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TOPICAL REVIEW

Competition in the development of nerve connections: a review of models

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Abstract

The establishment and refinement of neural circuits involve both the formation of new connections and the elimination of already existing connections. Elimination of connections occurs, for example, in the development of mononeural innervation of muscle fibres and in the formation of ocular dominance columns in the visual cortex. The process that leads to the elimination of connections is often referred to as axonal or synaptic competition. Although the notion of competition is commonly used, the process is not well understood—with respect to, for example, the type of competition, what axons and synapses are competing for, and the role of electrical activity. This article reviews the types of competition that have been distinguished and the models of competition that have been proposed. Models of both the neuromuscular system and the visual system are described. For each of these models, the assumptions on which it is based, its mathematical structure, and the extent to which it is supported by the experimental data are evaluated. Special attention is given to the different modelling approaches and the role of electrical activity in competition.

Contents

1. Introduction

During development and in adulthood, the establishment and refinement of neural circuits involve both the formation of new connections and the elimination of already existing connections (e.g. Wolff and Missler (1992), Bailey and Kandel (1993), Donoghue (1995), Lohof *et al* (1996), Strata and Rossi (1998), Moser (1999)). A well-studied case of this form of plasticity is the withdrawal of connections that takes place during development. Neurons—and other cell types—often are initially innervated by more axons than ultimately maintain

into adulthood (Purves and Lichtman 1980, Lohof *et al* 1996). This initial hyperinnervation followed by elimination is a widespread phenomenon in the developing nervous system and occurs, for example, in the development of connections between motor neurons and muscle fibres (e.g. Brown *et al* (1976), Jansen and Fladby (1990)) and in the formation of ocular dominance columns in the visual cortex (e.g. Hubel *et al* (1977), Wiesel (1982)). The process that reduces the amount of innervation onto a postsynaptic cell is often referred to as axonal or synaptic competition. However, neither term describes the process 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 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 a number of synapses, so that competition occurs not between single synapses but between groups of synapses. Notwithstanding, because of their widespread use in the literature, I will continue to use the terms axonal and synaptic competition.

Competition can be defined in various ways. One of the most general definitions was given by Van Essen *et al* (1990). In discussing the neuromuscular system, they defined competition as a process in which there are multiple participants whose behaviour 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.

In *independent competition*, the victors do not arise as a result of interactions between the participants. An example of this form of competition is a contest. In a contest, where the victors are chosen by judges based on a comparison of the performance of the participants, there are no interactions between the participants. One participant does not influence the performance of the other participants during the process of competition. In axonal competition, this would mean that the axons innervating the same postsynaptic cell do not affect each other and that the postsynaptic cell (e.g. the muscle fibre) would act as judge and decide, on the basis of some performance criteria, which axon(s) would win. Since axons do affect each other (see section 2), this form of competition is unlikely. Competition as in a contest is reminiscent of *competitive learning*, or winner-take-all learning, which was introduced by Kohonen (1982). In neural network models based on competitive learning, changes in synaptic strength are performed only for synapses impinging onto the target cell that is responding most strongly to a stimulus, and for synapses onto neighbours of the 'winning' cell. The term competitive refers to the (hypothetical) process by which the most responding target cell is chosen among those responding less strongly (see also Swindale (1996)).

In *interdependent competition*, victors emerge as a result of interactions—direct or indirect—between the participants (as in a boxing match, for example). In this case, the actions of one participant do affect the performance of the other participants during the process of competition. Interdependent competition is the type of competition that is considered in population biology. In population biology, where one studies the dynamics of populations of organisms, two species of organisms are said to compete if they exert negative effects on the growth of each other's population. A disadvantage of applying this definition to axonal competition is that it does not include independent competition, which is, at least in principle, a viable option, which should not be discarded just on the basis of terminology (see Ribchester (1992), and reply by Colman and Lichtman (1992)). Compared to the definition by Van Essen *et al* (1990), an advantage of the population biology definition is that nothing is said about the outcome of competition—all participants may emerge as 'victors' as a result of competition, i.e. negative interactions between the participants. In population biology, negative interactions

between species can come about in different ways (Yodzis 1989), leading to different types of competition:

- In *consumptive competition*, in systems of consumers and resources (e.g. predators and preys, respectively), each individual consumer tries to avoid the others and 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, Guillery 1988). In particular, it is believed that axons compete for neurotrophic factors, which are survival- or growth-promoting substances released by the postsynaptic cells upon which the axons innervate. During an earlier stage of development, when initial synaptic contacts are made, these neurotrophic factors have a well-established role in the regulation of neuronal survival (e.g. Fariñas *et al* (1994), Primi and Clarke (1996), Oppenheim (1996), Ma *et al* (1998)). But 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 2.1.5 and 2.2.3; 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); for more references, see section 3.3.2D). An important class of neurotrophic factors are the neurotrophins, with NGF (nerve growth factor) as its best-characterized member (Bothwell 1995, Lewin and Barde 1996).
- In *interference competition*, instead of hindrance through dependence on shared resources, there is direct interference between individuals. This occurs, for example, if there are direct negative interactions—e.g. aggressive or toxic interactions—between individuals. In axonal competition, nerve terminals could seek to destroy each other by releasing proteases (see sections 2.1.5 and 3.5).
  Interference competition also occurs if some essential resource can be obtained only by occupying, more or less exclusively, some portion of space (competition for space). Competition for space is primarily interference competition because each individual consumer is seeking to monopolize a portion of space, rather than to share resources (Yodzis 1989). In competition for space, the essential resource may be space itself, as in nest sites for hole nesting birds; or it may be another resource, such as, in the case of plants, light, which can only be obtained by occupying a certain amount of space above ground. In axonal competition, the essential resource may also be space itself or, for example, some essential extracellular matrix component (see section 3.4).

Although the notion of competition is commonly used in neurobiology, the process is not well understood—with respect to, for example, the type of competition, what axons and synapses are competing for, and the role of electrical activity—and only a few formal models exist. In population biology, in contrast, the concept of competition is well developed and has been studied by means of many formal models (e.g. MacArthur (1970), May (1974), Kaplan and Yorke (1977), Yodzis (1989), Keddy (1989), Van der Meer and Ens (1997), Grover (1997)). The concept of competition in population biology provides a useful framework for thinking about competition in neurobiology (Van Essen *et al* 1990, Ribchester and Barry 1994, Van Ooyen and Willshaw 2000), and in this paper I classify the different models according to the forms of competition that are distinguished in population biology (see also Ribchester and Barry (1994)). Since the innervation of mammalian skeletal muscle by its motor nerve (reviewed in Jansen and Fladby (1990), Sanes and Lichtman (1999), Ribchester (2001)) is the most accessible system for studying the development of nerve connections, most models of competition describe the neuromuscular system. But a number of competition models

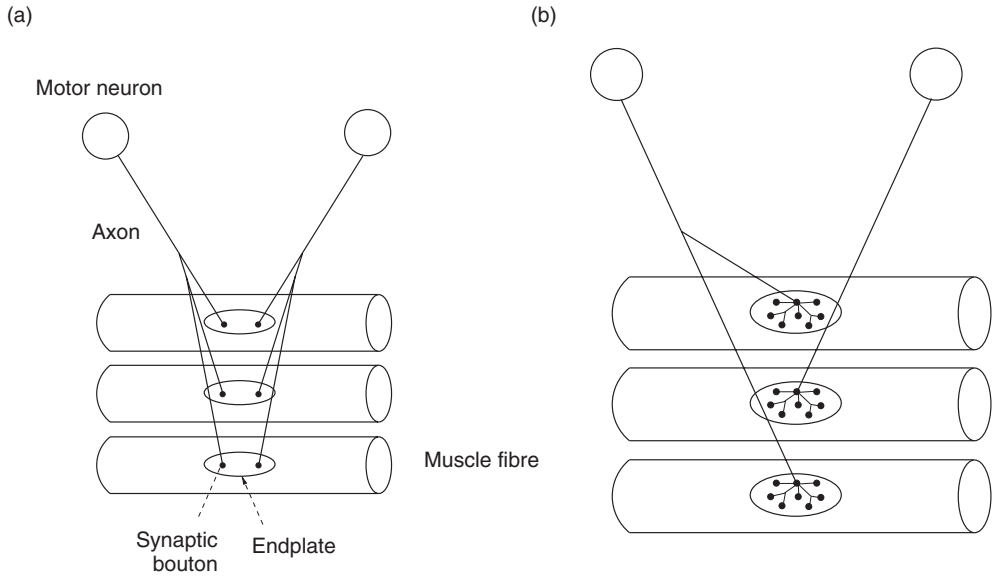

Figure 1. The development of connections between motor neurons and muscle fibres. (*a*) At birth, each muscle fibre is innervated by axons from several different motor neurons (polyneuronal innervation). (*b*) In adulthood, each muscle fibre is innervated by the axon from a single motor neuron (mononeuronal innervation). Note that the number of synaptic boutons of the remaining axon on each endplate has increased. Drawn after Purves (1994).

also exist for the visual system, and they are reviewed here as well, since their mathematical structure is in many ways similar to that of the models proposed for the neuromuscular system.

Before presenting the models, I briefly review the development of the neuromuscular and visual system, focusing on competition and the role of electrical activity.

2. Biological background

2.1. Neuromuscular system

2.1.1. Adult neuromuscular system. Skeletal muscles are made up of many individual cells, called muscle fibres. Muscle fibres are innervated by motor neurons. At the endplate—a discrete region near the midpoint of the muscle fibre—each muscle fibre is innervated by the axon from a single motor neuron (mononeuronal or single innervation) (figure 1(*b*)). Whilst each muscle fibre is innervated by a single motor neuron, a single motor neuron, through its axonal branches, typically contacts many muscle fibres. The number of fibres contacted by a given motor neuron is called the motor unit size. Motor neurons with successively higher firing thresholds—which are therefore less frequently activated—have successively larger motor units (size principle) (Henneman 1957, 1985).

Mononeuronal innervation enables optimal control of muscle force. Muscle contractions of increasing strength are generated by activating increasing numbers of motor neurons. To be able to do this—and without having wasted axon terminals (skeletal neuromuscular connections are so powerful that multiple innervation of the same fibre would be redundant)—it is necessary that a muscle fibre is innervated by only one motor neuron (e.g. Lichtman *et al* (1999)).

Mononeuronal innervation does not occur in all types of vertebrate muscle fibres. Twitch

fibres—the type that skeletal muscles are made of—are mononeuronally innervated. But tonic fibres are not. These are muscle fibres that, in contrast to twitch fibres, contract slowly and do not generate action potentials in response to nerve stimulation. They have multiple endplates as well as multiple axons at individual endplates (Lichtman *et al* 1985, Porter and Baker 1996). In some species, e.g. amphibians, even the endplates of twitch fibres are polyneuronally innervated (Trussell and Grinnell 1985, Werle and Herrera 1991, Grinnell 1995).

2.1.2. Development of mononeuronal innervation. 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 fibres. At birth, the endplate of each muscle fibre is contacted by axons from several different motor neurons (polyneuronal or multiple innervation) (figure 1(*a*)). During the subsequent few weeks, axons withdraw some of their branches until each muscle fibre is innervated by the axon from a single motor neuron (mononeuronal innervation) (figure 1(*b*)).

At the endplate, the terminal of an axon branch consists of multiple synapses, or synaptic boutons. 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 gradually retracted; when no boutons remain, the axon branch withdraws. The change from poly- to mononeuronal innervation is often called synapse elimination, but this term is unfortunate in the sense that there is contemporaneous addition and loss of synaptic boutons, and the synaptic area on the endplate actually increases during the elimination of polyneuronal innervation (Purves 1994, Sanes and Lichtman 1999). Input elimination would therefore describe the phenomenon more accurately (Sanes and Lichtman 1999).

During elimination of polyneuronal innervation, motor unit sizes, as well as the range of motor unit sizes, decrease, but there is no change in the number of motor axons innervating the muscle as a whole, i.e. there is no motor neuron death (Brown *et al* 1976, Balice-Gordon and Thompson 1988). Some motor neurons do die during development, but the period of cell death precedes the period of elimination of polyneuronal innervation (Oppenheim 1989, 1991).

2.1.3. Reinnervation experiments. In neonates and adults, muscles can be partially denervated by injuring some of the axons in the motor nerve. Reinnervation of the muscle by sprouting of intact axons and regeneration of damaged axons may then result in polyneuronally innervated muscle fibres (McArdle 1975, Brown *et al* 1981, Taxt 1983, Barry and Ribchester 1995). The subsequent elimination of polyneuronal innervation resembles that seen during normal postnatal development (McArdle 1975, Brown *et al* 1976, Betz *et al* 1979). Partial denervation experiments are used to investigate the mechanisms involved in the elimination of polyneuronal innervation.

2.1.4. Indications for 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, Fladby and Jansen 1987). Thus, individual motor axons appear to innervate more fibres as the result of the absence of other axons.

Competition for the endplate alone (postsynaptic competition) cannot account for all findings. If there was only postsynaptic competition, the withdrawal of axon branches at each endplate would occur independently of the withdrawal at other endplates. Postsynaptic competition alone therefore cannot explain why larger motor units reduce in size more than smaller ones (so reducing the range of motor unit sizes) and why branches at singly innervated

fibres—where there is no competition—can withdraw (Fladby and Jansen 1987). The latter observation led to the suggestion that there is a separate mechanism of intrinsic withdrawal, by which a certain number of the initial connections are withdrawn regardless of (postsynaptic) competition (Thompson and Jansen 1977, Fladby and Jansen 1987, Liu and Westerfield 1990). Thus, there also appears to be presynaptic constraints, so that each neuron can maintain only a limited number of axon branches. For example, after most of the motor units in the neonatal mouse soleus are removed, leading to incomplete innervation of the adult muscle, the average motor unit size found in the adult is independent of the remaining number of motor units (Fladby and Jansen 1987).

Competition seems to play a role also in the way in which, in some skeletal muscles, pools of motor neurons establish a topographic map—i.e. that motor neurons from nearby spinal levels project to nearby muscle sectors (e.g. Brown and Booth (1983), Bennett and Ho (1988), Gordon and Richmond (1990)). This topographic map can be re-established after denervation (e.g. DeSantis *et al* (1992), Laskowski and Sanes (1988)), and, in the re-establishment of the map, the outcome of the competition is influenced by the positional labels associated with axons from different levels in the spinal cord (Laskowski *et al* 1998).

