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Anodic Stimulation Misunderstood: Preferential Activation of Fiber Orientations with Anodic Waveforms in Deep Brain Stimulation

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Hypothesis: Fiber orientation influences activation thresholds and fiber orientations can be selectively targeted with DBS waveforms.

1 Introduction

Deep Brain Stimulation (DBS) is an established surgical intervention for movement disorders and a growing treatment option for psychiatric disorders.

Cathodic stimulation is primarily used in clinical DBS applications. Axons are understood to be more excitable during cathodic stimulation, and many studies report larger anodic thresholds compared to cathodic thresholds[1].

The activating function — second derivative of electric potential across nodes of Ranvier — can be used to approximate neural activation in response to extracellular electrical stimulation[2]. Positive second derivatives correspond to sites of action potential initiation (Figure 1).

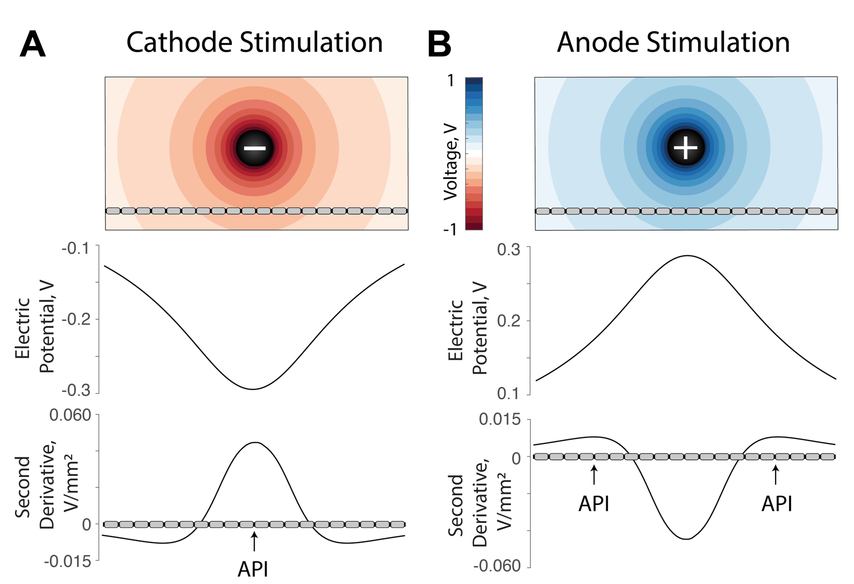

Figure 1. **A.** Electric potential and voltage second derivative plotted along a tangential axon given cathodic extracellular stimulation. Action potential initiation (API) occurs at the center node of the axon. **B.** For anodic stimulation, sites of API occur at nodes away from the center node relative to the electrode source. Flanking sites of API are referred to as virtual cathodes.

2 Methods

We used the finite element method in SCIRun (SCI Institute, Univ. of Utah, Salt Lake City, UT) to solve the bioelectric field problem for the Medtronic 3389 lead (Medtronic Inc., Minneapolis, MN).

The Hessian matrix of second spatial derivatives was calculated on a highly resolved grid from the electric potential solution. The eigenvalues of the Hessian tensor represent the activating function in the direction of the respective eigenvector.

We ran NEURON simulations along the directions of the principal eigenvectors using a modified NEURON model to verify the recruitment order determined from the primary, secondary, and tertiary eigenvalues and eigenvectors of the Hessian. We tested the impact of modifications to the stimulus waveform on activation thresholds for selective activation of fiber orientations.

