MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

MASSACHUSETTS GENERAL HOSPITAL

Harvard-MIT Health Sciences & Technology

TMS physics: Quantitative aspects of targeting and dosing

Intensive Course in Transcranial Magnetic Stimulation Jun 3rd, 2025

Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center

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Introduction

The TMS Setup

Coil

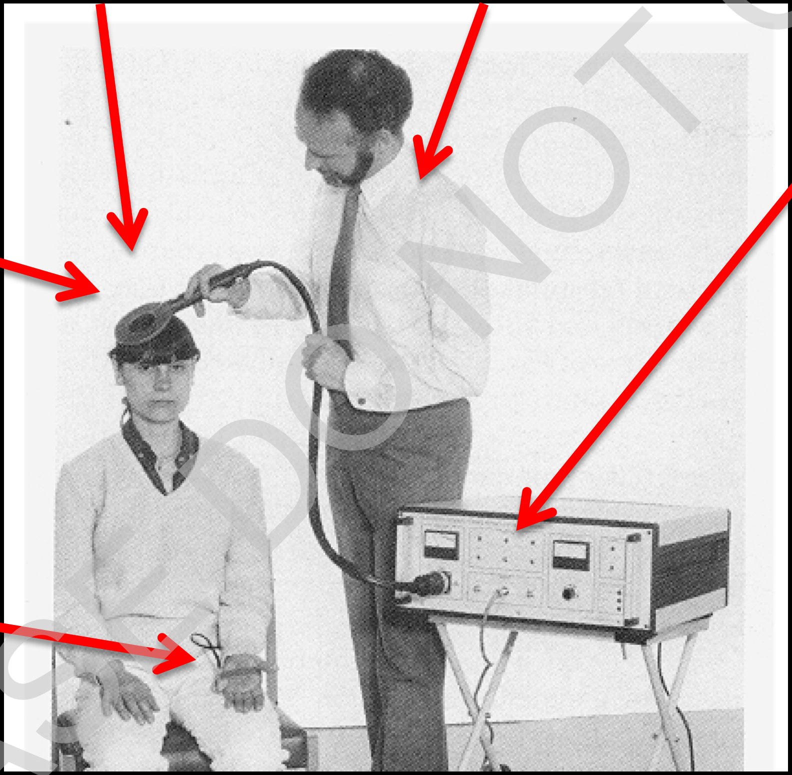
Creates magnetic and electric fields.

Electrodes

EMG records muscle activity.

Subject

Operator



Stimulator

Creates large currents.

From Barker et al. 1991 Journal of Clinical Neurophysiology

TMS variables: Recap

Variables that depend on "coil settings":

- Coil type (circular, figure-of-eight, other)
- Coil location
- Coil orientation and tilt

Variables that depend on "stimulator settings":

- Pulse waveform (monophasic, biphasic)
- Sequence (single, double, rTMS, patterned)
- Pulse direction (clockwise/counter; forward/backward)
- Intensity and dose

Subject (variability across individuals, subject state)

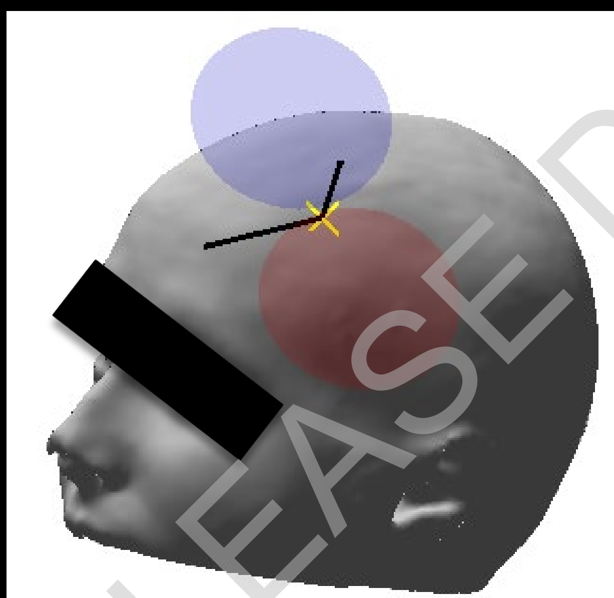
Concepts of TMS quantification

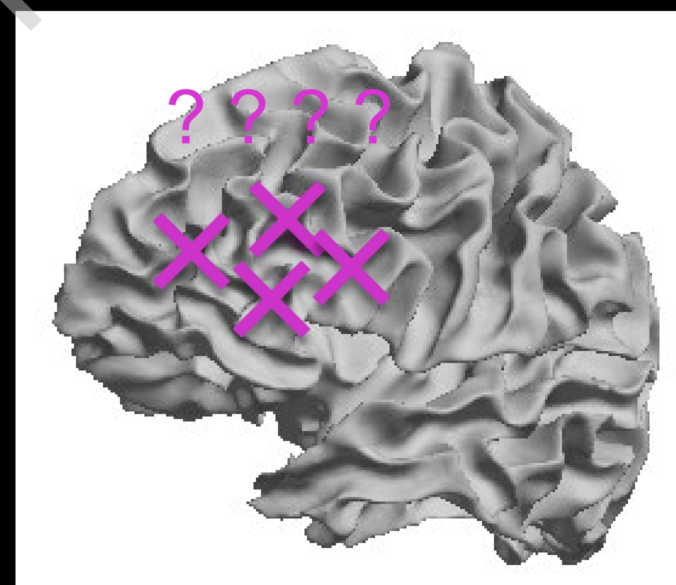
- How to stimulate a desired brain location?
  - This is called “targeting”.
- How to stimulate with a desired strength?
  - This called “dosing”.

    Depends on pulse strength, stimulus pattern, duration etc.
- Computational methods exist for quantifying spatial pattern and amplitude of the TMS stimuli.
  - This is the main topic of this talk.
- The effect of stimulus pattern (rTMS, theta burst) and duration is more challenging to model.
  - TMS+imaging is typically needed for quantification.

Introductory example to targeting & dosing

- Let us assume that you have selected a position and orientation for your TMS coil.
- Question: How strongly will you stimulate at different locations in the brain “X”?

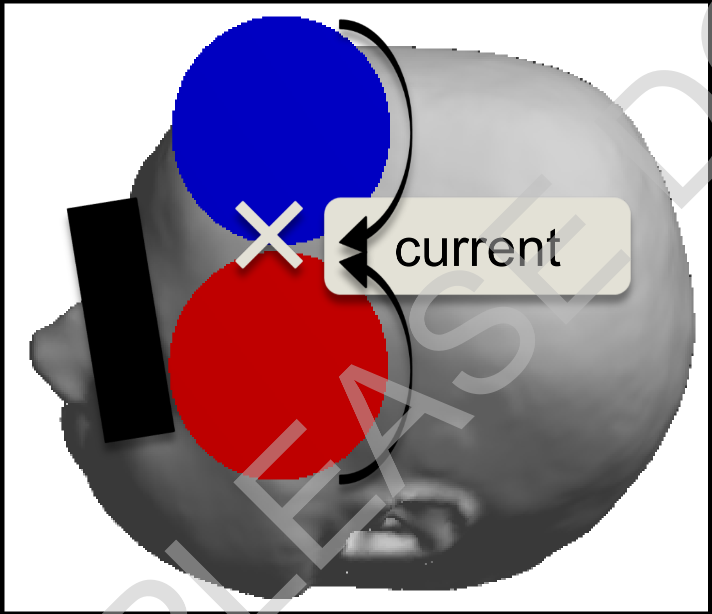




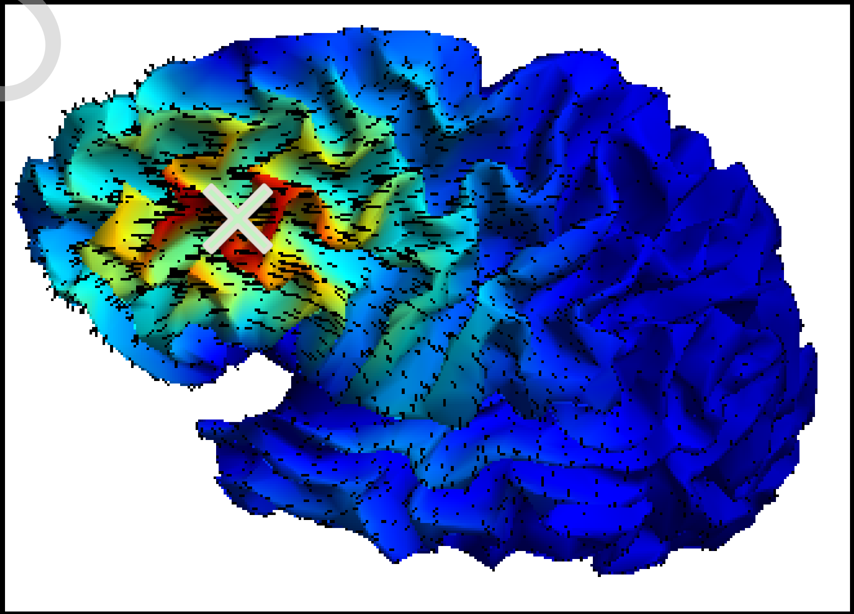
Computational modeling approach to targeting and dosing

- The electric field distribution can be estimated using computational methods presented in detail later.
  - It looks like the maximum field intensity is just under coil.
  - What is the value added in a more quantitative approach?

Simulated double coil

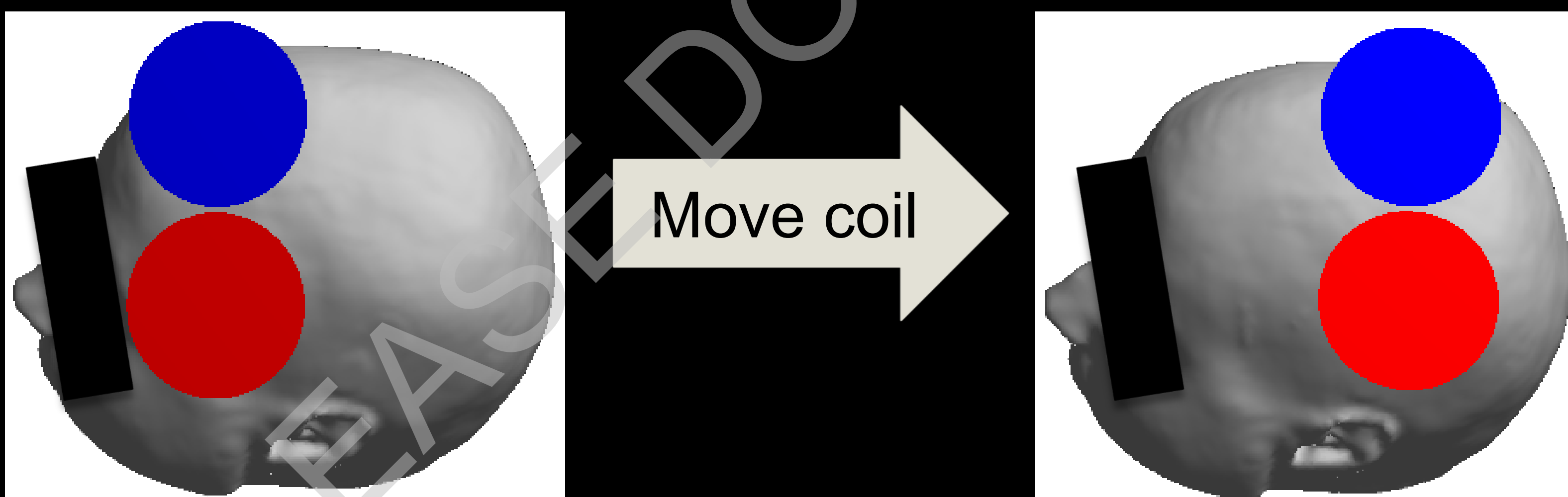


Maximum E-field = 68 V/m



Effect of coil location on TMS strength

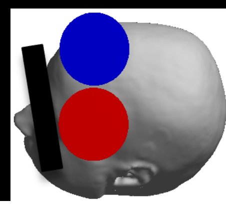
- Let's assume that stimulator output intensity is fixed.
  - Then, we move the coil between two locations.
    - Coil orientation is fixed Anterior-Posterior.
- Question: Is the E-field intensity the same in the brain?

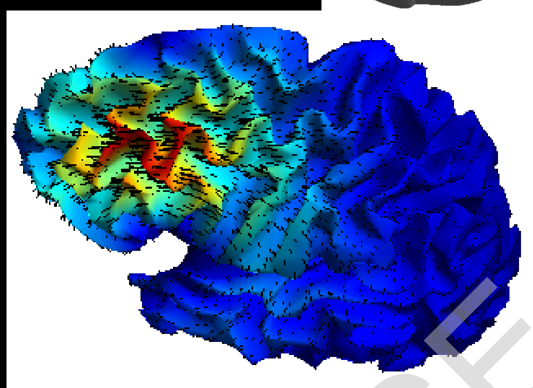


Effect of coil location on TMS strength (cont.)

Location #1

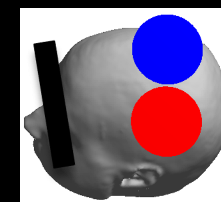
Max(E)=
68 V/m

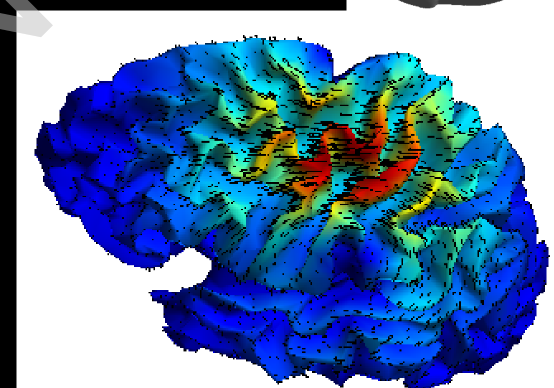




Location #2

Max(E)=
59 V/m



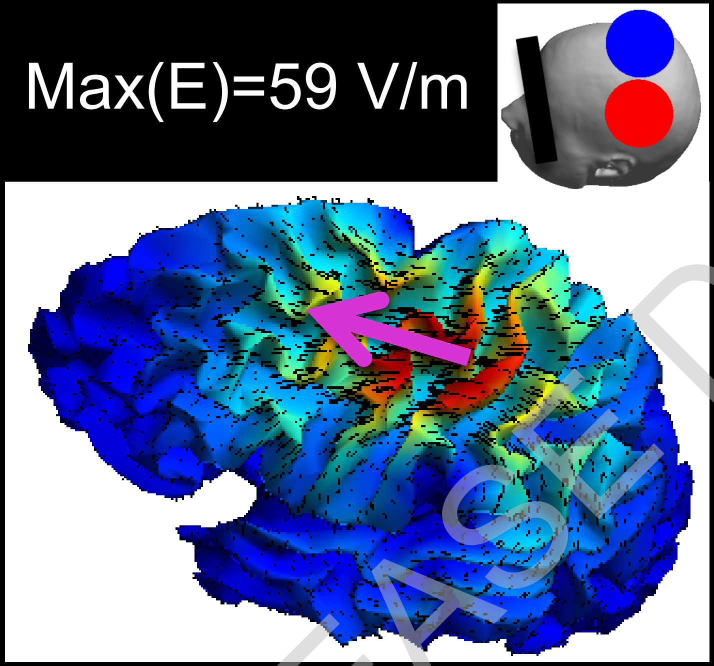


- The difference in E-field amplitude is over 10%.
  - Is 100% Motor Threshold (MT) same as 110% MT?

