J. theor. Biol. (2000) **206,** 195–210
doi:10.1006/jtbi.2000.2114, available online at http://www.idealibrary.com on IDEAL®

Development of Nerve Connections under the Control of Neurotrophic Factors: Parallels with Consumer–Resource Systems in Population Biology

ARJEN VAN OOYEN*† AND DAVID J. WILLSHAW‡

*Netherlands Institute for Brain Research, Graduate School Neurosciences Amsterdam, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands and ‡Institute for Adaptive and Neural Computation, Division of Informatics, University of Edinburgh, 5 Forrest Hill, Edinburgh EH1 2QL, U.K.

(*Received on* 16 *August* 1999, *Accepted in revised form on* 25 *May* 2000)

The development of connections between neurons and their target cells involves competition between axons for target-derived neurotrophic factors. Although the notion of competition is commonly used in neurobiology, the process is not well understood, 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 of consumer–resource systems. Here we show that a recently formulated model of axonal competition can be rewritten as a general consumer–resource system. This allows neurobiological phenomena to be interpreted in population biological terms and, conversely, results from population biology to be applied to neurobiology. Using findings from population biology, we have studied two extensions of our axonal competition model. In the first extension, the spatial dimension of the target is explicitly taken into account. We show that distance between axons on their target mitigates competition and permits the coexistence of axons. The model can account for the fact that in many types of neurons a positive correlation exists between the size of the dendritic tree and the number of innervating axons surviving into adulthood. In the second extension, axons are allowed to respond to more than one neurotrophic factor. We show that this permits competitive exclusion among axons of one type, while at the same time there is coexistence with axons of another type innervating the same target. The model offers an explanation for the innervation pattern found on cerebellar Purkinje cells, where climbing fibres compete with each other until only a single one remains, which coexists with parallel fibre input to the same Purkinje cell.

1. Introduction

The development of connections between neurons and their target cells often involves an initial stage of hyperinnervation followed by elimination of axons (Purves & Lichtman, 1980). In some cases, elimination continues until the target is innervated by just a single axon (e.g. in the innervation of muscle fibres, Jansen & Fladby, 1990), whereas in most cases several axons remain. Competition between innervating axons for target-derived neurotrophic factors, which are taken up by the axons via specific receptors at their terminals (Bothwell, 1995; Lewin & Barde, 1996) and which affect the

†Author to whom correspondence should be addressed. E-mail: a.van.ooyen@nih.knaw.nl

0022–5193/00/180195 + 16 $35.00/0

growth and branching of the axons (see Section 2.1), is thought to be involved in axon elimination (Grinnell *et al.*, 1979; Purves & Lichtman, 1985; Purves, 1988).

Although the notion of competition is commonly used in neurobiology, the process is not well understood, and only a few formal models exist (Gouzé *et al.*, 1983; Bennett & Robinson, 1989)—revised and further analysed by Rasmussen & Willshaw (1993) and Van Ooyen & Willshaw (1999a); Jeanprêtre *et al.* (1996); Harris *et al.* (1997); Elliott & Shadbolt (1996), 1998). 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 & Yorke, 1977; Yodzis, 1989; Van der Meer & Ens, 1997; Grover, 1997). In these models, one considers systems of consumers and resources where most types of resources are consumed by more than one species of consumer, so that there is competition between the consumer species.

In most models for the development of nerve connections, competition is based on fixed amounts of resources that become partitioned among the individual competitors (Gouzé *et al.*, 1983; Bennett & Robinson, 1989; Elliott & Shadbolt, 1996; Harris *et al.*, 1997). In other words, there is no production and no decay or consumption of resources, which is biologically unrealistic. We have recently formulated a model that is not based on fixed amounts of resources (Van Ooyen & Willshaw, 1999b; see also Jeanprêtre *et al.*, 1996). In this paper, we show analytically that there exist direct parallels between this model and consumer–resource systems in population biology (Yodzis, 1989). Stimulated by these parallels, we have investigated two extensions of the model. In the first extension, the spatial dimension of the target is explicitly taken into account. In the second extension, axons are capable of responding to more than one neurotrophic factor.

In Section 2, we summarize our axonal competition model (Van Ooyen & Willshaw, 1999b). In Section 3, we show that this model can be rewritten as a general consumer–resource system. The extensions of the model are studied in Sections 4 and 5.

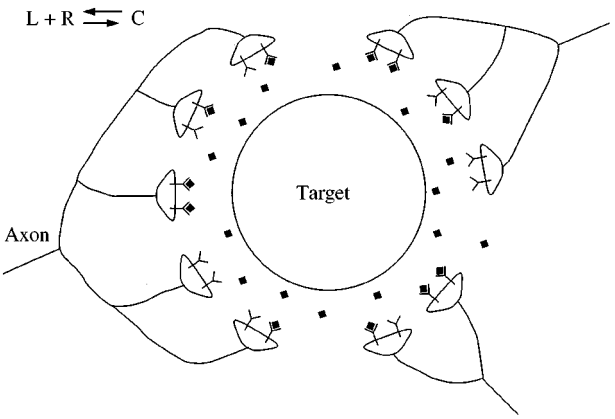

FIG. 1. Target cell with three innervating axons, each with a different degree of branching. The target releases neurotrophin, which binds to neurotrophin receptors at the axon terminals. The extracellular space around the target is assumed to be uniform with respect to the concentration of neurotrophin, i.e. is a single compartment. From Van Ooyen & Willshaw (1999b). (◆) neurotrophin (L); (⊣) unoccupied receptor (R); (⊣◆) neurotrophin–receptor complex (C).

2. Development of Nerve Connections under the Control of Neurotrophic Factors

In this section, we summarize the model by Van Ooyen & Willshaw (1999b). An important group of neurotrophic factors is the neurotrophin family, and from now on we will use the term neurotrophin instead of neurotrophic factor, although the model is not specific for any factor.

2.1. MODEL

We consider a single target cell at which there are n innervating axons each from a different neuron (Fig. 1). Neurotrophin is released by the target into the extracellular space at 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 then internalized and 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. If we assume standard reaction dynamics, the rates of change of the total number of neurotrophin–receptor complexes on axon i (C_i), the total number of unoccupied receptors

on axon i (R_i), and the extracellular concentration of neurotrophin (L) are

$$\frac{dC_i}{dt} = (k_{a,i}LR_i - k_{d,i}C_i) - \rho_i C_i, \quad (1)$$

$$\frac{dR_i}{dt} = \phi_i - \gamma_i R_i - (k_{a,i}LR_i - k_{d,i}C_i), \quad (2)$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n} (k_{a,i}LR_i - k_{d,i}C_i)/v, \quad (3)$$

where v is the volume of the extracellular space.

Following binding to receptor, neurotrophins locally increase the arborization of axons (e.g Cohen-Cory & Fraser, 1995), which will consequently cause an increase in the number of axon terminals. Increasing the number of axon terminals (on which the neurotrophin receptors are located) is likely to increase the axon's total number of receptors. Neurotrophins can also increase the axon's total number of receptors by (i) increasing the size of axon terminals (e.g. Garofalo *et al*., 1992) and (ii) upregulating the density of receptors (e.g. Holtzman *et al*., 1992).

In order for the total number of receptors to increase in response to neurotrophin, ϕ_i must increase in response to bound neurotrophin. We therefore assume that ϕ_i is an increasing function $f_i(C_i)$ of the amount of bound neurotrophin C_i. We call $f_i(C_i)$ the growth function. To take into account that axonal growth is relatively slow, ϕ_i lags behind $f_i(C_i)$ with a lag given by

$$\tau \frac{d\phi_i}{dt} = f_i(C_i) - \phi_i, \quad (4)$$

where the time constant τ for growth is of the order of days.

Because the precise form of the growth function is not known, Van Ooyen & Willshaw (1999b) studied four different classes of growth functions, all derived from the general growth function

$$f_i(C_i) = \frac{\alpha_i C_i^m}{K_i^m + C_i^m}. \quad (5)$$

Class O: for $m = 0$, $f_i(C_i)$ is a constant ($f_i(C_i) = \alpha/2$). *Class* I: for $m = 1$ and large K_i ($K_i \gg C_i$), growth is linear over a large range of C_i ($f_i(C_i) \approx \alpha_i C_i/K_i$). *Class* II: for $m = 1$ and smaller values of K_i ($K_i \not\gg C_i$), the growth function is a Michaelis–Menten function [$f_i(C_i) = \alpha_i C_i/(K_i + C_i)$]. *Class* III: for $m = 2$, the growth function is a Hill function [$f_i(C_i) = \alpha_i C_i^2/(K_i^2 + C_i^2)$]. Within each class of growth function, the specific values of the parameters (α_i and K_i), as well as those of the other parameters, may differ between the innervating axons. Various factors in the innervating axon influence the values of these parameters. For example, increased pre-synaptic electrical activity increases the axon's number of neurotrophin receptors (e.g. Birren *et al*., 1992), which implies that electrical activity affects growth (i.e. higher α_i or lower K_i), neurotrophic signalling (e.g. lower γ_i), or both. Because the level of electrical activity and other factors will differ between the axons, the parameter values between the axons will differ as well.

