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Encoding of pheromone intensity by dynamic activation of pheromone receptors

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Abstract

The perireceptor and receptor events in a model of the single olfactory receptor neuron of the male moth *Antheraea polyphemus* are studied. This first stage of signal transduction imposes limiting conditions on the amount of information the olfactory neuron can process. By employing basic concepts of information theory we compare the effectiveness of the odorant concentration coding in dependence on the level of temporal detail. We analyze two hypotheses, one in which the information is encoded in the average concentration of the activated receptors and the other in which it is encoded in its time-gradient. We show that each encoding scheme operates optimally at different levels of temporal resolution and discuss their biological meaning.

1 Introduction

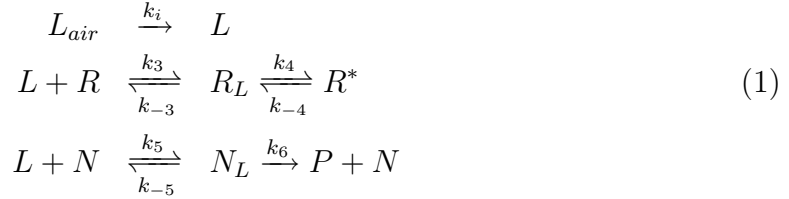
Orientation towards food and mate, especially in insects, is an olfactory-controlled behavior which relies on the detection of small amounts of odorant molecules delivered in turbulent atmospheric conditions, so that variation in magnitude and time is a major feature of the natural stimulus. This variation in the concentration of stimulus has been shown to be essential for locating the source of the stimulus (Kennedy et al., 1980, 1981; Willis and Baker, 1984).

In this paper we analyze how a well-studied receptor neuron of the male moth *Antheraea polyphemus* encodes its specific stimulus – the sexual pheromone emitted by conspecific females. Our study is based on a model of the perireceptor and receptor events involved in pheromonal transduction in this species (Kaissling, 2001; Kaissling and Rospars, 2004). The external stimulus is given by the spatio-temporal concentration of the major component of the sexual pheromone, the response of the system (the internal signal) is the concentration of activated receptor molecules borne by the dendritic membrane. We describe possible methods for reconstructing the stimulus from the response and we discuss the efficiency of the stimulus coding by employing an information-theoretic approach. This problem is biologically meaningful because the nervous system must solve it by gaining information on the stimulus from a proper processing of the initial information it receives, i.e. that encoded in the pheromonal receptors.

2 Theory and methods

2.1 The model

The model of odorant flux detector we consider here was developed by Kaissling and Rospars (2004) and represents a slightly modified version of the original model developed by Kaissling (1998, 2001). The network of chemical reactions (1) includes transfer of the external pheromone (or ligand) L_{air} from the surrounding air to the perireceptor space L , the reversible binding of L to a single-type of receptor molecules R , the reversible change of the complex R_L to an activated state R^* (the internal signal), a reversible binding of L to a deactivating enzyme N (see Kaissling and Rospars (2004) for details) and an irreversible odorant deactivation changing the complex N_L to $P + N$.



We denote the respective concentrations of the seven species involved by square brackets, e.g., $[L](t)$: for simplicity we omit to denote in the following the explicit dependence on the time variable t . The total concentration of the receptor molecules, $[R]_{tot} = [R] + [R_L] + [R^*]$, does not change over time, $[R]_{tot} = const.$, as well as the total concentration of the deactivating enzyme, $[N]_{tot} = [N] + [N_L]$, remains constant. The set of equations fully describing the evolution of the reactions (1) in time consist of five 1st-order ordinary differential equations (2)–(6) and two algebraic equations (7) and (8):

$$\frac{d[L]}{dt} = k_i[L_{air}] - k_3[L][R] + k_{-3}[R_L] - k_5[L][N] + k_{-5}[N_L] \tag{2}$$

