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How to label nerve cells so that they can interconnect in an ordered fashion

(ontogenesis/retinotopy/neural plasticity/induction of markers)

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ABSTRACT **We present a method for setting up topographically ordered mappings between two sheets of nerve cells. A set of chemical markers that express the neighborhood relationships within the presynaptic sheet is induced by the fibers into the postsynaptic sheet. The markers are used to guide the fibers to their terminal sites. A case for which this idea may be relevant is the retinotectal projection; our model exhibits types of plasticity found experimentally. The fact that the postsynaptic markers remain after removal of the projecting fibers suggests an important difference between development and regeneration. This paper concentrates on explaining the basic idea, and in addition presents a set of preliminary computer simulations.**

The problem we discuss is how the axons of a *presynaptic* sheet of nerve cells can come to connect with the cells of a *postsynaptic* sheet to produce an ordered mapping in a prespecified orientation. In a recent paper (1), we suggested that two different mechanisms are required: (*i*) a local one that employs a code (expressing the geometrical relationships within a sheet) to join neighboring presynaptic regions to neighboring postsynaptic regions; (*ii*) a global mechanism for placing the map in the required orientation, which must be specified genetically. We proposed a model for map-making which employs correlated neural activity as the code. On this model, maps are formed in a *systems-matching* fashion (2), that is, the axons cooperate to make ordered connections over the whole of the available postsynaptic sheet. Here we describe how the geometrical code can be realized in terms of molecular diffusion. We propose a model for inducing a fixed set of chemical markers (3–5) labeling the presynaptic cells through modifiable synapses onto the postsynaptic sheet. Given the correct starting conditions, which specify the orientation of the map, an ordered projection in the desired orientation will result. This model, though mathematically akin to our other suggestion (1), differs from it in two important respects: (*i*) because it works by molecular diffusion, it could be applied to developmental situations where spike activity is not yet possible; (*ii*) it has a *memory*, so in the regeneration situation the markers in the postsynaptic sheet are made up from those brought in by the regenerating fibers and those left over from a previous projection. In certain situations, very different types of map can be obtained merely by altering the relative effectiveness of these two ways of providing postsynaptic markers. In this paper, we are primarily concerned with explaining our idea, and we do so in terms of a simple analogy. We also discuss briefly its application to the topographically ordered projection of retina onto contralateral tectum in amphibia and fishes (6).

The analogy we employ describes a hypothetical trading situation. Traders from different parts of India travel to Britain to sell tea, each carrying the one blend of his home town. There is a limited number of basic types of tea, each grown on an isolated plantation. To make up the blend for a particular town, teas are taken from the plantations nearby, in amounts decreasing in proportion to the distance between town and plantation. Thus, two towns near to one another have *similar* blends, that is, several of the basic teas are found in both blends, in similar proportions. In this way, each trader is uniquely labeled by the tea he carries. Buyers, or customers, are scattered over Britain, and each makes up his own blend, from the teas delivered to him and also from his neighbors' blends. Consequently, neighboring buyers will also tend to have similar blends.

The rules of the market are as follows: Each trader keeps an order book containing a list of the few customers he is able to visit on a trip and the quantities to be delivered to each. After each trip he makes slight adjustments to the entries in his order book to meet his customers' demands better. In each case, he alters the quantity to be delivered in proportion to the similarity between his and the customer's blend. Because the total amount of tea he can carry on a trip is limited, the increase in some delivery quotas has to be balanced by the decrease in others, which can lead to loss of customers. He also plans to deliver samples to new customers living near his present ones, as a way of making new contacts in favorable parts of the market.

We shall now explain how trade develops. Selling is a self-reinforcing process because a trader who has delivered an increased amount of tea to a customer thereby brings the customer's blend nearer to his own, leading to an even larger increase on the next trip. However, the more a trader brings some customers under his influence, the more he has to give up others—for lack of tea. He concentrates on his few good customers, who will tend to be clustered together in a few small groups because customers with similar blends are usually neighbors. Where these groups will be also depends on the influence the other traders exert on his customers. The contacts he has in regions also served by traders carrying completely different blends will not usually develop because here buyers' tastes will be pulled in several different directions at once. The opposite will be true for the regions to which he and a neighbor both make deliveries; they carry similar blends and will cooperate in developing their contacts there.

