Supporting information: 4 simulation figures and extended methods

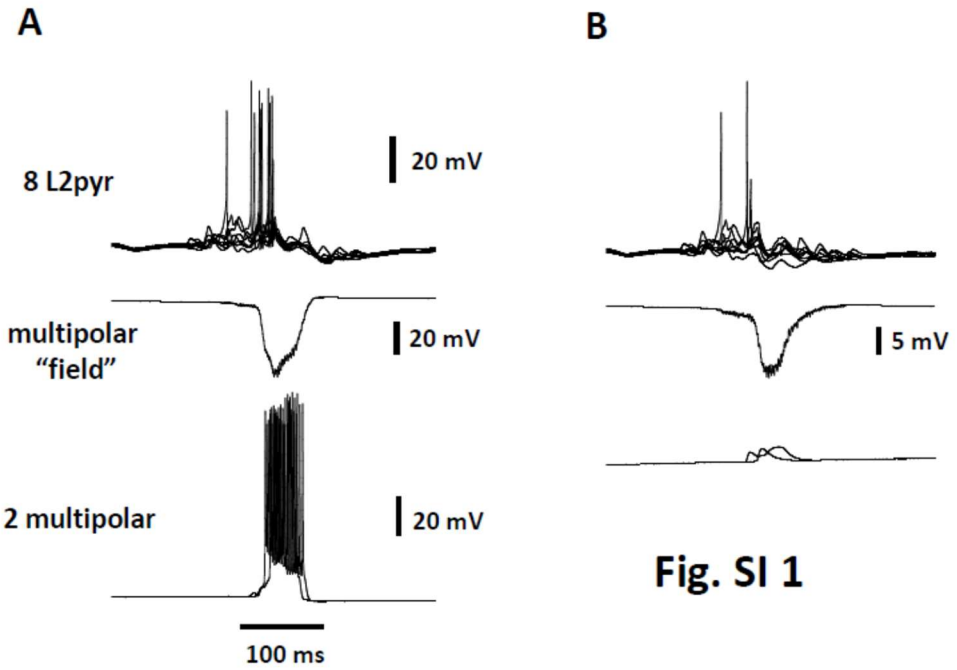

Fig. SI 1. *A threshold strength of persistent g_{Na} in multipolar neurons suffices for model endopiriform collective bursting and amplification of L2pyr activity.* Parameters in these simulations were as in Fig. 3, but with multipolar $g_{Na(P)}$ density 0.25 × transient g_{Na} density (in A), and 0.1 × transient g_{Na} density (in B). Note the profound difference in activities. Simulations piriformENDO105,106.

