CHAPTER

5

Network Formation Through Activity-Dependent Neurite Outgrowth: A Review of a Simple Model of Homeostatic Structural Plasticity

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OUTLINE

The Rewiring Brain
DOI: http://dx.doi.org/10.1016/B978-0-12-803784-3.00005-6

1 INTRODUCTION

Neuronal electrical activity plays an important role in the development of neurons into neural networks. Many processes that determine network connectivity and neuronal function are, on a variety of time scales and levels of organization, modulated by electrical activity. Cell death, cell differentiation, neurite outgrowth and branching, synapse formation and elimination, and ion channel and neurotransmitter expression are all influenced by electrical activity.[1–3] This activity-dependent maturation begins even before the onset of sensory responses, driven by intrinsically generated patterns of electrical activity.[4]

Electrical activity is a prominent factor not only during development but also in adulthood. Alterations in afferent activity in the mature brain, such as those caused by peripheral or central lesions (retinal lesions or stroke, for example), trigger extensive axon and dendrite remodeling and changes in synapse numbers, leading to massive adaptations in network connectivity.[5–9]

This chapter focuses on activity-dependent neurite outgrowth, a form of activity-dependent structural plasticity.[10] Structural plasticity is defined as encompassing all the structural changes that lead to the formation or deletion of synapses, such as neurite elongation and retraction and changes in dendritic spine numbers.[10] Both during development and in adulthood, the elongation, branching, and retraction of neurites (axons and dendrites) are under control of electrical activity.[5,7,11,12] Electrical activity exerts its effect on neurite outgrowth by modifying the level of intracellular calcium, particularly in the growth cone, a specialized structure at the tip of outgrowing neurites. Calcium, which enters the cell through voltage- and ligand-gated calcium channels, is the principal regulator of growth cone motility and neurite outgrowth.[11,13–15] Thus any factor that can change calcium influx, such as action potential firing, may also modulate neurite outgrowth.[14,16]

During development, a high intracellular calcium concentration, caused by membrane depolarization, a high neuronal firing rate, or stimulation by excitatory neurotransmitters, arrests neurite outgrowth or even causes retraction. Conversely, a low calcium concentration, due to a low firing rate, hyperpolarization, or inhibitory neurotransmitters, promotes neurite elongation.[17–21] In the adult nervous system, neurite outgrowth may be similarly affected by neuronal electrical activity. Raising activity causes axons to retract[22] or results in immobility of axonal filopodia,[23] whereas lowering electrical activity triggers axonal outgrowth.[24] Likewise, axons in the visual cortex start sprouting when cortical activity is reduced as a result of a focal retinal lesion.[7] Dendrites may respond to changes in electrical activity in the same way as axons. Increased neuronal activity caused by epileptic seizures results in dendritic retraction,[25] whereas decreased cortical activity induced by whisker ablation[5] or stroke[8] elicits dendritic outgrowth and remodeling.

Thus, both during development and in adulthood, the way in which electrical activity modulates neurite outgrowth seems to contribute to keeping neuronal electrical activity at a particular level (homeostasis). When the electrical activity of a neuron is above a desired value (homeostatic set-point), its neurites retract, breaking-up synaptic connections and so reducing neuronal activity. Conversely, when activity is below the desired value, neurites grow out, making new synaptic connections and so raising the neuron's activity. When the level of electrical activity or intracellular calcium is below a minimum level, however, neurites may also retract. In the hippocampus, e.g., a decrease in electrical activity

promotes axonal sprouting, whereas a complete block of activity has no growth-inducing effect and even prevents outgrowth.[26] Thus an optimal window of calcium or electrical activity may be necessary for neurite outgrowth, below and above which neurites retract.[11,21,27–31]

Activity-dependent neurite outgrowth leads to reciprocal interactions between network activity and connectivity. Changes in activity affect neurite outgrowth and thus synaptic connectivity, which in turn changes neuron and network activity. To help unravel the potential consequences of these interactions, we built the computational model that is described in this chapter,[32–35] which is one of the first models of homeostatic structural plasticity.[36] In the model, the neurite extensions of each neuron are represented by a circular neuritic field, which expands when the neuron's electrical activity is below a homeostatic set-point and retracts when the neuron's activity is above the set-point. Neurons connect synaptically when their neuritic fields overlap. In this chapter, I review studies that have employed the model and compare model results with empirical data on network formation and reorganization. I show that the model, simple as it is, has many emergent properties that are relevant for both neural development and adult plasticity.

2 MODEL

2.1 Overview

Our reason for building the neuritic field model was to explore what phenomena could emerge from activity-dependent neurite outgrowth. The model was inspired in part by developing cultures of dissociated cortex cells, in which initially disconnected cells assemble themselves, without external input, into synaptically connected network by neurite outgrowth and synaptogenesis.[37–40] In the model, growing neurons are described as expanding neuritic fields, representing both axons and dendrites, and neurons become synaptically connected when their neuritic fields overlap, with a connection strength proportional to the area of overlap. The outgrowth of each neuron depends on its own level of electrical activity. The neuritic field expands when the neuron's electrical activity is below a set-point, thereby increasing the field overlap and connectivity with other neurons. Conversely, the neuritic field retracts when activity is above the set-point, thereby reducing the connectivity with other neurons. Thus a reciprocal influence exists between electrical activity (fast dynamics) and outgrowth (slow dynamics): electrical activity determines outgrowth, while in turn outgrowth alters connectivity and thus activity. Through these interactions between outgrowth and activity, the initially disconnected neurons organize themselves into a synaptically connected network, guided only by the activity that is generated by the network itself; there is no external input.

2.2 Neuron Model

The electrical activity of the neurons is described by the shunting model.[41] In this model, excitatory inputs drive the membrane potential toward a maximum (the excitatory saturation potential), whereas inhibitory inputs drive the membrane potential toward a

minimum (the inhibitory saturation potential). Transformed into dimensionless equations, the model becomes[33]:

$$\frac{dX_i}{dT} = -X_i + (1 - X_i)\sum_{k=1}^{N} W_{ik}F(X_k) - (H + X_i)\sum_{l=1}^{M} W_{il}F(Y_l) \tag{5.1}$$

$$\frac{dY_j}{dT} = -Y_j + (1 - Y_j)\sum_{k=1}^{N} W_{jk}F(X_k) - (H + Y_j)\sum_{l=1}^{M} W_{jl}F(Y_l) \tag{5.2}$$

where X_i and Y_j are the membrane potentials of, respectively, the excitatory neuron i and the inhibitory neuron j, expressed in units of excitatory saturation potential; T is time, expressed in units of membrane time constant; N and M are the number of excitatory and inhibitory neurons, respectively; and H is the ratio of inhibitory to excitatory saturation potential. The terms $(1 - X_i)$ and $(1 - Y_j)$ imply that excitatory inputs drive the membrane potential toward 1. Similarly, the terms $(H + X_i)$ and $(H + Y_j)$ imply that inhibitory inputs drive the membrane potential toward $-H$. The Ws denote the connection strengths (all $W \geq 0$), with k and l the indices of the excitatory and inhibitory driver neurons, respectively; and i and j the indices of the excitatory and inhibitory target neurons, respectively. The term $F(X_i)$ is the firing rate, which is a sigmoidal function of the membrane potential:

$$F(X_i) = \frac{1}{1 + e^{(\theta - X_i)/\alpha}} \tag{5.3}$$

where α determines the steepness of the function and θ represents the firing threshold. The low firing rate when the membrane potential is subthreshold reflects spontaneous neuronal activity.

