(Transfer Report)

17th October 2015

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Abstract

The fruit fly uses its sense of smell to discover useful facts about the world. Previous experiences of different smells get stored in the fly brain along with information on whether the smell was associated with reward or punishment. Flies will use their sense of smell to decide whether to approach or retreat from a given odour. The place this information gets stored is the mushroom body, an area comprised of thousands of neurons that has been implicated in olfactory memory and decision-making. Experiments have shown the response of a fly to a given odour is determined by the activity of a small group of so called "output neurons" which receive their input from the mushroom body and are affected by neuromodulators such as dopamine and octopamine, with experimental evidence suggesting that dopamine and octopamine control reward based learning. David et al. observed that when imaging an output neuron ($M4\beta'$) before and after learning, this neuron exhibited a bi-directional change in firing rate depending on the reinforcement used (reward or punishment) in the experimental protocol. When the odour was paired with appetitive reinforcement the odour response of the output neuron decreased. Conversely, when the odour was paired with an aversive stimulus the odour response increased. The process of encoding odour valence is believed to be dependent on the activity of three types of neurons - Kenyon Cells, Mushroom Body Output Neurons and Dopaminergic Neurons. Each odour activates a unique subset of Kenyon Cells (KCs) in the mushroom body which are tasked with identifying an odour Dopaminergic neurons (DAs) are believed to signal reward or punishment and mushroom body output neurons (MBONs), depending on their type are believed to bias behaviour towards either approach or retreat. Previously, it has been shown that activation of glumatametergic MBONs simultaneous with activation of DA neurons induced appetitive or aversive memory depending on the DAs type (Perisse et al. 2013). The evidence appears to suggest that dopamine modulation leads to synaptic depression of the output of the KCs that represent the odour. Furthermore, the study by David et al. suggests there is a feedback loop from MBONs to DAs, which would make valence learning a recurrent circuit.

As a first step, I created a biologically plausible 3 compartment spiking model of the mushroom body based on known connectivity and firing rates, to test different hypothesis that seek to explain how plasticity drives odour valence learning.

We replicated in our simulations bi-directional change in firing rate observed in MBONs and we will further refine our model in the future after our experimental collaborator will test our predictions.

In the future, we will focus on uncovering the functional implications of a feedback loop for bidirectional valence learning. The ability to learn is an extraordinary achievement that unites animals of different complexity levels. By building a state of the art biologically plausible model of valence learning we hope to uncover learning principles that are shared across many different animals. The fly is an ideal organism to try to bridge the gap from stimulus learning to behavioural control. This is due to its small number of neurons (~5,000) that are involved which be simulated by currents computers and genetic tools that exists which allow us to silence, activate and record individual neurons.

1. Introduction

Like all living organisms, the fruit fly uses sensory information to navigate its world. To a first approximation a fruit fly's behaviour in response to a sensory input can be described as a decision making process of approach or retreat. One such sense that the fly uses to decide whether to approach or retreat is the sense of smell, which is a well-studied function, employed to gather information about the environment, find food, mating partners, and detect dangerous conditions signaled by harmful odours. From the stage of larvae, flies are attracted to most odours, but also show innate aversion to specific odours (Niewalda et al., 2008). The behaviour of larvae depends on experience: if an odour is associated with a sweetened reward and another odour offers no reward the flies will show a preference for the rewarded odour in a binary choice test. However, if an odour is associated with a punishment such as high-concentration salt taste, larvae can be conditioned aversively to odours (Niewalda et al., 2008). Understanding how memories of odours are generated and how they affect behaviour is an area of current research. Researchers are also beginning to understand how innate and learned olfactory behaviours interact with each other. However, until now there have been few computational driven approaches that have converted word models into mechanistic models that can explain the growing behavioural data and make predictions and testable hypotheses.