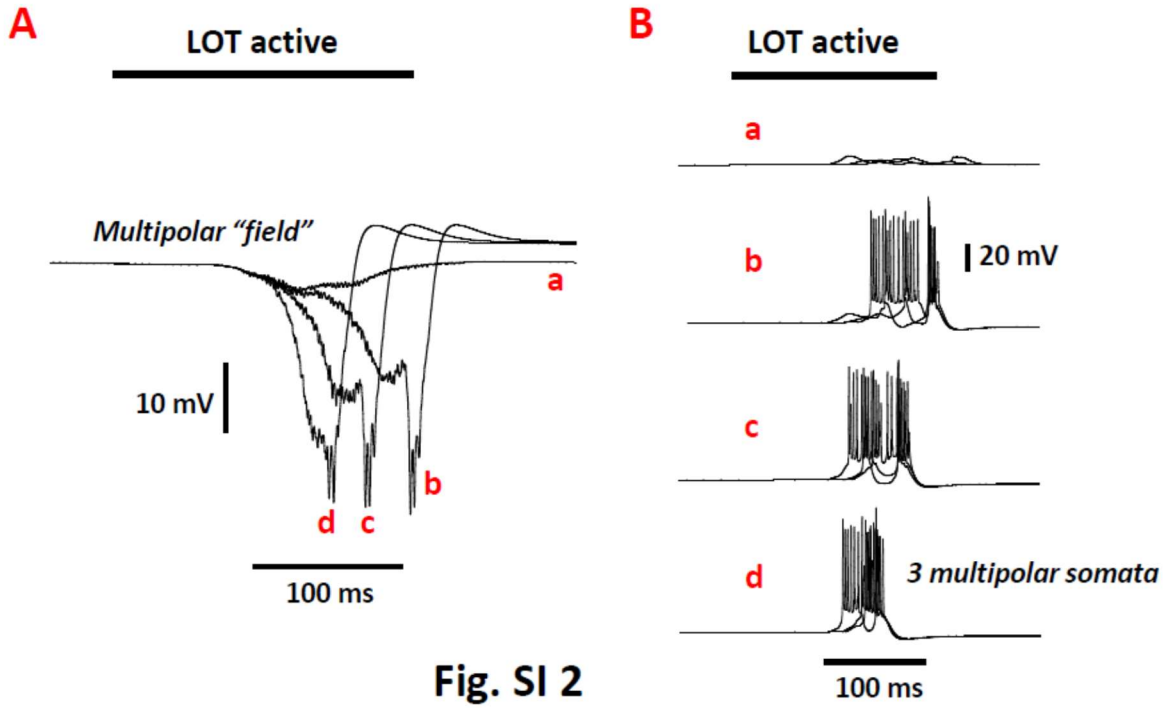

Fig. SI 2

Fig. SI 2. *With a fixed density of multipolar synaptic interconnections (above the percolation limit), a critical strength of multipolar recurrent synaptic excitation is necessary for collective bursting.* In each of the 4 simulations illustrated, all LOT afferents were active for 200 ms with mean interval between spikes = 300 ms. Each multipolar neuron contacted 12 others, chosen randomly. a: g_{AMPA} scaling = 0.75; b: 0.80; c: 0.85; d: 1.5. **A**: the multipolar "fields" (inverted average of multipolar somatic potentials, for the multipolar populations). **B:** somatic potentials of 3 multipolar neurons. Note the sharp transition between a and b, and the shortening latency as g_{AMPA} is further increased. Simulations piriformENDO41,43,42,39.

