Chapter 7

Conclusions

The aim of this thesis has to been to investigate the hypothesis that spontaneous waves of activity can guide development of the retinogeniculate pathway. In this chapter we summarise the main results from this thesis. We then give directions for future work and outstanding biological issues that will further help understand the processes underlying retinogeniculate development.

7.1 Discussion of the main results

All of the experimental results mentioned in this section refer to the work presented in Chapters 4, 5 and 6.

7.1.1 Replication of Keesing model results

The first experimental results presented in the thesis replicate the findings of the initial model of retinogeniculate development (Keesing et al., 1992). The original presentation of the model omitted values for most critical parameters as well as the method for generating retinal waves. Replication of their results therefore required finding suitable parameters and making appropriate assumptions about the retinal waves. Once the model was built, it also allowed us to investigate issues that were not previously addressed, such as the formation of projection columns in the LGN.

7.1.2 Normalisation

In contrast to most previous models of ocular dominance, we have shown here that presynaptic normalisation is crucial for ocular dominance development. Postsynaptic normalisation, used in many other models to provide competition between inputs from the two eyes, is redundant in the current model. The presynaptic normalisation should be implemented divisively for retinotopic projection columns to form in the model. Subtractive normalisation can also be used, but only if normalisation is slowly enforced and by placing appropriate upper bounds on individual weights. Postsynaptic normalisation may not be required simply because no positive between-eye correlations are generated by the retinal waves.

7.1.3 Spatio-temporal retinal wave properties

The spatial and temporal properties of spontaneous retinal waves affect development. First, we have shown that retinotopic map formation is reliant on a certain rate of wave generation. Ocular dominance, on the other hand, is more robust to changes in wave generation rate. Examination of the current biological data on temporal wave properties suggests that waves are not generated very often, and so the network needs to cope with long periods of silence between waves. This was achieved in the network by introducing a new weight modification rule, the active-covariance rule, which does not adapt weights when both pre- and postsynaptic activity are below threshold.

Second, the width of retinal waves also affects development. As the waves get wider, we find that the final receptive field size of postsynaptic units also increases, as more neighbouring presynaptic units are correlated. However, this also has the effect of inhibiting ocular segregation since units in different eyes are more likely to be jointly active. Network development is robust to wider waves though as long as narrower waves are used initially to establish the overall map layout. This increase in wave width during development is consistent with current biological data (Wong et al., 1993).

7.1.4 Monocular deprivation

The retinogeniculate model can also account for the results of monocular deprivation which shows that as an eye becomes less active, the number of postsynaptic cells responsive to that eye decreases. At the limit, when an eye never generates any spontaneous activity, no postsynaptic cells respond to that eye (Garraghty et al., 1988). These results are dependent on weakening presynaptic normalisation so that the weights are constrained to lie within, rather than strictly on, the constraint surface. This allows presynaptic units to disconnect from the postsynaptic sheet when their weights are never reinforced.

7.1.5 Segregation of on- and off-centre inputs

Postsynaptic units in the model can refine from initially receiving mixed on- and off-centre inputs to a mature state of receiving inputs from units of only one centre-sign. However, neighbouring postsynaptic units did not consistently organise into sublayers, in contrast with the natural system (Stryker & Zahs, 1983). The model also required on- and off-centre units to be anticorrelated for polarity segregation to occur. Although these correlations are present after the onset of visually-driven activity, they do not appear to be present in the developing retina (Mastronarde, 1989; Wong & Oakley, 1996). As the anticorrelations between on- and off-centre units in the model were weakened, in line with recordings from the developing retina, polarity segregation was inhibited.

7.1.6 Models of ocular dominance stripe formation

Most computer models of ocular dominance produce stripes of alternating eye input, similar to those found in the visual cortex. These stripes usually form as a result of positive between-eye correlations or some retinotopic bias in the unital weights. We have taken one of these models and extended the model into a three-dimensional output space (Obermayer et al., 1991). When the variance of the ocularity is low in comparison with the variance of the retinotopy features, we find that the ocularity feature maps onto the smallest axis of the postsynaptic block, the dorso-ventral axis, in a similar fashion to the mapping of ocularity in the LGN. This self organisation can, in principle, account for the overall layout of visual space and ocularity in the LGN. In practice however, factors such as limited axonal branching may prevent such global reorganisation.

7.2 Future work

In this section we consider several directions in which this work could be extended.

7.2.1 Modelling of the retina

The model retina used here is very simplistic and could be improved in several ways. First, we have considered the model retina to represent only a small patch of the natural retina. A larger-scale retina could include non-uniform sampling to investigate if the gradient of cell density in the retina is preserved in the mapping of visual space in the geniculate (Sanderson, 1971b). Second, if the contralateral retina is made larger than the ipsilateral retina, would the geniculate develop a monocular segment for the region of contralateral retina that is missing from the ipsilateral retina? Third, introducing further classification of presynaptic units as either X or Y ganglion cells would also allow us to investigate the issue of clustering of X and Y cells within geniculate layers.

In the work presented here, the retinal waves have been modelled simply as Gaussian functions of distance from a wavefront. We have not considered various other wave properties, such as their velocity and how they interact with other waves travelling across the retina (Feller et al., 1996). Including these other wave properties may introduce finer spatio-temporal correlations that can be exploited by the network.

