Cross-modal Sensory Information Integration in Modulation of Vertebrate Visual System Functions

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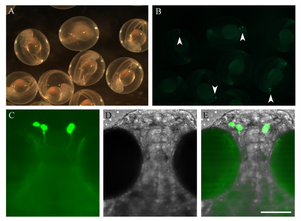
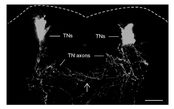
What We Know

The vertebrate retina receives centrifugal input from the brain. The input originates in different brain areas.

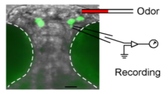
In zebrafish, the centrifugal input originates in the ***Terminal Nerve (TN)***. The cell bodies are located in the ***Olfactory Bulb (OB)*** and some of the axons enter the optic nerve and extend up to the neural retina. In the retina, the TN axons synapse with ***dopaminergic interplexiform cells (DA-IPC)*** and ***retinal ganglion cells (RGC)***.



Transgenic zebrafish that express GFP in the terminal nerve



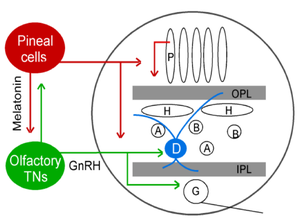
TN axon distribution in the brain (dorsal view)



In vivo TN recording while the fish receives olfactory stimulation

The function of the Olfacto-Retinal Circuit (ORC) is regulated by olfactory input.

- TN input alters GnRH signaling transduction and decreases dopamine release in the retina
- TN input increases outer retinal sensitivity (e.g., the amplitude of corneal full-field potentials) and inner retinal activity (e.g., firing of ganglion cells)
- Together, the olfactory input increases behavioral visual sensitivity
- TN projects axons to the pineal gland
- Pineal photoreceptor cell released melatonin diffuses to the OB and the neural retina
- Depletion of pineal melatonin alters the circadian rhythms of behavioral visual sensitivity but produces no effect on absolute rod and cone sensitivity



Interactions between pineal melatonin, olfactory GnRH signaling, the centrifugal visual pathway, and different retinal cells

Abbreviations: TN, terminal nerve; P, photoreceptor cells; H, horizontal cells; A, amacrine cells; B, bipolar cells; D, dopaminergic cells; G, retinal ganglion cells; OPL, outer plexiform layer; INL, inner plexiform layer

Understanding how this circuit works can have far reaching consequences:

- Provide more insight into the **cross-modal signaling interaction between different sensory systems** in vertebrates
- Create a **general-purpose tool for integrating arbitrary sensory input** in a machine learning context

What We Propose

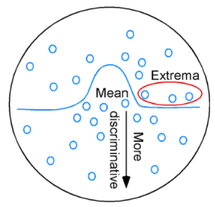
Based on wet bench experiments examining the circuit-level phenomena, we are working towards ***computational neural models*** that leverage the principles of the statistical ***extreme value theory*** (EVT) to simulate and predict the consequence of sensory integration in retinal function.

What is EVT?

Let $(s_1, s_2, \ldots, s_n)$ be a sequence of i.i.d. samples. Let $M_n = \max\{s_1, \ldots, s_n\}$. If a sequence of pairs of real numbers (a_n, b_n) exists such that each $a_n > 0$ and

$$\lim_{x\to\infty} P\left(\frac{M_n - b_n}{a_n} \le x\right) = F(x)$$

then if F is a non-degenerate distribution function, it belongs to one of three extreme value distributions.



Prior work suggests that it may be the extremes (border of circle), and not the means (center of circle), that produce strong responses in the brain.

- EVT applies regardless of the overall distribution
- Sampling the extrema in the tail of an overall distribution always results in an EVT distribution

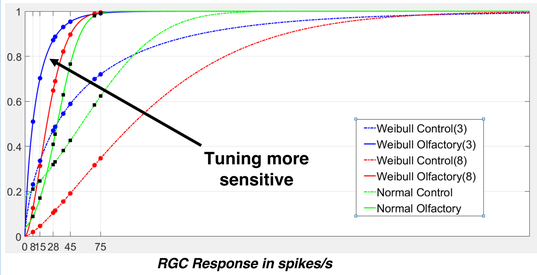
Why EVT?

- Evidence suggests that extremes, and not means, of cell responses direct activity in the brain [Freiwald et al. 2009].
- The sampling of the top-n RGC response results in an EVT distribution, and is ***Weibull*** if the data are bounded:

$$f(x;\lambda,k) = \begin{cases} \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} e^{-(x/\lambda)^k} & x \ge 0 \\ 0 & x < 0 \end{cases}$$

How is EVT different from central tendency modelling?