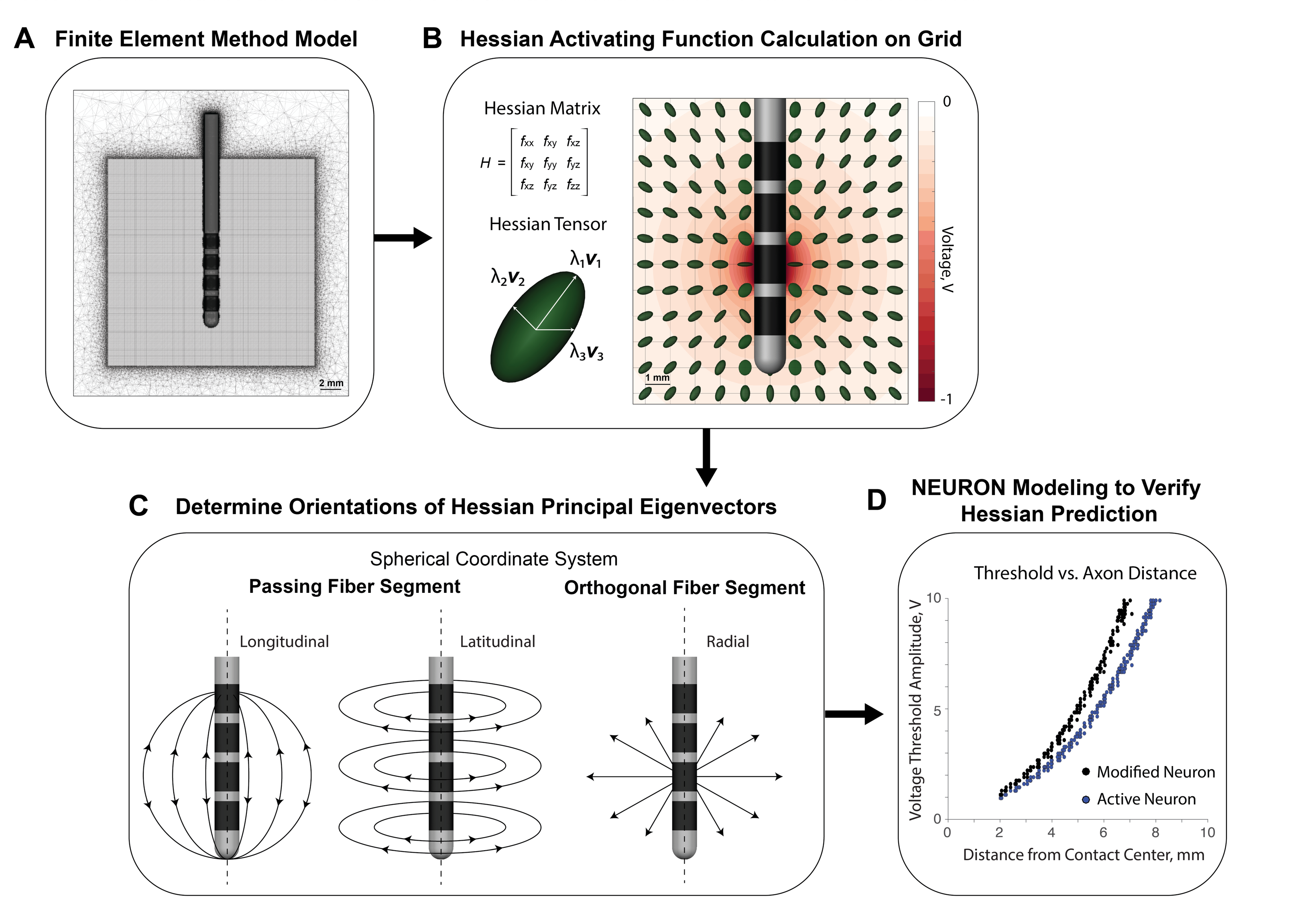

Figure 2. Methods flowchart. **A.** The finite element model consists of a tetrahedral mesh for the Medtronic 3389 lead. **B.** The Hessian matrix was derived from the electric potential solution and solved at every node on a 20 x 20 x 20 mm grid incorporated into the tetrahedral mesh. The Hessian matrix can be visualized as a tensor. **C.** Fiber orientations, determined from the principal eigenvectors of the Hessian, were classified using a spherical coordinate system. **D.** A modified NEURON model was created to restrict API to the center node of the axon for comparison to the Hessian-derived activating function. The modified axon fires at higher thresholds than the fully active axon.

3 Results

Cathodic stimulation and anodic stimulation each activate certain fiber orientations selectively. The likelihood that a particular fiber orientation will induce firing depends on the sign and the magnitude of the activating function.

