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Competition for tubulin between growing neurites during development

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Abstract

At its tip—called growth cone—a neurite is elongated by the assembly of tubulin into microtubules. We present a model of elongation (extended from Van Veen and Van Pelt, Bull. Math. Biol. 56 (1994) 249–273) in which tubulin is produced in the soma and transported to the growth cone by diffusion and active transport. The model accounts for competition observed between growing neurites of the same neuron and for 'dormant growth cones', and shows that cessation of growth in one neurite—e.g., when it encounters a target—can trigger the growth of the other neurites. The model makes testable predictions for the time course of outgrowth and the concentration of tubulin during competition. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Competition; Tubulin; Neurite outgrowth; Development; Morphology

1. Introduction

During development, neurons become assembled into functional networks by growing out axons and dendrites (collectively called neurites), which connect synaptically to other neurons. Neurite outgrowth—and the processes that influence it, e.g., electrical activity—therefore play a central role in determining what patterns of connections will develop. Despite the importance of neurite outgrowth, only relatively few formal models exist, most of which describe outgrowth and branching only in a statistical manner [7]. These statistical models do not clarify how the biological mechanisms involved in neurite outgrowth—the dynamics of the tubulin and

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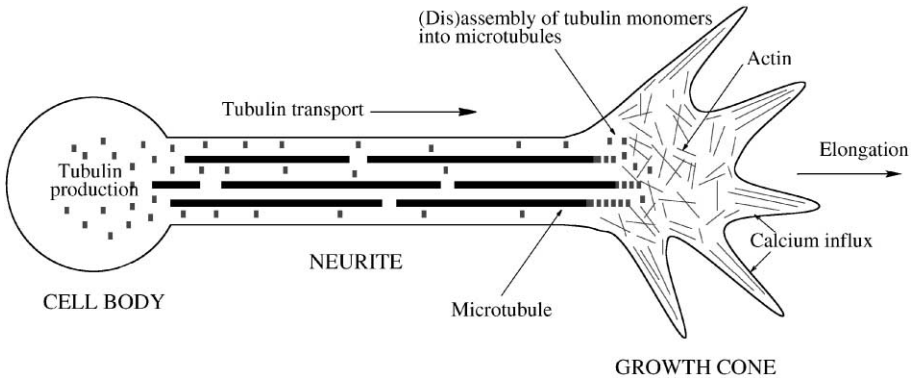

Fig. 1. The biology of neurite outgrowth. See further text.

actin cytoskeleton—may lead to the generation of neuritic structures; these models are therefore less amenable to direct experimental testing. Extending and further analysing an earlier model [8], we present a model that describes neurite outgrowth as the result of tubulin dynamics.

2. Biology of neurite outgrowth

The length of a neurite is determined by its microtubules, which are long polymers of tubulin present throughout the entire neurite (Fig. 1). Tubulin monomers are produced in the cell body and are transported down the neurite to the growth cone, which is a specialised structure at the tip of a growing neurite. In the growth cone, assembly of tubulin monomers elongates the microtubules and therefore the neurite. The rates of assembly and disassembly of tubulin are influenced by the actin cytoskeleton in the growth cone, by microtubule associated proteins (MAPs), and by (activity-dependent) changes in the calcium concentration [3,4].

3. Model

The model describes neurite elongation and retraction as the result of respectively assembly and disassembly of microtubules. We consider a simple compartmental model of a single neuron with n different neurites (Fig. 2). There is one compartment for the cell body and one compartment for the growth cone of each neurite. We model the time-dependent changes of the neurite length L_i ($i = 1, \ldots, n$), the concentration C_0 of tubulin in the cell body, and the concentration C_i of tubulin in the growth cone. Tubulin is produced in the cell body, at rate s, and is transported into the growth cones of the different neurites by diffusion and active transport, with diffusion constant D and rate constant f, respectively. At the growth cones, concentration-dependent assembly of tubulin into microtubules takes place, which elongates the

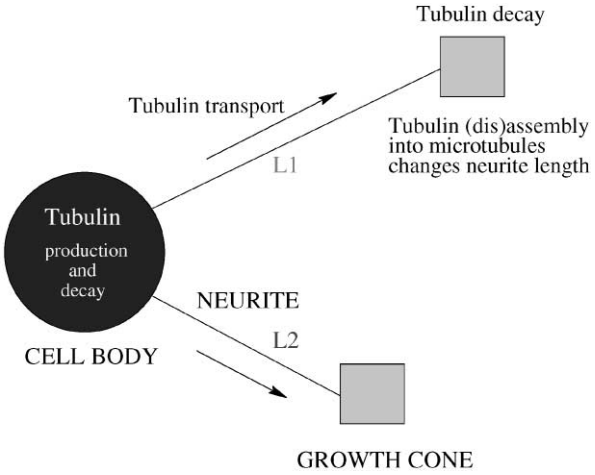

Fig. 2. The compartmental model of a single neuron with two neurites. See further text.

