Harnessing thermal fluctuations for selectivity gain

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***Abstract*—Selectivity of olfactory receptor neuron (ORN) is compared with that of its receptor proteins (*R*) with fluctuations of odor binding-releasing process taken into account. The binding-releasing process is modeled as *N* Bernoulli trials, where *N* is the total number of *R* per ORN. Dimensionless selectivities for both *R* and ORN are introduced and compared with each other. It is found the ORN's selectivity can be much higher then that of its receptor proteins. This effect is concentration-dependent. Possible application for biosensors is discussed.**

I. Introduction

In order to be useful, a chemical sensor must be able to discriminate between different substances it is exposed to. This ability, or selectivity can be achieved by different mechanisms. In industrial biosensors, high selectivity is usually ensured at the first stage of interaction between analyte and sensor. This is realized by covering with highly selective molecules the primary sensing surface. Those molecules could be highly specific enzymes [1], or antibodies [2].

For monitoring environment, another architecture has been developed in the olfactory system. Olfactory receptor neuron (ORN) is considered in sensory biology as the primary reception unit. And typical ORN is rather generalist then specialist [3], [4]. That means that an ORN increases its firing rate when exposed to different odors. The degree of increase depends on the substance presented, and this determines ORN's selectivity. Normally, discriminating ability increases when olfactory signal travels from primary reception units to higher brain areas, see Table I. It is well known that selectivity of a projection neuron, which receives stimulation directly from ORNs, is better than that of ORNs converging on it, [5]. At high odor concentration this happens due to mechanism of lateral inhibition in the olfactory bulb [6], [7]. At low odor concentration, when lateral inhibition seems not working, [8], another interesting mechanism has been proposed in [9]. Further, in the olfactory cortex, each scent is represented by specific activity in a neuronal assembly, and each neuron is involved in representation of many odors, [10]. Spatio-temporal pattern of activity in the assembly is essential for this final odor recognition [11], [12], [13].

From the physical point of view, the primary perception of odors happens in the set of N identical receptor proteins, R, expressed in the ORN's cilia. This set, or any individual R from it has its own selectivity, which is based on different chemical affinity between different odors and R. Is this selectivity the same as that of the corresponding ORN? Comparison of the two selectivities is not a trivial task due to different physical nature of response, see Table I. But any quantitative measure of selectivity can/should be expressed in dimensionless units. This allows for comparing selectivities for systems with qualitatively different physical nature of response as in the case of R and ORN. Below, we define such a dimensionless measure of selectivity for both R and ORN, and compare them. In this course we take into account that binding-releasing of odor molecules with R is subjected to thermal fluctuations since it is driven by Brownian motion. Also, we take into account that ORN is highly nonlinear processing unit due to presence of the firing threshold. Finally, we prove that due to this features the selectivity of ORN can be considerably higher than that of its receptor proteins. The degree of selectivity gain is calculated exactly for a simple ORN model. Possible implementation of this effect in artificial biosensors is discussed in conclusion.

constructive element	measure of response
receptor proteins	fraction of bound receptors
↓	
receptor neurons	mean firing rate
↓	
projection neurons	mean firing rate
↓	
olfactory cortex	activity in local cortical circuits (combinatorial code)

TABLE I
SELECTIVITY BUILD UP STEPS IN A BIOLOGICAL OLFACTORY SYSTEM

II. Definitions and assumptions

A. Model of ORN

In order to make possible a simple exact mathematical analysis we use an extremely simplified model. Namely, in this model, ORN has N identical receptor proteins R able to bind reversibly with odor molecules A. Each bound R contributes the same amount to the receptor potential, which is depolarization of ORN's excitable membrane. If the number $n(t)$ of bound R is above or equal to N_0, where $N_0 < N$, the firing threshold is achieved and the ORN fires output spikes with a constant frequency f. Otherwise, it is silent. We assume that binding-releasing of odor at any individual R is statistically independent of what happens with other receptor proteins.

