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CHAPTER 7

Competition in neurite outgrowth and the development of nerve connections

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Abstract: During the development of the nervous system, neurons form their characteristic morphologies and become assembled into synaptically connected networks. In both neuronal morphogenesis and the development of nerve connections, competition plays an important role. Although the notion of competition is commonly used in neurobiology, there is little understanding of the nature of the competitive process and the underlying molecular and cellular mechanisms. In this chapter, we review a model of competition between outgrowing neurites, as well as various models of competition that have been proposed for the refinement of connections that takes place in the development of the neuromuscular and visual systems. We describe in detail a model that links competition in the development of nerve connections with the underlying actions and biochemistry of neurotrophic factors.

Introduction

During the development of the nervous system, neurons form their characteristic morphologies and become assembled into synaptically connected networks. In many of the developmental phases that can be distinguished, competition plays an important role.

Axonal and dendritic morphogenesis

Neurons start growing out by projecting many broad, sheet-like extensions, called lamellipodia, which subsequently condense into a number of small, undifferentiated neurites of approximately equal length (Dotti et al., 1988). Eventually, one of the neurites (usually the longest) increases its growth rate — while at the same time the growth rate of the remaining neurites is reduced — and differentiates into an axon. All the neurites have the potential to develop into the axon (Dotti and Banker, 1987; Goslin and Banker, 1989; Bradke and Dotti, 2000a). In experiments in which the axon is transected at various distances from the soma, the longest neurite remaining after transaction usually becomes the axon, regardless of whether it was previously an axon or a dendrite (Goslin and Banker, 1989). Thus, axonal differentiation appears to be a competitive process in which the growth rate of the longest neurite is accelerated at the expense of all the other neurites, whose growth become inhibited (Dotti et al., 1988; Goslin and Banker, 1990; Bradke and Dotti, 2000b). These slower growing neurites become differentiated as dendrites.

The development of dendritic morphology proceeds by way of the dynamic behavior of growth cones — specialized structures at the terminal ends of outgrowing dendrites that mediate elongation and branching. Competition between dendrites is expected to occur with respect to elongation: the proteins upon which elongation depend (e.g., tubulin and microtubule-associated proteins) are produced in the soma and need to be divided between all the growing dendrites of a neuron. Competition could

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explain the observation that sometimes only one of the daughter growth cones propagate after branching, while the other stays dormant for a long time (Bray, 1973).

Axon guidance and synapse formation

Axons need to migrate to their targets, and one of the mechanisms by which this is achieved is by the diffusion of chemoattractant molecules from the target through the extracellular space (Tessier-Lavigne and Goodman, 1996). This creates a gradient of increasing concentration, which the growth cone at the tip of a migrating axon can sense and follow (Goodhill, 1997). Once the axons have arrived at their targets, they form synaptic connections by transforming their growth cones into synapses. This phase of synapse formation is followed by a phase of refinement, which includes both the formation of new synapses and the elimination of already existing synapses (Lohof et al., 1996). This process often involves withdrawal of some axons and thus a reduction in the number of axons innervating an individual target cell. In some cases, withdrawal of axons continues until the target is innervated by just a single axon, whereas in most other cases several innervating axons remain (Brown et al., 1976; Purves and Lichtman, 1985; Jansen and Fladby, 1990). Competition between innervating axons for target-derived neurotrophic factors is thought to be involved in the withdrawal of axons (Purves, 1988; see ''Neurotrophic factors'' through ''Visual System''). The cells that act as targets for the innervating axons release limited amounts of neurotrophic factors, which are taken up by the axons via specific receptors at their terminals and which affect the growth and branching of the axons (e.g., Cohen-Cory and Fraser, 1995; Funakoshi et al., 1995; Alsina et al., 2001).

To gain a real understanding of nervous system development and function, experimental work needs to be complemented by theoretical analysis and computer simulation. Even for biological systems in which all the components are known, computational models are necessary to explore and understand how the components interact to make the system work and how phenomena at one level of organization arise from processes at lower levels of organization. To understand how competition arises from the underlying molecular and cellular processes, we therefore need the guidance of appropriate mathematical and simulation models.

In this chapter, we review (i) a model of neurite elongation and competition between outgrowing neurites; and (ii) models of competition between innervating axons in the refinement of connections. For a model on the role of competition in axonal differentiation, see Samuels et al. (1996).

Competition in neurite elongation

Most models of the development of dendritic morphology describe neurite elongation and branching in a stochastic manner (e.g., Van Pelt et al., 1997; for a recent review, see Van Pelt et al. (2003)). Although these models are very successful at generating the observed variation in dendritic branching patterns, they do not clarify how the biological mechanisms underlying neurite outgrowth are involved. In this section, we review a model that studies the consequences of tubulin dynamics for neurite outgrowth.

The length of a neurite is determined by its microtubules, which are long polymers of tubulin present throughout the entire neurite. Tubulin is produced in the cell body and is transported down the neurite to the growth cone. Polymerization of tubulin, which occurs mainly in the growth cone, elongates the microtubules and thus the neurite. The rates of tubulin assembly and disassembly are influenced by the actin cytoskeleton in the growth cone, by microtubule associated proteins (MAPs), and by (activity-dependent) changes in the intracellular calcium concentration (Gelfand and Bershadsky, 1991; Schilstra et al., 1991; Sánchez et al., 2000).

In Van Veen and Van Pelt (1994) and Van Ooyen et al. (2001), the consequences for neurite outgrowth of the interactions between tubulin transport and (dis)assembly are explored. A simple compartmental model of a single neuron with n different neurites is considered. There is one compartment for the cell body and one compartment for the growth cone of each neurite i ($i = 1, \ldots, n$). The time-dependent changes in neurite lengths L_i, the concentration C_0

of tubulin in the cell body, and the concentrations C_i of tubulin in the growth cones are modeled. Tubulin is produced in the cell body at rate s and is transported into the growth cones of the different neurites by diffusion and active transport, with diffusion constant D and rate constant f, respectively. At the growth cones, concentration-dependent assembly of tubulin into microtubules takes place, which elongates the trailing neurite. Disassembly of microtubules into tubulin causes the neurite to retract. The rate constants a_i and b_i of assembly and disassembly, respectively, are taken slightly different in different neurites. These differences could arise as a result of differences between neurites in, for example, electrical activity (which affects the concentration of intracellular calcium), in the actin cytoskeleton of the growth cones, or in the state or concentration of MAPs. Finally, tubulin is also subjected to degradation, with rate constant g, both in the cell body and in the growth cone. Thus, the rates of change in L_i, C_i, and C_0 become

$$\frac{dL_i}{dt} = a_i C_i - b_i \tag{1}$$

$$\frac{dC_i}{dt} = b_i - a_i C_i + \frac{D}{L_i + k}(C_0 - C_i) + fC_0 - gC_i \tag{2}$$

$$\frac{dC_0}{dt} = s - \sum_{i=1}^{n} \frac{D}{L_i + k}(C_0 - C_i) - \sum_{i=1}^{n} fC_0 - gC_0 \tag{3}$$

where k is the distance between the centers of the cell body and growth cone compartment when $L_i = 0$.

