Influence of Dendritic Morphology on Axonal Competition

Arjen van Ooyen[1] David J. Willshaw[2]

[1]Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ, Amsterdam, The Netherlands, A.van.Ooyen@nih.knaw.nl
[2]Institute for Adaptive and Neural Computation, Division of Informatics, University of Edinburgh, 2 Buccleuch Place, Edinburgh EH8 9LW, UK, D.Willshaw@anc.ed.ac.uk

Abstract

The development of nerve connections involves competition among axons for survival promoting factors, or neurotrophins, which are released by the axons' target cells. To study the influence of the target's dendritic tree on axonal competition, we have extended our model of axonal competition (Van Ooyen & Willshaw 1999) to take into account the extracellular space around the dendrites. We show that spatial separation of innervating axons on the target's dendrites mitigates competition and permits the coexistence of axons. The model accounts for the finding that in many types of neurons a positive correlation exists between the size of the dendritic tree and the number of impinging innervating axons surviving into adulthood (Hume & Purves 1981; Purves & Hume 1981). Our results emphasize the importance of postsynaptic dendritic morphology in the development of specific patterns of nerve connections, on which the function of the nervous system depends.

Introduction

The development of connections between neurons and their target cells often involves an initial stage of superinnervation followed by elimination of axons (Purves & Lichtman 1980). Competition among innervating axons for target-derived neurotrophins is thought to be involved in the elimination of axons and the generation of different patterns of innervation (Purves & Lichtman 1985; Purves 1988). Neurotrophins are taken up by the innervating axons via specific receptors at their terminals (Bothwell 1995) and affect the growth and branching of the axons.

In many types of neurons, a positive correlation exists between the complexity of the dendritic tree and the number of impinging innervating axons surviving into adulthood (Hume & Purves 1981; Purves & Hume 1981). In the ciliary ganglion of adult rats, 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. In newborn animals, however, just as many axons, on average, innervate neurons that lack dendrites as innervate neurons that have complex dendritic trees. That is, multiple innervation is an unstable condition 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.

In this paper, we offer an explanation for this phenomenon, using a compartmental version of a model of axonal competition put forward by Van Ooyen & Willshaw (1999). We briefly summarize this model in the next section before introducing the compartmental version.

Competition for Neurotrophins

In Van Ooyen & Willshaw (1999), a single target cell (*e.g.* a neuron) is considered at which there are n innervating axons each from a different neuron (Fig. 1). Neurotrophin is released by the target into the extracellular space (which is considered to

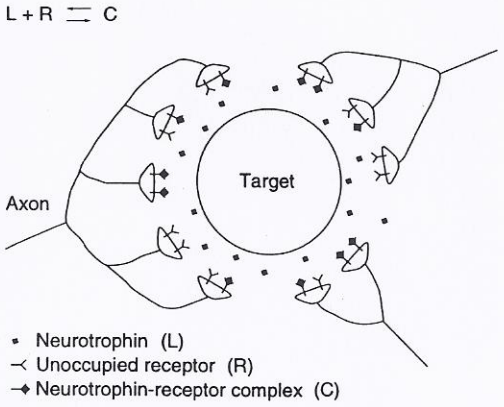

Figure 1: Target cell with three innervating axons, each with a different degree of branching. The target releases neurotrophin, which is bound by neurotrophin receptors at the axon terminals. The extracellular space around the target is assumed to be homogeneous with respect to the concentration of neurotrophin, i.e. the extracellular space is a single compartment.