$$\frac{d[R_L]}{dt} = k_3[L][R] - k_{-3}[R_L] - k_4[R_L] + k_{-4}[R^*] \tag{3}$$

$$\frac{d[R^*]}{dt} = k_4[R_L] - k_{-4}[R^*] \tag{4}$$

$$\frac{d[N_L]}{dt} = k_5[L][N] - k_{-5}[N_L] - k_6[N_L] \tag{5}$$

$$\frac{d[P]}{dt} = k_6[N_L] \tag{6}$$

$$[R] = [R]_{tot} - [R_L] - [R^*] \tag{7}$$

$$[N] = [N]_{tot} - [N_L]. \tag{8}$$

We assume, that at $t = 0$ the concentrations of L , R_L , R^* , N_L and P are zero, which gives the initial conditions. The values of the system parameters were determined by Kaissling (2001) and Kaissling and Rospars (2004), we summarize them in Tab. 1.

k_3	$= 0.209 \text{ s}^{-1} \mu\text{M}^{-1}$	k_{-3}	$= 7.9 \text{ s}^{-1}$
k_4	$= 16.8 \text{ s}^{-1}$	k_{-4}	$= 98 \text{ s}^{-1}$
k_5	$= 4 \text{ s}^{-1} \mu\text{M}^{-1}$	k_{-5}	$= 98.9 \text{ s}^{-1}$
k_6	$= 29.7 \text{ s}^{-1}$	k_i	$= 2900 \text{ s}^{-1}$
$[R]_{tot}$	$= 1.64 \mu\text{M}$	$[N]_{tot}$	$= 1 \mu\text{M}$

Tab. 1: Summary of the odorant flux detector model parameters, determined by Kaissling (2001) and Kaissling and Rospars (2004).

2.2 Information transmission and stimulus coding

The key question we investigate is: what is the efficiency of the stimulus-to-response transduction? Or, how well can the external signal $[L_{air}]$ be reconstructed from the $[R^*]$ signal? We describe the amount of the information transferred as a function of the level of temporal detail Δt (the temporal resolution) in $[L_{air}]$. $[L_{air}]$ is then realized by a piecewise constant function in time. The "time step" is equal to Δt , so we assume there is no finer detail below Δt , which is useful for examining the system's performance. Furthermore, we let the function $[L_{air}]$ be discrete-valued, thus it can take only one of n prescribed values $X = \{x_i\}_{i=1}^n$ in each time step (time "bin"), see Fig. 1. Of course, we can choose Δt so small and n so large that the trajectory looks continuous. We assign probability $p(x_i)$ to each possible value x_i and let the sequence of successive different $[L_{air}]$ values be independent realizations of random variable X . In the following, we let $\{x_i\}_{i=1}^n$ be equidistant, therefore the signal is fully described by the probability mass function $p(x_i)$ and Δt .

To measure the amount of information transferred we employ standard methods of information theory (Shannon, 1948; Cover and Thomas, 1991). The entropy (or the uncertainty) $H(X)$ (Cover and Thomas, 1991) can be assigned to $[L_{air}]$:

$$H(X) = - \sum_{i=1}^n p(x_i) \ln_2 p(x_i). \quad (9)$$

If the responses to the stimulation form another ensemble Y of m discrete states, $Y = \{y_j\}_{j=1}^m$, each with probability $p(y_j)$, then the conditional entropy $H(X|Y)$ is defined by employing the conditional probability $p(x_i|y_j)$ (Cover and Thomas, 1991)

$$H(X|Y) = - \sum_{j=1}^m p(y_j) \sum_{i=1}^n p(x_i|y_j) \ln_2 p(x_i|y_j). \quad (10)$$