2.3 Outgrowth and Connectivity

Neurons are located at random positions on a two-dimensional surface. Each neuron has a circular neuritic field, the radius of which is variable. When the fields of neurons i and j overlap, both neurons become connected with a strength

$$W_{ij} = A_{ij}S \tag{5.4}$$

where $A_{ij} = A_{ji}$ is the area of overlap, representing the total number of synapses formed reciprocally between neurons i and j; and S is a constant of proportionality, representing the strength of a single synapse. Synaptic strength may be taken to depend on the type of connection: S^{ee}, S^{ei}, S^{ie}, and S^{ii}, where, e.g., S^{ei} is the inhibitory-to-excitatory synaptic strength.

For both excitatory and inhibitory neurons, the change in neuritic field size depends on the neuron's own firing rate:

$$\frac{dR_i}{dT} = \rho G[F(X_i)] \tag{5.5}$$

where R_i is the radius of the neuritic field of neuron i and ρ determines the rate of outgrowth. The outgrowth function G (Fig. 5.1) is defined as

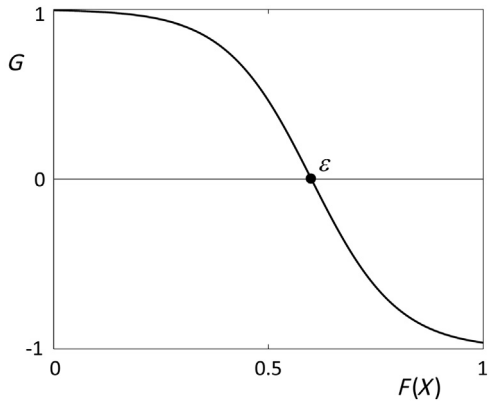

FIGURE 5.1 **Outgrowth function.** The function G (see Eq. 5.6) describes how the outgrowth of a neuritic field depends on the neuron's firing rate $F(X)$. A neuritic field expands when the firing rate is lower than ε and shrinks when the firing rate is higher than ε. At the homeostatic set-point ε, the neuritic field remains constant.

$$G[F(X_i)] = 1 - \frac{2}{1 + e^{[\varepsilon - F(X_i)]/\beta}} \tag{5.6}$$

where ε is the homeostatic set-point, i.e., the value of $F(X_i)$ for which $G = 0$; and β determines the steepness of the function. Depending on the value of $F(X_i)$, a neuritic field grows out [$G > 0$ if $F(X_i) < \varepsilon$], retracts [$G < 0$ if $F(X_i) > \varepsilon$], or remains constant [$G = 0$ if $F(X_i) = \varepsilon$]. In biological neurons, the effect of electrical activity on neurite outgrowth is mediated by calcium,[11,13–15] with the concentration of intracellular calcium acting as indicator of firing rate.[42–44]

2.4 Parameters

For the studies conducted by Van Ooyen and co-workers,[32–35,45] the fraction $M/(N + M)$ of inhibitory cells, if present, is in the range of 0.1–0.2.[46] The nominal values of the other parameters are $\rho = 0.0001$, $H = 0.1$, $\theta = 0.5$, $\alpha = 0.1$, $\beta = 0.1$, and $\varepsilon = 0.6$, for both excitatory and inhibitory neurons. Neurite outgrowth is on a time scale of days or weeks,[37,47] so connectivity is quasi-stationary on the time scale of membrane potential dynamics. The value of the outgrowth rate ρ is small enough for the quasi-stationarity approximation to be valid but not so small that it unnecessarily slows down the simulations. The neurons are initialized with no or small neuritic fields and with zero membrane potentials.

3 RESULTS

3.1 Network Assembly, Overshoot, and Homeostasis

Since the neurons are initialized with no or small neuritic fields, most neurons are initially disconnected or organized in small, isolated clusters (Fig. 5.2A). Consequently,

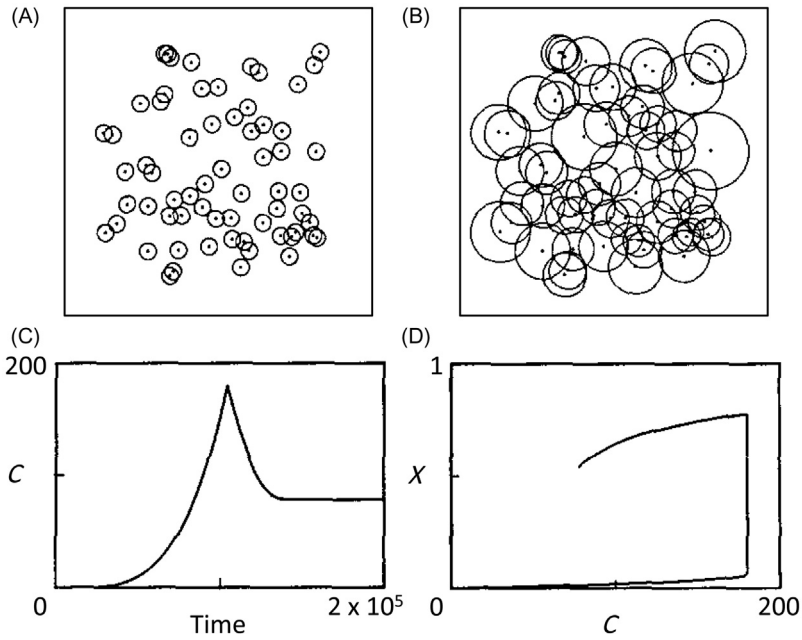

FIGURE 5.2 **Network assembly.** In this example, all cells are excitatory. (A) Early stage of network development. Neuritic fields are small, connectivity is low, and cells have a low level of electrical activity. (B) Network at equilibrium. The electrical activity of all cells is at the homeostatic set-point, and the neuritic field sizes remain constant. (C) Development of network connectivity $C = (1/2)\sum_{i=1,k=1}^{N} A_{ik}$ = total area of overlap (see Eq. 5.4) over time. (D) Network-averaged membrane potential X against network connectivity C. Electrical activity is initially low, so connectivity increases. When connectivity is strong enough, activity abruptly jumps to a much higher level. This level exceeds the homeostatic set-point, so connectivity and activity then decrease until activity is at the homeostatic set-point. Source*: Reproduced with permission from van Ooyen A, van Pelt J. Activity-dependent outgrowth of neurons and overshoot phenomena in developing neural networks. J Theor Biol. 1994;167:27–43. Elsevier.*

neuronal firing rates $F(X_i)$ are below the homeostatic set-point ε, so neuritic fields start expanding. As the neurons grow, they begin to form more and stronger connections, linking neurons together and slowly raising the level of activity in the network. At some degree of connectivity, network activity abruptly jumps to a much higher level (Fig. 5.2D). The activity of the neurons is then so high that $F(X_i) > \varepsilon$. As a consequence, neuritic field size and connectivity start decreasing and activity drops. As neurons adjust the size of their neuritic fields and react to the adjustments of their neighbors, the network eventually reaches a stable equilibrium in which the connectivity between cells is such that for all cells $F(X_i) = \varepsilon$ and neuritic fields and connectivity no longer change (Fig. 5.2B). The neurons thus self-organize, via a transient phase of high connectivity (overshoot) (Fig. 5.2C), into a stable network and achieve network-wide activity homeostasis, even though they can monitor only their own activity level. The neurons adapt to the local cell density, with neurons acquiring small neuritic fields in areas with a high cell density and large fields in areas with a low cell density (Fig. 5.2B). Because of differences in cell density, the developmental course of neuritic field size and electrical activity also varies among cells.[32]

