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Coding of periodic pulse stimulation in chemoreceptors

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Abstract

In natural conditions odorants released continuously by animals and plants are broken in discontinuous clumps and filaments. In the case of flying insects these discontinuities are perceived as periodic variations in the concentration of the stimulus. This periodicity has been shown to be essential to orientation and location of mate and food. We study analytically and numerically a model of the receplor-ligand interaction that takes place in the receptor neurons. We show that this model can account quantitatively for the range of optimum stimulus frequencies measured experimentally in the sex-pheromone system of moths. The results obtained suggest that the rate constants characterising the pheromone-receptor interaction are optimally adapted to the temporal characteristics of the signal it perceives.

Keywords: Temporal coding; Intensity coding; Olfaction; Receptor; Transduction; Neuron modelling

1. Introduction

The question of understanding how the olfactory system encodes a periodic stimulus is biologically meaningful, especially in insects. For example a male moth can locate a conspecific female using the sexual pheromone she emits. It has been shown in natural conditions that air turbulence physically breaks the initially continuous pheromone plume into spatially and temporally discontinuous patches (Murlis et al., 1992). For an insect flying and zigzagging in the plume the discontinuities appear as a periodic signal. The importance of this periodic stimulation has been experimentally studied and shown to be a necessary condition of odorant perception, because the moth cannot orient in an artificially made uniform cloud. Behavioural (Kennedy et al., 1980, 1981; Vickers and Baker, 1992; Willis and Baker, 1984) and neurophysiological (Christensen and Hildebrand, 1988; Marion-Poll and Tobin, 1992; Rumbo and Kaissling, 1989) experiments indicate that the optimum frequency is in the range 1–10 Hz. Our aim in the present paper is to investigate to what extent this optimum frequency can be explained by the characteristics of the peripheral sense organs.

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In moths these sense organs, called sensilla, are borne by the featherlike antennae which are much larger in males than in females (Kaissling, 1987). Several types of sensilla exist, the largest one, which are up to half a millimetre long, are responsible for the detection of the pheromone molecules. Each olfactory sensillum is a cylinder of cuticle, riddled with tiny holes, housing two receptor neurons (Steinbrecht, 1999). The membrane of each neuron bears receptor proteins and ion channels that can generate the electrical receptor potential, which is converted in action potentials at the initial segment of the axon (Fig. 1). The odorant molecules reach the receptors through the holes and the perireceptor space lying between the cuticle and the membrane. Chemosensory transduction is a remarkable biochemical and electrical process in which the presence of a single molecule (ligand) at the cell surface can be detected and amplified into an action potential. This is a multistage process (Krieger et al., 1997) that involves the association of the ligand with a receptor protein on the cell membrane. The production of this signaling complex triggers the activation of G-proteins, which in turn activate enzyme units that release second messenger molecules in the cytoplasm. The second messengers open a number of ion channels, resulting in a change of the membrane potential followed by the firing of one or more action potentials. In the present work we are interested in the initial ligand-receptor interaction which can be considered as merely amplified by the subsequent events in the transduction cascade. We will show, by extending our recent research on this topic (Rospars et al., 2000; Lánský et al., 2001), that this dramatically simplified system can nonetheless account for the main feature of the real system.

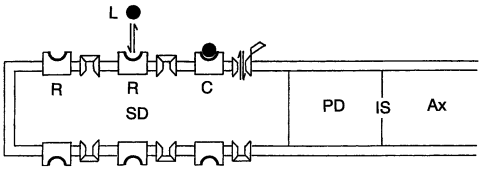

Fig. 1. Schematic representation of an olfactory receptor neuron. Only the first (receptor) and last (ion channel) components of the transduction cascade are shown. L, pheromone; R, pheromone receptor; C, pheromone-receptor complex (channel opening state); SD, sensory dendrite; PD, passive dendrite (without receptors); IS, initial segment (spike generator); Ax, axon.