Equation (10) quantifies the average uncertainty of the input (the stimulus), given the output (the response). The way to obtain $\{y_j\}_{j=1}^m$ from $[R^*]$ is presented below. Generally, information is defined as a reduction in uncertainty (Shannon, 1948), thus the quantity called mutual information, $I(X;Y)$, measures the information transferred by the system (the information channel, Shannon (1948))

$$I(X;Y) = H(X) - H(X|Y). \quad (11)$$

Ideally, if the transmission is free of errors, the uncertainty on the input, given the output, is zero: $H(X|Y) = 0$, thus the maximal value of the information transferred is $I(X;Y) = H(X)$. On the other hand, if X is completely independent of Y , then from formula (10) follows that $H(X|Y) = H(X)$, thus the minimal value of $I(X;Y)$ is zero. We define the normalized mutual information I_n confined to interval $[0, 1]$ describing the fractional part of the information transferred, by relation

$$I_n = \frac{I(X;Y)}{H(X)}. \quad (12)$$

Note, that $I(X;Y)$ does not quantify the information gain in real time, it only yields the average amount of bits gained per interval of length Δt . To obtain the average information flow η in bits per second we simply divide:

$$\eta = \frac{I(X;Y)}{\Delta t}. \quad (13)$$

3 Results and Discussion

In the following sections, we analyze two different approaches to the reconstruction of $[L_{air}]$ from $[R^*]$: coding by the average receptor count (denoted as count coding) and coding by the average receptor activation rate (denoted as rate coding). The properties of these code-reading mechanisms are illustrated on a simple type of stochastic stimulation. Ideally, one would discretize the values down to the molecular level to obtain the best possible resolution. This is however hardly possible, the value of $[R^*]$ corresponding to one activated receptor is approximately $10^{-6.2} \mu\text{M}$, and estimates of mutual information would thus require unrealistic amount of data. In order to obtain reasonable estimates of $I(X;Y)$ we use low values of discretization ($n = 4$), thus the shape of the curves is more important than their absolute values.

3.1 The count coding scheme

The first, and probably the simplest way to construct the ensemble of response states Y from the $[R^*]$ signal (and thus to 'read' the information about $[L_{air}]$) is to divide the time development of $[R^*]$ into "bins" of length Δt , (equal to Δt of $[L_{air}]$) and compute the average value of the activated receptors for each bin. Correspondingly, the averaged values of $[R^*]$ are discretized into m levels: $Y = \{y_j\}_{j=1}^m$, see Fig. 1. There are many ways to choose the discretization factor – our approach is to observe minimal and maximal value of the averaged $[R^*]$ and consequently to divide the range obtained (taking into account the impossibility of division below one activated receptor). Theoretically, choosing $m > n$ should not affect the value of $I(X;Y)$, however, we usually choose $m = n$ unless stated otherwise, mostly for numerical reasons (see below).

If the stimulus changes faster than the system stabilizes, the resulting values Y of $[R^*]$ at the current time bin are affected not only by the values X of $[L_{air}]$ at the