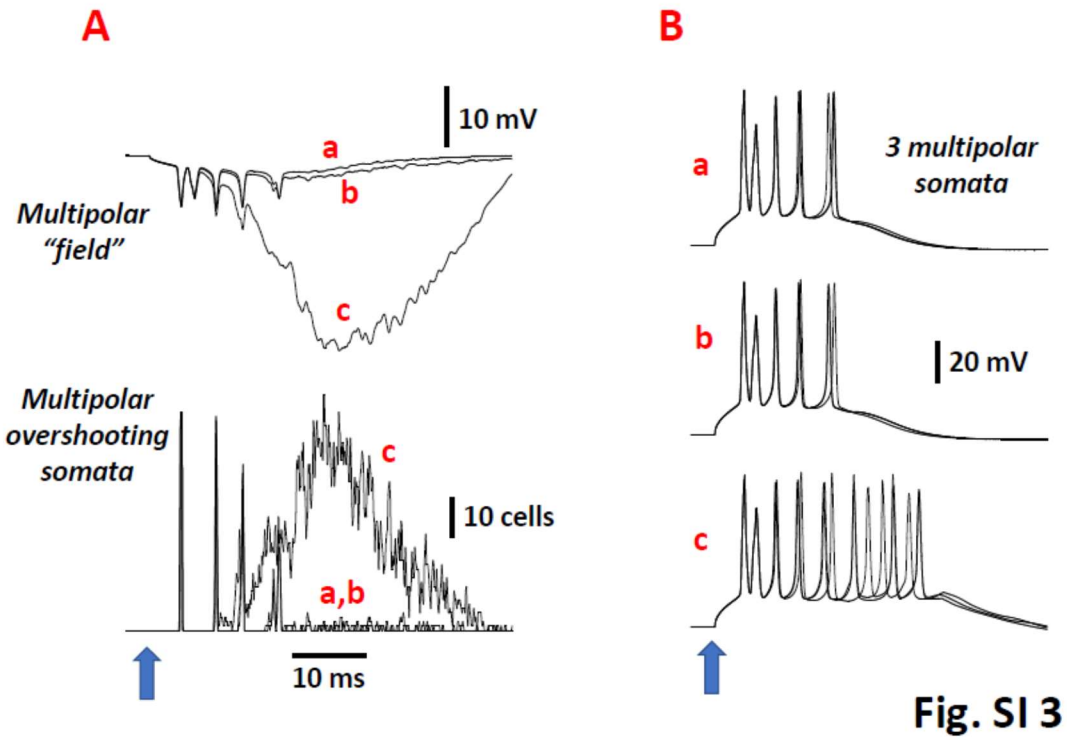

Fig. SI 3. *Further demonstration of the importance of g_{AMPA} (multipolar→multipolar)scaling for collective bursting.* In these 3 simulations, afferents were silent and a 5 ms, 0.6 nA depolarizing somatic current pulse was delivered to 50 multipolar neurons (arrows). a: each multipolar cell contacts 8 others, g_{AMPA} scaling 0.6; b: each multipolar cell contacts 12 others, g_{AMPA} scaling 0.6; c: each multipolar cell contacts 12 others, g_{AMPA} scaling 1.5: sustained firing now occurs. Simulations piriformENDO65,66,67.

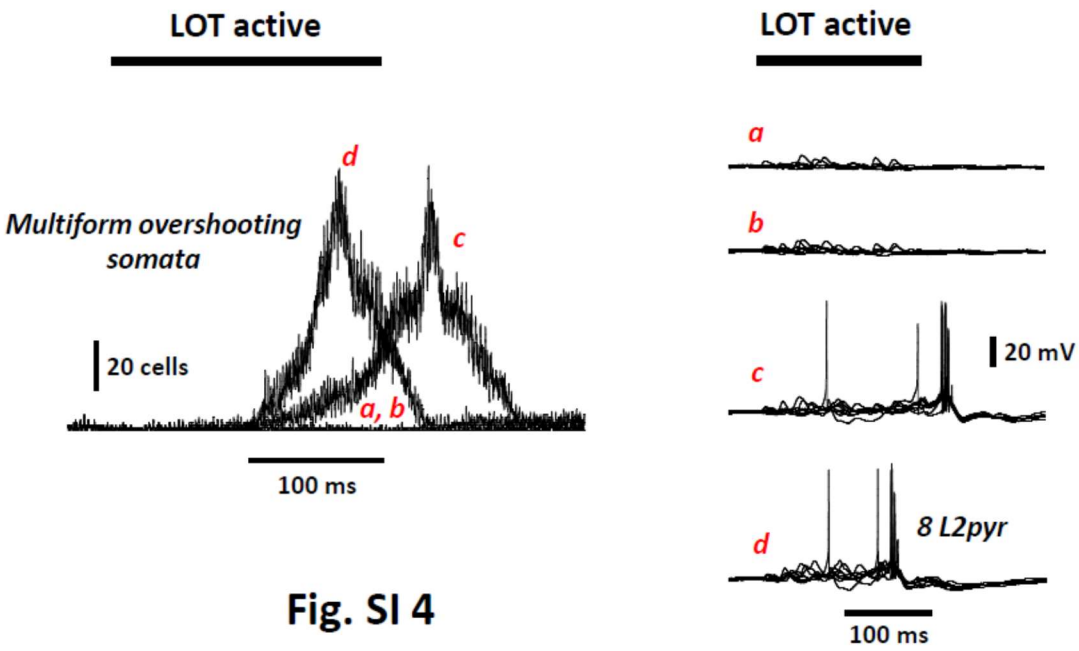

Fig. SI 4

Fig. SI 4. *Critical collective behavior of the multipolar (endopiriform) population as a function of afferent intensity, with consequent effects on the L2pyr population.* This figure extends Fig. 4 of the main text, although here bias currents to the multipolar neurons are different (Fig. 4: -0.25 nA, Fig. SI 4: -0.05 nA). In this figure, each model multipolar neuron contacts 3 others with scaling factor g_{AMPA} (multipolar→multipolar) = 0.6. The density of persistent g_{Na} was 0.5 × transient g_{Na}, as in Fig. 4. In each of the 4 simulations illustrated here, LOT afferents were active for 200 ms. a: mean interval between spikes in each LOT axon = 800 ms; b: 600 ms; c: 550 ms; d: 500 ms. Note the transition between b and c and the associated switch in L2pyr activities.

Detailed formulation of the (endopiriform) multipolar cell model.

Note that the programs for modeling all of the other cell types have a similar logical structure to this one, although cell architecture, conductance densities, and possibly membrane kinetics will vary from cell type to cell type. This model is a descendant of the one described in Ref. *(1)*.