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, while axons that do have neurotrophin ($C_i > 0$; equivalent to $\phi_i > 0$) are regarded as having survived. For class I, elimination of axons takes place until a single axon remains [single innervation, Fig. 2(a)], regardless of the rate of release of neurotrophin. The axon that survives is the one with the highest value of the quantity $\beta_i \equiv (k_{a,i}(\alpha_i/K_i - \rho_i))/(\gamma_i(k_{d,i} + \rho_i))$. If the growth function is a saturating function, i.e. classes II and III, more than one axon may survive [multiple innervation, Fig. 2(b) and (c)], depending on the parameters of the growth function and the rate of release of neurotrophin. For class III, stable equilibria for single and multiple innervation can coexist [Fig. 2(c)], and which of these will be reached in any specific situation depends on the initial conditions.

For the numerical simulations of the model and its extensions (see Sections 4 and 5), we take data available for nerve growth factor (NGF), the best characterized neurotrophin (Table 1). However, the results of our study are general and do not depend on specific choices for the parameter values.

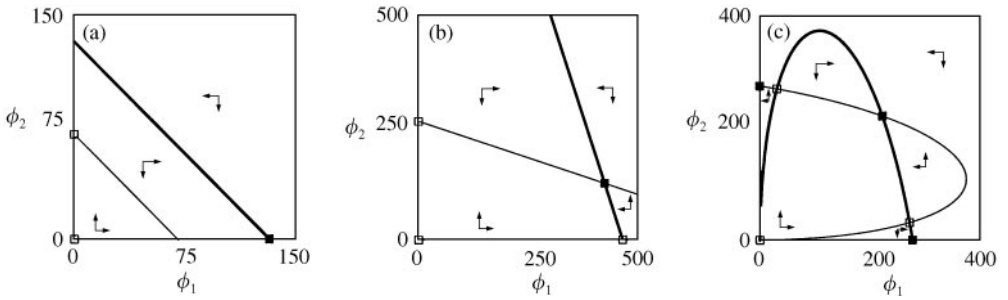

FIG. 2. For different classes of growth functions, the nullcline pictures for a system of two innervating axons, in the model of Section 2.1. The variables $\{R_i, C_i, i = 1, 2\}$ and L are at quasi-steady state. The —— are the nullclines of ϕ_1, the —— are the nullclines of ϕ_2. The x- and y-axes are also nullclines of ϕ_2 and ϕ_1, respectively. Vectors indicate direction of change; (■) stable equilibrium point and (□) unstable equilibrium point. Note that $\phi_i > 0 \Leftrightarrow C_i > 0$ and $\phi_i = 0 \Leftrightarrow C_i = 0$. From Van Ooyen & Willshaw (1999b). (a) *Class* I. The nullclines do not intersect at a point where both axons coexist. $\alpha_1/K_1 = 1.4$ and $\alpha_2/K_2 = 0.8$. (b) *Class* II. The nullclines intersect at a point where both axons coexist. The rate of release of neurotrophin, σ, is 10 times higher than the standard value. If we use the standard rate of release, the nullclines do not intersect, and only one axon will survive. $\alpha_1 = 700$, $\alpha_2 = 400$, and $K = 500$. (c) *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. $\alpha_1 = 300$, $\alpha_2 = 300$, and $K = 30$. For $K = 100$, for example, the stable equilibrium point where both axons coexist disappears.

TABLE 1
Units and parameter values used for the numerical simulations

Parameter	Value	Source
k_a	$4.8 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$	Sutter *et al.* (1979)
k_d	$1.0 \times 10^{-3}\ \mathrm{s^{-1}}$	Sutter *et al.* (1979)
γ	$2.7 \times 10^{-5}\ \mathrm{s^{-1}}$	Zupan & Johnson (1991)
ρ	$\sim 2.0 \times 10^{-5}\ \mathrm{s^{-1}}$	Layer & Shooter (1983)
δ	$\sim 1.0 \times 10^{-5}\ \mathrm{s^{-1}}$	Jeanprêtre *et al.* (1996)
σ	$2.0 \times 10^{-16}\ \mathrm{M\,s^{-1}}$	Blöchel, A. & Thoenen (1995) Jeanprêtre *et al.* (1996)
v	$1.7 \times 10^{-11}\ l$	
τ	~ 2 days	Bernd & Greene (1984)

Parameter values. These were taken from the data available for NGF (nerve growth factor). However, the results of our study are general and do not depend on specific choices for the parameter values. The rate constants (i.e. k_a and k_d) of the high-affinity NGF binding site are used because this mediates the biological response (Bothwell, 1995).

Units. Amounts of unoccupied receptor and neurotrophin-receptor complex are expressed in number of molecules. Neurotrophin concentration is expressed in M ($= \mathrm{mol}1^{-1}$). In the figures, time is given in hours (*hr*). The values of α_i and ϕ_i (or $\phi 1_i$ and $\phi 2_i$ in Section 5) are given in number of molecules hr^{-1}; the values of K_i are given in number of molecules. The dimension of $\eta_i \equiv \alpha_i/K_i$ is hr^{-1}. Only the parameter α_i (or η_i in Sections 4 and 5) is varied between axons. Unless otherwise indicated, the initial value of ϕ_i (or $\phi 1_i$ and $\phi 2_i$) for all axons is 10.0 molecules hr^{-1}. The initial values of number of unoccupied receptors, number of neurotrophin–receptor complexes, and neurotrophin concentrations are chosen so that when keeping ϕ_i (or $\phi 1_i$ and $\phi 2_i$) at their initial values, the system is in steady state.

3. Development of Nerve Connections as a Consumer–Resource System

We show that the model described in Section 2.1 can be rewritten as a consumer–resource system. The rate of change of ϕ_i (i.e. axonal growth) is of the order of days, so that on the time scale of ϕ_i, we can make quasi-steady-state approximations for the number of unoccupied receptors R_i and the number of neurotrophin–receptor complexes C_i (i.e. $\mathrm{d}R_i/\mathrm{d}t = \mathrm{d}C_i/\mathrm{d}t = 0$).

From eqn (1), this gives

$$\rho_i C_i = k_{a,i} L R_i - k_{d,i} C_i \tag{6}$$

and therefore

$$C_i = \frac{k_{a,i} L R_i}{k_{d,i} + \rho_i}. \tag{7}$$

Inserting eqn (7) into eqn (2) and making the quasi-steady-state approximation $dR_i/dt = 0$ gives

$$R_i = \frac{\phi_i}{\gamma_i + (k_{a,i}\rho_i/(k_{d,i} + \rho_i))L}. \tag{8}$$

Inserting eqn (8) into eqn (7) gives

$$C_i = \frac{\phi_i L}{\gamma_i(k_{d,i} + \rho_i)/k_{a,i} + \rho_i L}. \tag{9}$$

Now, define

$$h_i(L) \equiv \frac{\lambda_1 L}{\lambda_{2,i} + L}, \tag{10}$$

where

$$\lambda_1 = \frac{1}{v}, \quad \lambda_{2,i} = \frac{\gamma_i(k_{d,i} + \rho_i)}{\rho_i k_{a,i}}. \tag{11}$$

Further, define

$$g_i(L, \phi_i) \equiv \frac{f_i(C_i)}{\tau \phi_i}. \tag{12}$$

Inserting eqn (6) into eqn (3) and using eqns (9), (10), and (12), we can now describe the whole system given by eqns (1–4) as

$$\frac{d\phi_i}{dt} = \phi_i(g_i(L, \phi_i) - \lambda_3), \tag{13}$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n} \phi_i h_i(L), \tag{14}$$

where $\lambda_3 = 1/\tau$. Note that under the quasi-steady-state approximations, $\phi_i = \rho_i C_i + \gamma_i R_i$. Thus, variable ϕ_i is a measure for the total number of neurotrophin receptors (unoccupied plus bound to neurotrophin) on axon i.

Equations (13) and (14) are of the same form as those describing consumer–resource systems in population biology (Yodzis, 1989). Receptors, as it were, consume neurotrophin molecules (through binding of neurotrophin to receptor and subsequent degradation of the neurotrophin–receptor complex); as a result, the net number of receptors increases and the concentration of neurotrophin decreases. Variable ϕ_i corresponds to the size of the population of consumer species i, while variable L corresponds to the size of the resource population. In this system, there is only one type of resource and there are as many different consumer species as there are innervating axons. If the resource exists in isolation, it grows at rate σ and decays at rate δL. In the presence of ϕ_i, the resource is also consumed at rate $\phi_i h_i(L)$. In population biological terms, $h_i(L)$ is the functional response of the consumer, which describes how much resource is consumed per individual consumer per unit time. Here, the functional response is a type-II Holling response. The consumer grows in response to resource at rate $\phi_i g_i(L, \phi_i)$ and decays at rate $\lambda_3 \phi_i$. In population biological terms, $g_i(L, \phi_i) - \lambda_3$ is the numerical response of the consumer, which describes the change in the consumer population expressed per individual per unit time in response to (in general) both resource and consumer.

