

Olfactory Coding With All-or-Nothing Glomeruli

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Submitted 18 May 2007; accepted in final form 31 August 2007

Koulakov A, Gelperin A, Rinberg D. Olfactory coding with all-or-nothing glomeruli. *J Neurophysiol* 98: 3134–3142, 2007. First published September 12, 2007; doi:10.1152/jn.00560.2007. We present a model for olfactory coding based on spatial representation of glomerular responses. In this model distinct odorants activate specific subsets of glomeruli, dependent on the odorant's chemical identity and concentration. The glomerular response specificities are understood statistically, based on experimentally measured distributions of activation thresholds. A simple version of the model, in which glomerular responses are binary (the all-or-nothing model), allows us to account quantitatively for the following results of human/rodent olfactory psychophysics: 1) just noticeable differences in the perceived concentration of a single odor (Weber ratios) are as low as $dC/C \approx 0.04$; 2) the number of simultaneously perceived odors can be as high as 12; and 3) extensive lesions of the olfactory bulb do not lead to significant changes in detection or discrimination thresholds. We conclude that a combinatorial code based on a binary glomerular response is sufficient to account for several important features of the discrimination capacity of the mammalian olfactory system.

INTRODUCTION

Although the ability of the olfactory system to represent both the quality and intensity of odors has been thoroughly studied, the olfactory code remains unbroken. One of the main questions in studies of the sense of smell is how the odors are represented in the activity of central olfactory neurons. Experiments on anatomical connectivity (Axel 2005; Buck 2005; Grosmaître et al. 2006; Mombaerts 2004) and imaging of neuronal activity (Friedrich and Korsching 1997; Guthrie et al. 1993; Johnson et al. 1998; Meister and Bonhoeffer 2001; Rubin and Katz 1999; Uchida et al. 2000; Verhagen et al. 2007; Wachowiak and Cohen 2001; Xu et al. 2000) provide evidence for the spatial representation of olfactory information in the olfactory bulb (OB) (Adrian 1953; Kauer 1991; Shepherd 1994). Whether the information about odorants is relayed to higher brain areas in its spatial form or is translated by OB neurons into a more efficient representation, perhaps involving temporal correlations, is unclear. A definitive resolution of this question will allow investigators to directly probe neural representations of olfactory stimuli and ultimately build a testable model for the olfactory code.

Information about odorants in mammals is initially represented in the activity of olfactory receptor neurons (ORNs). Each ORN expresses one and only one type of olfactory receptor (OR) protein (Malnic et al. 1999; Rawson et al. 2000) whose binding specificity makes possible the recognition of a set of odorant molecules. ORNs can therefore be divided into classes expressing genetically distinct OR types. The number

of such types ranges from hundreds in humans to thousands in other vertebrates (Glusman et al. 2001; Man et al. 2004). All ORNs expressing the same gene for a particular OR protein project to one of two glomeruli, representing a convergence of many thousands of ORNs with identical ligand specificity onto the cohort of mitral/tufted cells within each glomerulus. The glomeruli in the olfactory bulb of mammals represent modules within which the first critical stage of olfactory information processing occurs. Glomerular processing is modified by several classes of local interneurons (Wachowiak and Shipley 2006) that can mediate center-surround inhibition to selectively enhance strong inputs and suppress weak inputs. The synaptic processing within the glomerulus of input signals from ORNs determines the rate and timing of action potentials by mitral/tufted cells, which carry the processed sensory signal to a variety of higher centers.

According to the spatial theory of odor coding olfactory information is represented in the spatial response patterns of glomeruli and their associated mitral/tufted neurons. Just as images on the retina evoke specific patterns of activation of retinal ganglion cells, different odorants are encoded in the spatial pattern of activity of mitral/tufted cells. Although the spatial code is simple it represents a powerful scheme, capable of encoding both intensity and quality of different odors, especially if different glomeruli are activated simultaneously in various combinations, leading to the notion of the combinatorial code (Firestein 2004; Khafizov et al. 2007; Mori et al. 2006).

As an alternative to the purely spatial coding hypothesis, a temporal theory of odor coding proposed that olfactory information is represented in the temporal pattern of neuronal spiking and/or in spiking synchronized to collective neuronal oscillations. Some implementations rely on the use of synchronization of spike timing with respect to the phase of oscillations (Brody and Hopfield 2003; Friedrich et al. 2004). Although evidence exists for the presence of correlations between mitral/tufted cell activity and local field potential oscillations (Bathellier et al. 2006; Galan et al. 2006; Hayar et al. 2005; Schoppa 2006), it is not clear whether this is how olfactory information is primarily transferred. The main argument in favor of the temporal coding theory is that coding in the temporal domain strongly increases the information capacity of the code. However, the information capacity of various types of olfactory codes has not been thoroughly investigated (Wilson and Mainen 2006).

In this study we investigate the discrimination capacity of the combinatorial spatial code. The main assumption we make

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is that the elementary unit of the olfactory code is the glomerulus. The mitral/tufted cells receiving excitatory inputs within the same glomerulus are assumed to send information into the olfactory cortex about how strongly a given glomerulus is activated. Alternatively, it could be possible that each mitral/tufted cell acts as an independent coder, making discrimination of odorant identity possible even within a single glomerulus. This hypothesis will not be pursued here.

