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Compartmental models of growing neurites

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Abstract

To investigate the morphological and electrical development of neurons using computer models it is useful to extend the compartmental modelling framework to include the situation where neurites (dendrites and axons) may change their length, diameter and membrane characteristics over time. This requires changing the size and other properties of existing compartments and adding new compartments during a particular computer simulation. We have been concerned with modelling the outgrowth of neurites when elongation and branching are controlled by the concentration of a substance in the growth cones. The substance is produced in the soma and diffuses or is actively transported along the growing neurites. We describe the technical issues involved in the compartmental modelling of this situation.

Keywords: Neuronal morphology; Dendrites; Compartmental models

1. Introduction

Our knowledge of the detailed functioning of neurons is likely to be enhanced if we can further understand the development of neuronal morphology and intrinsic neuronal properties. To this end we have been concerned with modelling the neurobiological mechanisms underlying the morphological development of neurons. This has

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necessitated the use of compartmental models for growing neurites (dendrites and axons) in which compartments are added, deleted and change in size over time. This contrasts with the static compartmental modelling framework used when simulating the electrical properties of mature dendritic trees. Our models also involve simulating the production, decay, diffusion and active transport of molecules along the growing neurites. Problems can arise in this compartmental modelling framework with the conservation of material and the stability of concentrations during transport, particularly with diffusion. In this paper, we consider some of the technical issues involved in such simulations. Examples from models of the outgrowth and branching of neurites are given.

2. An elongation model

A simple model of an elongating neurite was used to investigate how to simulate neurite development using a compartmental model. The situation consists of a single, unbranched neurite growing at a rate determined by the concentration of a substance at the neurite tip. This substance is produced in the cell body and diffuses down the growing neurite. The concentration of the substance is affected by a constant rate of decay in the soma and at the tip, and it is additionally consumed by the growth process at the tip. This particular model of neurite growth is set up in such a way that the length of the growing neurite can be calculated numerically without the need for a compartmental model. Thus, we have a baseline against which to check the accuracy of compartmental models.

For the compartmental model of the growing neurite, the equations describing the concentration in any compartment and the rate of change in length are:

$$\text{Soma:} \quad \frac{dC_0}{dt} = I - \gamma_0 C_0 + \hat{D}_{0,1}(C_1 - C_0), \tag{1}$$

$$\text{Intermediate:} \quad \frac{dC_i}{dt} = \hat{D}_{i,i-1}(C_{i-1} - C_i) + \hat{D}_{i,i+1}(C_{i+1} - C_i), \tag{2}$$

$$\text{Terminal:} \quad \frac{dC_n}{dt} = -\gamma_n C_n + \hat{D}_{n,n-1}(C_{n-1} - C_n) - \alpha_n C_n + \beta_n, \tag{3}$$

$$\frac{dL}{dt} = \alpha_n C_n - \beta_n, \tag{4}$$

where $\hat{D}_{ij} = DA_{ij}/V_i\Delta x_{ij}$ is the effective diffusion rate into compartment i from compartment j, A_{ij} is the cross-sectional area between the compartments, V_i is the volume of compartment i, Δx_{ij} is the distance between the centres of each compartment and D is the diffusion rate.

A number of questions arise when implementing a compartmental model of this situation: how long should individual compartments be? how should elongation take place? where should elongation take place?

