Modalities of Non-Invasive Modulation of Brain Function and Modeling Electrical Dose

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Center for Devices and Radiological Health
Office of Science and Engineering Laboratories

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IOM Workshop on Non-Invasive Modulation of the Central Nervous System

U.S. Food and Drug Administration
Protecting and Promoting Public Health

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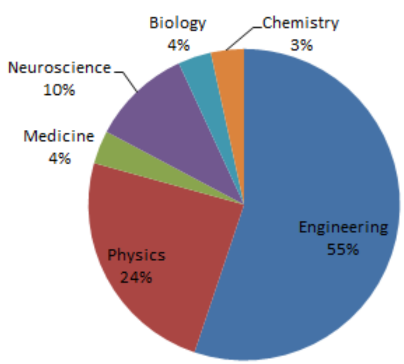
Regulatory Science in the FDA Division of Biomedical Physics

Regulatory science:
development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA regulated products

Who we are:

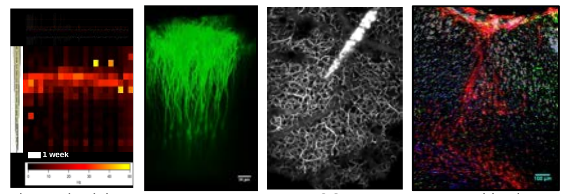
- 30 regulatory scientists
- 60 fellows, students, contractors

Field



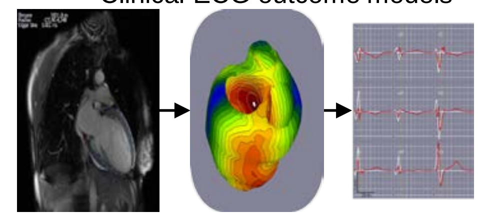
Biophysics

Neural implant reliability



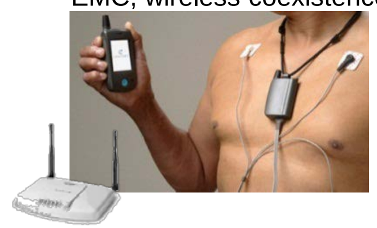
Electrophysiology TPM OCA Immunohistology

Clinical ECG outcome models



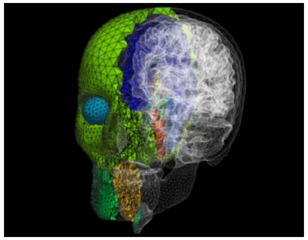
Electromagnetics

EMC, wireless coexistence



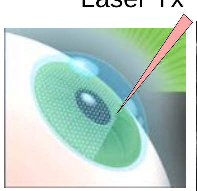
The Virtual Family

High resolution head model

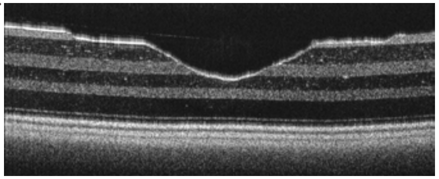


Optics

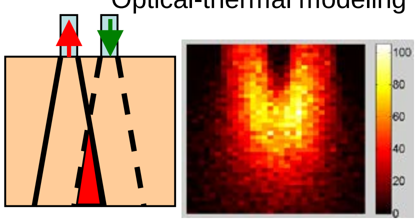
Laser Tx



Retina Phantom

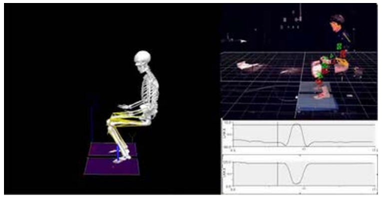


Optical-thermal modeling



Functional Performance & Device Use

Functional Models



Human Factors

Noninvasive Modulation of Brain Function

Possible Modalities

1. Electromagnetic
   - Transcranial DC
   - Transcranial AC
   - Magnetic Stimulation (low and high frequency)
2. Optical
   - Near IR
   - Channel Rhodopsin
3. Mechanical
   - Ultrasound

1. Transcranial DC, then and now

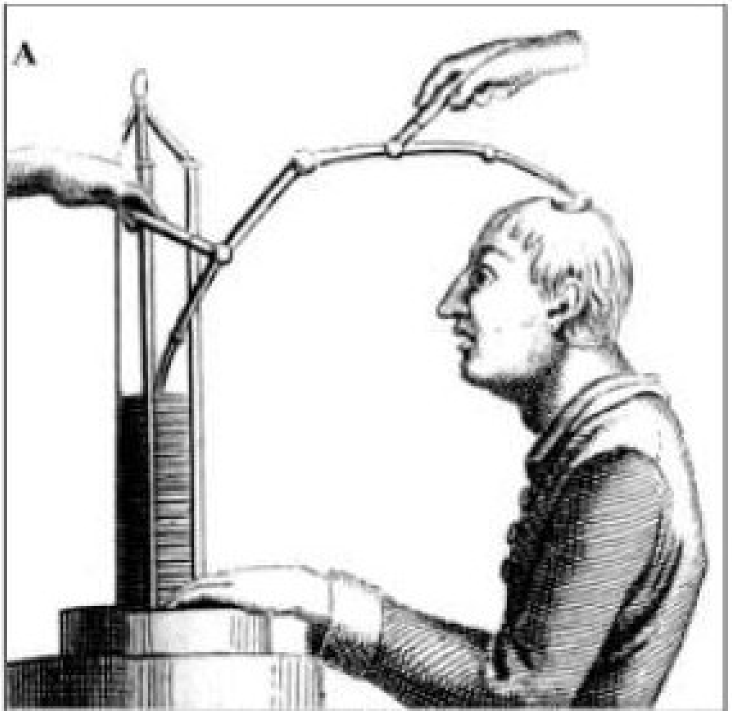
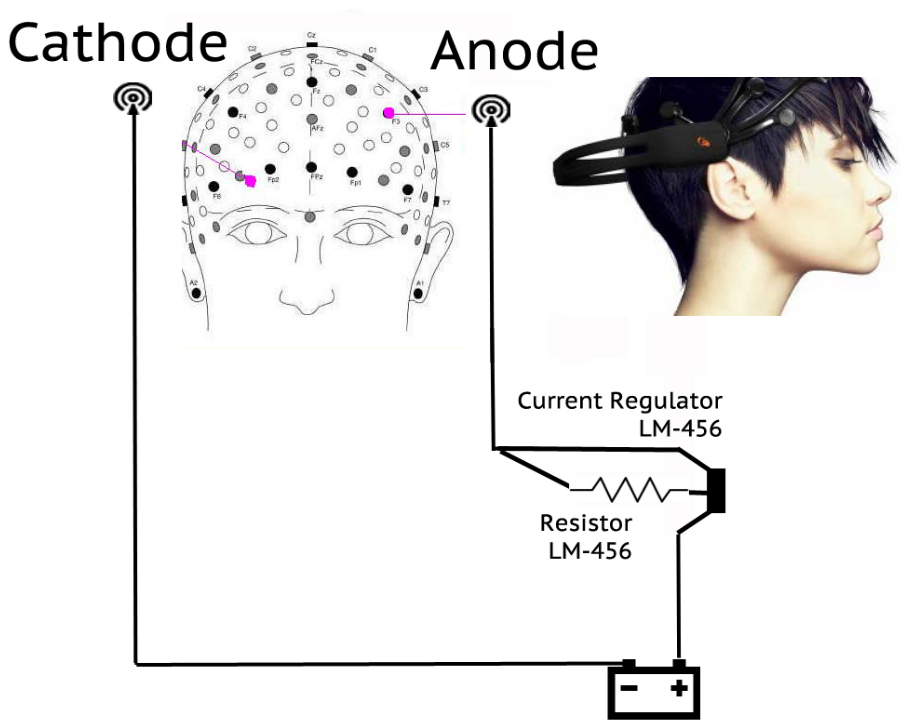


Plate V in Aldini J., Essai théorique et expérimental sur le galvanisme. Paris: Fournier Fils, 1804. Galvanism is being applied on the head of Luigi Lanzarini.



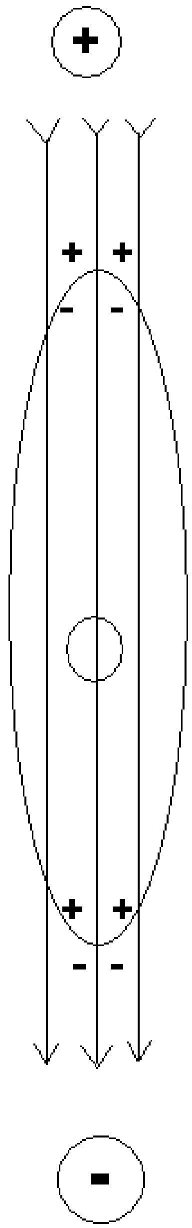
“DIY tDCS brain-boosting kit”

Parent, Can. J. Neurol. Sci. 2004; 31: 576-584

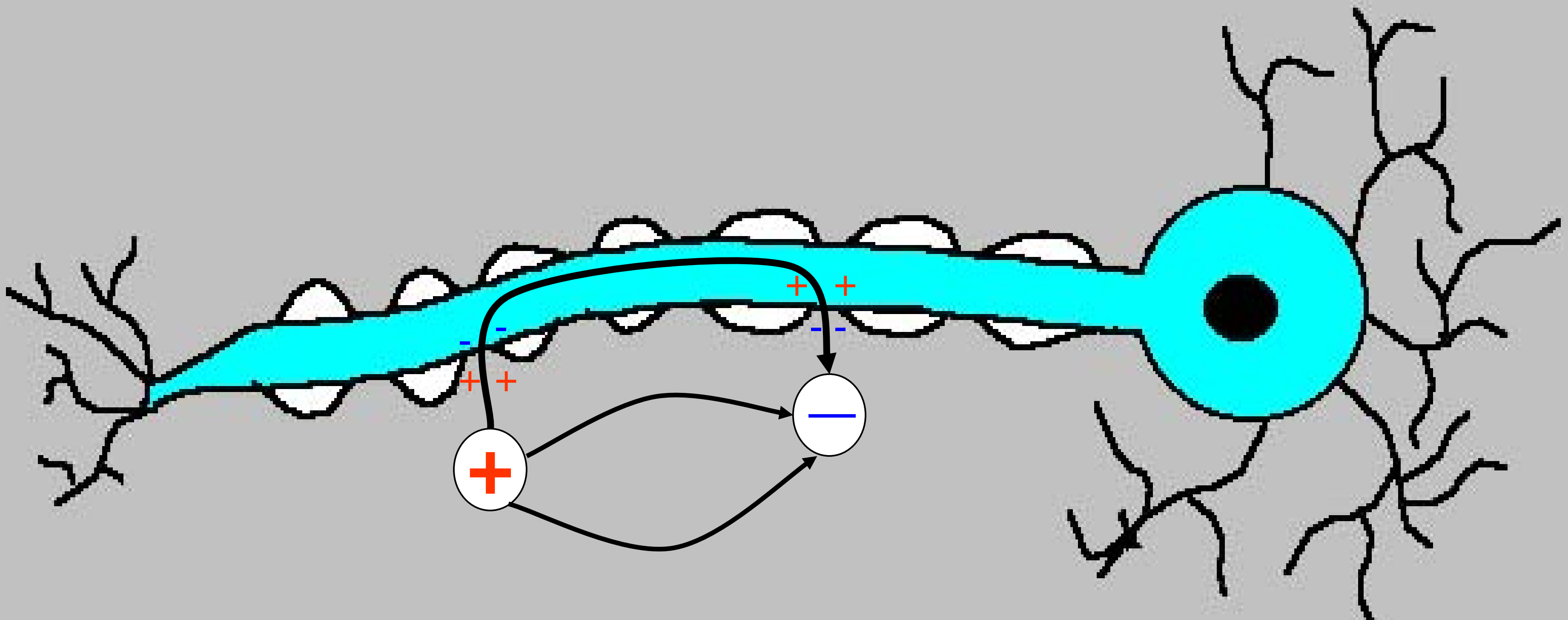
http://www.extremetech.com/extreme/121861-goflow-a-diy-tdcs-brain-boosting-kit

