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Point Process Filtering Estimates of Branching Rate for Neural Dendritic Morphology Generation

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Abstract

Current parametric approaches to dendritic morphology generation are limited in their ability to replicate realistic branching. A non-parametric approach applying a point process filter and the expectation-maximization algorithm offers a data-based solution that estimates the dendritic branching rate based on observations of bifurcation events in real neurons. Point processes can then be simulated using this branching rate estimate to indicate when a generated morphology should branch. Morphologies generated using this technique match both basic and emergent property distributions of the real neurons used as input into the algorithm. Further refinement of branching angles will allow for a flexible tool to generate realistic morphologies of a variety of neuronal stereotypes.

I. INTRODUCTION

Compartmental modeling in computational neuroscience allows for validation of our mechanistic understanding of neuronal function as well as a predictive capability for problems that are inconvenient to approach through experimentation [1]. Because the structure and function of neurons are intimately related [2], it is desirable for models to implement neuronal morphologies that are biologically accurate. Specifically focusing on the dendritic arbor, the geometry of dendritic processes will affect their electrical conductivity, the formation of synapses, and how synaptic inputs are integrated [3]. Previous stochastic methods have taken a parametric approach to morphology generation, with mixed results [4]. Here, a non-parametric approach is presented, which models dendritic branching as a point process in order to obtain an estimate of the branching rate as it varies with distance away from the soma. The resulting metrics can be used to generate morphologies of rat dentate granule cells with biologically realistic branching patterns.

II. PARAMETRIC SOLUTIONS AND THEIR LIMITATIONS

Traditional methods used to generate dendritic morphologies, such as the Hillman algorithm or Burke algorithm, take a parameter-driven flowchart approach [4]. First, a pathlength and

diameter are selected for the initial stem growing from the soma. The algorithm tests whether the dendrite should terminate or not (typically based on a diameter threshold) and if not, the dendrite then bifurcates into two daughter branches. Each daughter has an angle and pathlength selected for it from a measured distribution, and the process continues. Software tools are used to extract realistic distributions for branch pathlengths and branch angles from reconstructions of real neurons.

One issue for the flowchart approach is that it fails to account for potential interdependencies of parameters. For example, it assumes that branch pathlengths follow the same distribution regardless of where the branch is in relation to the soma. Additionally, compartment diameter is often an inaccurate marker for termination since there are some data sets in which the diameter values for the entire morphology have little variability. Given these difficulties, there is great room for improvement in parametric generation methods for dendritic morphologies.

III. METHODS

There are multiple biological mechanisms that may underlie more complicated branching dynamics that are unaccounted for by current morphology generation methods. One theory states that the dendrites choose to branch under a surplus of neurotrophic growth factors, which indicates conditions are right to send out multiple processes to attempt form synapses [5]. Other directive factors could originate from the cell body and avoidance of neighboring dendrites [6]. However, another important consideration is that the dendritic trees of granule cells will continue to change their shape even after the initial growth. Processes will extend and retract according to the potentiation of new synapses and the loss of existing ones [7]. As such, using a non-parametric approach such as a point process filter may be an effective way to capture the natural fluctuation of branching rate while still being agnostic to the exact mechanisms by which branching is determined.

A. State-Space Model

The state-space model used to model dendritic branching is a simplistic discrete Poisson-GLM of the branching rate as it relates to the bifurcation events we can observe as a point process in morphological reconstructions. It is a natural adaptation of the more common state-space model used to model neuronal spikes [8], except spikes are replaced with bifurcation events and interspike intervals are replaced with interbifurcation intervals, which is defined as the pathlength of the dendritic segment between two bifurcation points. Instead of discretizing time, this model discretizes distance: the total pathlength from the soma. Here, the state model for the log of the branching rate λ_k is assumed to be Gaussian where σ^2 is the state noise variance.

$$x_k = x_{k-1} + w \quad (1)$$

$$w = N\{0, \sigma^2\} \quad (2)$$

The observation model is a discretized Poisson process, $n_{k,r}$ that describes the number of bifurcation events that have occurred in the interval $(k, k+1)$, where R is the total number of point processes in the data set and N is the total number of bifurcations in the point process. $n_{k,r}$ is selected such that no more than 1 bifurcation event occurs in any given interval.

