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# Modeling Extracellular Fields for a Three-Dimensional Network of Cells using NEURON

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## Supplementary Document

### S1. Toy Neuron Model

We present here further details about the development of the toy neuron model (see section 3.5). NEURON codes for model development and for the linking of extracellular spaces, via the technique presented in this work, have been provided along with a flowchart that summarizes the various steps involved.

#### S1.1. Model Biophysics

As seen in Fig. 13, each neuron consists of a soma, axon, and two proximal dendrites, each of which divides into two distal dendrites. The soma is spherical and is attached to the axon at one end, and the two proximal dendrites at the other end. The axon has been modeled as being long and thin, with uniform diameter. The diameter of the proximal and distal dendrites is tapered with increasing distance from the soma. The morphological parameters for the neuron model are presented in table S1. The soma and the axon were endowed with Hodgkin-Huxley (HH) channels so as to enable them to produce action potentials. The dendrites were provided only passive leak channels. The reversal potential of the leak channels was set to  $-65$  mV, similar to that for the HH

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**Table S1: Morphological parameters for the toy neuron model**

Section	Parameter	Units	Value
soma	length	$\mu\text{m}$	20
	diameter	$\mu\text{m}$	20
	# of segments	-	1
axon	length	$\mu\text{m}$	1000
	diameter	$\mu\text{m}$	5
	# of segments	-	1001
proximal dendrites	length	$\mu\text{m}$	200
	diameter	$\mu\text{m}$	$2 \rightarrow 1$
	# of segments	-	201
distal dendrites	length	$\mu\text{m}$	100
	diameter	$\mu\text{m}$	$1 \rightarrow 0.2$
	# of segments	-	101

channels, thereby resulting in a resting membrane potential of around  $-65$  mV for the neuron.

### ***S1.2. NEURON Code For Creating The Individual Neurons***

The NEURON code presented below constructs a cell template, based on the biophysical parameters specified in the previous section. This template is then utilized to create two instances of the toy neuron.

```
// ***** Start of Template *****
begintemplate dummy_neuron
    public soma, axon, p_dend, d_dend
    create soma, axon, p_dend[1], d_dend[1]

    proc init() {
```

```

38     create soma, axon, p_dend[2], d_dend[4]
39     soma {
40         L = 20
41         nseg = 1
42         diam = 20
43         insert hh
44     }
45     axon {
46         L = 1000
47         nseg = 1001
48         diam = 5
49         insert hh
50     }
51     forsec "p_dend" {
52         L = 200
53         nseg = 201
54         diam(0:1) = 2:1
55         insert pas
56         e_pas = -65
57     }
58     forsec "d_dend" {
59         L = 100
60         nseg = 101
61         diam(0:1) = 1:0.2
62         insert pas
63         e_pas = -65
64     }
65
66     //Connecting all the sections together
67     //-- Axon to Soma
68     connect axon(1), soma(0)
69     //-- Primary Dendrites to Soma
70     for i = 0, 1 {
71         connect p_dend[i](0), soma(1)
72     }
73     //-- Secondary Dendrites to Primary Dendrites
74     for i = 0, 1 {

```

```

75         connect d_dend[i*2](0), p_dend[i](1)
76         connect d_dend[(i*2)+1](0), p_dend[i](1)
77     }
78 }
79 endtemplate dummy_neuron
80 // ***** End of Template *****
81
82 //Creating the Neurons
83 objref neuron[2]
84 for i = 0, 1 {
85     neuron[i] = new dummy_neuron()
86 }

```

87

### 88 ***S1.3. NEURON Code For Linking The Extracellular Fields***

89 The NEURON code below implements the coupling of extracellular fields of the two  
90 adjacent neurons, at regions where they are in close spatial proximity.

```

91 objref slist1, slist2, list_temp1, list_temp2
92 objref gmat, cmat, bvec, e, xl, layer, sl, lm
93
94 RATIO_ra_by_re = 0.01 // Specify
95 Re = Ra/RATIO_ra_by_re // Ohm.cm
96 xrxial_value = Re*1e-6/(PI*((diam/2)^2)*1e-8) // MOhm/cm
97
98 Re_Ohm = Re*1e-6*L*1e-4/(PI*((diam/2)^2)*1e-8) // MOhm
99 rlink = Re_Ohm/nseg // MOhm
100 glink = 1000/rlink // nS
101 ge_value = (glink*0.1)/area(0.5) // S/cm2
102
103 proc setExtra() {
104     forall {
105         insert extracellular
106         xc[0] = 0
107         xc[1] = 0