3.1 Recruitment Order based on Fiber Orientation

The positive Hessian eigenvalues predict that cathodic stimulation activates passing axons (longitudinal and latitudinal) and anodic stimulation activates axons leaving or approaching the electrode (orthogonal). Primary, secondary, and tertiary eigenvalues and eigenvectors for monopolar and bipolar stimulation for the Medtronic 3389 lead can be found in Figure 3.

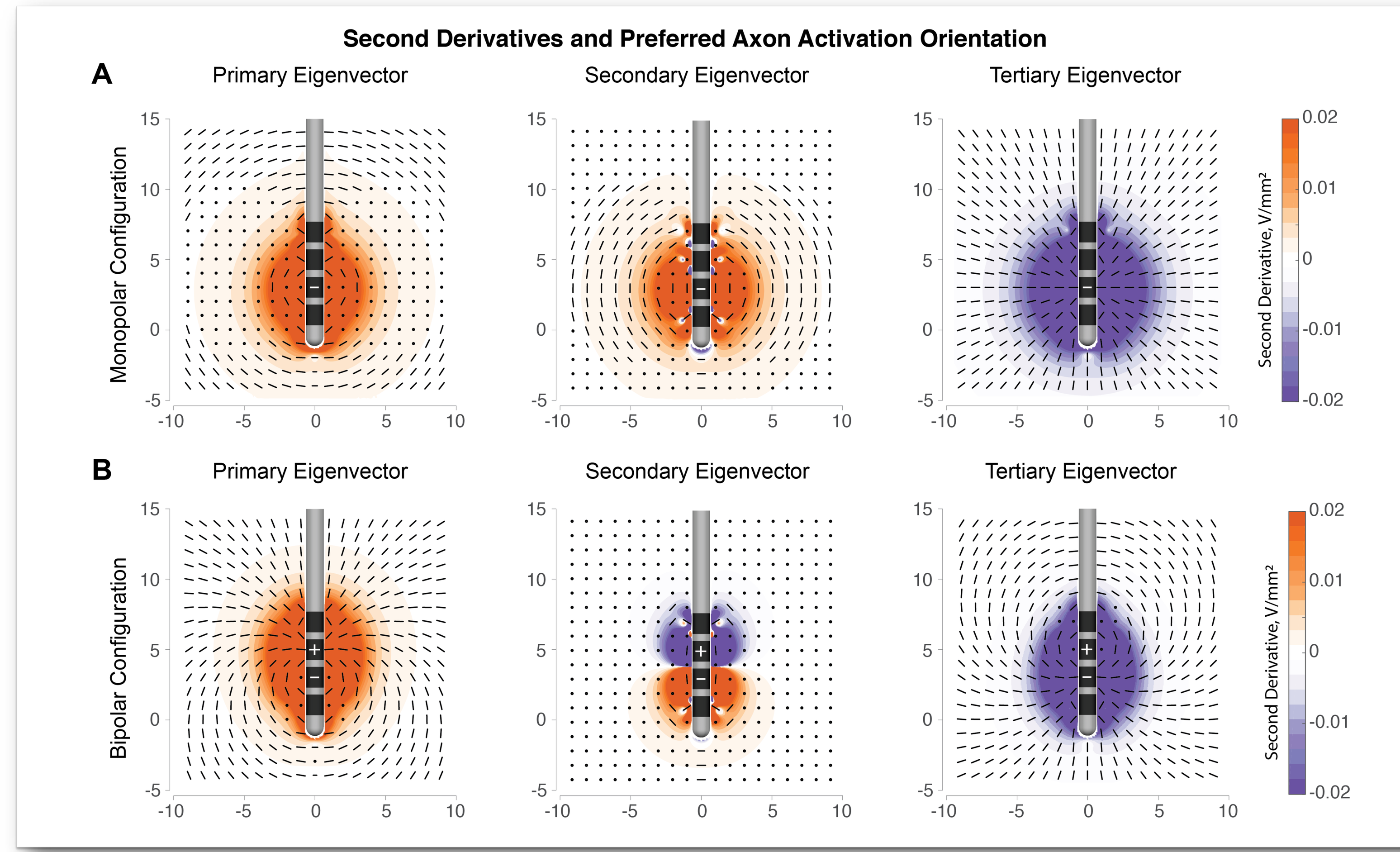

Figure 3. **A.** For monopolar cathodic stimulation, longitudinal and latitudinal fibers (passing fibers) have positive second derivatives, which correspond to an increased likelihood of firing. The orthogonal direction defined by the tertiary eigenvector has negative second derivatives. The tertiary eigenvalue magnitudes are twice that of the primary and secondary eigenvalues, implying large inhibition of orthogonal fibers. **B.** Anodic stimulation flips the preferential order of activation so orthogonal fibers are likely to initiate action potentials. Bipolar stimulation sees spatial selectivity of fiber orientations between the anode and the cathode electrodes.