Flies detect odours using olfactory receptor neurons (ORNs) housed in their antennae. The tuning of each OSN is determined by a single odorant receptor gene (Hallem & Carlson, 2006). Axons from the ORN expressing the same receptor always converge to the same site in the antennal lobe, which is a glomerulus. Their activity is picked up by inhibitory and excitatory projection neurons. Excitatory projection neurons (ePNs) deliver information to the calyces in the mushroom body while both inhibitory projection neurons (iPNs) and ePNs send information to the lateral horn which is a structure implicated in innate odour identification.

1.1 The mushroom body is the centre or associative learning in the fruit fly

The mushroom bodies are symmetrical structures with each mushroom body being composed of 2,000 KCs. Lesion experiments and synaptic blocking of mushroom bodies output have shown that that the mushroom body plays a critical role in memory formation and retrieval (Heisenberg et al. 1985).

Each odour activates a unique subset of these neurons (Honegger, Campbell, & Turner, 2011). The dendrites of the KCs form the cap or calyx of the MB, and their axons project anteriorly to form the stalk or peduncle before those axons terminate in one or more lobes, termed $\alpha\beta$ α', β', and γ lobe (Krashes et al. 2009). Each lobe contains a subset of the total number of KCs and they are believed to have unique roles in memory processing. In a previous study it has been shown by blocking different anatomical subdivisions of KCs, that the surface$\alpha\beta$ neurons are needed during retrieval of aversive and appetitive memory whereas α, β core neurons, when blocked only affect appetitive memory (Perisse et al., 2013).

1.1.1 The mushroom body recurrent activity is critical for stabalizing odour memories

Olfactory representations in the mushroom bodies are modulated by anterior paired lateral (APL) and dorsal paired medial (DPM) neurons. The gap-junctional connection between DPM and APL could guarantee that excitation from DPM is balanced by a similar magnitude of inhibition from APL. The gap junction between the APL and DPM neurons has been shown to play an essential part for the mushroom body during memory formation, constituting a recurrent neural network (Pitman et al., 2011).

1.2 Mushroom Body Output Neurons guide approach and retreat behaviours. Outputs from approximately 2,000 Kenyon cells of the mushroom body converge onto a population of only 34 mushroom body output neurons (MBONs), which fall into 21 anatomically distinct cell types (Aso et al., 2014) The dendrites of MBONs is restricted to few DAN zones. In the M4 MBON (David et. al 2015) where bi-directional change ofs firing rate has been observed with the axons from sugar rewarding dopaminergic neurons overlap with the dendrites of the MBON. In a recent study, MBONs were found to be broadly tuned, showing high levels of correlation between different MBON types. In comparison to representation in

the KCs, odours in the MBON were found to be much closer to one another. The odour representations in MBON of two groups of opposite valences was found (Hige, Aso, Rubin, & Turner, 2015). Reward learning was shown to potentiate the V3 MBON.

The M4 MBON exhibits bi-directional change in firing rate which makes it a prime candidate for modelling to test which hypothesis is best to explain experimental results from David et al. 2015. Optogenetic activation of the M4 neurons drove avoidance behaviour. Blocking the M4 neuron converted odour approach into odour retreat in naïve flies (flies that had an innate repulsion to an odour without learning). Aversive training potentiated the M4 response whereas appetitive training depressed it.

1.3 Dopaminergic Neurons convey reward and punishment signals

Dopaminergic neurons (DANS) are the most prevalent modulatory neurons that innervate the mushroom bodies. There are distinct dopaminergic neurons that provide positive and negative value signals. The two major clusters where most DANs reside are the PPL and the PAM clusters (Figure 1c). Positive reinforcement are provided by subsets of the approximately 100 DANs in the PAM cluster (Burke et al., 2012), . They predominately innervate nearby zones in the β, β', γ lobes.

Negative reinforcement such as from electric shock or bitter substances appears to be conveyed by DANs housed in the PPL cluster. Each PPL DAN that innervates the mushroom bodies projects presynaptic terminals on the vertical lobes α or α' or heel and surface of the peduncle (David Owald & Scott Waddell – in review).

