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SELECTIVITY IMPROVEMENT IN A MODEL OF OLFACTORY RECEPTOR NEURON WITH ADSORPTION-DESORPTION NOISE

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In biological olfactory systems, interaction of odorant molecules with olfactory receptor proteins is driven by Brownian motion. As a result, at chemical equilibrium, the total number of bound receptors changes randomly in time. Here we investigate the role of this effect, known in physics as adsorption-desorption noise, in the discriminating ability of olfactory receptor neurons. For this purpose we developed a computer program, which generates the adsorption-desorption process in a model neuron. We compared the processes resulting from two different odorants with different affinities for the receptor proteins. We took into account the threshold at which spikes are triggered and we calculated the neuronal selectivity due to the differences in the threshold-crossing statistics for the processes resulting from both odorants. We conclude that selectivity of the spiking response of the whole neuron is much greater than that of its receptor proteins in the near-threshold range of odorant concentrations.

Keywords: Olfactory Receptor Protein; Olfactory Receptor Neuron; Adsorption-Desorption Noise; Selectivity.

1. Introduction

In biological sensory systems, the selectivity, i.e. discriminating ability, between two signals builds up when these signals travel from the periphery to more central sensory areas, and finally it attains its maximum value in the multi-modal brain areas. This is also true for olfactory systems.[1] The progressive improvement of the discrimination of two stimuli along sensory pathways results ultimately from the initial difference between these two signals at the stage of primary reception of the stimuli. Therefore, it depends on the physical mechanisms, which underlie the primary reception. In the case of olfactory receptor neurons (ORNs), the primary

reception is due to the selective binding-releasing of odorant molecules to-from olfactory receptor proteins (ORs).[2–4] The ORs are located on the membrane of filaments (cilia), which protrude from the tip of ORNs. Most ORNs express a single olfactory receptor gene, so that all ORs on the ciliary surface of a given ORN are identical. The formation of the odorant-receptor complex triggers the transduction cascade, which provokes the opening of ion channels and the depolarization of the ORN membrane.[5,6] Depolarization to a critical potential level, the threshold, causes the initiation of an action potential, which travels along the ORN axon to the brain.

Thus, already in the ORN, several stages of processing of the olfactory signal involving many biochemical intermediates are present. Here we consider only the first and last stages of the whole transduction process, i.e. the initial binding-releasing of odor molecules by the OR and the final ORN firing. Our purpose is to compare the discriminating ability at these two stages. We take into account that the binding-releasing process is driven by Brownian motion and is, therefore, random. Different odorants generate stochastic processes with different characteristics, crossing the threshold at different times, and so generating different spike trains. We developed a computer model of this stochastic process, which allows us to determine the mean firing rates for different odorants and to compare the ORN selectivity in terms of output firing rates with that of ORs.

In a previous paper[7] one of us has shown analytically, that the discriminating ability of a chemical sensor can be improved substantially in some parameter range by means of proper processing of adsorption-desorption noise. Here we apply this approach to an ORN model which is an extremely simplified version of an ORN. We retain only the essential features of the biological ORN in order to study the problem at hand in as simple a setting as possible. We show numerically with this model that selectivity at the level of the ORN (expressed in terms of output firing rates) can be much better than that of a single OR at near-threshold concentrations range. In the present case the improvement in selectivity is exclusively due to differences in the threshold crossing statistics for two odorants.

2. Definitions of Odorant Selectivity

2.1. *Discriminating ability of a single receptor protein*

From a chemical point of view, the odorant molecules interact with receptor proteins according to an association-dissociation reaction, which is described by the following scheme

$$L + R \underset{k_-}{\overset{k_+}{\rightleftharpoons}} LR, \tag{2.1}$$

where L, R, LR denote the ligand (odorant molecule), the receptor protein, and the receptor-ligand binary complex, respectively.

In order to introduce numerical measures of selectivity for a receptor protein we denote the total number of receptor proteins in a single ORN as N. Let $[R]$ and $[LR]$ denote surface concentration of free and occupied ORs, respectively. If the ORN ciliary area is S, then $N = ([R] + [LR])S$, and the mean number of occupied proteins is $\overline{n} = [LR]S$. If an odorant L is applied at a certain concentration $[L]$, the mean relative amount s of proteins bound with odorant at chemical equilibrium is

$$s = \frac{[LR]}{[R] + [LR]} = \frac{\overline{n}}{N}. \tag{2.2}$$

If two odors, L_1 and L_2, are applied at the same concentration and it appears that $s_1 \neq s_2$, then we say that OR is able to discriminate between L_1 and L_2, and we express the OR selectivity as

