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Computation in the Olfactory System

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Abstract

Computational models are increasingly essential to systems neuroscience. Models serve as proofs of concept, tests of sufficiency, and as quantitative embodiments of working hypotheses and are important tools for understanding and interpreting complex data sets. In the olfactory system, models have played a particularly prominent role in framing contemporary theories and presenting novel hypotheses, a role that will only grow as the complexity and intricacy of experimental data continue to increase. This review will attempt to provide a comprehensive, functional overview of computational ideas in olfaction and outline a computational framework for olfactory processing based on the insights provided by these diverse models and their supporting data.

Key words: coding, contrast enhancement, convergence, dynamics, modeling, normalization, odor representation, synchrony

Introduction

In natural environments, airborne chemical stimuli are distributed unpredictably in time and space, and odorants from innumerable sources intermix freely. The olfactory system must be able to detect potential signals of interest within these chemically noisy environments, correctly extract these signals from a complex and changing odor background to form stimulus representations, compare these constructed representations to those of previously experienced odors, differentiate relevant from irrelevant stimuli, and cue an appropriate response. Many of the neural circuit elements comprising the olfactory system have been proposed to contribute to these processes in particular ways; for example, multiple feedback and feedforward interactions among olfactory structures, as well as between olfactory and non-olfactory areas, are thought to contribute to the filtering and construction of olfactory representations. Computational models of olfactory processing have been increasingly utilized to describe and interpret these complex and interrelated phenomena.

Primary olfactory sensory neurons (OSNs) number in the millions in rodents. Their axons are highly convergent, targeting specific, discrete neuropilar synaptic regions within the input layer of the olfactory bulb (OB) called glomeruli. In hamsters, for example, between 1300 and 4700 OSNs expressing the same odorant receptor complement converge upon each glomerulus (Schoenfeld and Knott, 2004). These large populations of redundant OSNs and their correspondingly high convergence ratios have been proposed to yield advantages such as an improved signal-to-noise ratio, a corresponding increase in effective stimulus sensitivity, and an increased range of tuning to different odorant concentrations (van Drongelen *et al.*, 1978; Duchamp-Viret *et al.*, 1989; Meisami, 1989; Cleland and Linster, 1999). The molecular receptive ranges or chemical receptive fields of these odorant receptors overlap substantially, such that the identity of odorants is not associated with the activation of a specific receptor but rather is represented by a distributed, combinatorial code (Adrian, 1953; Moulton, 1967; Stewart *et al.*, 1979; Kauer, 1991), now recognized as a pattern of activation across many receptors. Owing to the specific homotypic convergence of OSN axons, these odor-specific activity patterns can be most clearly observed in imaging studies of OB glomeruli (Friedrich and Korsching, 1997; Johnson *et al.*, 1998, 1999, 2004; Rubin and Katz, 1999; Meister and Bonhoeffer, 2001; Wachowiak *et al.*, 2002). These overlapping representations underlie two critical properties of the olfactory system that a labeled-line solution would not. First, the number of unique odor representations is not limited to the number of different receptor types (roughly 1000 in mice; Mombaerts, 1996) but can be estimated as m^n, where n denotes the number of receptor types and m denotes the number of recognizable states that each sensor can assume, ultimately limited by the signal-to-noise ratio of the system. Even if only two receptor states, active and inactive, were recognized, this would enable roughly 2^{1000} potential odor stimuli to be discriminated in mice. Second, the fact that structurally and perceptually similar odorant molecules will activate correspondingly overlapping sets of olfactory receptors (ORs) (Linster *et al.*, 2001b,

2002; Cleland *et al.*, 2002) establishes a basis for the recognition of stimulus similarity in the olfactory system. This is a prerequisite for basic postsensory cognitive processes such as generalization (Shepard and Chang, 1963; Shepard, 1987; Cleland *et al.*, 2002) and a tolerance for variance among repeated stimulus samples that a labeled-line system would have no clear means of generating.

Distributed patterns of activity in response to chemical stimuli are transmitted to the OB via OSN axons that terminate in the glomeruli of its input layer. The OB is believed to filter and transform these incoming sensory data, performing normalization, contrast enhancement, and similar operations before conveying the processed olfactory information to several different secondary olfactory structures via mitral cell axon collaterals (Cleland and Linster, 2003). Notably, the bulb constitutes the last common stage at which olfactory sensory representations can be processed before the signal diverges dramatically into these multiple secondary structures. It is clear from recent investigations that the perceptual qualities of odorants can be predicted, to a limited degree, from the patterns of activation that they evoke at the OB input layer (Linster and Hasselmo, 1999; Linster *et al.*, 2001b, 2002; Cleland *et al.*, 2002). However, several aspects of odor perception, for example, changes in perception and discrimination capacity due to odor intensity or prior experience, cannot be predicted solely by this first-order representation as reflected in glomerular activation patterns. Nor is the converse true; mitral cell responses in behaving animals cannot be predicted solely by the odor(s) presented but depend substantially on odor contingency (Kay and Laurent, 1999), as previously suggested in field potential recordings from the OB (Di Prisco and Freeman, 1985; Gray *et al.*, 1986; Freeman and Grajski, 1987; Grajski and Freeman, 1989). Furthermore, the OB receives substantial centrifugal projections from both cortical and neuromodulatory centers, and its responses to odor presentations are strongly regulated by these centrifugal inputs as well as odor learning and experience (Kay *et al.*, 1996; Kay, 2003, 2005; Ravel *et al.*, 2003; Wilson and Stevenson, 2003; Martin *et al.*, 2004; Wilson *et al.*, 2004). It is therefore safe to assume that the OB plays an important role in processing incoming sensory information. Accordingly, many models of OB signal processing have been developed, which are grouped here into studies of (1) filtering and contrast enhancement, (2) mechanisms underlying oscillations and spike synchronization, and (3) odor segmentation and associative memory function. In addition, a number of detailed biophysical models of bulbar neurons have been constructed, in many cases to address how their intrinsic properties underlie and interact with network properties.

