Competition in the Development of Nerve Connections

10

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During development, neurons and other target cells are often initially innervated by more axons than ultimately remain into adulthood. The process that leads to elimination of connections is referred to as axonal or synaptic competition. This chapter reviews the models of competition that have been proposed for the neuromuscular and the visual system, and describes in detail a model that links competition in the development of nerve connections with the underlying actions and biochemistry of neurotrophic factors.

10.1 Competition

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). A well-studied case of this form of remodeling is the withdrawal of connections that takes place during development. 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; see also section 10.2.2), the formation of ocular dominance columns (see chapter 12 and section 10.2.3), 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). Since 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 involve several 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 so that one or more of the participants emerge as victors. This definition leaves open the processes by which 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 others during

the competition. Lotteries are another example of this form of competition. Here the criteria for selection are random, and there is nothing a single ticket holder can do to influence the outcome. In axonal competition, this would mean that the axons innervating the same postsynaptic cell do not affect each other and that the postsynaptic cell would decide, on the basis of some performance or random criteria, which axon(s) would win. Since axons do affect each other (see section 10.2), and synapse elimination is nonrandom, 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. This is the type of competition that is considered in population biology, where two species of organisms are said to compete if they exert negative effects on the growth of each other's population. Ribchester (1992) and Ribchester and Barry (1994) extended this definition to neurobiology; they defined competition as the negative effects that one neuron or its synapses have on others. Based on how the negative interactions come about, two types of interdependent competition can be distinguished (Yodzis, 1989; see also figure 10.1):

• In *consumptive competition*, in systems of consumers and resources, each 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 believed that axons compete for target-derived neurotrophic factors (see section 10.2.1).

• In *interference competition*, instead of hindrance through dependence on shared resources, there is direct interference between individuals, e.g., direct

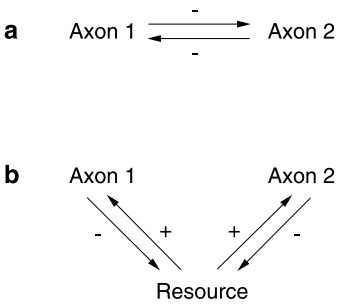

Figure 10.1
(*a*) Interference competition. (*b*) Consumptive competition. See the text for details. (Modified from Huisman, 1997.)

negative interactions, such as aggressive or toxic interactions. In axonal competition, nerve terminals could hinder each other by releasing toxins or proteases (see section 10.2.2). If some essential resource can be obtained only by occupying, more or less exclusively, some portion of space (competition for space), this is also primarily interference competition, because each consumer is seeking to monopolize a portion of space rather than to share resources (Yodzis, 1989).

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 discuss the different models of competition that have been proposed, both in the neuromuscular and in the visual system (for a more detailed review, see Van Ooyen, 2001). We classify the models according to the forms of (interdependent) competition that are distinguished in population biology (as described earlier). Before presenting the models, we briefly review the biology of neurotrophic factors—which play an important role in many models—and the development of the neuromuscular and the visual system, the two systems where competition is most widely studied.

10.2 Neurobiological Background

10.2.1 Neurotrophic Factors

During an early stage of development, when initial synaptic contacts are made, neurotrophic factors have a well-established role in the regulation of neuronal survival (see chapter 9). However, many studies now indicate that neurotrophic factors may also be involved in the later stages of development, when there is further growth and elimination of innervation (see sections 10.2.2 and 10.2.3; for a critical review, see Snider and Lichtman, 1996). 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. For instance, neurotrophins (i.e., neurotrophic factors of the NGF family, including BDNF, NT-3 and NT-4/5; Bothwell, 1995; Lewin and Barde, 1996), acting on their specific Trk receptors, may phosphorylate synapse-specific proteins and enhance transmitter release (Lohof et al., 1993). Similar effects are exerted by other neurotrophic factors, of the ciliary neurotrophic factor (CNTF) and glial cell line-derived neurotrophic factor (GDNF) classes (Ribchester et al., 1998; Stoop and Poo, 1996). It is of some interest that positive effects of neurotrophic factors on synaptic transmission and growth can be commuted to negative effects, depending on the relative levels of intracellular signaling molecules such as cyclic nucleotides (Boulanger and Poo, 1999; Poo, 2001).

10.2.2 Neuromuscular System

Adult System and Development

In adult mammals, each muscle fiber is innervated at the endplate—a discrete region near the midpoint of the muscle fiber—by the axon from a single motor neuron. This state is referred to as mononeuronal (μ) or "single" innervation (figure 10.2b). 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 (the size principle; Henneman, 1985).

During prenatal development, the axons of the motor neurons grow toward 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 (π) or "multiple" innervation (figure 10.2a). 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; Walsh and Lichtman, 2003). 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 contemporaneous addition and loss of synaptic boutons, the synaptic area on the endplate actually increases during the elimination

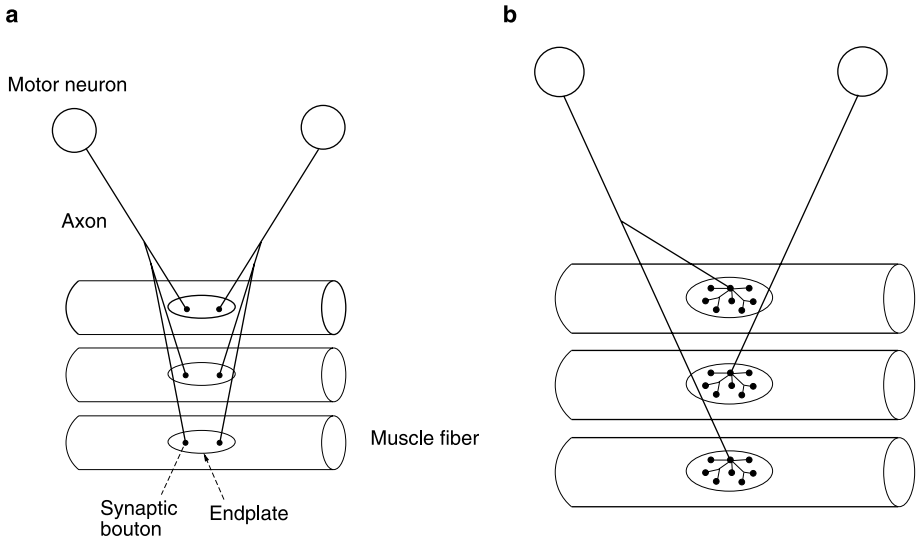

Figure 10.2
The development of connections between motor neurons and muscle fibers. (*a*) At birth, each fiber is innervated by axons from several different neurons. (*b*) In adulthood, each fiber is innervated by the axon from a single neuron. (From Van Ooyen, 2001.)

of polyneuronal innervation (Sanes and Lichtman, 1999). Motor unit sizes, as well as the range of sizes, decrease during elimination of polyneuronal innervation (Brown et al., 1976; Betz et al., 1979; Balice-Gordon and Thompson, 1988).