The assembly of initially unconnected model neurons into a connected network strongly resembles development in cultures of dissociated cortex cells, with respect to both activity and connectivity.[37,47–50] The first 3 weeks in vitro show a phase of steady neurite outgrowth and synapse formation,[37,48] with neuron firing and network activity abruptly appearing within a window of a few days[49] and network structure exhibiting a transition from local to global connectivity.[50] In the next week, this is followed by a substantial elimination of synapses until a stable connectivity level is reached.[37,48] Thus, as in the model, there is a transient overproduction (overshoot) of synapses during network development. Overproduction of structural elements followed by pruning is a general feature of nervous system development,[51] in vitro and in vivo, and occurs, e.g., with respect to dendritic length,[52] number of dendrites and axons,[53] and synapse numbers.[54] Variation in dendritic growth among individual cells is also seen in the cerebral cortex, with cells displaying clear, minor, or no overshoot in dendritic length.[52] Neurite outgrowth and synapse elimination in culture are controlled by electrical activity. Similarly to what is observed in the model,[32] chronic blockade of electrical activity enhances neurite outgrowth[55] and prevents subsequent synapse pruning.[37]

3.2 Relationship Between Activity and Connectivity

For a purely excitatory network ($M = 0$), the relationship between activity and connectivity and the changes in activity and connectivity during development can be predicted directly from Eq. (5.1).[32] For a given connectivity matrix $\mathbf{W}$, the equilibrium points of X_i are solutions of

$$0 = -X_i + (1 - X_i)\sum_{k=1}^{N} W_{ik}F(X_k) \tag{5.7}$$

If all cells have the same ε and the variations in X_i are small relative to the average membrane potential $\overline{X}$ of the network, then

$$0 = -\overline{X} + (1 - \overline{X})\overline{W}F(\overline{X}) \tag{5.8}$$

where $\overline{W}$ is the average connection strength. Rewriting this equation gives

$$\overline{W} = \frac{\overline{X}}{(1 - \overline{X})F(\overline{X})} \qquad 0 \le \overline{X} < 1 \tag{5.9}$$

Eq. (5.9), which defines a manifold (Fig. 5.3), provides the equilibrium value(s) of $\overline{X}$ for a given, fixed value of $\overline{W}$. Equilibrium states on branch CD of the manifold are unstable with respect to $\overline{X}$; equilibrium states on branches ABC and DF are stable. Because changes in $\overline{W}$ are slow, being caused by neuritic field outgrowth and retraction, $\overline{W}$ can be considered quasi-stationary on the time scale of membrane potential dynamics. That is, in the time that $\overline{X}$ relaxes to its equilibrium value, $\overline{W}$ hardly changes. In other words, at any given value for $\overline{W}$, $\overline{X}$ is at its equilibrium value. The slow evolution of $\overline{X}$, i.e., the changes in $\overline{X}$ that are brought about by changes in $\overline{W}$, therefore take place along the manifold.

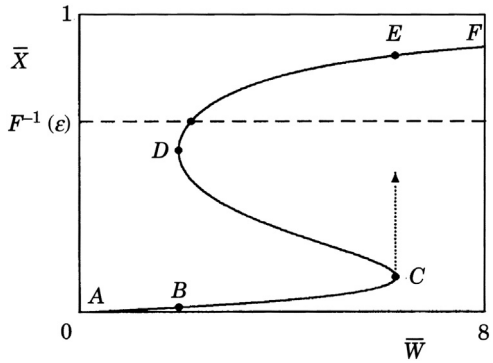

FIGURE 5.3 **Relationship between activity and connectivity.** The manifold (see Eq. 5.9) defines the equilibrium value(s) of the network-averaged membrane potential $\overline{X}$ for a given, fixed value of the network-averaged connectivity $\overline{W}$ in a purely excitatory network. Equilibrium values on branch CD are unstable with respect to $\overline{X}$; equilibrium values on branches ABC and DF are stable. The intersection point with the line $\overline{X} = F^{-1}(\varepsilon)$ (F^{-1} is the inverse of the firing rate function, see Eq. 5.3) is the equilibrium state of the whole system, at which $\overline{W}$ remains constant. See further text. Source: *Reproduced with permission from van Ooyen A, van Pelt J, Corner MA. Implications of activity dependent neurite outgrowth for neuronal morphology and network development. J Theor Biol. 1995;172 (1):63–82. Elsevier.*

If for all cells $F(X_i) = \varepsilon$, the neuritic fields, and therefore $\overline{W}$, remain constant (see Eqs. 5.5 and 5.6). Thus, at the intersection point with the line $\overline{X} = F^{-1}(\varepsilon)$ (F^{-1} is the inverse of F), $\overline{W}$ remains constant; above and below that line, it decreases and increases, respectively. Suppose that the intersection point is on branch DE (Fig. 5.3). During development, connectivity and activity are initially low, so $\overline{W}$ increases, and $\overline{X}$ follows the branch ABC until it reaches C, at which point it jumps to branch DE. However, $\overline{X}$ is then so high that the neuritic fields begin to retract and $\overline{W}$ to decrease until $\overline{X}$, moving along branch DE, reaches the intersection point. Thus, in order to arrive at an intersection point on branch DE, a developing network has to go through a phase in which connectivity is higher than in the final situation (overshoot).

A network that increases its connectivity starting from a quiescent state follows another trajectory (ABC) than a network that decreases its connectivity starting from an active state (FED), a phenomenon called hysteresis. In other words, a higher connectivity is needed to trigger activity in a quiescent network than to sustain it once the network has been activated. The existence of the hysteresis loop (i.e., the S-shaped curve of Fig. 5.3) hinges upon the firing rate function F having a (soft or hard) firing threshold and low spontaneous activity for subthreshold membrane potentials.[32] Interestingly, a very similar hysteresis loop between activity and connectivity was found in a detailed spiking and conductance-based large-scale network model of the human cortex.[56]

3.3 Slow Fluctuations in Activity

The level of electrical activity above which neurites retract may be different for different types of neurons,[11,57] which, translated to the model, means that there may be variation

among cells in ε. When such variation is present, the network can exhibit complex periodic behavior, with individual cells displaying slow oscillations in electrical activity that differ in frequency and amplitude.[34] Note that these oscillations are caused by the outgrowth and retraction of neuritic fields and thus occur on a time scale of days. Slow fluctuations in the electrical activity of individual cells, with periods of increased activity sometimes lasting as long as several days, have also been observed in developing cultures of dissociated cortex cells.[58]

3.4 Effect of Inhibition on Overshoot

In networks that contain both excitatory and inhibitory cells, overshoot still takes place and can even be enhanced.[33] To counterbalance inhibition, the cells need a higher excitatory connectivity, and thus a longer developmental time, to reach the activity level at which connectivity starts declining. In developing cultures of dissociated cortex cells, blockade of inhibitory GABAergic transmission indeed advances synapse elimination.[48]

Furthermore, in mixed networks, as opposed to purely excitatory networks, the decline in overall connectivity can be considerably delayed relative to the onset of network activity.[33] In parts of the network with many inhibitory cells, excitatory cells can still be growing out, while in parts with fewer inhibitory cells they are already retracting. Cells that receive inhibition become activated later and will retract later than cells without inhibition. These differences in growth mean that the average connectivity can still increase markedly after the onset of network activity. A delayed decline in connectivity relative to the onset of network activity is also observed in developing cultures.[37]

3.5 Multiple Equilibrium States

In contrast with purely excitatory networks, mixed networks do not under all initial conditions go to the same global end state with respect to electrical activity and connectivity. In a network with moderate inhibition and an initial connectivity that is higher than a certain level, connectivity will not be pruned but, instead, will continue to increase[33] (Fig. 5.4). As the excitatory connectivity increases, so does the inhibitory connectivity, which keeps activity low and stimulates further outgrowth. Moreover, if inhibitory cell density is high, inhibitory cells form connections among themselves, inhibiting each other's activity but stimulating each other's outgrowth, leading to more inhibition, lower activity, and further outgrowth of cells.