Extracellular Current Polarizes Cells

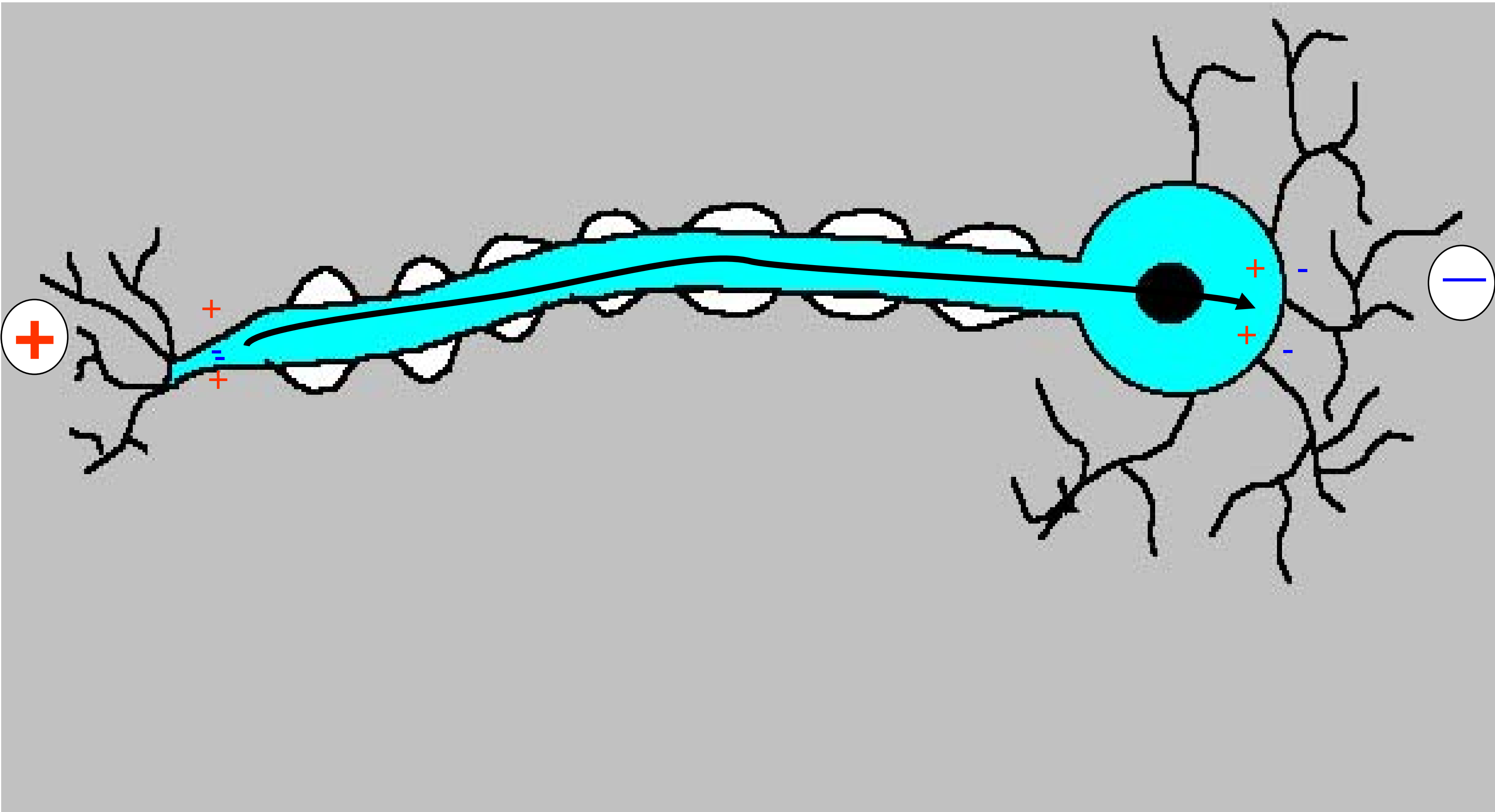
a. Location of current
b. Current polarizes cells at opposite ends.
c. Longer cells are polarized more at their ends
d. Cell alignment with direction of current flow gives maximum polarization
e. Geometry and branching
f. Waveform
g. Cell electrophysiology
h. Models are useful in predicting



