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A MARKER INDUCTION MECHANISM FOR THE ESTABLISHMENT OF ORDERED NEURAL MAPPINGS: ITS APPLICATION TO THE RETINOTECTAL PROBLEM

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This paper examines the idea that ordered patterns of nerve connections are set up by means of markers carried by the individual cells. The case of the ordered retinotectal projection in amphibia and fishes is discussed in great detail.

It is suggested that retinotectal mappings are the result of two mechanisms acting in concert. One mechanism induces a set of retinal markers into the tectum. By this means, an initially haphazard pattern of synapses is transformed into a continuous or piece-wise continuous projection. The other mechanism places the individual pieces of the map in the correct orientation.

The machinery necessary for this inductive scheme has been expressed in terms of a set of differential equations, which have been solved numerically for a number of cases. Straightforward assumptions are made as to how markers are distributed in the retina; how they are induced into the tectum; and how the induced markers bring about alterations in the pattern of synaptic contacts. A detailed physiological interpretation of the model is given.

The inductive mechanism has been formulated at the level of the individual synaptic interactions. Therefore, it is possible to specify, in a given situation, not only the nature of the end state of the mapping but also how the mapping develops over time. The role of the modes of growth of retina and tectum in shaping the developing projection becomes clear.

Since, on this model, the tectum is initially devoid of markers, there is an important difference between the development and the regeneration of ordered mappings. In the development of duplicate maps from various types of compound-eyes, it is suggested that the tectum, rather than the retina, contains an abnormal distribution of markers. An important parameter in these experiments, and also in the regeneration experiments where part-duplication has been found, is the range of interaction amongst the retinal cells.

It is suggested that the results of many of the regeneration experiments (including apparently contradictory ones) are manifestations of a conflict between the two alternative ways of specifying the orientation of the map: through the information carried by the markers previously induced into the tectum and through the orientation mechanism itself.

1. Discussion of marker theories

1.1. *Introduction*

One of the most intriguing biological problems yet to be solved is how ordered patterns of connections are set up in the nervous system. A case which has been investigated in detail is the topologically ordered projection of retina onto contralateral tectum in amphibia and fishes

(Gaze 1970). In recent years, an enormous amount of data has accumulated, tracing the normal sequence of development of retinotectal connections and showing how patterns of connections can be manipulated by surgical intervention.

In this paper we examine the idea that the retinotectal map is set up on the basis of markers (Sperry 1943, 1963; Gaze, Jacobson & Székely 1965) carried by the participating cells. The experimental evidence suggests to us that this is brought about by the induction of markers from retina into tectum, and we describe a formal model based on this idea. The model consists of the minimum of machinery required to produce correctly ordered mappings in the normal developmental situation. However, it accounts for other findings without needing extra hypotheses. We have already published an introductory paper on this topic (Malsburg & Willshaw 1977).

1.2. *Marker theories*

The fundamental problem is how the fibres put out by a sheet of *presynaptic* cells can make contact with the cells of a similar *postsynaptic* sheet in the sense of a topographically ordered mapping with a prespecified orientation. There are two different situations to be considered: the formation of ordered connections during normal development, and after regeneration following surgical interference with the mapping set up during development.

Several different solutions to this problem have been proposed (Sperry 1943; Prestige & Willshaw 1975; Willshaw & Malsburg 1976; Hope, Hammond & Gaze 1976). We shall discuss that class of hypotheses which we call *marker theories*. What all marker theories have in common is that there are two sets of distinguishing signs, or *markers* (presumably chemical in nature), assigned to the members of the two sheets. Within one sheet, the markers serve to distinguish one cell from another; and the two sets of markers are in some fixed correspondence, thus specifying which cells interconnect.

Perhaps the best known marker theory is Sperry's hypothesis of neuronal specificity (Sperry 1943, 1963). As applied to the retinotectal situation, he proposed that: (1) in early development the retinal cells undergo a process of differentiation, whereby each element acquires a unique marker; (2) the tectal cells undergo a comparable process of differentiation; (3) during development a matching process between correspondingly marked retinal and tectal cells takes place.

This hypothesis is what Prestige & Willshaw (1975) call a *direct-matching* theory: each cell has a characteristic affinity for each of the cells in the other sheet, with highest affinity for the one whose marker most nearly resembles its own.

In the rest of the chapter we discuss what led us to a new marker theory. We begin by enquiring whether the markers assigned to cells remain fixed or can be altered.

1.3. *Evidence for the reorganization of markers*

A popular way of examining this question has been to perform a *mismatch* experiment. This involves removing, from an adult, part of the retina, part of the tectum or parts of both and making the remaining cells re-establish a retinotectal projection. If the markers stay fixed, the cells originally paired together will re-establish contact, as far as is possible. Early experiments (Attardi & Sperry 1963) found this to be the case. In contrast, more recent experiments have revealed abnormal (but still ordered) patterns of connection. A half retina eventually established an expanded projection over the entire tectum (Schmidt, Cicerone & Easter 1978), a whole

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retina compressed its projection onto a half tectum (Gaze & Sharma 1970; Yoon 1971), and a half retina transferred its connections onto the foreign half tectum (Yoon 1972). If these mappings were set up by direct matching, some of the cells must have changed their markers.

A second experimental approach involves the rearrangement of cells in the adult tectum. Here, a piece of tectum is cut out and then replaced, either in a different orientation (Sharma & Gaze 1971; Yoon 1973; Levine & Jacobson 1974) or in exchange for another graft of similar size (Jacobson & Levine 1975*a*, *b*; Hope *et al.* 1976). The maps of the regenerated retinotectal connections were of two types. Sometimes that part of the field which normally mapped onto the graft had rotated or translocated in step with the graft; sometimes the field plot was normal. The first result indicates that the displaced tectal cells retained their markers; the second indicates that they did not.

Two important results come from developmental studies.

In larval *Xenopus*, there is an ordered projection of visual field on the tectum (Gaze, Keating & Chung 1974), which is present before retina and tectum have stopped growing. Since retina and tectum grow incongruently, these authors concluded that throughout development there is a progressive shifting of connections until the adult configuration is reached. This implies that the markers change continually throughout development.

This normal course of development of markers can be interfered with, as shown by the *classical compound-eye* experiments (Gaze, Jacobson & Székely 1963, 1965). Compound-eyes were made by fusing together two matching larval half-eyes, one from a left eye and one from a right eye. On recording from the adult, every tectal penetration received input from two visual regions arranged about a common axis of symmetry. Apparently each half-retina had connected in its normal orientation but had spread its connections, in order, across the whole tectum. This projection could not have resulted if retina and tectum each carried their normal set of markers.

Hunt & Jacobson (1973, 1974) have made compound-eyes from other combinations of larval half-eye: for example, a temporal left half-eye together with a nasal right half-eye rotated about 180°. These also sometimes developed double projections, which we call *new compound-eye maps*. One half-eye mapped in its normal orientation, whereas the other had one or both its axes reversed. Both projections were over the entire tectum. Similar double projections were sometimes developed by embryonic half-eyes (Hunt & Berman 1975; Feldman & Gaze 1975).

1.4. *Existing hypotheses concerning the reorganization of markers*

One proposal as to how reorganization of markers takes place is the *regulation hypothesis* (Gaze & Sharma 1970; Meyer & Sperry 1973): the removal of one end of a sheet of cells (as in the mismatch experiments) sets off a reorganization process ('regulation'), whereby the depleted sheet acquires the complete set of markers normally deployed over the full sheet. The depleted sheet is thus able to make ordered connections over the whole of the other sheet. The three types of mismatch result mentioned earlier have been taken to be evidence for regulation in the retina (Meyer & Sperry 1973), in the tectum (Yoon 1971; Meyer & Sperry 1973) and in both retina and tectum simultaneously (Yoon 1972). The concept of regulation has also been applied to the classical compound-eye experiments. It has been suggested that each half-retina regulated to acquire the set of markers normally possessed by a whole eye, and so could map as a whole eye over the entire tectum (Gaze *et al.* 1963).

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This idea of regulation may have been prompted by the analogy with morphogenesis. Production of abnormal morphologies following surgery can in some cases be predicted by using formal rules for the rearrangement of positional values attributed to the cells in the developing system (French, Bryant & Bryant 1976). Among these is a hypothesis for embryonic regulation to explain how a whole organ can regenerate from a part. However, the analogy between morphogenesis and the mapping problem must be drawn with caution. The arrangement of markers within a sheet is of secondary importance to the mapping problem. What *is* crucial is that the markers in one sheet be duplicated in the other. This could be done in a number of ways. For example, when a half-retina regenerates an expanded projection over a whole tectum, it could be that the retinal markers have changed, or the tectal markers, or both.

Quite apart from this consideration, regulation does not deal satisfactorily with the two other classes of experiment we mentioned. In the tectal graft experiments, regulation presumably predicts normal maps, but rotated or translocated part-maps were also found. If each half of a new compound-eye acquired a full set of markers (as was postulated for the classical compound-eyes), it would project over the entire tectum, in its normal orientation. But in fact only one of the two half-eyes mapped in its normal orientation.

1.5. *Systems-matching*

Gaze & Keating (1972) pointed out that in the mismatch and the classical compound-eye experiments the retinal fibres spread out as an ordered system to cover the whole tectum, whatever the relative size of retina and tectum may be; *systems-matching* occurred (each half of a compound-eye is regarded as a separate system). They suggested that such projections could be obtained by a competitive mechanism, without invoking regulation. Prestige & Willshaw (1975) showed that competitive mechanisms working on fixed sets of markers will produce some but not all types of systems-matching. To produce all types, an extra condition must be introduced, such as one equalizing the number of presynaptic sites with the number available postsynaptically. This is a form of regulation.

In fact, systems-matching can be obtained without the use of markers. In the neural activity model, which we proposed earlier (Willshaw & Malsburg 1976), retina and tectum are regarded as uniform media. The desired orientation of the map is specified by the initial pattern of synaptic contacts. In the arrow model (Hope *et al.* 1976), each tectal cell contains information only about *relative*, rather than absolute position. The shortcoming of these mechanisms is that when they are applied to the graft transplantation experiments they do not predict translocated maps. The neural activity model predicts normal maps. The arrow model predicts a normal map after translocation and a rotated part-map after rotation. Finally, the new compound-eye maps cannot be explained by supposing that each half-retina systems-matches in its normal orientation across the entire tectum.

2. A model involving the induction of markers

2.1. *Introduction*

Any formulation of a marker theory based on Sperry's original idea (Sperry 1943, 1963) needs two sets of postulates: one specifying how the two sheets of cells acquire their markers initially, and one specifying how markers can be changed by experimental intervention.

But if cells in one sheet acquired their markers from those in the other sheet, they would have

a built-in capacity for altering their markers – and thus altering the mapping between the sheets – following surgical intervention. We suggest that, once the first contacts have been made, the presynaptic fibres are guided to make synaptic contact in the postsynaptic sheet by the markers that they themselves induce there through these synapses.

This inductive mechanism, which works on a microscopic level, can be used to connect neighbouring presynaptic regions to neighbouring postsynaptic regions. The map's global properties – size, position and orientation – must be determined separately (Willshaw & Malsburg 1976). Size and position are fixed by the boundary conditions. For orientation a separate mechanism is needed. In the absence of an orientation mechanism, completely continuous maps may not result.

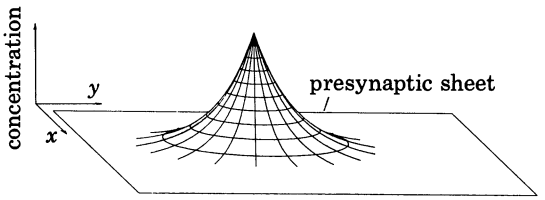

FIGURE 1. The distribution of concentrations of molecules produced at a single source in the presynaptic sheet and spreading out over its surface. Through the combined effects of a number of sources of molecules of different types scattered over the sheet, each cell acquires a unique marker.

2.2. *The model*

There is a continuous exchange of information between cells. This may or may not involve an actual interchange of material. Nonetheless, we suppose that communication is by means of a number of transportable substances, or *molecules*. The molecules are produced within the presynaptic sheet and are transported by axonal flow to the postsynaptic sheet, into which they are induced through the contacts made there by the presynaptic fibres.

There are several different types of molecule, at least one type for each spatial dimension. Each type is synthesized at a steady rate within one isolated region of the presynaptic sheet. The molecules have a limited lifetime and are free to diffuse within the presynaptic sheet; that is, they are exchanged in some way between neighbouring cells. The distribution of molecules presynaptically is assumed to have reached a stationary state. The concentration of each molecule type is at a maximum at its source and falls off with distance from the source, with a characteristic length given by the rate of diffusion and the time constant of molecular decay (figure 1).

In this way, markers are assigned to presynaptic cells. Each cell carries several different molecules, whose concentrations vary in small steps in going from one cell to the next. One may visualize the concentrations in a cell as components of a vector in a multidimensional space.

The concentration vectors cannot be used as a code for position in the presynaptic sheet if the locations of the sources are unknown. But they could, in principle, be used to order the presynaptic terminations according to the relative positions of their cells of origin, thus giving a map of the presynaptic sheet drawn to an arbitrary scale and in an arbitrary orientation; the concentration vectors encode *neighbourhood relations*.

We do not tackle the question of how the fibres find the postsynaptic sheet. So let us start from the situation where the axons have already established tentative synapses, in a haphazard fashion. Through these synapses, each presynaptic cell continually injects molecules, in

proportions given by its concentration vector, into all the postsynaptic cells it contacts. Molecules are also exchanged between postsynaptic cells, and in this way they too acquire markers.

Each synapse is characterized by two quantities. One of them is its *strength*, which specifies the rate of transfer of molecules from fibre to cell. The other is its *fitness*, which is numerically equal to the *similarity* between the presynaptic and the postsynaptic cell. The similarity is a function of the concentrations of the molecule types common to both cells, and it measures how closely the proportions of the molecules in one cell approach those in the other. The similarity function is defined to have a maximum value of 1 when these proportions are identical and a minimum of 0 when the cells have no molecule types in common.

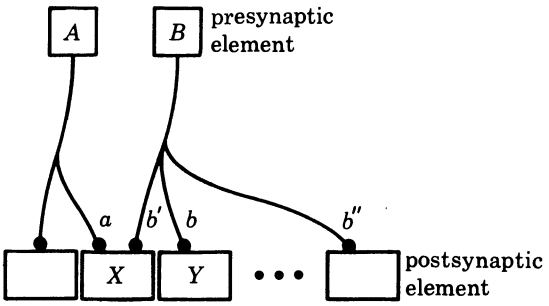

FIGURE 2.

A rule is needed for the continuous modification of synaptic strengths. As applied to the synapses made by a particular axon on the postsynaptic cells at a particular time, it can be stated in three parts.

(1) The strength of each synapse is increased according to its fitness. The greater its fitness, the higher its rate of growth.

(2) If this rule were to act alone, synapses would grow without bounds. Therefore, a *sum rule* operates to keep the total strength of synapses available to the axon at a constant value; the strengthening of some synapses leads to the weakening of others.

(3) The axon puts out branchlets to make new synapses in the neighbourhood of existing ones, and those synapses which have shrunk to a certain lower limit are abolished.

A mathematical statement of how the various components of the modification rule are fitted together is given in the appendix.

2.3. *How the model functions*

In order to show how the mechanism acts to rearrange contacts, we must explain the ways in which synapses can interact with each other. The basic form of interaction is of a synapse with itself. Axon *A* (figure 2) injects through synapse *a* into cell *X* molecules in proportions characteristic of its own mixture. In doing this, it brings *X*'s collection of molecules nearer its own, thereby favouring the strengthening of synapse *a*.

Whether this synapse does become strengthened, however, depends on the intersynaptic interactions, which are of three types.

Competition acts between the contacts made by the same axon on different postsynaptic cells (for example, the synapses *b*, *b′* and *b″* made by *B* in figure 2). It is a direct consequence of the sum rule, and results in the synapses with relatively high fitnesses being strengthened at the expense of the others.

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The other types of interaction are mediated by the postsynaptic concentrations. Consider two synapses, say a and b, which are located on neighbouring postsynaptic cells and which have different parent cells, A and B. If A and B are near neighbours, they will inject similar collections of molecules into X and Y. Since there is an interchange of molecules between neighbouring postsynaptic cells, the tendency of each of these two synapses to grow is reinforced by the molecules injected through the other one. This is an effect of *cooperation*. If the places of origin of A and B are not so close together, the molecules injected by A and by B will be of the same kind but in different proportions. The concentrations in this postsynaptic region cannot simultaneously resemble those in A and those in B. Either A or B will be favoured, leading to reinforcement of one synapse and suppression of the other, an effect of *interference*. If A and B are so far away that they have no molecules in common, they act independently of one another. The extent of these two interactions depends on the form of the similarity function used. For a given similarity function, the range of interaction of any kind depends on the extent of the individual molecular gradients.