7.2.2 Scaling up the network

The size of the retinogeniculate model was relatively small to keep the computational demands of the simulations fairly low. Given the encouraging results from the current model, it may be worth scaling up the size of the model on two counts. First, the two models presented in this thesis should be merged so that we use retinal waves (rather than feature vectors) to generate activity for two two-dimensional retinae innervating a three-dimensional LGN. This new model would be much closer to the natural system than either of the two models investigated in this thesis. Second, the number of units in each layer could be increased, respecting also the relative numbers found in the retina and geniculate during early development. This is not straightforward however, given the ongoing cell death during development and variation in population sizes between animals (Williams et al., 1986; Wong & Hughes, 1987; Spear, Kim, Ahmad, & Tom, 1996). The relative dimensions of the geniculate could also be taken into account when designing the new model (Elgeti, Elgeti, & Fleischhauer, 1976). Making a model which respects the relative numbers of cells in the retina and LGN would allow for comparisons of convergence and divergence with the natural system.

7.2.3 Polarity segregation

The failure to segregate on- and off-centre inputs using correlations similar to those present in the developing retina is likely to be due to the choice of weight modification rule and neighbourhood update. Given the promising initial results of polarity segregation using a BCM rule with one postsynaptic unit (Lee & Wong, 1996), it is worth investigating performance in the network with both the BCM rule and competitive rules. Competitive rules such as the Obermayer/Goodhill rule use a form of neighbourhood weight update which, unlike the growth rule used in this thesis, should only update the weights of active presynaptic units. This should encourage neighbouring postsynaptic units to develop similar polarity preferences and possibly form polarity sublaminae. This sublamination could also be enhanced by implementing either of the possible forms of polarity bias mentioned in Chapter 5.

7.2.4 Temporal correlations

The spontaneous waves of activity correlate the activity of retinal units both in space and time. In this thesis we have concentrated on the spatial aspects of this correlated activity, without considering the short-term temporal correlations created by the waves moving across the retina. The models presented in this thesis can therefore be regarded as 'snapshot' models, since there is no information stored from one iteration to the next. The temporal coincidence of pre- and postsynaptic activity is crucial to weight adaptation (Markram et al., 1997), and exploiting these correlations may be important for segregation of inputs. For example, X and Y ganglion units have considerably different temporal signatures after the onset of vision which could be detected by using temporal information in the weight modification rule (Földiák, 1991; Barrow & Bray, 1992; Wallis, Rolls, & Földiák, 1993).

7.3 Outstanding biological issues

During the course of this thesis, several biological issues have been raised which have not yet been addressed experimentally. Some of these experiments may be possible with current techniques, but it is likely that most have not been performed because there are no suitable techniques currently available. Some topics which deserve future attention are now described.

7.3.1 Retinal waves

More detailed measurements of the patterns of the retinal waves will allow us to investigate the roles of waves in other aspects of retinogeniculate development. For example, are there any differences in firing patterns of X and Y retinal ganglion cells, and does this drive LGN units to become responsive to just X or Y inputs? Measurements of the direction in which waves tend to travel will help to test the hypothesis that wave directions are related to retinal eccentricity and can guide overall retinotopic layout (Trevelyan, Thompson, & Willshaw, 1993). Some of these questions may also be answered as more details of the mechanisms responsible for generation and propagation of the waves are discovered (Wong, 1995; Feller et al., 1996).

7.3.2 Development of topography

Most topographic models show a progressive refinement of both individual receptive field size and overall retinotopic order. How does model refinement correspond to development in the natural system? Most work on this topic has focused on the development of unit responses rather than overall map formation. To answer this question, maps of visual space should be taken at different times during map development. In the case of retinogeniculate development, projection column maps should also be taken. Pictures of the initial map layout will indicate the amount of order in the system before activity-dependent processes begin to reorganise the pathway. Subsequent maps will then show the amount of reorganisation and refinement. These maps could be generated using retrograde labelling of neighbouring geniculate cells (I. Thompson, personal communication). Producing such maps of visual space in the LGN during the period of retinogeniculate development is complicated however due to the large increase in LGN volume at this time (Elgeti et al., 1976). This may mean that it is possible to create these maps only after development of the retinogeniculate pathway and the LGN has stabilised. Topographic maps of the mature LGN under altered conditions, such as activity blockade and monocular deprivation, would, however, be useful for comparison with both control maps and model predictions.

7.3.3 Development of on- and off-centre units

The segregation of LGN layers into polarity-specific sublaminae is believed to be activity-dependent (Cramer et al., 1996; Cramer & Sur, 1997). There are two outstanding questions related to this segregation. First, why do on-centre cells always go into the dorsal region of a lamina and off-centre cells to the ventral region? This could indicate some form of activity-independent mechanism at work, although it has yet to be found. Second, how does the relative firing rates of on- and off-centre units compare to the number of on- and off-centre geniculate units? Wong and Oakley (1996) report that during P16–24, off-centre cells fire around three to four times more often than on-centre cells. If polarity segregation can be regarded as analogous to ocular segregation, do the results from monocular deprivation also apply, namely that the more often a presynaptic unit fires, the more postsynaptic units connect to it? On this basis, we would expect to find many more off-centre than on-centre geniculate cells. Visual inspection of existing maps however seems to show that the sublayers are approximately the same size (Stryker & Zahs, 1983).

7.3.4 Propagation of waves to other areas

The aim of this thesis has been to see how activity-driven processes can guide development of the retinogeniculate pathway. A central assumption of this work is that these processes not only apply to retinogeniculate development, but also to neural development in general. With reference to the visual system, we would therefore expect that the general principles guiding retinogeniculate development also underlie geniculocortical development. It would be therefore be interesting to see the effects of modifying or blocking retinal wave activity upon the development of cortical cell receptive fields. Given the existence of spontaneous waves in other areas (Wong, 1993), similar blockade experiments could be performed in other sensory modalities. The results of these experiments will help to understand the extent to which neural development is guided by general activity-driven processes.