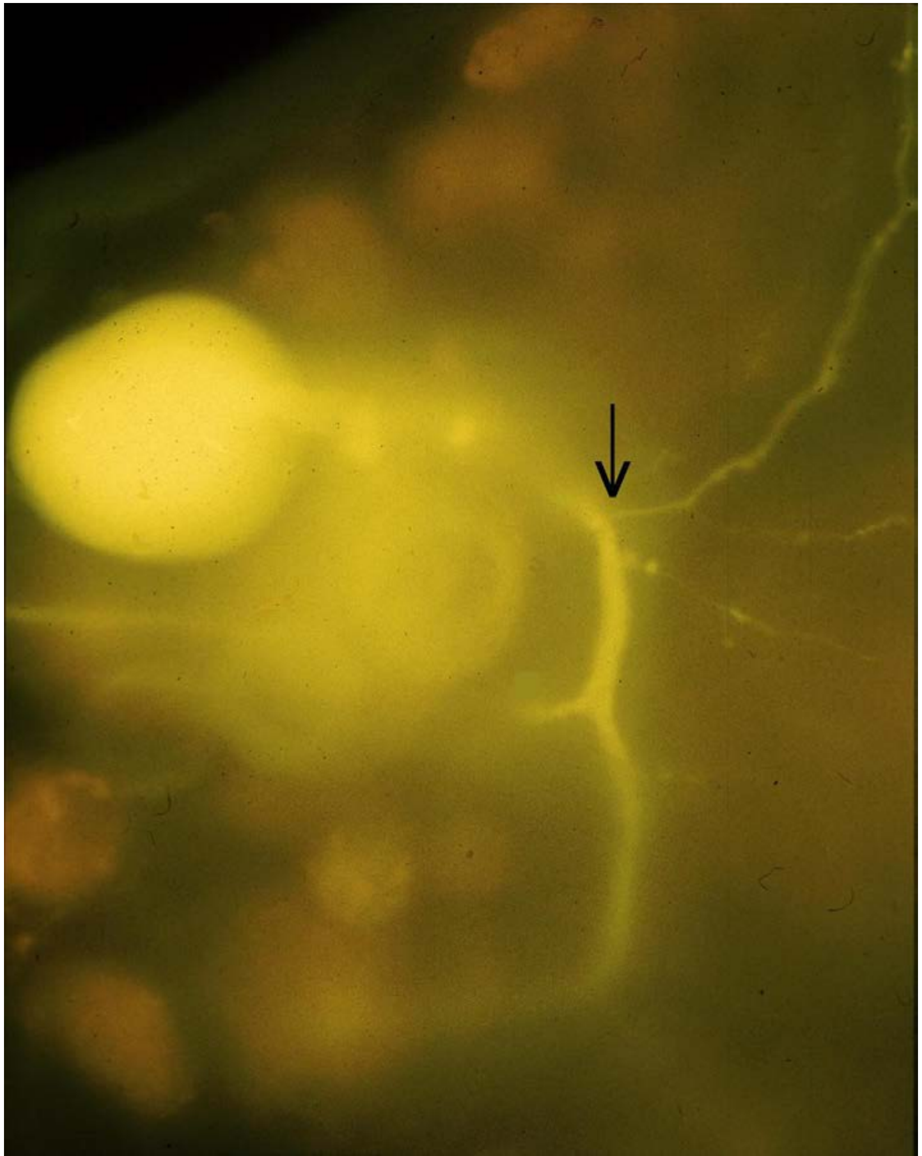
Local Nerve Stimulation

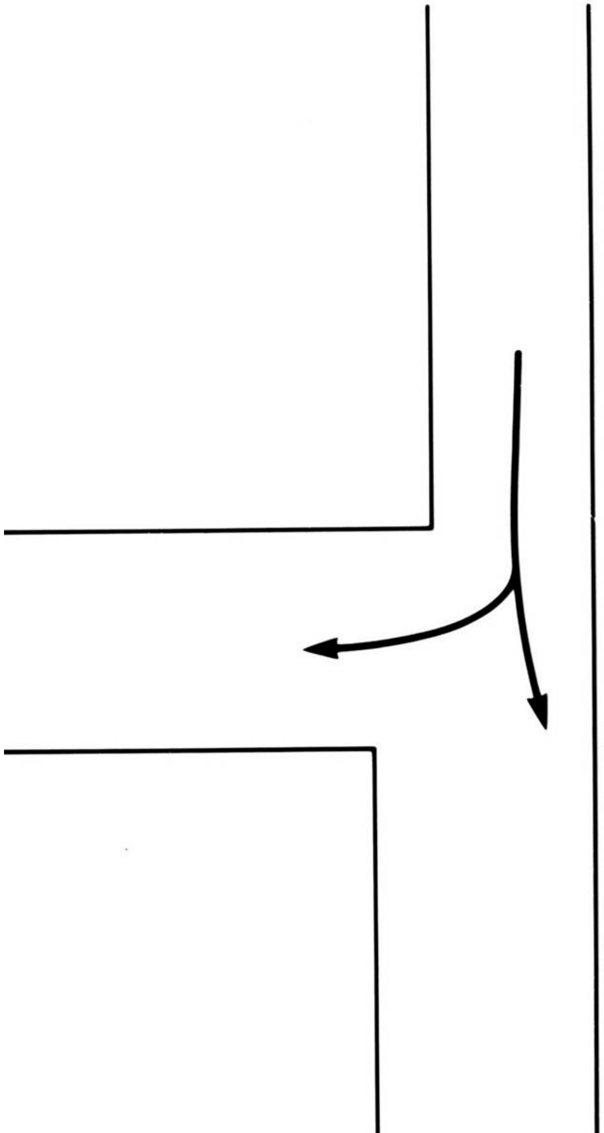


Electric Field Stimulation

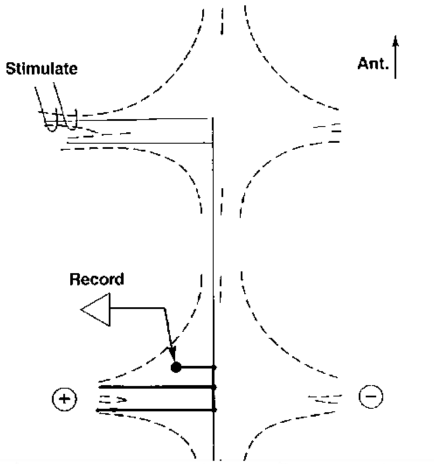


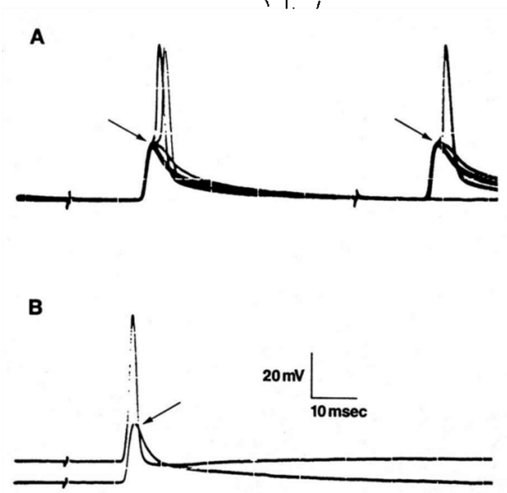
Modulation at Branch Point Failure Site



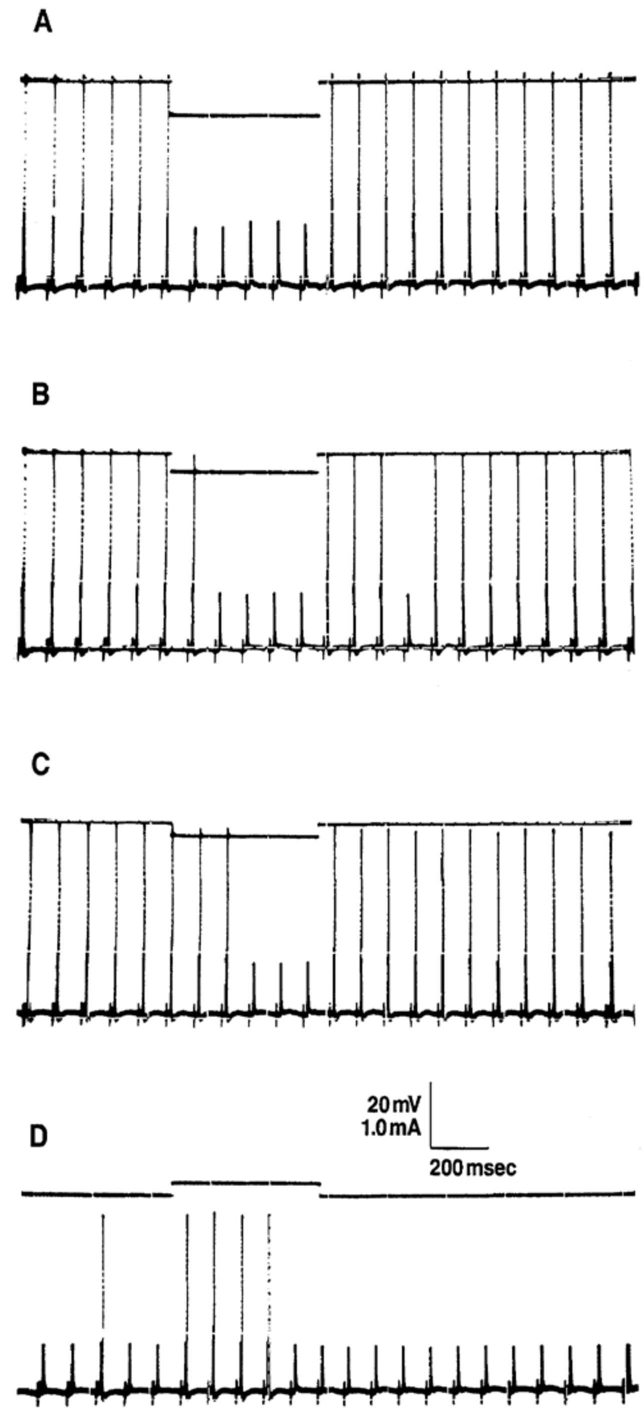


DC Blocks or Relieves Block

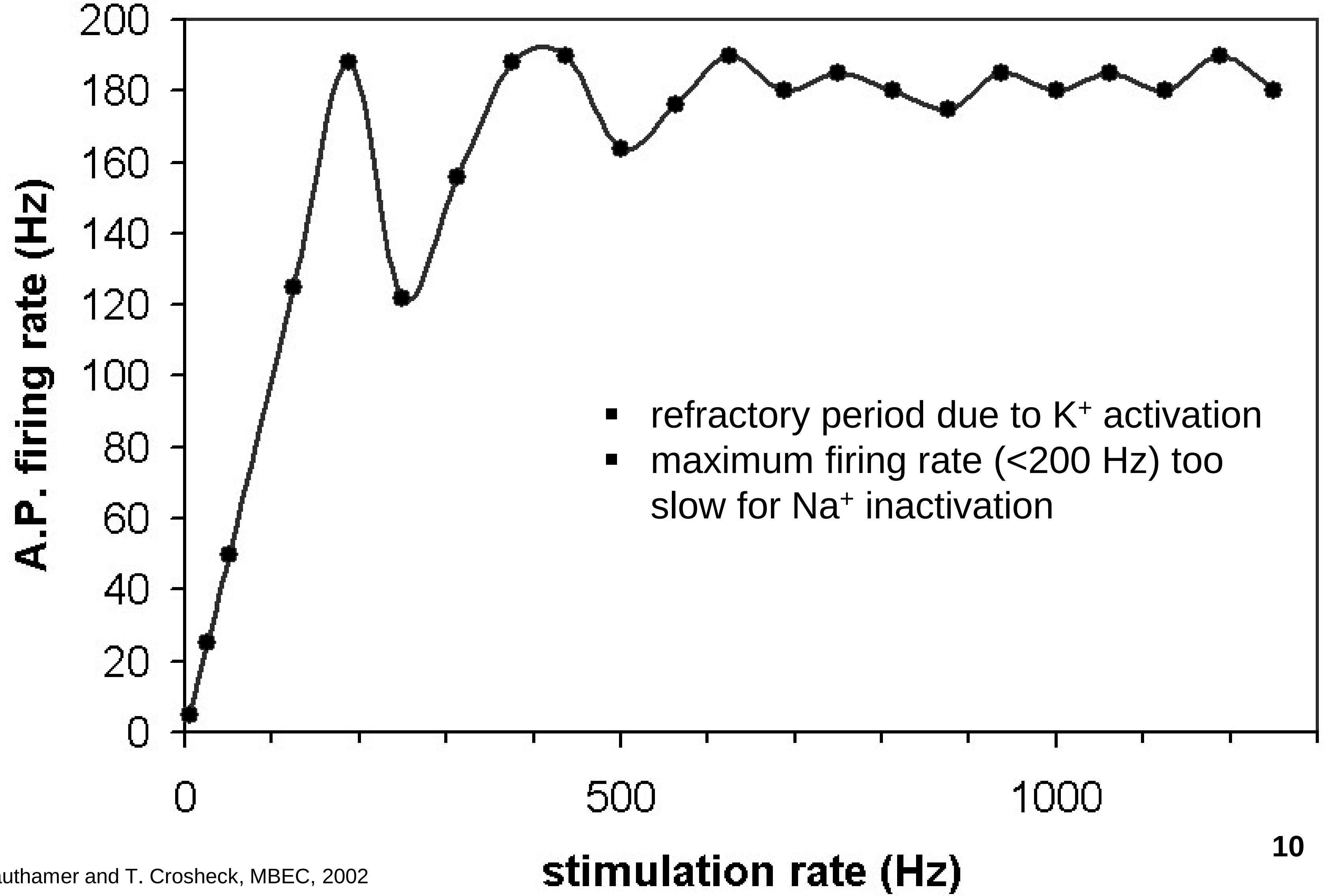




63 mV/cm is minimum field for producing block



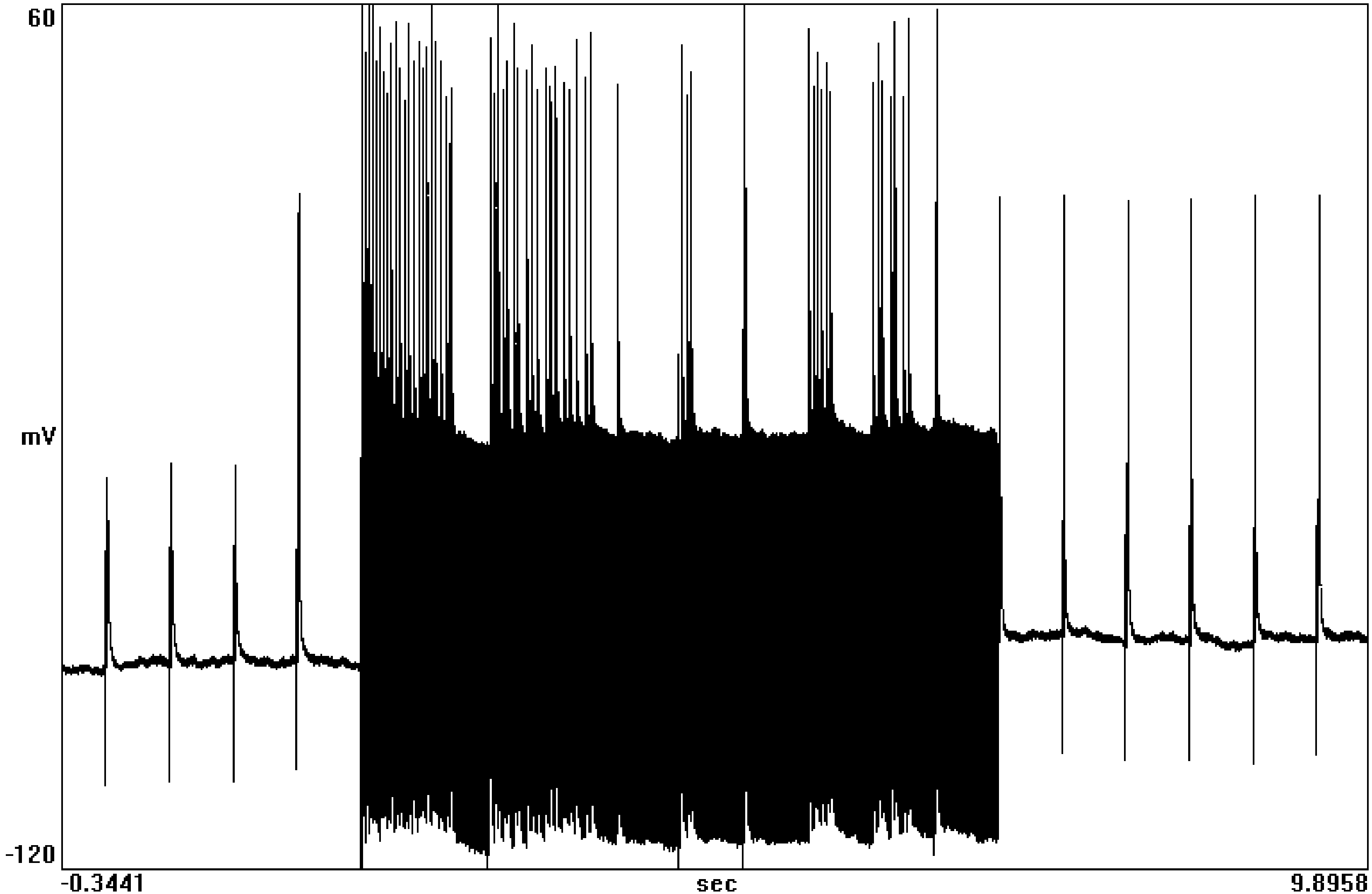
AC I/O for Unmyelinated Cell Model



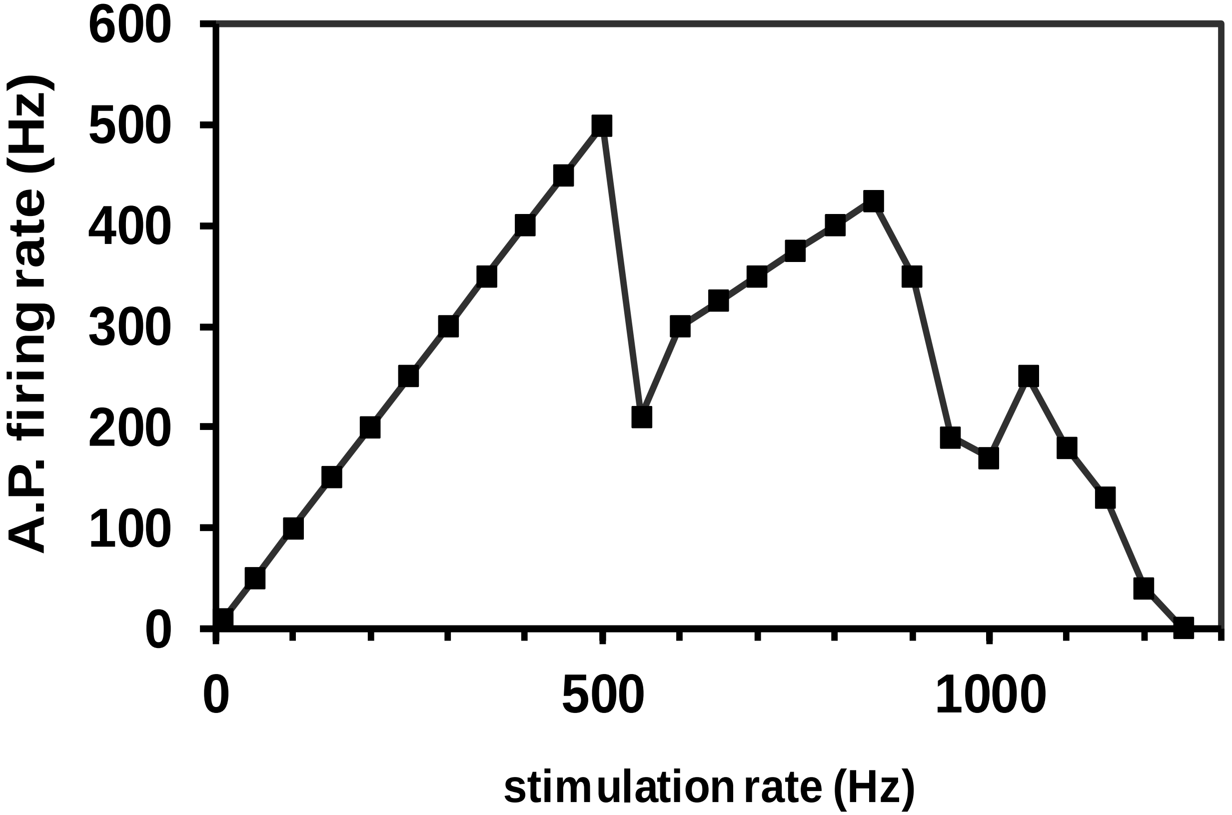
- refractory period due to K^+ activation
- maximum firing rate (<200 Hz) too slow for Na^+ inactivation

from V. Krauthamer and T. Crosheck, MBEC, 2002

