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REVIEW ARTICLE

Activity-dependent neural network development

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Abstract. Electrical activity plays a pivotal role in the development of neurons into functional neural networks. Besides changes in synaptic strength, many other processes are activity-dependent. They influence neuronal function and connectivity, on multiple time scales as well as on multiple levels of specificity, both during development and in adulthood. A number of these processes are reviewed here, together with some simulation models. Their relevance for the current thinking about neural networks is discussed.

1. Introduction

In the course of development neurons become assembled into functional neural networks. Electrical activity plays a central role in this process, and its effects are not restricted to mere changes in synaptic strength. Many processes that determine connectivity and neuronal function are, on various time scales, modulated by electrical activity: e.g. naturally occurring cell death, trophic factor production and responsiveness, number and effectiveness of transmitter receptors, neurite outgrowth and growth cone behaviour, neuronal morphology, gene expression and differentiation of neurons, neuron-glia interactions, synaptogenesis, secondary elimination of synapses, and changes in synaptic strength.

As a result of these activity-dependent processes, a reciprocal influence or feedback loop (a characteristic of self-organizing systems) exists between the development of neuronal form, function and connectivity on the one hand, and neuronal and network activity on the other hand (also see van Pelt *et al* 1994). A given network may generate activity patterns which modify the organization of the network, leading to altered activity patterns which could further modify structural or functional characteristics, and so on (e.g. Von der Malsburg and Singer 1988). Furthermore, in the initial stages of development, activity patterns that are not evoked by external input (endogenous or 'spontaneous' activity: see Corner 1990) play an important role, as has been demonstrated in a number of cell and tissue culture experiments (e.g. Corner and Ramakers 1992). A developing network is thus a dynamic system in which the structure, number of elements, and functional characteristics of the elements are variable, in part being under control of the system's own activity. The presence of such feedback loops has implications not only for the emergence of network organization and function, but also for the functioning of the mature system: processes that are involved in development often appear to remain operative in adulthood.

In this review I will describe (i) the dependency of various developmental processes upon electrical activity, (ii) the indications that these processes are still operative in the mature state, and (iii) a number of illustrative simulation models (without the pretention of being complete).

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2. Cell death and trophic factors

During development, up to about twice as many neurons are produced in many structures as will survive into adulthood (e.g. Oppenheim 1991). This process of overproduction followed by death occurs in regions of the peripheral as well as central nervous system. The survival of neurons depends to a great extent on whether or not they have obtained adequate amounts of specific neurotrophic factors (Purves 1988, Oppenheim 1991), which seem to act by suppressing an intrinsic cell suicide program (Johnson and Deckwerth 1993). The survival requirements of developing neurons include factors that are produced by their target cells. They are taken up through the synapses of the presynaptic cell and reach the soma by retrograde axoplasmic transport. In addition to affecting survival, trophic influence can affect axonal and dendritic arborization, the production and choice of neurotransmitter, the expression of receptors, and a variety of electrical membrane properties, both in development and in adulthood (for references see Clarke 1991).

The synthesis of neurotrophic factors is regulated by electrical activity. For example, the synthesis of the neurotrophins NGF (nerve growth factor) and BDNF (brain derived neurotrophic factor) by neurons in the central nervous system is up-regulated via the excitatory neurotransmitter glutamate and down-regulated via the inhibitory neurotransmitter GABA (Zafra *et al* 1990, Lu *et al* 1991, Thoenen 1991). The responsiveness to trophic stimulation may also be regulated by electrical activity, since depolarization increases the expression of the receptors for neurotrophic factors (Black 1993). Moreover, different excitatory receptor subtypes mediate trophic or *regressive* influence: stimulation of ionotropic receptors (see section 3) decreases survival, whereas metabotropic receptor activity is necessary for survival (Black 1993; for a review on the trophic effects of excitatory neurotransmitters and depolarization, see Balázs *et al* 1992). Electrical activity and trophic factors may interact via levels of intracellular calcium ($[Ca^{2+}]_i$). Depolarization causes Ca^{2+} entry, and neurons that have low $[Ca^{2+}]_i$ are more dependent on trophic factors than those with high $[Ca^{2+}]_i$ (Koike and Tanaka 1991). The expression of endogenous BDNF, which enhances cell survival, is increased by the activation of voltage-sensitive Ca^{2+} channels (Ghosh *et al* 1994). At very high $[Ca^{2+}]_i$, however, neuronal death is increased. In connection with these observations, the 'calcium set-point hypothesis' of neuronal survival and dependence on neurotrophic factors has been proposed (Franklin and Johnson 1992), which states that: (i) at $[Ca^{2+}]_i$ substantially below resting levels, neurons do not survive, even in the presence of neurotrophic factors; (ii) at normal $[Ca^{2+}]_i$ neurons survive only if adequate amounts of trophic factors are available; (iii) at modestly elevated $[Ca^{2+}]_i$ neurons will survive even in the absence of trophic factors; and (iv) at very high $[Ca^{2+}]_i$ neuronal death is increased. Finally, both the uptake of trophic substances and the transport through axons might themselves be activity-dependent, the former also via the activity-dependent regulation of neurite outgrowth and branching patterns (see section 4), which influences the number of synapses and thereby the attainment of trophic substances.

In addition to the mechanisms described above, by which the electrical activity in afferent nerve fibres modulates the effects of retrogradely transported neurotrophic factors, the afferents themselves may also produce specific neurotrophic factors that are anterogradely transported through their axons and synaptically released, possibly in an activity-dependent manner (Linden 1994).

The neurotrophic factors that are retrogradely transported through an axon may affect not only the parent neuron but also the synapses impinging on it. Cutting axons can cause withdrawal of synapses from the damaged cells (for references see Clarke 1991). Neurons deprived of retrograde trophic support will then in turn fail to provide trophic support to

the neurons one stage further upstream. Similarly, anterograde trophic effects might be transmitted further downstream. Thus, there could exist a network of trophic interactions comparable in complexity to neural networks based on electrical activity, with both systems reciprocally influencing each other at multiple levels (Clarke 1991).

The roles of trophic interactions and neuronal death are most pronounced during development: establishment of neuronal circuits, formation of morphogenetic patterns, control of neuronal numbers, matching the number of presynaptic and postsynaptic cells, and eliminating wrongly connected cells (Oppenheim *et al* 1992, Raff 1992). The rapid regulation of neurotrophic substances by neuronal activity, however, allowing the conversion of short-term signalling into long-term changes, suggests that their function is much more than merely regulating neuronal survival during development (Thoenen 1991; also see Lindsay *et al* 1994). Trophic interactions may also be involved in memory and learning in adulthood (Thoenen 1991, Black 1993, Tancredi *et al* 1993).

2.1. Models

Understanding the implications of trophic interactions at the network level requires mathematical and simulation models (Clarke 1991).