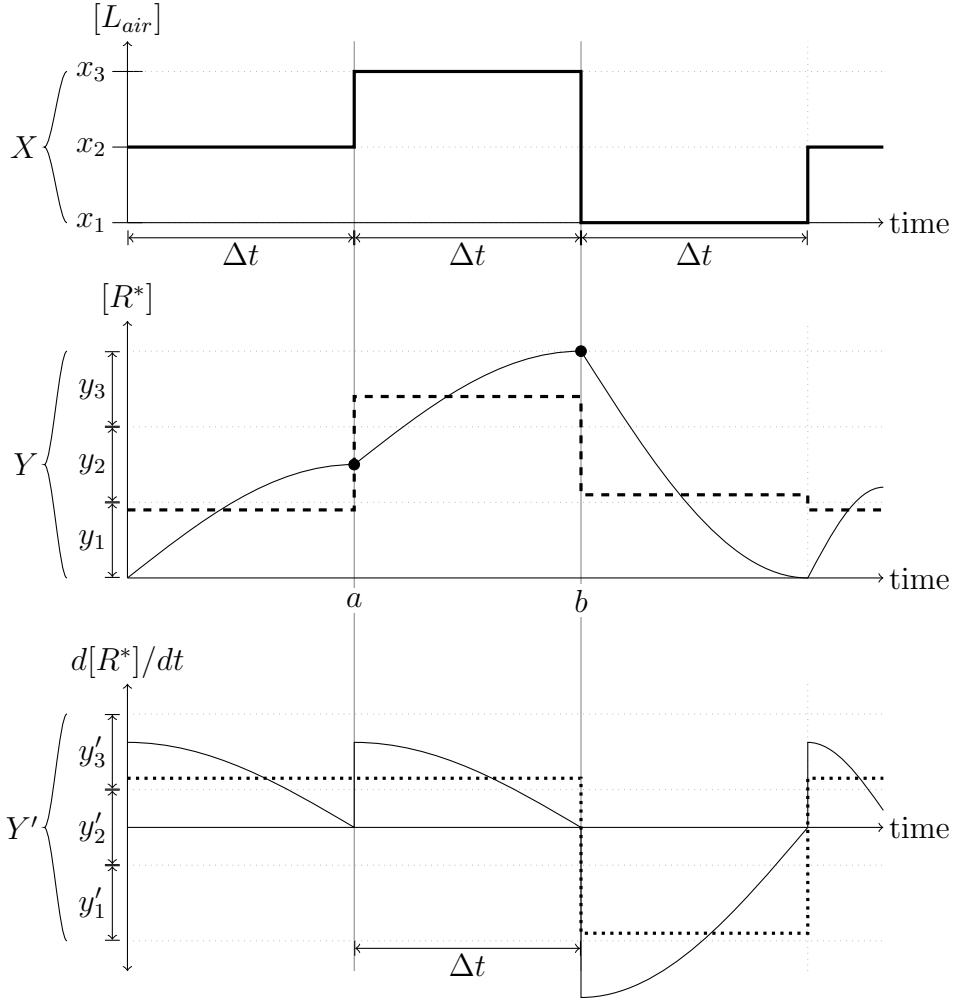


Fig. 1: Schematic illustration of stimulus and response discretization. The external stimulus $[L_{air}]$ is a piecewise constant function (thick solid line), with "time step" Δt , taking one of $\{x_i\}_{i=1}^3$ equidistant values, selected independently for each interval using the probability mass function $p(x_i)$. The response $[R^*]$ to such stimulation is shown below with thin solid line. The discretization of $[R^*]$ into ensemble $Y = \{y_j\}_{j=1}^m$ (count coding) is performed in the following steps: 1) mean values of $[R^*]$ in subsequent time steps Δt are computed (thick dashed line); 2) these mean values are assigned into different bins y_j . The ensemble $Y' = \{y'_j\}_{j=1}^m$ (rate coding) is obtained similarly from the derivative $d[R^*]/dt$ shown below (thin solid line): average time-gradient values in time steps Δt are computed (thick dotted line) and discretized.

corresponding bin, but also by the values X at the preceding bins. In other words, the information transfer in this system has a memory – the current state is affected by its history. We will deal with the memory effects later in more detail. For the case of the count coding scheme we assume, that only the value of Y at the "current" time bin is used to reconstruct the true value of the corresponding X , i.e., the code-reader

has no capacity to process several y_j 's at a time. The memory effect is therefore the main source of errors in otherwise deterministic $[L_{air}]$ to $[R^*]$ transduction.