$$n_{k,r} = \text{Poisson}(\lambda_k \Delta) \quad (3)$$

The conditional intensity function is as follows, where μ is the log of the background branching rate and β is a gain parameter.

$$\lambda_k \Delta = \exp(\mu + \beta x_k) \quad (4)$$

B. Branch Rate Estimation

The point process filter algorithm presented in Mendel (1995) and Brown et al. (1998) [9, 10], was used to obtain an estimate of the posterior density of the branching rate. This was done via a one-step prediction and recursive nonlinear filtering to obtain the best estimate of $x_{k,k}$. Later observations of bifurcations can be helpful in estimating the branching rate at shorter pathlengths. Because of this, a fixed interval smoother was used to obtain $\bar{x}_{k|K}$.

One Step Prediction:

for $k = 1, 2, \dots, K$

$$\bar{x}_{k|k-1} = \bar{x}_{k-1|k-1} \quad (5)$$

$$W_{k|k-1} = W_{k-1|k-1} + \sigma^2 \quad (6)$$

Recursive Nonlinear Filter:

for $k = 1, 2, \dots, K$

$$\bar{x}_{k|k} = \bar{x}_{k|k-1} + W_{k|k-1} \sum_{r=1}^R \left[\beta (n_{k,r} - \lambda_k (\mu + \beta \bar{x}_{k|k-1}) \Delta) \right] \quad (7)$$

$$W_{k|k-1}^{-1} = W_{k|k-1}^{-1} + R \beta^2 \lambda_k (\mu + \beta \bar{x}_{k|k-1}) \Delta \quad (8)$$

Fixed Interval Smoother:

for $k = K-1, K-2, \dots, 1$

$$A_k = W_{k|k} W_{k+1|k}^{-1} \quad (9)$$

$$\bar{x}_{k|K} = \bar{x}_{k|k} + A_k [\bar{x}_{k+1|K} - \bar{x}_{k+1|k}] \quad (10)$$

$$W_{k|K} = W_{k|k} + A_k \left[W_{k+1|K} - W_{k+1|k} \right] A_k^T \quad (11)$$

C. Expectation-Maximization

Estimation of the branching rate and optimization of the parameters μ , β , and σ^2 were performed recursively by using the expectation-maximization approach described in Smith and Brown, 2003 [11].

D. Morphology Generation

To randomly generate morphologies, a point process variable was simulated at the maximum branch rate. First, a Poisson process was constructed using the maximum branching rate of λ_{max} . Upon a second pass, each bifurcation event in this Poisson process was only kept with probability λ_k/λ_{max} . With neural spiking data, this technique is known as spike thinning [12].

However, because of the variability of this process, there existed the possibility that the resulting dendritic tree contains only a few initial bifurcations and nothing more. Therefore, the generated morphologies were screened so that only the morphologies with a certain number of bifurcation events were accepted. This range was based on the total number of bifurcation events present in the Claiborne data set, so the range was set from 10 to 25 bifurcations.

E. Evaluation of Performance

To evaluate the goodness of fit, a direct KS-plot comparing the time-rescaled distribution of branch occurrences was deemed inappropriate since the relatively low number of branch events made the confidence intervals extremely large. Instead, a comparison of the distributions of the emergent properties was made, which is a standard practice in evaluating the performance of morphology generation algorithms [13]. Here, the distributions of overall interbifurcation pathlengths, the total number of bifurcations per morphology, and the total dendritic length were all computed. Additionally, a Sholl analysis of the resulting morphologies was performed to compare the distribution of branches based on Euclidean distance away from the soma. This is performed by counting the number of intersections the morphology has with concentric spheres drawn around the soma at different radii, then plotting the number of intersections against the radii.