Filtering and contrast enhancement

The high convergence ratio between OSNs expressing a particular odorant receptor and their target glomeruli in the OB (Figure 1A) is believed to improve the signal-to-noise ratio during odorant detection (van Drongelen *et al.*, 1978), potentially overcoming the limiting noise inherent in the transduction mechanisms of individual OSNs (Lowe and Gold, 1995). In principle, this improves the coding capacity of the olfactory system, increasing the number of different odor-specific patterns that can be discriminated, as well as improves the effective maximum sensitivity of the system (Duchamp-Viret *et al.*, 1989; Duchamp-Viret *et al.*, 2000) (Figure 1B). This property may also contribute toward increasing the range of odor ligand concentrations that can be represented by OB glomeruli without saturation (Figure 1C). Specifically, the modeling of signal transduction and convergence properties among OSNs suggested that regulation of the intracellular gain between G protein–coupled odorant receptors and their cyclic nucleotide-gated channel effectors could underlie both an extremely high sensitivity for odorant stimuli and a substantial broadening of the dose–response profile of OB glomeruli (Cleland and Linster, 1999). This hypothesis provides a possible solution to the conundrum of how collective concentration–response curves measured by glomerular imaging can be substantially broader than those measured in individual OSN recordings (Duchamp-Viret *et al.*, 1990; Friedrich and Korsching, 1997; Bozza *et al.*, 2002), enabling preservation of the ratios of activation levels among glomeruli across broader concentration ranges and hence potentially facilitating the recognition of odor quality across changes in concentration. Another approach has been suggested by Anton and colleagues (1991). Noting that the activity of each glomerulus is sampled and conveyed centrally by a number of mitral cells (on the order of 50 in hamsters; Schoenfeld and Knott, 2004), and that mitral cell firing frequencies do not scale monotonically with concentration as do those of OSNs (Harrison and Scott, 1986; Meredith, 1986; Wellis *et al.*, 1989), these authors proposed that the synaptic circuitry within each glomerulus could compute a frequency-to-spatial transformation on the incoming information. That is, the number of responding mitral cells within a glomerulus, rather than their firing rates, would reflect the firing rates of the sensory neurons projecting to that glomerulus in response to odor stimulation (Figure 1D).

Contrast enhancement is a common property of sensory systems that narrows (sharpens) sensory representations by specifically inhibiting neurons on the periphery of the representation, thus enhancing the contrast between signal and background (Figure 2A). A number of computational models have investigated the contrast enhancement potential of OB circuitry, most of which, by analogy with the retina, have investigated the potential role of lateral inhibitory projections. Classically, bulb models have emphasized lateral inhibition mediated by mitral cell lateral dendrites (Rall and Shepherd, 1968; Shepherd and Brayton, 1979; Schild, 1988; Urban, 2002; Davison *et al.*, 2003). These lateral dendrites form reciprocal synapses with inhibitory granule cell spines in the external plexiform layer of the bulb, forming a network through

