Assignment for Meeting 4

Involved a lot of computation, but they gloss over details to not scare away physicians and neuroscientists:
Luján J L, Chaturvedi A, Malone D A, Rezai A R, Machado A G, McIntyre C C. Axonal pathways linked to therapeutic and nontherapeutic outcomes during psychiatric deep brain stimulation. Human Brain Mapping 33: 958–968, 2011.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/lujan2011.pdf

Lots of computation here too:
Capogrosso M, Wenger N, Raspopovic S, Musienko P, Beauparlant J, Bassi Luciani L, Courtine G, Micera S. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. Journal of Neuroscience 33: 19326–19340, 2013.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/capogrosso2013.pdf

Built on Capogrosso et al. 2013, and also involved lots of computation, but they don't provide many methodological details:
Barra B, Conti S, Perich M G, Zhuang K, Schiavone G, Fallegger F, Galan K, James N D, Barraud Q, Delacombaz M, Kaeser M, Rouiller E M, Milekovic T, Lacour S, Bloch J, Courtine G, Capogrosso M. Epidural electrical stimulation of the cervical dorsal roots restores voluntary upper limb control in paralyzed monkeys. Nature Neuroscience 25: 924–934, 2022.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/barra2022.pdf

Note: first author is often early career, did most of the work. Last author is often the one with most experience and judgment, runs the lab, brings in the money.

Brain Stimulation (2010) 3, 65–77

BRAIN STIMULATION

www.brainstimjrnl.com

ORIGINAL RESEARCH

Patient-specific models of deep brain stimulation: Influence of field model complexity on neural activation predictions

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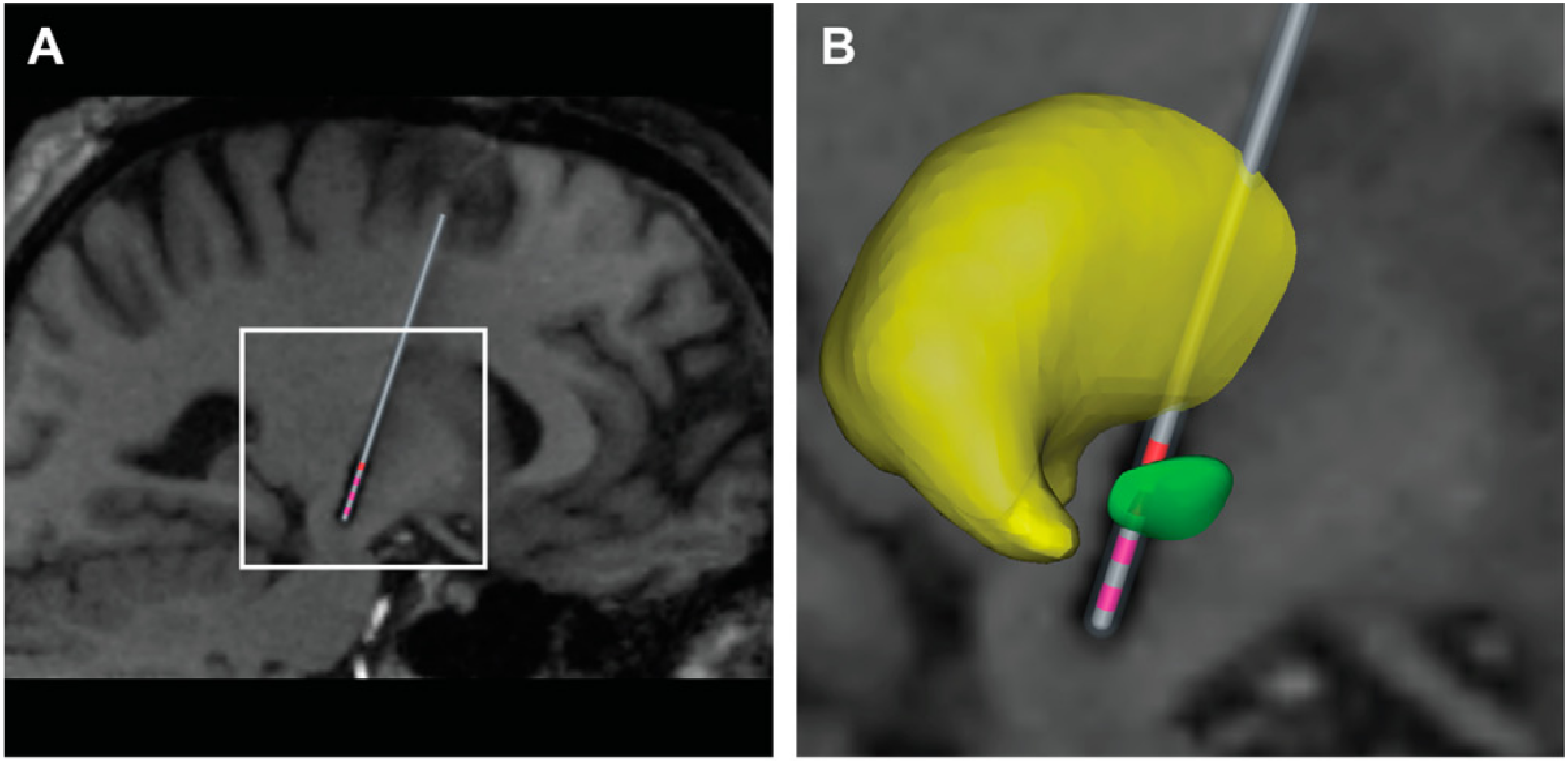
[c]*Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH, USA*

