Using the Nonlinear Dendritic Transfer Function

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Introduction

This document describes the MATLAB code used for generating a nonlinear dendritic transfer function in Singh & Zald (2015). This code takes biophysical parameters intrinsic to the dendrite such as capacitance, resistance etc. and the dendritic spacing to approximate the peak evoked somatic EPSP for desired input combinations. The basic unit of input is the induced local depolarization from a stimulus as we consider a time invariant transformation between temporally spaced input sequences (neurotransmitter binding) rather than a continuously varying input current. This condition allows dendritic responses to a stimulus set to be independent of previous and subsequent inputs permitting a direct input-output transformation as in artificial neural networks. We term this transformation the "dendritic transfer function". Based upon empirical results, transformations within a branch interact nonlinearly, while those between branches are independent mimicking a multi-layer neural network. The basic form of this transformation is a threshold corresponding to NMDA-mediated spike generation, before which the function is linear (passive propagation) and beyond which the function is highly nonlinear (concave) and saturable via the recruitment of active currents (spikes). The basis for the model is the separation of time-scales between fast-ionic (AMPAR-mediated), leak, and slow-ionic (NMDAR-mediated) responses which allow dynamics to be segregated into discrete steps based upon a known distribution of their durations. By considering input to as the AMPAR-induced depolarization rather than current, we may further restrict the model to two components: linear currents (i.e. leaky K^+) and nonlinear slow currents (NMDAR-mediated) to obtain this separation. The base equation we seek to reduce is then:

$$(1)\ C_m \frac{dV}{dt} = \frac{-V}{R_m} + \frac{g_{NMDA}(E_{NMDA}-V)}{1+Exp[-(V-V_{mid})/k_s]}$$

The Model: Constants

Users will need the following information about the neuron: membrane capacitance (C_m), membrane resistance (R_m), the functional length constant of decay (λ) and the spatial organization of the branch. We used a diameter of 1μm and a width of 10μm for basal dendrite compartments and the following parameters:

C_m=1μF/cm^2 =$\pi * 10^{-14}$F

R_m=10KΩ cm^2 = π^{-1}*$10^{11}\Omega$

Users will also need the following information regarding NMDAR channels: NMDAR reversal potential (E_{NMDA}), NMDAR conductance (g_{NMDA}), the NMDAR channel's mid-opening (V_{mid}), the opening slope (k_s) and the parameters of its (multi-exponential) opening distribution: the exponents themselves (T_{On}) and their weights (A_{On}) within the distribution. All potentials are translated so that the resting potential is zero. We used the following parameterization:

E_{NMDA}=70mV (translated from 0mV)

g_{NMDA}=3.9nS

k_s=2.5mV^{-1}

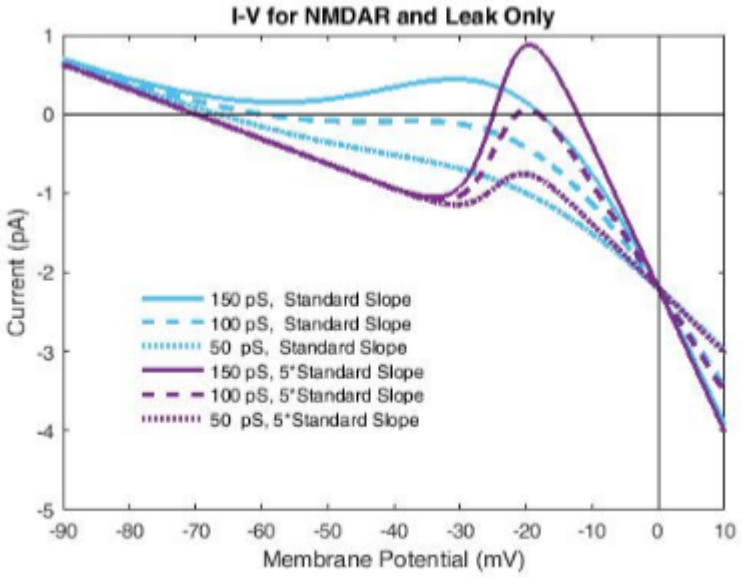
V_{mid}=46.3mV (translated from -23.7 mV)

λ=77μm

T_{On}=[4.86 28.9 7472]ms

A_{On}=[0.4474 0.2105 0.3421]

Although we do not do so in the present code, a superior strategy may be to define V_{mid} as the middle fixed point of the first equation (under Introduction). The reduction to just passive leak and NMDAR-mediated currents following initial excitatory transmission requires a decrease of k_s over the traditional value used to model the voltage-dependence of NMDA conductance in order to preserve the bistability (Figure 3D below):