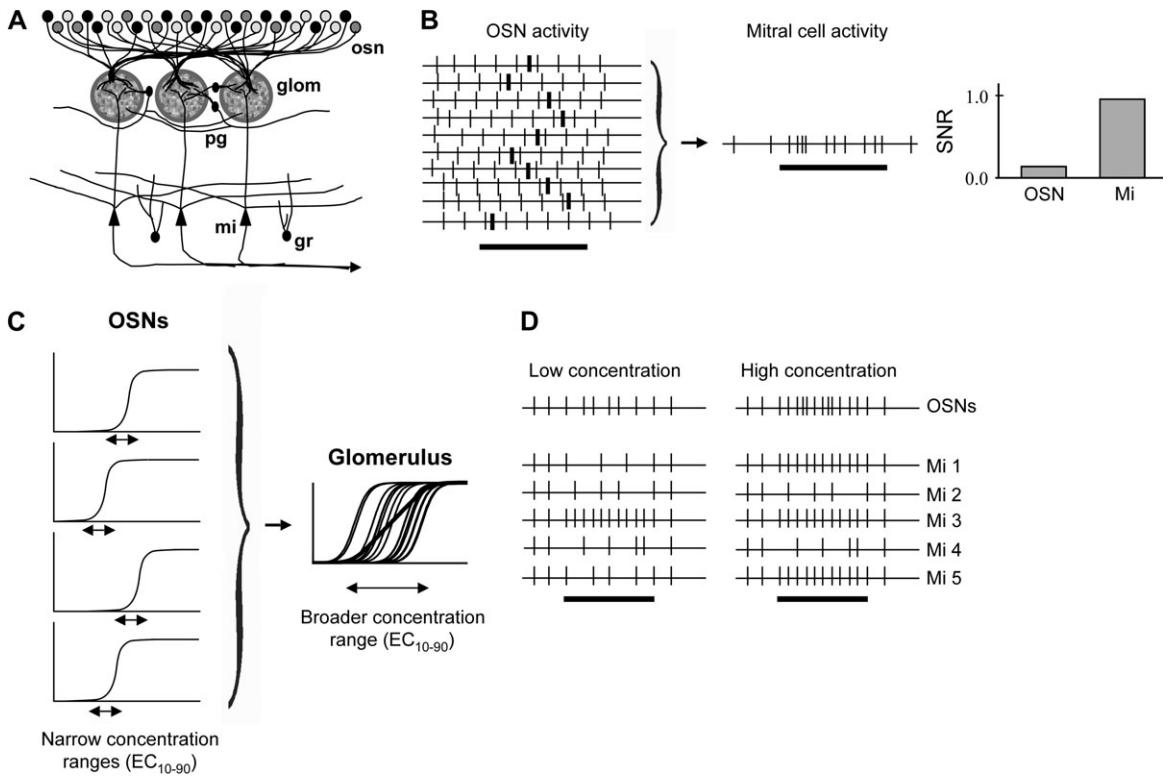

Figure 1 Glomerular computations and convergence. **(A)** Simplified structure of the OB as represented in most computational models. Large populations of olfactory sensory neurons (osn) expressing the same receptor (particular shades of gray) converge onto common glomeruli (glom) in the OB, within which they synapse onto the dendrites of periglomerular (pg) and mitral (mi) cells. Mitral cells also excite granule cells (gr) via their lateral dendrites, and granule cells in turn inhibit mitral cells; functionally, this mediates lateral inhibition among mitral cells. PG cells are primarily associated with one or a small number of glomeruli and project axons to a few other glomeruli; these have also been suggested to mediate lateral inhibition between mitral cells. A number of other cell types have also been characterized in the bulb, such as short axon and tufted cells, that are rarely included in computational models; furthermore, established heterogeneity within the cell types modeled has usually been neglected. **(B)** The high convergence of OSN axons onto mitral cells within each glomerulus significantly improves the signal-to-noise ratio in mitral cells as compared to OSNs. Even if a weak odorant stimulus were to evoke only a single additional spike in each OSN above its basal rate of spiking (OSN activity; bold lines), this high convergence ratio can generate a robust odor response in a postsynaptic mitral cell (mitral cell activity), hence enabling mitral cells to reliably represent odor stimuli at lower concentrations than can OSNs (van Drongelen *et al.*, 1978). Horizontal bars depict the time of odorant presentation. The signal-to-noise ratio (SNR: ratio of stimulus-evoked spikes to all spikes) that can be measured in mitral cells is improved (larger) compared to that measured in OSNs. **(C)** While OSN concentration–activation curves are steep, enabling accurate representations of ligand–receptor binding over a range of roughly 1-log-unit concentration, the considerably broader curves observed in glomeruli can be explained if the convergent OSN population is nonuniform in spare receptor capacity or other determinants of intracellular gain (Cleland and Linster, 1999). If OSNs with identical odorant selectivity but exhibiting different functional spare receptor capacities (different half-activation values) project onto a single glomerulus, the summed concentration–activation curve of that glomerulus can span several log units of concentration. **(D)** Frequency-to-spatial transformation by local glomerular circuits proposes that different populations of mitral cells within each glomerulus are activated as a function of the average firing rate of the convergent OSNs (Anton *et al.*, 1991). Low-concentration odorants (left panel) evoke weak activity in a given receptor-specific OSN subpopulation, generating increased activity in only one mitral cell. In contrast, a high-concentration odor stimulus (right panel) evokes greater activity in the OSN population and hence generates measurable excitatory responses in three mitral cells. Horizontal bars depict the time of odorant presentation.

which mitral cells inhibit one another as well as themselves (Isaacson and Strowbridge, 1998), although the region receiving this inhibition is not clearly localized (Luo and Katz, 2001; Debarbieux *et al.*, 2003; Djurisic *et al.*, 2004). Subsequent models proposed that contrast enhancement was instead mediated by lateral inhibition mediated by the relatively superficial periglomerular (PG) cells (Linster and Gervais, 1996; Linster and Hasselmo, 1997) (Figures 1A and 2B). This hypothesis offered the substantial advantage that lateral inhibition could be delivered onto mitral cells in the glomerular region of their apical dendrites, a location better capable of preventing spike initiation in these cells owing to the close proximity of excitatory and inhibitory inputs (Liu, 2004; Mel and Schiller, 2004). In a model based on this hypothesis, Linster and Hasselmo (1997) further showed that if the activation of PG cells is modulated by cholinergic inputs from the horizontal limb of the diagonal band, a relatively stable number of active mitral cells can be maintained independent of the intensity of olfactory input or the set of OSNs activated by the odorant. In this model, granule cells served instead to modulate the gain of mitral cell activity and were necessary in order to obtain stable average firing rates. Indeed, subsequent studies have shown that PG cells are appropriately modulated by acetylcholine (Castillo *et al.*, 1999),