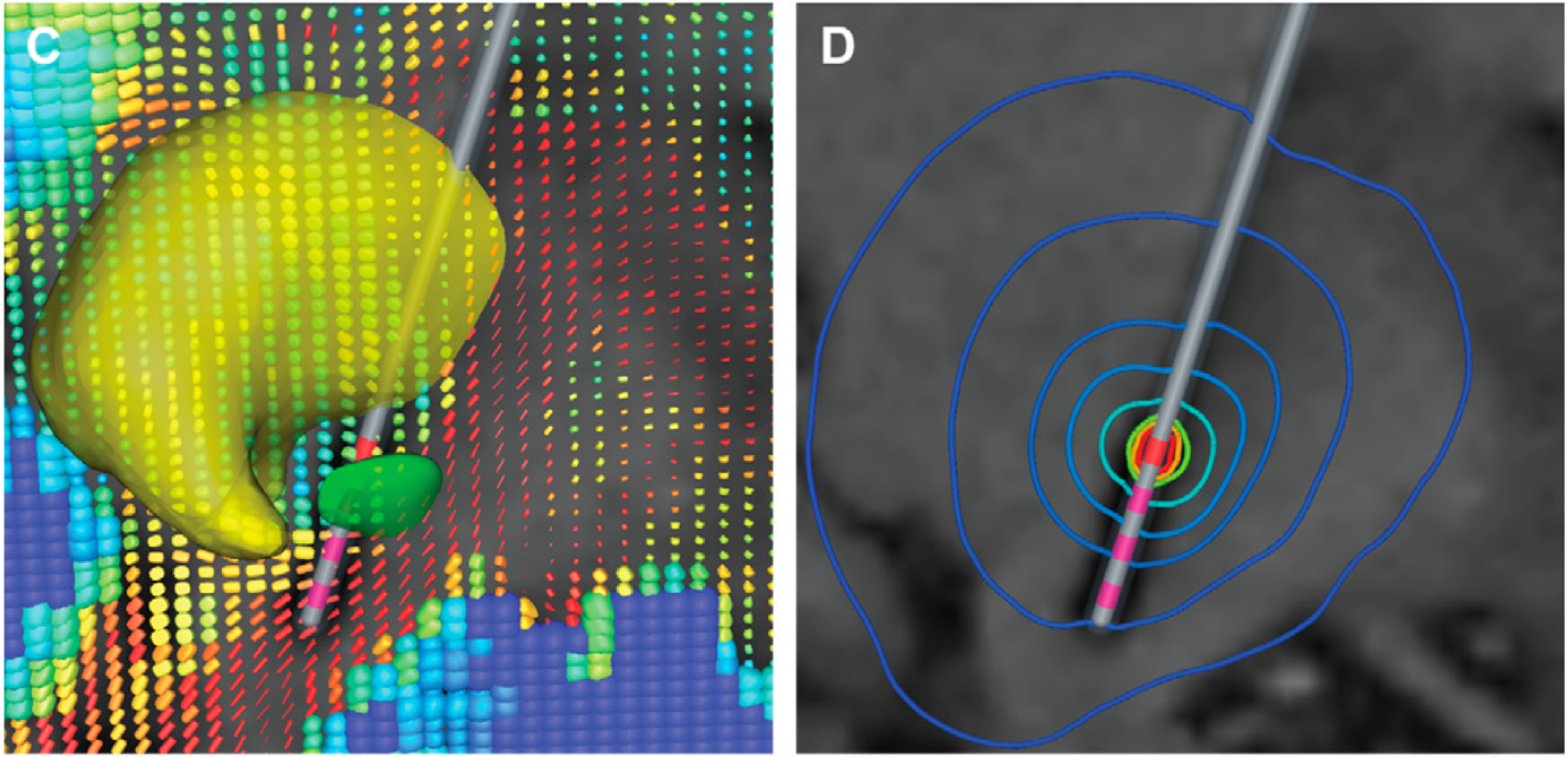
Chaturvedi A, Butson C R, Lempka S F, Cooper S E, McIntyre C C. Patient-specific models of deep brain stimulation: influence of field model complexity on neural activation predictions. Brain Stimulation 3: 65–67, 2010. https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/chaturvedi2010.pdf



Chaturvedi et al. Fig. 1. Patient-specific DBS model.