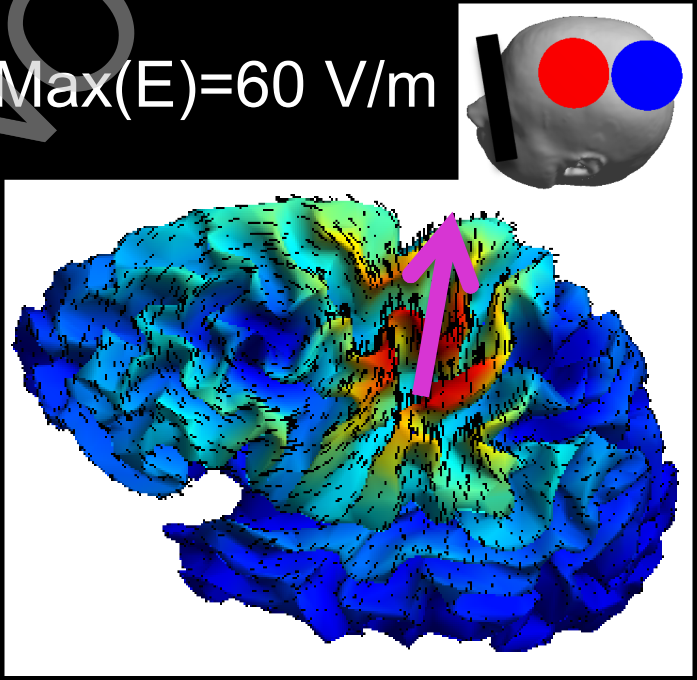
Effect of coil orientation: Rotation

- Let us assume that the coil is rotated 90 degrees while keeping the location fixed:

Max(E)=59 V/m



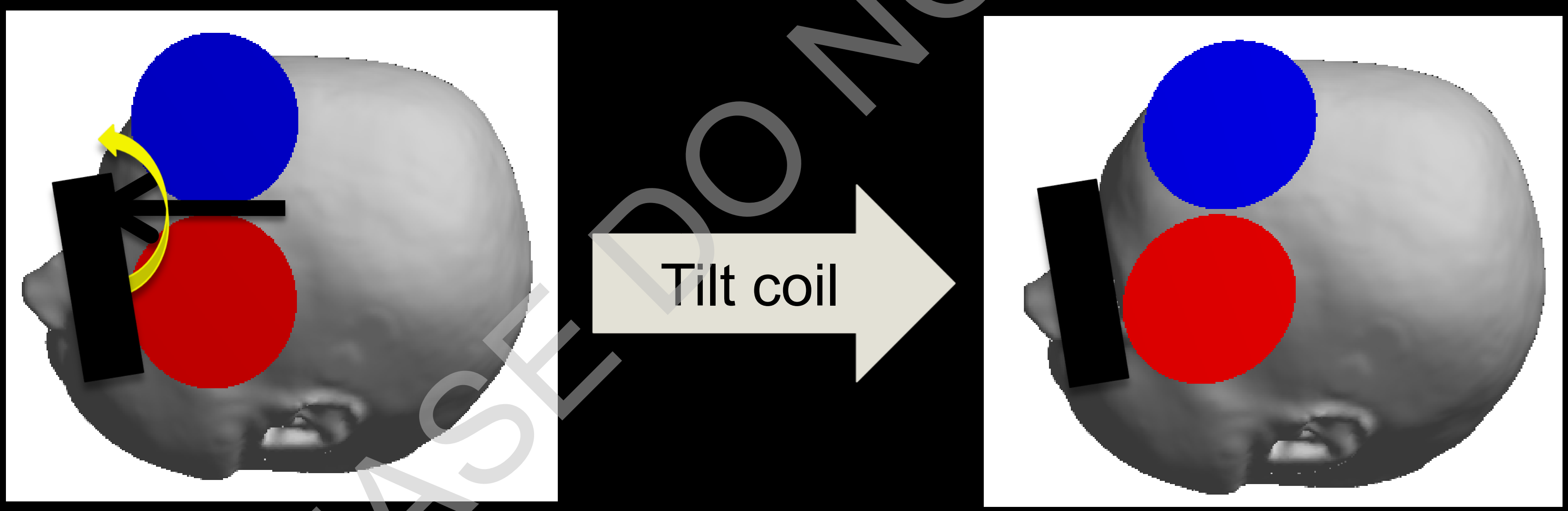
Max(E)=60 V/m



The amplitude remains same but shape and direction change!

Effect of coil orientation: Tilt

- Assume location is fixed but coil is tilted in the left-right direction by 20 degrees.

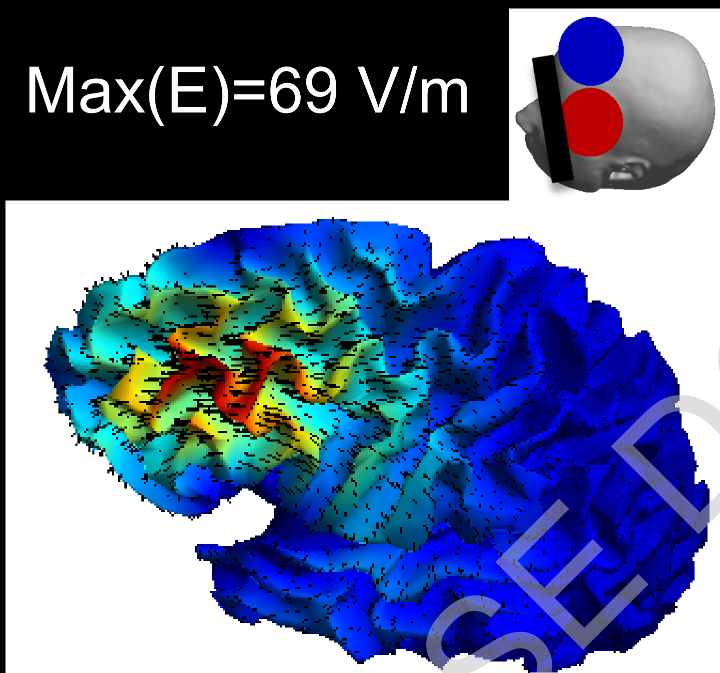


Effect of coil orientation: Tilt

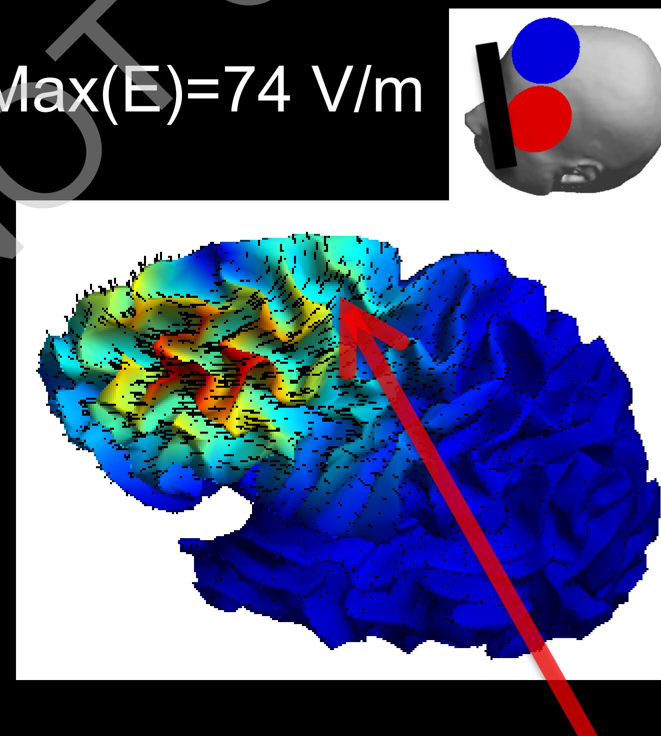
Case#1: NO TILT

Case#2: WITH TILT

Max(E)=69 V/m



Max(E)=74 V/m

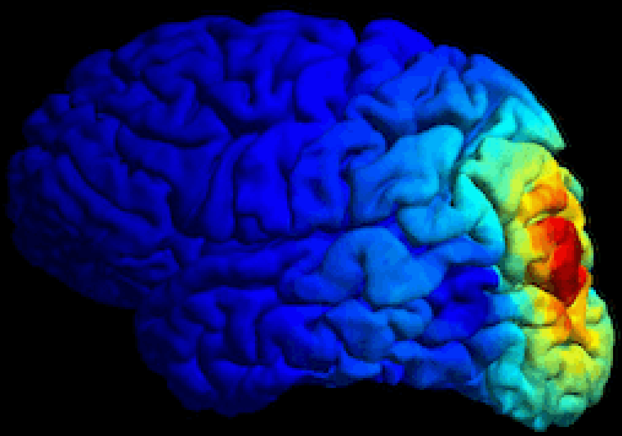


- Tilting the coil changes the maximum amplitude and the shape of the electric field as well!

Introductory example conclusions

The shape and strength of the TMS electric field pattern in the brain varies when the coil is moved -> Even if the stimulator output intensity is fixed!

The E-field distribution depends on:
-coil POSITION and ORIENTATION
-coil GEOMETRY
-DISTANCE to the brain location
-CONDUCTIVITIES of tissue compartments
-SHAPES of tissue compartments

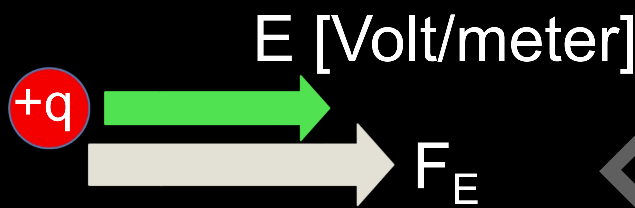


TMS physics background

Electromagnetic fields and forces

Electric force on a charge +q

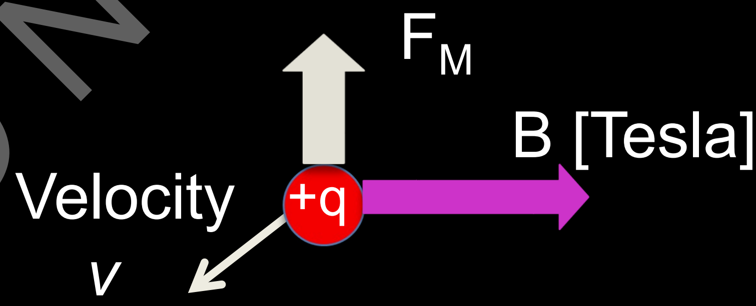
$$\mathbf{F}_E = q\mathbf{E}$$



- E-field is parallel to the force.
- E will accelerate charge if initially at rest!

Magnetic force on a charge

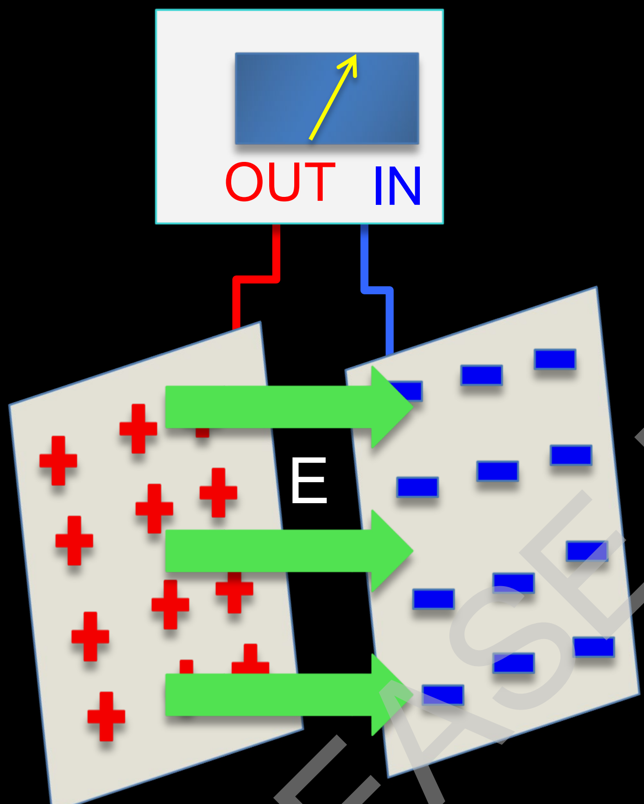
$$\mathbf{F}_M = q\mathbf{v} \times \mathbf{B}$$



- B-field is perpendicular to the force.
- B will only turn the direction of a moving charge!

Static charges generate static E-fields

Voltage source



Conducting plates

Earth surface has an electric field of 100 V/m!

How large are TMS E-fields?
Should we feel more stimulated?

The Earth's electric field around you

The human body is a relatively good conductor ->
you tend to make an isopotential surface (also with ground).

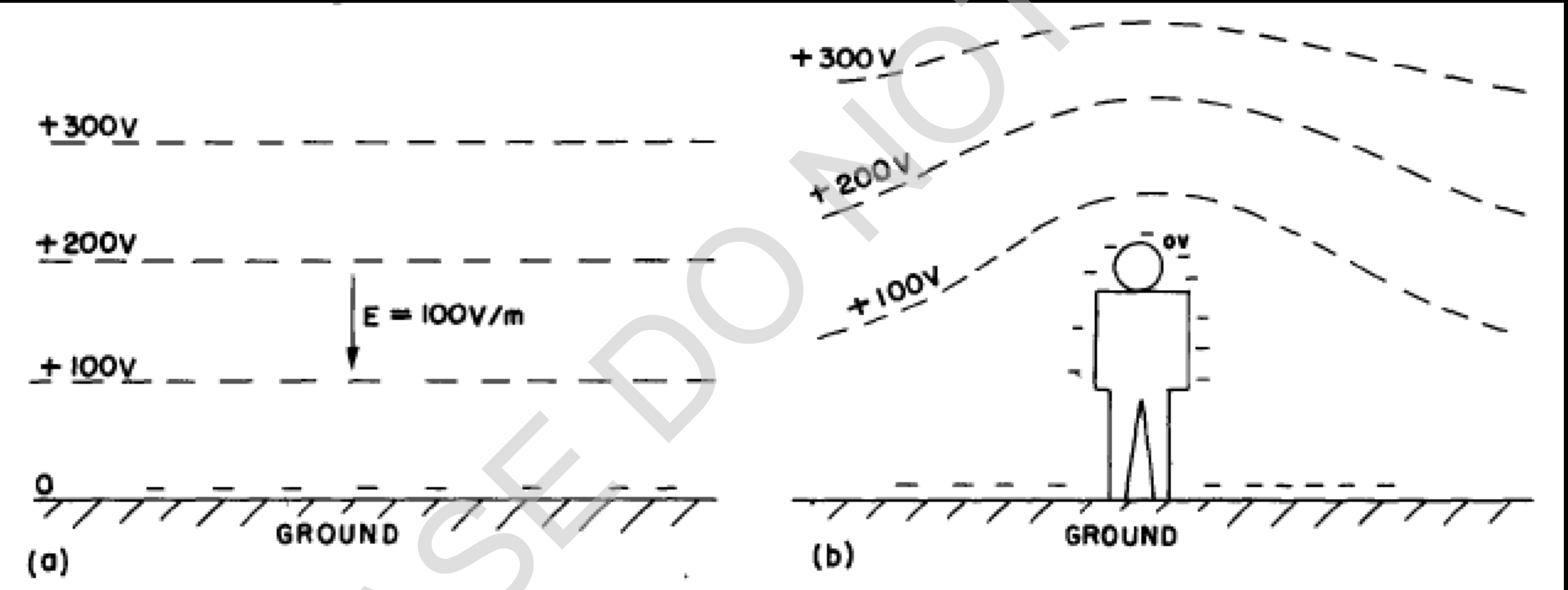
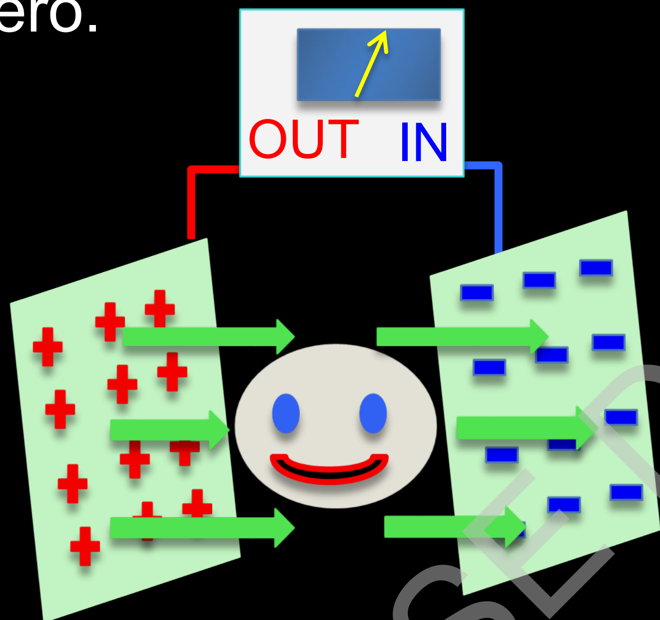


Fig. 9–1. (a) The potential distribution above the earth. (b) The potential distribution near a man in an open flat place.