$$\mu = \left| \log \frac{s_1}{s_2} \right|. \tag{2.3}$$

Note that definition (2.2), (2.3) is given for a whole population of ORs expressed in a single neuron, and deals with mean number of occupied proteins. Since our purpose is to compare the selectivity of a single OR to that of an ORN, it is worthwhile to explain what this definition (2.2), (2.3) means for a single OR. For this purpose one must take into account that receptor-odorant interactions are driven by Brownian motion. At any moment in time, any OR can be either free, or occupied with an odorant molecule, and this process is random. Therefore, one can introduce the probability p for a single OR to be occupied at any moment in time. It can be easily proven that p is equal to s as introduced in (2.2). Indeed, due to the probabilistic nature of the binding-releasing process, at any moment of time there is a probability, P_k, that exactly k ORs are occupied, and $N - k$ are free. Then the instantaneous relative amount of ORs bound with odorant is $\frac{k}{N}$. In order to find the mean relative amount of ORs bound with odorant, which is s, one adds all possible relative amounts multiplied by their probabilities. The probability P_k can be found as the corresponding term in the binomial distribution:

$$P_k = C_N^k \, p^k (1-p)^{N-k}, \quad k = 0, 1, 2, \ldots, N.$$

Now s can be found by averaging all possible relative concentrations from the set $\left\{\frac{0}{N}, \frac{1}{N}, \frac{2}{N}, \ldots, \frac{N}{N}\right\}$ over the binomial distribution:

$$\begin{aligned} s &= \sum_{0 \le k \le N} P_k \cdot \frac{k}{N} \\ &= \sum_{0 \le k \le N} C_N^k p^k (1-p)^{N-k} \cdot \frac{k}{N} \\ &= \sum_{0 \le k \le N} \frac{N!}{k!\,(N-k)!} p^k (1-p)^{N-k} \cdot \frac{k}{N} \\ &= \sum_{1 \le k \le N} \frac{(N-1)!}{(k-1)!\,(N-k)!} p^k (1-p)^{N-k} \end{aligned}$$

$$= p \sum_{1 \le k \le N} \frac{(N-1)!}{(k-1)!\,(N-k)!} p^{k-1}(1-p)^{N-k}$$
$$= p \sum_{0 \le k \le N-1} \frac{(N-1)!}{k!\,(N-1-k)!} p^{k}(1-p)^{N-1-k}$$
$$= p.$$

Thus, (2.3) can be rewritten as follows

$$\mu = |\log(p_1/p_2)|, \tag{2.4}$$

which means that the selectivity of a single OR for two odorants can be defined as the logarithm of the ratio of the probabilities that the OR is occupied by these odorants.

It is helpful to discuss here our definition of selectivity of single OR given in Eqs. (2.3) and (2.4). In chemistry, selectivity/specificity of association-dissociation reaction, like (2.1), is normally expressed in terms of dissociation constant, K_d, which is defined as

$$K_d = \frac{[L][R]}{[LR]} = \frac{k_-}{k_+}, \tag{2.5}$$

where concentrations are taken at equilibrium. For two different odorants the dissociation constants may differ. In this case the receptor can discriminate between those odorants. The discriminating ability, μ_{K_d}, based on the K_d values might be expressed as

$$\mu_{K_d} = |\log(K_{d2}/K_{d1})|, \tag{2.6}$$

where K_{d1}, K_{d2} are the dissociation constants for the first and second odor, respectively. From definitions (2.2) and (2.5) one obtains that the probability of an OR to be bound with an odorant presented at concentration $[L]$ is

$$p = \frac{1}{1 + K_d/[L]}. \tag{2.7}$$

Thus, there is monotonic dependence between p and K_d, and therefore, definition of μ either in terms of K_d, or p is equally suitable from a mathematical point of view. Moreover, the μ value, as defined in (2.4), can be given in terms of the dissociation constants as

$$\mu = \left| \log \frac{1 + K_{d2}/c}{1 + K_{d1}/c} \right|,$$

where c is the concentration of any one of two ligands. But the equivalence of both (2.4), and (2.6) is not complete from a biological point of view. First, the definition of selectivity in terms of K_d, as given in (2.6), is concentration-independent, whereas the observed selectivity in frogs is decreasing with increasing concentration.[1] Second, as it is clear from Eq. (2.5), in order to determine K_d one needs access to three concentrations, namely, $[R]$, $[L]$ and $[LR]$, whereas an ORN interacts with

the external world through its ORs only, and can have access to the values $[R]$ and $[LR]$, but not to $[L]$. Knowing $[R]$ and $[LR]$, it is possible to determine p as shown in (2.2), therefore, we base our definition of selectivity on p, which is biologically more relevant.