2.1.5. What mediates the competition in the development of mononeuronal innervation? This question cannot yet be answered conclusively, although a number of possibilities have been proposed:

Consumptive competition: neurotrophic factors. 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 *et al* 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. Although GDNF may not be the endogenous mediator of neuromuscular synaptic competition (Ribchester 2001), and the interpretation of these kinds of experiments is often complicated by non-specific effects of such treatments, the idea that competition is mediated by muscle-derived neurotrophic factors has nevertheless been strengthened by the findings of Nguyen *et al* (1998).

Interference competition: competition for space. 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 N-CAM, has been disrupted (Sanes *et al* 1998).

Interference competition: direct negative interactions. One possibility is that an activated muscle globally releases proteases that destroy or disconnect nerve terminals (O'Brien *et al* 1978). In this scenario, the electrical activity of an axon, possibly via stimulating the local release of protease inhibitors, might serve to make it resistant to proteolytic breakdown (see section 3.5). Many proteases and protease inhibitors are located at the neuromuscular junction (Hantai *et al* 1988), and various proteases have been proposed to play a key role in synapse destabilization (Liu *et al* 1994b, Tyc and Vrbova 1995, Zoubine *et al* 1996). Another possibility

is that axon-derived, or axon-stimulated local release of, protease mediates direct negative interactions between axons (Sanes and Lichtman 1999) (see section 3.5).

2.1.6. Role of electrical activity. Regarding the role of activity in synapse elimination—which occurs at a time when muscles are becoming active—at least two questions can be asked (Ribchester 2001).

(1) Does the overall level of activity affect the rate of synapse elimination?
(2) Do differences in the activity of innervating axons confer competitive advantages on the more active axons?

Concerning question (1), 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, Callaway and Van Essen 1989, Blondet *et al* 1989, Barry and Ribchester 1995, Ribchester and Taxt 1984), while stimulating activity accelerates synapse elimination (O'Brien *et al* 1978, Thompson 1983, Zhu and Vrbova 1992, Vyskocil and Vrbova 1993), although there are some nuances to these findings (see Ribchester (2001)).

Concerning question (2) 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) (see also Callaway *et al* (1989)) using selective blocking found the opposite. Experiments in tissue culture, too, show opposing results (Magchielse and Meeter 1986, Nelson *et al* 1993). The view that active synapses have a competitive advantage is also supported by Balice-Gordon and Lichtman (1993, 1994). 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, they suggest that electrically active synapses are the stimulus for removing the AChRs underlying the less active synapses, which are then eliminated (see sections 3.5.3 and 3.5.4). However, in regeneration experiments, Ribchester (1988, 1993) showed that inactive terminals are capable of competitively displacing other—active and inactive—terminals. Recently, Costanzo *et al* (2000) also found that, during regeneration, activity is not necessary for competitive synapse elimination. Making the regenerating nerve, the intact nerve, and the muscle endplate completely silent, they demonstrated that silent synapses from the regenerating nerve can displace other silent synapses from the intact nerve. Electrical activity also seems not to be sufficient for synapse elimination. Barry and Ribchester (1995) found that following recovery from chronic nerve conduction block, many reinnervated muscle fibres in partially denervated muscles retain polyneuronal innervation, in spite of the resumption of normal neuromuscular activity.

In conclusion, activity is influential but does not seem to be decisive (Costanzo *et al* 2000, Ribchester 2001). To reconcile the different findings concerning activity, one possibility is that activity is just one of the many influences in competition, while the actual competition is governed by other factors, e.g. neurotrophic factors and their receptors (Costanzo *et al* (2000); see also section 3.3.2D).

2.2. Visual system

2.2.1. Adult visual system. Retinal axons from the two eyes project to the lateral geniculate nucleus (LGN) of the thalamus. The LGN is composed of two or more layers, each of which receives axons from either the left or the right eye. In turn, the axons from the LGN project to layer IV of the visual cortex. Like the different layers in the LGN, cells in layer IV respond

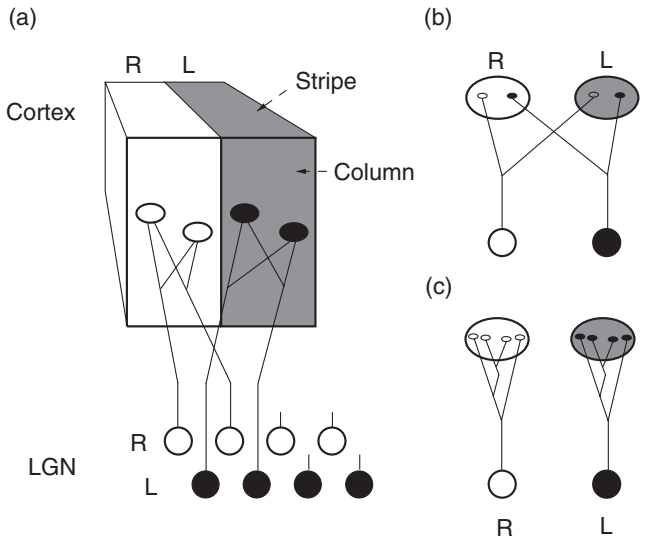

Figure 2. The development of ocular dominance columns. (*a*) The adult visual system. The LGN of the thalamus is composed of two or more layers, each of which receives axons from either the left or the right eye. The axons from the LGN project to layer IV of the visual cortex. Like the different layers in the LGN, cells in layer IV respond preferentially to input from either the left or the right eye (ocular dominance). (*b*) In the immature system, the arbors of the geniculate axons overlap extensively within layer IV. (*c*) During further development, remodelling of axonal arbors takes place so that each cortical cell receives axons from either left-eye or right-eye geniculate neurons. Note that the number of branches (and thus synapses) of the remaining axon on each cortical cell has increased. Drawn after Gilbert (1992) and Lichtman *et al* (1999).

preferentially to input from either the left or the right eye; in other words, they show ocular dominance (figure 2(*a*)). Unlike the mononeuronal innervation of muscle fibres, a single cortical cell is typically innervated by a number of LGN cells (of the same ocular dominance) (e.g. Tanaka (1985), Gilbert (1992)). Within layer IV and perpendicular to the cortical surface, cells with the same ocular dominance are stacked on top of each other, forming so-called ocular dominance columns. Parallel to the cortical surface, columns of the same ocular dominance are grouped together and form a pattern of alternating stripes. For a more detailed description of the visual system and its development, the reader is referred to Reid (1999), Lichtman *et al* (1999), and Swindale (1996), and references therein.

The functional significance of ocular dominance columns is not clear. In addition to ocular dominance stripes, positions in the retina are projected in a topographical manner to the cortex (Roskies *et al* 1995), and ocular dominance stripes might be a 'side effect' of that: experimental results (Fawcett and Willshaw 1982) and modelling results (e.g. Von der Malsburg and Willshaw (1976), Goodhill (1993)) show that mechanisms that ensure corresponding topographic mappings from the two retinas onto a single sheet of cells usually also produce ocular dominance stripes (see also Swindale (1996)).

2.2.2. Development of ocular dominance columns. The formation of eye-specific layers in the LGN and ocular dominance columns in the cortex requires anatomical remodelling of axonal arbors during development (figures 2(*b*), (*c*)). Initially, the retinal axons from the two eyes overlap extensively within the LGN, before gradually segregating to form eye-specific layers. Similarly, the arbors of geniculate axons are initially evenly distributed within layer IV,

before becoming restricted to eye-specific columns. 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.

2.2.3. Competition. The formation of eye-specific layers and columns appears to be a competitive process. For example, when kittens are reared with one eye closed (monocular deprivation), the ocular dominance stripes associated with the closed eye become smaller than those associated with the open eye (see further section 2.2.4). As in the neuromuscular system, the formation of eye-specific regions might involve competition between axons or axon branches for target-derived neurotrophic factors. Continuous infusion of the neurotrophin NT-4/5 or the neurotrophin BDNF in the cat visual cortex prevents the formation of ocular dominance columns (Cabelli *et al* 1995), presumably because the geniculate axon branches fail to retract. As expected when axons compete for neurotrophic factor, removal of neurotrophic factor by application of neurotrophic factor antagonists prevents the formation of ocular dominance column by eliminating inputs from both eyes (Cabelli *et al* 1997). In monocular deprivation experiments in cat, excess neurotrophic factor mitigates the relative increase of the ocular dominance stripes associated with the open eye (Carmignoto *et al* 1993, Hata *et al* 1996), presumably by overwhelming the competitive disadvantage of the closed eye. Infusion of the neurotrophin NGF abolishes the effects of monocular deprivation in the rat LGN (Domenici *et al* 1993) and visual cortex (Yan *et al* 1996).

2.2.4. Role of electrical activity. The segregation process into eye-specific layers and columns is influenced by the neural activity impinging on the LGN and cortex. Neural activity arises not only from visual stimulation through photoreceptor activation but also from spontaneously occurring activity (i.e. not visually driven activity) in retinal ganglion cells; and treatments that block all activity have different effects compared to those that block only visually driven activity. When all activity in both eyes of kittens is blocked by injection of tetrodotoxin (TTX, which blocks the generation of action potentials), ocular dominance columns do not form at all (Stryker and Harris 1986). But when only the visually driven activity is blocked, 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 spontaneously occurring activity in the immature retina may instruct the early segregation of axonal arbors into ocular dominance columns. Immature retinal ganglion cells generate waves of activity that propagate across the retina (Wong *et al* 1993). Since waves are generated independently in each retina, activities from the two eyes—and therefore also the neural activities to the LGN and cortex—are likely to be asynchronous, which could provide a signal for segregation. Inconsistent with a critical role for spontaneous activity are the findings by Crowley and Katz (1999), who showed that total removal of retinal influence (by eye removal) in ferrets early in visual development does not prevent the normal development of ocular dominance columns. To reconcile these finding with those by Stryker and Harris (1986), one possibility is that blockade of all activity by TTX results in increased non-specific neurite outgrowth (see also Kater *et al* (1988), Van Ooyen *et al* (1995), Van Oss and Van Ooyen (1997)), which may mask already established columns rather than disrupt their formation (Crowley and Katz 1999). Recently, Crowley and Katz (2000) showed that, in ferret, ocular dominance columns appear much earlier during development—already less

than 7 days after geniculocortical innervation of layer IV—than previously thought, and that these early columns were unaffected by experimentally induced imbalances in retinal activity . They proposed that axon guidance cues are sufficient to initially establish columns, and that neuronal activity is subsequently required for their maintenance and plasticity.

Although activity might not be necessary for the initial formation of ocular dominance columns, it does certainly play a role in their plasticity. 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 dramatically smaller than those formed by the open eye's input (e.g. in kittens: Wiesel and Hubel (1963), Shatz and Stryker (1978)), indicating that segregation is a competitive process and that the open eye has a competitive advantage. However, when the postsynaptic cortical cells are silenced, the closed eye has a competitive advantage (Reiter and Stryker 1988). In addition to affecting ocular dominance, activity—e.g. spontaneously occurring retinal waves—may play a role in the synapse elimination that occurs in sharpening up the initial, coarse topographic maps, which are formed by gradient-dependent mechanisms during early development (see e.g. Roskies *et al* (1995), Goodhill and Richards (1999)). For an extensive review on the development of topography and ocular dominance columns, as well as on the various formal models that have been proposed, see Swindale (1996).

In conclusion, just as the role of activity in the development of the neuromuscular system, activity is influential in the development of the visual system but might not be decisive.

2.3. Other parts of the nervous system

An initial excess and subsequent decrease in the number of connections that an individual target cell receives occurs in many parts of the nervous system, not just in the neuromuscular and visual system (Purves and Lichtman 1980). In neonatal rat cerebellum, for example, individual Purkinje cells are initially innervated by several climbing fibres, which, during subsequent development, compete with each other until only a single one remains (Crepel 1982). In the ciliary ganglion of newborn rabbits, all neurons—irrespective of their number of dendrites—are initially innervated by approximately the same number of axons. But during subsequent axon elimination, neurons that lack dendrites lose all but one of their innervating axons. In contrast, neurons with many dendrites remain innervated by the largest number of axons (Hume and Purves 1981, Purves and Hume 1981, Purves 1994). Submandibular ganglion cells in the rat are initially innervated by five or more axons, but this number reduces to one or two over the first month after birth (Lichtman 1977). Changes in the number of connections also occur in the olfactory bulb, hippocampus, and spinal cord (Purves 1994, Lohof *et al* 1996).

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 of the models is to explain the change from polyneuronal to mononeural innervation during development. In the visual system, the main aim is to explain the development of ocular dominance. Since the ways in which competition is modelled in both systems have many similarities, models of both systems are reviewed together.

The presentation of the models is structured as follows:

- The models described in section 3.1 (and, in part, also in section 3.2) enforce competition rather than implement its putative underlying mechanisms; that is, these models explore

the consequences of imposing certain constraints or 'rules' that are introduced to ensure competition between axons.

- The models described in the other sections directly implement the underlying mechanisms. To classify these models—all of which implement a form of interdependent competition—I use the different forms of competition that are distinguished in population biology (see section 1):
  - *Consumptive competition* (section 3.3), in which the individual competitors hinder each other through their dependence on shared resources.
  - *Interference competition*, in which the competitors compete for space (section 3.4) or in which there are direct negative interactions between the competitors (section 3.5).

For each model, I describe what assumptions the model is based upon, how these assumptions are supported by the experimental data, what the model can explain and predict, and what the role of electrical activity is. For each model, I also identify its underlying positive feedback loop—this is what enables one or more competitors to outcompete the others. All the models are given in sufficient detail to show the differences and similarities in modelling approach and mathematical structure. (In presenting the equations, I use each author's own mathematical terminology.) I shall provide criticism for each model, but that does not imply a negative value judgement on the work, merely a general reminder that more modelling and experimental work needs to be done in order to understand competition.