1.3.1 Dopaminergic Neurons convey reward and punishment signals in different areas of the mushroom body

Distinct DANs convey the effects of sugar and water reward as opposed to the same neurons representing subjective value such as in the case of negative reinforcing DANs. The sugar and water responsive DANs project to unique zones on the MB lobes, thus suggesting that learning-related plasticity is represented in different places along the axon of an individual KC.

It is believed that since DANs reaches a subset of KCs axons, they modify KC output synapses onto MBONs in their respective zone. Thus water memories and sugar memories are predicted to have unique KC-MBON connections that represent them.

1.3.2 Dopaminergic Neurons modulated learning changes odour drive to KC-MBON synapses

Previously it has been shown that presynaptically expressed dDA1 receptors in KCs have affinity to dopamine which drives learning through plasticity. A hypothesis has been proposed by which learning modifies subsets of KC-MBON pathways which in naive flies are balanced. Appetitive responding DAs promotes odor approach by depressing odor drive to 'avoidance' MBONs and possibly by strenghtening approach pathways. Conversely, aversive responding DAs promotes odo

1.3.3 Dopaminergic Neurons modulated learning changes in odour drive to KC-MBON synapses

Previous studies have shown that dopamine-drive plasticity occurs during reinforcement learning at the KC-MBON-DA junction. Aversive learning has been shown to depress odour-drive to the vertical lobe MBONs. Two competing theories could explain the effect of dopamine on the KC-MBON synapse. According to the first, dopamine always depresses the synapse. In this case potentiation would occur through the mechanism of lateral disinhibition from MBONs encoding opposite valences. This hypothesis is supported by anatomy that shows that generally DANs overlap with the dendrites of MBONs that bias towards In the second scenario, dopamine can exercise bi-directional control over the synapse leading to both potentiation and depression. This level of control would have computational benefits, allowing dopamine to 'fine-tune' the synapse until it reaches a target value.

We have built models for both scenarios and in the next section we shall describe the constraints of the model and the predictions it makes.