In Galli-Resta and Resta (1992) a model for the regulation of cell death has been developed. Cells are generated according to a specific scheme and die around a certain age unless trophic influence saves them. By assuming that trophic interactions between connected structures are mutual, i.e. trophic factors are supplied from the target to the input cells and vice versa, apparently conflicting experimental findings with respect to the regulation of target and input size can be reconciled. The model predicts both outcomes that support the size-matching hypothesis (i.e. a linear relationship between target and input size) and outcomes that strongly deviate from this linear relation.

Trophic interactions are used in a model of the establishment of connections between motor neurons and muscle fibres (Rasmussen and Willshaw 1993—a revised model of that of Bennett and Robinson 1989). During development of the nervous system, the axons of motor neurons branch into a number of terminals, so that each muscle fibre is connected by terminals from several different neurons. Withdrawal of terminals takes then place until each fibre is innervated by a single axon. In the model, competition for a postsynaptic (trophic) substance produced by each fibre together with competition for a presynaptic substance lead to such a single innervation pattern, as well as to a maximal number of terminals that a neuron can maintain (there is no neuronal death nor effects of activity). Intrinsic withdrawal, as observed in some experiments, appears as a side effect of the competitive mechanism. For related models, see references in Rasmussen and Willshaw (1993).

Trophic interactions are also used in a model of the mapping of neurons from spinal segments onto targets in the periphery (Liestøl *et al* 1993). In the model, each postsynaptic cell produces a limited amount of trophic factor so that more connections onto a cell leads to a reduced survival chance of each connection. An increase in the number of connections of a given presynaptic cell also decreases the survival chance of each connection. Together with chemoaffinity (no activity-dependent processes are assumed) these interactions generate an innervation pattern resembling that of the biological system. In the model, the final pattern is sensitive to the initial distribution of presynaptic fibres onto their targets. This sensitivity is markedly reduced if neurons are allowed to die depending on the sum of the survival chances of their connections.

In a model for the self-organization of neural assemblies into clusters of cells with characteristic, input-related responses, synapses degenerate unless they receive sufficient

trophic factor, which is distributed from postsynaptic cells under an activity-dependent Hebb-like rule (Kerszberg *et al* 1992). A pattern of connections emerges with short-range excitation and longer-range inhibition. Synaptic stabilization based on post- and presynaptic trophic factors is also used in a model of the self-organization of cortical maps (Tanaka 1990).

In developing neural networks, the number of elements of the system itself can change, as new cells are added and others may die. This could lead to novel dynamics. In Kaneko (1994) and Kaneko and Yomo (1994) systems with a growing number of elements are considered. Cells compete for a resource term which is supplied from the environment. The ability to obtain this depends on the internal state of the cell, and cells divide and die depending on their state. During development, simultaneous death of many cells is seen (due to *interaction* among cells) resembling the 'programmed' cell death seen in many biological systems.

Neuronal death and pruning of connections might have conceptual links with structural plasticity in artificial neural networks in which, in contrast to conventional learning algorithms, the architecture of the network itself (number of elements, pattern of connections) varies during learning, e.g. in Kohonen networks (Fritzke 1991) and feedforward networks (Refenes and Vithlani 1991, Hirose *et al* 1991, Romaniuk and Hall 1993, Odri *et al* 1993, Bartlett 1994, Nabhan and Zomaya 1994, Fahner and Eckmiller 1994).

3. Receptors and ion channels

The roles of ion channels and neurotransmitter receptors in mediating rapid electrical signalling have been appreciated for a long time. More recently it has been recognized that they are also involved in much slower processes, and that electrical activity (via neurotransmitter release and receptor actions) can modulate itself, and can even influence neuronal differentiation during development.

Transmitter receptors can be divided into two families according to how the receptor and effector function (i.e. gating ion channels) are coupled (Schwartz and Kandel 1991). In the family of gated ion channel or ionotropic receptors, the recognition site and channel are different parts of the same protein. This family includes several glutamate receptor types (AMPA, kainate, NMDA) and the GABA receptors, which mediate neuronal excitation and inhibition, respectively. The family of G-protein coupled or metabotropic receptors contains the serotonin, dopamine and neuropeptide receptors, but also one of the glutamate receptor types (Schoepp *et al* 1990). Here, recognition is carried out by a separate molecule that is coupled via a G-protein to an effector molecule, which typically produces a diffusible second messenger (e.g. cAMP). This second messenger in turn triggers changes in a variety of proteins.

Second messengers can induce the opening or closure of ion channels (in some instances the G-protein can act directly on an ion channel), thus modulating the signalling properties of the cell. These changes, which depend on transiently elevated concentrations of second messenger, last from seconds to minutes, usually much longer than the changes in membrane potential produced by ionotropic receptors. As second messengers can diffuse intracellularly, they can affect channels in distant parts of the cell (also see Kasai and Petersen 1994).

Another class of proteins upon which second messengers act are neurotransmitter receptors (of both families, so that interactions between ionotropic and metabotropic receptors—e.g. different types of glutamate receptors—are possible). In this way, a receptor can regulate its own effectiveness, as well as that of a receptor for another neurotransmitter.

For example, after prolonged exposure to its own transmitter, a receptor can become desensitized. Also the number of receptors can be regulated, usually on a time scale of hours (for references see Shaw *et al* 1989) with down-regulation following agonist stimulation or increases in electrical activity, and up-regulation following antagonist treatment or decreases in electrical activity. This type of regulation is not restricted to G-protein coupled receptors. In adult rat neocortex, for example, an increase in neural activity or agonist stimulation decreases the number of AMPA receptors (a type of glutamate receptors) while increasing the number of GABA receptors (Shaw and Scarth 1991, Shaw and Lanius 1992; for the effects of depolarization on AMPA receptors in cerebellar granule cells, see Condorelli *et al* 1993). Such control of receptor number and sensitivity may be regarded as a form of homeostasis of neuronal activity (also see Turrigiano *et al* 1994).

Through second messenger systems, electrical activity can act on proteins that regulate the expression of genes (Armstrong and Montminy 1993) including those related to channels and receptors. This can cause more enduring effects in neuronal excitability lasting days or weeks, or which can even lead to persistent changes in cellular function (neuronal differentiation). Stimulation of gene expression often occurs via Ca^{2+} dependent mechanisms. Changes in $[Ca^{2+}]_i$ can occur either through second messengers mobilizing Ca^{2+} ions from intracellular stores, or directly via Ca^{2+} flux through NMDA channels and voltage-sensitive Ca^{2+} channels which open upon membrane depolarization (in this way, the activity of ionotropic receptors can also lead to long-lasting changes). Already the early differentiation of neurons is dependent upon neurotransmitter actions and membrane polarization (for references see Harris 1981). Ion flux in immature cells triggers later steps of development, including developmental changes in ion channels and receptors (Spitzer 1991). For example, Ca^{2+} influx elicited by depolarization has been shown to influence neurotransmitter levels, the choice of neurotransmitter phenotype and properties of potassium channels (for references see Spitzer 1991). Electrical activity may be crucial for the full maturation of inhibitory transmission (in cultured rat neocortex: Corner and Ramakers 1992; in mouse cerebellar cultures: Seil and Drake-Baumann 1994). In cultured cerebellar granule cells, glutamate stimulates GABA receptor mRNA expression, whereas treatment with NMDA receptor antagonists does the opposite (Memo *et al* 1991). In adult monkey visual cortex, GABA and its receptor are regulated, possibly through changes in gene expression, in an activity-dependent manner, with down-regulation following afferent deprivation (Jones 1993). Thus, both during development and in adulthood, levels of electrical activity are likely to control the balance between excitation and inhibition.