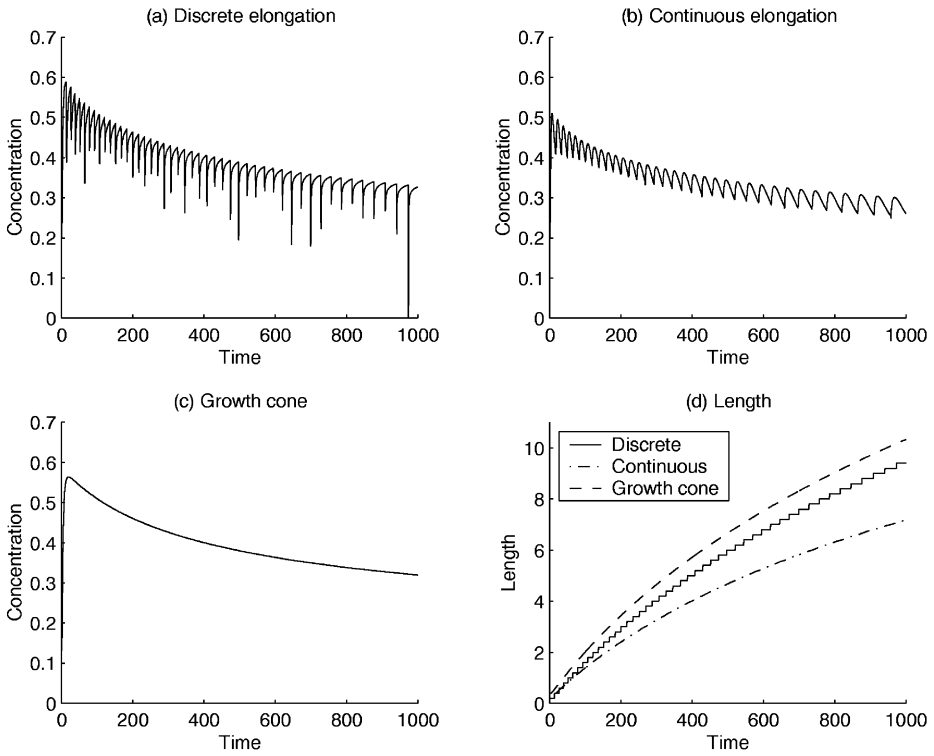

Fig. 1. Simulation of growth of a single neurite using three different compartmental modelling schemes. (a)–(c) show concentration over time of the growth-determining substance in the terminal tip for the different schemes (note that the transients to zero in (a) are truncated due to the data storage resolution). (d) shows the length of the neurite over time for the three schemes. In all cases, diameter = 1.0 throughout, $\Delta x = 0.2$, $I = 0.5$, $\gamma_0 = \gamma_n = 0.4$, $\alpha_n = 0.05$, $\beta_n = 0.01$, $D = 0.5$, $\mathrm{d}t = 0.04$ (all units arbitrary).

For this model, the only quantity of interest is the concentration of the growth-determining substance along the neurite. Thus, the first question is largely answered by the need for diffusion of the substance along the neurite to be numerically stable, if its concentration is to be calculated at, say, the midpoint of each compartment. Using simple forward Euler integration to determine the concentration of the substance in each compartment, then for a given compartment length, Δx, a suitably small integration time step, $\mathrm{d}t$ is determined by the rate of diffusion, D, so that $\mathrm{d}t < \Delta x^2/2D$. How and where elongation should take place is less obvious and three different schemes were tried:

Discrete elongation (*DE*): All compartments have a fixed length, Δx. The terminal compartment accumulates required length changes at each time step until such changes reach Δx, at which time a new terminal compartment of length Δx is added. To conserve the amount of growth-determining substance in the neurite, the concentration of the substance in the new compartment is initially zero.

Continuous elongation (*CE*): All compartments have a fixed length, Δx, except the terminal compartment which elongates at a rate determined by the concentration of the substance there. Once the terminal compartment's length reaches $2\Delta x$ it is split into two compartments, each of length Δx.

Growth cone (*GC*): The terminal compartment has fixed length Δx and can be regarded as equivalent to the growth cone. The immediately proximal compartment elongates as per DE. All other compartments have fixed length, Δx.

An example of the results from the different schemes is shown in Fig. 1. The DE scheme has the desirable property that all diffusion calculations are over the same length, Δx, and all concentration calculations are for fixed volumes. It has the less desirable property of the instantaneous creation of a terminal compartment containing none of the diffusing substance. Thus a trace of the terminal concentration over time contains frequent transients to and from zero. CE addresses this issue but introduces both a variable length for diffusion calculations and a variable volume for concentration calculations in the terminal compartment. This produces small oscillations in the terminal concentration and, more importantly for this model of growth, results in a lower average terminal concentration with a consequently shorter neurite than that produced by DE. The GC scheme addresses this problem by retaining a fixed volume terminal compartment. This scheme produces neurites of the same total length as DE, but with a very stable terminal concentration.