The analysis of the model shows that small differences between neurites in their rate constants of assembly and/or disassembly (e.g., as a result of differences between neurites in intracellular calcium concentration) lead to competition between growing neurites of the same neuron. This competition emerges as a result of the interactions between tubulin-mediated neurite elongation and transport of tubulin. If one of the neurites has a higher rate constant for tubulin assembly and/or a lower rate of disassembly, it can slow down (Fig. 1a) or even prevent (Fig. 1b) the outgrowth of the other neurites for a considerable period of time (i.e., they are dormant), by using up all the tubulin produced in the soma. Only after the fastest growing neurite has reached a certain length (the longer the neurite, the smaller the amount of tubulin that is transported by diffusion per unit of time) can the tubulin concentration in the growth cones of the other neurites increase, causing them to grow out. The smaller the rate of production of tubulin in the cell body, the bigger this period of dormancy.

Van Ooyen et al. (2001) showed that stopping the outgrowth of the fastest growing neurite (e.g., representing the physiological situation that a neurite has reached its target) can "awaken" the dormant growth cones, which then, after a characteristic delay, start growing out (Fig. 1c). The length of the delay is determined by the time it takes for the tubulin concentration to build up to the value where the rate

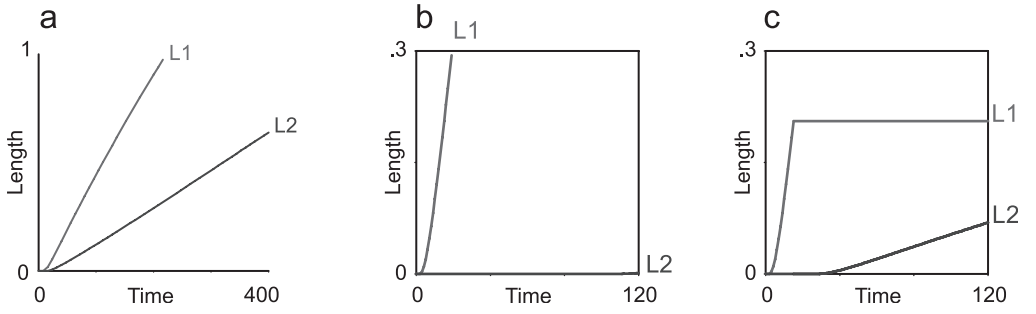

Fig. 1. Results of the compartmental model of a single neuron with two neurites. Neurite 1 has a higher rate constant for tubulin assembly. As a result, neurite 1 can slow down (a) or even prevent (b) the growth of the other neurite. Stopping the growth of neurite 1 triggers, after a time delay, the growth of the other neurite (**c**). Parameters (all units arbitrary): $b_1 = b_2 = 0.01$, $D = 0.5$, $g = 0.1$, $s = 0.07$, $f = 0$, and $k = 1$. In (a), $a_1 = 0.09$ and $a_2 = 0.06$. In (b) and (c), $a_1 = 0.3$ and $a_2 = 0.05$. (Modified from Van Ooyen et al. (2001)).

of assembly (a_iC_i) is bigger than the rate of disassembly (b_i).

The model can account for the occurrence of "dormant growth cones" (Bray, 1973), the observation that after branching only one of the daughter growth cones propagates. The prediction of the model that there should be competition between growing neurites of the same neuron has recently been confirmed experimentally (Costa et al., 2002). These findings show that (1) when one neurite stops growing out, other neurites — after a certain delay, as in the model — start growing out; and (2) when more neurites are growing out at the same time, the rate of outgrowth is smaller than when only a single neurite is growing out. To test whether this is indeed due to competition for tubulin, as our model suggests, the concentration of tubulin in growth cones should be monitored during outgrowth. The model predicts that the concentration of tubulin in growth cones that are not growing out should be below the critical value [the concentration of tubulin at which assembly (a_iC_i) just equals disassembly (b_i)].

Competition between innervating axons

The establishment and refinement of neural circuits involve both the formation of new connections and the elimination of existing connections (e.g., Lohof et al., 1996). Neurons, and other cell types, are initially innervated by more axons than they ultimately maintain into adulthood (Purves and Lichtman, 1980; Lohof et al., 1996). This is a widespread phenomenon in the developing nervous system and occurs, for example, in the development of connections between motor neurons and muscle fibers (reviewed in Jansen and Fladby, 1990; Sanes and Lichtman, 1999; Ribchester, 2001), the formation of ocular dominance columns, and the climbing fiber innervation of Purkinje cells (Crepel, 1982).

The process that reduces the amount of innervation onto a postsynaptic cell is often referred to as axonal or synaptic competition, although neither term describes the competitors adequately (Colman and Lichtman, 1992; Snider and Lichtman, 1996). Because a single axon can branch to innervate, and compete on, many postsynaptic cells simultaneously, competition is perhaps better described as occurring between axon branches rather than between axons. By further arborization, the contact between an axon branch and a postsynaptic cell can comprise several synapses or synaptic boutons, so that competition occurs not between single synapses but between groups of synapses.

Defining synaptic competition has exercised a number of authors. In discussing the neuromuscular system, Van Essen et al. (1990) gave one of the most general definitions of competition: a process in which there are multiple participants whose behavior is governed by certain rules such that one or more of the participants emerge as victors. This definition leaves open by what processes the victors arise. Based on whether or not there are interactions between the participants, Colman and Lichtman (1992) distinguished two ways by which victors can come about, leading to two types of competition:

(1) In *independent competition*, victors do not arise as a result of interactions (either direct or indirect) between the participants, but are chosen (by "judges") based on a comparison of the performance or desirable features of the participants (e.g., as in a beauty contest). In this form of competition, one participant cannot influence the performance of the other participants during the process of competition. Because axons do affect each other (see, e.g., "Neuromuscular system"), this form of competition is unlikely.

(2) In *interdependent competition*, victors emerge as a result of direct or indirect interactions between the participants, affecting their performance. Based on how the negative interactions come about, two types of interdependent competition can be distinguished (Yodzis, 1989; see Fig. 2).

(2a) In *consumptive competition*, in systems of consumers and resources, each individual consumer hinders the others solely by consuming resources that they might otherwise have consumed; in other words, consumers hinder each other because they share the same resources. In neurobiology, competition is commonly associated with this dependence on shared resources (Purves and Lichtman, 1985; Purves, 1988, 1994). In particular, it is

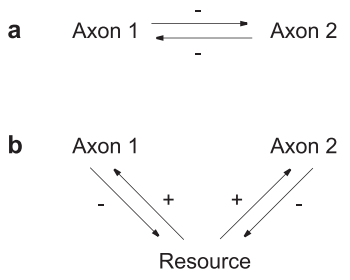

Fig. 2. (a) Interference competition. (b) Consumptive competition. See text for details. (Modified from Huisman (1997).)

believed that axons compete for target-derived neurotrophic factors (see "Neurotrophic factors" through "Visual System").

