ESANN'1994 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 20-21-22 April 1994, D-Facto public., ISBN 2-9600049-1-4, pp. 91-96

Stochastic model of odor intensity coding in first-order olfactory neurons

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Abstract. We study how the concentration of an odorant is coded by olfactory neuroreceptors using a two-point stochastic model. This model describes the main variables involved (activation of odorant receptor sites, receptor potential and firing frequency) and gives their mean and variance. It accounts well for the basic properties of olfactory neuroreceptors.

1. INTRODUCTION

Building biophysical models that explain the generation of the membrane potentials is a classical endeavor of neurophysiology. Stochastic models of neurons have been also intensively investigated [6]. Models of *single* neurons are relevant in sensory physiology because intensity of stimulation (here odor concentration) is encoded by the frequency of action potentials fired by first-order neurons (neuroreceptors). By contrast, the quality of an odor is a property of the population of neuroreceptors, and the experimenter cannot tell the nature of the odor from the recording of any single neuron (an important exception is the neuroreceptor to sex pheromones in Insects). Olfactory coding begins by the binding of odorant molecules to receptor proteins borne by the neuroreceptor dendritic membrane. Then a membrane depolarization is evoked, called *receptor potential.* When this potential is high enough, action potentials (spikes) are generated and propagated along the axon to the brain [1]. Modeling the olfactory neuroreceptor has been a neglected topic. The only reported effort to our knowledge has been made by Kaissling and only a brief summary is available in [1]. This situation prompted us to develop our own approach.

We model the olfactory neuroreceptor using a three-fold approach. First, the dependency of the spike firing frequency on the concentration C of an odorant is studied. Second, a stochastic approach is used to describe the variability of the processes involved, a prominent feature in experimental recordings. In our model, the variability results from the random bombardment of the neuroreceptor by identical odor molecules. Third, this model uses a two-point description of the neuron [3, 4], whereas most models that describe the dynamics of interspike intervals (ISIs) model the evolution of the membrane potential at only one point [6]. Here, we consider separately the dendritic compartment and the initial segment of the axon.

2. GENERATION OF THE RECEPTOR POTENTIAL IN DENDRITES

2.1. Occupation and activation of receptor sites

There is only one odorant substance M at concentration C, and the

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neuroreceptor bears n single-site receptors R, either identical or belonging to different classes. In both cases R is first occupied by M; then, if the interaction is strong enough, R is activated; finally M is released. In our simplification release is independent of activation [2].

Occupation and release. Each receptor is occupied and released independently of others according to the stochastic reaction schemes $M + R \xrightarrow{\lambda} MR$ and $MR \xrightarrow{\mu} M + R$, where the occupation parameter λ is a linear function of C. A receptor site occupied (respect. free) at time t has a probability $\mu\Delta t + o(\Delta t)$ (respect. $\lambda\Delta t + o(\Delta t)$) of being occupied (respect. released) in $(t,\ t+\Delta t]$. The stochastic process giving the number of occupied sites X_n defined by these probabilities, is a birth and death process with transition rates $\lambda_n(i) = \lambda(n-i)$ and $\mu_n(i) = \mu i$, for $i = 0, 1, \ldots, n$. The mean number of occupied sites and its steady state values are

$$E(X_n(t)) = n\lambda\alpha(1 - \exp(-t/\alpha)) \underset{t\to\infty}{=} n\lambda\alpha \qquad (1)$$

where the number of occupied sites at time $t = 0$ is 0 and $\alpha = (\lambda + \mu)^{-1}$. The variance of the number of occupied sites at time t is

$$\mathrm{Var}(X_n(t)) = n\mu\lambda\alpha^2 - \alpha(\mu - \lambda)\, n\lambda\alpha \exp(-t/\alpha) - n\lambda^2\alpha^2 \exp(-2t/\alpha) \qquad (2)$$

and its limiting value for $t \to \infty$ is $n\mu\lambda\alpha^2$. In order to simplify the computational problems, the process X_n with discontinuous trajectory can be approximated by a diffusion process X_n^* with similar statistical properties. With a proper choice of the initial value of X_n^*, its mean is (1) and its variance is

$$\mathrm{Var}\ (X_n^*(t)) = n\mu\lambda\alpha^2\Big(1 - \exp(-2t/\alpha)\Big). \qquad (3)$$

The variances (2) and (3) become identical for $t\to\infty$. Then $X_n^*(t)$ reaches a steady state which follows the normal distribution $N(n\lambda\alpha,\ n\lambda\mu\alpha^2)$.

Activation. We assume that an occupied receptor AR can be activated to AR^* with probability p, independently of its past behavior. Then, all properties of the process Y_n that describes the number of activated sites at time t can be derived directly from those for process X_n by $Y_n = pX_n$.