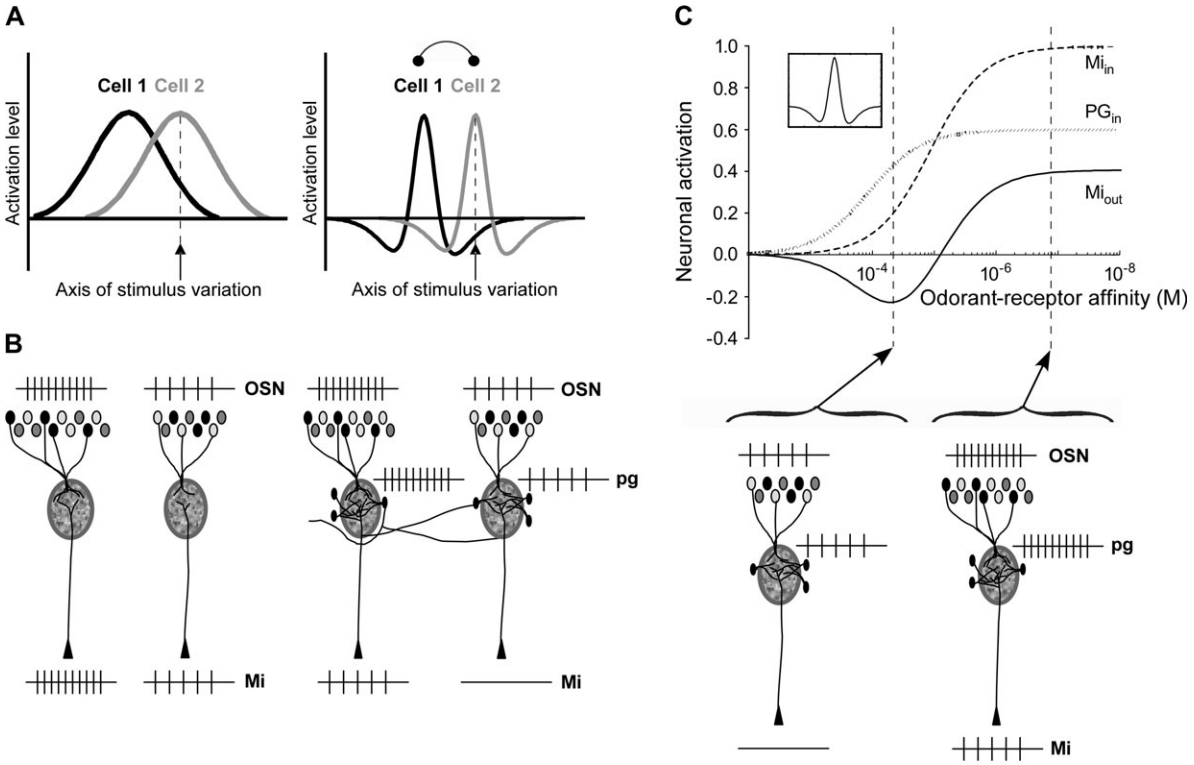

Figure 2 Contrast enhancement. **(A)** Contrast enhancement is a phenomenon observed in most sensory systems by which marginally activated neurons are excluded from a stimulus-specific ensemble by inhibition, hence sharpening the sensory representation and differentiating it from other, similar representations. In the absence of contrast enhancement, the tuning curves of cells 1 and 2 substantially overlap (left panel), and the stimulus represented by the vertical line evokes activity in both cells. If contrast enhancement is enabled, for example, by the addition of lateral inhibition such that each cell inhibits the other, the two cells both become more narrowly tuned, and their receptive fields may no longer overlap. The stimulus represented by the vertical line now evokes activity only in cell 2, while cell 1 is inhibited (right panel). **(B)** Computational models of the OB have proposed that inhibitory PG cells could mediate contrast enhancement in the glomerular layer of the OB. In these models, PG cells receive direct sensory input within a given glomerulus and inhibit mitral cells in neighboring glomeruli via axonal projections. If an odor stimulus activates a range of neighboring glomeruli, increasing the level of PG cell–mediated inhibition would lead to concomitantly sharpened representations among mitral cells. Left panel: in the absence of PG cell–mediated inhibition, mitral cell activity directly reflects OSN activity. Right panel: the addition of inhibitory projections mediated by PG activity inhibits the more weakly activated mitral cell out of the active ensemble. With strong contrast enhancement, only the most strongly activated mitral cells become activated by odor inputs, while weakly activated mitral cells are inhibited. **(C)** Nontopographical contrast enhancement based on local glomerular computations (Cleland and Sethupathy, 2004). In this model, contrast enhancement is generated within the stimulus-response profile of each individual glomerulus, resulting in sharpening of the odor-evoked representation across the glomerular layer. Within each glomerulus, mitral (Mi_{in}) and periglomerular (PG_{in}) cells have the same tuning curves but different response properties and both receive parallel input from OSNs. Mitral cell output (Mi_{out}) is additionally shaped by PG-mediated dendrodendritic inhibition, such that only the most strongly excited mitral cells are activated (lower right panel), while more weakly excited mitral cells exhibit net inhibitory responses (lower left panel). The shape of the Mi_{out} curve generates the familiar on-center/inhibitory-surround function of contrast enhancement (inset).

and some of the behavioral predictions from these models have been confirmed in rats (Linster *et al.*, 2001a; Linster and Cleland, 2002).

Contrast enhancement, the effects of which have been directly observed in the OB (Yokoi *et al.*, 1995), can be functionally defined as a process of competition between neurons proportional to the similarity of the information that they mediate. Simplified models of the olfactory system, based on one-dimensional odor subspaces, have been able to implement contrast enhancement using lateral inhibition (Linster and Gervais, 1996; Linster and Hasselmo, 1997, 1999; Linster and Smith, 1997; Linster and Cleland, 2001; Cleland and Linster, 2002) as well as spike synchrony (Cleland and Linster, 2002) and have been effective at interpreting behavioral and physiological data derived from single monotonically varying odorant series (Yokoi *et al.*, 1995; Linster and Hasselmo, 1999; Cleland *et al.*, 2002; Cleland and Narla, 2003). However, to escape this limitation and model more realistic, high-dimensional odor spaces (Hudson, 1999; Korsching, 2001; Alkasab *et al.*, 2002), subsequent models have relied upon networks constructed so that the strength of PG-mediated inhibition is effectively proportional to receptive field similarity rather than the physical proximity of glomeruli. One network model based on this assumption has been shown to best reproduce calcium imaging data obtained from honeybee OSNs and projection neurons (analogous to mitral cells), while networks based on nearest-neighbor lateral inhibition performed comparably to networks based on random inhibitory projections (Linster *et al.*, 2005). Another such model has successfully reproduced

mixture processing properties measured in rats (Wiltrout *et al.*, 2003; Linster and Cleland, 2004). One set of models has proposed a means for contrast enhancement to be effected by spike synchronization, independent of the underlying firing rates (Linster and Cleland, 2001; Cleland and Linster, 2002). Finally, nontopographical models of contrast enhancement are also capable of distributing inhibition in proportion to receptive field similarity, but they approach the problem differently, relying on intraglomerular computations and broad feedback inhibition to effect contrast enhancement via a ''winner-take-most'' algorithm in which the most active neurons inhibit those that are less active (Figure 2C; Cleland and Sethupathy, 2004). Furthermore, unlike mechanisms based upon lateral projections, nontopographical contrast enhancement does not require a built-in foreknowledge of the similarities in molecular receptive ranges expressed by different OB glomeruli in order to distribute inhibition correctly and is entirely independent of the physical location of glomeruli within the OB.

Mechanisms underlying oscillations and spike synchronization

While recent models have begun to favor glomerular-layer mechanisms for contrast enhancement, granule cell activity also clearly shapes mitral cell response patterns and hence the presumptive odor representations that emerge from the OB. Specifically, several computational models of the OB have suggested that the temporal pattern of spiking among mitral cells may play a role in odor representation (Schild, 1988; Meredith, 1992; White *et al.*, 1992, 1998; White and Kauer, 2001). While it is clear that temporal response patterns in mitral cells do change as a function of odor identity, there is as yet no broadly accepted theory of how these response patterns may contribute to the representation of odorant stimuli. Figure 3A illustrates an example of how odor identity could be represented by temporal patterning in mitral cells. Each of four odors A–D evokes characteristic temporal spike patterns in two mitral cells (left panel). If the instantaneous spike rates of these mitral cells are plotted against each other during the odor response, each odor evokes a different trajectory representative of the odor (right panel).