3.1. Constant total synaptic strength

Computational models of the development of nerve connections—especially models of the formation of ocular dominance columns—typically enforce competition rather than model its putative underlying mechanisms explicitly (for a review, see Miller (1996); see also Elliott *et al* (1996a), Swindale (1996)). These models usually describe physiological plasticity (changes in synaptic strength, as a result of Hebbian learning) rather than anatomical plasticity (changes in axonal arborization), and competition is often enforced by keeping the total synaptic strength onto a postsynaptic cell constant. Hebbian learning together with enforcing competition between input connections has also been used in studying the development of the neuromuscular system (Stollberg 1995) (section 3.1.1). Enforcing competition between the *output* connections of a neuron, by keeping the total synaptic strength of the output connections constant, was used by Willshaw (1981) in a model of the neuromuscular system that also implemented interference competition between a muscle fibre's input connections (see section 3.5.1).

To see how competition between input connections 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 activity level $x_i(t)$ of the ith input. Thus

$$\Delta w_i(t) \propto y(t)x_i(t)\Delta t. \tag{1}$$

If two inputs (e.g. two eyes) innervate a common target and if the activity level in both inputs is sufficient to achieve potentiation, then this rule causes both pathways to be strongly potentiated, and no segregation (ocular dominance) occurs. What is required is some form of competition, so that when the synaptic strength of one input grows, the strengths of the other one shrinks. A common method to achieve this is to constrain the total synaptic strength (synaptic normalization). More specifically, synaptic normalization is the constraint that $\sum_i^n w_i^p(t) = K$, where K is some constant and p is usually taken to be 1 or 2; $p = 1$ conserves

the total synaptic strength, whereas $p = 2$ conserves the length of the weight vector. 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. For a particular normalization constraint, there are various ways in which that constraint may be enforced. In multiplicative normalization (Von der Malsburg 1973, Von der Malsburg and Willshaw 1976, Willshaw and Von der Malsburg 1976), each synaptic strength $w_i(t + \Delta t)$ is multiplied by an amount so as to enforce the constraint. In subtractive normalization (Miller *et al* 1989, Miller and Stryker 1990), an amount is subtracted from each synaptic strength so as to enforce the constraint. For both multiplicative and subtractive normalization, it is also possible to implicitly enforce the normalization constraint by including a decay term in equation (1) (Miller and MacKay 1994).

The final outcome of development may differ depending on whether multiplicative or subtractive normalization is used (Miller and MacKay 1994). If two equivalent input populations (e.g. two eyes) innervate a common target, multiplicative normalization prevents their segregation (i.e. formation of ocular dominance) if there are positive correlations between the two populations (positive between-eye correlations are likely to be present when the two eyes are open), whereas subtractive normalization allows segregation under these circumstances. Segregation under multiplicative normalization can occur only if there are anticorrelations between the two populations.

With competitive learning (see section 1)—where changes in synaptic strength are performed only for synapses impinging onto the target cell that is responding most strongly to a stimulus, and for synapses onto neighbours of the 'winning' cell—normalization constraints are also used to prevent synapses from growing without bounds. As with simple Hebbian learning, the outcome of competitive learning shows important differences depending on whether multiplicative or subtractive normalization is used (Goodhill and Barrow 1994).

Experimental evidence for multiplicative normalization has been found in cultures of cortical neurons (Turrigiano *et al* 1998). In these cultures, the strengths of all synapses onto a pyramidal neuron are scaled down when the overall activity level of the neuron is increased, and are scaled up when the overall activity level of the cell is decreased. In addition to scaling synaptic strength, activity can regulate the excitability of the whole neuron, in such a way that when the activity of a neuron is high, ionic conductances in the neuron are modified to decrease activity, and when the activity of a neuron is low, ionic conductances are modified to increase activity (for reviews on such homeostatic plasticity, see Van Ooyen (1994) and Turrigiano (1999)). Since the effect of synaptic strength is weighted by the excitability of the postsynaptic cell, such regulation of neuronal excitability is functionally similar to activity-dependent scaling of synaptic strength (Miller 1996).

3.1.1. Stollberg (1995). Stollberg (1995) used a form of synaptic normalization to study the establishment of the size principle (i.e. that motor neurons with higher firing thresholds innervate larger numbers of muscle fibres—see section 2.1.1). The model considers the relative strengths of synapses impinging on a muscle fibre. The relative synaptic strength is assumed to increase when synapse and muscle fibre are either both active or both inactive, and to decrease in all other situations. Furthermore, it is assumed that the absolute collective strength increases during development. Early on during development, the absolute collective synaptic strength is low, so that the muscle fibres are not activated. The synapses that are then active will be eliminated. These synapses are mostly those from lower threshold neurons because they are activated more often; whenever a neuron with a particular threshold is active, all the neurons in the same pool with a lower threshold are active as well. The removal of the synapses from lower threshold neurons thus produces the size principle. (The elimination of inactive

synapses when the muscle fibre is active was shown not to be dominant.) During the course of development, also more fibres in the model become mononeuronally innervated, although many remain polyneuronally innervated, and it seems that the model does not guarantee mononeuronal innervation for all fibres. Barber and Lichtman (1999) proposed a related model of the establishment of the size principle (section 3.5.4).

3.2. Modified Hebbian learning rules

With equation (1), only increases in synaptic strength can take place; decreases in synaptic strength—and competition—are brought about by enforcing synaptic normalization afterwards. Another approach for achieving competition, which does not impose synaptic normalization, is to modify the simple Hebbian learning rule 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.

If we assume that the postsynaptic activity level $y(t)$ must be above some threshold θ_y to achieve LTP, and otherwise yield LTD; and assume a similar possibility for the presynaptic activity level $x_i(t)$, then a suitable synaptic modification rule is (Miller 1996)

$$\Delta w_i(t) \propto [y(t) - \theta_y][x_i(t) - \theta_x]\Delta t. \tag{2}$$

If both $y(t)$ and $x_i(t)$ are above their thresholds (θ_y and θ_x, respectively), LTP occurs; if one is below its threshold and the other is above, LTD occurs. (To prevent LTP when both $y(t)$ and $x_i(t)$ are below their thresholds, $\Delta w_i(t)$ is often set to zero in this case.) For LTD to achieve competition, the synaptic strength lost through LTD must roughly equal the strength gained through LTP. This can only be achieved with appropriate input correlations, which makes simple LTD a fragile mechanisms for achieving competition (Miller 1996).

Another mechanism that ensures that when some synaptic strengths increase, others must correspondingly decrease (i.e. competition) is to make one of the thresholds variable. If the threshold θ_x^i increases sufficiently as the postsynaptic activity $y(t)$ or synaptic strength $w_i(t)$ (or both) increases, conservation of synaptic strength can be achieved (Miller 1996). Similarly, if the threshold 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). This results in temporal competition between input patterns, rather than spatial competition between different sets of synapses.

Yet another mechanism that can balance synaptic strengths is based on a form of—experimentally observed—long-term synaptic plasticity that depends on the relative timing of pre- and postsynaptic actions potentials (spike-timing dependent plasticity, or STDP) (Zhang *et al* 1998). Presynaptic action potentials that precede postsynaptic spikes strengthen a synapse, whereas presynaptic action potentials that follow postsynaptic spikes weaken it. Synapses subject to STDP in effect compete for control of the timing of postsynaptic action potentials (i.e. competition in the time domain) (Song *et al* 2000). Synapses of inputs that fire the postsynaptic neuron with short latency or that act in correlated groups become strengthened, while others become weakened. As a consequence of the intrinsic nonlinearity of the spike-generation mechanisms, STDP has the effect of keeping the total synaptic input to the neuron roughly constant, independent of the presynaptic firing rates. However, for this to work, it is still necessary to impose a hard limit on the maximum strength of individual synapses allowed.

3.3. 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 modelling competition. 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 section 2). Synaptic normalization is too rigid a constraint compared with the plasticity of the developing nervous system, and models based on this constraint may therefore become too restricted in the range of phenomena they can produce (see also Swindale (1996) and e.g. Elliott and Shadbolt (1998b)). If Hebbian learning rules are modified only to enforce competition and not to represent a possible physiological mechanism this is equally unsatisfactory. Modelling the actual mechanism of competition can give the models more flexibility and potentially a larger explanatory and predictive power. It will also be easier to interpret and extend these models because its variables and parameters are more directly linked to biological processes and mechanisms.

In models that implement consumptive competition (*resource models*), competition between input connections does not have to be enforced but comes about naturally through their dependence on the same target-derived (i.e. postsynaptic) resource. There are two ways in which this can be modelled:

- In *fixed resource models* (section 3.3.1), 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 (as with synaptic normalization) and can increase during development when resource becomes partitioned among the input connections.
- In *variable resource models* (section 3.3.2), even the total amount of resource is not constrained to remain constant, which is a further step towards biological realism. 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 also closer to other consumer–resource systems in biology: organisms need a continuous supply of food (resource) to sustain themselves.

3.3.1. Constant amount of resource. Two fixed resource models of the development of neuromuscular connections (Gouzé *et al* (1983) and the dual constraint model (Bennett and Robinson 1989, Rasmussen and Willshaw 1993)) and one of the development of ocular dominance columns (Harris *et al* 1997) are described. The models proposed by Gouzé *et al* (1983) and Harris *et al* (1997) consider only competition for a postsynaptic resource, whereas the dual constraint model combines competition for a postsynaptic resource with competition for a presynaptic resource (i.e. a presynaptic cell has a fixed amount of resource to distribute among its output connections). Electrical activity plays the most explicit role in the model by Harris *et al* (1997).

3.3.1A. Gouzé et al (1983). This model is one of the earliest to implement competition for a postsynaptic resource. In the model, there are N motor neurons and M muscle fibres. A motor neuron is indexed by n, a muscle fibre by m, and a nerve terminal by nm. The model assumes the following:

(1) Nerve terminals compete for a postsynaptic resource μ, present at concentration μ_m. The total amount of postsynaptic resource is kept constant.
(2) At each nerve terminal, a postsynaptic stabilization factor s is produced from μ. The production of s is autocatalytic and increases with the mean firing rate I_n of the neuron.

(3) A nerve terminal becomes stabilized when the concentration s_{nm} of s reaches a threshold value S.

In terms of differential equations:

$$\frac{\mathrm{d}s_{nm}}{\mathrm{d}t} = kI_n\mu_m s_{nm}^{\alpha} \tag{3}$$

$$\frac{\mathrm{d}\mu_m}{\mathrm{d}t} = -k\sum_{n=1}^{N} I_n\mu_m s_{nm}^{\alpha} \tag{4}$$

where k is a constant and α is an exponent >1 to express the autocatalytic character of the reaction. Since there is no degradation, there is a fixed amount of resource at each muscle fibre m ($\mu_m + \sum_{n=1}^{N} s_{nm} =$ constant). Assuming a Poisson distribution for the initial number of nerve terminals per muscle fibre and a normal distribution for the initial values of μ_m and s_{nm} (I_n may be taken the same for all n), Gouzé *et al* (1983) showed that the exponent α will amplify the initial differences in s_{nm} and that as a result only one nerve terminal per muscle fibre becomes stabilized.

The weak points of the model are that (i) no explicit process is suggested for the autocatalytic reaction; (ii) it uses a threshold value for the stabilization of a terminal; and (iii) it is very parameter sensitive—the value of S has to be set relative to the values of the other parameters to ensure single innervation. Also, the model shows that motor unit size increases with I_n, which is not in agreement with the size principle (see section 2.1.1).

3.3.1B. Dual constraint model. Based on experimental results that suggest a role for both a postsynaptic and a presynaptic resource in the development of neuromuscular connections (see section 2.1.4), the dual constraint model—first proposed by Bennett and Robinson (1989) and later extended and clarified by Rasmussen and Willshaw (1993)—combines competition for both these types of resources. A role for a presynaptic resource was first suggested by Willshaw (1981) (section 3.5.1) and later also by Smalheiser and Crain (1984).

Description of the model. There are N motor neurons and M muscle fibres. A motor neuron is indexed by n, a muscle fibre by m, and a terminal by nm. Each motor neuron has a presynaptic resource A (e.g. a receptor), which is located in all its terminals, in amount A_{nm}. Each muscle fibre has a postsynaptic resource B (e.g. a neurotrophin molecule), in amount B_m, for which motor neuron terminals compete. In the synaptic cleft, a reversible reaction takes place between A and B to produce binding complex C, in amount C_{nm}. Thus

$$A_{nm} + B_m \rightleftharpoons C_{nm}. \tag{5}$$

The binding complex C is essential to the maintenance of a terminal: the size of the terminal is assumed to be directly proportional to C_{nm}. For the rate of change of C_{nm} the following equation is assumed:

$$\frac{\mathrm{d}C_{nm}}{\mathrm{d}t} = \alpha A_{nm}B_m C_{nm}^{\mu} - \beta C_{nm} \tag{6}$$

where α and β are rate constants. Including C_{nm}^{μ} (with $\mu > 0$) in the rate of the forward reaction incorporates a positive feedback: larger terminals favour the forward reaction and so can become larger still. 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. Including C_{nm}^{μ} (with $\mu > 0$) is needed to achieve single innervation (Bennett and Robinson 1989, Van Ooyen and Willshaw 1999a)

The total amount A_0 of presynaptic substance in each motor neuron and the total amount B_0 of postsynaptic substance in each muscle fibre are fixed. Molecules of A can be located in the cell soma and in the terminals of the neuron, either bound or unbound. Thus, the conservation equation for A is

$$A_0 = A_n + \sum_{j=1}^{M} A_{nj} + \sum_{j=1}^{M} C_{nj} \tag{7}$$

where A_n is the amount of A located in the cell soma of motor neuron n.

The amount A_{nm} of unbound presynaptic substance is assumed to be proportional to (i) the size C_{nm} of the terminal (thus incorporating a second positive feedback); and (ii) the amount A_n of presynaptic factor in the cell soma, yielding

$$A_{nm} = K C_{nm} A_n \tag{8}$$

where K is a constant. Bennett and Robinson (1989) did not discuss what process could give rise to the distribution of A given by equation (8). Rasmussen and Willshaw (1993) showed that anterograde transport of A down the axon in combination with retrograde transport of A from the terminal could give rise to such a distribution. The role of the combination of both positive feedback loops (one in equation (6) and one in equation (8)) in achieving single innervation has not been analysed.

