# DrosOlf Logic: A Literature Review Proposing a Novel Synthesis of Results from Three Recent Axel Lab Publications

**Siddhant Sanghi**
Columbia University
New York, NY 10027
ss5943@columbia.edu

**Abstract**

Wang et al. in 'Evolving the Convergent Olfactory System through Machine Learning' (2021) propose that there exists a functional logic of the Drosophila Olfactory System that accurately models the sequential neural connectivity of the Olfactory Receptor Neuron (ORN)-Projection Neuron (PN)-Kenyon Cell(KC) connections in the Drosophila olfactory system in a three-layer input-contraction-expansion ANN architecture. Further, the authors claim that there is a similar neural architectural logic for the Mouse olfactory system as in the Drosophila. This literature review coins that convergent logic as **DrosOlf Logic**, hypothesizing the different biological regions corresponding to the three-layer ANN architecture for odor identity and odor valence pathways for the Mouse on the basis of biological evidence in Wang and Boboila et al.'s 'Transient and Persistent Representations of Odor Value in Prefrontal Cortex' (2020). Further, the ongoing Hebbian Plasticity implemented for the KC-output layer in the Drosophila ANN from Wang et al.'s paper, could explain the Piriform-output representational drift in Schoonover et al.'s 'Representational Drift in the Primary Olfactory Cortex' (2021). In fact, the representational drift could be empirical evidence for Neuroplasticity. Finally, this review discusses the remarkable resemblance that **DrosOlf Logic** bears to the design principle for the U-Net Convolutional Neural Network Architecture (Ronneberger et al., 2015) for Computer Vision, discussing the possibility of a shared functional logic between neural pathways for vision and olfaction.

## 1 Introduction

Since winning the 2004 Nobel Prize in Physiology for his 1991 paper on the discovery of a nine-hundred-gene family that coded for olfactory receptors, Richard Axel has focused the efforts of his lab on completely understanding olfactory neural pathways in mice and fruitflies. The Axel Lab conducts cutting-edge research on olfaction in the brain, and in the last two years has published several papers out of which this literature review will focus on three papers and the possible connections between their results. The publications listed chronologically are **1. 'Transient and Persistent Representations of Odor Value in Prefrontal Cortex'** (Wang and Boboila et al., 2020) **2. 'Representational Drift in the Primary Olfactory Cortex'** (Schoonover et al., 2021) **3. 'Evolving the Convergent Olfactory System through Machine Learning'** (Wang et al., 2021). Henceforth, this review will use numbers 1-3 to refer to the three different papers listed above.

Paper 1 examines representations of odors in piriform cortex and two downstream areas, Orbitofrontal Cortex (OFC) and Medial Prefrontal Cortex (mPFC) during reward-based appetitive learning [1]. The authors observed a largely unchanging representation of odor identity in piriform, a transient neural representation of positive odor value (rewarded (CS+) odors) in the OFC and persistent representations of positive and negative odor value (rewarded (CS+) and unrewarded (CS-) odors) in the mPFC. Moreover, the OFC and mPFC function sequentially in the learning of appetitive reward-based associations in the odor-reward based task.

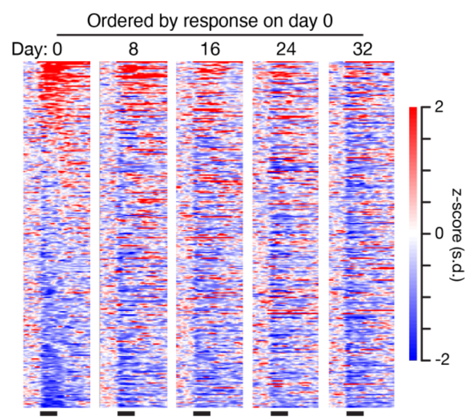


Figure 1: Odor response heat maps for 300 randomly selected odor-unit pairs, ordered by response magnitude on day 0, representing representational drift over 32-day period [2]

Paper 2 challenges the role of the piriform cortex in odor identity determination due to continuous representational drift in the piriform [2]. Although piriform activity can be used to discriminate between odorants at any time point, odor-evoked responses drift over periods of days to weeks (Fig. 1). Fear conditioning does not stabilise this representation, and daily exposure to the same odorant slows the rate of drift but when exposure is stopped the rate increases again. This could mean that the piriform may not be the center for odor identity, or there may be a region downstream with a stable odor identity representation or this drift is evidence for plasticity in that the ensembles for a particular odorant with daily exposure would continue to fire with slower rate of drift of pattern than if exposure to that odorant was halted. Possibly the instability might be a property of unstructured cortices like the piriform. It is important to consider that this result could possibly affect Paper 1's finding that odor identity representation was largely unchanging in the pirifrom.

