selectivity of Single Receptor Protein

The discriminating ability of a receptor protein can be defined as follows. Let during two separate experiments two different odors $O$ and $O'$ are presented to a given receptor or a set of them at the same concentration. Denote as $p$ and $p'$ the probability to find a receptor bound with odor $O$ and $O'$. If $p \neq p'$ then we say that this receptor is able to discriminate between $O$ and $O'$. Otherwise, it cannot. The same is with the ORN expressing this receptor. Suppose that $p > p'$. Then the discriminating ability at the level of single receptor protein can be characterized numerically as

$$\mu = \log \frac{p}{p'}.$$  

(2)

Selectivity of ORN

In the ORN expressing concrete receptor protein, one may observe convergence of signals from individual receptor proteins onto the ORN’s interior, see Fig. 2, and farther onto the axonal hillock where it is decided whether to fire or not. The degree of convergence is characterized by the total number $N$ of receptors per neuron. The firing threshold can be expressed as the minimal number $N_0$ of receptors which must be bound with odor in order to ensure depolarization necessary for triggering. Since odor binding-releasing is driven by the Brownian motion, the firing threshold will be achieved irregularly and this will result in irregular/random spiking of ORN.

In a simplified model of ORN, see Fig. 2, the ORN’s discriminating ability between the $O$ and $O'$ can be defined as follows. Let the ORN during two separate experiments is exposed to $O$ and $O'$ at equal concentrations. Denote $F$
FIGURE 2. Simplified model of olfactory receptor neuron as single cilium with firing threshold. $N$ — is the total number of receptors, $N_0$ — is the threshold number. The neuron starts firing if the number of bound receptors exceeds $N_0$.

and $\bar{F}'$ the ORN's mean firing rate if O and O' are presented. Then the ORN’s ability $\delta$ to discriminate between O and O’ can be defined as follows

$$\delta = \log \frac{\bar{F}}{\bar{F}'}.$$  \hspace{1cm} (3)

It was shown, [9], that in situation when the dose-response dependence is of threshold type and probabilistic, a considerable selectivity gain is possible. For the model ORN, the following mathematically rigorous estimate has been obtained, [10, 11, 12]:

$$\delta > \frac{\left( p_0 - p \right) N \mu}{1 - p}, \quad p_0 = \frac{N_0}{N}. \hspace{1cm} (4)$$

The numbers $N$ and $N_0$ can be high. E.g., $N = 2{,}500{,}000$, $N_0 = 250$ for moth, (J.-P. Rospars, private communication). For frog, $N = 25{,}000$, $N_0 = 35$, [13]. Estimate (4) suggests that ORN’s selectivity can be much higher than that of its receptor proteins, provided $p_0 - p > 0$. The latter is achieved if the odors O and O’ are presented at sub-threshold concentration. Namely, the mean number of bound receptors is below the threshold one. In this case, the firing threshold is achieved due to random fluctuations, and this process appeared to be more selective than random binding-releasing at a single receptor. Conclusion (4) has been checked by means of direct numerical simulation of odor binding-releasing in a set of receptors, [14].

**TRADE-OFF BETWEEN SENSITIVITY AND SELECTIVITY**

Define the selectivity gain, $G_t$, as follows

$$G_t = \frac{\delta}{\mu}. \hspace{1cm} (5)$$

Then from (1) and (4) one obtains the following estimate

$$G_t > \frac{1}{G_n} - p \frac{N \mu}{1 - p}.$$  \hspace{1cm} (6)

The right-hand side of inequality (6) is the decreasing function of $G_n$. Therefore, the better is the sensitivity gain the less optimistic are estimates (4), (6) for selectivity. Consider situation when all N receptors should be bound to ensure triggering ($N_0 = N$). In this case $G_n = 1$ (no sensitivity gain) and we have from (6)

$$G_t > N,$$

which is quite optimistic for selectivity.

The estimate (6) depends on the probability $p$ that a receptor is bound with odor O. This probability can be calculated based on association-dissociation rate constants $k_+, k_-$ between the odor and receptor, and odor’s concentration, $c$:

$$p = \frac{c k_+}{c k_+ + k_-}.$$ 

If concentration $c$ is very low, then $p$ is very low as well and (6) turns into the following:

$$G_t G_n > N,$$

which again demonstrates the trade-off between selectivity and sensitivity. Finally, if concentration $c$ increases drawing $p$ to the $\frac{c k_+}{c k_+}$, then the estimate (6) turns into $G_t > 0$, which promises nothing as regards selectivity gain.
CONCLUSIONS AND DISCUSSION

We have considered here a set of identical receptor proteins belonging to a single ORN as converging on its interior and made some conclusions about sensitivity and selectivity gain in the ORN itself, see Equations (1), (4), (6). The main conclusion is that due to convergence one may have either high selectivity or high sensitivity. Increasing one of them results in decreasing the other one. While the sensitivity gain does not depend on the stimulus intensity, the selectivity decreases with increasing concentration, see Equations (4), (6). This conforms with experimental observations, [15, 16]. Concentration at which a selectivity gain might be expected, must be sub-threshold: the firing threshold can be achieved due to fluctuations, but the time-averaged concentration is less than the threshold one. This strong limitation on the concentration range may cast doubt on a possibility that the mechanism discussed here could operate in a real biological system. In this connection I would like to say that the suitable concentration depends on the threshold $N_0$, which itself could be adjustable. The evident mechanisms for this are adaptation and inhibition of the ORN. Interesting, that in the olfactory system, ORN’s output is subjected to feedback presynaptic inhibition, [17]. For the secondary neurons, this inhibition acts similarly as elevation of ORN’s firing threshold.

Conclusions made here about the trade-off between sensitivity and selectivity and the selectivity gain itself are obtained by means of mathematical analysis of the binding-releasing stochastic process, [12]. The binding-releasing noise, normally considered as negative factor in signal processing, is crucial for the selectivity gain discussed.

As to my knowledge, no experimental attempt was made to compare the ORN selectivity with that of its receptor proteins. This is not surprising because measuring selectivity of a receptor protein belongs to chemistry, while discriminating ability of ORN — to sensory biology. The selectivity gain predicted in [12] and here is made possible due to the threshold manner of the ORN response to converging inputs from its receptors. This offers an experimental procedure for checking the prediction. Namely, the selectivity of individual receptor protein ($\mu$) can be estimated while measuring the ORN output in the form of receptor potential, with spike-triggering mechanism blocked. The ORN selectivity ($\delta$) can be estimated through mean firing rate as defined in (3).

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