1.4 Previous modelling attempts of olfactory learning

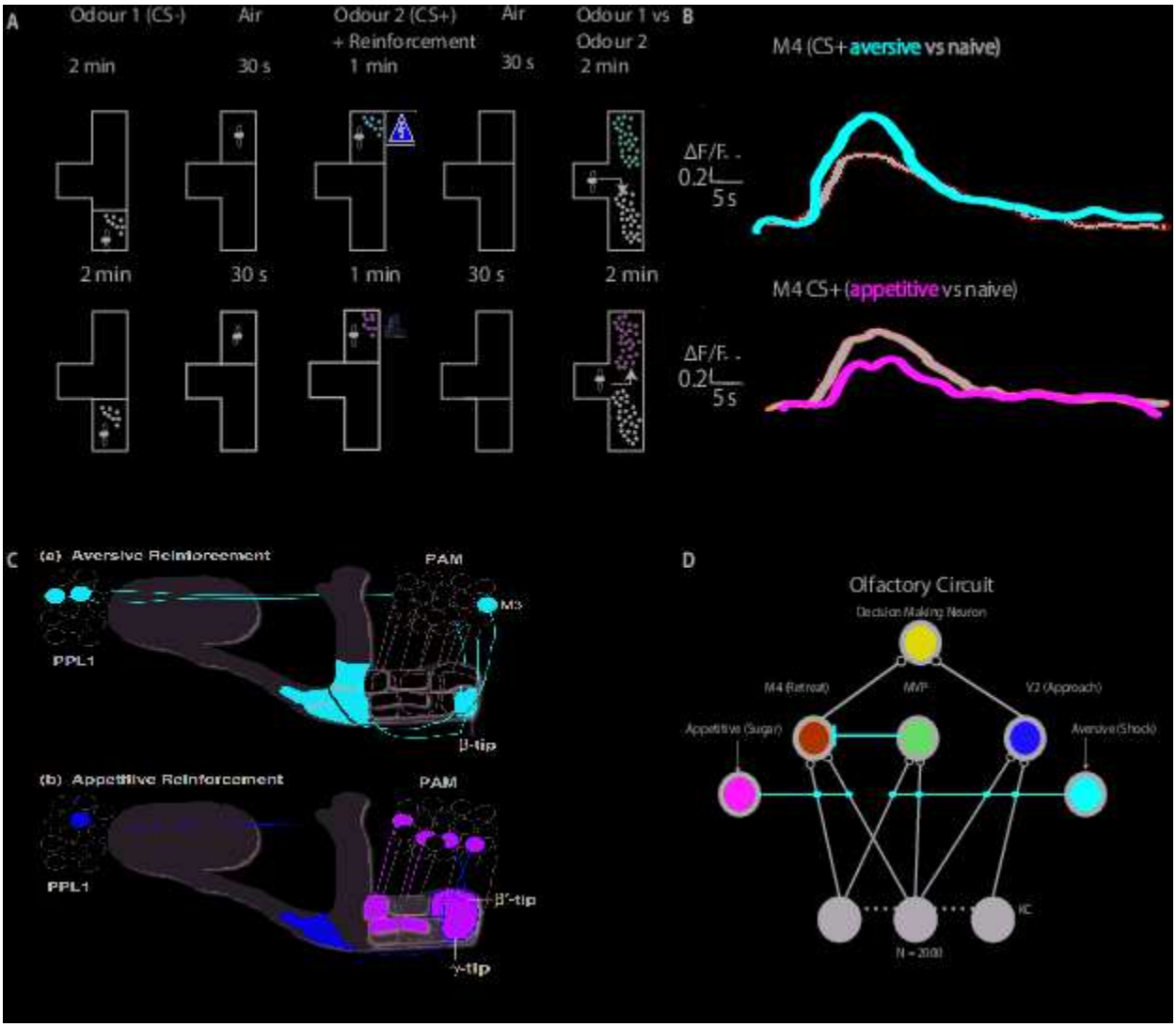

Figure 1: a) In the learning paradigm a fly is shown an odour (CS+) together with a reinforcement which can be either sugar or shock. After a 30s break the fly is given another odour (CS-). Subsequently the fly is tested for odour preference when given a choice between the CS+ and CS-.
b) Calcium imaging experiment befor and after learning has show na bidirectional change in firing rate with the firing rate increasing for aversive learning and decreasing for appetitive learning.
c) (a) DA neurons representing aversive reinforcement. Studies [5,6,7] suggest that neurons in PPL1 convey negative reinforcement whereas live- imaging data [49] corroborate that DA neurons innervating the lower stalk and junction are strongly activated by shock. In this illustration a selection of DA neurons innervating these MB zones and the MB-M3 neurons on the tip of the γ lobe are activated (red). (b) DA neurons representing appetitive reinforcement. DA neurons in PAM innervate many discrete zones in the β, β' and γ lobes [7]. Ca2+ imaging of sugar-evoked activity suggests only some zones receive appetitive reinforcement [7]. Those DA neurons innervating the β and γ lobe tips are modulated by OA through OAMB [12] (yellow outline). OA- dependent reinforcement also requires OCTb2R in the aversive MB-MP1 neurons (yellow). Some of the PAM-DA neurons on the β' and γ lobe tips are also required to mediate the OA-independent reinforcing effects of nutrient value.
d) The valence learning olfactory circuit is made of a group of approx 2.000 KCs which are task with odour identification. There are two groups of dopaminergic4neurons that signal either shock or sugar and depress connections between KCs and MBONs. M4 MBON bias towards retreat behaviour while V2 MBONS bias towards approach behaviour. The MVP MBON neuron inhibits the M4 neuron.

2. Methods

We shall now describe the methods used in this study. Experiments were performed by David Owald at the CNCB and motivated the simulations which were created by the author.

