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Oscillations in a neurite growth model with extracellular feedback

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HIGHLIGHTS

- A new model of neurite outgrowth accounting extracellular signalling is proposed.
- The model predicts three different scenarios of the neurite development.
- It has been demonstrated that the elongation dynamics is angle-specific.

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ABSTRACT

We consider the influence of extracellular signalling on neurite elongation in a model of neurite growth mediated by building proteins (e.g., tubulin). The tubulin production dynamics were supplied by a function describing the influence of extracellular signalling, which can promote or depress neurite elongation. We found that this extracellular feedback could generate neurite length oscillations consisting of a periodic sequence of elongations and retractions. The oscillations prevent further outgrowth of the neurite, which becomes trapped in the non-uniform extracellular field. We analysed the characteristics of the elongation process for different distributions of attracting and repelling sources of the extracellular signalling molecules. The model predicts three different scenarios of neurite development in the extracellular field, including monotonic and oscillatory outgrowth, localised limit cycle oscillations and complete growth depression.

1. Introduction

Neural development and dendritic morphogenesis underlie the formation of specific network structures, synaptic connectivity and information processing in the brain [1–4]. Abnormalities in neuronal development and regeneration are implicated in several neurological disorders, such as autism, schizophrenia and epilepsy [5–9]. The generation of certain morphological patterns involves complex intracellular molecular cascades that are modulated by extracellular signalling. Neurite elongation and branching lead to the formation of specific dendritic patterns, guided by extracellular growth factor molecules released by the other cells. The most significant neurotrophic factors that stimulate neurite outgrowth are GDNF, BDNF and NGF [10,11,12]. An inverse process called retraction is also important for the development and functioning of the nervous system. Retraction may be caused by lysophosphatidic acid [13] and some types of signalling molecules, such as semaphorins, netrins, and ephrins [14,15]; glutamate [16]; and others [17]. The elongation process depends on building proteins (e.g., tubulin, actin) produced in the cell soma. Those proteins are transported to the growth cone by diffusion and active transport and then assembled in microtubules, resulting in elongation of the neurite. In the extracellular space, the neurite is guided by growth factors, which provide a direction for its growth. Neurite growth can also be influenced by many other factors, including cell adhesion and binding to extracellular matrix components [18,19].

Many mathematical models have been proposed to simulate neural development features (reviewed in [4]). Based on microtubule assembly and depolymerisation, these models describe the production, degradation, and transport processes of proteins construction. The neurite length dynamics of these models are based on the evolution of tubulin concentration in the neurite compartments including the growth cone [20–22] or the evolution of the tubulin spatial concentration profile along the neurite [23,24], or the models have focused on the description of the mechanical properties of the neurite outgrowth [19,25,26]. The model of neurite outgrowth

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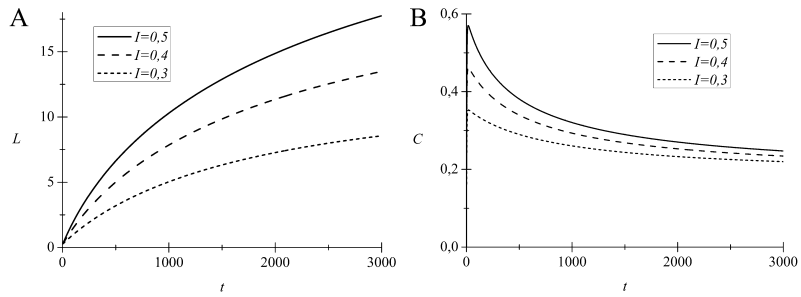

Fig. 1. Evolution of the neurite length (A) and tubulin concentration (B) in the growth cone for different values of the tubulin production rate. Parameter values: $d = 0.2$, $\gamma_0 = \gamma = 0.4$, $\alpha = 0.05$, $\beta = 0.01$, $D = 0.5$, $l1 = 0.1$, $\Delta t = 0.01$ (all units arbitrary).

proposed in [27] is based on the assumption that the elongation can be controlled by membrane expansion and endocytosis. Depending on the coupling between the microtubules and the vesicle dynamics, different regimes corresponding to dendritic and axonal growth were found. The models mentioned above merely incorporated intracellular processes that underlie the outgrowth. The extracellular signalling described in other modelling studies accounts for different aspects of neural morphogenesis, such as neurite branching and navigation (e.g., [28]). However, the extracellular influence on the elongation and retraction processes remains poorly understood.