To summarize, the neuron does not have a static set of properties, even in adulthood, but changes under influence of its own activity. These interactions are reciprocal: electrical activity depends on ion channels and receptors, the properties of which, in turn, can be modified by electrical activity. This loop operates on various time scales, not only during development, but also during the functioning of the adult brain.

3.1. Models

To study what impact such a feedback loop could have, Abbott *et al* (Abbott *et al* 1993, LeMasson *et al* 1993, Abbot and LeMasson 1993) have developed model neurons (single as well as multi-compartmental) in which the maximal conductance $\bar{g}_j$ of each ionic current is not fixed, as in most models, but dynamic and regulated by the neuron's own activity, with the intracellular Ca^{2+} concentration as an indicator of activity levels. The behaviour

of $\bar{g}_j$ obeys

$$\tau_j \frac{d\bar{g}_j}{dt} = f_j([Ca^{2+}]) - \bar{g}_j \quad (1)$$

where τ_j is much larger (minutes to hours) than the time constants of the other processes in the neuron; $f_j([Ca^{2+}])$ is the steady-state value of $\bar{g}_j$, which depends sigmoidally on the calcium concentration

$$f_j([Ca^{2+}]) = \frac{G_j}{1 + exp(s([Ca^{2+}] - C_T)/\Delta)} \quad (2)$$

where G_j, C_T and Δ are parameters determining the form of the sigmoid, and s is $+1$ for inward and -1 for outward currents, so that a negative feedback loop exists from activity to current strength (stability criterion). This regulation scheme stabilizes the activity of the neuron (lobster stomatogastric ganglion neurons have indeed been found to regulate their conductances to maintain stable activity patterns: Turrigiano *et al* 1994). If, for example, the amount of extracellular potassium is increased so that an isolated, periodic bursting neuron (single compartment) goes into a fast, tonic firing mode, the resulting increase in electrical activity and $[Ca^{2+}]_i$ will, via equations (1) and (2), readjust the maximal conductances so that the initial behaviour is restored (although possibly with a completely different set of conductances). This type of regulation also causes the intrinsic properties to shift in response to external stimulation or the presence of other neurons. An example of the latter is given by a network of two neurons, which, when uncoupled, are identical bursters. When they are symmetrically coupled, however, their activity in the network is no longer identical. The coupling shifts their intrinsic properties: the behaviour of one of the neurons, when again uncoupled, has changed from bursting to tonic firing. Thus, the coupling has spontaneously differentiated the neurons to form a circuit in which one acts as a pacemaker and the other as a follower. In a multi-compartmental version of the model with soma, axon and dendritic tree, in which equations (1) and (2) act locally, a realistic pattern of membrane conductances (i.e. the strongest sodium current near the soma, intermediate along the axon, and smallest on the dendritic tree) spontaneously arises when the dendritic tree is randomly stimulated with excitatory inputs. This pattern emerges purely as a result of the morphology of the neuron.

In Bell (1991), the ion channels in dendritic compartments are also treated more dynamically: during learning, the conductances are changed so as to optimize an objective function of local current flow. It is shown that these rules give rise to motion sensitive receptive fields. Interestingly, Zohary *et al* (1994) have found that the increase in perceptual sensitivity of monkeys practising a motion detection task is accompanied by an increase in sensitivity of directionally selective neurons.

Taken together, this type of dynamic regulation of intrinsic properties may play an important role in network adaptation and development. Along with activity-dependent synaptic plasticity, the existence of activity-dependent neuronal properties suggests that plasticity at 'nodes' (i.e. neurons) may be an important element in network learning (Abbott *et al* 1993, and references therein).

Using globally coupled networks of chaotic elements, Kaneko (1994) has studied such a case: synaptic change is not assigned to the interaction between i and j, but to the coupling w_i at node i, so that the coupling strength, for a given i, takes the same value for every j. Given an update rule for w_i, common inputs, applied to a subset of elements, increase the degree of synchronization of oscillations of these elements, which persists even if the inputs are removed. Thus, clustering according to inputs is obtained.

Tawel (1992) has studied a neuron that adaptively participates in the learning process of a feedforward backpropagation network. During learning, both the synaptic weights and the steepness of the sigmoidal activation function of the individual neurons are optimized, so that in the end each neuron attains its own characteristic activation function (stimulus-response properties of individual neurons in the adult cortex can indeed be modified: see references in Zohary *et al* 1994). The method appears to reduce the learning time significantly.

Another intrinsic property that can improve learning is the phenomenon that a neuron can decrease its activity when repeatedly stimulated (i.e. habituation or adaptation, e.g. through desensitization of receptors). It was implemented in the Neocognitron (van Ooyen and Nienhuis 1993), which is a multi-layered feedforward network for visual pattern recognition (Fukushima 1980). A type of competitive learning is used to train the network. After learning is completed, the model has a hierarchical structure in which simple features of the input patterns are combined step by step into more complicated features, with the cells in the highest layer each responding to only one input pattern (if learning was successful). Habituation improves pattern discrimination because cells will become less responsive to the more frequent features among a set of input patterns, so that circuits for detecting them will not be reinforced. Circuits for relatively infrequent features (i.e. discriminating features) develop preferentially. Without habituation, features shared by different patterns are preferentially learned.

Neuromodulators (e.g. neuropeptides and hormones; see section 3) modify the intrinsic properties of neurons (e.g. Kaczmarek and Levitan 1987). In Coolen *et al* (1993) a simplified form of neuromodulation is implemented in Ising-spin neural networks: a modulator-specific subset of neurons is prevented from transmitting signals. Neuromodulation, which is present both during learning and recall, enables associative memories to perform selective pattern reconstruction. Which of the stored patterns will be candidates for reconstruction depends on the similarity of the modulation setting at the moment the patterns were learned with that present during the recall phase.

The modulatory system need not be separate from the system it modulates (i.e. intrinsic neuromodulation). In molluscs, it has been found that neurons within a central pattern generator circuit can, by their own activity, dynamically modulate synaptic strengths within that same circuit during its normal operation (Katz *et al* 1994).