High Frequency Firing in Unmyelinated Cell



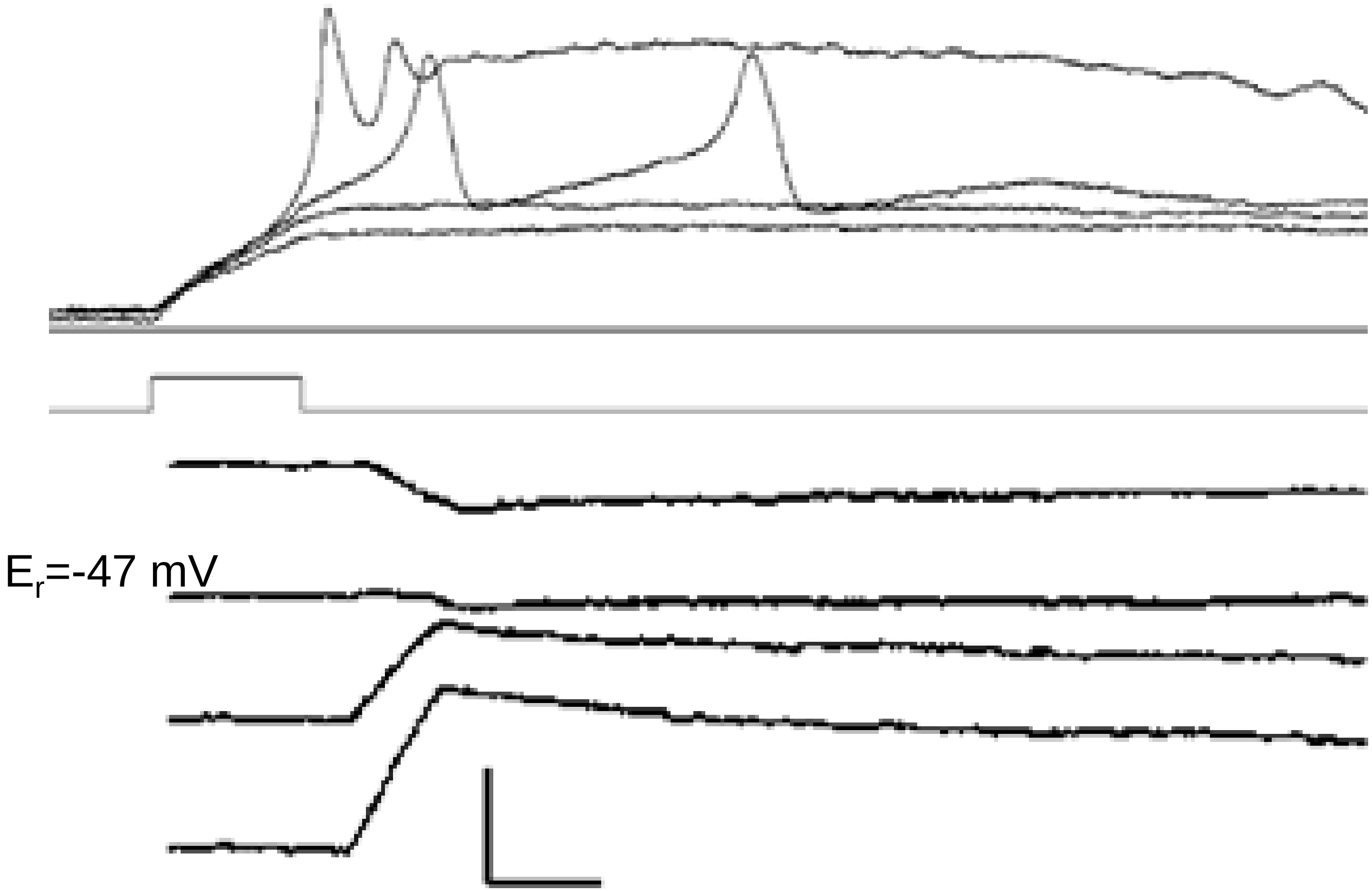
AC I/O for Myelinated Fiber Model – High Frequency Block



- refractory period due to Na^+ inactivation
- maximum firing rate (~500 Hz) causes Na^+ inactivation and refratoriness

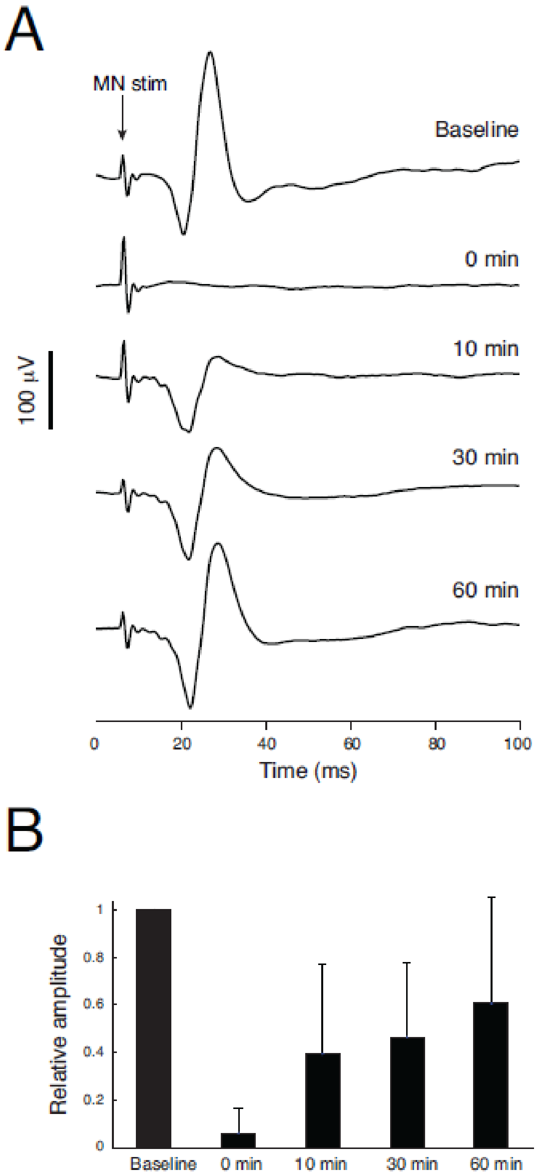
Krauthamer, Crosheck MBEC, 2002

2. Light: NIR (1889nm) on DRG Cells



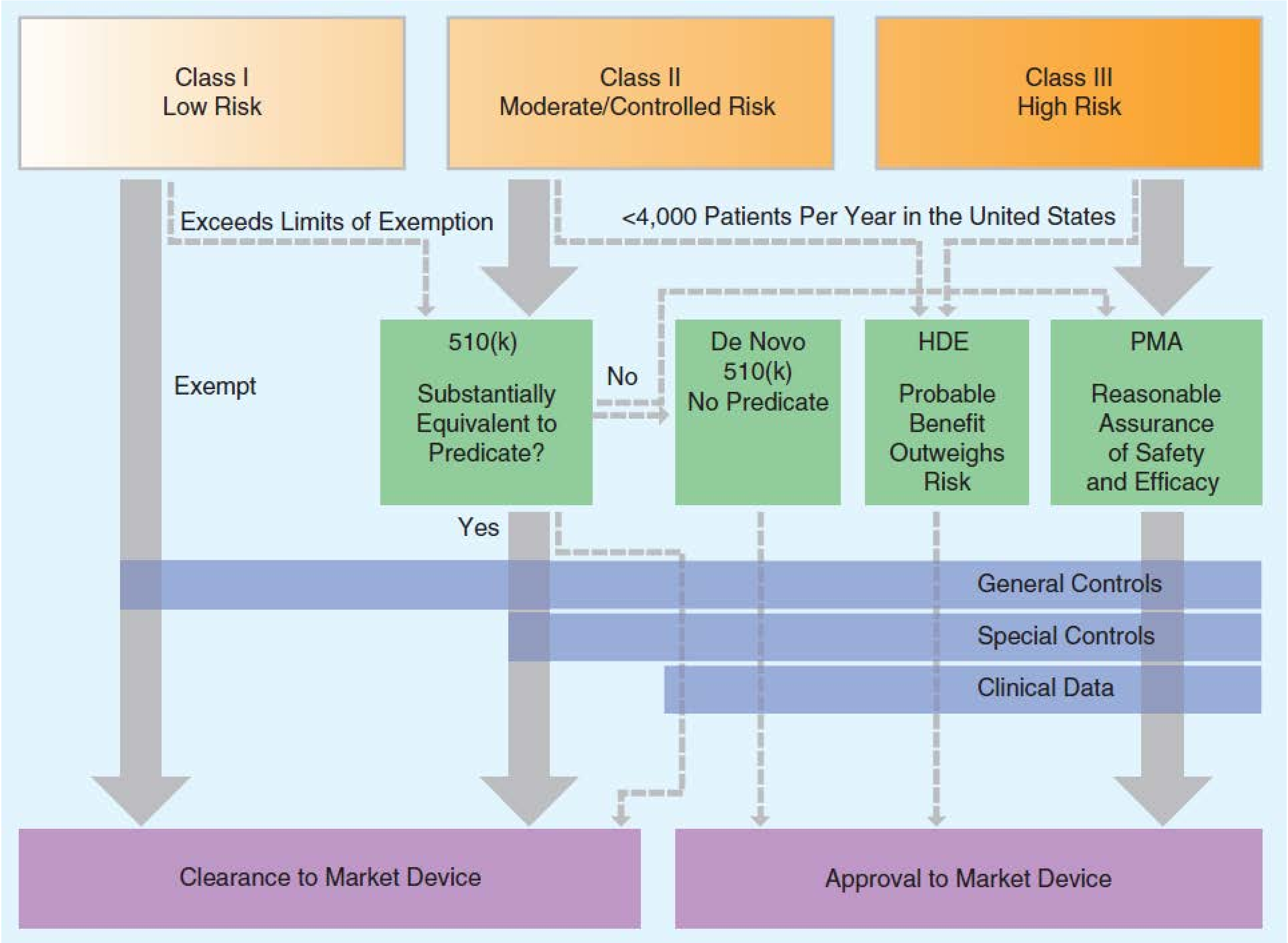
Katz, Ilev, Krauthamer, Kim, Weinreich, NeuroReport 2010, 21:662-666

3. Ultrasound Alters Evoked Potentials



Somatosensory evoked potentials recorded from epidural cortical electrodes following HIFU. SSEP amplitude drops following application.