From "*Feynman Lectures on Physics, Vol. 2*"

Stimulation with static E-field?

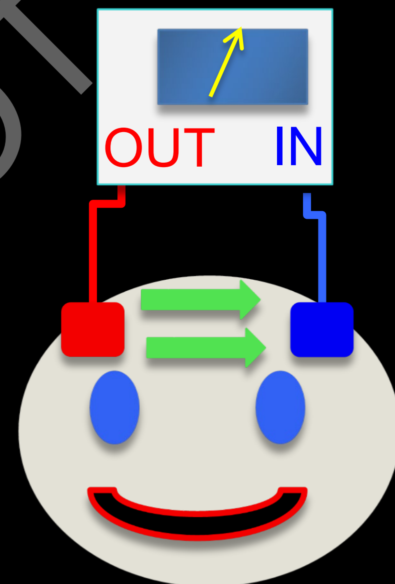
In a static case, the E-field inside a perfect conductor is zero.



•Human head is a relatively good conductor.

•External static E-fields do not penetrate to brain (much)!

What about tDCS then?

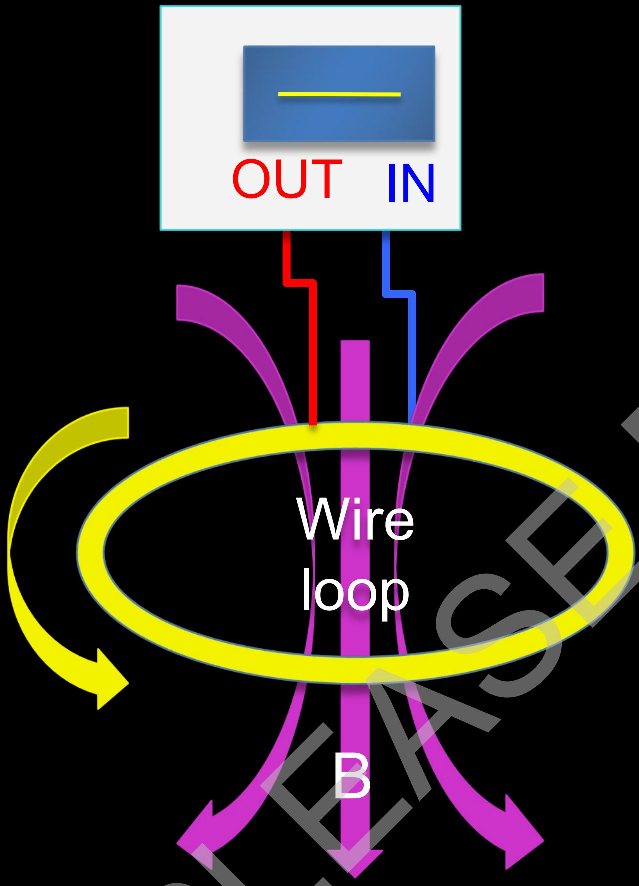


•Physical contact between head and electrodes needed!

•The potential at the contacts is forced to be different!

Static currents generate static B-fields

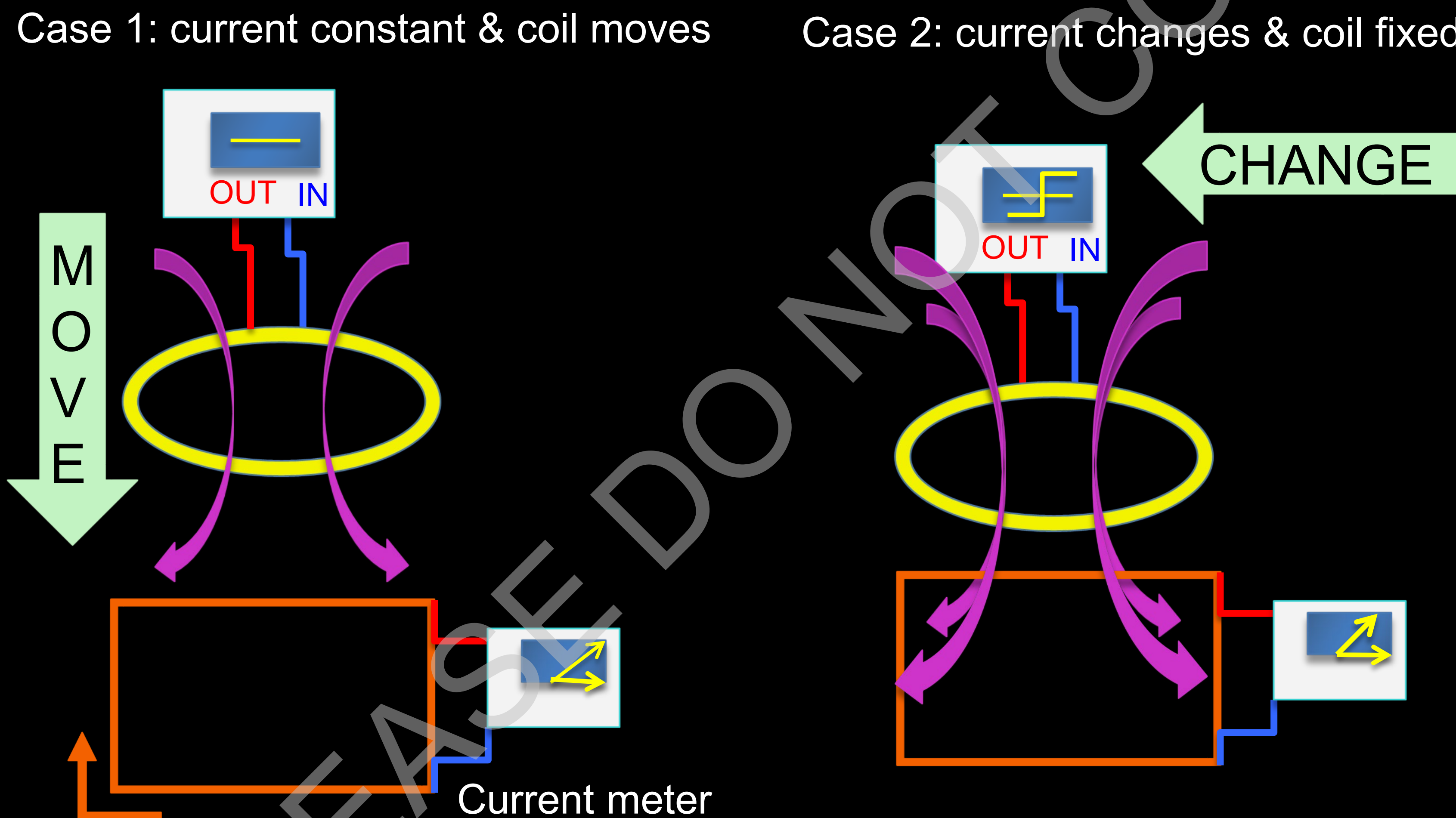
DC source:



Does static B-field stimulate the brain?

A 3T scanner at MGH Martinos Center
Currents flow in superconducting medium!
(3 Tesla >10^5 times earth's B-field)

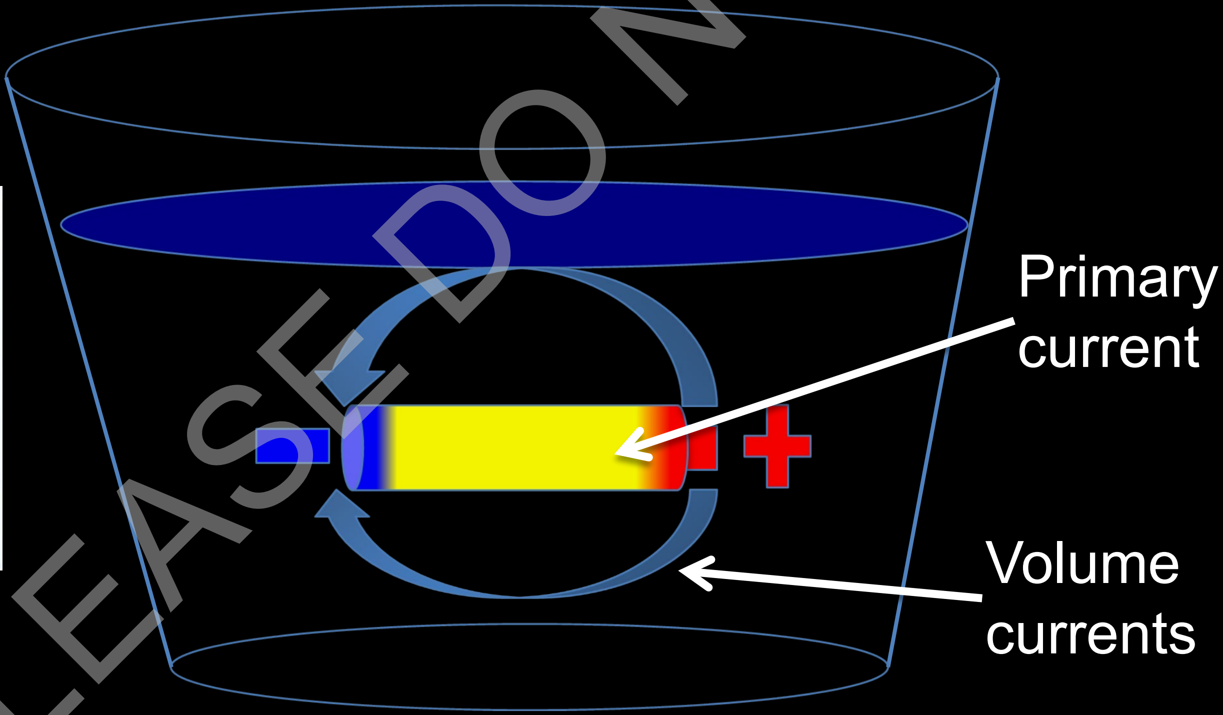
Time-varying B-fields create E-fields!



Time-varying B-field induces E-field that drives current in the loop!

Volume conductors

- To get charges going, we must have a current source.
- What happens if a battery gets into a glass of salt water?
  - Ionic currents in the water flow to “close the circuit”.



Ohm's law

The volume currents are determined by Ohm's law:

$$J = \sigma E$$

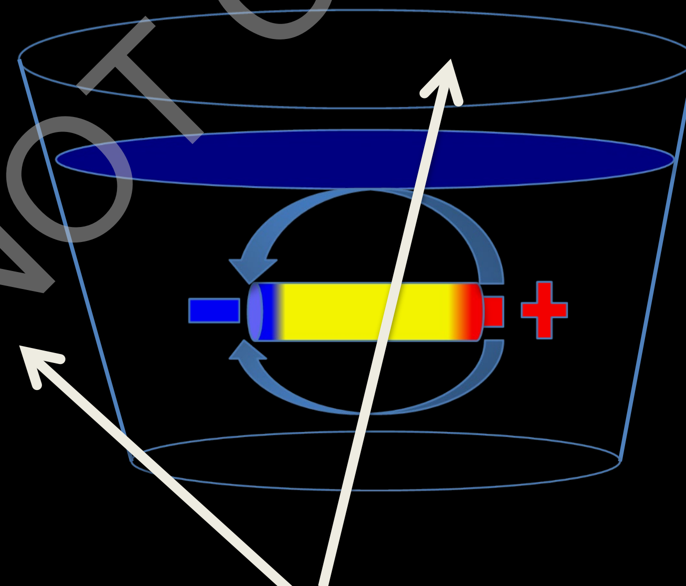
" J " is current density [Ampere / m^2]
" σ " is conductivity [Siemens / m]
" E " is the electric field [Volt / m]

Values of conductivity " σ " at temperature of 20℃:

Copper: 5.96×10^{7} S/m
Sea water: 4.8 S/m
Air: 3×10^{-15} to 8×10^{-15} S/m

(From Wikipedia)

Battery in a glass:



Conductivity " σ " is zero outside the glass -> Current must be zero too!

This sets boundary conditions for E-field created by the battery.

Conductivity boundaries: Simple example

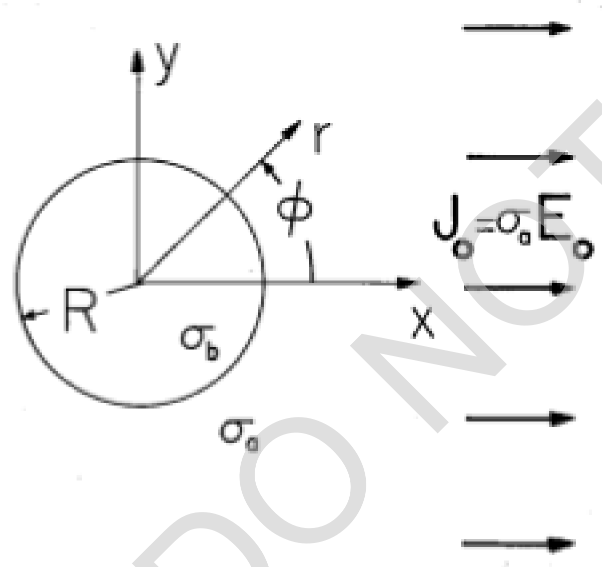


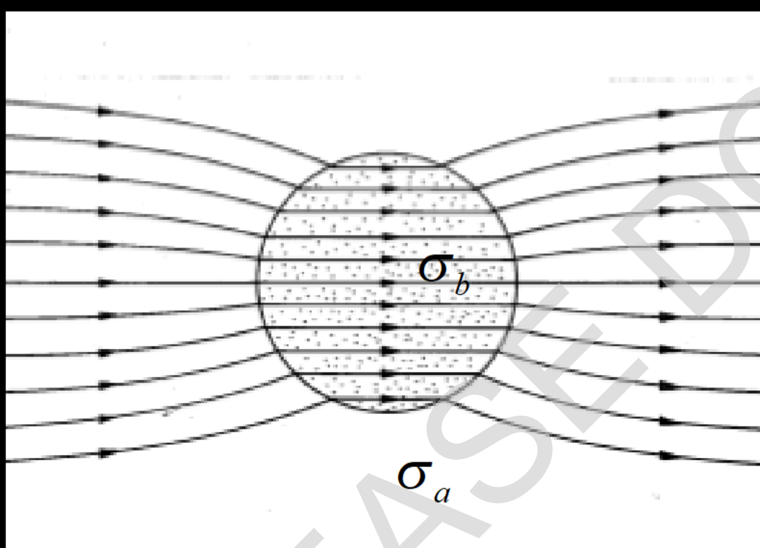
Fig. 7.5.1 Conducting circular rod is immersed in a conducting material supporting a current density that would be uniform in the absence of the rod.