In a simplified model, it was shown that mixed networks have two equilibrium states: an attractor A at a relatively low level of connectivity and an attractor B at high connectivity[35] (Fig. 5.5A and B). In attractor A, the cells have a constant level of electrical activity, whereas in attractor B they exhibit fast oscillations in activity (Fig. 5.5C) (resulting from interactions between excitation and inhibition,[59,60] not from neuritic field outgrowth and retraction). Although activity oscillates, the time-averaged activity in attractor B is at the set-point level, so there are no net changes in neuritic field sizes or connectivity

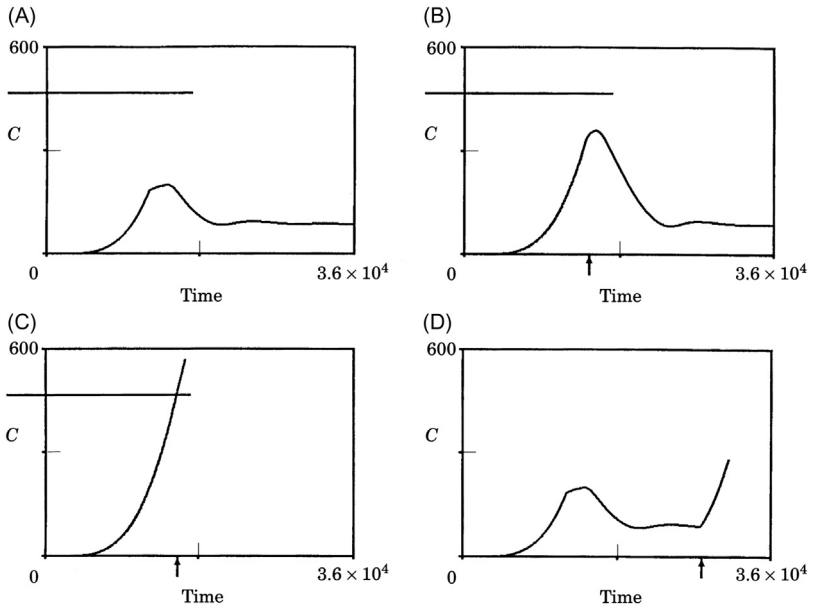

FIGURE 5.4 **Failure of connectivity pruning.** (A) Normal development. Total connectivity $C = \sum_{p=1,q=1}^{N+M} A_{pq}$ (see Eq. 5.4). (B) Electrical activity is blocked until the time indicated by the *arrow*. During the activity block, connectivity increases. Once activity is allowed to return, connectivity is pruned back to its normal equilibrium value. (C) If electrical activity is blocked for a longer period so that connectivity becomes higher than the critical value indicated by the *horizontal line*, connectivity is not pruned but continues to increase once activity returns. (D) Activity is blocked in a normally developed network at the time indicated by the *arrow*. Source*: Reproduced with permission from van Ooyen A, van Pelt J, Corner MA. Implications of activity dependent neurite outgrowth for neuronal morphology and network development. J Theor Biol. 1995;172(1):63–82. Elsevier.*

(Fig. 5.5D). Attractor B may be interpreted as a pathological state, with epileptic-like activity. During normal development, with a low initial level of connectivity, the network ends up, via an overshoot in connectivity, in attractor A (Fig. 5.5B). However, with high initial connectivity, which could be brought about by temporarily blocking electrical activity, the network goes to attractor B (Fig. 5.5B). Furthermore, the higher the level of inhibition during development (number of inhibitory cells, strength of inhibitory synapses), the more likely the network is to end up in attractor B.

The latter finding may provide an explanation for the experimental observation that hypoxic-ischemic encephalopathy in rat pups, which causes a preferential loss of excitatory cells and synapses (and thus a relatively high level of inhibition), can lead to epileptiform activity later on in adulthood.[61,62] Similarly, enhanced rather than reduced tonic $GABA_A$ inhibition is found in typical absence epilepsy.[63] The presence of two stable attractors may also explain that following chronic blockade of electrical activity in developing cultures of dissociated cortex cells (resulting in a high density of synapses), synapse elimination fails to occur once the block is removed and activity returns to control levels.[55,64]

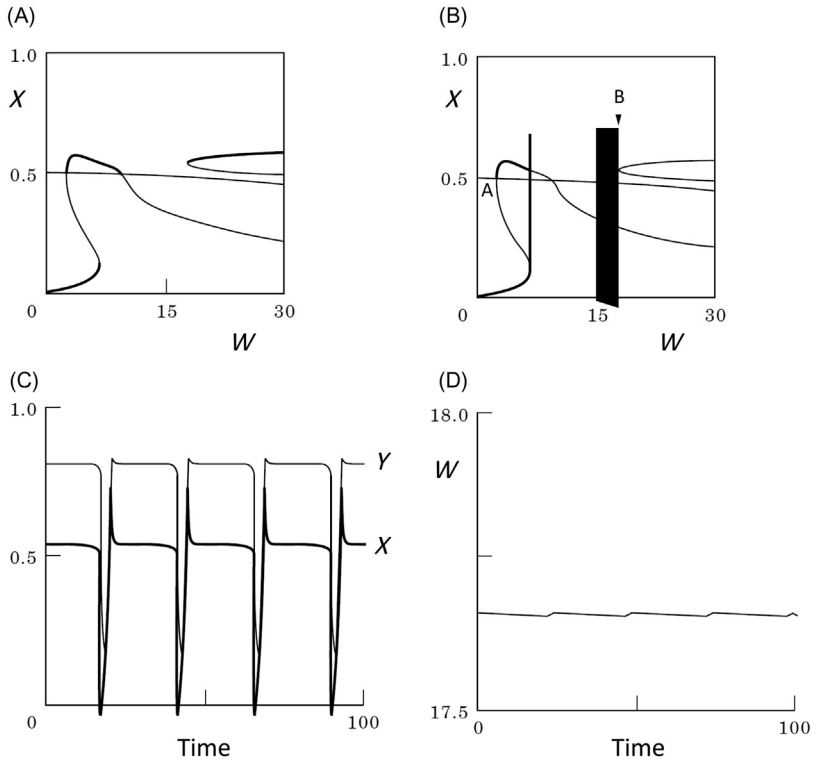

FIGURE 5.5 **Two attractors.** (A) The manifold shows the equilibrium value(s) of the excitatory activity X for a given, fixed value of the connectivity W in a simplified network with excitation and inhibition[35] (compare with Fig. 5.3). The *bold lines* indicate stable and the *thin lines* unstable points with respect to X. The *thin, nearly horizontal line* denotes points where W is at equilibrium. (B) The *bold lines* now depict development over time, not stability as in (A). The whole system has two attractors. With a low initial level of connectivity ($W = 0$), the network ends up, via an overshoot in connectivity, in a point attractor (marked with an A), in which W and X are constant. With a high initial level of connectivity ($W = 15$), the network ends up, via oscillations in X and a slow increase in W (since the changes in W are much slower than those in X, no separate oscillations are visible), in a limit cycle attractor (marked with a B and an *arrow*), in which W is nearly constant but X oscillates. (C) Excitatory activity X and inhibitory activity Y in the limit cycle attractor. (D) Connectivity W in the limit cycle attractor. Source: *Reproduced with permission from van Oss C, van Ooyen A. Effects of inhibition on neural network development through activity-dependent neurite outgrowth. J Theor Biol. 1997;185(2):263–280. Elsevier.*