2.1 Connectivity

We used experimental . It is believed that the $M4\beta'$ neurons receives input from the

2.1 Mushroom Body Kenyon Cells model

We created a spiking model of the mushroom body valence learning circuit. The three main components that required modelling were the Kenyon Cells, the MBONs and DAs. To simulate an odour we first select randomly 200 neurons that are activated when an odour is shown, to ensure 10% sparseness (Andrew Lin et al. 2014). We subsequently generated spike trains which are tuned to known statistics of KC spikes (Turner et al. 2008). KC during spontaneous activity show very frugal spiking activity that averages around ~0.1 Hz. When an odour is shown, arandom sample of KCs fire at approximately 2 Hz with a large number of spikes occurring in the first 100 ms. To generate the KC spike train we use a Poisson inhomogeneous process described by the following equation:

$$P(\text{spike during } \Delta\text{t}) = e^{-r(t)\Delta t} \tag{1}$$

Where r(t) is a function that describes the firing rate profile of KCs.

2.2 Mushroom Body Output Neurons model

We shall now describe how we modelled MBONs. There are 34 MBONs separable in two populations: the approach MBONs and the retreat MBONs. We follow this convention in our model and we begin our simulations with only 2 MBONs: one that biases for approach and one that biases for retreat. They both get approximately equal input from KCs. To simulate the MBONs we use knowledge gathered from a recent paper that performed whole cel recording in an MBON (Higue et al. 2015). To model the KC firing patterns we used experimental data (Turner, Bazhenov, & Laurent, 2008) and generated spike patterns that closely resemble observed spike patterns (Fig 2a)Ldi). The paramater values for the MBON model used are as follows:

Parameter	Default Value	Symbol
MBON Membrane Time Constant	20 ms	τ_m
MBON Spiking threshold	-40 mV	V_{th}
MBON Resting membrane potential	-60 mV	V_{inh}
MBON Excitatory conductance	0 mV	E_{ex}
MBON Inhibitory conductance	-80 mV	E_{inh}

It has been recently been shown after recording from all 32 MBONs that when their responses are analzyed the highest degree of separation occurs between odour of different valences, rather than odour of different identtiy. Therefore, the coding space of MBONs is believed to be of the valence. A naive odour can be imagined to exist in an odour space where approach and retreat drives are balanced. We have generated 4 different odours that were in a neutral state (Figure 4). MBONs sample approximately ~800 of KCs of the total number depending on their type and approximately 80 KCs that respond to an odour drive the input to the approach and retreat MBONs. The KC-MBON synapses have random strength at the begining of the simulation which places an odour close to the line of balanced drive towards approach and retreat. Training an odour with appetitive or aversive reinforcement will change the position occupied by the odour in the valence space.

Figure 2: This figure shows the odor valence space coded by MBONs. The black line represents a perfect balance between retreat and approach drive corresponding to both MBONs populations firing at the same rate. The green area corresponds to a higher drive towards approach. Conversely, the red area corresponds to a higher retreat drive from MBONs. The yellow area represents a neutral drive when the odor elicits a response that is +- 10 Hz distance to the line that represents perfect balance.

2.3 Linear Integrate and Fire Neuron Model

We describe the neuron models we used in the computational simulations. We begin by describing the Linear Integrate and Fire neuron model used in every simulation and the parameters used in each simulation. The LIF neuron equation is as follows:

$$\tau_m \frac{dV}{dt} = (V_{rest} - V) + g_{ex}(E_{ex} - V) + g_{inh}(E_{inh} - V) \tag{2}$$

Here V is the membrane potential of the neuron as a function of time , $\tau_m$is the membrane time constant, $V_{rest}$is the resting membrane potential, $E_{ex}$is the excitatory reversal potential and $E_{in}$is the inhibitory reversal potential. $g_{ex}$and $g_{inh}$are the synaptic conductances. A

They are modelled according to the following equations:

$$\tau_{ex} dg_{ex} = -g_{ex} \tag{3}$$

$$\tau_{inh} \frac{dg_{inh}}{dt} = -g_{inh} \tag{4}$$

$\tau_{ex}$and $\tau_{inh}$are the synaptic time constants for the excitatory and the inhibitory conductance, respectively. When the neuron receives an action potential from a presynaptic cell the postsynaptic conductance increases by the following formulas: $g_{ex} \rightarrow g_{ex} + \Delta g_{ex}$ and $g_{inh} \rightarrow g_{inh} + \Delta g_{inh}$.

