

# Neural Systems: Analysis and Modeling

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## VOLUME LEARNING: SIGNALING COVARIANCE THROUGH NEURAL TISSUE

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### ABSTRACT

The finding that rapidly diffusible chemical signals produced at post-synaptic terminals can cause changes in efficacy at spatially distant pre-synaptic terminals completely alters the framework into which Hebbian learning fits. These signals diffuse through the extra-synaptic space to alter synaptic efficacies under appropriate contingencies. We have analysed the resulting model of plasticity within a volume of neural tissue. As a special case, we show that rather than having the scale of developing cortical structures such as ocular dominance columns set by intrinsic cortical connectivity, it is set by a more dynamic process tying diffusion and pre-synaptic activity.

### 1 INTRODUCTION

The traditional view of communication between nerve cells has focused narrowly on how pre- and post-synaptic elements at a particular terminal interact. Although horizons had to be broadened to accommodate neuromodulators such as acetylcholine and serotonin, which act at a distance from their synaptic terminal of origin, a more dramatic shift is forced by recent evidence that nitric oxide (NO) is a fast acting messenger important for learning and long-term potentiation (LTP) which can readily diffuse through extra-synaptic space.

Data (eg O'Dell *et al*, 1991, Schuman *et al*, 1991) suggest that NO plays the rôle traditionally accorded to a retrograde signal in the familiar Hebbian synapse: pre-synaptic activity coupled with post-synaptic depolarisation leads to the latter's emission of a retrograde signal which in turn leads to the modulation of pre-synaptic efficacy. However that NO can diffuse readily through cell

membranes implies a completely different theoretical account of plasticity. Any pre-synaptic terminal can feel the effects of the local concentration of NO, whether or not its own post-synaptic terminal is depolarised - the NO itself takes on a role as a Hebbian conjunction detector. This role had been assigned previously to the N-methyl-D-aspartate receptor.

We call this kind of synaptic change *volume learning* since plasticity operates within a complete, diffusion defined, region. This shift makes a theoretical difference - it is not merely the chemical instantiation of a conventionally understood process - indeed it was originally suggested on theoretical grounds (Gally *et al*, 1990). Of course, the same would hold for other similarly diffusible substances. This paper explores some of the consequences of such a mechanism of plasticity. The next section describes the model and section 3 studies what determines cortical scale in volume learning.

## 2 THE MODEL OF VOLUME LEARNING

Consider a region  $\mathcal{R}$  containing plastic synapses  $\mathcal{S}$ . Each synapse  $s \in \mathcal{S}$  is idealised as having a coordinate  $r^s \in \mathcal{R}$  and a real valued strength  $w_{i^s j^s}^s(t)$ , where  $i^s$  and  $j^s$  identify the pre- and post-synaptic cells respectively and  $t$  is time. The local concentration of NO is  $\mathcal{N}(r, t)$  and it changes according to:

$$\frac{\partial \mathcal{N}(r, t)}{\partial t} = \mathcal{D} \nabla^2 \mathcal{N}(r, t) - \kappa \mathcal{N}(r, t) + p(r, t) \quad (1)$$

where where  $\nabla^2$  is the Laplacian,  $\mathcal{D}$  is NO's diffusion constant,  $\kappa$  the destruction rate, and  $p(r, t)$  the production rate.

NO is a small, membrane permeable molecule, for which this simplistic isotropic model of diffusion is probably not too unrealistic. Since it is an oxygen free radical, it is destructive to tissue at a high concentrations. There are protective mechanisms that help limit this toxicity. Two feedback control mechanisms are of particular interest: NO is also known as endothelial derived relaxation factor (EDRF) because of its rôle in causing the relaxation of surrounding arterioles and consequently increasing blood flow to the region surrounding its site of production. Hæmoglobin has a high affinity for NO, and so will remove it from a region - this is modeled here by the uniform destruction rate - the more NO, the more hæmoglobin, the more chelation of NO. Another theoretically interesting mechanism which we do not model here is that NO down-regulates (Manzoni *et al*, 1992) the receptor on the post-synaptic terminal which is one of the first steps in the chemical cascade that leads to its production. The more NO, the less sensitive the receptor to pre-synaptic firing, the less NO gets produced.

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According to the model, NO is produced through local activity at the synapse filtered through the current weights, ie  $p(\mathbf{r}, t) = \mathcal{K} [\sum_{s \in \mathcal{S}: \mathbf{r}=\mathbf{r}^s} x_{is}(t) w_{is,js}^s(t)]$  where  $x_{is}(t)$  is the firing rate of the relevant pre-synaptic cell and  $\mathcal{K}$  is a constant. This is obviously a gross simplification – even with NO, the post-synaptic terminal retains some unmodeled capacity as a Hebbian conjunction detector.

The local concentration of NO and pre-synaptic activity interact to cause weight changes. This is modeled as:

$$\frac{dw_{is,js}^s(t)}{dt} = \delta [x_{is}(t) - \theta] [\mathcal{N}(\mathbf{r}, t) - \mathcal{F}(x_{is}(t), \theta)]$$

where  $\theta$  is a fixed excitatory threshold,  $\mathcal{F}(x, \theta)$  is the function that picks thresholds for potentiation and depression, and  $\delta$  is the learning rate.

