A mathematical model of MAP2 dependent elongation and branching in growing dendrites

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Introduction

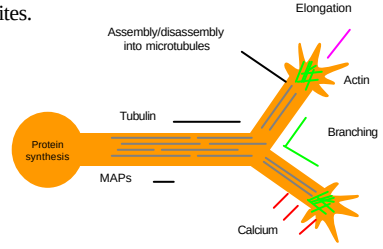
The formulation of a biophysical model of neurite elongation and branching is presented. Our model describes neurite outgrowth as a function of the ***production***, ***transport*** and (***dis***)***assembly*** of tubulin into microtubules, regulated by MAP-2 and calcium.

In the understanding of the form and function of the neuron, its development is an important factor. During growth, the major decisions are made in how to grow, where the inputs end up situated and how the neuron functions. This means that to study the neuron in its later, fully mature life, understanding how the neuron arrived in that state is an important indication of its function.

The aim is to create a multi-faceted biophysical model capable of generating proper neurite growth. This will be of use to researchers who wish to examine the growth, form, and function of developing neurons. The model serves as an important extension of previous models which are either statistical [3] and generate accurate morphologies but do not describe the biophysics of growth, or models with only a single biophysical element [4].

Foundations of the Model

The initial model is an amalgam of models of neurite elongation [2,4] and the biophysical MAP-2 dendritic branching model of Hely et al [1]. The model encompass three essential elements: *Tubulin*, *MAP-2* and *Calcium* in the dendrites.



- ***Tubulin*** is assembled into ***microtubules*** which are affected by MAP-2.
- ***MAP-2*** aids in the bundling or assembly of microtubules and can be in three states:
  - ***Unbound***, where the chemical is free to diffuse within the neurite.
  - ***Bound***, where the chemical is attached to microtubules creating bundles, essential in the elongation of the neurite.
  - ***Phosphorylated***, where MAP-2 destabilises the microtubule bundles, promoting branching of the neurite.
- ***Calcium*** determines the phosphorylation state of MAP-2

The Formulae

There are three sets of equations controlling the model. A set each for calcium, tubulin, and a larger set for MAP-2.

The calcium equations all follow the format of *Influx+(-)Diffusion-Decay.*

$$\frac{dC_i}{dt} = I + \frac{\hat{D}_C(C_{i-1} - C_i)}{dx} + \frac{\hat{D}_C(C_{i+1} - C_i)}{dx} - d_C C_i$$

The tubulin equations follow a similar pattern with the addition of active transport and production in the soma. At the neurite tips they also deal with assembly and disassembly into microtubules:

$$\frac{dT_t}{dt} = \frac{\hat{D}_T(T_{t-1} - T_t)}{dx} + aT_{t-1} - d_T T_t - a_T T_t B_t + b_T$$

The MAP-2 equations are all interdependent and are governed by conversion rates (U=unbound, B=bound, P=bound & phosphorylated):

$$\frac{dU_t}{dt} = \frac{\hat{D}_U(U_{t-1} - U_t)}{dx} - d_U U_t - c_1 U_t + c_2 B_t$$

$$\frac{dB_t}{dt} = c_1 U_t - c_2 B_t - c_3 F B_t + c_4 G P_t - d_B B_t \qquad F = \frac{C_t^2}{k_F + C_t^2}$$

$$\frac{dP_t}{dt} = c_3 F B_t - c_4 G P_t - d_P P_t \qquad G = \frac{C_t^2}{k_G + C_t^2}$$

The elongation rate in the growth cone is a function of available tubulin and bound (stabilising) MAP-2:

$$\frac{dL}{dt} = a_L T_t B_t - b_L$$

Branching probability is function of relative amount of phosphorylated MAP-2 indicating microtubule instability:

$$B_{PR} = k_B \frac{P_t}{P_t + B_t}$$

References

[1] Hely , T. Graham, B. Van Ooyen, A. 2001. A computational model of dendritic elongation and branching based on MAP-2 phosphorylation. *J. Theor. Biol.*, 210:375-384

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[3] J van Pelt and HBM Uylings, Natural variability in the geometry of dendritic branching patterns, in *Modeling in the Neurosciences: From Ionic Channels to Neural Networks*, RR Posznanski Ed (1999) Harwood, Amsterdam.

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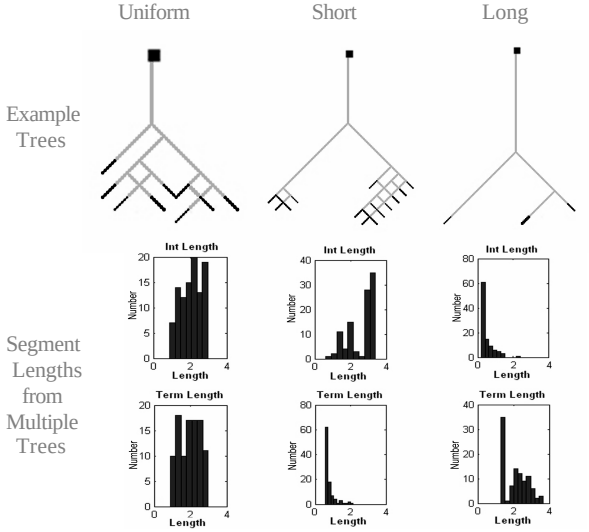
Current Results of Model

The model has been implemented and can currently generate several different topological classes with small changes in parameter values. These have been broadly classified into uniform segment lengths, short terminals with long intermediates, and long terminals with short intermediates.



Initial results from the model would suggest that one of the main factors in determining the topology of a neurite is the rate of phosphorylation of MAP-2.

These topologies have direct relations to neurites studied in vitro and in vivo. There are broad classifications of neurites which can be directly compared to those grown here such as the apical dendrite of a pyramidal neuron which equates to long intermediates with short terminals.

Conclusions

- This initial model only describes microtubule dynamics but provides a first stage in developing more complex biophysical models of neurite outgrowth.
- Details such as the relationship between MAP-2 and elongation and branching rates are largely hypothetical. Experiments that could test these elements of the model are highly desirable.
- The model indicates key components of elongation and branching.
- The final aim is to have a fully integrated 3-d environment with guidance cues, a realistic growth cone, filopodia, synapse formation.

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