Competition

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). This competition for the endplate (postsynaptic competition), however, cannot explain why larger motor units decrease in size more than smaller ones (thus reducing the range of motor unit sizes) and why sometimes branches at singly innervated fibers—where there is no competition—apparently withdraw (Fladby and Jansen, 1987). This process of "intrinsic withdrawal" has not yet been observed directly, but Keller-Peck et al. (2001b) have argued that the asynchronous pattern of synapse loss observed within motor units precludes intrinsic withdrawal as an integral component of synapse elimination. It should now be possible to resolve this issue by repeating the earlier studies of Betz et al. (1979) and Fladby and Jansen (1987) using thy1-YFP transgenic mice, which have endogenously fluorescent motor axons and synapses, facilitating repeated visualization of identified neuromuscular junctions (Feng et al., 2000). If confirmed, the existence of intrinsic stimuli to synapse elimination would imply that there are also presynaptic constraints that restrict the number of axon branches each neuron can maintain.

What mediates the competition in the development of mononeuronal innervation? We discuss this for both consumptive and interference competition.

Consumptive Competition

Muscles might release diffusible neurotrophic factors for which axons compete (Snider and Lichtman, 1996). Several factors produced by muscles are capable of retarding elimination of polyneuronal elimination when applied to postnatal muscles (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 2 weeks later than normal. Exogenous administration of GDNF to neonatal muscle also delays elimination of π-junctions, but the pattern of innervation, together with the decline in sensitivity, suggested that the predominant effect of this growth factor is to stimulate or maintain nerve branch points, rather than synaptic terminals per se (Keller-Peck et al., 2001a). It remains uncertain where the receptors for GDNF are located and how their expression is regulated. However, the observation that small but significant enhancements in neurotransmitter release occur in response to low concentrations of GDNF suggests that immature synaptic terminals at least express the receptor (Ribchester et al., 1998). It is not known whether nodes of Ranvier, or other sites of neural sprouting, also express GDNF receptors.

Interference Competition: Competition for Space

Until recently, the notion that competition occurs only for space at the endplate was controversial because some observations of developing neuromuscular junctions in vivo revealed that as one terminal is withdrawn, the space it occupied is left vacant rather than being taken over by another terminal (Balice-Gordon and Lichtman, 1994). However, a takeover of existing space clearly occurs during reinnervation of partially denervated muscle (Costanzo et al., 2000). Moreover, very recent observations made by Lichtman and colleagues, utilizing transgenic thy1-YFP mice, suggest that both processes—takeover and withdrawal without takeover—occur at the same or different junctions during neonatal synaptic competition as well (Walsh and Lichtman, 2003). At present, it remains to be seen whether takeover will turn out to be the predominant mechanism, as in reinnervated muscle (Barry and Ribchester, 1995; Costanzo et al., 1999, 2000).

However, attempts to identity molecules that might mediate a spatial competition have so far been unsuccessful (Ribchester, 2001). For example, normal elimination of synapses occurs in various transgenic animals in which expression of cell surface or extracellular matrix molecules, such as neural cell adhesion molecules (N-CAMs), has been disrupted (Sanes et al., 1998). But since synapse elimination must, at some stage in the process, involve weakening of the adhesive bonds between synaptic membranes and molecules in the extracellular matrix, the notion of interference competition based on access to synaptic space should therefore still receive attention. Intraneuritic tension-adhesion mechanisms have been posited to account for morphogenesis in the brain (Van Essen, 1997), and such mechanisms may be accessible to experimental investigation at a cellular level, using the neuromuscular junction as a paradigm. Mechanical stimulation (stretch) of motor nerve endings regulates transmitter release at neuromuscular junctions, and this effect is mediated by integrins, receptors for adhesion molecules (Kashani et al., 2001). Integrins are implicated in synapse formation, growth, and specificity in *Drosophila* muscle (Beumer et al., 1999).

Interference Competition: Direct Negative Interactions

Another possibility is axon-derived or axon-stimulated release of interfering molecules. For

instance, proteases might mediate direct negative interactions between axons (Sanes and Lichtman, 1999). Many proteases and protease inhibitors are located at the neuromuscular junction (Hantai et al., 1988), and various proteases have been proposed to play a role in synapse destabilization (e.g., Zoubine et al., 1996). Highly selective proteases could also work indirectly, mediating the kind of spatial competition indicated earlier.

Role of Electrical Activity

Does the overall level of activity affect the rate of synapse elimination? Blocking activity (by interfering with input activity, synaptic transmission, or muscle activity) delays or prevents synapse elimination (Thompson et al., 1979; Brown et al., 1982; Ribchester and Taxt, 1984; Callaway and Van Essen, 1989; Barry and Ribchester, 1995), while stimulating activity accelerates synapse elimination (O'Brien et al., 1978; Thompson, 1983; Zhu and Vrbova, 1992; Vyskocil and Vroba, 1993; for a review, see Ribchester, 2001).

Do differences in the activity of innervating axons confer competitive advantages on the more active axons? Here the findings are less clear-cut. Selectively stimulating motor neurons in neonates, Ridge and Betz (1984) found that the more active axons have a competitive advantage over the less active ones, whereas Callaway et al. (1987), using selective blocking, found the opposite. Experiments in tissue culture also show opposing results (Magchielse and Meeter, 1986; Nelson et al., 1993). Based on observations that synapse elimination begins with elimination of AChRs (the postsynaptic receptors for acetylcholine, the neurotransmitter in motor neurons) and that in adults partial but not complete paralysis of the endplate leads to the elimination of the terminals overlying the silent patches, Balice-Gordon and Lichtman (1993, 1994) suggested that electrically active synapses are the stimulus for removing the AChRs underlying the less active synapses, which are then eliminated. However, 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). Thus, differences in activity are not strictly necessary for synapse elimination.

Electrical activity also seems to be insufficient for synapse elimination. Barry and Ribchester (1995) found that following recovery from chronic nerve conduction block, many reinnervated muscle fibers in partially denervated muscles retain polyneuronal innervation, in spite of the resumption of normal neuromuscular activity. Following on from this, Costanzo et al. (1999) showed that the synaptic efficacy per unit area was similar in the coinnervating inputs to the muscle fibers, whatever the relative synaptic area covered by each motor nerve terminal.