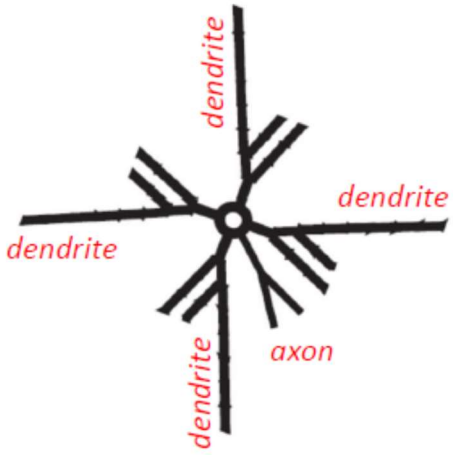

Fig. SI 5. *Schematic of the multipolar cell architecture (not to scale).* There are 59 compartments, 1 for the soma, 6 for the branching axon, 13 for each of the branching dendrites.

The endopiriform multipolar neuron has a compartmental structure as shown in Fig. SI 5. All compartments are cylindrical. The model was based on an earlier basket cell model, with soma dimensions in microns: radius 7.5, length 20; axon compartmental dimensions = radius 0.8 tapering to 0.5, length 50; dendritic compartmental dimensions = radius 1.06 tapering to 0.42, length 40. To convert this structure to a multipolar cell, the dendritic compartments were doubled in length, then doubled in area (to account for spines).

A consistent set of units for the model consists of mV, ms (or ms^{-1} for rate functions), nF, nA, μS.

We simulated electrical and calcium-mediated activity with the standard discrete compartmental cable equation *(2)*. Electrotonic parameters were membrane capacitance density 0.9 $\mu F/cm^2$, membrane resistivity R_m = 50,000 Ω-cm^2 for soma/dendrites and 1,000 Ω-cm^2 for the axon, internal resistivity R_i = 250 Ω-cm for soma/dendrites and 100 Ω-cm for the axon. Synaptic and leak conductances are taken to be ohmic, with reversal potentials in mV: leak -65, K^+ (and $GABA_B$) -85, Na^+ 50, Ca^{2+} 125, anomalous rectifier (h-current) -40, AMPA and NMDA 0, $GABA_A$ -75.

As per usual, for compartment *k*,

$$C_k \, dV_k / dt = \sum_m \gamma_{m,k} (V_m - V_k) - I_{ionic,k}$$

where C_k is the membrane capacitance of compartment k, the V's are transmembrane potentials of various compartments (and the extracellular space is assumed isopotential), the sum is taken over all compartments directly connected to compartment k, and $I_{ionic,\,k}$ is the ionic transmembrane current for the respective compartment. This latter term includes the leak, synaptic currents, and active transmembrane currents.

Active transmembrane currents included these: transient g_{Na}, persistent g_{Na}, 5 types of g_K, 2 types of g_{Ca}, and the anomalous rectifier. The g_K types were $g_{K(DR)}$, the delayed rectifier; $g_{K(A)}$ ("A" current); $g_{K(M)}$ ("M" current); $g_{K(C)}$ ("C" current), and $g_{K(AHP)}$ (slow afterhyperpolarization). The g_{Ca} types were $g_{Ca(L)}$ (high-threshold) and $g_{Ca(T)}$ (low-threshold "T" type). Membrane kinetics for all channel types except $g_{K(AHP)}$ depended on transmembrane voltage. $g_{K(C)}$ depended on $[Ca^{2+}]_i$ as well; and $g_{K(AHP)}$ depended on $[Ca^{2+}]_i$ but not on voltage.

The voltage-dependent kinetics of the different transmembrane currents were simulated with a standard Hodgkin-Huxley type of scheme, where there are activation ("*m*") and possibly inactivation ("*h*") state variables, specific to each conductance type, having kinetics that depend on membrane voltage only. The conductance in a given compartment depends on a scaling constant, say $g_{K(A)}$ (dropping the compartmental subscript "k"), multiplied by powers of "m" and "h" for that conductance and that compartment. The state variables each evolve according to the differential equations:

$$dm / dt = \alpha_m \times (1 - m) - \beta_m \times m \;\; ; \;\; dh / dt = \alpha_h \times (1 - h) - \beta_h \times h$$

The α's and β's are designated the forward and backward rate functions, respectively; they are functions of transmembrane voltage and of course have different properties for each conductance type. An equivalent formulation of these kinetics uses the relations of the sort:

$$m_\infty (V) = \alpha_m (V) / [\alpha_m (V) + \beta_m (V)] \; ; \;\; \tau_m (V) = 1 / [\alpha_m (V) + \beta_m (V)] \; ,$$

(likewise for h_∞ and τ_h). Here, m_∞ is the steady-state value that m would obtain if V were held constant, and τ_m is the respective time constant. (It is easy to show that these numbers are well-defined). Hence, kinetic properties can be defined by the rate functions (of voltage), or by steady-state values and time constants. We use both formulations below.