Haus, Hermann A., and James R. Melcher, *Electromagnetic Fields and Energy.* (Massachusetts Institute of Technology: MIT OpenCourseWare). http://ocw.mit.edu (accessed Monday, July 16, 2012 4:56 PM). License: Creative Commons Attribution-NonCommercial-Share Alike.

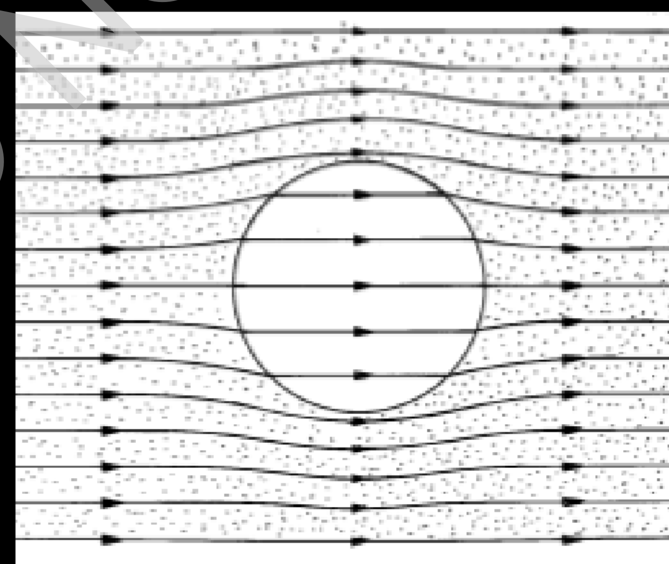
Conductivity boundaries: Simple example (cont)

In the quasi-static (low-frequency) approximation:
Electric current density must be continuous across boundary.

$\sigma_a < \sigma_b$



$\sigma_a > \sigma_b$

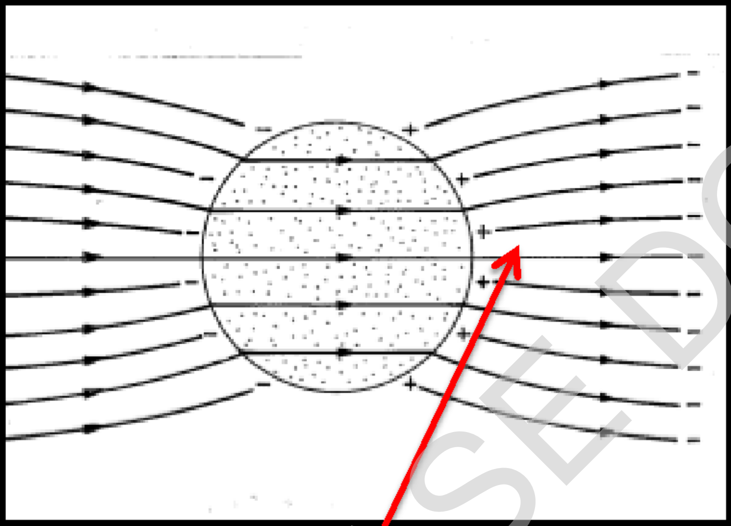


The conductive object alters the path of the current!

Conductivity boundaries: Simple example (cont)

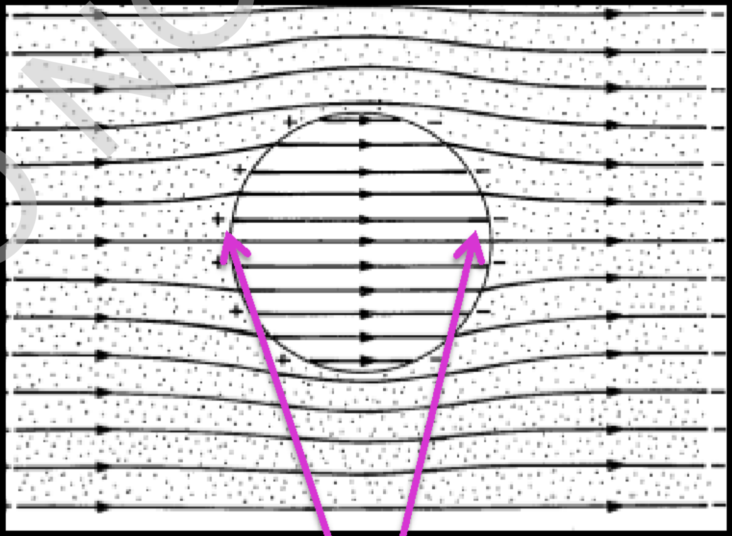
Tangential component of E-field is continuous across boundary.
Normal component of E-field is in general discontinuous!

$\sigma_a << \sigma_b$



E-field HIGHER inside region of LOWER conductivity!

$\sigma_a >> \sigma_b$



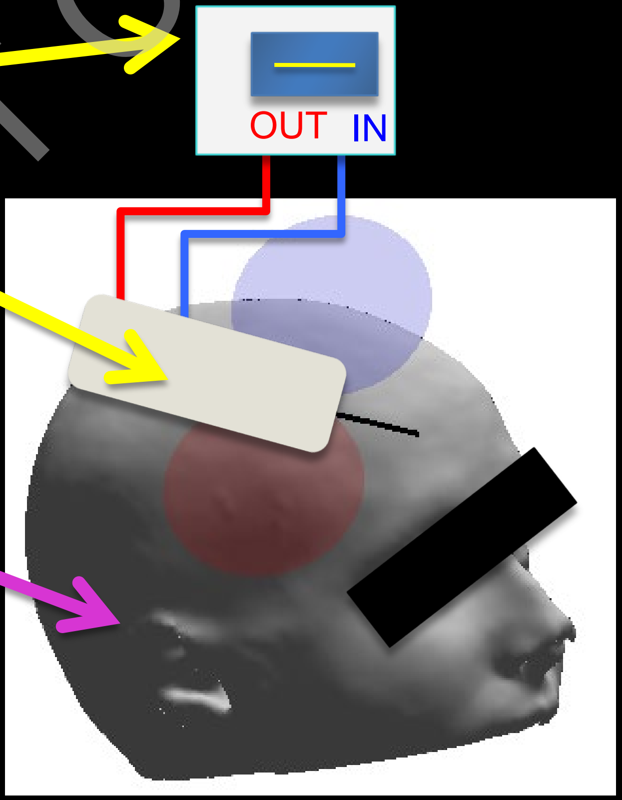
Charge accumulation at boundary creates secondary E-fields.

The effects of a TMS pulse: Physics and physiology

Current sources and volume conductors in TMS

The stimulator and the coil are the current source.

The subject's head is the volume conductor.

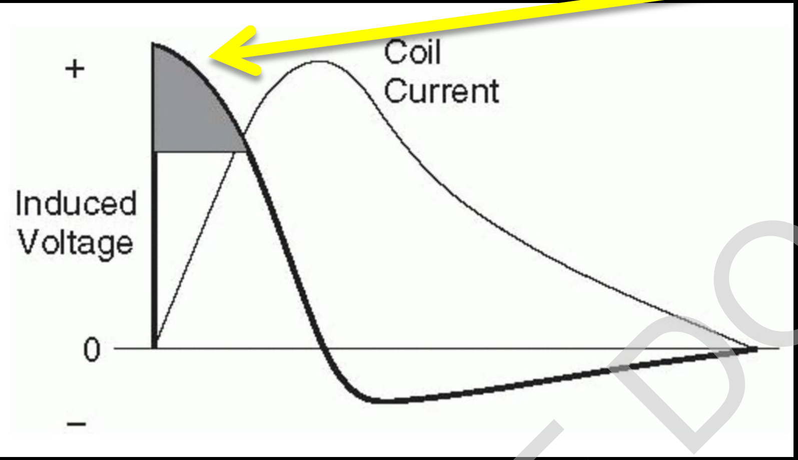


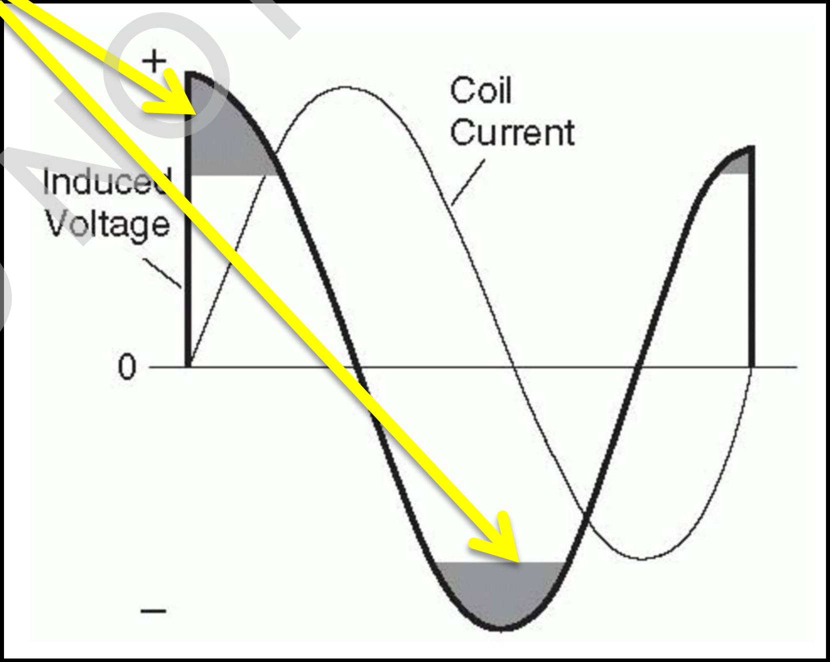
Since the TMS E-field is created by induction, contactless operation possible!

Pulse waveforms

- Monophasic
- Bi-phasic

Large effect on neuronal membrane potentials!

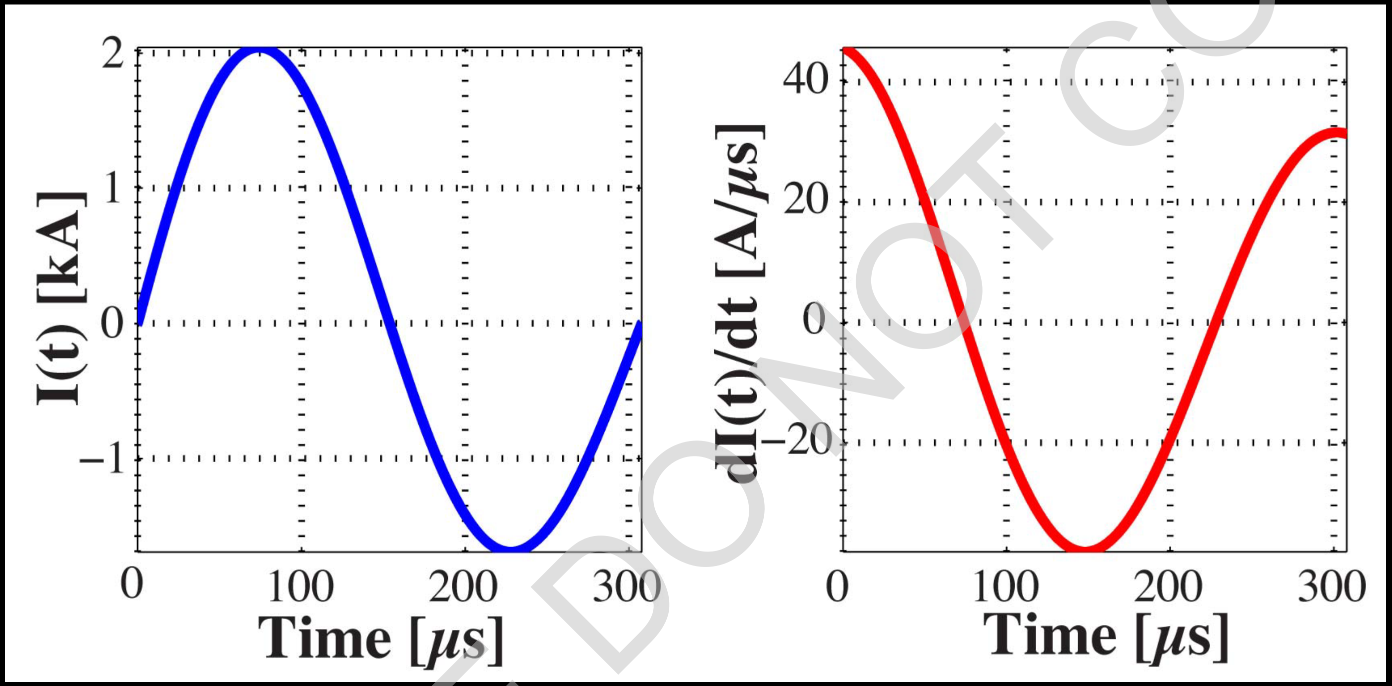




Note: the E-field ~ dB/dt
-> never fully "mono-phasic"

From Wassermann, Eric M. et al, *Oxford Handbook of Transcranial Stimulation, 1st Edition*

Bi-phasic TMS pulse: A closer look



- Peak current amplitude ~ kA (kiloAmpere)
- Peak magnetic field ~ T (Tesla)
- Electric field strength in brain ~ 100 V/m (Volts/meter)
- Pulse frequency ~ kHz (kiloHertz)

Basic TMS coils

Circular / Single
(diffuse stimulation)

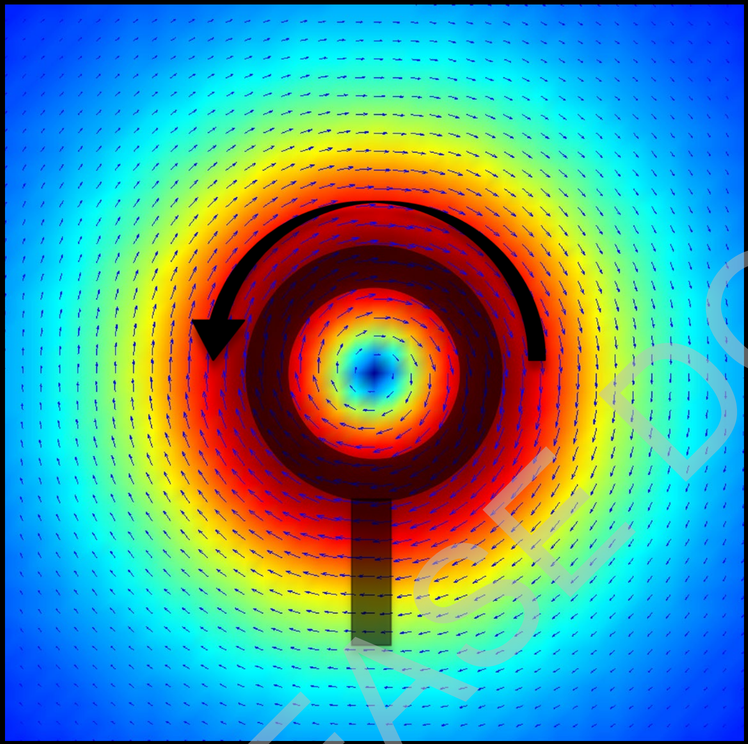
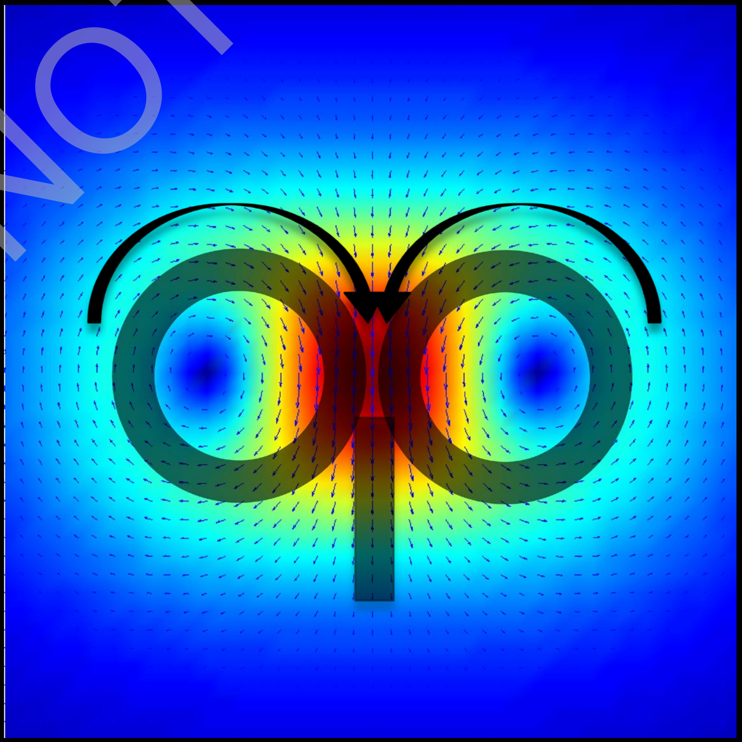


