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Competition Amongst Neurons for Neurotrophins

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Abstract. In the development of nerve connections, neurons are believed to compete for target-derived neurotrophic factors which support their survival and maintenance of their synapses. We introduce a mathematical framework for neurotrophin release and its uptake by the innervating neurons. We explore the idea that central to the action of neurotrophins is their capacity to upregulate their own receptors.
Using nerve growth factor (NGF) as the paradigm case, we show theoretically how the form of the upregulation determines the nature and outcome of the competitive process. Under some conditions, the target structure becomes singly innervated; under others, multiple innervation results, the amount of multiple innervation depending on the supply of neurotrophins. The finding that electrical activity increases the numbers of receptors means that competition for neurotrophin amongst synapses leads to the survival of the more active ones. Reduction in receptor upregulation or in the supply of neurotrophin (which may occur in ageing and disease-related neurodegeneration), can lead to a complete loss of innervation.
Our model encompasses previous models of neuronal competition during development and couples the field of neurobiology to that of population biology, where the notion of competition is better developed.

1 Introduction

During the development of the nervous system, neurons become assembled into networks by making synaptic connections with other neurons. In many cases there is not a simple, inflexible pairing together of particular pre- and postsynaptic elements but there is competition among neurons. The crucial question concerns the nature of this competition.

In order to survive, neurons and synapses need to obtain sufficient amounts of so-called neurotrophic factors. These survival-promoting substances are released in limited amounts by the neurons' target elements. They are taken up by the innervating neurons, which are thought to compete for them. Neurons or synapses that fail to obtain sufficient amounts will die. The notion of competition has been used to explain axonal elimination during, for instance, the innervation of mammalian skeletal muscle [1], cerebellar Purkinje cells [2], autonomic ganglion cells [3] and the formation of ocular dominance columns [4].

An important class of neurotrophic factors are the neurotrophins, with NGF (nerve growth factor) being its best characterised member [5]. Neurotrophins bind to their specific receptors at the synaps, resulting in activation of the receptor. The ligand-receptor complex is then internalised, and the neurotrophin and activated receptor are retrogradely transported to the cell body. The activated receptor, by triggering a signalling cascade, has direct local effects in the synapse on growth and maintenance, and on somatic processes such as neuronal survival.

A key observation is that neurotrophins can upregulate their own receptors: exposure to NGF causes a slow increase in the number of its receptors [5, 6, 7, 8, 9]. Correspondingly, the amount of receptors increases markedly as initial target contact is made [10]. Thus neurons that get a good supply of neurotrophin increase their number of receptors and become even more competent to bind neurotrophin, and so might outcompete neurons that do not. The number of neurotrophin receptors is also increased by membrane depolarization in the innervating neurons [11].

Although the notion of competition is commonly used, it is usually applied in a rather unspecified manner to cover any situation where neurons appear to hinder each other. The underlying mechanisms and the nature of the competitive process are largely unknown. Only a few formal models exist, for a few systems only, such as the neuromuscular junction [12]. In contrast, in the field of theoretical population biology the concept of competition (in the sense of different consumers competing for the same resources) is well developed, and has been studied by means of many mathematical models [13]. Benefiting from the insights obtained in population biology, we have developed a novel model to investigate the nature of neuronal competition.

2 Model

A single target is considered, at which there are n synapses, each from a different neuron. The maintenance of the synapses depends on the neurotrophic factor released by the target. Although all neurotrophins have many properties in common, the model is specifically based on NGF (nerve growth factor). We model the neurotrophin concentration (L) in the extracellular medium of the target cell, assumed to be uniform, and for each synapse i the concentration of unoccupied (R) and occupied receptors (C). The dynamics, which apply to any type of neurotrophin, are described by the following set of equations:

$$\begin{aligned}
\frac{dC_i}{dt} &= k_i^a L R_i - k_i^d C_i - \rho_i C_i \\
\frac{dR_i}{dt} &= \phi_i - \gamma_i R_i - k_i^a L R_i + k_i^d C_i \qquad (1) \\
\frac{dL}{dt} &= \sigma - \delta L - \textstyle\sum_{j=1}^{n} (k_j^a L R_j - k_j^d C_j),
\end{aligned}$$

There are parameters for the rate of neurotrophin release (σ), degradation and diffusion away of neurotrophin (δ), production of receptors (ϕ), turnover of unoccupied receptors (γ), association and dissociation of neurotrophin to the receptor (k^a and k^d), and degradation of the occupied receptor (ρ). As the functional response of neurotrophins is mediated by receptor activation (see Introduction), the state of a synapse is determined by the amount of occupied (i.e., activated) receptor, C; if $C = 0$ the synapse cannot be maintained.

