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How patterned neural connections can be set up by self-organization

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An important problem in biology is to explain how patterned neural connections are set up during ontogenesis. Topographically ordered mappings, found widely in nervous systems, are those in which neighbouring elements in one sheet of cells project to neighbouring elements in a second sheet. Exploiting this neighbourhood property leads to a new theory for the establishment of topographical mappings, in which the distance between two cells is expressed in terms of their similarity with respect to certain physical properties assigned to them. This topographical code can be realized in a model employing either synchronization of nervous activity or exchange of specific molecules between neighbouring cells. By means of modifiable synapses the code is used to set up a topographical mapping between two sheets with the same internal structure. We have investigated the neural activity version. Without needing to make any elaborate assumptions about its structure or about the operations its elements are to carry out we have shown that the mappings are set up in a system-to-system rather than a cell-to-cell fashion. The pattern of connections develops in a step-by-step and orderly fashion, the orientation of the mappings being laid down in the earliest stages of development.

1. THE RETINO-TECTAL PROJECTION AND SYSTEMS-MATCHING IN LOWER VERTEBRATES

Many parts of the vertebrate nervous system are known to interconnect in a topographically ordered, or continuous, fashion. The maps so formed are in many cases two dimensional: in higher vertebrates there is a map of the retina on the surface of the striate cortex (Talbot & Marshall 1941), and on the surface of the superior colliculus (Apter 1945; Cooper, Daniel & Whitteridge 1953). In lower vertebrates optic nerve fibres go mainly to the superior colliculus, here called the optic tectum, which is also retinotopically organized (Gaze 1958). We also mention the two dimensional somatotopic organization of the somatosensory cortex (Rose & Mountcastle 1959) and of the motor cortex (Woolsey 1952) and, as an example of maps between central structures, the ordered intertectal projection in amphibia (Gaze, Keating, Székely & Beazley 1970). The preservation of the tonotopic organization of the cochlea in the auditory pathway (Rose, Galambos & Hughes 1959) provides an example of a one dimensional mapping.

A system which has been investigated in great experimental detail is the ordered projection of the retina onto the contra-lateral tectum in amphibia and fishes. In these animals it has been possible to perform various surgical manipulations on the retina and the tectum and to investigate by behavioural, histological and electrophysiological means the retinotectal projection produced after successful regeneration of the optic nerve (Gaze 1970). If one can suppose that the mechanisms arranging nerve connections during embryogenesis are also operative during regeneration then such experiments provide a way of discovering and testing theories for the formation of nerve connections in this system. Many of the experiments carried out are of the 'mismatch' type (discussed by Prestige & Willshaw 1975), in which a portion of retina or tectum (or both) is removed from an adult animal. The results of these experiments indicate that in many cases 'systems-matching' (Gaze & Keating 1972) takes place during regeneration, that is, the whole of the retina (or what remains of it after surgery) maps in a continuous fashion and in a predictable orientation across the whole of the tectum (or what remains of it). Recent work has shown that the retino-tectal system also displays systems-matching during development. In experiments on *Xenopus laevis*, Gaze, Keating & Chung (1974) found that from an early stage the whole of the visual field is projected in topographical order over the entire tectum, which order is maintained as the retina and tectum develop to maturity. Since retina and tectum grow in different ways and at different rates it was concluded that the only way the systems could remain matched throughout development was for the synaptic relations between retina and tectum to be constantly changing.

A number of theories for the establishment of topographical mappings during development or regeneration have been put forward (Weiss 1928; Sperry 1943; Gaze, Jacobson & Székely 1965; Prestige & Willshaw 1975). Perhaps the best known of these is Sperry's theory of neuronal specificity. He proposed that during embryogenesis each retinal ganglion cell and each tectal cell acquires a unique chemical label and that during regeneration or development pairs of pre- and postsynaptic cells with matching specificities are able to couple together. The mismatch experiments are explained in the context of this theory by making the additional assumption that the effect of the surgery is to cause the cells to be systematically relabelled, thus enabling new pairs of cells to be matched. In their paper, Prestige & Willshaw (1975) drew the distinction between two types of theory employing sets of labels to set up topographical mappings. In one of them, the Sperry-type, the search for a partner is carried out by each axon independently. In the other one axons compete for sites, and vice versa, by means of which certain forms of systems-matching can be accomplished. Neither type, however, uses the fact that the prospective partners of neighbouring presynaptic cells are themselves neighbours in the postsynaptic array. As a consequence, such mechanisms are more general than they need to be; all possible one-to-one mappings can be set up using them, not just the topographical ones.