Figure-of-eight / Double
(focal stimulation)

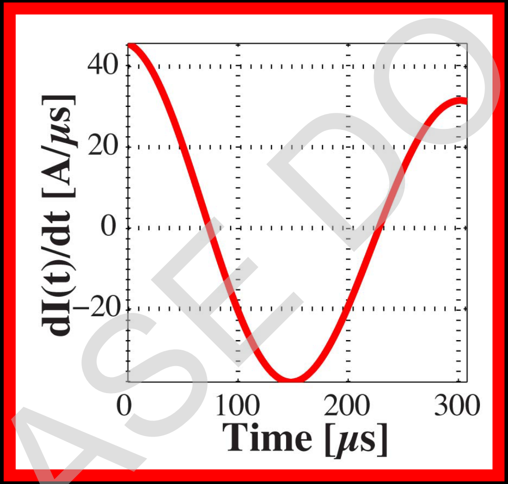


Quasi-static TMS-induced electric fields

For any coil type (with currents in kHz regime)

$$\mathbf{E}(\mathbf{r}) = \left(-dI(t)/dt\right) \times \mathbf{L}(\mathbf{r})$$

Electric field = Current rate of change × Coil "sensitivity profile"



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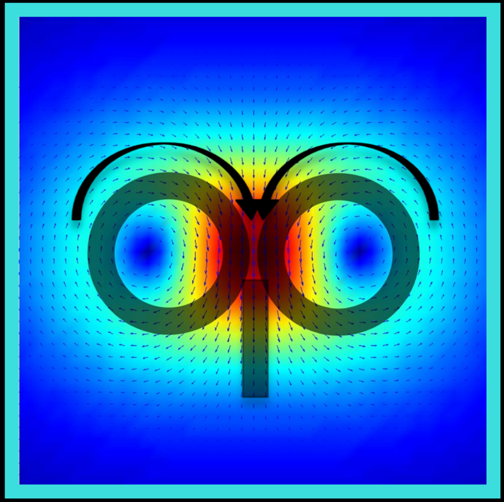


The coil sensitivity is also called the "lead field" due to EEG/MEG analogy

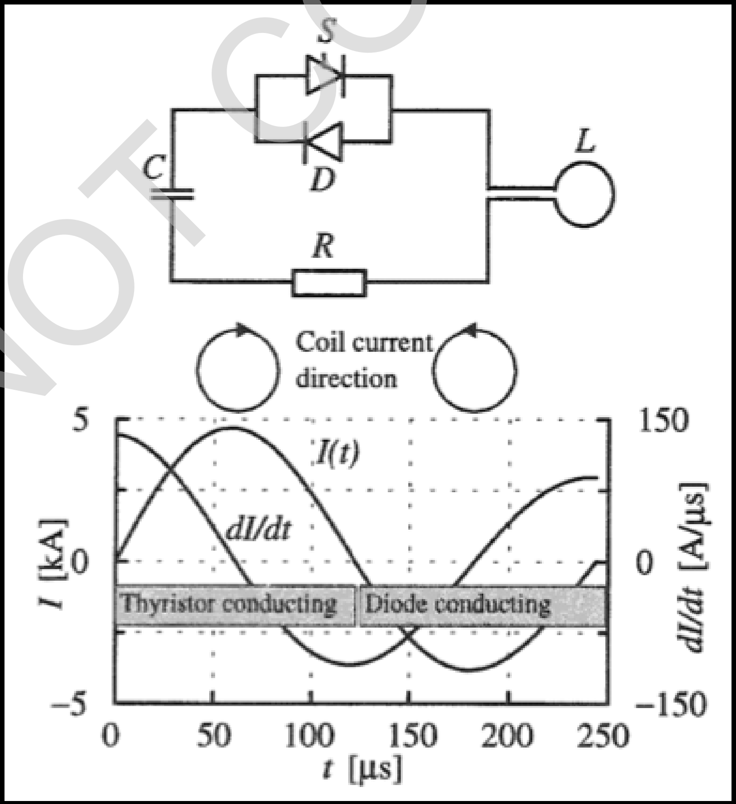
What determines dI/dt?

The bi-phasic current waveform is a damped sinusoid:

$$I(t) = (U_0 / L\omega)\exp(-\alpha t)\sin(\omega t))$$

U_0 = charging voltage (~stimulator output intensity)
R = coil & circuit resistance
L = coil inductance
C = condensator capacitance
α = damping constant = $R/2L$
ω = pulse frequency = $\sqrt{(LC)^{-1} - \alpha^2}$

Taking derivative: $dI/dt_{max} = (U_0/L)$



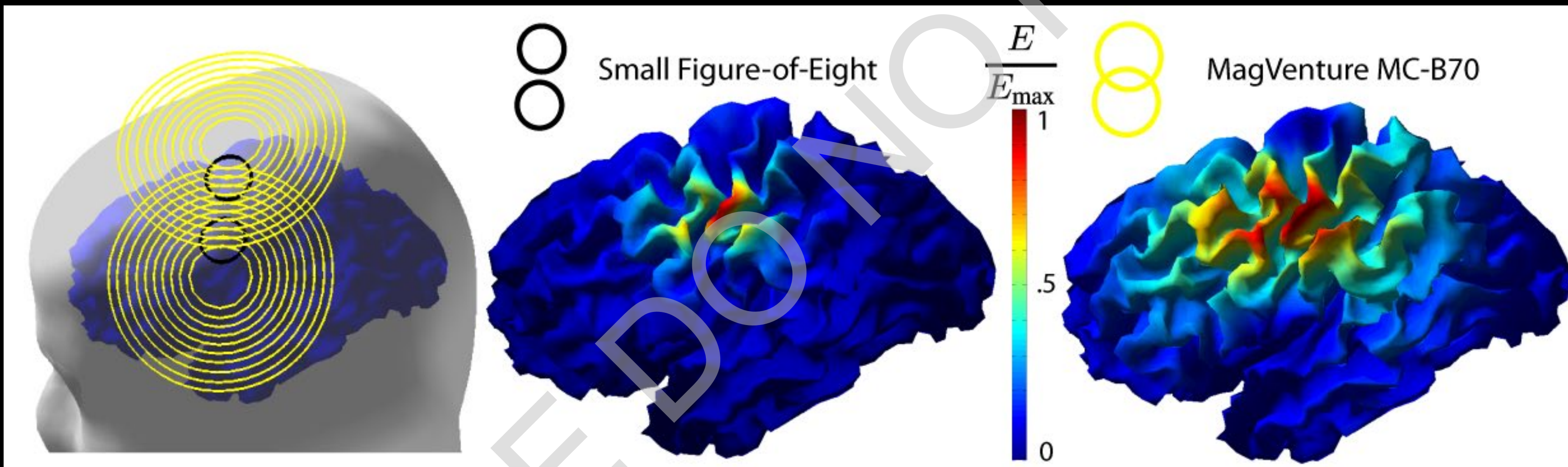
From Ilmoniemi *et al.* 1999 Crit. Rev. Biomed. Eng

Maximum dI/dt during the pulse
Is proportional to stimulator output intensity!

What determines coil "sensitivity profile"?

The coil sensitivity is a vector field: $\mathbf{L}(\mathbf{r}) = \left[\ \mathbf{L}_x(\mathbf{r})\ \ \mathbf{L}_y(\mathbf{r})\ \ \mathbf{L}_z(\mathbf{r})\ \right]$

Coil sensitivity magnitude examples:



The sensitivity profile $\mathbf{L}(\mathbf{r})$ depends on:

1) Coil wire winding

2) Head shape, tissue conductivities.

Inside homogeneous conductivity compartment E-field maximal at boundary -> NO 3D focusing for TMS/TES!

Linearity: Physics *vs.* physiology

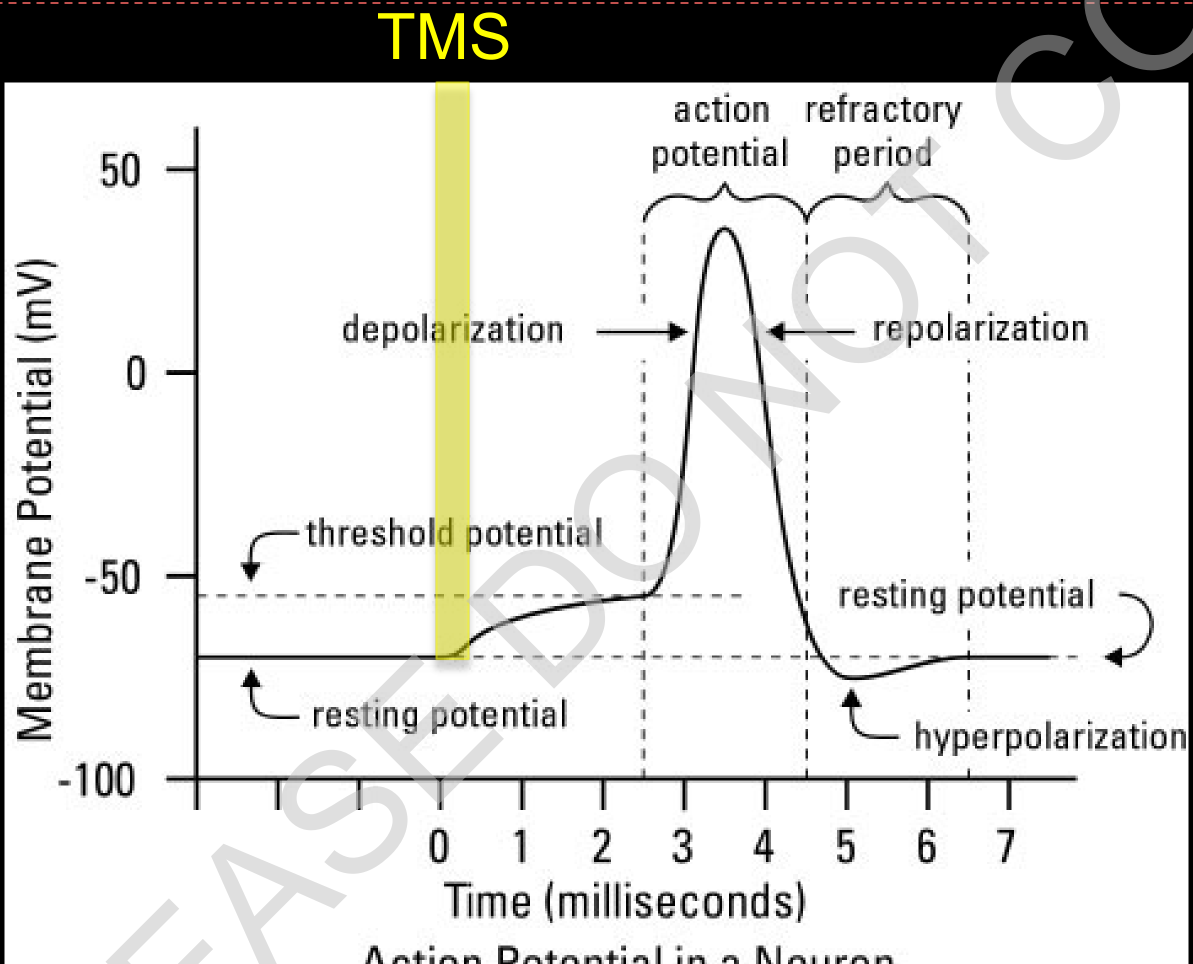
- The TMS-induced E-fields are physically well defined, but:
  - The medium is assumed to be passive and usually purely resistive.
  - This will predict the E-fields well in a "human-like phantom" where tissue shapes and conductivities match real values.

- Neurons are active elements!
  - The duration of the pulse / stimulation, orientation of the electric field w.r.t. the neuron's axis -> all matter!
  - The physiological output (neuronal activity) is not linearly correlated with the physical input (TMS).

- Software packages such as "NEURON" can be used to model the active membrane properties.
  - Not routinely done due to obvious complexities
  - Can provide valuable insights into mechanisms of action

Aberra A et al. Brain Stim 2020;13(1):175–89.

Physiology: neuronal action potential

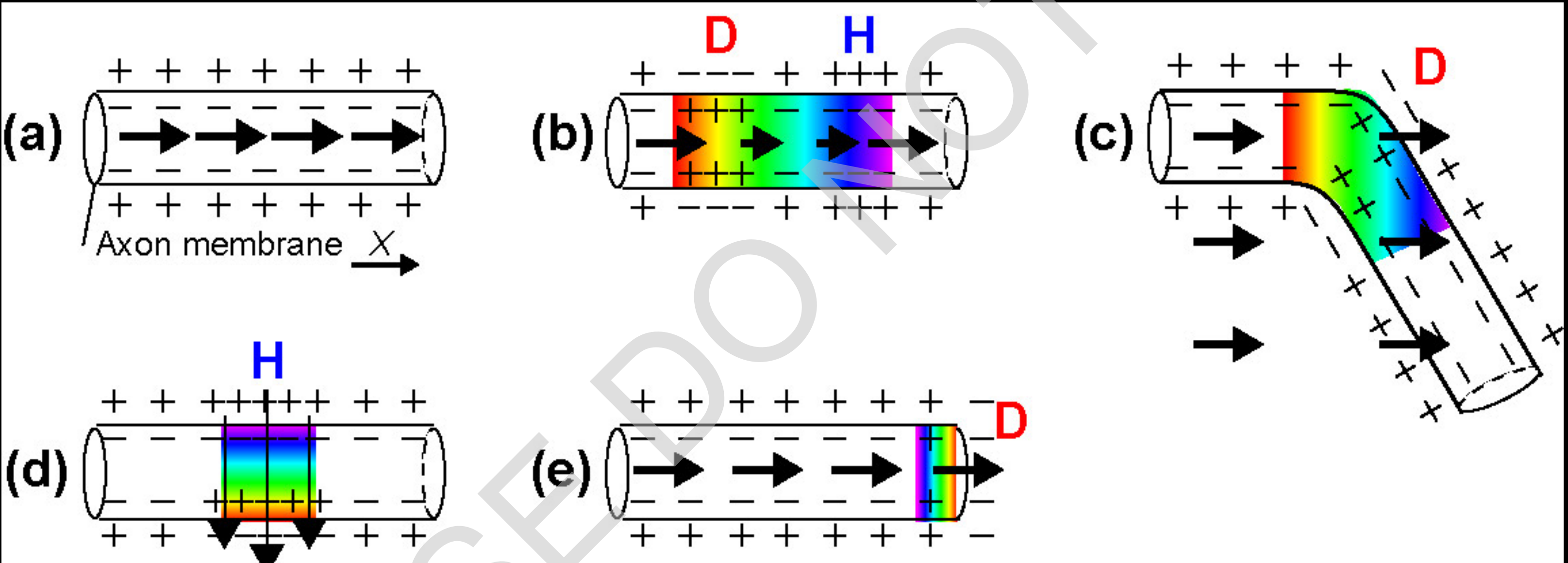


Action Potential in a Neuron

Both supra- and sub-threshold stimulation possible!