Some evidence indicates that processing of sensory inputs within glomeruli can operate in an all-or-none fashion, particularly in the peri-threshold range of odorant concentrations (Chen and Shepherd 2005; Shepherd 2004). LeVetean and MacLeod (1966) recorded odor-elicited large-amplitude field potentials from the glomerular layer of the rabbit olfactory bulb. Application of repeated odorant stimuli produced field potential responses with an all-or-nothing character. Another line of evidence for all-or-nothing glomerular responses comes from studies of activity-dependent labeling of odorant-activated glomeruli with 2-deoxyglucose (Sharp et al. 1975; Stewart et al. 1979). At very low odor concentrations a small number of glomeruli responded but their labeling was found to be very dense. This is consistent with the hypothesis that glomerular activation can occur in an all-or-nothing manner, particularly in the range of odorant concentrations at or just above threshold. Therefore we will assume initially that glomeruli have binary responses and as such can be either active (ON) or inactive (OFF). This assumption is made to simplify the presentation of our results. Later we relax this assumption by allowing graded activation of a single glomerulus.

The assumption of binary glomerular activation puts a strong restriction on the olfactory code. Perhaps the only remaining feature of the code is its combinatorial complexity. Having made these assumptions we address several results of human and rodent olfactory psychophysics. We ask whether the odorant discrimination capacity observed in these experiments can be explained *only* based on the combinatorial olfactory code. A positive answer to this question will make a strong case for the parsimony of a spatial code. We will address experiments on the human Weber ratio (just noticeable relative differences in concentration) (Cain 1977), the robustness of olfactory discrimination to lesions observed in rodents (Bisulco and Slotnick 2003; Slotnick and Bisulco 2003), and the number of monomolecular odors that can be detected simultaneously (Jinks and Laing 1999). We select this particular set of experiments because they encompass olfactory tasks particularly relevant to the animal's behavior, such as detection of odors, detection of odor gradients, and recognition of odor components in mixtures. Also modeling of the outcomes of these experiments can be accomplished through statistical description of glomerular responses to individual odorants. The psychophysical sensitivities measured in these olfactory discrimination tasks are therefore related by our model to the parameters of statistical distributions of glomerular thresholds that could be assayed electrophysiologically, thus making our model falsifiable. Although we propose a combinatorial coding scheme as a parsimonious description of the system, we do not exclude the role of temporal coding. Therefore we build the case only for sufficiency of the combinatorial code.

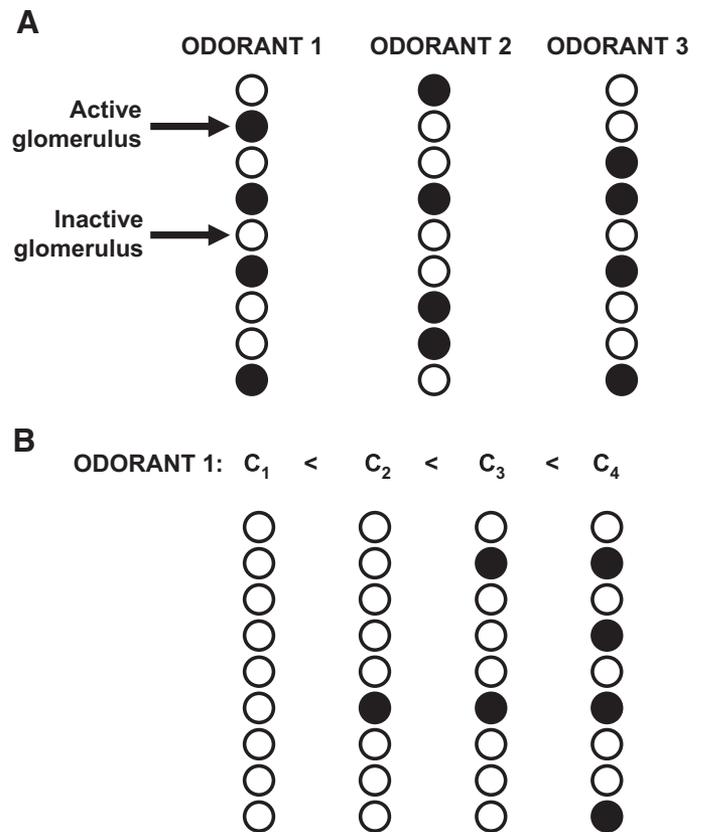


FIG. 1. Responses of independent glomeruli. *A*: different odors activate different subsets of glomeruli. *B*: increase in concentration of the same odorant leads to recruitment of additional glomeruli.

RESULTS

For the purposes of this study we define the glomerulus as a locus in the olfactory bulb that receives inputs from receptor cells expressing the same genetically distinct type of olfactory receptor. Thus two glomeruli receiving inputs from the same receptor neurons in two olfactory bulbs, left and right, will be included in the same independent glomerulus in our model. The number of independent glomeruli defined in this way is equal to the number of genetically distinct types of olfactory receptor proteins expressed by the receptor cells. For humans this number is about $N = 350$ (Glusman et al. 2001; Man et al. 2004; Menashe et al. 2006). For mice and rats the number of independent glomeruli is about $N = 1,000$ (Man et al. 2004; Zhang et al. 2004).

