frontiers

Supplementary Material

Kilohertz frequency deep brain stimulation is ineffective at regularizing the firing of model thalamic neurons

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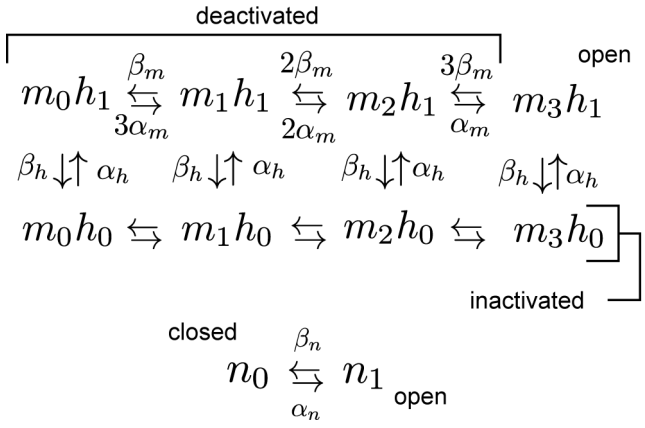
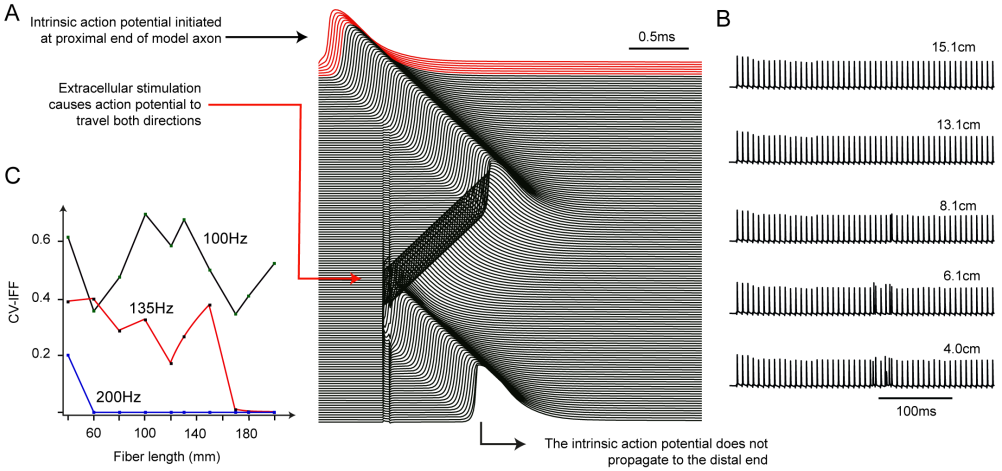
1 Supplementary Figures and Tables