In this letter, we propose a neurite growth model that is capable of neurite elongation and retraction, driven by extracellular signalling. Such signals coming from the extracellular space may activate specific pathways that regulate different aspects of neuronal development (axon and dendrite growth), synapse formation and plasticity [29]. To model the intracellular dynamics, we used the tubulin-based compartmental model [22]. The extracellular signals are treated as a non-uniform field of molecules released by neighbouring cells and sensed by the growth cone. We assume that these molecules generate a feedback signal, which changes the rate of tubulin production. These changes depend on the type of extracellular molecules (whether they attract or repel the growth and, hence, promote or depress it). We analysed the computational consequences of this extracellular feedback and found that it could significantly affect the growth dynamics. In particular, certain extracellular concentration profiles may induce spontaneous neurite length oscillations. These oscillations may delay neurite growth, or the neurite may be completely trapped, oscillating with a particular frequency in a specific region of space.

2. Materials and methods

We investigate the tubulin-based compartmental model proposed in [22], supplied with extracellular feedback as follows:

$$\begin{cases} \dfrac{dC_0}{dt} = I - \gamma_0 C_0 + \hat{D}_{01}(C_1 - C_0); \\ \dfrac{dC_i}{dt} = \hat{D}_{i,i-1}(C_{i-1} - C_i) + \hat{D}_{i,i+1}(C_{i+1} - C_i); \\ \dfrac{dC_n}{dt} = -\gamma_n C_n + \hat{D}_{n,n-1}(C_{n-1} - C_n) - \alpha \cdot C_n + \beta; \\ \dfrac{dL}{dt} = \alpha \cdot C_n - \beta; \\ \dfrac{dI}{dt} = -\delta(I - I*) + F(S(x,y,t)). \end{cases} \quad (1)$$

Here, the variable C_i describes the concentration of available (free) tubulin in the ith segment of the neurite ($i = 0,1,\ldots,n$), and L is the variable length of the neurite. The parameter γ determines the tubulin degradation rate, α is an association constant, β is a dissociation constant, $\hat{D}_{ij} = (DA_{ij}/V_i\Delta x_{ij})$ is the diffusion rate from segment j to segment i, A_{ij} is the cross-section area between segments, V_i is the volume of segment i, Δx_{ij} is the distance between the centres of the nearest-neighbour segments, and D is the diffusion constant.

Neurotrophic factors affect the cell metabolism via the growth cone. After binding to the receptor, they form a complex that activates PI3-kinase and Akt. Akt activation leads to the CREB-mediated synthesis of actin and tubulin, accelerating outgrowth. In the growth cone, PI3-kinase induces Ras, which is a pathway that stimulates actin polymerisation [11,12,17]. In our model, the extracellular feedback is provided by the last equation. We assume that the rate of tubulin production, I, is variable relative to an equilibrium level, I^*, with a characteristic time scale, $1/\delta$. The influence of extracellular signalling is described by the function $F(S(x,y,t))$, where $S(x,y,t)$is an effective (average) concentration of the growth factors in the growth cone at a point (x,y) in the *2D* area at a time point t. We suppose that the sources of extracellular molecules (e.g., other cells) are uniformly distributed in the *2D* area and characterised by a parameter p. These sources are divided into those that promote the growth of the neurite ($p = +1$) and those that depress it ($p = -1$), each occurring with an equal probability.

The concentration of signalling molecules diffusing from each source to the growth cone can be calculated by the following formula [30]:

$$C^f(r,t) = \frac{q}{4\pi D_1 r} \cdot \left(1 - \frac{2}{\sqrt{\pi}} \int_0^{\frac{r}{\sqrt{4D_1 t}}} e^{-x^2} dx \right), \quad (2)$$

where q describes the constant rate of growth factor production, r is the distance between the source and the growth cone, and D_1 is the diffusion rate of the extracellular signalling molecules. Examples of the extracellular signal distributions are shown in Fig. 2A–C as two-dimensional colour maps. Next, we calculate the overall influence of the molecules coming from all sources, accounting for these molecules at the growth cone location as a sum weighted by the signs, p_k, of the corresponding sources:

$$S(x,y,t) = \sum_{k=1}^{N} p_k \cdot C_k^f(r(x,y),t). \quad (3)$$

We estimate the action of this effective concentration on the growth cone by the activation function $F(S)$, here given the form of logistical curve for illustration:

$$F(S) = A\left(\frac{1}{1 + \exp\left(\frac{-2\pi(S-B)}{C}\right)} - 1/2 \right), \quad (4)$$