We therefore arrived at the hypothesis that the observed one-to-one corre-

spondence between pre- and postsynaptic cells is not determined genetically and that the ontogenetic mechanism is made up of two independent parts. The one part ensures that as a result of an optimizing process neighbouring presynaptic cells come to connect with neighbouring postsynaptic cells. If this condition is obeyed for all pairs of neighbouring cells the resulting mapping will be a topographical one. The other part is concerned with the determination of the position, size and orientation of the final mapping by means of boundary and initial conditions in a way that leads to systems-matching. The boundary conditions may vary from case to case, especially in the experiments mentioned above, so that the same genetical program for the topographic part can in different situations lead to quite different retinal points being connected to a given tectal location, without the need for relabelling.

After having made this division of the ontogenetical problem into a microscopic mechanism leading to topographic order and macroscopic boundary conditions, we now propose a specific model for the microscopic mechanism in which use is made of the concepts of neural excitation and inhibition and of self-organization with the help of modifiable synapses.

2. A MODEL WORKING BY SELF-ORGANIZATION

We shall talk about two two dimensional sheets of elements, intended to represent a pre- and a postsynaptic sheet of nerve cells. The presynaptic elements are able to put out axons and make synapses with elements of the postsynaptic sheet, thereby building up a mapping between the two sheets. The basic requirement of the model is for distances between cells to be encoded in the system. This can be done in two ways: either in terms of the relative concentrations of certain molecules which are being continuously transferred between adjacent cells or by having a system where electrical activity between adjacent cells is correlated. This introductory paper is not an appropriate place to discuss both models in detail. However, we would like to have a specific model in mind, for only then are we able to make firm predictions about its behaviour. General theories, often containing hidden assumptions, are frequently open to various interpretations. Following an earlier suggestion (Lettvin; cited in Chung 1974), we shall discuss the neural activity model. It should be born in mind, however, that a molecular realization is an alternative possibility. We discuss this point elsewhere (Malsburg & Willshaw 1976, in preparation).

Our model is based on the idea that the geometrical proximity of presynaptic cells is coded in the form of correlations in their electrical activity. These correlations can be used in the postsynaptic sheet to recognize axons of neighbouring presynaptic cells and to connect them to neighbouring postsynaptic cells, hence producing a continuous mapping.

The first problem is to produce correlations between activity in neighbouring cells. By 'neural activity' we here mean spike activity measured in, say, impulses

per second. (In fact, the exact nature of the activity is not critical to our argument.) We start by assuming that there are short range excitatory connections between the cells in a sheet so that activity in neighbouring cells becomes mutually reinforced. To prevent activity from spreading too far we must also provide longer range inhibitory interconnections. (Such a scheme of interconnections has already been used by one of us in a model for orientation specificity in the striate cortex (Malsburg 1973).) As a result, if the cells which are active happen to be grouped together they fire strongly, whereas widely dispersed activity is relatively weak. We now assume that the two sheets are interconnected by modifiable synapses of the correlation type, as used in theoretical work by Hebb (1949), and many others (Marr 1969; Willshaw, Buneman & Longuet-Higgins 1969; Malsburg 1973), being facilitated in proportion to the product of the activities in the

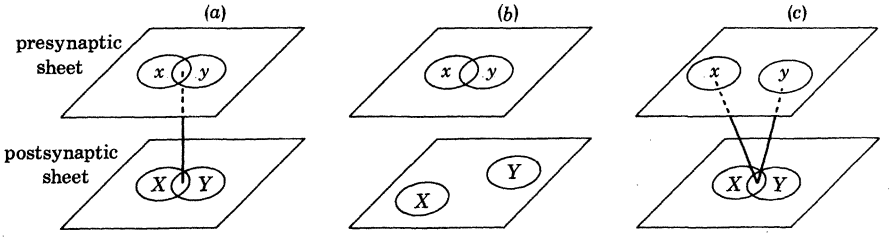


FIGURE 1. Ways in which the two clusters of cells, x and y, in the presynaptic sheet can connect with the two postsynaptic clusters, X and Y, respectively. We denote the cells common to clusters x and y by $(x \cap y)$ and the synapses between x and X by $(x \to X)$.

Configuration (a) is favoured more than (b) for two reasons: since x and y overlap they share axons and thereby synapses. It is therefore unlikely that X and Y occupy disconnected regions on the postsynaptic surface. Secondly, the synapses $((x \cap y) \to (X \cap Y))$ in (a) are reinforced by the occurrence of x *and* by the occurrence of y.