```

```

108
109         xg[0] = 1e-9    // Infinite Resistance
110         xg[1] = 1e-9    // Infinite Resistance
111
112         xrxial[0] = xrxial_value          // MOhm/cm
113         xrxial[1] = 1e9    // Infinite Resistance
114     }
115
116     print "_____ "
117     print "Extracellular Mechanism Inserted"
118     print "_____ "
119 }
120 setExtra()
121
122 proc setExtraLink() {
123     // connected sections in neuron 1
124     slist1 = new SectionList()
125     // connected sections in neuron 2
126     slist2 = new SectionList()
127
128     // ensure that the order is the same
129     neuron[0].axon slist1.append()
130     neuron[1].axon slist2.append()
131     neuron[0].soma slist1.append()
132     neuron[1].soma slist2.append()
133     neuron[0].p_dend[0] slist1.append()
134     neuron[1].p_dend[0] slist2.append()
135     neuron[0].d_dend[0] slist1.append()
136     neuron[1].d_dend[0] slist2.append()
137     neuron[0].d_dend[1] slist1.append()
138     neuron[1].d_dend[1] slist2.append()
139
140     nsecs = 0 // will contain total connected secs
141     forsec slist1 {
142         nsecs += nseg
143     }
144     print "_____ "

```

```

145     print "Total Connected Segments = ", 2*nsegs
146     print " _____"
147
148     gmat = new Matrix(2*nsegs, 2*nsegs, 2)
149     cmat = new Matrix(2*nsegs, 2*nsegs, 2)
150     bvec = new Vector(2*nsegs)
151     xl = new Vector()
152     layer = new Vector(2*nsegs)
153     layer.fill(1)
154
155     forsec slist1 {
156         for (x, 0) {
157             xl.append(x)    // for neuron 1
158             xl.append(x)    // for neuron 2
159         }
160     }
161
162     e = new Vector(2*nsegs)
163     sl = new SectionList()
164
165     list_temp1 = new List()
166     forsec slist1 {
167         for (x, 0) {
168             list_temp1.append(new SectionRef())
169         }
170         slist1.remove()
171     }
172     list_temp2 = new List()
173     forsec slist2 {
174         for (x, 0) {
175             list_temp2.append(new SectionRef())
176         }
177         slist2.remove()
178     }
179
180     for i = 0, nsegs-1 {
181         list_temp1.object(i).sec sl.append()

```

```

182         list_temp2.object(i).sec sl.append()
183     }
184
185     ge = ge_value // S/cm2
186
187     for (i=0; i<(2*nsegs); i=i+2) {
188         gmat.x[i][i] += ge
189         gmat.x[i+1][i+1] += ge
190         gmat.x[i][i+1] += -ge
191         gmat.x[i+1][i] += -ge
192     }
193
194     lm = new LinearMechanism(cmat, gmat, e, bvec, sl, xl,
195 layer)
196
197     print "_____ "
198     print "Extracellular Connected Via Link"
199     print "_____ "
200 }
201 setExtraLink()
202

```

203 As described in section 3.5, the neurons have been oriented such that one primary  
 204 dendrite of each of the two neurons, along with the distal dendrites emerging from  
 205 them, are considered to be at a sufficiently large distance from the other neuron to not  
 206 have their extracellular spaces affected directly by it. This constraint was imposed to  
 207 demonstrate an element of heterogeneity in the coupling of the extracellular regions of  
 208 the two neurons. The exact nature of coupling between the two neurons can be made as  
 209 complex as necessary, with the technique being amenable to any such requirements.  
 210 The toy neuron model simply being an illustrative example, we have chosen to limit its  
 211 complexity here by assigning equal coupling strengths between the various regions at  
 212 which the two neurons are in close spatial proximity. This assumes that the two



neurons maintain a constant spatial separation throughout their morphology. If the need arises for differential coupling, potentially based on the distance of separation and/or other factors, the implementation requires only a minor modification to reflect the same. In the above implementation, this would translate into the dynamic evaluation of the parameter '*ge\_value*' for each segment, with the value being a function of the distance of separation.

In the case of a network/syncytial model, variations in the boundary conditions are easily feasible within the presented framework. The extracellular boundary conditions, in NEURON, can be altered as required by modifying the values of the resistive, capacitive and voltage components (see Table 1 and Fig. 2) that define the extracellular features of each cell. Variations can be introduced, such as between peripheral and non-peripheral cells, or across the ends of a tissue/network, depending on the modeling requirements.