(2b) In *interference competition*, instead of hindrance through dependence on shared resources, there is direct interference between individuals: e.g., direct negative interactions, such as aggressive or toxic interactions. In axonal competition, nerve terminals could hinder each other by releasing toxins or proteases (e.g., Zoubine et al., 1996; Sanes and Lichtman, 1999).

Although the notion of competition is commonly used in neurobiology, there is little understanding of the type of competitive process or the underlying molecular mechanisms. In this chapter, we review some of the models of competition that have been proposed, both in the neuromuscular and in the visual system (for more detailed reviews, see Van Ooyen (2001) and Van Ooyen and Ribchester (2003)). We classify the models according to the different forms of (interdependent) competition. Before presenting the models, we briefly discuss neurotrophic factors — which play an important role in many models — and the development of the neuromuscular and visual system, the two systems where competition is most widely studied.

Neurotrophic factors

During an earlier stage of development, when initial synaptic contacts are made, neurotrophic factors have a well-established role in the regulation of neuronal survival (e.g., Farinas et al., 1994; Primi and Clarke, 1996; Ma et al., 1998; for a review, see Clarke, 2003). But many studies now indicate that neurotrophic factors are also involved in the later stages of development, when there is further growth and elimination of innervation (e.g., Snider and Lichtman, 1996; see further "Neuromuscular system" through "Visual System"). For example, neurotrophic factors have been shown to regulate the degree of arborization of axons (e.g., Cohen-Cory and Fraser, 1995; Funakoshi et al., 1995; Alsina et al., 2001). In addition to their decisive role in the fate of neurons and the disposition of their connections, neurotrophic factors have well-defined roles in modulating synaptic transmission (e.g., Poo, 2001).

Neuromuscular system

In adult mammals, each muscle fiber is innervated at the endplate by the axon from a single motor neuron (see Fig. 3). This state is referred to as mononeuronal or "single" innervation. However, a single motor neuron, through its axonal branches, typically contacts many muscle fibers. The motor neuron and the group of muscle fibers it innervates is referred to as the motor unit, and the number of fibers contacted by a given motor neuron is called the motor unit size. Motor neurons with higher firing thresholds — which may therefore be less frequently activated — have progressively larger motor units (size principle; Henneman, 1985).

During prenatal development, the axons of the motor neurons grow towards their target muscle, and near the muscle each axon arborizes to innervate a large number of muscle fibers. At birth, the endplate of each muscle fiber is contacted by axons from several different motor neurons, a state referred to as polyneuronal or "multiple" innervation. During the subsequent few weeks, axonal branches are removed or withdrawn until the motor endplate of each muscle fiber is taken over by the synaptic boutons derived from a single motor axon collateral (Brown et al., 1976; Betz et al., 1979; Keller-Peck et al., 2001a). Thus, during the elimination of polyneuronal innervation, the number and size of the synaptic boutons of the winning axon increase, while the synaptic boutons of the losing axon are either gradually retracted or "nipped" off from their parent neuron (Keller-Peck et al., 2001b). With

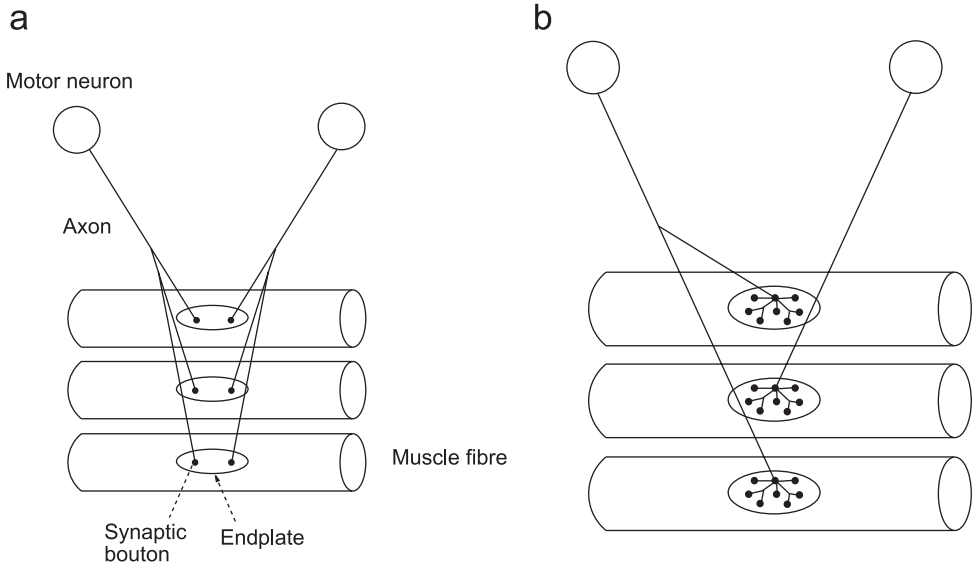

Fig. 3. The development of connections between motor neurons and muscle fibers. (a) At birth, each fiber is innervated by axons from several different neurons. (b) In adulthood, each fiber is innervated by the axon from a single neuron. (From Van Ooyen (2001).)

contemporaneous addition and loss of synaptic boutons, the synaptic area on the endplate actually increases during the elimination of polyneuronal innervation (Sanes and Lichtman, 1999).

The elimination of polyneuronal innervation appears to be a competitive process. Following removal of some motor axons at birth, the average size of the remaining motor units after elimination of polyneuronal innervation is larger than normal (Thompson and Jansen, 1977; Betz et al., 1979; Fladby and Jansen, 1987). Axons may compete for neurotrophic factors released by muscles (Snider and Lichtman, 1996). Several factors produced by muscles are capable of retarding elimination of polyneuronal elimination (English and Schwartz, 1995; Kwon and Gurney, 1996; Jordan, 1996). For example, transgenic mice overexpressing the neurotrophic factor GDNF show extensive polyneuronal innervation at a relatively late postnatal stage (Nguyen et al., 1998). Mononeuronal innervation is eventually established, but about two weeks later than normal.

Electrical activity influences competition, but does not appear to be decisive (for reviews, see Van Ooyen, 2001; Ribchester, 2001). When motor endplates are made completely silent by blocking nerve conduction and synaptic transmission during nerve regeneration, inactive terminals appear capable of competitively displacing other — active or inactive — terminals (Ribchester, 1988, 1993; Costanzo et al., 2000).

Visual system

In the adult visual system, the different layers of the lateral geniculate nucleus (LGN) receive axons from either the left or the right eye. Like the different layers in the LGN, columns of cells in layer IV of the visual cortex (to which the axons from the LGN project) respond preferentially to input from either the left or the right eye (ocular dominance). The formation of eye-specific layers and columns requires anatomical remodeling of axonal arbors during development. Initially, the retinal axons from the two eyes overlap extensively within the LGN. Similarly, the arbors of geniculate axons are initially evenly distributed within layer IV. Just as in the elimination of polyneuronal innervation in the neuromuscular system, the refinement of connections to the LGN

and cortex involves both the retraction of axonal side branches that project to the wrong region and the elaboration of branches that project to the correct region, and the total number of synapses onto a postsynaptic cell actually increases during the period in which elimination takes place.

