

Theory and Mathematics of NemaSys

Neuronal cable theory

We describe here the theory and mathematics underlying the NemaSys simulator, for the special case in which each neuron is assumed to be a single, isopotential compartment, and the membrane resistance is assumed to be Ohmic. Assuming N neurons connected by electrical and chemical synapses, the voltage V_i of each neuron obeys

$$C_i \frac{dV_i}{dt} = -G_i^L [V_i - E_i^L] - \sum_{j=1}^N G_{ij}^E [V_i - V_j] - \sum_{\lambda} G_{ij}^\lambda(V_j) [V_i - E_i^\lambda] - I_i^S(t)$$

where the term on the left represents capacitive membrane current, involving the whole-cell membrane capacitance C . The first term on the right involves a constant leak conductance G^L , modeling the passive effects of the soma membrane, and the leak reversal potential E^L . The second term represents the current due to non-rectifying electrical (E) synapses, and involves a constant conductance G^E and the (linear) voltage difference between cells. The third term represents the current due to ion type λ , flowing across the postsynaptic membrane i due to neurotransmitter released from j . The fourth term is the current due to sensory input, which depends implicitly upon the post-synaptic membrane potential V_j as discussed below.

Connective neuroanatomy

The number of interconnections between each pair of neurons has been tabulated by White et al. (1986), and put in machine-readable form by Achacoso and Yamamoto (1992). To impose these anatomical constraints on the net synaptic connection between a given pair of cells ij , the total conductance between two neurons ij is scaled by the anatomy data

$$G_{ij}^E = N_{ij}^E g_{ij}^E$$
$$\hat{G}_{ij}^\lambda = N_{ij}^\lambda g_{ij}^\lambda$$

where N^E (N^λ) represents the number of electrical (chemical), given by the anatomy (White et al., 1986). This allows a fitness search over the average strength of single electrical and chemical synapses between each pair of cells, which is much more constrained than a search over all real conductance values. The anatomical data imply no self-synapses, thus the connection matrices N_{ij} each have zeros along the diagonal?

Synaptic physiology

It is reasonable in *C. elegans* to assume that synaptic connections are fast compared to neuronal time constants and variations in sensory input (Wicks et al. (1996), the conductance to ion type λ in the post-synaptic cell i is assumed to be a sigmoid function of pre-synaptic voltage V_j , and given by

$$G_{ij}^\lambda(V_j) = \hat{G}_{ij}^\lambda \sigma \left[\beta_{ij}^\lambda (V_j - \bar{V}_j) \right]$$

The sigmoid function we defined to be $\sigma(z) = 1/(1 + \exp(-z))$, so that the minimum conductance is zero and the maximum conductance is scaled by an overall factor. This factor represents the

total postsynaptic conductance when all the ligand-gated channels are open. We describe below why the center of synaptic activation in nematodes is a parameter tied to the presynaptic cell j only. The steepness parameter β_{ij} retains both indices for generality. Synaptic time delays may be included via a second-order differential equation, which is integrated along with the voltage degrees of freedom (Koch and Segev, 1998).

Dale's principle

Post-synaptic current flows in response to postsynaptic channel openings, and the corresponding reversal potential E^λ depends upon intracellular and extracellular ion concentrations associated with the post-synaptic cell only. To reflect this in the notation, the label λ specifies the postsynaptic ion, so that the reversal potential E^λ depends only on the post-synaptic cell, labeled by i . This physiological constraint limits the way variations in driving potential can affect cells in the network.

Each neuron may receive synaptic input from all neuron types in general. Regarding synaptic output, we assume Dale's principle: Each neuron releases only excitatory (+) or inhibitory (−) neurotransmitter. If we further make the strong assumption that there is only one ion associated with excitation, e.g., Na, and only one ion associated with inhibition, e.g., K, then there are only two corresponding reversal potentials, and each cell may be labeled according to (+) or (−). More generally, λ may index an assortment of ion currents and channel types.

Sensory currents

We are primarily interested in the behaviors of chemotaxis, thermotaxis, and mechanical touch and tap reflex. Each of these behaviors involves movement on a flat two-dimensional surface, the Petri dish environment of most nematode experiments.

In most modeling work, including our previous work on chemotaxis (Ferree et al., 1997; Ferree and Lockery, 1998; 1999), it has been assumed that currents due to sensory stimuli are proportional to the stimulus.

$$I_i^S(t) = \beta_i^S S(t)$$

This simple prescription is easy to introduce, but is not correct because it neglects the effects of the driving potential.

A more physiological prescription is to assume that the membrane conductance is a sigmoidal function of stimulus intensity

$$G_i^S(t) = \hat{G}_i^S \sigma[\beta_i^S S(t)]$$

and that the current involves this conductance multiplied by a driving potential.

$$I_i^S(t) = G_i^S(t) [V_i - E_i^S]$$

This way of introducing sensory input has the following effect. Even if the conductance is effectively a linear function of stimulus intensity, the current involves the product of stimulus intensity and postsynaptic potential. This kind of system is nonlinear, and is sometimes referred to as bilinear. It can be shown analytically that bilinear systems have an infinite Volterra series solution, in which successive kernels are simple convolutions of the first-order linear kernel. Hence this kind of system, though nonlinear, may be amenable to analyses like those developed for linear networks (Ferree and Lockery, 1998; 1999).

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