4. Neurite outgrowth

4.1. Neurite outgrowth, electrical activity, and neurotransmitters

During early development neurons attain their characteristic morphology of branched axons and dendrites (the conventional view is that dendrites always conduct information towards the soma and axons away; in fact, neurons have a more varied repertoire: see e.g. Andersen (1985), Shepherd (1990, 1991), Regehr *et al* (1993), Stuart and Sakmann (1994)). Around the cell body, protrusions of the cell membrane emerge which later develop into neurites (neurite is a general term for both axon and dendrite). The one with the highest outgrowth rate usually becomes the axon, while the others turn into dendrites (Sargent 1989, Craig and Banker 1994). At the tip of a growing neurite is a highly specialized motile structure, the growth cone, which typically consists of a flat lamellipodium and numerous filopodial extensions. It is capable of path finding, elongating, retracting, branching and initiating synaptogenesis. Neurite outgrowth and growth cone behaviour are therefore essential to the development of neuronal morphology and the pattern of synaptic connections. Apart from providing space for other cells to synapse upon, dendritic and axonal trees influence the

current flow through the cell and, thereby, its electrical properties.

Neuronal morphology results from the genetic potentialities along with environmental inputs such as growth factors, substrate adhesion molecules, and local cell interactions (for the latter see e.g. Gao *et al* 1991, Baptista *et al* 1994). Numerous studies have demonstrated that electrical activity and neurotransmitters can directly affect neurite outgrowth and neuronal morphology. They could play important roles, therefore, not only in information coding but also in defining the structure of the networks in which they operate (Mattson 1988).

Electrical activity of the neuron reversibly arrests neurite outgrowth or even produces retraction (Cohan and Kater 1986, Fields *et al* 1990, Schilling *et al* 1991, Grumbacher-Reinert and Nicholls 1992). Similarly, depolarizing media and neurotransmitters affect neurite outgrowth of many cell types (e.g. Sussdorf and Campenot 1986, McCobb *et al* 1988, Lipton and Kater 1989, Mattson and Kater 1989, Neely 1993) with, in general, excitatory neurotransmitters inhibiting outgrowth and inhibitory ones antagonizing the effects of excitatory neurotransmitters. In cultured hippocampal pyramidal neurons, for example, glutamate causes a dose-dependent reduction in dendritic length (Mattson *et al* 1988) (axonal outgrowth is also affected, but at higher concentrations) which can be antagonized by GABA or the suppression of electrical activity by anticonvulsant drugs (Mattson 1988). Dendritic outgrowth continues when neurons are exposed to GABA plus glutamate at a concentration of glutamate that normally causes dendritic regression (Mattson 1988). Excess inhibition, however, suppresses outgrowth. When GABA and its potentiator diazepam are added, the outgrowth of both the axon and dendrites is suppressed. This supports the notion that an optimal level of electrical activity is required for neurite outgrowth. Moreover, it may be not merely the frequency of impulses that is important, but also its pattern. In mouse sensory neurons, phasic stimulation is more effective in inhibiting neurite outgrowth than is stimulation with the same number of impulses at a constant frequency (Fields *et al* 1990).

The influences of electrical activity and neurotransmitters act on the level of both single neurite and whole cell. Specific cues such as neurotransmitters could act locally on individual growth cones, e.g. local application of glutamate to individual dendrites results in local dendritic regression (Mattson *et al* 1988), whereas action potentials may simultaneously regulate the behaviour of all the growth cones and neurites of a given neuron (Kater and Guthrie 1990, Cohan and Kater 1986; also see Stuart and Sakmann 1994). The conditions under which neurites grow out may be different for different neurons (Kater *et al* 1990). Even different neurites of the same neuron, e.g. axons and dendrites, can have different growth properties (Kater and Guthrie 1990).

In addition to the effects described above, neurotransmitters can regulate the direction of neurite outgrowth (Zheng *et al* 1994, Smith 1994). Neurites growing from cultured Xenopus neurons turn towards an acetylcholine (ACh) source. They are able to detect a gradient in neurotransmitter concentration, a phenomenon whereby Ca^{2+} in the growth cone seems to play a crucial role. Besides detecting neurotransmitter molecules, growth cones are also capable of releasing them (Young and Poo 1983), a characteristic they share with the presynaptic terminal.

Neurite outgrowth, growth cone motility, shape and direction of outgrowth are also regulated by trophic factors such as NGF (e.g. Jacobson 1991). Applied electric fields, too, influence nerve growth, with respect both to branching (McCaig 1990a) and to the rate of elongation (McCaig 1990b). Nitric oxide (NO), an endogenously produced free-radical gas, which has been implicated as an intercellular messenger subserving long-term potentiation (LTP) (see section 5), also reversibly causes growth cone collapse and neurite retraction (Hess *et al* 1993). It may play a role in activity-dependent processes, as its production

depends upon Ca^{2+} (Schuman and Madison 1994b).

Taken together, these data show that the growth cone is a structure capable of integrating multiple cues, a process comparable to the classical integration of multiple synaptic inputs (Kater and Guthrie 1990).

4.2. Calcium

The morphological responses to neurotransmitters and electrical activity are most likely mediated by changes in $[Ca^{2+}]_i$ (Cohan *et al* 1987, Kater *et al* 1988, Mattson 1988, Kater *et al* 1990, Kater and Guthrie 1990, Kater and Mills 1991). Depolarization leads to Ca^{2+} entry, and a number of aspects of growth cone motility, such as assembly and disassembly of microtubules, are thought to be regulated by Ca^{2+}. In connection with these observations, the Ca^{2+} theory of neurite outgrowth has been proposed (e.g. Kater *et al* 1988, 1990, Kater and Guthrie 1990), which states that low $[Ca^{2+}]_i$ at the growth cone stimulates outgrowth, higher concentrations cause a cessation of outgrowth, and still higher concentrations lead to regression of neurites. Since outgrowth is also blocked if $[Ca^{2+}]_i$ is too low, there appears to be an optimal level. Differences in reaction among cells and neurites may be attributable to differing Ca^{2+} regulating characteristics.

4.3. Morphology and polarity

Electrical activity determines not only whether or not a neuron grows out, but also the morphology of its growth cones. In addition to blocking outgrowth, electrical stimulation decreases the number of filopodia and causes the lamellipodium to retract (Cohan and Kater 1986). Since the form of the growth cone can affect branching (also see van Veen and van Pelt 1992), electrical activity and neurotransmitters can regulate the branching pattern of the dendritic and axonal tree (Brewer and Cotman 1989, Kater *et al* 1990). During normal development, neurotransmitters released by afferent axons could alter the dendritic morphology of growing neurons. For example, in a system where hippocampal pyramidal cells are grown on a mat of axons from entorhinal cortex, glutamate released from entorhinal axons inhibits dendritic outgrowth in pyramidal cells (Mattson 1988).