- Central tendency modelling focuses on the mean of the distribution but completely ignores the extrema



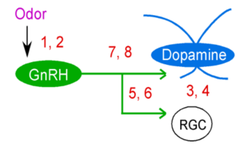
Cumulative Distribution Functions for zebrafish with / without olfactory stimulation at light intensity 10^{-5} & 10^{-6} resp. showing the difference between central tendency modelling (green) and EVT (red and blue)

Modelling Effort

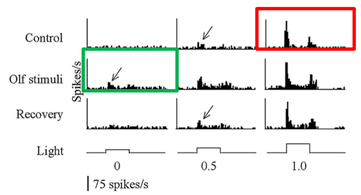
For modeling the effect of olfactory stimulation on zebrafish visual sensitivity, we used data from the study by [Huang et al. 2005]. This data represents single unit RGC responses (On-Off) before and after olfactory stimulation at varying light intensity.

Experimental setup for RGC recordings in response to olfactory and TN stimulation. The numbers correspond with the following conditions:

1,2 - sham or odor stimulation
3,4 - activation or inhibition of dopamine receptors
5,6 - activation or inhibition of GnRH receptors
7,8 - manipulation of dopamine and/or GnRH receptors

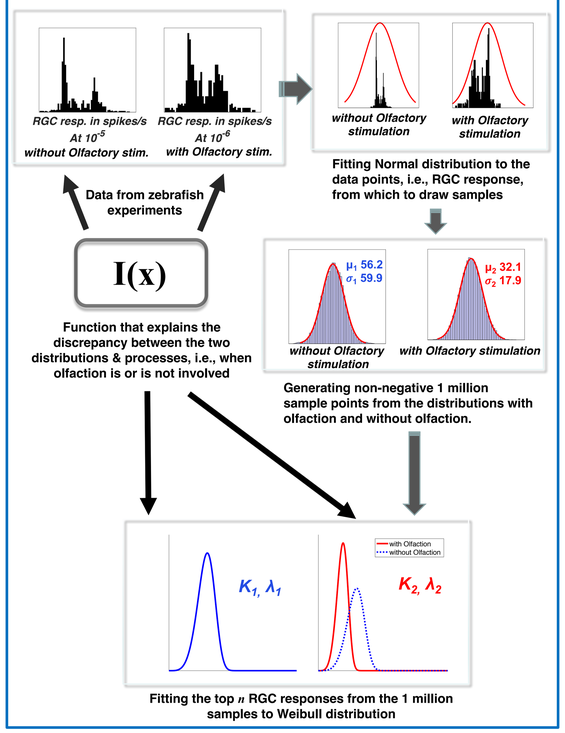


Our work focused on the ***threshold light intensity 10^{-6} with olfactory stim.*** **(green box)**, designated by "0" in the figure for olfactory stimulation and ***10^{-5} without olfactory stim.*** **(red box)** designated by "1.0" in figure:



Histograms of light-evoked RGC responses before (top) and during (middle) olfactory stimulation, and after 5 min. of recovery (bottom). Threshold RGC responses are indicated by arrows.

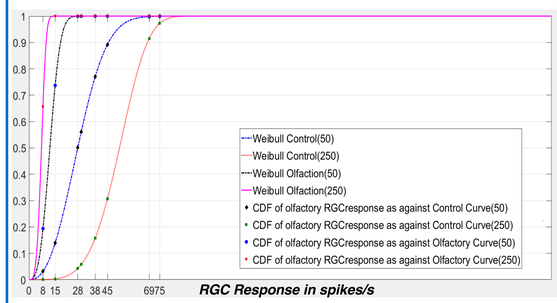
Our modeling effort can be summarized as:



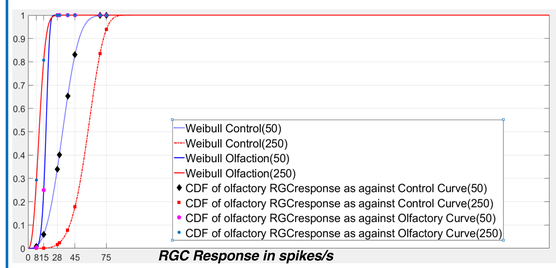
Results

Observations:

- Tuning is always more sensitive when there is olfactory stimulation
- Tail size matters
- Similar patterns for Markov Chain Monte Carlo and Random Sampling



Cumulative Distribution Functions for zebrafish with / without olfactory stimulation at light intensity 10^{-5} & 10^{-6} resp. with simulated points through MCMC



Cumulative Distribution Functions for zebrafish with / without olfactory stimulation at light intensity 10^{-5} & 10^{-6} resp. with simulated points through Random sampling

References

- [Huang et al. 2005] Luoxiu Huang, Hans Maaswinkel and Lei Li (2005). ***Olfactoretinal centrifugal input modulates zebrafish retinal ganglion cell activity: a possible role for dopamine-mediated Ca2+ signalling pathways.*** JPhysiol 569.3, 939-948.
- [Coles. 2001] S. Coles. ***An introduction to statistical modeling of extreme values.*** Springer, 2001.
- [Freiwald et al. 2009] Winrich A. Freiwald, Doris Y. Tsao, and MargaretS. Livingstone (2009). ***A Face Feature Space in the Macaque Temporal Lobe***, Nature Neuroscience, vol. 12, no. 9, September, 2009.

Acknowledgement

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