As in the neuromuscular system, the formation of eyespecific layers and columns may involve competition between axons or axon branches for target-derived neurotrophic factors. Continuous infusion of the neurotrophins NT-4/5 or BDNF in the cat visual cortex prevents the formation of ocular dominance columns (Cabelli et al., 1995). In monocular deprivation experiments in cat and rat, excess neurotrophic factor mitigates or abolishes the relative increase of the ocular dominance stripes associated with the open eye (e.g., Yan et al., 1996).

Many studies indicate that spontaneous activity in the retina influences the formation of ocular dominance columns (e.g., Feller, 2002; Wong and Lichtman, 2003). This is, however, inconsistent with the finding that eye removal in ferrets early in visual development does not prevent the development of ocular dominance columns (Crowley and Katz, 1999). Crowley and Katz (2000) showed that, in ferret, ocular dominance columns appear much earlier during development than previously thought, and that these early columns are unaffected by imbalances in retinal activity.

Review of models

Models in which competition plays an important role have been proposed for both the neuromuscular and the visual system. In the neuromuscular system, the main aim is to explain the change from polyneuronal to mononeural innervation of muscle fibers. In the visual system, the main aim is to explain the development of columnar organization of synaptic connectivity, especially ocular dominance. The presentation of the various models is structured on the basis of how competition is implemented: through synaptic normalization and modified Hebbian learning rules, dependence on shared resources, or interference. For each model, we identify its underlying positive feedback loop; this is what enables one or more competitors to outcompete the others.

Competition through synaptic normalization and modified Hebbian learning rules

Many models enforce competition rather than implement its putative underlying mechanisms (for a review, see Miller (1996)). That is, these models explore the consequences of imposing certain "rules" that are introduced to ensure competition between axons. These models usually describe changes in synaptic strength (physiological plasticity) rather than changes in axonal arborization (anatomical plasticity). To see how competition can be enforced, consider n inputs with synaptic strengths $w_i(t)$ $(i = 1, \ldots, n)$ impinging on a given postsynaptic cell at time t. Simple Hebbian rules for the change $\Delta w_i(t)$ in synaptic strength in time interval Δt state that the synaptic strength should grow in proportion to the product of the postsynaptic activity level $y(t)$ and the presynaptic activity level $x_i(t)$ of the ith input:

$$\Delta w_i(t) \propto y(t)\, x_i \Delta t \tag{4}$$

According to Eq. (4), only increases in synaptic strength can take place, and if the activity level of two inputs (e.g., two eyes) both are sufficient to achieve potentiation, then both pathways are strongly potentiated (and no ocular dominance can occur). To achieve that when the synaptic strength of one input grows, the strengths of the other one shrinks (i.e., competition), $\sum_i^n w_i(t)$ should be kept constant (synaptic normalization). At each time interval Δt following a phase of Hebbian learning, in which $w_i(t + \Delta t) = w_i(t) + \Delta w_i(t)$, the new synaptic strengths are forced to satisfy the normalization constraint, either by multiplying each synaptic strength with a certain amount (multiplicative normalization; Willshaw and Von der Malsburg, 1976) or by subtracting from each synaptic strength a certain amount (subtractive normalization; Miller et al., 1989). The final outcome of development may differ depending on whether multiplicative or subtractive normalization is used (Miller and MacKay, 1994). Multiplicative, but not subtractive, normalization prevents the development of ocular dominance if

there are positive between-eye correlations (which are likely to be present when the two eyes are open).

Another approach for achieving competition is to modify Eq. (4) such that both increases in synaptic strength (long term potentiation, or LTP) and decreases in synaptic strength (long term depression, or LTD) can take place. Assume that $y(t)$ and $x_i(t)$ must be above some thresholds θ_y and θ_x, respectively, to achieve LTP, and otherwise yield LTD (Miller, 1996); i.e.,

$$\Delta w_i(t) \propto [\, y(t) - \theta_y][x_i(t) - \theta_x]\Delta t \qquad (5)$$

A stable mechanism for ensuring that when some synaptic strengths increase, others must correspondingly decrease is to make one of the thresholds variable. If θ_x^i increases sufficiently as $y(t)$ or $w_i(t)$ (or both) increases, conservation of synaptic strength can be achieved (Miller, 1996). Similarly, if θ_y increases faster than linearly with the average postsynaptic activity, then the synaptic strengths will adjust to keep the postsynaptic activity near a set point value (Bienenstock et al., 1982).

Yet another mechanism that can balance synaptic strengths is based on (experimentally observed) spike-timing dependent plasticity (STDP; reviewed in Bi and Poo (2001)). Presynaptic action potentials that precede postsynaptic spikes strengthen a synapse, whereas presynaptic action potentials that follow postsynaptic spikes weaken it. Subject to a limit on the strengths of individual synapses, STDP keeps the total synaptic input to the neuron roughly constant, independent of the presynaptic firing rates (Song et al., 2000).

Consumptive competition: competition for target-derived resource

Keeping the total synaptic strength onto a postsynaptic cell constant (synaptic normalization) is a biologically unrealistic way of modeling competition during development. In both the neuromuscular and the visual system, the total number of synapses onto a postsynaptic cell increases during competition as the winning axons elaborate their branches and the losing axons retract branches (see "Visual system" and "Review of models"). In models that implement consumptive competition, competition between input connections does not have to be enforced but comes about naturally through their dependence on the same target-derived resource. There are two ways in which this can be modeled:

(1) In *constant resource models*, the total amount of postsynaptic resource is kept constant. The total amount of resource is the amount taken up by the input connections (i.e., the total synaptic strength if resource is "converted" into synaptic strength) plus the amount left at the target. Thus, the total synaptic strength is not kept constant and can increase during development when resource becomes partitioned among the input connections.
(2) In *variable resource models*, even the total amount of resource is not constrained to remain constant. In these models, there is continuous production of neurotrophin and continuous uptake or binding of neurotrophin. Continuous uptake or binding ("consumption") of neurotrophin is needed to sustain the axonal arbors and synapses; this view of the way in which the resource exerts its effects is closer to the biology of neurotrophins.

Constant amount of resource

Bennett and Robinson (1989) and Rasmussen and Willshaw (1993). The dual constraint model combines competition for a postsynaptic resource with competition for a presynaptic resource. Each muscle fiber has a postsynaptic resource B, and each motor neuron has a presynaptic resource A, which is located in its cell soma and in all its terminals. The total amount A_0 of presynaptic substance in each motor neuron is fixed. The total amount B_0 of postsynaptic substance in each muscle fiber is also fixed. In the synaptic cleft, a reversible reaction takes place between A and B to produce binding complex C. The rate of the forward reaction that produces C depends on the amounts of pre- and postsynaptic resource, but also on the amount of C itself. This incorporates a positive feedback that is needed to achieve single innervation. The justification given by Bennett and Robinson (1989) for including this

positive feedback is that electrical activity in the nerve terminal could produce electromigration of molecules B in the endplate — so that larger terminals will attract more molecules.