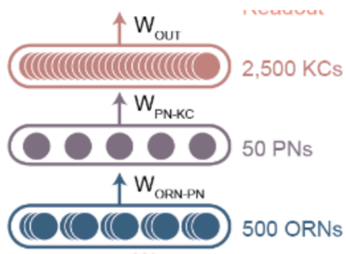


Figure 2: **DrosOlf Logic** ANN Architecture: input-contracting-expanding layers (from down to up) [3]

Paper 3 discusses the convergent evolution of the olfactory system of fly and mouse through a Machine Learning lens. This paper seeks to answer whether the anatomic connectivity and functional logic of olfactory circuits would evolve in artificial neural networks (ANNs) trained to perform olfactory identity and value classification tasks [3]. The input-contraction-expansion functional logic of three-layer ANN architecture, termed **DrosOlf Logic** in this review, is seen to be common for both fruitfly and mouse. ANNs trained to classify odor identity recapitulate the connectivity inherent in the olfactory system. When trained to both classify odor identity and to impart innate valence onto odors, the network develops independent pathways for identity and valence classification. Further, incorporation of Hebbian plasticity in the KC-output layer could possibly be a simulation of the representational drift spoken of in Paper 2.

This literature review proposes that Paper 3 consolidates research from Papers 1 and 2 in order to create a holistic image of olfactory pathways in the mouse brain, discussed in the next two sections.

## 2 Origin and Significance of DrosOlf Logic

From Paper 3, we know that architecture of olfactory systems, in vivo and in silica, is based upon two essential features or the **DrosOlf Logic** of contraction-expansion: convergence of several ORNs onto a small number of glomeruli followed by an expansion onto much larger number of third order neurons [3].

From Paper 3, past research proposed a goal of the olfactory system as construction of a high-dimensional representation in the expansion layer (KCs in the Drosophila mushroom body or pyramidal cells in the Mouse piriform cortex) to understand behavioural significance of odors [3]. This notion implies the following: 1. Hebbian plasticity, whose performance scales linearly with dimensionality, would try to maximize expansion layer dimension to optimize performance 2. Odor representations by PNs must be uncorrelated to maximize dimensionality for KC layer, and the only uncorrelated connectivity pattern is an identity mapping from OR types to PN output, which is exactly seen in singular OR expression and OR-specific projection through olfactory glomeruli.

Interestingly, **DrosOlf Logic** for high-dimensional odor representation from Paper 3 shows that ubiquitous features of biological olfactory pathways arise as the special method of removing glomerular layer correlations to maximize the expansion layer dimension for better understanding of the odor's relevance to behavior [3].

## 3 DrosOlf Logic seen in Mouse Odor Identity and Value Pathways

The three-layer input-contracting-expanding ANN architecture of **DrosOlf Logic**, represents biologically plausible regions in the Mouse odor identity classification pathway in Paper 3. The input layer is made of Olfactory Receptor Neurons (ORNs) that converge to form glomeruli in the Olfactory Bulb (OB), and then diverge through sparse random projections onto the Piriform cortex, analogous to the ORN-Projection Neuron-Kenyon Cell **DrosOlf Logic**. There is evidence of emergence of independent pathways for odor identity and odor valence in the Drosophila ANN from the paper, and in the case of the Drosophila, for the joint task of odor identity and value classification, the Kenyon Cell (KC) Layer is split into Kenyon Cells and Lateral Horn Neurons (LHNs), which means that the identity is not needed for the valence classification, which is different in the case of the Mouse.