2.4 The three factor learning rule

Here we introduce a learning rule based on evidence that STDP has been observed in the locust mushroom bodies (Cassenaer and Laurent 2007). In this dopamine modulated STDP model, coincident pre-post firing create a temporal 'tag' to the participating synapses i.e those KCs which have activated the MBON, synapses which depressed if the reward or punishment occurs soon afterward. Figure 3 illustrates the learning rule. The synaptic conductances are strenghtened in the presence of dopamine.

STDP equation:

$$S_i(t) = \sum_k \delta(t - t^*_{i,k}) \tag{5}$$

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = -\frac{x_j(t)}{\tau_+} + S_j(t) f \tag{6}$$

$$\frac{\mathrm{d}y_i(t)}{\mathrm{d}t} = -\frac{y_i(t)}{\tau_-} + S_i(t) \tag{7}$$

$$\frac{\mathrm{d}tag_{ij}(t)}{\mathrm{d}t} = A_+ x_j(t) S_i(t) - A_- y_i(t) S_j(t) \tag{8}$$

The synaptic tag, which we will refer to as 'tag' is updated as follows:

$$\frac{\mathrm{d}w_{ij}(t)}{\mathrm{d}t} = \frac{dtag_{ij}(t)}{dt} * d(t) \tag{9}$$

Since we are interested in investigating the functional role of the feedback loop from the MBON to the DA neuron we model the DA neuron as an integrate and fire neuron too. The dopamine concentration which modulates synaptic chance is a function of the number of spikes that occur within a time period.

Synaptic change thus is the result of dopamine concentration value multipled by snatpic time value at each time point

Weight chance occur on

Parameter	Default Value	Symbol
STDP max potentiation amplitude	0.006 mV	A_+
STDP max Depression amplitude	0.005 mV	A_-
STDP Depression time constant	20 ms	τ_-
STDP Potentiation time constant	0 ms	τ_+
Dopamine receptor DA1 time constant	20 ms	τ_{DA1}

Figure 3: a) KC-MBON STDP learning rule, reproduced from Cassenaer and Laurent [Cassenaer and Laurent 2012]. In gray, the normal STDP rule in KC-MBON synapses, where δt is the time of the postsynaptic spike minus the presynaptic spike, and the y axis shows the percent change in KC-evoked EPSP size in MBONs following five trials in which pre- and postsynaptic spikes were paired at the given δt. In blue, the STDP ruleo bserved when octopamine is injected 1s after pairing. b)Dopamine modulated spike-timing dependent learning rule: Near-coincident pre- and postsynaptic spikes causes synaptic depression. c) i) Raster plot showing KCs firing in response to an odour ii) M4 neuron memebrane potentia during appetitive training iii) Excitatory(green) and Inhibitory(currents) during appetitive training d) i) (The relative timing of firings of the pre and post synaptic neurons induce changes in the synaptic 'tag' variable according to the dopamine modulated STDP learning rule. ii) The synaptic tag decays to zero (top), but if extracellular dopamine are present during the critical time window (middle) the maximal synaptic conductance w is modified (iii)

3. Results

The main aim of my DPhil is to develop mechanistic models that will help us understand how memories of stimuli and their value are used by the fruit fly to guide its behaviour.

David Owald et al. at the CNCB observed that when calcium imaging an output neuron that biases behaviour towards retreat, the activity changed both after appetitive and after aversive training. While dopamine modulation from appetitive coding dopaminergic neurons can explain the decrease in firing rate during appetitive training, we can test in our model whether disinhibition can explain an increase in firing rate. To test a hypothesis that suggests decreased lateral inhibition from the MVP2 output neuron is the reason for this observed increase of firing rate. Indeed antomical studies have shown there exists an inhibitory connection from the MVP2 to the M4 neuron. Odour exposure in our simulation lasts for 10 seconds.

