Title: Is the olfactory bulb computationally similar to the retina?

Author information:

Ambarish S. Ghatpande
Monell Chemical Senses Center, Philadelphia, PA 19104
email:aghatpande@monell.org


Keywords: olfactory bulb, lateral inhibition, sparse inhibition, computational role

Acknowledgements: I thank Dr. Graeme Lowe for helpful discussions, Dr. M. Ramaswami for pointing out the paper by Root et al. and Dr. Alan Gelperin for his generous support.
Abstract The computational role of the olfactory bulb remains a mystery after sixty years of physiological research. Recently, Fantana et al. (2008) have proposed a new model of bulb function based on sparse inhibitory connections between glomeruli, the functional units of the bulb, rather than the existing lateral inhibition model. I present a summary of their model here and its implications along with comparison to recent work in the very similar *Drosophila* olfactory system.

The vertebrate olfactory bulb and its insect analog, the antennal lobe, are the first brain areas to receive odor information from the nose and antennae respectively. Approximately twenty million olfactory receptor neurons located in the nose send their axons to the bulb of the rat. Each receptor neuron bears cilia that express only one of a possible thousand different G-protein coupled odorant receptors. Each odorant receptor is capable of binding several different volatile small molecules. The entire population of receptor neurons is capable of binding a very large number of different odorants. Although we have a fairly good understanding of how odor input to the bulb is organized, we do not yet understand the computational rules the olfactory bulb uses to transform this high-dimensional odor input into an output useful to the rest of the brain. Recently, Fantana et al. have directly addressed this fundamental question by combining functional imaging of the bulb to record olfactory inputs with extracellular recordings of the bulbar output neurons, while delivering 200 different olfactory stimuli to the nose of anesthetized rats (Fantana et al. 2008). Their conclusions about olfactory bulb function are quite different than a previous widely accepted model, which proposed
a computational role for the bulb quite similar to that of the retina, as described a little later (Yokoi et al. 1995).

As mentioned earlier, the bulb receives axonal projections from receptor neurons located in the roof of the nose. These receptor neuron axons are sorted into bundles at the bulbar surface according to the type of odorant receptor they express. These axon bundles enter specialized neuropil regions called glomeruli that cover the entire surface of the bulb and form synapses with second-order neurons (Figure 1). One class of these second-order neurons, viz. the mitral cells sends their apical dendrites into glomeruli and form synapses with the incoming axons. These same mitral cells carry the processed bulbar output via their own axons to several downstream areas. Mitral cells receive GABAergic inhibitory inputs at two levels. One class of inhibitory interneurons, the periglomerular cells, surrounds the glomeruli and sends their dendrites into them. Periglomerular cell dendrites form synapses with receptor neuron axons as well as forming two-way or reciprocal dendrodendritic synapses with mitral cell apical dendrites. These cells mediate intraglomerular inhibition between the ~25 mitral cells innervating a single glomerulus. Another class of GABAergic interneurons, the axon less granule cells, form reciprocal dendrodendritic synapses with the secondary dendrites of mitral cells at a deeper level in the bulb. Granule cells are thought to mediate most of the interglomerular inhibition. Thus, a glomerulus with its associated mitral cells and synaptically connected periglomerular and granule cell partners may be thought of as a single functional unit. Since each of these units receives input from a unique odorant receptor it forms a distinct channel of olfactory information. The rodent olfactory bulb is
a network of approximately two thousand such information channels connected to one another primarily through inhibitory synapses that granule cells form on mitral cell secondary dendrites.

The retina and the olfactory bulb share several cellular and synaptic features (DeVries and Baylor 1993). Over the years, bulb investigators have proposed and examined whether the input-output rules governing these two structures are similar. Lateral inhibition is a very well known input-output rule of the retina which arises partly due to a syncytial layer of inhibitory interneurons, similar to the granule cell layer of the bulb (DeVries and Baylor 1993). Lateral inhibition gives rise to the excitatory center, inhibitory surround receptive fields of some retinal neurons. Light falling on the center of their receptive field excites these neurons, while light falling on the surrounding region inhibits them. Analogous to these retinal center-surround receptive fields, bulbar mitral cells are proposed to receive excitation from the single central glomerulus to which they project their apical dendrites, while receiving inhibition via granule cells on their secondary dendrites from surrounding excited glomeruli. This excitatory center and inhibitory surround rule has been proposed for the olfactory bulb for a long time but has not been extensively tested. The question remains, do granule cells give rise to lateral inhibition in the bulb?

Fantana et al. set out to answer this question. To illustrate their line of reasoning, based on the predictions of the lateral inhibition model, consider the diagram shown in Figure 1B. The experiment they devised was to record the spiking of mitral cells that innervate
the ‘red’ glomerulus while activating the ‘yellow’, ‘green’ or ‘blue’ glomeruli by delivering different odors to the nose. If most of the glomeruli adjacent to the ‘red’ glomerulus are connected to it via shared granule cells, then it is expected that the mitral cells of the ‘red’ glomerulus should respond (i.e. show a change in spiking behavior) to activation of the adjacent ‘yellow’ and ‘green’ glomeruli. Furthermore, it is expected that this response should diminish with increasing radial distance from the ‘red’ glomerulus, such that activating the ‘blue’ glomerulus should not influence the spiking of mitral cells of the ‘red’ glomerulus.