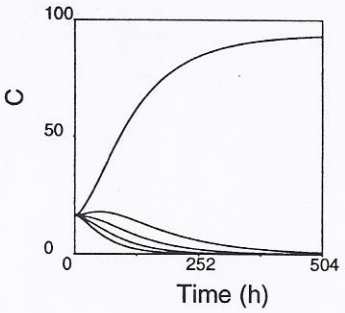

Figure 2: Axon elimination in single compartment model (Fig. 1). The axon with the highest value of α_i among the initial five axons survives. $\alpha_1 = 1.4$, $\alpha_2 = 0.8$, $\alpha_3 = 0.6$, $\alpha_4 = 0.4$, $\alpha_5 = 0.2$. The values of all the other parameters are identical among the axons. The amount of neurotrophin-receptor complex, C, is in number of molecules.

be a single compartment) at rate σ and is removed by diffusion and degradation with rate constant δ. In addition, at each axon i, neurotrophin is bound to receptor, with association and dissociation constants $k_{a,i}$ and $k_{d,i}$, respectively. Bound neurotrophin (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. Assuming standard reaction dynamics, the rates of change of the total amount of neurotrophin-receptor complex on axon i (C_i), the total amount of unoccupied receptor on axon i (R_i), and the extracellular concentration of neurotrophin (L) are

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

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

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

The term $(k_{a,i}LR_i - k_{d,i}C_i)$ represents the net amounts of receptor and neurotrophin being converted into complex; v is the volume of the extracellular space, which is assumed to be homogeneous with respect to the concentration of neurotrophin.

Neurotrophins, following binding to receptor, enhance axonal growth: they increase the arborization of axons (and hence the number of axon terminals, where the neurotrohpin receptors are located)(Edwards *et al.* 1989; Diamond *et al.* 1992; Schnell *et al.* 1994; Cohen-Cory & Fraser 1995), enlarge the size of the axon terminals (Garofalo *et al.* 1992), and possibly upregulate the density of neurotrophin receptors (Lindsay *et al.* 1990; Holtzman *et al.* 1992). In all these effects of neurotrophins on axonal growth, the axon's total amount of receptor will increase. Therefore, the amount of unoccupied receptor that is inserted into the axon per unit time, ϕ_i, must be an increasing function, $f_i(C_i)$ (called growth function), of the amount of bound neurotrophin, C_i. One of the functions studied in Van Ooyen & Willshaw (1999) is $f_i(C_i) = \alpha_i C_i$. To take into account that axonal growth is relatively slow, ϕ_i lags behind $f_i(C_i)$ with a lag given by

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

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

The precise values of the parameters of growth (α_i) and neurotrophic signalling ($k_{a,i}$, $k_{d,i}$, ρ_i, and γ_i) will vary among axons. For example, increased presynaptic electrical activity increases the axon's amount of neurotrophin receptor (Birren *et al.* 1992; Cohen-Cory *et al.* 1993), which implies that increased presynaptic electrical activity affects growth (i.e. higher α_i) or neurotrophic signalling (e.g. a lower γ_i) or both.

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 or died. For $f_i(C_i) = \alpha_i C_i$, elimination of axons takes place until either no or one axon remains (single innervation) (Fig. 2). No more than one axon can survive, regardless of the supply of neurotrophin, σ. The axon that survives is the one with the highest value of the quantity $\beta_i \equiv (k_{a,i}(\alpha_i - \rho_i))/(\gamma_i(k_{d,i} + \rho_i))$, which we interpret as the axon's competitive strength. The activity dependence of β_i means that the most active axon survives provided that the variation due to other factors does not predominate.

If $f_i(C_i)$ is a saturating function, several axons may survive. In this case, there is a dependence on the rate of release of neurotrophin, σ: the larger σ, the more innervating axons survive. Increased electrical activity of the target cell (i.e. postsynaptic activity) increases σ (Lu *et al.* 1991), which implies that increased postsynaptic electrical activity increases the number of surviving axons. As in the previous case, axons with higher presynaptic electrical activity have an advantage in survival. Thus, axon survival depends on both pre- and postsynaptic electrical activity. Based on axonal competition, new learning rules for changing connectivity in neural networks may be formulated.