Single innervation is a stable state of the model, and there is an upper limit — proportional to A_0/B_0 — on the number of terminals that can be supported by each motor neuron (Rasmussen and Willshaw, 1993). So if the initial amount of polyneuronal innervation is larger than this limit, then terminals will withdraw, even in the absence of competition (''intrinsic withdrawal''; Fladby and Jansen, 1987). Van Ooyen and Willshaw (1999a) showed that polyneuronal states can also be stable and can coexist with single innervation states.

Weak points of the dual constraint model are that (1) it does not make clear the identity of the pre- and postsynaptic resource; (2) a stronger biological justification for the positive feedback loops is needed; and (3) without electrical activity (i.e., no dependence on C in the forward reaction), no competitive elimination of connections takes place, which is not in agreement with recent experimental findings (see ''Neuromuscular system'').

Harris et al. (1997, 2000). This model of the development of ocular dominance columns incorporates a combination of Hebbian synaptic modification and activity-driven competition for neurotrophins. In the model, each cortical cell has a fixed pool of neurotrophin to distribute over its input connections. The higher the connection strength, the faster the uptake of neurotrophin. Connection strength increases due to Hebbian LTP at a rate that depends on the amount of neurotrophin taken up (together with the previous assumption, this creates a positive feedback loop). Connection strength decreases due to heterosynaptic LTD. The model shows that ocular dominance columns develop normally — even with positive inte-reye correlations in activity (compare ''Competition through synaptic normalization and modified Hebbian learning rules'') — when available neurotrophin is below a critical amount and that column development is prevented when excess neurotrophin is added. A criticism of the model is that it incorporates only physiological plasticity, while anatomical plasticity is (mainly) involved in the formation of ocular dominance columns.

Variable amount of resource

Elliott and Shadbolt (1998a, b). This model of the development of the visual system explicitly describes anatomical plasticity and implements a role of electrical activity, both in the release and in the uptake of neurotrophin. The model incorporates a positive feedback: neurotrophin increases the number of synapses, while more synapses mean a higher uptake of neurotrophin. The model permits the formation of ocular dominance columns, even in the presence of positively correlated interocular images (compare ''Competition through synaptic normalization and modified Hebbian learning rules''). A high level of neurotrophin released in an activity-independent manner prevents the formation of ocular dominance columns. A criticism of the model is that electrical activity directly increases the uptake of neurotrophin, rather than by increasing the number of neurotrophin receptors (Birren et al., 1992; Salin et al., 1995) or the number of synapses (Ramakers et al., 1998).

Jeanprêtre et al. (1996). This model implements neurotrophic signalling in a fully dynamical way, incorporating production, degradation, and binding of neurotrophin. In the model, there is a single target that releases neurotrophin and at which there are a number of innervating axons. Each axon has a variable called ''axonal vigor,'' which represents its ability to take up neurotrophin and which is proportional to its total number of neurotrophin receptors. The rate of change of vigor depends on the vigor itself (i.e., positive feedback) and increases with the fraction of receptors occupied by neurotrophin, over and above some threshold (the threshold is a constant that represents the value of the axonal vigor that gives zero growth). The system will approach a stable equilibrium point in which a single axon — the one with the lowest threshold — survives. Criticisms of the model are that (1) the rate of change of axonal vigor (including the positive feedback) is postulated but not explicitly derived from underlying biological mechanisms; and (2) the thresholds do not emerge from the underlying dynamics but need to be assumed.

Van Ooyen and Willshaw (1999b). Independently from Jeanprêtre et al. (1996), Van Ooyen and Willshaw (1999b) proposed a model of competition

that implements neurotrophic signaling in a fully dynamical way and that does not have the above-mentioned drawbacks. For a detailed description of the model, see ''Detailed description of Van Ooyen and Willshaw's model.''

Interference competition

In the following models, all of which describe the neuromuscular system, interference competition involves direct negative interactions: nerve terminals are destroyed or disconnected by the punitive effects of other axons.

Willshaw (1981). Based on a proposal by O'Brien et al. (1978), Willshaw (1981) assumed that each terminal injects into its endplate a degrading signal, at a rate proportional to its own ''survival strength'' (the size of the terminal is thought to be proportional to this strength), that reduces the survival strength of all the terminals (including itself) at that endplate. The survival strength of each terminal also increases, at a rate proportional to that strength (positive feedback). Further, the total amount of survival strength supported by each motor neuron is kept constant, i.e., synaptic normalization of the total strength of the output connections.

The model can account for (1) the elimination of polyneuronal innervation; (2) the decrease in spread of motor unit size; (3) the competitive advantage of the terminals of smaller motor units over those of larger ones (Brown and Ironton, 1978); and (4) the increase in motor unit size after neonatal partial denervation (Fladby and Jansen, 1987).

Criticisms of the model are that (1) the positive feedback is not accounted for biologically; and (2) it uses synaptic normalization of output connections, which implies that not all fibers will show an increase in their total input survival strength during development (see ''Neuromuscular system'').

Nguyen and Lichtman (1996). This model, which was not given in mathematical terms, has many similarities with Willshaw's (1981) model, except that there is an explicit role for electrical activity. In the model, each active synapse, by activating its underlying acetylcholine receptors (AChRs) in the endplate, generates two postsynaptic signals: (1) a punishment signal that spreads over short distances and eliminates AChRs of neighboring synaptic sites — which instigates the removal of the overlying nerve terminal; and (2) a more locally confined protection signal that neutralizes the punishment signal. The strength of both signals is proportional to the level of activity. Thus, when postsynaptic sites at the same endplate have a different level of activity, the less active ones will generate a weaker protection signal (and a weaker punishment signal) than the more active ones, so that the less active ones lose more AChRs. The loss of AChRs further reduces local postsynaptic activity, leading to an even weaker protection signal, more loss of AChRs, and eventually the removal of the overlying nerve terminal. This positive feedback loop can bring about the removal of all nerve terminals but the most active one. When all the postsynaptic sites are equally active or when they are all inactive, all nerve terminals will be maintained.

A criticism of this model is that it relies heavily on electrical activity while recent experimental results suggest that activity might not play such a decisive role (see ''Neuromuscular system''). Barber and Lichtman (1999) put the ideas of Nguyen and Lichtman (1996) into mathematical terms, although the punishment and protection signals are not explicitly modeled. In addition to accounting for the elimination of polyneuronal innervation, this model is also able to reproduce the size principle (see ''Neuromuscular system'').