The numerical response in axonal competition is affected by the form of the growth function $f_i(C_i)$. In Van Ooyen & Willshaw (1999b), competition is studied for different forms of $f_i(C_i)$, using a general growth function [eqn (5)]. Inserting this general growth function into eqn (12) and using eqn (9) gives

$$g_i(L, \phi_i) = \frac{\phi_i^{m-1}(\lambda_{4,i} L)^m}{(\lambda_{2,i} + L)^m + (\lambda_{5,i}\phi_i L)^m}, \tag{15}$$

where

$$\lambda_{4,i} = \frac{(\alpha_i/\tau)^{1/m}}{K_i \rho_i}, \quad \lambda_{5,i} = \frac{1}{K_i \rho_i}. \tag{16}$$

For class I of the general growth function ($m = 1$ and $K_i \gg C_i$, and hence $\lambda_{2,i} + L \gg \lambda_{5,i}\phi_i L$),

$$g_i(L, \phi_i) = g_i(L) = \frac{\lambda_{4,i} L}{\lambda_{2,i} + L}, \tag{17}$$

which is a type-II Holling response.

For class II ($m = 1$ and $K_i \not\gg C_i$),

$$g_i(L, \phi_i) = \frac{\lambda_{4,i} L}{\lambda_{2,i} + L + \lambda_{5,i}\phi_i L}, \tag{18}$$

which is a form of a consumer-dependent response (Abrams, 1994), since it also depends on ϕ_i. For class III ($m = 2$), $g_i(L, \phi_i)$ is also of this form.

The form in which the classical Lotka–Voltera competition equations are given, i.e. without direct reference to what the consumer species are competing for, is obtained from eqns (13) and (14) by making a quasi-steady-state approximation for the resource, i.e. $\mathrm{d}L/\mathrm{d}t = 0$. This gives an expression for L in terms of ϕ_i, which can then be inserted into eqn (13). For example, for class I, if we assume for simplicity that all $\lambda_{2,i}$ are the same and δ can be neglected, the quasi-steady-state approximation for the resource gives

$$h(L) = \frac{\sigma}{\sum_{i=1}^{n} \phi_i}. \tag{19}$$

Using this and eqn (10), we obtain

$$L = \frac{\sigma\lambda_2}{(\lambda_1 \sum_{i=1}^{n} \phi_i) - \sigma}. \tag{20}$$

Inserting eqn (20) into eqn (13), using eqn (17), gives

$$\frac{\mathrm{d}\phi_i}{\mathrm{d}t} = \phi_i \left(\frac{\lambda_{4,i}}{(\lambda_1/\sigma)\sum_{i=1}^{n} \phi_i} - \lambda_3 \right). \tag{21}$$

For $n = 2$, for example, the nullclines of ϕ_1 and ϕ_2, obtained by setting $\mathrm{d}\phi_i/\mathrm{d}t = 0$ in eqn (21), are parallel lines (excluding the nullclines $\phi_i = 0$, $i = 1, 2$), and hence, only one axon can survive. For class II, the expression obtained for $\mathrm{d}\phi_i/\mathrm{d}t$ shows that the nullclines can intersect so that coexistence is possible [see Fig. 2(b)].

We now summarize the parallels between the development of nerve connections and consumer–resource systems.

1. Neurotrophin corresponds to resource.
2. The number of axons corresponds to the number of different consumer species.
3. The number of neurotrophin receptors of a given axon determines the population size of that species.
4. The way in which neurotrophin affects axonal growth (i.e. increases the axon's total number of neurotrophin receptors) determines the numerical response of the consumer.
5. The kinetics of neurotrophin binding to receptor, degradation of neurotrophin–receptor complex, and turnover of receptor determine the functional response of the consumer.
6. Axonal competition for neurotrophins is a form of what in population biology is called consumptive competition: consumer species hinder one another through their dependence on shared resource(s).
7. Survival of a single axon corresponds to the classical competitive exclusion result from theoretical population biology, which says that in equilibrium one type of resource can maximally sustain one consumer species. Survival of several axons corresponds to coexistence of consumer species.
8. For class III, the coexistence of several stable equilibria 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 (Van Ooyen & Willshaw, 1999b). The ability of an axon to regenerate corresponds to the property of invasibility in population biology. Invasibility is defined as follows (Yodzis, 1989). Suppose we remove a consumer species S from a system of coexisting consumer species and allow the remaining species to reach a new attractor. Species S is then able to invade the reduced system if after introducing a few individuals of species S, the system approaches a new attractor in which S is represented.
9. Although not included in the model, axons can also exert direct negative effects on the growth of other axons (e.g. Nguyen & Lichtman, 1996), which corresponds to interference in population biology. Interference is the presence of direct aggressive interactions between members

of the competing species; it can exist in addition to competition for available resources (Yodzis, 1989).

[The parallels drawn under (1), (2), (6), (7), and (9) can partly also be found in earlier, qualitative comparisons between population biology and neurobiology (Ribchester & Barry, 1994; Van Essen *et al.*, 1990)].

Stimulated by the parallels between the development of nerve connections and consumer–resource systems, we have studied two extensions of our axonal competition model, and these will be discussed in Sections 4 and 5.

4. Effect of Spatial Dimension on Competition

The classical result of competitive exclusion is obtained in models that ignore spatial distributions of consumer and resource species. These, however, could come into play in permitting consumer species to coexist, and recent research in population biology has focused on discovering the various ways competitive exclusion can be foiled. Inspired by this, we have investigated how axonal competition is affected when the spatial dimension of the extracellular space around the target is explicitly taken into account, so that the concentration of neurotrophin is no longer necessarily uniform across the extracellular space. To this end, we consider two compartments in the extracellular space (which in the model described in Section 2.1 is considered as a single compartment), where each compartment has a single innervating axon (Fig. 3). We deliberately use this relatively simple two-compartment model (see Section 6) in order to clearly demonstrate how competition is affected.

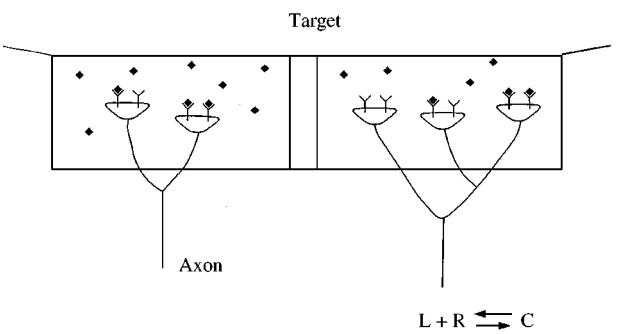

FIG. 3. Two-compartment model of Section 4.1. Target may represent soma or dendrite. (◆) Neurotrophin (L); (—≺) unoccupied receptor (R); (—◆) neurotrophin–receptor complex (C).

4.1. COMPARTMENTAL MODEL

Axon i grows in compartment i ($i = 1, 2$), in which L_i is the concentration of neurotrophin. Replacing L in eqns (1) and (2) by L_i gives the rates of change of C_i and R_i, respectively. Neurotrophin is released in each compartment at rate σ and is removed by degradation with rate constant δ. Each compartment has volume v_c and cross-sectional area A. The distance between the centres of the compartments is l. Between compartments, diffusion of neurotrophin takes place. If we approximate the concentration gradient between the compartments by $(L_2 - L_1)/l$, then the amount of neurotrophin that flows from one compartment to the other per unit time is (Fick's law)

$$I = -AD\frac{L_2 - L_1}{l}, \tag{22}$$

where D is the diffusion coefficient of neurotrophin. The change in the concentrations L_1 and L_2 caused by the flow I is I/v_c. Modifying eqn (3) to take into account diffusion, we obtain the rates of change of L_1 and L_2:

$$\frac{dL_1}{dt} = \hat{D}(L_2 - L_1) + \sigma - \delta L_1 - (k_{a,1}L_1R_1 - k_{d,1}C_1)/v_c, \tag{23}$$

$$\frac{dL_2}{dt} = \hat{D}(L_1 - L_2) + \sigma - \delta L_2 - (k_{a,2}L_2R_2 - k_{d,2}C_2)/v_c, \tag{24}$$

where $\hat{D} = AD/(lv_c)$.

Equation (4) again describes axonal growth. We use class I of the general growth function, i.e. $f_i(C_i) = \eta_i C_i$ (where, in terms of the parameters of the general growth function, eqn (5), $\eta_i = \alpha_i/K_i$), which does not permit axons to coexist if the extracellular space is uniform with respect to the concentration of neurotrophin, i.e. is a single compartment. The values of all parameters except η_i are the same for both axons. For the parameter values, see Table 1.