In mouse brains the odor value representation task begins with the input piriform layer and so another input-converging-expanding ANN with different biological regions representing the three-layer **DrosOlf Logic** needs to be created. This ANN should have input layer as piriform, followed by convergence to the Orbitofrontal Cortex (OFC) layer for transient representation of only the rewarded positive-value (CS+) odors and then divergence to the Medial Prefrontal Cortex (mPFC) layer for a persistent representation of rewarded positive-valued odors (CS+) as well as unrewarded negative-valued odors (CS-), as per Paper 1's findings on the olfactory value representation circuit that fit in with the three-layer ANN architecture for odor value classification circuitry.

Thus, inspired by **DrosOlf Logic** from Paper 3, two ANNs - one for odor identity classification and one for odor valence classification - can be created for olfactory circuitry in the Mouse brain. Paper 3's **DrosOlf Logic** provides some supporting evidence that the odor value representation circuit is probably simply made up of three regions and can be completely explained by the Piriform-OFC-mPFC sequential circuit with necessary flow of information from each layer to the next.

## 4 Neuroplasticity could explain the Representational Drift in Piriform Output

In Paper 3, the authors were able to incorporate ongoing Hebbian plasticity in the KC-output layer of the ANN for Drosophila (or the Piriform-output layer for Mouse) without losing out on odor identity classification accuracy, which remained at 80% [3]. The fact that task accuracy for the ANN was not hampered can show that plasticity is biologically plausible. In fact, this Hebbian Plasticity could possibly explain the representational drift of odor identity in the Piriform in Paper 2. Paper 2 claims that daily exposure to the same odorant slows the rate of drift, but when exposure is halted that rate increases once again [2]. This slowing down and speeding up of the rate of representational drift for odor identity in the piriform is strongly reminiscent of the Hebbian plasticity rule of 'Neurons (or neuronal ensembles) that fire together wire together, and those that fire out of sync, lose their link'.

Paper 2 shows that the Piriform exhibits representational drift, stabilization based on some kind of history with daily exposure to the same odorant, and subsequent drift of previously stabilized representations on halting of exposure to odorant stimulus. This information propounds a model in which Piriform functions as a quick learning system which continually learns and overwrites itself. Paper 2 calls the Piriform a possible 'scratch pad' for odor identity which rapidly encodes memory traces upon limited odorant exposure without a mechanism to stabilize traces and store memories over a long time course. In a quick learning system, experience with one odorant can drive plastic changes that alter the representations of other odors. Then, representational drift in piriform is a consequence of continual learning and simultaneous overwriting.

Paper 2 questions the role of Piriform in odor identification due to the continual drift in representations, but Paper 1 and Paper 3 seem to provide some rationale for the piriform's role in odor identification. Paper 1's choice of OFC and mPFC was chosen on the basis of anterograde and retrograde tracing of neural connections in the olfactory learning circuitry downstream of the piriform, owing to its importance in information collection on the identity of an odor, which would be needed downstream to determine odor value, too. Paper 3's successful incorporation of KC-output plasticity without hindrance to task performance can explain the plastic representational drift, where the drift is evidence of neuroplasticity.

In fact, more research into Machine Learning algorithms possibly even neural networks (call them **Olfactory Neural Networks (ONNs)**), that model the scratch-pad like piriform layer in a fast learning environment, could revolutionize efficient learning inspired by the Olfactory system. Just like Computer Vision (CV) models human vision and Natural Language Processing (NLP) models human language, there ought to be a human olfactory-learning-based branch of Machine Learning called **Olfacto-Computation (OC)**.

## 5 Similarity of DrosOlf Logic to U-Net Architecture

In this final discussion section of the review, we will discuss the remarkable resemblance that **DrosOlf Logic** bears to the design principle for the U-Net Convolutional Neural Network Architecture [4] for Computer Vision. **DrosOlf Logic** is the input-contracting-expanding paradigm of anatomical connectivity and functional logic which is emergent biologically and in the ANN from Paper 3.

The U-Net architecture for image segmentation (Fig. 3 below) takes advantage of contracting and symmetrically expanding paths to optimize information about both localisation and context of image pixels. The down-sampling gives more information on localisation, and the subsequent up-sampling provides more information about overall context, which tackles the localisation-context conundrum in a smart manner. The fact that **DrosOlf Logic** bears similarity in design principle to U-Net even though there is difference in the kind of input data (odor vectors vs image vectors) and kind of network (ANN vs CNN), reflects some possible universality of this kind of input-contracting-expanding logic as a neural organisation logic for efficient functional activity. It is known that there is a striking biological resemblance in visual and olfactory sensory processing [5-6], and the similar logic to tackling olfactory identity classification and image segmentation could be computational evidence of this biological similarity in functional logic and neural connectivity between olfaction and vision.