IV. DATA SET

Dendritic morphologies were taken from NemoMorpho.org [14], an online database for neuron reconstructions obtained from experimental work. In particular, a pool of 42 rat dentate gyrus granule cells from Rihm and Claiborne (1990) [15] was selected as the data set. The data was discretized using a step of 1 μm , with a maximum observation length of $N = 669 \mu\text{m}$. A separate point process was constructed for each terminal path (soma to dendritic tip) in the morphology, for a total of $R = 709$ point processes consisting of ones and zeros indicative of bifurcation events. The last bifurcation point in each point process corresponded to the terminal point, and the remaining values until the maximal point process length were set at 0.

V. RESULTS AND DISCUSSION

The expectation-maximization algorithm was performed until each parameter value converged with a tolerance of 0.001. The final parameter values were $\sigma^2 = 0.008$, $\beta = 0.858$, and $\mu = -5.489$. Using the point process filter and fixed interval smoother we obtained the estimate for the branching rate, $\lambda_k = \exp(\mu + \beta x_k)$ shown in Fig. 2. This matched our expectation that the branching rate would be higher at shorter pathlengths from the soma.

After the branch rate estimation, 50 example dendritic morphologies were generated by simulating Poisson point processes. The resulting morphologies are compared to the real Claiborne morphologies and some example morphologies produced by traditional stochastic algorithms, i.e. L-NEURON, in Figure 3. The morphologies generated using this method have noticeable improvements to early branching behavior and branch termination. Note that many of the branch angles shown in the new morphologies are fixed for demonstration purposes, since the primary concern was the branch occurrence, not the branching angles. Biologically realistic branch angles and arbor shape will be the focus of future work.

In Figure 4, which plots the histogram peaks for the distributions, it is evident that the distributions do not quite match the distributions for the Claiborne data set exactly, indicating that this model does not perform as a complete characterization of the branching behavior. But overall, the ability of this generation method to reproduce the distributions of multiple emergent properties is an encouraging result. A comparison of the interbifurcation pathlengths shows that both distributions are exponentially distributed, which lends support to the decision to model this as a Poisson process. However, the generated morphologies show an overrepresentation of shorter pathlengths. The distribution of total dendritic length shows a similar tendency for shorter branch pathlengths than the Claiborne set. The Sholl analysis for both sets of morphologies follow a similar path, indicating similar branching dynamics, but may suggest that the initial branch events are occurring later than they should in the generated morphologies. However, this metric must be viewed cautiously, since the fixed branch angles could be biasing the results. Finally, the total number of bifurcation events show a comparable distribution across the range accepted by the screening process.

One concern for the estimated branching rate was related to how the point processes were constructed from the Claiborne reconstructions. For each morphology in the data set, a

separate point process was constructed for each terminal path, i.e. the path from the soma to a particular dendritic tip. This meant that the early bifurcations were counted multiple times in the data at the exact same pathlength k . This contrasts with bifurcation events observed at pathlengths further from the soma, which would be spread out across more pathlength values since there are more unique observations. This could potentially be addressed in future work by increasing the observation variance at lower branch orders, effectively smoothing the effects of duplicate observations.

The point process approach offers a promising data- based solution towards generating realistic dendritic morphologies. Further modifications to the model, such as adding a history component based on previous bifurcation events or adding a neighbor component that takes into account when neighboring branches decide to bifurcate, could provide more information needed to get a better estimate of the branching rate.

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Figure 1.
Bifurcation events modeled as a point process with discretized pathlength. The last bifurcation event to occur is the branch termination.

Figure 2.

Estimated branching rate, $\lambda_k = \exp(\mu + \beta x_k)$ as it varies with pathlength from the soma.

Granule Cell Morphologies (Claiborne 1990)

Comparable L-Neuron Morphologies

New Morphologies

Figure 3.

Example morphologies, both reconstructed from histological measurements and generated stochastically. In the new morphologies, the occurrence of bifurcation events obtained by spike thinning a maximum rate Poisson process according to the λ_k/λ_{max} values from Fig. 2.

Figure 4.

A comparison of various distributions of the new generated granule cell dendritic morphologies (dashed) and the real Claiborne data set (solid). A: Interbifurcation pathlengths. B: Total Dendritic Length. C: Sholl Analysis. D: Total number of bifurcation events.