Detailed description of Van Ooyen and Willshaw's Model

Van Ooyen and Willshaw (1999b) proposed a model of (consumptive) competition that implements neurotrophic signalling in a fully dynamical way. Unlike Jeanprêtre et al. (1996), they did not need to assume a priori thresholds. Important variables in the model are the total number of neurotrophin receptors that each axon has and the concentration of neurotrophin in the extracellular space. In the model, there is positive feedback loop between the axon's number of receptors and amount of bound neurotrophin. Unlike in Jeanprêtre et al. (1996), this positive feedback — which enables one or more axons to outcompete the

others — was derived directly from underlying biological mechanisms. Following binding to receptor, neurotrophins can increase the terminal arborization of an axon (see "Neurotrophic factors") and therefore the axon's number of synapses. Because neurotrophin receptors are located on synapses, increasing the number of synapses means increasing the axon's total number of receptors. Thus, the more receptors an axon has, the more neurotrophin it will bind, which further increases its number of receptors, so that it can bind even more neurotrophin — at the expense of the other axons.

Instead of increasing the terminal arborization of an axon, neurotrophins might increase the axon's total number of receptors by increasing the size of synapses (e.g., Garofalo et al., 1992) or by upregulating the density of receptors (e.g., Holtzman et al., 1992).

Description of the model

A single target cell is considered at which there are n innervating axons each from a different neuron (Fig. 4). Neurotrophin is released by the target into the extracellular space at a (constant) rate σ and is removed by degradation with rate constant δ. In addition, at each axon i, neurotrophin is bound to receptors with association and dissociation constants $k_{a,i}$ and $k_{d,i}$, respectively. Bound neurotrophin (the neurotrophin-receptor complex) is also degraded, with rate constant ρ_i. Finally, unoccupied receptor is inserted into each axon at rate ϕ_i and is degraded with rate constant γ_i. Thus, the rates of change in the total number R_i of unoccupied receptors on axon i, the total number C_i of neurotrophin–receptor complexes on axon i, and the extracellular concentration L of neurotrophin are

$$\frac{dC_i}{dt} = (k_{a,i}LR_i - k_{d,i}C_i) - \rho_i C_i \tag{6}$$

$$\frac{dR_i}{dt} = \phi_i - \gamma_i R_i - (k_{a,i}LR_i - k_{d,i}C_i) \tag{7}$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n}(k_{a,i}LR_i - k_{d,i}C_i)/v \tag{8}$$

where v is the volume of the extracellular space. Axons that will end up with no neurotrophin ($C_i = 0$) are assumed to have withdrawn.

The biological effects of neurotrophins — all of which, as explained above, can lead to an axon getting a higher total number of receptors — are triggered by a signaling cascade that is activated upon binding of neurotrophin to receptor (Bothwell, 1995). In order for the total number of receptors to increase in response to neurotrophin, the rate ϕ_i of insertion of receptors must be an increasing function, f_i (called growth function), of C_i. To take into account that axonal growth is relatively slow ϕ_i lags behind $f_i(C_i)$, with a lag given by

$$\tau\frac{d\phi_i}{dt} = f_i(C_i) - \phi_i, \tag{9}$$

where the time constant τ for growth is of the order of days. Setting immediately $\phi_i = f_i(C_i)$ does not change the main results. Van Ooyen and Willshaw (1999b) studied different classes of growth functions, all derived from the general growth function

$$f_i(C_i) = \frac{\alpha_i C_i^m}{K_i^m + C_i^m}. \tag{10}$$

Depending on the values of m and K, the growth function is a linear function (class I: $m = 1$ and K_i much greater than C_i) or a saturating function: a Michaelis-Menten function (class II: $m = 1$ and K_i not much greater than C_i) or a Hill function (Class III: $m = 2$). Within each class, the specific values of the parameters α_i and K_i, as well as those of the other parameters, will typically differ between the innervating axons — e.g., as a result of differences in activity or other differences. For example, increased presynaptic electrical activity can increase the axon's total number of receptors (by upregulation: Birren et al., 1992; Salin et al., 1995; or by stimulating axonal branching: Ramakers et al., 1998), which implies that, for example, α_i is increased or γ_i is decreased.

Results of the model

For class I, starting with any number of axons, elimination of axons takes place until a single axon remains (single innervation), *regardless of the rate σ of*