The glomerular responses in our approach are defined by the set of binary numbers r_i , where the index i runs from 1 to N . The numbers indicate whether a given glomerulus is activated ($r_i = 1$) or not activated ($r_i = 0$) by the odor. Note that we assume that a glomerulus carries one bit of information, but do not specify how information is transferred to other parts of the brain. Information transfer may be realized by modulation of the firing rate, changes in synchrony between mitral cells of the same glomerulus, or other means.

Different odors activate different subsets of glomeruli (Fig. 1A), thus resulting in combinatorial encoding of stimulus quality. For increasing concentration of the same odorant, we assume that glomeruli are sequentially recruited, i.e., the number of glomeruli that are active increases with increasing intensity of the stimulus. We therefore assume that no glomerulus can be

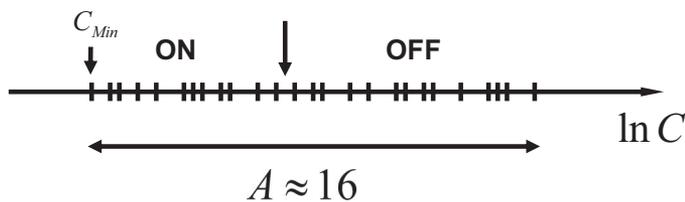


FIG. 2. Thresholds for activation of the set of glomeruli by a monomolecular odorant (vertical marks). For a given odorant concentration (longer vertical arrow) the glomeruli with smaller thresholds are active (ON). Width of the distribution of thresholds (in logarithmic scale) is $A \approx 16$. C_{Min} is the minimal glomerular threshold for this odorant. Note that some glomeruli represented by high thresholds may never be activated because these thresholds are above the saturated vapor pressure for this odorant (see text).

deactivated by an increased concentration of the same odor (Fig. 1B).

Our model can be restated in terms of the activation thresholds for the glomeruli. Thresholds $\theta_i(O)$ are defined as the concentrations of the odorant O at which glomerulus number i is activated. For each monomolecular odorant there is a set of N such thresholds, which completely define the response of our model olfactory system to that particular odorant. Indeed, for each value of concentration C the glomeruli satisfying $\theta_i(O) \leq C$ are activated (ON), whereas those with $\theta_i(O) > C$ are not active (OFF). A possible set of odorant thresholds is shown in Fig. 2. Following Hopfield (1999) we will assume that the thresholds are distributed uniformly on the logarithmic scale of concentration.

The width of the distribution of glomerular thresholds is defined by parameter A in our model (Fig. 2). One possible way to estimate the value of this parameter is to observe the recruitment of ORNs as a function of concentration. To interpret the data on ORN recruitment we will assume that receptor neurons expressing the same olfactory receptor are all activated at the same value of a monomolecular odor concentration, although this may not be universally the case (Grosmaître et al. 2006). The similarity in receptor neuron activation is consistent with the main postulate of our model according to which the elementary unit of olfactory response is the glomerulus. Therefore the differences in the responses of ORNs projecting to the same glomerulus could not be transmitted further or interpreted by the nervous system. It is assumed therefore that glomerular activation threshold is equal to the activation threshold for the ORNs projecting to this glomerulus. Because glomerular responses are identified in our model with the ORN responses one could use the range of activation of ORNs to determine parameter A . The data available for the rat show that about 36% of ORNs are recruited when the concentration varies within about 2.75 orders of magnitude (decimal logarithm units) (Duchamp-Viret et al. 2000). This number is obtained after averaging over several odorants. This recruitment rate corresponds to the full activation of 100% of cells within about 7.6 orders of magnitude of concentration. In natural logarithm units this range translates into the width of distribution of glomerular thresholds of about $A_{rat} = 7.6 \ln 10 = 17.6$. Interestingly, a similar estimate for the frog based on data in Duchamp-Viret et al. (2000) yields $A_{frog} = 14.2$. Thus this parameter has a potential to vary weakly between species. The results below are only slightly affected when the parameter varies between the frog and the rat values. Therefore in this study we will adopt a median value between the rat and the

frog $A = 16$ that corresponds to about 7 orders of magnitude in decimal logarithm units. It is interesting that a similar value of 6 orders of magnitude of concentration is observed for the width of distribution of human psychophysical thresholds for detection of different odors (Devos and Laffort 1990; Walker et al. 2003). It appears that various behaviorally relevant variability ranges are in close agreement with each other.

Our model thus has two essential numerical parameters: the number of independent glomeruli N , which is variable from species to species, and the dynamic range of the olfactory system $A \approx 16$. Using these two parameters we address below several psychophysical experiments.

Just noticeable changes in concentration

We will first deduce the Weber ratio [the just noticeable difference (JND) in relative concentration]. For a given concentration C the fraction of glomeruli whose thresholds are below C is $(\ln C - \ln C_{Min})/A$, as illustrated in Fig. 2. Here C_{Min} is the minimum glomerular threshold for a given odorant introduced in Fig. 2. The total number of recruited glomeruli (in the ON state) is therefore

$$n = N \frac{\ln C - \ln C_{Min}}{A} \quad (1)$$

To determine JND in concentration we note that in the all-or-nothing model the change in concentration is detected if it leads to the recruitment of at least one new glomerulus. The condition $\Delta n = 1$ leads in combination with Eq. 1 to the following expression for the Weber ratio

$$\frac{\Delta C}{C} \approx \Delta \ln C = \frac{A}{N} \quad (2)$$

In other words the Weber ratio is equal to the average distance between neighboring thresholds on the logarithmic scale of concentrations. The estimate for the value of the Weber ratio for humans can be obtained by taking $N = 350$ and $A \approx 16$, which results in $\Delta C/C \approx 4.6\%$. This result compares favorably with experimental findings of Cain (1977), who measured $\Delta C/C$ to be in the range between 4 and 16%. In particular, when an odorant was delivered using an air-dilution olfactometer, the Weber ratio could reach 4.2% (see Fig. 3 in Cain 1977).