trailing neurite. Disassembly of microtubules into tubulin causes the neurite to retract. The rate constants a_i and b_i for assembly and disassembly, respectively, are typically different in different neurites, e.g., as a result of differences between neurites in electrical activity (which affects the concentration of intracellular calcium), in the actin cytoskeleton of the growth cones, or in the state or concentration of MAPs. Finally, tubulin is also subjected to degradation, with rate constant g, both in the cell body and in the growth cone. Thus, the rates of change of L_i, C_i, and C_0 become

$$\frac{\mathrm{d}L_i}{\mathrm{d}t} = a_i C_i - b_i, \tag{1}$$

$$\frac{\mathrm{d}C_i}{\mathrm{d}t} = b_i - a_i C_i + \frac{D}{L_i + k}(C_0 - C_i) + fC_0 - gC_i, \tag{2}$$

$$\frac{\mathrm{d}C_0}{\mathrm{d}t} = s - \sum_{i=1}^{n} \frac{D}{L_i + k}(C_0 - C_i) - \sum_{i=1}^{n} fC_0 - gC_0, \tag{3}$$

where k is the distance between the centres of the cell body and the growth cone compartment when $L_i = 0$. In [8] there is no degradation of tubulin—which is biologically not plausible and which makes the mathematical analysis more difficult—and no active transport of tubulin. We analysed the model by means of phase–plane analysis, bifurcation analysis, analytical tools, and simulation.

4. Results

Competition between growing neurites for tubulin can occur for a wide range of parameter settings. If one of the neurites has a higher rate constant for tubulin

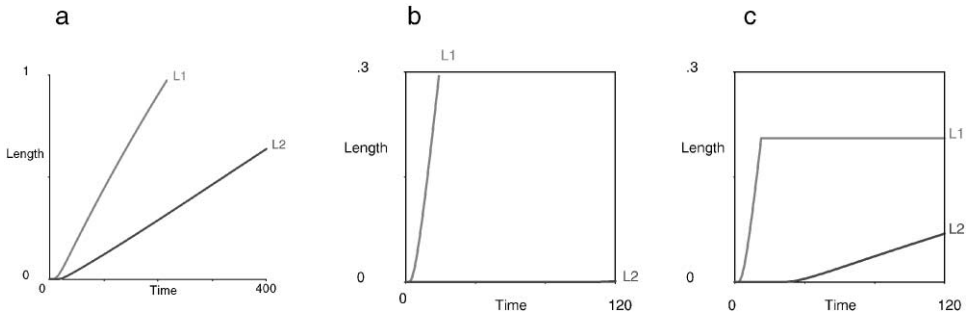

Fig. 3. Results of the compartmental model of a single neuron with two neurites. Neurite 1 has a higher rate constant for tubulin assembly. As a result, neurite 1 can slow down (a) or even prevent (b) the growth of the other neurite. Stopping the growth of neurite 1 triggers the growth of the other neurite (c). Parameters (all units arbitrary): $b_1 = b_2 = 0.01$, $D = 0.5$, $g = 0.1$, $s = 0.07$, $f = 0$, and $k = 1$. In (a), $a_1 = 0.09$ and $a_2 = 0.06$. In (b) and (c), $a_1 = 0.3$ and $a_2 = 0.05$.

assembly and/or a lower rate constant for disassembly, it can slow down (Fig. 3a) or even prevent (Fig. 3b) the outgrowth of the other neurites for a considerable period of time (i.e., they are 'dormant'), by using up all the tubulin produced in the soma (also reported in [8]). Only after the fastest growing neurite has reached a certain length can the tubulin concentration in the growth cones of the other neurites increase, causing them to grow out. The smaller the rate of production of tubulin in the cell body, the longer this period of dormancy.

Stopping the outgrowth of the fastest growing neurite (e.g., representing the physiological situation that a neurite has reached its target) can 'awaken' the dormant growth cones, which then, after a characteristic delay, start growing out (Fig. 3c). The length of the delay is determined by the time it takes for the tubulin concentration to build up to the value where the rate of assembly ($a_i C_i$) is bigger than the rate of disassembly (b_i).

Preliminary results show that the higher the relative contribution of the active component (parameter f) to the transport process, the smaller the competitive effects.

The model can account for the occurrence of 'dormant growth cones' [1] and for recent experimental findings in tissue culture (G.J.A. Ramakers, unpublished results), which show competitive effects between elongating neurites of the same neuron: (i) when one neurite stops growing out, other neurites—after a certain delay, as in the model—start growing out; and (ii) when more neurites are growing out at the same time, the rate of outgrowth is smaller than when only a single neurite is growing out.

5. Discussion

Competition between growing neurites emerges in the model as a result of the interactions between tubulin-mediated neurite elongation and transport of tubulin produced in the cell body. In more detailed compartmental models [2], in which each

neurite is divided into many compartments, we found very similar results as those reported here.

The model can account for recent experimental findings which show competitive effects between elongating neurites of the same neuron (G.J.A. Ramakers, unpublished results). To test whether this is indeed due to competition for tubulin, as our model suggests, we are planning to monitor the concentration of tubulin in growth cones during outgrowth. The model can predict what the concentration of tubulin should be during competition, and can also predict the time course of outgrowth following cessation of outgrowth in other neurites.

Our results are also relevant for understanding the formation of nerve connections, by showing how changes in the growth of a subset of a neuron's neurites (e.g., as a result of changes in electrical activity, or as a result of neurites finding their targets) can affect the growth of its other neurites. In general, competition for resources—between neurites of the same neuron as studied here or between neurites of different neurons for target-derived resources [5,6]—plays an important role in the development of neuronal connectivity.

The present work is part of an ongoing project to develop biologically realistic models for the development of neuronal morphology.

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