Analysis of the mitral cell-granule cell reciprocal synapse: adaptation and divisive scaling

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INTRODUCTION

The mammalian olfactory bulb (OB) is an attractive system for exploring how cellular physiology transforms complex stimuli at the sensory periphery into percepts that are identifiable, discriminable, and carry emotional valence (Laurent, 2001). Although there is debate as to whether the neural code in the OB is fundamentally rate or time based, it is generally agreed that the bulb employs many of the same "canonical" neural tuning and noise reduction strategies described for other peripheral sensory structures such as the retina. These include, but are not limited to; a robust axonal convergence of ORN axons into anatomically distinct glomeruli, and an extensive lateral network that allows communication between the bulb's principal neurons - the mitral cells. In addition to these classical kinds of computations, there is substantial evidence that the bulb utilizes various oscillations to both represent stimuli and to provide a respiration locked-reading frame to temporally reformat synaptic activity (Margrie and Schaefer, 2003).

Numerous theoretical studies have demonstrated that oscillatory activity is exceptionally robust in networks of mutually inhibitory, weakly coupled neurons (Hoppenensteadt and Izhikevich, 1997). Although such connectivity is realized in the bulb through lateral inhibition mediated by granule cells (Margrie *et.al*, 2001), there is also a second kind of inhibitory coupling connecting mitral cells to themselves via recurrent dendrodendritic inhibition(Isaacson and Strowbridge, 1998). This self inhibition is mediated through a "short-loop" synaptic circuit in which a secondary dendrite of a mitral cell releases glutamate onto an adjacent granule cell dendrite (Schoppa et.al ,1998), which in turn controls the graded release of GABA back onto the original mitral cell dendrite (fig 1 and fig.2).

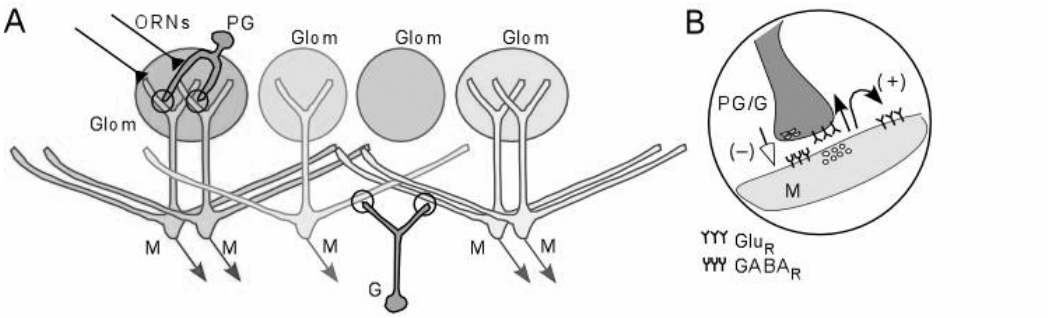

Figure 1. *Schematic of recurrent inhibition in the olfactory bulb.* **A** shows the major lateral connections of the bulb, including the dendrodendritic mitral cell(M)-granule cell(G) synapse. **B** shows an expanded view of this synapse, indicating forward, glutamatergic, and "reverse," GABAergic synaptic transmission (Modified with permission from Schoppa and Urban (2003))

Although the full functional implications of this reciprocal inhibition are at present unknown, a reasonable first approximation is that it functions as a ligand mediated after-hyperpolarizing current (AHP) and confers on the mitral cell properties typical of AHPs mediated by voltage dependent conductances. These effects include spike frequency adaptation and a redistribution of interspike intervals. In the present study, we use a computational model to investigate the nature of hyperpolarizations mediated by graded recurrent inhibition, and their effects on firing rate and spike distributions. In addition, we use this model to examine some of the dynamical consequences of self-inhibition, including increased sensitivity to the slope of input transients. We conclude with a demonstration that a divisive like computation can be implemented at this reciprocal synapse.

MODEL

Here we model a single mitral cell and granule cell as classic integrate and fire neurons with both deterministic thresholds and reset values. The only external input is delivered to the mitral cell in the form of synaptic noise (poisson distributed EPSPs of given average frequency). The coupling between mitral cell and granule cell is realized as a reciprocal interaction which is excitatory in forward direction (from mitral to granule cell) and is inhibitory in reverse direction (granule cell to mitral cell).The model includes a rendering of reciprocal connectivity which captures both sub and suprathreshold granule cell transmitter release (fig. 1 and fig. 2).