One of the most widely studied features of OB processing has been the dynamic oscillatory activity patterns observed in the bulb in response to odor stimulation, particularly given the observation that mitral cell spiking is correlated in time with these field oscillations (Freeman and Grajski, 1987; Eeckman and Freeman, 1990; Kay *et al.*, 1996; Kashiwadani *et al.*, 1999; Kay, 2003). Some researchers have proposed that odor quality may be represented in dynamic attractors formed in the OB (Freeman, 1979, 1987, 1994; Li and Hopfield, 1989; Erdi *et al.*, 1993; Fukai, 1996; Hoshino *et al.*, 1998; Breakspear, 2001). Models of these phenomena have traditionally evaluated these responses as coupled oscillators, attributing the dynamics to reciprocal feedback interactions between mitral cell secondary dendrites and granule cells (Figure 3B; Freeman, 1979, 1987, 1994; Li and Hopfield, 1989; Grobler and Erdi, 1991; Erdi *et al.*, 1993; Ermentrout and Kleinfeld, 2001). However, several studies have focused on intraglomerular mechanisms such as gap junctions mediating the synchronization of mitral cells emerging from the same glomerulus (Schoppa and Westbrook, 2001, 2002; Schoppa and Urban, 2003; Christie *et al.*, 2005; Hayar *et al.*, 2005). Indeed, a recent model of these intraglomerular interactions supports these proposals, suggesting that reciprocal coupling among mitral cell apical dendrites could be instrumental in generating local spike synchronization (Migliore *et al.*, 2005). It is also increasingly clear that the dynamics of the OB are tightly coupled with those of the piriform cortex and that both depend on mutual feedback between the two structures (Gray and Skinner, 1988; Neville and Haberly, 2003; Martin *et al.*, 2004); combined bulb–cortex models have suggested possible roles for these interactions (Fukai, 1996; Li and Hertz, 2000). Other aspects of piriform cortical dynamics have also been modeled (Wilson and Bower, 1992; Liljenstrom and Hasselmo, 1995; Claverol *et al.*, 2002; Xu and Principe, 2004), albeit with less focus on their functional role (but see Granger and Lynch, 1991).

Recently, models of these field oscillatory properties have begun to emphasize their relationship to the regulation of spike timing in mitral cells (Davison *et al.*, 2003; Margrie and Schaefer, 2003), suggesting that patterns of spike synchronization among mitral cells responding to the same sensory input are important contributors to the odorant representation at this level. In the example shown in Figure 3C, the average firing rates of the two model mitral cells do not contribute to the differentiation of odors A and B. However, the phase of firing during oscillatory cycles does contribute odor identity information sufficient to discriminate these two odors. This type of coding scheme was first proposed for the insect antennal lobe by Laurent and coworkers (Laurent, 1996; Laurent *et al.*, 1996; Stopfer *et al.*, 1997), supported by behavioral data demonstrating that a reduction in the synchronization of projection neuron action potentials impaired odor discrimination in honeybees (Stopfer *et al.*, 1997). This phenomenon was subsequently studied in genetically modified mice (Nusser *et al.*, 2001) and has been modeled by several groups. These models have primarily served to illustrate and emphasize the circuit properties and mechanisms by which the regulation of spike synchronization among secondary neurons could contribute to odor representations. Specifically, some models have explored the biophysical bases of slow temporal patterning and fast oscillogenesis among secondary olfactory neurons (Bazhenov *et al.*, 2001), while others have demonstrated how the regulation of spike synchronization among secondary neurons can influence the readout of information at the next level of processing (Perez-Orive *et al.*, 2004; Sivan and Kopell, 2004), facilitate contrast enhancement, and underlie

