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A Computational System for Simulating and Analyzing Arrays of Biological and Artificial Chemical Sensors

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Abstract

We have designed an approach for modeling olfactory pathways by which one can explore how the properties of individual receptors affect the information coding capacity of an entire system. The effect of receptor tuning breadth on system performance was explored explicitly. We presented model sensory arrays with sets of stimuli randomly and uniformly distributed in an 'olfactory space'. Arrays of uniformly sized model receptors responding to 25–35% of the stimuli gave the best performance as measured by the ability to capture the most information about the stimulus set. Arrays of variably sized model receptors that were both more broadly and more narrowly tuned than this optimum could, however, perform better than uniform arrays. This method and the results obtained using it suggest a framework for considering the growing body of evidence on the functional properties of individual olfactory receptor and relay neurons from a systems coding perspective.

Introduction

The peripheral olfactory system consists of a large, diverse array of sensory neurons and first-order relay neurons, each of which responds to many different stimuli (Gesteland *et al.*, 1965; Getchell, 1974; Duchamp *et al.*, 1974; Revial *et al.*, 1978, 1982; Wellis *et al.*, 1989; Mori *et al.*, 1992; Sato *et al.*, 1994; Hirono *et al.*, 1994; Bozza and Kauer, 1998; Malnic *et al.*, 1999). In the olfactory epithelium, single, mono- molecular stimuli elicit time-varying changes in the activity levels of a population of olfactory receptor neurons (ORNs) (Revial *et al.*, 1978, 1982; Sicard, 1986; Sato *et al.*, 1994; Youngentob *et al.*, 1995; Duchamp-Viret *et al.*, 1999; Vogler and Schild, 1999). The axons of these primary sensory neurons project to the olfactory bulb, where they segregate according to which olfactory receptor (OR) protein they express (Mombaerts *et al.*, 1996). In the olfactory bulb, ORNs synapse directly onto mitral/tufted (M/T) cells, the output cells of the olfactory bulb, as well as onto periglomerular interneurons. A substantial fraction of the output cells also appear to be involved in representing each stimulus by modulating their activity over time (Kauer, 1974b; Meredith and Moulton, 1978; Harrison and Scott, 1986; Hamilton and Kauer, 1989; Wellis *et al.*, 1989; Wellis and Scott, 1990; Imamura *et al.*, 1992; Mori *et al.*, 1992; Katoh *et al.*, 1993; Cinelli *et al.*, 1995). The representation of stimuli across such broad arrays of neurons is an example of a distributed or population code (Kauer, 1987, 1991; Schild, 1988; Buck, 1996; Laurent, 1997, 1999; Hildebrand and Shepherd, 1997; Mori *et al.*, 1999; Christensen and White, 2001; Kauer and White, 2001). The fundamental property of this type of coding is that the ability of the entire system to make fine discriminations depends not on any single component, but, rather, how an animal perceives its chemical environment emerges from a synthesis of information from many components at each level of the pathway. This coding paradigm has the advantage of accounting for not only the physiological data described above, but also for a number of other olfactory system characteristics, including plasticity and tolerance of large lesions (Lu and Slotnick, 1998). In attempting to understand how a coherent odor perception emerges from this representation, one is presented with the challenge of formally relating the response properties of individual neurons to the global, system-wide representation (Schild, 1988; Rolls *et al.*, 1996; Alkasab *et al.*, 1999).

What methods can be used as the basis for describing such relationships? One candidate approach is information theory (IT), which uses Bayesian reasoning to quantitatively assess the contributions of individual elements to overall system representations. IT was originally developed to quantify data transmission over noisy electrical channels (Shannon and Weaver, 1949), but since it provides a methodology for measuring the statistical relationship between two systems, the theory has been successfully used to study encoding of sensory information in neural systems (Bialek *et al.*, 1991; Theunissen and Miller, 1991; Atick *et al.*, 1992; Abbott *et al.*, 1996; Rolls *et al.*, 1996; Yamada *et al.*, 1996; Rieke *et al.*, 1997; Maynard *et al.*, 1999). IT techniques have been applied most often to analysis of the fine temporal

structure of sequences of action potentials [as reviewed by Borst and Theunissen (Borst and Theunissen, 1999)], but they have also been used to explore distributed coding (Theunissen and Miller, 1991; Brunel and Nadal, 1998; Maynard *et al.*, 1999; Eurich and Wilke, 2000). Both its quantitative nature and its ability to characterize relationships among numerous component elements recommend IT analysis to the study of olfactory coding (Alkasab *et al.*, 1999). Here, we examine how an IT approach may be used to measure the degree to which receptors in biological systems or sensors in artificial systems contribute to the overall performance of olfactory arrays.

In this paper, we establish a theoretical framework and modeling approach for simulating arrays of chemosensors, modeling their responses to stimuli and quantitatively assessing the coding capacity of the array using IT measures. Using these methods, we can explore how the properties of idealized individual sensors that model biological ORNs affect the distributed representation of an entire array. By systematically changing model sensors and quantifying array performance, we have begun to characterize some of the possible relationships between one sensor property—breadth of tuning—and the representation of odorant stimuli by the entire olfactory receptor array. This method also potentially offers an approach for quantifying how measured response profiles of individual biological ORNs represent fundamental properties of the chemical world.

Methods

Models of odorant stimuli

The difficulty in describing the crucial physico-chemical properties that define chemical stimuli as odors has long hampered our understanding of olfactory systems. A particular difficulty has been discovering which combinations of physical parameters of odorant molecules (e.g. molecular weight, polarity, charge, chemical structure, or more complex properties based on reactivity) determine ORN response. These parameters are expected to be different for neurons expressing different olfactory receptor proteins. As a simplified example, an ORN with responses that vary with changes in the polarity of a stimulus molecule may be indifferent to the charge or molecular weight of the stimulus, while the responses of another ORN may change with another aspect of molecular structure. For biological ORNs, it seems most likely that these parameters will correspond to complex combinations of physico-chemical properties which determine the interaction between an odorant and the OR protein. No comprehensive set of parameters has yet been found for all odorant sets, although changes in responses with changing carbon chain length appear to be relevant for some ORNs and second-order neurons (Imamura *et al.*, 1992; Katoh *et al.*, 1993; Sato *et al.*, 1994; Yokoi *et al.*, 1995; Zhao *et al.*, 1998; Rubin and Katz, 1999; Uchida *et al.*, 2000).

We do not yet know even the number of parameters needed to characterize general olfactory stimuli. However, we can estimate certain bounds on this dimensionality for biological olfactory systems. Attempts to find stimulus parameters that account for frog and zebrafish neuronal responses to limited odorant sets have met with some success (Revial *et al.*, 1983; Sicard and Holley, 1984; Friedrich and Korsching, 1998). These studies, which have used variations of principal component analysis applied to single unit responses, suggest that there are at least three relevant parameters in the studied systems, although these methods do not identify the physical parameters themselves. At the other extreme, the number of different OR genes in rodents may be as large as 1000 (Ressler and Sullivan, 1993), although it is not yet known how many of them are expressed at any one time. If each OR type corresponds to its own independent parameter and if ORNs are simply active or inactive, an olfactory system could describe 2^{1000} different stimuli, which is more than the estimated number of atoms in the universe (Dyson, 1979). Thus, it is unlikely that the responses of neurons expressing different receptors are completely independent of one another. It is reasonable, therefore, to propose that the dimensionality of 'olfactory space' is greater than three, but much less than 1000.