Finally, users will need to describe the post-decay boundaries (b_u and b_l) and curvatures (a_u and a_l) of dendritic saturation. Generally the curvatures of either side should be equal ($a_u = a_l$). We applied a post-decay saturation boundary using parameters measured at the soma. However, it is likely that saturation occurs before the soma so the actual saturation boundary will likely be specific to distance from the soma. For instance, one choice would be the NMDAR reversal potential subjected to spatial decay. In our particular case, however, we used:

b_u=16mV

b_l=-16mV

a_u=a_l=0.5

The Model: Functions

For the model's full derivation see the original paper (Singh & Zald, 2015). However the premise may be briefly described as follows. First linear (fast ionic) currents propogate toward the soma and local depolarization consists of temporal decay within a compartment (based upon the NMDAR inter-opening distribution) and spatial decay in the accumulation of currents between compartments (based upon the functional length constant). These linear currents may be represented by a linear transformation of input determined by positions within the branch. As reported in the paper, we found that the using the same length constant for spatial for somatic propagation as with the inter-compartmental contribution to NMDA spikes underestimated the spatial dependence. As such we only used half decay with i,j denoting the synaptic sites:

$$(2)\ \ \phi\ (x_{j->i}) = e^{-\frac{2|x_i - x_j|}{\lambda}}$$

Expected temporal decay at channel opening (with n the number of components in A_{On}, T_{On}:

(3) $\phi_i = \sum_{k=1}^{n} A_k \frac{R_m C_m}{T_k + R_m C_m}$

We combine these into a constant symmetric matrix which is characteristic to the branch topology (not dependent upon activation). The vector of activations at channel opening is then the initial depolarization/synaptic input (v) multiplied by the branch's decay matrix (Φ):

(4) V_{On}=Φv

With $\Phi_{i,j}$=$\phi(x_{j->i})$ if i not equal to j and otherwise ϕ_i. In Singh & Zald 2015 we also derive the expected NMDA spike amplitude as:

(5) $V_{NMDA}(V_{On_i}) = (\frac{gE}{g+R_m^-1})\ \frac{1}{1+Exp[-[V_{On}(i)-V_{mid}+k_s ln(gR_m+1)]/k_s]}$

The decay from each synaptic site to the soma is:

(6) $\delta_i = e^{-\frac{x_{j->soma}}{\lambda}}$

We also include a soft saturation function G(V) to mimic the saturation of dendritic current:

(7) G(v)=ln(1+$e^{-a_l(V-b_l)}$)/a_l-ln(1+$e^{-a_u(V-b_u)}$)/a_u +b_l

and the final resultant somatic depolarization is the sum of linear and nonlinear components, plus saturation:

(8) $T(v) = G(\sum_{i=1}^{n} \delta_i[v_i + V_{NMDA}(\Phi v)_i])$

The Code

The code consists of 5 MATLAB files: DendTranBranch, NormalDend, LengthMat, SigZ, and Spike. DendTranBranch is the master file while LengthMat computes Φ, SigZ computes the soft boundary function G(v) and Spike computes V_{NMDA}. The function NormalDend runs DendTranBranch with some normal parameters. In addition to the parameters discussed above, the function DendTranBranch also requests the length to the soma from the branch's starting point ("branchtosoma") and the inter-stimulus interval (ISI). The ISI is only for simulating responses to paired-pulse electrodes and should otherwise be set to 0. The variable "Distance" requests a row vector containing the distance from the most proximal synapse to the branch point for the initial entry and the distance between synapses for all subsequent entries for a total length equal the number of synapses considered (n). Input is a matrix with n columns with each row corresponding to a vector of synaptic inputs at some interval of interest (i.e. time). As a transfer function, the model does not have a dependence upon the sequence of input vectors so the result is the same for running each time point separately (a single columnn vector) or simultaneously as a matrix. The master function (DendTranBranch) outputs a row vector with each entry equal the somatic depolarization due to the corresponding column of the synaptic input matrix. Parameters used in DendTranBranch should be in base units: F, S, Ω, s etc. and output is in Volts. Normal DendTran requires the following variables: Input, b_u, b_l, a_u, a_l, distance, branchtosoma, and ISI. For synapses with zero input, g_{NMDA} is always set zero so that spikes remain dependent upon neurotransmitter binding. For paired-pulse stimulation we use the method described in the paper by Gomez-Gonzalez and colleagues which we reference in the original paper. This approach gives the second pulse's NMDAR conductance as:

(9) $g_{NMDApulse}$ max(1, 1.6*(1-$\frac{ISI}{100ms}$))

We allow spikes from paired-stimulation to sum linearly prior to spatial decay with the restriction that they not pass the NMDAR reversal potential (E_{NMDA}) which forms a strict upper boundary.