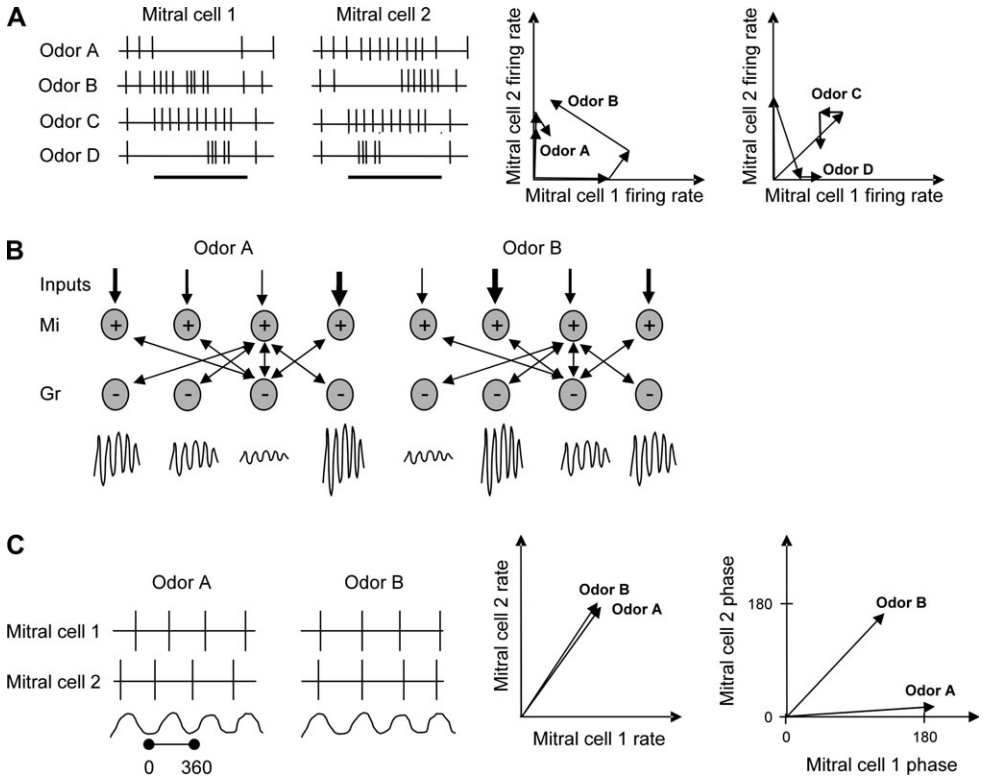

Figure 3 Oscillations and synchrony. **(A)** Any given mitral cell in the OB may respond to different odorant stimuli (A, B, C, and D) with a variety of temporally complex spike patterns including interwoven excitatory and inhibitory phases. It has been proposed that these temporal patterns may contribute to odor representations in the vertebrate OB and the analogous insect antennal lobe (Laurent, 1999; Laurent *et al.*, 2001). If the instantaneous firing rates of two cells are depicted as a function of each other, a distinct trajectory (in time) can be plotted for each odorant stimulation. For clarity, three discrete epochs are depicted rather than a continuous function; the three time windows depicted during odorant presentation (left panels; horizontal bar) correspond to the three vectors comprising each trajectory in the graphs (right panels). In contrast, if average firing rates over the application of the stimulus were plotted, the responses to the three odorants could not be differentiated (not shown). **(B)** The reciprocal synaptic interactions between mitral (Mi) and granule (Gr) cells have often been simulated as a system of coupled oscillators driven by external inputs. In such models, the variance among the stimulus amplitudes across these inputs generates a map of field oscillations with variable amplitudes and fixed phase lags across the OB. For clarity, bidirectional connections are depicted from only a single column. Oscillation amplitudes across the OB are representative of the odor stimulus (compare the patterns evoked by the two odors). **(C)** Field oscillatory dynamics are believed to reflect and/or influence spike timing in mitral cells, potentially resulting in odor-specific populations of mitral cells based on spike synchrony rather than overall activity. While the overall activity patterns evoked by odors A and B are very similar, selection for spikes relatively synchronized with one another and with the oscillatory field potential reveals two clearly odor-specific subpopulations. Consequently, when the firing rates of the two cells are plotted against one another, the representations of the two odors are nearly indistinguishable (middle panel). In contrast, when the relative phases of the two cells are plotted, clearly different representations of the two odors can be observed (right panel).

the salience of olfactory stimuli (Linster and Cleland, 2001; Cleland and Linster, 2002).

Odor segmentation and associative memory function

Odor segmentation is the general term for the problem of how the olfactory system is able to segregate and identify different odorants that are encountered simultaneously. As most odors comprise multiple separate odorant molecules, it is far from clear how the olfactory system can parse the multitude of odorant stimuli present at any given time and attribute each to appropriately separate sources. One approach has been to hypothesize that odors emitted from different sources can be segregated by OB circuitry based upon their differential fluctuations in time (Fort and Rospars, 1992; Hendin *et al.*, 1998; Hopfield, 1999). Odor segmentation could thereafter be performed in the OB using source-separation algorithms dependent upon associative memory function. Generally, such models hypothesize that associative memories for patterns of OB activity evoked by known odorants become embedded in bulbar circuitry and can then be used to recognize these patterns when they recur, even in degraded form. Specifically, a model by Hendin *et al.* (1998) illustrates how, if the glomerular layer feeds into a mitral-granule cell layer for which appropriate dynamics for an associative memory function have been implemented, each odor can be separately represented in successive inhalation cycles when multiple (known) odors are presented at the same time.

Olfactory associative memory functions have been more commonly attributed to the piriform cortex, one of the

targets of mitral cell axons projecting from the OB. Specifically, the piriform cortex has been proposed to mediate the associative memory functions necessary for odor-context learning (Haberly and Bower, 1989; Hasselmo *et al.*, 1990; Haberly, 2001) and hierarchical clustering (Ambros-Ingerson *et al.*, 1990). For example, cortical short-term synaptic depression can be employed to filter out stable background odorants, whereas long-term synaptic plasticity can store associations between neurons responding to the same odor stimuli (Figure 4). Indeed, the extensive intrinsic feedback network in this cortex and its integration with afferent inputs closely resembles the structure of traditional theoretical associative memory networks as first described by Marr (1971). Several laboratories have constructed models of piriform cortex, implementing these associative memory functions (Haberly and Bower, 1989; Ambros-Ingerson *et al.*, 1990; Hasselmo *et al.*, 1990; Barkai and Hasselmo, 1994; Hasselmo *et al.*, 1997) as well as exploring the role of cortical cholinergic modulation in their regulation (Hasselmo *et al.*, 1990, 1997; Patil and Hasselmo, 1999; Linster and Hasselmo, 2001; Linster *et al.*, 2003).

Detailed biophysical models

Most models of the olfactory system to date have emphasized network-level interactions and the properties of OB and piriform cortical circuitry using simplified cellular models conducive to these larger scale simulations. However, several relatively detailed biophysical models of olfactory neurons—particularly OSNs and mitral cells—have also been constructed. Biophysical (or compartmental) models focus on membrane and cellular properties rather than network phenomena; to this end, they include substantial morphological, biophysical, and/or physiological detail. For example, membranes are modeled with membrane resistivity and capacitance values drawn from experimental data, with realistic or data-derived lengths, diameters, and morphological branching patterns along with models of passive and active ion channels inserted in appropriate regions of the model