Basic principles of TMS activation

The "activating function" depends on the E-field gradient along the axon (D=depolarization, H=hyperpolarization)



Ilmoniemi et al. (1999) Crit Rev Biomed Eng ***27****:241-84*

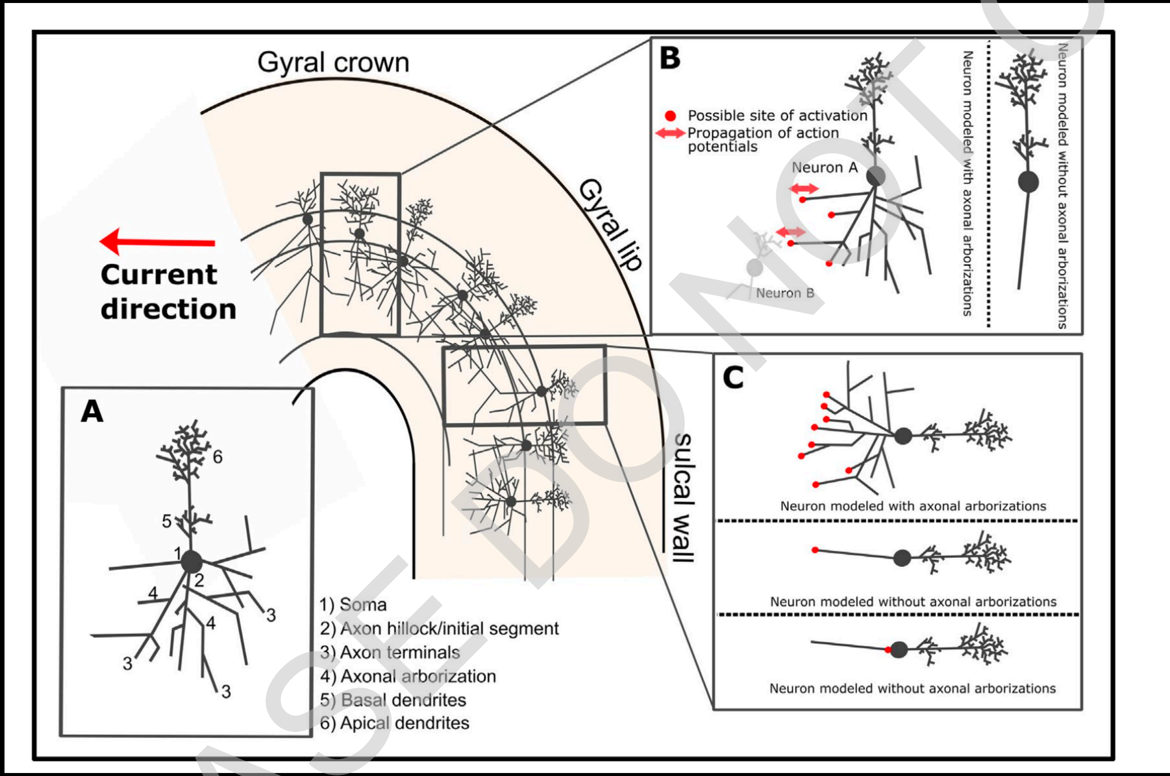
Possible loci: axon terminals, bends etc.
Gradients also created by volume conductor non-uniformities!

Where does TMS stimulate?

- At low intensities, the activation most likely transsynaptic.
  - This is called the I-mechanism: additional 2 ms latency compared with electrical stimulation (TES).
- At high intensities, the activation can be direct.
  - This is called the D-mechanism: no additional latency.
- In practice, the net effect of TMS is a some kind of combination of these!
  - TMS introduces “neuronal noise” to the cortical area.

Where does TMS stimulate (cont)

- The most recent "TMS mechanisms" review:

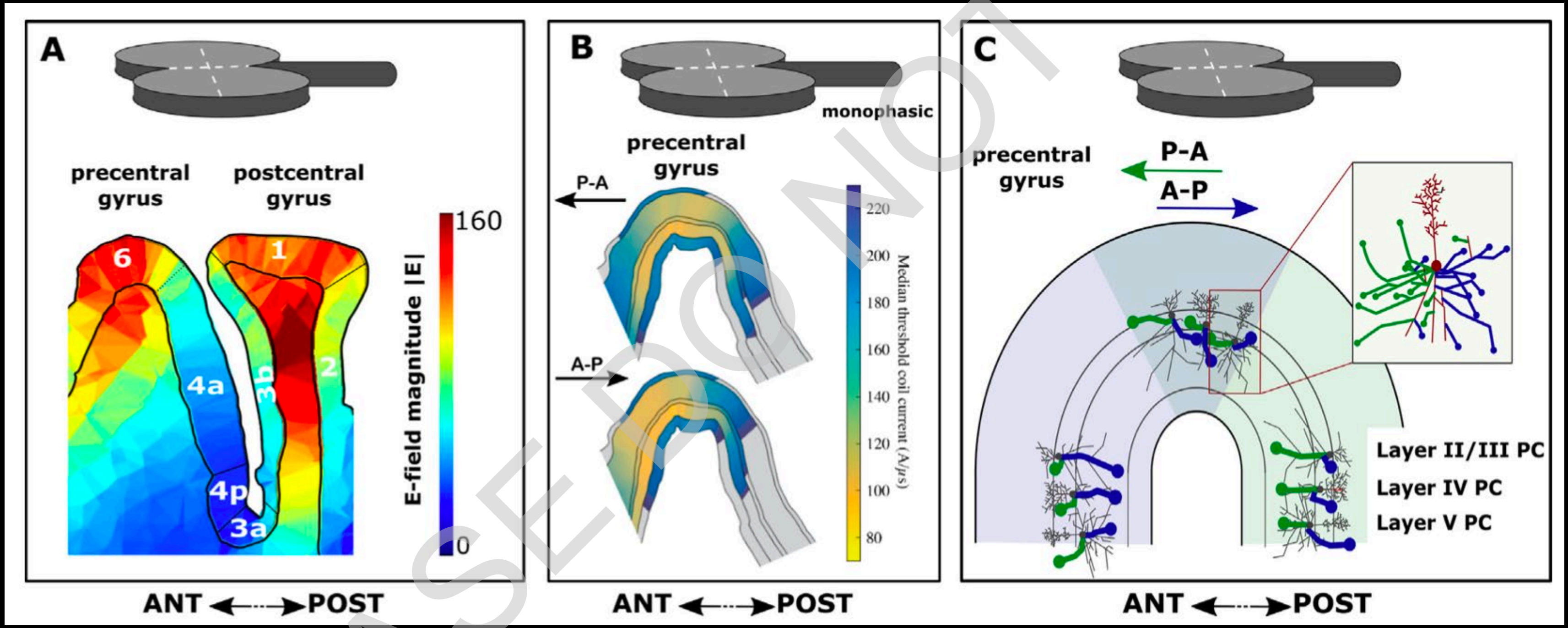


Siebner HR et al. Clin Neurophysiol. 2022 Aug;140:59-97.

- Axonal bends may be activated also activated at higher thresholds
- Coupling of accurate E-field and neuronal models is necessary!

Where does TMS stimulate (cont)

- Some practical predictions: PA vs AP stimulation

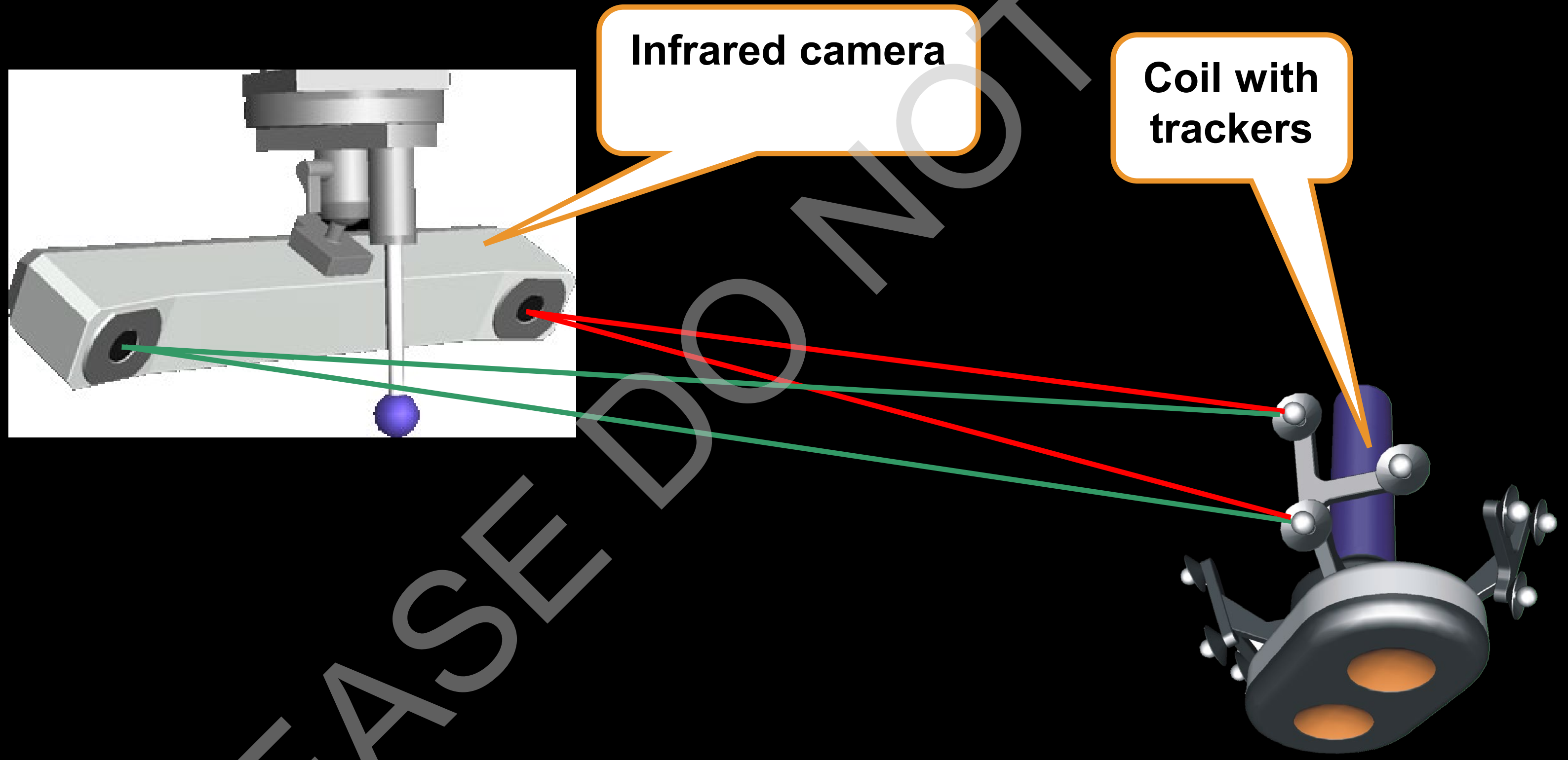


Siebner HR et al. Clin Neurophysiol. 2022 Aug;140:59-97.

- The E-field direction with respect to axonal element determines the site of lowest activation thresholds!

Modeling of TMS-induced E-fields in practice

Navigators



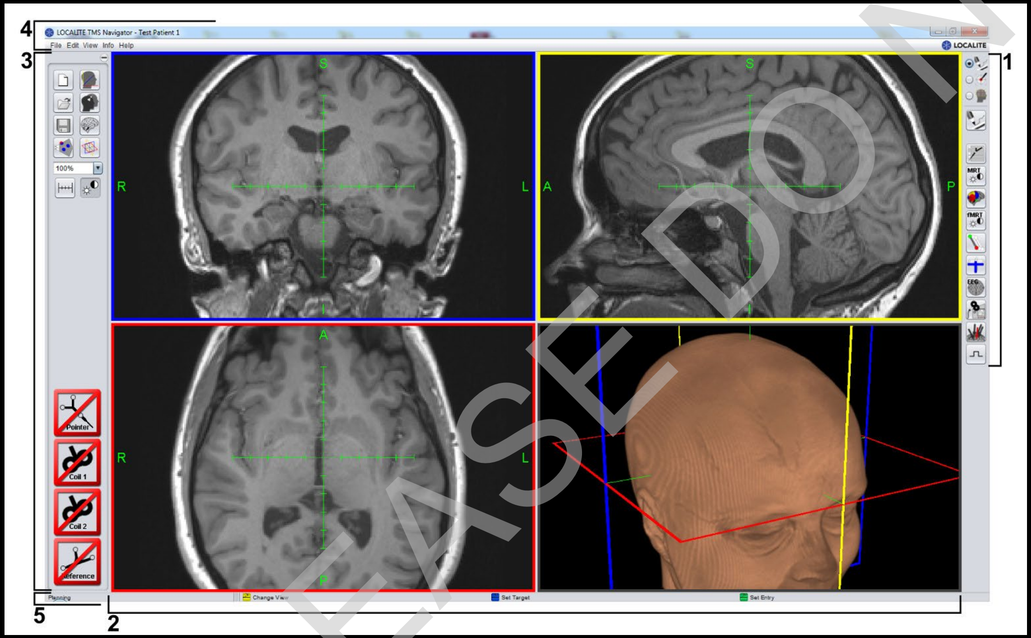
Ruohonen & Karhu (2010) Neuropysiol Clin 40:7-17