In deriving the expression for the Weber ratio we assumed that a change in the activation of a single glomerulus is sufficient to detect a change in odorant concentration. For the purely ON-OFF model this is the minimum possible detectable response, which implies that we have used the ideal observer in our estimate. We then asked how much our result would change if activation of more than one glomerulus was necessary to evoke a psychophysical response, i.e., that the glomerular array is considered by a nonideal observer. Thus we obtained the result for the Weber ratio in the case when JNDs in the number of active glomeruli is given by $\Delta n \neq 1$. In this case an analog of Eq. 2 can be derived

$$\frac{\Delta C}{C} \approx \frac{A}{N} \Delta n \quad (3)$$

This equation implies that if, say, detection of activation of two glomeruli is necessary to evoke psychophysical response

($\Delta n = 2$) the Weber ratio is twice as large as in the purely ON-OFF case ($\Delta n = 1$).

Effects of bulbar lesions

We will next examine the effects of lesions of the olfactory bulb on the detection of odors. Experimental studies suggest that extensive bulbar lesions lead to no significant effect on detection and discrimination of odors (Bisulco and Slotnick 2003; Slotnick and Bisulco 2003). Here we suggest that this conclusion follows naturally from the ON-OFF model. The model therefore reproduces the observed robustness of olfactory discrimination after lesions of the olfactory bulb.

Consider the detection task first. The presence of the odorant is detected in our model if at least one glomerulus is activated. The minimal perceived concentration is therefore determined by the minimum value in the set of N thresholds $\theta_n(O)$ for different glomeruli (Figs. 2 and 3). If the lesion removes a fraction f of all glomeruli, chosen randomly, the minimum threshold shifts to the next lowest available threshold, which is spared by the lesion. The average shift in the detection threshold is given by

$$\frac{\Delta C_{Min}}{C_{Min}} = \frac{A}{N} \frac{f}{1-f} \tag{4}$$

For a 50% bulbar lesion (50% of glomeruli are removed, $f = 0.5$) it coincides with the Weber ratio given by Eq. 2, which for rats is equal to $\Delta C/C = 0.016$ in this model ($N = 1,000$). The shift in the detection threshold given by Eq. 4 is indeed insignificant, which renders the olfactory system robust to lesions. The robustness stems from the broad tuning of different glomeruli: If some of them are removed, others can still detect an odorant.

The ability to detect a given odorant implies that two different odorants can be discriminated in this model. Indeed, if each odorant is presented at the perceptual threshold, it will activate a single glomerulus. By detecting which glomerulus is active an ideal observer could infer what odorant is present. If

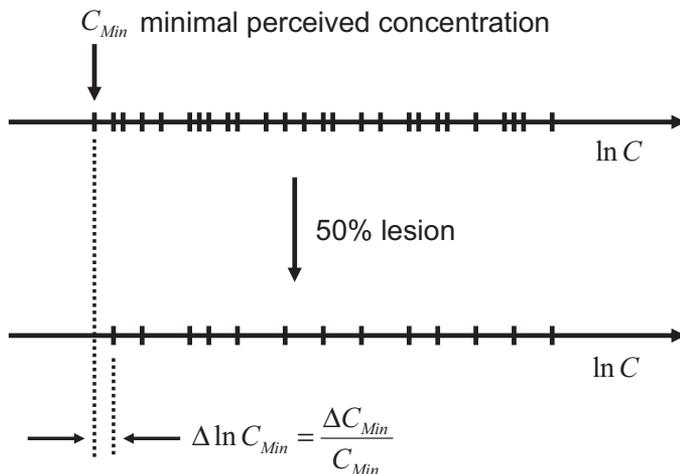


FIG. 3. Robustness of a combinatorial code to lesions. Detection threshold for a given odorant is determined by the minimum threshold out of the set of N different glomeruli. A lesion of the olfactory bulb removes a subset of the glomeruli. Detection threshold in the lesioned bulb is determined by the next lowest available threshold that survives the lesion. Shift in the detection threshold due to a lesion is small and is of the order of the Weber ratio.