B. Selectivity of receptor proteins

Consider two separate experiments in which two odors A_1 and A_2 are presented at the same concentration c to the set of R. Due to thermal fluctuations, the instantaneous number

$n(t)$ of bound R will change randomly. In the equilibrium, the mean number of bound receptors is $p_i N$, where $0 \le p_i \le 1$, $i = 1, 2$. Any of p_i can be found as $p = c/(c + K_D)$, where K_D is the corresponding dissociation constant. If A_1 has more affinity with R than does A_2, then $p_1 > p_2$:

$$p_1 = p_2 + \Delta p, \quad \Delta p > 0. \tag{1}$$

In this case we say that R is able to discriminate between A_1 and A_2 and characterize this ability by the following dimensionless selectivity:

$$S_R = \Delta p \,/\, p_1. \tag{2}$$

Actually, the quantity p here gives the probability that any R is bound with odor molecule (binding probability) if observed at any moment.

C. Selectivity of ORN

We assume here that the concentration c ensures that mean number of bound receptors $p_1 N$, $p_2 N$ is close to the firing threshold N_0. In this case, the instantaneous number $n(t)$ will cross the threshold N_0 randomly due to thermal fluctuations both for A_1 and A_2. If we observe the ORN activity during some fixed time interval T, its mean firing rate will be $F = fT_a/T$, where $T_a < T$ is the total time the $n(t)$ spends above N_0, both for A_1 and A_2. From (1) it follows that $T_{a1} > T_{a2}$, which results in $F_1 > F_2$. The latter means that ORN is able to discriminate between A_1 and A_2. The dimensionless selectivity of ORN is as follows

$$S_{ORN} = (F_1 - F_2) \,/\, F_1 = \Delta T_a \,/\, T_{a1}, \tag{3}$$

where $\Delta T_a = T_{a1} - T_{a2}$.

III. Selectivity gain

Here we compare selectivity of ORN with that of its receptor proteins. For this purpose define selectivity gain g as follows:

$$g = S_{ORN} \,/\, S_R = (\Delta T_a \, p_1) \,/\, (\Delta p \, T_{a1}). \tag{4}$$

For *poor selectivities* both Δp and ΔT_a are small. Taking this into account the latter can be rewritten as a derivative:

$$g(p) = \frac{p}{T_a} \frac{d\,T_a}{d\,p}, \tag{5}$$

where T_a is the amount of time spent above the threshold during period T for a given binding probability p.

It seems evident that

$$T_a = T \, \mathbf{Prob}\{n(t) \ge N_0\}, \tag{6}$$

where

$$\mathbf{Prob}\{n(t) \ge N_0\} = \sum_{N_0 \le k \le N} \binom{N}{k} p^k (1-p)^{N-k}. \tag{7}$$

Eq. (5), after substituting (6) and (7) turns into the following:

$$g(p) = \frac{p \sum\limits_{N_0 \le k \le N} \frac{1}{k!(N-k)!} p^{k-1} (1-p)^{N-k-1} (k - Np)}{\sum\limits_{N_0 \le k \le N} \frac{1}{k!(N-k)!} p^k (1-p)^{N-k}}. \tag{8}$$

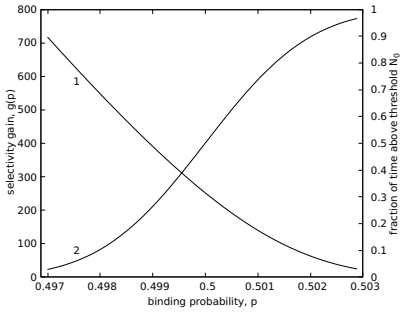

Fig. 1. Dependence of selectivity gain, 1, and fraction of time spent above the threshold, 2, on the binding probability. Here $N = 100\,000$, $N_0 = 50\,000$.