Using equations (7) and (8), we obtain

$$A_{nm} = K C_{nm} \frac{A_0 - \sum_{j=1}^{M} C_{nj}}{1 + K \sum_{j=1}^{M} C_{nj}}. \tag{9}$$

Molecules of B can either be unbound in the endplate membrane or bound in one of the terminals. Thus, the conservation equation for B is

$$B_0 = B_m + \sum_{i=1}^{N} C_{im}. \tag{10}$$

Introducing equations (9) and (10) into (6) gives a set of differential equations for how C_{nm} changes over time. For the initial conditions, Bennett and Robinson (1989) chose a random set of terminals whereby each terminal had the same initial value of C_{nm}, so that symmetry was broken only by the spread in initial motor unit sizes. Rasmussen and Willshaw (1993) broke the symmetry also by variation in the initial values of C_{nm}.

Results of the model. By means of simulation, Bennett and Robinson (1989) showed that after an initial phase in which all terminals grow, a state of single innervation is reached in most cases. Using perturbation analysis, Rasmussen and Willshaw (1993) showed that single innervation is indeed a stable state of the model. They also showed that there is an upper limit—proportional to A_0/B_0—on the number of terminals that can be supported by each motor neuron. So if the initial amount of polyneuronal innervation is larger than this limit, then terminals will withdraw, even in the absence of competition, i.e. there is intrinsic withdrawal. They suggested that intrinsic withdrawal should not be regarded as a separate non-competitive mechanism (Thompson and Jansen 1977, Fladby and Jansen 1987) but rather as a side effect of the competitive mechanism.

Neither Rasmussen and Willshaw (1993) nor Bennett and Robinson (1989) analysed whether polyneuronal innervation can also be a stable state of the model. Using bifurcation and phase–space analysis, Van Ooyen and Willshaw (1999a) showed that, for certain parameter settings, polyneuronal states can be stable and can coexist with single innervation states.

Which of these states will be reached depends on the initial amounts of binding complex C in the terminals. The coexistence of stable polyneuronal and single innervation states offers an explanation for partial denervation experiments that show that persistent polyneuronal innervation occurs after reinnervation and recovery from prolonged nerve conduction block (Brown *et al* (1982), Barry and Ribchester (1995); see section 2.1.6), while under unblocked conditions single innervation develops (see section 2.1.3 and figure 3). The model by Van Ooyen and Willshaw (1999b), section 3.3.2D, offers a related explanation for persistent polyneuronal innervation.

To study the formation of topographic maps in the projections from motor neuron pool to muscle (see section 2.1.4), Bennett and Robinson (1989) considered a situation in which the rate constant α of the forward reaction (see equation (6)) takes on different values according to which motor neuron n and which muscle fibre m are involved. This situation is possible if the properties of the presynaptic and postsynaptic substance depend on respectively which motor neuron and which muscle fibre synthesizes them. A topographic map will emerge if these properties change according to position of motor neuron and muscle fibre. In simpler and more general models with a graded affinity between axons and postsynaptic sites (designed for the visual system), Prestige and Willshaw (1975) showed that a topographic map emerges if both the number of axon branches that can contact a postsynaptic cell and the number of postsynaptic sites that an axon can contact are limited; in other words, if, as in Bennett and Robinson (1989), there is both a postsynaptic and a presynaptic constraint causing competition.

Weak points of the dual constraint model are that (i) it does not make clear the identity of the pre- and postsynaptic resource; (ii) a stronger biological justification for the positive feedback loops is needed; and (iii) without electrical activity ($\mu = 0$ in equation (6)), no competitive elimination of connections takes place (see also figure 3(c)), which is not in agreement with recent experimental findings (see section 2.1.6).

Further analyses and extensions of the model. By giving a more specific interpretation of the dual constraint model, Joseph and Willshaw (1996) were able to offer an alternative justification for the dependence of the rate of the forward reaction (in equation (6)) on the size C_{nm} of a motor neuron terminal. They assumed that molecule A represents the protein agrin, and molecule B the acetylcholine receptor (AChR). AChR diffuses freely in the muscle membrane, but when agrin binds to agrin-specific receptors in the muscle, AChRs immobilize and aggregate (Axelrod *et al* 1976, Wallace 1988). Aggregation is an activity-dependent process because it requires Ca^{2+}, which enters the muscle following AChR activation by acetylcholine (the neurotransmitter in motor neuron terminals). The number of aggregated AChRs is represented in the model by C_{nm}, which determines the size of the terminal. However, because agrin does not bind directly to AChR, a different reaction scheme between A and B is required; nonetheless, this reaction scheme also produces equation (6) for the rate of change of C_{nm}. But the rate of the forward reaction is now proportional to the size of the terminal because of the dependence of aggregation on Ca^{2+} influx into the muscle, which is proportional to the amount of AChR activation and therefore to the area of the terminal. Joseph and Willshaw (1996) used the model to explain that, during reinnervation, the regenerating nerve displaces more terminals from the intact nerve when the muscle is paralysed than when it is not (Ribchester 1993). Under conditions of paralysis in the model—which means no Ca^{2+} influx into the muscle—there is a change in the dependence of the rate of the forward reaction on the size of an individual terminal, which gives the small reinnervating terminals some initial advantage in the competitive process.

By combining elements from the models by Joseph and Willshaw (1996) and Kerszberg and Changeux (1993)—so that Ca^{2+} now inhibits AChR production globally and stimulates

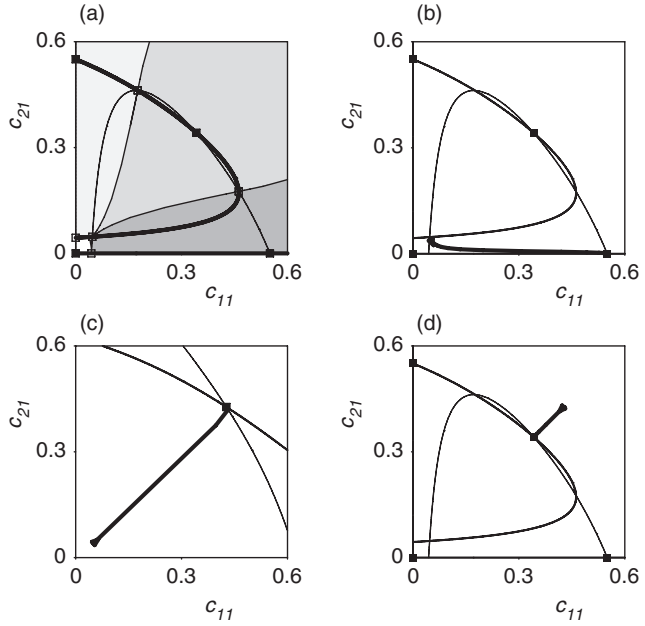

Figure 3. To explain how a nerve conduction block can lead to persistent polyneuronal innervation in the dual constraint model (section 3.3.1B), we consider a system consisting of two motor neurons—indexed as 11 and 21—that both contact the same, single muscle fibre (i.e. $N = 2$, $M = 1$). Note that this means that there is competition for postsynaptic substance only. The parameter settings are such that both single and polyneuronal innervation are stable states of the system (for parameter values, see Van Ooyen and Willshaw (1999a)). c_{nm} is the non-dimensional quantity representing the amount of binding complex ($c_{nm} \equiv C_{nm}/B_0$). If $c_{nm} = 0$, the axon terminal does no longer exist. In (*b*)–(*d*), triangles mark the starting points of trajectories (bold curves). (*a*) The bold and the thin curves are the nullclines of c_{21} and c_{11}, respectively. Intersection points of these lines are the equilibrium points of the system. Filled boxes indicate stable equilibrium points; open boxes indicate unstable equilibrium points. Also drawn are the stable manifolds of the saddle points, which are the lines separating the basins of attraction of the stable equilibrium points. The white area is the basin of attraction of the equilibrium where $c_{11} = c_{21} = 0$ (no innervation), the light grey area that of the equilibrium where $c_{21} > 0$ and $c_{11} = 0$ (single innervation), the dark grey area that of the equilibrium where $c_{11} > 0$ and $c_{21} = 0$ (single innervation), and the intermediate grey area that of the equilibrium where both $c_{11} > 0$ and $c_{21} > 0$ (polyneuronal innervation). (*b*) Normal development: the system goes to a state of single innervation. Although there is also a stable polyneuronal innervation point, this is not reached with normal, low initial values of c_{nm}. For clarity, in (*b*)–(*d*) the unstable equilibria are not indicated. (*c*) As does blocking electrical activity in the neuromuscular system (Thompson *et al* 1979, Duxson 1982, Taxt 1983, Ribchester 1993), blocking activity in the model results in stable polyneuronal innervation. When nerve conduction is blocked, $\mu = 0$ in equation (6), and polyneuronal innervation is the only stable equilibrium. (*d*) Subsequent restoration of activity means that the nullclines are again as in (*a*) and (*b*), but now the starting values of c_{nm} are those reached as in (*c*)—i.e. in the basin of attraction of the polyneuronal equilibrium point. The system goes to this equilibrium and will remain there forever, i.e. persistent polyneuronal innervation. From Van Ooyen and Willshaw (1999a).

AChR aggregation locally—Joseph *et al* (1997) were able to explain the results produced by focal blockade of postsynaptic AChRs (Balice-Gordon and Lichtman 1994) (see section 2.1.6). In the model, a synapse on the blocked region of a partially blocked endplate is unstable because the positive effect of calcium on receptor aggregation is missing while the negative, global effect of calcium on receptor production is still present. When the endplate is completely blocked, the

negative effect of calcium is also missing, creating again a stable situation. For an alternative, but related, explanation of the focal blockade experiments, see sections 3.5.3 and 3.5.4.

3.3.1C. Harris et al (1997). Harris *et al* (1997) proposed a model of the development of ocular dominance columns that incorporates an interesting combination of Hebbian synaptic modification and activity-driven competition for neurotrophins. The model assumes the following:

(1) Each cortical cell has a fixed pool of neurotrophin to distribute over its input connections.
(2) Connection strength increases due to Hebbian LTP and decreases due to heterosynaptic LTD.
(3) The more neurotrophin a synapse has taken up, the higher the rate at which its connection strength increases (Korte *et al* 1995).
(4) The higher the connection strength, the faster the uptake of neurotrophin.

In the description of the model, a single cortical cell i will be considered, which receives input from both right and left eyes.

From assumption (1)

$$N_i^{\mathrm{f}} + (n_i^{\mathrm{r}} + n_i^{\mathrm{l}}) = N_i \tag{11}$$

where N_i is the total amount of neurotrophin available at cortical cell i, $(n_i^{\mathrm{r}} + n_i^{\mathrm{l}})$ is the sum of the amounts currently taken up by the right and left eye inputs, and N_i^{f} is the amount of free neurotrophin left at cell i (see figure 4). The equations controlling connection strength and neurotrophin level are given for the input from the right eye; identical equations hold for the left eye. A maximum level of connection strength is assumed, which is set arbitrarily to 1:

$$w_i^{\mathrm{r}} + f_i^{\mathrm{r}} = 1 \tag{12}$$

where w_i^{r} is the current connection strength of the input from the right eye, and f_i^{r} is the free store of raw material still available at the connection.

From assumptions (2) and (3), there is a reversible interchange between connection strength and free store of raw material:

$$f_i^{\mathrm{r}} \underset{K^-}{\overset{K^+}{\rightleftharpoons}} w_i^{\mathrm{r}}$$

with

$$K^+ = k^+ n_i^{\mathrm{r}} v_i a^{\mathrm{r}} \tag{13}$$

$$K^- = \beta_1 v_i \tag{14}$$

where k^+ and β_1 are constants, v_i is the firing rate in cortical cell i, and a^{r} is the activity in the thalamic input from the right eye. Using equations (12)–(14), we obtain for the rate of change of w_i^r

$$\frac{\mathrm{d}w_i^{\mathrm{r}}}{\mathrm{d}t} = k^+ n_i^{\mathrm{r}} v_i a^{\mathrm{r}} (1 - w_i^{\mathrm{r}}) - \beta_1 v_i w_i^{\mathrm{r}}. \tag{15}$$

From assumption (4),

$$N_i^{\mathrm{f}} \underset{\beta_2}{\overset{w_i^{\mathrm{r}}}{\rightleftharpoons}} n_i^{\mathrm{r}}$$

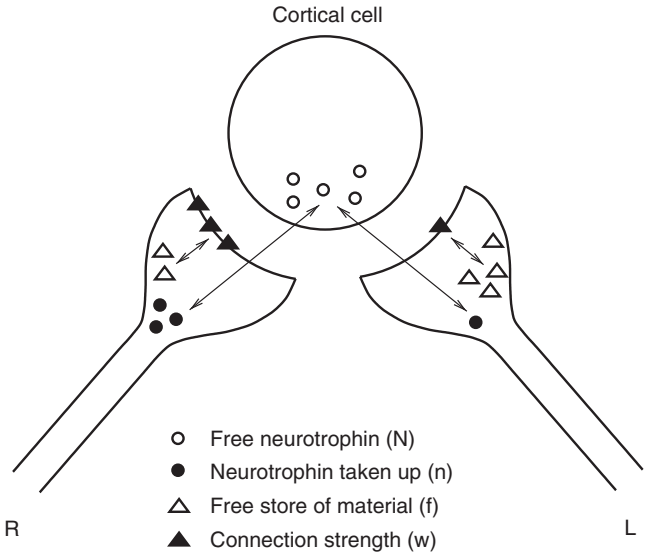

Figure 4. The model by Harris *et al* (1997) (section 3.3.1C). Each cortical cell i receives input from both the left (L) and the right (R) eye. The connection from each eye has a fixed total amount of material available, so that—for the right eye, for example—the current connection strength w_i^{r} plus the free store of raw material f_i^{r} remains constant. The rate at which raw material is reversibly transformed into connection strength is affected by the amount n_i^{r} of neurotrophin taken up by the connection. Each cortical cell has a fixed total amount of neurotrophin available, so that the amounts taken up by the right and left eye connections ($n_i^{\mathrm{r}}, n_i^{\mathrm{l}}$) plus the amount of free neurotrophin left at cortical cell i remains constant. Drawn after Harris *et al* (2000).

and, using equation (11)

$$\frac{\mathrm{d}n_i^{\mathrm{r}}}{\mathrm{d}t} = [N_i - (n_i^{\mathrm{r}} + n_i^{\mathrm{l}})]w_i^{\mathrm{r}} - \beta_2 n_i^{\mathrm{r}} \tag{16}$$

where β_2 is a constant. Equations (15) and (16) form the crucial part of the model.