Neurotransmitters may orient the site of axon formation (Mattson *et al* 1990). Early in development, hippocampal neurons extend several short neurites (Dotti et al 1988) which, at the time they first appear, cannot be specified as either axonal or dendritic. The length of these initial neurites appears to determine which one will become the axon. In experiments in which the axon is transected at various distances from the soma, the longest neurite remaining after transection usually becomes the axon, regardless of its previously being an axon or dendrite (Goslin and Banker 1989). A similar process may be involved during normal development: when one of the neurites exceeds, by chance, the others by a critical length, it becomes specified as the axon (Goslin and Banker 1989). Neurotransmitters, electrical activity and other factors that regulate neurite length might therefore play a role in the differentiation of neurites into axons and dendrites (i.e. polarity).

The acquisition of axonal characteristics is correlated with the selective segregation of the protein GAP-43 to the growth cone of a single neurite (Goslin and Banker 1990). It may be a candidate for the regulatory protein in the conceptual model of Goslin and Banker (1990), which states that the rate of neurite elongation depends on the concentration of some protein, whose distribution is in turn determined by length. The transport of GAP-43 to the growth cone is an active process and therefore largely independent of neurite length, while the return to the soma might be a diffusion process, so that, according to this hypothesis,

the growth cone of the longest neurite would receive more protein, and the neurite would grow longer still. Interestingly, GAP-43 is sensitive to changes in membrane polarization (Dekker *et al* 1989) and in Ca^{2+} levels (Aloyo *et al* 1983); GAP-43 could modulate Ca^{2+} signals in growth cones and synapses, and regulate membrane and cytoskeletal assembly (for references see Fields and Nelson 1992). Direct indications that Ca^{2+} plays a role in the formation of axon-dendrite polarity have been obtained by Mattson *et al* (1990). A *localized* influx of Ca^{2+} suppresses axon formation, in neurons that have not yet established their polarity, as well as in neurons from which the axon is transected at short distances from the soma (which causes Ca^{2+} to enter). When a Ca^{2+} gradient is present in the neuron, the axon will not form where the Ca^{2+} concentration is highest. In this way, a local encounter with neurotransmitter (or any other factor causing a local increase in Ca^{2+}) could influence the site at which an axon will be formed. It may be that a neurite becomes an axon just because it has a low $[Ca^{2+}]_i$ and therefore grows more rapidly than the other neurites (also see Mattson *et al* 1990). Indeed, $[Ca^{2+}]_i$ is lower in axons than in dendrites (Guthrie *et al* 1988).

4.4. Adhesion molecules

Adhesive and repulsive interactions among cell surface molecules (e.g. on growth cones and neurites), and among cell surface molecules and molecules in the extracellular matrix also participate in growth cone behaviour (e.g. Letourneau 1991), neurite extension, retraction and guidance, as well as in neurite fasciculation and neuronal migration (Jessell 1991). The adhesion molecules of the immunoglobulin superfamily (e.g. neural cell adhesion molecule: N-CAM), cadherins (e.g. N-cadherin), and integrins promote neurite outgrowth; N-CAM and cadherins are involved in cell-cell adhesion, whereas integrins mediate adhesion of cells to glycoproteins (e.g. fibronectin and laminin) in the extracellular matrix. Not all the actions of these molecules, however, involve adhesion (Schwab *et al* 1993). For example, myelin, tenascin and cytotactin induce an avoidance reaction or neurite retraction (e.g. Edelman and Cunningham 1990). Most of these interactions are probably established in an activity-independent fashion (Smith 1994). However, in the neuromuscular junction it has been found that blockade of activity increases the level of axonal polysialic acid (PSA: the major glycoprotein on N-CAM modulating adhesiveness) resulting in axonal defasciculation and increased branching (Landmesser *et al* 1990). Since PSA is widely expressed in the developing nervous system, this form of activity-dependent axon behaviour may be more general (Hockfield and Kalb 1993).

4.5. The mature system

Neurotransmitters are also likely to play important roles in plastic changes in neuronal morphology during adulthood (Mattson 1988). There are growing indications that the adult brain is not structurally static, but rather in a state of continual morphological change (for references see Mattson 1988, Purves *et al* 1986). This is to be contrasted to the view that neural changes are encoded in functional alterations of synaptic networks that are anatomically fixed (see Purves and Voyvodic 1987). For example, dendrites of individual neurons in the superior cervical ganglion of young adult mice are, when followed over intervals of up to three months, subject to continual change: some branches retract, others elongate, while still others appear to be newly formed (Purves *et al* 1986). This implies that the synaptic connections made onto these cells must also undergo substantial rearrangements. The dendritic tree of pyramidal cells in the visual cortex of adult rats changes in response

to changes in environmental conditions (Uylings *et al* 1978). The dendritic extent per neuron in the human cortex may increase steadily through old age (Beull and Coleman 1979, Coleman and Flood 1986); it has been interpreted as a compensatory response to neuronal death (Curcio *et al* 1982, Coleman and Flood 1986).

Polarity in mature neurons displays a surprising degree of plasticity. Axotomy or deafferentation leads to profound changes in polarity, and membranes that normally are postsynaptic can form presynaptic specializations (for references see Craig and Banker 1994). Mechanisms involved in the specification of polarity thus continue to operate in adulthood (Craig and Banker 1994). Alterations in these mechanisms may contribute to the pathology of some neurological diseases. The reorganization of the microtubule system appears to be an important pathological feature of Alzheimer's disease (for references see Craig and Banker 1994). Neuronal damage and death in Alzheimer's disease may result from excessive rises in $[Ca^{2+}]_i$ (Mattson 1992, Mattson *et al* 1993)

To summarize, electrical activity and neurotransmitters influence neurite outgrowth and growth cone behaviour in a variety of ways. These influences are not only important during development, but probably also provide mechanisms for neural plasticity in adulthood (Kater and Guthrie 1990).

4.6. Models

Hentschel and Fine (1994a, b) have demonstrated, using models of isolated, single cells, that growth under the control of diffusible factors such as Ca^{2+} can lead to the emergence of dendritic forms from initially spherical cells. Local outgrowth and retraction of the cell membrane are taken to depend upon the local concentration of Ca^{2+} close to the internal surface of the membrane:

$$V(s) = aC(s)^{\alpha} - bC(s)^{\beta} \tag{3}$$

where $V(s)$ is the growth velocity normal to the surface at point s, $C(s)$ is the submembrane Ca^{2+} concentration at that point, a and b are the rate constants for outgrowth and retraction, respectively, and α and β reflect the cooperativety of the dependence on Ca^{2+} (set at 1 and 2, respectively); equation (3) is a phenomenological description of the theory of Kater *et al* in that the outgrowth rate increases as the Ca^{2+} concentration rises to some optimum value, above which it decreases and even becomes negative at still higher levels. The local Ca^{2+} concentration results from influx and active extrusion. At spontaneously occurring convexities in the membrane, the local concentration will become larger than at concavities, because of the larger surface to volume ratio. These protrusions of the membrane will not decay because of the existence of a positive feedback loop: Ca^{2+} influx increases with increased submembrane Ca^{2+} concentrations, as a consequence of the presence of voltage-sensitive Ca^{2+} channels and the influence of Ca^{2+} on the membrane potential. This leads, if the growth rate has a positive dependence upon the Ca^{2+} concentration, to continued outgrowth and branching. The development in the model resembles that of living neurons: outgrowth starts with broad and irregular as well as with short and fine extensions of the membrane (lamellipodia and filopodia, respectively) followed by the emergence of distinct processes (neurites) which spontaneously form enlargements at the top (growth cones). The extension of these processes is often punctuated by periods of retraction. Growth under reduced electrical excitability (which affects the Ca^{2+} permeability) results in longer, thinner neurites. Similar changes are seen in cultured cerebellar Purkinje cells when electrical activity is blocked by TTX (Schilling *et al* 1991). Increasing the (voltage-independent)

Ca^{2+} permeability leads to more compact dendrites with broader growth cones.