Of course, in reality, the glomeruli are neither colored nor is it possible to exclusively target mitral cells innervating a single defined glomerulus. The authors, therefore, recorded from mitral cells in a small region directly beneath the center of the bulb’s dorsal surface, assuming these mitral cells should be innervating a few glomeruli located directly above them. The dorsal surface of the bulb was chosen because it is readily accessible to their imaging technique allowing them to simultaneously record glomerular activation by different odors.

Next, the authors ideally needed the ability to activate all the glomeruli within reach of their target mitral cell secondary dendritic fields. This is a demanding task in the rat olfactory bulb since each has ~1800 glomeruli with unknown sensitivity profiles to a nearly infinite number of odorants. They addressed this problem by developing a sophisticated odor delivery machine capable of emitting 100 different odors. In experiments extending 40 hours, they screened ~200 monomolecular odors for their
ability to activate any of the estimated 200 dorsally located glomeruli. To measure glomerular activation, the authors captured images of changes in reflected red light from the exposed dorsal surface of the bulb, a technique known as intrinsic optical signal imaging (IOS). The IOS signal is thought to arise from changes that occur in the blood flow and oxygenation levels of active regions of the brain, viz., glomeruli on the bulbar surface in the current experiments (Meister and Bonhoeffer 2001).

Based on IOS imaging the authors identified 40 odors that were relatively effective at activating dorsal glomeruli. Given that odor space is practically infinite, it was not surprising that most dorsal glomeruli (75%) failed to respond to any of the 40 odors. Of the remaining, individual glomeruli responded to anywhere between 1 to 20 odors in the panel. In total, they obtained 50 active, evenly distributed, dorsal glomeruli with their 40-odor panel.

In separate experiments, they recorded the extracellular spiking of 179 mitral cells in the center of the bulbar dorsal surface. Since these cells reside directly beneath the center, their secondary dendrites are expected to radiate to almost every region of the exposed dorsal surface. These centrally located mitral cells should therefore receive lateral inhibition from a substantial fraction of the dorsal glomerular units activated by the 40-odor panel. To identify reproducible change in a mitral cell’s firing pattern with odor application, the authors developed a highly sensitive measure based on the timing of individual spikes within each inhalation cycle rather than using a less sensitive conventional firing rate measure. They were surprised to find that half the centrally located mitral cells were unresponsive to any of the 40 odors. Of the remaining half,
individual cells were responsive anywhere from 1 to 10 odors with an average of 2 and a median of 3 odors per cell.

Having obtained odor response spectra for 179 centrally-located mitral cells and knowing the location of dorsal glomeruli that responded to every odor in the panel, the authors then fit the obtained response spectra of each mitral cell to two models. One, the lateral inhibition model, assumed a weak but radially uniform inhibition with the strength dependent on the distance from the mitral cell’s own glomerulus (shown in Fig. 1B). Another, the sparse-inhibition model, assumed that the inhibitory inputs to each cell were few in number and not necessarily radially distributed (shown in Fig. 1C). The lateral inhibition model fit the odor response spectra of most mitral cells poorly. The sparse inhibition model that relaxed the assumption of adjacency but allowed the contribution of a few glomeruli anywhere on the dorsal surface fit most odor response spectra well. Based on these results, the authors suggest that interglomerular inhibition in the bulb is unlike lateral inhibition in the retina. It does not have a dense but weak inhibitory surround. Instead, inhibition is much more restricted: it flows between a few specific glomeruli that strongly inhibit one another but are not necessarily adjacent.

These results clearly outline an alternative to the current model of lateral inhibition in the olfactory bulb (Yokoi et al. 1995). What are the implications of this new model of interglomerular inhibition for the olfactory system? Lateral inhibition, as described in the retina, removes redundant spatial information, thereby improving the information-carrying capacity of the retinal output. The need for lateral inhibition is not readily
apparent in the olfactory bulb. It is thought to improve ‘contrast’ between closely related odors that have been shown to activate adjacent glomeruli. What might a bulb that employs sparse inhibition achieve? As envisioned by the authors, such an output essentially reformats the information originally coming from the nose rather than just enhancing contrast. Using some unknown chemical-ecological logic, perhaps unique to each species, the bulb combines input of glomeruli receiving chemically diverse inputs to generate a unique representation of the stimulus and transfers that representation to the olfactory cortex. Thus, the consequences of lateral versus sparse inhibition for bulbar output are fundamentally different.

One limitation of the present work is that the evoked IOS, although odor-specific, arises due to presynaptic and astrocytic activity (Gurden et al. 2006; Petzold et al. 2008). It is possible that the 40-odor panel might not effectively activate mitral-granule circuits underlying the IOS-active glomeruli. If this is shown to be true, the present conclusions will need to be revised. This potential drawback will be resolved as new techniques are discovered that allow for visualization of odor-evoked postsynaptic activity in glomeruli and confirm the reliability of IOS in reporting activated glomerular functional units.