The model shows that ocular dominance columns develop normally—even with positive inter-eye correlations in activity (cf section 3.1)—when available neurotrophin is below a critical amount and that column development is prevented when excess neurotrophin is added. Harris *et al* (2000) showed that the model can also account for the experimental results that column formation is prevented by removal of neurotrophin (Cabelli *et al* 1997) and that the shift to the open eye in monocular deprivation experiments is mitigated by excess neurotrophin (Carmignoto *et al* 1993, Hata *et al* 1996) (see section 2.2.3).

A criticism of the model is that it incorporates only physiological plasticity and that it does not explicitly describe anatomical plasticity, while the latter is (mainly) involved in the formation of ocular dominance columns and its breakdown following infusion of neurotrophin (see section 2.2, and also Elliott and Shadbolt (1998b)). Essential features of the model are assumptions (1), (3), and (4). Assumption (4) is motivated by evidence that neurotrophin can be released in an activity-dependent manner (Blochl and Thoenen 1995), although this says something about the amount available and not directly about the rate constant for uptake. Moreover, if the released neurotrophin diffuses too far, the connections from both eyes would profit from increased release, which would invalidate assumption (4).

3.3.2. Variable amount of resource. As opposed to the models in section 3.3.1, in variable resource models it is not required that the total amount of resource should remain constant. There is continuous production and uptake or binding of neurotrophin; continuous uptake or binding is needed to sustain the axonal arbors and synapses. The models are formulated in terms that usually have a clear biological interpretation (production, decay, growth). Elliott and Shadbolt (1998a) and Elliott *et al* (1996a) proposed models of competition in the development of the visual system, whereas the models by Jeanprêtre *et al* (1996) and Van Ooyen and Willshaw (1999b) were not intended to model a particular system and study in general competition for a target-derived neurotrophic factor. Although the model by Elliott *et al* (1996a) is significantly different from the other models in this section—in that resource is not explicitly modelled—I still consider it here because the amount of resource is interpreted in terms of postsynaptic activity, which is variable.

3.3.2A. Elliott et al (1996a). Elliott *et al* (1996a) used an approach from statistical mechanics to model sprouting and retraction of axonal processes (i.e. anatomical plasticity). The model consists of a sheet of presynaptic cells and a sheet of postsynaptic cells, whereby each presynaptic cell has axonal projections over a preferred region of the postsynaptic sheet. The energy of the network is defined as

$$E = -\tfrac{1}{2} \sum_{\langle ij \rangle} \sigma_i \sigma_j \tag{17}$$

where i and j index axonal processes of presynaptic cells and $\sigma_i = +1(-1)$ denotes activity (inactivity) of the presynaptic cell from which process i emerges. The symbol $\langle ij \rangle$ means that the product $\sigma_i \sigma_j$ contributes to the sum if and only if the axonal processes are attached to the same or to adjacent postsynaptic cells. The energy E_i of any particular axonal process i is defined implicitly in equation (17). Thus, axonal processes that have the same activation state as axonal process i, and that are attached to the same or to adjacent postsynaptic cells, decrease the energy E_i, while processes of opposite states of activation increase it. Low energy is interpreted as high trophic support: a postsynaptic cell is stimulated to release neurotrophin when the axons innervating it are active (e.g. Zafra *et al* (1991)). The sum over nearest postsynaptic neighbours represents local diffusion through the target field.

After a pattern of presynaptic activity is established, active presynaptic cells are selected to undergo, with a certain probability, sprouting and retraction such that the energy of the network is minimised. Only active presynaptic cells are selected because active processes are assumed to require greater trophic support than inactive ones. Energy minimisation thus corresponds to cells searching for the greatest trophic support by sprouting into postsynaptic regions of high support and retracting from postsynaptic regions of low support. Energy minimisation implements competition because pairs of axonal processes of opposite activation increase the energy. The model was used to study the development of ocular dominance columns, the plasticity of adult somatosensory maps, and various pharmacological manipulations of the developing visual system (Elliott *et al* 1996a–c, 1997).

A criticism of the model is that it implements only a very crude approximation of competition for neurotrophin. Furthermore, Miller (1998) showed that the energy function used in this model is mathematically equivalent to the energy function used in models that are formulated in terms of synaptic strength modification of anatomically fixed connections (Miller *et al* 1989). However, Elliott *et al* (1998) argued that this equivalence of energy functions does not entail equivalence of models and that there are significant dynamical differences.

3.3.2B. Elliott and Shadbolt (1998a). Elliott and Shadbolt (1998a) proposed a model (improved from Elliott and Shadbolt (1996)) of the development of the visual system that explicitly describes anatomical plasticity and incorporates the role of electrical activity. Their model will be described for the case of a single target (e.g. a cortical cell) with a number of innervating axons (e.g. from the LGN).

Description of the model. The model is formulated in discrete time steps initially and then transformed into differential equations. The variable in the model is the number s_i^n of synapses that axon i has on the target at time step n. The target releases neurotrophin, in amount r^n

$$r^n = T_0 + T_1 f^n \tag{18}$$

where T_0 is a constant representing the activity-independent component of release, T_1 is a constant for the activity-dependent component, and $0 \leqslant f^n \leqslant 1$ is the mean activity of a synapse averaged over all synapses impinging onto the target:

$$f^n = \frac{\sum_i s_i^n a_i^n}{\sum_i s_i^n} \tag{19}$$

where $a_i^n \in [0, 1]$ is the level of electrical activity of axon i. The uptake u_i^n of neurotrophin by axon i increases with its number of synapses and its level of activity:

$$u_i^n = Q^n r^n s_i^n g(a_i^n) \rho_i^n \tag{20}$$

where Q^n is a constant of proportionality, g is some function describing the dependence of neurotrophin uptake on the axon's electrical activity, and ρ_i is the affinity of each synapse for the neurotrophin and is interpreted as the number of neurotrophin receptors. It is further assumed that the total uptake of neurotrophin by all axons completely exhausts the available pool of neurotrophin at each time step. This means that $\sum_i u_i^n = r^n$, which defines Q^n as

$$Q^n = \frac{1}{\sum_i s_i^n g(a_i^n) \rho_i^n}. \tag{21}$$

The function g is

$$g(a_i^n) = a + a_i^n \tag{22}$$

where a is a constant determining the capacity of an inactive axon to take up the neurotrophin. Uptake of neurotrophin increases the number of synapses (for references, see section 3.3.2D):

$$s_i^{n+1} - s_i^n = \epsilon(u_i^n - s_i^n) \tag{23}$$

where ϵ is a constant determining the growth rate. Note that for an axon to sustain its synapses it needs to take up neurotrophin; if $u_i^n = 0$, the number of synapses decreases. Equations (20) and (23) incorporate a positive feedback: neurotrophin increases the number of synapses, and more synapses mean a higher uptake of neurotrophin. Putting all the equations together, we have

$$s_i^{n+1} - s_i^n = \epsilon s_i^n \left[\left(T_0 + T_1 \frac{\sum_j s_j^n a_j^n}{\sum_j s_j^n} \right) \frac{(a + a_i^n)\rho_i^n}{\sum_j s_j^n (a + a_j^n)\rho_j^n} - 1 \right]. \tag{24}$$

From equation (24) a differential equation is obtained by omitting n everywhere and replacing the left side by $\mathrm{d}s_i/\mathrm{d}t$. For the number ρ_i of neurotrophin receptors per synapse, two cases were considered. Either ρ_i was a fixed number or it was proportional to the recent time average $\bar{a}_i^n$ of the axon's activity, i.e.

$$\rho_i = \lambda \bar{a}_i^n \Big/ \sum_x s_{xi}^n \tag{25}$$

where λ is an arbitrary constant and x is the index of a target (two or more targets need to be considered in this case). Dividing by the axon's total number of synapses means that the receptors are distributed over the axon's synapses.

Results of the model. Elliott and Shadbolt (1998a) analysed mathematically the case for two innervating axons and a single target. Both choices of the number ρ_i of neurotrophin receptors give essentially identical results and numerically they found little qualitative difference when more than two innervating axons were considered. When the activity-independent uptake of neurotrophin dominates the activity-dependent uptake (the limit $a \to \infty$), then both axons survive. When the activity-dependent uptake is sufficiently strong (a sufficiently small), single innervation occurs, where the axon with the highest activity level a_i wins the competition. When both axons have the same mean activity level but are not necessarily active at the same time, then if the activity-dependent release of neurotrophin dominates ($c \equiv T_0/(aT_1) < 1$), single innervation always develops, for all values of $p < 1$, where p is the probability that both axons have the same activity in any given time interval (only binary activity is considered; $p = 0.5$ represents uncorrelated activity). The two fixed points of single innervation, where either of the axons is present, are both stable; the fixed point of multiple innervation is unstable. Which of these stable points will be reached in any specific situation depends on the axons' initial number of synapses. Conversely, if the activity-independent release dominates ($c > 1$), then both axons survive, for all values of $p < 1$. The stability of the fixed points is now exactly the reverse from above.

Elliott and Shadbolt (1998b) extended the simple system with only one target cell to a full model consisting of two sheets of LGN cells, one representing the left eye and the other representing the right eye, and one sheet of cortical cells. Further: (i) each LGN cell was constrained to arborize over a fixed square patch of cortical cells; (ii) equation (25) was used for the number of neurotrophin receptors per synapse; and (iii) the neurotrophin released by the cortical cells was assumed to diffuse through the target field. They showed that this model permits the formation of ocular dominance columns, even in the presence of positively correlated interocular images (with synaptic normalization this would have been possible only with subtractive normalization—see section 3.1). In accordance with the simple system, they found that a high level of neurotrophin released in an activity-independent manner prevents the formation of ocular dominance columns. To compare their results with neurotrophin infusion experiments (see section 2.2.3), a high level of neurotrophin released in an activity-independent manner was taken to represent the level of neurotrophin availability by exogenous cortical infusion.

In a further study, Elliott and Shadbolt (1999) used their competition model to show that spontaneous retinal activity can drive the segregation of afferents into eye-specific laminae (LGN) and columns (cortex), as well as the refinement of topographic and receptive fields in the retinogeniculocortical pathway. Again, afferent segregation and receptive field formation are disrupted in the presence of exogenous neurotrophins.

Criticisms of the model are the following. (i) In equation (19), the activity-dependent release by the target is dependent not just on its level of activity but on its level of activity *divided* by the total number of synapses impinging onto the target. Why this is so and how this normalization affects the results is not made clear. (ii) In the model, electrical activity directly increases the uptake of neurotrophin (equation (20)). Although electrical activity can increase uptake by increasing the number of neurotrophin receptors (Salin *et al* 1995, Birren *et al* 1992) or, by stimulating axonal branching, the number of synapses (Ramakers *et al* 1998), this is not the way in which it was modelled in equation (20).

3.3.2C. Jeanprêtre et al (1996). Jeanprêtre *et al* (1996) were the first to model neurotrophic signalling in a fully dynamical way: the model describes changes in the extracellular concentration of neurotrophin resulting from production, degradation, and binding of neurotrophin.

A single target is considered at which there are n innervating axons. Neurotrophin is released by the target into the extracellular space and is removed by the axons through receptor-mediated uptake. The model also considers removal of neurotrophins other than by the innervating axons: i.e. by degradation and diffusion and by receptor-mediated uptake by neural and non-neural cells (e.g. glia) in the target area. The variables in the model are the 'axonal vigour', x_i for axon i, and the concentration S of neurotrophin in the extracellular space. The axonal vigour represents the ability of each axon to take up neurotrophin and is proportional to the total number of neurotrophin receptors (occupied plus unoccupied) at each axon. Focusing on the essential elements of the model, ignoring receptor-mediated uptake of neurotrophin other than by the innervating axons, we obtain

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = x_i G_i(x_i)\left[\frac{S}{K_{d,i}+S} - \frac{S_i^T}{K_{d,i}+S_i^T}\right] \tag{26}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = Q - AS - \sum_{i=1}^{n} \frac{x_i S}{K_{d,i}+S} \tag{27}$$

where Q is the rate of release of neurotrophin; A is the rate constant for degradation; $S/(K_{d,i}+S)$ is the fraction of occupied receptors, which follows from assuming Michaelis–Menten kinetics, where $K_{d,i}$ is a constant of the binding reaction; $G_i(x_i)$ is a function with the only restriction that it always remains between two positive constants; and S_i^T is a constant that represents the value of S that gives zero growth of the vigour of axon i. Thus, in equation (27), the amount of neurotrophin that is removed by axon i increases with the number $x_i S/(K_{d,i}+S)$ of occupied receptors. In equation (26), the rate of change of vigour depends on the vigour itself (i.e. positive feedback) and increases with the number of occupied receptors, over and above some threshold $S_i^T/(K_{d,i}+S_i^T)$.

By means of a Lyaponov function, they showed that the system will approach a stable equilibrium point in which a single axon—the one with the lowest value of S_i^T—survives. Although well known from models of population dynamics (Yodzis 1989), they rightly emphasized that the widespread intuitive belief that competition is a consequence of resources being produced in limiting amounts is too simplistic. For example, the number of surviving axons cannot be increased by increasing the rate of release of neurotrophin. The higher release becomes again limiting by the resulting increase in axonal vigour.

Criticisms of the model are that (i) it can only explain single innervation; however, Kohli and Clarke (1997) showed that if axonal vigour is bounded—i.e. a ceiling on $G_i(x_i)$ is imposed—multiple innervation also becomes possible; (ii) equation (26), which specifies the rate of change of axonal vigour (including the positive feedback), is postulated but not explicitly derived from underlying biological mechanisms; (iii) the thresholds do not emerge from the underlying dynamics but need to be assumed; and (iv) in this formulation, axons have only a single target, whereas in many biological systems each axon often innervates a number of targets.

