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Dose–Response Relationships in an Olfactory Flux Detector Model Revisited

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Abstract

A simple model of an odorant flux detector including odorant uptake, activation of odorant receptor molecules and enzymatic odorant deactivation can produce different types of static dose–response relationships. Depending on the binding characteristics of the odorant to the receptor molecule and to the deactivating enzyme, the receptor occupation by the odorant as related to the odorant uptake is quasi-hyperbolic, linear or, close to saturation, steeper than linear. In Rospars *et al*. (2003, Chem. Senses, 28: 509–522) a note contributed by both of us stated erroneously that an equation describing these relationships given previously (Kaissling, 1998, Chem. Senses, 23; 99–111; Kaissling, 2001, Chem. Senses, 26: 125–150) was incorrect. We show here that the difference in equations was due to a simplifying assumption in Rospars *et al*. (2003) about the deactivating enzyme, we summarize briefly the properties of the correct equation of Kaissling (1998, 2001) and we discuss the relation with the model studied in Rospars *et al*. (2003).

Key words: chemoreceptors, dose–response relationships, flux detectors, odorant deactivation, pulsed odorant stimulation, receptor occupation modeling

Model of a flux detector

Olfactory organs which adsorb from the air space but do not desorb odorant molecules need a mechanism for odorant deactivation in order to avoid accumulation of active stimulus molecules at the receptor cells. Here, we consider a network of chemical reactions including the uptake of the odorant or ligand L, its reversible binding to a receptor R, the reversible change of the complex LR to an activated state LR′ (Minor and Kaissling, 2003), a reversible binding of L to a hypothetical deactivating enzyme N, and an irreversible odorant deactivation by changing of the complex LN to P + N (Figure 1).

This is a slightly extended version of the network considered in Kaissling (1998, figure 7) where the activation of the complex LR was not included. In the 1998 network the deactivating enzyme was called E. The present network is a simplified version of the system of Kaissling (2001, figure 1) since the complex FB_{red} (Kaissling, 2001) of pheromone and binding protein (PBP) is considered here as ligand L and since the pheromone degrading enzyme is neglected. This simplification is possible since in the 2001 model the pheromone adsorbed by the olfactory hairs is rapidly bound to the PBP and thereby largely protected from degradation by a pheromone degrading enzyme. It should be noted that the degrading enzyme (called E in Kaissling, 2001) is not to be confused with the above deactivating enzyme N. The latter was postulated since the deactivation process shows significant saturation at high odorant uptake.

The concentration of the seven species or states considered are denoted between brackets: [L], [R], [LR], [LR′], [N], [LN], [P].

Dose–response relation at constant stimulation

The correct equation for static dose–response relationships is (cf. Kaissling, 1998, equation 18; 2001, equation 4)

$$\frac{[\mathrm{LR}']}{[\mathrm{LR}']_{\max}} = \frac{1}{\frac{K_{\mathrm{d3}}Q_4}{K_{\mathrm{m5,6}}}\left(\frac{k_6[\mathrm{N}]_{\mathrm{tot}}-1}{U}\right)+1} \quad (1)$$

with

$$[\mathrm{LR'}]_{\max} = (1-Q_4)[\mathrm{R}]_{\mathrm{tot}}$$

the maximum concentration of activated receptor LR′ (see Rospars *et al.*, 2003, equation B4);

$$K_{\mathrm{d3}} = k_{-3}/k_3$$

the dissociation constant of ligand and receptor;

$$\text{Uptake}: \quad L_{air} \longrightarrow L$$

$$\text{Activation}: \quad L + R \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} LR \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} LR'$$

$$\text{Deactivation}: \quad L + N \underset{k_{-5}}{\overset{k_5}{\rightleftarrows}} LN \xrightarrow{k_6} P + N$$

Figure 1 Model of reactions of a flux detector system. L_{air}, ligand in air space; L, ligand taken up, accumulating in the surrounding of the receptors; LR, ligand bound to receptor R; LR′, activated receptor–ligand complex; LN, ligand bound to enzyme N; P, deactivated ligand. Rate constants numbered after Kaissling (2001).