Hence (dropping compartmental subscripts), the ionic current depending on membrane channels (excluding synaptic currents), and using "g" parameters as scaling constants and using a consistent set of units, will be:

$$g_L (V + 65) + [g_{Na(F)} m_{Na(F)}^3 h_{Na(F)} + g_{Na(P)} m_{Na(P)}^3] (V - 50) +$$

$$[g_{K(DR)} m_{K(DR)}^4 + g_{K(A)} m_{K(A)}^4 h_{K(A)} + g_{K(M)} m_{K(M)} + g_{K(C)} m_{K(C)} \mathbf{\Gamma}(\chi) +$$

$$g_{K(AHP)} m_{(AHP)}] (V + 85) + [g_{Ca(L)} m_{Ca(L)}^2 + g_{Ca(T)} m_{Ca(T)}^2 h_{Ca(T)}] (V - 125) +$$

$$+ g_{AR} m_{AR} (V + 40)$$

In the above equation, χ stands for $[Ca^{2+}]_i$ in the respective compartment, and **Γ** a function thereof, to be defined below.

Kinetics of voltage-dependent membrane conductances are as follows:

Transient $g_{Na:}$: $m_\infty = 1 / [1 + \exp((-V - 38) / 10)]$;

$\tau_m = 0.0125 + 0.1525 \exp((V + 30)/10)$ if $V < 30$ mV

$= 0.02 + 0.145 \exp((-V-30)/10)$ otherwise.

$h_\infty = 1 / [1 + \exp((V + 58.3)/6.7)]$

$\tau_h = 0.225 + 1.125 / [1 + \exp(V + 37)/15)]$

Persistent $g_{Na:}$: activation kinetics as above (but for other principal cell types, there may be shifts along the voltage axis); there is no inactivation.

Delayed rectifier: $m_\infty = 1 / [1 + \exp((-V - 27) /11.5)]$;

$\tau_m = 0.25 + 4.35 \exp((V + 10)/10)$ if $V < -10$ mV

$= 0.25 + 4.35 \exp((-V-10)/10)$ otherwise.

A current:: $m_\infty = 1 / [1 + \exp((-V - 60) / 8.5)]$;

$\tau_m = 0.185 + 0.5 / [\exp((V + 35.8)/19.7) + \exp((-V-79.7)/12.7)]$

$h_\infty = 1 / [1 + \exp((V + 78.0)/6.0)]$

$\tau_h = 0.5 / [\exp((V + 46)/5) + \exp((-V-238)/37.5)]$ if $V < -63$ mV

$= 9.5$ otherwise.

Anomalous rectifier: $m_\infty = 1 / [1 + \exp((V + 75) /5.5)]$;

$\tau_m = 1 / [\exp(-14.6 - 0.086\ V) + \exp(-1.87 + 0.07\ V)]$

C current (voltage-dependent part): if $V < -10$ mV then

$\alpha_m = 0.106 \exp((V + 50)/11 - (V + 53.5)/27)$

$\beta_m = 4 \exp((-V - 53.5)/27) - \alpha_m$; otherwise

$\alpha_m = 4 \exp((-V - 53.5)/27)$ and $\beta_m = 0$

M current: $\alpha_m = 0.02 / [1 + \exp((-V - 20)/5)]$

$\beta_m = 0.01 \exp((-V - 43)/18)$

High-threshold g_{Ca} *(*$g_{Ca(L)}$*):* $\alpha_m = 1.6 / [1 + \exp(-0.072\ (V - 5))]$

$\beta_m = 0.1\ ((V + 8.9)/5) / [\exp(V + 8.9)/5) - 1]$

Low-threshold g_{Ca} *(*$g_{Ca(T)}$*):* $m_\infty = 1 / [1 + \exp((-V - 52)/7.4)]$

$\tau_{m-} = 1 + 0.33 /[\exp((V + 27)/10) + \exp((-V-102)/15)]$

$h_\infty = 1 / [1 + \exp((V + 80)/5)]$

$$\tau_h = 28.3 + 0.33 /[\exp((V + 48)/4) + \exp((-V - 407)/50)]$$

Scaling factors for membrane conductances (as in multipolar.f). These are given in units of mS/cm^2.