3.3.2D. Van Ooyen and Willshaw (1999b). Independently from Jeanprêtre *et al* (1996), Van Ooyen and Willshaw (1999b) proposed a model of competition that implements neurotrophic signalling in a fully dynamical way. Unlike Jeanprêtre *et al* (1996), they did not need to assume *a priori* thresholds and could explain both single and multiple innervation. Important variables in their 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

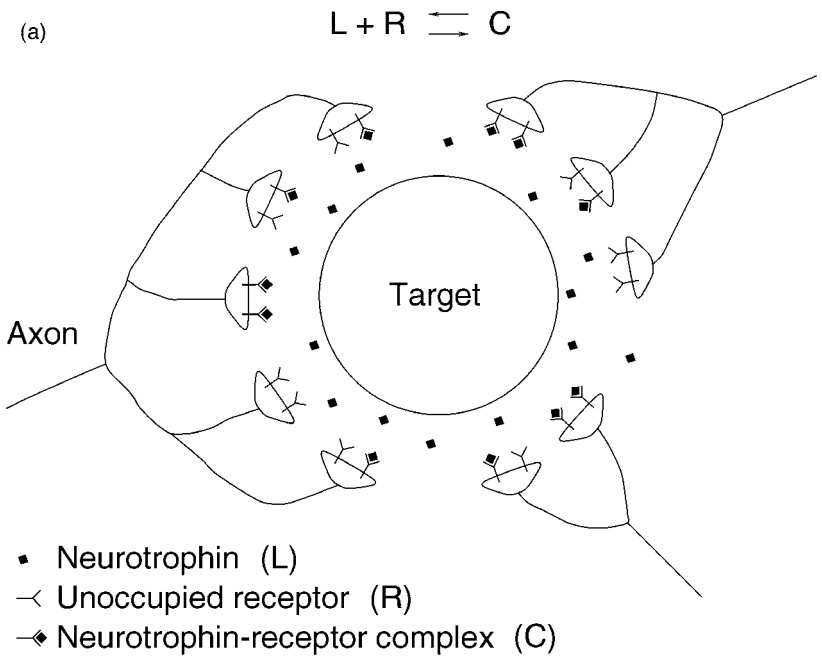

Figure 5. The model by Van Ooyen and Willshaw model (section 3.3.2D) (from Van Ooyen and Willshaw (1999b); see this paper for parameter values). (*a*) Target cell with three innervating axons, each with a different degree of branching. The target releases neurotrophin, which binds to neurotrophin receptors at the axon terminals. For three different classes of growth functions (as defined in section 3.3.2D), (*b*)–(*d*) show the development of innervation for a system of five innervating axons, where each axon has a different competitive strength, β_i (defined in section 3.3.2D). 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 quasi-steady state; in (*e*) and (*f*), $\beta_1 > \beta_2$; in (*g*), $\beta_1 = \beta_2$). 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 curves are the nullclines of ϕ_1 and the light curves 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 of the system. A filled square indicates a stable equilibrium point; an open square indicates an unstable equilibrium point. Vectors indicate direction of change. (*b*) Class I: elimination of axons takes place until a single axon remains. 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 (the stable equilibrium point at ($\phi_1 = 0, \phi_2 = 0$) is not indicated because it too close to another, unstable point). For a sufficiently higher value of K_i, for example, the stable equilibrium point where both axons coexist would disappear.

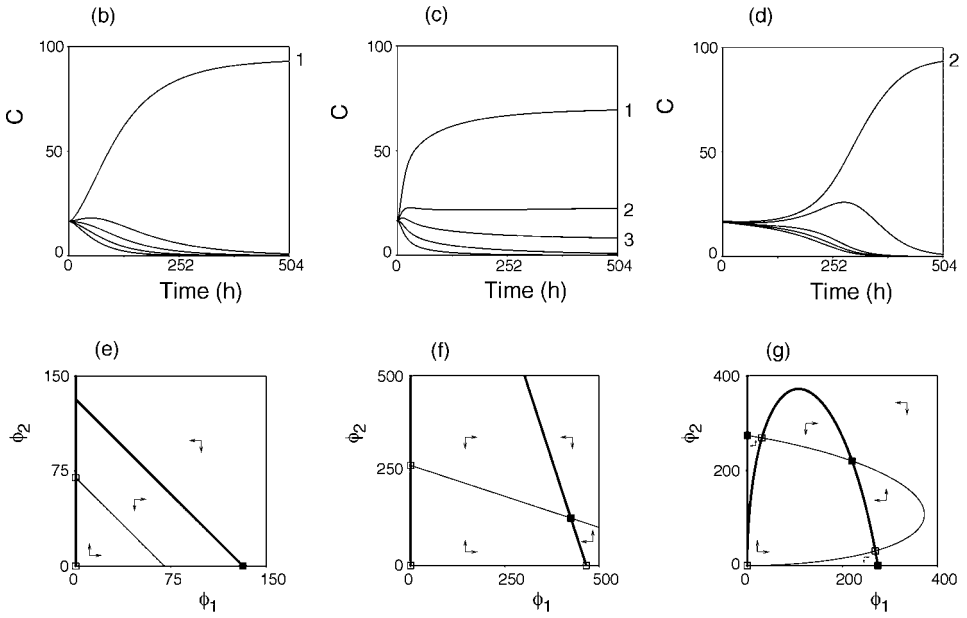

Figure 5. (Continued)

the others—was derived directly from underlying biological mechanisms. Following binding to receptor, neurotrophins can increase the terminal arborization of an axon (Campenot 1982a, b, Edwards *et al* 1989, Yasuda *et al* 1990, Yunshao *et al* 1992, Diamond *et al* 1992, Cohen-Cory and Fraser 1995, Causing *et al* 1997, Schnell *et al* 1994, Funakoshi *et al* 1995) 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 by 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 (figure 5(a)). 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 of 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

$$\frac{dC_i}{dt} = (k_{a,i}LR_i - k_{d,i}C_i) - \rho_i C_i \tag{28}$$

$$\frac{dR_i}{dt} = \phi_i - \gamma_i R_i - (k_{a,i}LR_i - k_{d,i}C_i) \tag{29}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \sigma - \delta L - \sum_{i=1}^{n} (k_{\mathrm{a},i} L R_i - k_{\mathrm{d},i} C_i)/v \tag{30}$$

where v is the volume of the extracellular space. The term $(k_{\mathrm{a},i} L R_i - k_{\mathrm{d},i} C_i)$ represents the net amount of neurotrophin that is (continuously—to counter $\rho_i C_i$) being bound to receptor. Axons that 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 signalling 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

$$\tau \frac{\mathrm{d}\phi_i}{\mathrm{d}t} = f_i(C_i) - \phi_i \tag{31}$$

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

$$f_i(C_i) = \frac{\alpha_i C_i^m}{K_i^m + C_i^m}. \tag{32}$$

Depending on the values of m and K, the growth function is a linear function (class I: $m = 1$ and $K_i \gg C_i$), a Michaelis–Menten function (class II: $m = 1$ and $K_i \not\gg C_i$), 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 (e.g. 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 release of neurotrophin (see figure 5). The axon that survives is the one with the highest value of the quantity $\beta_i \equiv (k_{\mathrm{a},i}(\alpha_i/K_i - \rho_i))/(\gamma_i(k_{\mathrm{d},i} + \rho_i))$, which is interpreted as the axon's competitive strength. For class I, only in the 'degenerate' case when two axons have *exactly* the same parameter values can they coexist. If the growth function is a saturating function—classes II and III—more than one axon may survive (multiple innervation); the higher the rate σ of release of neurotrophin, the more axons survive. For class III, stable equilibria for 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 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 coexistence of several stable equilibria for class III implies that an axon that is removed from a multiply innervated target may not necessarily survive ('regenerate') when replaced with a low number of neurotrophin receptors (figures 6(*a*), (*b*)).

The model can account for the following observations:

- Following a stage of hyperinnervation, 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

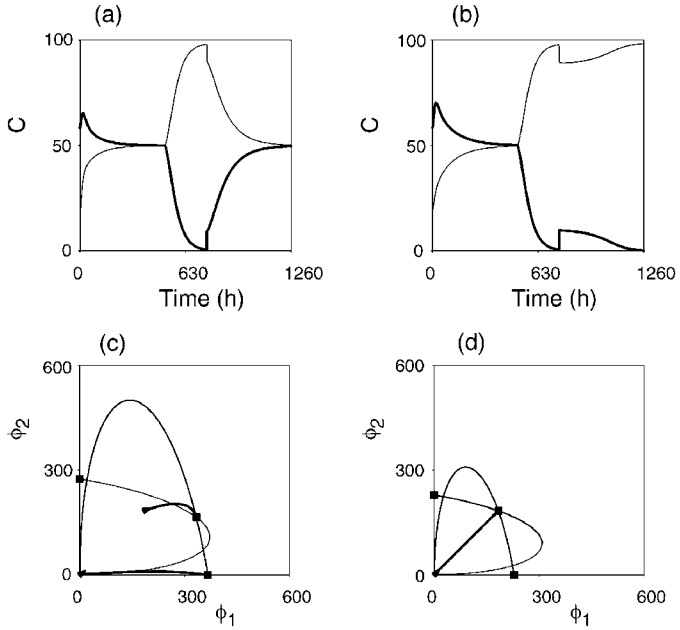

Figure 6. The implications of the coexistence of stable states of single and multiple innervation for class III in the model by Van Ooyen and Willshaw (1999b) (section 3.3.2D). In (*a*), (*b*), removal of an axon from a multiply innervated target and subsequent replacement, for (*a*) class II and (*b*) class III (see section 3.3.2D). At $t = 504$ h, axon 1 (bold curve) is removed by setting $\alpha_1 = 0$. At $t = 756$ h, axon 1 is replaced by setting α_1 back to its original value, with initial conditions $\phi_1 = 30$, $R_1 = \phi_1/\gamma$, and $C_1 = 0$. Only for class II the replaced axon can survive. For class III, in order for the replaced axon to survive, a much higher initial value of ϕ_1 would be required. From Van Ooyen and Willshaw (1999b). The phase–space plots of (*c*) and (*d*) illustrate how, for class III, persistent multiple innervation can arise after recovery from nerve conduction block, in a system of two innervating axons. For explanation of nullclines and symbols, see figure 5 (for clarity, the unstable equilibria are not indicated). The basins of attraction of the equilibrium points are comparable with those in figure 3(*a*). The triangles mark the starting points of trajectories (bold curves). As shown in (*c*), under normal conditions—with electrically active axons that have a different level of activity (represented by $\alpha_1 = 400$ and $\alpha_2 = 300$; other parameter values as in figure 5(*g*)) and a low initial number of receptors (i.e. ϕ_i is low: $\phi_1 = \phi_2 = 0.25$)—single innervation develop. When activity is blocked (values of α_i lower and the same: e.g. $\alpha_1 = 250$ and $\alpha_2 = 250$), as in (*d*), the same initial conditions lead to multiple innervation. Subsequent restoration of activity means that the nullclines are again as in (*c*), but now the starting values of ϕ_i are those reached as in (*d*)—i.e. in the basin of attraction of the polyneuronal equilibrium point. The system goes to this equilibrium and will remain there forever, i.e. persistent polyneuronal innervation. Another way in which persistent multiple innervation can arise following a nerve conduction block is through altering the rate of release of neurotrophin, σ, which also changes the sizes of the basins of attraction of the equilibria.

reinnervation and recovery from prolonged nerve conduction block (Barry and Ribchester (1995), see sections 2.1.6 and 3.3.1B). In terms of the model, conduction block changes the sizes of the basins of attraction of the equilibria (via changes in the competitive strength β_i or in the rate σ of release of neurotrophin), so that the system can go to an equilibrium of multiple innervation, while under normal conditions single innervation develops. Once the conduction block is removed, the system will remain in the basin of attraction of the multiple innervation equilibrium (see figures 6(*c*), (*d*)). The dual constraint model, section 3.3.1B, offers a related explanation for persistent multiple innervation.

- Increasing the amount of target-derived neurotrophin delays the development of single innervation (class I) (see section 2.1.5) or increases the number of surviving axons (classes II and III) (e.g. in epidermis: Albers *et al* (1994)).

Further, the following points should be noted:

- If the biological interpretation is that the axon's total number of neurotrophin receptors changes because of changes in its arborization, then this means that, during competition, a winning axon elaborates its branches and a losing axon retracts branches (as described for biological systems in sections 2.1.2 and 2.2.2).
- For competition to occur, it is not necessary that there is presynaptic or postsynaptic activity, or that there is activity-dependent release of neurotrophin (cf Snider and Lichtman (1996)). The axon's competitive strength, β_i, can be influenced also by other factors than presynaptic activity. Thus, both presynaptic and postsynaptic activity may be influential but are not decisive (Ribchester 1988, Costanzo *et al* 2000). The fact that inactive postsynaptic cells often appear to have increased rather than decreased neurotrophin release (Pittman and Oppenheim 1979, Snider and Lichtman 1996) poses no problem for the occurrence of competition in the model.
- For class III, the dependence on initial conditions means that it is difficult for innervating axons to displace existing axons, even if the innervating axons have a higher competitive strength than the existing axons. This form of plasticity is required in learning, where new experiences should be unable to overwrite the memories already laid down (Lichtman *et al* 1999). When axons should occupy targets that already have innervation—as in regeneration—the model suggest that it is more efficient to increase the number of receptors on the regenerating axons than to increase the amount of neurotrophin (which also affects the existing axons).
- Decreasing the difference in competitive strengths between the different axons delays the development of single innervation or increases the number of surviving axons (the latter only for classes II and III).
- The model can be, and is (Ribchester, personal communication), tested experimentally. The model predicts that axons that are being eliminated will have a small number of neurotrophin receptors. The shape of the growth function—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 it has over all its synapses. In relating axon survival to neurotrophin concentration, the model predicts, for example, that the smaller the value of K_i of the growth function, the lower the concentration of neurotrophin needed to rescue more axons.