This commercial system has many different stable states; the typical one having many, but not all, pairs of neighboring Indian towns trading with neighboring British towns; the set of trading relations maps India onto Britain in a piecewise continuous fashion, with no definite orientation prevailing. To induce a completely continuous map in a predetermined orientation, a minimum of order must be present amongst the

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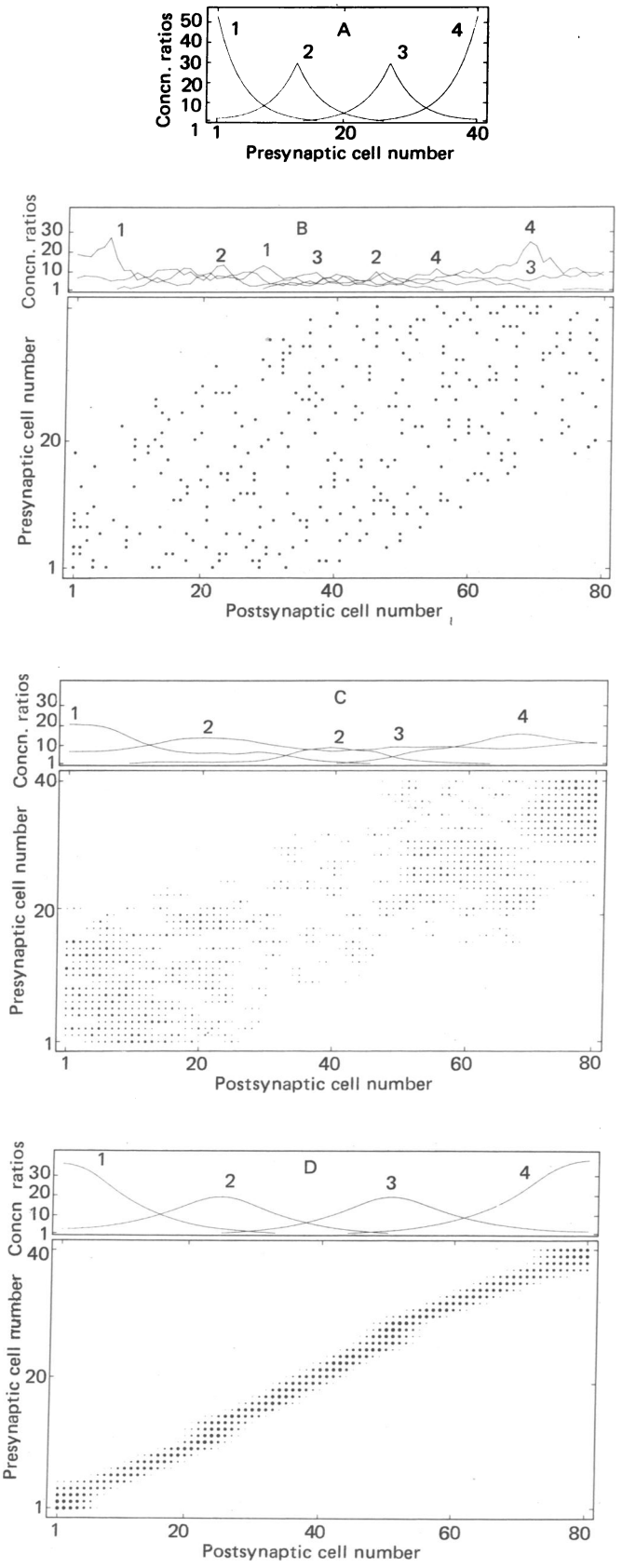