It is impossible to derive the consequences of the modification rules by analytical methods. However, qualitative arguments can be of help, as follows. Of the postsynaptic cells contacted by a given presynaptic cell, those least similar to it are eliminated (competition), leaving the high similarity cells which will be grouped together, since neighbouring cells have similar concentration vectors. The presynaptic cells which contact a given postsynaptic region will be neighbours (cooperation). Furthermore, most postsynaptic cells will receive innervation from just one presynaptic region (interference).

The optimal configuration is one where neighbouring presynaptic cells project to neighbouring postsynaptic cells. This represents a topographically ordered projection of one sheet onto the other. However, this globally optimal state will not in general be reached from an initially random distribution of synapses. We discuss this point once we have described some illustrative computer calculations.

2.4. *Computer results*

We carried out computer calculations to represent the establishment of connections between two chains of 80 cells, under a number of different conditions.

There are certain technical advantages in programming the one-dimensional system. An 80×80 system was manageable in computing requirements and also reasonably large. Our treatment can easily be generalized to two dimensions. (This is in contrast to theories of map-making based on a time of arrival mechanism. Timing works in one dimension, but is inadequate for two.) Apart from one special case, which we mention later, all the problems that our theory has to face in two dimensions are present in the one-dimensional case.

We have done some two-dimensional calculations, which all work as predicted from the one-dimensional case.

As a first illustration, let us take a chain of 80 presynaptic cells which are marked by seven different molecule types each produced at a different presynaptic location. The distribution of molecules across the chain is shown in figures 3*a* and *b* for two different diffusion lengths. We can now construct the *interaction matrix* for a given presynaptic marker distribution. An entry in a matrix (figure 3*c*) indicates that the cell identified with the row has molecules in common with the cell identified with the column; that is, these two cells interact with each other if they have contacts in the same postsynaptic region. Presynaptic cells which are near-neighbours cooperate with each other; presynaptic cells which are not near-neighbours interfere. The

important parameter is the range of interaction, which is equal to the width of the band in the matrix. The interaction matrices for the marker distributions of figures 3*a* and *b* are shown, superimposed, in figure 3*c*.

Taking the presynaptic cells to be marked by the set of gradients of figure 3*b*, let us suppose that each axon initially makes a small number of contacts at random amongst the postsynaptic cells. Figure 4*a* shows the matrix of initial connections. Initially, the induced concentrations, displayed above the matrix, are very weak and irregularly distributed.

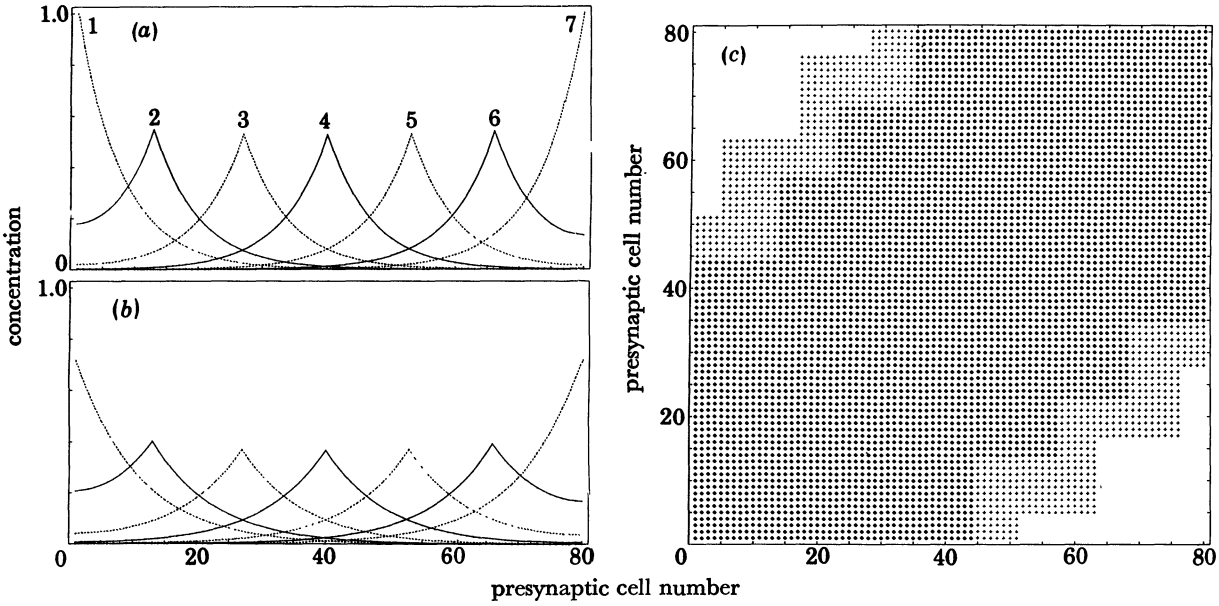

FIGURE 3. Sources for 7 different molecules were placed approximately equidistantly along a chain of 80 presynaptic cells – at positions 1, 13, 26, 40, 53, 66 and 80. This figure shows the stable distribution of molecules diffusing out from these sources, under two different conditions. The diffusion length constant is $\lambda = \sqrt{(d/a)}$, where d is the diffusion constant and a is the decay constant. Units of length and time are the cell spacing and the step length. All concentrations are normalized so that the maximum has a value 1.0. Molecules whose concentrations are less than 1% of the total are discarded. (*a*) Presynaptic marker distribution for $d = 0.3, a = 0.006. \lambda = \sqrt{50} \approx 7$. (*b*) Marker distribution for $d = 0.3, a = 0.003. \lambda = 10$. (*c*) The interaction matrix for these two cases. A '◆' in a matrix entry indicates that the corresponding pair of cells interact when marked according to *a*. The extent of interaction for cells marked as in *b* is greater than for *a*. The extra pairs of cells involved are indicated by '+'s in the matrix.

We now wish to know how the contacts are modified whilst molecules are being induced into the postsynaptic sheet. Figure 4*b* shows the situation after a few modification steps. Note the appearance of weak synapses on each side of a strong synapse. This shows the facility of each axon to sprout. Comparison of 4*b* with 4*c* enables us to identify the various types of interaction. The black regions which first become apparent in figure 4*b* show that neighbours in one sheet are cooperating to connect with neighbours in the other. Consider now presynaptic cells 1–20. By competition, they give up all their contacts which are not in the postsynaptic region 1–25; by interference they dissuade other presynaptic cells from connecting there.

The shape of the mapping and the profile of induced concentrations emerge simultaneously. The end configuration for this case is shown in figure 4*d*. This is a stable state, by which we mean that the average change in synaptic strengths per iteration has fallen below a small, preset, value. In this final state, parts of the presynaptic chain project in a continuous fashion

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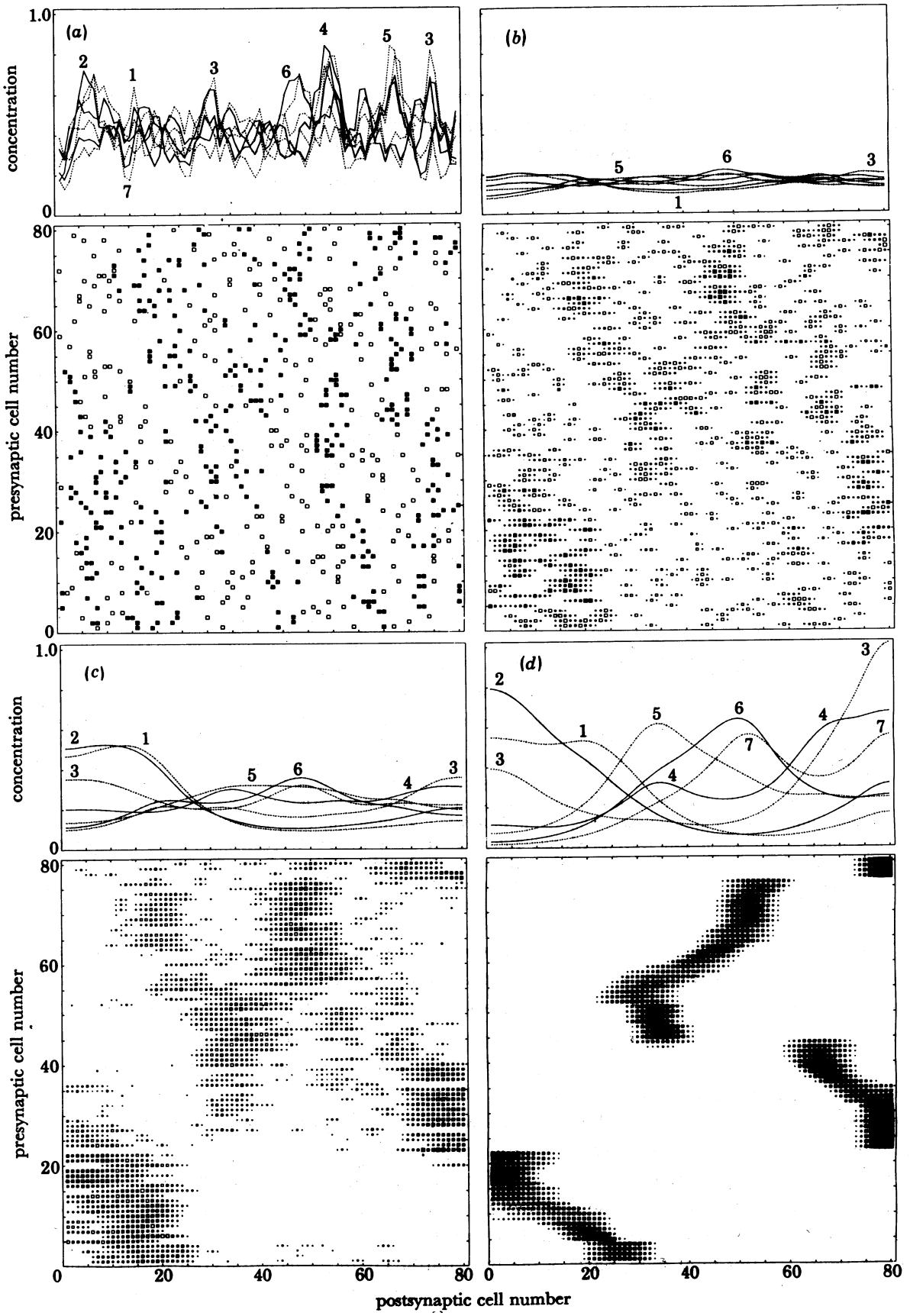

FIGURE 4. For description see opposite.

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onto the postsynaptic chain, but there is no global order; we shall call this a *piece-wise continuous* projection.

2.5. *Provision of orientation information*

The mechanism for ordering synaptic contacts just described contains nothing to favour one particular orientation in the final map. It is therefore not surprising that this mechanism on its own produces maps which are piece-wise continuous, where no consistent orientation prevails. Orientation information must be supplied in addition.

We cannot be as specific about the nature of the orientation mechanism as we were for the neighbourhood mechanism. What we do suggest is that orientation information is supplied in the form of *starting conditions*: that there is a mechanism which introduces a systematic bias in the initial pattern of connections. In the one-dimensional case, this could give rise to two blank areas in the diagonally opposite corners of the matrix of initial connections (figure 5*a*).

With this configuration as starting conditions, after a short time the synapses begin to show organization in an ordered fashion, with the induced concentrations also showing order (figure 5*b*). Cooperation is now much stronger. Figure 5*c* gives a later stage, and the end configuration is shown in figure 5*d*. There is an ordered map of presynaptic cells onto postsynaptic cells, and a rough copy of the presynaptic concentration profiles (figure 3*b*) has become induced into the postsynaptic chain.

The amount of initial synaptic order required for the eventual production of an ordered map depends on the degree of interaction between presynaptic cells. Suppose that the synaptic bias is so slight and the range of interaction so small that many non-interacting fibres make initial contact in roughly the same postsynaptic region. Then it is quite possible for portions of the presynaptic sheet to map independently across the postsynaptic sheet. Reduction of the range of interaction by having the presynaptic cells marked as in 3*a* rather than 3*b* leads to some parts of the postsynaptic chain receiving projections from more than one presynaptic region (figure 6). Both projections are in the desired orientation. In order to obtain a single continuous projection, the initial pattern of synapses must be made more ordered. Alternatively, as we have seen, the range of interaction can be increased.

2.6. *The logic for the orientation mechanism*

In setting up the matrix of figure 5*a* we had to decide in what form the information for specifying the orientation of the map should be supplied. One way would be for the fibres from a particular small region to initially make exclusive contact, in the desired orientation, on a

FIGURE 4. Showing the development of a map between two full-size chains of cells from random starting conditions. Certain features of this figure are common to all other mapping figures. Each figure is made up of a connectivity matrix and a plot of the distributions of markers induced postsynaptically. All concentration plots of a series are drawn to the same scale (unless otherwise stated). Plots for odd-numbered molecules are indicated by broken lines, even-numbered by continuous lines. Where possible, sections of the concentration profiles are labelled by the number of the appropriate molecule type. Each square in the connectivity matrix indicates a synapse between the presynaptic and the postsynaptic cells identified with the matrix row and column respectively. Square area is proportional to synaptic strength. The synapses coloured black are those which are subsequently strengthened, because they have above average fitness. (*a*) The starting configuration. Each of the 80 presynaptic cells, carrying molecules as prescribed in figure 3*b*, has made 8 contacts at random amongst the 80 postsynaptic cells. Here the induced concentration profiles have been enlarged 80 times to emphasize the initial lack of order. (*b*) The state of the mapping after 50 steps of iteration. The very small squares denote synapses which have just been formed by sprouting. (*c*) After 150 steps. Definite hills and valleys begin to emerge in the concentration plots. (*d*) After 2000 steps: a stable configuration.

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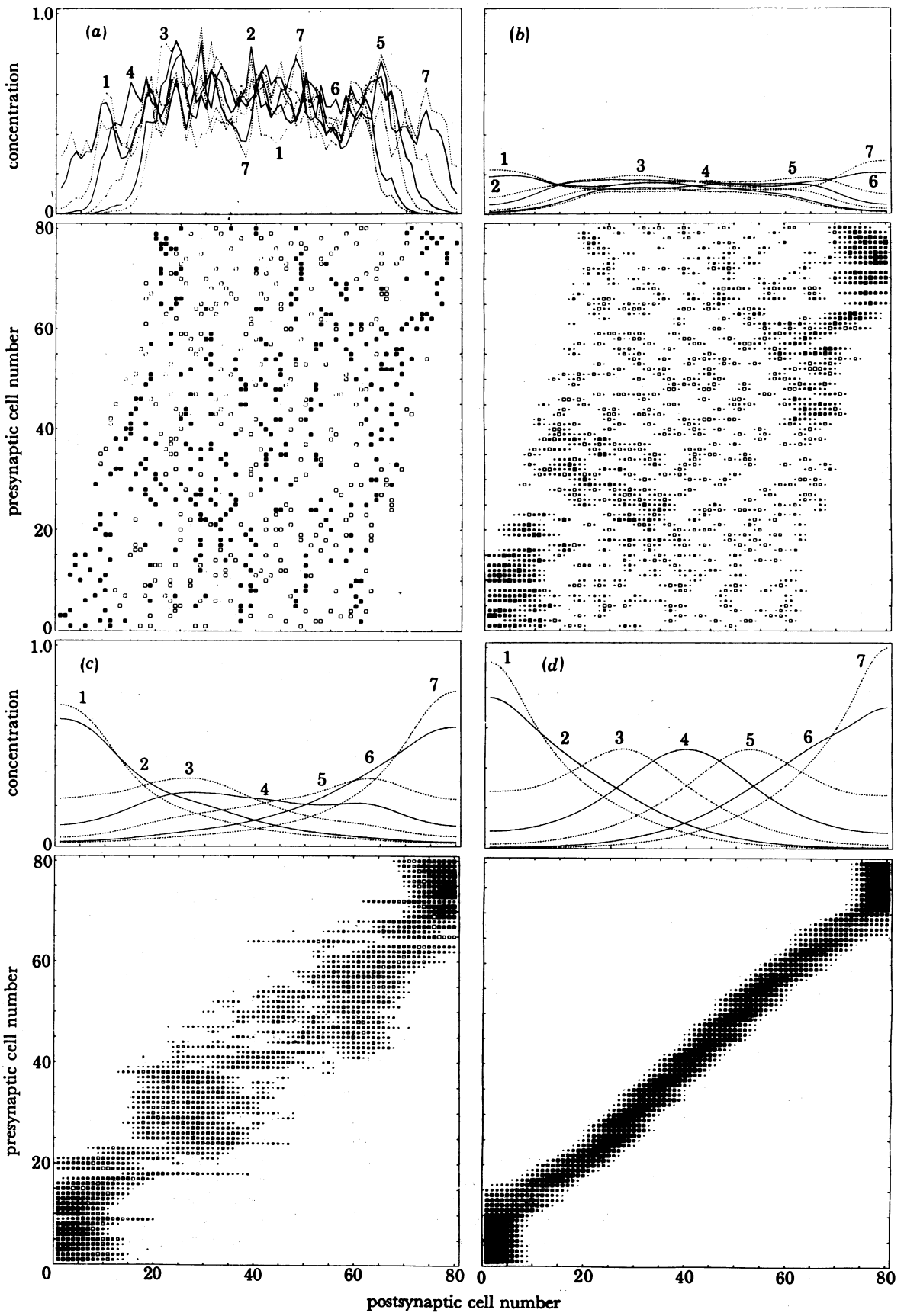

FIGURE 5. For description see opposite.

