Competition for Neurotrophic Factors: Mathematical Analysis

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Neurotrophic factors, particularly the neurotrophin gene family of neurotrophic factors, are implicated in activity-dependent anatomical plasticity in the visual cortex and at the neuromuscular junction. Accumulating evidence implicates neurotrophic factors as possible mediators of activity-dependent competition between afferents, leading to the segregation of afferents’ arbors on the target space. We present a biologically plausible mathematical model of competition for neurotrophic factors. We show that the model leads to anatomical segregation, provided that the levels of neurotrophic factors released in an activity-independent manner, or the levels available by exogenous infusion, are below a critical value, which we derive. Above this critical value, afferent segregation breaks down. We also show that the model segregates afferents even in the presence of very highly correlated patterns of afferent activity. The model is therefore ideally suited for application to the development of ocular dominance columns in the kitten visual cortex.

1 Introduction

Activity-dependent, competitive interactions between afferents innervating the same target structure are a common feature of the development of the vertebrate nervous system. The molecular bases of these interactions during target innervation are broadly understood, but much remains to be discovered concerning the mechanisms that lead to the segregation of afferents’ arbors on the target structure during later stages of development. One attractive model is that just as retrograde neurotrophic factors (NTFs) regulate neuronal differentiation and survival during the early stages of development, they might also regulate synaptic growth and survival during later stages (Purves, 1988, reviewed in Snider & Lichtman, 1996). If endogenous NTFs are in limited supply, then competition between afferents will occur not only during target innervation but perhaps also during synaptic remodeling. Furthermore, exogenous infusion of NTFs might prevent or temper competitive interactions between afferents, and thus either prevent or slow down segregation.

Evidence is now accumulating that implicates NTFs in competitive plas-
ticity phenomena. Ventricular infusion of nerve growth factor (NGF) abolishes the effects of monocular deprivation in the rat lateral geniculate nucleus (LGN) (Domenici, Cellerino, & Maffei, 1993) and visual cortex (Maffei, Berardi, Domenici, Parisi, & Pizzorusso, 1992; Berardi et al., 1993; Yan, Mazow, & Dafny, 1996) and tempers them in the cat visual cortex (Carmignoto, Candea, Comelli, & Maffei, 1993). Cortical infusion of the neurotrophin NT-4/5, but no other neurotrophin, prevents the atrophy of LGN cell bodies in the ferret following monocular deprivation (Riddle, Lo, & Katz, 1995), and cortical infusion of brain-derived neurotrophic factor (BDNF) or NT-4/5 prevents the anatomical segregation of geniculocortical afferents into ocular dominance columns in the cat (Cabelli, Hohn, & Shatz, 1995). In addition, blockade of the endogenous ligands of the trkB receptor (BDNF and NT-4/5) also inhibits the formation of ocular dominance columns (Cabelli, Shelton, Segal, & Shatz, 1997). At the vertebrate neuromuscular junction, exogenous application of basic fibroblast growth factor and ciliary neurotrophic factor prevents the elimination of polyneuronal innervation (English & Schwartz, 1995), and application of BDNF slows the anatomical but not the physiological segregation of motor neurons (Kwon & Gurney, 1996).

Since afferent segregation in the visual cortex (Reiter, Waitzman, & Stryker, 1986; Stryker & Harris, 1986) and at the neuromuscular junction (Srihari & Vrbova, 1978; Thompson, Kuffler, & Jansen, 1979) is known to depend on both pre- and postsynaptic activity, it is important that the production or release, or both, of NTFs should depend on electrical activity. In the rat visual cortex, dark rearing reduces the level of BDNF mRNA (Castren, Zafra, Thoenen, & Lindholm, 1992; Schoups, Elliott, Friedman, & Black, 1995), but the level of NGF mRNA remains unchanged except for a transient increase during a narrow time window (Schoups et al., 1995), and monocular deprivation also decreases the expression of BDNF mRNA (Bozzi et al., 1995). At the developing neuromuscular junction, activity blockade increases the expression of both BDNF mRNA (Koliatsos, Clatterbuck, Winslow, Cayouette, & Price, 1993) and insulin-like growth factor-1 mRNA (Caroni & Schneider, 1994), while at the adult neuromuscular junction, activity blockade decreases the expression of NT-4/5 mRNA and electrical stimulation increases it (Funakoshi et al., 1995). Nothing is known about the release of neurotrophic factors from either muscle cells or neurons in the visual cortex. However, in the hippocampus, NGF and BDNF are released by a constitutive mechanism, mainly associated with cell bodies, and also by an activity-dependent mechanism that depends on Na+ influx and intracellular but not extracellular Ca2+ (Blöchl & Thoenen, 1995, 1996; Griesbeck, Blöchl, Carnahan, Nawa, & Thoenen, 1995; Goodman et al., 1996).

In this article, we develop and analyze a mathematical model of retrograde neurotrophic interactions. Our aim is to construct a plausible model that does not impose competition between afferents by using the conventional device of synaptic normalization (von der Malsburg, 1973). Instead,
we build a model in which competition occurs in a dynamical fashion (see also Bienenstock, Cooper, & Munro, 1982; Bennett & Robinson, 1989; Elliott & Shadbolt, 1996). Previously we made preliminary attempts to construct such a model (Elliott & Shadbolt, 1996), but the resulting model suffered from a number of undesirable features, to be discussed later. Our present model overcomes these difficulties by being formulated in a very different manner, and it constitutes a more general and more powerful neurotrophic model. We show that a key parameter of the model governs the capacity of the model to segregate afferents, even in the presence of very strongly correlated patterns of afferent activity, and we show that when either exogenous levels of NTF or the levels of NTF available by activity-independent release exceed a certain, critical value, afferent segregation suddenly breaks down. In the next section, we formulate and study the model, and in the last section we discuss the model's assumptions and some general issues raised.

2 A Model of Neurotrophic Interactions

In this section, we formulate and analyze our model of activity-dependent neurotrophic interactions. We first formulate it as an abstract mathematical system and then discuss the validity and biological plausibility of the assumptions behind the model. Next, we study some exact solutions of the model. This is followed by a fixed-point analysis, which demonstrates the existence of a parameter regime in which the model always leads to afferent segregation, independent of the strength of correlations in afferent activity, except for perfectly correlated activity. We then extract a random walk approximation to the model, which is used to estimate the number of time steps above which afferent segregation could occur, but below which afferent segregation cannot occur. Finally, we present results of numerical simulations of the model.

For the purposes of analytical ease and tractability, we will usually restrict attention to the case of two afferents innervating a target structure. Numerical results, for the purposes of comparison to analytical results, will therefore also be restricted to two afferents. However, numerically we find little qualitative difference between models of two or more afferents, so this justifies, a posteriori, the restriction to the two-fferent case. Furthermore, two afferents are often enough to represent familiar examples of neuronal development: two eyes innervating the optic tectum or, via the LGN, the visual cortex, or the not untypical case of two motor neurons’ initially innervating a muscle fiber.

We provide a summary of the key symbols used in the derivation and analysis of our model in Table 1.

2.1 Formulation of the Model. Let letters such as \( i, j, \) and \( k \) denote afferent cell positions and letters such as \( x \) and \( y \) denote target cell positions; the vector character of these positions is left implicit for notational simplicity.
Table 1: Key Symbols Used in the Derivation and Analysis of the Model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>i, j, k</td>
<td>Afferent cell positions</td>
</tr>
<tr>
<td>x, y</td>
<td>Target cell positions</td>
</tr>
<tr>
<td>s_{xi}</td>
<td>Number of synapses from afferent i to target x</td>
</tr>
<tr>
<td>a_i</td>
<td>Activity of afferent i</td>
</tr>
<tr>
<td>n</td>
<td>Time-step number in discrete time</td>
</tr>
<tr>
<td>t</td>
<td>Continuous time</td>
</tr>
<tr>
<td>r_x</td>
<td>NTF released from target x</td>
</tr>
<tr>
<td>T_0, T_1</td>
<td>Activity-independent release of NTF from target cells</td>
</tr>
<tr>
<td>f_x</td>
<td>Mean activity of a synapse averaged over all synapses on target x</td>
</tr>
<tr>
<td>d_x</td>
<td>NTF available at target x following diffusion</td>
</tr>
<tr>
<td>Δ_{xy}</td>
<td>Function characterizing the diffusion of NTF</td>
</tr>
<tr>
<td>ρ_i</td>
<td>Number of receptors per synapse on afferent i</td>
</tr>
<tr>
<td>w_{xi}</td>
<td>NTF taken up by afferent i from target x following diffusion</td>
</tr>
<tr>
<td>g</td>
<td>Function characterizing the dependence of NTF uptake on activity</td>
</tr>
<tr>
<td>a</td>
<td>Parameter characterizing activity-independent NTF uptake</td>
</tr>
<tr>
<td>τ</td>
<td>An exponential decay constant</td>
</tr>
<tr>
<td>ϵ</td>
<td>A &quot;learning rate,&quot; depending on τ</td>
</tr>
<tr>
<td>s_i</td>
<td>Number of synapses from afferent i in one-target cell case</td>
</tr>
<tr>
<td>c</td>
<td>Critical parameter influencing model’s behavior, c = T_0/(aT_1)</td>
</tr>
<tr>
<td>y_i, χ</td>
<td>Variable-transformed versions of s_i and t, respectively</td>
</tr>
<tr>
<td>δ_i, δ_{xi}</td>
<td>Perturbations about fixed points or initial conditions</td>
</tr>
<tr>
<td>p, q</td>
<td>Probability that a_i = a_j for two afferents (q = 1 – p)</td>
</tr>
</tbody>
</table>

Let the number of synapses from afferent i to target x be denoted by s_{xi}. All synapses are taken to possess fixed and equal efficacies; this is justified since we consider anatomical and not physiological plasticity. Let the activity of afferent i be denoted by a_i ∈ [0, 1]. We will formulate our model initially in discrete time steps. Thus, time-dependent variables such as a_i and s_{xi} will possess superscripts to denote the time step: a_i^n and s_{xi}^n for time step n. We will then make the transition to continuous time, and time-dependent variables will be written as, for example, a_i(t) and s_{xi}(t). For notational simplicity we will not normally indicate this time-dependence explicitly.