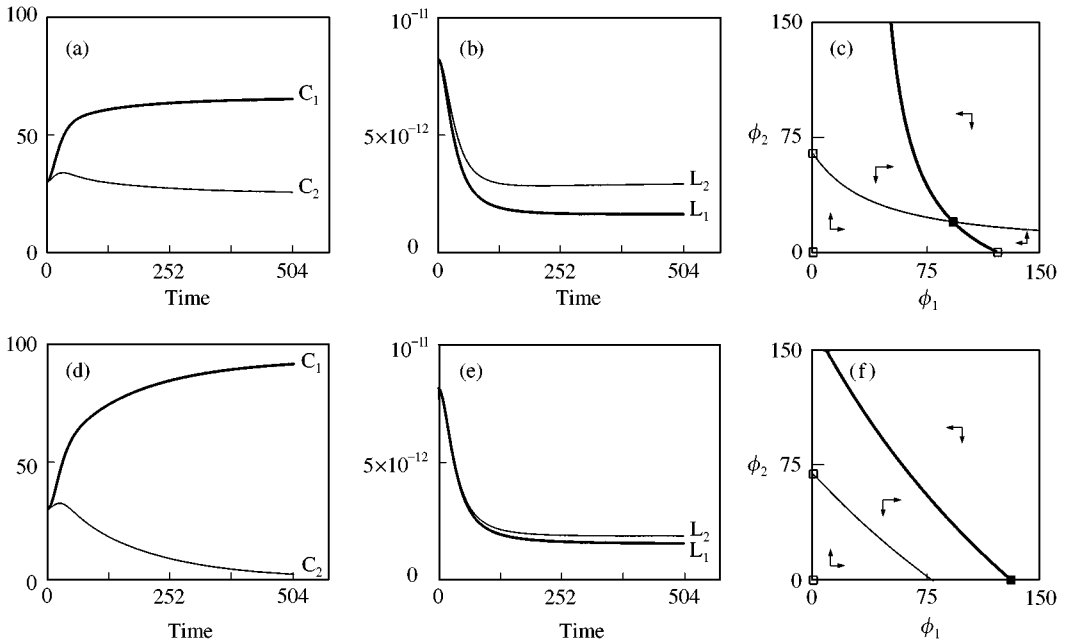

FIG. 4. Coexistence of axons and competitive exclusion depending on the value of $\hat{D}$, in the two-compartment model of Section 4.1. (a)–(c) Coexistence, $\hat{D} = 0.2$. (d)–(f) Competitive exclusion, $\hat{D} = 2$. In (c) and (f), the —— are the nullclines of ϕ_1 and the —— the nullclines of ϕ_2. The x- and y-axes are also nullclines of ϕ_2 and ϕ_1 respectively. For explanation of symbols, see Fig. 2. $\eta_1 = 1.4$ and $\eta_2 = 0.8$. $v_c = v/2$.

4.2. RESULTS

In the two-compartment model, axons can coexist even with class I of the growth function. Coexistence occurs for relatively small $\hat{D}$, i.e. if the axons are far apart (l large) or if the diffusion coefficient D is small [Fig. 4(a)–(c)]. In the limit for $\hat{D} = 0$, there is no interaction between the compartments and, consequently, no competition between the axons. For relatively large $\hat{D}$, i.e. if the axons are close to each other (l small) or if the diffusion coefficient D is large, only a single axon can survive [Fig. 4(d)–(f)]. In the limit for infinitely large $\hat{D}$, the neurotrophin concentration in both compartments will always be the same, i.e. the model will become effectively identical to the single compartment model.

We now study exclusion and coexistence using phase-plane analysis. Because the rate of change of ϕ_i is of the order of days, we can make quasi-steady-state approximations for the other variables on the time scale of ϕ_i (i.e. $\mathrm{d}C_i/\mathrm{d}t = \mathrm{d}R_i/\mathrm{d}t = \mathrm{d}L_i/\mathrm{d}t = 0$, $i = 1, 2$). Using these approximations, we can draw the nullclines of ϕ_1 and ϕ_2, i.e. the lines depicting the solutions of $\mathrm{d}\phi_1/\mathrm{d}t = 0$ and $\mathrm{d}\phi_2/\mathrm{d}t = 0$, respectively. The intersection points of the nullclines are the equilibrium points of the system. For small $\hat{D}$, there is an intersection point where both axons coexist [Fig. 4(c)]. Figure 5(a) shows the value of ϕ_2 in this intersection point for different values of $\hat{D}$. Around $\hat{D} = 0.45$, a transcritical bifurcation occurs, where the coexistent equilibrium point disappears. For $\hat{D} < 0.45$, both axons survive; for $\hat{D} > 0.45$, only one axon survives.

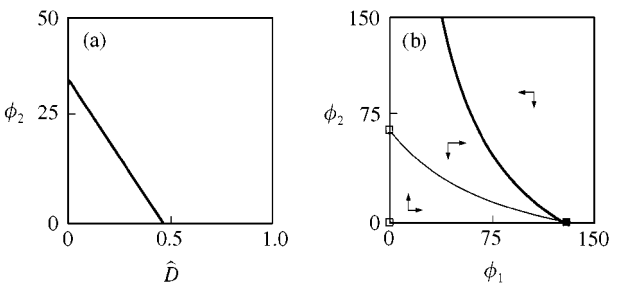

FIG. 5. (a) The value of ϕ_2 in the coexistent equilibrium point of Fig. 4(c) drawn for different values of $\hat{D}$. (b) The nullcline picture at the bifurcation point $\hat{D} = 0.45$. For explanation lines and symbols, see Fig. 4.

The possibility of coexistence in the multi-compartment model can also be shown analytically. At equilibrium, $\mathrm{d}\phi_i/\mathrm{d}t = 0$. For class I in the single-compartment model, the solutions of this equation are, from eqns (13) and (17), $\phi_i = 0$

or $g_i(L) - \lambda_3 = 0$. Taking the second solution for all n axons defines a system of n equations with only one free variable, L. Because all $\lambda_{4,i}$ are typically distinct, at most one equation can be satisfied. Hence, no more than one ϕ_i can be non-zero at equilibrium, i.e. competitive exclusion. In the multi-compartment model, in contrast, taking the second solution $g_i(L_i) - \lambda_3 = 0$ for all n axons defines a system of n equations with n free variables L_i. A number of these equations may be satisfied simultaneously, meaning that coexistence is possible.

Spatial separation ($\hat{D}$ small) and coexistence of innervating axons becomes possible if the target cell has an extensive dendritic tree. Thus, the larger the dendritic tree, the more innervating axons can survive. If the target cell lacks dendrites, the innervating axons are confined to the relatively small surface area of the soma ($\hat{D}$ large), and only one innervating axon typically survives (see further Section 6).

5. Axons Responding to More than One Neurotrophin

In consumer–resource systems in population biology, consumer species often utilize more than one type of resource. In this section, we investigate the parallel situation in neurobiology: innervating axons that are capable of responding to more than one type of neurotrophin (e.g. Barde, 1989; McManaman *et al.*, 1989; Lindsay *et al.*, 1994). We examine two possibilities through which axons can respond to more than one type of neurotrophin. (1) Individual axons have a single type of neurotrophin receptor, but this can bind to more than one type of neurotrophin. (2) Individual axons have more than one type of neurotrophin receptor, and each type of receptor binds exclusively to one type of neurotrophin.

To study (1) and (2), we consider a single target that releases two types of neurotrophin and at which there are two different groups of innervating axons. For (1), axons from one group have one type of receptor, while axons from the other group have another type. The different receptor types bind the neurotrophins with different affinities. For (2), all axons have the same two types of receptor but in axons from different groups they are present in different proportions. We deliberately use small numbers of neurotrophin and receptor types to obtain a better understanding of how axonal competition is affected. We use class I of the growth function, i.e. $f_i(C_i) = \eta_i C_i$ (where, in parameters of eqn (5), $\eta_i = \alpha_i/K_i$), and a single compartment for the extracellular space; these are conditions that do not permit axons to coexist if they respond to only one neurotrophin.