(A) Sagittal view of post-operative patient MRI with patient-specific electrode location and trajectory. White bounding box is region of interest for B-F.

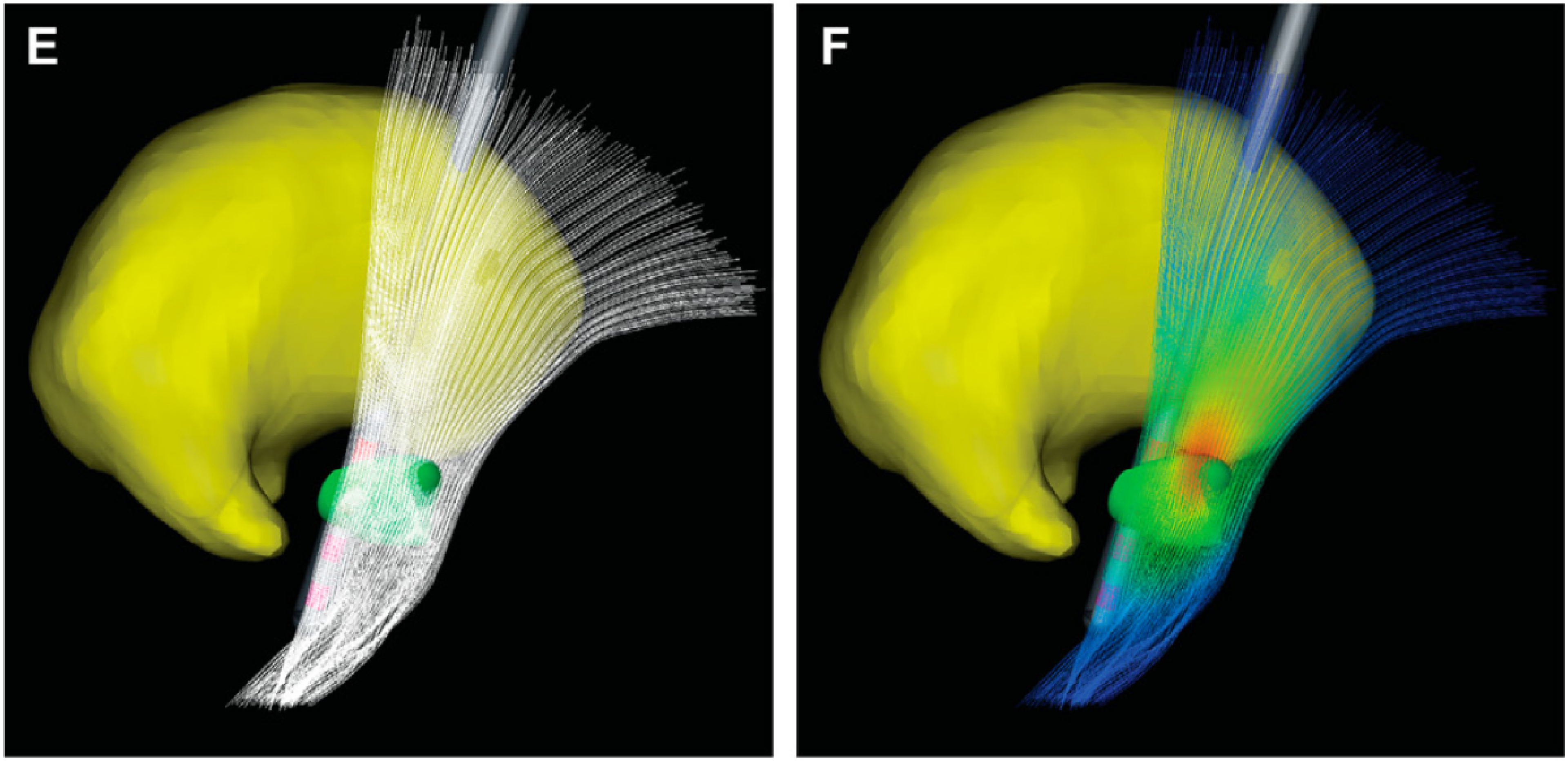
(B) 3D nuclei placed within the same patient-specific modeling environment (thalamus – yellow; subthalamic nucleus – green).



Chaturvedi et al. Fig. 1.

(C) DTI (diffusion tensor image) showing each tensor as an ellipsoid. Colors indicate fractional anisotropy (blue-0; red-1), shapes indicate magnitude and direction of water diffusion (spherical – isotropic; cylindrical – anisotropic).

(D) Isolines showing potential distribution near active contact 3 (blue – low voltage; red – high voltage).



Chaturvedi et al. Fig. 1.

(E) 240 fiber trajectories in the internal capsule (white lines), created using DTI tractography.