CDRH Regulatory Pathways



Welle CG and Krauthamer V, "FDA Regulation of Invasive Neural Recording Electrodes", IEEE PULSE, MARCH/APRIL 2012, pp. 37-41

Models Used for Assurance of Device Safety and Effectiveness

	Human Trial	Animal Model	In Vitro Model (phantom)	Computer Model
cost	very high	moderate	low	low (after development)
time	long	moderate	short	short
ability to vary parameters	not easy	limited	limited	high (good learning tool)
testing involving harm	no, unethical	restricted	yes	yes
simplifying assumptions	none	none	many and always	always (limiting)
relevance	direct	variable (species)	limited	variable (depends on validation)
testing of disease state	yes	difficult	simplified states	yes
experimental control	difficult	good	high	high
interpretation of data and ability to predict	not easy	yes	limited	Yes – can predict device and drug interactions

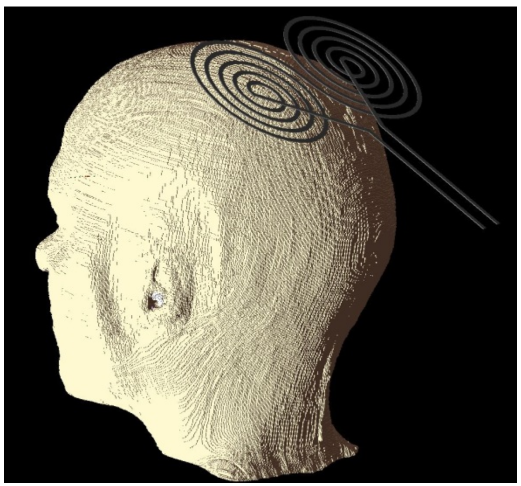
Modeling exposure of different brain locations to electric fields

Modeling electric field in the brain

- "Macroscopic" modeling (Organ level)
  - External source (e.g., TMS, tDCS, tACS)
  - Anatomical precision
  - Electrical properties of brain & anisotropy
- "Microscopic" level (Neuronal response)
  - What is the physiological response associated to a given electric field?
- Model Validation
- Regulatory Science: the "MIDA" model

Macroscopic modeling

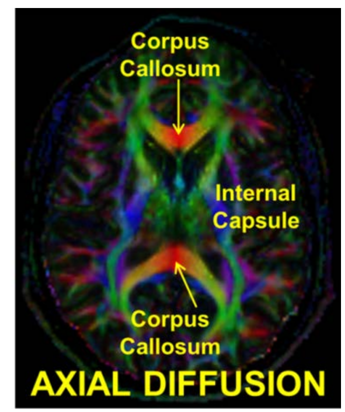
External source (TMS)



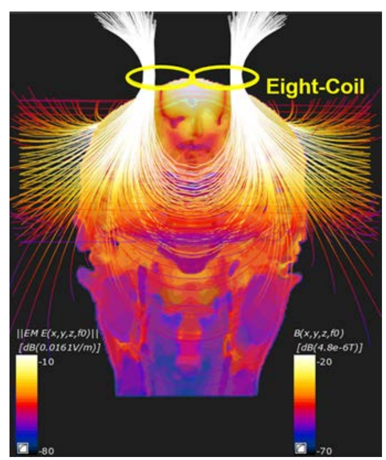
Electrical properties of brain (gray vs. white matter, anisotropy)

Brain GM

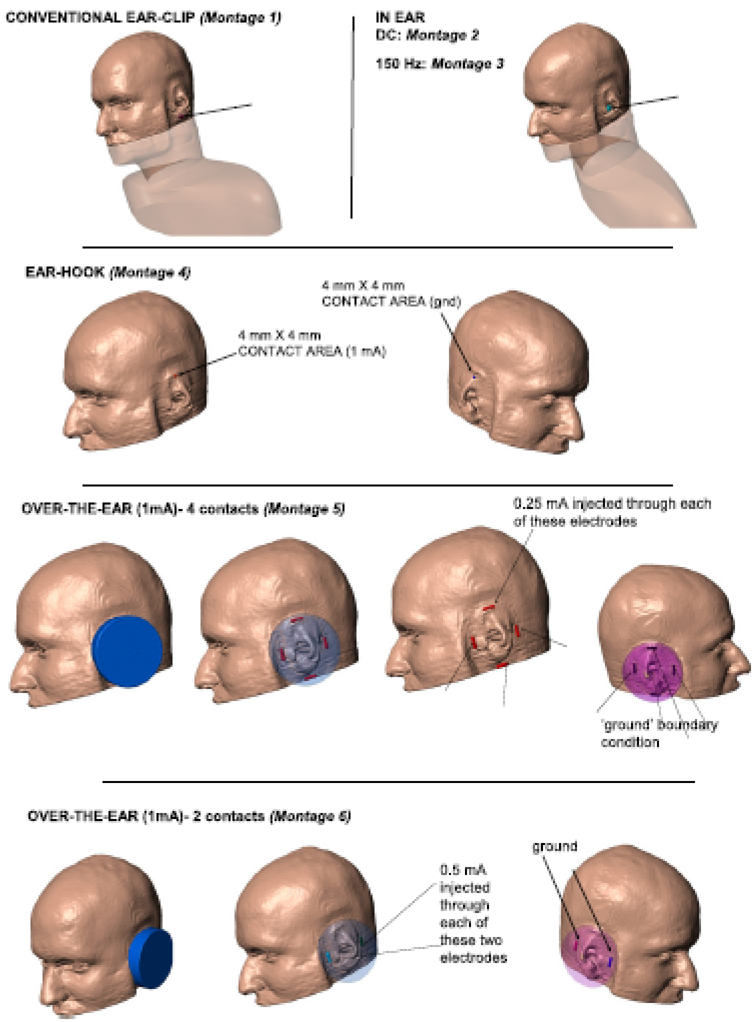
Brain WM

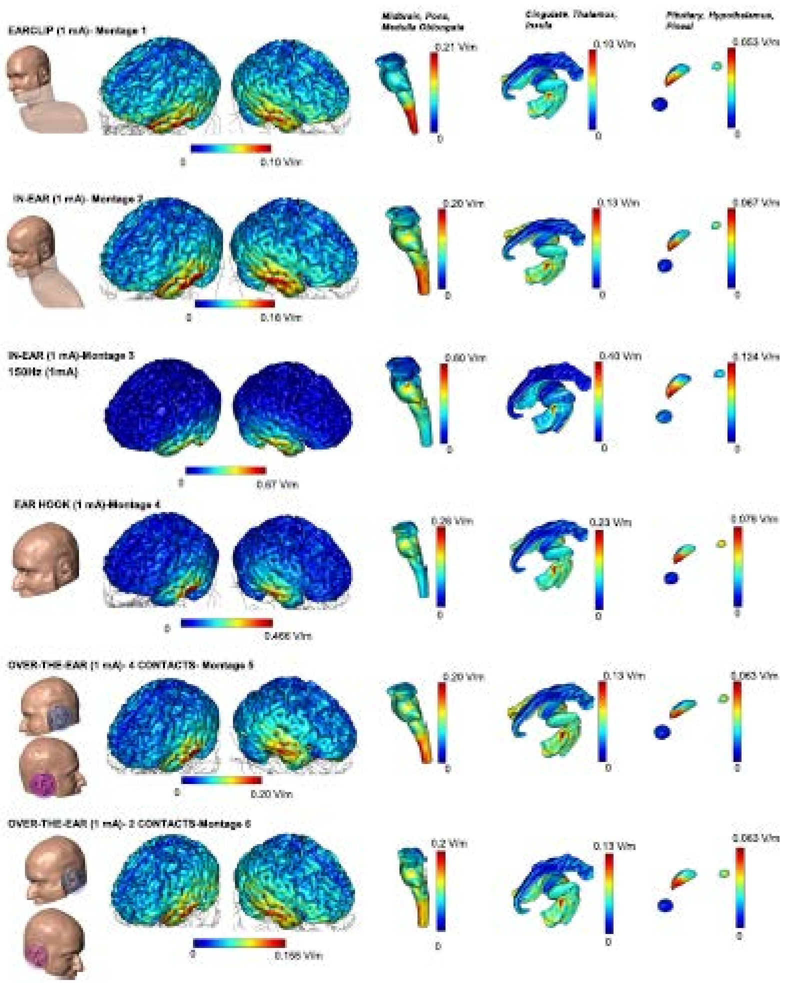


Anatomical precision: where is the electric field?