Cathodic Waveform:

As predicted, neurons in the primary and secondary eigenvector directions (passing) fire APs, whereas neurons in the tertiary eigenvector direction (orthogonal) do not.

Anodic Waveform:

Orthogonal neurons fire at lower thresholds than the passing fibers did under cathodic stimulation. The longitudinal and latitudinal neurons, which fired with a cathodic pulse, do not fire with anodic stimulation.

Clinical Charge Balanced Waveform:

Both passing fibers and orthogonal fibers are activated by the cathodic and anodic phases of the balanced waveform, respectively.

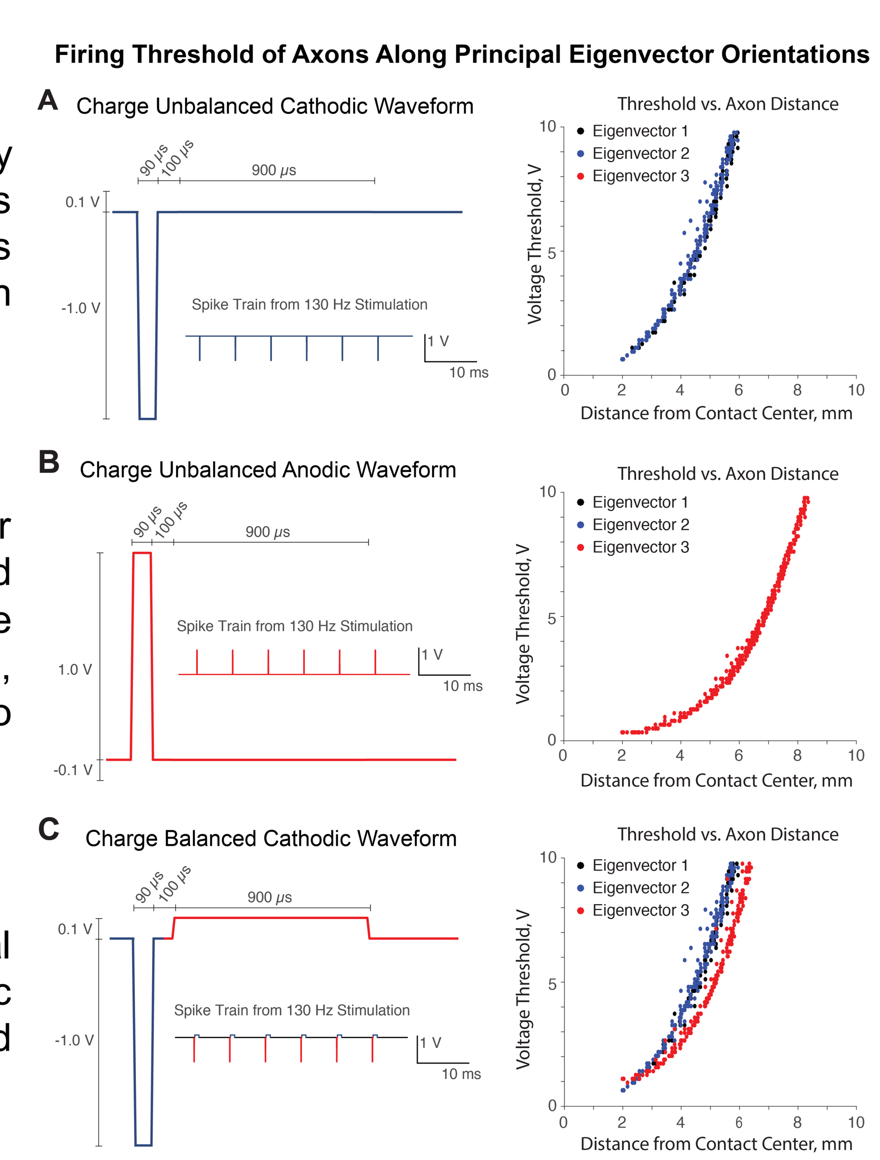

Figure 4. An unbalanced cathodic pulse causes firing of neurons oriented in the primary and secondary eigenvector directions. Neurons in the tertiary eigenvector orientation do not fire, as predicted by the eigenvalues. **B.** An unbalanced anodic pulse reverses the fiber orientation recruitment from the cathodic pulse. **C.** In a 10% charge balancing cathode-first stimulus regime, neurons at all orientations fire at similar thresholds.

3.2 Selective Activation of Neurons Based on Changes in Waveform