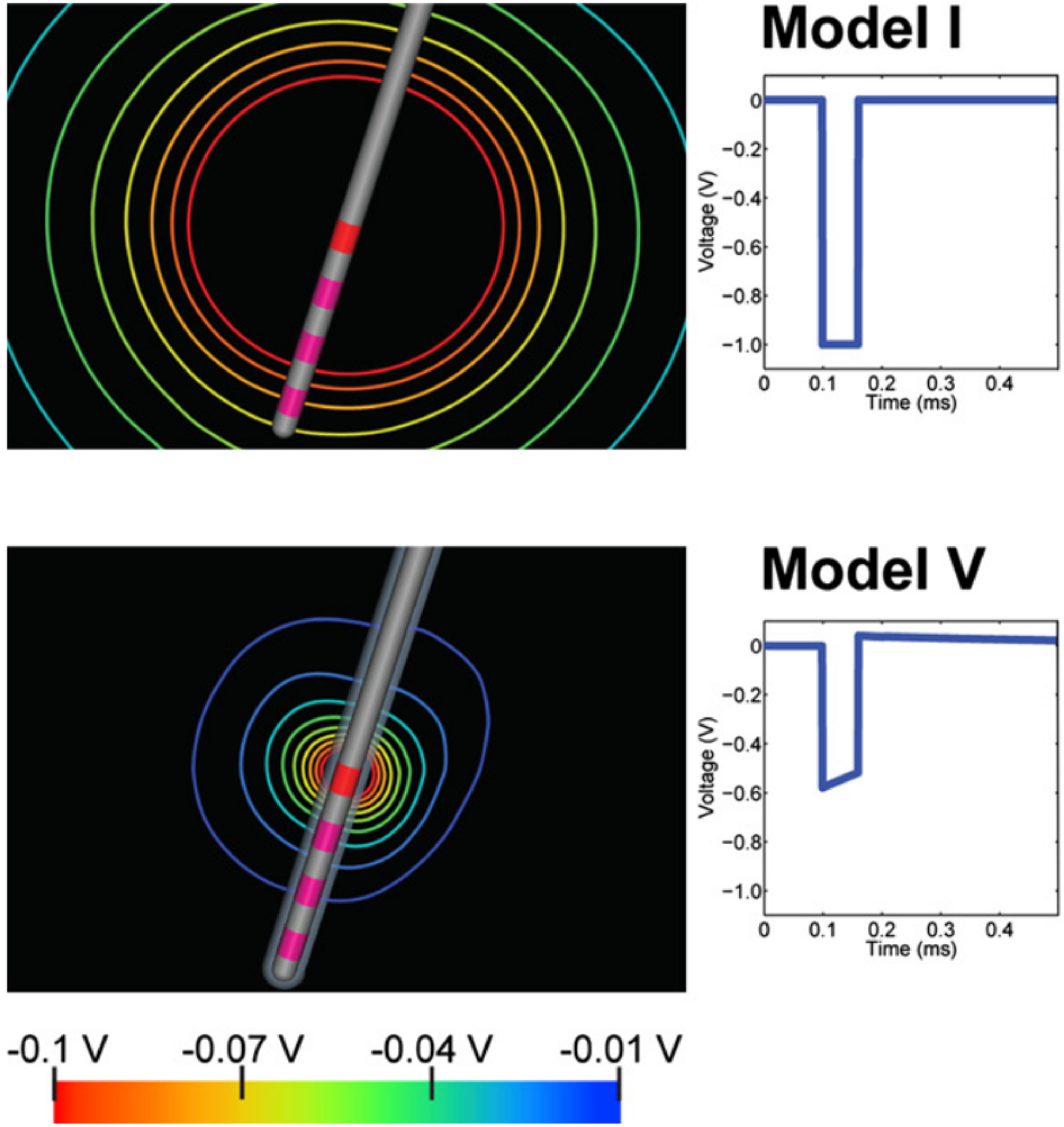
(F) FEM voltage solutions along the 240 fibers after being stimulated with a 25 V cathodic stimulus at contact 3.

Chaturvedi et al. Fig. 2.

Top left: Isopotential contours at peak of a -1V stimulus pulse for the simplest model (assumes electrode-tissue interface is perfect, brain is like a pudding with uniform, isotropic conductivity.

Top right: Corresponding stimulus waveform.

Bottom: Includes effects of electrode encapsulation and capacitance, and brain tissue nonuniformity and anisotropy.