In conclusion, activity is clearly influential in synaptic competition—particularly in regard to its effects on the rate of synapse elimination—but activity does not seem to be decisive (Costanzo et al., 2000; Ribchester, 2001). To reconcile the different findings, one possibility is that activity is just one of many influences in competition. Perhaps its main influence is restricted to critical periods during the competitive process, while the actual competition is governed by other factors, e.g., neurotrophic factors, adhesion molecules, and their receptors (Costanzo et al., 2000; see also section 10.4).

10.2.3 Visual System

Adult System and Development

In the adult visual system, the different layers of the lateral geniculate nucleus (LGN) receive axons from

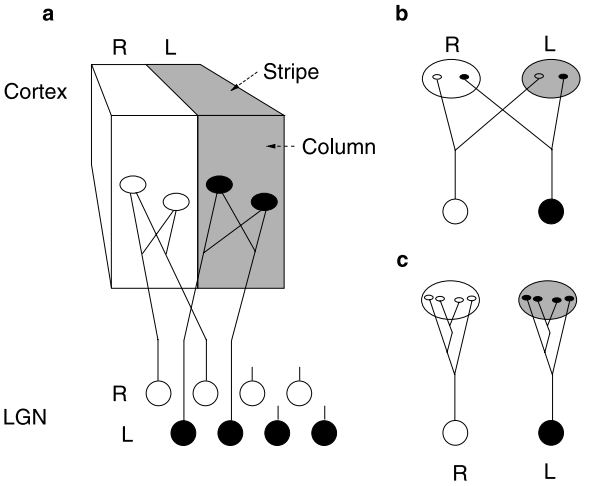

Figure 10.3
The development of ocular dominance columns. (*a*) The adult visual system. The lateral geniculate nucleus (LGN) of the thalamus is composed of two or more layers, each of which receives axons from either the left or the right eye. In the visual cortex, cells in layer IV respond preferentially to input from either the left or the right eye. (*b*) In the immature system, the arbors of the geniculate axons overlap extensively within layer IV. (*c*) During further development, remodeling of axonal arbors takes place so that each cortical cell receives axons from either the left-eye or right-eye geniculate neurons. (From Van Ooyen, 2001.)

either the left or the right eye (figure 10.3a). 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; see also chapter 12).

The formation of eye-specific layers and columns requires anatomical remodeling of axonal arbors during development (figures 10.3b and 10.3c). 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.

Competition

As in the neuromuscular system, the formation of eye-specific layers and columns might 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), presumably because the LGN axon branches fail to retract. In monocular deprivation experiments (see the following section) in cats and rats, 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; see also chapter 12).

Role of Electrical Activity

The process of segregation into eye-specific regions is influenced by neural activity, which arises not only from visual stimulation through photoreceptor activation but also from spontaneous activity in retinal ganglion cells. When all activity in both eyes of kittens is blocked by tetrodotoxin, ocular dominance columns do not form at all (Stryker and Harris, 1986). When only the visually driven activity is blocked, however, as in macaque monkeys reared in complete darkness, a normal pattern of ocular dominance columns is found (LeVay et al., 1980). In fact, in monkeys at least, ocular dominance columns are present prior to birth and eye opening (Horton and Hocking, 1996). Taken

together, these observations suggest that spontaneous activity in the retina may instruct the formation of ocular dominance columns. This is 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). Recently, Crowley and Katz (2000) showed that in ferrets, ocular dominance columns appear much earlier during development than previously thought, and that these early columns are unaffected by imbalances in retinal activity. They proposed that axon guidance cues are sufficient to initially establish columns.

Although activity might not be necessary for the initial formation of ocular dominance columns, the prevailing view is that it does play a decisive role in their later plasticity. For example, when vision through one eye is prevented by suturing the eyelids shut after birth, the stripes or patches formed by the sutured eye's input become smaller than those formed by the open eye's input (e.g., Shatz and Stryker, 1978; see also chapter 12). However, even this bastion of synaptic plasticity seems to be under renewed assault (Wickelgren, 2000; Crowley and Katz, 2000; Crair et al., 2001). In conclusion, just as activity has a role in the development of the neuromuscular system, activity is also influential in the development of the visual system, but it may not be overwhelmingly decisive.

10.3 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 here is structured on the basis of how competition is implemented: through synaptic normalization and modified Hebbian learning rules (section 10.3.1), dependence on shared resources (section 10.3.2), or interference (section 10.3.3). For each model, we identify its underlying positive feedback loop; this is what enables one or more competitors to outcompete the others. To show the differences and similarities in modeling approach, mathematical equations are given for one model of each type.

10.3.1 Competition Through Synaptic Normalization and Modified Hebbian Learning Rules

Many models—especially those of the formation of ocular dominance—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:

$$\Delta w_i(t) \propto y(t) x_i(t) \Delta t. \tag{10.1}$$

According to Eq. (10.1), only increases in synaptic strength can take place, and if the activity levels of two inputs (e.g., two eyes) are both sufficient to

achieve potentiation, then both pathways are strongly potentiated (and no ocular dominance can occur). To achieve the situation 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 by a certain amount (multiplicative normalization; Willshaw and Von der Malsburg, 1976) or by subtracting a certain amount from each synaptic strength (subtractive normalization; Miller et al., 1989). The final outcome of development may depend 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). Experimental evidence for multiplicative normalization has been found in cultures of cortical neurons (Turrigiano et al., 1998; see also chapter 8).

Another approach for achieving competition is to modify Eq. (10.1) so 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 $\gamma(t)$ and $x_i(t)$ must be above some thresholds θ_γ and θ_x, respectively, to achieve LTP, and otherwise yield LTD (Miller, 1996); i.e.,

$$\Delta w_i(t) \propto [\gamma(t) - \theta_\gamma][x_i(t) - \theta_x]\Delta t. \tag{10.2}$$

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 $\gamma(t)$ or $w_i(t)$ (or both) increases, conservation of synaptic strength can be achieved (Miller, 1996). Similarly, if θ_γ 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; see also chapter 12).

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).

10.3.2 Consumptive Competition: Competition for a Target-Derived Resource

Keeping the total synaptic strength on 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 on a postsynaptic cell increases during competition as the winning axons elaborate their branches and the losing axons retract branches (see section 10.2). 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 *fixed-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 the 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 the resource becomes partitioned among the input connections.