2. Analytical results

2.1. Pulsed stimulation

The ligand molecules L are uniformly diluted in the carrier medium (water or air) which is in direct contact with the receptors. The concentration of ligand is described by alternating square pulses, in the form

$$L(t)=\begin{cases} L_{\mathrm{H}}, & \text{for } t\in[j(t_{\mathrm{L}}+t_{\mathrm{H}}),j(t_{\mathrm{L}}+t_{\mathrm{H}})+t_{\mathrm{H}}) \\ 0 & \text{elsewhere} \end{cases} \tag{1}$$

where $j=\{0, 1,...\}$, t_{H} is the duration of the pulses (at concentration L_{H}), it is the inter-pulse duration. The stimulation frequency is

$$f=(t_{\mathrm{L}}+t_{\mathrm{H}})^{-1} \tag{2}$$

It is clear that f can be changed either by modifying t_{L} or t_{H}. In order to conform to actual experimental practice, we may assume that the values of L_{H} and t_{H} are fixed in Eq. (1). Then the only variable in this stimulation protocol is the length of absence of stimulation, t_{L}. Of course, this assumption implies that the amounts of ligand delivered per stimulation cycle are the same for different stimulation frequencies, but the amounts delivered per unit of time are different. When the interpulse t_{L} decreases and tends to zero, f increases and tends to a limiting value, $f_{\max}=t_{\mathrm{H}}^{-1}$ which corresponds to a permanent stimulation.

2.2. Concentration of signaling complex as a function of time

A patch of sensory membrane uniformly covered with identical receptors R of concentration N is considered (sensory dendrite SD of Fig. 1). Ligand molecules can bind to receptors R and create a ligand-receptor complex denoted by C with concentration C and referred to as the

signaling complex. Let us denote by $R(t)$ the concentration of free ('not interacting') receptors and by $C(t)$ the concentration of bound ('interacting') receptors at time t. We assume in Eq. (1) that up to time origin no ligand is present at the vicinity of the receptors, which means that the initial conditions are $R(0)=N$ and $C(0)=0$.

In the investigated model it is assumed that the transduction cascade is triggered by mere binding, $\mathrm{L}+\mathrm{R}\underset{k_{-1}}{\overset{k_1}{\rightleftarrows}}\mathrm{C}$, where k_1 and k_{-1} are the binding and release rate constants, respectively (Lauffenburger and Linderman, 1993). Taking into account that $R(t)+C(t)=N$ is constant for any t, only one equation is sufficient to describe the reaction (Rospars et al., 2000),

$$\frac{\mathrm{d}C(t)}{\mathrm{d}t}=-(k_{-1}+k_1L(t))C(t)+k_1L(t)N \tag{3}$$

Eq. (3) takes into account the limited number of receptor sites and implicitly assumes that the concentration $L(t)$ is not influenced by the binding and release of ligand molecules. For a constant stimulation ($t_\mathrm{L}=0$) at level L_H, the asymptotic level of bound receptors is

$$C_\infty=\frac{k_1NL_\mathrm{H}}{k_{-1}+k_1L_\mathrm{H}} \tag{4}$$

Solving Eq. (3) for stimulation protocol described by Eq. (1), the level of bound receptors in the first stimulation interval, [0, t_H] is

$$C(t)=C_\infty(1-\exp(-(k_{-1}+k_1L_\mathrm{H})t)) \tag{5}$$

and at the end of the first stimulation period [0, $t_\mathrm{H}+t_\mathrm{H}$], it reaches the value

$$C(t_\mathrm{H}+t_\mathrm{L})=C_\infty(1-\exp(-(k_{-1}+k_1L_\mathrm{H})t_H))\exp(-k_{-1}t_\mathrm{L}) \tag{6}$$

Similarly,

$$C(2t_\mathrm{H}+t_\mathrm{L})=C_\infty(1-\mathrm{e}^{-(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}})(1+\mathrm{e}^{-(k_{-1}t_\mathrm{L}+(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H})}) \tag{7}$$

holds and in general, we can write

$$C((n+1)t_\mathrm{H}+nt_\mathrm{L})=C_\infty(1-\mathrm{e}^{-(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}})(1+\mathrm{e}^{-k_{-1}t_\mathrm{L}+k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}}+\ldots\mathrm{e}^{-n(k_{-1}t_\mathrm{L}+(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H})}) \tag{8}$$

which can be rewritten as

$$C((n+1)t_\mathrm{H}+nt_\mathrm{L})=C_\infty(1-\mathrm{e}^{-(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}})\times\frac{1-\mathrm{e}^{-(n+1)(k_{-1}t_\mathrm{L}+(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H})}}{1-\mathrm{e}^{-(k_{-1}t_\mathrm{L}+(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H})}} \tag{9}$$