◆ Human Brain Mapping 00:000–000 (2011) ◆

Axonal Pathways Linked to Therapeutic and Nontherapeutic Outcomes During Psychiatric Deep Brain Stimulation

J. Luis Lujan,[1] Ashutosh Chaturvedi,[1,2] Donald A. Malone,[3,4] Ali R. Rezai,[4] Andre G. Machado,[4] and Cameron C. McIntyre[1,2,4]*

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[2]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio 44106*
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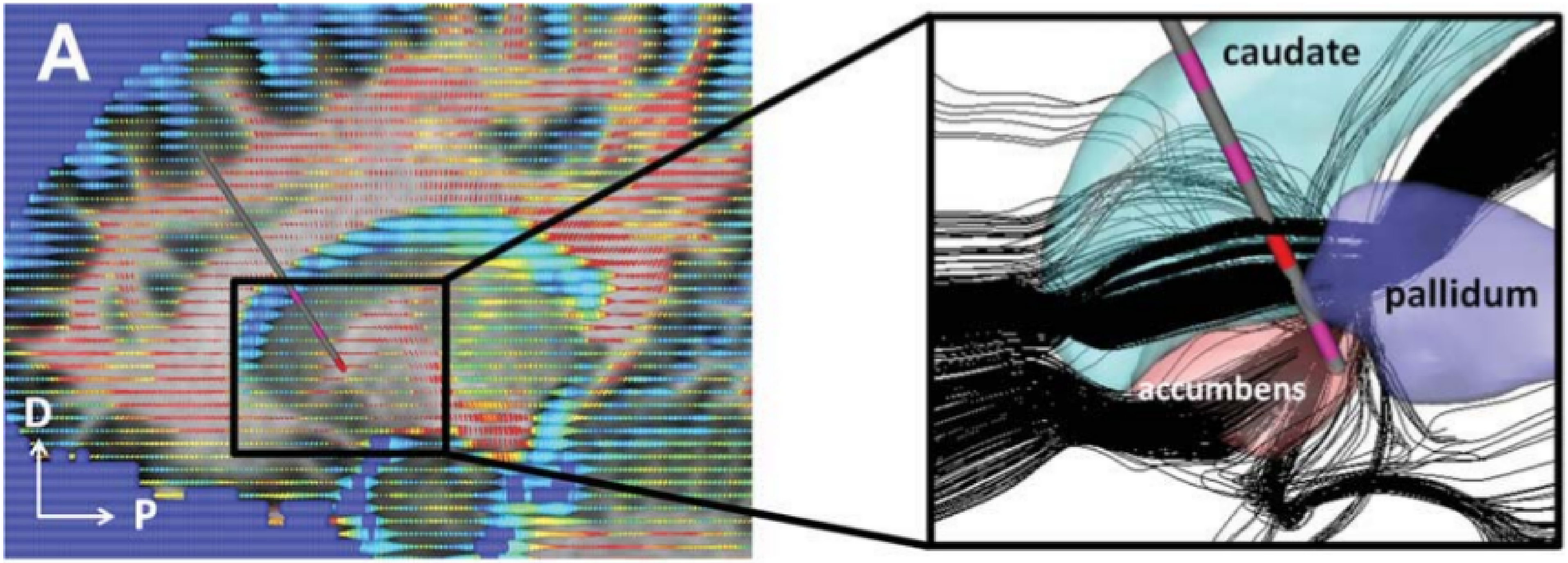
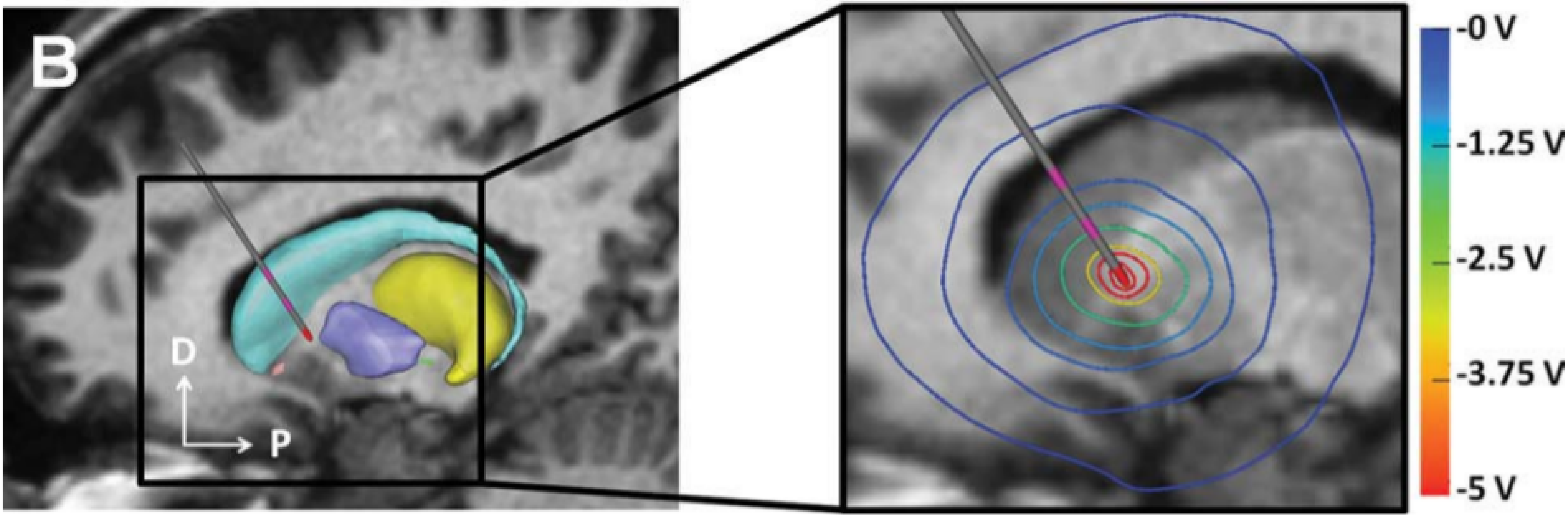
Luján J L, Chaturvedi A, Malone D A, Rezai A R, Machado A G, McIntyre C C. Axonal pathways linked to therapeutic and nontherapeutic outcomes during psychiatric deep brain stimulation. Human Brain Mapping 33: 958–968, 2011. https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/lujan2011.pdf