#### ***S1.4. Flowchart Describing Steps Followed For Toy Model***

Fig. S1 shows a flowchart that summarizes the series of steps involved in developing the toy model. The steps involved in the coupling of the extracellular spaces of the two neurons, which form the crux of the present work, have been encapsulated within the dashed box. The only main prerequisite is to have the models of the individual neurons that need to be coupled extracellularly. The various stages, and also the terminology used for the various parameters (in red), are closely linked to the NEURON code presented in the previous section. Certain stages in the workflow have been represented via colored boxes, and these correspond to the stages where user input is required. The other stages are capable of continuing in their default configuration,

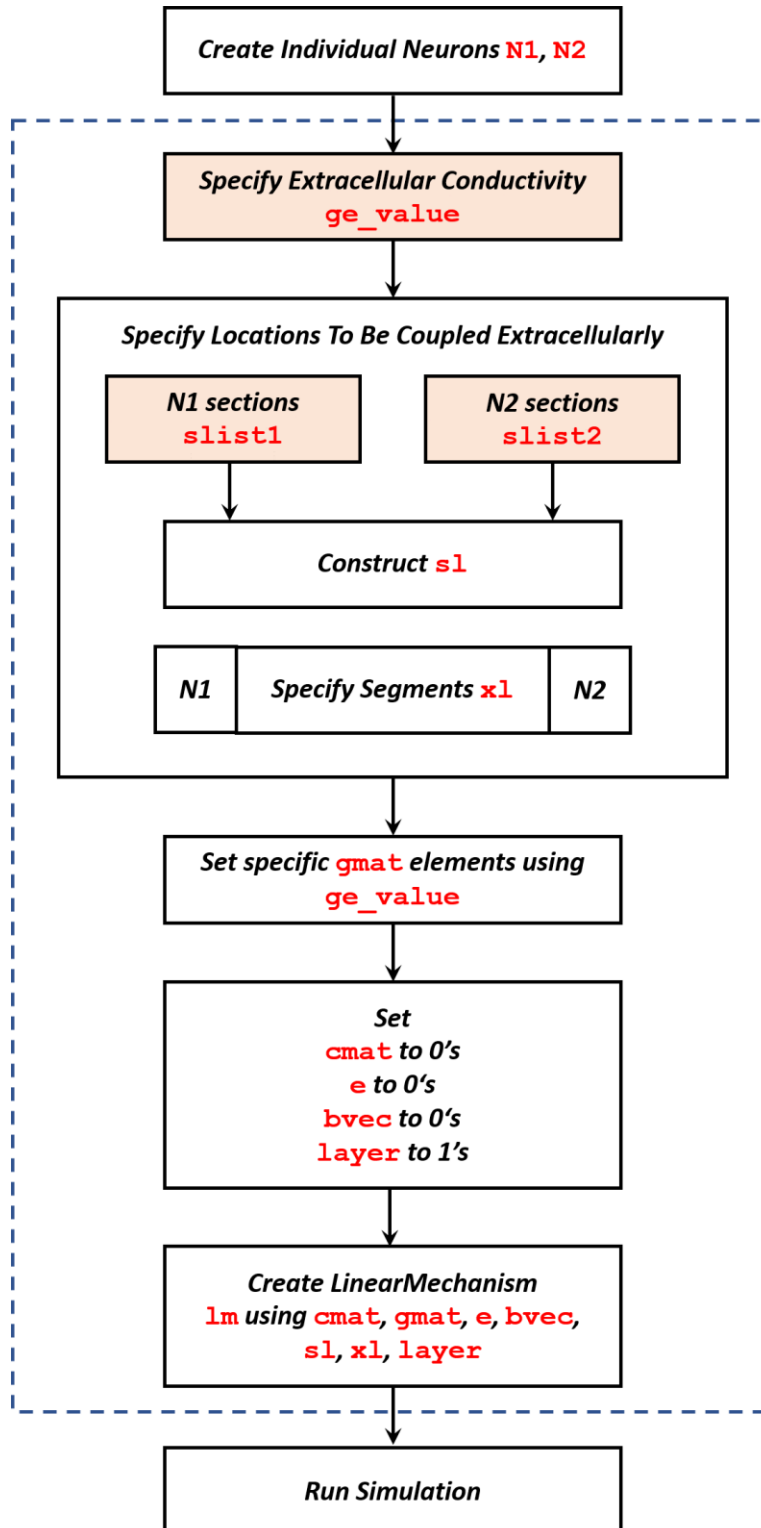


Figure S1: Flowchart summarizing the steps involved in developing the toy model. The dashed box encapsulates the steps involved in the coupling of the extracellular fields, and corresponds to the NEURON code presented in section S1.3. The colored boxes indicate the minimal stages where user input is required. The terms in red correspond to the variable names employed in the NEURON code.

237 coupling. This offers a degree of automation if the modeler simply wishes to reuse the  
238 existing extracellular coupling mechanism between different pairs of neurons. The  
239 process can be further streamlined by creating templates for the coupling mechanism  
240 and instantiating these wherever required. This would, in essence, be similar to creating  
241 templates for cells as employed in section S1.2, and may be advisable when handling  
242 large neuronal networks. But the wider capabilities and flexibility of the technique  
243 presented here is more evident when the modeler opts to explicitly tweak the individual  
244 parameters as dictated by the biophysical requirements of their model. The flowchart  
245 only attempts to present a very basic and easily reusable implementation of the  
246 technique.