Given the uncertainty about the sizes, shapes and dimensionalities of olfactory space, we have made a number of assumptions for the present discussion. We created a generalized framework for modeling odorants and olfactory receptors, and have used IT analyses to examine some of the properties of their interactions. We begin by describing a set of stimuli in which each model odorant is represented by a point in a multi-dimensional experimental space (see Figure 1). This space is intended to model olfactory 'odorant space', not perceptual 'odor space'; that is, its dimensions are the set of physical parameters of stimuli which determine the response profiles of the sensors rather than behavioral dimensions (though in other experiments, analogous analyses might be performed in a perceptual space). Each stimulus in our model is specified by the values of these parameters, just as each odorant is defined according a set of physical parameters. In our simulations, we have used a three-dimensional experimental space, but the technique is not limited to this number: spaces of two, four or more dimensions are straightforward to implement (although high-dimensional spaces are demanding to compute and impossible to visualize). A three-dimensional experimental space means that the responses of all model receptors can be separated based on three independent stimulus parameters. Within this space, a cubic experimental volume is defined in which stimuli are uniformly randomly distributed; no stimuli occur outside this experimental volume. The arrangement of stimuli in this experimental volume is independent of the likelihood of each stimulus occurring, although the probability of occurrence is an important consideration in calculating IT measures.

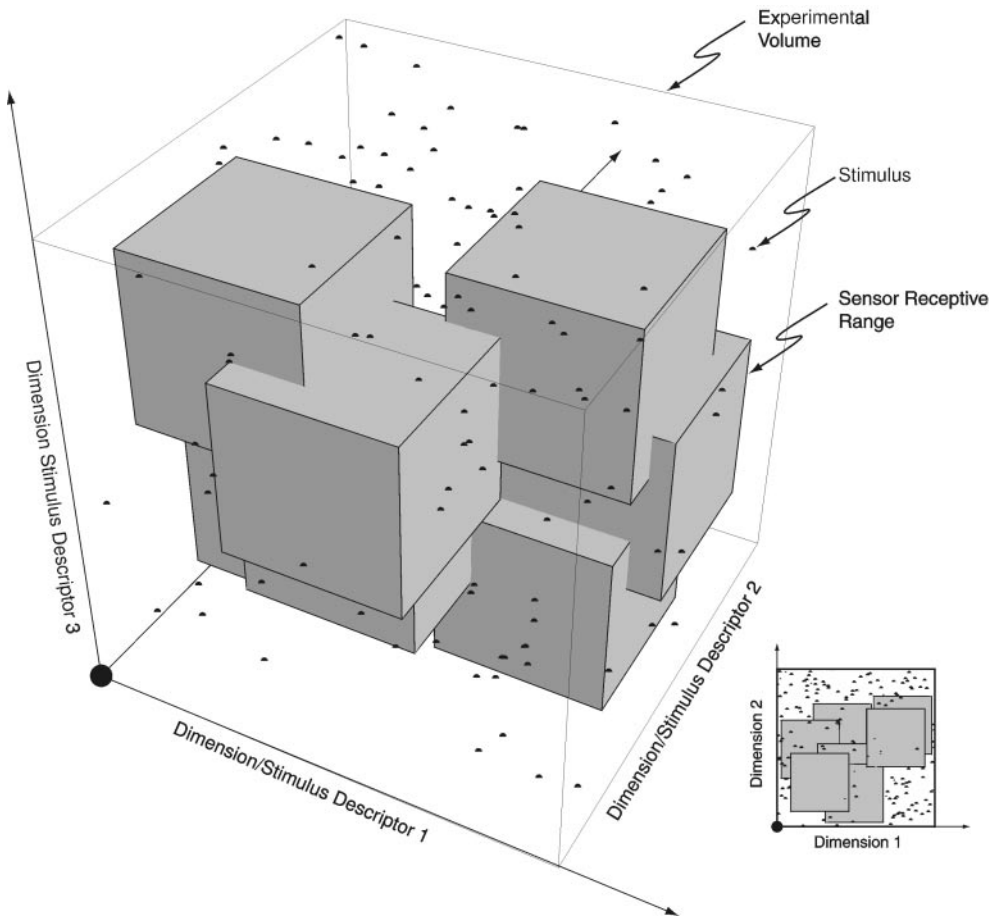

Figure 1 Model sensors and stimuli in a three-dimensional experimental space. Stimuli and sensor receptive ranges are restricted to a cubic experimental volume. The dimensions of this space correspond to hypothetical physico-chemical measures of the stimuli relevant to their interaction with the sensors: for example, they might represent polarity, charge, or molecular weight. The eight sensors have cubic receptive ranges (gray cubes), each of which occupies 5% of the experimental volume. Two hundred stimuli (black dots) are randomly distributed in this volume according to a uniform distribution (not all are visible). Stimuli that fall outside the eight cubic receptive ranges of the sensors are undetected by this array. The lower-right inset is a two-dimensional schematic representation of this three-dimensional arrangement, as would be seen from above the experimental volume along dimension 3 (i.e. through the top of the cube).

Models of receptors

In general, the physiological study of biological olfactory systems centers around methodically observing response profiles and relating the qualitative and quantitative attributes of odorants to changes in neuronal activity. In the study of ORNs and M/T cells, a variety of techniques have been used to measure neuronal responses as different odorant stimuli are applied under controlled conditions. These include intracellular electrophysiological recording (Getchell, 1977; Wellis *et al.*, 1989), intracellular calcium measurements (Restrepo *et al.*, 1993; Bozza and Kauer, 1998; Leinders-Zufall *et al.*, 1998), extracellular action potential measurement (Kauer, 1974; Meredith and Moulton, 1978; Harrison and Scott, 1986; Mori *et al.*, 1992; Duchamp-Viret *et al.*, 1999), 2-deoxyglucose uptake (Stewart *et al.*, 1979; Johnson *et al.*, 1998), and *in vivo* imaging (Cinelli *et al.*, 1995; Friedrich and Korsching, 1997; Joerges *et al.*, 1997; Rubin and Katz, 1999; Wachowiak and Cohen, 2001). Such responses have often been summarized as positive (excitatory), negative (suppressive), or null (no change) responses based on changes in action potential firing rate, membrane potential amplitudes or other time-varying signals. In addition to temporally complex firing patterns, olfactory neurons, like all CNS neurons, show variation in responses to repeated applications of the same stimulus. This variability comes from several sources: the inherent noise of the neuron (Harrison and Scott, 1986; Lowe and Gold, 1995), changes in stimulus conditions, errors in the measurement process and changes in the system as a result of prior odorant exposure (Getchell and Shepherd, 1978; Baylin and Moulton, 1979; Kurahashi and Menini, 1997; Friedrich and Laurent, 2001). Upon different presentations, therefore, ostensibly identical odorant stimuli can give rise to apparently different responses.

We have sought to create a framework which can capture these complexities without becoming unwieldy. In our

model, a sensor—which represents an ORN—maps stimuli (points in the experimental space, as described in the previous section) to the probabilities of all possible responses (i.e. a probability density function). These responses could be binary (positive/null) responses, ternary (positive/negative/null) responses, labeled responses ('A', 'B', 'C', etc.) or complex time-varying signals. In the experiments described here, we have modeled the sensors as giving either positive or null responses. We have also made the receptive range (RR) of each sensor a cube in the experimental space: that is, a neuron gives a positive response (with probability 1) to all stimuli that fall within the cube, and a null response (also with probability 1) to all stimuli outside it (see Figure 1). The RR of each sensor is randomly placed within the experimental volume, and is required to be completely contained by the experimental volume to which stimuli are restricted. One consequence of this arrangement is that the center of the RRs of larger sensors are biased toward the center of the space (since they must remain completely inside the experimental volume). We can express the size of sensor RRs as a percentage of the experimental volume; this size is therefore also equivalent to the percentage of stimuli to which the sensor gives a positive response, since the stimuli are randomly distributed within the volume. Refinements of this scheme are possible (e.g. richer response sets, probabilistic responses, more complex RR shapes), but they do not alter the fundamental methodology: the input to a sensor is a stimulus and the output of the sensor is a probability density function of responses.