Modifying the cathodic and anodic portions of the DBS waveform can selectively target fiber orientations.

- Cathode-first stimulation: We found that using a charge-balancing amplitude of 2.5% and 5% will prioritize firing of longitudinal and latitudinal axons. A 10% balancing pulse amplitude will activate all fiber orientations similarly. A 100% balancing pulse amplitude will preferentially activate orthogonal fibers.
- Anode-first stimulation: the orthogonal neurons will be preferentially activated regardless of the balancing pulse amplitude.

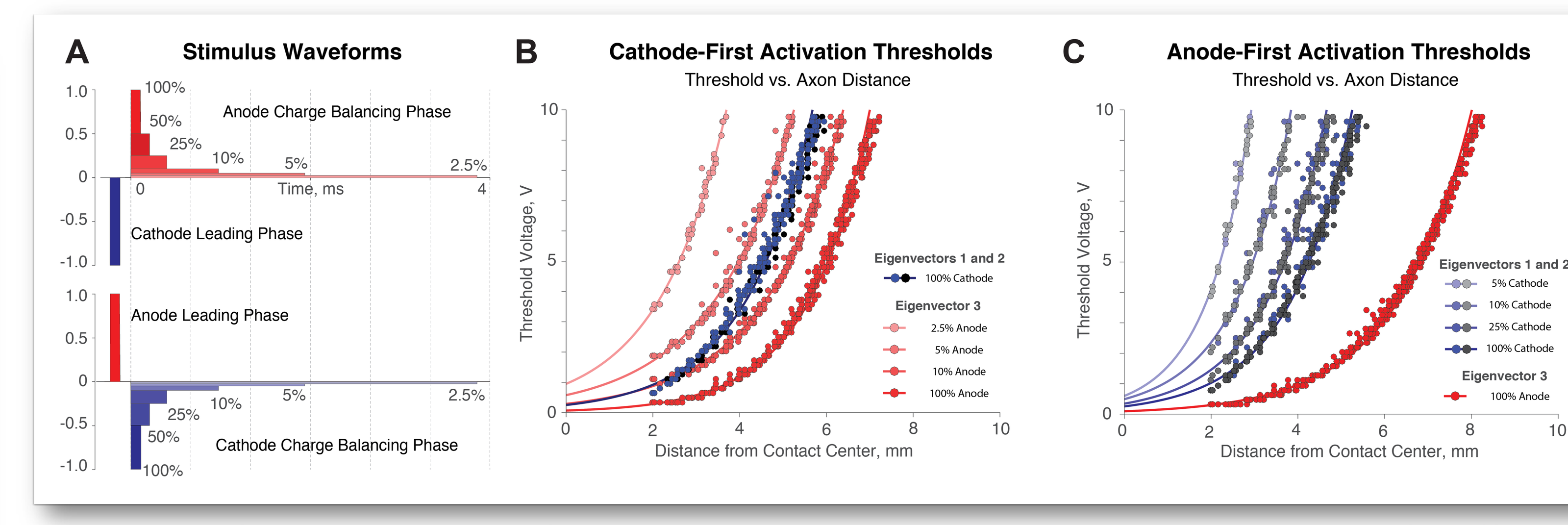

Figure 5. **A.** Cathode- and anode- first stimulus regimes with varying charge-balancing phases of 100%, 50%, 25%,10%, 5%, and 2.5% of the leading phase amplitude. **B.** Cathode-first stimulation with varying amplitudes of the anodic charge balancing phase. Changes to the balancing either select against or in favor of orthogonally oriented fibers (third eigenvector). **C.** Anode-first stimulation with varying amplitudes of the charge-balancing phase. Orthogonal fibers are highly excitable in all anode-first waveform scenarios.