For large n (i.e. large t), the concentration of the signaling complex reaches a periodic steady state in which each pulse gives rise to a distorted response with a saw-like appearance (Fig. 2). The asymptotic maximum level of bound receptors (peak of saw teeth) is the limit of expression (Eq. (9)) for $n\to\infty$,

$$C_\mathrm{max}=\frac{C_\infty(1-\exp(-(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}))}{1-\exp(-(k_{-1}t_\mathrm{L}+(k_{-1}+k_1L_\mathrm{H})t_\mathrm{H}))}, \tag{10}$$

with $C_\mathrm{max}=C_\infty$ if $t_\mathrm{L}=0$ (continuous stimulation) and $C_\mathrm{max}<C_\infty$ otherwise. For the minimum we have

$$C_\mathrm{min}=C_\mathrm{max}\exp(-k_{-1}t_\mathrm{L}). \tag{11}$$

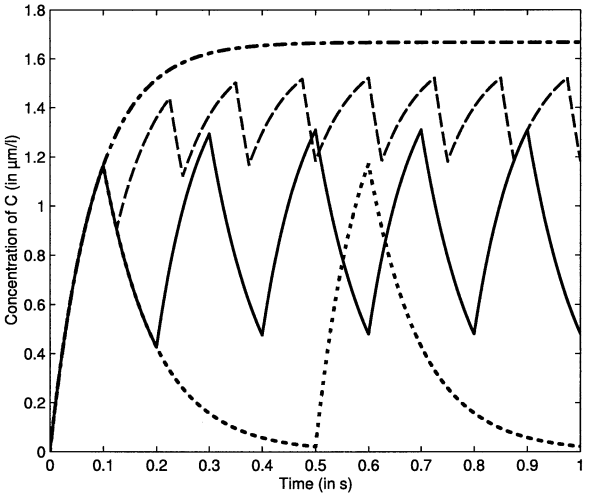

Fig. 2. Concentrations of signaling complex $C(t)$ as a function of time for different frequencies of stimulation $f=2$, 5, 8, 10 Hz. The figure shows both, the transient and steady-state behaviour of the system. Trend to $C_\infty=1.66$ µmol/l (peak) and to zero (drought) is apparent. Parameters: $N=10$ µmol/l, $k_1=0.2$ µmol/l per s, $k_{-1}=10$ per s, $L_\mathrm{H}=10$ µmol/l (midrange value), $t_\mathrm{H}=0.1$ s and different $t_\mathrm{L}=0.4$ (2 Hz, dotted line), 0.1 (5 Hz, solid line), 0.025 (8 Hz, dashed line), 0 (10 Hz, dash-dot line) s, frequency calculated according to Eq. (2).

Between these two extremes, the function $C(t)$ alternatively exponentially grows (with time constant $k_{-1}+k_1L_H$ and asymptotic level C_∞),

$$C(t) = C_\infty - (C_\infty - C_{min})\exp(-(k_{-1} + k_1L_H)(t - j(t_L + t_H))) \quad (12)$$

for $t \in [j(t_L+t_H), j(t_L+t_H)+t_H)$, $j \gg 1$ and decays (with time constant k_{-1} and asymptotic level zero),

$$C(t) = C_{max}\exp(-k_{-1}(t - j(t_L + t_H) - t_H) \quad (13)$$

for $t \in [j(t_L+t_H)+t_H, (j+1)(t_L+t_H))$, $j \gg 1$. Obviously, the durations of growth and decay are equal to t_H and t_L, respectively, and due to the simplicity of the model there is no delay in reaction to the stimulation change.

From extremes (Eqs. (10) and (11)) the amplitude A of $C(t)$ can be defined as half of the difference $C_{max}-C_{min}$,

$$A = \frac{C_\infty}{2}\,\frac{(1 - e^{-(k_{-1}+k_1L_H)t_H})(1 - e^{-k_{-1}t_L})}{1 - e^{-(k_{-1}t_L+(k_{-1}+k_1L_H)t_H)}}, \quad (14)$$

which tends to zero for $t_L \to 0$ (high frequency of stimulation) and to $C(t_H)/2$ for $t_L \to \infty$ (low frequency), see Fig. 3. It follows from Eqs. (4) and (14) that the amplitude A and the relative amplitude $A_r = 2A/C_\infty$ have the same shape of dependence on the frequency of stimulation $1/(t_H+t_L)$.