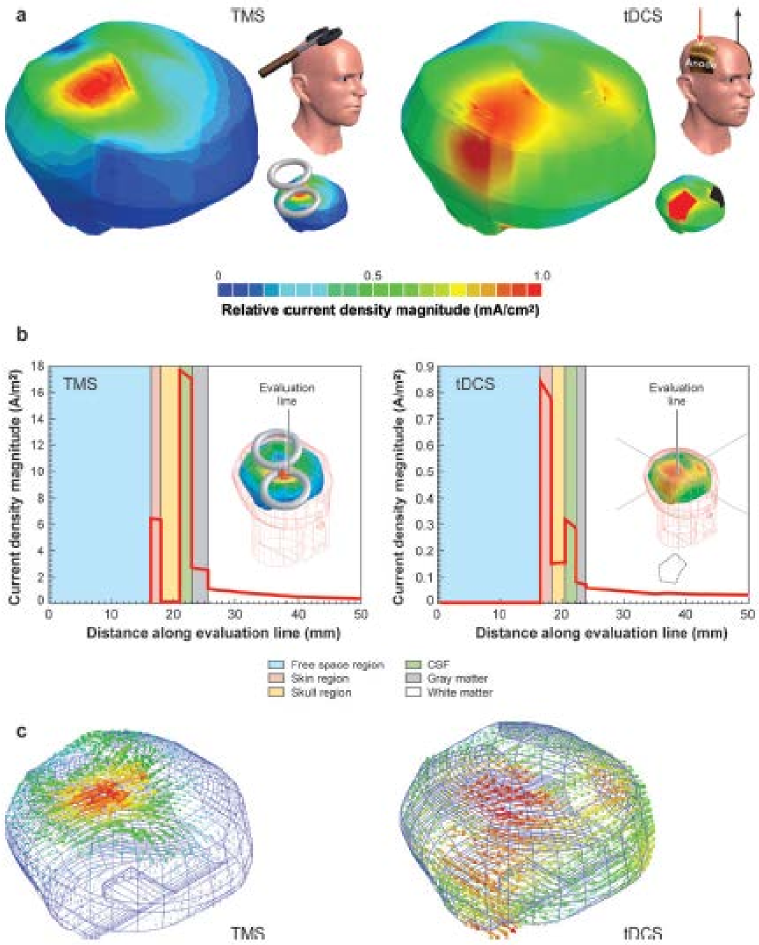
Electric field and source configuration





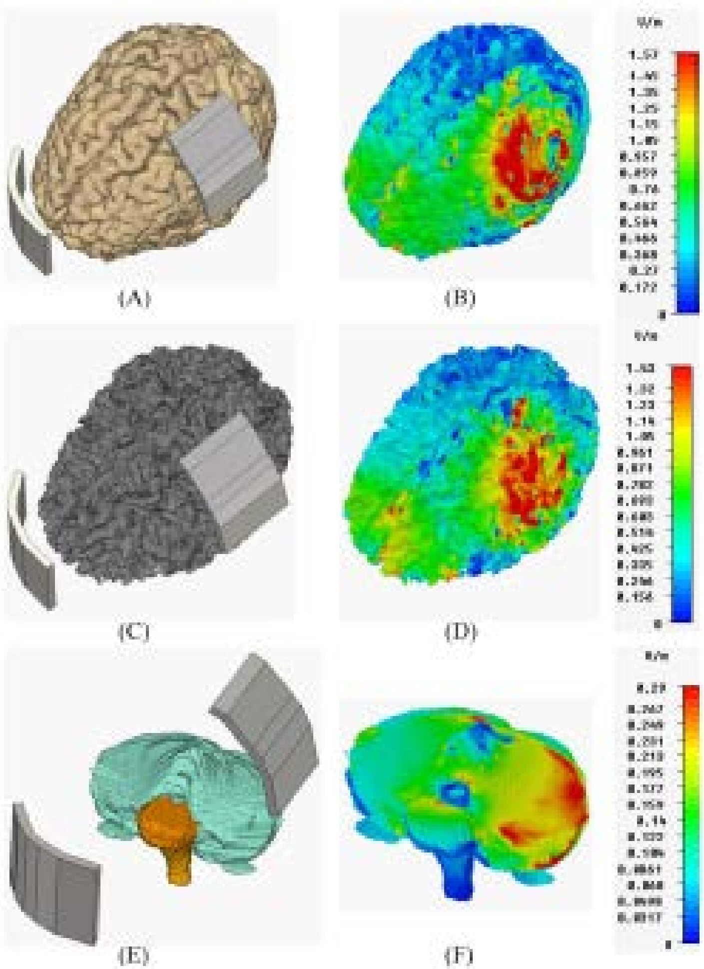
A. Datta et al., NeuroImage 65 (2013) 280–287

Electric field and technology (e.g., TMS vs. tDCS)



Wagner et al., Annu. Rev. Biomed. Eng. 2007. 9:527–65

Computational modeling in support of clinical studies



doi:10.1093/brain/awu343 BRAIN 2015: 138; 428–439 | 428
BRAIN
A JOURNAL OF NEUROLOGY

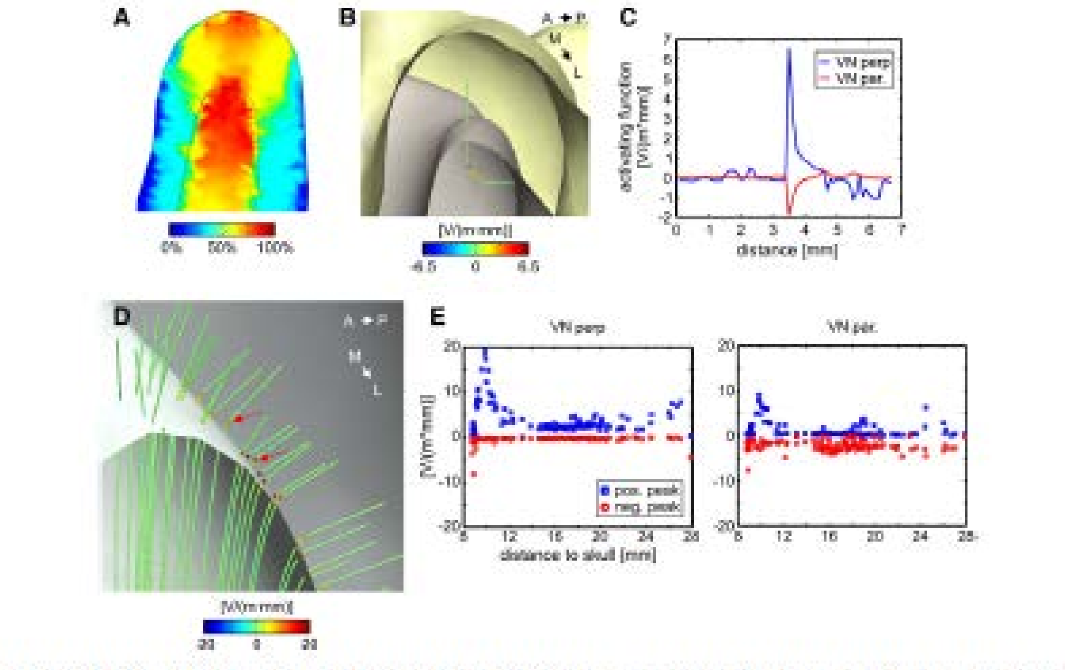
Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex

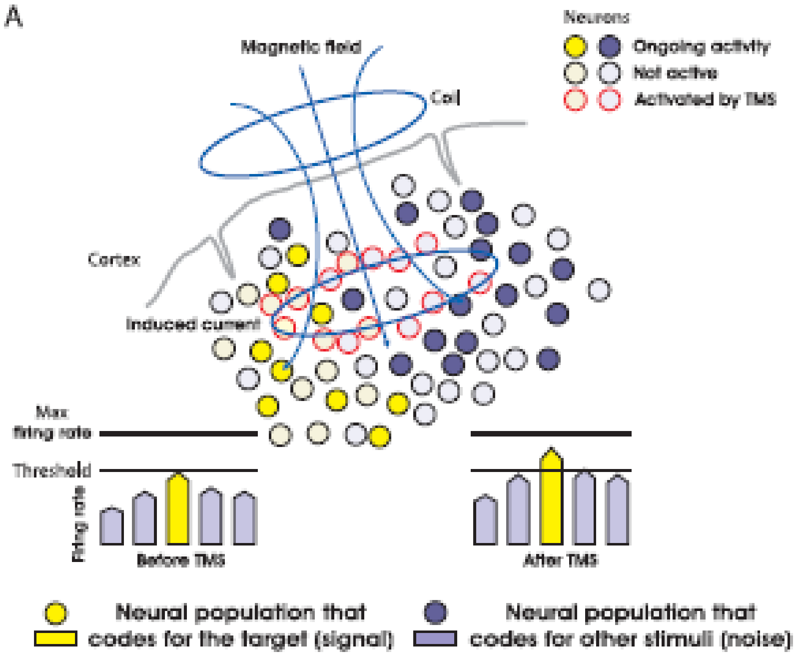
Nadia Bolognini,[1,2] Silvia Convento,[1] Elisabetta Banco,[2,3] Flavia Mattioli,[4] Luigi Tesio[3,5] and Giuseppe Vallar[1,2]

- Clinical and technological “pull & push”
- Modeling can help to understand underlying mechanisms

Parazzini et al., IEEE TransBiomEng 2011

From Macroscopic to Neuronal response

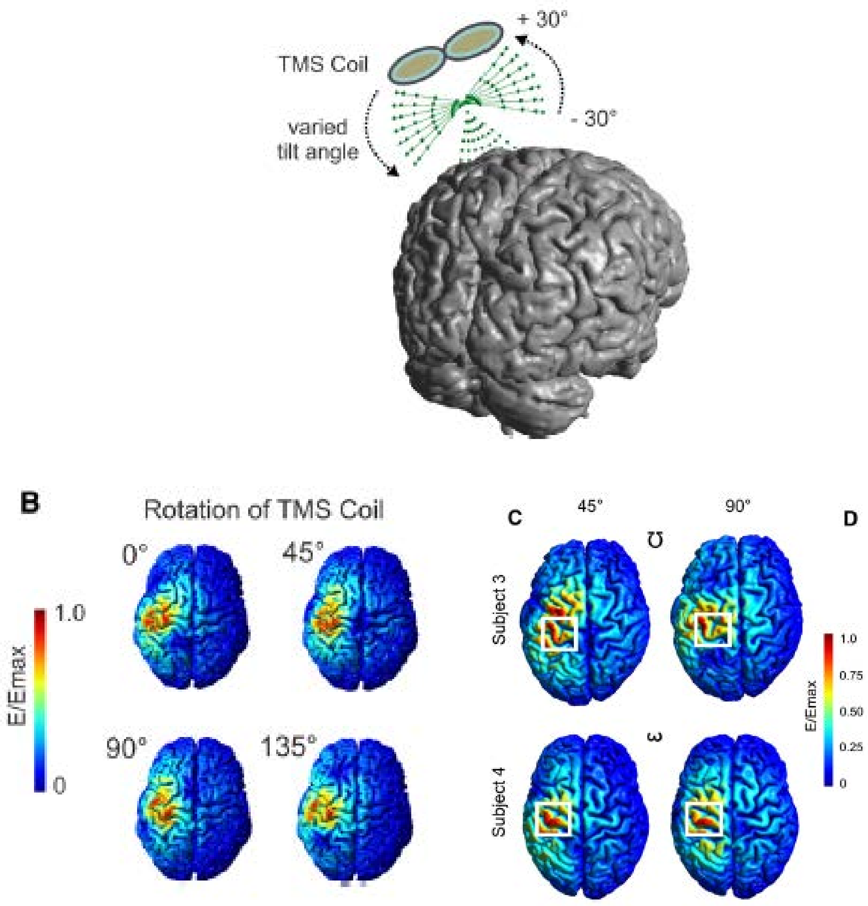


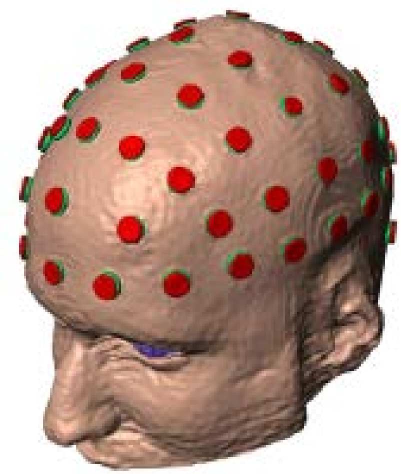


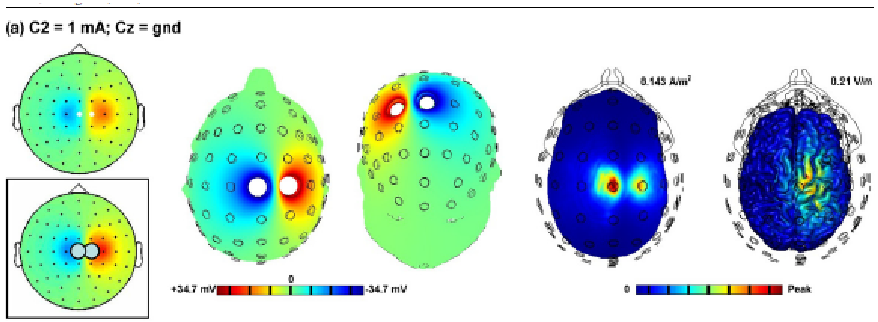
A. Opitz et al., NeuroImage 58 (2011) 849–859