Criticisms of the model are that (i) rather than study a number of different classes of growth functions, it would be better to derive the critical properties of the growth function responsible for producing a particular result; (ii) in this formulation, axons 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 between branches of the same axon (as in the dual constraint model); and (iii) the effects of activity have not yet been studied explicitly (for example, σ can be made dependent on postsynaptic activity).

Further analyses and extensions of the model. 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 fibres, where they are completely intermingled (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. Modelling local release of neurotrophin along the target and diffusion of neurotrophin in the extracelluar 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). This can explain that (i) when coexisting axons are found on mature muscle cells they are physically separated (Kuffer *et al* 1977, Lømo 1980, Lo and Poo 1991) and (ii) a positive correlation exists between the size of the dendritic tree and the number of innervating axons surviving into adulthood (Hume and Purves 1981, Purves and Hume 1981, Purves 1994). The latter is not a matter of available space because in, for example, the ciliary ganglion of adult rabbits, all neurons—with no dendrites at all or with many dendrites—are initially innervated by the same number of axons.

In another extension of the model, Van Ooyen and Willshaw (2000) considered a single target that releases two types of neurotrophin (e.g. Barde (1989), McManaman *et al* (1989), Lindsay *et al* (1994)) and at which there are two types of innervating axons. Each axon type can respond to both neurotrophin types. The following two situations were examined. (i) 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. (ii) 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 (i) and (ii), 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 (i), this means that each type of receptor should bind preferentially, but not necessarily exclusively, to one type of neurotrophin. For (ii), 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. This occurs, for example, on Purkinje cells (Crepel 1982), where climbing fibres compete with each other during development until only a single one remains, which coexists with parallel fibres innervating the same Purkinje cell.

In population biology, the concept of competition is well developed (see section 1). 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. $\mathrm{d}R_i/\mathrm{d}t = \mathrm{d}C_i/\mathrm{d}t = 0$), they showed that equations (28)–(30) can be rewritten as

$$\frac{\mathrm{d}\phi_i}{\mathrm{d}t} = \phi_i(g_i(L, \phi_i) - \lambda_3) \tag{33}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \sigma - \delta L - \sum_{i=1}^{n} \phi_i h_i(L) \tag{34}$$

where the function $g_i(L, \phi_i)$ encompasses the growth function, and the function $h_i(L) \equiv \lambda_1 L/(\lambda_{2,i} + L)$ includes the binding kinetics of neurotrophin to receptor (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 for 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, and $g_i(L, \phi_i) - \lambda_3$ is the numerical response of the consumer. For class I of the general growth function, $g_i(L, \phi_i) = g_i(L) = \lambda_{4,i} L/(\lambda_{2,i} + L)$.

Equations (33) and (34), for class I, also show the similarities with the model by Jeanprêtre *et al* (1996). Variable x_i corresponds to ϕ_i (especially if $\rho_i = \gamma_i$), variable S is L, and $S/(K_{d,i} + S)$ has a similar form as $h_i(L)$ and $g_i(L)$. One difference is that the expression with S_i^T, in equation (26), varies among axons, unlike the corresponding λ_3, in equation (33). Van Ooyen and Willshaw's model also encompasses the dual constraint model (with only a postsynaptic resource): for class III, the isocline picture is qualitatively the same as that of the dual constraint model (cf figures 3(a) and 5(g)).

3.4. Interference competition: competition for space

Competition for space occurs if some essential resource can be obtained only by monopolizing some portion of space. The resource may be space itself or may be some immobile resource. The model by Van Essen *et al* (1990) and the induced-fit model by Ribchester and Barry (1994), both of the neuromuscular system, can be classified as incorporating a form of competition for space; this is most explicit in the model by Van Essen *et al* (1990).

3.4.1. Van Essen et al (1990). Van Essen *et al* (1990) incorporated 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. The notion of a scaffold was motivated by experiments showing that the basal lamina at the endplate persists for long periods after denervation and is recognized by regenerating axons as a site for differentiation of synapses (e.g. Marshall *et al* (1977), Sanes *et al* (1978)).

In the model (figure 7), each endplate is a one-dimensional structure of fixed length, consisting of a number of equally spaced positions. A terminal occupies a number of these positions and grows by occupying more positions, at the expense of the size of other terminals. Scaffold—an immobile structure, which does not diffuse—is formed from a precursor that is synthesized by the muscle fibre and is continuously incorporated into the basal lamina underneath nerve terminals, but not in vacant positions of the endplate. There is also a continuous turnover of scaffold, which is greater in vacant positions than in innervated positions. In the presynaptic terminal, a scaffold-recognition signal is generated that is proportional to the scaffold concentration immediately underneath; this signal can spread over a small distance within the presynaptic terminal. The growth of each terminal is simulated as a stochastic process, whereby the probability that a terminal will increase or decrease its size depends on a weighted average of the scaffold-recognition signals arising within a small distance from each end of the terminal. The higher this average, the higher the probability of growth and the smaller the probability of retraction.

Starting with polyneuronal innervation, the model showed that even after many iterations, a high percentage (20% in the reported simulation) of muscle fibres remained polyneuronally innervated, so it is not clear whether this model can account for single innervation. Nerve terminal elimination occurred relatively rapidly, however, if the probability of growth was also made proportional to the size of the terminal (positive feedback)—but in this case it seems that the scaffold did not play a critical role anymore.

3.4.2. Induced-fit model. By analogy with enzyme–substrate and antigen–antibody binding, Ribchester and Barry (1994) proposed a model of synaptic competition based on induction of

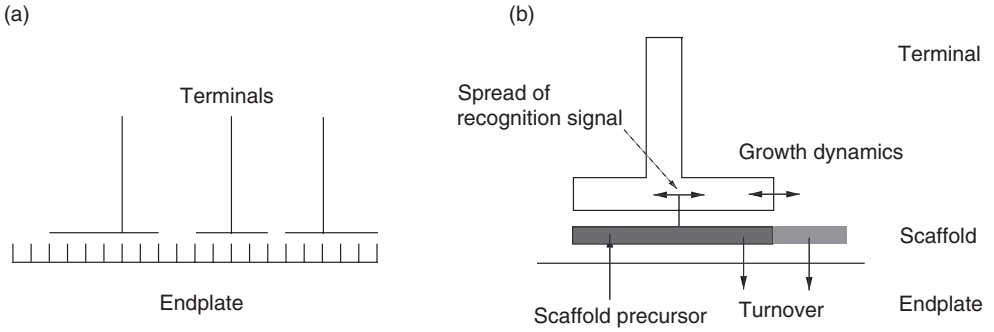

Figure 7. The model by Van Essen *et al* (1990) (section 3.4.1). (*a*) An endplate consisting of a number of equally spaced positions. A terminal occupies a number of these positions and grows by occupying more positions, at the expense of the size of the other terminals. (*b*) Signals and mechanisms involved in the growth (or retraction) of each terminal. Drawn after Van Essen *et al* (1990).

selective adhesion between nerve terminal and muscle endplate. The model, which was not given in mathematical terms, assumes the following:

(1) Nerve terminals from different axons have different isoforms of an adhesion molecule. Each endplate may express a number of different complementary isoforms.
(2) Nerve terminals induce a conformational change in the complementary adhesion molecules in the endplate so that goodness-of-fit increases. (Instead of a conformational change, the endplate could be induced to increase the expression of the appropriate complementary isoform.)
(3) Competing nerve terminals can occupy synaptic space because there is a partial fit between uncomplementary isoforms.
(4) With time, a conformational change in, or expression of, a particular isoform becomes more permanent; this could represent a form of positive reinforcement.
(5) Electrical activity in a terminal accelerates the conformational change or synthesis of the appropriate complementary isoform.

The model was used to explain that nerve conduction block delays or inhibits elimination of polyneuronal innervation in partially denervated and reinnervated muscle (see figure 8) (Taxt (1983), Barry and Ribchester (1994, 1995); see also sections 2.1.3 and 2.1.6).

To test whether the model can indeed explain mononeuronal innervation as well as results from denervation experiments, it should be expressed in more specific, mathematical terms. It is also not clear what molecules could be involved, but isoforms of N-CAM were suggested. However, normal elimination of synapses occurs in various transgenic animals in which expression of cell surface molecules, such as N-CAM, has been disrupted (Sanes *et al* 1998).

The induced-fit model is reminiscent of the marker induction model of the establishment of ordered nerve connections between retina and optic tectum (Willshaw and Von der Malsburg 1979). In this model, molecular markers of several different types label the retinal cells, with nearby retinal cells carrying similar collections of markers. During development, the markers are induced, through the synapses formed, onto the optic tectum. At each tectal site, the markers from the various retinal cells that are innervating it become blended together with markers from neighbouring tectal sites. A positive feedback loop is set up whereby the pattern of retinotectal connections is gradually refined according to the match between the patterns of retinal and tectal markers at each synapse, leading to changes in the profile of markers across

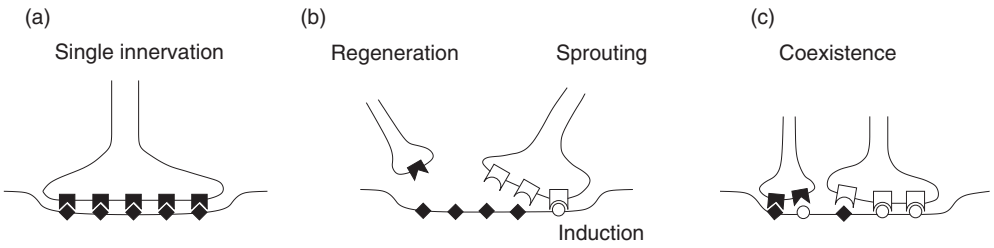

Figure 8. The induced-fit model of synaptic competition (section 3.4.2), as applied to explain that conduction block delays or inhibits elimination of polyneuronal innervation in partially denervated and reinnervated rat muscle. (*a*) The initial state of single innervation. Complementary adhesion molecules cause a tight bond between the motor nerve terminal and the muscle fibre. (*b*) After denervation of the muscle fibre by injuring the axon, the muscle fibre may become reinnervated by regeneration of the damaged axon and by sprouting of intact axons. The goodness-of-fit of the regenerating axon depends on how long the new sprout from the intact axon had had time to respecify the isoforms (induction) on the endplate, and also on how active the sprout had been. Thus, under conduction block—which is assumed to slow down the induction process—a regeneration axon can be maintained for longer, so that multiple innervation (*c*) will persist for longer. Drawn after Ribchester and Barry (1994).

the tectum, and then to further changes in the pattern of connections, and so on. By this means, an initially disordered pattern of retinotectal connections is gradually refined into an ordered map of retina onto tectum, at which point the retinal marker profiles have become replicated across the tectum.

3.5. Interference competition: 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 (this idea is the least explicit in the model by Liu *et al* (1994a), section 3.5.2). In addition to interference, two models incorporate a presynaptic constraint. In the model by Willshaw (1981), the total synaptic strength supported by each motor neuron is kept constant (i.e. synaptic normalization as in section 3.1, but now of the total strength of the output connections). In the model by Barber and Lichtman (1999), the total amount of presynaptic resource is kept constant (as in the dual constraint model, section 3.3.1B). Except in the model by Willshaw (1981), electrical activity plays a decisive role in all models.

3.5.1. Willshaw (1981). This is the first 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 axon terminal injects into its endplate a degrading signal that reduces the 'survival strength' of all the terminals (including itself) at that endplate. The size of a terminal is thought to be proportional to its survival strength. In particular, the model assumes that:

(1) Each terminal has a survival strength S_{IJ} for the contact between axon I and fibre J.
(2) Each terminal injects into its endplate a degrading signal at a rate proportional to its own survival strength. The total rate of release into fibre J is thus proportional to the sum $\sum_i S_{iJ}$ of the survival strengths of the f_J terminals there. This total signal reduces the survival strengths of all the terminals there, all being affected equally. The rate at which each terminal on fibre J is degraded is proportional to the mean strength $M_J = \frac{1}{f_J}\sum_i S_{iJ}$.

(3) The survival strength of each terminal increases at a rate proportional to that strength (positive feedback).
(4) The total amount of survival strength supported by each motor neuron is kept constant. Thus, for each I, $\sum_j' S_{Ij} =$ constant, where $\sum_j'$ denotes a sum over all fibres contacted by the axon in question.

From assumptions (2) and (3) it follows that

$$\frac{\mathrm{d}S_{IJ}}{\mathrm{d}t} = -\alpha M_J + \beta S_{IJ} \tag{35}$$

where α and β are rate constants. From assumption (4) it follows that

$$\sum_j' \frac{\mathrm{d}S_{Ij}}{\mathrm{d}t} = \sum_j' (-\alpha M_j + \beta S_{Ij}) = 0. \tag{36}$$

Equation (36) gives an expression for β, which can be substituted in equation (35), yielding

$$\frac{\mathrm{d}S_{IJ}}{\mathrm{d}t} = \alpha \left(\sum_j' M_j \right) \left(\frac{S_{IJ}}{\sum_j' S_{Ij}} - \frac{M_J}{\sum_j' M_j} \right). \tag{37}$$

The model can account for the elimination of polyneuronal innervation, whatever the initial distribution of survival strengths. At each endplate, the terminal whose survival strength represents the largest fraction of the total strength available to its motor neuron is likely to survive. From equation (37), it can be seen that when polyneuronal innervation is eliminated, no further change in survival strengths will occur: no polyneuronal innervation means $M_J = S_{IJ}$ for all innervated fibres, and $M_J / \sum_j' M_j$ becomes equal to the first term within the brackets, so that $\mathrm{d}S_{IJ}/\mathrm{d}t$ becomes zero. In addition to accounting for the elimination of polyneuronal innervation, the model accounts for (i) the decrease in spread of motor unit size during the elimination of polyneuronal innervation (e.g. Brown *et al* (1976)); (ii) the competitive advantage of the terminals of smaller motor units over those of larger ones (Brown *et al* 1976, Brown and Ironton 1978); and (iii) the increase in motor unit size after neonatal partial denervation (Thompson and Jansen 1977, Fladby and Jansen 1987). To be able to account for the above phenomena, it is essential that the total amount of survival strength available to each motor neuron is kept constant. This assumption is also essential for the elimination of polyneuronal innervation: without it, elimination proceeds until the terminal that initially has the largest survival strength remains, so that some neurons might lose all their initial axon terminals.