This was implemented with the following rule:

$$\textit{If}\ \ V_g(t) \geq V_{gthresh} \rightarrow\ P_{rel}=1,\ N=N_{max}$$

$$\textit{If}\ \ K < V_g(t) < V_{gthresh}\ \text{ and } V_m(t) \geq V_{mthresh} \rightarrow P_{rel}=1,\ N=.5N_{max}$$

$$\textit{Else}\ P_{rel}=0$$

Where V_g (t), $V_{gthresh}$ denote the granule cell voltage and threshold, V_m(t), $V_{mthresh}$ denote the mitral cell voltage and threshold, and K is a fixed voltage above resting potential. P_{rel} and N_{max} denote release probability and total quanta in the releasable pool, respectively. N is the number of quanta released, and differs for sub and suprathesholds granule cell voltages. All simulations were performed in Matlab.

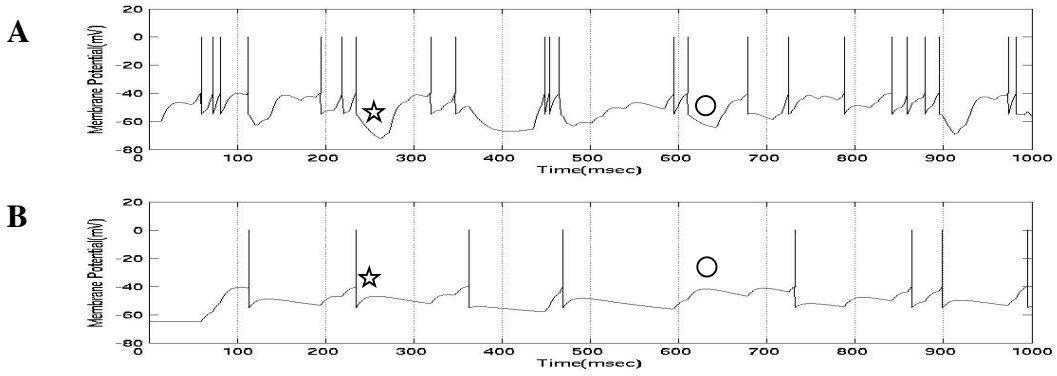

Figure 2. A) *Mitral Cell response for poisson distributed synaptic input with average frequency of 100 Hz* **B)** *Granule Cell response*. Both types of inhibitory events, supratheshold and subthreshold can be seen in the above plot. ☆Supratheshold. ○Subthreshold.

SIMULATION RESULTS

The first simulation was a standard I-O characterization of our reciprocally inhibited, integrate and fire mitral cell. The mitral cell was driven by poisson distributed barrages of synaptic input with mean frequencies ranging from 10 to 200 Hz. In the absence of reciprocal inhibition, mean firing rate varied linearly (6.31 spikes/s/Hz) with synaptic input frequency (fig. 3). With reciprocal inhibition intact, the FI characteristic was scaled divisively (2.18 spikes/s/Hz, see below). In addition, reciprocal inhibition caused a significant redistribution of mitral cell ISIs in response to 50 Hz synaptic input (fig. 2), with the peak ISI shifting from 7ms without inhibition (CV=0.85) to 45ms with inhibition (CV=0.58).

A **B**

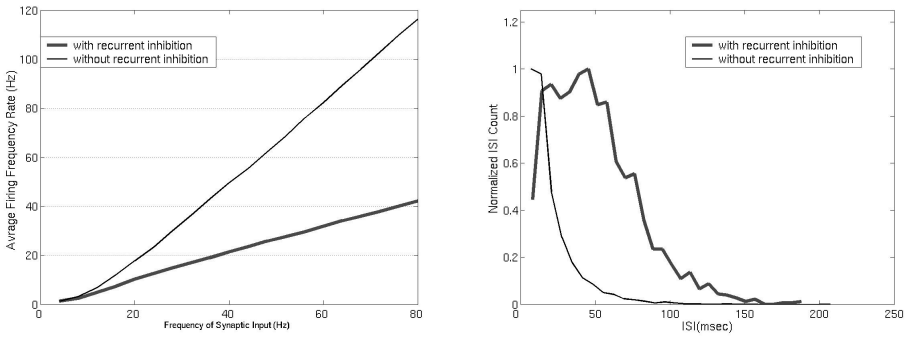

Figure 3. A) *Firing rate as a function of synaptic input frequency*. Bold trace is with recurrent inhibition, light trace is without. **B)** *Normalized mitral cell ISI distributions with 50Hz synaptic noise as input*. Bold trace is the ISI histogram (30 bins) in the presence of recurrent inhibition (peak at t=45ms, CV=.58). Light trace is the ISI histogram without recurrent inhibition (peak at t=7ms, CV=.85).