Figure 4: A) During appetitive training the dopamine modulated STDP rule targets the KC-M4 synapses i) In our simulation an odour is shown for 1 s while appetitive reinforcement is provided after 100 ms ii) A raster plot of the KC spikes used to represent the 1s long odouriii) The membrane potential of the M4 synapse during appetitive training is shown iv) The excitatory (green) and inhibitory(current) are shown with appetitive training decreasing the amount of excitatory current that reaches the M4 neuron due to the decrease in maximum excitatory conductance at the affected synapses compared to before training v) A selection of 'weights' are shown that represent the efficacy of the KC-M4 synapses (blue) undergoing depression. For reference, a KC-MVP synapse is shown that undergoes no depression B During aversive training dopamine modulated STDP targets the KC-MVP synapse leading to disinhibition of the M4 neuron i) An odour is shown for 1 s paired with aversive reinforcement ii) The restor plot of the KC spikes used to represent the 1s odour iii) The membrane potential of the MVP neuron during aversive training is shown iv) The excitatory(green) and inhibitory(red) currents are shown with aversive training decreasing the amount of inhibitory current that reaches the MVP neuron v) A selection of 'weights' are shown that represent the efficacies of KC-MVP synapses (purple). An unchanged KC-M4 synapse(blue) is shown for reference C) After appetitive training the odour is shown again this time by itself and the activity of the appetitively trained M4 neuron is measured and compared to the M4 neuron in the naive state D) After aversive training the odour is shown again and the activity of the M4 neuron is measured and compared to the naive state M4 neuron. We observe a bi-directional change in response in accordance to experimenta evidence.

3.1 Bi-directional change in firing rate can occur when dopamine only depresses the KC-MBON synapse

During appetitive training KC-M4 synaptic weights decrease (Fig5A,v) . After learning the response from the M4 neuron shows a decreased firing rate profile compared to the naive state(Fig3C). Appetitive learning through decrease of drive towards retreat has changed the odour representation in an area that translates into approach behaviour (Fig 3D).

During aversive training aversive training, synaptic connections between KC and the MVP2 output neuron suffered depression. This in turn meant that the MVP2 neuron fired less and inhibition to the M4 neuron decreased.

In the first model I developed I wanted Our results show that a dopamine modulated learning rule where dopamine shifts the learning rule into a regime where both pre before post and post before pre spike pairs lead to LTD is sufficient to explain bi-direction change in firing rate.

Figure 5: A) After appetitive training the odour is shown again this time by itself and the activity of the appetitively trained M4 neuron is measured and compared to the M4 neuron in the naive state B) After aversive training the odour is shown again and the activity of the M4 neuron is measured and compared to the naive state M4 neuron. We observe a bi-directional change in response in accordance to experimenta evidence.

3.2 Lateral inhibition between output neurons can enhance odour discrimination

In our simulations we have shown that lateral inhibition can explain bi-directional change in firing rate observed experimentally. The functional requirement for this could be to enhance odour discrimination. Random connectivity