FIG. 1. The development of a continuous mapping between a chain of 40 presynaptic cells and one of 80 postsynaptic cells. Indices ρ and τ are reserved for pre- and postsynaptic cells, respectively. Molecules of types 1, 2, 3, and 4 are produced at fixed rates in presynaptic cells 1, 13, 27, and 40, respectively. Each presynaptic cell also produces a small amount of the comparison molecule 5. The concentration $C_{\rho m}(t)$ of molecule m in cell ρ obeys the diffusion equation:

$$\frac{dC_{\rho m}}{dt} = -\alpha C_{\rho m} + d(C_{\rho-1,m} - 2C_{\rho m} + C_{\rho+1,m}) + Q_{\rho m},$$

in which α and d are decay and diffusion constants and $Q_{\rho m}$ gives the source contribution (if any). The concentration $C_{\tau m}(t)$ for postsynaptic cell τ obeys the same equation, with the last term now representing contributions from the presynaptic cells: $Q_{\tau m} = \Sigma_\rho C_{\rho m} T_{\rho\tau}$, in which the synaptic strength $T_{\rho\tau}$ specifies the rate of transport from axon ρ into cell τ. The vector $\mathbf{V}_\rho$ holds the concentration ratios $(C_{\rho 1}, C_{\rho 2}, C_{\rho 3}, C_{\rho 4})/C_{\rho 5}$. $\mathbf{V}_\tau$ is defined in the same way. Starting from a given synaptic distribution, the set of coupled diffusion equations for the postsynaptic concentrations is solved iteratively. After each step, axon ρ has its synaptic strengths adjusted as follows: (*i*) Each synaptic strength $T_{\rho\tau}$ is altered in proportion to the difference between the similarity $S(\rho, \tau)$ and the mean similarity $\overline{S}(\rho)$:

$$\Delta T_{\rho\tau} = h[S(\rho,\tau) - \overline{S}(\rho)],$$

in which $S(\rho,\tau) = 1 - 0.1\ \Sigma_{m=1}^{4} |\log(\mathbf{V}_{\rho m}) - \log(\mathbf{V}_{\tau m})|$ and $\overline{S}(\rho) = \Sigma_\tau S(\rho,\tau)/N - k$, summed over ρ's N synapses; h and k are constants. (*ii*) Very weak synapses are removed, and ρ is then made to establish new synapses with cells next to the ones it already contacts. (*iii*) A process of normalization is carried out to keep the total strength of synapses available to ρ at a constant value T. (A weak synapse is defined as a synapse of strength less than ½% of T.) (*A*) The pattern of the four concentration ratios in the presynaptic sheet. Ratios less than 1 are set equal to 1 and are left out of the picture. (*B*) The initial pattern of synaptic contacts. A black spot indicates the presence of a synapse between a particular axon (row) and cell (column). Each axon has made eight contacts at random within a particular large region of the postsynaptic chain—this is one way of supplying orientation information. The pattern of postsynaptic concentrations induced through these synapses is shown above—after a very short diffusion time. (*C*) An intermediate state in the calculation. Spot area is proportional to synaptic strength. (*D*) The final continuous map. Parameter values used: $\alpha = 0.02$, $d = 0.30$, $h = 0.01$, $k = 0.03$, $T = 1.00$; source strengths were $Q = 100$ for molecules 1–4, $Q = 0.45$ for molecule 5.

initial trading contacts. An efficient way of providing this would be to supply each trader with very rough starting directions (e.g., "Start off in Wales") or to give the buyers instructions to the same effect. Alternatively, the fashion of drinking tea could be made to spread out from one region, where it was introduced by traders from a small region of India (containing at least three towns), the orientation of the initial part-map imposing itself on the rest of the map as it develops.

It is now time to translate our tea trade story into biological language to show that it is an appropriate analogy of a possible model. Traders from India and their customers in Britain become the elements of a presynaptic and a postsynaptic sheet of nerve cells, respectively. Each tea constituent becomes one of a number of types of marker molecules that are being continually synthesized in certain isolated cells in the presynaptic sheet and that from there diffuse out over the sheet, decaying gradually. This sets up a collection of local gradients in the presynaptic sheet, and each cell there can be identified by its unique *concentration vector*, which records the concentrations of the various molecules within that cell. Traders' routes represent the presynaptic axons, along which some of the molecules are sent by axonal transport to the postsynaptic sheet. The rate of diffusion from a fiber into a cell is specified by the strength of the synapse between them (represented by an individual delivery quota of tea). Molecules also diffuse within the postsynaptic sheet, and so the concentration vectors identifying the cells here will depend on the quantities of molecules delivered from the presynaptic sheet and the quantities interchanged. Synaptic strengths are modified in proportion to the similarity between the appropriate pre- and postsynaptic concentration