For computational purposes, an array of sensors can be treated as a single sensor. That is, if sensor A and sensor B each can give only positive and null responses, then the array of sensors A and B would have four possible response states: positive/positive, positive/null, null/positive and null/null. The response profile of a sensor array is then just the probability of each of these response combinations for each stimulus, and array responses to a stimulus set can be tabulated as for a single sensor.

Information theory measures

From these descriptions of stimulus sets and response profiles, the performance of sensors and arrays in response to a set of stimuli can be evaluated using IT measures. First, the entropy of the stimulus set is calculated from the set of probabilities of occurrence of each stimulus. Entropy quantifies the complexity of the stimulus set; it measures the average *a priori* difficulty in randomly guessing which stimulus is present. In comparing two stimulus sets, the set which is more complex has greater entropy, and its state is more difficult to guess without other information. A profile of sensor responses to a stimulus set also has an entropy; this is calculated from the probability of each sensor response among the responses to the entire stimulus set. The entropy of the response profile to a stimulus set quantifies the maximum capacity of the sensor to carry information about the state of the stimulus set. The mutual information (MI) (also known as 'transinformation') between sensor responses and the stimulus set measures the extent to which complexity in a set of possible stimuli can be accounted for by the complexity in the responses; that is, the correlated complexity. To calculate the MI between a stimulus set and sensory responses, one needs to know the response profile of the sensor; that is, the conditional probability of the sensor giving each response to each of the stimuli. All of these measures, including their mathematical definitions, are described in more detail in a previous review (Alkasab *et al.*, 1999).

MI has a number of advantages as a measure of coding performance. First, MI is an entropy measure—it directly quantifies the reduction in uncertainty that is possible by utilizing a sensor. That is, if a stimulus set has an *a priori* entropy of 10 bits and a sensor has a MI with that stimulus set of 2 bits, then the uncertainty about the state of the stimulus is reduced to 8 bits if one observes the output of that sensor. Secondly, it measures how well a sensor or array makes discriminations averaged over repeated stimulus applications. It therefore provides a link between instantaneous response profiles and long-term performance. Finally, MI allows one to account for the probability of occurrence of each stimulus; this corresponds to the likelihood of encountering each odorant in the natural world. Most chemical environments consist of some frequently encountered stimuli and a larger set of detectable but rarely met odorants. Other neuronal sensory systems have been observed to take advantage of these differences in frequency of stimuli in the natural world. IT predicts that systems which fail to account for the statistics of the natural world cannot describe the world with optimal efficiency (Atick, 1992; Rieke *et al.*, 1995; Olshausen and Field, 1996). For these experiments, we have specified that each stimulus has an equal likelihood of being presented to the system; distributions which match what is known about natural chemical environments more closely are also easily implemented within our system.

Experimental approach

We use these models to explore how the performance of a chemosensory array depends on the tuning breadths of its individual components. In this paper, because we are interested in the general properties of ensembles of sensors, we create many random arrangements of sensors and stimuli, and calculate the mean performance across these arrangements. This process is illustrated in Figure 2, which shows the details of the steps in generating a plot of performance against sensor size. First, the properties of the array and stimulus set are specified (step 1). In this example, 32 stimuli are randomly distributed according to a uniform distribution in a cubic experimental volume within a three-dimensional experimental space (step 2). We specify that each stimulus is equally likely, which means that the