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similar small postsynaptic region, all other contacts being made at random. The mapping could then be made to spread out as if from a seed crystal, the orientation of the initial part-map eventually imposing itself on the entire mapping. Such a scheme, however, relies on just a few key cells, and would go awry if they were damaged or were missing. We examined this possibility in connection with our neural activity model for map-making (Willshaw & Malsburg 1976), and so we shall not discuss it in detail here.

A more reliable procedure, which was used in the simulations, is to nudge each fibre gently towards its target region, so that its initial contacts are restricted to a particular large part of the postsynaptic sheet. This introduces a very small amount of order in the initial distribution of synapses, as in figure 5*a*.

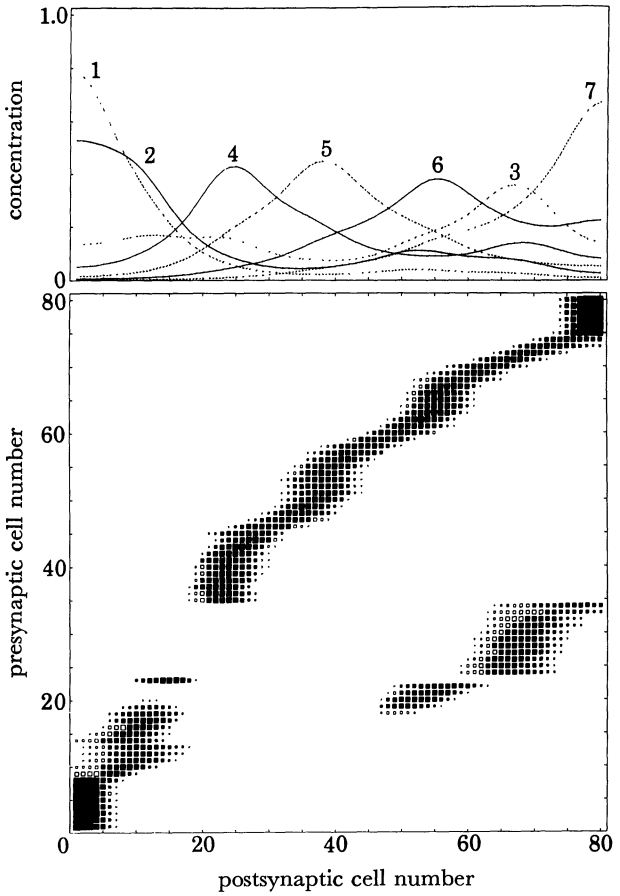

FIGURE 6. The mapping developed after 800 steps using the starting conditions of figure 5*a* but with presynaptic fibres marked as in 3*a* rather than 3*b*.

FIGURE 5. The establishment of a mapping under conditions similar to those for figure 4 except that a small amount of order has been placed in the starting conditions. (*a*) Starting configuration. Each presynaptic cell has made 8 contacts at random amongst a certain 60 of the 80 cells. Here the induced concentrations have been enlarged 100 times. A trace of order is present at the ends of the concentration profile. There, the 'wrong' molecules have been suppressed by the lack of the appropriate synapses.

The next three pictures show the mapping at the stages strictly analogous to those shown for the previous calculation. (*b*) After 50 steps of iteration. Note that growth is mainly restricted to the ends of the post-synaptic sheet. (*c*) After 150 steps. Note the misplacement of the synapses made by fibres 18 and 64. (*d*) The stable configuration after 2000 steps. The bunching of contacts at the ends is a genuine edge effect.

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There are a number of logically different ways for controlling where a fibre makes its initial contacts. It may be that (1) each fibre is able to recognize the collection of postsynaptic *cells* which it might contact initially. Alternatively (2), each fibre may prefer to go to a particular postsynaptic *location*, regardless of what cells are there. The difference between these two possibilities is made clear when we interchange two groups of postsynaptic cells before the initial conditions are set up. If (1) holds, the initial synaptic configuration will be different from normal because the fibres which initially contact the transposed cells will now contact them in their new positions. If (2) holds, it is immaterial how cells are arranged in the postsynaptic sheet, and so the initial synaptic configuration will be as normal. The same thought-experiment can be done for the presynaptic cells. Therefore, there are in all four different ways of supplying *orientation information.*

2.7. *Regeneration and memory*

We now come to the feature which distinguishes the logic of our molecular model from that of our earlier neural activity model (Willshaw & Malsburg 1976). The postsynaptic sheet has

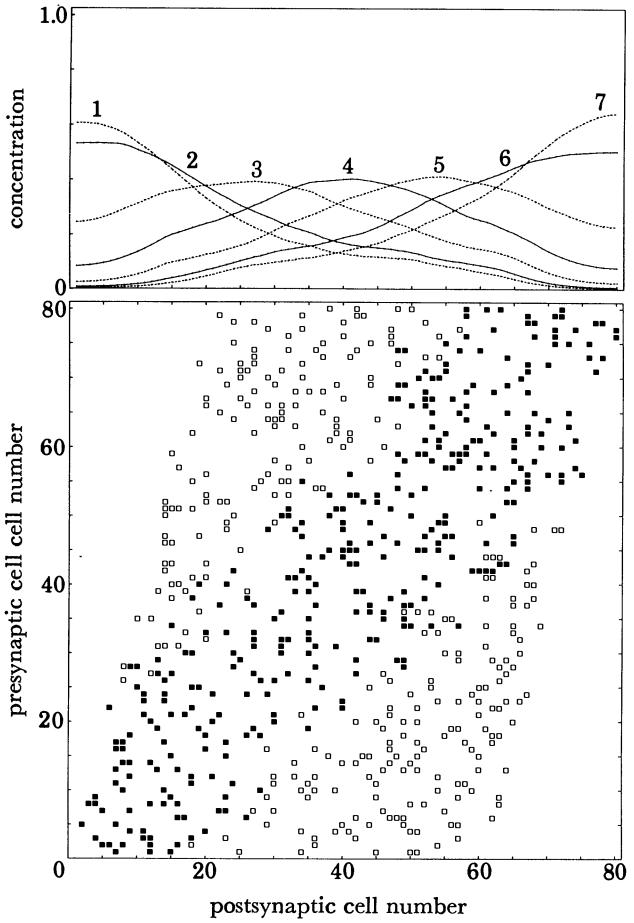

FIGURE 7. The system in the state shown in figure 5*d* had all its connections destroyed. Fibres were then allowed to innervate as they did originally (i.e. as for 5*a*). This figure shows the initial configuration in the regeneration. Note that, compared to 5*a*, the regenerating fibres already have strong preferences (indicated by the black squares in the matrix) for their original target areas. In this example, the equations for molecular induction, diffusion and decay were iterated 100 times before allowing synaptic modification to start. This weakened the previously induced information, and this is why the postsynaptic gradients are flattened copies of those in 5*d*. The ordered mapping which was established very quickly is identical to that in 5*d* and is not shown.

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a *memory*: since the information induced postsynaptically is in the form of molecular concentrations, it would be likely to survive severance of connections between the two sheets, for some time at least. Let us suppose that the state depicted in figure 5*d* has been reached. Now destroy all connections and then allow the fibres to reinnervate the postsynaptic sheet. The initial distribution of synapses is as before. But the postsynaptic cells are now primed to favour certain fibres above others (figure 7). A stable mapping is produced relatively quickly, and is comparable with that existing before the surgery was performed.

In this regeneration situation, information to orientate the map is being supplied twice over: once in the initial pattern of synapses and once in the surviving postsynaptic concentrations. Either way of providing this information is sufficient on its own to give a correctly oriented map. As we showed in §2.5, if there is an initial bias in the synapses the postsynaptic sheet can be *naïve*, that is, initially devoid of markers. Conversely, if the postsynaptic chain has already been primed, the initial synaptic distribution can be random. These two ways of supplying information to orientate the map can also be made to *conflict* with one another; by arranging, for example, that the initial pattern of synapses in regeneration favours one orientation and the initial induced concentrations favour another. In some situations of conflict, the final pattern of connections re-established can be predicted; in other cases it will be very sensitive to fine details, which prevents any general prediction from being made.

The next chapter deals with certain regeneration experiments. As we shall show, the idea of *conflict* is essential for the understanding of many of the experimental findings.

3. Regeneration

3.1. *The mismatch experiments*

The basic facts to account for are:

(1) half a retina eventually regenerates ordered connections over the entire tectum (Horder 1971; Schmidt *et al.* 1978);
(2) a whole retina comes to compress its projection, in order, on to a half tectum (Gaze & Sharma 1970; Yoon 1971, 1976);
(3) half a retina can transfer its connections in order onto the foreign half tectum (Horder 1971; Yoon 1972);
(4) some of these situations have a time course. For example, fibres from a half retina regenerating onto a whole tectum first establish connections in roughly their original target areas, and later slide across to cover the whole tectum (Schmidt *et al.* 1978). Such findings could explain why in some mismatch experiments no spread or compressed maps were found (Attardi & Sperry 1963).

In terms of our model, performing a mismatch experiment is a simple way of introducing a conflict. Let us remove presynaptic cells 41–80 from the system as shown in figure 5*d*, cut through all connections and then allow the surviving fibres to reinnervate the postsynaptic sheet, with starting conditions as given in figure 8*a*. The conflict arises because the fibres initially make contact over most of the 80 postsynaptic cells whereas their initial preferences are for cells 1–40 only. As the process of synaptic modification proceeds, the fibres first tend towards their original sites (figure 8*b*). They then gradually spread their connections in order over the entire postsynaptic chain (figure 8*c* and *d*).

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In this case, the relative strengths of the two opponents in the conflict are comparatively unimportant. It is true that the more powerful the initial induced information is, the more quickly the regenerating fibres will return to their original positions. But thereafter it is a straightforward matter for them, by sprouting contacts onto neighbouring cells, to spread over the entire chain.

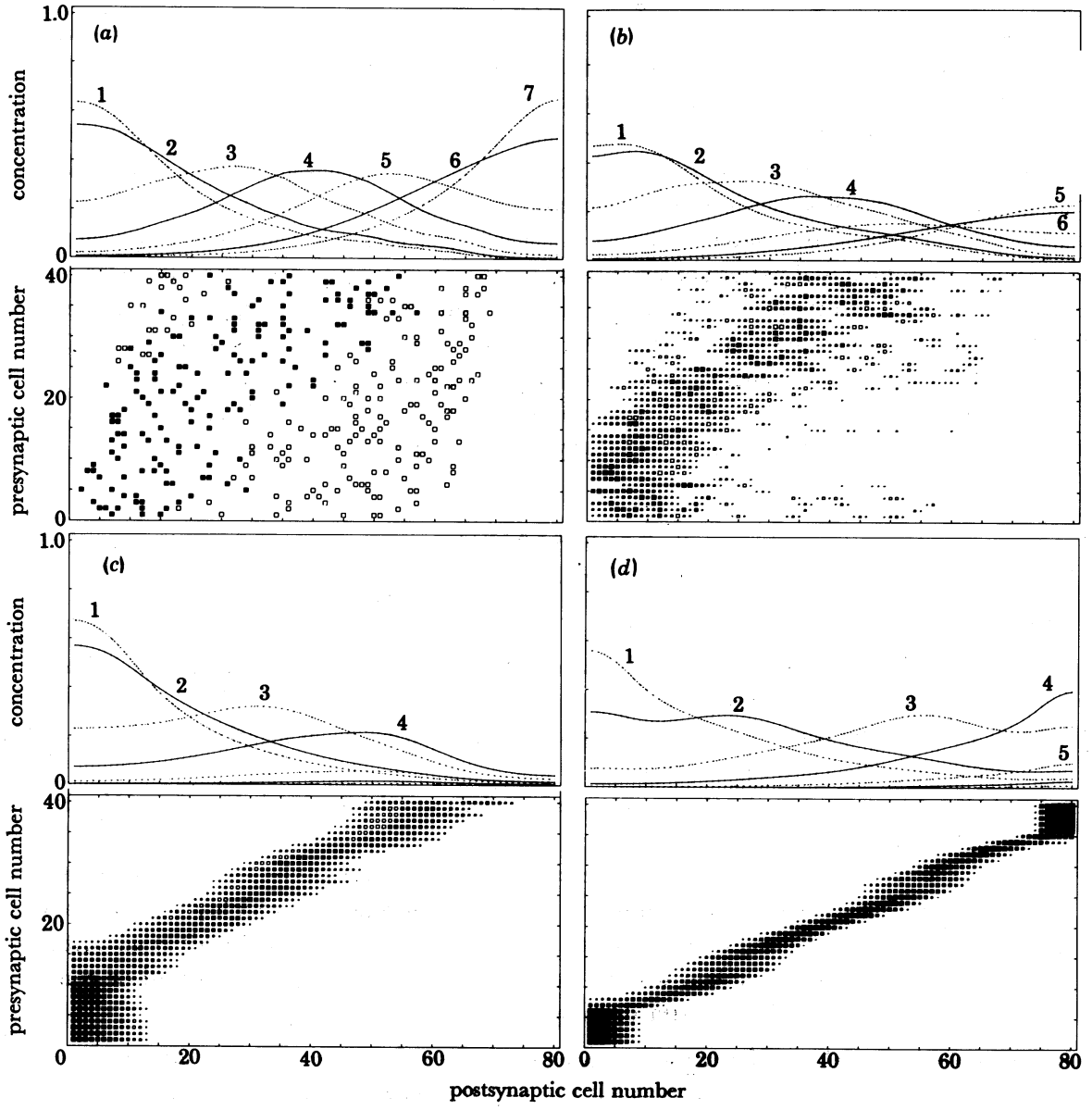

FIGURE 8. Presynaptic cells 1–40 regenerating onto postsynaptic cells 1–80. Presynaptic cells 41–80 were removed from the system shown in figure 5*d* and all connections were destroyed. The surviving 40 presynaptic cells were made to form synapses according to the usual rule. (*a*) Starting configuration. Postsynaptic iteration was carried out for 50 steps before synaptic modification commenced, (*b*) After 50 steps. Molecules of types 5, 6 and 7, being only sparsely represented in presynaptic cells 1–40 (see figure 3*b*), are disappearing from the postsynaptic chain. (*c*) After 350 steps. The white edge to the synaptic band indicates a progressive shifting of synaptic connections across the entire postsynaptic chain. (*d*) The stable configuration resulting after 5000 steps. This 'systems-matching' has set off a reorganization of markers in the *postsynaptic* chain.

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In general, however, the relative strengths of the orientation information and the initial induced information are of great importance. An example is provided by the experiment complementary to the one just described: allow connections to re-establish after *postsynaptic* cells 41–80 have been removed from the adult system and all connections have been destroyed (figure 9*a*). An extreme case is where the surviving induced information is exceptionally strong.