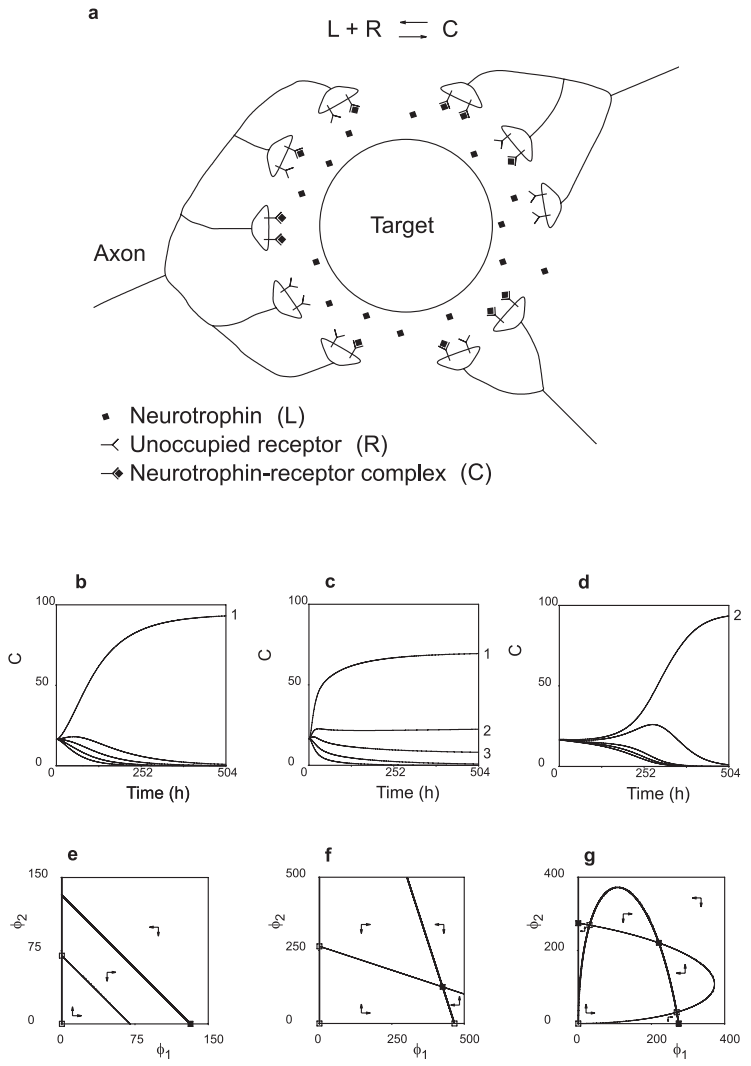

Fig. 4. The model of Van Ooyen and Willshaw (see ''Detailed description of Van Ooyen and Willshaw's model''). (a) Target cell with three innervating axons. The target releases neurotrophin, which binds to neurotrophin receptors at the axon terminals. For three different classes of growth functions, (b)–(d) show the development of innervation for a system of five innervating axons, where each axon has a different competitive strength β_i. Figures (e)–(g) show the nullcline pictures for a system of two innervating axons [the variables R_i, C_i, $i=1,2$ and L are set at quasisteady state; in (e) and (f), $\beta_1 > \beta_2$; in (g), $\beta_1=\beta_2$]. Variable C is expressed in number of molecules, variable ϕ in number of molecules h^{-1}. Axons that at the end of the competitive process have no neurotrophin ($C_i=0$; equivalent to $\phi_i=0$) are assumed to have withdrawn. In (e)–(g), the bold lines are the nullclines of ϕ_1 and the light lines are the nullclines of ϕ_2 (the x and y-axes are also nullclines of ϕ_2 and ϕ_1, respectively). Intersection points of these lines are the equilibrium points. A filled square indicates a stable equilibrium point, an open square an unstable equilibrium point. Vectors indicate direction of change. (b) Class I. Elimination of axons takes place until the axon with the highest value of the competitive strength β_i survives. (c) Class II. For the parameter settings used, several axons survive. (d) Class III. Dependence on initial conditions: although axon one has the highest value of the competitive strength, axon two survives because its initial value of ϕ_i is sufficiently higher than that of axon one. (e) Class I. The nullclines do not intersect at a point where both axons coexist. (f) Class II. The nullclines intersect at a point where both axons coexist. For a sufficiently lower rate of release of neurotrophin, for example, the nullclines would not intersect, and only one axon would survive. (g) Class III. There is a stable equilibrium point where both axons coexist, as well as stable equilibrium points where either axon is present. For a sufficiently higher value of K_i, for example, the stable equilibrium point where both axons coexist would disappear. (From Van Ooyen (2001).)

release of neurotrophin (see Fig. 4). For class I, the number of surviving axons cannot be increased by increasing σ because an increased amount of neurotrophin will become again limiting as a consequence of the resulting increase in the size of the winning axon — which shows that the widely held belief that competition is the result of resources being produced in limited amounts is too simplistic. The axon that survives is the one with the highest value of the quantity $\beta_i \equiv (k_{a,i}(\alpha_i/K_i - \rho_i))/(\gamma_i(k_{d,i} + \rho_i))$, which is interpreted as the axon's competitive strength. If the growth function is a saturating function — classes II and III — more than one axon may survive (multiple innervation); and then the higher the rate σ of release of neurotrophin, the more axons survive. For class III, stable equilibria of single and multiple innervation can coexist, and which of these will be reached in any specific situation depends on the initial conditions. For classes I and II, there is just one stable equilibrium point for any set of parameter values and therefore no dependence on initial conditions. For all classes, axons with a high competitive strength β_i survive, and the activity dependence of β_i (e.g., via α_i) means that these are the most active ones provided that the variation due to other factors does not predominate.

The model can account for the following:

- The development of both single and multiple innervation.
- The coexistence of stable states of single and multiple innervation (class III) in skeletal muscle. This can explain, in denervation experiments, the occurrence of persistent multiple innervation after reinnervation and recovery from prolonged nerve conduction block (Barry and Ribchester, 1995; Van Ooyen, 2001).
- Increasing the amount of target-derived neurotrophin delays the development of single innervation (class I) (see "Neuromuscular system") or increases the number of surviving axons (classes II and III) (e.g., in epidermis; Albers et al., 1994).
- Decreasing the difference in competitive strengths between the different axons (which could be brought about by blocking their activity) delays the development of single innervation or increases the number of surviving axons (the latter only for classes II and III).
- Both presynaptic and postsynaptic activity may be influential but are not decisive (Ribchester, 1988; Costanzo et al., 2000). For competition to occur, it is not necessary that there is presynaptic activity: differences in the axons' competitive strengths β_i can arise also as a result of differences in other factors than activity. It is also not necessary that there is postsynaptic activity, or activity-dependent release of neurotrophin (compare Snider and Lichtman (1996)).
- For class III, an interesting observation is that the coexistence of several stable equilibria for class III implies that an axon that is removed from a multiply innervated target may not necessarily be able to reinnervate the target ("regenerate") when replaced with a low number of neurotrophin receptors (Fig. 5).

Influence of the spatial dimension of the extracellular space

Van Ooyen and Willshaw (1999b) assumed that the concentration of neurotrophin is uniform across the extracellular space, so that all axons "sense" the same concentration. This is a good assumption if all the axons are close together on the target structure, as, for example, at the endplate on muscle fibers (Balice-Gordon et al., 1993). However, if the target structure is large (e.g., a large dendritic tree), the spatial dimension of the extracelluar space should be taken into account. Modeling local release of neurotrophin along the target and diffusion of neurotrophin in the extracellular space, Van Ooyen and Willshaw (2000) showed that distance between axons mitigates competition, so that if the axons are sufficiently far apart on the target, they can coexist (i.e., even under conditions — e.g., a class I growth function — where they cannot coexist with a uniform extracellular space).

Axons responding to more than one type of neurotrophin

Van Ooyen and Willshaw (2000) considered a single target that releases two types of neurotrophin and at which there are two types of innervating axons

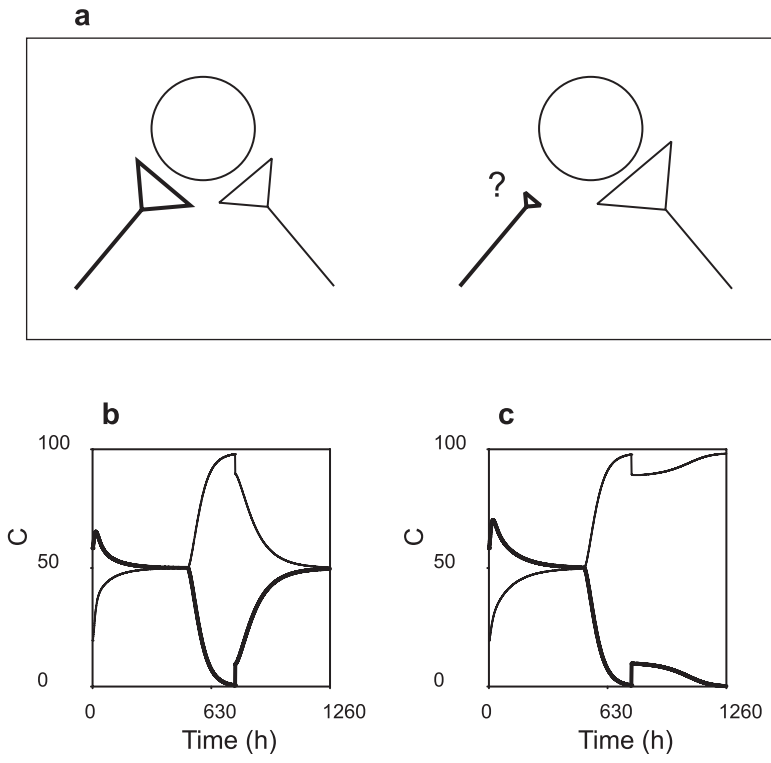

Fig. 5. Removal of an axon from a multiply innervated target and subsequent replacement (a), for class II (b) and class III (c). At $t = 504$ h, axon 1 (bold line) is removed. At $t = 756$ h, axon 1 is replaced (with initial conditions $\phi_1 = 30$, $R_1 = \phi_1/\gamma$, and $C_i = 0$). Only for class II can the replaced axon survive. For class III, in order for the replaced axon to survive, a much higher initial value of ϕ_1 would be required. For notations, see Fig. 4. (Modified from Van Ooyen (2001).)