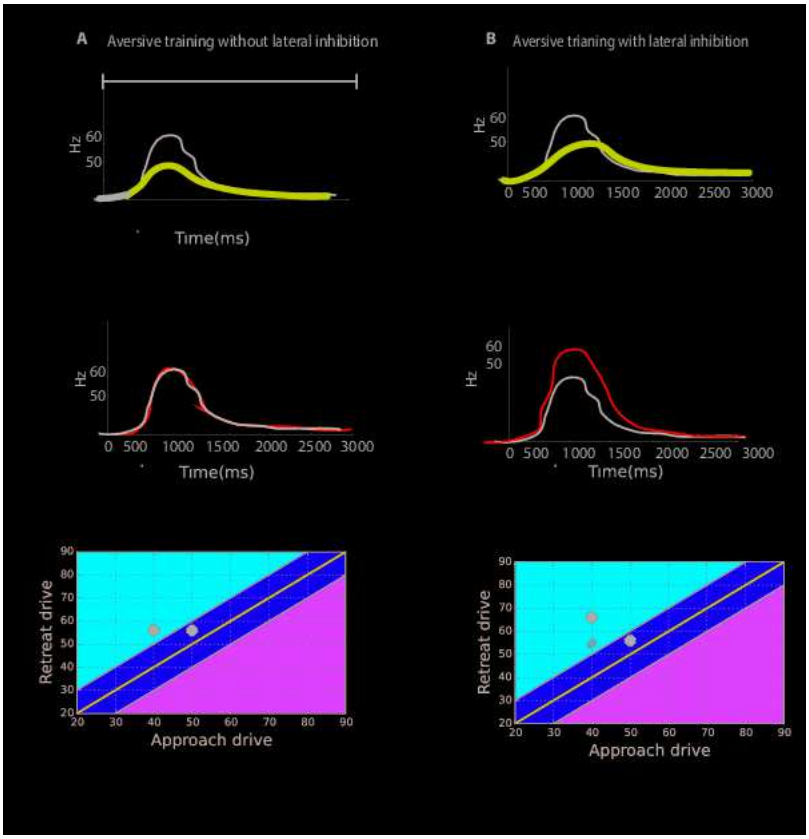

Figure 6: To see the functional implications of lateral inhibition we pair an odour with aversive reinforcement and perform the simulation for 1 second with and without inhibition. A) Odour retrieval test without lateral inhibition In order: Response of approach neuron to odour after aversive training vs naive response, Response of retreat neuron to odour after aversive training vs. naive response B) Odour retreival test with lateral inhibition. In order: Response of retreat neuron to odor after aversive training vs. naive; Response of approach neuron after aversive training vs. naive; Odor projected in valence space before and after training

3.3 Trained odour can change thee valence of untrained odour

We next wanted to test what is the effect of training an odour

Figure 7: A) After appetitive training the odour is shown again this time by itself and the activity of the appetitively trained M4 neuron is measured and compared to the M4 neuron in the naive state B) After aversive training the odour is shown again and the activity of the M4 neuron is measured and compared to the naive state M4 neuron. We observe a bi-directional change in response in accordance to experimenta evidence.

4. Future Work

4.1 The functional role of the MBON - DA feedback loop

We began preliminary work on investigating the MBON - DA feedback loop. Anatomical work by David et al 2015 have shown that the M4 retreat biasing MBON has axons projecting to appetitive DA neurons. Our simulaitons predict that the feedback loop would have to be inhibitory for stable learning. In the case of an excitatory feedback loop, when showing an odour, KCs would activate the M4 neuron which in turn would lead to depression, according to our learning rule. This would make a naive odour become appetitive (Figure 5).

When we tested an inhibitory MBON - DA connection we found that inhibition wou

My ultimate goal is to create a state of the art model of the olfactory circuit that can give an account for learning a stimulus from the first layer together with transformation that occur until the the odour representation reaches the layer that controls behaviour. This will mean building a circuit that models antennae (ORNs), the antennal lobe (PNs) & the mushroom bodies(KCs, MBONs and DAs).

The first step will be to adding more realistic temporal dynamics in my network model. Currently, Kenyon Cells spikes are generated by a simple algorithm that creates spike trains of a given firing rate and temporal profile. However, in the future I would like to model the Kenyon Cells are neurons with dynamics that change over time. This is because there is evidence that recurrent activity in the mushroom bodies involving the APL and DPM neurons and perhaps recurrent activity between KCs themselves are critical in stabilizing memories and in retrieving them (Krashes et al 2009).

0.1 4.2 Simulating odours of different concentration

An unanswered question in the drosophila learning field is how would the fruit fly react if it is shown odour mixtures of opposite valences. Would a 50% appetitively train odour - 50as neutral. Furthermore would the fly change its behaviour as a function of the concentration ratio?

5. Timeline

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