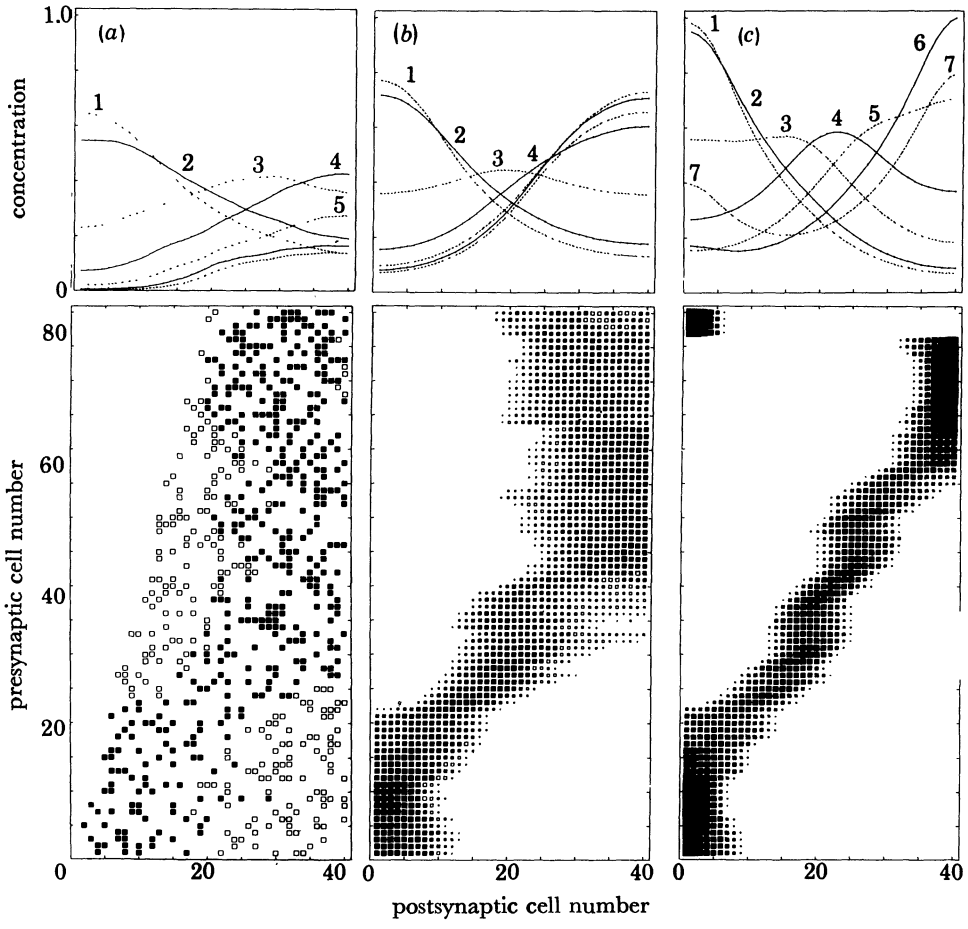

FIGURE 9. Presynaptic cells 1–80 regenerating onto postsynaptic cells 1–40. Once again, the 'surgery' was carried out on the system shown in figure 5*d*. This time, postsynaptic cells were removed. (*a*) Initial configuration. Here each fibre initially made 8 synaptic contacts at random along as much of its prescribed part of the postsynaptic chain as is now available. Initial postsynaptic iteration of 50 steps was carried out. (*b*) After 350 steps. The high-numbered presynaptic cells are all endeavouring to contact the same postsynaptic cells. (*c*) Stable configuration reached after 5000 steps. An almost completely continuous mapping results. Fibres 76–80 can maintain contact on the lowest-numbered postsynaptic cells because they do not interfere with the other postsynaptic cells which have synapses there. Leaving aside the blemish produced by fibres 76–80, the 7 molecular gradients seen in 5*d* have now been fitted, in an orderly arrangement, into the reduced postsynaptic space.

Then, the surviving postsynaptic cells will attract their original presynaptic partners. The other presynaptic cells will then have to place their contacts where they will not interfere with the contacts already established. No continuously ordered map will result. This situation can be remedied by weakening the effect of the induced postsynaptic information, which is done in our calculations by iterating the equations for the postsynaptic concentrations a few extra times before allowing synaptic modification to start. The amount of initial iteration used for

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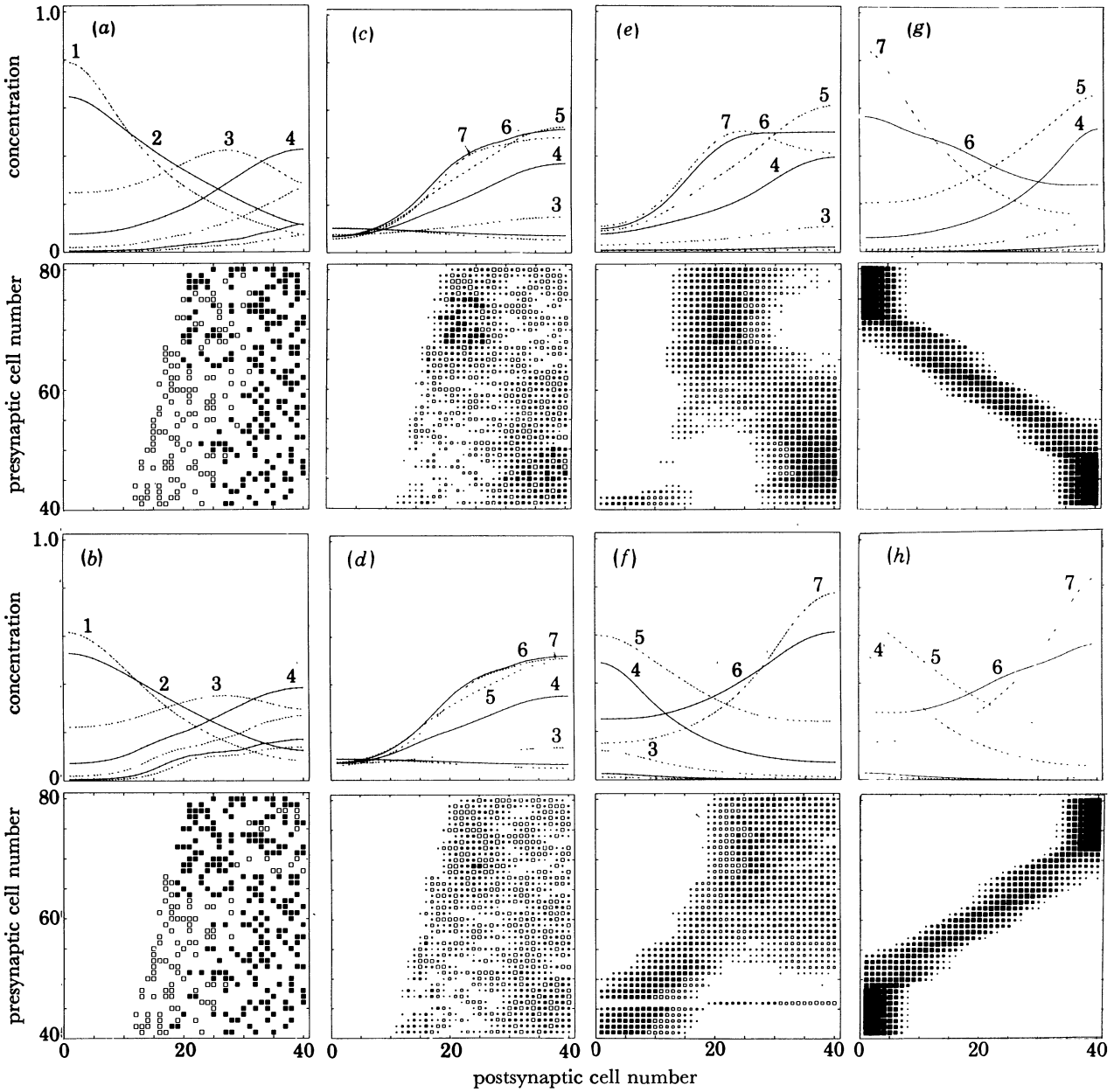

FIGURE 10. Presynaptic cells 41–80 regenerating onto postsynaptic cells 1–40. 'Surgery' performed on the system shown in figure 5*d*. (*a*) Initial configuration after only 5 steps of initial iteration. Therefore, the initial induced information has a relatively strong influence. (*b*) Initial configuration after 50 steps of initial iteration. This weakens the influence of the induced information. (*c*), (*d*) After 100 steps of iteration in the situations of strong (*c*) and weak (*d*) induced information. Molecules of types 1–3 are disappearing and being replaced by types 5–7, because the presynaptic fibres have almost none of the lower-numbered molecules. (*e*), (*f*) After 300 steps in the strong (*e*) and the weak (*f*) cases. (*g*), (*h*) Stable configurations after 4000 steps. Strong initial induced information has reversed the map (*g*), with a corresponding reversal of order of the postsynaptic gradients. In (*h*) the orientation mechanism has predominated, and a mapping in the normal orientation has resulted.

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figure 9*a* was not quite enough to give a completely ordered map. Figure 9*b* shows an intermediate state, and figure 9*c* gives the end configuration, where just a small part of the presynaptic sheet is incorrectly mapped.

The conflict becomes more serious when the principles of the previous two experiments are combined to leave each of the cells remaining without any of its original partners: destroy all connections and remove presynaptic cells 1–40 *and* postsynaptic cells 41–80 from the system in the state shown in figure 5*d*. There is now a direct conflict. The orientation mechanism favours the establishment of a map in one orientation, and if that mechanism is strong enough a continuous map in that orientation results (figure 10*b*, *d*, *f*, *h*). But the induced information favours the opposite orientation. The induced information in 10*a* is stronger than in 10*b*, and in the series 10*a*, 10*c*, 10*e*, 10*g* a map in the reversed orientation results. Horder & Martin (1977) found this type of map when they ablated temporal retina and caudal tectum (to which *nasal* retina normally projects), leaving a band of intact fibres projecting to the caudal edge of the rostral remnant. Our interpretation of this result is that leaving some fibres intact has strengthened the initial induced information to such an extent that the 'wrong' orientation is favoured.

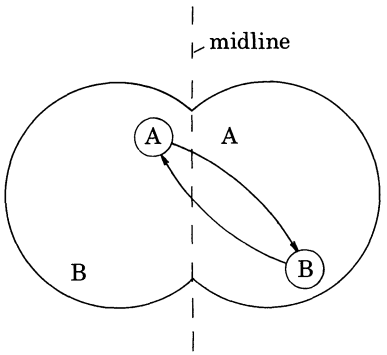

FIGURE 11. Representing the interchange of grafts between tecta. The encircled regions, at locations A and B, were exchanged. If the same set of markers is distributed over each tectum, mirror-symmetrically arranged about the midline, the transplantation operation will give rise to each tectum having two regions which carry the same markers. If different markers are in right and left tecta no duplication can be produced.

3.2. *Do two retinae carry matching sets of markers?*

In the next sections, we shall discuss a number of experiments which are variations on the mismatch theme. In some of these, the tectum receives innervation from both ipsilateral and contralateral retinae. We therefore wish to know how the markers in the two retinae are related.

Jacobson & Levine (1975*b*) transferred grafts between the two tecta. They found that the graft and the tectal region mirror-symmetrically related to the graft's original position sometimes received a projection from the same part of the visual field. Therefore, the two tecta must normally carry identical sets of markers, mirror-symmetrically arranged (figure 11). Since we are proposing that the tectum acquires its markers from the retina, the retinal markers must be arranged similarly.

When Levine & Jacobson (1975) removed one tectum from an adult goldfish and then deflected the optic nerve ipsilaterally, they found that only small portions of the two retinae were represented on the remaining tectum. The entire tectum was usually divided up between the two eyes, but sometimes just a small tectal region was innervated binocularly. In these

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double projections, the ipsilateral and contralateral fields were always in register. Once again, this suggests to us that the two retinae carried matching sets of markers. Why large portions of the two retinae did not, apparently, project to the tectum is not clear to us.

3.3. *Duplications in the map*

Gaze & Sharma (1970) were the first to show that after removing the caudal half of the tectum and mapping the regenerated projection, some points in the tectum received a projection from two distinct retinal areas. They found this result only when the optic nerve was left intact. When it was cut or crushed, a continuous map resulted. Our interpretation of this result is that leaving the optic nerve intact amounts to increasing the strength of the induced information, which can result in duplication, as discussed in § 3.1. Figure 9*c* shows a small amount of duplication. The duplication can be increased by performing fewer initial iterations on the equations for the postsynaptic concentrations.

Duplication was also seen by Schmidt (1978). Having allowed a temporal half-retina to make an ordered map over the whole of a normal tectum, he removed this half-retinal projection and led in the entire ipsilateral projection. He found that almost every tectal penetration was associated with two regions of the visual field systematically separated along the naso-temporal axis. He interpreted this result as the superposition of an expanded half-retinal and a normal projection. Our interpretation is that there is a severe conflict here. Initially, the whole tectum is primed to make preferential connections with just half the retina, whereas it receives contacts from the whole retina. Therefore, a tectal region could become connected to two, non-interfering, retinal regions.

In both sets of experiments, the orientation and extent of the duplicated part-map will depend on factors such as where the cut was made and how extensive the range of presynaptic interaction is. This might explain why in the intact optic nerve experiments some authors found a duplication in the normal orientation and others did not (Gaze & Sharma 1970; Udin 1977). In order to obtain results comparable to Schmidt's (figure 12), we had to decrease the interference range by using presynaptic cells marked as in figure 3*a*. It should be possible to use the findings of duplication experiments to measure the range of interaction in the retina.

3.4. *Dual innervation*

An inductive mechanism prescribes that the reorganization of markers following surgical intervention always takes place in the postsynaptic sheet. This differs from the regulation hypothesis, which states that the reorganization occurs in the sheet which has undergone surgery. Schmidt (1978) has obtained direct evidence against the regulation hypothesis, in the case of a goldfish half-retina regenerating into a whole tectum. He diverted the entire ipsilateral projection into a tectum which was already holding an ordered expanded projection from the contralateral temporal half-retina. If regulation had taken place in the half-retina, the new retina would be expected to spread its connections in order over the whole tectum. Schmidt found that the temporal half of the new retina mapped in register (in the mirror-symmetrical sense) with the existing temporal half, across the whole tectum. The other retinal half made no connections there. He concluded that it was the tectum which had had its markers changed, although it had not undergone surgery. Schmidt (1978) has done the complementary experiment of diverting the optic nerve from a *half* retina to innervate a tectum already holding an ordered projection from a *whole* retina. The half-retina projected in register with the corresponding half of the incumbent retina, across just half the tectum.

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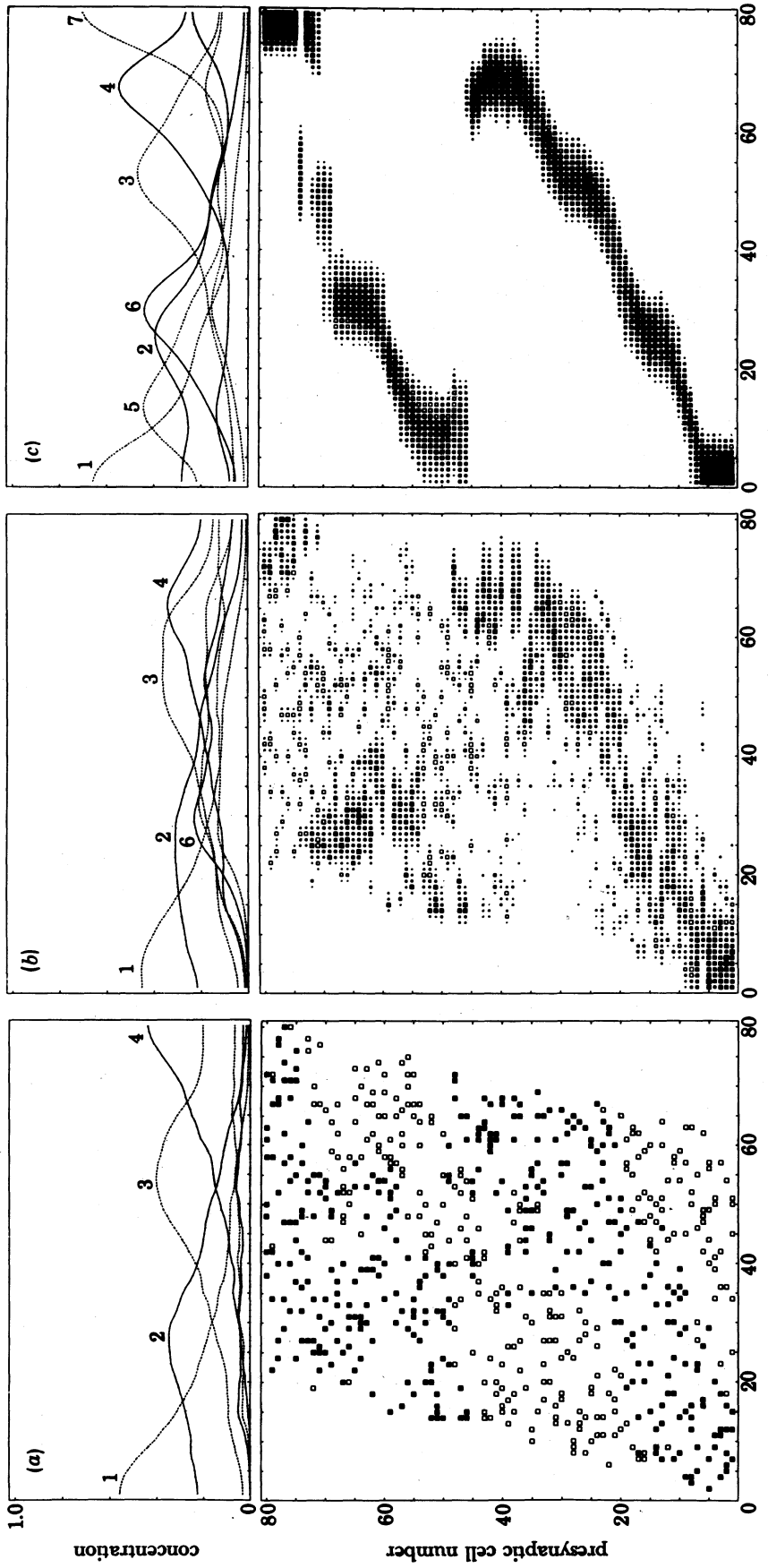

FIGURE 12. Regeneration of 80 presynaptic cells onto 80 postsynaptic cells which originally had a projection from 40 presynaptic cells similar to that shown in figure 8*d*. Presynaptic cells marked as in figure 3*a*. (*a*) Initial configuration. (*b*) After 50 steps. A double representation begins to form on the postsynaptic chain. Note the intrusion of molecules of type 6 in the induced concentrations, which corresponds to the arrival of the overlaid projection. (*c*) After 400 steps (not the final configuration). In the concentration profiles, the presence of the double projection is indicated by the overlap of the hills for molecules 5 and 6 with those for molecules 1 and 2.