3.6 Differentiation Between Excitatory and Inhibitory Cells

Although in the model there are no intrinsic differences between excitatory and inhibitory cells with respect to outgrowth rules, they nevertheless differentiate, with the neuritic fields of inhibitory cells becoming smaller than those of excitatory cells[33] (Fig. 5.6A–C). The mechanism is as follows. Each cell will attain a neuritic field size for which the input from overlapping cells is such that $F(X_i) = \varepsilon$. An excitatory cell that receives inhibition therefore needs more excitatory input than a cell that is not inhibited, and thus grows a larger neuritic field. As a result, each inhibitory cell will become

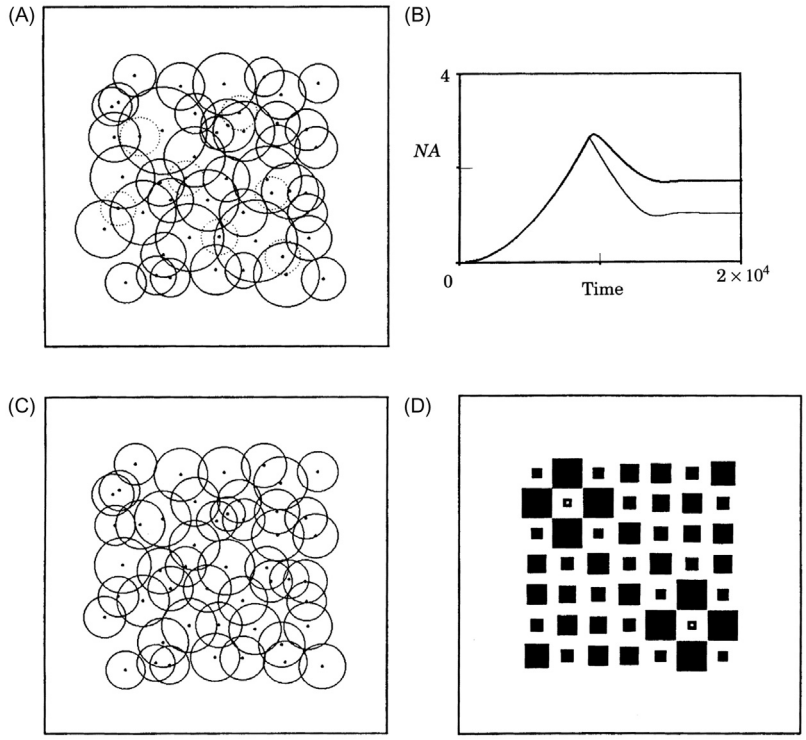

FIGURE 5.6 **Influence of inhibitory cells.** (A) Mature network showing the neuritic fields of excitatory cells (*continuous lines*) and inhibitory cells (*dotted lines*). (B) The average neuritic field area of excitatory cells (*thick line*) and that of inhibitory cells (*thin line*) over time. Cell size starts differentiating once the network has become active. (C) Same placing of cells as in (A), but all former inhibitory cells are now excitatory. (D) Cells on grid positions. The diameter of a square is proportional to the area of the neuritic field (scaled to the maximum area found in the network). Cells with a *white dot* in the middle are inhibitory. All networks have torus boundary conditions. Source*: Reproduced with permission from van Ooyen A, van Pelt J, Corner MA. Implications of activity dependent neurite outgrowth for neuronal morphology and network development. J Theor Biol. 1995;172(1):63–82. Elsevier.*

surrounded by large excitatory cells, whereas the inhibitory cell itself can remain small because a small neuritic field already yields sufficient overlap with its large surrounding cells. In other words, an inhibitory cell becomes small by increasing the size of its direct neighbors. Differences in cell size emerge irrespective of initial size: inhibitory cells may start at the same size as excitatory cells or may be introduced in a well-advanced or mature excitatory network.

In the cerebral cortex, the dendrites and axons of inhibitory neurons are, on the whole, indeed smaller than those of excitatory neurons.[65] Pyramidal cells, which are excitatory, have large apical dendrites and long axons, and often form long-range connections.[66] Nonpyramidal cells, which are generally smaller, are mostly inhibitory and mainly make local connections.[46]

3.7 Patchy Connectivity Structure

By inducing outgrowth, inhibitory cells enhance the degree of connectivity among their neighboring cells.[33] To obtain sufficient input, excitatory cells that receive inhibition need to grow larger neuritic fields and hence become more tightly connected among each other than uninhibited cells. In other words, inhibitory cells impose a kind of clustered connectivity structure onto the network (Fig. 5.6D), somewhat resembling the patchy organization of lateral connections observed in the neocortex.[67,68]

Guided by intrinsically generated electrical activity,[69] the cortex self-organizes from a diffuse network into a network with local neuronal clusters of corticocortical connections.[70] Inhibitory neurons may help shape these patchy connectivity patterns.[71] A conceptual model has been proposed in which basket interneurons (inhibitory cells) veto pyramidal neurons (excitatory cells) to form connections within circular domains.[71] The model requires pyramidal axons to step over a zone of inhibition, which indeed is the effect of inhibition in the neuritic field model, as inhibition favors outgrowth. In the same vein, double bouquet cells, another type of inhibitory cells, have been suggested to impose a microcolumnar organization upon the cerebral cortex.[72]

In the neuritic field model, when inhibitory cells are in the position that they can connect among themselves, they inhibit each other's activity but stimulate each other's outgrowth,[33] leading to the formation of long-range inhibitory connections, as found in the cortex.[73,74] Thus the distribution of inhibitory cells has a large impact on the connectivity structure (neuronal clusters, long-range inhibition) that arises in the network. Excitatory and inhibitory synaptic strength (S; see Eq. 5.4) also influence network structure.[32] When synaptic strength is low, cells develop into a single interconnected network. When synaptic strength is high, separate, mutually disconnected subnetworks emerge, because contact with fewer cells is then sufficient to reach set-point activity.

3.8 Self-Repair of Connectivity After Lesions

After cell loss (which, in the brain, could be caused by stroke or neurodegeneration), the remaining cells, especially those in the neighborhood of the deleted cells, lose connections and consequently undergo a drop in activity [$F(X_i) < \varepsilon$]. This triggers neuritic field outgrowth and formation of new connections until activity is restored [$F(X_i) = \varepsilon$]. The more cells are deleted, the larger the compensatory increase in neuritic field size, and the bigger the average neuritic field size in the network.[33]

Some brain regions lose neurons through old age, and in these regions there is indeed a steady increase of dendritic extent per neuron.[75] Accordingly, no increase in dendritic extent occurs in brain regions that do not lose neurons with age.[76] Stroke also leads to cell loss and deprives neurons surrounding the stroke site of horizontal input.[8,9] Similarly to what is observed in the model, the deprived neurons remodel their dendritic arbors, withdrawing branches from the infarct and extending branches toward intact areas.[8,77] In this way, cells may form new connections and restore their level of activity. In agreement with such a process of compensatory sprouting, dendritic remodeling is inversely correlated with distance from the infarct.[8] The farther a cell is from the infarct, the less it will be affected by a loss of input, and the less remodeling is needed.