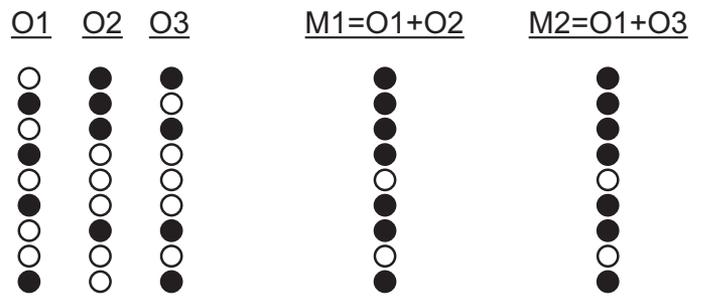


FIG. 4. Responses to mixtures in the ON-OFF model. Responses of glomerular array to the mixtures are given by the maximum over the responses to individual components, reproducing hypoadditivity observed in the majority of olfactory neurons (Duchamp-Viret et al. 2003). Three monomolecular odorants mixed in different combinations (M1 and M2) evoke the same response in the glomerular array, leading to the failure to identify the presence of the individual components in the mixture.

more than one glomerulus is activated by each odorant, discrimination becomes more reliable. Thus from the standpoint of the ideal observer used in this model, both detection and discrimination are equivalent and robust to lesions.

Number of components in the mixture that can be detected

We will now address the number of monomolecular odorants that can be identified simultaneously in our model. The basic problem with identifying monomolecular odorants in the odor mixture is illustrated in Fig. 4. Assume that the subject is presented with a mixture of two odorants: O1 and O2. This mixture is identified as M1 in Fig. 4. A possible response of the glomeruli to the mixture includes a maximum of the glomerular activation evoked by either O1 or O2 when presented separately. This form of additivity between components of odor mixtures is observed in 60–70% of ORNs and is called *hypoadditivity* (Duchamp-Viret et al. 2003), a term derived from prior psychophysical studies of odor intensity in single compounds and odor mixtures (Cometto-Muniz et al. 1999; Laska and Hudson 1993). In the case of hypoadditivity the response of a glomerulus to the mixture of odorants is equal to the maximum of the responses of this glomerulus to components of the mixture measured individually, i.e., when no other components of the mixture are present.

For binary glomeruli, hypoadditivity is equivalent to calculating a logical *or* function over binary strings representing responses of glomerular arrays to individual components. Logical *or* function is defined as the maximum of two or more binary (Boolean) variables (Quine 1982), representing, e.g., the activation of individual glomeruli to individual mixture components. Throughout the remainder of the paper we will use hypoadditivity to describe responses to mixtures. The impact of other forms of additivity, such as synergy and suppression, which are observed in fewer ORNs (Duchamp-Viret et al. 2003), is discussed in the supplementary materials.¹

When the subject is presented with another mixture M2, in which O2 is replaced by O3, the pattern of activation may be exactly the same as in the response to M1 (Fig. 4). In this event the presence of O2 cannot be distinguished reliably from O3 in the mixture. The quantitative question that arises in this case is at what number of monomolecular odorants in the mixture such ambiguity may arise.

¹ The online version of this article contains supplemental data.

To identify the number of monomolecular odorants at which the ON-OFF model fails to differentiate the presence of one of them in a mixture we notice the following condition in Fig. 4. If one adds O2 to mixture M2, the glomerular response is unchanged. This implies that *no* glomeruli are recruited by adding an extra odor to the mixture. The failure of the observer to identify an extra odor occurs when $\Delta g < 1$, where Δg is the average number of glomeruli recruited by the new odor.

Consider a mixture of S odorants. Our goal is to determine the number $g(S)$ of glomeruli activated by this mixture on average. We will then use the criterion $\Delta g \equiv g(S + 1) - g(S) < 1$ to determine at what number of odorants S the olfactory system fails to detect the presence of individual components, as discussed in the previous paragraph. To accomplish this goal we will relate $g(S)$ to the number of glomeruli $g(S + 1)$ active when another component, called O , is added to the mixture. Assume that the component O , when present alone, activates n glomeruli. In the presence of other odorants the number of newly recruited by component O glomeruli is expected to be smaller than n . Indeed, other components of the mixture activate a fraction $x = g(S)/N < 1$ of all glomeruli, and xn of the glomeruli recruited by the component O . The latter glomeruli are already activated by the mixture and cannot be recruited by O . Therefore one expects that the number of glomeruli newly recruited by O is $n - xn$ rather than n . The equation that determines the rate of recruitment when new components are sequentially added to the mixture is

$$g(S + 1) = g(S) + n - xn \quad (5)$$

Using $x = g(S)/N$ this equation can be solved to result in the number of glomeruli recruited when an S component mixture is presented

$$g(S) = N \left[1 - \left(1 - \frac{n}{N} \right)^S \right] \quad (6)$$

Here n is the average number of glomeruli activated by a single monomolecular odorant, given by Eq. 1. This number is assumed to be similar for different components. A more general equation, which includes a possibility of different numbers of glomeruli activated by each component n_s , is

$$g(S) = N \left[1 - \prod_{s=1}^S \left(1 - \frac{n_s}{N} \right) \right] \quad (7)$$

Here the product is taken over all components present in the mixture.

As we mentioned, the olfactory system described here fails to detect a substitution of one of the odors if $\Delta g \equiv g(S + 1) - g(S) < 1$. Using Eq. 6 we obtain from this condition the maximum number of odorants in the mixture which can be detected

$$S^* = \frac{\ln n}{\ln [N/(N - n)]} \quad (8)$$

Equation 8 is illustrated in Fig. 5A (solid line).