Tractography was done in STN DBS to isolate fiber tracts associated with clinical benefits (hyperdirect pathway) and side effects (internal capsule). Preferential activation of orthogonal fibers with anodic stimulation can be used to target fiber tracts associated with therapeutic benefit, and widen the therapeutic window.

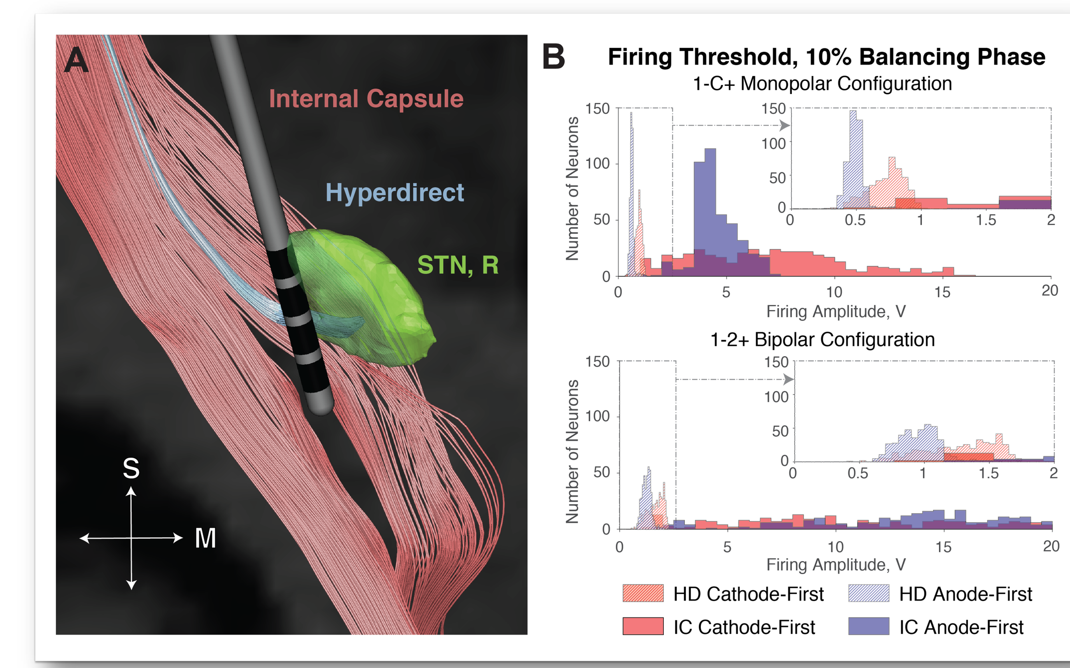

Figure 6. **A.** Visualization of HD and IC tracts with respect to the STN (right) and lead. **B.** Firing threshold histograms for HD and IC tracts given cathodic and anodic stimulation for 10% balancing. Anodic stimulation reduces threshold voltage of orthogonally oriented fibers. As a result, the HD is activated at a smaller voltage with anodic stimulation rather than cathodic stimulation. The orthogonal components of the IC are activated at lower thresholds as well, but bipolar stimulation reduces the spread of activation in the IC.

4 Conclusions

- We demonstrated the activation of passing fibers with cathodic stimulation versus selective activation of orthogonal fibers with anodic stimulation.
- Orthogonal fibers are activated by anodic stimulation at lower thresholds than passing fibers given the same amplitude of cathodic stimulation.
- This study might explain the existence of virtual cathodes in tangential fibers, which are present during anodic stimulation at more distal nodes (Figure 1B).
- Anodic stimulation has the potential for clinical benefit.

5 Future Directions

- Exploration of preferential activation of fiber orientation in clinical scenarios.
- The Hessian could be used as a novel metric for the Volume of Tissue Activated that considers activation in all fiber orientations.

6 References and Acknowledgements

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