These two results provide additional evidence that the markers in the two retinae of a normal animal are related in a mirror-symmetrical fashion: in the maps under discussion, the mirror-related parts of the two retinae project in register, and the retinal regions in one eye which have no mirror counterpart in the other eye project monocularly.

3.5. *A serendipitous finding*

This was obtained by Feldman, Keating & Gaze (1975) while doing developmental studies on *Xenopus*. They had removed one eye at stage 29, and after metamorphosis attempted to deflect fibres from the remaining eye to innervate the ipsilateral tectum. In most cases, fibres from the whole retina grew to both tecta. In one animal, the visual projection to one tectum was normal, indicating that the retina contained a normal set of markers. But on the other tectum, an ordered projection from only part of the retina was found, and this was expanded over the entire tectum. These authors concluded that a part-retina is still able to form an expanded projection on the tectum, even though it contains just a part-set of markers. Since the retinal cells had retained their markers, the tectal cells must have changed theirs in order to accommodate an ordered expanded projection. This result is predicted by an induction mechanism.

3.6. *Time considerations*

The speed of reaching the model's final state will depend on the factors controlling the relative strengths of the two conflicting ways of providing orientation information. Such factors may vary from experiment to experiment, so it is possible that apparently identical experiments might find different time courses. These factors may also vary from species to species. Yoon (1976) investigated, in goldfish, the time course of a retina regenerating onto a half-tectum on which it had previously set up a compressed projection. He found that the retinal fibres compressed into the half-tectum more quickly than in the establishment of the original compressed projection. Cook & Horder (1974) performed the same experiment on a different type of goldfish, and found no such difference. We have to conclude that in their experiment the induced information had a comparatively weak influence.

3.7. *The tectal graft transplantation experiments*

The second important way of producing a conflict is to do a tectal graft rotation or translocation experiment.

Two different types of result have been obtained. Sometimes the map of regenerated connections was normal and continuous; sometimes that part of the visual field which mapped onto the graft became rotated or translocated in step with the graft (Sharma & Gaze 1971; Yoon 1973; Levine & Jacobson 1974; Jacobson & Levine 1975*a*, *b*; Hope *et al.* 1976). Jacobson & Levine (1975*a*, *b*) successfully translocated grafts between tecta in 27 frogs. In 13 cases a normal continuous map was seen; in the other 14 cases evidence for translocation of the appropriate part of the projection was found. The problem now is to account for both types of projection.

Let us perform a graft rotation experiment on our model. We start with the system as in figure 5*d*. We then turn round the portion of the postsynaptic chain comprising cells 20–70, cell 20 now being next to cell 71. We destroy all connections and then allow the fibres to re-innervate the postsynaptic chain. The logic of the orientation mechanism must now be specified. Let us assume that orientation information is determined by the postsynaptic *cells* (figure 13*a*).

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The conflict arises because the postsynaptic cells are primed to accept fibres so as to give a continuous map with the middle section rotated, whereas the initial pattern of synapses, although slightly altered by the graft rotation, favours a normal continuous map. The conflict can be resolved in favour of a normal or a piece-wise continuous map; as already shown, piece-wise continuous maps are stable states of the system. The starting conditions of figure 13*a* lead to the end configuration of figure 13*b*.

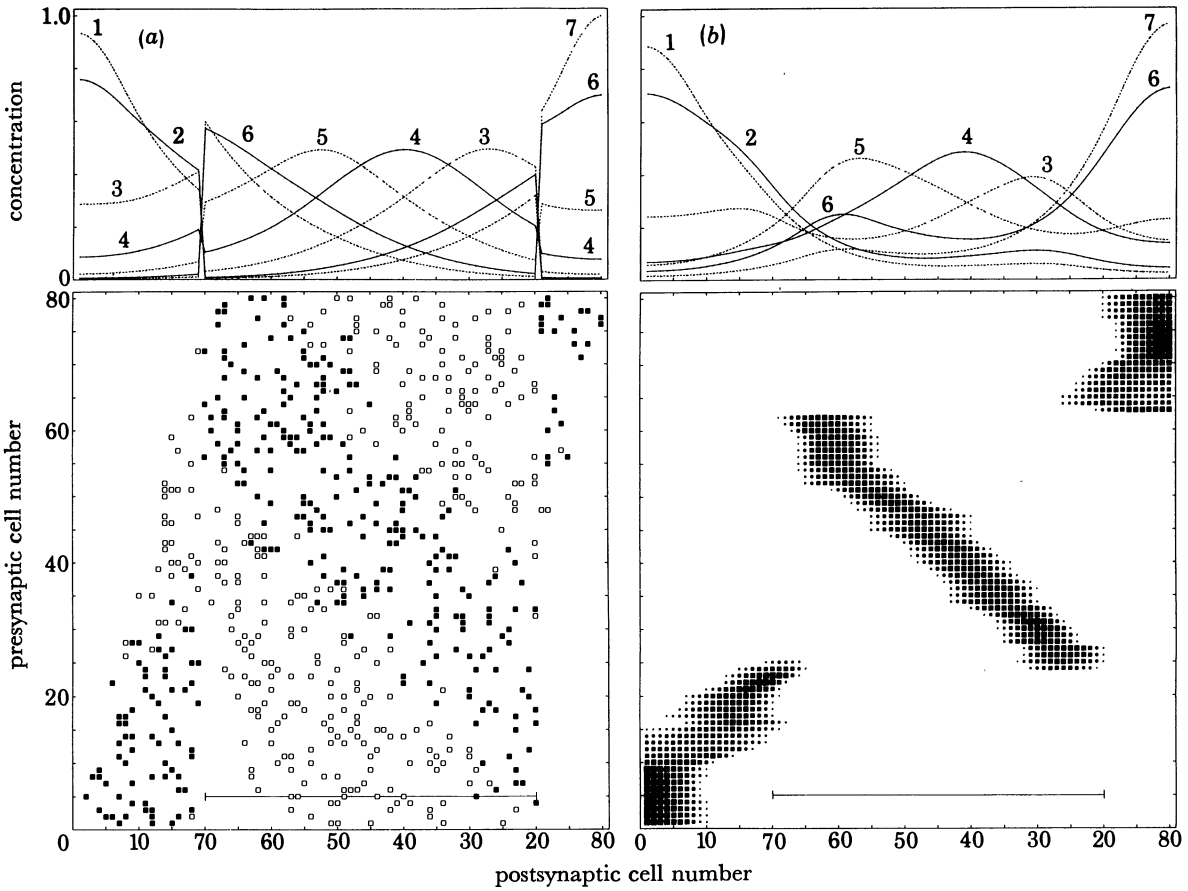

FIGURE 13. Regeneration of a mapping after inversion of part of the postsynaptic chain. (*a*) The starting system was once again that shown in figure 5*d*. The part of the postsynaptic chain stretching from cell 20 to cell 70 was turned around and all connections were destroyed. The horizontal line drawn in the matrix indicates those cells affected. Postsynaptic *cells* rather than *locations* were assumed to determine the initial pattern of reinnervation. Hence the blank space in the bottom left part of the matrix. No initial iteration was performed on the equations for the postsynaptic concentrations. The initial concentrations are therefore faithful copies (with inversion in the inverted region) of those of figure 5*d*. The distribution of the black regions in the connection matrix show that there is a strong initial preference of fibres for a piece-wise continuous map. (*b*) Stable end configuration after 1600 steps.

On weakening the initial induced information, the starting conditions of 14*a* are obtained. In this example, there is a time course. Early on, part of the map over the graft is rotated (figure 14*b*). As time goes on, the map is gradually cleaned up (figure 14*c*) until the continuous state shown in figure 14*d* is reached.

When we repeated these calculations with orientation information depending on post-synaptic *location*, similar results were found. The two different orientation mechanisms seem

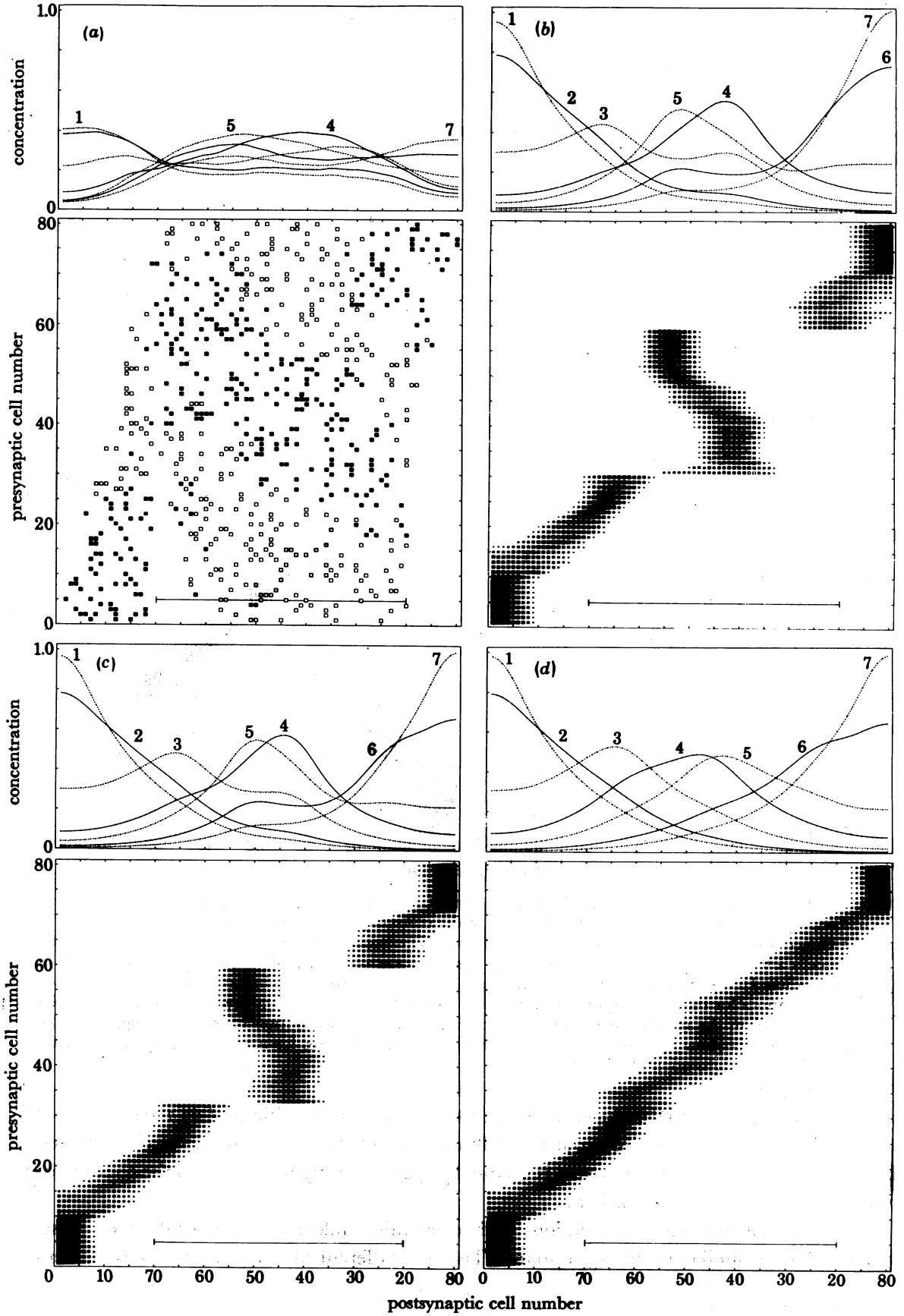

FIGURE 14. The manipulation done in the previous series was repeated after first iterating the equations 100 times before modification commenced. This weakened the induced information. (*a*) Initial configuration. The initial preference of fibres for a piece-wise continuous map is now not so strong. (*b*)–(*d*). After 1500, 3000 and 4000 steps respectively.

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therefore to have the same effect. A difference would be seen if the postsynaptic grafts were very large. In the limiting case of rotating the entire tectum, a rotated map must be produced if orientation information is determined by the cells, however strong the induced information is.

In general, however, either a normal continuous or a piece-wise continuous map is possible. In the retinotectal situation, the factors determining which type of map will result (such as the exact size and shape of the graft and the effect of the tectal incisions) may be difficult to keep constant. Therefore, both types of map could be found in apparently identical rotation experiments. The same analysis holds for the translocation experiments.

The tectal graft experiments have been much discussed of late in connection with whether the tectum contains pre-programmed markers or is merely a uniform medium. The production of rotated or translocated mappings after graft transplantation in the adult is no evidence for genetically programmed markers, because the markers could have been brought in by the presynaptic fibres during development. The ideal experiment to answer this question would be to rotate or translocate a portion of a tectum which had never received a retinal input. This seems to be a difficult experiment to perform. A more feasible experiment is to remove the information presumed to have been induced on the adult tectum, before doing a rotation or translocation manipulation. Regeneration of a correspondingly rotated or translocated mapping would then be strong evidence for pre-programmed tectal markers.

Experiments by Hunt (1976) on *Xenopus* have a bearing on this point. He constructed *scrambled* maps, maps with apparently no retinotopic order, by the technique of repeatedly rotating the eye during larval stages 28–31. He then performed a tectal graft transplantation experiment on the adult, removed the scrambled projection and allowed a normal set of optic fibres, from the ipsilateral eye, to innervate the tectum. In some cases he obtained the piece-wise continuous maps sometimes found in the normal graft transplantation experiments; the map was continuous except that the part of the field normally associated with the graft had translocated or rotated along with the graft. These results have been taken to show that the tectal markers which give rise to this piece-wise continuous map must have been pre-programmed into the tectum; and that they could not have been placed there by induction from the retina because prior to the graft transplantation tectal cells had not received a normal retinal input.

In order to evaluate these results, it is essential to know how the markers for the scrambled map are arranged across the tectum. Is there a scrambled distribution of markers emanating from a roughly normal distribution in the retina (as in figure 4*d*), or are the markers normally distributed in the tectum and abnormally distributed in the retina (J. T. Schmidt, personal communication)? Double innervation experiments of the type done by Schmidt (1978) could answer this question.

We have 'repeated' Hunt's experiments with our model. We took the map shown in figure 4*d* to represent a scrambled map. We rotated postsynaptic cells 20–70, destroyed all connections and allowed reinnervation to take place. Synaptic modification started immediately, so the initial induced information exerted a strong effect. A classical rotated part-map was obtained (figure 15). We must admit, however, that this result is due to the presence of a particular type of disorder in our scrambled map. It is therefore essential to examine the details of the scrambling in scrambled biological maps.

When the same manipulation was repeated after first weakening the initial induced information, a normal continuous map was obtained. Hunt found this type of map in a minority of cases.