For small separations of x and y configuration (c) is unstable: the action of the lateral inhibition ensures that x and y are never active at the same time and so synapses $(x \to (X \cap Y))$ and $(y \to (X \cap Y))$ compete against each other, to the benefit of neither set of synapses. For larger separations of x and y configuration (c) is excluded by the mode of growth of the mapping, which is discussed in §3.

appropriate pre- and postsynaptic cells. Finally, to drive the system, we assume that at any one time, as a result of some random process, a few presynaptic cells are spontaneously active. These will fire most strongly if clustered together, and the response evoked in the post-synaptic layer will also be at its strongest if due to cells closely grouped together. Since the stronger a cell fires the greater the modification of its synapses, the synapses of tight clusters of presynaptic cells evoking activity in tight postsynaptic clusters will be selectively reinforced. We also insist that to prevent a steady build-up in all synaptic strengths, leading to instabilities, the total strength associated with each postsynaptic cell is limited. Thus when some synapses increase in strength others are made to decrease. Apart from the modification of existing synapses, we also need a facility for forming new synapses to offset the loss of the seldom modified synapses, which, over time, drift

to zero strength. One way of doing this is to assume that axons are continually putting out branchlets to contact neighbouring cells, such contacts being withdrawn if not immediately reinforced.

For the self-organizing component of the model the initial pattern of connections can be random; no form of preference of fibres for cells need be introduced at this stage. Over a sufficient period of time the axonal arborizations, initially spread out over the entire postsynaptic surface, gradually narrow down until small clusters of presynaptic cells come to be exclusively connected with small clusters of cells located somewhere in the post-synaptic sheet. We shall be referring to this refining of diffuse patterns of connections as the process of *organization*. In particular, overlapping presynaptic clusters will be connected to overlapping postsynaptic clusters (see figure 1), and if this is true for all overlapping clusters the two sheets will be interconnected in a topographically ordered fashion.

3. Boundary and initial conditions; orientation of the map

The mechanism which was described in the last section acts on a local level. All macroscopic features of the emerging mapping, such as its size and orientation, have to be determined by boundary conditions. Special care must also be taken that the development of the mapping does not get trapped in local optima, which could result if map formation started at different centres, producing extensive but incompatible part-maps. Further improvement could then only be made by partial destruction and reorientation of some of the part-maps, which cannot be carried out by a microscopic mechanism.

The problem of local optima is solved by initially restricting development to one region of nucleation, from which a continuous mapping then spreads out over the whole of both surfaces.

The other question is how to determine genetically the final orientation of the mapping. There is nothing in the local mechanism to specify one orientation rather than another, and if no systematic trends are introduced in the initial pattern of connections then the final orientation of the map is the result of chance. On the other hand, a slight but systematic bias within the initial connections towards a certain orientation will suffice to determine which end of the presynaptic array connects to which of the postsynaptic array. Such a bias could be established by a trace of spatial order within the afferent fibres or by weak preferences of some fibres for particular postsynaptic regions. It is enough if this initial bias is present within the nucleating region because the orientation of this region will impose itself on the rest of the projection developing later on. This paper is not attacking the question of *how* orientation information is produced by the nervous system; the point here is that since the maps observed do have definite orientation this information *must* be provided genetically, and it would be most efficient to specify the

orientation of the nucleating region only. We therefore introduce the idea of *polarity markers*, namely that the cells of a particular small presynaptic region initially establish contact, in the required orientation, with a small postsynaptic region. It should not be thought, however, that with the polarity markers we are invoking precise preprogrammed cellular specificity, and thereby introducing redundancy of principle. Precise cellular specificity fails as an explanation of systems-matching. The weak specificity introduced here contains only enough information to specify orientation; the chosen presynaptic region can make initial connections with any small postsynaptic region, not just that region to be connected to it in the final mapping.

The condition for maintaining just one nucleation region in the postsynaptic sheet is that organization must proceed by the catalysing action of organized cells on their neighbours via lateral excitation, and in no other way. In other words, spontaneous organization of isolated cells must be suppressed, although these cells can be fired by presynaptic activity that happens to activate many of their dispersed afferent fibres. There are several ways of doing this. For example, synapses could be modified according to a function of pre- and postsynaptic activity which disfavours small signals, or the random fluctuations could be kept within bounds by slowing down the speed of organization. In our simulations we have adopted the first solution, and have a *modification threshold*, which the pre- and post-synaptic activity must exceed before modification can take place. The threshold is set so that postsynaptic activity induced by correlated activity from as yet unorganized presynaptic cells is not reinforced.