2. In *variable-resource models*, it is not imposed that even the total amount of resource should 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, and is also closer to other consumer–resource systems in biology; organisms need a continuous supply of food (resource) to sustain themselves.

Fixed-Resource Models

Dual Constraint Model (Bennett and Robinson, 1989; Rasmussen and Willshaw, 1993)

Based on experimental results that suggest a role for both a postsynaptic and a presynaptic resource in the development of neuromuscular connections (see section 10.2.2), the dual constraint model combines competition for both these types of resources. Each muscle fiber m has a postsynaptic resource B (in amount B_m), and each motor neuron n has a presynaptic resource A, which is located in its cell soma (in amount A_n) and in all its terminals nm (in amount A_{nm}). In the synaptic cleft, a reversible reaction takes place between A and B to produce binding complex C:

$$A_{nm} + B_m \rightleftarrows C_{nm}, \tag{10.3}$$

with

$$\frac{dC_{nm}}{dt} = \alpha A_{nm} B_m C_{nm}^{\mu} - \beta C_{nm}, \tag{10.4}$$

where α and β are rate constants. The size of the terminal is assumed to be proportional to C_{nm}. Including C_{nm}^{μ} (with $\mu > 0$) in Eq. (10.4) incorporates a positive feedback and 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.

The total amount A_0 of presynaptic substance in each motor neuron is fixed:

$$A_0 = A_n + \sum_{j=1}^{M} A_{nj} + \sum_{j=1}^{M} C_{nj}, \tag{10.5}$$

where N and M are the total numbers of neurons and muscle fibers, respectively. The amount A_{nm} is assumed to be proportional to C_{nm} (thus incorporating a second positive feedback) and A_n:

$$A_{nm} = KC_{nm}A_n, \tag{10.6}$$

where K is a constant.

The total amount B_0 of postsynaptic substance in each muscle fiber is also fixed:

$$B_0 = B_m + \sum_{i=1}^{N} C_{im}. \tag{10.7}$$

Introducing Eqs. (10.5), (10.6), and (10.7) into Eq. (10.4) gives a set of differential equations for how C_{nm} changes over time.

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; see section 10.2.2).

Polyneuronal states can also be stable and can coexist with single innervation states (Van Ooyen and Willshaw, 1999a). This offers an explanation for partial denervation experiments that show that persistent polyneuronal innervation occurs after reinnervation and recovery from prolonged nerve conduction block (see section 10.2.2), while under unblocked conditions single innervation develops (see also section 10.4).

Weak points of the dual constraint model are that (1) it does not make clear the identity of the pre- and postsynaptic resources; (2) a stronger biological justification for the positive feedback loops is needed; and (3) without electrical activity [$\mu = 0$ in Eq. (10.4)], no competitive elimination of connections takes place, which is not in agreement with recent experimental findings (see section 10.2.2).

Joseph and Willshaw (1996) and Joseph et al. (1997) gave a more specific interpretation of the dual constraint model in which A represents the protein agrin, B the acetylcholine receptor (AChR), and C aggregated AChRs. They were able to explain the results produced by focal blockade of postsynaptic AChRs (Balice-Gordon and Lichtman, 1994; see also section 10.2.2).

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 owing 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 owing to heterosynaptic LTD.

The model shows that (1) ocular dominance columns develop normally—even with positive intereye correlations in activity (compare section 10.3.1)—when the available neurotrophin is below a critical amount and (2) 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-Resource Models

Elliott and Shadbolt (1998a,b)

This model of the development of the visual system explicitly describes anatomical plasticity and incorporates a role for electrical activity, both in the release and in the uptake of neurotrophin. For the case of a single target (e.g., a cortical cell) with a number of innervating axons (e.g., from the LGN), the rate of change in the number s_i of synapses that axon i has on the target is given by

$$\frac{ds_i}{dt} = \varepsilon s_i \left[\left(T_0 + T_1 \frac{\sum_j s_j a_j}{\sum_j s_j} \right) \frac{(a + a_i)\rho_i}{\sum_j s_j (a + a_j)\rho_j} - 1 \right], \tag{10.8}$$

where ε is a rate constant, T_0 is a constant representing the activity-independent component of release of neurotrophin by the target; T_1 is a constant for the activity-dependent component; $\sum_j s_j a_j / \sum_j s_j$ is the mean activity of a synapse, where a_j is the level of activity of axon j; $(a + a_i)\rho_i$ represents the capacity of an axon to take up neurotrophin, where a is a constant for activity-independent uptake and ρ_i is the number of neurotrophin receptors per synapse. Equation (10.8) 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 section 10.3.1). 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 it is not clear why the activity-dependent release of neurotrophin is taken to depend on the mean activity of the synapse, rather than on the level of activity of the target. Also, in the model, electrical activity directly increases the uptake of neurotrophin, rather than by increasing the number of neurotrophin receptors (Salin et al., 1995; Birren et al., 1992) or the number of synapses (Ramakers et al., 1998).

Jeanprêtre et al. (1996)

Jeanprêtre et al. (1996) were the first to model neurotrophic signaling in a fully dynamical way, implementing production, degradation, and binding of neurotrophin. They considered a single target that releases neurotrophin and at which there are a number of innervating axons. In the model, 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 in 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 yields 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 in 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 the description of this model, see section 10.4.

10.3.3 Interference Competition

Competition for Space

Competition for space occurs if some essential resource can be obtained only by monopolyzing some portion of space. The resource may be space itself or it may be some immobile resource.

Van Essen et al. (1990)

This model incorporates competition for space together with the idea that the increase in size of a motor neuron terminal depends on how much ''scaffold'' is incorporated in the underlying basal lamina at the endplate. In the model, a terminal occupies a certain amount of space on the endplate and grows (as a stochastic process) by occupying more space at the expense of the size of other terminals. It is not clear whether the model can account for single innervation, because even after many iterations, a high percentage of muscle fibers remained polyneuronally innervated.

Induced-Fit Model (Ribchester and Barry, 1994)

In the induced-fit model, which was not given in mathematical terms, nerve terminals from different axons have different isoforms of an adhesion molecule, and each endplate may express a number of different complementary isoforms. Nerve terminals induce a conformational change in (or increase the expression of) the complementary adhesion molecules in the endplate so that goodness-of-fit increases. Electrical activity in a terminal accelerates the con-

formational change. The model was proposed to explain that a block in nerve conduction delays or inhibits elimination of polyneuronal innervation in partially denervated and reinnervated muscle (Taxt, 1983; Barry and Ribchester, 1994, 1995; see also section 10.2.2).