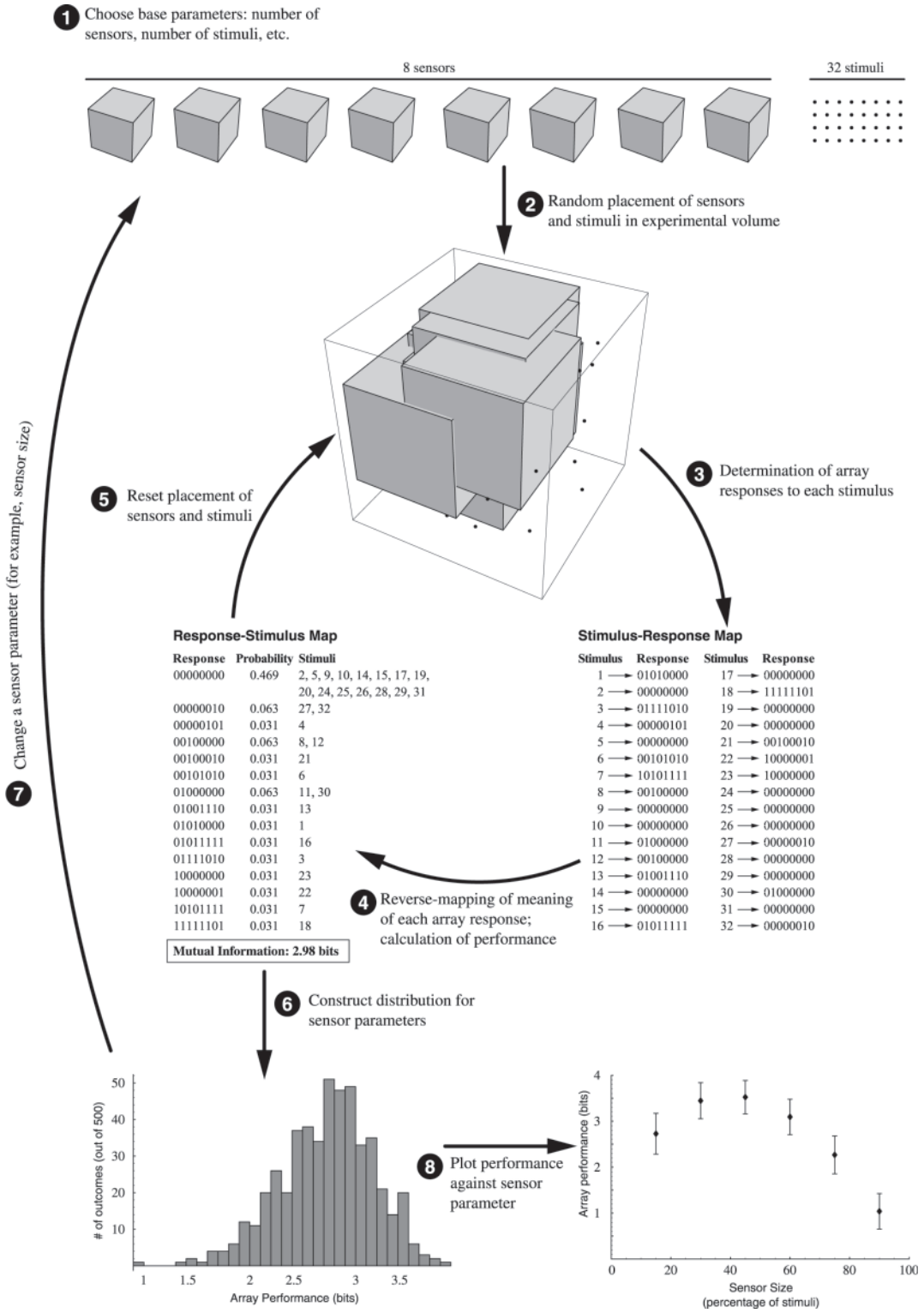

Figure 2 Method for using sensor array models to determine the effect of sensor parameters on array performance. In step 1, the parameters of the model are chosen: in this case, 32 stimuli and 8 positive/null sensors of a particular size (such that each sensor RR contains 20% of the stimuli) are randomly placed in a cubic experimental volume in a three-dimensional space (step 2). In step 3, the array response to each stimulus is determined. From this table, each response actually evoked by the stimulus set is associated with its probability of occurrence and the stimuli which evoked it (step 4), and the mutual information between this sensor array and the stimulus set is computed. New random locations for the stimuli and sensors are found (step 5), and steps 3 and 4 are repeated (in this case, for 500 cycles). The results from step 4 are plotted in a histogram to show the distribution of performance across the realizations (step 6) of this combination of sensor array parameters and stimuli. Then, in step 7, a parameter of the model (sensor size, in this case) is incremented, and the process is repeated. The plot of performance against the independently varying parameter is then constructed (step 8).

stimulus set has an entropy of 5 bits. The array consists of eight positive/null sensors; the RR of each sensor occupies 15% of the volume of the experimental volume. Since the stimuli are equally likely to be placed anywhere within the experimental volume, we expect each RR, on average, to contain 15% of the stimuli. The RRs of the sensors are also randomly placed within the experimental volume such that the entirety of each RR is contained within the boundaries of the volume. From this random placement of sensors and stimuli, the array response evoked by each stimulus is determined (step 3)—the stimulus–response map. This map is then reversed to list the realized sensor states and the stimuli which evoked them—the response–stimulus map (step 4). Note that although 256 responses are theoretically possible for an array of eight binary sensors, only 15 are actually observed for this array in response to this stimulus set. From the response–stimulus map, the MI is calculated to be 2.98 bits. The sensors and stimuli are then reshuffled to be placed randomly again within the experimental volume (step 5). The cycle of randomly rearranging sensors and stimuli and computing the performance of the resulting array is repeated hundreds or thousands of times, and the distribution of the results plotted in a histogram (step 6); in this case, the performance (i.e. the mean of the distribution) is 2.72 ± 0.44 (mean ± SD) bits for 500 repetitions. Next, the parameter of interest is incremented, and the process is repeated (step 7). In this case, the RR of each sensor is enlarged to a volume of 30% of the experimental volume. The stimuli and sensors of this new size are randomly placed, and the performance is evaluated for another 500 repetitions. This is repeated for arrays of sensors of RRs occupying 45, 60, 75 and 90% of the experimental volume. These results are then compiled into a plot (step 8) of array performance against sensor size for eight-sensor arrays discriminating 32 stimuli.

Results

Varying sensor response breadth

To explicitly explore how RR size affects the performance of entire olfactory arrays of various sizes, we conducted a series of experiments using simple models in a three-dimensional experimental space. Sets of 1024 stimuli were randomly distributed according to a uniform distribution within a cubic experimental volume in this space. This design is intended to simulate the 'generalist olfactory problem' of discriminating a large number of (possibly unknown) stimuli. For each array, the RRs of sensors were also randomly distributed such that the entirety of each RR was contained within the cube. The sensors in an array had uniform size; each responded one of two ways: either positive or null. Each of the set of 1024 stimuli was specified to be equally likely, which makes the entropy of the discrimination task 10 bits. For each array size and sensor breadth, we computed the performance of 1500 random placements of stimuli and sensors for arrays between 8 and 48 sensors and 300 repetitions for arrays of 64 and 128 sensors. The results of systematically varying sensor RR size from 5 to 95% of the experimental volume for arrays of 8, 16, 24, 32, 48, 64 and 128 sensors are shown in Figure 3A. For each array size, performance is poorest at the extremes of sensor RR size (5 and 95% of the experimental volume) and is greatest for arrays of sensors with RRs between 25% (for the 128-sensor array) and 35% (for the 8-sensor array). The peaks of the curves shift to the left as array size increases—that is, the optimal RR size is smaller for larger arrays. Figure 3B shows the distribution of the results of 300 trials with an array of 128 sensors of size 25%. For every array size (i.e. number of sensors), the difference in performance between each pair of different sensor sizes was significant. In addition, the performance differences between arrays with different numbers of the same-sized sensors were also significant. (For all comparisons, Welch's approximate t-test was used and $P < 0.001$.) Since changing the positions of receptors had a smaller effect on performance than changing RR size, we conclude that the breadth of response of sensors in an array is more important in determining the information capacity than the specific placement of sensors relative to the stimuli.

Arrays containing different numbers of sensors were affected by this changing sensor RR size in different ways. Increasing the number of sensors increases performance (i.e. curves are higher for larger arrays), but MI measures for larger arrays show diminishing increases in performance as more sensors are added. The peak performance for arrays of each size is plotted in Figure 3C. One of the characteristics of a distributed code is that MI increases in proportion to the logarithm of the number of sensors in the ensemble (Abbott and Dayan, 1999). For arrays of 8, 16, 24 and 32 sensors, this relationship holds; for these four points, the data were fit by the relationship $I_{max} = 1.56 \log_2(N) - 0.13$ ($R^2 = 0.998$). However, for larger arrays, maximum performance falls below this line. From this, we conclude that as arrays get larger, new sensors contribute less new information. Note that none of the arrays reach the maximum of 10 bits of performance. This is a partly a result of the random distribution of sensor RRs and stimuli; by chance, some stimuli will be so close to one another that they cannot be distinguished, which pulls the performance below 10 bits. If these arrays were tested against larger stimulus sets (with greater entropy), this upper limit on performance would be higher, such that 128-sensor arrays would achieve performances of >10 bits.

These results can be applied to the characterization of biological olfactory codes in several ways. First, the RR breadth which results in the maximum average MI (i.e. the sensor size which leads to the greatest discrimination among the stimuli) for each array size is quite large, such that each sensor gives a positive response to >250 stimuli (out