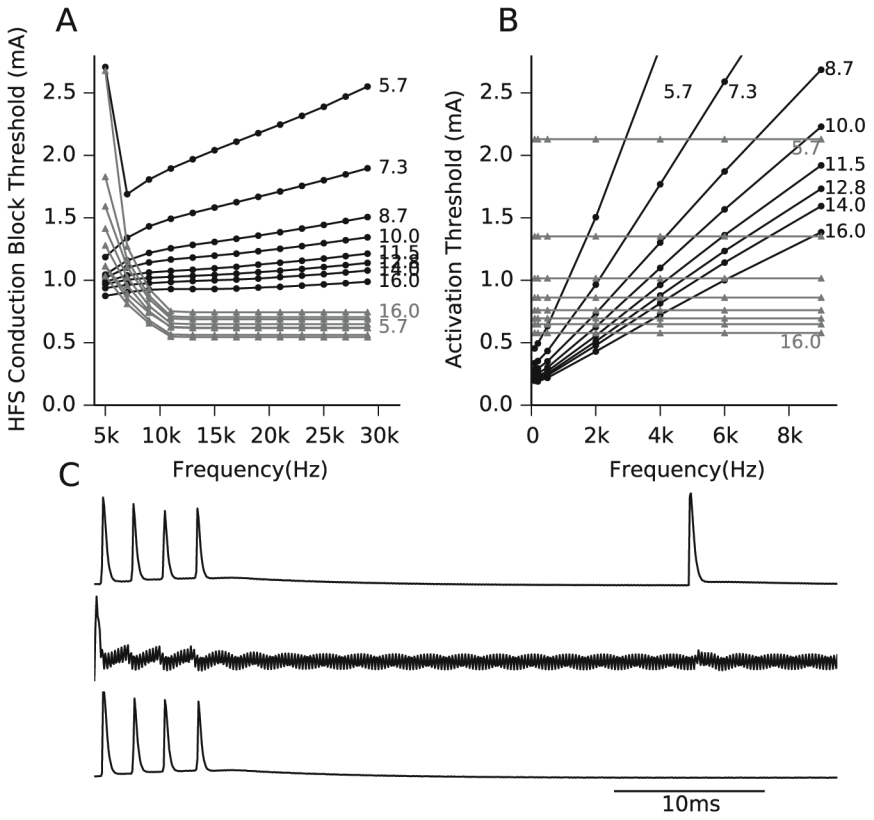
1.1 Supplementary Figures



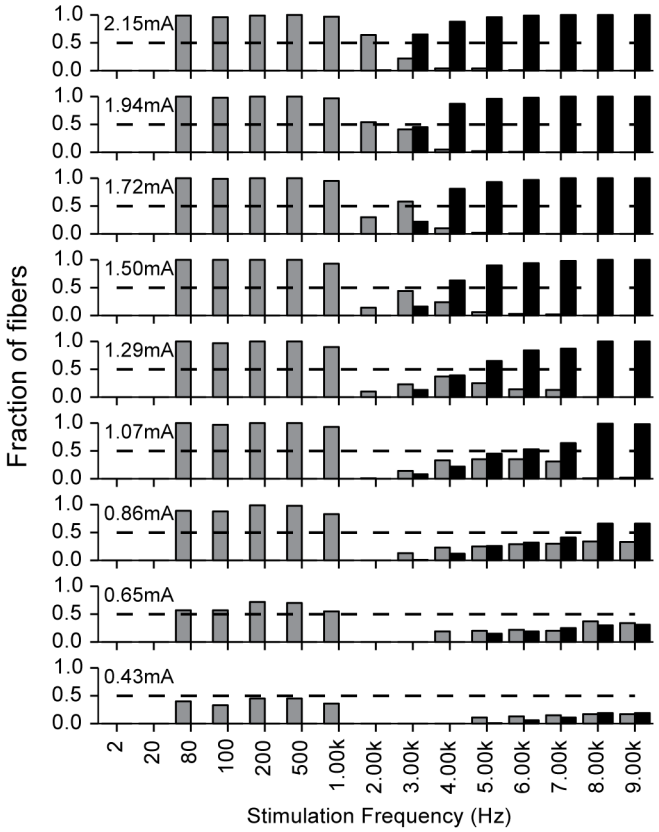
Supplementary Figure 1. Kinetic schemes used to describe the gating variables of sodium and potassium.



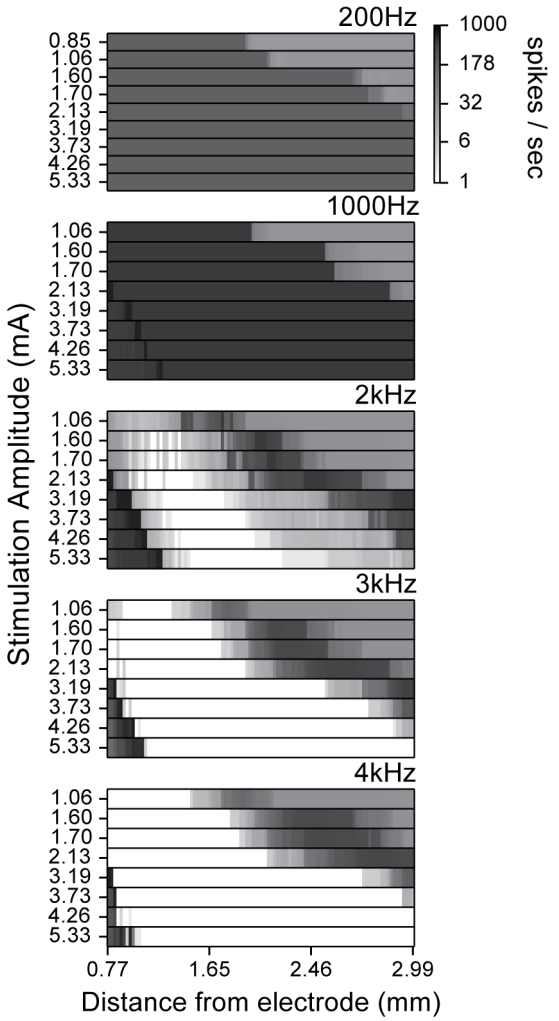
Supplementary Figure 2. Ability to suppress action potentials depends on the length of the model fiber. Using output regularity as a measure of DBS efficacy we conducted simulations with different axonal lengths and measured the efficacy of high frequency stimulation at frequencies used in the clinic. We observed that the intrinsic action potential generated by intracellular stimulation at the proximal end of the model axon was suppressed completely at 135 Hz only when fibers were longer than 170 mm with the extracellular electrode placed 40 nodes away from the ends of the axon in all simulations. (A**)** Example of modeled intrinsic action potential propagation and suppression by high frequency stimulation; traces are the membrane voltage measured in each node of Ranvier. (B) Transmembrane voltage for model axons of different lengths stimulated at the same frequency. (C) Regularity of neuronal firing measured as the coefficient of variation of the instantaneous firing frequency versus the length of the model axon measured for multiple frequencies. 100 Hz was not sufficient to mask the intrinsic action potential at any length.