$$Q_4 = k_{-4}/(k_4 + k_{-4})$$

$$K_{m5,6} = (k_{-5} + k_6)/k_5$$

the Michaelis constant of ligand and deactivating enzyme;

$$[N]_{tot} = [N] + [LN]$$

the total concentration of deactivating enzyme;

$$[R]_{tot} = [R] + [LR] + [LR']$$

the total concentration of receptor molecules, where

$$[LR'] = [LR]k_4/k_{-4}$$

(see Kaissling, 2001, equation A26; Rospars *et al.*, 2003, equations B1 and B2); U, the odorant uptake (measured as concentration per s of odorant taken up);

$$U_{sat} = k_6[N]_{tot}$$

the odorant uptake at which $[LR] = [LR']_{max}$.

According to equation (1), the static value of $[LR']/[LR']_{max}$ depends on the uptake U and on the quantity

$$K = K_{d3}Q_4/K_{m5,6}$$

The dose–response relationships differ in three cases, $K < 1$ (receptors half-saturate at lower U than enzyme), $K = 1$ and $K > 1$ (enzyme half-saturates at lower U than receptors). The relationships for the three cases are shown in semilog (Figure 2a) and log–log plots (Figure 2b). For $U << U_{sat}$, the relationship between $[LR']$ and U is linear; in all three cases it is

$$\frac{[LR']}{[LR']_{max}} = \frac{U}{KU_{sat}}$$

The relationships differ from each other when U approaches U_{sat}. For $K < 1$ the relationship saturates similarly to a hyperbolic one, for $K = 1$ it remains linear, and for $K > 1$ it becomes steeper than linear. All dose–response curves end at $U = U_{sat}$ where N works with maximum velocity. At $U > U_{sat}$ the deactivation process is overloaded by the ligand. No equilibrium between odorant uptake and deactivation can be reached, and the ligand concentration [L] increases permanently.

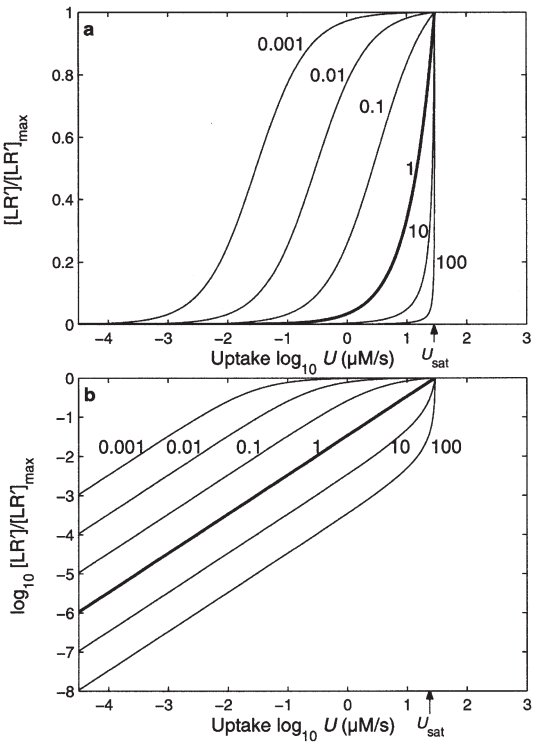

Figure 2 Plots of static dose–response curves according to equation (1). The relative number of activated receptor molecules $[LR']/[LR']max$ is plotted over the odorant uptake U in semilog **(a)** and double log **(b)** axes. The ratio $K = K_{d3}Q_4/K_{m5,6}$ is given besides each curve. For the values of $K < 1$, $K = 1$ and $K > 1$ the dose–response relationships are quasi-hyperbolic, linear and, close to saturation, steeper than linear, respectively. Parameter values: $[R]_{tot} = 1.64$ μM, $k_6 = 29.7$/s, $[N]_{tot} = 1$ μM, $U_{sat} = 29.7$ μM/s.

In Kaissling (2001) it was assumed that $K = 1$, i.e. that receptor molecules and deactivating enzyme half-saturate at the same ligand concentration. (The same relation holds true numerically in Rospars *et al.*, 2003.)