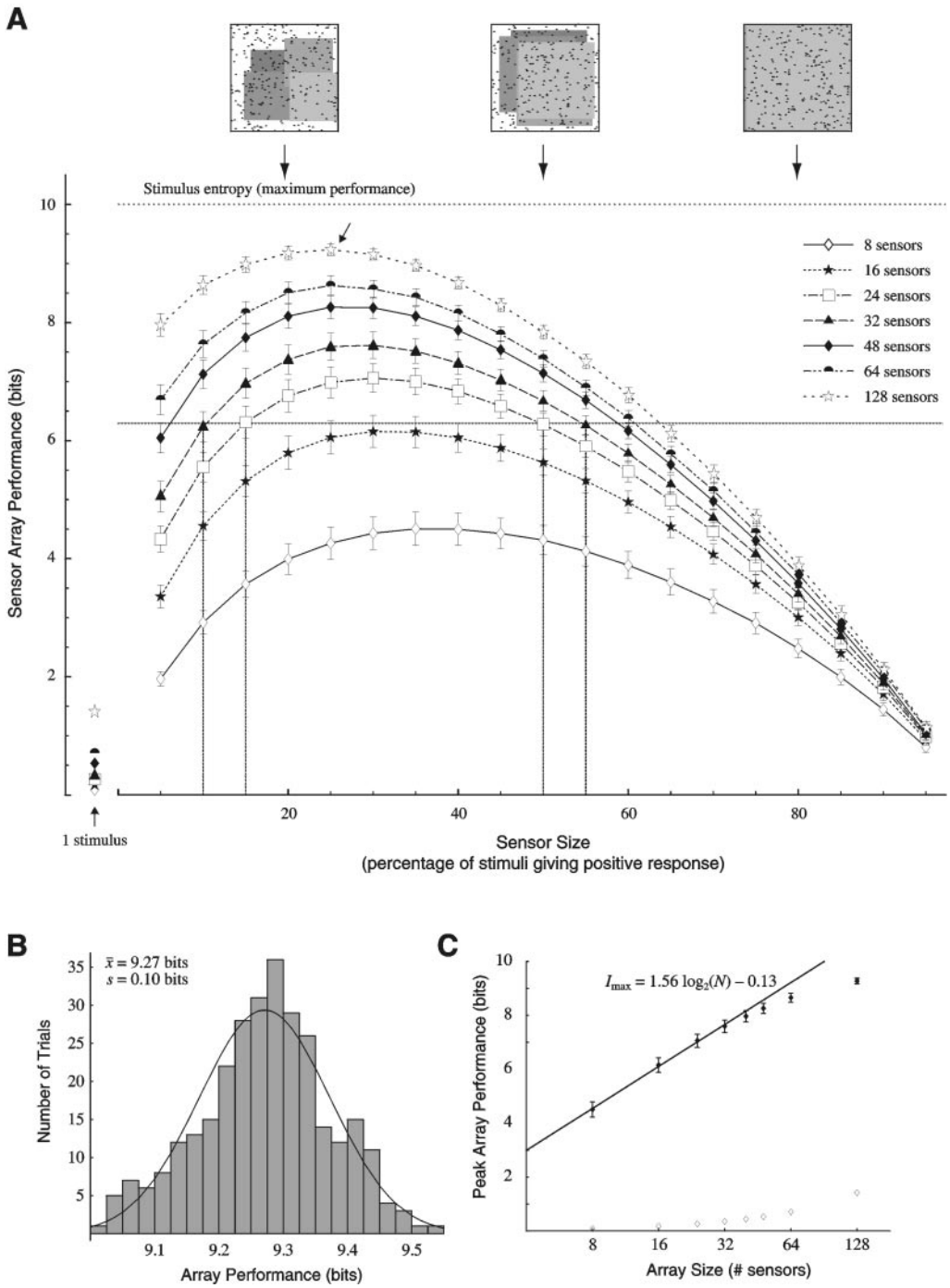

Figure 3 Effects of sensor breadth and array size on array performance. **(A)** For each array containing different numbers of sensors, there is a size for sensors in the array which maximizes MI. Each point is the mean of 1500 trials with randomly placed sensors and stimuli for arrays of 8, 16, 24, 32 and 48 sensors, and 300 trials for arrays of 64 and 128 sensors; error bars represent the standard deviation of each distribution. The performance of each neighboring sensor size and array size is significantly different ($P < 0.001$ for each comparison). Above, two-dimensional schematic representations show the relative sizes of sensors and the experimental volume. Each shaded square occupies 20, 50 or 80% of the experimental volume. In three dimensions, the cubic receptive ranges occupy corresponding fractions of the volume (and are expected to give positive responses to an equivalent fraction of stimuli). At the left are the computed MI values for arrays in which each sensor is activated by a single stimulus ('1 stimulus'). Vertical lines indicate non-optimal sensor sizes for arrays of 24 or 32 sensors which give equivalent performance of 6.3 bits. **(B)** The distribution of performance results is shown for 300 trials of arrays of 128 sensors of size 25% (indicated by arrow in A). The probability density function of a normal distribution with the corresponding estimated mean (9.27 bits) and SD (0.10 bits) is overlaid. **(C)** The peak performance of arrays is plotted against the number of sensors in the array. Arrays of 8, 16, 24 and 32 broadly tuned sensors (filled diamonds) show an increase in maximum performance proportional to the log of the sensor size; this increase is fit by the line $I_{max} = 1.56 \log_2(N) - 0.13 (R^2 = 0.998)$. At higher sensor counts, array performance deviates downward from this relationship. Arrays of sensors each of which responds to one stimulus (open diamonds) show lower performance and a slower increase in performance with increasing array size.

of 1024). In the context of biological olfactory systems, this result suggests that in an olfactory system that must discriminate many disparate odorants (i.e. those that span a broad range among the measures that determine their interactions with ORNs), neurons which only respond to one or two stimuli would be disadvantageous compared with more broadly tuned receptors. A system of narrowly tuned sensors, in which each sensor responds to exactly one stimulus, is represented at the left of Figure 3A. (Such arrays are limited to representing a number of odorants equivalent to the number of different receptor types.) A system of receptors with larger RRs, on the other hand, could encode many more odorants than the number of receptor types. Finally, our results are predicated on a uniformly random distribution of stimuli in both space and time. In physical terms, this would correspond to a set of odorants which were distributed evenly across physical parameters, and occur with equal likelihood. While this is not a good model of natural chemical environments, the results are nonetheless consistent with evidence from both amphibians and mammals, which suggests that olfactory neurons do tend to be broadly tuned: olfactory neurons are generally found to respond to more than one member of even small stimulus sets (Gesteland *et al.*, 1965; Duchamp *et al.*, 1974; Getchell, 1974; Revial *et al.*, 1978, 1982; Sicard and Holley, 1984; Sato *et al.*, 1994; Bozza and Kauer, 1998; Malnic *et al.*, 1999; Duchamp-Viret *et al.*, 1999, 2000).

As large as these optimal RRs seem, they are smaller than what would be predicted by considering the optimal breadth of an individual sensor. The MI of an individual binary sensor is greatest if it responds to exactly half of the stimuli. An array of independent, binary sensors would have a symmetric curve with an optimum RR size of 50%. The observed asymmetry of the curves in Figure 3 suggests that the relationships between sensors within the array play a major role in determining array performance (i.e. sensors are not independent). When a sensor is added to an ensemble, it makes a contribution to the total MI only if it conveys new information about the stimulus. The new sensor conveys no new information if its response can be predicted from the response of the rest of the array. The extent to which two sensors (or an array and a sensor) carry the same information can be termed their information redundancy. One way to quantify this redundancy in a noiseless case is to determine the MI between the additional sensor and the array. If it is high relative to the entropy of the new sensor, then the responses of the new sensor could be predicted from the existing array, and the new sensor has little new information. Conversely, if the MI between the array and the new sensor is low (i.e. if the response of the new sensor could not be predicted from the response of the array), then the sensor does convey new information and it can make a positive contribution to the performance of an array. Thus, we can use the MI between sensors to quantify the extent to which they carry redundant information.

This redundancy depends on the degree to which sensor RRs overlap. Clearly, sensors which substantially overlap will have redundant information; less obviously, sensors whose RRs do not overlap at all have greater information redundancy than sensors whose RRs partially overlap. This relationship between RR overlap and information redundancy explains some of the features of Figure 3A. Each curve represents a balance between optimizing the RRs of individual sensors and optimizing their RR overlap. Each individual sensor would be most informative if it were activated by half the stimuli. When we restrict sensor RRs to be completely within the experimental volume, however, every RR in an array has a high likelihood of containing the region at the center of the volume, resulting in many stimuli that activate all of the sensors (which therefore cannot be discriminated from one another). Smaller sensors allow central stimuli to activate different subsets of sensors, permitting them to be discriminated. However, if the sensor RRs become so small that they do not overlap at all, then many stimuli will activate no sensors, and therefore also not be discriminated.