5.1. INDIVIDUAL AXONS HAVING ONE RECEPTOR TYPE

Consider a single target at which there are two different groups of axons. One group, consisting of axons $i = 1, \ldots, n$, has receptor type $R1$; the other group, consisting of axons $i = n+1, \ldots, n+m$, has receptor type $R2$. The target releases two types of neurotrophin, $L1$ and $L2$, which bind to both $R1$ and $R2$, but with different affinities. At axons $i = 1, \ldots, n$, we have the following binding reactions:

$$L1 + R1_i \underset{k11_{d,i}}{\overset{k11_{a,i}}{\rightleftharpoons}} C11_i,$$

$$L2 + R1_i \underset{k21_{d,i}}{\overset{k21_{a,i}}{\rightleftharpoons}} C21_i,$$

where $k11_{a,i}$ and $k21_{a,i}$ are the association constants, $k11_{d,i}$ and $k21_{d,i}$ are the dissociation constants, and $C11_i$ and $C21_i$ are the neurotrophin–receptor complexes. The neurotrophin –receptor complexes $C11_i$ and $C21_i$ are degraded with rate constants $\rho 11_i$ and $\rho 21_i$, respectively. The receptors $R1_i$ and $R2_i$ are inserted at rates $\phi 1_i$ and $\phi 2_i$, respectively, and are degraded with rate constants $\gamma 1_i$ and $\gamma 2_i$, respectively. In analogy with eqns (1), (2), and (4), we obtain for axons $i = 1, \ldots, n$,

$$\frac{dC11_i}{dt} = (k11_{a,i} L1R1_i - k11_{d,i} C11_i) - \rho 11_i C11_i, \tag{25}$$

$$\frac{dC21_i}{dt} = (k21_{a,i} L2R1_i - k21_{d,i} C21_i) - \rho 21_i C21_i, \tag{26}$$

$$\frac{dR1_i}{dt} = \phi 1_i - \gamma 1_i R1_i - (k11_{a,i} L1R1_i - k11_{d,i} C11_i) - (k21_{a,i} L2R1_i - k21_{d,i} C21_i), \quad (27)$$

$$\tau \frac{\phi 1_i}{dt} = \eta_i (C11_i + C21_i) - \phi 1_i. \quad (28)$$

Note that in eqn (28) class I of the growth function is used (see Section 2.1), where $C11_i + C21_i$ is the total amount of bound neurotrophin on axon i.

At axons $i = n+1, \ldots, n+m$, we have the following binding reactions:

$$L2 + R2_i \underset{k22_{d,i}}{\overset{k22_{a,i}}{\rightleftharpoons}} C22_i,$$

$$L1 + R2_i \underset{k12_{d,i}}{\overset{k12_{a,i}}{\rightleftharpoons}} C12_i.$$

In analogy with eqns (25–28), we obtain for axons $i = n+1, \ldots, n+m$,

$$\frac{dC22_i}{dt} = (k22_{a,i} L2R2_i - k22_{d,i} C22_i) - \rho 22_i C22_i, \quad (29)$$

$$\frac{dC12_i}{dt} = (k12_{a,i} L1R2_i - k12_{d,i} C12_i) - \rho 12_i C12_i, \quad (30)$$

$$\frac{dR2_i}{dt} = \phi 2_i - \gamma 2_i R2_i - (k22_{a,i} L2R2_i - k22_{d,i} C22_i) \quad (31)$$

$$- (k12_{a,i} L1R2_i - k12_{d,i} C12_i), \quad (32)$$

$$\tau \frac{\phi 2_i}{dt} = \eta_i (C22_i + C12_i) - \phi 2_i. \quad (33)$$

In analogy with eqn (3), we obtain for the rates of change of the neurotrophin concentrations,

$$\frac{dL1}{dt} = \sigma 1 - \delta 1 L1 - \sum_{i=1}^{n} (k11_{a,i} L1R1_i - k11_{d,i} C11_i)/v - \sum_{i=n+1}^{n+m} (k12_{a,i} L1R2_i - k12_{d,i} C12_i)/v, \quad (34)$$

$$\frac{dL2}{dt} = \sigma 2 - \delta 2 L2 - \sum_{i=n+1}^{n+m} (k22_{a,i} L2R2_i - k22_{d,i} C22_i)/v - \sum_{i=1}^{n} (k21_{a,i} L2R1_i - k21_{d,i} C21_i)/v, \quad (35)$$

where $\sigma 1$ and $\sigma 2$ are the rates of release of $L1$ and $L2$, respectively, and $\delta 1$ and $\delta 2$ are the rate constants for degradation of $L1$ and $L2$, respectively. We assume that except for η_i there is no variation in parameter values between axons.

For simplicity (see Section 6), we take $\gamma 1 = \gamma 2 \equiv \gamma$, $\delta 1 = \delta 2 \equiv \delta$, and $\sigma 1 = \sigma 2 \equiv \sigma$. For the different neurotrophin–receptor combinations, we assume that all constants except the association constants are identical, i.e. $k11_d = k21_d = k22_d = k12_d \equiv k_d$ and $\rho 11 = \rho 21 = \rho 22 = \rho 12 \equiv \rho$. For the association constants, we assume that $k11_a = k22_a \equiv k_a$ and that $k21_a$ and $k12_a$ are a fraction of k_a, i.e. $k21_a = k12_a = qk_a$, where $0 \leqslant q \leqslant 1$. For $q = 0$, there is no cross-reactivity, i.e. the different receptors are specific for a given type of neurotrophin: $L1$ binds only to $R1$, and $L2$ only to $R2$. For $q = 1$, $L1$ and $L2$ bind equally well to both $R1$ and $R2$. For $0 < q < 1$, $L1$ and $L2$ bind to both $R1$ and $R2$, but with different association constants. In other words, q expresses receptor specificity and thus overlap in resource (i.e. neurotrophin) utilization between the two groups of axons. As in the previous models, axons that at the end of the competitive process have no neurotrophin (i.e. for $i = 1, \ldots, n$, $C11_i + C21_i = 0$, which is equivalent to $\phi 1_i = 0$; for $i = n+1, \ldots, n+m$, $C22_i + C12_i = 0$, which is

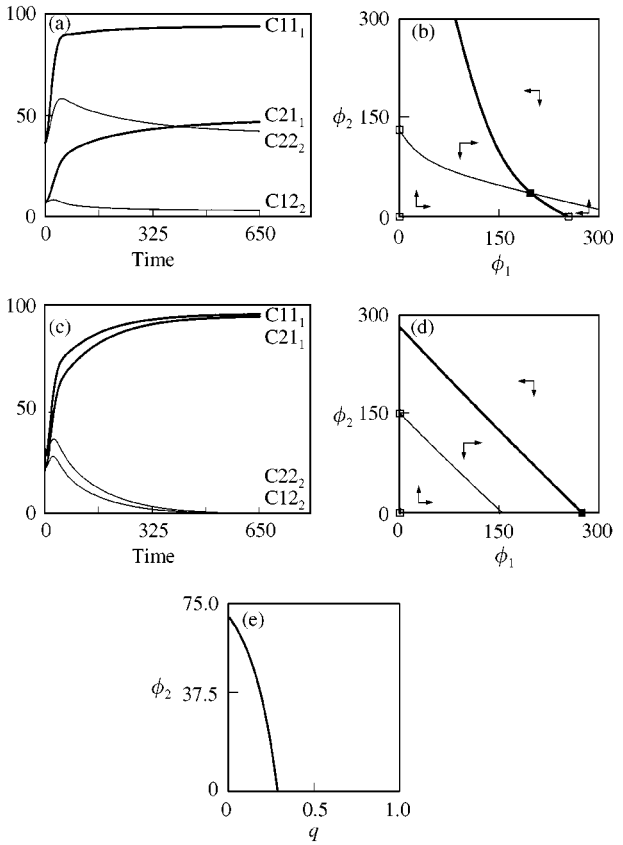

FIG. 6. Coexistence of axons and competitive exclusion depending on the value of q, in the two-neurotrophin model of Section 5.1. System of two innervating axons ($n = m = 1$). Axon 1 has receptor type $R1$; axon 2 has receptor type $R2$. (a, b) Coexistence, $q = 0.2$. (c, d) Competitive exclusion, $q = 0.8$. In (b) and (d), the —— are the nullclines of ϕ_1 and the —— the nullclines of ϕ_2. $\eta_1 = 1.4$ and $\eta_2 = 0.8$. The x- and y-axes are also nullclines of ϕ_2 and ϕ_1, respectively. For explanation symbols, see Fig. 2. (e) The value of ϕ_2 in the coexistent equilibrium point of (b) drawn for different values of q.

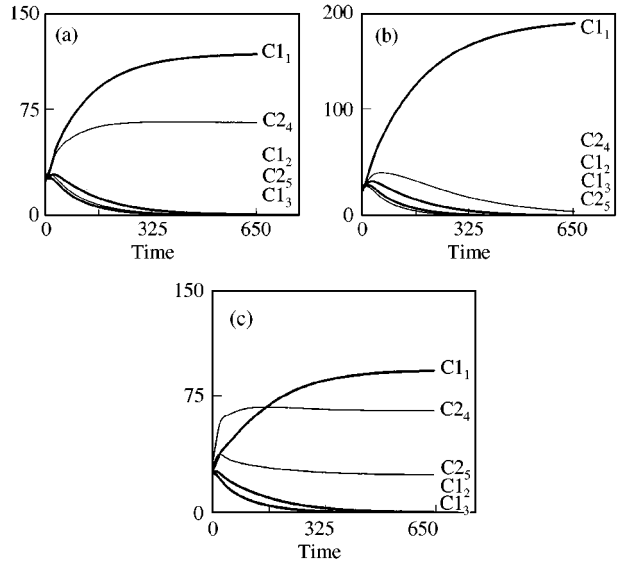

FIG. 7. System of five innervating axons ($n = 3$, $m = 2$), in the two-neurotrophin model of Section 5.1. Axons 1, 2, and 3 have receptor type $R1$; axons 4 and 5 have receptor type $R2$. $C1_i \equiv C11_i + C21_i$ and $C2_i \equiv C22_i + C12_i$. (a) Competitive exclusion within each group, but coexistence between groups. The axons with the highest values of η_i within each group survive (axons 1 and 4), $q = 0.2$. (b) Competitive exclusion. The axon with the overall highest value of η_i survives (axon 1), $q = 0.8$. In (a) and (b), $\eta_1 = 1.4$, $\eta_2 = 0.8$, $\eta_3 = 0.6$, $\eta_4 = 1.0$, and $\eta_5 = 0.5$. (c) The second group of axons has class II of the growth function, the first group class I. Axons 1, 4, and 5 survive. $q = 0.2$, $\eta_1 = 1.4$, $\eta_2 = 0.8$, $\eta_3 = 0.6$, $\alpha_4 = 150$, $\alpha_5 = 90$, and $K_4 = K_5 = 40$.

equivalent to $\phi 2_i = 0$) are assumed to have withdrawn. For the parameter values, see Table 1.