Map formation resulting from the growth of a nucleation region ensures that disconnected presynaptic regions are not connected to the same postsynaptic region despite the fact that the limited range of inhibition permits several presynaptic clusters to be active at the same time. A postsynaptic cell C, which is in the process of organization, is activated almost exclusively by lateral excitation from already organized neighbouring cells. These in turn can only be activated by their 'correct' presynaptic region. At the same time, presynaptic clusters from random positions will also be active, and although they do modify synapses, their total effect, taken over the ensemble of possible stimuli, is small, since the total synaptic strength available to C is limited and so the different modifications interfere with each other. The 'correct' synapses, however, are strengthened with each stimulation, and will in the end win out.

4. Computer simulation experiments

We have so far attempted to explain our proposed mechanism entirely by qualitative arguments. A good test of the logic of the arguments is to produce a formal demonstration of their feasibility. It is fairly easy to write down a set of coupled differential equations to describe the relevant events, but these are not soluble by analytical methods. We therefore wrote computer programs to give

us numerical solutions for a model system. The simplifications we made in doing this were:

(1) Limitations of computing time and space meant that we could only simulate small systems: the number of cells in a sheet varied between 36 and 64.

(2) To save computing time weak diffuse activity in the presynaptic sheet was ignored.

(3) We employed a simplified idea of a synapse: we assumed that initially each axon not marking polarity made a contact of roughly equal strength with each postsynaptic cell and that during organization all the synapses were retained, despite the fact that many of them had zero strength.

None of these assumptions is a serious oversimplification, although an extra argument is needed to interpret assumption (3) for a larger, physiologically more

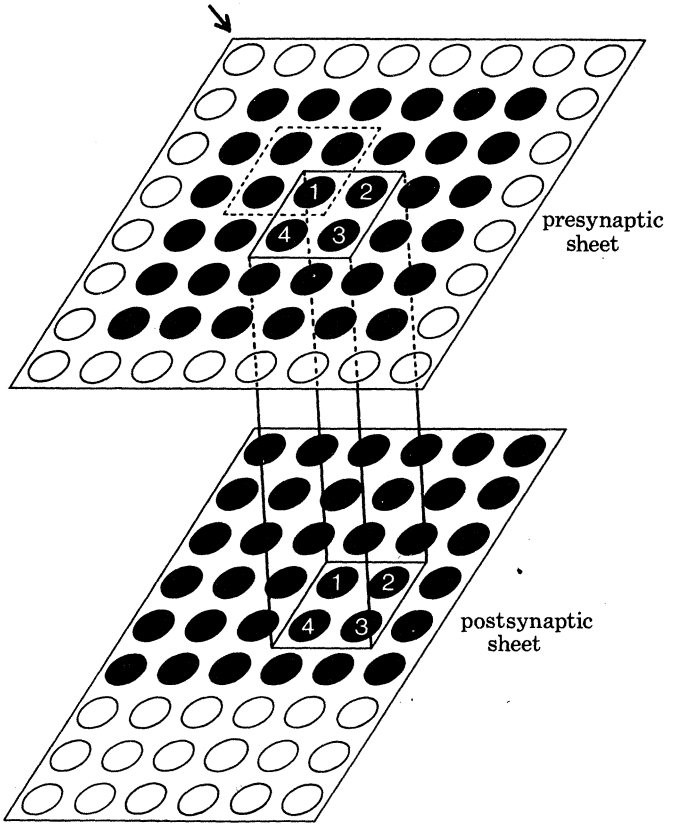


FIGURE 2. The two sheets which are to interconnect. Filled circles (●) represent the members of the two 6 × 6 sheets involved in the mappings for figures 3*a* and 4. The pairs of polarity markers used for 3*a* are labelled 1, 2, 3, 4; for figure 4 the same postsynaptic polarity markers were chosen, but this time their partners are the four cells enclosed by the dotted line drawn on the presynaptic sheet. The cells added in the calculations for figures 3*b*, *c* and *d* are denoted by unfilled circles (○). The arrow indicates the corner of the presynaptic sheet to be placed top left in the maps of figures 3 and 4.

realistic, system. We discuss this point in the next section. We did an extra calculation to check the validity of assumption (2).

To enable the reader to repeat our calculations we have listed in the appendix the steps taken in our calculations and the parameter values used.