Luján et al. Fig. 2A.

Left: DTI (diffusion tensor image) showing each tensor as an ellipsoid. Colors indicate fractional anisotropy (blue-0; red-1), shapes indicate magnitude and direction of water diffusion (spherical – isotropic; cylindrical – anisotropic).

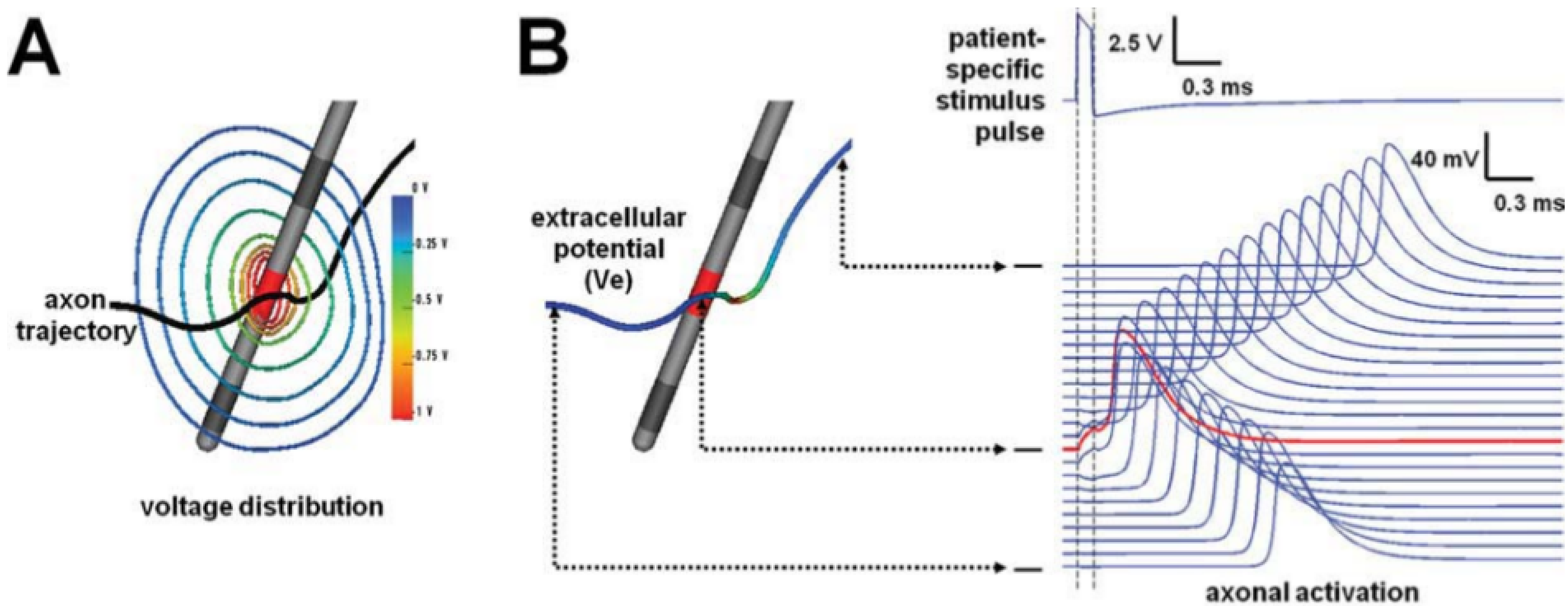
Right: Axon trajectories (black lines) inferred from DTI by streamline tractography from seed points near the patient-specific electrode location.



Luján et al. Fig. 2B.

Left: Deep brain nuclei near stimulating electrode, clockwise from nucleus accumbens (small, pink): caudate nucleus (light blue), thalamus (yellow), globus pallidus (purple).