5.1.1. *Results*

We first study a system of two innervating axons where axon 1 has receptor type $R1$ and axon 2 has receptor type $R2$ (i.e. $n = m = 1$). In contrast to the model with one type of neurotrophin (and a single extracellular compartment) (see Section 2.1), in this model both axons can coexist. Coexistence occurs for relatively small q, i.e. if there is little cross-reactivity and, consequently, little overlap in neurotrophin utilization between the axons [Fig. 6(a) and (b)]. For $q = 0$, the axons depend entirely on different neurotrophins, so that there is no interaction between the axons and, consequently, no competition. For relatively large q, i.e. if there is a large overlap in neurotrophin utilization, no more than one axon can survive [Fig. 6(c) and (d)]. For $q = 1$, there is complete overlap in neurotrophin utilization, i.e. there are no differences between the two groups of axons. Because we assume only variation between axons in η_i (the parameter of the growth function of class I), the axon that survives is the one with the highest value of η_i.

As in Section 4.2, to study this system of two innervating axons using phase-plane analysis, we make quasi-steady-state approximations for all the variables except ϕ_i (i.e. $dC11_i/dt = dC21_i/dt = dC22_i/dt = dC12_i/dt = dR1_i/dt = dR2_i/dt = dL1/dt = dL2/dt = 0$, $i = 1, 2$). For relatively small q, there is an intersection point where both axons coexist [Fig. 6(b)]. Figure 6(e)

shows the value of ϕ_2 in this intersection point for different values of q. Around $q = 0.28$, a bifurcation occurs, where the coexistent equilibrium point disappears. For $q < 0.28$, both axons survive; for $q > 0.28$, only one axon survives.

We now consider the more general case in which there is more than one axon in each group (i.e. $n > 1$ and $m > 1$). For relatively large q, in total only one axon survives [Fig. 7(b)]. For relatively small q, there is competitive exclusion within each group of axons but coexistence between groups: in total two axons survive, one from each group [Fig. 7(a)]. For class I of the growth function, there are no conditions under which more than one axon from each group can survive. For classes II and III, more axons may survive. For example, if the axons from the second group have a class II growth function, more than one axon may survive from this group, while from the first group, with a class I growth function, only one axon survives [Fig. 7(c)].

5.2. INDIVIDUAL AXONS HAVING TWO RECEPTOR TYPES

Again, we consider a single target at which there are two different groups of axons. The two groups have both receptor types, but they are present in different proportions. One group, consisting of axons $i = 1, \ldots, n$, has more $R1$ than $R2$; the other group, consisting of axons $i = n + 1, \ldots, n + m$, has more $R2$ than $R1$. The target releases two types of neurotrophin, $L1$ and $L2$; $L1$ binds only to $R1$, and $L2$ only to $R2$.

At all axons, we have the following binding reactions:

$$L1 + R1_i \underset{k11_{d,i}}{\overset{k11_{a,i}}{\rightleftharpoons}} C11_i,$$

$$L2 + R2_i \underset{k22_{d,i}}{\overset{k22_{a,i}}{\rightleftharpoons}} C22_i.$$

For all axons, we obtain

$$\frac{dC11_i}{dt} = (k11_{a,i} L1R1_i - k11_{d,i} C11_i) - \rho 11_i C11_i, \tag{36}$$

$$\frac{dR1_i}{dt} = \phi 1_i - \gamma 1_i R1_i - (k11_{a,i} L1R1_i - k11_{d,i} C11_i), \tag{37}$$

$$\frac{dC22_i}{dt} = (k22_{a,i} L2R2_i - k22_{d,i} C22_i) - \rho 22_i C22_i, \tag{38}$$

$$\frac{dR2_i}{dt} = \phi 2_i - \gamma 2_i R2_i - (k22_{a,i} L2R2_i - k22_{d,i} C22_i). \tag{39}$$

For axons $i = 1, \ldots, n$, we assume that

$$\tau \frac{\phi 1_i}{dt} = \eta_i (C11_i + C22_i) - \phi 1_i, \tag{40}$$

$$\phi 2_i = p \phi 1_i, \tag{41}$$

where $0 \leqslant p \leqslant 1$ and $C11_i + C22_i$ is the total amount of bound neurotrophin on axon i.

For axons $i = n + 1, \ldots, n + m$, we assume that

$$\tau \frac{\phi 2_i}{dt} = \eta_i (C11_i + C22_i) - \phi 2_i, \tag{42}$$

$$\phi 1_i = p \phi 2_i. \tag{43}$$

For $p = 0$, axons $i = 1, \ldots, n$ have only $R1$ and axons $i = n + 1, \ldots, n + m$ only $R2$. For $p = 1$, there are no differences between both groups of axons. For $0 < p < 1$, both groups have both $R1$ and $R2$, but in different amounts. In other words, p expresses overlap in neurotrophin utilization, as does q in the previous model (see Section 5.1).

For the rates of change of the neurotrophin concentrations, we obtain

$$\frac{dL1}{dt} = \sigma 1 - \delta 1 L1 - \sum_{i=1}^{n+m} (k11_{a,i} L1R1_i - k11_{d,i} C11_i)/v, \tag{44}$$

$$\frac{dL2}{dt} = \sigma 2 - \delta 2 L2 - \sum_{i=1}^{n+m} (k22_{a,i} L2R2_i - k22_{d,i} C22_i)/v. \tag{45}$$

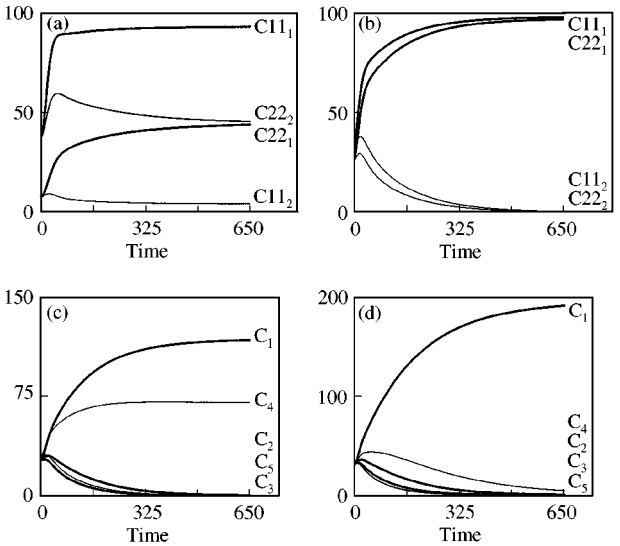

FIG. 8. Coexistence of axons and competitive exclusion in the two-neurotrophin model of Section 5.2. In (a) and (b), a system of two innervating axons ($n = m = 1$). Axon 1 has more $R1$ than $R2$; axon 2 has more $R2$ than $R1$. $\eta_1 = 1.4$ and $\eta_2 = 0.8$. (a) Coexistence, $p = 0.2$. (b) Competitive exclusion, $p = 0.8$. In (c) and (d), a system of five innervating axons ($n = 3$, $m = 2$). Axons 1, 2, and 3 have more $R1$ than $R2$; axons 4 and 5 have more $R2$ than $R1$. $\eta_1 = 1.4$, $\eta_2 = 0.8$, $\eta_3 = 0.6$, $\eta_4 = 1.0$, and $\eta_5 = 0.5$. $C_i \equiv C11_i + C22_i$. (c) Competitive exclusion within each group, but coexistence between groups. The axons with the highest value of η_i within each group survive (axons 1 and 4), $p = 0.2$. (d) Competitive exclusion. The axon with the overall highest value of η_i survives (axon 1), $p = 0.8$.

For simplicity (see Section 6), we take $k11_{a,i} = k22_{a,i} \equiv k_a$, $k11_{d,i} = k22_{d,i} \equiv k_d$, $\rho 11_i = \rho 22_i \equiv \rho$, $\gamma 1_i = \gamma 2_i \equiv \gamma$, $\delta 1 = \delta 2 \equiv \delta$, and $\sigma 1 = \sigma 2 \equiv \sigma$. For the parameter values, see Table 1.