2.2. *Discriminating ability of ORN*

In order to define selectivity at the level of spike train generation, we must specify how the number of odorant-receptor complexes is transformed into a spike rate. Here we assume that the membrane depolarization at which a spike is fired is reached when the number of bound ORs is equal to N_0. When the number of bound ORs is equal or higher than N_0, the ORN fires with constant frequency, F_0, and when it is lower, it does not fire at all.

Consider first the deterministic case. Then the number of bound receptors, $\overline{n}$, is

$$\overline{n} = sN \equiv pN,$$

where s is defined in (2.2). So, for any odorant, the ORN will either fire with fixed rate, or it will be silent. This gives rise to the expectation that ORN's discrimination is of a binary type, which means that the ORN behaves as a mere detection device, responding by yes or no to the presence of odorants. For example, if $\overline{n_1} < N_0 < \overline{n_2}$, for odorants L_1 and L_2, respectively, then L_1 will not be detected and L_2 will be detected.

In the stochastic case, which is more realistic, the behavior of the system is very different. Then the number, $n(t)$, of ORs bound with odorant changes continuously due to the stochastic nature of the binding-releasing process at any individual OR. As a consequence of these random fluctuations in $n(t)$, it happens that $n(t)$ is greater than threshold N_0, even when the mean number of odorant-receptor complexes, $\overline{n}$, is less than N_0. So, the ORN will fire spikes from time to time, these firing events being randomly distributed in time. The ORN will fire irregularly in accordance with the irregularities in the threshold crossing process. This gives rise to a mean firing rate, F, which is defined as the mean number of spikes per unit time, provided the observation period, T, is long enough to include many moments of crossing threshold.

We consider this mean firing rate as the output signal of the ORN stimulated with an odorant. The length of time, $n(t)$ spends above the threshold depends on the odorant applied, which causes difference in mean firing rates for different odorants, hence the ORN selectivity. The role of fluctuations will be more pronounced for just subthreshold stimuli, because such stimuli give rise to frequent threshold crossing events.

Our purpose is to estimate the ORN selectivity for two odorants, which differ in their affinity to the same OR, delivered at concentrations yielding subthreshold activity. When fluctuations are taken into account, the neuron fires from time to time for both stimuli. Denote F_1 and F_2 the mean firing rates for odorants L_1

and L_2. Then, in analogy with (2.3), expecting $F_1 > F_2$, we define the selectivity of the ORN as

$$\nu = \log \frac{F_1}{F_2}.$$

For determining values of F_1 and F_2 we use numerical simulation of the binding-releasing stochastic process (2.1) as described in the next section. Then we can compare the ORN selectivity to that of single OR.

3. Methods

3.1. *Simulation of the stochastic process*

3.1.1. *Principle of the algorithm*

For each value of concentration we determine the number of ORs bound with odorants L_1 and L_2 at any moment of time, t, in the following way. At time $t = 0$ we chose an initial state in which the number of occupied receptors is equal to the mean number of occupied receptors for each odorant. Having the number of bound receptors $n(t)$ at moment t, we calculate this number at moment $t + dt$, where dt is the time step, by determining what happens with each OR during time interval dt. If a receptor is occupied at moment t then the probabilistic meaning of rate constants in scheme (2.1) tells us that at moment $t + dt$ it will be free with probability $k_- \cdot dt$, and it will stay occupied with probability $1 - k_- \cdot dt$. If the receptor is free at moment t, then it will be occupied at $t + dt$ with probability $k_+ \cdot c \cdot dt$, and will stay free with probability $1 - k_+ \cdot c \cdot dt$, where c is the odorant concentration. The same procedure is applied to the second odorant with k_- changed to k'_-. In order to make a decision about any occupied receptor the program generates a random number ξ, distributed uniformly in the interval $[0; 1]$. If $\xi \leq k_- \cdot dt$, then the corresponding receptor becomes free, and it stays occupied if $\xi > k_- \cdot dt$. Similarly, if ξ generated for a free OR satisfies the inequality $\xi \leq k_+ \cdot c \cdot dt$, then it becomes occupied, and it stays free if $\xi > k_+ \cdot c \cdot dt$. This allows one to generate trajectory $n(t)$ on the interval $[0; t_{\max}]$ for each odorant and concentration.