Each target cell x, at time step n, is taken to release an amount of NTF given by

$$r_x^n = T_0 + T_1 f_x^n,$$  \hspace{1cm} \text{(2.1)}

where $0 \leq f_x^n \leq 1$ is a function of the afferent input at time-step n. Thus, there is an activity-independent component given by $T_0$ and an activity-dependent component, up to a maximum of $T_1$. The simplest, parameter-free choice for the function $f$ is

$$f_x^n = \frac{\sum_i s_{xi}^n a_i^n}{\sum_i s_{xi}^n}.$$  \hspace{1cm} \text{(2.2)}
which represents the mean activity of a synapse averaged over all synapses. This has the disadvantage that a target cell possessing only one synapse may be induced to release the maximum amount of NTF. However, in practice, we will find that target cells rarely reach such states. Other choices for $f$ are possible, such as a logistic function. This would overcome the disadvantage of the unrealistic release properties inherent in equation 2.2, but a logistic function would introduce two parameters, and its mathematical form would considerably complicate our analysis. In the following we will use only the form given in equation 2.2.

We assume that the NTF released by target cells rapidly diffuses through the target field, so the amount available at each target cell following diffusion in time-step $n$ is given by

$$d^n_x = \sum_y \Delta_{xy} r^n_y,$$

(2.3)

where $\Delta_{xy}$ is a function characterizing the diffusion process and is normalized so that $\sum_y \Delta_{xy} = 1 \forall x$. This equation represents the raw release of NTF from target cells convolved with the diffusion function. Biologically, this amounts to the assumption that NTF diffuses from each target cell independent of the diffusion from all other target cells, and that the amount available, after diffusion, at each target cell is just the sum of the amounts reaching that cell from all other cells.

The NTF available at any given target cell following diffusion is assumed to be rapidly taken up by the afferents synapsing on it. We take the uptake by afferent $i$ from target $x$ at time-step $n$ to be proportional to the number of terminals $i$ has on $x$, $s_{xi}$, and to the “affinity” of each terminal for the factor at time-step $n$, $\rho^n_i$. The uptake is also assumed to be a function of afferent activity. The affinity is interpreted as the number of receptors for the NTF possessed by each terminal. We will consider two possibilities:

$$\rho^n_i = \begin{cases} \lambda, & \text{Case 1 (cell death)} \\ \lambda \bar{a}^n_i / \sum_x s_{xi}, & \text{Case 2 (no cell death)} \end{cases}$$

(2.4)

where $\lambda$ is an arbitrary constant and $\bar{a}^n_i$ denotes the recent time average of the activity of afferent $i$ computed at time-step $n$. The cell death case assumes a fixed number of receptors per terminal, independent of the total number of terminals. The no-cell-death case, on the other hand, assumes that the number of receptors per terminal is inversely proportional to the total number of terminals supported by the afferent and proportional to the recent time average of the activity of the afferent. This means that the efficacy of uptake per terminal by afferents with smaller axonal arbors is greater than that of afferents with larger axonal arbors. These two possibilities are called cell death (CD) and no cell death (NCD) because we will find that the CD case permits afferents to retract all their terminals, which we interpret as
indicating the death of afferent cells, while the NCD case does not permit complete retraction, except when the recent time average of afferent activity falls to zero.

The uptake, at time-step \( n \), by afferent \( i \) from target \( x \) is then taken to be

\[
u_{xi}^n = Q^n_x d^n_x s^n_x g(a^n_i) \rho^n_i,
\]

where \( Q^n_x \) is a constant of proportionality and \( g \) is some function describing the dependence of NTF uptake on afferent activity. We assume complete uptake by all afferents, so that the available pool of NTF at each target cell is exhausted at each time step. This means that \( \sum_i u_{xi}^n = d^n_x \), which defines \( Q^n_x \) as

\[
Q^n_x = \left[ \sum_i s^n_i g(a^n_i) \rho^n_i \right]^{-1}.
\]

A particularly simple form for the function \( g \) is

\[
g(a^n_i) = a + a_i^n,
\]

where \( a \) is a constant determining the capacity of an inactive afferent to take up the NTF. Although other forms are possible, the simple form defined by equation 2.7 satisfies the basic requirement that the level of afferent activity determines the capacity for uptake, subject to a resting level of uptake. We will thus use this form.

Putting all this together, we have that the uptake of NTF by afferent cell \( i \) from target cell \( x \) following diffusion is given by

\[
u_{xi}^n = \sum_y \Delta y \left( T_0 + T_1 \frac{\sum_j s^n_{xy} d^n_j}{\sum_j s^n_{xy}} + \sum_j \frac{s^n_{ij} (a + a^n_i) \rho^n_j}{\sum_j s^n_{ij} (a + a^n_i) \rho^n_j} \right).
\]

We will assume that the number of synapses between afferent \( i \) and target \( x \) at time-step \( n + 1 \) is equal to the recent time average of the uptake of NTF by afferent \( i \) from target \( x \), computed at time-step \( n \), so that

\[
s^{n+1}_{xi} = \bar{u}_{xi}^n.
\]

This, together with equation 2.8, defines a set of coupled, nonlinear recurrence relations defining the evolution of the \( s^n_{xi} \). The order of the recurrence relations depends on the time averaging in equation 2.9. The simplest selection for the recent time average of some set of time-dependent quantities \( w^n \) is

\[
\bar{w}^n = \frac{1}{1 + l} \sum_{m=n-l}^n w^m,
\]
where \( l \) is some nonnegative integer defining the number of time steps over which the time average is taken. The order of the associated recurrence relations would then just be \( l \). This choice, however, has at least three difficulties. First, it is biologically implausible since it assumes a strict cutoff with non-decaying contributions from time steps prior to the cutoff. Second, from a mathematical point of view, high-order recurrence relations are difficult to analyze. Third, from a computational perspective, large \( l \) would be very memory intensive, so only simulations of small collections of afferent and target neurons could be performed.

An alternative and biologically plausible time average can be defined by convolving the quantities \( w^n \) with a decaying exponential. In continuous time, the time average of \( w(t) \) is thus given by

\[
\bar{w}(t) = \frac{1}{\tau} \int_{-\infty}^{t} dt' w(t') e^{-\frac{(t-t')}{\tau}},
\]

where \( \tau \) is a decay constant that sets the time scale for the time average. The overall factor of \( 1/\tau \) ensures that \( \bar{w}(t) = w \) when \( w(t) = w \), a constant. In discrete time, this becomes

\[
\bar{w}^n = (1 - e^{-1/\tau}) \sum_{m=-\infty}^{n} w^m e^{-\frac{(n-m)}{\tau}}.
\]

Defining \( \phi = e^{-1/\tau} \), the time average at one time step is simply related to the time average at the previous time-step through

\[
\bar{w}^{n+1} = (1 - \phi) \bar{w}^{n+1} + \phi \bar{w}^n.
\]

Thus, in addition to being biologically plausible, the time average defined by equation 2.12 results in only first-order recurrence relations, which are more mathematically tractable, and also an averaging procedure that is not computer memory intensive.

Using equation 2.9 together with equation 2.13, we have,

\[
\bar{u}_{x_i}^{n+1} = u_{x_i}^{n+1} = (1 - \phi) u_{x_i}^{n} + \phi \bar{u}_{x_i}^{n} = (1 - \phi) u_{x_i}^{n} + \phi s_{x_i}^{n},
\]

which gives,

\[
\bar{u}_{x_i}^{n+1} - u_{x_i}^{n+1} = \epsilon (u_{x_i}^{n} - s_{x_i}^{n}),
\]

where \( \epsilon = 1 - \phi \) is a learning rate that emerges automatically from the
time-averaging process. Inserting $u^{n+1}$ from equation 2.8, we have,

$$s_{x_i}^{n+1} - s_{x_i}^n = \epsilon s_{x_i}^n \left[ \sum_y \Delta_{xy} \left( T_0 + T_1 \sum_j s_{yi}^n \frac{(a + a_j^y)\rho_j^n}{\sum_j s_{yj}^n (a + a_j^y)\rho_j^n} - 1 \right) \right]. \tag{2.16}$$

which constitute a set of first-order recurrence relations in the $s_{x_i}^n$. In the continuous time limit, these recurrence relations give the first-order differential equations,

$$\frac{ds_{x_i}}{dt} = \epsilon s_{x_i} \left[ \sum_y \Delta_{xy} \left( T_0 + T_1 \sum_j s_{yi}\frac{a + a_i}{\sum_j s_{yj}(a + a_i)\rho_j} - 1 \right) \right]. \tag{2.17}$$

that is, we interpret equation 2.16 as constituting a one-step, Euler method for numerically integrating equation 2.17, where we have absorbed the step size into a redefinition of $\epsilon$. (In fact, the continuous time limit in equation 2.17 follows straightforwardly from taking the time derivative of equation 2.11 with $\dot{w} = u_{x_i}$ and $\dot{s}_{x_i} = u_{x_i}$, in which case we obtain that $\epsilon = 1/\tau$, without absorbing a step size.) These equations represent the final form of our model for both the CD and the NCD cases.

### 2.2 Exact Solutions.

We now extract some exact solutions from the set of equations defined by equation 2.17 and examine their behavior. For increased tractability, we assume that there is no diffusion of NTF between target cells, so that $\Delta_{xy} = \delta_{xy}$, the Kronecker delta function. For the neuromuscular junction, this is likely to be a reasonable approximation, since it appears that motor neurons compete for muscle fibers on a fiber-by-fiber basis, rather than for groups of neighboring fibers. In the visual cortex, such an assumption would similarly result in LGN cells’ competing for cortical neurons on a neuron-by-neuron basis, which would be inconsistent with the extended size of ocularity domains. While this is unsatisfactory, we do not expect the inclusion of diffusion otherwise to affect significantly the dynamics of our model; this is discussed in the next section. To obtain exact solutions, we also restrict to the CD case, so that $\rho_i = \lambda \forall i$, since analysis of the NCD case appears to be more difficult. We may then safely consider only one target cell and drop the subscript $x$ so that $s_i$ denotes the number of synapses between afferent $i$ and the one target cell. Then,

$$\frac{ds_i}{dt} = \epsilon s_i \left[ \left( T_0 + T_1 \sum_j s_{ij}\frac{a + a_i}{\sum_j s_{ij}(a + a_i)\rho_j} - 1 \right) \right]. \tag{2.18}$$

from which we see that the ratio $s_i/s_j$ evolves as

$$\frac{d}{dt} \left( \frac{s_i}{s_j} \right) = \epsilon \frac{s_i}{s_j} \left( T_0 + T_1 \sum_k s_{ik}\frac{a + a_k}{\sum_k s_k(a + a_k)} \right) \frac{1}{\sum_k s_k(a + a_k)} (a_i - a_j). \tag{2.19}$$
and the sum $\sum_k s_k$ evolves as

$$
\frac{d}{dt} \sum_k s_k = \epsilon \left[ \left( T_0 + T_1 \frac{\sum_k s_k a_k}{\sum_k s_k} \right) - \sum_k s_k \right] 
\leq \epsilon \left( T_0 + T_1 - \sum_k s_k \right). 
$$

(2.20)

Therefore, the sum evolves to a value bounded from above by $T_0 + T_1$. (This upper bound also applies to each target cell in the NCD case.) In the limit that $a \to \infty$, so that the resting uptake of NTF by afferents dominates the activity-dependent component of uptake, the ratio $s_i/s_j$ remains fixed. This shows that if segregation is to occur, then $a$ must be sufficiently small. Also, when $a_i > a_j$, the ratio $s_i/s_j$ grows; when $a_i < a_j$, it decays; and when $a_i = a_j$, it remains fixed. So if, say, $\tilde{a}_i$ always exceeds $\tilde{a}_j$, then $s_i/s_j \to \infty$, and since $\sum_k s_k$ remains finite, $s_j \to 0$. We therefore restrict to the nontrivial case when the afferents have the same mean activities.