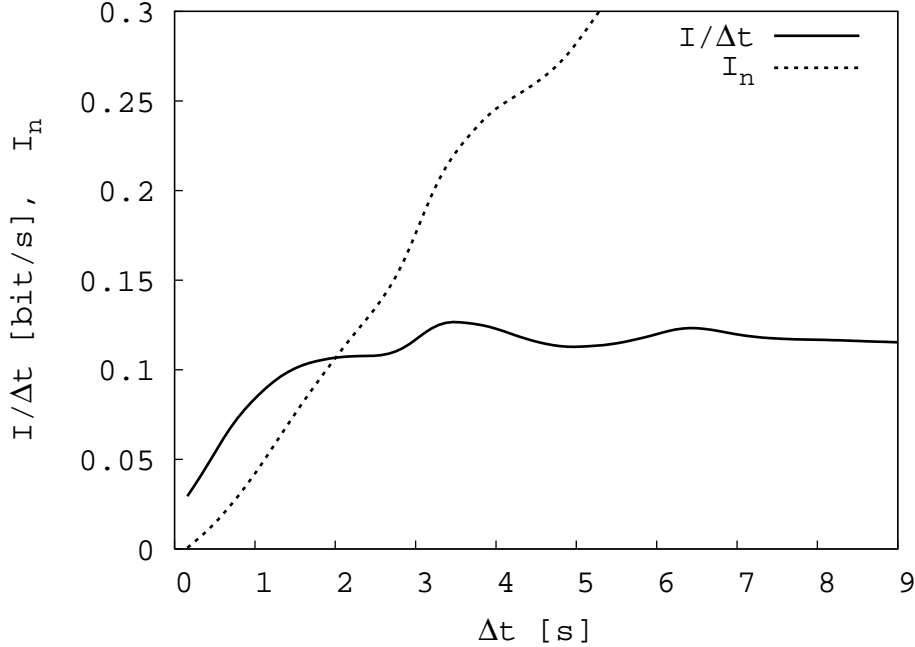


Fig. 2: Effectiveness of the count coding scheme as a function of time resolution Δt . The number of discretization levels is $n = m = 4$, X is drawn from the uniform distribution with maximum value $\frac{3}{4}[L_{air}]_{max}$. The mutual information flow I/dt is nearly flat for $\Delta t > 2$ s. The normalized mutual information I_n increases monotonously and saturates to unity for $\Delta t \approx 20$ s: for $\Delta t > 20$ s the decoding is essentially "error-free". The quantities decrease rapidly towards very small values of Δt , as expected.

The estimate of the amount of information the count coding scheme reveals is shown in Fig. 2 for the simple case when all values of X are distributed equally likely. We see that the mechanism is most effective in describing the low-frequency component of the stimulation, below 1 Hz. The mutual information $I(X; Y)$ steadily increases to its maximum value and the information flow I/dt remains almost constant. On the other hand, this mechanism does not reveal much of the more detailed structure (higher than 1 Hz) of the external signal.

3.2 The rate coding scheme

As mentioned in the previous section, the sequence $\{Y\}$ of the averaged values of $[R^*]$ is not statistically independent due to the memory effect in stimulus-to-response transduction. To approach the problem correctly from the information-theoretic point of view, we would have to compute (estimate) the complete form of the mutual

information $I(X; Y)$ in the general case (Cover and Thomas, 1991)

$$I(X; Y) = \lim_{k \rightarrow \infty} \frac{1}{k} I(\{X_i\}_{i=1}^k; \{Y_i\}_{i=1}^k) \quad (14)$$

Formula (14) is known to be notoriously hard to estimate, even when further limiting conditions are applied on the form of information transmission and on the type of dependence in $\{Y\}$. The amount of data needed to estimate $I(X; Y)$ grows exponentially with increasing k and even in cases where limit is guaranteed to exist the convergence may be arbitrarily slow. Furthermore, equation (14) implies, that the decoding mechanism would have to process several y'_j s at a time in order to gain additional information due to their inter-dependence.

To overcome the above mentioned difficulties we suggest here the "rate coding" scheme, that benefits from the memory effect, yet employs only local properties, i.e., processes only one bin at a time. The main idea is, that at least part of the value of the derivative of $[R^*]$ with respect to time is the direct consequence of the memory effect and may thus be utilized to reveal some different or additional information compared to the values of concentration. Both coding schemes may be used cooperatively, e.g., large positive value of the derivation suggests that the average value of $[R^*]$ is underestimated. In this section, for comparing the two suggested decoding mechanisms, we analyze information transmission based solely on the rate coding scheme. Similarly to the count coding mechanism, we compute the average derivative in each time bin, $[R^*]_D$, and discretize its value into m levels: $Y = \{y_j\}_{j=1}^m$ – we employ again the equidistant discretization based on the $\min[R^*]_D$ and $\max[R^*]_D$.