The method of calculation we chose is a straightforward consequence of the probabilistic nature of rate constants. Special care was taken to insure the numerical precision of the algorithm (see next subsection). Detailed descriptions of this method and other more sophisticated and maybe faster methods, can be found in Smith.[8] The calculation time required to obtain a single trajectory for a single odorant is about 15 hours with an Intel 2.7 GHz processor. Most of the calculations were performed in parallel with a multiprocessor Linux cluster.

3.1.2. *Enhanced algorithm*

The simulation algorithm becomes unacceptably imprecise if the numerical value of any of the quantities

$$k_- \cdot dt, \quad 1 - k_- \cdot dt, \quad k_+ \cdot c \cdot dt, \quad 1 - k_- \cdot dt \tag{3.1}$$

becomes very small. This can be explained as follows. Standard pseudo-random numbers generator produces at each call an integer number $n \in \{0, \ldots, \texttt{RAND\_MAX}\}$, where RAND_MAX is system-specific. In Borland C, RAND_MAX = 32767. The above-mentioned $\xi \in [0; 1]$ is then obtained as $\xi = n/(\texttt{RAND\_MAX} + 1)$. As a result, ξ does not spread over the whole continuum $[0; 1]$, but takes values from the discrete set $\{0, 1/(\texttt{RAND\_MAX}+1), 2/(\texttt{RAND\_MAX}+1), \ldots, 1\}$, instead. If one of the quantities from (3.1), say, $a \equiv k_+ \cdot c \cdot dt$ appears between adjacent discrete points $m/(\texttt{RAND\_MAX}+1)$ and $(m + 1)/(\texttt{RAND\_MAX} + 1)$, then the probability of a free receptor to become occupied during time dt will be equal to $m/(\texttt{RAND\_MAX} + 1)$ instead of a. Since $\hat{a} \equiv [a \cdot (\texttt{RAND\_MAX}+1)]/(\texttt{RAND\_MAX}+1) = m/(\texttt{RAND\_MAX}+1)$, where $[x]$ denotes the integral part of x, then one obtains the relative deviation $\frac{a-\hat{a}}{a}$ of probability a. The upper bound for $a - \hat{a}$ is $1/(\texttt{RAND\_MAX} + 1)$. Thus the deviation may be ignored if

$$a \gg 1/(\texttt{RAND\_MAX} + 1).$$

Unfortunately, not all possible values of quantities in (3.1) satisfy the above criterion. Example, with the values of tables 1-2 one has $a = k_+ \cdot c_{\min} \cdot dt = 7.11 \cdot 10^{-8}$, whereas $1/(\texttt{RAND\_MAX} + 1) = 3.05 \cdot 10^{-5}$ for RAND_MAX specified above. Since simulations were partially performed in the Borland C system with that small RAND_MAX value, an enhanced algorithm was used, which is explained below for quantity a, corresponding to the probability that a free receptor becomes occupied during time step dt.

Instead of considering quantity a, we consider $A = a \cdot \texttt{RAND\_MAX}$. In order to determine at a single time step the destiny of a free OR, a random integer number n between 0 and RAND_MAX is drawn. If $n < [A]$, then OR becomes occupied (outcome O_3 in Fig. 1, right). If $n > [A]$, then OR remains free (outcome O_1). If $n = [A]$, outcome O_2, then the destiny is still not determined. In this case consider value $B \equiv (A - [A]) \cdot (\texttt{RAND\_MAX} + 1)$, and get new a random number n' between 0 and RAND_MAX. If $n' < [B]$, outcome O_{23}, then OR becomes occupied. If $n' > [B]$, outcome O_{21}, then OR remains free. If $n' = [B]$, outcome O_{22}, then the procedure of magnification can be repeated with $C \equiv (B - [B]) \cdot (\texttt{RAND\_MAX} + 1)$, instead of B, and so on. In this calculation we stop at B, treating outcome O_{22} similarly to O_{23}. The possible deviation from correct transition probabilities when using this

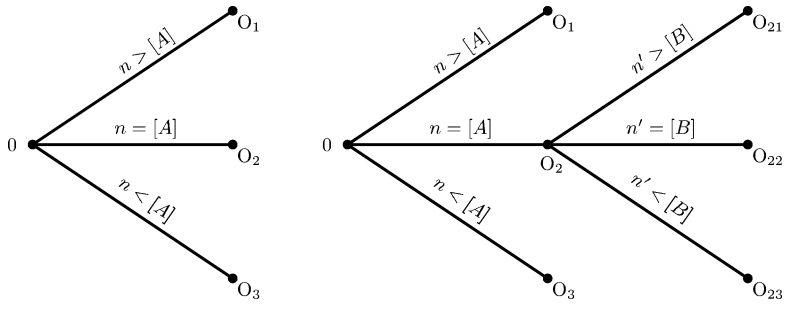

Fig. 1. Structure of single trial in plain (left), and enhanced (right) Monte Carlo method.