With initial conditions given at $t = t_1$, equation 2.18 may be transformed into a more transparent form by using the new variables $y_i = \frac{1}{T_1} e^{\epsilon (t-t_1)} S_i$ and $\chi = e^{\epsilon (t-t_1)}$. Defining $ac = T_0 / T_1$, we obtain

$$
\frac{dy_i}{d\chi} = \frac{\sum_j y_j (ac + a_i) (a + a_i) y_i}{\sum_j y_j (a + a_j) \sum_j y_j}.
$$

(2.21)

While the “critical” point $c = 1$, corresponding to $aT_1 = T_0$, dramatically simplifies this equation, in fact the behavior of the solutions at this point is untypical. We shall return to this issue. We will find in both the CD and NCD cases that the size of the parameter $c$ determines whether afferent segregation occurs. Modulo the factor of $a$, $c$ is simply the ratio of the activity-independent release (or, equivalently, the exogenous infusion) to the maximum activity-dependent release of NTF. It therefore has a fairly direct biological interpretation.

From equation 2.21 we immediately obtain the result that

$$
\frac{dy_i}{dy_j} = \frac{a + a_i y_i}{a + a_j y_j}.
$$

(2.22)

Thus, if the $a_i$ are constant in the time interval $[t_1, t_2]$, which corresponds to the $\chi$-interval $[\chi_1, \chi_2]$, where $\chi_1 = 1$, then we have that

$$
\left( \frac{y_i(\chi_2)}{y_i(\chi_1)} \right)^{1/(a + a_i)} = \left( \frac{y_j(\chi_2)}{y_j(\chi_1)} \right)^{1/(a + a_j)}.
$$

(2.23)
1948 T. Elliott and N. R. Shadbolt

\[ y_j(\chi_2) = y_j(\chi_1) \left( \frac{y_j(\chi_2)}{y_j(\chi_1)} \right)^{\frac{\mu_j}{\rho_j}} = A_{ji} y_j^{p_{ji}}(\chi_2), \]  

(2.24)

where \( A_{ji} = y_j(\chi_1)/y_j^{p_{ji}}(\chi_1) \) and \( p_{ji} = (a + a_i)/(a + a_j) \). For \( a_i = b \forall i \), where \( b \) is some constant, we have that \( p_{ji} = 1 \forall i, j \). Thus, equation 2.24, together with the result that \( \sum_k [y_k(\chi_2) - y_k(\chi_1)] = (ac + b)(\chi_2 - \chi_1) \), gives

\[ y_i(\chi_2) = y_i(\chi_1) \left[ 1 + \frac{1}{\sum_k y_k(\chi_1)} (ac + b)(\chi_2 - \chi_1) \right], \]  

(2.25)

or

\[ s_i(t_2) = s_i(t_1) \left[ e^{-\epsilon (t_2 - t_1)} + \frac{T_1}{\sum_k s_k(t_1)} (ac + b) \left( 1 - e^{-\epsilon (t_2 - t_1)} \right) \right]. \]  

(2.26)

For arbitrary \( a_i \), but still constant in \([t_1, t_2] \), equation 2.24 allows us to decouple the differential equations in equation 2.21 to obtain

\[ \int_{y_i(\chi_1)}^{y_i(\chi_2)} \frac{\left( \sum_i A_{ji} y_j^{p_{ji}-1} \right) \left( \sum_j A_{ji} p_{ji} y_j^{p_{ji}-1} \right)}{1 + A_{ji} p_{ji} y_j^{p_{ji}-1}} \ dy = (ac + a_i)(\chi_2 - \chi_1), \]  

(2.27)

where \( p_{ji} = (ac + a_j)/(ac + a_i) \). (Such simple decoupling does not appear to be possible in the NCD case because equation 2.22 contains additional factors on the right-hand side.) In general, the multiple exponents in the integrand prevent the integral from being evaluated exactly. This difficulty may be avoided by assuming that the \( a_i \) take only two possible values, so that the \( p_{ji} \) take only two values. This is essentially equivalent to assuming that in the time interval \([t_1, t_2] \), there are only two afferents, since different afferents with identical activity would be indistinguishable in terms of the evolution equations. We therefore restrict to the explicit case of only two afferents. For notational convenience, in expressions or sentences in which the subscripts \( i \) and \( j \) appear simultaneously, but in which neither \( i \) nor \( j \) is summed over, we will use the subscript \( j \) to denote the afferent not denoted by the subscript \( i \), so that when \( i = 1, j = 2 \) and when \( i = 2, j = 1 \).

For the two-afferent case, equation 2.27 becomes

\[ \int_{y_i(\chi_1)}^{y_i(\chi_2)} \frac{(1 + A_{ji} y_j^{p_{ji}})(1 + A_{ji} p_{ji} y_j^{p_{ji}-1})}{1 + A_{ji} p_{ji} y_j^{p_{ji}-1}} = (ac + a_i)(\chi_2 - \chi_1). \]  

(2.28)

Substituting \( z = y_j^{p_{ji}-1} \), writing \( b_{ji} = (p_{ji} - 2)/(p_{ji} - 1) \), \( \beta_{ji} = \frac{1}{p_{ji}}(p_{ji} + 1 - \frac{1}{p_{ji}}) \), and \( y_{ji} = (1 - \beta_{ji})/(1 - p_{ji}) \), and assuming that \( a \neq 0 \) and \( ai \neq aj \) to avoid the
points \( b_{ji} = 1 \) and \( b_{ji} = 2 \), we obtain

\[
\frac{A_{ji}}{p_{ji}^p}[y_{pji}^{p}(\chi_2) - y_{pji}^{p}(\chi_1)] + \beta_{ji}[y_{ji}(\chi_2) - y_{ji}(\chi_1)]
\]

\[
-\gamma_{ji} \int_{y_{pji}^{p-1}(\chi_1)}^{y_{pji}^{p-1}(\chi_2)} dz \frac{z^{-b_{ji}}}{1 + A_{ji}p_{ji}^p z} = (ac + a_{ji})(\chi_2 - \chi_1) .
\]  

(2.29)

The integral on the left-hand side of this equation must, in general, be evaluated by a power series expansion. However, for \( b_{ji} \) an integer, the integral can be evaluated in closed form. If \( b_{ji} = -l \), an integer, then \( p_{ji} = \left(\frac{b_{ji} + 2}{b_{ji} + 1}\right) \). If \( l \geq 0 \), then an elegant assignment is \( a = l + 1, a_i = 0, a_j = 1 \). If \( l < -2 \), then we may select \( a = -(l + 2), a_i = 1, a_j = 0 \). Since we require that \( a \) is not too large from equation 2.19, we shall simply take \( a = 1 \). Thus, we have two selections of parameters:

Selection 1: \( l = 0, b_{ji} = 0, p_{ji} = 2, a_i = 0, a_j = 1 \).

Selection 2: \( l = -3, b_{ji} = 3, p_{ji} = \frac{1}{2}, a_i = 1, a_j = 0 \).

These two cases fortunately represent opposite patterns of afferent activity, and thus permit a (quasi-)analytic study of the solutions to equation 2.21 and an examination of the parameter regimes in which afferent segregation might occur. For \( p_{ji} = 2 \) (selection 1) we obtain the exact solution,

\[
A_{ji}(p_{ji}^p)^2[y_{pji}^{p}(\chi_2) - y_{pji}^{p}(\chi_1)] + p_{ji}^p(3p_{ji}^p - 2)[y_{ji}(\chi_2) - y_{ji}(\chi_1)]
\]

\[
+ \frac{(p_{ji}^p - 1)(p_{ji}^p - 2)}{A_{ji}} \log \frac{1 + A_{ji}p_{ji}^p y_{ji}(\chi_2)}{1 + A_{ji}p_{ji}^p y_{ji}(\chi_1)}
\]

\[
= (p_{ji}^p)^2(ac + a_{ji})(\chi_2 - \chi_1) .
\]  

(2.30)

and for \( p_{ji} = \frac{1}{2} \) (selection 2) we have,

\[
A_{ji}(3 - 2p_{ji})[y_{pji}^{1/2}(\chi_2) - y_{pji}^{1/2}(\chi_1)] + [y_{ji}(\chi_2) - y_{ji}(\chi_1)]
\]

\[
+ A_{ji}^2(2p_{ji}^e - 1)(p_{ji}^e - 1) \log \frac{A_{ji}p_{ji}^{e}y_{ji}^{1/2}(\chi_2) + y_{ji}^{1/2}(\chi_1)}{A_{ji}p_{ji}^{e}y_{ji}^{1/2}(\chi_2) + y_{ji}^{1/2}(\chi_1)}
\]

\[
= (ac + a_{ji})(\chi_2 - \chi_1) .
\]  

(2.31)

It is straightforward to transform these into solutions for the \( s_i \). Although these equations represent exact solutions, they are implicit in the \( s_i \), so, given \( s_i(t_1), s_i(t_2) \) must be determined numerically. However, for the specific point \( c = 1 \), at which \( p_{ji}^e = p_{ji} \), the coefficients of the log terms in equations 2.30
and 2.31 vanish, leaving quadratic equations whose solutions are trivial. At this point, for \( p_{ji} = 2 \) (selection 1) we obtain the explicit solution,

\[
y_i(\chi_2) = \frac{y_i(\chi_1)}{y_j(\chi_1)} \left\{ \sqrt{\left[ y_i(\chi_1) + y_j(\chi_1) \right]^2 + 2y_j(\chi_1)(\chi_2 - \chi_1) - y_i(\chi_1)} \right\}. \tag{2.32}
\]

and for \( p_{ji} = \frac{1}{2} \) (selection 2) we have,

\[
y_i^{1/2}(\chi_2) = \frac{1}{y_i^{1/2}(\chi_1)} \left\{ \sqrt{\left[ y_i(\chi_1) + y_j(\chi_1) \right]^2 + 2y_i(\chi_1)(\chi_2 - \chi_1) - y_j(\chi_1)} \right\}. \tag{2.33}
\]

This simplification occurs because the coefficient of the integral in equation 2.29 vanishes at \( c = 1 \), which reflects a cancellation in the integrand in equation 2.27, which in turn reflects the simplification that occurs in equation 2.21 at \( c = 1 \).