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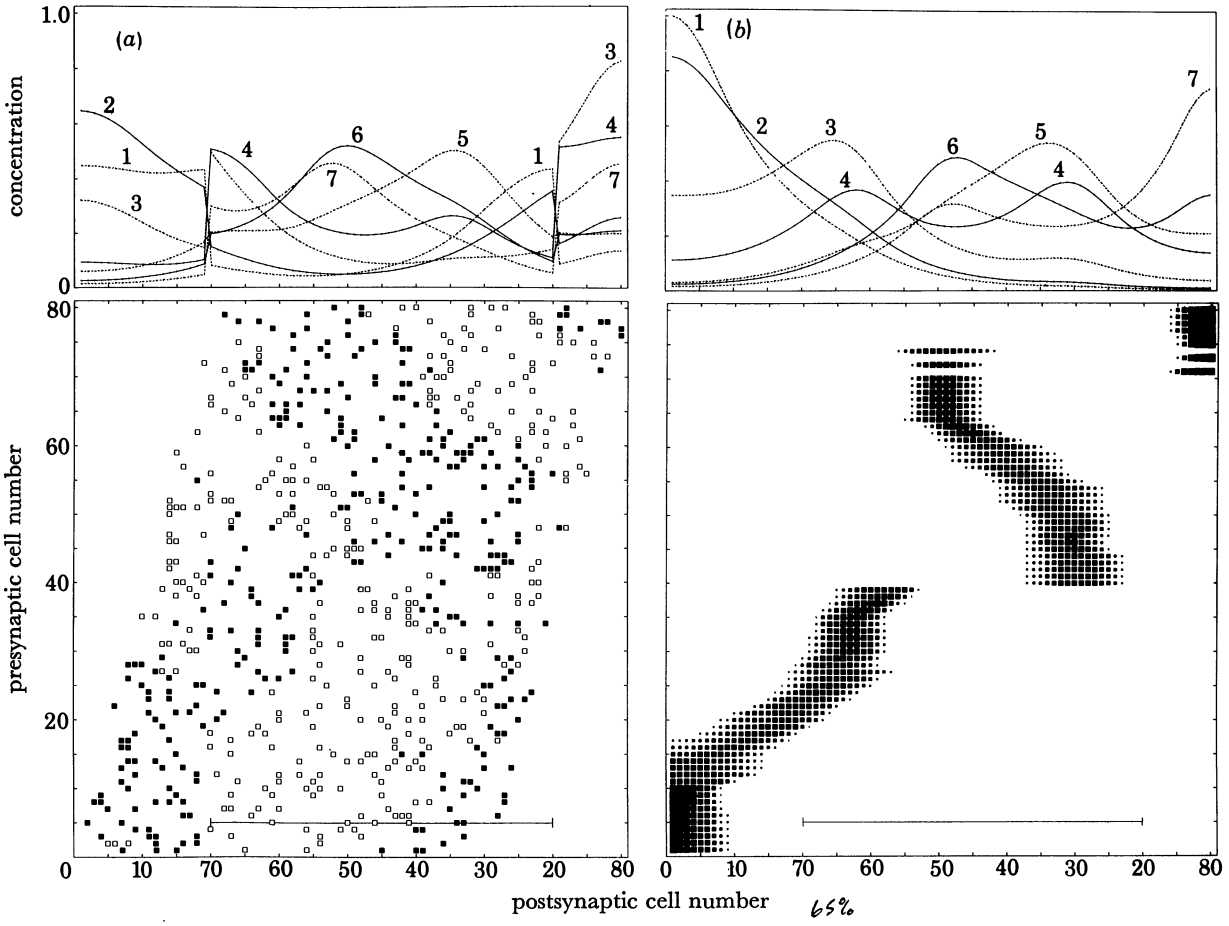

FIGURE 15. A 'graft rotation' carried out on a system which had reached the discontinuous state shown in figure 4*d*. (*a*) Initial configuration. Pattern of reinnervation determined by postsynaptic *locations*, so in the initial pattern of synapses there is no indication that part of the postsynaptic chain has been inverted. No initial iteration. The initial concentrations are therefore carbon copies (with appropriate inversion) of those given in figure 4*d*. (*b*) Stable configuration reached after 4000 steps. Fibres 40–80 have returned to roughly the partners they had in 4*d*, whereas most of the others have not. The result is a distorted version of the classical piece-wise continuous map shown in figure 13*b*.

3.8. *Mismatch and graft rotation combined*

In recent work on goldfish, Yoon (1977) incorporated in the same experiment the two types of conflict that we have discussed. He found that the compressed projection from a whole retina onto a half tectum remained compressed when part of the tectum was rotated by 90° or 180°. In the cases when the graft survived, the projection regenerated to it was found to be rotated by the corresponding amount.

In a complementary set of experiments, the projection onto a tectum containing a rotated graft was found to undergo compression after removal of part of the tectum, which included part of the graft. The projection to the graft retained its rotated orientation while shifting and compressing. These results are predicted by an inductive mechanism, and are not in accordance with the regulation hypothesis. For example, in Yoon's first experiment, regulation states that the tectal cells had changed their markers in order to produce the initial compressed map. If then markers are plastic, subsequent rotation of part of the tectum should result in an ordered compressed map, rather than the piece-wise continuous map found by Yoon.

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4. Development

4.1. *The development of the normal projection*

The development of retinotectal connections differs from regeneration in that the tectum has not had the chance to be programmed by a previous retinal projection.

Furthermore, account must be taken of the disparate modes of growth of retina and tectum. In *Xenopus*, the retina grows in rings (Straznicky & Gaze 1971), whereas the tectum grows in a curvilinear fashion, rostrally to caudally and laterally to medially (Straznicky & Gaze 1972).

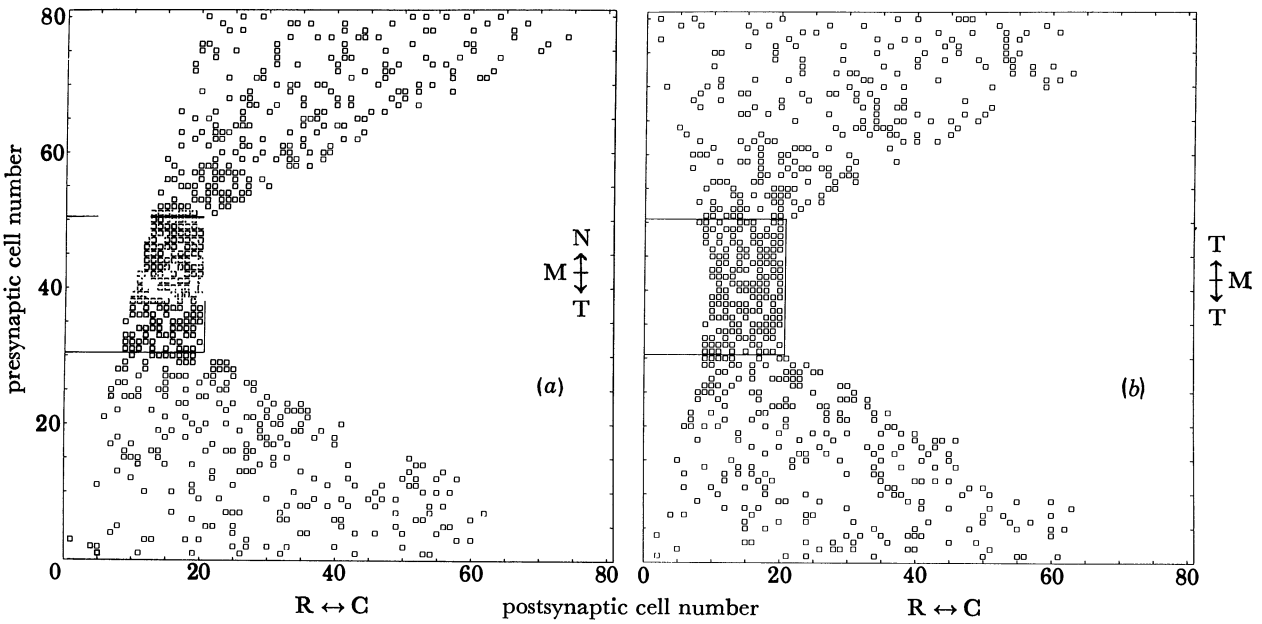

Figure 16. (*a*) Shows the synapses which each fibre makes on initially innervating the postsynaptic chain during normal development. The rule of growth is that initially presynaptic cells 31–50 contact postsynaptic cells 1–20. These initial synapses are enclosed by a small square. At regular intervals thereafter, 1 cell is added to each end of the presynaptic chain and 2 are added to the high-numbered (caudal) end of the postsynaptic chain. Fibre 40 cannot initially contact cells with a higher number than 20 because these have not yet been born at the time when it puts out its initial contacts; fibre 60 can only make contacts up to cell 40; and so on. (*b*) Pattern of initial connections for the development of a map from a 'double-temporal' chain. Since the orientation mechanisms for the two 'temporal half-eyes' are mirror-symmetrically related, the matrix of connections is symmetrical about a horizontal line drawn between presynaptic cells 40 and 41. Notation R, rostral; C, caudal; T, temporal; N, nasal; M, mid-line.

Therefore, cells which are to connect together in the adult are born at different times. Even so, Gaze *et al.* (1974) found, from very early stages of development, an ordered projection of field onto tectum, oriented as in the adult. They concluded that this implies a gradual shifting of connections throughout development. They also found systematic distortions in the retinotectal projection. In adult *Xenopus*, the nasal and temporal half-retinae occupy roughly equal tectal areas. But up to stage 63/64, the nasal half-retina took up significantly more than half the tectum. Receptive field size also varied. At very early stages, fields were enormous, and gradually shrunk as development proceeded; and fields were consistently larger rostrally than caudally.

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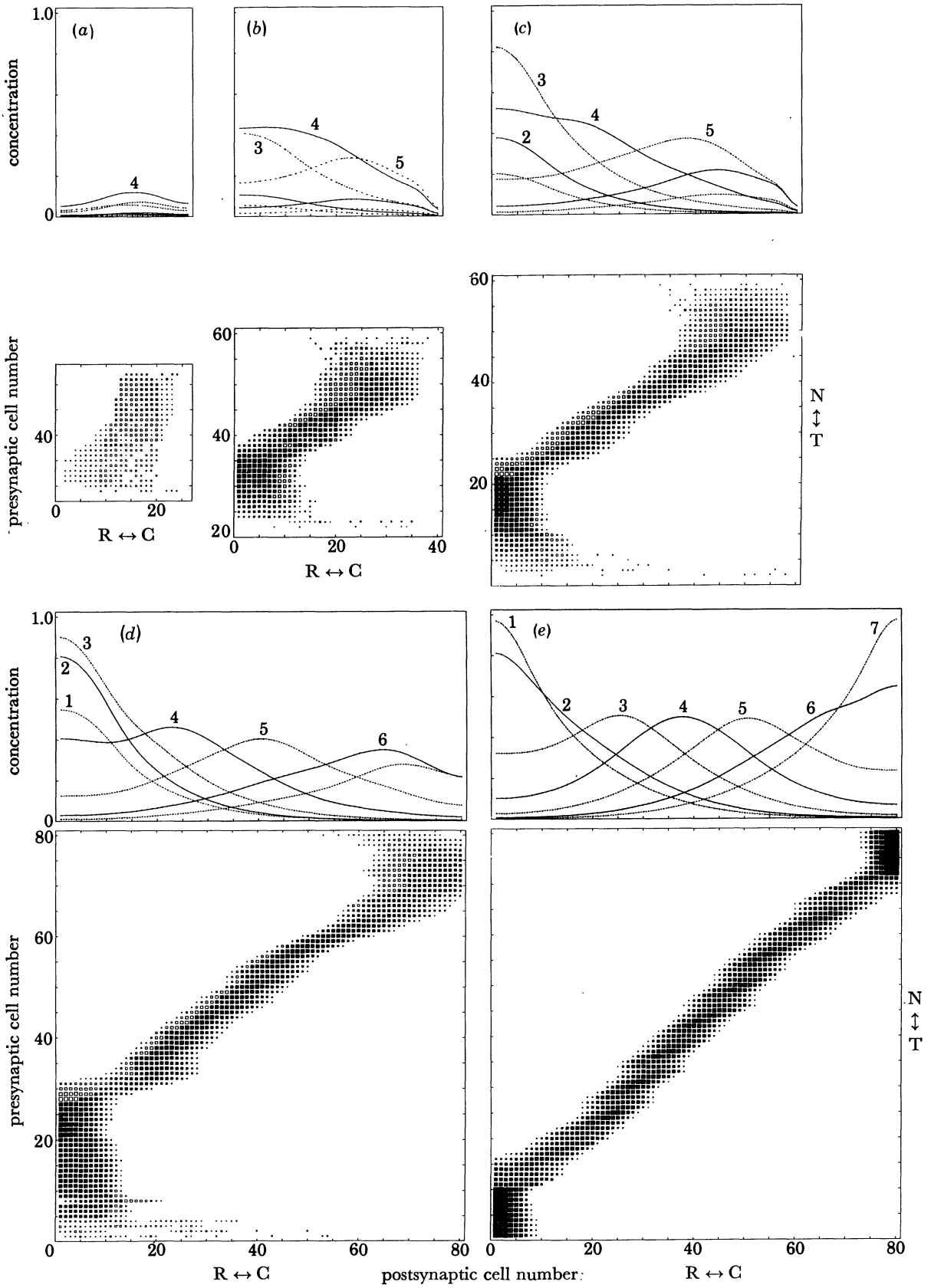

FIGURE 17. For description see opposite.

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We investigated a one-dimensional analogue of the developing retinotectal projection. The two chains of cells represent the nasotemporal axis of the retina and the rostrocaudal axis of the tectum. Temporal retina and rostral tectum are represented by low-numbered cells. Initially there are only 20 cells in each chain, presynaptic cells 31–50 and postsynaptic cells 1–20. The chains are gradually augmented whilst the mapping is set up, by a periodic addition of cells to both ends of the 'retina' and to 'caudal' 'tectum'.

We assume that the process of marking the presynaptic cells is complete before development commences. This may not be true in reality but it is not a serious simplication.

The initial contacts made by each fibre are shown in figure 16*a*.

The initial orientation information is very imprecise. Rostral cells, in fact, have no contacts at all. There is, however, enough orientation information there to start out the mapping in the correct direction (figure 17*a*). After a few modification steps there is a roughly ordered map of the total length of the presynaptic chain, now comprising 40 cells, on the total available postsynaptic chain (figure 17*b*). Once this state has been reached, differences between innervation of the rostral and the caudal ends become apparent. New temporal fibres, arriving at the rostral end, find fibres already there, and endeavour to dislodge them. This can only be done by a gradual shifting of all fibres to new sites. Whilst shifting is going on, the temporal fibres will be closely packed rostrally, giving large 'receptive fields' there. At the caudal end, as new nasal fibres arrive, new cells become available. Each fibre can therefore take up a lot of room. The nasal half of the presynaptic chain occupies more than half of the postsynaptic chain, and its receptive fields are small (Figures 17*a–e*).

For a strict comparison with the maps of Gaze *et al.* (1974), which show the relation between tectum and visual field rather than retina, we would have to rescale our maps. Assuming that throughout development always the same field angle is projected onto the retina, in a uniform fashion (Easter, Johns & Baumann 1977), this would involve redrawing the presynaptic axes of all the connectivity matrices to the same length. This would produce maps with even greater distortions; in particular the receptive field size would be seen to shrink as development proceeds.

We conclude that the nonlinearities observed in the developing retinotectal map of *Xenopus* are not surprising given the way retina and tectum grow. These are the only nonlinearities our model can produce under normal conditions. The magnitude of the nonlinearities will depend on how the rates of growth of retina and tectum compare with the rate of synaptic modification.

Chung & Cooke (1975) rotated *Xenopus* tecta about 180° at stage 37, which is just before optic nerve fibres invade the tectum. This operation did not affect the orientation of the retinotectal map subsequently formed, but it did cause temporal rather than nasal retina to occupy more than half the tectum during development. This indicates to us that the rotated tectum grew

FIGURE 17. Stages in the development of a mapping under normal conditions. In this case cells are added every 30 steps of iteration. We have supposed that new presynaptic cells build up their total synaptic strength gradually (over 300 steps in this case), rather than exerting their full effect as soon as they are added to the presynaptic chain. (*a*) After 100 steps. Each chain now has 26 cells. The mapping is very diffuse, but there is a tendency for fibres to make connections from bottom left to top right in the matrix. (*b*) After 300 steps. 40 cells in each chain. The synapses of the outermost presynaptic cells are very weak, because of the slow growth of new synapses. (*c*) After 600 steps. 60 cells in each chain. Contacts made at the rostral end of the postsynaptic chain are very bunched. (*d*) After 1000 steps. Each chain has its full complement of cells. The mapping is continuous but distorted and the induced gradients are not spread uniformly across the postsynaptic chain. (*e*) Stable configuration after 6000 steps.