method for generating stochastic trajectories can be estimated. The probabilities of outcomes O_1, O_2, O_3 are $(\texttt{RAND\_MAX} - [A])/(\texttt{RAND\_MAX} + 1)$, $1/(\texttt{RAND\_MAX} + 1)$, $[A]/(\texttt{RAND\_MAX} + 1)$, respectively. If single trial is stopped at this stage (Fig. 1, left), then outcomes O_1 and O_3 can be treated as "OR remains free" and "OR becomes occupied", respectively, while O_2 cannot be treated unequivocally due to large single bin width if trials are made in accordance with the scheme in Fig. 1, left. An additional toss for outcome O_2 results in outcomes O_{21}, O_{22}, O_{23} with probabilities $(\texttt{RAND\_MAX} - [B])/(\texttt{RAND\_MAX} + 1)$, $1/(\texttt{RAND\_MAX} + 1)$, $[B]/(\texttt{RAND\_MAX} + 1)$, respectively. Now we treat outcomes O_1 and O_{21} as "OR remains free", and O_3 and O_{23} as "OR becomes occupied". The corresponding probability is as follows

$$p(\mathrm{O}_3 \textbf{ or } \mathrm{O}_{23}) = p(\mathrm{O}_3) + 1/(\texttt{RAND\_MAX} + 1) \cdot [B]/(\texttt{RAND\_MAX} + 1).$$

After substituting B instead of $[B]$ one obtains

$$p(\mathrm{O}_3 \textbf{ or } \mathrm{O}_{23}) = a.$$

The latter expression for $p(\mathrm{O}_3 \textbf{ or } \mathrm{O}_{23})$ differs from the former one by $(B - [B])/(\texttt{RAND\_MAX} + 1)^2$, hence simulation in accordance with the scheme of Fig. 1, right, gives transition probabilities, which deviate from the desired ones not more than by

$$1/(\texttt{RAND\_MAX} + 1)^2.$$

Examples of trajectories are shown in Fig. 2.

3.2. *Processing of calculated trajectories*

In our paradigm, the ORN fires with constant rate F_0 when the number of bound ORs is above N_0. If the trajectory spends periods of time above the threshold,

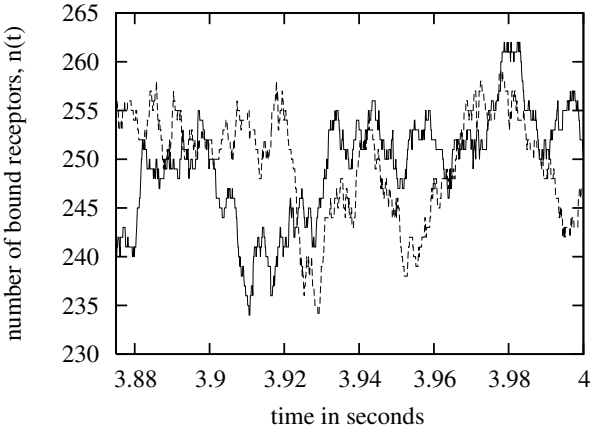

Fig. 2. Example of two trajectories calculated for two different odorants L_1 (continuous line) and L_2 (dotted line). Concentration $c = 3.78028e \cdot 10^{-9}$ M for both odorants. Compare this with experimental curve in Miyanaga *et al.*[9] Fig. 3c.

Table 1. Values of constants characterizing model ORN and odors.

Number of ORs per ORN, N	2 500 000
Threshold number of activated ORs per ORN, N_0	240, 250 or 260
Constant firing rate, when above threshold, F_0	7 Hz
Rate constants, k_+	$209\,000\,\mathrm{s}^{-1}\,\mathrm{M}^{-1}$
k_-	$7.9\,\mathrm{s}^{-1}$
k'_-	$8.295\,\mathrm{s}^{-1}$

Table 2. Numerical values of parameters used for calculations.

Range of concentrations, $c_{\min}$	$3.40225 \cdot 10^{-9}$ M
$c_{\max}$	$4.15831 \cdot 10^{-9}$ M
Concentration increment, Δc	$3.78028 \cdot 10^{-11}$ M
Simulation time, $t_{\max}$	26.4 s
Time step, dt	0.0001 s

we calculate the total amount of time, T_1 and T_2, it spends there for each of two odorants during the simulation period $[0; t_{\max}]$. Having T_1 and T_2, we estimate the number of spikes, produced during the simulation period as F_0T_1 and F_0T_2, which gives for selectivity ν at a given concentration

$$\nu = \log \frac{T_1}{T_2}. \tag{3.2}$$

The mean firing rate F is calculated as

$$F_i = F_0 \cdot T_i / t_{\max}, \quad i = 1, 2,$$

where F_0 and $t_{\max}$ are given in Tables 1 and 2, respectively.