We can now examine the evolution of the \( s_i, i = 1, 2 \), in one or two time intervals during each of which the \( a_i, i = 1, 2 \), are constant. We set \( T_1 = 1 \) without loss of generality since \( T_0 \) sets the overall scale for the \( s_i, i = 1, 2 \). Because we have solutions that require that \( a = 1 \), we therefore have that \( c = T_0 \). We shall examine the solutions as a function of the parameter \( c \), which determines the ratio between the activity-independent and the maximum activity-dependent release of NTF by target cells. We will restrict attention to the region \( 0 < c \leq 1 \); we will consider \( c > 1 \) in subsequent sections. We take \( \epsilon = 0.018 \), which means that \( \phi^{250} \sim 0.01 \), and we consider time intervals \( \Delta t \) of unit size. The quantity

\[
T_0 + T_1 \frac{\sum_j s_i a_j}{\sum_j s_j}
\tag{2.34}
\]

sets the overall scale for \( \sum_j s_j \), and, assuming that \( \bar{a}_i = \frac{1}{2}, i = 1, 2 \), it has an average value given by \( T_0 + \frac{1}{2}T_1 = \frac{1}{2} + c \). Thus, we employ the initial conditions at \( t = 0 \) given by \( s_i(0) = \frac{1}{2}(1 + 2c), i = 1, 2 \).

Figure 1 shows the changes in the \( s_i, i = 1, 2 \) that occur during the time interval \([0, 1]\) when one afferent, \( i \), is “on” (\( a_i = 1 \)) and the other, \( j \), is “off” (\( a_j = 0 \)), plotted as a function of \( c \), obtained by numerically solving equations 2.30 and 2.31 by Newton iteration. At \( c = 0 \), \( p_{ji} = a_j/a_i \), which is undefined for \( a_i = 0 \), so we avoid this point. Figure 1a shows the shift in the two solutions, \( \Delta s_i = s_i(t) - s_i(0), i = 1, 2, \) at \( t = 1 \). We see that one \( (s_i) \) increases, while the other \( (s_j) \) decreases, with the extent of the change increasing with \( c \). Figure 1b shows the relative difference between the two solutions, \( \Delta q = (s_i - s_j)/(s_i + s_j), \) at \( t = 1 \). The relative difference is marginally larger (less than 1%) for \( c = 10^{-3} \) (the smallest value of \( c \) we consider) than for \( c = 1 \).
A Model of Neurotrophic Interactions

Figure 1: The change in the system after one time step in which one afferent is on and the other is off, for the CD case, for initial conditions $s_i = \frac{1}{2}(1 + 2c), i = 1, 2$. The shifts (a) from the initial conditions and (b) the relative difference are shown. The shift increases as a function of $c$, but the relative difference decreases as a function of $c$.

In Figure 2 we take $a_i = 1$ and $a_j = 0$ in the time interval $[0, 1]$, but then reverse the afferents’ activities, so that $a_i = 0$ and $a_j = 1$ in the time interval $(1, 2]$. Figure 2a shows the change $\Delta s_{ij}, i = 1, 2$, and Figure 2b shows the relative difference $\Delta s_{ij}$, both at $t = 2$. This figure shows that for $c \sim 1$, the changes that accrued during the first time period are almost entirely reversed in the second, while for $c \sim 0$, the changes are not completely reversed. This suggests that statistical fluctuations in afferent activity may
result in changes that might accumulate in the $s_i$, $i = 1, 2$, for $c$ sufficiently small, but that might not accumulate in the $s_i$, $i = 1, 2$, for $c$ close to unity. Hence, afferent segregation might be possible for $c$ sufficiently small, while it might not be possible for $c$ close to unity.

To investigate the role of the initial conditions $s_i(0) = \frac{1}{4}(1 + 2c)$, $i = 1, 2$, in this behavior, we drop the $c$-dependence and consider only $s_i(0) = \frac{1}{4}$.
Figures 3 and 4 show the equivalents of Figures 1 and 2 for this case. We see that the relative difference $\Delta_{ij}$ increases rather than decreases as a function of $c$. However, it is important to notice that Figures 3a and 4a indicate that both the $s_{ij}, i = 1, 2$, grow for most values of $c$. This is because the sum $\sum_j s_j(0)$ is not matched to the support provided by the target cell; the target cell initially provides a large, generalized stimulus for growth that prevents significant competitive interactions between the two afferents. Once the sum $\sum_j s_j$ reaches a level that matches the support provided, however, the evolution of the $s_{ij}, i = 1, 2$, basically reverts to that exhibited in Figures 1 and 2. This is demonstrated in Figure 5, where the stimuli used to generate Figure 4 are applied 2500 times in succession.

2.3 Fixed-Point Analysis. The analysis performed so far has only hinted at the possibility that afferent segregation might be possible for $c$ sufficiently small and might not for $c$ sufficiently large; the results in Figure 5 demonstrate this, but they are derived from repeated, numerical re-solution of equations 2.30 and 2.31. Furthermore, we have studied the solutions only for strictly anticorrelated patterns of afferent activity and only for $0 < c \leq 1$. Moreover, we have studied analytic solutions for the CD case only. In order to characterize the solutions of equation 2.17 more generally, we now perform a fixed-point analysis, although we will continue to consider only two afferents, and either one (CD case) or two (NCD case) targets cell. We also continue to assume that $\Delta_{xy} = \delta_{xy}$.

2.3.1 The CD Case. Equation 2.18 manifestly possesses a fixed point at $s_i = 0$. We must determine whether this point is stable or unstable to small perturbations about it. We set $s_i = \delta_i$ and $s_j = (T_0 + \frac{1}{2}T_1) + \delta_j = T_1(ac + \frac{1}{2}) + \delta_j$, where, as before, $j$ denotes the afferent not denoted by $i$, and $\delta_i$ and $\delta_j$ are small perturbations. We then linearize the evolution equations to obtain

\[
\frac{d\delta_i}{dt} = \epsilon \delta_i \left( \frac{ac + a_i}{ac + \frac{1}{2}} \frac{a + a_i}{a + a_j} - 1 \right),
\]  
\[ \text{(2.35)} \]
\[
\frac{d\delta_j}{dt} = \epsilon T_1 \left( \frac{a_j}{2} - 1 \right) - \epsilon \left( \frac{ac + a_i}{ac + \frac{1}{2}} - 1 \right) \delta_j + \epsilon \frac{1}{ac + \frac{1}{2}} \left[ \left( ac + a_i \right) \delta_i - \frac{ac + a_i}{a + a_j} \delta_j \right].
\]  
\[ \text{(2.36)} \]

The second of these indicates that $T_1(ac + \frac{1}{2})$ is not a fixed point for $s_j$ unless we average over afferent activity and assume that the average values of $a_i$ and $a_j$ are both 0.5. To perform the averaging over afferent activity, we will consider binary activity only, so that $a_i \in \{0, 1\}, i = 1, 2$. Let $p$ be the probability that both afferents have the same activity in any given time
Figure 3: As Figure 1, but with initial conditions $s_i = \frac{1}{2}$, $i = 1, 2$. (a) The shift from the initial conditions is now positive for both afferents, for most values of $c$. This means that both afferents experience a generalized stimulus for growth. (b) The relative difference increases as a function of $c$.

interval. Then we have four possible activity patterns with probabilities given by:

\[
P(a_i = 0 \& a_j = 0) = \frac{p}{2},
\]

\[
P(a_i = 0 \& a_j = 1) = \frac{1-p}{2},
\]

\[
P(a_i = 1 \& a_j = 0) = \frac{1-p}{2},
\]

\[
P(a_i = 1 \& a_j = 1) = \frac{p}{2},
\]
assuming an unbiased distribution of “on” and “off” states. Averaging equations 2.35 and 2.36 over these activity patterns, we obtain,

\[
\frac{d}{dt} \langle \delta_i \rangle = \epsilon \langle \delta_i \rangle \frac{(c - 1)(1 - p)}{(2ac + 1)(a + 1)},
\]

\[
\frac{d}{dt} (\langle \delta_i \rangle + \langle \delta_j \rangle) = -\epsilon (\langle \delta_i \rangle + \langle \delta_j \rangle),
\]

where \(\langle \rangle\) denotes the averaging. We thus see that for \(c < 1\), the point \(s_i = 0, s_j = T_1(ac + \frac{1}{2})\) is a stable fixed point (an “attractor”) of equation 2.18.
Figure 5: As Figure 4, except that the two alternating activity patterns used to generate Figure 4 are applied 2500 times in succession. After reaching a point at which the afferents match the support provided by the target cell, the behavior of the system basically reverts to that in Figures 1 and 2. We see strict segregation of the afferents for $c$ less than approximately 0.45. Increasing the number of times that the activity patterns in Figure 4 are applied increases this value.

averaged over afferent activity, for all values of $p < 1$. For $c > 1$, this point is unstable (a “saddle”), again for all values of $p < 1$. 
A Model of Neurotrophic Interactions

By symmetry, the fixed point $s_i = 0, s_j = T_1(ac + \frac{1}{2})$ is paired with another fixed point at $s_i = T_1(ac + \frac{1}{2}), s_j = 0$.