Compartmental Model

We investigate how axonal competition is affected if the extracellular space around the target is not homogeneous with respect to the concentration of neurotrophin. To this end, we divide the extracellular space into two spatially adjacent compartments, each with a single innervating axon (Fig. 3). We deliberately use this simple two-compartment model to demonstrate clearly how competition is affected. Axon i grows in compartment i ($i = 1, 2$), in which L_i is the concentration of neurotrophin. The rates of change of C_i and R_i are given by eqns (1) and (2), respectively, in which L is replaced by L_i.

Neurotrophin is released in each compartment at rate σ and is removed by degradation with rate constant δ. Each compartment has length Δx and cross-sectional area

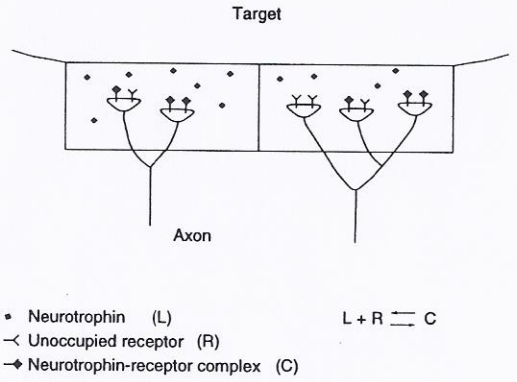

Figure 3: Extracellular space is divided into two compartments, each with a single innervating axon. The target may represent a soma or a dendrite.

A. Between compartments diffusion of neurotrophin takes place. The amount of neurotrophin that flows from one compartment to the other per unit area and unit time is (Fick's law)

$$J = -D\frac{L_2 - L_1}{\Delta x}, \qquad (5)$$

where D is the diffusion coefficient of neurotrophin and Δx is the distance between the centres of the compartments. As A is the area across which diffusion occurs, the total amount of neurotrophin that flows per unit time from one compartment to the other is AJ. The resulting change in the concentrations L_1 and L_2 is determined by the volume $v_c = A\Delta x$ of each compartment. Adding a diffusion term to eqn (3), we obtain the rates of change of L_1 and L_2:

$$\frac{dL_1}{dt} = \hat{D}(L_2 - L_1) + \sigma - \delta L_1 - (k_{a,1}L_1R_1 - k_{d,1}C_1)/v_c \quad (6)$$

$$\frac{dL_2}{dt} = \hat{D}(L_1 - L_2) + \sigma - \delta L_2 - (k_{a,2}L_2R_2 - k_{d,2}C_2)/v_c, \quad (7)$$

where $\hat{D} = D/(\Delta x)^2$.

Equation (4) again describes axonal growth. The growth function used is $f_i(C_i) = \alpha_i C_i$. Recall that this growth function leads to the survival of only one axon in the model in which the extracellular space is considered to be a single compartment.

Parameter values used are as in Van Ooyen & Willshaw (1999).