Direct Negative Interactions

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)

This is the first published formal model of the elimination of polyneuronal innervation in the neuromuscular system. 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). Furthermore, 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 section 10.2).

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 in the endplate, generates two postsynaptic signals: (1) a punishment signal that spreads over short distances and eliminates the 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 except the most active one. When all the postsynaptic sites are equally active or when they are all inactive, all nerve terminals will be maintained.

The model can account for the observation that when the AChRs of a portion of an endplate are blocked, the blocked AChRs and their directly overlying nerve terminals are eliminated only when a substantial portion remains unblocked (Balice-Gordon and Lichtman, 1994). A criticism of this model (and the next one) is that it relies heavily on electrical

activity, while recent experimental results suggest that activity might not play such a decisive role (see section 10.2.2).

Barber and Lichtman (1999)

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 their model, each synaptic area, A_{mn} for the area that neuron n makes on muscle fiber m, is subjected to two effects: (1) loss of synaptic area, in an amount E_{mn}, through the punishing effect of other axons; and (2) gain or loss of synaptic area, in an amount U_{mn}, through utilization of neuronal resources. Thus,

$$\frac{dA_{mn}}{dt} = -\alpha E_{mn} + \beta U_{mn}, \tag{10.9}$$

where α and β are rate constants.

It is assumed that axons are able to compete effectively only during asynchronous activity and that the punishing effect of an axon is proportional to the amount of neurotransmitter it releases (which in turn is proportional to the axon's terminal size at the endplate and to its mean firing rate), so that

$$E_{mn} = \sum_{i \neq n} f_i A_{mi}(1 - \tau^2 f_n f_i), \tag{10.10}$$

where f_i and f_n are the firing rates of neurons i and n, respectively; the neurons are asynchronously active during a fraction $(1 - \tau^2 f_n f_i)$ of the time, where τ is a constant.

The total amount R of presynaptic resource in each motor neuron is kept constant, so that

$$R = R_{a,n} + f_n \sum_j A_{jn}^{\gamma}, \tag{10.11}$$

where $R_{a,n}$ is the amount of free resource left in motor neuron n and $\gamma < 1$ represents the assumption that large synaptic areas are disproportionally less taxing on the resources of the neuron. This total amount of presynaptic resource in each neuron is divided among all its connections, with large synaptic areas receiving a greater share, so that

$$U_{mn} = R_{a,n} \frac{A_{mn}}{\sum_j A_{jn}} = \left(R - f_n \sum_j A_{jn}^{\gamma} \right) \frac{A_{mn}}{\sum_j A_{jn}}. \tag{10.12}$$

In addition to accounting for the elimination of polyneuronal innervation, the model is able to reproduce the size principle (see section 10.2.2) because the presynaptic resource is utilized more heavily with increased activity of the neuron. The competitive advantage of higher frequency axons early in development is overcome at later stages by the greater synaptic efficacy of axons firing at a lower rate.

10.4 One Model in More Detail

Van Ooyen and Willshaw (1999b) proposed a model of (consumptive) competition that implements neurotrophic signaling in a fully dynamical way. Unlike Jeanprêtre et al. (1996) (see section 10.3.2), 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 this model, there is a positive feedback loop between the axon's number of receptors and the amount of neurotrophin bound. Unlike the model of 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 their receptors, neurotrophins can increase the terminal arborization of an axon (see section 10.2.1) and therefore the axon's number of syn-

apses. 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.

Neurotrophins might increase the axon's total number of receptors not only by enhancing the terminal arborization of an axon but also 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).

10.4.1 Description of the Model

A single target cell is considered at which there are n innervating axons, each from a different neuron (figure 10.4a). Neurotrophin is released by the target into the extracellular space at a (constant) rate σ and is removed by degradation with a 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 a rate constant ρ_i. Finally, unoccupied receptors are inserted into each axon at a rate ϕ_i and are degraded with a 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

$$\frac{dC_i}{dt} = (k_{a,i}LR_i - k_{d,i}C_i) - \rho_i C_i \tag{10.13}$$

$$\frac{dR_i}{dt} = \phi_i - \gamma_i R_i - (k_{a,i}LR_i - k_{d,i}C_i) \tag{10.14}$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n}(k_{a,i}LR_i - k_{d,i}C_i)/v, \tag{10.15}$$

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

$$\tau\frac{d\phi_i}{dt} = f_i(C_i) - \phi_i, \tag{10.16}$$

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

$$f_i(C_i) = \frac{\alpha_i C_i^m}{K_i^m + C_i^m}. \tag{10.17}$$

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, which can be either 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 among the innervating axons as a result, for example, 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 and Salin et al., 1995; or by stimulating axonal branching: Ramakers et al., 1998),