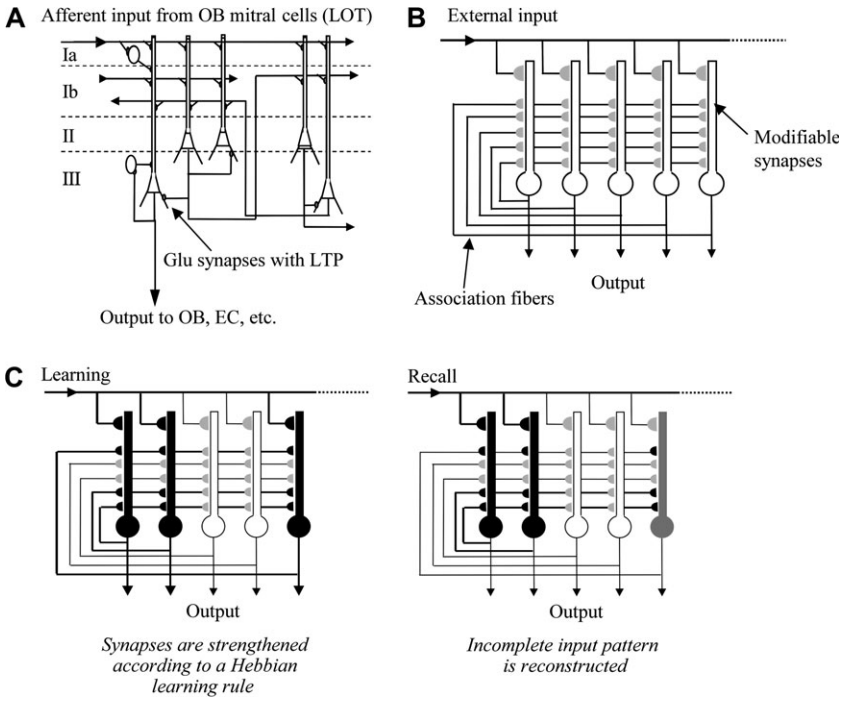

Figure 4 Associative memory function in olfactory cortex. **(A)** Piriform cortex exhibits the fundamental anatomical features necessary for the implementation of associative memory: extrinsic input from the OB to each pyramidal cell via the lateral olfactory tract (LOT) and extensive intrinsic excitatory connections among pyramidal cells. These intrinsic associative connections are subject to synaptic plasticity, also crucial for associative memory function, and exhibit long-term potentiation (LTP). Additionally, several classes of local inhibitory interneurons have been described in the piriform cortex. Piriform pyramidal neurons project back to the OB, as well as to other structures such as the entorhinal cortex (EC). **(B)** Schematic representation of an associative memory network. The critical features are (1) external inputs to associative neurons, (2) all-to-all excitatory connections among these neurons (association fibers), and (3) a learning rule that modifies the strengths of these connections when external inputs are being learned by the network (modifiable synapses). **(C)** Learning and recall in an associative memory network. Learning (left panel). An olfactory stimulus activates a subset of pyramidal cells (three dark cells) via distributed afferent projections from the OB to the PC. During learning, excitatory synaptic connections between pyramidal cells activated by that odorant are strengthened via a Hebbian plasticity rule (dark semicircles denote strengthened synapses). Recall (right panel). After learning a pattern, if a noisy or degraded example of that pattern is presented to the system, the stored odorant pattern can be reconstructed due to the previously strengthened connections. Dark semicircles denote previously strengthened synapses. Owing to the previously strengthened synapses, activation of just two dark cells secondarily activates a third cell (gray), reconstructing the previously learned pattern.

neuron. Biophysical models usually can be directly interrelated with electrophysiological data. However, they are often poor choices for large-scale models, due to the large numbers of weakly defined parameters as well as their substantial computational costs. Several detailed OSN models have illustrated how ligand–receptor binding and nonlinear transduction processes can underlie the experimentally observed response properties of these cells (Malaka *et al.*, 1995; Rospars *et al.*, 1996; Vermeulen *et al.*, 1996, 1997; Lansky and Rospars, 1998; Vermeulen and Rospars, 1998; Kaissling, 1998, 2001; Cleland and Linster, 1999; Rospars *et al.*, 2000; Kaissling and Rospars, 2004). Compartmental models of mitral cells have been used to elucidate intrinsic cellular phenomena, such as the localization of spike initiation in mitral cells (Shen *et al.*, 1999; Chen *et al.*, 2002) and the effects of intraglomerular gap junctions (Migliore *et al.*, 2005), as well as synaptic phenomena such as long-term potentiation at the OSN–mitral synapse (Ennis *et al.*, 1998). Other compartmental models have focused on bridging the gap between cellular and systems properties in both vertebrate and insect systems (Bhalla and Bower, 1993; Davison *et al.*, 2000, 2003; Bazhenov *et al.*, 2001; Cleland and Sethupathy, 2004). These detailed models make a clear case that the morphological and biophysical properties of OB neurons underlie and define their computational capabilities. While many emergent network properties are best studied with simple cellular models, biophysical models have revealed computational mechanisms that are beyond the capacity of these simpler models to elucidate. Ultimately, reconciliation of these detailed models with large-scale functional models will be necessary for progress in the understanding of olfactory processing.

Synthesis

Computational models of the olfactory system have contributed immensely to the framing of experimental problems and the construction of complex hypotheses regarding its function. Here, we briefly outline a working hypothesis of olfactory system function, integrating the insights derived from the models reviewed above and constrained by their supporting data sets.

Inhaled odorants bind to specific populations of ORs expressed on the apical surface of primary OSNs, which are distributed across the nasal epithelium. ORs are broadly tuned for odorant ligands, such that even simple monomolecular odorants activate a number of receptor types to differing degrees, producing combinatorial patterns of activation among OR classes that reflect odor quality. While the pattern of OSN activation depends primarily upon the ligand–receptor affinities of multiple OR populations for the various molecular moieties (odotopes) of odors' component molecules, it also is likely influenced by other factors such as the fluid dynamics of inhalation, the net molecular sorptiveness of odorant molecules, and the behavioral regulation of odor sampling (reviewed in Schoenfeld and Cleland, 2005). Other physical factors that affect the pattern of OSN activation include the concentration of odorants as well as interference caused by overlaps among the representations of multiple odotopes that are simultaneously presented to the olfactory epithelium. Different odotopes may compete for receptors for which they have not only different affinities but also different efficacies (Duchamp-Viret *et al.*, 2003; Araneda *et al.*, 2004; Oka *et al.*, 2004; Sanz *et al.*, 2005), such that a reduction in the activation of an OR gene–specific OSN population may as well connote an increased concentration of a relatively antagonistic odotope as a reduced concentration of an agonist odotope. In short, the pattern of OSN activation in any natural scene context is likely to be an unknown composite of multiple, overlapping, and degraded primary odorant representations. It is from this unpromising raw material that the olfactory system must detect and identify relevant stimuli.