While other schemes are certainly possible, these three variations highlight the problems that must be considered when building a compartmental model of growing neurites. For this model, gradually incrementing particular compartment lengths, rather than instantaneously adding new compartments of some fixed length, removes large transients in the substance concentration, but care is needed in where the elongation takes place. GC produces the best results and may be most realistic in that actual growing neurites are tipped by a growth cone with elongation taking place behind it. Numerical calculations of neurite length confirm that DE and GC produce accurate steady-state lengths.

This simple growth model actually captures certain features seen in the growth of real neurites, such as apparent competition for growth between two branches supplied by the same source of growth-determining substance. This is explored in detail in van Ooyen et al. [1].

3. A branching model

We have used this style of developmental compartmental modelling to simulate an elongating and branching dendritic tree in which now the diffusing substance controls the probability that a terminal will branch, rather than the rate of elongation. As with the above elongation model, the substance is produced in the cell body and diffuses along the growing tree. It decays in the cell body and in the terminal tips. Any terminal will bifurcate in a discrete time step with a probability proportional to the concentration of the substance in the terminal. Each terminal branch elongates at some fixed

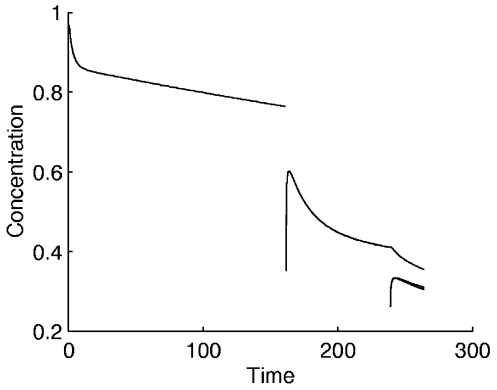

Fig. 2. Concentration over time of the branch-determining substance in the terminal tips. Neurite initially contains a single branch which bifurcates at around time 170. One of these daughter branches then bifurcates at time 230. Diameter = 1.0 throughout, $\Delta x = 1.0$, $I = 1.0$, $\gamma_0 = 0.45$, $\gamma_n = 0.55$, $\alpha_n = \beta_n = 0$, $D = 60$, $K = 0.032$, $dt = 0.005$ (all units arbitrary).

rate. Thus this model is described by Eqs. (1)–(3) above, plus the probability that terminal n will branch at time t: $P_n(t) = KC_n(t)$.

The compartmental model used to simulate this is based on the GC scheme. Terminal compartments have fixed size and elongation takes place at a fixed rate by changing the length of the compartment immediately proximal to each terminal. A branching event results in the terminal compartment being replaced by four new compartments, consisting of a terminal and proximal compartment for each of the two new daughter branches. The amount of branch-determining substance in the old terminal compartment is divided equally between the four new compartments. An example of the terminal concentrations over time in a growing tree are shown in Fig. 2.

This scheme introduces a number of artifacts. A branch event takes place within a single time step and results in daughter branches with a certain minimum length. This is necessary to provide, for each new branch, both a growth cone in which to measure the concentration of the branch-determining substance and a proximal compartment that elongates as the branch grows. It also ensures stability of diffusion as diffusion lengths are never too small. However, this introduction of new compartments with each branching event instantaneously increases neurite volume and results in large transients in the terminal concentration, as with the DE scheme. These transients quickly settle and hopefully do not significantly distort the final form of the tree. While in reality the formation of new branches takes a finite time, dendritic branches do apparently have a certain minimum length [3].

Data from real dendritic trees often indicate a decrease in branching probability with the increasing number of terminals in the tree and with the number of branch points between a particular terminal and the cell body [2]. Such competitive effects between different branches are seen in this compartmental model due to the differential diffusion of the controlling substance from its source in the soma to the terminal tips.

4. Conclusions

Care is required in the construction of a compartmental model of a growing neurite to ensure that the elongation of compartments and addition of new compartments are handled sensibly within the context of the variables that need to be calculated accurately. Here, we have been concerned with the diffusion of a growth- or branch-determining substance along a growing neurite. Other transport mechanisms, such as fast and slow active transport, need also to be considered for modelling neuritic development. The use of implicit integration schemes, such as would be needed if the simulation of electrical properties was included, would require efficient schemes for the reconstruction of the coefficient matrix every time a compartment was added or deleted. In summary, compartmental modelling of neuronal development introduces new computational concerns beyond those addressed in the standard compartmental modelling framework.

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