Dose–response at pulsed stimulation

In Rospars *et al.* (2003) the model of Kaissling (2001) was studied for examining its responses to pulsed stimulation. For simplicity it was assumed that the enzyme N is an 'external species, i.e. with constant concentration despite entering in different reactions, in contrast to R, whose free amount is decreased by bound and activated states' (Rospars *et al.*, 2003, p. 520). A similar assumption was made in the 'generalized flux detector' model in Rospars *et al.* (2000), an intermediate between concentration and flux

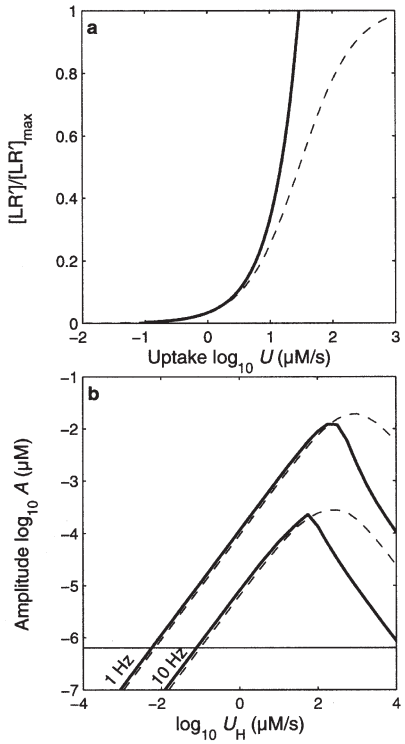

Figure 3 Comparison of the exact solution (thick solid line) and the approximated solution (dashed line) based on the simplifying assumption of constant free N, for $K = 1$ and constant **(a)** and periodic **(b)** stimulations. (a) Semilog plot of static dose–response curves, as in Figure 2a. The approximated solution differs from the exact one, given by equation (1), only by the absence of the –1 term in the denominator; see equation (B3) in Rospars *et al*. (2003). (b) Amplitude of the periodic oscillations of the activated receptor complex LR′ as a function of the height U_H (in μM/s) of periodic 20 ms pulses of ligand molecules, at 1 Hz and 10 Hz (cf. Rospars *et al*. 2003, figure 8A). The two solutions diverge at high uptake values, close to the maximum amplitudes. The horizontal line at $A = 10^{-6.2}$ μM corresponds to activation of a single receptor molecule. Parameter values: $[R]_{tot}$, k_6, $[N]_{tot}$, as in Figure 2; other parameter values, which play a role in (**b**), are the same as those determined in Kaissling (2001, figure 2): $k_3 = 0.209/(s.\mu M)$, $k_{-3} = 7.9/s$, $k_4 = 16.8/s$, $k_{-4} = 98/s$, $k_5 = 4/(s.\mu M)$, $k_{-5} = 98/s$, $K = 1$.

detectors. With this assumption (not made by Kaissling, 1998, 2001) an equation of the static dose–response relation similar to equation (1) was obtained, except that the –1 term was missing. This equation exclusively produces true hyperbolic dose–responses (Figure 3a, dashed line).

The exact solution and the approximated one (assuming N is an ″external species″) are compared for constant stimulations in Figure 3a, and for pulsed ones in Figure 3b. These figures show, as expected, that using the simplifying assumption affects the conclusions about the responses to both constant and pulsed stimulations but only at high values of stimulus uptake, i.e. when concentration of the complex LN becomes high. With constant stimulation the exact and approximated solutions are identical for uptake values U up to 5 μM/s. With periodic pulses of 20 ms duration, they are identical for pulse heights U_H up to 100 μM/s. In particular, the quantitative results given on the average concentration and amplitude of [LR′] under pulsed stimulation (50 ± 4 molecules at 2 Hz; see Rospars *et al.*, 2003, table 4) remain unchanged, the pulse height used being 0.1 μM/s. Therefore, whether N is considered as an external species or not, the conclusion that the network can resolve repetitive pulses at 2 Hz but not at 10 Hz still holds true.

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