We will now examine the maximum number of detectable components in the intermediate range of concentrations. In this case, as follows from Eq. 1, single components activate a small fraction of the bulb, i.e., $n \ll N$. In this regime the maximum number of components Eq. 8 becomes

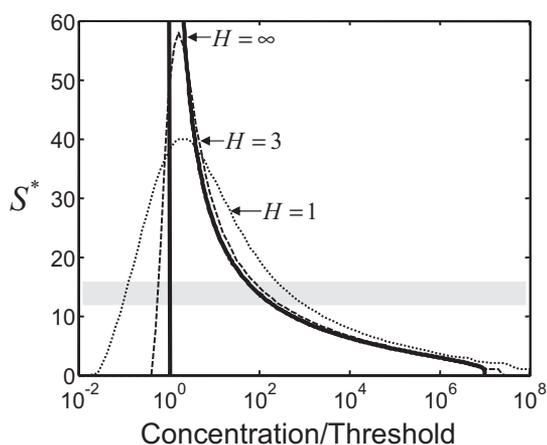


FIG. 5. Maximal number of components in a mixture that permits detection of a single component. Horizontal axis represents the ratio of the concentration and the detection threshold for each individual component in the mixture that is equal to the minimum glomerular threshold for this component. Note that the absolute value of the detection threshold may be different for different odorants as observed in Devos and Laffort (1990). Solid line shows the results for the ON-OFF model (Eq. 8). Results for the models involving graded glomerular activation are shown by the dashed (Hill coefficient $H = 3$) and dotted ($H = 1$) lines for comparison. Experimentally observed range of values is shown by the gray region.

$$S^* \approx \frac{N}{n} \ln n = A \frac{\ln(A^{-1}N \ln [C/C_{Min}])}{\ln [C/C_{Min}]} \quad (9)$$

The magnitude of the maximum number of odorants is therefore determined by the dynamic range of the natural logarithm of distinguishable concentrations $A \approx 16$, which corresponds to about 7 orders of magnitude of concentration.

Experimentally the maximum number of monomolecular odorants in a mixture at which the presence or absence of a single component can be detected is between 12 and 16 (Jinks and Laing 1999). In these experiments mixtures of ≤ 16 monomolecular odorants were presented to human subjects. The concentrations of the individual components were chosen so that their perceived intensities were similar, leading to the conclusion that the number of activated glomeruli was approximately the same in the framework of our model. A single most familiar component of the odor mixture was replaced with a different randomly chosen odor and the human subject was asked to press a “yes” or “no” button on the computer screen indicating whether the selected component is present. The performance of the subjects fell to a chance level between 12 and 16 components in the mixture. From the perspective of the ON-OFF model this number is consistent with the concentration of individual components of about 10^2 times the threshold for detection (Fig. 5). Our model predicts that with increasing concentration of individual odorants, the number of detectable components should decrease. The overall order of magnitude of the number of odorants detectable in a mixture is determined by the natural logarithm of the range of concentrations distinguished by the olfactory system, which is given by the parameter $A \approx 16$ (see Eq. 9).

What happens if a change in activation of $\Delta n > 1$ glomeruli is needed to detect a substitution of a monomolecular odor component in the mixture (compare with Eq. 3)? The number of components in the mixture at which a psychophysical detection threshold is reached in this case is given by an expression similar, but more general than Eq. 8

$$S^* = \frac{\ln(n/\Delta n)}{\ln[N/(N-n)]} \quad (10)$$

The number of components at which the psychophysical detection of single added odors falls to chance thus depends logarithmically on the detectable change in the activation of glomeruli Δn . This dependence is weaker than that of the Weber fraction (Eq. 3), which was directly proportional to Δn . We conclude that the maximum number of components at which replacement of a single component in the mixture can be detected is weakly dependent on the number of glomeruli that are needed to cause a psychophysical response and is mostly determined by parameter $A \approx 16$, especially in the intermediate range of concentrations.

Graded glomerular response

Here we will find the conditions under which glomerular responses can be considered binary. To account for the graded nature of the response of glomerulus number i as a function of concentration $r_i(C)$ we assume that it is described by the Hill equation

$$r_i(C) = \frac{C^H}{C^H + (K_i)^H} = \frac{1}{1 + e^{H(\ln K_i - \ln C)}} \quad (11)$$

Here H and K_i are the Hill exponent and the saturation concentration, respectively, for this glomerulus. We normalized the response by the maximum value to make a comparison with the ON-OFF case easier. Saturation concentration K_i is defined here as the concentration of the odorant at which glomerular response is equal to one half of the maximal value.

The second equality in Eq. 11 emphasizes that as a function of the logarithm of concentration the Hill equation actually takes the form of a logistic function. The steepness of the logistic function is determined by the Hill exponent: The response increases from 0 to 1 within the range of the logarithm of concentration proportional to $1/H$. As the Hill exponent increases the glomerular response becomes sharper, until, in the limit $H \rightarrow \infty$, it becomes infinitely sharp, as in the ON-OFF model considered earlier. At what value of the Hill exponent can one consider the conclusions of the ON-OFF model to be valid?