The resulting estimates of the same quantities as in the case of the count coding are shown for comparison in Fig. 3 under the same circumstances. We see that the mechanism is most effective in describing the high-frequency component of the stimulation, above 1 Hz. The normalized mutual information I_n never saturates, but due to small values of Δt the information flow is greater than in the case of count coding. Both quantities decrease rapidly towards very small values of Δt , as expected. The amount of information transferred below $\Delta t = 0.1$ s corresponds to the lower-than 10 Hz-frequency component of the stimulation signal – details on smaller scale than $\Delta t = 0.1$ s are not transferred because the change in the $[R^*]$ corresponds to less than one receptor molecule (Kaissling and Rospars, 2004).

4 Conclusions

We conclude that each of the considered mechanism works best on a different time scale. The count coding carries information about the mean value of $[L_{air}]$ and works better as the system approaches the steady-state. On the other hand, the rate coding works best in the transient state and describes accurately the finer temporal details of the stimulus (see Fig. 4), this is also confirmed by experimental observations (Kramer, 1997). Furthermore, it is known that at least two different pheromonal receptor neurons exist which can follow periodic stimuli at different frequencies (up to 2 and

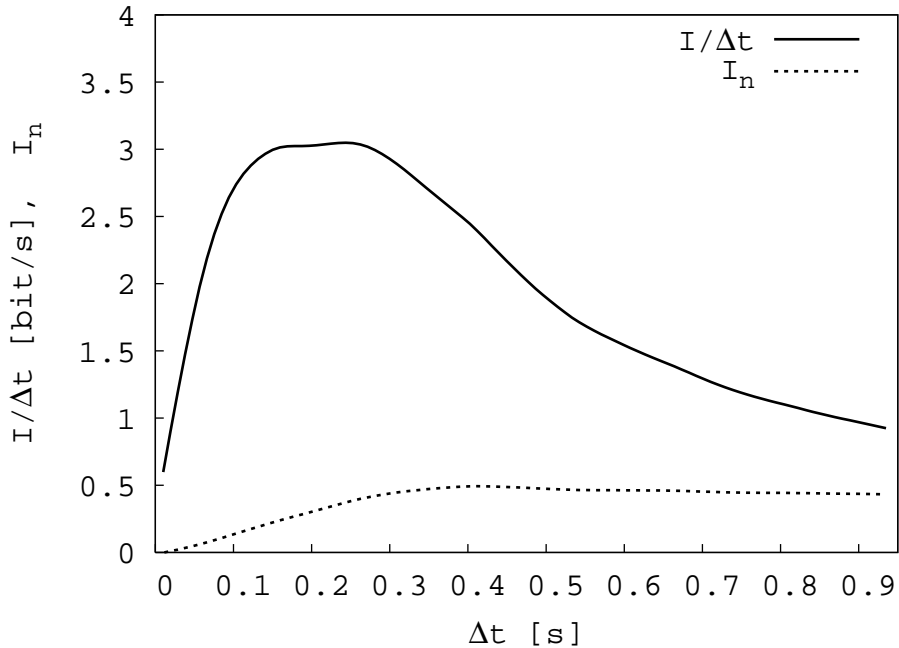


Fig. 3: Efficiency of the rate coding scheme as a function of time resolution Δt . The number of discretization levels is $n = m = 4$. X is drawn from the uniform distribution with maximum value $\frac{3}{4}[L_{air}]_{max}$, the values are approximated over several runs of 4000 time steps Δt . The mutual information flow I/dt is optimal around $\Delta t = 0.2$ s and the absolute values are greater than in the case of the count coding scheme (due to much smaller values of Δt). The coding scheme is never fully error-free: the normalized mutual information I_n never saturates to one, the maximum is around $\Delta t = 0.4$ s then it slowly decreases. Both quantities decrease rapidly towards very small values of Δt , as expected. The amount of information transferred below $\Delta t = 0.1$ s corresponds to the lower-than 10 Hz-frequency component of the stimulation signal.