In the model of Hentschel and Fine, the effects of cytoskeleton elements such as microtubules, which form a rigid, continuous internal core within the neurite, are not explicitly taken into account. In van Veen and van Pelt (1994), neurite elongation is described as resulting from polymerization of microtubules, with a constant production of tubulin at the soma and a diffusion-based transport to the growth cone, where polymerization takes place with a tubulin concentration-dependent assembly rate and a fixed disassembly rate. This leads to a constant elongation rate in a cell with a single neurite. When more neurites are present, also transient or complete retraction of segments can occur if assembly/disassembly rate constants differ among the neurites. In large trees, the maximal number of sustainable terminal segments is positively related to the production rate of tubulin. Although not implemented in the model, the (dis)assembly rate is dependent upon Ca^{2+} (for references see van Veen and van Pelt 1994), as is the morphology of the growth cone (see section 4.3). The latter affects branching events (see van Veen and van Pelt 1992), the occurrence of which is probably random in time: a growth model which assumes that a tree grows via a sequence of random branching events (one at a time) is sufficient to explain the observed variance in dendritic trees (van Pelt *et al* 1992).

A neuron does not grow in isolation but, rather, in interaction with its environment (including, of course, other cells). Electrical activity resulting from synaptic interactions can, in both models, modulate dendritic outgrowth via Ca^{2+} influx elicited by depolarization. We have made a start at unravelling the possible implications for neuronal morphology and network development of electrically interacting cells whose outgrowth depends on their electrical activity (van Ooyen and van Pelt 1993, 1994a,b,c). The electrical activity is governed by the shunting model (e.g. Carpenter 1989), which for a purely excitatory network becomes:

$$\frac{dX_i}{dT} = -X_i + (1 - X_i)\sum_{j}^{N} W_{ij}F(X_j) \tag{4}$$

where X_i is the membrane potential, $F(X_j)$ is the mean firing rate, which depends sigmoidally on the membrane potential, W_{ij} is the connection strength between neuron i and j ($W_{ij} \geqslant 0$), and N is the total numbers of neurons. Neurons reside on a two-dimensional surface, and are initially disconnected. Growing neurons are modelled as expanding circular areas ('neuritic fields', as yet without distinguishing axons from dendrites). When two such fields overlap, W between the cells is proportional to the area of overlap. The growth of the radius (R) of each field depends on the firing rate of the neuron:

$$\frac{dR_i}{dt} = \rho\left[1 - \frac{2}{1 + \exp((\epsilon - F(x_i))/\beta)}\right] \tag{5}$$

where ϵ is the firing-rate at which $dR_i/dt = 0$, ρ is the rate of outgrowth, and β determines the non-linearity. Depending on $F(X_i)$, a neuritic field will grow out ($F(X_i) < \epsilon$), retract ($F(X_i) > \epsilon$) or remain constant ($F(X_i) = \epsilon$). This is a phenomenological description of the theory of Kater *et al* (see section 4.2) to the effect that the neuron's electrical activity, via Ca^{2+}, affects its outgrowth (excluding that low levels of activity can also block outgrowth). Note, that connection strength is not directly modelled but is a function of neuritic field size, and that, when a field expands, the connection strengths to other cells increase simultaneously.

Several interesting properties arise as the result of interactions among outgrowth, excitation and inhibition:

Overshoot. A general feature of nervous system development is that virtually all elements show an initial overproduction (so-called overshoot phenomena; for references see van Ooyen and van Pelt 1994a). In both purely excitatory and mixed networks, we found such a transient overproduction with respect to connection strength. For a given connectivity W in a purely excitatory network, the equilibrium points are solutions of (see equation (4))

$$0 = -X_i + (1 - X_i) \sum_j^N W_{ij} F(X_j) \qquad \forall i. \tag{6}$$

If the variations in X_i are small (relative to $\bar{X}$, the average membrane potential of the network), the average connection strength $\bar{W}$ can be written as a function of $\bar{X}$:

$$\bar{W} = \frac{\bar{X}}{(1 - \bar{X})F(\bar{X})} \qquad 0 \leqslant \bar{X} < 1 \tag{7}$$

which gives the equilibrium manifold of $\bar{X}$ ($\mathrm{d}\bar{X}/\mathrm{d}T = 0$) as depending on $\bar{W}$ (figure 1). The presence of this hysteresis loop underlies the emergence of overshoot (see figure 1), and hinges upon the firing-rate function having some form of threshold along with low, but non-zero values for sub-threshold membrane potentials (also see Pakdaman *et al* 1994). With respect to the development of activity and connectivity, the model shows similarities with developing *in vitro* cultures of dissociated cells: an initial phase of neurite outgrowth and synapse formation while activity is low, a rather abrupt onset of network activity when the synapse density reaches a critical value, followed by a phase of neurite retraction (Purkinje cells in cerebellar cultures: Schilling *et al* 1991) and/or elimination of synapses (cerebral cortex cells: van Huizen *et al* 1985, 1987, van Huizen 1986).

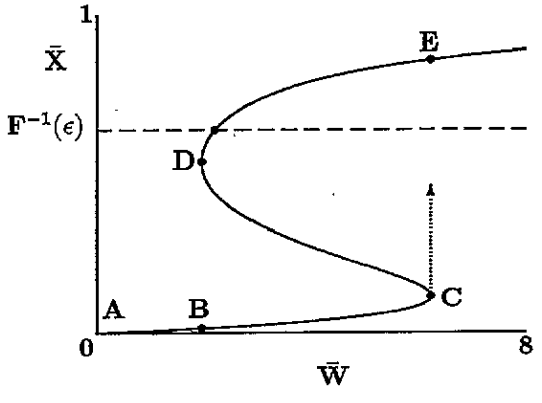

Figure 1. Hysteresis. Equilibrium manifold of $\bar{X}$ ($\mathrm{d}\bar{X}/\mathrm{d}T = 0$) as depending on $\bar{W}$ ($\bar{W} = \frac{1}{N}\sum_{i,j}^{N} W_{ij}$), according to equation (7) (states on CD are unstable with respect to $\bar{X}$, the others are stable). At the intersection point with the line $\bar{X} = F^{-1}(\epsilon)$ (F^{-1} is the inverse of F), $\bar{W}$ remains constant; above and below that line, it decreases and increases, respectively (see equation (5)). Connectivity is quasi-stationary on the time scale of membrane potential dynamics, and, starting at A, $\bar{X}$ will follow the branch ABC, until it reaches C, where it jumps to the upper branch, thus exhibiting a transition from quiescent to activated state. If the equilibrium point is on DE, $\bar{W}$ decreases again, and a developing network has to go through a phase in which $\bar{W}$ is higher than in the final situation, thus exhibiting a transient overshoot in $\bar{W}$. An intersection point on CD results in regular oscillations that follow the path ABCEDBCEDBC....