4. Results

We model the neuron as a set of N identical ORs, which bind odorant molecules independently (see Fig. 3). Two odorants, L_1 and L_2 with different affinities for the OR are considered. They are characterized by their binding rate k_+, which is the same for both odorants, and their releasing rate k_- for L_1 and k'_- for L_2, with $k'_- > k_-$, which means that L_2 has the lowest affinity for the OR. The numerical values of all parameters, including threshold N_0 above which the neuron fires with constant frequency F_0, are given in Table 1. The values of N, k_+ and k_- are those for the moth ORN responsive to the sexual pheromone as given by Kaissling.[10,11] The corresponding K_d are $37.8\,\mu$M for L_1 and $39.7\,\mu$M for L_2.

As stated in the previous section, the effects due to randomness of the binding-releasing process should be more pronounced if the mean number of bound receptors is just subthreshold. For this reason we studied a range of odorant concentrations in this region. We chose the left end of the concentration range below the threshold value for the more affine odorant, and its right end above the threshold. The range chosen spans from subthreshold to suprathreshold values also for the less affine

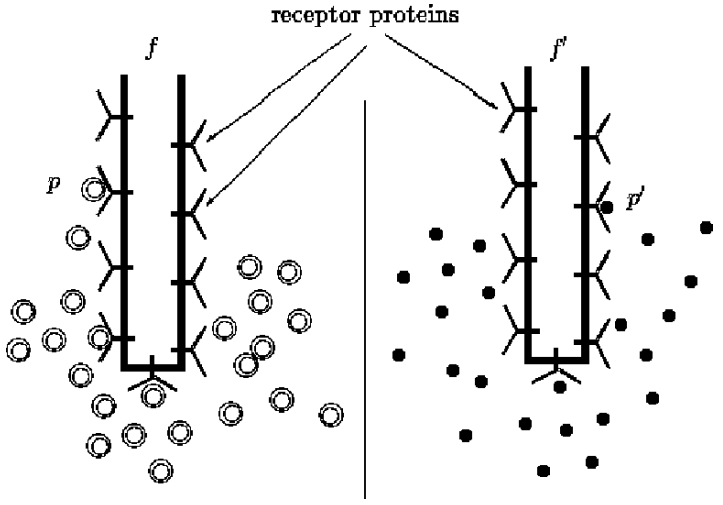

Fig. 3. Definition of ORN selectivity. It is assumed that the neuron fires at a constant rate when threshold is achieved. The mean firing rate depends on the temporal properties of the threshold crossing process, which depends on the odorant presented.

odor. Twenty one equidistant concentration values in the range chosen were used for simulation, from $c_{\min}$ to $c_{\max}$ (see Table 2).

First, we calculated the stochastic trajectories for each odorant interacting with the receptors characterized by the parameters given in Table 1 for 21 different concentrations as given in Table 2.

Second, the trajectories obtained (see Fig. 2) were processed as described in the Methods section. The firing rates for increasing odorant concentrations were determined. Figure 4 shows that the firing rate increases with concentration according to a sigmoid curve.

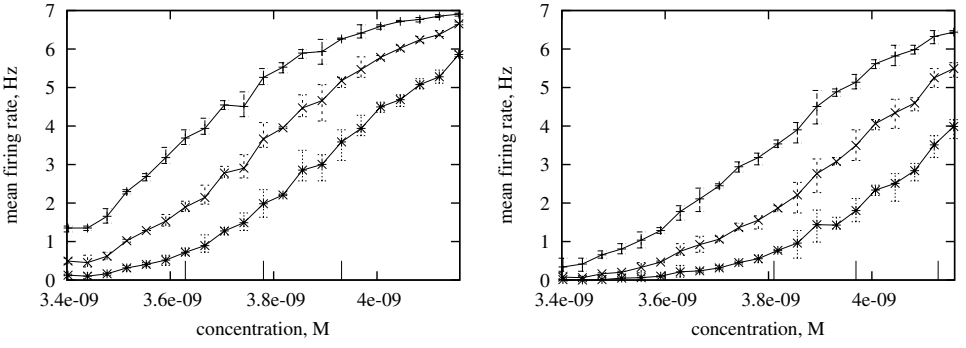

Fig. 4. Mean firing rate of an ORN versus concentration for three different threshold values N_0 for more (left) and less (right) affine odor. Curves from top to bottom correspond to $N_0 = 240$, 250, 260. Three vertical bars at the X-axis denote concentration values at which the mean number of bound receptors equal 240, 250 and 260. Compare this with Fig. 5.