To make a connection to the ON-OFF model we construct the integrated population response, which represents the number of active glomeruli in the case of graded responses (Firestein et al. 1993; Meister and Bonhoeffer 2001; Wachowiak and Cohen 2001)

$$n = \sum_{i=1}^N r_i(C) \quad (12)$$

The glomeruli whose saturation concentration K is far below C contribute unity to the sum, thus playing the role of ON units. Glomeruli, for which C is much smaller than the threshold, contribute little to the population activity, playing the role of OFF units (Fig. 6). The graded contribution between 0 and 1 is expected for glomeruli in the range of $\ln K$ of width $1/H$ around the current value of logarithm of concentration (Fig. 6). A glomerulus therefore gets recruited when the odorant concentration passes the neighborhood of the saturation concentration. Thus in the case of graded glomerular responses, the saturation

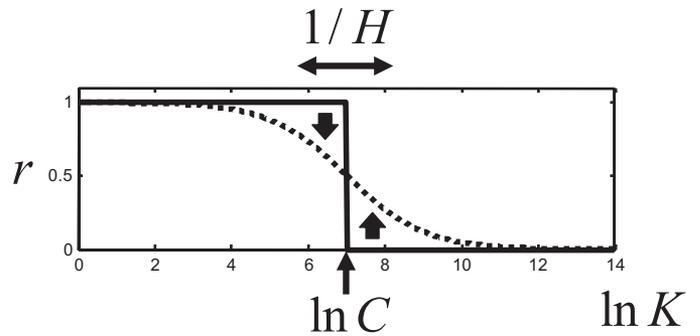


FIG. 6. Response of a population of glomeruli to an odorant at concentration C as a function of the saturation concentration K . Solid line: responses in the ON-OFF model (Hill coefficient $H \rightarrow \infty$). Dotted line: responses for $H = 1$ (Eq. 11). Total integrated response of the population is the same for the cases illustrated by dotted and solid lines. This is because changes in response are of the opposite sign for glomeruli whose saturation concentrations are above and below the odorant concentration (up and down arrows). For this reason the ON-OFF model is valid to describe the population response when the condition represented by Eq. 13 is satisfied.

concentration K plays the role of threshold for glomerular activation. When the summation in Eq. 12 is evaluated for the pure ON-OFF model ($H \rightarrow \infty$), it renders the number of active glomeruli similar to Eq. 1. If one considers the case of $H \sim 1$ one notices that the total population activity given by Eq. 12 does not differ much from the pure ON-OFF case ($H \rightarrow \infty$). This is because the contribution from suprathreshold glomeruli is lowered (Fig. 6), whereas the subthreshold glomeruli contribute more, leading to compensation and no substantial change in the integral population activity due to the finite Hill coefficient. This cancellation is possible if the range of thresholds for glomerular activation A is substantially larger than the range of graded response for a single glomerulus $1/H$

$$A \gg 1/H \quad (13)$$

In other words, the dynamic range for the entire population should substantially exceed the dynamic range for a single detector. If this condition is satisfied the ON-OFF model captures the essential behavior of the population activity. For the activation thresholds distributed within 7 orders of magnitude in concentration ($A \approx 16$) and the Hill coefficients ranging between about 0.5 and 4.4 (Firestein et al. 1993; Wachowiak and Cohen 2001) one expects the condition Eq. 13 to be met and the ON-OFF model to accurately represent the population activity even if the glomerular responses are graded.

We also examined the effects of graded glomerular responses on the number of components in a mixture that can be detected. To this end we evaluated the change in the response of the glomerular array caused by the replacement of a single component. The response to individual components was described by Eqs. 11 and 12. As in the ON-OFF case we assumed that the activation pattern for a mixture is given by the maximum over the responses obtained for individual components, which corresponds to hypoadditivity (Duchamp-Viret et al. 2003). We also assumed that substitution of a component can be detected if the total variation of the glomerular response vector is equal to one, similar to the pure ON-OFF case. Of course, the variation in the total response vector in the continuous case can be below or above one and becomes an additional parameter of the model. We have chosen this variation to be one to make a comparison to the pure ON-OFF case. The

critical number of components discriminated in a mixture obtained under these conditions is shown in Fig. 5 by the dashed ($H = 3$) and dotted ($H = 1$) lines. The main effect of graded glomerular responses is in smearing the ON-OFF dependence by approximately $1/H$. For moderate concentrations of components the analytical result (Eq. 8) gives an adequate approximation to the results obtained in the case of graded glomerular responses. We conclude that the ON-OFF model may give a good approximation for the number of components in the mixture that can be detected even if the actual responses of glomeruli are graded. Also, except for the small range of the values of components' concentration around threshold for detection, the ON-OFF model underestimated the number of components that can be detected (Fig. 5). This is because additional information about the mixture composition was provided by the graded responses of glomeruli.

Experimental predictions

The first prediction of our model pertains to the experiments with bulbar lesions. Although we argued that shifts in the detection threshold due to lesions are small (Eq. 4) our model predicts that the Weber fraction may be substantially increased. Indeed the Weber fraction according to Eq. 2 is inversely proportional to the number of available glomeruli. A 50% random lesion will therefore lead to an increase in the Weber fraction by a factor of 2. Similarly, a 90% indiscriminate lesion will result in a tenfold increase in the just noticeable differences in concentration. We suggest that these effects could be observed in psychophysical measurements in surgically manipulated rats.

In the experiments with odor mixtures our model predicts that with increasing concentration of individual monomolecular components, the number of detectable odors should decrease. This prediction is evident from Fig. 5.