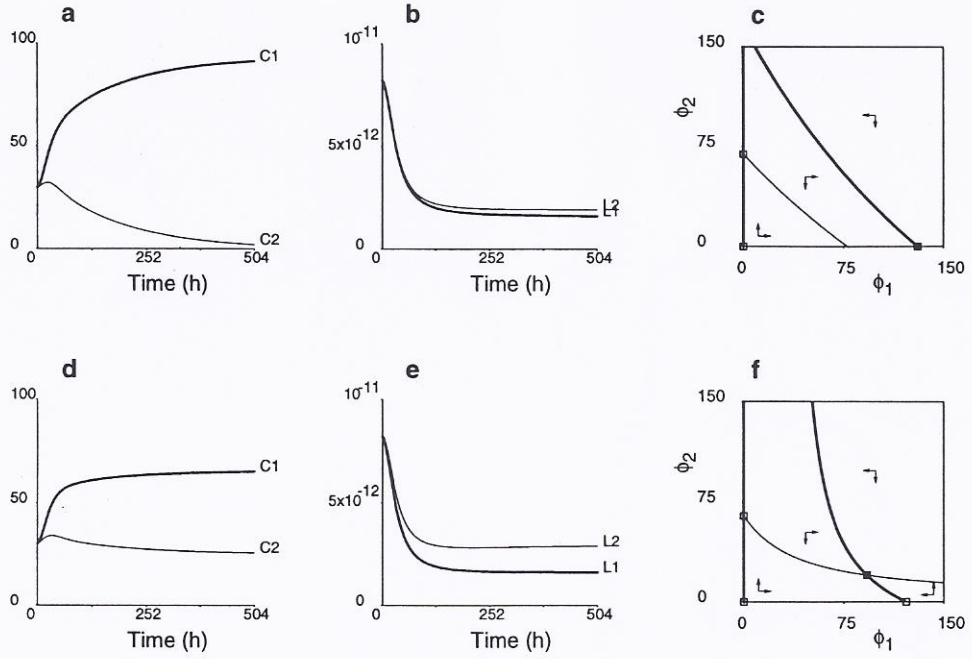

Figure 4: Survival of a single axon (**a-c**) and coexistence of axons (**d-f**) depending on $\hat{D}$. In **a-c**, $\hat{D} = 2.0$; in **d-f**, $\hat{D} = 0.2$. If an axon has no neurotrophin-receptor complex (i.e. $C_i = 0$, equivalent to $\phi_i = 0$), it has died or withdrawn. The values of C_i are in number of molecules; the values of the concentration of neurotrophin, L_i, in mol/l. In **c** and **f**, the bold lines are the null-isoclines of ϕ_1, and the thin lines those of ϕ_2. Filled squares indicate stable, and open squares unstable equilibrium points. $\alpha_1 = 1.4$, $\alpha_2 = 0.8$. The values of all the other parameters are the same for both axons. The value of v_c is the same in all figures; v_c is a scale factor, which does not affect the outcome of the competition.

Results

In the compartmental model, no more than one axon can survive if $\hat{D}$ is relatively large, i.e. if the axons are close to each other (Δx small) or if the diffusion coefficient D is large (Fig. 4a-c). In the limit for infinitely large $\hat{D}$, the neurotrophin concentrations in both compartments are always the same, i.e. the model will become effectively identical to the single compartment model (Van Ooyen & Willshaw 1999).

As the rate of change of ϕ_i (axonal growth) 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. $\frac{dC_i}{dt} = \frac{dR_i}{dt} = \frac{dL_i}{dt} = 0, i = 1, 2$). Using these approximations, we can draw the null-isoclines for ϕ_1 and ϕ_2, i.e. the lines depicting the solutions of $\frac{d\phi_1}{dt} = 0$ and $\frac{d\phi_2}{dt} = 0$, respectively. The intersection points of the ϕ_1 and ϕ_2 null-isoclines are the equilibrium points of the system.

For large $\hat{D}$, there is no equilibrium point where both axons coexist (Fig. 4c), unless the rate of release of neurotrophin, σ, is very much higher [i.e. if the electrical activity of the target cell is increased, which increases σ (Lu *et al.* 1991)].

Both axons can survive if $\hat{D}$ is relatively small, i.e. if the axons are far apart (Δx large) or if the diffusion coefficient D is small (Fig. 4d-f). In the limit for $\hat{D} = 0$, there is no interaction or competition between the axons.

Fig. 4f shows that for small $\hat{D}$ the null-clines intersect at a point where both axons coexist. In Fig. 5, the value of ϕ_2 in this coexistent equilibrium point is drawn 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. Thus, if the target cell lack dendrites, the competing axons are confined to the relatively small surface area of the soma ($\hat{D}$ large), and only one axon will survive. If the target cell has an extensive dendritic tree, spatial separation of the innervating axons becomes possible ($\hat{D}$ small), and several axons may survive.