As previously discussed (Wilson and Mainen 2006), the current lateral inhibition model of bulb function has several predictions. It is useful to examine the present findings in that light:

1) Lateral inhibition predicts that receptor neurons are more broadly tuned, i.e. respond to more odors than their corresponding mitral cells. Fantana et al. found a few glomeruli that were activated by up to 20 odors while the most broadly tuned mitral
cells they encountered responded to at most 10 odors. This is consistent with receptor neurons being more broadly tuned, though it is not definitive. A definitive test for a few known receptor neuron-principal neuron combinations (principal neurons are the insect analog of mitral cells) has recently been carried out in fruit flies. The results indicate that in fact, principal neurons are more broadly tuned than their corresponding receptor neurons (Bhandawat et al. 2007). Neither lateral nor sparse inhibition models predict these results that require the presence of lateral excitatory inputs. Does this mean that the insect antennal lobe and the vertebrate olfactory bulb have different input-output rules? Might there be a third model of bulbar function? Better methods of labeling and recording bulbar activity in vivo will be required to explain these apparent contradictions.

2) Yet another prediction of the lateral inhibition model is the one directly tested by the authors: that of radially uniform inhibition. Interestingly, a recent report that examined lateral inhibition in the Drosophila antennal lobe found that inhibition was uniformly distributed over all glomeruli and scaled with the strength of total receptor neuron output (Olsen and Wilson 2008). Although the extent and uniformity of inter versus intra-glomerular inhibition is very much a matter of active investigation in the antennal lobe (Root et al. 2008), the report by Olsen and Wilson suggests lateral inhibition in the antennal lobe is different than either the lateral or sparse inhibition model of bulb function. Further experiments in both systems should resolve these fundamental issues.

3) There is evidence that both insect as well as vertebrate olfactory systems have specialist channels of information (Wilson and Mainen 2006). These are odorant
receptors specifically attuned to odorants / pheromones that are crucial for specific species. Thus, bulbar circuitry is expected to have specialized glomerular units that respond to very few odors and are not highly interconnected with other more generalized glomerular units. In their work, Fantana et al. have tested only a limited subset of dorsal glomeruli. It remains to be seen if their conclusions are valid for other areas of the olfactory bulb.

In conclusion, Fantana et al. have suggested a new model of olfactory bulb function that will stimulate further work aimed at understanding the computational role of this crucial part of an important sensory system. Their results have also highlighted apparent functional differences with the antennal lobe of insects and the need to reconcile them.
References


Figure Legend

**The olfactory bulb circuit and two models of bulb function:** 

**A.** Simplified diagram of the olfactory bulb and its neuronal connections is shown. Odorant receptor neurons in the nose are shown in various colors which indicate that each receptor neuron expresses only one of a thousand-possible odorant G-protein coupled receptors on their cilia. The axons of all receptor neurons expressing one kind of receptor collect together and enter one of two glomeruli on the surface of each olfactory bulb. Each glomerulus is innervated by ~ 25 mitral cell apical dendrites that synapse with the receptor neuron axons. A population of inhibitory periglomerular cells surrounds each glomerulus and sends their dendrites into the glomerulus to form synapses with receptor neuron axons and dendrodendritic synapses with mitral cell apical dendrites. At a deeper level, each mitral cell also bears long, radiating secondary dendrites that receive inhibitory input from GABAergic granule cell dendritic spines. The dendrodendritic synapses formed between mitral and periglomerular or granule cell spines are capable of receiving excitatory input from mitral cells and releasing GABA from nearby sites on the same spine. 

**B.** In a lateral inhibition model, each mitral cell is connected to all or most adjacent glomeruli. This is accomplished through granule cells that form dendrodendritic synapses with mitral cells innervating adjacent glomeruli. This model predicts that extracellular spikes recorded from mitral cells of the ‘red’ glomerulus will be strongly influenced when the ‘yellow’ or ‘green’ glomeruli are activated by odor rather than the ‘blue’ glomerulus. The connections between adjacent glomeruli are stronger and the strength falls with increasing radial distance shown as a blue colored zone around the secondary dendrites, with darker color indicating a stronger connection between glomerular units. 

**C.** The sparse inhibition model proposed by Fantana *et al.* (2008). In this model, only a few glomeruli are strongly connected to one another through shared granule cells. Thus, mitral cells of the ‘red’ glomerulus are disynaptically connected to mitral cells of the ‘green’ and ‘blue’ glomeruli (connections shown as blue ovals on secondary dendrites), but are not connected to the ‘yellow’ glomerulus. Here, inhibition operates between specific glomeruli that need not be adjacent to one another. Intense color indicates a stronger connection than a faint colored oval.
A

receptor neurons

glomerulus

periglomerular cell

apical dendrite

secondary dendrites

mitral cell

granule cells

B

Lateral Inhibition

activation by odor

C

Sparse Inhibition