As exposure to neurotrophins has been found to upregulate their own receptors, the production rate of receptors, ϕ, is not a fixed parameter but a dynamical variable that changes in response to neurotrophin. We model it with

$$\tau \frac{d\phi_i}{dt} = f_i(C_i) - \phi_i, \tag{2}$$

where $f_i(C_i)$ is the dose-response function determining the steady-state value of ϕ_i. The time constant τ is of the order of many hours or even days, reflecting the fact that the number of receptors changes slowly in response to neurotrophin, since it involves slow processes such as the expression of genes. The dynamics of C, R, and L are orders of magnitude faster, and on the time scale of the dynamics of ϕ they are essentially in equilibrium. In the analysis of the model we make a quasi steady-state approximation for these variables.

3 Results

If there were no upregulation, i.e., $f_i(C_i)$ is a constant or a decreasing function, all synapses would survive. Although f_i has been investigated experimentally [14], its exact functional form is not known. We therefore studied three basic and well-known types of dose-response curves consistent with upregulation. The values of the parameters of the curves could differ between innervating neurons, and may depend on, among other things, the level of their electrical activity.

Type I: monotonically increasing function. We use $f_i(C_i) = \alpha_i C_i$. We find that, generically, at most one C_i can be non-zero, i.e., at most one synapse can be maintained in equilibrium (see Appendix and Fig. 1a). This is irrespective of initial conditions or supply of neurotrophins (value of σ). Our result is analogous to the well-known "competitive exclusion" principle from population biology saying that k different resources can maximally sustain k different species ($k = 1$ in our case). The synapse with the highest value of $\beta_i \equiv (\alpha_i - \rho_i)k_i^a / \gamma_i \delta(k_i^d + \rho_i)$ will outcompete all others. It can, however, never be maintained in equilibrium if $\beta_i \leq 1/\sigma$.

Competitive exclusion could explain that during development cells lose all but one of their innervating axons, as is the case for skeletal muscle, cerebellar Purkinje cells, and autonomic ganglion cells lacking many dendrites.

Type II: Michaelis-Menten function. This dose-response curve, described by $f_i(C_i) = \alpha_i C_i/(K_i + C_i)$, is also monotonically increasing but gradually saturates towards an upper bound. Depending on the parameter settings, either one synapse will survive (competitive exclusion), or, which is now also possible, several different synapses (coexistence, see Fig. 1b). The more synapses can coexist the larger σ and the smaller K_i. In the limiting case, all synapses will survive. Again, there is no dependence on initial conditions. For large K (with values of α increased correspondingly), the model becomes equivalent to the model with the type I curve. When only one synapse survives, it will the one with the highest value of $\beta_i' \equiv (\alpha_i/K_i - \rho_i)k_i^a/\gamma_i\delta(k_i^d + \rho_i)$. A synapse can, however, never be maintained in equilibrium if $\beta_i' \leq 1/\sigma$. The order in which synapses survive if σ is increased is determined by the values of β_i'.

A type II curve could explain that, in addition to single innervation, many kinds of neurons retain several input axons.

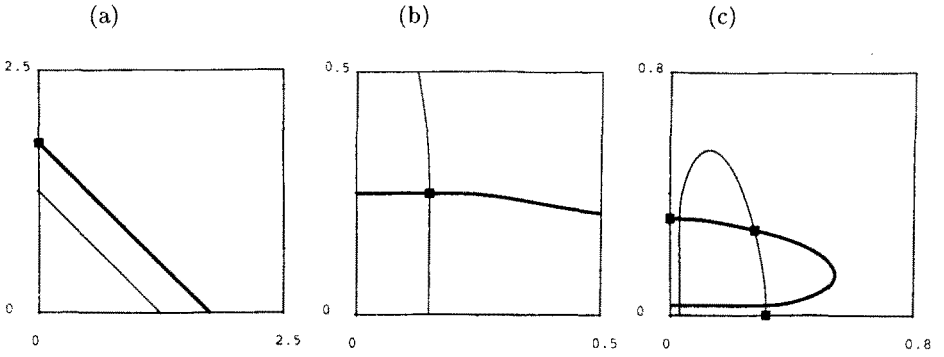

Fig. 1. For $n = 2$ the nullclines $\frac{d\phi_1}{dt} = 0$ (thin line) and $\frac{d\phi_2}{dt} = 0$, with quasi-steady state conditions of the other variables; x-axis: ϕ_1, y-axis: ϕ_2; ■ indicate stable equilibrium point. **a.** Type I: competitive exclusion. **b.** Type II: coexistence. **c.** Type III: coexistence and exclusion. Notice that $\phi_i = 0$ means $C_i = 0$.