OSNs expressing the same OR and hence sharing the same molecular receptive range project their axons to specific glomeruli within the OB input layer (Mombaerts *et al.*, 1996). Hence, the primary olfactory representation can be conveniently measured by imaging glomeruli: that is, the axonal arborizations of convergent OSNs in the OB glomerular layer. Some glomerular imaging techniques are explicitly presynaptic (Friedrich and Korsching, 1997; Wachowiak *et al.*, 2002), even those that are not are likely to reflect predominantly presynaptic activity due to the disproportionate number of OSNs arborizing within each glomerulus compared with the number of bulbar neurons arborizing therein (Shepherd and Greer, 1998; Schoenfeld and Knott, 2004); glomeruli, of course, do not contain cell bodies. Under simple experimental conditions, these glomerular response profiles are predictive of odor quality, as measured behaviorally (Johnson and Leon, 2000; Linster *et al.*, 2001b; Cleland *et al.*, 2002; Leon and Johnson, 2003). However, this concordance is not robust even to changes in odorant concentrations and certainly cannot be expected to persist in the context of a complex olfactory natural scene.

Mitral cells, along with middle and deep tufted cells, are the principal output neurons of the OB. They are directly postsynaptic to OSNs, and as such the pattern of mitral/tufted cell activation across the bulb constitutes the secondary olfactory representation. In mammals, mitral cells sample from only a single glomerulus, hence a glomerulus along with its associated mitral cells and interneurons has been referred to as an "odor column" (Shepherd and Greer, 1998) that derives its receptive field primarily from a single population of convergent OSNs. However, the mitral/tufted activation pattern also depends on the activity of several classes of bulbar interneurons and hence is substantially transformed with respect to the primary olfactory representation. For example, some form of normalization of stimulus concentrations is clearly evident in the concentration–response profiles of mitral cells. Mitral cell activity patterns are

relatively stable across concentrations compared with the changes in OSN responses (Chalansonnet and Chaput, 1998), and when they are affected by odorant concentration changes, these changes are often complex and difficult to predict. Some mitral cells progress from excitation to inhibition with increasing concentrations, while others become more excited, often exhibiting shorter latencies to first spike; other cells display yet other profiles (Harrison and Scott, 1986; Meredith, 1986; Wellis *et al.*, 1989; Chalansonnet and Chaput, 1998). What is clear, however, is that mitral cells do not monotonically increase their activity in response to increased stimulus intensities, nor, consequently, is there likely to be a substantial broadening of mitral cell activity across the bulb owing to the recruitment of lower affinity receptors. These are two essential ways in which the structure of the secondary (mitral) olfactory representation differs from that of the primary representation as measured among OSNs, and this transformation provides essential constraints to models of bulbar mechanisms.

Normalization, the process by which sets of values are rescaled to a common or tractable range, requires a negative feedback loop that is effectively global in scope; that is, the strength of feedback inhibition should be scaled to the average activity across the bulb rather than to local activation levels if the profiles of relative activation among odor columns are to be preserved. Contrast enhancement, in turn, requires the delivery of inhibition onto odor columns proportional to the activation of columns exhibiting similar receptive fields (molecular receptive ranges). In the OB, the synaptic triad connecting OSN arbors, PG cell dendritic spines, and mitral cell dendrites in close proximity (reviewed by Shepherd and Greer, 1998) coupled with the lateral excitatory network mediated by external tufted and short axon cells (Aungst *et al.*, 2003; Hayar *et al.*, 2004) can effect both normalization and contrast enhancement between the primary and secondary olfactory representations (Cleland and Sethupathy, 2004). Briefly, OSNs activate mitral cells, external tufted cells, and PG cell dendritic spines in parallel, and these PG spines deliver inhibition onto mitral cell apical dendrites, closely apposing the excitatory OSN inputs. Nontopographical contrast enhancement models (Cleland and Sethupathy, 2004) predict that PG cell–mediated feedforward inhibition of the mitral cell will predominate when the odor column is weakly activated, while direct OSN activation of the mitral cell will predominate when the odor column is strongly activated (Figure 2C), consistent with recordings from rabbit mitral cells (Yokoi *et al.*, 1995). Normalization is effected via the activation of external tufted cells, which proportionately excite a lateral excitatory network of external tufted and short axon cells, thereby broadly inhibiting mitral cell activity across the bulb via sign-inverting PG cells.

The net activation of mitral cells is then translated into trains of action potentials, the precise timing of which appears to be regulated by coordinated oscillations measurable in field recordings across the OB. These bulbar oscillations are thought to depend on an extensive excitatory–inhibitory network of mitral cell secondary dendrites and granule cell interneurons, as well as reciprocal cortical connections that modulate bulbar activity according to behavioral state (Kay, 2003; Ravel *et al.*, 2003; Lagier *et al.*, 2004; Martin *et al.*, 2004). Mitral cell spike synchronization patterns can mediate a second level of feature extraction to the odor representation, as follower neurons in diverse central olfactory structures (Cleland and Linster, 2003) process incoming mitral cell spikes via synaptic learning rules, the best known of which rely upon precise spike timing (Song *et al.*, 2000; Cleland and Linster, 2002). Centrifugal modulatory inputs also influence olfactory processing and learning mechanisms within the OB (Sullivan *et al.*, 2000; Linster and Cleland, 2002; Yuan *et al.*, 2003), emphasizing the active role of the OB in shaping and transforming odor signals and the importance of behavioral state.

Conclusions

Computational models have an established and growing role within systems neuroscience. As our understanding of neural processing and interactions becomes more sophisticated, computer models of these systems are increasingly necessary in order to understand and interpret experimental results. In the olfactory system in particular, computational modeling will no doubt be essential to understand the integration of the many factors influencing the construction and transformation of odor representations.

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