We first calculated how 36 presynaptic cells, arranged as a 6×6 square sheet, would develop a projection onto an identical square of 36 postsynaptic cells. Four pairs of cells were chosen to mark polarity. The 72 cells involved are marked by filled circles (●) in figure 2.

To depict a particular mapping between the two sheets we calculated, weighting by the appropriate synaptic strengths, the mean coordinates of the presynaptic

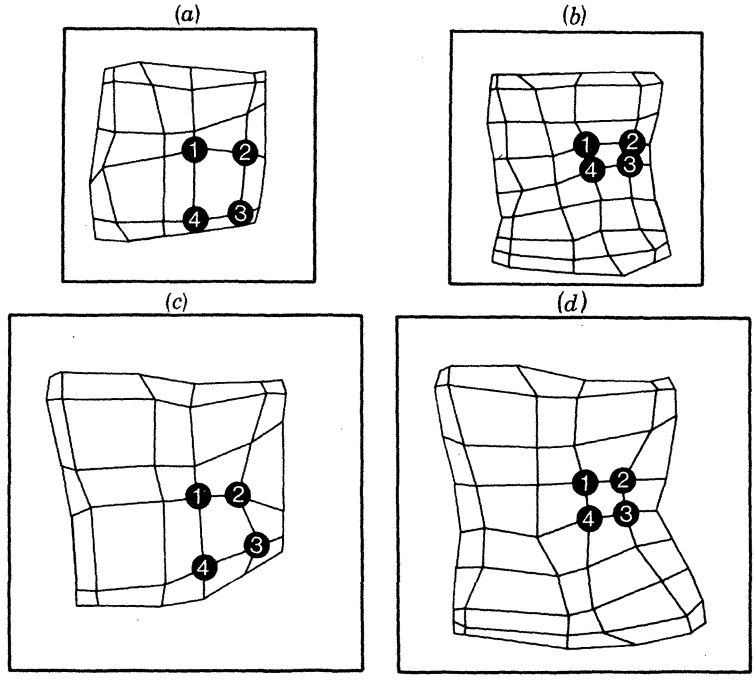


FIGURE 3. Maps of postsynaptic cells drawn on the presynaptic sheet for various model systems. In each diagram the thick black line tracing out a square denotes the boundary of the presynaptic sheet, oriented with the corner marked by the arrow in figure 2 placed top left. For each postsynaptic cell the centre of the cluster of presynaptic cells connected to it was plotted out. Points associated with neighbouring post-synaptic cells were then joined by a straight line. Since only cluster centres were plotted, the post-synaptic maps so constructed are necessarily smaller than the appropriate presynaptic sheets; the half-width of the distribution of presynaptic cells connected to a given postsynaptic cell never exceeded $\frac{9}{10}$ of the presynaptic cell interspacing. Postsynaptic polarity marker positions are indicated as in figure 2.

(*a*) The mapping between the two 6×6 sheets which has developed after 15000 trials. Figures 3*b*, *c* and *d* show the new mappings obtained after performing on the system in the state shown in 3*a* the three manipulations described in the text. (*b*) The mapping between 36 presynaptic and 54 postsynaptic cells after 9000 trials. (*c*) The mapping between 64 presynaptic and 36 postsynaptic cells after 10000 trials. (*d*) The mapping between 64 presynaptic and 54 postsynaptic cells after 15000 trials.

cells connected to each postsynaptic cell. These coordinate positions were then plotted on a map of the presynaptic sheet, now regarded as a continuum. This way of presenting our results is closely analogous to the electrophysiological maps of the tectum projected on to the visual field favoured by neurophysiologists (Gaze 1970). (The analogy is not exact since we do not have a counterpart to the projection of retina onto visual field.) Figure 3*a* shows the map obtained after 15000 trials. Note that the polarity markers have shifted from their initial positions, showing that they are only there to give the map the desired orientation, and so their positions are not rigidly determined. The choice of cells to mark polarity is relatively free. Choosing, for example, the four cells in the middle of the presynaptic surface (as we have done here) does not oblige us to take the corresponding middle four postsynaptic cells as their respective partners.

To demonstrate the model's systems-matching properties we now show the results of three manipulations, in which cells were added to one or both sheets of a system which had already attained an ordered mapping and then the way the enlarged system rearranged its connections was followed for a few more thousand trials. In each case the starting configuration was that shown in figure 3*a*, and to avoid introducing bias, once again the new cells were all given synapses, of roughly equal strength, with all cells from the opposite sheet. The three manipulations were:

(1) We increased the number of postsynaptic cells from 36 to 54 by adding 3 rows of 6 cells to make a 6×9 oblong sheet, leaving the presynaptic sheet unchanged.