Multimodality of receptors. Most neuroreceptors are unspecialized and likely bear several types of receptor sites. For m types of receptors with frequencies n_j, $(n_1 + \ldots + n_m = n)$, each type of receptor is characterized by the triplet $\{\lambda_j,\ \mu_j,\ p_j;\ j = 1, \ldots, m\}$, with $\alpha_j = (\lambda_j + \mu_j)^{-1}$. The total number of activated sites $Y_n(t)$ is the sum over all subsets of the number of activated sites derived from (1) for any subset j. Then, the mean value of Y_n is,

$$E(Y_n(t)) = \sum_{j=1}^{m} p_j n_j \lambda_j \alpha_j (1 - \exp(-t/\alpha_j)) \underset{t\to\infty}{=} \sum_{j=1}^{m} p_j n_j \lambda_j \alpha_j. \qquad (4)$$

The asymptotic mean number of activated receptors under the condition that $\lambda_j \to \infty$ for each j can be defined as the saturation level, L; it is

$$L = \sum_{j=1}^{m} p_j n_j. \qquad (5)$$

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L differs for neuroreceptors bearing different populations of receptor sites.

2.2. Receptor potential

When a receptor site is activated it triggers the opening of ionic channels that depolarize the dendritic membrane. This receptor potential can be simulated by a process $Y = Y(t)$ related to the number of activated receptors Y_n or Y_n^*. In doing this the dependence of the contribution of each activated receptor to Y on the location of the receptor and on the actual value of the membrane potential is neglected. This simplification does not influence the qualitative behavior of the model but it will have to be removed when parametrization of the model is performed.

3. GENERATION OF ACTION POTENTIALS

3.1. Model of the axon initial segment

The one-dimensional models are based on two assumptions. The first is that after spike generation, the membrane potential Z at the axon initial segment (here called *axonal potential)* is reset, e.g. to the resting potential. The second assumption, implicitly contained in the unidimensionality of the models, is that the receptor potential Y is also reset after the spike. Consequently, the ISIs are independent random variables. Whereas the first assumption is well founded, because the falling phase of the action potential is an active mechanism that restores the resting potential (here taken as the zero level), the second one (resetting of the receptor potential) is unrealistic. A simplified solution to this problem is to divide the neuron into two compartments, the somatodendritic part and the initial segment, which allows resetting Z without resetting Y [4]. We assume that Y depends only on odor stimulation, not on Z, so that the dendritic ionic current and potential are not affected by the spike generating mechanism.

The initial segment A can be described by a circuit with a generator, a resistor R_A, a capacitor C_A, and a switch in parallel, which is the simplest realistic description of a neuron membrane. Then, Z is given by the stochastic differential equation $C_A \mathrm{d}Z(t) + R_A^{-1} Z(t)\mathrm{d}t = I(t)\mathrm{d}t$, with $Z(t_0) = 0$, where $Z(t_0)$ is the resetting potential and $I = I(t)$ is the input current due to the receptor potential. If a "slowly changing" stimulus is applied at time t_0 and the switch is open, I flows across the resistor and charges the condenser, and Z can be approximated in the form,

$$Z(t) = \frac{1}{C_A}\int_{t_0}^{t} \exp\left(-\frac{t-u}{\tau_A}\right) I(u)\mathrm{d}u \cong \frac{I(t)\tau_A}{C_A}\left(1 - \exp\left(-\frac{t-t_0}{\tau_A}\right)\right) \qquad (6)$$

where $\tau_A = R_A C_A$ is the time constant of the axonal membrane. "Slowly changing" means that the variation of I has been small during the charging of the condenser, whose time scale is given by τ_A. The switch closes when Z exceeds a certain threshold S (emission of a spike). The condenser discharges and Z resets to 0 (end of the spike). Then the switch opens and the condenser charges again; A is again submitted to the dendritic current and the process

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of spike emission can continue. In model (6), the voltage at A is reset after the spike and then exponentially tracks the receptor potential. If $Z(t)$ does not exceed S for a long period, then the axonal and receptor potentials become identical.

3.2. Firing frequency

Let t_1, t_2, ..., t_k denote the moments when process $Z(t)$ reaches the threshold $S > 0$ and their differences, $\Delta_{k+1} = t_{k+1} - t_k$, the corresponding sequence of ISIs. From (6), the time dynamics of Z, starting at time t_0, is

$$Z(t) = Y(t)\left(1 - \exp\left(-\frac{t - t_k}{\tau_A}\right)\right),\ t \in (t_k,\ t_{k+1}],\ Y(t_0) = y_0. \qquad (7)$$

The moment of the next spike t_{k+1} is the realization of random variable

$$T_{k+1} = \inf\{t > t_k;\ Z(t) \geq S \mid Z(t_k) \geq S,\ Z(t_k + 0) = 0\} \qquad (8)$$

which can be rewritten, by using (7), into the form $T_{k+1} =$

$$= \inf_{t > t_k}\left\{ Y(t)\left(1 - \exp\left(-\frac{t - t_k}{\tau_A}\right)\right) \geq S \mid Y(t_k) = \frac{S}{1 - \exp(-\Delta_k/\tau_A)}\right\} \qquad (9)$$

where Y is assumed to have a continuous trajectory (diffusion process). It follows from (9) that the length of the next ISI depends on the actual value of the receptor potential at the moment of last firing and thus on the length of the previous ISI. This feature is the main difference between the *partial reset* (two-point) model and those with *total reset* (one-point). If $Y(t_k)$ is very high then Δ_k is very short. If Y changes slowly with respect to time constant τ_A, the next ISI, Δ_{k+1}, will be also short with high probability. On the other hand, if Δ_k is long, $Y(t_k) \cong S$ and consequently the next ISI will not be very short. For this reason the model produces positively correlated sequences of ISIs and consequently coefficient of variation greater than 1, as we verified by simulation [3].