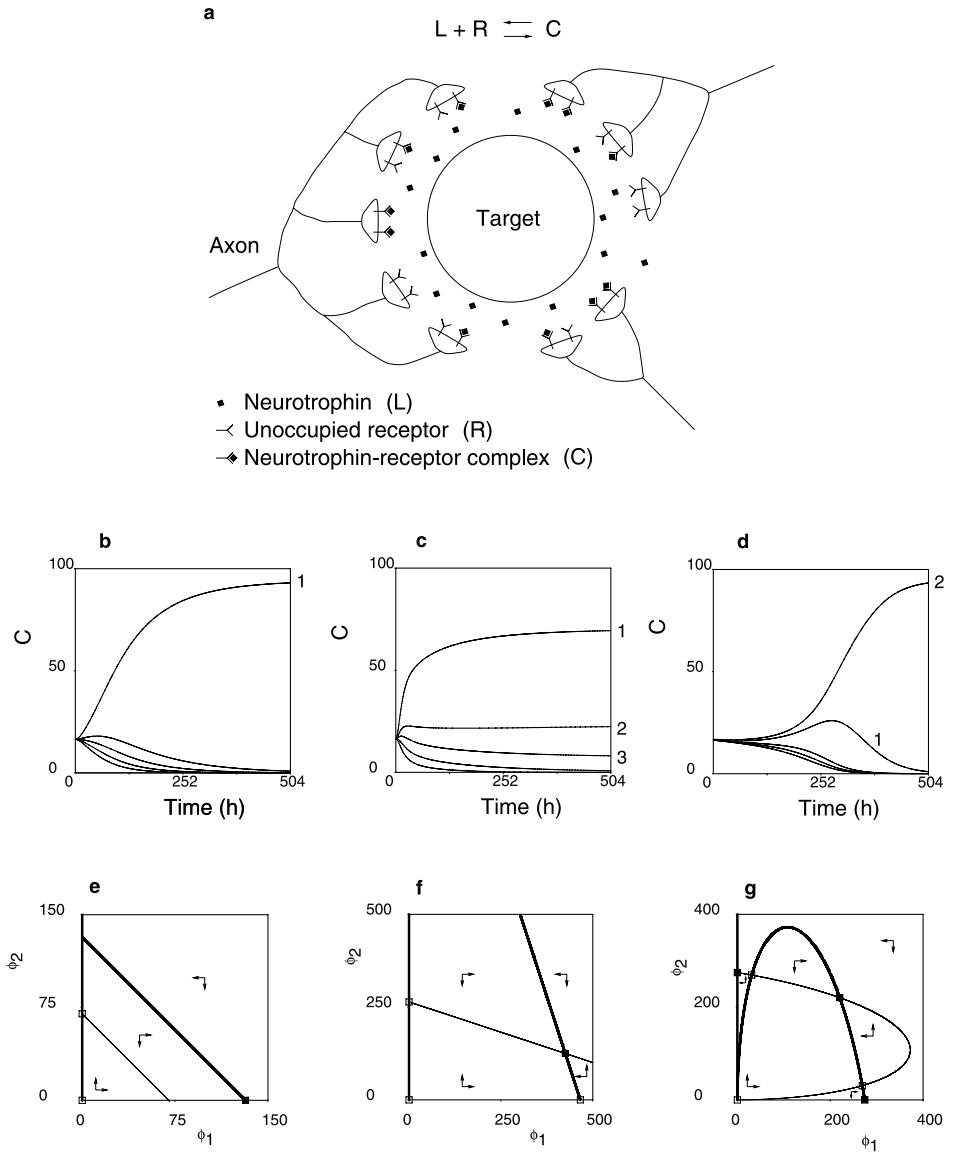

Figure 10.4

The model of Van Ooyen and Willshaw (see section 10.4). (*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. (*e–g*) The nullcline pictures for a system of two innervating axons [the variables R_i, C_i, $i = 1, 2$ and L are set at

which implies that, for example, α_i is increased or γ_i is decreased.

10.4.2 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 neurotrophin release (see figure 10.4). For class I, the number of surviving axons cannot be increased by increasing σ because an increased amount of neurotrophin will again become 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. Persistent multiple innervation is found in denervation experiments after reinnervation and recovery from prolonged nerve conduction block (Barry and Ribchester, 1995; see section 10.2.2 and figure 10.5).
- Increasing the amount of target-derived neurotrophin delays the development of single innervation (class I) (see section 10.2.2) 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 develop-

quasi-steady state; in (*e*) and (*f*), $\beta_1 > \beta_2$; in (*g*), $\beta_1 = \beta_2$]. The variable C is expressed in number of molecules and ϕ in number of molecules hr^{-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). The 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 1 has the highest value of the competitive strength, axon 2 survives because its initial value of ϕ_i is sufficiently higher than that of axon 1. (*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 neurotrophin release, 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.)

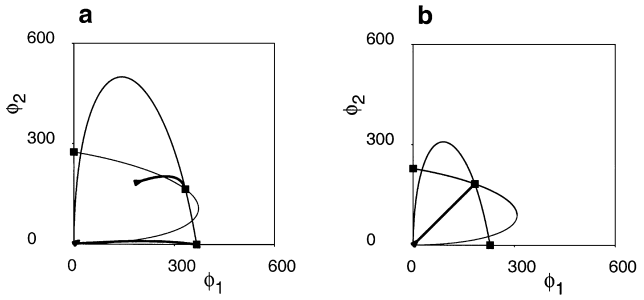

Figure 10.5
For class III, persistent multiple innervation can arise after recovery from nerve conduction block. Shown are the phase-space plots for a system of two innervating axons; for notations, see figure 10.4. The triangles mark the starting points of the trajectories (bold lines). As shown in (*a*), under normal conditions—with electrically active axons that have a different level of activity (values of α_i high and different) and a low initial number of receptors—single innervation develop. When activity is blocked (values of α_i lower and the same), as in (*b*), the same initial conditions lead to multiple innervation. Subsequent restoration of activity means that the nullclines are again as in (*a*), but now the starting values of ϕ_i are those reached as in (*b*), i.e., in the basin of attraction of the polyneuronal equilibrium point. The system goes to this equilibrium and will remain there; i.e., there is persistent polyneuronal innervation. (From Van Ooyen, 2001.)

ment 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; see section 10.2.2). For competition to occur, it is not necessary that there be presynaptic activity; differences in the axons' competitive strengths β_i can also arise as a result of differences in other factors than activity. It is also not necessary that there be postsynaptic activity or activity-dependent release of neurotrophin (compare Snider and Lichtman, 1996).

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 it is replaced with a low number of neurotrophin receptors (figure 10.6). To stimulate reinnervation, the model suggests that it is more efficient to increase the number of receptors on the regenerating axons than to increase the amount of neurotrophin, because the latter treatment also makes the existing axons stronger.

10.4.3 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 valid 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

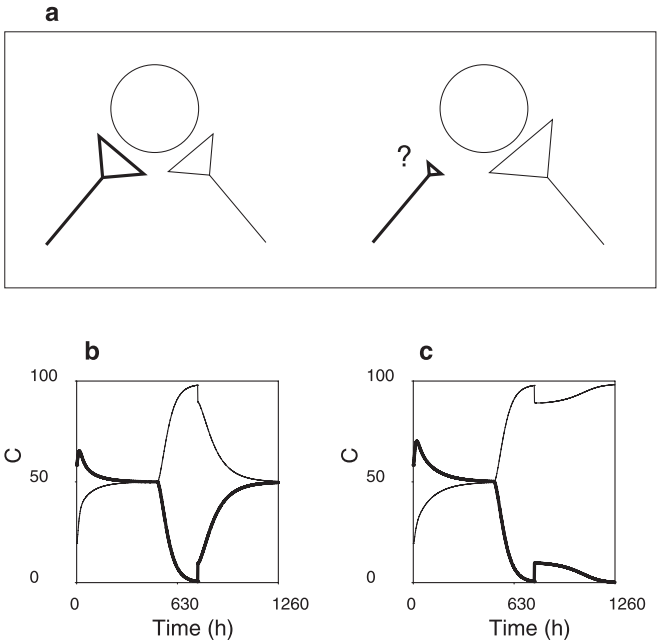

Figure 10.6
(*a*) Removal of an axon from a multiply innervated target and subsequent replacement, for class II (*b*) and class III (*c*). At $t = 504$ hr, axon 1 (bold line) is removed. At $t = 756$ hr, axon 1 is replaced (with initial conditions $\phi_1 = 30$, $R_1 = \phi_1/\gamma$, and $C_1 = 0$). 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 figure 10.4. (Modified from Van Ooyen, 2001.)

that the distance between axons mitigates competition, so that if the axons are sufficiently far apart on the target, they can coexist (even under conditions, e.g., a class I growth function, where they cannot coexist with a uniform extracellular space; see figure 10.7). This can explain why (1) when coexisting axons are found on mature muscle cells they are physically separated (Kuffer et al., 1977; Lo and Poo, 1991) and (2) in adulthood a positive correlation exists between the size of the dendritic tree and the number of innervating axons, while in newborn animals neurons of all sizes are innervated by approximately the same number of axons (e.g., in the ciliary ganglion of rabbits; Hume and Purves, 1981; Purves, 1994).