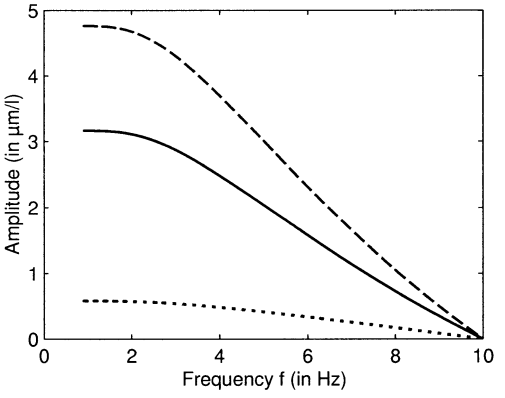

Fig. 3. Amplitude of the response A as a function of the stimulation frequency f (for its correspondence with t_L see Fig. 2) for different pulse heights $L_H = 10$ (dotted), 100 (solid) and 1000 (dashed) µmol/l. Parameters: Same N, k_1, k_{-1} as in Fig. 2, $t_H = 0.1$ s.

2.3. Tuning

The effect of the periodicity of the stimulation can be best appreciated by determining the pattern, which yields in some sense the optimal response of the system. Such a stimulation must meet two conditions. First, the amplitude A of concentration of the signaling complex must be sufficiently large. Obviously, the largest amplitude is achieved for longest t_L (and t_H), in other words for the slowest frequency of the stimulation, because it permits to reach the asymptotic levels C_∞ (peak) and zero (trough). Second, the stimulation must maximise the rate of change of the signaling complex in time to avoid that a constant (or almost constant) level be kept for a long period, because experimental evidence shows that in this case the stimulus is not perceived. However, this speed is lowest for long t_L (and t_H) and it increases when these intervals are shortened. Thus, the shortening of t_L has opposite effects on the amplitude and the rate of change, therefore, these effects must balance for some 'optimum' value of t_L. These observations suggest to take the product of the amplitude and of the rate of change in time as a suitable candidate to determine the optimal response. The rate of change of the evolution of the signaling complex between two stimulus alternation is given by the slopes of the tangents at the points of stimulation changes, $2A/t_H$ (growth, see Eq. (12)) and $-2A/t_L$ (decay, Eq. (13)). Assuming that t_H is constant, the suggested measure of the tuning γ caused by periodic stimulation (1) is proportional to the product of the amplitude A and of the rate given above (Lánský et al., 2001),

$$\gamma(t_L) \propto \frac{A^2}{t_L}. \quad (15)$$

After substituting Eq. (14) into Eq. (15) and after eliminating constants which have no influence on the position of maxima, the function to investigate is in the form

$$\gamma(t_L) = \frac{1}{t_L}\left(\frac{1 - e^{-k_{-1}t_L}}{1 - qe^{-k_{-1}t_L}}\right)^2, \quad (16)$$

where $q = \exp(-(k_{-1}+k_1L_H)t_H))$ is a constant independent of t_L. Using for the tuning of the stimulation the relative amplitude A_r (with respect to the maximum amplitude, which is $C_\infty/2$), instead of the amplitude A, has no effect on the position of the maxima. In practice we used the relative value $\gamma_r = \gamma/\max(\gamma)$ which varies between 0 and 1. Function Eq. (16) can be numerically searched for an optimum silent interval t_L (i.e. for an optimum frequency) under the assumption that the other characteristics of stimulation (t_H and L_H) are fixed (Fig. 4). This procedure can be repeated for different fixed characteristics t_H and L_H (Fig. 5).

It is clear that an increase of the amplitude with decreasing stimulation frequency is an intrinsic property of our model. On the other hand, the decrease of the response due to slow variation of the stimulation is included in the tuning function in an ad hoc manner.