Replacing $Y(t)$ in (7) by (4), we get the mean value of the *axonal potential* Z_n in the time between two consecutive spikes, $t \in (t_k, t_{k+1}]$

$$\mathrm{E}(Z_n) = \left(1 - \exp\left(-\frac{t - t_k}{\tau_A}\right)\right)\sum_{j=1}^{m}\left\{p_j n_j \lambda_j \alpha_j\left(1 - \exp\left(-\frac{t - t_0}{\alpha_j}\right)\right)\right\}. \qquad (10)$$

This equation encompasses different types of activity according to C. Three regions, without sharp boundaries, can be defined by the asymptotic mean receptor potential. If it is high above the threshold $\sum p_j n_j \lambda_j \alpha_j \gg S$ which corresponds to a strong stimulation, the firing frequency f is approximated from (10) by solving the equation $\mathrm{E}(Z_n(t)) = S$

$$f^1 = -\tau_A \ln\left(1 - S/\sum_{j=1}^{m} p_j n_j \lambda_j \alpha_j\right) \qquad (11)$$

In this case the neuron fires rather regularly with fluctuations, related to those of Y_n around its mean, which are characterized by variance $\mathrm{Var}(Y_n(\infty))$. In the second region, characterized by condition $\sum p_j n_j \lambda_j \alpha_j \ll S$, the firing pattern is Poissonian. Finally, in the inter-mediate

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region, where the asymptotic mean is close S, the characteristics of firing are difficult to specify without simplification or simulations.

4. DISCUSSION

4.1. Mean behavior of the olfactory neuroreceptor

Equation (11) shows how the firing frequency f varies with increasing odor concentration C, λ being proportional to C. For low C, f remains zero, then rises to f_s at concentration C_s for which the mean receptor potential crosses threshold S. Above C_s, f is approximately linearly proportional to the receptor potential (1) or (4). However, below C_s spikes are also occasionally generated because of the random fluctuations of the receptor potential. It can be shown by simulation that the firing frequency resulting from noise increases almost linearly from 0 to f_s [3].

Several properties found experimentally in real neuroreceptors are predicted by our model. First, in both cases the plot of firing frequency *vs.* log C is a *sigmoid* curve. In the case of neuroreceptors bearing only one type of receptor sites, it is a logistic curve, and in the general case of m types of receptor sites per neuroreceptor, it is a summation of logistic curves, which may be also sigmoid. Second, the *saturation levels* (5), the *slope* of the sigmoid curves at the inflection point and the *sensitivity* of the neuroreceptor, defined by the abscissa of the inflection point, are all expected to vary in neuroreceptors bearing different populations of receptor sites, in agreement with observations.

4.2. Stochastic behavior of the olfactory neuroreceptor

Firing laws. Our model predicts other properties depending on the stimulus intensity. For low asymptotic mean values of the receptor potential, it generates spikes forming a Poisson process. When the steady state of Z is approximately at the same level as the threshold S, the model predicts that the distribution of ISIs becomes similar to Gamma, Inverse Gaussian or lognormal distributions. Finally, with increasing C, the intervals between firings should become shorter and also more regular.

Serial dependency, both positive and negative, and *coefficients of variation* larger than one, have been often observed in real neurons. The model predicts positive serial dependency of ISIs. These features are not found in classical models with total reset. Firing of spikes in *bursts* is frequently observed [5]. Bursting, exceptionally long ISIs and high serial correlations are related phenomena. It can easily be accounted for by two-compartment models. If the correlation time of Y, i.e. the time after which the receptor potential is no longer influenced by its previous values, is long (relatively to τ_A), the trajectory of Y may be expected to change smoothly. When Y is high above the threshold S, it stays there for a certain time and the model produces a sequence of short ISIs, i.e. a burst. Similarly, when Y falls below S it yields a very long ISI.

Spontaneous activity, i.e. spikes in the absence of overt stimulation, can be

recorded from neuroreceptors. We have shown that the neuroreceptors spontaneously fire bursts of spikes (not spikes), according to a Poisson process [5]. According to our model this means that the neuroreceptors alternate at rest between a state close to the resting potential (between bursts) and a state close to the threshold (within bursts).

4.3. Perspectives

The model presented is based on numerous simplifications and several factors have not been explicitly taken into account, such as detailed biochemical mechanisms of transduction and detailed biophysical membrane properties. Some of these factors can be easily fit in the model, whereas others do not call for a new model but for extensions of the present one. However, our assumptions lead to a basically correct account of the neuroreceptor behavior, which suggests that essential features of the real mechanisms have been retained.

References

More detailed credit to previous work in this field can be found in the following list of references:

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