vectors, the total strength available to each presynaptic cell being kept constant. The presynaptic sources can be arranged in many ways. There could be just a few long-range gradients [at minimum two for two dimensions, as proposed by Sperry (3, 4)], or many short-range ones. The precision in the final map depends on the number of presynaptic elements marked uniquely; the fine details of the presynaptic gradients need not be reproduced in the postsynaptic sheet. There are many logically different ways of supplying orientation information; these must first be evaluated by experiment for the case in question.

The rule we use for the modification of synapses is analogous to the one proposed by Hebb (7), and captures the general idea of the specificity of one cell for another. Presynaptic sum rules, or conservation of axonal innervation, have often been discussed by neurobiologists (8–10).

To show that this model works, we made calculations on the computer for systems of 50–100 cells. An example is shown in Fig. 1. Our choice of the form of the sum rule and of the similarity function, of the distribution of the presynaptic sources and of the way orientation information is supplied was arbitrary to some extent; we have tested other alternatives that work equally well.

It is worth pointing out that this model, like others (1, 10), is *nonlinear*, in the sense that two presynaptic sheets may interfere with each other when developing their projections on the same postsynaptic sheet.

With reference to the retinotectal projection in amphibians and fishes, we can make the following generlizations.

(*i*) Provided that consistent information for orientation of the map is supplied, a continuous map of the whole of the presynaptic sheet is set up across the whole of the postsynaptic sheet in the given orientation. It is as if the presynaptic fibers cooperate (although they do not do so explicitly) to spread their contacts in an ordered fashion over the whole of the available postsynaptic surface; that is, systems-matching (2) occurs. The addition of more cells to the sheets during development will cause the overall pattern of connections to be adjusted in order to preserve the systems-matching property. The visual map in *Xenopus laevis* has been found to develop in this manner (11). Once the model has reached the stable state of a continuous mapping, a *mismatch* (10) experiment can be performed by destroying all connections, removing cells from one end of a sheet, and then allowing the projection to be reestablished. As might be expected, the sheets will eventually come to systems-match, as found experimentally, (12, 13).

(*ii*) In distinction to the neural activity model (1), the molecular model has a *memory;* the information encoded postsynaptically is in the form of molecular concentrations and so will persist for some time following severance of connections between the two sheets. Thus, in the regeneration situation the postsynaptic markers are made up from the molecules brought in by the regenerating fibers *and* those left over from the previous projection. Suppose a normal continuous map has developed, and now cut out a portion of the postsynaptic sheet and replace it in a different orientation, destroying all connections in the process. The subsequent regeneration of connections takes the form of a struggle. The fibers try to impose a map with a consistent orientation over the whole of the postsynaptic sheet, as they did in the original development of contacts. But to do this they must overwrite the markers of the displaced cells, which are already primed to attract their original partners, and are thus attempting to set up a part-map in an orientation conflicting with that desired by the fibers. If the fibers prevail, the original map will be restored. Otherwise a piecewise continuous map will result; as we have mentioned, such maps are stable states of the system. In the biological situation, whether a normal or a piecewise continuous map results will depend on the factors controlling the relative speed with which the two determinants of the postsynaptic concentrations can reestablish their influence. Such temporal factors may be difficult to control, so it is quite possible that both types of map would be obtained from the same experimental situation, as has been found after rotation of tectal grafts in adult goldfish (14, 15). A similar analysis holds for graft translocation experiments (16, 17).

The idea that the information deposited by a previous projection is important in determining future patterns of connections is supported by recent work by Schmidt (18). For example, when a tectum holding an expanded contralateral projection from a half-retina is also innervated by the whole ipsilateral retina, the two corresponding retinal halves project in register over the entire tectum, and the other half, from the whole retina, makes no connections.

We are preparing a more comprehensive account of the application of our model to the retinotectal situation. It will include our interpretation of various compound-eye experiments (19–21).

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