C. Miniussi et al. / Neuroscience and Biobehavioral Reviews 37 (2013) 1702–1712

Model validation







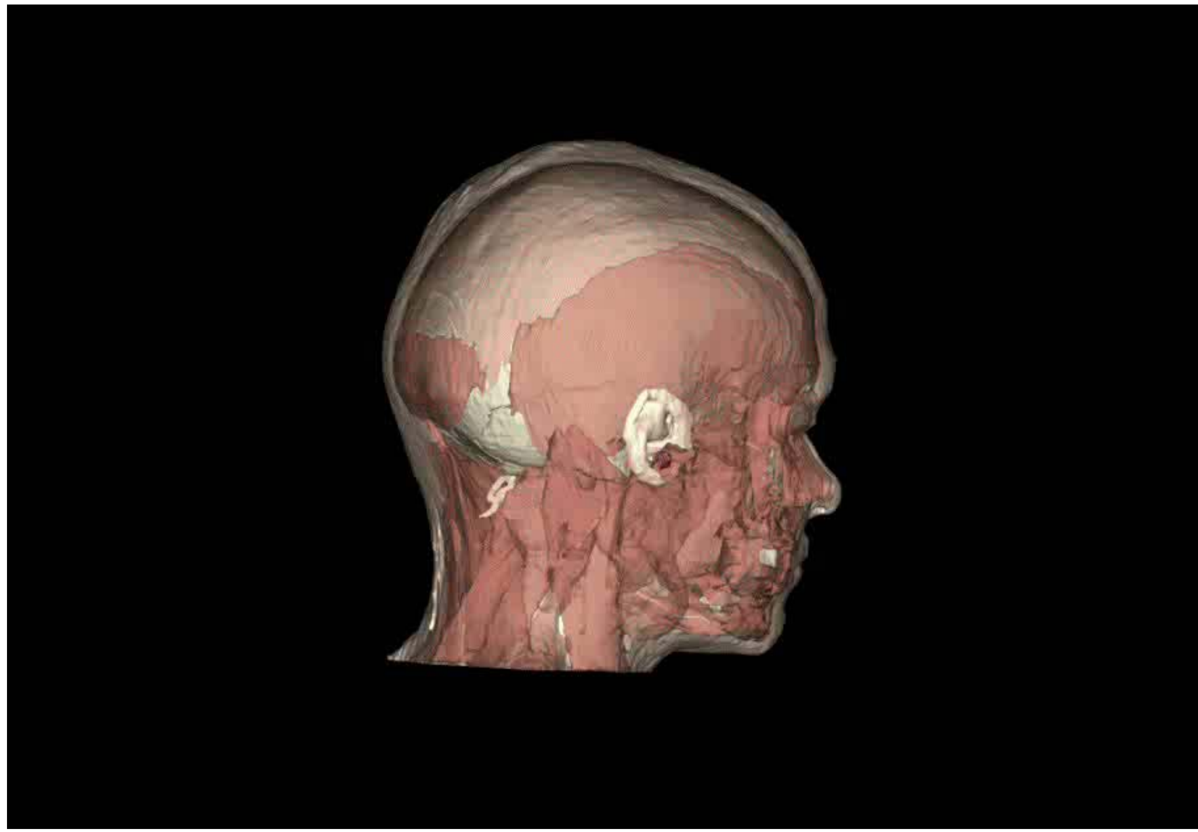
A. Opitz et al. / NeuroImage 81 (2013) 253–264

A. Datta et al. J. Neural Eng. 10 (2013) 036018

Modeling electric field in the brain: Regulatory Science

MIDA: A Multimodal Imaging-based Detailed model of the Anatomy of the human head and neck.

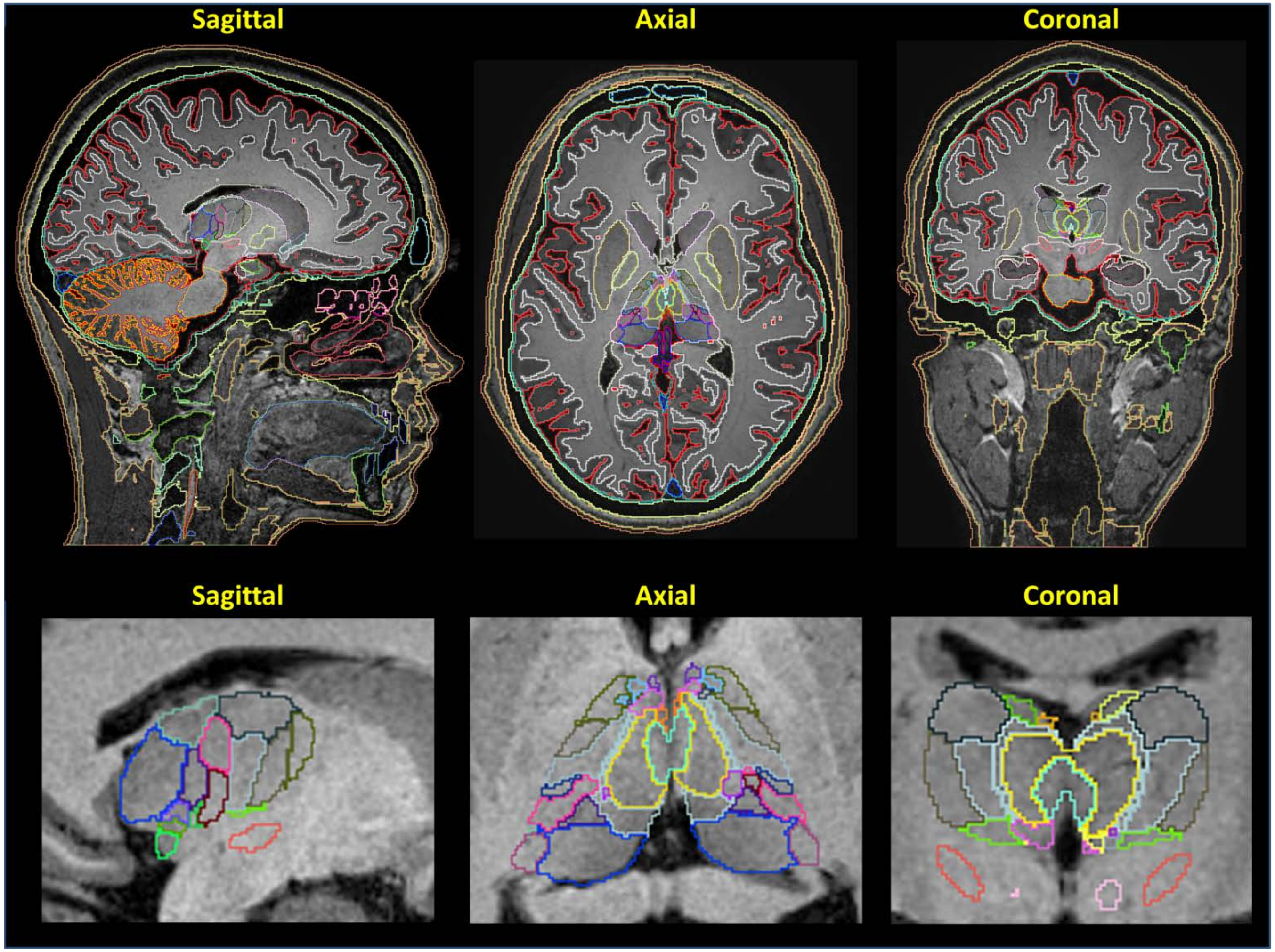
US Food and Drug Administration (FDA),
IT'IS Foundation, Zurich, Switzerland
ETH Zurich, Switzerland
Medical University of Vienna, Austria
Massachusetts General Hospital, Harvard Medical School, USA.

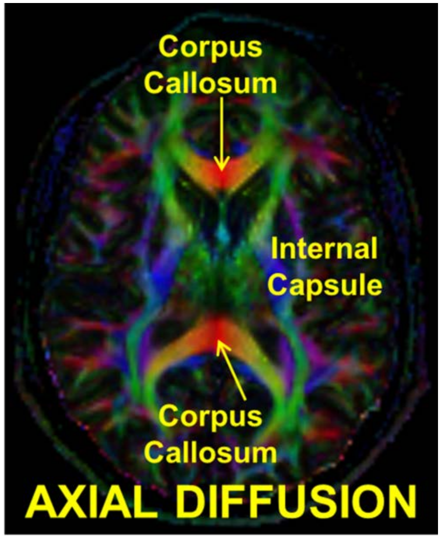


Model of human head and neck freely available for the scientific community
MIDAmodel@fda.hhs.gov

Iacono MI, Neufeld E, Akinnagbe E, Wolf J, Oikonomidis IV, Sharma D, Wilm BJ, Wyss M, Pruessmann KP, Jakab A, Makris N, Cohen ED, Kuster N, Kainz W, Angelone LM. Submitted