Criticisms of the model are that (i) the positive feedback (assumption (3)) is postulated and not accounted for biologically; (ii) it uses synaptic normalization of output connections (assumption (4)), which implies that not all fibres will show an increase in their total input survival strength during development (see section 2.1.2); (iii) in obtaining the degrading signal (see assumption (2)), which is divided by the number of terminals present at an endplate, a mathematical discontinuity is introduced when a terminal withdraws (see also Gouzé *et al* (1983)); and (iv) the effects of electrical activity are not considered.

3.5.2. Liu et al (1994a). In this model, which was not given in mathematical terms, axons vie to escape the punitive effects of a target-derived toxic factor, which may be a protease that disconnects nerve terminals. This idea is supported by observations that several protease inhibitors can partly prevent synapse elimination at the neuromuscular junction (Connold *et al* 1986, Vrbova and Fisher 1989, Liu *et al* 1994b). The model was applied to both the neuromuscular and the visual system (Liu *et al* 1994a).

In the model, an electrically activated postsynaptic cell releases proteases globally, resulting in a strength reduction of all its inputs. Presynaptic activity, in contrast, causes local release of protease inhibitor, which offers protection to the protease; thus, the surviving axons will be the ones that are active most often. There is no positive feedback loop, and how the model can generate single innervation is not clear. It is possible that proteases could also mediate direct negative interactions between axons (Sanes and Lichtman 1999); however, the model would then become very similar to the model described in the next section.

3.5.3. Nguyen and Lichtman (1996). Also not given in mathematical terms, this model, as well as the one in section 3.5.4, has many similarities with Willshaw's (1981) model (section 3.5.1), except that there is an explicit role for electrical activity. Interference is incorporated by punishment and protection signals (whose identities are not further specified), and more active synapses prosper by punishing their less active neighbours. The model (see also Balice-Gordon and Lichtman (1994), Jennings (1994)) is based on observations that levels of AChRs—the postsynaptic receptors for acetylcholine, the neurotransmitter in motor neuron terminals—begin to decline before the overlying nerve terminal withdraws (Balice-Gordon and Lichtman (1993), Culican *et al* (1998); see also section 2.1.6). In the model (figure 9), a decrease in AChRs instigates the removal of the overlying nerve terminal. By activating its underlying AChRs, each active synapse generates two postsynaptic signals: (i) a punishment signal that spreads over short distances and eliminates AChRs of neighbouring synaptic sites; and (ii) a more locally confined protection signal that neutralizes the punishment signal. The strength of both signals is proportional to the level of activity; at inactive sites, no signals are generated. 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. Such a positive feedback loop can bring about the removal of all nerve terminals but the most active one. When the postsynaptic sites are equally active, they generate equally strong punishment signals, but also equally strong protection signals, so that all nerve terminals are maintained. All terminals are maintained also when all the postsynaptic sites are inactive, because then neither the punishment signal nor the protection signal is generated. Thus, elimination requires the presence of active neighbouring sites.

The model can explain the following observations. (i) 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). (ii) AChRs are lost from denervated portions of incompletely reoccupied endplates following reinnervation (Stanco and Werle 1997), whereas AChRs at completely denervated endplates are relatively stable (Moss and Schuetze 1987).

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 (section 2.1.6). AChRs, too, are unlikely to play a pivotal role: synapse formation and elimination occur normally in mutant zebrafish lacking nicotinic AChRs (Liu and Westerfield 1990).

3.5.4. Barber and Lichtman (1999). Barber and Lichtman (1999) put the ideas of Nguyen and Lichtman (1996) (section 3.5.3) into mathematical terms. However, the punishment and

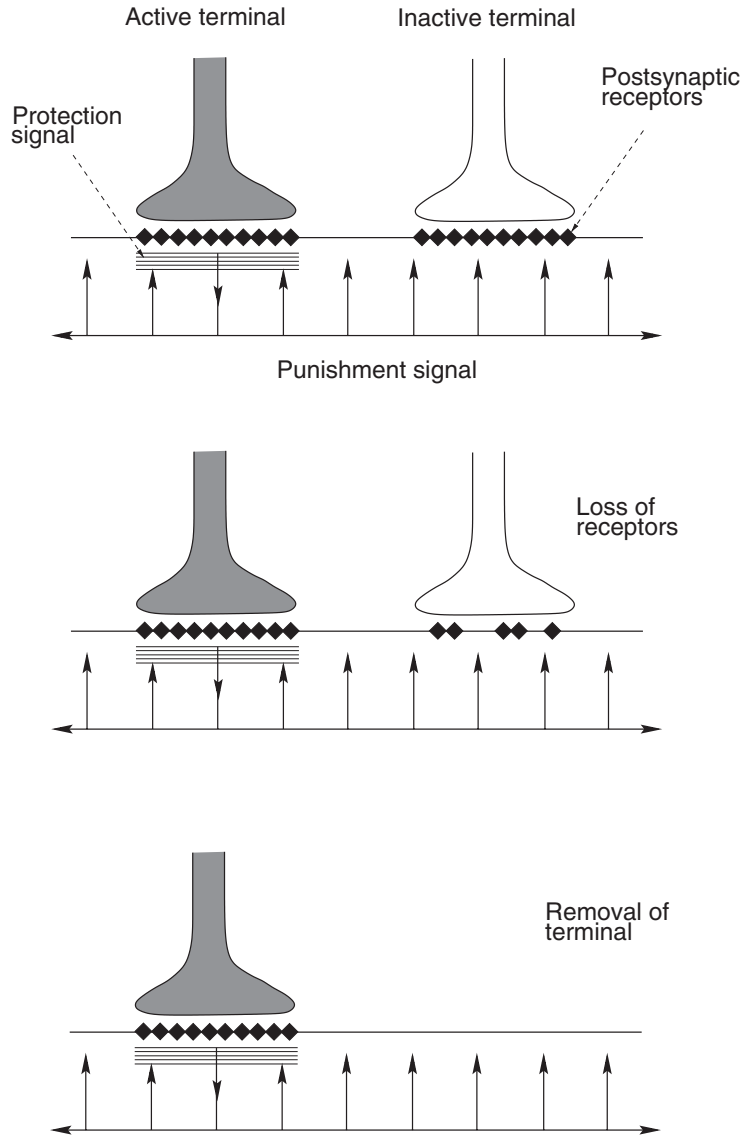

Figure 9. The model by Nguyen and Lichtman (1996) (section 3.5.3). The punishment signal, generated by the active terminal, causes selective loss of receptors beneath the inactive terminal—which lacks a protection signal—leading to its subsequent removal. Drawn after Nguyen and Lichtman (1996).

protection signals are not explicitly modelled, and there is the extra element of keeping the total amount of presynaptic resource constant (as in the dual constraint model, section 3.3.1B). The main aim of the model was to reconcile two paradoxical results regarding the role of activity: (i) the more active neurons maintain the smallest motor units—i.e. the size principle (Henneman 1957, 1985, Callaway *et al* 1987, 1989); and (ii) activity drives competition at individual endplates (Balice-Gordon and Lichtman 1994, Ribchester and Taxt 1983). The model was developed from the following assumptions:

(1) The ability of an axon to eliminate competing axons is proportional to the amount of neurotransmitter it releases; this amount is proportional to the axon's total synaptic area (i.e. terminal size) at the endplate and to its activity (mean firing rate).
(2) Axons are only able to compete effectively during asynchronous activity.
(3) The total amount of presynaptic resource in each motor neuron is kept constant; this constrains the amount of neurotransmitter available for release and the total synaptic area the neuron can support.
(4) The amount of presynaptic resource in each neuron is divided among all its connections, with large synaptic areas receiving a greater share.
(5) Large synaptic areas are disproportionally less taxing on the resources of the neuron.

Each synaptic area, A_{mn} for the area that neuron n makes on muscle fibre m, is thus subjected to two effects: (i) loss of synaptic area, in amount E_{mn}, through competition; and (ii) gain or loss of synaptic area, in amount U_{mn}, through utilization of neuronal resources. Thus,

$$\frac{\mathrm{d}A_{mn}}{\mathrm{d}t} = -\alpha E_{mn} + \beta U_{mn} \tag{38}$$

where α and β are rate constants.

From assumptions (1) and (2),

$$E_{mn} = \sum_{i \neq n} f_i A_{mi} (1 - \tau^2 f_n f_i) \tag{39}$$

where f_i and f_n are the firing rates of neuron 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. From assumption (3), the conservation equation for the total amount R of presynaptic resource is

$$R = R_{\mathrm{a},n} + f_n \sum_j A_{jn}^{\gamma} \tag{40}$$

where $R_{\mathrm{a},n}$ is the amount of free resource left in motor neuron n and $\gamma < 1$ represents that large synaptic areas are disproportionally less taxing on the resources of the neuron (assumption (5)). From assumption (4), the amount of free resource is divided among all the neuron's connections, so that

$$U_{mn} = R_{\mathrm{a},n} \frac{A_{mn}}{\sum_j A_{jn}} = \left(R - f_n \sum_j A_{jn}^{\gamma} \right) \frac{A_{mn}}{\sum_j A_{jn}}. \tag{41}$$

In addition to accounting for the elimination of polyneuronal innervation, the model is able to reproduce the size principle, because the presynaptic resource is more utilized with increased activity of the neuron. A competitive advantage of higher frequency axons early in development is overcome at later stages by greater synaptic efficacy of axons firing at a lower rate. In the model, early competition is dominated by active axons that battle against other active axons, whereas later on the main changes in connectivity are dominated by relatively inactive axons that battle other inactive axons. The way the size principle is generated in this model has similarities to the way it is generated in the model by Stollberg (1995) (section 3.1.1), as the model by Barber and Lichtman (1999) can also be viewed as being driven by correlations in presynaptic and postsynaptic activity.

In addition to the criticisms given for the previous model (section 3.5.3), which are also valid here, assumptions (2) and (5) do not have strong experimental support.

4. Discussion

Models of competition in the development of nerve connections, both in the neuromuscular and in the visual system, have been reviewed. The models differ with respect to:

(1) *The type of competition*. This can be none (enforcing competition), consumptive competition, or interference competition (competition for space, direct negative interactions). In some instances, depending on the objectives of the model, it might be sufficient to enforce competition rather than to model the putative underlying mechanisms. But if the objective is to understand competition and to relate to experiments, then modelling underlying mechanisms is important. However, even if the main objective is to understand not competition *per se* but a process in which it is involved (for example, the formation of ocular dominance columns and topographic maps), the specific way in which competition is modelled could make a difference. Considering that already the way in which the normalization constraint is enforced makes a difference as to when ocular dominance columns can develop (see section 3.1), differences might also be expected if underlying mechanisms are explicitly modelled. For example, Harris *et al* (1997) and Elliott and Shadbolt (1998b) showed that models implementing the putative underlying mechanisms 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 experimental studies are necessary to find out what type(s) of competition is (are) involved in the formation of nerve connections. Recent findings (see sections 2.1.5 and 2.2.3), both in the neuromuscular and in the visual system, have supported a role for neurotrophic factors (in consumptive competition). More types of competition may be involved at the same time, e.g. consumptive competition plus direct negative interactions (see section 2.1.5).

(2) *The specific underlying mechanisms*. The role of electrical activity and the mechanisms that create the positive feedback loop differ between models.
In both the neuromuscular and the visual system, electrical activity may be just one of the influences in competition—competition can occur without pre- and postsynaptic electrical activity, see section 2—while the actual competition is driven by other factors, e.g. neurotrophic factors and their receptors. However, in many of the reviewed models (but not all, e.g. Willshaw (1981), Jeanprêtre *et al* (1996), Van Ooyen and Willshaw (1999b)), electrical activity plays a decisive role.
Most models proposed for the development of neuromuscular connections can produce the change from polyneuronally to mononeuronally innervated muscle fibres, but the extent to which the positive feedback loop—the most essential part of the models, enabling one of the axons to outcompete the others—is biologically justified varies between models. In addition to elimination of polyneural innervation, a model has to account for the size principle, the reduction of motor unit sizes, the effects of electrical activity, and the occurrence of stable polyneuronal innervation under some circumstances. Models differ as to their ability to account for all these observations (or have not yet considered them). Similarly, in models proposed for the development of ocular dominance columns, the biological justification of the positive feedback loop differs between models.

(3) *The modelling approach*. Even if the same type of competition is modelled, the modelling approach may differ. For example, consumptive competition can be implemented in a fixed or a variable resource model (see section 3.3). Although under some conditions both types of models can be expressed in terms of the other, a variable resource model

has the advantage that its variables and parameters are better 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 these models, e.g. explicit modelling of the extracellular space and diffusion.

Models can improve our intuitive ideas about competition. For example, the widely held belief that competition is a consequence of resources being produced in limited amounts is too simplistic. For instance, in the model by Jeanprêtre *et al* (1996) and in the model by Van Ooyen and Willshaw (1999b) for class I of the growth function (i.e. axonal vigour is unbounded), the number of surviving axons cannot be increased by increasing the amount of neurotrophin: the higher amount of neurotrophin becomes again limiting by the resulting increase in axonal vigour of the winning axon. Examination of models have also shown that activity-dependent release of neurotrophin and presynaptic activity are not necessary for competition to occur, although activity can be influential (see sections 2.1.6 and 2.2.4). In experiments testing the role of electrical activity, it is important to know exactly how activity has been changed: postsynaptic activity (and whether inactive postsynaptic cells have increased or decreased release of neurotrophin—see Snider and Lichtman (1996), and section 3.3.2D: *results of the model*), the absolute level of presynaptic activity, and the relative difference in activity between innervating axons.

Challenges for further modelling studies, of both the neuromuscular and the visual system, include (i) modelling the role of electrical activity in competition (pre- and postsynaptic; and accounting for the observation that activity is influential but may be not decisive); (ii) combining physiological plasticity (changes in synaptic strength) with anatomical plasticity (changes in axonal arborization) (see also Harris *et al* (2000)); (iii) combining different types of competition (e.g. consumptive competition plus direct negative interactions), and (iv) studying whether explicitly modelling the putative underlying mechanisms of competition makes a difference in models in which competition is involved.

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