We have tested this explanation explicitly by designing an experiment in which arrays of 32 sensors were measured for their ability to discriminate three stimulus sets: 1024 stimuli uniformly distributed throughout the experimental volume to which stimuli are restricted, 512 stimuli uniformly distributed in the inner 50% of this volume (i.e. a cube in the center of the experimental volume whose volume is half of the full volume), and 512 stimuli uniformly distributed in the outer 50% of the volume (i.e. the outer 'shell' of the experimental volume). Sensors remain distributed throughout the entire experimental volume. The results of this experiment are shown in Figure 4. The central curve of Figure 4 (diamonds, solid line) is a replication of the results for a 32-sensor array from Figure 3A. When stimuli are restricted to the central half of the experimental volume, smaller sensors are at an advantage, resulting in a left-shifted curve. Conversely, for stimuli on the periphery of the experimental volume, larger sensors are advantageous, and the curve shifts to the right. From these data, one possible explanation for Figure 3A is that each curve starts at the far left with small sensors with little overlap, resulting in poor performance. As sensor RR increases, the overlap of sensors becomes sufficient for the array to discriminate stimuli and performance improves. Eventually, sensor size increases enough that there is a central region within which stimuli activate many sensors in the array; obviously, no stimuli within this region can be discriminated. As sensor size increases further and the size of this region increases, performance degrades. These considerations can also explain why the optimum RR size is larger for smaller arrays: the RRs of smaller arrays need to be large to overlap with those of their neighbors, and so the performance benefit of overlapping is realized at larger RR sizes. The relationship between RR overlap and information redundancy can also

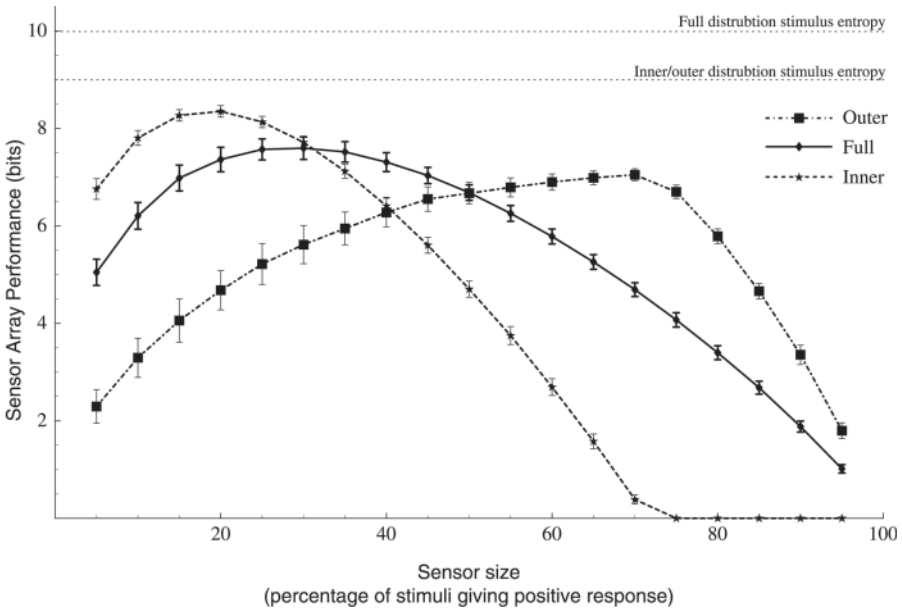

Figure 4 Relationships among placement of stimuli, sensor size, and array performance. Array performance versus sensor size in arrays of 32 sensors was measured for three different distributions of stimuli. In the experiment labeled 'Inner', 512 stimuli were uniformly distributed in the inner 50% of the experimental volume. In the experiment labeled 'Full', 1024 stimuli were uniformly distributed throughout the volume, and in the experiment labeled 'Outer', 512 stimuli were distributed in the outer 50% of the volume. These results demonstrate that arrays of smaller sensors perform better in discriminating centrally located stimuli, while arrays of larger sensors are better for discriminating peripheral stimuli.

explain why increased array size does not give a constant performance improvement. If an array is already large, when a new sensor is added to it, it is unlikely to find an advantageous RR position, and it is therefore likely to contribute almost all redundant information.

Considerations of RR overlap and information redundancy have direct application to descriptions of distributed olfactory codes as well. Clearly, an array of olfactory neurons will have the greatest coding capacity if each neuron contributes unique information; this requires some overlap of response profiles. IT analysis indicates that performance is enhanced when multiple sensors/receptors are involved in the detection of any given stimulus, which is what is generally observed in studies of biological olfaction: at each level of an olfactory system, a substantial fraction of the neurons respond to any one odorant (Adrian, 1950; Gesteland *et al.*, 1965; Kauer, 1974; Meredith and Moulton, 1978; Stewart *et al.*, 1979; Hamilton and Kauer, 1985, 1989; Harrison and Scott, 1986; Wellis *et al.*, 1989; Wellis and Scott, 1990; Imamura *et al.*, 1992; Mori *et al.*, 1992; Katoh *et al.*, 1993; Cinelli *et al.*, 1995; Johnson *et al.*, 1998). The IT analysis further indicates that when testing with limited sets of stimuli (compared with the entire odorant universe), some neurons expressing different ORs may appear to have similar response profiles because their RRs overlap substantially. A small test stimulus set might not include stimuli which would allow the distinct but overlapping RRs to be discriminated, and the two receptors would appear to be functionally identical (White *et al.*, 1999).

Sensor Heterogeneity

In investigations of responses from primary and secondary olfactory neurons, the breadth of response profiles have been found to vary (Duchamp *et al.*, 1974; Revial *et al.*, 1978; Imamura *et al.*, 1992; Mori *et al.*, 1992; Katoh *et al.*, 1993; Bozza and Kauer, 1998; Krautwurst *et al.*, 1998; Duchamp-Viret *et al.*, 1999; Malnic *et al.*, 1999), although the limited size of stimulus sets makes it difficult to draw conclusions about the true RRs of these neurons. Using the tools described here, we explored the effect that heterogeneity of receptor response breadth may have on the ability of sensor arrays to encode olfactory information. In this study, we created arrays of 24 and 36 sensors, where each array contained a mix of sensors of two RR sizes: one class of sensors which respond to many stimuli and another class of sensors which respond to few. The different sizes were chosen such that a homogeneously sized population of sensors of either size would yield approximately the same performance (dashed vertical lines in Figure 3A). For an array of 24 sensors, we chose RRs of size 15 and 50% because, from Figure 3A, homogeneous arrays of sensors of each size have approximately equal performance of 6.3 bits. Homogeneous arrays of 36 sensors of either size 10 or 55% also have a MI of 6.3 bits. We constructed arrays with different numbers of small and large sensors and observed the performance for various degrees of mixing. These results are summarized in Figure 5. For arrays of 24 and 36 sensors, heterogeneous mixtures of both large and small sensors outperform homogeneous arrays of either size. An array