There is, in addition, another fixed point of equation 2.18, averaged over afferent activity, given by $s_i = T_1(ac + \frac{1}{2}), s_j = 0$. Expanding about this point as usual, and averaging the linearized equations as before, we obtain

$$\frac{d}{dt}((\delta_i) + (\delta_j)) = -\epsilon((\delta_i) + (\delta_j)),$$

$$\frac{d}{dt}((\delta_i) - (\delta_j)) = -\epsilon((\delta_i) - (\delta_j)) \frac{2a(c - 1)(1 - p)}{(2a + 1)^2(2ac + 1)}. \tag{2.44}$$

For $c < 1$, this point is unstable (a “saddle”), while for $c > 1$ this point is stable (an “attractor”), for all values of $p < 1$.

These three fixed points provide a complete understanding of the evolution of the $s_i, i = 1, 2$, determined from equation 2.18 averaged over all afferent activity patterns. For $c < 1$, except when $s_i = s_j$ initially, afferent segregation always occurs, for all values of $p < 1$. Conversely, for $c > 1$, except when either $s_i = 0$ or $s_j = 0$ initially, afferent segregation never occurs, for all values of $p < 1$. For $c = 1$, the entire line $\sum_j s_j = T_1(ac + \frac{1}{2})$ is a stable attractor, with flow approaching it from either below or above along straight lines projecting radially outward from the origin. Biologically, this means that afferent segregation breaks down when the activity-independent release (or exogenous supply) of NTF exceeds a certain, critical value (e.g., Cabelli et al., 1995; English & Schwartz, 1995; Kwon & Gurney, 1996). Although numerical simulation could establish that segregation breaks down beyond some point, only analysis can establish precisely at which point segregation breaks down.

Figure 6 shows the flow derived from equation 2.18 by averaging over afferent activity. In Figure 6a we set $c = \frac{1}{2}$ and $T_1 = 1$ and $a = 1$, in Figure 6b we set $c = 1$ and $T_1 = \frac{3}{2}$, and in Figure 6c we set $c = \frac{1}{2}$ and $T_1 = \frac{1}{2}$, and we have changed the values of $T_1$ in Figure 6b and Figure 6c so that the fixed points are at the same positions as in Figure 6a. For visual impact, we have analytically continued to the region $p < 0$ and set $p = -3$. This has the effect of accentuating the flow; the figure is qualitatively identical for $0 \leq p < 1$.

2.3.2 The NCD Case. To perform the fixed-point analysis for the NCD case, we drop the $\bar{a}_i$ term in $\rho_i, i = 1, 2$, which is equivalent to assuming that the time averages of all afferents’ activities are fixed and equal. For studies of normal development, this is a reasonable assumption. We restrict to two target cells and, as usual, two afferent cells. We will employ an equivalent convention for target cells as that used for afferent cells: that in expressions or sentences in which the subscripts $x$ and $y$ appears simultaneously, but in which neither $x$ nor $y$ is summed over, the subscript $y$ denotes the target cell not denoted by the subscript $x$. 
Figure 6: Flows derived from the fixed-point analysis of the linearized, afferent-activity-averaged equations for the CD case. For (a) $c < 1$, segregated final states attract almost all the flow, while for (c) $c > 1$, an unsegregated final state attracts almost all the flow. At (b) $c = 1$, the flow consists of straight lines projecting radially from or toward the origin, with flow either upward or downward, depending on the initial conditions, toward the line $\sum_j s_j = T_1(ac + \frac{1}{2})$ (dashed line).
One fixed point is at $\mathbf{s}_{xi} = 0, \mathbf{s}_{xj} = T_1(ac + \frac{1}{2}), \mathbf{s}_{yi} = T_1(ac + \frac{1}{2}), \mathbf{s}_{yj} = 0$, and this is paired with another fixed point at $\mathbf{s}_{xi} = T_1(ac + \frac{1}{2}), \mathbf{s}_{xj} = 0, \mathbf{s}_{yi} = 0, \mathbf{s}_{yj} = T_1(ac + \frac{1}{2})$. The $x$-behavior decouples from the $y$-behavior at each of these points, and it is easy to establish that these two fixed points are identical to the equivalent fixed points in the CD case. Thus, for $c < 1$, these points are stable attractors, while for $c > 1$ they are unstable saddles, for all values of $p < 1$.

The analysis of the fixed point at $\mathbf{s}_{xi} = \frac{1}{2}T_1(ac + \frac{1}{2}), \mathbf{s}_{xj} = \frac{1}{2}T_1(ac + \frac{1}{2}), \mathbf{s}_{yi} = \frac{1}{2}T_1(ac + \frac{1}{2}), \mathbf{s}_{yj} = \frac{1}{2}T_1(ac + \frac{1}{2})$ is, however, not identical to the equivalent point in the CD case. Expanding and linearizing about this point, and averaging over afferent activity patterns as usual, after lengthy algebra we obtain,

\[
\frac{d}{dt} \begin{pmatrix} \langle \delta_{xi} \rangle \\ \langle \delta_{xj} \rangle \\ \langle \delta_{yi} \rangle \\ \langle \delta_{yj} \rangle \end{pmatrix} = \frac{\epsilon}{4} \begin{pmatrix} q\alpha - 3 & -q\alpha - 1 & q\beta - 1 & -q\beta + 1 \\ -q\alpha - 1 & q\alpha - 3 & -q\beta + 1 & q\beta - 1 \\ q\beta - 1 & -q\beta + 1 & q\alpha - 3 & -q\alpha - 1 \\ -q\alpha - 1 & q\alpha - 3 & -q\beta + 1 & q\beta - 1 \end{pmatrix} \begin{pmatrix} \langle \delta_{xi} \rangle \\ \langle \delta_{xj} \rangle \\ \langle \delta_{yi} \rangle \\ \langle \delta_{yj} \rangle \end{pmatrix},
\]

(2.45)

where $q = 1 - p$, the $\delta_{xi}$, and so forth, denote small perturbations about the fixed points, and $\alpha$ and $\beta$ are given by

\[
\alpha = \frac{1 + 4a - 2ac}{(2a + 1)^2(2ac + 1)},
\]

(2.46)

\[
\beta = \frac{1}{(2a + 1)^2}.
\]

(2.47)

Because of the symmetries in this matrix, we can read off the eigenvectors and associated eigenvalues by inspection:

- Eigenvector: $(1, -1, -1, 1)^T$, Eigenvalue: $\epsilon q(\alpha - \beta)/2$
- Eigenvector: $(1, -1, 1, -1)^T$, Eigenvalue: $\epsilon q(\alpha + \beta) - 2)/2$
- Eigenvector: $(1, 1, 0, 0)^T$, Eigenvalue: $-\epsilon$
- Eigenvector: $(0, 1, 0, 1)^T$, Eigenvalue: $-\epsilon$.

where the superscript $T$ denotes the transpose. The first eigenvalue in this list reduces to

\[
-\epsilon \frac{2a(c - 1)(1 - p)}{(2a + 1)^2(2ac + 1)},
\]

and the second is

\[
-\epsilon \left(1 - \frac{1 - p}{(2a + 1)(2ac + 1)}\right).
\]
Thus, two eigenvalues are negative definite, one eigenvalue is negative semidefinite, and the remaining eigenvalue changes sign at \( c = 1 \). For \( c < 1 \), this fixed point is therefore an unstable saddle, and for \( c > 1 \), it is a stable attractor. Although the analysis is more complicated, this fixed point behaves identically to the equivalent fixed point in the CD case.

The NCD case is essentially identical to the CD case. There are three fixed points in each case. Two correspond to segregated final states, and the other corresponds to an unsegregated final state. For \( c < 1 \), the segregated final states are stable and attract almost all the flow, while for \( c > 1 \), the unsegregated final state is stable and attracts almost all the flow.

In the CD case we proved that the limit \( a \to \infty \) prevents afferent segregation (see equation 2.19), but this proof does not go through for the NCD case, unless we assume that \( \rho_i = \rho_j \forall i, j \). The fixed-point analysis, however, for both the CD and the NCD cases, proves that the limit \( a \to \infty \) behaves identically to the point \( c = 1 \), at least for the afferent-activity-averaged equations, since (at least) one of the eigenvalues of each of the matrices determining the linear flow becomes zero when either \( a \to \infty \) or \( c = 1 \). Thus, it is important to realize that the transition from segregation to nonsegregation that occurs at \( c = 1 \) is valid only for finite \( a \), since if we take the limit \( a \to \infty \) in the expression for \( c \), \( c = T_0/(aT_1) \), we obtain \( c = 0 \) always, which (wrongly) predicts segregation always.

### 2.4 Random Walk Approximation.

The fixed-point analysis performed above indicates that the transition from segregation to nonsegregation is discontinuous and occurs at the point \( T_0 = aT_1 \) for all values of \( p < 1 \). As \( p \) approaches unity, the flow slows down, so that it takes longer to segregate (for \( c < 1 \)) or longer to abolish partial segregation (for \( c > 1 \)). Biologically, the time needed to segregate or abolish segregation might be important, because if the capacity for plasticity is under some form of control, then the required time might exceed the time during which the system is able to change. We now examine this issue. To do this, we extract a random walk approximation. We do this for the CD case only. While we thus consider the time taken to segregate in models to be important, we are generally skeptical about claims that models are temporally realistic inasmuch as the time-step sizes that they use can be compared to real times in real biological systems. Because models typically contain many parameters, it is usually easy to adjust some of them (particularly the “learning rate”) so that the models’ time steps can be compared to real times.

Provided that \( \epsilon \) is sufficiently small, the one-step Euler method defined by equation 2.16 provides a good approximation to the solutions of equation 2.17 with time steps \( \Delta t \) of unit size. Given initial conditions \( s_i^0 \), if we wish to calculate \( s_i^{n+1} \), then we can insert either \( s_i^n \) or \( s_i^0 \) into the right-hand side of the one-step Euler method corresponding to equation 2.18, since the difference between the resulting values is of order \( \epsilon^2 \), which we can take to be negligible for \( \epsilon \) sufficiently small. Using \( s_i^0 \) instead of \( s_i^0 \), however, has
the considerable advantage that $\Delta s_i^{n+1} = s_i^{n+1} - s_i^n$ depends only on the $s_i^n$, which are fixed, and the afferents' activities only at time-step $n$, and not at any earlier times steps through $s_i^0$. Thus, the $\Delta s_i^{n+1}$ are strictly independent of the $\Delta s_i^n$ provided that the $a_i^n$, and the $\Delta s_i^{n+1}$ take values from the same, possibly infinite set as the $\Delta s_i^n$. These are exactly the conditions that define the evolution of the $s_i$ as a random walk away from their initial values.