A more compact formula can be obtained from (8) by using binomial cumulative probability function:

$$cdf(N_0, N, p) = \sum_{0 \le k \le N_0} \binom{N}{k} p^k (1-p)^{N-k}.$$

By applying this in (8) one obtains after transformations:

$$g(p) = N \frac{p}{1-p} \left(\frac{cdf(N - N0, N-1, 1-p)}{cdf(N - N0, N, 1-p)} - 1 \right). \tag{9}$$

IV. Numerical examples

Numerical estimates of the derivative $dg(p)/dp$ for several sets of pares (N, N_0) supports the idea that

$$dg(p) \,/\, dp < 0, \quad 0 \le p \le 1.$$

Since p increases with odor concentration, from the latter, one could expect higher selectivity gain for smaller concentrations. On the other hand, denominator $cdf(N - N0, N, 1-p)$ in (9) gives exactly the fraction of time $n(t)$ spends above the threshold. This fraction determines the ORN's level of output (mean firing rate), and it decreases with decreasing concentration and p. So, we have here a trade-off between selectivity and sensitivity: with decreasing concentration and binding probability p one gets higher selectivity, but lower sensitivity, see also Fig 1. Which values of p might be of practical interest depends on concrete values of the total number N of binding sites in a sensor and the minimal number N_0 of bound sites required for having activity at its output end.

In the Table II we put some examples of selectivity gain. The first two rows of the Table II give examples for a moth pheromone ORN. The possible value for the number of receptor proteins R per ORN is taken from [14]. Based on data from [14] it is possible to conclude that several hundreds could be a good value for N_0. Actually, the threshold value for a biological ORN depends on many factors not considered here, like ionic composition on both sides of the excitable membrane, which may be variable, and presence of inhibitory stimulation, which can be fast or slow. Therefore, values in Table II are rather illustrative than conclusive.

N	N_0	p	$g(p)$	time above N_0
2556000	200	$7.5{\cdot}10^{-5}$	16.6	28%
2556000	250	$7.5{\cdot}10^{-5}$	61	0.03%
100000	10000	0.1	84	50%
1000000	100000	0.1	266	50%
10000000	1000000	0.1	841	50%

TABLE II
SELECTIVITY GAIN EXAMPLES

V. CONCLUSIONS AND DISCUSSION

In this note, we discussed a possible utilization of thermal noise for improving odor discrimination. Consideration is made for a simplified model of olfactory receptor neuron. Selectivity of ORN is compared with that of its receptor proteins. It is concluded that the former can be much higher than the latter if thermal fluctuations of odor molecules binding-releasing process are taken into account.

This is not the only case when Brownian motion is used beneficially in living objects, see e.g. [15] for muscles contraction. Also, this is not the only case when fluctuations processing instead of filtering them out is proposed for improving discriminating ability. Actually, this note falls into the promising and developed area of fluctuation enhanced sensing, see [16], [17].

The model of ORN described in Sec. II-A is a very simplified toy model. Actually, under receptor protein R we have in mind a ligand-gated ion channel found in insects, [18]. We leave in the model the main source of non-linearity, namely, the firing threshold and this is enough to demonstrate the idea. Another sources of non-linearity can be found in ORN due to its internal biochemical mechanisms, especially, if ORN expresses G protein–coupled receptors, [19]. This additional non-linearity seems working in the same direction as the main one: improving ORN selectivity as compared with that of its receptor proteins.

A less evident limitation is that the effect of selectivity gain considered here can be observed in the narrow range of odor concentrations, or binding probabilities p, see Fig. 1. This range depends on the firing threshold level N_0. The latter is variable in living objects due to adaptation and inhibition [20]. In practical realizations, intended to work in wide concentration range, a possibility of tuneable threshold should be considered. Actually, a scent description includes both identity (odor species) and intensity (concentrations). This note offers nothing as regards concentration. Understanding how odor intensity is represented in olfactory system might help to resolve the above mentioned limitation. Possible steps in this direction are made in [21], [22].

Size of industrial biosensors constantly decreases. In small devices, noise represents an essential part of output. Utilizing noise for improving device characteristics could be a better choice than averaging out signal fluctuations. As we can see from three bottom rows of Table II, selectivity gain due to the mechanism discussed here can be quite large. Exploiting this mechanism opens a perspective of using as primary odor recognition sites in biosensors simple molecules with low discriminating ability, but cheaper, and with better performance characteristics like durability and robustness. High selectivity can be achieved due to selectivity gain at further stages of noisy signal processing.

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