3.9 Neurogenesis-Induced Network Reorganization

The model network can also cope with insertion of new cells (neurogenesis) in a mature network, in which electrical activity is at the homeostatic set-point. The newly added cells grow out and become electrically active as a result of the input they receive from the network. At the same time, the activity of the preexisting cells, especially those surrounding the newly inserted cells, increases above the set-point because of the extra input they receive from the new cells. These changes in activity trigger adjustments in neuritic field size and connectivity of both new and preexisting cells, until the activity of all cells has returned to the homeostatic set-point. In the adult brain, insertion of newborn cells takes place in the dentate gyrus of the hippocampus,[78] and, as in the model, induces structural adaptations in preexisting circuits as cells become synaptically integrated.[79,80]

3.10 Neuronal Death During Development

Experimental findings have shown that neurite retraction occurs not only when activity is above a set-point value but also when it is below a certain minimum value.[11,26] If a growth function is used in which neurite retraction also takes place when neuronal activity is very low, the initial activity (connectivity) should be high enough to stimulate outgrowth.[45] However, even when initial activity is high enough, some cells, after transiently growing out, may still lose all of their connections and become silent (such cells are effectively "dead"), resembling the neuronal death seen during normal neural development.[81] Interestingly, experimental studies showed that neurons are especially vulnerable to cell death when their intracellular calcium concentration is substantially below resting level,[82] possibly as a result of diminished calcium influx due to low electrical activity.

3.11 Differentiation of Intrinsic Properties

In addition to neurite outgrowth, the maximal conductances of ion channels are regulated by activity.[83,84] Activity modifies the maximal conductances of ion channels in such a way that excitability is decreased when neuronal activity is high and increased when neuronal activity is low. In a model that extends the neuritic field model with activity-regulated maximal conductances, and that uses spiking neurons rather than firing rates (see Eq. 5.3), cells self-assemble into a coupled network exhibiting a rich repertoire of activity patterns.[85] Although all the cells are governed by the same activity-dependent rules for growth and conductance change, they nevertheless differentiate, with cells acquiring different firing patterns and distinct mixtures of conductances. Thus the interplay between outgrowth and changes in intrinsic properties leads to the formation of a highly differentiated network.

3.12 Self-Organized Criticality

Experiments have uncovered an intriguing dynamical state characterized by so-called neuronal avalanches in a variety of neural systems, including acute and cultured cortical slices,[86,87] developing cultures of dissociated cortex cells,[40] the developing retina,[88] and the

neocortex in vivo.[89] Neuronal avalanches are spontaneous bursts of activity that have power-law size and duration distributions.[86,87] The number of events of a given size (e.g., in terms of number of electrodes on which activity is recorded) falls as the size to the power $-3/2$, and the number of events of a given duration falls as the duration to the power -2. Power laws typically emerge in systems when they are close to a transition in behavior (i.e., when they are critical). Simple models have shown that the experimentally observed power laws can arise if connectivity is such that every neuron that fires an action potential causes, on average, one other neuron to fire.[90] With this connectivity, the network is critical in the sense that activity neither dies out nor increases over time.

How do networks develop and maintain patterns of connectivity that satisfy this criticality condition? In a version of the neuritic field model in which neuronal activity is generated by a Poisson spiking model,[44] the activity bursts in the network at equilibrium, when neuritic field sizes and connectivity are stable, exhibit the same power-law dependencies for size (as measured in number of action potentials) and duration as observed experimentally.[86,87] The property of the model that neurons grow out when activity is low and withdraw when activity is high forces the network to find a middle ground between all-to-all connectivity (producing excessive activity) and local connectivity (producing insufficient activity), and this is what provides the potential for critical, power-law behavior.[44] The self-organization of the model into a critical state with neuronal avalanches has also been demonstrated analytically.[91] Moreover, the neuritic field model can account for the different activity stages through which developing cultures of dissociated cortex cells traverse until they reach criticality.[92] In the mature brain, criticality may enhance information coding and transmission.[93–95]

3.13 Retinal Mosaics

The vertebrate retina contains several cell types distributed in multiple layers, with each cell type typically occupying only a single layer.[96] Furthermore, cells of a given type are positioned semiregularly within a layer, forming what is known as a retinal mosaic, so named because of the way the cell bodies and their dendrites tile the surface. Retinal mosaics ensure that the visual field is uniformly sampled and that there are no holes in visual space.

One of the mechanisms underlying mosaic formation is lateral migration.[96,97] During development, retinal cells arrive randomly spaced in their destination layer, but then start to move laterally within the layer, possibly as a result of neurite interactions as cells grow out,[98–100] until they form a regular mosaic. This mechanism was investigated in a version of the neuritic field model that was extended with an equation for lateral movement.[101] In the extended model, cell bodies repel each other in proportion to their neuritic overlap:

$$\frac{\mathrm{d}\mathbf{C}_i}{\mathrm{d}T} = \eta \sum_{k=1}^{N} u(\mathbf{C}_i - \mathbf{C}_k) W_{ik} \tag{5.10}$$

where $\mathbf{C}_i$ is a vector denoting the two-dimensional position of cell i; η determines the rate of movement; N is the total number of cells; W_{ik} is the connection strength from cell k to

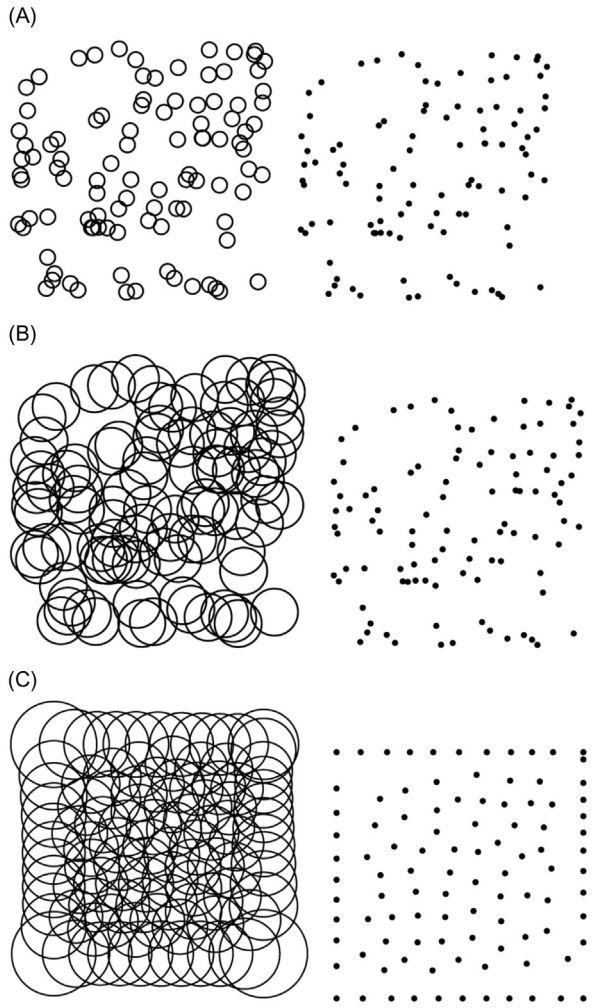

FIGURE 5.7 **Retinal mosaic development.** On the left, the neuritic fields; on the right, the positions of the cell bodies. The same network is shown at three stages of development. All cells are excitatory. (A) Neuritic fields have grown out, but cells have not yet moved, so the mosaic is still random. (B) Neuritic fields have grown enough to cause some small cell movement and a slight increase in mosaic regularity. (C) Neuritic sizes are uniform and the mosaic is highly regular. Cells at the border become larger because the network was not simulated with torus boundary conditions. Source*: Reproduced with permission from Eglen SJ, van Ooyen A, Willshaw DJ. Lateral cell movement driven by dendritic interactions is sufficient to form retinal mosaics. Network. 2000;11(1):103–118. Taylor & Francis Ltd., www.tandfonline.com.*

cell i; and $u(\mathbf{V})$ is the vector $\mathbf{V}$ normalized to unit length, except that $u(\mathbf{0}) = \mathbf{0}$. Elements of $\mathbf{C}_i$ are bounded to keep each cell body within the surface. All cells are excitatory.