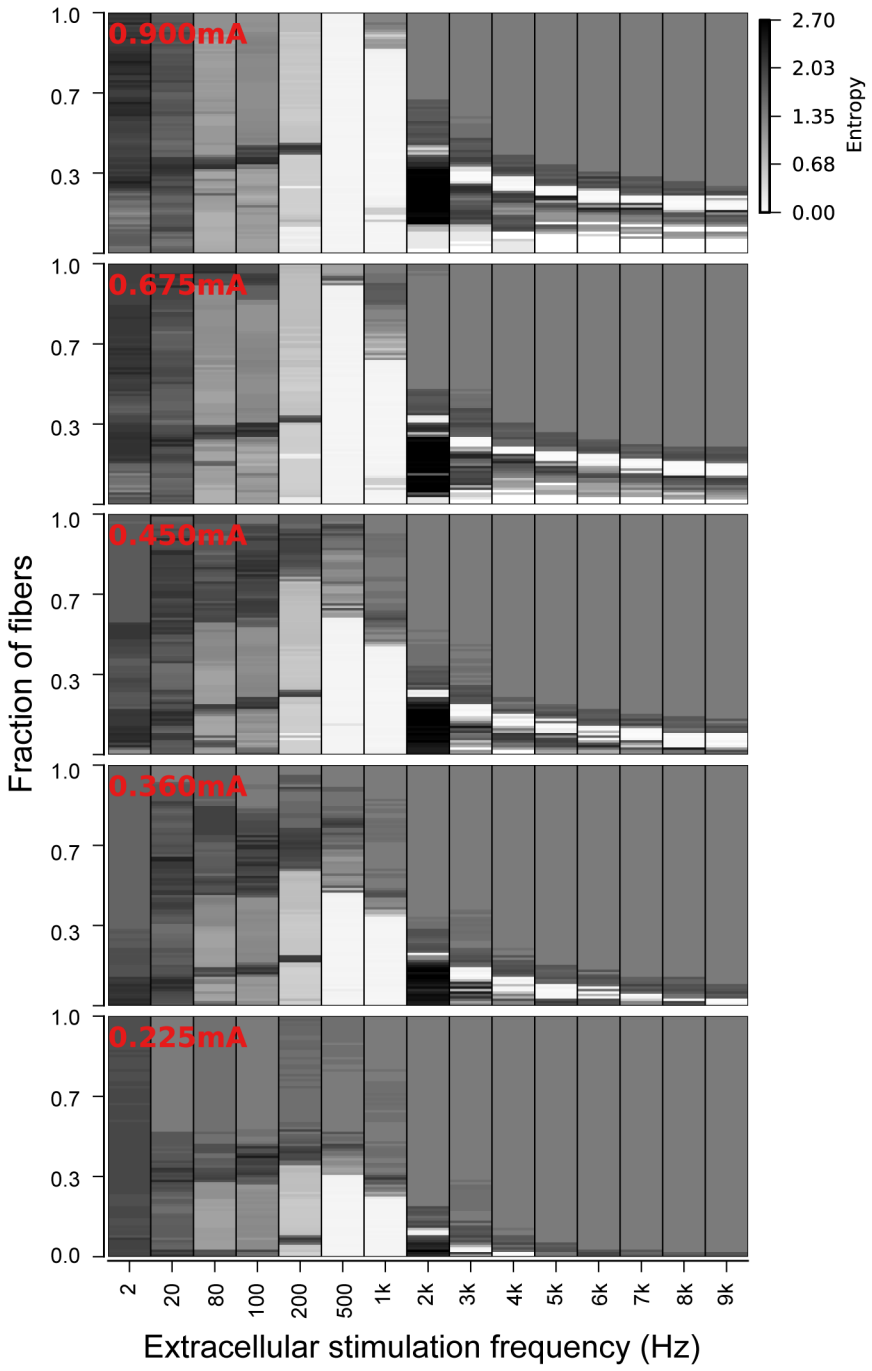
Supplementary Figure 3. Conduction block and activation threshold – as a function of extracellular stimulation frequency – for model axons with different diameters (μm). (A) Conduction block for fiber 1mm from the electrode. Black circles are for a sinusoidal stimulation waveform, as used in Bhadra et al. 2007, and gray triangles for a cathodic square monophasic wave with a pulse width of 90 μs. (B) Activation threshold for extracellular stimulation of a fiber at 3 mm using a single stimulation cycle. (C) Voltage recorded during one of the simulations in A for (from top to bottom) nodes 0, 25 and 50 where node 0 is where the intracellular stimulation is delivered, node 25 is closest to the stimulating electrode and node 50 the distal end of the model axon where the output was recorded. Example is a 10 μm axon stimulated at 9 kHz and 1.14mA at an electrode to axon distance of 1 mm.