To address the dynamical utility of our reciprocal synapse, we computed the ratio of the 3rd to 1st interspike interval (ISI) as a measure of early spike adaptation for conditions where stimuli were either instantaneous steps of 50pA, or ramped currents of duration 0-1000ms. For all current ramps duration was adjusted to ensure that the total charge transfer was constant. In figure 4 ISI adaptation is shown both with (bold traces) and without (light traces) reciprocal inhibition. Without inhibition, ISI adaptation rose steeply between the 0ms and 10ms ramp conditions, indicating that although there is an accelerating nonlinearity, the dynamic range of adaptation as a function of input current slope is relatively small. In contrast, with reciprocal inhibition, ISI adaptation overshoots its steady state value and its dynamic range includes ramp durations up to 20 ms, consistent with the view that this form of inhibition makes mitral cells more robust discerners of input transients (Margrie et al, 2003).

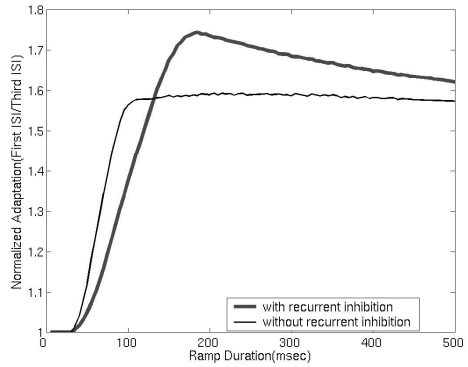

Figure 4. *Mitral cell ISI adaptation in response to ramped current steps*. Graph depicts the ratio of the third ISI to the first ISI, normalized to the ratio for the instantaneous step current condition (0ms ramp duration). Bold trace shows adaptation with recurrent inhibition, light trace shows adaptation without recurrent inhibition.

Finally, we investigated whether reciprocal inhibition may effect a form of divisive scaling. Preliminary results in our lab and others (Schoppa *et.al,* 1998*)* demonstrate that the dendrodendritic synapse of a mitral cell onto a granule cell may be a locus of short term plasticity, owing to the fact that NMDA receptors are present in the post-synaptic membrane. By simulating a synaptic conductance increase or decrease, we discovered that modulation of IPSP amplitude is translated into firing rate modulations in the mitral cell (fig. 5).

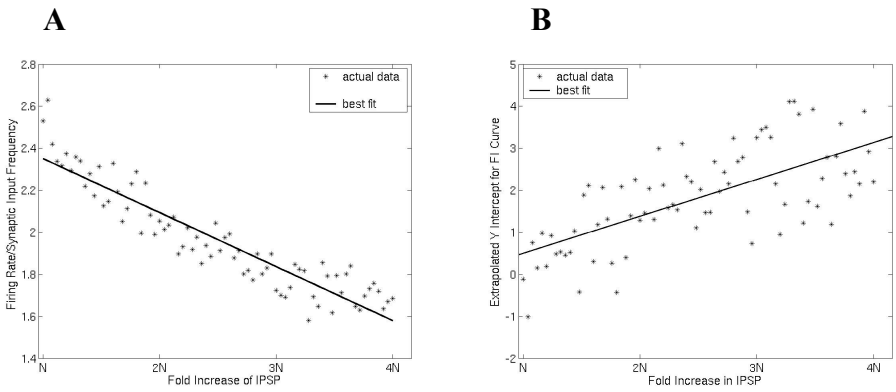

Figure 5. *Reciprocal inhibition as divisive scaling factor*. **A)** Change in the slope of FI curve with respect to increasing IPSP amplitude (R^2=0.85) .**B)** Change in the extrapolated Y intercept for FI curves with respect to increasing IPSP amplitude (R^2=0.45).

DISCUSSION

Our results demonstrate that reciprocal inhibition at the mitral cell-granule cell synapse has important dynamical consequences. Perhaps our most novel result is that a mitral cell coupled to itself through dendrodendritic inhibition can effect a form of divisive scaling *via* additive scaling of IPSP amplitude. We have found that this scaling is robust across a physiological range of IPSP sizes (fig. 5), suggesting that this synapse may be performing a kind of gain modulation. The general usefulness of such a computation has been described by Chance et al (2002), and in the context of the bulb may allow short term plastic events at reciprocal synapses to function as gain modulating signals.

We are currently in the process of making our model more mechanistic by including NMDA-like kinetics in the post synaptic granule cell. In addition we are perfecting techniques to address the issue of dendrodendritic synaptic plasticity experimentally with paired whole cell recordings.

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