(2) The 6×6 sheet of presynaptic cells was enlarged by adding a band of cells around the outside to make an 8×8 sheet. The postsynaptic sheet was left unchanged.

(3) Both sheets were enlarged, to 64 and 54 cells respectively, as described in (1) and (2) above.

The cells added in these manipulations are marked by unfilled circles (○) in figure 2.

Figures 3*b*, *c* and *d* show the three new mappings obtained in this manner. The most striking point about all four maps shown is that the topographical ordering is in each case perfect; each pair of neighbouring postsynaptic cells is mapped onto neighbouring points on the presynaptic surface. To see how the mapping changes size as the relative sizes of the two sheets alter, the reader should observe the location of the small area marked out by the four postsynaptic polarity markers. In figures 3*a* and 3*c* this area is situated in the bottom right-hand quarter. In figures 3*b* and 3*d* we find that it has shrunk and has moved up to accommodate the new post-synaptic cells coming in at the bottom.

To emphasize that the polarity markers specify only the relative orientation of the two sheets, and not individual connections, we show in figure 4 another sequence of maps of the development of a topographical projection between two 6×6 sheets. The postsynaptic polarity markers were those used in the

previous calculations, but this time we took their partners from the diagonally opposing quarter of the other sheet, that is, the quarter indicated in figure 2 by the arrow. Various stages in the growth of the mapping are shown. We only plotted out the positions of those postsynaptic cells which had established organized connections. After 5000 trials, only the polarity markers and a few neighbours have established definite contact, in the region of the presynaptic polarity markers

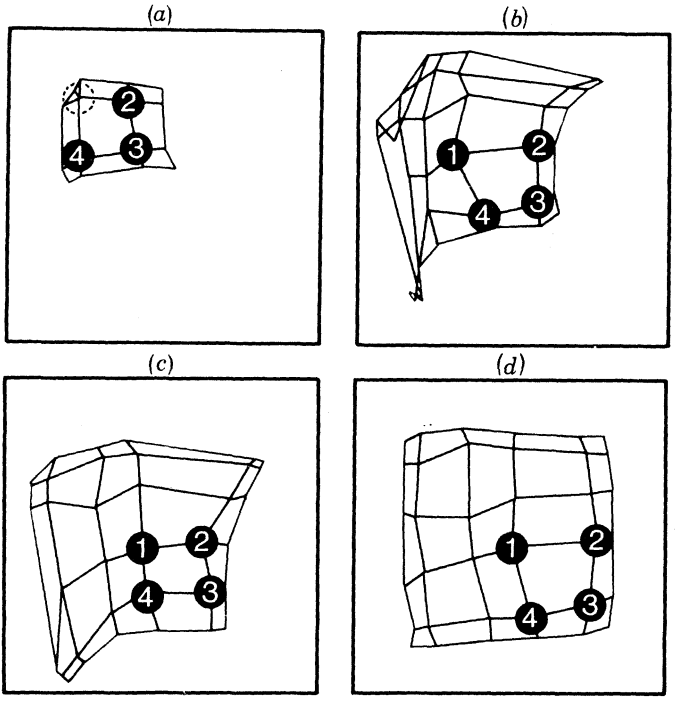


FIGURE 4. The development of a mapping between two 6 × 6 sheets in the case when the two sets of polarity markers occupied non-corresponding regions on the two surfaces. Conventions as in figure 3. Only the positions of those postsynaptic cells which had established definite contacts were plotted.

(*a*) By 5000 trials only the polarity markers and their neighbours had established definite contact. The mapping set up by this stage is between cells in the top left hand quarter of the presynaptic sheet and those in the bottom right hand quarter of the postsynaptic sheet. (*b*) After 20000 trials. To accommodate the new cells which have established contact, albeit in a disorganized manner, the map of the postsynaptic sheet has shifted down and to the right. (*c*) By 30000 trials positions of all postsynaptic cells could be plotted out, but the map is distorted. (*d*) After 50000 trials. A stable and ordered map is produced.

(figure 4*a*). As time goes on, the map enlarges and gets shifted down and to the right (figure 4*b*). By 30000 trials all positions can be mapped out (figure 4*c*), and by 50000 trials a stable and orderly map is seen (figure 4*d*).