5.2.1. *Results*

We obtain very similar results as in the previous model (see Section 5.1.1). In a system of two innervating axons (i.e. $n = m = 1$), there is coexistence for relatively small p (i.e. if axon 1 has mainly receptor type $R1$ and axon 2 mainly receptor type $R2$) [Fig. 8(a)] and competitive exclusion for relatively large p (i.e. if the difference in receptor content between both axons is smaller) [Fig. 8(b)].

In the more general case, in which there is more than one axon in each group (i.e. $n > 1$ and $m > 1$), two axons survive for relatively small p, one from each group [Fig. 8(c)]. For relatively large p, on the other hand, only one axon survives [Fig. 8(d)].

6. Discussion and Conclusions

We have shown analytically that there exist formal parallels between consumer–resource systems in population biology (Yodzis, 1989) and the development of nerve connections under the control of neurotrophins (Van Ooyen & Willshaw, 1999b). This allows neurobiological phenomena to be interpreted in population biological terms and, conversely, approaches from population biology (where competition is better understood) to be applied to neurobiology.

The notion that there could be useful analogies between the development of nerve connections and the dynamics of populations in ecosystems is not new. For example, Purves & Lichtman (1985) suggested that the interactions between neurons during development resemble more those between organisms in an ecosystem than those between elements in an electrical circuit. Jeanprêtre *et al.* (1996) compared single innervation to competitive exclusion in population biology. In a qualitative fashion, Ribchester & Barry (1994) indicated how the principles used to describe competition in ecosystems might be used as a basis for further experimental investigation of synaptic competition. By adopting a definition of competition from population biology (Keddy, 1989), they identified several important questions concerning synaptic competition: what the resources are, whether competition is based on consumption of resources (consumptive competition) or on control of access to resources (spatial competition), and whether competition also involves direct negative interactions between synapses (interference). Similar ideas can be found embedded in Van Essen *et al.* (1990).

To account for perceptual categorization, Edelman (1987), in his theory of neuronal group selection, also applied population thinking to neurobiology, but at a different level of organization. His theory proposes that the key principle governing brain organization is a population one and that in its operation the brain is a selective system. According to this theory, the brain is functionally organized into cellular populations

containing individually variant networks, or neuronal groups, upon which selection acts during development.

Unlike previous comparisons between neurobiology and population biology, the parallels we have drawn are based on formal, analytical arguments. We have shown that competition in nervous systems and ecosystems can be described by similar underlying equations. Inspired by these parallels, we studied two extensions of our axonal competition model (Van Ooyen & Willshaw, 1999b).

First, the findings from theoretical population biology concerning the importance of the spatial dimension in competition led us to investigate how axonal competition is affected when the spatial dimension of the extracellular space around the target is taken into account, so that the concentration of neurotrophin is no longer necessarily uniform across the extracellular space. Although we modelled only two compartments, the main result—that competitive exclusion does not occur if the innervating axons are sufficiently far apart on the target cell—is not expected to change if the model is made more accurate by dividing the extracellular space into additional compartments. In agreement with the model are the *in vitro* and *in vivo* observations that coexisting nerve terminals from different motor neurons are physically separated on mature muscle cells (Kuffer *et al*., 1977; Lømo, 1980; Lo & Poo, 1991). With neurons as target cells, spatial separation and coexistence of innervating axons become possible only if the target has an extensive dendritic tree. Indeed, in many types of neurons, a positive correlation exists between the size of the dendritic tree and the number of innervating axons surviving into adulthood (Hume & Purves, 1981; Purves & Hume, 1981; Purves, 1994). In the ciliary ganglion of adult rabbits, for example, neurons that lack dendrites are innervated by a single axon, whereas neurons with many dendrites are innervated by the largest number of axons. That is not a matter of available space because in newborn animals all neurons are innervated by approximately the same number of axons. Thus, multiple innervation is unstable for neurons that lack dendrites, whereas no net elimination of axons takes place on neurons that have many dendrites. It is not understood how the presence of dendrites mitigates competition and permits the coexistence of axons. Our results show that competition for neurotrophin released locally along the target's dendrites (Wetmore *et al*., 1991), together with diffusion of neurotrophin, provides a plausible mechanism. Interestingly, not only the size of the dendritic tree could affect axonal innervation but, by influencing the spatial pattern of the concentration of neurotrophin, also the tree's specific morphology.

In the second extension of our model, we investigated how axonal competition is affected if the axons are capable of responding to more than one type of neurotrophin (e.g. Barde, 1989; McManaman *et al*., 1989; Lindsay *et al*., 1994); in ecosystems, this corresponds to consumer species utilizing more than one type of resource. We examined the following two situations. (1) Individual axons have only a single type of neurotrophin receptor, but this can bind to more than one type of neurotrophin. Different types of axons have different receptor types. (2) Individual axons have more than one type of neurotrophin receptor, and each receptor type binds exclusively to one type of neurotrophin. Different types of axons have these receptor types in different proportions. Our results show that for both (1) and (2), different types of axons can coexist if they respond to the neurotrophins with sufficiently different affinities, i.e. if the axons' overlap in neurotrophin utilization is below a certain level. For (1), this means that there is a limit on the degree of cross-reactivity, i.e. each type of receptor should bind preferentially, but not necessarily exclusively, to one type of neurotrophin. For (2), this means that there is a limit on the similarity in receptor content between different types of axons. These kinds of limits on the similarity of coexisting axons with respect to neurotrophin utilization correspond to what is called in population biology limiting similarity (Yodzis, 1989). In analysing (1) and (2), we made, for reasons of simplicity, assumptions for the parameters (see Sections 5.1 and 5.2), but all these assumptions can be relaxed without compromising the main results. What counts is the axons' degree of overlap in neurotrophin utilization, and this can be influenced by many parameters. The main conclusions are also expected to be valid in models that are extended to more than two types of neurotrophin and receptor.

By having axons respond with different affinities to more than one type of neurotrophin, our 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 [see Figs 7(a), (c) and 8(c)]. The model can thus account for the emergence of an innervation pattern such as is found on cerebellar Purkinje cells (Crepel, 1982): climbing fibres compete with each other during development until only a single one remains, which coexists with parallel fibres innovating the same Purkinje cell. More than one type of neurotrophin can indeed be involved in setting up this innervation pattern, as in the developing cerebellum a variety of neurotrophins and receptors are expressed (Hofer *et al*., 1990; Ernfors *et al*., 1992; Rocamora *et al*., 1993; Gao *et al*., 1995; Segal *et al*., 1995; Lindholm *et al*., 1997).

We thank Michael Corner for critical reading of the manuscript. We thank an anonymous referee for valuable suggestions on the manuscript.

REFERENCES

ABRAMS, P. (1994). The fallacies of "ratio-dependent" predation. *Ecology* **75,** 1842–1850.

BARDE, Y. A. (1989). Trophic factors and neuronal survival. *Neuron* **2,** 1525–1534.

BENNETT, M. R. & ROBINSON, J. (1989). Growth and elimination of nerve terminals at synaptic sites during polyneuronal innervation of muscle cells: a trophic hypothesis. *Proc. R. Soc. Lond. B* **235,** 299–320.

BERND, P. & GREENE, L. A. (1984). Association of ^{125}I-nerve growth factor with PC12 pheochromocytoma cells. Evidence of internalization via high-affinity receptors only and for long-term regulation by nerve growth factor of both high- and low-affinity receptors. *J. Biol. Chem.* **259,** 15 509–15 516.

BIRREN, S. J., VERDI, J. M. & ANDERSON, D. J. (1992). Membrane depolarization induces p140^{trk} and NGF responsiveness, but not p75^{LNGFR}, in MAH cell. *Science* **257,** 395–397.

BLÖCHEL, A. & THOENEN, H. (1995). Characterization of nerve growth factor (NGF) release from hippocampal neurons: evidence for a constitutive and an unconventional sodium-dependent regulated pathway. *Eur. J. Neurosc.* **7,** 1220–1228.

BOTHWELL, M. (1995). Functional interactions of neurotrophins and neurotrophin receptors. *Ann. Rev. Neurosci.* **18,** 223–253.

COHEN-CORY, S. & FRASER, S. E. (1995). Effects of brain-derived neurotrophic factor on optic axon branching and remodelling *in vivo*. *Nature* **378,** 192–196.

CREPEL, F. (1982). Regression of functional synapses in the immature mammalian cerebellum. *Trends Neurosci.* **5,** 266–269.

EDELMAN, G. M. (1987). *Neural Darwinism. The Theory of Neuronal Group Selection.* New York: Basic Books, Inc., Publishers.

ELLIOTT, T. & SHADBOLT, N. R. (1996). A mathematical model of activity-dependent, anatomical segregation induced by competition for neurotrophic support. *Biol. Cybernet.* **75,** 463–470.