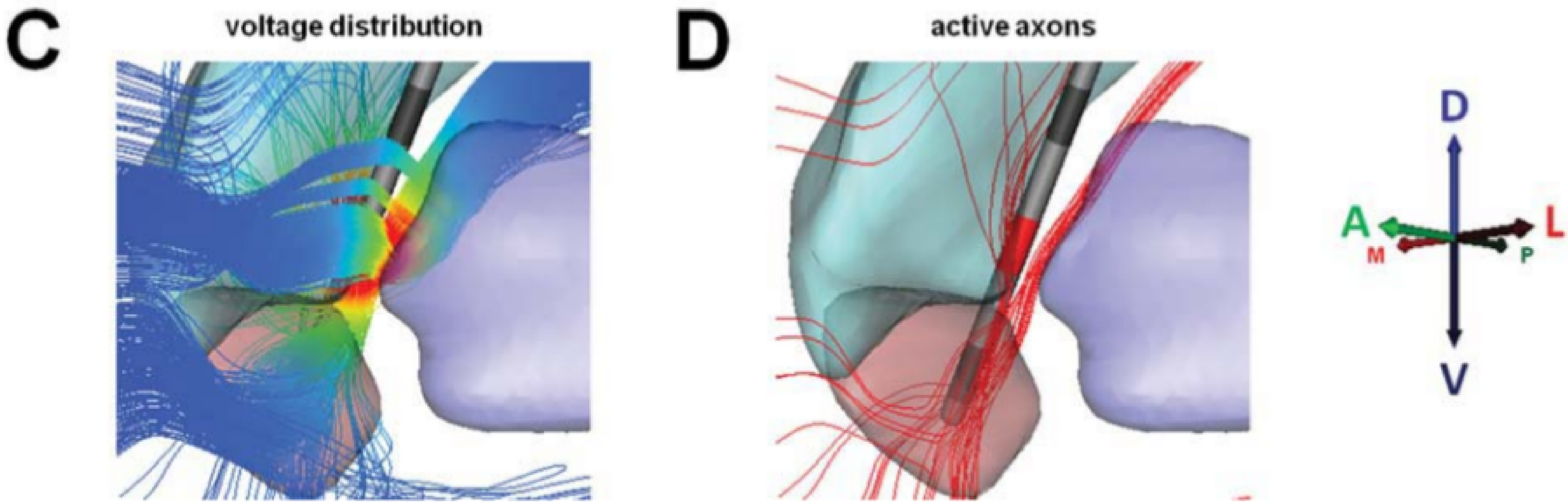
Right: Isopotential controus produced by monopolar stimulation in the ventral anterior internal capsule.



Luján et al. Fig. 3.

A. Trajectory of a myelinated axon passing near a DBS electrode. Patient-specific stimulation produces electric field with indicated contours. Color scale ranges from 0V (blue) to -1V (red).

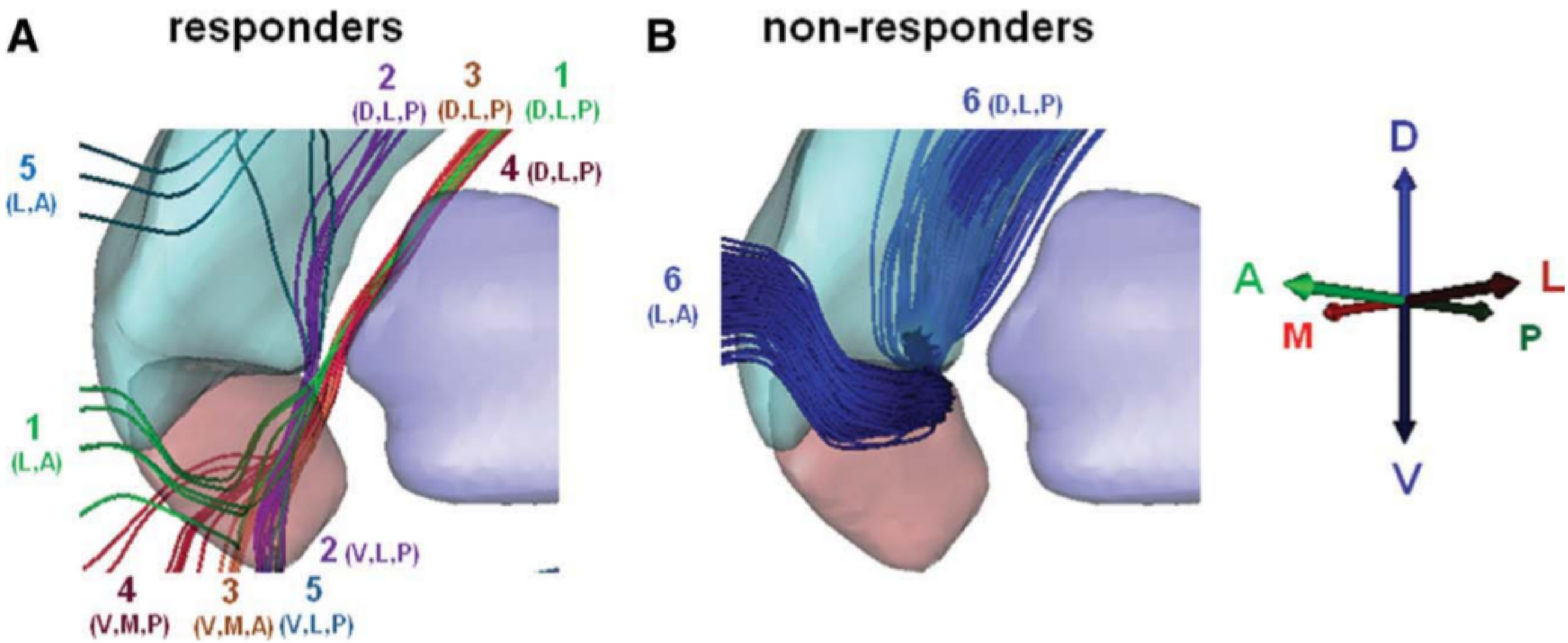
B. Left: Axon redrawn in color to show stimulus-induced extracellular potential. Stimulation triggers a spike at the node of Ranvier where the second spatial derivative of extracellular potential is largest (not where extracellular potential is most negative).