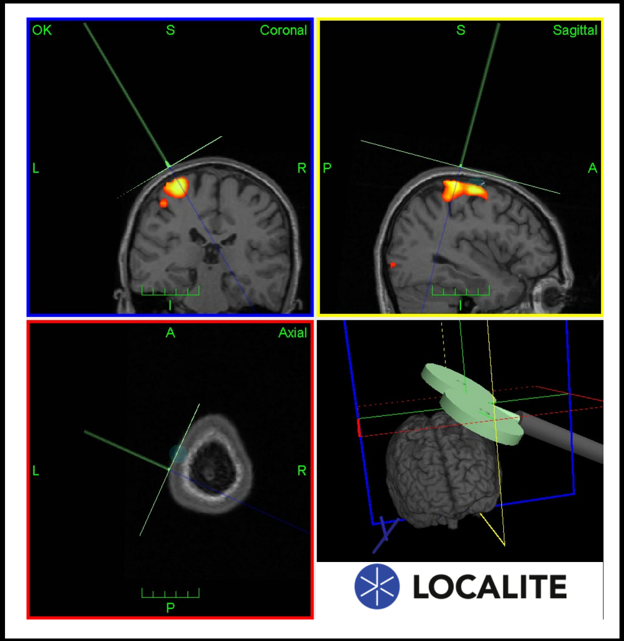
Navigators

Provide tools to track coils w.r.t subject's head

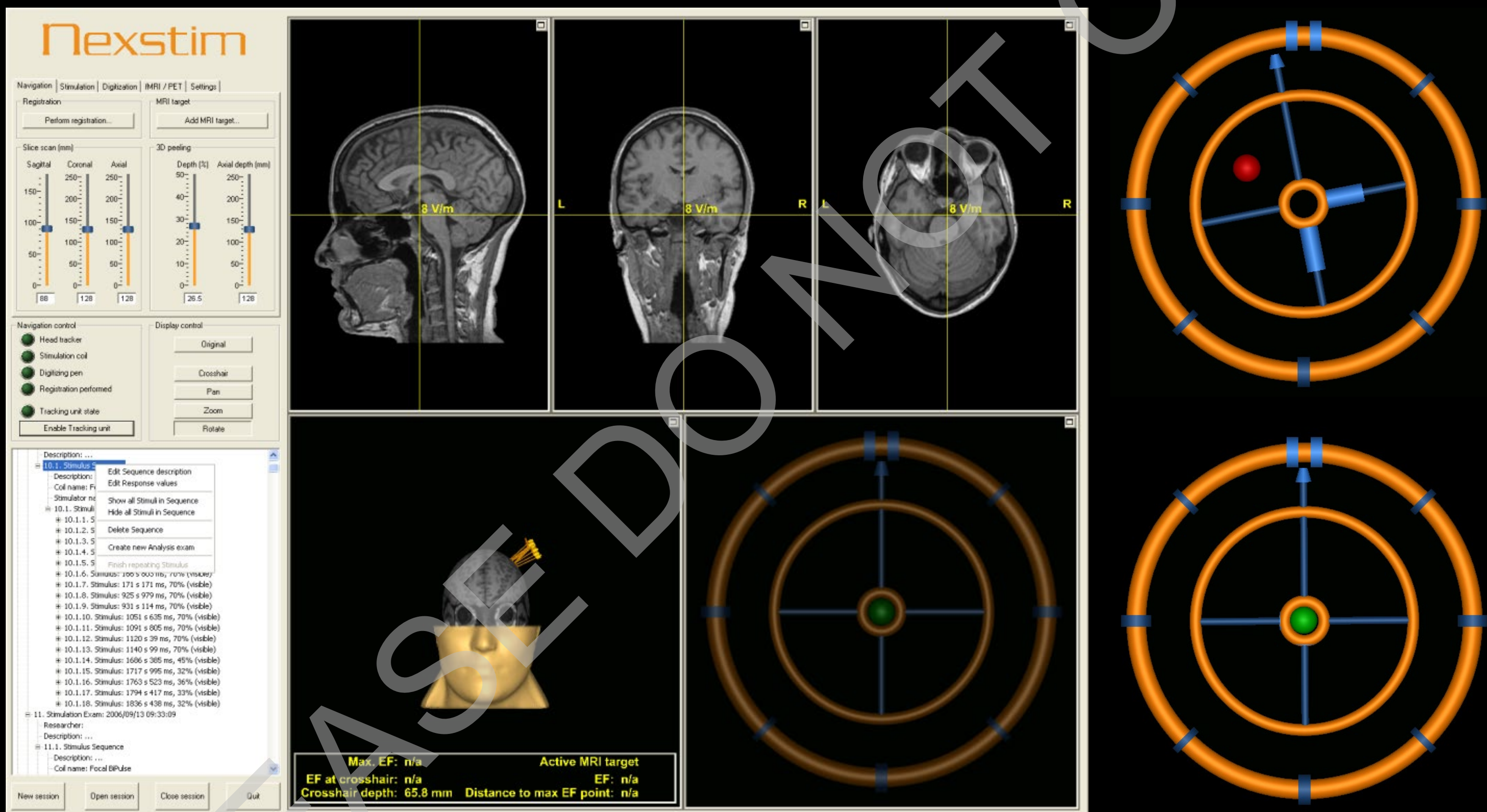
Co-register anatomy with MRI data

Targeting stimulation using fMRI, MNI coordinates etc



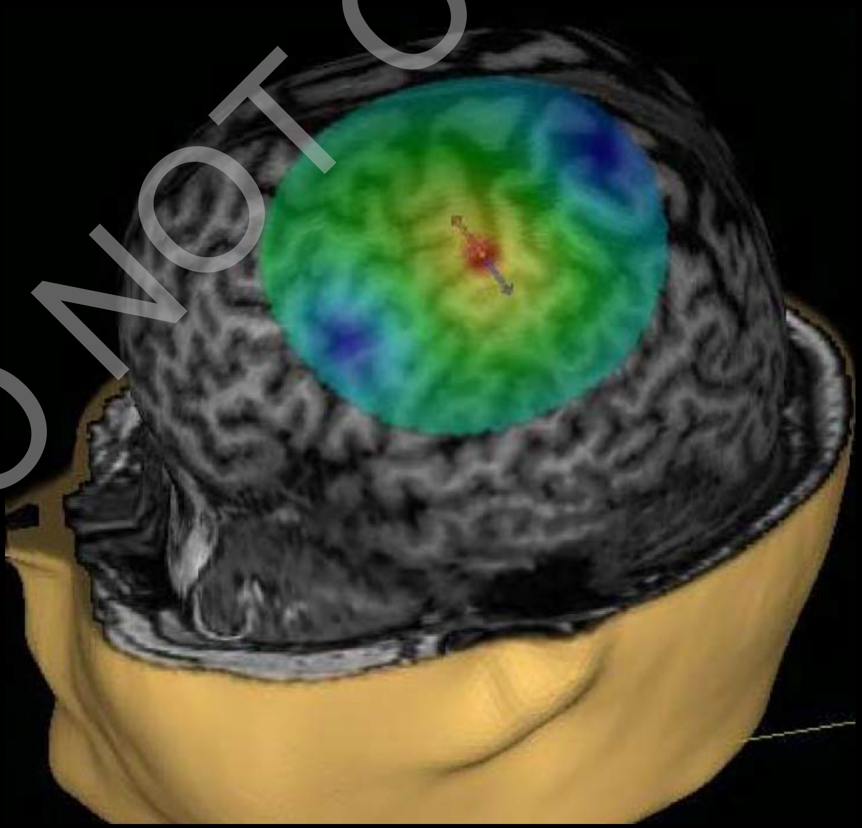


Navigators (cont)



State-of-the-art

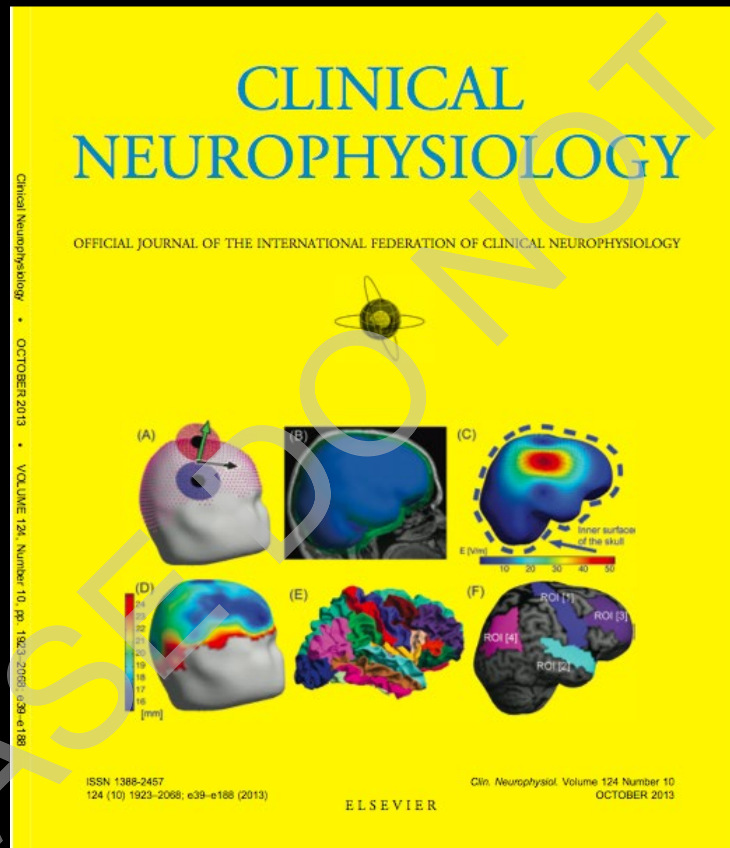
- Navigators typically use spherical head models.
- Spherical models:
  - Computationally efficient.
  - Suitable for on-line targeting.
  - May be less accurate where skull is not spherical.



ALL models are approximations of reality!

Comparison of spherical and realistically shaped boundary element head models for transcranial magnetic stimulation navigation

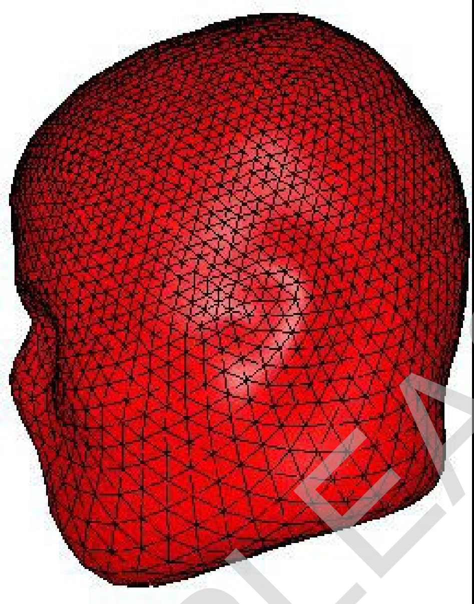
Nummenmaa A, Stenroos M, Ilmoniemi RJ, Okada YC, Hämäläinen MS, Raij T.

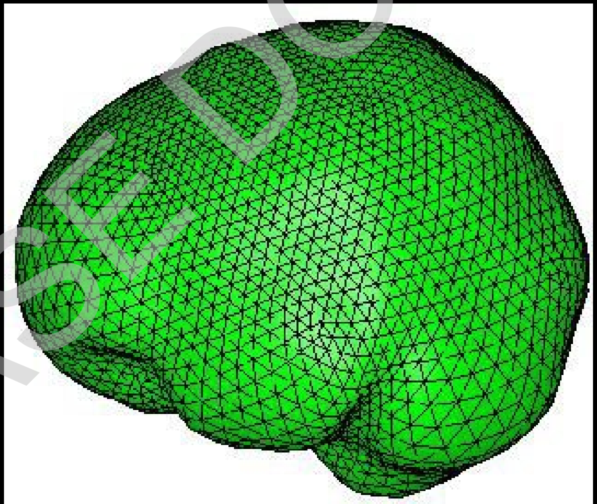


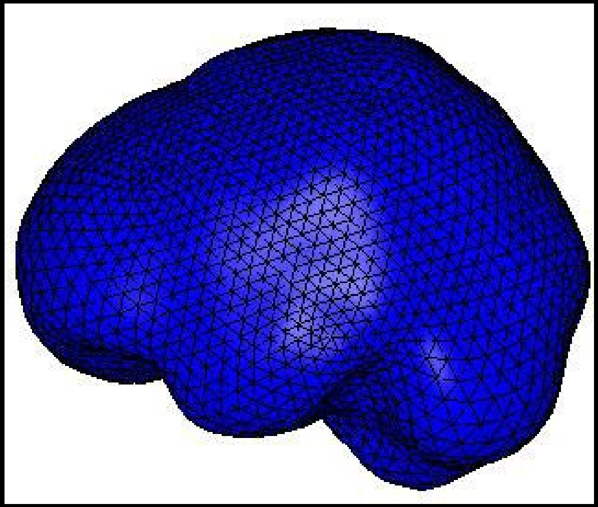
Clin Neurophysiol. 2013 Oct;124(10):1995-2007.

Practical realistic calculations: The BEM

- BEM = Boundary Element Method (or Model)
  - In present "standard approach" 3 layers (compartments):
    - Scalp, Skull & Brain (Outer skin , Out. skull, Out. Brain=In. skull)
  - Conductivity of each layer assumed homogeneous & isotropic
    - Conductivity values : ~0.3 S/m (Scalp & Brain) ~0.006 S/m