When the method of information transmission by the mitral cells is established, the values of the parameters of our model could be confirmed electrophysiologically. Thus the distribution of glomerular thresholds could be assessed from experimental measurements of the activation thresholds for individual mitral cells. To this end the responses of mitral cells as functions of odorant concentration could be fitted with the Hill equation (Eq. 11). In the previous section we suggested that in the case of graded glomerular response the role of activation thresholds is played by the saturation concentration K . The distribution of concentration thresholds for different mitral cells could be used to verify the linear recruitment of mitral cells with the logarithm of concentration. The width of the distribution interval A could be confirmed to have the value of about 16 accepted in this study. Such electrophysiological observations could be used to confirm the assumptions about the statistical features of the olfactory code that are used in our model.

DISCUSSION

In this work we examine a simplified model for olfactory coding involving ON-OFF glomeruli. The detection of odor concentration and composition in this model is possible by examining binary strings, representing glomerular response patterns. Our study therefore examines the purely combinato-

rial component of the olfactory code. We conclude that the results of psychophysical studies probing the discrimination capacity of human and rodent olfactory systems can be understood on the basis of this simplified model. In some cases, such as human Weber ratios, the simplified model predicts a somewhat better performance than displayed by humans (Eq. 2; Cain 1977). We thus suggest that a spatial combinatorial code is sufficient to explain the discrimination capacity of human/rodent olfaction.

There are olfactory psychophysics results different from the three phenomena we choose to relate to our model (Cain 1988; Doty and Laing 2003). Human odor detection thresholds vary over several orders of magnitude (Cain 1988; Devos and Laffort 1990; Walker et al. 2003) and are significantly lower than the odor identification threshold (Hummel et al. 2006; Keller and Vosshall 2004). Interactions among components of binary odorant mixtures are frequently nonlinear. The mixture may smell more intense than the stronger component sampled alone, may smell intermediate in intensity between the two components sampled alone, or may smell less intense than the weaker component sampled alone (Cain et al. 1995; Lawless 1997; reviewed in Wise et al. 2007). In addition, there are important effects of the temporal parameters of odor sampling relative to the respiratory or sniffing cycle (Johnson et al. 2006; Mainland and Sobel 2006; Verhagen et al. 2007). Finally, humans cannot reliably identify the odors of components of mixtures containing more than three compounds (Goyert et al. 2007; Jinks and Laing 2001).

We selected three phenomena among the array of results in olfactory psychophysics because our theory is statistical in nature and relates most directly to data sets where large numbers of odors and subjects have been tested and quantitative data reported. Studies using small sets of odors and subjects may contain perceptual results—unique to the set of odors or panel of subjects tested—that are not represented in our theory in its present form. In further work we will attempt to extend our theory to a larger set of psychophysical results.

In estimating the range of glomerular threshold distribution A we have made several assumptions. First, we extrapolated glomerular recruitment rate from lower to higher concentrations. If, for example, the recruitment rate were significantly lower for higher odorant concentrations than our estimate one would expect a larger, $A = 16$ value of the distribution width. Relaxing this assumption, however, will not appreciably affect our results because they rely on the recruitment rate at the lower odorant concentrations, for which the experimental evidence in Duchamp-Viret et al. (2000) is available. Another assumption pertains to a lack of sampling biases in assaying the ORN responses. We assumed in particular that the ORNs recorded in Duchamp-Viret et al. (2000) represented many different glomeruli taken randomly. This assumption was based on the broad spatial distribution in the nasal cavity of ORNs projecting to the same glomerulus. Alternatively, the sampling of ORNs in Duchamp-Viret et al. (2000) could reflect a bias toward certain groups of glomeruli. In this case two dramatically different options are available. First, it is possible that the particular group of glomeruli for which recordings of ORNs have bias is not particularly different from other glomeruli in terms of their affinity to the tested odorant. In this case it is possible to accept the estimate of $A = 16$ obtained for this particular group as representative for the entire population.

In the other extreme, the sampled group of glomeruli belongs to the population with a particular range of affinities to the given odorant. If this range is not overlapping with other glomerular groups, our estimate for the width of distribution is expected to be lower than the actual value.

Duchamp-Viret et al. (2000) reported that odorants delivered at the saturated vapor pressure activate only about 50% of ORNs in the rat. This feature can be incorporated in our model if about 50% of glomerular thresholds in Fig. 2 are above the saturated vapor concentration. Because parameter $A = 16$ is used in this study to calculate the rate of recruitment of glomeruli by odorants, our model does not require that the entire dynamic range is actually exploited by the olfactory system. On the contrary, that only a fraction of glomeruli are active makes a combinatorial encoding of odorants possible even at the saturated vapor pressure. This allows different odorants to smell differently when they are delivered at the maximal concentration (Gross-Isseroff and Lancet 1988). When 50% of glomeruli are active, the binary glomerular code allows representation of the maximal number of combinations and thus encoding the maximal number of odorants.

Additional features can be added to our model for a spatial code, such as more complex interactions between mixture components. In this case the olfactory code is expected to become more powerful and the discrimination capacity should increase. Our estimates therefore provide lower bounds for the discrimination capacity of the spatial code. Because these lower bounds appear to be in good agreement with experiments, the spatial code provides a both simple and powerful scheme for representing olfactory information.

ACKNOWLEDGMENTS

We thank G. Shepherd, C. Stevens, and P. Wise for helpful comments on some of the issues in the paper.

GRANTS

This work was supported by grants from the Whitehall Foundation to A. Gelperin and D. Rinberg.

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