Oscillations. For some values of ϵ, the model generates sustained oscillations in overall activity and connectivity (see figure 1). Networks in which the cells have different ϵ values

exhibit complex patterns: the oscillations of the cells can differ in frequency, phase and amplitude (Van Ooyen and van Pelt 1994c).

In the following we consider networks in which ϵ is the same for all cells and in the range that does not cause oscillations.

'Critical period'. Networks with inhibition in which activity is blocked, thus inducing a high $\bar{W}$, do not necessarily decrease $\bar{W}$ after the block has been removed: when the average $F(X) < \epsilon$ due to inhibition, $\bar{W}$ will increase still further. If the time that the network spent under electrical silence is longer than a certain critical period (and $\bar{W}$ larger than a certain value), $\bar{W}$ can no longer decrease.

Each cell in the model seeks to maintain its set-point of electrical activity ($F(X) = \epsilon$) by means of adjusting the size of its neuritic field. This homeostatic principle leads to the following properties:

Compensatory sprouting. Excitatory cell death in the model will be accompanied by an increased neuritic field of the surviving neurons. In human cortex the dendritic extent per neuron increases steadily through old age (Beull and Coleman 1979, Coleman and Flood 1986). This has been interpreted as a compensatory response to neuronal death (Curcio *et al* 1982, Coleman and Flood 1986).

Network size. In excitatory networks with a low synaptic strength, cells develop into a single interconnected network, whereas a high synaptic strength yields loosely connected sub-networks (van Ooyen and van Pelt 1994a). Inhibitory cells increase the degree of connectivity, and, by inducing outgrowth, can help to selectively connect sub-networks.

Neuritic field size. Cells surrounded by many others will become small, whereas isolated cells must grow large fields to contact sufficient cells (figure 2(*c*)). In mixed networks, the neuritic field of an inhibitory cell tends to become smaller than that of an excitatory cell, even though their growth properties are identical. To receive sufficient excitation, a cell connected to an inhibitory cell must grow a larger field than does one that is not inhibited. An inhibitory cell can therefore remain small because it will become surrounded by large excitatory cells (figure 2(*a, b, d, e*)). These in turn will also be surrounded by relatively small cells, and so on, thus giving rise to a characteristic distribution of cell sizes.

Distribution of inhibitory cells. When inhibitory cells are able to contact each other, they are electrically inhibited but their outgrowth will become stimulated. In this way, not only the number of inhibitory cells is important but also their distribution.

Differences among cells. Local variations in cell density and number of inhibitory cells generate a great variability among individual cells, with respect to their neuritic field size at equilibrium, and to the developmental course of field size and firing behaviour.

To summarize, neurotransmitters and electrical activity, by means of their effect on neurite outgrowth, have considerable potential for controlling the development of neuronal form and network circuitry in assemblies of interacting cells.

5. Synapses

In addition to activity-dependent changes in neuronal circuitry that are based on morphological alterations, the efficacy of synaptic transmission in existing connections can be modulated by electrical activity. Hebb (1949) has proposed that coinciding pre- and