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caudally to rostrally instead of rostrally to caudally. Our conclusion is in line with experiments done at earlier stages. When these authors rotated the anterior (rostral) part of presumptive tectum at stage 22, tectal histogenesis in the rotated part was seen to progress caudally to rostrally.

The fact that retina and tectum grow whilst the retinotectal projection develops imparts a sequential order to the system. This makes it easier for a developing system to form a normal continuous map than it is for a fully grown, but naïve, system. As we described in § 2.5, a naïve system may no longer produce a continuous map when the range of presynaptic interaction is

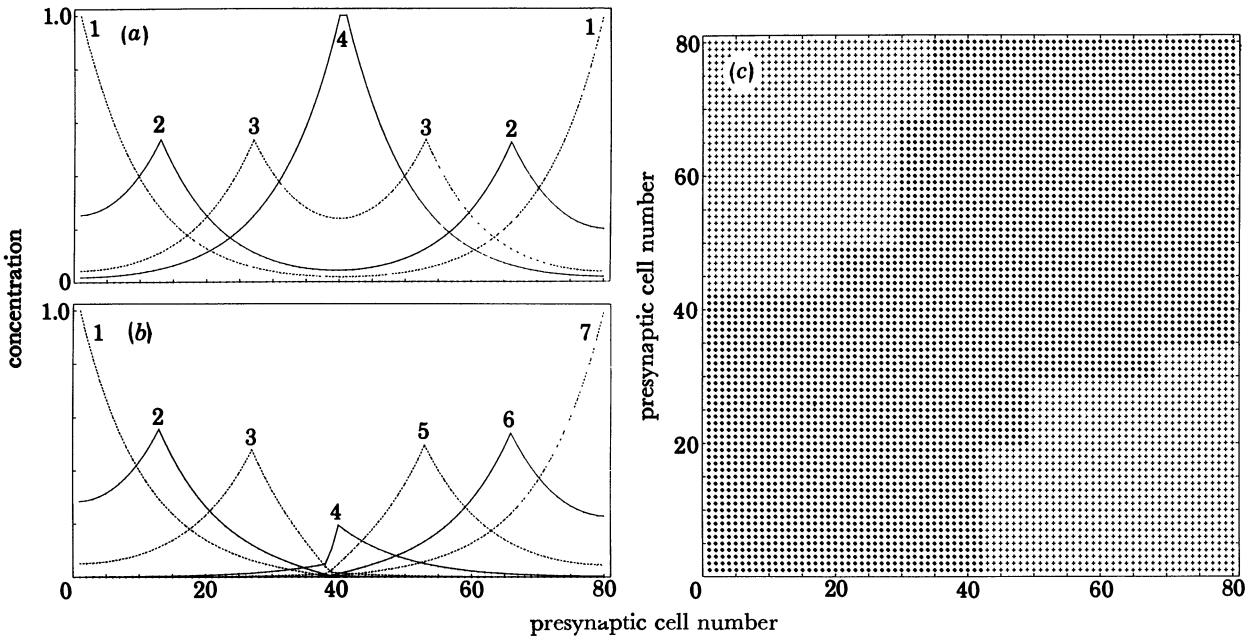

FIGURE 18. (*a*) Presynaptic markers for a 'compound-eye'. Sources of the same type are at positions arranged approximately symmetrically about the centre of the chain. Diffusion parameters as in figure 3*b*. (*b*) The distribution of markers shown in figure 3*b* was altered by placing an obstacle between cells 38 and 39. This had the effect of allowing only 50% of the molecules attempting to cross between 38 and 39 to arrive at the other side. The resulting marker distribution is shown here. (*c*) Interaction matrices for (*a*) and (*b*). In this case, the cells marked as in (*b*) have the narrower range of interaction of the two, as indicated by the '◆'s in the matrix. Comparison with figure 3*c* shows that the presence of an obstacle reduces the range of interaction.

reduced (figure 6). But in development, as long as there is sufficient time for each incoming fibre to have its contacts reorganised to lie next to those of its neighbours, an ordered and continuous map results. We repeated our developmental calculations with the presynaptic cells marked as for figure 6, and by slowing down the rate of growth of the two chains we obtained a sequence of development similar to that of figure 17. The minimum range of interaction which will give an ordered map is determined by the rate of growth of the chains.

As figure 17 also indicates, to obtain a correctly ordered map in development it would be sufficient to allow the first few fibres to specify the initial orientation of the map and allow all other connections to be made at random.

4.2. *The classical compound-eye experiments*

Each half of a classical compound-eye (Gaze *et al.* 1963) projects over the entire tectum in its normal orientation. The double projections obtained from double-nasal eyes are commonly

called double-nasal (NN) maps. There are also double-temporal (TT) and double-ventral (VV) maps (Straznicky, Gaze & Keating 1974). Compound-eyes made out of dorsal halves do not make an optic nerve.

We assume that the original eyes had matching sets of markers. Then the compound-eye contains two sets of identical markers, symmetrically arranged in the two half-eyes (figure 18*a*). On our model, fibres from each half are directed independently to the tectum and project each half-eye in its normal orientation (figure 16*b*). The presence of duplicate markers and mutually consistent orientation information leads to a map in which each pair of fibres carrying the same markers projects to the same tectal site (figure 19). Extension to the two-dimensional case is straightforward.

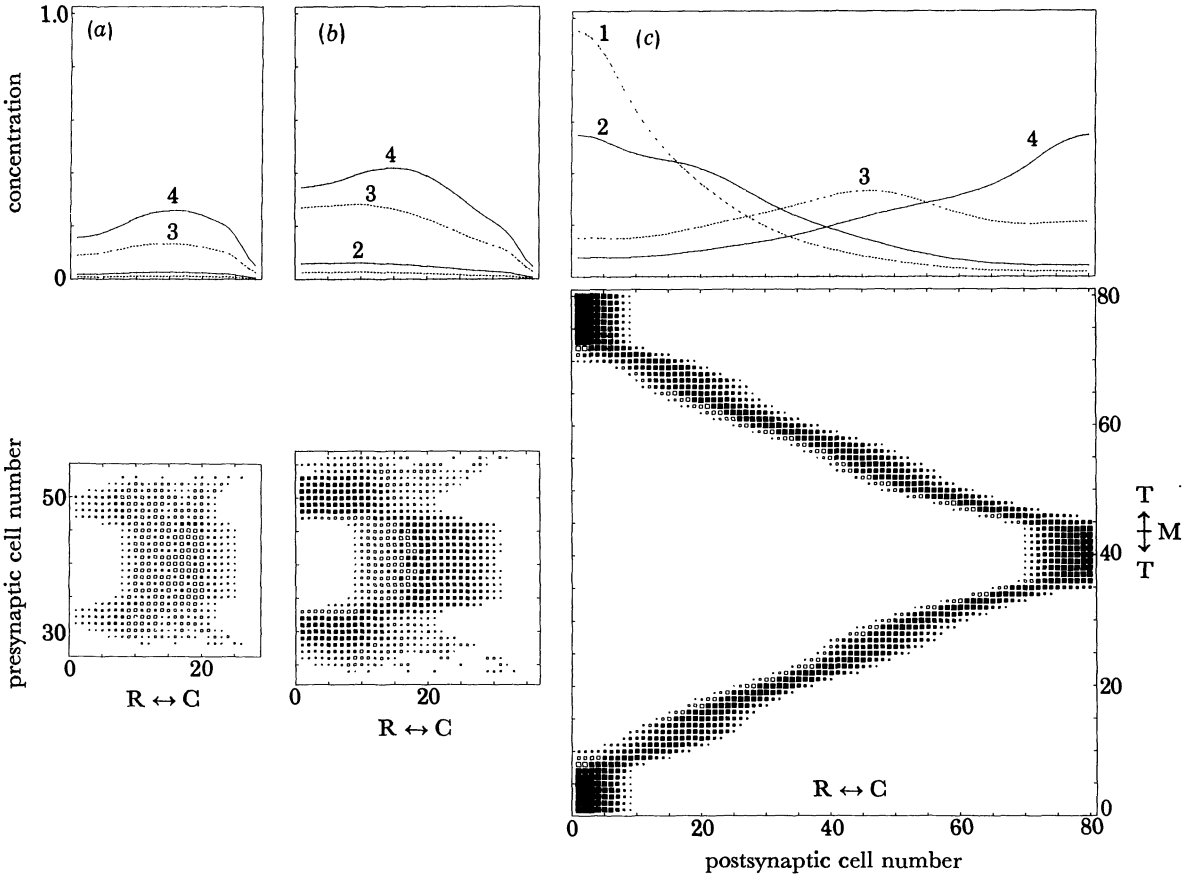

FIGURE 19. The development of a mapping made by a 'double-temporal' chain. Presynaptic fibres marked as in figure 18*a*, initial synaptic configuration as specified by figure 16*b*. Other conditions identical with those used for the sequence of normal development shown in figure 17, except that new cells are added every 50 steps. (*a*) After 200 steps of iteration. Initially the map is very imprecise, 28 cells in each chain. (*b*) After 400 steps. Each chain has 36 members now. (*c*) Stable configuration after 3000 steps. The profiles of the four types of molecules in the presynaptic chain have now become induced into the postsynaptic chain.

This argument applies under the assumptions stated to the maps formed by NN, TT and VV eyes, and also to the compound-eye type maps found after fusion of embryonic whole eyes (Hunt & Jacobson 1974).

4.3. *The new compound-eye maps: transection and transrepolarization*

In a new compound-eye map, each half-eye projects across the entire tectum, but only one half projects in its normal orientation. Fibres of completely different retinal origins therefore project to the same tectal region, and so these maps cannot be accounted for in terms of symmetries in the distribution of the original retinal markers. One possible interpretation is that the markers in one half-eye had been systematically altered. But there is a simpler way of accounting for these results.

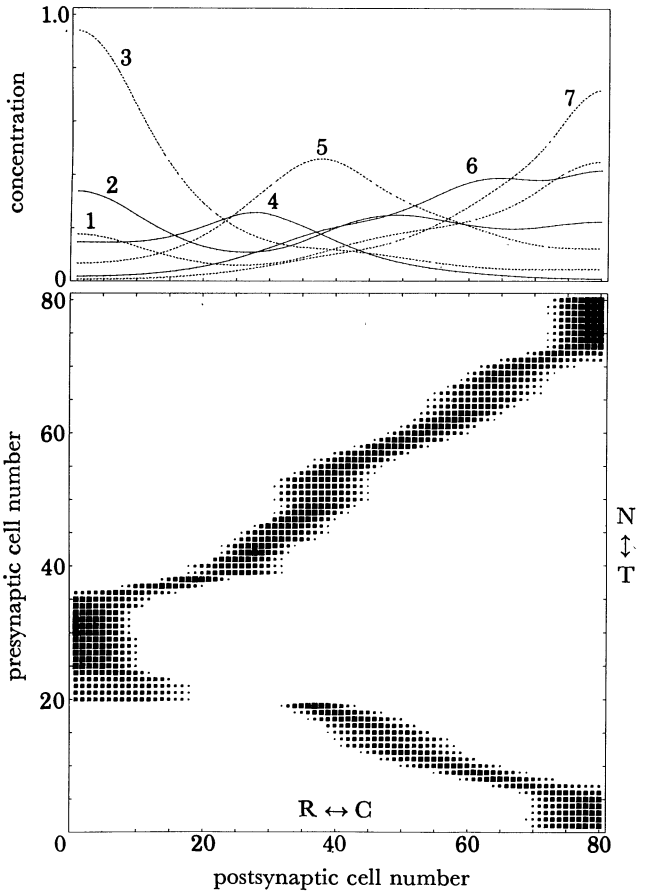

FIGURE 20. The development of a mapping under the conditions used for normal development (figure 17) except that an obstacle was placed in the presynaptic chain, as shown in figure 18*b*. The stable configuration after 2000 steps is shown here. Note that the projection is 'double-nasal' rather than 'double-temporal'.

The easiest way of producing a new compound-eye map is to *transect* the embryonic eye – slit it down the vertical or the horizontal midline. Vertically slit eyes often yield NN maps (Hunt & Jacobson 1974). As in the normal map, the nasal extremity projects caudally. But the temporal extremity also projects caudally, and the vertical midline now projects rostrally. A particularly puzzling fact is that the compound-eye maps found after vertical transection are *always* NN.

Our interpretation of this result is based on the fact that the disparate modes of growth of retina and tectum introduce an asymmetry. Referring back to figure 16*a*, the initial distribution of synapses made by each fibre during development would favour the establishment of

an NN map. NN maps are not produced in normal development because interference prevents fibres from non-neighbouring presynaptic regions from maintaining contacts on the same postsynaptic cells. We suggest that the effect of cutting through the larval eye is to shorten the range of interaction between fibres, in the direction perpendicular to the cut. This will reduce the tendency for a fibre to interfere with one situated at the mirror-symmetrical position at the other side of the cut. The likelihood of producing a mirror-image projection is further increased if there is a source of molecules near the cut in the retina. This would impose some mirror symmetry in marker values of cells near the cut.

In our calculations we represented the effect of the cut by placing in the middle of the presynaptic chain a partial obstruction to the flow of molecules. This gave us the marker distribution shown in figure 18*b*, which we employed in running a developmental sequence. Figure 20 shows the final stable map. We think that this would pass for a double-nasal map in an electrophysiological mapping experiment. It seems to be impossible to get a double-temporal map by this method.

The slitting operation must not abolish the continuity of markers over the slit. In the absence of continuity, the two half-eyes would spread their connections across the tectum independently and would each come to map in their normal orientation across the whole of the tectum.

Our suggestion can now be applied to the case of slitting the larval retina along the horizontal midline. In vertical transection, that half-retina whose outer edge normally projects to the growing edge of the tectum retains its orientation in the double projection. Therefore, since the tectum grows laterally to medially (Straznicky & Gaze 1972), after horizontal transection the half-retina whose outer edge normally projects medially will retain its orientation in the double map. This is the ventral half, and indeed horizontally transected eyes can give VV but never DD maps (Hunt & Jacobson 1974). It is worth noting that normal maps could still be obtained under these conditions if the growth of retina and tectum were slowed down sufficiently.

Other combinations of compound-eye have been made by Hunt & Jacobson (1973) and Hunt & Frank (1975). Hunt & Frank placed a nasal left half-eye together with a temporal right half-eye rotated about 180°. Later on in development they removed one half-eye. They found that the orientation of the map developed by the surviving half depended on how long the two halves were left together, and concluded that one half-retina had reprogrammed the other ('transrepolarization'). We suggest that it is the tectum which sends the fibres off to abnormal positions, just as for the transection situation. We cannot give a detailed argument here as this problem is one of the few for which a two-dimensional analysis is needed. It is interesting that in these experiments the critical period for determining the final orientation of the map is the period when the tectum is first being innervated by optic nerve fibres.

Compound-eye maps have also been developed by larval half-eyes (Hunt & Berman 1975; Feldman & Gaze 1975). The orientation of the map is related to the type of fragment. Nasal half-eyes yielded NN maps, temporal halves TT maps. Our interpretation is that the retina subsequently grows as normal, eventually replacing the excised half, but the operation has conferred an advantage on the unexcised half. This starts to map onto the tectum in its usual orientation, and then the postsynaptic concentrations induced by it force the fibres from the newly regenerated half-retina to connect in the reverse orientation. Interference will, however, prevent the formation of perfect double projections.

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5. Physiological considerations

The experiments we have discussed all refer to the phenomenology of mappings between retina and tectum. Any theory of these phenomena in terms of microscopic processes can be regarded as substantiated only after the exact nature of these processes is confirmed. Before that, a theory is justified if it is able to encompass a large number of phenomenological details with only a few microscopic hypotheses; and if the microscopic elements it contains are plausible. We now discuss this second point.

5.1. *Markers*

The markers must be transportable; they must be stable once their source has been removed; the effects of two sets of markers must superpose. The most obvious candidates for markers are molecules, and this is the possibility we examine. But other types of markers are possible.

Only very general properties are required for marker molecules. They must be subject to continuous synthesis, and decay. The latter could be hydrolysis, enzymatic decomposition or uptake by foreign cells. Molecules are transported along the fibres of projection and within the two sheets. The latter could be passive diffusion within and between cells or some sort of more active exchange, say, by contacts between membranes. Such gap junctions are often observed in embryonic structures (Loewenstein 1970). The velocity of axonal transport from retina to tectum must only be high enough to make up for tectal loss of molecules. No rapid signal transmission is required, as the marker distribution within the retina is assumed to have reached a stationary state.