In the simulations described so far we assumed that each stimulus consisted of a single cluster of activity. In reality there will be more than one cluster present; each postsynaptic cell can simultaneously receive input from disconnected

presynaptic regions, and so one-to-one maps might not result. To investigate this we did an extra simulation, similar to that which gave the map shown in figure 3*a*. The polarity markers used were the four middle cells in each sheet, and this time the typical stimulus was activity in two pairs of adjacent cells, each pair being randomly chosen from the presynaptic sheet. As time went on, although synapses were modified by dispersed activity, the strong effects from the 'correct' cells eventually won out, and by 15000 trials a perfectly ordered mapping, comparable with that of figure 3*a*, had developed. This calculation, together with the arguments already given, justifies our decision to ignore dispersed presynaptic activity in our main body of simulations.

5. Physiological considerations

With the present computer techniques, only small numbers of cells can be simulated, and so one must attempt to extrapolate from our calculations to real size systems.

We made no attempt to represent the complex three dimensional geometry of axonal growth. This led to the unrealistic assumption, in the computer model, that each pair of pre- and postsynaptic cells is interconnected, although their synapse may be of zero strength. In reality this large number of synapses can be reduced drastically, for the following reason.

Owing to the lateral excitation within the postsynaptic sheet, two fibres can influence each other without sharing contact with the same postsynaptic cell. If each axon ramifies on a small scale in the way that we have suggested, then in the synaptic modification procedure the axonal branches will be moved around as some synapses grow and some decay. Therefore, each presynaptic cell need not have a contact with each postsynaptic cell. However, the number of contacts made at the start must suffice to bring each axon within sensing range of its target area. The sensing range S is determined by and roughly equal to the range of the postsynaptic lateral excitation. It can be several times the radius T of the target area, which gives the precision in the final mapping. The region in which an axon must have some contacts if it is to home in on its target area has an area πS^2. Therefore, each axon must initially make at least $N/\pi S^2$ contacts at random among N postsynaptic cells. Although there are at present many unknowns, it is instructive to give a numerical example. Taking N to be 10^6, and arbitrarily setting T at 10 and S four times as great (meaning that approximately 3200 regions can be distinguished), the number of contacts each axon must initially make is about 200. Certainly, our calculation gives a pessimistic estimate since an axon can also be attracted to its target area through the mediation of the axon of a neighbouring presynaptic cell. This reduces further the initial density of contacts required.

The inhibition in the postsynaptic layer is merely there to stop the excitation from spreading too far, and so its range must be slightly greater than the range of excitation.

6. Conclusions

The purpose of this paper is to show that it is possible to devise a theory for the establishment of ordered neural connections displaying systems-matching properties which exploits the already existing order within the two sheets of cells to be matched. Our theory of self-organization can be viewed as marking one end of a spectrum of possible theories, at whose other extremity stand the theories of neuronal specificity. In these theories emphasis is laid on the labelling of cells and a set of relabelling rules to cater for new conditions, whereas there is little or no interaction between cells in the same sheet. In our theory such interactions play a crucial rôle, and the amount of labelling is no more than the minimum required for correct orientation of the map. A simpler type of mechanism, such as one assigning unique and unmodifiable labels to cells, is incapable of explaining systems-matching.

The prime value of our paper is to show that such theories of self-organization do in fact work, and they should now be taken seriously. They have the advantage of requiring only an extremely small amount of information to be specified genetically, and we have not had to make embarrassing assumptions about regulation, that is, relabelling of cells according to global observations to make mappings possible under new conditions. The computer simulations are intended to demonstrate the logical consistency of our assumptions, and should be regarded primarily as an aid to thought.

By working our theory through we have been able to make a number of generalizations, which are independent of the precise details of implementation of our neural activity model.

(1) The mapping develops in a step-by-step and orderly fashion.

(2) The axonal arborizations initially ramify diffusely over the postsynaptic surface and then become more restricted in extent as the mapping develops.

(3) Whereas the pattern of connections reflected in the final map is not laid down straightaway, the orientation of the map is already fixed at the earliest stages of development.

(4) Provision of the correct starting conditions, that is, the correct polarity markers, is essential for successful development of the map; inconsistent orientation information leads to peculiar maps. This leads to the speculation that the remarkable series of maps obtained in the transrepolarization experiments (Hunt & Frank 1975) reflects the working out of a set of mutually incompatible polarity markers arising from putting together incompatible hemiretinae. We are at present exploring this possibility.

Appendix

Here is a description of the calculations performed on the computer.