We may most simply calculate the mean and variance of a random variable $W$ corresponding to a random walk process by using its probability-generating function $G_W(r) = E[r^W]$, where $E$ denotes the expectation value. Then the mean, $\mu_W$, and variance, $\sigma_W^2$, are given by

$$\mu_W = \left. \frac{dG_W}{dr} \right|_{r \uparrow 1},$$

and

$$\sigma_W^2 = \left. \left[ \frac{d^2G_W}{dr^2} + \left( \frac{dG_W}{dr} \right)^2 \right] \right|_{r \uparrow 1},$$

when these limits exists.

As in the fixed-point analysis, we assume binary afferent activity with probabilities given by equations 2.37 through 2.40. The corresponding step sizes $\Delta s_i^n$ take values from the set $\{\Theta_{00}, \Theta_{01}, \Theta_{10}, \Theta_{11}\}$, where the first subscript denotes the value of $a_i$ and the second the value of $a_j$. Taking $a = 1$ and $T_1 = 1$, and employing the initial conditions $s_i^0 = \frac{1}{2}(1 + \delta_i)(1 + 2c)$, where $\delta_i$ is such that $|\delta_i| \leq 1$ and represents a small perturbation about the value $\frac{1}{2}(1 + 2c)$ used earlier, and taking $\delta_i + \delta_j = 0$, so that one afferent is just above and the other is just below this value, the $\Theta_{i,j}$ take the following values:

$$\Theta_{00} = \frac{e}{4}(1 + \delta_i),$$

$$\Theta_{01} = -\frac{e}{4} \frac{1 + \delta_i}{3 - \delta_i} [(1 + \delta_i) + 2(1 - \delta_i)c],$$

$$\Theta_{10} = \frac{e}{4} \frac{1 + \delta_i}{3 + \delta_i} [(1 + 3\delta_i) + 2(1 - \delta_i)c],$$

$$\Theta_{11} = \frac{e}{4}(1 + \delta_i).$$

The probability-generating function of the random variable $\Delta s$ for an arbitrary afferent and an arbitrary, single time step is thus given by

$$G_{\Delta s}(r) = \frac{1}{2}p \left( r^{\Theta_{00}} + r^{\Theta_{11}} \right) + \frac{1}{2} (1 - p) \left( r^{\Theta_{01}} + r^{\Theta_{10}} \right).$$
and the random variable
\[ S_i = \sum_{m=1}^{N} \Delta s_i^m, \]  
(2.55)

which denotes the shift of afferent \( i \) away from its initial value \( s_i^0 \) after time-step \( N \), has a probability-generating function given by
\[ G_{S_i}(r) = [G_{\Delta S}(r)]^N, \]  
(2.56)

the mean, \( \mu_i \), and variance, \( \sigma_i^2 \), of which are given by
\[ \mu_i = \frac{1}{2} Ne(1 - p)(1 - c)\delta_i \frac{1 - \delta_i^2}{9 - \delta_i^2}, \]  
(2.57)

and
\[ \sigma_i^2 = \frac{1}{4} Ne^2 (1 + \delta_i)^2 \left\{ \frac{1}{4} p + (1 - p^2) \frac{(1 - \delta_i)^2}{(9 - \delta_i^2)^2} \delta_i^2 (1 - c)^2 \right\} \]
\[ + \frac{1 - p}{9 - \delta_i^2} \left[ \frac{1}{4} (1 + 3\delta_i)(1 + \delta_i) + (1 + 2\delta_i)(1 - \delta_i)c + (1 - \delta_i)^2 c^2 \right]. \]  
(2.58)

There are two things to notice about the expression for \( \mu_i \). First, for \( c < 1 \) and \( \delta_i > 0 \) (\( \delta_i < 0 \)), \( s_i \) is expected to increase (decrease) and \( s_j \) is expected to decrease (increase). This expectation is consistent with the nature of the fixed points in Figure 6a. However, for \( N \) sufficiently large, if \( \delta_i > 0 \), then \( s_i \) is expected to become negative. This is an artifact of the assumption of fixed-step sizes. Analytically, as \( s_i \) approaches zero, the rate of change of \( s_i \) decreases, violating the fixed-step size assumption. Similarly, for \( N \) sufficiently large, if \( \delta_i > 0 \), then \( s_i \) is expected to exceed the average value of \( \sum s_i \), which is \( \frac{1}{2} + c \). Again, this is an artifact of the assumption of fixed-step sizes. For \( c > 1 \), all these results are reversed: \( s_i \) and \( s_j \) are expected to evolve toward each other, in accord with the fixed-point analysis. However, for \( N \) sufficiently large, \( s_i \) and \( s_j \) are expected to move toward each other but overshoot, so that one becomes large and positive and the other large and negative. Again, this is an artifact of the fixed-step size assumption.

Second, for \( \delta_i = 0 \), we have that \( \mu_i = 0 \). That is, there is no expected shift away from the initial conditions when both afferents start with \( s_i = s_j = \frac{1}{4} (1 + 2c) \). This is in accord with the fixed-point analysis. However, our analysis of the exact solutions above indicated that even for \( \delta_i = 0 \), specific patterns of afferent activity might induce segregation. This analysis used anticorrelated afferent activity with activity patterns reversing at each time step. In this case, for \( c \) near to unity or below, segregation does indeed
occur, as shown in Figure 5. However, such activity patterns are such that the $a_{i}^{n+1}$ are not independent of the $a_{i}^{n}$, since $a_{i}^{n+1} = 1 - a_{i}^{n}$ ∀n, but the random walk approximation requires the assumption of strict independence for its validity. The fixed-point analysis also requires this assumption of independence for the averaging over afferent activity to be valid. For the $a_{i}^{n+1}$ independent of the $a_{i}^{n}$, as both the random walk and the fixed-point analysis require, segregation does not occur for $\delta_{i} = 0$.

In Figure 7, for $\epsilon = 0.018$ (as before), $N = 10^6$, and $\delta_{i} = 0.01$ we show graphs of the interval $[\mu_{i} - \sigma_{i}, \mu_{i} + \sigma_{i}]$ by showing graphs of $\mu_{i}$ and $\mu_{i} \pm \sigma_{i}$, for $0 \leq \epsilon \leq 1$, for three different values of $p$. Since both $\mu_{i}$ and $\sigma_{i}$ are proportional to $\epsilon$, the quantitative features of these graphs are independent of $\epsilon$, except for the scale of the vertical axes. As $p$ increases, the intervals broaden and are pulled downward. Each graph in this figure shows a minimum value of $\epsilon$, $c_{seg}$, below which the expected shift is not consistent with zero and above which the expected shift is consistent with zero. (There is also a value for $c > 1$ beyond which the expected shift becomes significantly negative for $\delta_{i} > 0$, but, as explained above, this is an artifact and is ignored.) We take this as the value of $c$ below which afferent segregation could occur within the number of time steps permitted and above which afferent segregation cannot occur within the number of time steps permitted. Strictly speaking, this interpretation violates the assumption of linearization required to derive the random walk approximation. However, we will find reasonable qualitative agreement with numerical results.

The value of $c_{seg}$ can be calculated by solving $\mu_{i} = \sigma_{i}$, from which we obtain a messy expression that we do not reproduce here. To be real valued, the expression requires that

$$p \leq \frac{N\delta_{i}^{2}}{9 + (1 + N)\delta_{i}^{2}}. \quad (2.59)$$

As $N \to \infty$, $p$ may approach unity, as expected from the fixed-point analysis. For finite $N$, the range of values of $p$ in which afferent segregation might be possible within the number of time steps permitted is reduced. Figure 8 shows a graph of $p$ plotted as a function of $c_{seg}$ for $\delta_{i} = 0.01$ and for a range of values of $N$. The qualitative character of the curves is unchanged by changing $\delta_{i}$; broadly speaking, decreasing (increasing) $\delta_{i}$ for fixed $N$ has the same effect as decreasing (increasing) $N$ for fixed $\delta_{i}$.

### 2.5 Numerical Simulations.

We now turn to numerical simulations of the model defined by equation 2.17. We consider two afferents and either one target cell for the CD case or two target cells for the NCD case. In the latter case, we continue to assume that NTF does not diffuse through the target field. We also continue to assume that $a = 1$ and $T_{1} = 1$ so that the numerical results can be compared to the analytical results discussed above. We take the initial conditions as before, $s_{i}^{0} = \frac{1}{4}(1 + \delta_{i})(1 + 2\epsilon)$, $t = 1, 2$, except that we...
Figure 7: The expected shift, $\mu_i \pm \sigma_i$, from the initial conditions given by the random walk approximation. The dashed line is $\mu_i$, and the solid lines are $\mu_i \pm \sigma_i$. Shifts for three different values of $p$ are shown: (a) $p = 0.3$, (b) $p = 0.5$, and (c) $p = 0.7$. In each case $N = 10^6$ and $\delta_i = 0.01$. 
Figure 8: Graphs of $p$ against $c_{seg}$ for five different values of $N$. Moving from bottom left to top right: $N = 10^5$, $N = 10^6$, $N = 10^7$, $N = 10^8$, and $N = 10^9$. For each value of $N$, the associated curve divides the $c$-$p$ plane into two pieces. The upper piece is the region in which afferent segregation is predicted by the random walk approximation not to be possible within the number of steps, $N$, permitted. For each value of $N$, $\delta_i = 0.01$.

Now take the $\delta_i, i = 1, 2$, to be random numbers in the interval $[-0.01, 0.01]$ and we do not assume that $\delta_i + \delta_j = 0$. Afferent activity is binary valued, $a_i \in \{0, 1\}, i = 1, 2$, and such that the probability that both afferents have the same activity in any given time step is $p$. In each time step, one afferent, $i$, is assigned activity $a_i = 0$ with probability 0.5; otherwise it is assigned activity $a_i = 1$. The other afferent, $j$, is assigned activity $a_j = a_i$ with probability $p$; otherwise it is assigned activity $a_j = 1 - a_i$. We take the time steps to be of unit size and $\epsilon = 0.018$.