Initially, cells are randomly distributed across the surface (Fig. 5.7A). As neuritic fields grow out, cells gradually begin to repel each other, slowly settling into a regular

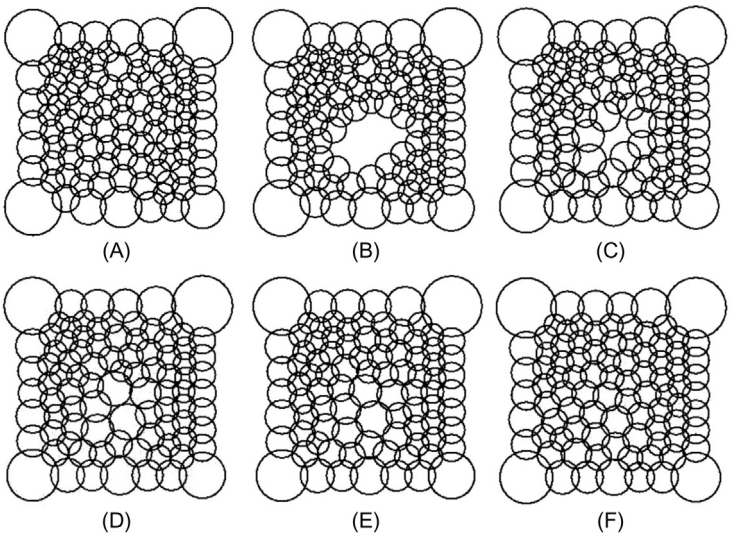

FIGURE 5.8 **Lesioning retinal cells.** After the network has developed (A), 10 central cells are removed (B). The neighboring cells move into this vacated area and expand to cover up the hole (C and D). All the cells in the network increase their neuritic fields a little in order to adapt to the new situation (E and F). All cells are excitatory. Source: *Still frames reproduced with permission from www.anc.ed.ac.uk/~stephen/mosaics/index.html, Stephen Eglen.*

hexagonal-like mosaic layout (Fig. 5.7B and C), in which cell position and neuritic field size remain stationary.[101] The amount of cell movement is small and in line with what is observed experimentally.[98] The regularity of the mosaic, however, is higher than observed experimentally, but reducing the precision with which cells detect neuritic overlap can remedy this.[101] The network can cope with changes in the number of cells.[96] If cells are added, the network automatically reorganizes, with cells getting closer together but maintaining an equally regular pattern. Similarly, if cells are deleted (i.e., a local lesion), the neighboring cells move in and expand to occupy the empty area, restoring mosaic regularity (Fig. 5.8), in agreement with experimental findings.[102]

Cell mosaics are not restricted to the retina and have, e.g., also been discovered in rat cerebellum and avian tectum.[103] Lateral cell movement due to neurite interactions may also in these cases be a possible mechanism for mosaic formation.

3.14 Developmental Changes in Burst Patterns

A computational study into the development of firing patterns applied the neuritic field model to simulate the self-assembly of 10,000 neurons, both excitatory and inhibitory, into a connected network.[104] Instead of the firing rate model (see Eq. 5.3), an integrate-and-fire model[105] was used, as well as a model of synaptic facilitation and depression.[106,107] Synaptic facilitation is the short-term enhancement of synaptic strength due to the prolonged elevation of presynaptic calcium levels following synaptic activity. Synaptic

depression is the short-term decrease in synaptic strength as a result of the depletion of neurotransmitter vesicles after synaptic activity. The focus of the study was on bursts of activity, where bursts are defined as periods of activity in which the network-average per neuron firing rate is higher than a given threshold. As connectivity developed in the model, bursts initially had a low firing rate and long duration, but then gradually evolved into more intense and shorter ones later on,[104] precisely as had been observed in developing cultures of dissociated cortex cells.[58] Thus the experimentally observed change in burst shape during development can be explained by activity-dependent neurite outgrowth and dynamical synapses, without the need for such features as LTP/LTD, detailed neuronal morphology, or specific patterns of connectivity.

3.15 Developmental Transitions in Cognition

An important question in psychology is how developmental transitions in cognition can arise even though brain growth may be gradual. Children show stages in development during which their cognitive abilities remain more or less stable,[108] interspersed with rapid transitions when cognition changes discontinuously and qualitatively new knowledge is acquired. In the network governed by the neuritic field model, electrical activity shows such a discontinuous change as connectivity gradually increases. Beyond a critical connectivity value, the network suddenly jumps from a state of low activity to a state of high activity (Figs. 5.2D and 5.3). The implications of this growth-related bifurcation for cognition have been studied[109,110] in Exact ART,[111] a neural network model based on the Adaptive Resonance Theory (ART).[112] ART specifies network structures and learning rules for unsupervised classification of input patterns. In an ART network, which uses the shunting model as neuron model (Eqs. 5.1 and 5.2), input patterns that are alike according to some criterion are classified into one category. The network constructs categories during the presentation of input patterns and remains adaptable to unknown patterns. Increasing the range and strength of excitatory and inhibitory connections in Exact ART revealed that the network exhibits qualitatively different dynamical regimes affecting the way learned categories are represented.[109,110] At low connectivity, representations of learned categories are mainly local, whereas at high connectivity they are mostly distributed. A change in representation is an important condition for learning qualitatively new knowledge. Thus a gradual, continuous developmental change in connectivity could lead to a relatively rapid, discontinuous change in cognitive abilities.

4 DISCUSSION

By adapting their neuritic field size, neurons in the model endeavor to reach and maintain a desired level (homeostatic set-point) of electrical activity. Neuritic field size expands when the neuron's electrical activity is below the set-point and shrinks when the neuron's electrical activity exceeds the set-point. By increasing its neuritic field size, the neuron enhances its afferent connectivity and potentially also its level of electrical activity; by decreasing its neuritic field size, the neuron achieves the opposite. In this way, each

neuron is pursuing its own goal of attaining a set-point level of activity, with the resulting network connectivity arising from many neurons simultaneously seeking to support their activity need.[1] This local striving for a desired level of electrical activity leads to many, seemingly unrelated, emergent properties: global homeostasis of network activity, even though neurons can monitor only their own activity level; a transient phase of high network connectivity (overshoot); developmental neuronal death; self-organized criticality; patchy network connectivity; retinal mosaics; formation of a normal or a pathological network (epileptic-like oscillatory electrical activity) depending on early level of inhibition, with too much inhibition leading to an abnormal mature network; differentiation in neuritic size between excitatory and inhibitory cells; differentiation in intrinsic firing patterns; developmental changes in network bursts; developmental transitions in cognition; self-repair of connectivity and restoration of activity following cell loss (stroke, neurodegeneration); and reorganization of connectivity during integration of newborn cells (adult neurogenesis).

The model shows the power of bottom-up modeling. In a bottom-up approach, instead of starting with a particular goal or predescribed behavior that the model should reproduce, one explores the emergent properties and phenomena resulting from the interactions among the constituents of the model.[3,113,114] Without this type of modeling, it would have been difficult to surmise that all of the above listed findings could have been different manifestations of the same underlying process, namely homeostatic activity-dependent neurite outgrowth.