10 Hz respectively, Meng et al. (1989)). So we predict that different post-receptor transduction mechanisms operate in these two neuron types that are respectively sensitive to the two different aspects of the signal we have compared.

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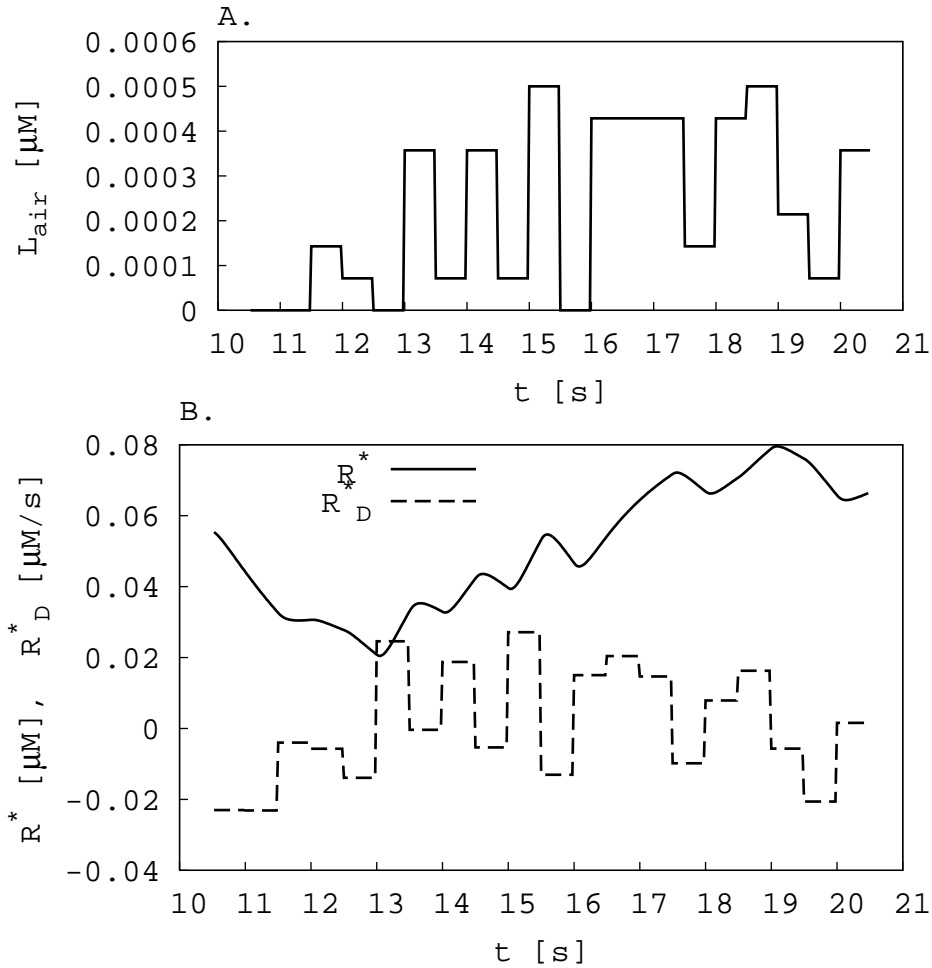


Fig. 4: Efficiency of the rate coding scheme for $\Delta t = 0.2$ s. Part A shows the spatio-temporal characteristic of the external stimulus $[L_{air}]$. Part B. compares the corresponding response $[R^*]$ and the averaged values $[R^*]_D$ of $d[R^*]/dt$. It can be seen that the rate coding scheme carries most of the information about the stimulus.

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