Judicious choice of  $\theta$  and  $\mathcal{F}$  can lead to arbitrary Hebbian rules – including potentiation and forms of hetero- and homo-synaptic depression. Typically a higher concentration of NO would be expected to be required to cause an inactive pre-synaptic terminal to be depressed than to cause an active one to be potentiated. It is the balance between these thresholds combined with the nature of the input firing that sets the cortical spatial scale.

One facet of this class of reaction-diffusion equation (Turing, 1952) is its ability to support travelling wave solutions (eg Fisher, 1937) in which information is transmitted through space much faster than would be expected from diffusion alone. This effect may be important in development since the diffusion coefficients in cells of the chemicals used for non-local signaling are tiny (Murray, 1989). For this to work, there should be a short term effect of local NO concentrations within a region of co-localised pre-synaptic activity such that low concentrations enhance its release whereas high concentrations suppress it. NO production from a small patch could then rapidly spread out throughout the volume, diffusing passively wherever presynaptic terminals are quiet.

It is a moot point whether this effect is required or even desirable. Nevertheless, waves may be important in the early stages of activity controlled development when relatively global signals are needed.

### **3 CORTICAL SCALE**

Hebbian mechanisms have frequently been proposed as governing the activity dependent development of such structures as topologically ordered maps and ocular dominance (OD) columns from lateral geniculate nucleus to visual cortex (see eg Montague *et al*, 1991 for references). Pre-synaptic firing consequent either on the statistics of the visual input and/or the intrinsic connections in

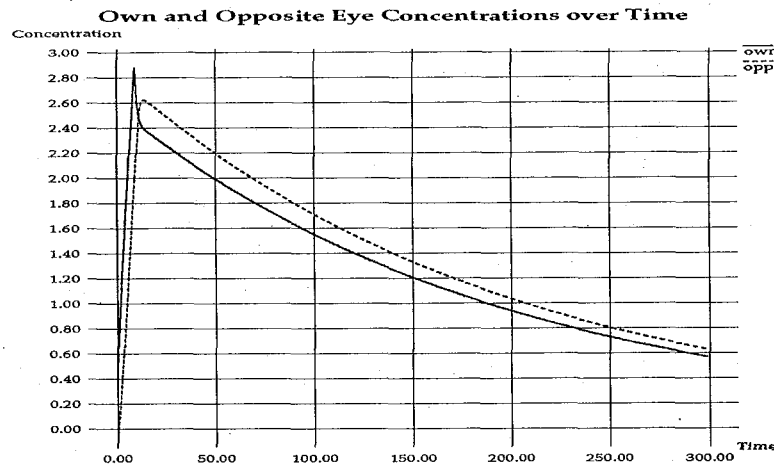
the retina reports the input neighbourhood relations. Traditionally, the neighbourhood relations in the post-synaptic layer have been modeled as coming from intrinsic cortical connections. However volume learning offers an alternative explanation – neighbourliness is reported directly through the diffusion process. Not only does this not require these connections to be extant and functioning at the time the maps are developing, but also it turns out that pre- and/or post-synaptic weight normalisation, the potentially unphysiological bane of traditional accounts, can be dispensed with. What remains therefore is to understand how the thresholds set cortical scales and what determines observable phenomena such as the width of OD stripes.

For the latter, we performed simulations starting from random innervation with relatively small domains controlled mostly by one or other eye, and with positive correlations within an eye and zero or anti-correlations between the eyes (Montague *et al*, 1991). They suggested that if the development rate is reasonably low, the characteristic size of a domain seems to grow up to a certain point at which it stabilises. If the development rate is too high, then one or other of the eyes can sometimes capture large chunks of cortex, or even the whole of it. Note that there is no artificial synaptic normalisation scheme preventing this from happening. This is a strong hint that there is some minimum size of a domain which is stable to the random perturbations induced in the simulation. Domains smaller than this are not stable – they need to club together with neighbouring patches.

We tested a simple version of this hypothesis using a discrete approximation and looking for the instability of regular stripes or patches of certain widths from two 1d retinae to perturbations from the state in which cells in both eyes fire for equal times. The figure shows the concentration of NO (assuming saturated weights) at the centre of a patch of seven cells when its 'parent' eye is on for ten times steps but the opposing eye is on for eleven.

Note from the curve that the own-eye concentration rise more steeply, which arises since in the opposite-eye case the NO has to diffuse. Also once it reaches a peak, the concentrations decrease according to the decay constant of NO in the tissue – if there were no decay then this idealised system would reach steady state. Importantly, for this patch width, the curve for the opposite-eye case ultimately lies above that for the own-eye. As the size of the patch grows, the point at which the curves cross over gets later and later, and the total difference between the two curves changes sign. Depending on the precise nature of the learning rule, when this difference is negative, there will be a tendency for the opposite eye to decrease the weight of the own-eye synapses, effectively extending its local patches into the own-eye cortical turf. Conversely, if the difference is positive, the patch will tend to be stable to this perturbation. This implies exactly the phenomenon of a minimum stable stripe width.

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**Figure 1** Concentrations for own- and opposite-eye cases over time at the middle of stripes of width 7 cells. Diffusion constant  $D = 5.0$ , decay rate  $\lambda = 0.995$ .

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