First we characterize the general behavior of the model in the $c$-$p$ plane. To this end we consider 21 different values of $c$ uniformly distributed in the interval $[0, 1]$, and similarly for $p$. For each pair of values of $c$ and $p$, we solve equation 2.17 numerically $10^5$ times using different random selections of initial conditions. We numerically integrate equation 2.17 rather than numerically solve the exact but implicit expressions in equations 2.30 and 2.31 for the CD case because it is computationally faster to do the former; for the NCD case, we are forced to employ numerical integration. Each solution consists of $10^6$ individual time steps. For each point in the $c$-$p$ plane, we define a segregation probability, $S$, which is the ratio of the number of times segregation is observed to the total number of times the differential equations are solved.
In Figure 9 we show contours of $S$ in the $c$-$p$ plane. Figure 9a shows contours for the CD case, and Figure 9b shows contours for the NCD case. The “wobbles” in the contours are artifacts of poor resolution along both the $c$- and the $p$-axes and would also be smoothed by increasing the number of simulations at each point. However, increasing the resolution and the number of simulations significantly would make the generation of the contours computationally intractable. The shape of the contours in Figure 9 is in good qualitative agreement with those derived from the random walk approximation shown in Figure 8. Quantitatively, however, there is poor agreement, since the random walk approximation significantly overestimates the maximum number of steps below which segregation is not expected. This disagreement is not too surprising, since the random walk approximation assumes fixed-step sizes. Figure 9 indicates that the transition from segregation to nonsegregation is not abrupt but possesses a continuous profile, because the number of time steps permitted is not infinite. However, the transition is nevertheless very rapid.

Typical examples of the evolution of the $s_i$, $i = 1, 2$, for three different values of $c$ are shown in Figure 10, for the CD case, for uncorrelated activity ($p = 0.5$), obtained by numerical integration. In Figure 10a, for $c = 0.8$, we see segregation of the two afferents, so that $s_i \rightarrow 0$ for one of them. In contrast, in Figure 10b, for $c = 1.0$, the “critical” value at which equation 2.21 becomes dramatically simplified and the fixed points flip from being attractors to being saddles or vice versa, the evolution seems to be chaotic, with afferents appearing to segregate, but then, after varying lengths of time, suddenly reversing roles, with one rapidly growing and the other rapidly decaying. Figure 10c, for $c = 1.2$, exhibits some of the chaotic behavior of Figure 10b, but the afferents never approach segregation.

Figure 11 shows examples of the evolution for the NCD case, again for uncorrelated afferent activity. Here we consider two target cells, but show for clarity the evolution associated with only one target cell; the evolution associated with the other target cell is the reverse of that shown. This figure shows that the transition from segregation (Figure 11a, $c = 0.92$) to nonsegregation (Figure 11c, $c = 0.98$) is smooth, with intermediate, partially segregated states being present rather than the chaotic oscillations of the CD case (Figure 11b, $c = 0.95$).

To rule out the possibility that the behavior exhibited in Figure 10b is due to a numerical instability associated with the numerical integration, we show, in Figure 12, the results obtained from the exact and explicit analytic solutions in equations 2.32 and 2.33. Figure 12 reveals qualitative similarities to Figure 10b, but there are quantitative differences. The chaotic oscillations are still present but are, in fact, enhanced. Thus, the numerical integration results, for $c = 1$ in the CD case, tend to overestimate the average oscillation period. However, this quantitative difference is not important. Numerical solution of the exact but implicit equations 2.30 and 2.31 for $c = 0.8$ and $c = 1.2$ reveals both qualitative and quantitative similarity to the numerical
Figure 9: Contours of the segregation probability $S$ in the $c$-$p$ plane obtained by full numerical simulations of the (a) CD case and the (b) NCD case. From bottom left to top right in each case: $S = 0.95$, $S = 0.75$, $S = 0.50$, $S = 0.25$, and $S = 0.05$. Almost all points under the $S = 0.95$ contours segregate, while almost all points above the $S = 0.05$ contours do not segregate.

integration results. Thus, possible numerical instabilities associated with the numerical integration do not appear to be significant.

Finally, although the fixed-point analysis of the afferent-activity-averaged equations for the NCD case results in the same fixed points with identical properties as for the CD case, Figures 9 to 11, while demonstrating much qualitative similarity between the CD and the NCD cases, exhibit some
Figure 10: Three examples of the typical behavior of the CD case for $p = 0.5$, for different values of $c$: (a) $c = 0.8$, (b) $c = 1.0$, and (c) $c = 1.2$. The transition from segregation to nonsegregation is characterized by chaotic oscillations.
Figure 11: Three examples of the typical behavior of the NCD case for $p = 0.5$, for different values of $c$: (a) $c = 0.92$, (b) $c = 0.95$, and (c) $c = 0.98$. The transition from segregation to nonsegregation is smooth and continuous, with partially segregated states in between.
quantitative differences. In the fixed-point analysis, the various \( \rho_i \) basically make no contribution at first order except to expand and rotate the coordinate system, which is why the NCD fixed points are identical in character to the CD fixed points. However, the dynamics associated with the \( \rho_i \) are important, since they ensure that, for example, two afferents will each win one of two target cells. In the CD case, this never happens: one afferent always wins both target cells, and the other always retracts all its terminals. In addition, to perform the analysis in the NCD case, we dropped the \( \bar{a}_i \) term from \( \rho_i \). Numerically, fluctuations in this term will contribute and will serve to “smear” the transition point \( c = 1 \) over a range of values of \( c \). Thus, while we expect qualitative similarity in terms of the parameter regime in which segregation is expected, we would not expect exact quantitative agreement.

3 Discussion

We have shown that a mathematical model of retrograde neurotrophic interactions leads to the segregation of afferents’ arbors on the target space even for very strongly correlated afferent activity patterns. Segregation occurs provided that the level of NTF released in an activity-independent manner, or, equivalently, the level of NTF available by exogenous infusion, is not too high, relative to the resting uptake of NTF by afferents and the maximum amount of NTF available by activity-dependent release.

A key assumption in our model is that the (recent average) level of NTF taken up by an afferent from part of the target structure determines the
number of synapses the afferent projects to that part of the target structure. Thus, we assume that a (local) decline in NTF levels results in a (local) atrophy of the afferent’s axonal arbor, and, similarly, a (local) increase in NTF levels results in a (local) growth of the afferent’s axonal arbor. Evidence exists that indicates this assumption is not unreasonable. NTFs can promote axonal growth: retinotectal afferent arbors in *Xenopus* grow in response to increased levels of BDNF (Cohen-Cory & Fraser, 1995). Furthermore, localized atrophy or growth of axonal arbors in response to NGF shortage or supply, respectively, has been observed (Campenot, 1982a,b).

A further key assumption in our model is that the uptake of NTFs depends in part on afferent activity. To our knowledge, no experimental evidence exists to suggest whether this is a plausible assumption. However, much evidence suggests that competitive interactions between afferents depend, at least in part, on the relative rather than the absolute levels of afferent activity. For example, monocular deprivation has a profound effect on LGN cells driven by the deprived eye, while binocular deprivation has little or no effect (Guillery & Stelzner, 1970; Guillery, 1972). Although it is possible that activity might affect the ability of afferents to utilize, rather than to take up, NTFs (Meyer-Franke, Kaplan, Pfrieger, & Barnes, 1995; discussed in Snider & Lichtman, 1996), it is unlikely that this could lead to differences depending on relative levels of activity, unless an enhanced capacity to utilize NTFs also enhances the rate of uptake. For example, if activity affects only the ability of afferents to utilize NTFs, then deprived-eye LGN cells should undergo atrophy whether or not the other eye is deprived. That is, activity-mediated utilization would appear to be noncompetitive.

The status of our assumption regarding NTF uptake is therefore that of a tentative postulate, driven by theoretical considerations concerning the possible mechanisms of afferent competition. Analysis of our model demonstrates that activity-dependent uptake of NTF is the driving force behind competitive dynamics, since if the activity-independent component of uptake dominates the activity-dependent component (the limit $a \to \infty$), then afferent segregation cannot occur. This should be regarded as a prediction: if it were possible pharmacologically to dissect out and remove the postulated activity-dependent component of afferent NTF uptake, so that only the activity-independent component remains, then we predict that in an otherwise normal preparation, afferent segregation would not occur.

Another assumption is that of rapid diffusion of NTF through the target field. This assumption is not critical; it serves to make the equations and the resulting analysis more tractable. Slowing the rate of diffusion, allowing NTF to accumulate over time, and introducing some method of degrading NTF so that its levels do not grow unboundedly would not significantly alter the dynamics of our model, although the time taken to segregate would be increased. A model based on such an approach, using nitric oxide (NO) as a retrograde messenger, has been presented (Montague, Gally, & Edelman, 1991), and arguments concerning the theoretical advantages conferred
by spatial and temporal averaging have been advanced (Gally, Montague, Reeke, & Edelman, 1990; Edelman & Gally, 1992). However, inhibition of NO synthase in the visual system does not alter ocular dominance plasticity (Reid, Daw, Czepita, Flavin, & Sessa, 1996; Ruthazer, Gillespie, Dawson, Snyder, & Stryker, 1996), so the status of NO as a relevant retrograde messenger is unclear.

In the NCD case, we assumed that the affinity of each terminal for NTFs is proportional to the time average of the afferent’s activity and inversely proportional to the total number of terminals supported by the afferent. The affinity of a terminal for NTFs was interpreted as proportional to the number of receptors for the NTFs possessed by the terminal. We therefore assumed that NTF receptors are regulated by afferent activity. Evidence indicates that kindling and seizures in the rat result in an elevation of the mRNAs for trkB and trkC, the receptors for BDNF, neurotrophin-3 (NT-3) and NT-4/5 (Bengzon et al., 1993; Dugich-Djordjevic et al., 1995; Salin et al., 1995), suggesting that afferent activity might regulate NTF receptors. Furthermore, depolarizing media directly influence NTF receptor expression in cell culture (Birren, Verdi, & Anderson, 1992; Cohen-Cory, Elliott, Dreyfus, & Black, 1993).