10.4.4 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 (see figure 10.8). 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

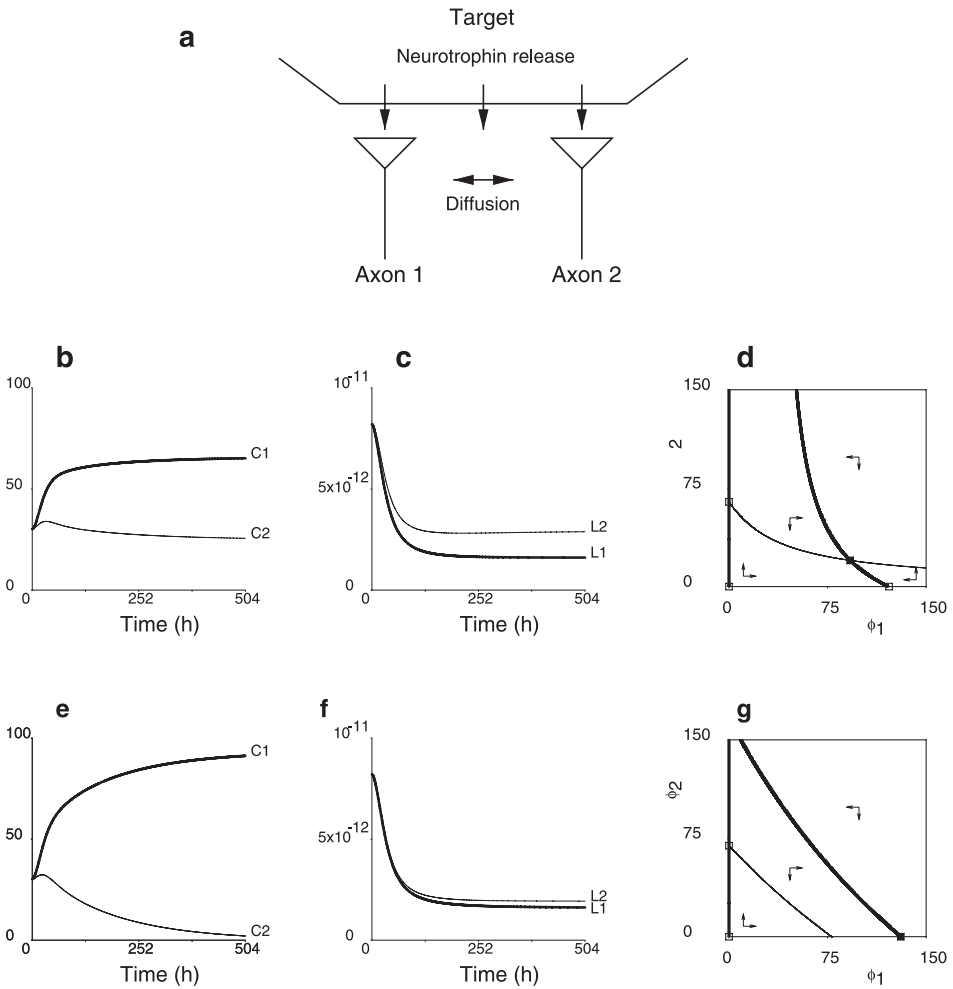

Figure 10.7

Influence of distance between axons on competition. (*a*) There is release of neurotrophin along the target and diffusion of neurotrophin in the extracellular space. Both axons have a class I growth function. (*b–d*) If the axons are relatively far apart, both survive. (*e–g*) If the two axons are close to each other, only one will survive. (*c*, *f*) The neurotrophin concentrations L_i (in mol l^{-1}) near the axons. (*d*, *g*) The null-isoclines, in which the bold lines are the null-isoclines of ϕ_1 and the thin lines those of ϕ_2. For other notations, see figure 10.4. (Modified from Van Ooyen and Willshaw, 2000.)

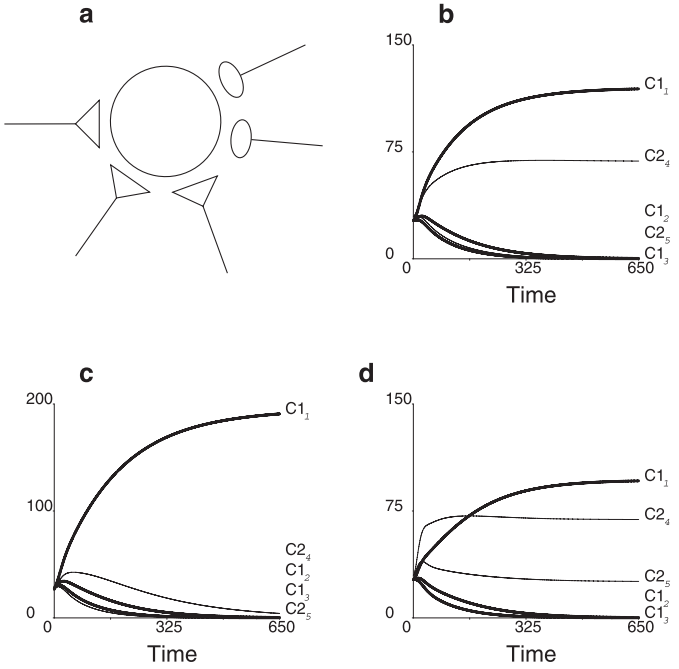

Figure 10.8
(*a*) System of five innervating axons where the target releases two types of neurotrophin, L1 and L2. Axons 1, 2, and 3 have receptor type R1 (which binds preferentially, but not exclusively, to L1), and axons 4 and 5 have receptor type R2 (which binds preferentially, but not exclusively, to L2). In (*b*–*d*), $C1_i$ ($C2_i$) 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 hours. For other notations, see figure 10.4. (*b*) When the receptor specificity is high, there is competitive exclusion within each group, but coexistence among groups. (*c*) When the receptor specificity is low, only one axon overall survives. In (*d*), the second group of axons (axons 4 and 5) has a class II growth function, the first group (axons 1, 2, and 3) class I. Axons 1, 4, and 5 survive. (Modified from Van Ooyen and Willshaw, 2000.)