Transient g_{Na}: 400 (axon), 60 (soma and proximal dendrites), 30 → 10 (rest of the dendrites)

Persistent g_{Na}: Varies, depending on the simulation

Delayed rectifier: 400 (axon), 100 (soma and proximal dendrites), 20 (rest of the dendrites)

A current: 1 (axon), 2 (soma), 1 (dendrites)

AHP current (slow, gated by Ca^{2+}*)* 0 (axon), 0.12 (soma and dendrites)

Anomalous rectifier: 0 (axon), 0.02 (soma and dendrites)

C current: 10 (soma), 0 elsewhere

M current: 8 (axon), 6 (soma and dendrites)

High-threshold g_{Ca} *(*$g_{Ca(L)}$*):* 0 (axon), 0.5 (soma and proximal dendrites), 2.5 (distal dendrites)

Low-threshold g_{Ca} *(*$g_{Ca(T)}$*):* 0 (axon), 0.05 (soma and proximal dendrites), 0.5 (distal dendrites)

$[Ca^{2+}]_i$ dynamics and slow AHP conductance. $[Ca^{2+}]_i$ (denoted "chi" in the code, and "χ" here) rises with Ca^{2+} current through high-threshold ($g_{Ca(L)}$) channels, into a thin cylindrical shell in each soma-dendritic compartment. For each soma-dendritic compartment, a parameter "cafor" is defined as 52×10^6 / [compartment area in $microns^2$] (respectively 26×10^6 / [compartment area in $microns^2$] for the soma). For compartment k, then,

$d\chi_k / dt$ = "cafor" × [high-threshold inward I_{Ca} in nA for compartment k] - $\beta_\chi \times \chi_k$

The relaxation parameters β_χ are 0.05 for dendrites and 0.02 for the soma, corresponding to decay time constants of 20 ms and 50 ms, respectively. Note the model does not include Ca^{2+} currents in the axon.

The quantities χ_k are coupled to K^+ currents as follows. First, for $g_{K(C)}$, the term $\mathbf{\Gamma}(\chi)$, which appears in the equation for total ionic current, is equal to min (1, $0.004 \times \chi$). (This formulation allows for saturation, in case χ becomes very large, as it can do during plateau potentials.) Second, for $g_{K(AHP)}$, the forward rate function in compartment k is α_m = min ($2\times10^{-5}\times \chi_k$, 0.01), again allowing for saturation. The backward rate function is constant at 0.001, corresponding to relaxation with time constant 1 second.

Formalism for major synaptic conductances. The major synaptic conductances developing across multipolar cell membranes are mediated by AMPA and $GABA_A$ receptors, excitatory and inhibitory respectively. A unitary AMPA conductance follows an alpha function and is equal to g_{AMPA} t exp (-t / τ), where τ g_{AMPA} is a scaling constant that depends on the presynaptic cell type, and which varies with the simulation, t is time in ms, and τ is a time constant in ms (in this case,

2 ms). A unitary $GABA_A$ conductance also has a scaling constant, rises in one integration time step, and decays exponentially: for multipolar neurons, the decay time constant is 6 ms.

Connectivity of multipolar neurons. The endopiriform cells synaptically contact each other, and they send output to, and receive input from: piriform layer 2 pyramids, layer 3 pyramids, and deep basket (fast-spiking) cells. A deep basket cell is excited by 10 randomly chosen multipolars with g_{AMPA} scaling 0.5; a multipolar cell is inhibited by 15 deep basket cells, with $g_{GABA(A)}$ scaling 1.0. The other connectivity parameters were varied in different simulations.

References for Supporting Information

1) R.D. Traub, E.H. Buhl, T. Gloveli, M.A. Whittington, M.A., Fast rhythmic bursting can be induced in layer 2/3 cortical neurons by enhancing persistent Na^+ conductance or by blocking BK channels. *J. Neurophysiol.* **89**, 909-921 (2003).

2) F.A. Dodge, J.W. Cooley, Action potential of the motoneuron. *IBM J. Res. Dev*. **17,** 219-229 (1973).