Modeling the human head: the MIDA model

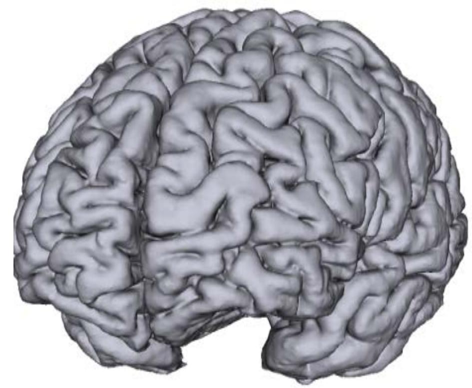




Iacono et al., IEEE EMBS 2014

Gray Matter and White Matter

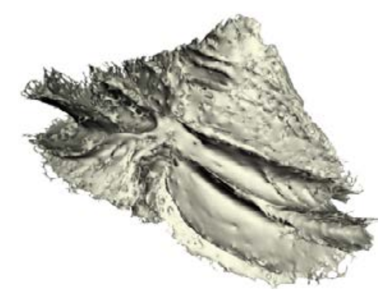
Brain GM



Brain WM

Cerebellar GM

Cerebellar WM

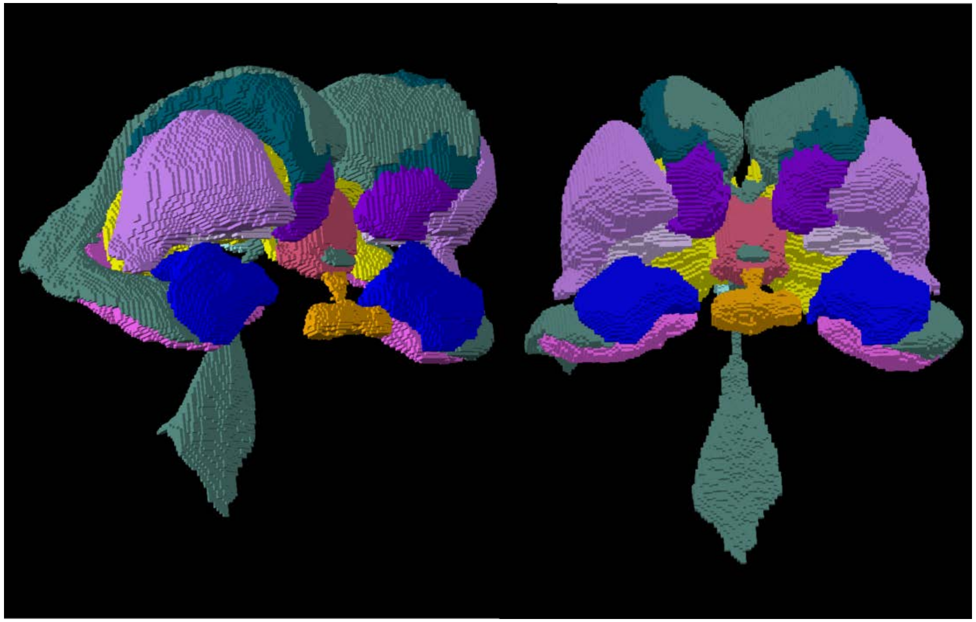


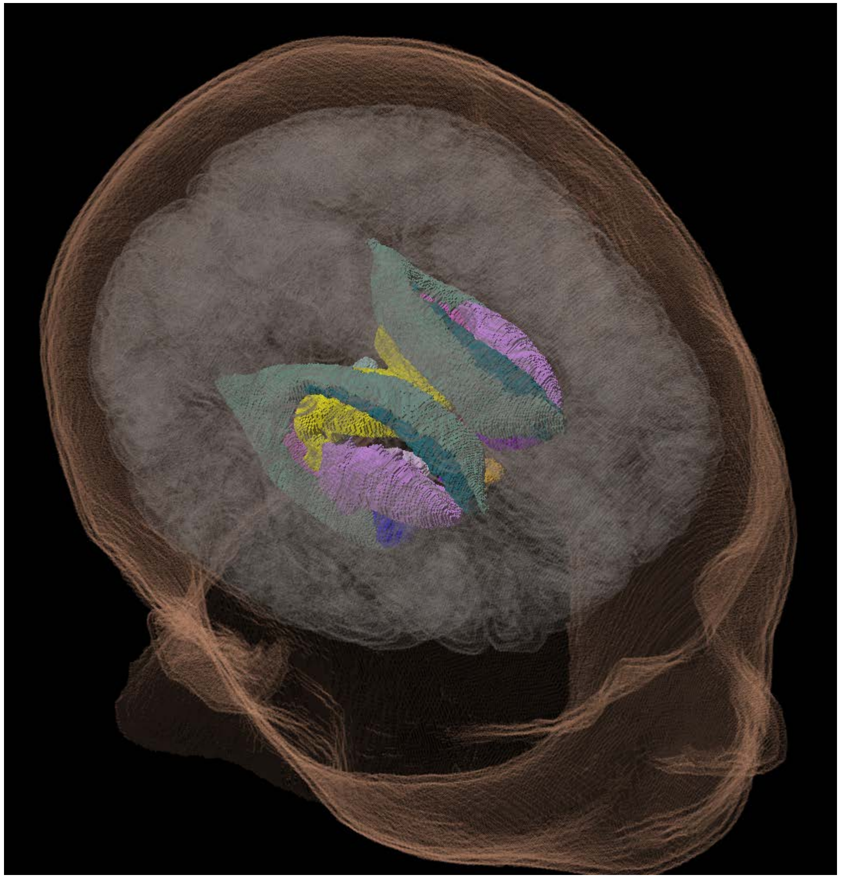
Iacono et al., MIDA Model, submitted

Deep Brain

MIDA model

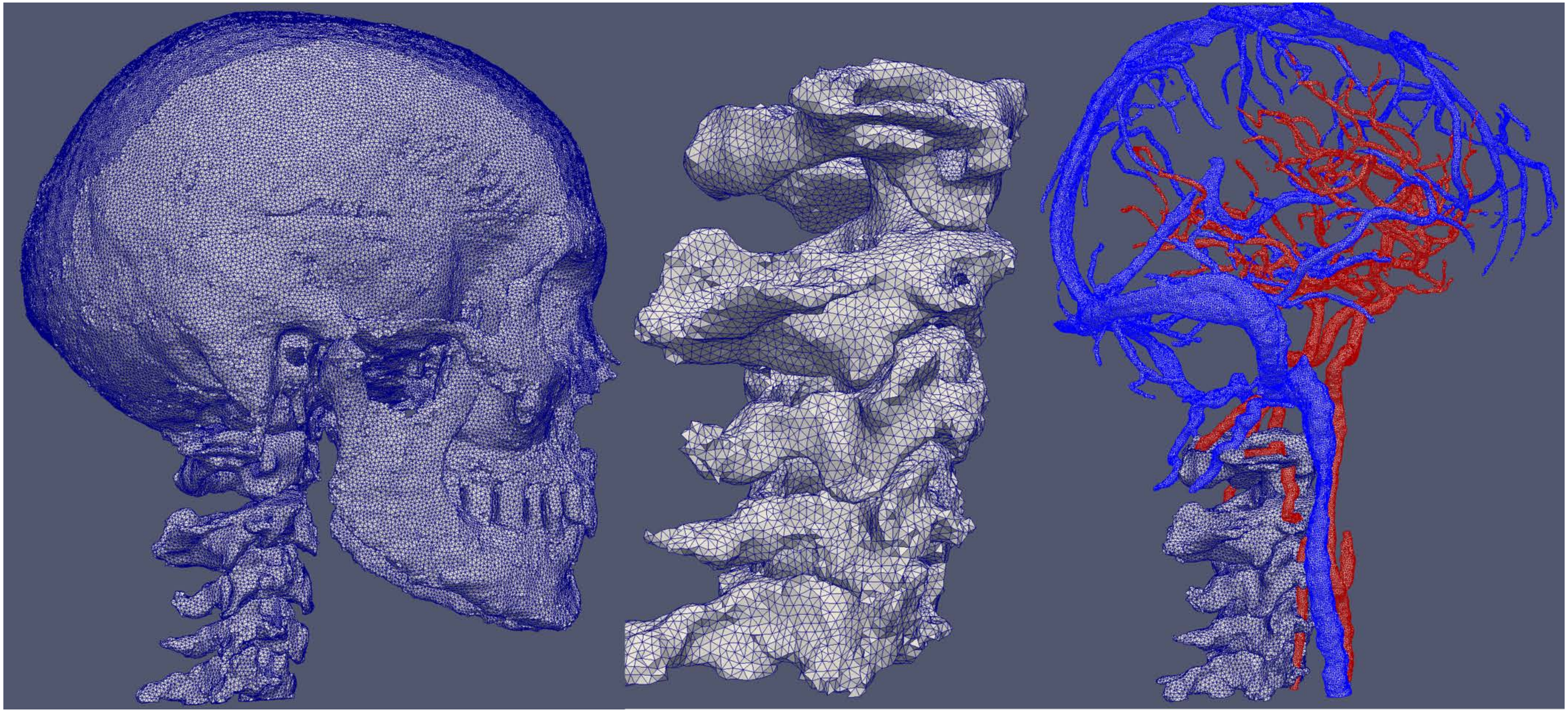
Basal Ganglia, Thalamus, & Limbic System





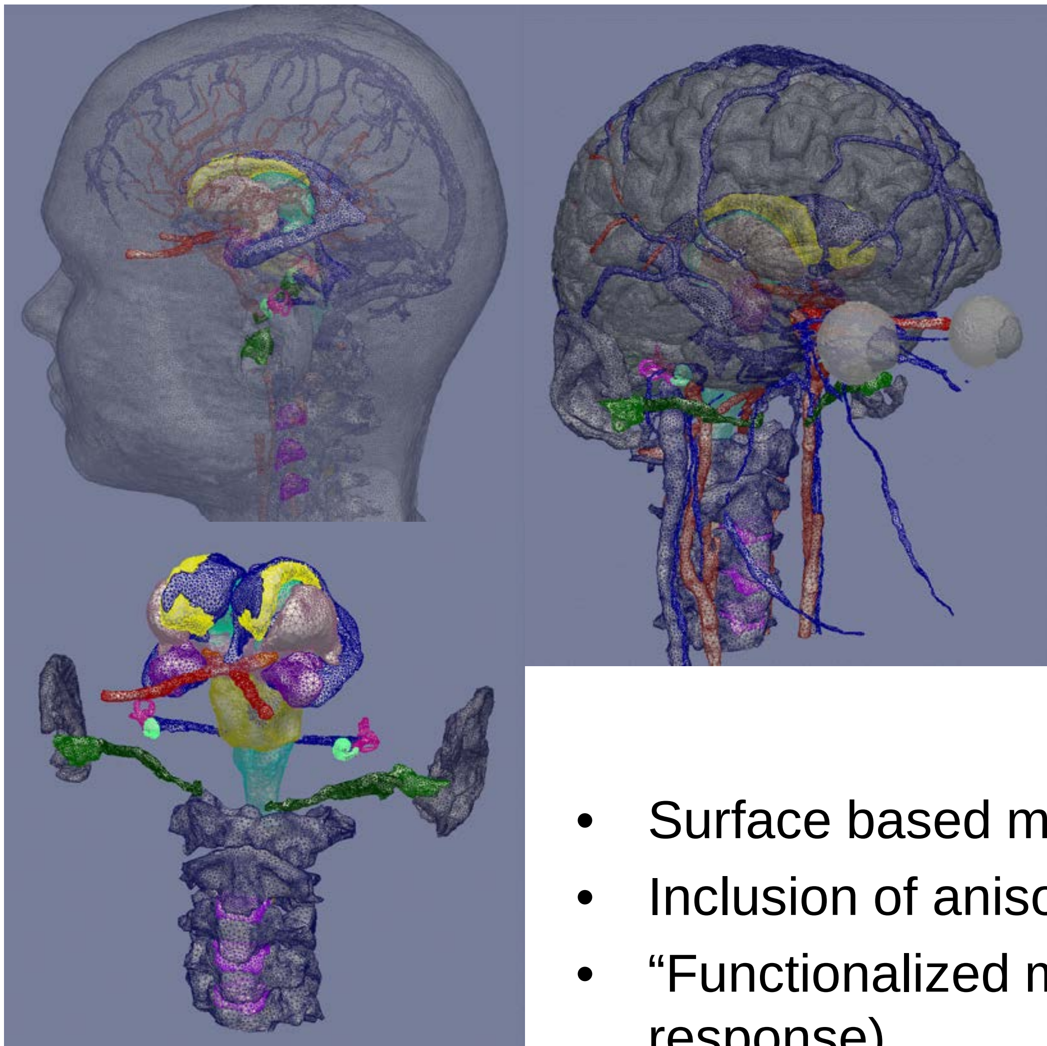
Iacono et al., MIDA Model, submitted

Bones and Vessels

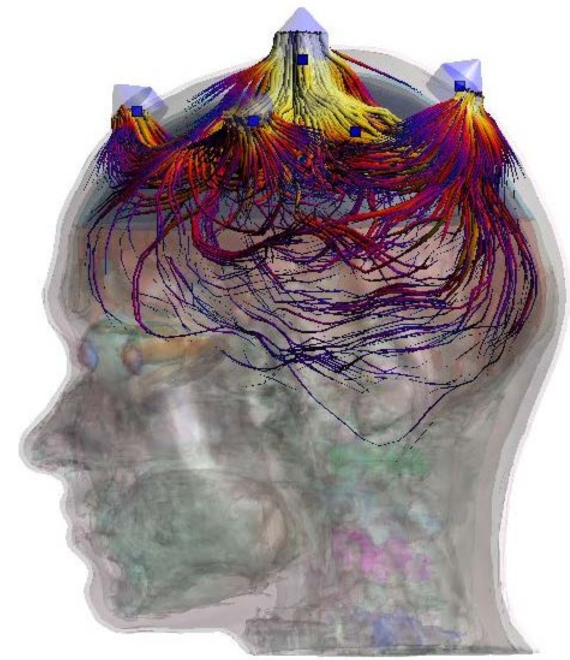


Iacono et al., MIDA Model, submitted

Case study – tACS



Iacono et al., MIDA Model, submitted



Neufeld et al., IEEE NER 2015

- Surface based models
- Inclusion of anisotropic properties
- “Functionalized model” (Neuronal response)

Summary

- Overview of non-invasive neuromodulation devices (EM, optics, ultrasound)
- What is known and unknown about engineering neuromodulation devices
- Modeling exposure of different brain locations to electric fields

Thank you!