Type III: sigmoidal function. We use the Hill equation, $f_i(C_i) = \alpha_i C_i^m/(K_i + C_i^m)$ with a Hill coefficient, $m = 2$, which also saturates but has a particularly low response at low C. Independent of the parameter settings, for each synapse there is a stable equilibrium point where only this synapse is present and all others are extinct. In contrast to the case with the type II function, coexistence equilibrium points can be present at the same time (see Fig. 1c), depending on the parameter settings. Which equilibrium point is approached, a coexistence equilibrium point (if present) or one where only one of the synapses survives, depends on the initial values of ϕ_i. The nullcline configurations (Fig. 1c) are similar to those found in the dual constraint model of the neuromuscular junction [12], which describes competition among motor neurons in the innervation of muscle fibres. Changing the values of β_i' changes the basin of attractions of the equilibrium points.

Electrical activity. For a neuron i the actual values of the parameters of the dose-response function, as well as those of the other parameters, will depend on, among many other things, the level of the neuron's electrical activity. Membrane depolarization increases the number of receptors [9], which implies a higher ϕ_i (and thus a higher α_i or lower K_i), or a lower γ_i. A high level of activity thus means a high β_i (β_i'), giving active innervating neurons a competitive advantage.

With both Type I and Type II curves, a synapse can displace existing synapses if its value of β_i. is higher. As a consequence, the average value of β_i and the level of electrical activity for the surviving synapses will increase during development. This selection process is reminiscent of a competitive mechanism for affinity selection of T-cell clones for antigen during the course of an immune response. With a Type III curve a synapse with a higher β_i' can also invade provided its initial value of ϕ_i is high enough.

4 Discussion

The model shows how the dynamics of neurotrophin signalling leads to neuronal competition. The model integrates other models of competition (e.g. [12] and [15]), and opens up an important area of neurobiology to the concepts from population biology. Notice that our model involves a continuous supply of neurotrophin (resource) that is used up and constantly required by the synapses. Models that are based on a fixed amount of neurotrophin that becomes divided up, however, also falls into our general framework. We obtain this by choosing $\sigma = \delta = 0$, and $\rho_i = 0$ for all i, and thus having the conservation law $L = L_0 + \sum_i^n C_i$, where L_0 is the total amount of neurotrophin. With this choice, we obtain very similar results for all types of dose-response curves.

The nature of the competitive interactions is determined by the way neurotrophins regulate their own uptake. Experimental studies should focus on measuring this, also for other neurotrophins than NGF. Differences in dose-response functions for different cell types or neurotrophins could explain different innervation patterns.

To illustrate the main points, we studied simplified neurons without explicitly modelling neuritic extensions. Target neurons with an extensive dendritic tree, resulting in a non-uniform distribution of neurotrophin through local release, local uptake and diffusion, may mitigate competition. In this way, the morphology of the dendritic tree could also determine the pattern of innervation.

5 Appendix

Making a quasi steady-state approximation for L, R, and C (i.e., $\frac{dL}{dt} = \frac{dR}{dt} = \frac{dC}{dt} = 0$) yields $\phi_i = C_i[\rho_i + b_i/(\sigma - a)]$, where $a = \sum_j^n \rho_j C_j$ with n the total number of synapses, and $b_i = \gamma_i \delta(k_i^d + \rho_i)/k_i^a$. We consider the dose-response function $f_i(C_i) = \alpha_i C_i$. In equilibrium all synapses i have to satisfy $\frac{d\phi_i}{dt} = 0$, and thus for each i (using the quasi steady-state expression for ϕ_i), $C_i = 0$ or

$\alpha_i - \rho_i - b_i/(\sigma - a) = 0$. When considered for all i, the latter equation is a linear system of n equations in one unknown, a. Generically, at most one of these can be satisfied. Hence, at most one C_i can be non-zero, i.e., at most one synapse can be maintained in equilibrium.

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