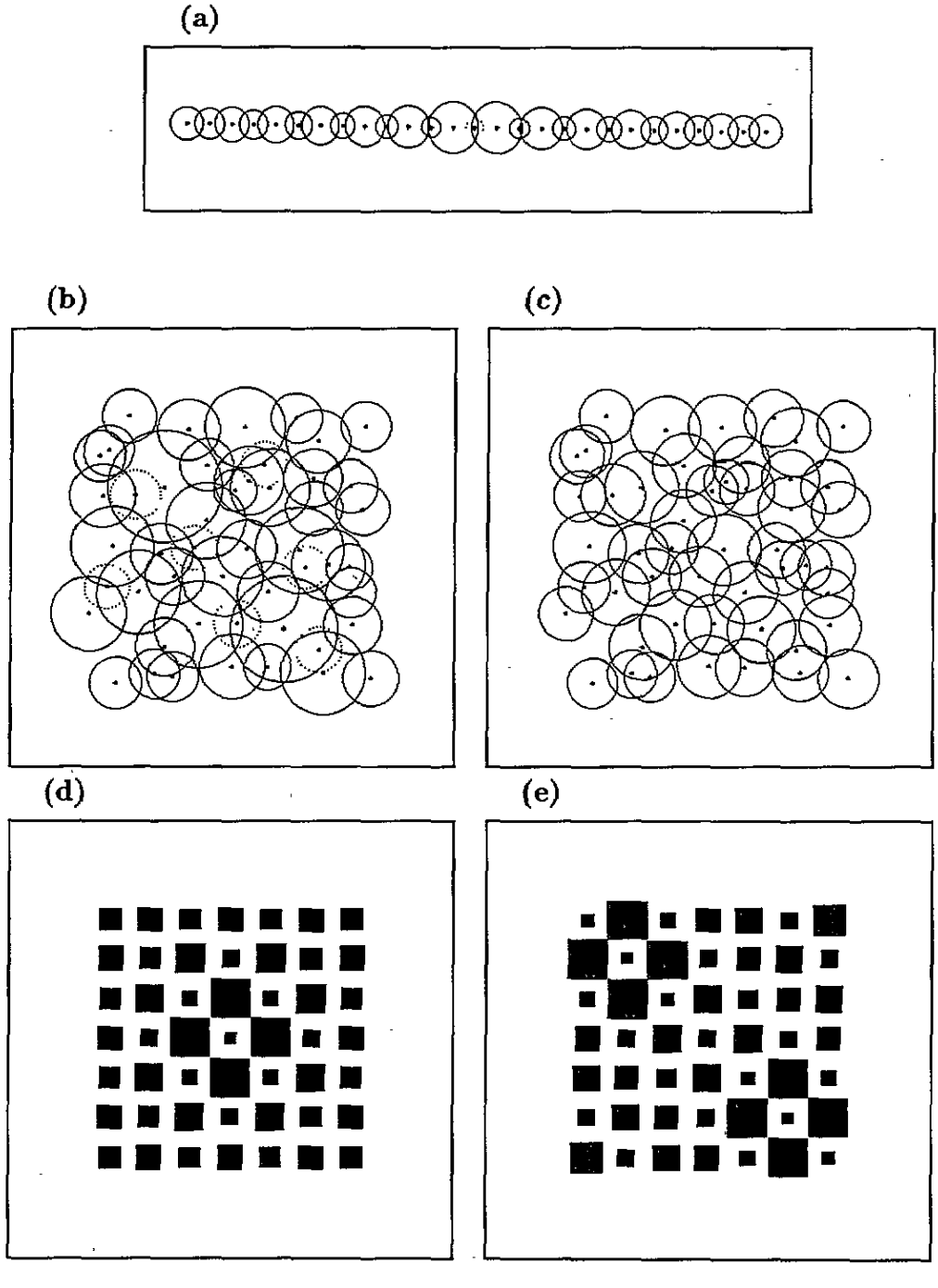

Figure 2. Neuritic fields. Torus boundary conditions. (*a*) String of excitatory cells with one inhibitory cell in the middle (dashed line). (*b*) Mixed network. Dashed line indicates inhibitory cell. (*c*) Same placing of cells as in (*b*) but all former inhibitory cells are now excitatory. (*d*) Cells on grid positions. Diameter of square is proportional to area of neuritic field. Scaled to maximum area. The small cell in the middle (surrounded by large cells) is inhibitory. (*e*) Two inhibitory cells (the small ones surrounded by large cells).

postsynaptic activity leads to changes in synaptic strength. In most neural network models some form of Hebbian learning is used (see e.g. Brown *et al* 1990). Synaptic mechanisms resembling Hebbian learning (i.e. long-term synaptic potentiation or LTP) are found in the hippocampus, and probably in many other areas. The Hebbian properties of LTP derive from the properties of the NMDA glutamate receptor and its associated Ca^{2+} channel: Ca^{2+} influx requires the coincidence of receptor activation by presynaptically released glutamate and depolarization of the postsynaptic membrane to expel Mg^{2+} that normally blocks the channel at resting potential. If LTP involves a presynaptic increase in neurotransmitter release, some retrograde signal from post- to presynaptic neuron is necessary. Diffusible messengers such as arachidonic acid, nitric oxide and carbon monoxide have been implicated (Hawkins *et al* 1993, Schuman and Madison 1994b). As such signals can diffuse widely, not only the synapses where LTP is induced, but also those of nearby neurons would be strengthened. Indeed, when LTP is triggered in a single synapse by simultaneously stimulating both the pre- and postsynaptic neuron, synapses on neighbouring neurons are strengthened as well (Bonhoeffer *et al* 1989, Schuman and Madison 1994a). Thus, LTP may not be as specific as had previously been thought (Barinaga 1994) which may have important consequences for learning and memory (also see Montague *et al* 1991).

Synaptogenesis and elimination of synapses are controlled by electrical activity (e.g. Purves and Lichtman 1980, Constantine-Paton 1990, Shatz 1990). For further information on synaptic plasticity, the reader is referred to, for example, Fields and Nelson (1992) and references therein. Many models of activity-dependent development deal with the emergence of ocular dominance columns (e.g. Von der Malsburg 1979, Swindale 1980, Miller *et al* 1989, Obermayer *et al* 1990, Goodhill and Willshaw 1990).

6. Glial cells

The central nervous system is composed of an intimately associated network of neurons and astrocytes (a type of glial cells). Although glial cells outnumber neurons, relatively little attention has been paid to their function in development and information processing. Only recently have studies suggested that their function may not be limited to the rather passive role of providing structural and trophic support. Astrocytes possess functional neurotransmitter receptors, and hence are potentially capable of monitoring neuronal activity. They can also directly influence neuronal activity (Nedergaard 1994) and may be involved in non-vesicular release of neurotransmitters (Attwell *et al* 1993). Müller (1992) gives a review of the evidence for glial participation in activity-dependent plasticity.

7. Discussion

Many seemingly unrelated processes in the development of the nervous system interact through their dependence on electrical and neurotransmitter mediated signals (in many cases with Ca^{2+} as underlying messenger) (also see Harris 1981). This is of importance for development, but also for learning and memory in the mature state (see e.g. Stryker 1990), as many of these processes remain operative in the adult brain. Activity-dependent plasticity operates on multiple levels of specificity, ranging from single connections to whole cells, i.e. from synapses, populations of synapses (see section 5), neurites and branching patterns to intrinsic neuronal properties and cell death. Electrical activity (fast dynamics) changes neuronal form, function and connectivity also on multiple time scales (slow dynamics): from minutes (e.g. modulating channels), hours (e.g. number and effectiveness of receptors)

to days or weeks (e.g. gene expression and neurite outgrowth) and persistently (neuronal differentiation). Thus, in contrast to conventional neural network models in which the structure and elements are fixed and only the parameters of the model (e.g. connection strength) can change, the nervous system is a more truly variable system in which the properties of the constituting elements (e.g. morphology and electrical characteristics) as well as their number and interactions are subject to change (also see Hogeweg and Hesper 1986). This provides possible mechanisms for learning beyond changes in synaptic strength.

A generic connectionist model is a graph consisting of nodes (e.g. neurons) and edges or links (e.g. synaptic connections) between them (Farmer 1990). Learning in neural network models occurs via changes in connection strength in such a way that all the connections to a given node can be modified independently ('edge learning'). This is fundamentally different in connectionist models of the immune system (B-cell immune networks, e.g. De Boer and Perelson, 1991), where the only means of modifying connection strength is by changing a node parameter (i.e. lymphocyte concentration; lymphocyte types are here the nodes of the network), so that all the connection strengths to a given node change simultaneously ('node learning'). However, as we have seen, many activity-dependent properties in neurons also seem to operate on the node level, or on levels intermediate between node and edge (also see Stuart and Sakmann (1994) who suggest that propagation of somatic action potentials into the dendritic tree may be important for changes in synaptic strength - that is, on a node basis). This suggests that some form of node learning may also be important for the functioning of neural networks (also see Abbott *et al* 1993), although as yet most models have individual neurons that do not adaptively participate in the learning process (but see references in section 3, and so-called weightless neural networks, e.g. Aleksander 1991; also see Finkel and Edelman (1985), who have a node rule to modify the amount of neurotransmitter release: all the terminals of the presynaptic neuron are influenced simultaneously).

The feedback mechanisms in a neuron (e.g. regulation of receptor number and sensitivity, neurite outgrowth) seem to contribute to the homeostasis of neuronal activity (in contrast to Hebbian synaptic potentiation, which acts to modify activity) or, more generally, to the optimization of some locally defined condition. Are neurons essentially pursuing their own goals, and must learning and memory be viewed as emerging from many neurons simultaneously striving to support their own needs? (Klopf 1982). Since no agreement exists upon what constitutes information processing in neural cells (Kohonen 1992) and many neuronal properties seem to have no place in the existing neural network models, it may be worthwhile to pursue fundamentally different models (e.g. adaptive neurons, node learning). In this, we might do well to allow ourselves to be inspired by the many developmental mechanisms that are still operative in the adult brain.

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