Luján et al. Fig. 3.

C. Extracellular potentials calculated from patient-specific models of current and voltage spread in brain tissue were used as forcing functions in models of axons in the ventral anterior internal capsule. Nucleus accumbens (small, pink), caudate nucleus (light blue), thalamus (yellow), globus pallidus (purple).

D. DBS-activated axons in one patient. Diagram on right is a 2-D projection of three orthogonal axes (dorsal-ventral, anterior-posterior, and lateral-medial, bigger means closer to the reader).



Luján et al. Fig. 5.

Activated pathways common to at least 75% of patients with therapeutic (A) or nontherapeutic (B) response to DBS. Nucleus accumbens (small, pink), caudate nucleus (light blue), thalamus (yellow), globus pallidus (purple).

In the study by Luján et al.

- How many patient-specific electrodes were involved?
- How many axon models were used, and how many patient-specific DBS electric fields were they subjected to?
- How many simulations using NEURON were executed?
- Where was the computer that executed these simulations?

Reading a Scientific Paper

- Title
- Authors and affiliations
- Abstract
- Introduction
  - Statement of the problem/hypothesis
  - Scientific context (existing evidence, current understanding)
- Methods
  - Experimental subjects (animals, human subjects)
  - "Experimental preparation": organ / tissue / cell / protein / gene / computational model
  - Experimental manipulations: behavioral, surgical, pharmacological, diet, electrical stimulation . . .
  - Data collected, analysis methods
- Results (experimental observations)
- Discussion
  - Principal conclusions
  - Limitations or weakesses of this study
  - Future work
- Acknowledgments
- Conflicts of Interest
- References
  - >>> and <<<
- Having read this paper, what new thoughts do you have?

Reading a Scientific Paper

Now let's take a closer look at Luján et al..

Extracellular Stimulation of a Neuron

Download

```
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/
  rehs2024/extracellular_stim_and_rec.zip
```

Extract the zip file into an empty folder.

In a terminal, cd to that folder, then execute

```
nrnivmodl
```

That should compile the file `xtra.mod`

Next execute the command

```
nrngui initxstim.hoc
```

or, if you prefer to use NEURON from Python, execute

```
python3
```

and then at the Python prompt execute

```
from neuron import h, gui
h.load_file("initxstim.hoc")
```

Assignment for Meeting 5

Following the outline a few slides back, examine the corresponding parts of one of these papers. In the Introduction, Methods, Results, and Discussion sections, identify one or two items that seemed noteworthy to you.

Capogrosso M, Wenger N, Raspopovic S, Musienko P, Beauparlant J, Bassi Luciani L, Courtine G, Micera S. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. Journal of Neuroscience 33: 19326–19340, 2013.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/capogrosso2013.pdf

Barra B, Conti S, Perich M G, Zhuang K, Schiavone G, Fallegger F, Galan K, James N D, Barraud Q, Delacombaz M, Kaeser M, Rouiller E M, Milekovic T, Lacour S, Bloch J, Courtine G, Capogrosso M. Epidural electrical stimulation of the cervical dorsal roots restores voluntary upper limb control in paralyzed monkeys. Nature Neuroscience 25: 924–934, 2022.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/rehs2024/barra2022.pdf

Assignment for Meeting 5 *continued*

Of the various issues raised by these authors
Capogrosso M, Lempka S F. A computational outlook on neurostimulation. Bioelectronic Medicine 6: 10, 2020.
https://www.neuron.yale.edu/ftp/ted/nsgoutreach/capogrosso2020.pdf
which three seem most important to you, and why?