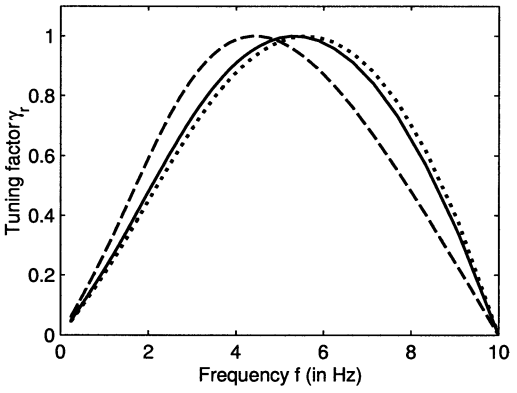

Fig. 4. Tuning curve γ_r as a function of the stimulation frequency f (for its correspondence with t_L, see Fig. 2) for different pulse heights $L_H = 0.1$ (dotted), 10 (solid), and 1000 (dashed) μmol/l. For lower stimulations slower frequency is optimal. Parameters: Same N, k_1 and k_{-1} as in Fig. 2, $t_H = 0.1$ s.

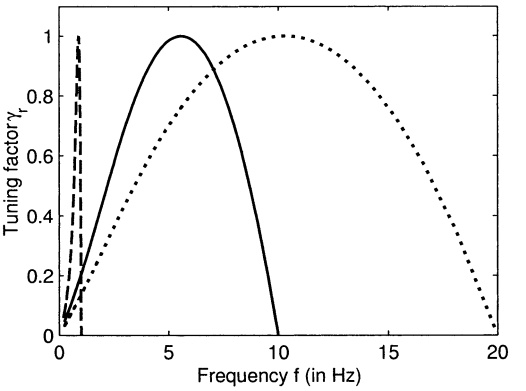

Fig. 5. Tuning curve γ_r as a function of the stimulation frequency f (for its correspondence with t_L, see Fig. 2) for different pulse durations $t_H = 0.05$ (dotted), 0.1 (solid) and 1 (dashed) s. For shorter pulses faster frequency is optimal. The curves are independent of L_H. Parameters: Same N, k_1 and k_{-1} as in Fig. 2.

3. Numerical results

3.1. Parameters and variables

The total concentration of receptors N and the rate constants k_1 and k_{-1} are intrinsic parameters of the system which are considered as fixed, while L_H, t_H and t_L are extrinsic parameters which can be modified. For this reason we investigated only the effect of these extrinsic parameters on the shape of the response and mainly the role of the durations t_H and t_L of 'on' and 'off' intervals. In our recent papers (Rospars et al., 2000; Lánský et al., 2001) on comparison of concentration detectors with other types of chemoreceptors, the numerical values of the parameters N, k_1 and k_{-1} characterising the membrane were based on extensive experimental observations presented in Kaissling (1998a) for the sex-pheromone receptor neuron of the male moth *Antheraea polyphemus.* The same parameters are used here: $k_1 = 0.2$ μmol/l per s, $k_{-1} = 10$ per s, $N = 10$ μmol/l (the concentration of the receptor proteins is expressed with respect to the volume of the hair lumen). The biologically meaningful range of the variable L is (0.1, 1000) μmol/l (see Section 4).

3.2. Concentration of signaling complex as a function of time

For short t_H and longer t_L, the asymmetric shape of $C(t)$ is apparent in Fig. 2. The periodic steady state is definitely achieved after less than 0.5 s. Fig. 2 also clearly illustrates a strong dependence of the response amplitude on the stimulation frequency. When the frequency of stimulation increases the modulation of the number of activated receptors decreases; for 10 Hz (continuous stimulation for $t_L = 0$ with $t_H = 0.1$ s) the peak-to-peak variation is smoothed out. For very short t_L, the curves coincide asymptotically at the level 1.66 μmol/1. This dependence of the amplitude on the stimulation frequency is illustrated in Fig. 3.

3.3. Tuning

We are interested in the stimulation frequency f that yields the largest relative effect of the concentration of the signaling complex. For determining this optimum frequency, the values of the relative tuning function γ_r, based on Eq. (16) are plotted against f (by decreasing t_L). For a fixed pulse duration $t_H = 0.05$ s (not shown) the optimal stimulation frequency is approximately 5 Hz for $L_H = 1000$ μM/l (upper range) and 10 Hz for L_H smaller than 10 μM/1 (lower range). For longer pulse durations (Fig. 4) the optimum frequency tends to about 5 Hz independently of L_H. By varying the pulse duration t_H various optimum frequencies can be obtained (Fig. 5) which, in this case, are independent of constant L_H. The optimum frequencies found are approximately 25 Hz at 20 ms (not shown), 10 Hz at 50 ms, 5 Hz at 0.1 s and less than 1 Hz for $t_H = 1$ s.