The assumption that the affinity of a terminal is inversely proportional to the number of terminals amounts to the assumption that, for fixed mean activity, an afferent possesses a fixed number of NTF receptors that are re-distributed around its axonal arbor in response to sprouting or retraction. Although no evidence bears directly on this assumption, some indirect evidence does suggest that it is not implausible. Recently it has been established that at the Drosophila neuromuscular junction, the expression of the cell adhesion molecule fasciclin II (Fas II) by motor neurons controls the size of motor neuronal arbors: mutants that express approximately 50% lower levels of Fas II than controls possess arbors with approximately twice as many synaptic boutons (Schuster, Davis, Fetter, & Goodman, 1996a,b). The synaptic efficacy of motor neurons in such mutants is unchanged, suggesting that the same levels of synaptic machinery as in controls are simply distributed over a larger number of boutons (Schuster et al., 1996b). However, if the mutation reducing Fas II by 50% is combined with one that expresses the cAMP response element-binding protein activator, then synaptic efficacy is also increased (Davis, Schuster, & Goodman, 1996). The fact that only mutants with reduced Fas II have motor neurons with the same synaptic efficacy as controls thus suggests that the assumption of a fixed number of NTF receptors, for fixed mean activity, is not implausible.

In this model, we have considered only the possible role of NTFs in activity-dependent, competitive, anatomical changes. We have specifically ignored any possible physiological changes that might precede anatomical changes (Bailey & Kandel, 1993). However, evidence is accumulating that implicates NTFs not only in competitive, anatomical plasticity but also in physiological plasticity. For example, at the neuromuscular junction, BDNF
A Model of Neurotrophic Interactions

and NT-3 rapidly potentiate synaptic transmission (Lohof, Ip, & Poo, 1993), and in the rat visual cortex, BDNF blocks long-term depression (Akaneya, Tsumoto, & Hatanaka, 1996) and, in addition to NGF, enhances excitatory transmission (Carmignoto, Pizzorusso, Tia, & Vicini, 1997). In the hippocampus, BDNF and NT-3 elevate intracellular Ca\(^{2+}\) levels (Berninger, Garcia, Inagaki, Hahnel, & Lindholm, 1994), and NGF, BDNF, NT-3, and NT-4/5 all potentiate or modulate synaptic transmission (Knipper, Leung, Zhao, & Rylett, 1994; Lessmann, Gottman, & Heumann, 1994; Kang & Schuman, 1995). Furthermore, BDNF-knockout mice exhibit significantly impaired long-term potentiation (LTP) (Korte et al., 1995). This impairment can be reversed by a virus-mediated reexpression of the BDNF gene (Korte et al., 1996). These results, the last two especially (Korte et al., 1995, 1996), suggest that NTFs might, in addition to their neurotrophic properties, act as retrograde messengers during LTP, inducing rapid physiological presynaptic changes. The non-Hebbian character of LTP in the hippocampus and the rat visual cortex suggests that if NTFs do act as retrograde messengers during LTP, they diffuse widely through the target field and act on, or are taken up by, active afferents (Bonhoeffer, Staiger, & Aertsen, 1989; Kossel, Bonhoeffer, & Bolz, 1990). If NTF-mediated physiological plasticity is competitive in character, then NTFs might provide a natural bridge between physiological and anatomical plasticity. It would be of considerable interest to extend the present model in order to take account of these possibilities.

In the CD case, we find a discontinuous transition from segregation to nonsegregation. Although such a discontinuity is also predicted for the NCD case, in fact it is not observed, because the \(\rho_i\) and the \(\bar{a}_i\) play an important role in the dynamics and serve to smooth out the transition. A discontinuous transition, although a logical possibility, is unlikely to occur in real, biological systems. Segregation in both cases also occurs even in the presence of very highly correlated patterns of afferent activity. This is likely to be unrealistic. Preliminary indications are that these difficulties do not exist in full-scale simulations of large numbers of afferent and target neurons, which include the diffusion of NTF through the target field. However, mathematical analysis of the model, including NTF diffusion, is very much more complicated than the analysis considered here.

Another difficulty is that the transition from segregation to nonsegregation in the CD case is chaotic, involving oscillations in the sizes of afferents’ arbors. While this is, again, a logical possibility, it is almost certainly biologically implausible. One way of overcoming this difficulty is to discretize the \(s_{xi}\). This is natural in a model of anatomical plasticity, in which the \(s_{xi}\) represent the (possibly scaled) numbers of synapses between afferents and target cells. Such discretization thus has the effect of setting a limit below which the \(s_{xi}\) are deemed to be zero. Once set to zero, they can never regrow. This would serve to eliminate the oscillatory behavior at \(c = 1\). However, since the CD case permits cell death, it is of no interest for studying afferent segregation in later development. For this, the NCD case is required, and
this does not exhibit a chaotic transition from segregation to nonsegregation.

It might be considered that the existence of specific classes of fixed points in our model (perfectly segregated or exactly balanced innervation in the two-afferent case) is biologically unrealistic, since in the striate cortex, for example, many different balances of control between the two eyes exist. However, it should be realized that our model indicates only that if competition and plasticity occur for indefinitely long, then afferents either will segregate perfectly or will achieve perfectly balanced innervation. The random walk approximation gives insight into how long segregation or the abolition of partial segregation might take. If these processes are long compared to the duration of the period in which the developing system is plastic, then the system will not have time to reach the fixed points. This would be reflected in the continued presence of neurons falling, for example, into many different ocular dominance classes. Furthermore, diffusion of NTF through the target field is likely to affect the dynamics of segregation. Indeed, preliminary results indicate that large-scale simulations of the formation of ocular-dominance columns can retain considerable binocular overlap at ocular-dominance column boundaries, even when the termination of the critical period for plasticity is not considered.

One result for which the present model cannot account, is the fact that infusion of the γ-aminobutyric acid (GABA_A) receptor agonist muscimol into the striate cortex during development causes a paradoxical shift of ocular dominance toward the deprived eye (Reiter & Stryker, 1988; Hata & Stryker, 1994). Since we postulate that the uptake of NTFs is activity dependent, active-eye afferents should take up more NTFs than inactive-eye afferents (assuming comparable axonal arborisations), despite the fact that excess GABAergic stimulation via muscimol infusion would be expected to cause a marked decline in the levels of NTFs available from target cells (Zafra, Castren, Thoenen, & Lindholm, 1991). A plausible way of extending our model to overcome this difficulty is to assume that more active afferents require greater neurotrophic support than less active afferents (Elliott & Shadbolt, 1996). In this case, more active afferents receiving inadequate neurotrophic support for their level of activity and extent of axonal arborizations would be expected to undergo an atrophy of their axonal arborizations. Less active afferents, on the other hand, might receive sufficient neurotrophic support to maintain their axonal arborizations, or, at least, they might atrophy less quickly than those of more active afferents. In combination, the result would be that the more active afferents would retract, leaving the less active afferents in control. Evidence supports the view that electrical activity exerts a regressive influence on the size of axonal arborizations (Cohan & Kater, 1986; Sussdorf & Campenot, 1986; Lipton & Kater, 1989; Mattson & Kater, 1989; Fields, Neale, & Nelson, 1990).

This account of the paradoxical shift of ocular dominance toward the deprived eye requires only that the postsynaptic cortical neurons play a permissive role in synaptic plasticity, by regulating the production and re-
lease of NTFs according to the balance of excitatory and inhibitory synaptic input (Zafra et al., 1991). An alternative view is that cortical neurons might play an instructive role in the plasticity of geniculocortical afferents. For example, the disparity in activity between the undeprived-eye afferents and the muscimol-silenced cortical neurons might lead to a long-term depression of the active, but not the inactive, geniculocortical synapses via mechanisms involving the N-methyl-D-aspartate receptor (discussed in Shatz, 1997). However, neither this account nor our own can explain the paradoxical shifts in ocular dominance that occur following cortical BDNF infusion in kittens (Galuske, Kim, Castren, Thoenen, & Singer, 1996) or cortical NGF infusion in adult cats (Gu, Liu, & Cynader, 1994). Although it is possible that no single unitary mechanism exists to account for all these paradoxical results, it is also possible that both muscimol and NTF infusion might interfere with inhibitory circuitry and cause paradoxical shifts (discussed in Thoenen, 1995).

Recent data indicate that NTFs affect not only axonal arborizations, but also dendritic arborizations (McAllister, Katz, & Lo, 1995, 1996, 1997; see also Snider, 1988). However, BDNF and NT-3 exert opposing influences on dendritic development, with these influences reversing in different cortical layers (McAllister et al., 1997). In contrast, while BDNF and NT-4/5 do affect ocular dominance column development, NGF and NT-3 do not (Cabelli et al., 1995, 1997). It therefore seems premature to attempt to construct a model of the action of any particular NTF in the striate cortex. However, this does not preclude the possibility of theoretically exploring the general implications of neurotrophic interactions for development, plasticity, and competition, which is what we have attempted to do here.

An interesting neurotrophic model of the elimination of polyneuronal innervation at the vertebrate neuromuscular junction has been presented (Bennett & Robinson, 1989). It is similar to our model inasmuch as it considers the role of neurotrophic molecules and their receptors in development. However, the model does not consider the role of afferent activity in the process of synaptic rearrangement at the neuromuscular junction. Recently a neurotrophic model of the development of ocular dominance columns has been presented (Harris, Ermentrout, & Small, 1997). Unfortunately, this model appears to suffer from a number of difficulties. First, it disregards anatomical plasticity, yet the evidence for the breakdown of segregation of LGN afferents following exogenous infusion of NTFs is anatomical, not physiological (Cabelli et al., 1995). Also, the model assumes a constant pool of available NTF, so that NTF production and release is not regulated by neuronal activity. Finally, the model makes the rather implausible assumption that the uptake of NTF by afferents depends on the afferents' synaptic efficacy.

We have also presented a rather simpler model of neurotrophic interactions than the one presented here (Elliott & Shadbolt, 1996). There are, however, a number of difficulties with our earlier model. First, hand set-
ting was required to prevent uncontrolled growth or uncontrolled decay of afferents. The present model dynamically controls growth and decay. Second, segregation of afferents occurred even when afferent activity was perfectly correlated. This indicates that the postulated mechanisms underlying plasticity in that model are likely to be wrong. In the present model, segregation does not occur in the presence of perfectly correlated patterns of afferent activity. With such patterns, afferents grow in such a way that the ratio of their numbers of synapses remains fixed. Last, growth in the absence of afferent activity was not possible in our earlier model. However, much evidence suggests that afferent growth is possible even when afferent activity is silenced with tetrodotoxin (e.g., Brown & Ironton, 1977; Sretavan, Shtz, & Stryker, 1988; Antonini & Stryker, 1993). Afferent inactivity in the present model does not prevent growth. We thus regard the present model as superior to our earlier model. Future work on our latest model will involve its application to full-scale simulations of the development of ocular dominance columns and the possible inclusion of physiological plasticity.

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