The results of the model do not depend critically on the neuritic fields being described as circles. Other approaches for characterizing the neuritic extent of a neuron give essentially the same results.[32] Also, modeling axonal and dendritic fields separately, in which case connectivity among excitatory cells and among inhibitory cells is no longer necessarily symmetrical, does not alter the main findings.[33] Even assuming that the length of neurites is constant and that only the numbers of dendritic spines and axonal boutons, the pre- and postsynaptic parts of synapses, change in a homeostatic manner, would produce similar results, with spine and bouton number instead of neurite extent characterizing the size of a neuron (see further below). The precise form of the outgrowth function is also not essential, as long as high activity induces neuritic field shrinkage and low activity induces neuritic field expansion. The results are also robust when, instead of the shunting model, another model is used to describe neuronal electrical activity. For example, in a detailed spiking and conductance-based model of the human cortex,[56] the same type of hysteresis loop between activity and connectivity was found as in the neuritic field model,[32] implying that the results that rely on hysteresis, such as overshoot, can also be observed in more detailed models.

4.1 Future Experimental Studies

To determine the relationship between neuronal electrical activity and rate of neurite outgrowth (growth function, see Eq. 5.6) more quantitatively, one could continuously stimulate neurons at different frequencies and measure their morphological response. Alternatively, since intracellular calcium mediates the effect of electrical activity on neurite

outgrowth,[11,13–15] one could challenge neurons with different rises in intracellular calcium by means of calcium uncaging.[13] This may also reveal differences in growth response between axons and dendrites or between different cell types (excitatory, inhibitory). For example, different types of neurons may have their homeostatic set-point at different levels of electrical activity or intracellular calcium. Further open questions concern the way the set-point is encoded biologically and how cells measure the deviation between the actual level of activity or calcium and the set-point level.[115] Lastly, in interpreting the results from experimental studies, one should realize that with an optimal calcium window for neurite outgrowth, an increase in calcium or electrical activity could lead to either stimulation or suppression of outgrowth, depending on the resting value of calcium.

To correlate activity history with neuronal morphology, one could simultaneously monitor electrical activity and morphology in developing networks in vitro or in vivo, using advanced techniques such as optogenetics, two-photon microscopy, calcium imaging, and multielectrode arrays, which enable measuring activity and neurite morphology over extended periods of time.[7,116–119] With these techniques, many specific questions can be investigated to test the model results. Do the slow fluctuations in electrical activity as observed in developing cultures of dissociated cortex cells[58] correlate with periodic changes in neurite outgrowth, as in the model[34]? Does synaptic input from inhibitory cells increase the dendritic extent of excitatory cells, as the model predicts[33]? Similarly, do excitatory cells in networks in which inhibition is blocked show less variation in dendritic extent than excitatory cells in networks with intact inhibition? Does cell loss cause a drop in activity and trigger a compensatory increase in the axonal and dendritic extents of the remaining cells, as seen in the model[33]?

In the model, external input, from sources outside the network, changes the distribution of neuritic field sizes.[32,33] If a cell receives external excitatory input, it needs less input from other cells in the network to attain the set-point level of activity and hence can do with a smaller neuritic field. Does external excitatory input indeed give rise to smaller dendrites in developing or mature networks? Does continual external input prevent networks from reaching critical connectivity? A network that has grown in the presence of external input is not expected to be in a critical state when the external stimulation is removed. Likewise, does external stimulation of the developing retina influence mosaic regularity, since retinal cells that receive external excitatory input would grow out less and repel other cells less than retinal cells without external input?

4.2 Future Modeling Studies

In the model, no distinction is made between axons and dendrites. One way to do this is to provide each neuron with two neuritic fields, one for the axonal extensions and one for the dendritic extensions.[92] If wanted, the axonal and dendritic fields can be given different growth parameters or functions. Simulations with separate axonal and dendritic fields show that the results presented here do not critically depend on neurons having a single neuritic field.[33]

A further step toward a more detailed description of growing neurons is to employ, not circular neuritic fields, but spatial functions describing the density of the neuron's axonal

and dendritic branches. The connectivity between two neurons can then be calculated by estimating the number of synapses formed in the area of spatial overlap between the axonal and dendritic density fields.[120]

Instead of using fields, one can model the actual morphology of elongating and branching neurites, as in a compartmental modeling approach[121–123] or as in the program NETMORPH.[124,125] In NETMORPH, a simulation tool for building synaptically connected networks with realistic neuron morphologies, axonal and dendritic morphologies are created by stochastic rules for the behavior of individual growth cones, the structures at the terminal tips of neurites that mediate elongation and branching. The growth of terminal branches can be made dependent on the time-averaged local membrane potential at the growth cone. This membrane potential will be influenced by both the firing rate at the soma and the local synaptic potentials at the neurite.

Using neuritic fields is one way to abstract away from detailed neuronal morphology. Another way is to describe each neuron as having separate axonal synaptic elements (representing boutons) and dendritic synaptic elements (representing spines), which can combine to form synapses.[126,127] In the synaptic element model, with growth rules partly inspired by the neuritic field model, neurons generate new elements when neuronal electrical activity is below the set-point, and delete elements, including those bound in synapses, when activity is above the set-point or below a certain minimum level. A growth function with a minimum and a set-point level was also used in the neuritic field model.[45]

A promising further line of modeling work is to combine activity-dependent neurite outgrowth with other activity-dependent properties, such as intrinsic ion channel conductances, which are also regulated in a homeostatic manner.[84,85,128] Even early developmental processes, such as differentiation of cell identity, are partly governed by electrical activity.[129] For example, during development, GABA-induced depolarization (GABA is excitatory early on) is necessary for proper excitatory synapse formation and dendritic development,[130] a mechanism that may contribute to balancing excitation and inhibition. Electrical activity influences neuronal identity not only during development but also in adulthood: the relative proportions of different types of inhibitory interneurons are continuously adjusted in response to neuronal activity.[131] In the neuritic field model, the identity of cells, i.e., whether they are excitatory or inhibitory, is fixed and has to be set before-hand. It would be interesting to make this aspect of network development also dependent on electrical activity and part of the self-organization process. One can envisage a model of self-organization in which neurite outgrowth, intrinsic cellular conductances, and ratio of inhibitory to excitatory cells are all controlled by electrical activity in a homeostatic manner. Such a model may also include homeostatic and Hebbian synaptic plasticity.[83,132] The interactions among these different types of activity-dependent processes, operating at different time and spatial scales, may generate extremely rich dynamics.[133,134]

The possible roles of activity-dependent neurite outgrowth, or structural plasticity in general, in cognitive processes such as learning and memory have not been studied extensively.[109,110] A form of memory could occur when, after the application of external input, the networks were pushed into a different stationary state with respect to neuritic field sizes and connectivity. For this to be feasible, however, different solutions of neuritic field size distributions must exist in which the electrical activity of all cells is at the homeostatic

set-point. Whether these multiple equilibrium points exist for the circular neuritic field model is unknown.

Homeostatic activity-dependent neurite outgrowth provides a mechanism by which unconnected neurons can self-organize into a connected network and offers a way of automatically creating, without parameter tuning, balanced connectivity in large-scale networks in which neuronal activity is neither too high nor too low. In general, activity-dependent neurite outgrowth may act as a central organizing principle driving both the development of networks and the reactive and compensatory structural changes induced by neurogenesis, deafferentiation, and neurodegeneration in adulthood.

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