Now, we can compare the behaviour of the optimal system as determined in Figs. 4 and 5 with the suboptimal behaviours illustrated in Fig. 2. It follows from Fig. 2 that to achieve the largest change in the number of activated signaling complexes, the periods t_L and t_H have to be balanced and the same result follows from Fig. 5 for other pairs of t_L and t_H. Furthermore, for the situation illustrated in Fig. 2, the optimum length of absence of ligand was found to be $t_L = 0.1$ s (solid line). The same figure shows that choosing t_L smaller than this value decreases the amplitude (dashed line). On the other hand, choosing t_L greater than 0.1 s leads to an increase of the amplitude (dotted line), but this increase is smaller and smaller because the shape of $C(t)$ becomes less and less linear. This gives a pictorial interpretation of the tuning factor γ.

4. Discussion

A noteworthy feature of the present approach is that it is based on a very simplified model of the olfactory system. The whole transduction process is reduced to a mere receptor-ligand interaction $L + M \leftrightarrows C$. This so-called concentration detector model implicitly assumes that the ligand has free access to the receptors and can enter and leave the perireceptor space without any hindrance, in both directions. In reality this is not the case for pheromone sensilla because a physically distinct perireceptor space is created by the multiporous hair cuticle that houses the sensory dendrite: the pheromone molecules must cross this barrier and when they reach the perireceptor space they can no longer leave it. As a result they accumulate there and must be destroyed by enzymatic processes (Kaissling, 1998b, 2001). For this reason, the receptor neuron is not a mere concentration detector but a flux detector (Kaissling, 1998a). However, in Rospars et al. (2000) we showed that the two main effects of interposing this perireceptor space were (i) to increase the ligand concentration L there with respect to the concentration in the environment L_{air}, and (ii) to introduce a lag in the response with respect to the stimulus (it never exceeds a quarter of the stimulation period). With the parameters chosen for describing the perireceptor space, L was found to be 10^6 times greater than the external concentration L_{air}, e.g. delivered by the stimulating apparatus in physiological experiments. So, except for the time lag, the concentration detector is an acceptable description of the more realistic flux detector provided L at the vicinity of the receptor is taken 1 million times greater than L_{air}, in the species considered. Behavioural and physiological experiments indicate that L_{air} goes from 300 molecules per cubic

centimetre of air at the sensory threshold (10^{-7} μmol/l) to 30 billions at sensory saturation (10^{-3} μmol/l). Consequently, with a constant level of the stimulation laying in this interval, as assumed here, the level in the perireceptor space is in the range (0.1, 1000) μmol/l. The responses of the models can be expected to be gradual in this region. It is worth mentioning that at sensory threshold, only 15 molecules are captured by the whole antenna, which is an exquisite sensitivity.

In *A. polyphemus*, as in other species investigated, the physiologically effective frequencies of stimulation lay approximately in the interval (1, 10) Hz (Rumbo and Kaissling, 1989; in this work $t_H = 20$ ms). The model presented here is compatible with these observations and suggests that the optimum frequency of stimulation can be accounted for by fundamental characteristics of the receptor-ligand interaction only. Thus it might illustrate the idea that in the pheromone detecting system, as far as the ability to follow the stimulation frequency is concerned, the most important single process and main bottleneck in the whole chain of sensory events, from biochemical and electrical transductions in the receptor neurons (Rospars et al., 1996) to interneuron processing in the central nervous system (especially in the brain antennal lobes; Hildebrand and Shepherd, 1997), is the initial one, when ligand molecules interact with the layer of receptor proteins. If this idea is right, the neural processes in the pheromone system would be able to amplify without distortion the evolution in time of the initial signal, i.e. the formation of the signaling complex. Several different amplification mechanisms are used to fulfill this function, especially the multistep biochemical cascade in the sensory dendrite and the convergence of multiple receptor neurons on single projection neurons in the antennal lobes.

For the range of frequencies (1, 10) Hz experimentally observed the model predicts that the optimal pulse duration is in the range 50 ms–0.8 s (see Fig. 5). This is in reasonably good agreement with field experiments indicating that in natural odor plumes the stimulus bursts are of short duration, typically tens of milliseconds up to about half a second (Murlis, 1997). Thus the model does not conflict with the idea that the moth pheromone receptor system might be optimally adapted to the time characteristics of the signal it perceives.

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