ELLIOTT, T. & SHADBOLT, N. R. (1998). Competition for neurotrophic factors: mathematical analysis. *Neural Comput.* **10,** 1939–1981.

ERNFORS, P., MERLIO, J.-P. & PERSSON, H. (1992). Cells expressing mRNA for neurotrophins and their receptors during embryonic rat development. *Eur. J. Neurosci.* **4,** 1140–1158.

GAO, W.-Q., ZHENG, J. L. & KARIHALOO, H. (1995). Neurotrophin-4/5 (NT-4/5) and brain-derived neurotrophic factor act at later stages of cerebellar granule cell differentiation. *J. Neurosci.* **15,** 2656–2667.

GAROFALO, L., RIBEIRO-DA-SILVA, A. & CUELLO, C. (1992). Nerve growth factor-induced synaptogenesis and hypertrophy of cortical cholinergic terminals. *Proc. Nat. Acad. Sci. U.S.A.* **89,** 2639–2643.

GOUZÉ, J.-L., LASRY, J.-M. & CHANGEUX, J.-P. (1983). Selective stabilization of muscle innervation during development: a mathematical model. *Biol. Cybernet.* **46,** 207–215.

GRINNELL, A. D., LETINSKY, M. S. & RHEUBEN, M. B. (1979). Competitive interaction between foreign nerves innervating frog skeletal muscle. *J. Physiol.* (*Lond*) **289,** 241–262.

GROVER, J. P. (1997). *Resource Competition.* London, New York: Chapman & Hall.

HARRIS, A. E., ERMENTROUT, G. B. & SMALL, S. L. (1997). A model of ocular dominance development by competition for trophic factor. *Proc. Nat. Acad. Sci. U.S.A.* **94,** 9944–9949.

HOFER, M., PAGLIUSI, S. R., HOHN, A., LEIBROCK, J. & BARDE, Y.-A. (1990). Regional distribution of brain-derived neurotrophic factor mRNA in the adult mouse brain. *EMBO J.* **9,** 2459–2464.

HOLTZMAN, D. M., LI, Y., PARADA, L. F., KINSMAN, S., CHEN, C.-K., VALLETTA, J. S., ZHOU, J., LONG, J. B. & MOBLEY, W. C. (1992). p140^{trk} mRNA marks NGF-responsive fore-brain neurons: evidence that *trk* gene expression is induced by NGF. *Neuron* **9,** 465–478.

HUME, R. I. & PURVES, D. (1981). Geometry of neonatal neurones and the regulation of synapse elimination. *Nature* **293,** 469–471.

JANSEN, J. K. S. & FLADBY, T. (1990). The perinatal reorganization of the innervation of skeletal muscle in mammals. *Prog. Neurobiol.* **34,** 39–90.

JEANPRÊTRE, N., CLARKE, P. G. H. & GABRIEL, J.-P. (1996). Competitive exclusion between axons dependent on a single trophic substance: a mathematical analysis. *Mathl. Biosci.* **133,** 23–54.

KAPLAN, J. L. & YORKE, J. A. (1977). Competitive exclusion and nonequilibrium coexistence. *Am. Nat.* **111,** 1030–1036.

KEDDY, P. (1989). *Competition.* London, New York: Chapman & Hall.

KUFFER, D., THOMPSON, W. & JANSEN, J. K. S. (1977). The elimination of synapses in multiply-innervated skeletal muscle fibres of the rat: dependence on distance between end-plates. *Brain Res.* **138,** 353–358.

LAYER, P. G. & SHOOTER, E. M. (1983). Binding and degradation of nerve growth factor by PC12 pheochromocytoma cells. *J. Biol. Chem.* **258,** 3012–3018.

LEWIN, G. R. & BARDE, Y.-A. (1996). Physiology of the neurotrophins. *Annu. Rev. Neurosci.* **19,** 289–317.

LINDHOLM, D., HAMNER, S. & ZIRRGIEBEL, U. (1997). Neurotrophins and cerebellar development. *Perspect. Dev. Neurobiol.* **5,** 83–94.

LINDSAY, R. M., SHOOTER, E. M., RADEKE, M. J., MISKO, T. P., DECHANT, G., THOENEN, H. & LINDHOLM, D. (1990). Nerve growth factor regulates expression of the nerve growth factor receptor gene in adult sensory neurons. *Eur. J. Neurosci.* **2,** 389–396.

LO, Y.-J. & POO, M.-M. (1991). Activity-dependent synaptic competition in vitro: heterosynaptic suppression of developing synapses. *Science* **254,** 1019–1022.

LØMO, T. (1980). What controls the development of neuromuscular junctions? *Trends Neurosci.* **3,** 126–129.

MACARTHUR, R. H. (1970). Species packing and competitive equilibrium for many species. *Theor. Popul. Biol.* **1,** 1–11.

MCMANAMAN, J. L., CRAWFORD, F., CLARK, R., RICHKER, J. & FULLER, F. (1989). Multiple neurotrophic factors from skeletal muscle: demonstration of effects of bFGF and comparisons with the 22-kdalton CAT development factor. *J. Neurochem.* **53,** 1763–1771.

MAY, R. M. (1974). *Stability and Complexity in Model Ecosystem*, Monographs in Population Biology, Vol. 6, Princeton, NY: Princeton University Press.

NGUYEN, O. T. & LICHTMAN, J. W. (1996). Mechanisms of synapse disassembly at the developing neuromuscular junction. *Curr. Opin. Neurobiol.* **6,** 104–112.

PURVES, D. (1988). *Body and Brain: A Trophic Theory of Neural Connections.* Cambridge, MA and London: Harvard University Press.

PURVES, D. (1994). *Neural Activity and the Growth of the Brain.* Cambridge: Cambridge University Press.

PURVES, D. & HUME, R. I. (1981). The relation of postsynaptic geometry to the number of presynaptic axons that innervate autonomic ganglion cells. *J. Neurosci.* **1,** 441–452.

PURVES, D. & LICHTMAN, J. W. (1980). Elimination of synapses in the developing nervous system. *Science* **210,** 153–157.

PURVES, D. & LICHTMAN, J. W. (1985). *Principles of Neural Development*. Sunderland, MA: Sinauer.

RASMUSSEN, C. E. & WILLSHAW, D. J. (1993). Presynaptic and postsynaptic competition in models for the development of neuromuscular connections. *Biol. Cybernet.* **68,** 409–419.

RIBCHESTER, R. R. & BARRY, J. A. (1994). Spatial *versus* consumptive competition at polyneuronally innervated neuromuscular junctions. *Exp. Physiol.* **79,** 465–494.

ROCAMORA, N., GARCIA-LADONA, F. J., PALACOS, J. M. & MENGOD, G. (1993). Differential expression of brain-derived neurotrophic factor, neurotrophin-3, and low-affinity nerve growth factor receptor during the postnatal development of the rat cerebellar system. *Mol. Brain Res.* **17,** 1–8.

SEGAL, R. A., POMEROY, S. L. & STILES, C. D. (1995). Axonal growth and fasciculation linked to differential expression of BDNF and NT3 receptors in developing cerebellar granule cells. *J. Neurosci.* **15,** 4970–4981.

SUTTER, A., RIOPELLE, R. J., HARRIS-WARRICK, R. M. & SHOOTER, E. M. (1979). Nerve growth factor receptors. Characterization of two distinct classes of binding sites on chick embryo sensory ganglia cells. *J. Biol. Chem.* **254,** 5972–5982.

VAN DER MEER, J. & ENS, B. J. (1997). Models of interference and their consequences for the spatial distribution of ideal and free predators. *J. Anim. Ecol.* **66,** 846–858.

VAN ESSEN, D. C., GORDON, H., SOHA, J. M. & FRASER, S. E. (1990). Synaptic dynamics at the neuromuscular junction: mechanisms and models. *J. Neurobiol.* **21,** 223–2249.

VAN OOYEN, A. & WILLSHAW, D. J. (1999a). Poly- and mononeuronal innervation in a model for the development of neuromuscular connections. *J. theor. Biol.* **196,** 495–511.

VAN OOYEN, A. & WILLSHAW, D. J. (1999b). Competition for neurotrophic factor in the development of nerve connections. *Proc. R. Soc. Lond. B* **266,** 883–892.

WETMORE, C., CAO, Y., PETTERSSON, R. F. & OLSON, L. (1991). Brain-derived neurotrophic factor: subcellular compartmentalization and interneuronal transfer as visualized with anti-peptide antibodies. *Proc. Nat. Acad. Sci. U.S.A.* **88,** 9843–9847.

YODZIS, P. (1989). *Introduction to Theoretical Ecology*. New York: Harper & Row.

ZUPAN, A. A. & JOHNSON JR., E. M. (1991). Evidence for endocytosis-dependent proteolysis in the generation of soluble truncated nerve growth factor receptors by A875 human melanoma cells. *J. Biol. Chem.* **266,** 15 384–15 390.