Supplementary Figure 4. Summary plots for populations of 10 μm diameter fibers (100 axons with 81 nodes of Ranvier and intrinsic activity) as in Figure 9 of the manuscript. Bar plots of fraction of fibers undergoing conduction block (black) and fibers with regular output (gray).



Supplementary Figure 5. Firing rates in response to extracellular stimulation at different frequencies and amplitudes in a model with intrinsic activity. Each row represents the firing rate of 100 fibers in response to extracellular stimulation at a particular frequency. The fibers are sorted by proximity to the electrode.



Supplementary Figure 6. Summary entropy colormaps for populations of 5.7µm diameter fibers (100 axons with 81 nodes of Ranvier and intrinsic activity) stimulated with sinusoidal waveforms of increasing amplitudes. Note that although conduction block arises (white bands for frequencies above 1 kHz), the frequency-block threshold relation is inverted in relation to stimulation with cathodic monophasic pulses.

1.2 Supplementary Tables

Parameter	Units	Node	MYSA	FLUT	STIN
Fiber diameter – D	μm	5.7			
Diameter – d	μm	1.9		3.4	
Individual segment length	μm	1	3	35	70.5
Number of segments in continuous section	-	-	-	-	6
Periaxonal space width	μm	-	0.002	0.004	
Number of myelin lamella – nl	-	-	80		
Membrane capacitance – C_n,C_i	μF/cm^2/lamella	2	0.67	1.19	
Myelin capacitance - C_m	μF/cm^2/lamella	-	0.1		
Myelin conductance - g_m	S/cm^2	-	0.001		
Intraaxonal resistivity - ρ_a	Ωcm	70			
Periaxonal resistivity – ρ_{pa}	Ωcm	-	70		
Passive membrane conductances – ρ_{Lk},g_i	S/cm^2	0.007	0.001	0.0001	
Maximum fast Na^+ conductance – g_{Na+}	S/cm^2	3.0	-	-	-
Maximum fast K^+ conductance – g_{K+}	S/cm^2	0.08	-	-	-
Maximum persistent Na^+ conductance – g_{Nap}	S/cm^2	0.01	-	-	-
Na^+ Nernst potential – E_{Na+}	mV	50	-	-	-
K^+ Nernst potential – E_{K+}	mV	-90	-	-	-
Leakage reversal potential – E_{Lk}, E_i	mV	-90	-80		
Rest potential – E_{rest}	mV	-80			

Supplementary Table 1. Model details. The inter-nodal segment – STIN – is divided in 6 segments which is represented in NEURON by 6 connected sections with the same parameters and a single segment. The intermodal length is 500μm. The actual myelin sheath capacitance of the model is $C_m/(nl\times 2)$ and the actual myelin conductance in a similar way.

Fiber number	Simulation duration		Stimulation Frequency
	1s	***20s***	
10	0	0.05	200Hz
30	0.02	0.05	

40	0	0.05	
50	0.98	1.28	
70	1.34	1.94	
10	1.59	1.62	
30	1.96	2.14	
40	2.09	2.12	2000Hz
50	1.74	1.91	
70	1.42	1.95	
10	0	0	
30	1.2	1.03	
40	2.19	2.35	4000Hz
50	2.01	2.17	
70	1.55	1.96	

Supplementary Table 2. Entropy was slightly underestimated (mean absolute error of 0.19 bits/s) when using short simulation times.