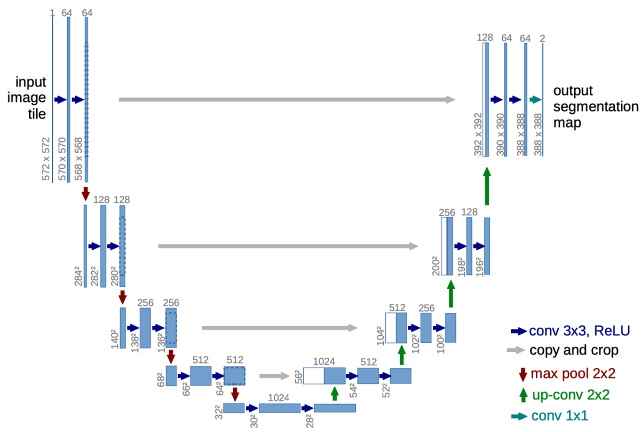


Figure 3: U-Net Architecture: contracting and expanding paths tackle localisation-context conundrum [4]

## 6 Conclusion

In conclusion, thus, there is a strong interconnectivity between results of the three papers discussed in this review, like the ability of Paper 3's **DrosOlf Logic** to model the discovered odor value representation pathway from Paper 1 and the power of Paper 3's implementation of Hebbian plasticity in posing a possible explanation to Paper 2's representational drift in the piriform cortex. Further, there is a vast scope for exploration at the confluence of computation and the olfaction in the future: olfaction-inspired **Olfacto-computation (OC), Olfactory Neural Nets (ONNs)** and so much more.

Ultimately, this kind of literature review facilitates conversations across papers published in the same lab that could provide challenges to conclusions made by other papers or answers to questions raised by other papers, in a bid to create a more holistic understanding of the results.

## 7 Acknowledgements

I would like to thank the following members and ex-members of the Axel Lab for their support and guidance and help in paper access: current postdoc Cristian Boboila (co-author of Paper 1), ex-member Peter Wang (author of Paper 3 and co-author of Paper 1, currently at Stanford) and Richard Axel. Further, I would like to thank Professor Christos Papadimitriou and TAs for a highly engaging seminar course on Computation and the Brain, one of my favorites at Columbia.

## References

[1] Wang PY, Boboila C, Chin M, Higashi-Howard A, Shamash P, Wu Z, Stein NP, Abbott LF, Axel R. 'Transient and Persistent Representations of Odor Value in Prefrontal Cortex'. *Neuron*. 2020 Aug 13:S0896-6273(20)30577-8. https://doi.org/10.1016/j.neuron.2020.07.033.

[2] Schoonover CE, Ohashi SN, Axel R, Fink AJP. 'Representational drift in primary olfactory cortex'. *Nature*. 2021 Jun 9. https://doi.org/10.1038/s41586-021-03628-7.

[3] Wang PY, Sun Y, Axel R, Abbott LF, Yang GR. 'Evolving the olfactory system with machine learning'. *Neuron*. 2021 Oct 6:S0896-6273(21)00682-6. https://doi.org/10.1016/j.neuron.2021.09.010.

[4] Ronneberger O, Fischer P, Brox T. 'U-Net: Convolutional Networks for Biomedical Image Segmentation'. 2015 May 18. https://arxiv.org/pdf/1505.04597.pdf

[5] Lankford, C. et al. 'A Comparison of the Primary Sensory Neurons Used in Olfaction and Vision'. *Front. Cell. Neurosci*. 2020 Nov 5. https://doi.org/10.3389/fncel.2020.595523

[6] Korshunov, K. et al. 'Illuminating and Sniffing Out the Neuromodulatory Roles of Dopamine in the Retina and Olfactory Bulb'. *Front. Cell. Neurosci*. 2020 Aug 31. https://doi.org/10.3389/fncel.2020.00275