The strength of the synaptic connection between cell i in a sheet of M presynaptic cells and cell j in a sheet of N postsynaptic cells is specified by the entry s_{ij} in the $M \times N$ matrix s. The activity H_j^* in postsynaptic cell j is determined by its membrane depolarization H_j, and is calculated according to a linear threshold model of a nerve cell (Malsburg 1973). At time t, cell j is deemed to fire if its depolarization exceeds a fixed threshold value θ. Its activity $H_j^*(t)$ is defined as

$$H_j^*(t) = \begin{cases} H_j(t) - \theta & \text{if} \quad H_j(t) > \theta, \\ 0 & \text{otherwise.} \end{cases}$$

To calculate the membrane depolarization we assume that its rate of change $\partial H_j/\partial t$ is proportional to the sum of the excitatory effects of active presynaptic cells, the excitation and inhibition supplied by nearby active postsynaptic cells and a decay term due to losses in the membrane itself. It is helpful to define the quantities $A_i^*(t)$, e_{kj} and i_{kj}. The variable $A_i^*(t)$, used to describe the state of the presynaptic cells, has value 1 if cell i is active at time t and 0 otherwise. The time independent parameters e_{kj} and i_{kj} specify the short range excitation and inhibition exerted by postsynaptic cell k on postsynaptic cell j.

We can then write a set of N coupled equations.

$$\frac{\partial H_j(t)}{\partial t} + \alpha H_j(t) = \sum_i A_i^*(t)\, s_{ij}(t) + \sum_k H_k^*(t)\, e_{kj} - \sum_k H_k^*(t)\, i_{kj} \quad \text{for} \quad j = 1,2,3,\ldots, N.$$

The first sum represents the contributions from the presynaptic cells; the other two are the excitatory and inhibitory contributions from the postsynaptic cells. The parameter α is the membrane time constant. To ensure that cells which do not mark polarity have initially no particular preference for any cell in the opposite sheet, all initial values of the entries in s are chosen from a set of random numbers normally distributed about a positive mean. The numbers are then adjusted to give synapses between polarity marker cells above-average strengths. The following procedures are carried out for each successive trial, during which the postsynaptic cells are stimulated by a given set of presynaptic cells.

(1) A small cluster of c presynaptic cells is chosen at random from the whole set of overlapping clusters of that size covering the presynaptic sheet. These cells constitute the input to the postsynaptic sheet during this trial. (This is where we assume that dispersed patterns of activity that can also occur have no significant effect.)

(2) For each of the N postsynaptic cells a stationary solution for its membrane depolarization is found by iterating the set of coupled equations until the mean change in depolarization per unit of time becomes less than 0.5 %.

(3) Only those synapses between cells firing sufficiently strongly are strengthened. The increase in strength Δs_{ij} of synapse s_{ij} is given by

$$\Delta s_{ij} = h A_i^* H_j^*$$

provided that H_j^*, as calculated in step 2, exceeds the modification threshold ϵ, and where the constant h sets the speed of organization.

(4) The synaptic strengths are then renormalized so as to keep the mean strength associated with each postsynaptic cell at a constant value S, thus

$$\frac{1}{M}\sum_{i=1}^{M} s_{ij} = S \quad \text{for} \quad j = 1, 2, \ldots, N.$$

The parameters c, α, θ, h, ϵ, S and the entries in the matrices i and e are constants, whose values have to be found by trial and error. The values used in the main body of calculations were

$$c = 2, \quad \theta = 10.0, \quad \alpha = 0.5, \quad h = 0.016, \quad \epsilon = 2.0, \quad S = 2.50.$$

A postsynaptic cell could influence other postsynaptic cells up to a distance 3 units away, the distance between the two cells with coordinates (x, y) and (x', y') being defined as the sum $|x-x'|+|y-y'|$. The postsynaptic excitatory and inhibitory constants took the following values

distance between cells j and k	1	2	3
e_{kj}	0.05	0.025	—
i_{kj}	—	—	0.06

For the initial values in the matrix s a set of MN random numbers were first chosen from a normal distribution of mean 2.50 and standard deviation 0.14. The values of the entries designating synapses between polarity markers were then increased fivefold, and then all the numbers were normalized, as in step (4) given above.

For the extra simulation to investigate the disruptive effect of dispersed presynaptic activity, the stimuli used were chosen equiprobably from the set of 1800 pairs of pairs of neighbours which can be formed from the members of a 6×6 sheet. Under these conditions, four instead of two presynaptic cells were active per trial, and to cater for this θ and ϵ were doubled, to take the values 20.0 and 4.0, and h was decreased to 0.005. All other parameters retained the values given above.

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