(see Fig. 6). Each axon type can respond to both neurotrophin types. The following situations were examined. (1) Individual axons have only a single type of neurotrophin receptor, but this can bind to more than one type of neurotrophin. Different types of axons have different receptor types. (2) Individual axons have more than one type of neurotrophin receptor, and each receptor type binds exclusively to one type of neurotrophin. Different types of axons have these receptor types in different proportions. The results show that, for both (1) and (2), different types of axons can coexist (i.e., even under conditions — e.g., a class I growth function — where they cannot coexist with a single type of neurotrophin) if they respond to the neurotrophins with sufficiently different "affinities." For (1), this means that each type of receptor should bind preferentially, but not necessarily exclusively, to one type of neurotrophin. For (2), this means that the receptor content between different types of axons should be sufficiently different. By having axons respond with different affinities to more than one type of neurotrophin, the model can account for competitive exclusion among axons of one type while at the same time there is coexistence with axons of another type innervating the same target (Figs. 6b, d). This occurs, for example, on Purkinje cells, where climbing fibers compete with each other during development until only a single one remains, which coexists with parallel fibers innervating the same Purkinje cell (Crepel, 1982).

Discussion

We have shown that competition between growing neurites can emerge as a result of the interactions

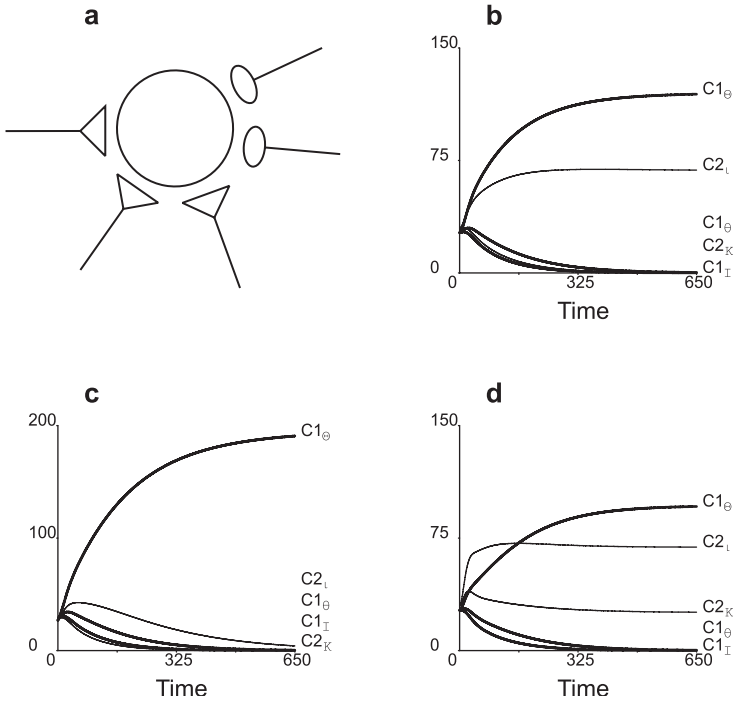

Fig. 6. System of five innervating axons (a), where the target releases two types of neurotrophin, $L1$ and $L2$. Axons 1, 2, and 3 have receptor type $R1$ (which binds preferentially, but not exclusively, to $L1$), and axons 4 and 5 have receptor type $R2$ (which binds preferentially, but not exclusively, to $L2$). $C1_i$ ($C2_i$) is the total number of $R1$–$L1$ and $R1$–$L2$ ($R2$–$L1$ and $R2$–$L2$) complexes for axon i. Except in (d), all axons have a class I growth function. Time is in h. For other notations, see Fig. 4. When the receptor specificity is high, there is competitive exclusion within each group, but coexistence between groups (b). When the receptor specificity is low, only one axon overall survives (c). In (d), the second group of axons has a class II growth function, the first group class I. Axon 1, 4, and 5 survive. (Modified from Van Ooyen and Willshaw (2000).)

between the transport of tubulin and the tubulin-mediated elongation of neurites. The model can account for "dormant growth cones" and for recent experimental findings in tissue culture showing competitive effects between outgrowing neurites (Costa et al., 2002). These results are also relevant for understanding the formation of nerve connections, because it shows that changes in the growth of a subset of a neuron's neurites (e.g., as a result of changes in electrical activity, or as a result of neurites finding their targets) can affect the growth of the neuron's other neurites (see, e.g., Gan and Macagno (1997)).

At their target, axons from different neurons compete for target-derived resources. The model by Van Ooyen and Willshaw (1999b) of axonal competition suggests that the regulation of axonal growth by neurotrophins is crucial to the competitive process in the development, maintenance, and regeneration of nerve connections. Among the many axonal features that change during growth in response to neurotrophin (degree of arborization and consequently the number of axon terminals; size of terminals; and density of receptors) the consequent change in the axon's total number of neurotrophin receptors, changing its capacity for removing neurotrophin, is what drives the competition. The form of the dose–response curve between neurotrophin and axonal arborization (or better, the total amount of neurotrophin receptors) determines what patterns of innervation can develop and what the capacity for axon regeneration will be.

In the model by Van Ooyen and Willshaw (1999b), axons have only a single target, whereas in the neuromuscular system, for example, each axon innervates a number of targets. This means that

there will also be competition between branches of the same axon for neurotrophin receptors, which are produced in the soma. Kasthuri and Lichtman (2003) showed that fate of axon branches is strictly related to the identity of the axons with which they compete. When two neurons co-innervate multiple target cells, the losing axon branches in each contest belong to the same neuron and are at nearly the same stage of withdrawal. An interesting question is whether this observation can be accounted for by competition between axon branches for neurotrophin receptors.

Furthermore, the effects of electrical activity, such as the activity-dependent release of neurotrophin, have not yet been studied explicitly in Van Ooyen and Willshaw's model.

In general, a challenge for future modeling studies is to investigate whether explicitly implementing the putative underlying mechanisms of competition makes a difference in models in which competition is involved. For example, Harris et al. (1997) and Elliott and Shadbolt (1998b) showed that implementing the putative underlying mechansism of activity-dependent competition permits the formation of ocular dominance columns in the presence of positively correlated interocular images. Ocular dominance columns do not occur under these conditions when competition is enforced using multiplicative normalization.

Further challenges for modeling competition include (1) accounting for the observation, in the visual system as well as in the neuromuscular system, that activity is influential but may not be decisive; and (2) combining physiological plasticity (changes in synaptic strength) with anatomical plasticity (changes in axonal arborization) (see Elliott et al., 2001).

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