The marker molecules in the two sheets may be of the same type, or they may be complementary. They must be suitable for the calculation of similarities. This may not be a restriction on the nature of the molecules at all, as quite different similarity evaluating mechanisms can be imagined.

5.2. *Sources*

One of the disturbing features of marker theories has always been the requirement for a very high degree of correspondence between the presynaptic and the postsynaptic marker distributions. It is difficult to imagine a way in which this correspondence could be genetically programmed prior to the existence of a fibre projection system.

We have shown here that the postsynaptic marker distribution can be induced by the fibre system itself. This means that no separate genetic mechanism for reproducing markers in the postsynaptic sheet is required. Since reproducibility is not needed, all precision requirements, such as, that the markers are graded uniformly across the retina, no longer apply; even a marker distribution changing randomly in time can lead to a topographic map. We have successfully tested such a model.

But this freedom in the choice of marker distribution provides few criteria for deciding what distribution is actually present in the retina. The basic requirement is that markers be unique and continuous in space. We were therefore led to the assumptions of isolated point sources (or line sources) and lateral transport. The problem then is to specify the location and number of sources. How the sources are determined genetically is a common morphogenetic problem, and it could be solved by a mechanism of the type proposed by Meinhardt & Gierer (1974). The markers in the two retinae must be related approximately mirror-symmetrically.

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5.3. *The similarity function*

Any theory of direct matching must contain an equivalent to our similarity function. The similarity function used in this paper was selected for the simple interpretation it can be given in molecular terms. We imagine that presynaptic and postsynaptic membranes are held together by molecules of the same type binding together, one anchored in the presynaptic, the other in the postsynaptic membrane. The measure of similarity is given by the number of bindings per unit of subsynaptic surface.

To compute this number we made several assumptions. The different molecules in the two synaptic membranes are tightly packed, and therefore their total surface density is constant and independent of the total concentrations within the presynaptic and the postsynaptic cells. The molecules in the presynaptic membrane are representative of the various molecule types found in the presynaptic cell itself. But the molecules appearing in the postsynaptic membrane are restricted to the types possessed by the presynaptic cell. Finally, all the bindings which can be made *are* made. Let the density of molecules of type i be d_i in the presynaptic membrane and d'_i in the postsynaptic membrane. Then the density of bindings made between molecules of type i is the minimum of d_i and d'_i. The total density of bindings, and therefore the similarity, is the sum Σ_i minimum (d_i, d'_i) over all molecule types in the presynaptic cell, as was used in our simulations.

We have tested successfully several other similarity functions (see, for example, Malsburg & Willshaw 1977). Our mechanism is therefore not unique, but it does have a simple biological interpretation.

5.4. *Synapses*

Various interpretations could be put on the quantity we call synaptic strength. At one extreme, one could imagine that between each pair of presynaptic and postsynaptic cells there is just one synaptic structure, whose subsynaptic area (or some other graded property) accounts for the quantity 'synaptic strength'. At the other extreme it could be supposed that there is a multitude of synaptic structures between these two cells, all having the same synaptic weight. In this case, synaptic modification could arise merely from movement of unitary synapses, rendering creation and destruction unnecessary. Our presynaptic sum rule would then acquire a natural interpretation. However, this possibility is not strictly compatible with our simulations, where synaptic weight was allowed to 'jump' from one termination area of a presynaptic fibre to a second, non-contiguous, area, without touching the intervening space. We have done other simulations where 'jumping' was not allowed. The system is more likely to become trapped in local optima because it is now no longer guaranteed that each axon will concentrate all its synapses in the same small postsynaptic region. Otherwise its behaviour is the same.

It is worth pointing out that for the neighbourhood part of the mechanism discussed in this paper the role of the postsynaptic sheet is entirely passive, it being simply a diffusive medium. It is therefore quite conceivable that the mechanism could act within every cross-section of the optic nerve. This could explain the high degree of retinotopic order within the optic nerve of some species (Cook & Horder 1977). If there is a completely continuous retinal map already present in the optic nerve, the mechanism ensuring continuity must be able to operate there rather than only at the level of the tectum.

The rule allowing the sprouting of new synapses only in places adjacent to existing ones ensures that a fibre can only react to favourable situations if it can actually 'feel' them with its

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terminal processes. In this way, terminal arbors move around on the postsynaptic sheet by creating synapses on one side and retracting them on the other. Compact areas of arborization may split in two or merge into one. We view sprouting as a continuously ongoing process. The ability of a fibre to sprout is retained in the equilibrium state.

Sprouting would not be required if all synapses which could be made are always present but most of them are inactive, as has been suggested by Wall (1977). This is certainly a possibility, but we think that in the retinotectal application it would be an inefficient use of neural wiring.

5.5. *The sum rule*

Several authors have proposed that nerve cells are limited in their capacity to make synaptic contact. In the class of competitive mechanisms discussed by Prestige & Willshaw (1975), ordered mappings can only be produced when each cell makes only a limited number of contacts. Schneider (1973; also Devor & Schneider 1975) introduced the idea of conservation of terminal arbor in order to account for the retinotopic maps produced following retinal lesions in neonatal hamsters. Raisman (1977) showed that in rat the number of synapses made by the fimbriae on the septum is always the same, independent of the degree of denervation of the fimbriae. This suggests that there is a control operating on the number of postsynaptic (septal) sites available for contact and no control on the number of synapses each fimbrial input can make.

6. Conclusions

The original problem we set ourselves was to resolve the following apparent contradiction. On the one hand, the observation that after translocation of part of the tectum retinal fibres could return to find their original partners suggested that cells carried fixed markers. But contrary to this, the mismatch experiments indicated that if there were markers then they were labile. We have shown that this is not a real contradiction, and to resolve it we have proposed that the retinal cells induce into the tectum a set of markers which are then used for setting up ordered connections.

The neural activity model (Willshaw & Malsburg 1976) is inadequate for the retinotectal problem. But it may act in other situations where visual experience plays a role, such as the establishment of intertectal connections (Keating 1977).

Our inductive model contains just that amount of machinery required for a sheet of presynaptic cells of arbitrary size to map in order and in a specified orientation across the whole of a second, postsynaptic, sheet of arbitrary size. If any of the components of the mechanism were removed, ordered maps would no longer be obtained.

The following results, which are incompatible with the regulation hypothesis, can be accounted for by our minimal model without needing extra hypotheses: that fibres from a half-retina regenerating onto a whole tectum return to their 'normal' positions before expanding to innervate the whole tectum; the continuous maps sometimes seen in the tectal graft transplantation experiments; the 'serendipitous' map; the maps produced by Yoon which are both rotated and compressed; the map of a half-retina on the foreign half-tectum found in an abnormal orientation; the double innervation maps found by Schmidt; the nonlinearities seen in the developing retinotectal map in *Xenopus*.

In specifying the form of our model, the only important decision we had to make which was not forced by our original problem concerned the range of interaction amongst the presynaptic

cells. Taking it to be of the same order as the width of the presynaptic sheet leads to a straightforward interpretation of the mirror-image maps found after transection, and probably the transrepolarization maps as well when our model is extended to two dimensions. Other results then follow: vertical transection must give a double-nasal rather than a double-temporal map; horizontal transection must give a double-ventral map. The rather surprising double representation results obtained by Gaze & Sharma and by Schmidt are also accounted for.

We have difficulty in accounting for the results by Cook & Horder of experiments involving regeneration of the projection of a whole retina onto a half-tectum. It is too early to judge what the recent scrambled maps produced by Hunt can say about inductive mechanisms.

It might be argued that the orientation mechanism need act only during the earliest stages of development: as long as the initial part-map is correctly oriented, a completely ordered map will result; and in regeneration, fibres are guided to the tectum by means of the information previously induced there. But in a number of regeneration situations, a bias in the initial synaptic contacts is needed to specify the orientation of the map. A case in point is the establishment of an ordered projection from a half-retina onto a foreign half-tectum in the normal orientation.

We chose to construct a model which was sufficiently precise for it to be implemented as a computer programme because we felt that only in this form could its implications be clearly worked out. However, this meant that, for the purpose of our calculations, we had to specify details which are not crucial to the argument. The nature, number and distribution of the sources (apart from their bearing on the range of interaction), the details of the calculation of similarity, the way the sum rule is implemented and the manner in which sprouting can occur are all factors which may have different implementations from the ones we have envisaged.

A number of predictions can be made at the microscopic level. There must be markers, which could be molecules; there must be exchange of markers between cells in the same sheet and they must be transported from presynaptic to postsynaptic sheet; the synaptic modification mechanism must involve both presynaptic and postsynaptic sides. (If the markers are molecules they will not necessarily be represented by only one or two molecule types whose concentrations vary monotonically across the whole of the cellular sheet. Therefore, they may be difficult to identify.)

The range of interaction must be determined, particularly because it has a bearing on the precision of the orientation information to be supplied. The more interference there is, the less precise the initial distribution of synapses need be, and *vice versa*. The interaction range must be large enough (or the orientation information precise enough) for ordered maps to be formed in the naïve situation (Feldman, Gaze & Keating 1971); and the interaction range must be small enough (or the orientation information sufficiently imprecise) for duplicated maps to be obtained as discussed in § 3.3.

For each of the experimental situations discussed, it has been possible to make definite proposals as to how the markers in the retina are related to those in the tectum. The outcome of further experiments can therefore be predicted. Possible manipulations are: bringing in a projection from a known type of retina to innervate a virgin tectum; to innervate a tectum which previously held a retinal projection; to innervate a tectum in the presence of an existing retinal projection.

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Appendix. Algorithm used in the calculations

Nomenclature

There are synaptic contacts between some members of a chain of N_R presynaptic cells and some of a chain of N_T postsynaptic cells. $W_{\rho\tau}$ gives the strength of the synaptic contact between presynaptic cell ρ and postsynaptic cell τ. There are M different types of molecule flowing within and between the two chains.

Formalism

The change $\Delta C_{\chi m}$ in the concentration $C_{\chi m}$ of molecule m in the χth cell in a chain (presynaptic or postsynaptic), from time t to $t+\Delta t$ is given by the following diffusion equation.

$$\Delta C_{\chi m} = [-aC_{\chi m} + d(C_{\chi-1,m} - 2C_{\chi m} + C_{\chi+1,m}) + Q_{\chi m}]\,\Delta t, \tag{1}$$

where a and d are decay and diffusion constants. The first term in this equation represents losses. The second term specifies the process of exchange of molecules between cell χ and its neighbours. The interpretation of the third term depends on to which chain of cells this equation is being applied.

For the selection ξ from the M molecules we define the set of time-varying *normalized concentrations*. $\hat{C}_{\chi m}$ is the normalized concentration of molecule m in cell χ, and is calculated as

$$\hat{C}_{\chi m} = C_{\chi m}/\Sigma_{m'} C_{\chi m'}, \tag{2}$$

where the sum is taken over all molecules in the selection ξ. All values of $\hat{C}_{\chi m}$ which fall below the small number ϵ are set to 0. This limits the extent of the molecular gradients. The normalized *concentration vector* $\hat{\mathbf{C}}_\chi$ has the set of normalized concentrations $\hat{C}_{\chi m}$ as components.

For the presynaptic chain (where we use the index ρ), the third term in equation (1) represents the contributions from the various presynaptic sources. $Q_{\rho m} = Q$ if there is a source for molecule m at cell ρ, where Q is a constant; $Q_{\rho m} = 0$ otherwise.

For the postsynaptic chain (where we use the index τ), the third term in equation (1) gives the flow of molecules induced into cell τ from the presynaptic cells: $Q_{\tau m} = \Sigma_\rho \hat{C}_{\rho m} W_{\rho\tau}$, where $\hat{C}_{\rho m}$ is normalized over all M molecules. The synaptic strengths therefore specify the rates of transfer of molecules from fibre to cell.

The *similarity* between cells ρ and τ is

$$S(\rho,\tau) = \Sigma_m \min(\hat{C}_{\rho m}, \hat{C}_{\tau m}), \tag{3}$$

where the normalized postsynaptic concentrations $\hat{C}_{\tau m}$ are calculated with respect to those molecule types common to both cells ρ and τ. The *fitness* of a particular synapse is numerically equal to the similarity between the appropriate presynaptic and postsynaptic elements.

The adjustment of synaptic strengths made at each step in the calculation is a two-part operation:

(i) The synaptic weight $W_{\rho\tau}$ is changed by an amount $\Delta W_{\rho\tau}$, calculated as

$$\Delta W_{\rho\tau} = h[S(\rho,\tau) - \bar{S}(\rho)].$$

$\bar{S}(\rho)$ is a mean similarity calculated over the n postsynaptic cells which fibre ρ contacts: $\bar{S}(\rho) = (1/n)\Sigma_{\tau'} S(\rho,\tau') - k$; k and h are constants. This is a molecular analogue of the Hebb (1949) rule for synaptic modification.

(ii) The new synaptic values are then scaled so as to keep the total synaptic strength available to each presynaptic element at a constant value W. The resulting synaptic strengths are therefore

$$W'_{\rho\tau} = (W_{\rho\tau} + \Delta W_{\rho\tau})\,W/(W + \Sigma_{\tau'} \Delta W_{\rho\tau'}).$$

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The algorithm

For the given distribution of sources, the set of equations obtained by applying equation (1) to each of the N_R presynaptic cells is iterated until stable solutions are obtained; that is, the average change in concentration values between successive steps is less than 0.1 %. The presynaptic concentration vectors $\hat{C}_\rho$ (normalized over all M molecule types) are then constructed.

For the set of n_R presynaptic cells and n_T postsynaptic cells used in the calculation, initial values are entered in the matrix of connections to specify the initial synaptic configuration. It is supposed that each fibre initially contacts at random n_0 of the cells in a particular section of the postsynaptic chain. Fibre ρ makes its initial contacts amongst the postsynaptic cells numbered from $\rho[(N_T - N_L)/N_R]$ to $\rho[(N_T - N_L)/N_R] + N_L$ or n_T, whichever is the smaller. The value of N_L sets the amount of bias within the initial synaptic configuration. With N_L set to N_T, for example, there is no bias at all.

Initially all synapses are of equal strength and the total strength available to each fibre has the constant value W.

The following sequence of operations is then performed repeatedly.

(1) With the values for synaptic strengths and presynaptic concentrations as given, the set of equations obtained by applying equation (1) to each of the n_T postsynaptic cells is iterated for a fixed number of times (t_d).

(2) The normalized postsynaptic concentrations are calculated according to equation (2).

(3) Each synapse is modified in strength by the two-step process already outlined, similarities being calculated as in equation (3).

(4) All synapses of strength less than 0.5 % of W are discarded, and then each fibre pushes out a contact of strength 1 % of W onto each of the cells adjoining the ones it already contacts, provided that (*a*) the strength of the existing contact exceeds 2 % of W, and (*b*) it does not already have a synapse at this new site.

This cycle of four operations is repeated until the postsynaptic concentrations have stabilized, the criterion for stability being as for the presynaptic concentrations.

Parameter values

General. $N_R = 80$, $N_T = 80$, $M = 7$. The values of n_R and n_T used are supplied in the text, where appropriate.

Presynaptic concentrations. $a = 0.006$ (figures 3*a*, 18*a*, 18*b*), $a = 0.003$ (figure 3*b*), $d = 0.3$, $\epsilon = 0.01$, $Q = 100.0$.

Establishment of initial contacts. $n_0 = 8$, $N_L = 60$ (for an initial bias in the synaptic contacts), $N_L = 80$ (no initial synaptic bias).

Postsynaptic concentrations. $\Delta t = 1$, $t_d = 5$; a, d, ϵ as for the presynaptic chain.

Synaptic modification. $W = 1.00$, $h = 0.01$, $k = 0.03$.

Supplementary remarks

(i) For the developmental calculations, each new fibre is allowed to build up its synapses gradually. t' steps after the birth of its parent cell, a fibre has contacts of strength W', where

$$W' = \begin{cases} (t'/300)W & \text{for } 0 < t' < 300, \\ W & \text{otherwise.} \end{cases}$$

(ii) To represent the effects of an obstacle in the presynaptic chain (figure 18*b*) it is supposed that only 50% of the molecules sent between cells 38 and 39 reach their destination. This entails replacing $\Delta C_{38,m}$ and $\Delta C_{39,m}$ in equation (1) by $\Delta C'_{38,m}$ and $\Delta C'_{39,m}$, where

$$\Delta C'_{38,m} = \Delta C_{38,m} - 0.5\, C_{39,m},$$

$$\Delta C'_{39,m} = \Delta C_{39,m} - 0.5\, C_{38,m}.$$

The algorithm was written in FORTRAN V and run on a UNIVAC 1108 computer.

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