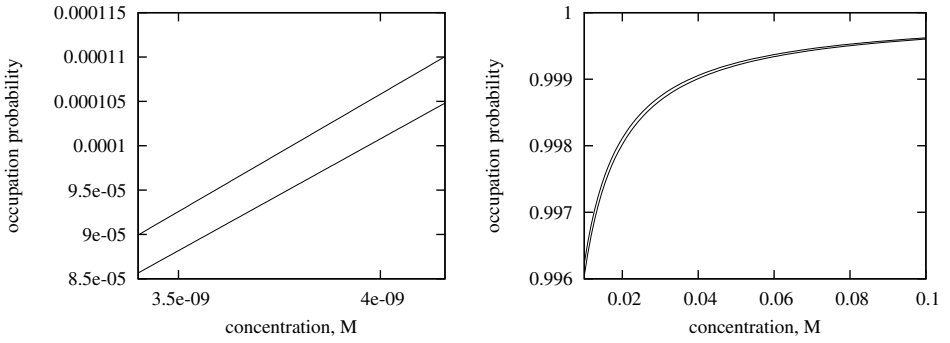

Fig. 5. Probability that an OR is occupied with first (upper curve) and second odorant versus concentration, calculated as in Eqs. (2.2) or (2.7).

This contrasts with the probability of a single OR to be bound to the odorant (see Fig. 5). The sigmoid character of curves in Fig. 4 is a new property, which emerges due to the threshold-type reaction of ORN, and to statistical properties of the threshold crossing process.

For a very small concentration (on the left of the range studied) the firing rate tends to zero. For a concentration on the right end of the range studied (or greater), the firing rate tends to asymptote F_0. As might be expected, the dose-response curves are shifted to the right when the threshold is increased.

Third, the selectivity for the OR μ (2.4) and for the ORN ν (3.2) were calculated and compared for different thresholds. As result, we obtained selectivity values versus concentrations c of odorants for various threshold values N_0 from 240 to 260 (Fig. 6). In addition, we calculated neuronal selectivity values versus

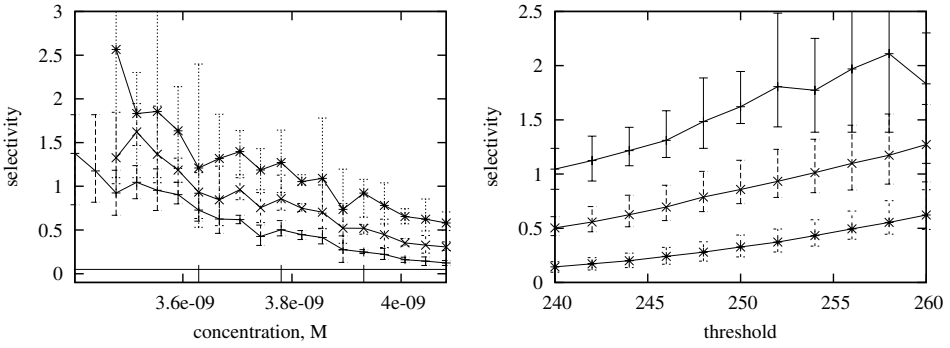

Fig. 6. (a) Selectivity of an ORN (3 upper curves) and its membrane-bound ORs (lower straight line) versus concentration. Curves from bottom to top correspond to thresholds $N_0 = 260$, 250, 240, respectively. The single primary receptor selectivity [see Eqs. (2.4), (2.7)] is equal to 0.0487859 and 0.048785 at left and right ends, respectively. (b) Selectivity of ORN versus threshold value N_0 for three different concentrations. Curves from top to bottom correspond to concentrations $3.51566 \cdot 10^{-9}$ M, $3.78028 \cdot 10^{-9}$ M, $4.0449 \cdot 10^{-9}$ M, respectively.

threshold number for three different concentrations. Figure 6a shows that, in the range of concentrations studied, the ORN selectivity ν is much higher than the OR selectivity μ. For example, at concentration $c = 10^{-4}$ M and threshold $N_0 = 250$, the ORN selectivity ν is 16.5 times larger than the OR selectivity μ. Contrary to μ, which is almost independent of concentration, ν increases when the concentration decreases. When the firing rate tends to the asymptote F_0, ν tends to μ. Figure 6a shows also that ν increases when the threshold is increased.