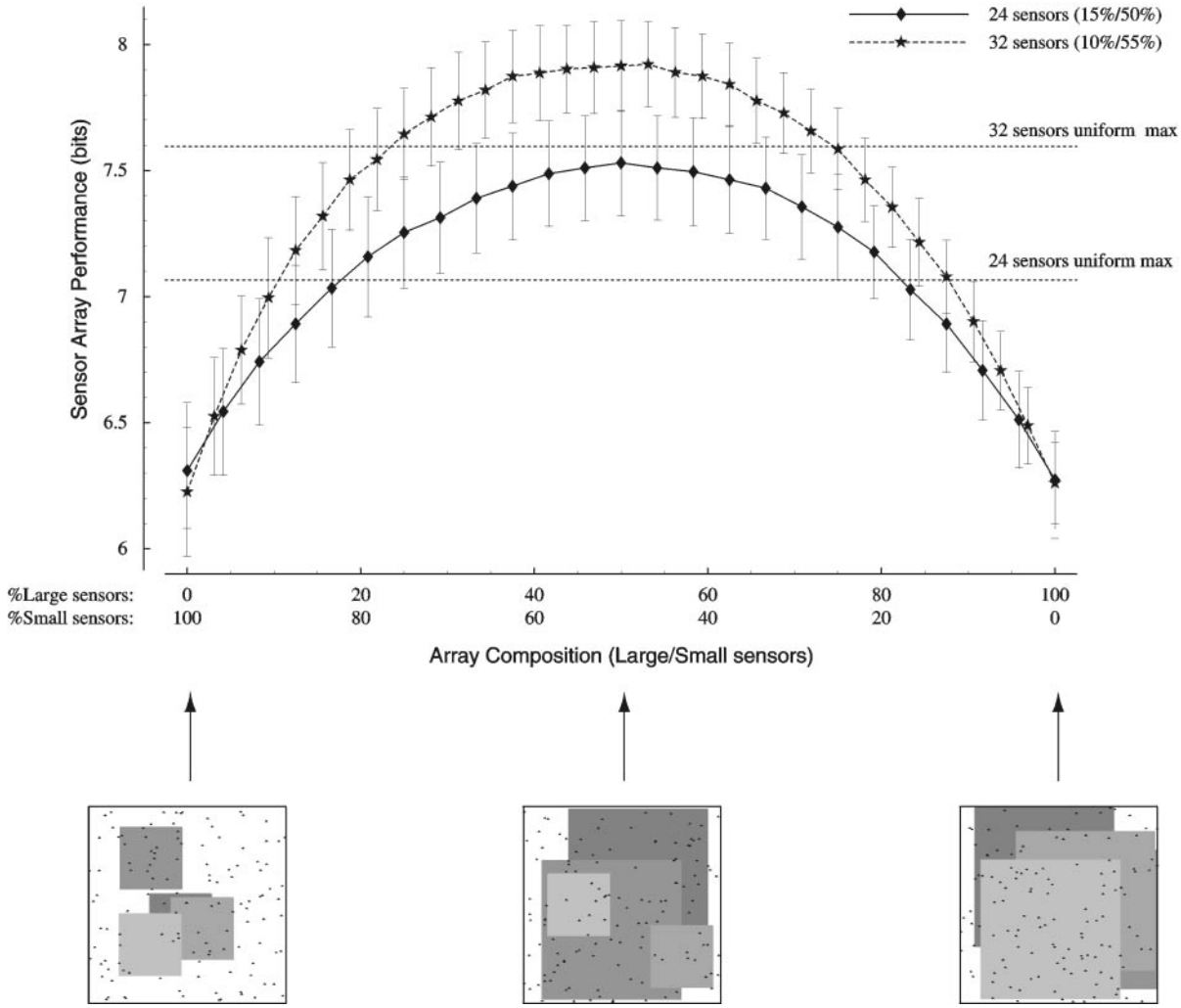

Figure 5 Effect of mixing sensor sizes on array performance. Arrays containing different proportions of large and small sensors (volumes 15 and 50% for a 24-sensor array and 10 and 55% for a 32-sensor array) show maximum performance when the array contains an approximately equal mixture of large and small sensors. Each point represents the mean of 500 trials (error bars are the standard deviation of the population). The horizontal dotted lines show the performance of homogeneous arrays of the optimum sensor size. At bottom are two-dimensional representations of the relative proportions of large and small sensors to the entire experimental volume.

of 12 large and 12 small sensors conveys 7.5 ± 0.2 bits of information as compared with 6.3 bits for an array of 24 large sensors or 24 small sensors. An array of 18 large and 18 small sensors conveys 7.9 ± 0.2 bits as compared with 6.3 bits for an array of 36 large or 36 small sensors. These heterogeneous arrays also performed better than homogeneous arrays of the optimum size: 7.1 ± 0.2 bits for 24 sensors ($P < 0.001$) and 7.6 ± 0.2 bits for 36 sensors ($P < 0.001$) (dashed horizontal lines in Figure 5).

One possible explanation for this observation also relates to the consequences of RR overlap for array performance. As discussed above, arrays of small sensors are likely to have sub-optimal performance because they do not overlap sufficiently: too many stimuli do not activate any sensors. Larger sensors overlap too much: a significant proportion of the stimuli activate all (or nearly all) of the sensors. This is demonstrated by the results of Figure 4, which show that, on average, smaller sensors perform best in discriminating stimuli in the central region (where the sensor RRs overlap most), whereas large sensors tend to give the best performance in outer regions of the experimental volume (where they overlap least). In a heterogeneous array, the strengths of the small sensors compensate for the weaknesses of the large sensors, and vice versa. Small sensors are likely to contribute to making discriminations among centrally located stimuli with which large sensors might have difficulty. Reciprocally, the presence of large sensors means that discriminations can be made among stimuli in the periphery of the space which would be impossible with small sensors alone. This suggests the possibility that more broadly tuned receptors permit detection of stimuli in regions of the olfactory space where

the inter-stimulus distance is large, while finely tuned receptors allow discrimination in regions of greater stimulus density. This could be tested by using different stimulus distributions.

Discussion

Recent studies of the response properties of neurons in which particular ORs have been identified (Zhao *et al.*, 1998; Krautwurst *et al.*, 1998; Malnic *et al.*, 1999; Murrell and Hunter, 1999; Araneda *et al.*, 2000) and other studies in which the responses of individual ORNs have been examined (Duchamp *et al.*, 1974; Revial *et al.*, 1978, 1982; Hirono *et al.*, 1994; Sato *et al.*, 1994; Bozza and Kauer, 1998; Duchamp-Viret *et al.*, 1999) show that the receptor cells and the receptor proteins they express generally respond to more than one compound. Ensembles of these neurons encode the detailed information about the chemical environment on which animals base their olfactory behaviors. In this paper, we have begun to explore in a formal, systematic way how the discriminatory power of these ensembles can emerge from the tuning properties of the individual receptors.

Our goal has been to create a framework in which to explore relationships between the response properties of individual olfactory neurons and coding properties of arrays. To do this, we created a system in which we could both define the response profiles of model olfactory sensors and evaluate statistically the performance of sensor arrays. Individual model sensors are defined as having continuous RRs in a multi-dimensional space. We have chosen such simple sensors because this assumption reduces large numbers of theoretically possible responses to a sparser subset. For example, an array of 32 binary sensors with positive/null responses has 2^{32} possible states, and therefore could encode more than 4×10^9 different stimuli. However, this presumes that the response of each sensor is completely independent of the others; if the sensors are limited to having contiguous RRs in a space of dimensionality of <32, then the sensors cannot be independent, and many array states cannot be evoked by any stimulus. Specifically, if the RRs of a pair of sensors do not intersect, all of the states of the array in which both are activated cannot be elicited by any stimulus. Therefore, each pair of non-overlapping RRs reduces the number of available array states. The same argument applies to larger combinations of the sensors as well, which further reduces the number of realizable states. The ability of an array of receptors that is restricted in this way to discriminate among a defined stimulus set can be quantified using a MI measure. We have used this measure because it allows a comparison between the coding contributions of individual sensors and the overall performance of the array. Together, this combination of easily manipulated models and a statistical framework for evaluating overall performance comprise a powerful tool for exploring the properties of distributed codes.