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 (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 among 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 (figure 10.8b,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).

10.4.5 Parallels with Population Biology

In population biology, competition has been studied in many formal models (e.g., Yodzis, 1989; Grover, 1997). Parallels with axonal competition would allow results from population biology to be applied to neurobiology. Van Ooyen and Willshaw (2000) showed that the equations describing axonal competition are of the same form as those describing consumer–resource systems (Yodzis, 1989). By making quasi-steady-state approximations—on the slow time scale of ϕ_i—for R_i and C_i (i.e., $dR_i/dt = dC_i/dt = 0$), they showed that Eqs. (10.13)–(10.16) can be rewritten as

$$\frac{d\phi_i}{dt} = \phi_i[g_i(L, \phi_i) - \lambda_3] \tag{10.18}$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n} \phi_i h_i(L), \tag{10.19}$$

where function $g_i(L, \phi_i)$ encompasses the growth function, and function $h_i(L) \equiv \lambda_1 L/(\lambda_{2,i} + L)$ includes the kinetics of binding neurotrophin to receptors. (All λs are constants.) Note that under the quasi-steady-state approximations, $\phi_i = \rho_i C_i + \gamma_i R_i$. Thus ϕ_i is a measure of the total number of neurotrophin receptors (unoccupied plus bound to neurotrophin) on axon i. In population biological terms, ϕ_i is the size of the population of consumer species i; L is the size of the resource population; $h_i(L)$ is the functional response of the consumer, which describes how much resource is consumed per individual consumer per unit of time; and $g_i(L, \phi_i) - \lambda_3$ is the numerical response of the consumer, which describes the change in the consumer population expressed per individual per unit of time in response to (in general) both resource and consumer. For class I of the general growth function, $g_i(L, \phi_i) = g_i(L) = \lambda_{4,i} L/(\lambda_{2,i} + L)$.

The form in which the classical Lotka-Voltera competition equations are given, i.e., without direct reference to what the consumer species are competing for, is obtained from Eqs. (10.18) and (10.19) by making a quasi-steady-state approximation for the resource, i.e., $dL/dt = 0$. This gives an expression for L in terms of ϕ_i, which can then be inserted into Eq. (10.18). For example, for class I, if we assume for simplicity that all $\lambda_{2,i}$ are the same and δ can be neglected, we obtain

$$\frac{d\phi_i}{dt} = \phi_i \left[\frac{\lambda_{4,i}}{(\lambda_1/\sigma) \sum_{i=1}^{n} \phi_i} - \lambda_3 \right]. \tag{10.20}$$

10.5 Discussion

The model by Van Ooyen and Willshaw (1999b) links competition in the development of nerve connections with the underlying actions and biochemistry of neurotrophins. It can account for the development of single and multiple innervation, as well as for several other experimental findings, including the observation that activity is influential but not decisive in competition.

The model 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 can change during growth in response to neurotrophin [the degree of arborization (and consequently the number of synapses), the size of synapses, and the density of neurotrophin receptors], the consequent change in the axon's total number of neurotrophin receptors, which changes its capacity for removing neurotrophin, is what drives the competition.

Being a variable resource model (see section 10.3.2), this model has the advantage that its variables and parameters are directly interpretable in terms of the underlying biology (e.g., release, degradation, and binding of neurotrophin; insertion and turnover of receptor). This makes it also more straightforward to extend the model.

Future Modeling Studies

Axons in the model by Van Ooyen and Willshaw (1999b) have only a single target, whereas in the neuromuscular system, for example, each axon innervates a number of targets, so that there will also be competition among branches of the same axon for neurotrophin receptors (which are produced in the soma). Furthermore, the effects of activity have not yet been studied explicitly (e.g., the activity-dependent release of neurotrophin).

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 mechanism 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) (as in Elliott et al., 2001).

Future Experimental Studies

Further experimental studies are necessary to find out what type(s) of competition is (are) involved in the formation of nerve connections. More types of competition may be involved at the same time, e.g., consumptive competition plus interference competition. Recent findings (see sections 10.2.2 and 10.2.3), both in the neuromuscular and in the visual system, have supported a role for neurotrophic factors in consumptive competition.

The model by van Ooyen and Willshaw (1999b), which implements consumptive competition for neurotrophins, can be tested experimentally. The model predicts that axons that are being eliminated will have a low number of neurotrophin receptors. The shape of the growth function [i.e., the dose-response curve between neurotrophin and axonal growth; see Eq. (10.17)], which determines what type of innervation can develop, can be determined experimentally in vitro by measuring, for different concentrations of neurotrophin, the axon's total number of neurotrophin receptors over all its synapses.

In assessing the role of electrical activity in competition, it is important to know exactly how activity has been changed, including postsynaptic activity (and whether decreased levels of activity increase or decrease the release of neurotrophin; see Snider and Lichtman, 1996), the absolute level of presynaptic activity, and the relative differences in activity among innervating axons. The models suggest that all these could in principle have different effects.

Finally, synapse elimination is thought to be a process distinct from "Wallerian" degeneration—a synchronous, obliterative response to nerve injury in which nerve terminals are degraded and undergo phagocytosis (e.g., Winlow and Usherwood, 1975). However, an interesting alternative paradigm with

the potential to offer insights into mechanisms of synapse elimination is provided by the Wld^S mutant mouse and its transgenic derivatives (Ribchester et al., 1995; Gillingwater and Ribchester, 2001). These mice have slow Wallerian degeneration or none. Sciatic nerve axotomy in Wld^S mice induces synaptic boutons to withdraw from motor endplates in a fashion that strongly resembles synapse elimination. Very recently, the Wld^S genotype has been used to form the genetic background for thy1-CFP transgenic mice, in which motor axons and synaptic terminals endogenously express cyan fluorescent protein (Gillingwater et al., 2002). These mice, which have endogenously fluorescent synapses that are protected from Wallerian degeneration, offer many advantages that should facilitate further descriptive, experimental, and computational analyses of synapse elimination and its molecular mechanisms.

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