Fourth, the latter effect is studied in more details in Fig. 6b. It shows that the increase in selectivity with increasing threshold occurs at all odorant concentrations in the range studied.

The dependencies obtained suggest that the selectivity of a chemoreceptor neuron can be much higher than that of its receptor proteins. Additionally, it is observed that the ORN selectivity increases, if the odorant concentration decreases, and vice versa. Selectivity improvement is more pronounced at low concentrations. On the other hand, at low concentrations, the threshold is crossed rarely and the firing rate becomes low. At very low concentrations the spike rate may be too low to have a physiological meaning.

5. Discussion

Biological systems operate at temperatures that are well above the absolute zero, therefore thermal fluctuations are inevitable in any biological process. If the process involves association-dissociation of molecules, then the fluctuations bring about random variations in the number of associated molecules. The influence of these variations on chemotaxis has recently been studied experimentally in single-cell organisms.[9] Chemical senses of multi-cell organisms as well involve odorant binding of ligands to specialized ORs on the ORN surface. These ORNs are thus subjected to random variations in the number of ligands during primary reception. The statistical nature of the binding-releasing of odorants can be observed directly in electrophysiological recordings at very low stimulus intensity (see Minor and Kaissling[12]). It has been suggested that the subthreshold fluctuations of the membrane potential they induce lower the sensory threshold and so extend the dynamic range of responses towards low stimulus concentrations.[13]

In the present work we performed numerical simulations of the odorant binding-releasing stochastic process in order to investigate the influence on neuronal selectivity of the random nature of binding-releasing processes. We take into account these properties by means of direct numerical simulations. Our conclusion is that the selectivity of ORNs, as defined in Sec. 2.1, can be significantly higher than that of its ORs. This conclusion is based on a simplified neuronal model. It ignores most of the detailed processes involved in olfactory transduction, such as odorant binding proteins (OBPs), G-proteins, effector enzymes, second messengers, calcium and chloride channels, feedback reactions etc. However, it is not necessary to consider the overall complexity of transduction to analyze its most basic properties. For

example, as far as dose-response curves are concerned, it can be shown[14] that the most important step in olfactory transduction is the first one the receptor-ligand interaction. The subsequent steps merely amplify this initial interaction. This example illustrates why a simplified model is adequate to analyze the influence of random fluctuations on selectivity.

Further research of this effect should check its role in the framework of a more realistic model of the early steps of transduction, like in Rospars *et al.*[15] The present work specifies the key parameters that need to be taken into account in such models and in physiological experiments. It is, thus, a useful guide when tackling with more intricate situations. From this point of view it is worth mentioning some restrictions of the approach followed which can be solved in more complex models.

First, in our present model, selectivity improvement occurs only in a near-threshold concentration range, it disappears above this range, and, below it, the mean firing rate becomes too small to be physiologically significant. This results from simplifications made in the model of ORN, especially the fact that the firing rate does not depend on how much above threshold the number of bound ORs is, which is not the case in real ORNs. Introducing here a functional dependence similar to that proposed to describe frog[16] and rat[14] ORN responses could widen the range of concentrations where the effect takes place and make the selectivity improvement more pronounced.

Second, our approach does not include adaptation processes. Adaptation is present in ORNs and takes several forms depending on the nature of the stimuli (brief pulse, long pulse or brief repetitive pulses[17]). Depending on the mechanism involved the sensory threshold may or may not be modified by adaptation. If the threshold is modified, the selectivity enhancement might be less pronounced in an adapted ORN. Alternatively, some ORN types might be tuned to have maximum selectivity enhancement in their adapted state. These developments are outside the scope of the present paper. They call for less simplified models which are still in development.[18,19]

Third, the mechanism proposed here for enhancing the discrimination between odorants is only one among many. Other mechanisms in ORNs could play a role, especially those involving cooperativity. For example, OR clustering has been shown to improve concentration-response relationship, as described by others,[20,21] and other proteins in the transduction cascade might be involved as well. Another example is provided by the voltage-gated sodium channels in the axon action-potential generator whose cooperation produces the voltage firing threshold. This threshold, which can be expressed in terms of the number of ORs bound with ligand, as explained in Sec. 2.2 above, determines in turn the smallest stimulus intensity that can be signaled to secondary neurons in the antennal lobes (AL) of insects and olfactory bulbs (OB) of vertebrates. However, the interactions taking place in the neural network of the AL/OB, provides a higher level form of cooperation between ORNs. It is likely the major mechanism involved in odor discrimination (e.g. Linster *et al.*[22]).

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