This framework may be used to examine results describing the response properties of biological olfactory receptor neurons (Revial *et al.*, 1978; Krautwurst *et al.*, 1998; Zhao *et al.*, 1998; Duchamp-Viret *et al.*, 1999; Malnic *et al.*, 1999). In all of these studies, although relatively small numbers of odorants were tested, receptor neurons were generally shown to respond to more than one stimulus. This suggests that the neurons would, in fact, respond to more odorants if additional ones could have been presented (White *et al.*, 1999). Our results suggest that this property of broad tuning might be an advantageous adaptation for a generalist chemosensory system: a system of sensors which respond to a high proportion of possible stimuli (between 20 and 40%) provides substantially greater coding capacity than a system with more selective sensors (between 1 and 10%). Another theoretical study of the binding properties of arrays of biological receptors also predicts such broadly tuned sensors (Lancet *et al.*, 1993). While such a generalist olfactory system might not be able to capture all of the information about the chemical environment, it can provide an efficient mechanism for covering broad regions of the olfactory space. It seems that biological systems might use sensors with relatively large RRs to generate the distributed code by which they describe the environment (though sensors with small RRs may be involved for specialized detection and discrimination).

In addition, considerations of sensor heterogeneity are relevant to the study of biological olfactory systems because they suggest that diversity of RR size may be advantageous. In experimental studies, differences in receptor breadth may be difficult to characterize completely because of the difficulty of obtaining response profiles to stimulus sets that comprise a significant fraction of the complete odorant universe for a given species. In spite of the difficulties of observing these differences, they may play a significant role in the distributed representation of olfactory information. Since it is unlikely in a system composed of hundreds of different receptor proteins that all the proteins would evolve with optimal tuning widths, it may be adaptive and biochemically efficient to generate a diversity of binding specificities. In addition, arrays of biological olfactory receptors might be intrinsically diverse. Olfactory receptors are in a constant state of turnover as a result of injury, apoptosis and renewal (Graziadei and Graziadei, 1979a,b); if the RR of a receptor neuron changes as it ages, this could have a profound impact on information coding in the olfactory system. It could even be that changes in response breadth over time that accompany the life cycle of ORNs provide advantages for the stimulus coding process.

Our study also suggests some bounds on the distribution of receptor tuning breadths. Unfortunately, there are as yet only a few studies of the response properties of ORNs expressing defined receptor proteins (Malnic *et al.*, 1999;

Araneda *et al.*, 2000). This is due to a variety of technical difficulties. First, the number of possible stimuli which might be tested is large (some speculate on the order of 10^4 for a macrosmatic animal) and needs to be defined for the particular species being studied. Since there is no systematic description of olfactory stimuli, meaningful sampling of this large set is not yet possible. Secondly, because the time course of an olfactory response is generally longer than for the other senses, relatively few stimuli with few repetitions can be tested in each preparation. This combination makes it difficult to assess RR size for olfactory neurons, since differences could arise as an artifact of the selection of a particular stimulus set or measurement technique. However, our results suggest that when sufficient data sets from populations of odorants and sensors become available, they will show significant differences in tuning breadths across populations of receptors—some olfactory neurons will be found to respond to small sets of odorants and others to larger sets (Kauer, 1980; Hildebrand and Shepherd, 1997). In fact, a recent study of response profiles of olfactory receptor neurons by Duchamp-Viret and colleagues (Duchamp-Viret *et al.*, 2000) showed some evidence for bimodality in sensor breadth for the rat, but not for the frog. A distribution of tuning widths follows naturally from the large repertoire of receptor genes (Sharon *et al.*, 1998; Fuchs *et al.*, 2001): the inevitable variation in receptor response properties results in a population of receptors which have many tuning widths. Thus, biological olfactory systems might exploit the advantages of distribution of receptor breadths as a side effect of the expansion of the olfactory genome.

Since so little is known about general properties of olfactory stimuli, we made relatively arbitrary decisions in designing our model systems. Though our experiments illustrate some critical aspects of the relationship between sensors and array performance, the results are sensitive to the chosen distributions of stimuli. In particular, the fact that stimuli (and sensors) were constrained to a cubic experimental volume created an unintended difference between central and peripheral stimuli (Figure 4). In addition, the uniform distribution of stimuli and sensors resulted in a 'ceiling effect' (Figure 3C) which affected high levels of performance. The results reiterate that knowledge of stimulus distributions and their relationships to sensor properties are critically important for understanding olfactory function. We intend to explore these relationships further by examining other stimulus distributions and the characteristics of sensor arrays that best discriminate them.

These initial studies suggest several additional avenues of further research. First, the responses of the sensors modeled here are simpler than those in biological olfactory systems in a number of ways. They give simple positive or null responses, while olfactory neurons in general are clearly capable of more complex output, including graded and time-varying events (Kauer, 1974; Kauer and Shepherd, 1977; Harrison and Scott, 1986; Meredith, 1986; Hamilton and Kauer, 1989; Wellis *et al.*, 1989; Laurent *et al.*, 1996, 2001). Our model neurons have a maximum information carrying capacity of 1 bit per stimulus application, which means that the maximum information carrying capacity of an N-sensor array would be N bits if there were no information redundancy among the sensors. Sensors with more complex responses will lead to systems with larger coding capacities. We are particularly interested in modeling arrays of sensors with time-varying responses to explore the evolution of information across an olfactory system over time (Laurent *et al.*, 2001).

Secondly, olfactory receptors are subject to noise that arises at several different levels, from the interaction between the odorant and receptors, to the generation of the primary transduction currents and to spike generation. For M/T cells, in addition to noise from the receptor neurons, there is noise from the propagation of the receptor neuron spikes from the epithelium to the bulb, noise of synaptic transmission from the receptor axon terminal, noise from the generation of M/T cell spikes and noise from the global bulbar neuronal network. All of these sources can reduce the capacity of the system for carrying information about the stimuli. In addition, noise can have effects on information capacity across an array—noise in common between sensors (correlated or common-mode noise) has a different impact on the total capacity of the array than non-correlated noise independent to each of the sensors, since the effects of uncorrelated noise can be reduced by convergence of multiple sensors of the same response type (van Drongelen *et al.*, 1978). One might hypothesize that the large size of biological arrays compensates for these sources of noise; models which explore this balance can explicitly test that idea. The effect of other factors in olfactory coding can also be tested using this technique: graded olfactory neuron responses, multiple binding sites, temporally complex patterns of activity and the effects of concentration all lend themselves to representation in model systems.

In spite of the simplicity of the models used here, this approach of exploring the properties of networks from a formal statistical perspective is helpful for defining the limits of the initial representation of chemical stimuli in olfactory systems. Many data suggest that the representations of perceived odors tend to be distributed widely across the components of the olfactory pathway. Our approach provides a framework for analytically characterizing the growing understanding of the functional properties of individual neurons and for considering those properties in the context of system-wide coding. We anticipate using these techniques to approach a wide variety of questions, from the evolution of biological olfactory systems to the rational design of sensor arrays for artificial olfactory systems. These paths might lead us to a definitive description of how the pieces of the olfactory response can be put together to form the whole of a description of the chemical world.

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