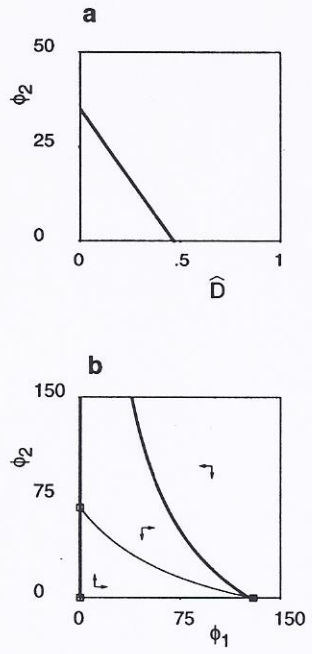

Figure 5: **a**. The value of ϕ_2 in the coexistent equilibrium point (see Fig. 4f) drawn for different values of $\hat{D}$. **b**. The isocline picture at the bifurcation point $\hat{D} = 0.45$. For explanation lines and symbols, see Fig. 4. See further text.

Discussion

The development of connections between neurons and their targets involves competition among innervating axons for target-derived neurotrophins. To study how the dendritic tree of the target cell affects the competition, we have formulated a compartmental version of our model of axonal competition (Van Ooyen & Willshaw 1999). The extracellular space around the target's dendrites and soma is divided into several compartments, and in each compartment there is local release of neurotrophin from the target, along with diffusion of neurotrophin between compartments. We show that if the innervating axons are spatially near each other on the target, they compete more strongly than if they are further separated, in which case coexistence of axons becomes permissible. Spatial separation of axons is possible if the target cell has an extensive dendritic tree. Thus, the model can account for the finding that in many types of neurons a positive correlation exists between the size of the dendritic tree and the number of impinging innervating axons surviving into adulthood. Although the present study does not exclude the role of other factors in axonal competition (such as the form of the axonal growth function), our results emphasize the importance of postsynaptic dendritic morphology in the development of specific patterns of nerve connections. New learning rules for changing connection strengths between neurons may be formulated based on axonal competition and its dependence on pre- and postsynaptic electrical activity.

References

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.

Bothwell, M. (1995) Functional interactions of neurotrophins and neurotrophin receptors. *Ann. Rev. Neurosc.* **18**, 223-253.

Cohen-Cory, S., Elliott, R. C., Dreyfus, C. F. & Black, I. B. (1993) Depolarizing influences increased low-affinity NGF receptor gene expression in cultured Purkinje neurons. *Expl Neurol.* **119**, 165-173.

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

Diamond, J., Holmes, M. & Coughlin, M. (1992) Endogenous NGF and nerve impulses regulate the collateral sprouting of sensory axons in the skin of the adult rat. *J. Neurosci.* **12**, 1454-1466.

Edwards, R. H., Rutter, W. J. & Hanahan, D. (1989) Directed expression of NGF to pancreatic β cells in transgenic mice leads to selective hyperinnervation of the islets. *Cell* **58**, 161-170.

Garofalo, L., Ribeiro-da-Silva, A. & Cuello, C. (1992) Nerve growth factor-induced synaptogenesis and hypertrophy of cortical cholinergic terminals. *Proc. Natl. Acad. Sci. USA* **89**, 2639-2643.

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 forebrain 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.

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. Neurosc.* **2**, 389-396.

Lu, B., Yokoyama, M., Dreyfus, C. F. & Black, I. B. (1991) Depolarizing stimuli regulate nerve growth factor gene expression in cultured hippocampal neurons. *Proc. Natl. Acad. Sci. USA* **88**, 6289-6292.

Purves, D. & Lichtman, J. W. (1980) Elimination of synapses in the developing nervous system. *Science* **210**, 153-157.

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. (1985) *Principles of neural development.* Sunderland, Massachusetts: Sinauer.

Purves, D. (1988) *Body and brain: a trophic theory of neural connections.* Cambridge, Massachusetts, and London: Harvard University Press.

Schnell, L., Schneider, R., Kolbeck, R., Barde, Y-A. & Schwab, M. E. (1994) Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. *Nature* **367**, 170-173.

Van Ooyen, A. & Willshaw, D. J. (1999) Competition for neurotrophic factor in the development of nerve connections. *Proc. Royal. Soc. B.* **266**, 883-892.