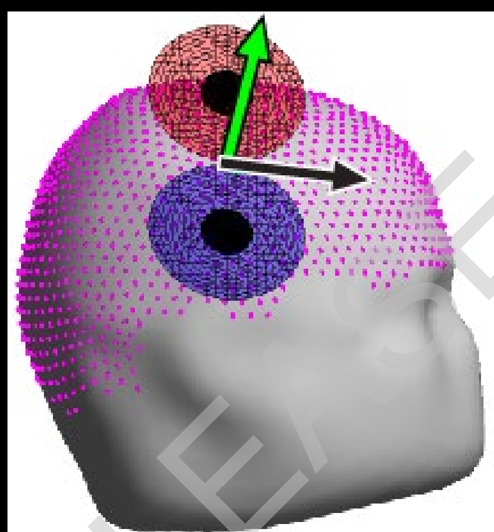


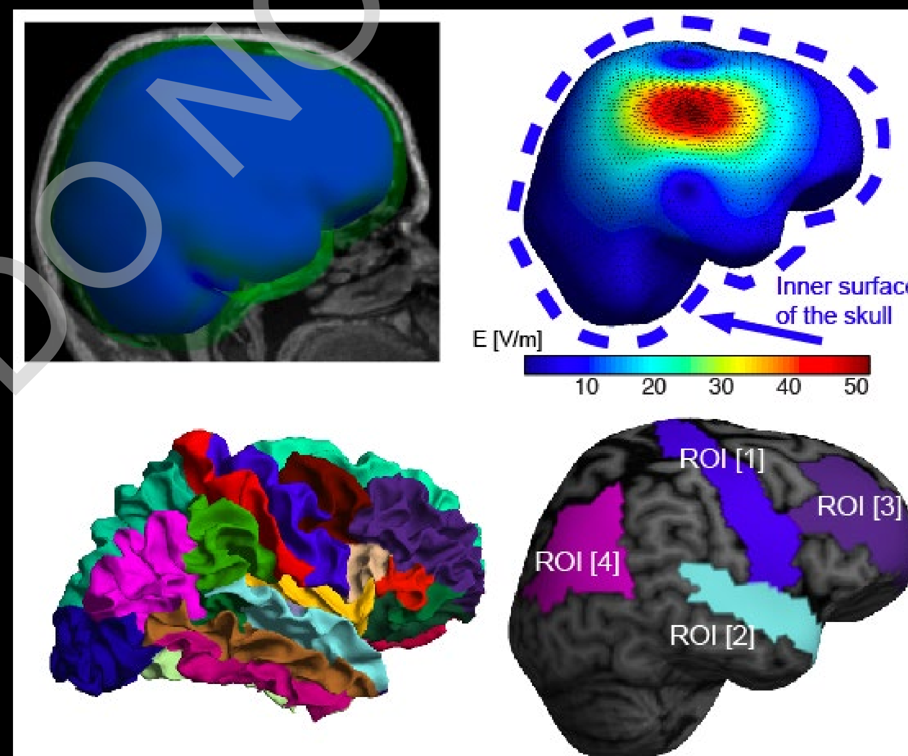


Spherical vs. realistic head models

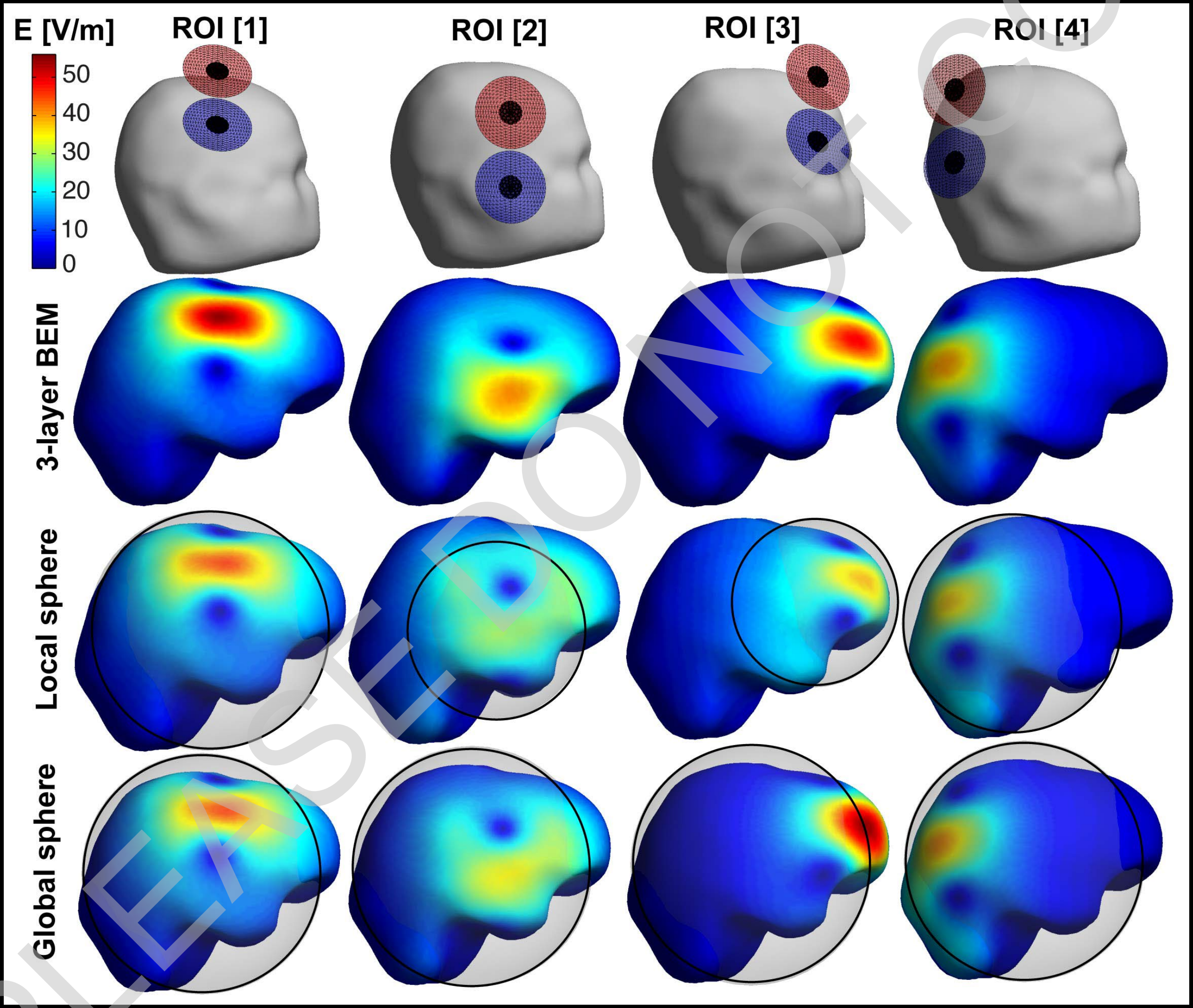
- We compared locally and globally fitted spherical models to three and one layer Boundary Element Models (BEM)

Three layer BEM:
(brain, skull, skin)





Spherical vs. realistic head models (cont).

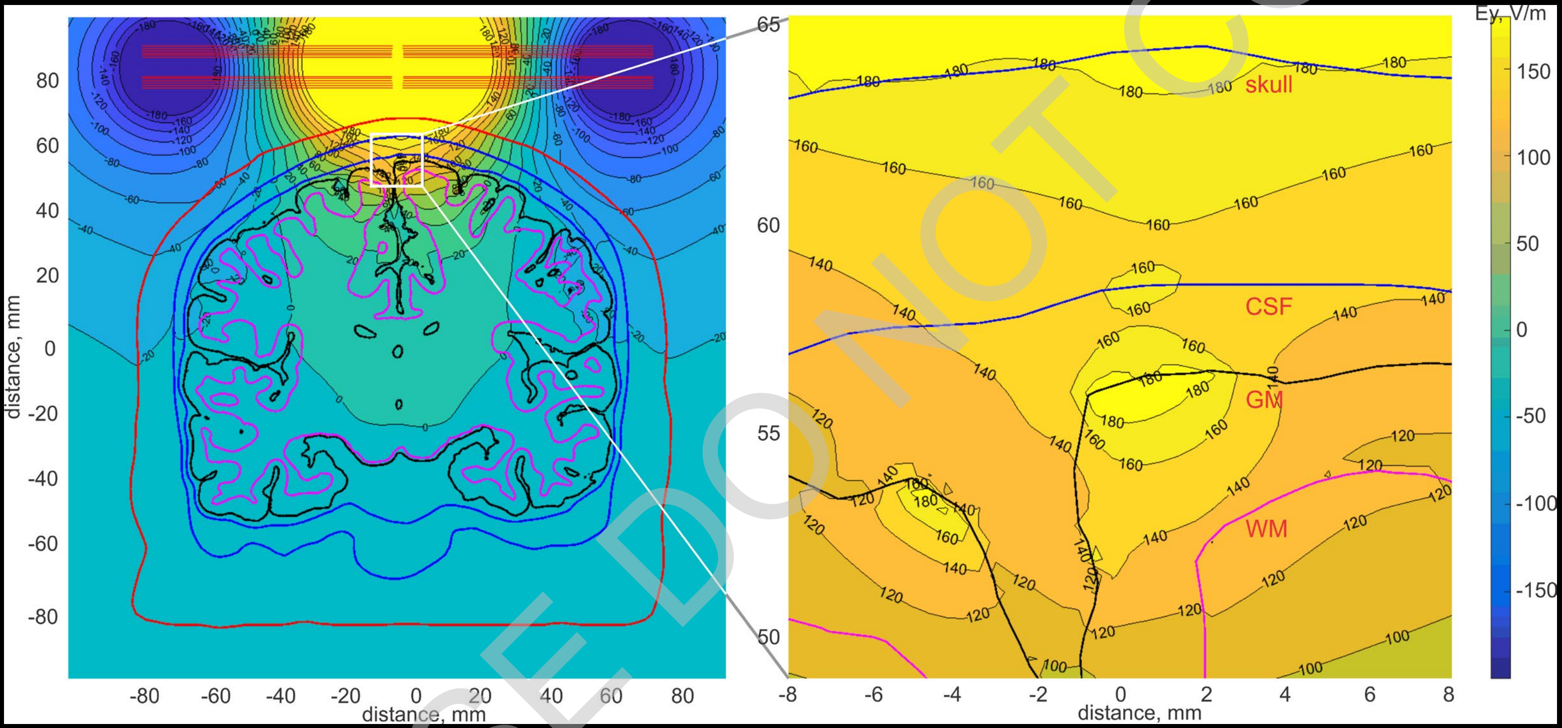


BEM vs. sphere findings

- Inner skull surface is the most important boundary
  - TMS quite insensitive to the exact value of skull conductivity
- Shape of inner skull is important where the head is not spherically symmetric
  - Main differences in temporal and frontal regions
- Fitting of a sphere to a skull surface can be tricky
  - Spherical approximations can be further improved
- If feasible, the three-layer model is recommended

High-resolution BEM modeling

Makarov, S., Noetscher, G., Raij, T., Nummenmaa, A., 2018, IEEE Trans. Biomed. Eng



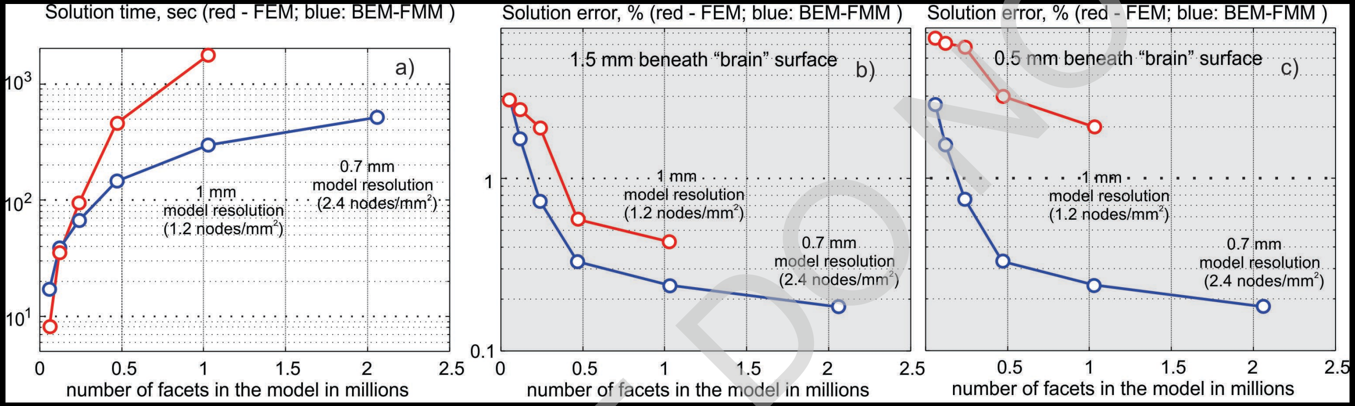
New method developed to obtain accuracy of the numerical commercial Finite Element Method (FEM) solver (Ansys Maxwell)

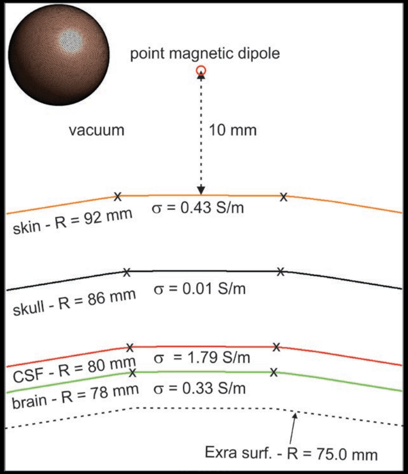
Highly detailed models with the convenience of the surface-based approach through fast-multilevel multipole (FMM) method

Comparison of BEM-FMM with FEM

The computational performance was compared with SimNIBS 2.1.1

Spherical mode (analytical solution) was used as gold standard





Computational performance of BEM-FMM is superior especially for high-resolution models and close to conductivity boundaries!

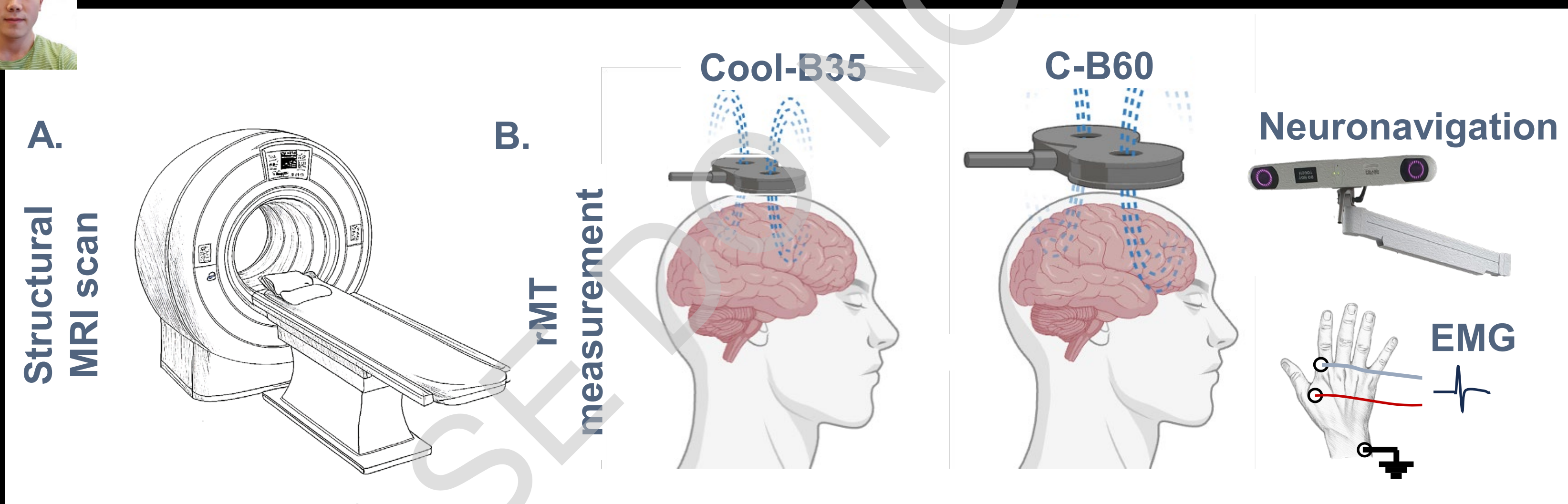
Further improvements have been made to SimNIBS 4 and BEM-FMM → both FEM and BEM can be made numerically "sufficiently accurate"

Thet, A., Saturnino, G.B., Burnham, E., Noetscher, G. Nummenmaa, A., and Makarov, S. 2019, J. Neural Eng

E-field modeling as a quantitative tool

Q: is the individual cortical E-field distribution a “reliable measure” of excitability?

→ lots of ”variables”: coil model, head model, numerical solver, navigation data, EMG responses!



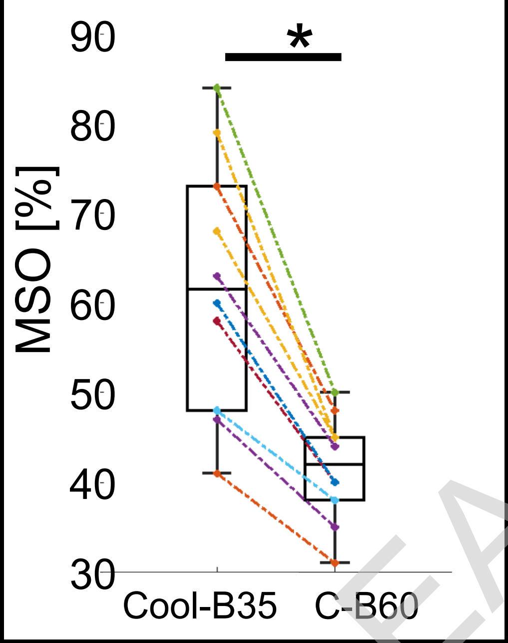
Idea: test the predictions by measuring resting Motor Threshold (rMT) with two different TMS coils

Kim et al. 2025, In preparation

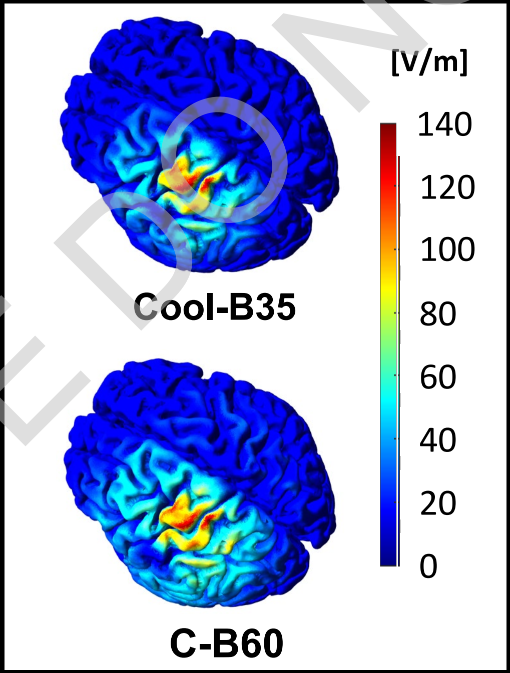
Comparing rMT and E-fields between two coils

- Ten (10) healthy volunteers went through the motor mapping / rMT
- The latest E-field modeling tools developed with Dr. Makaroff

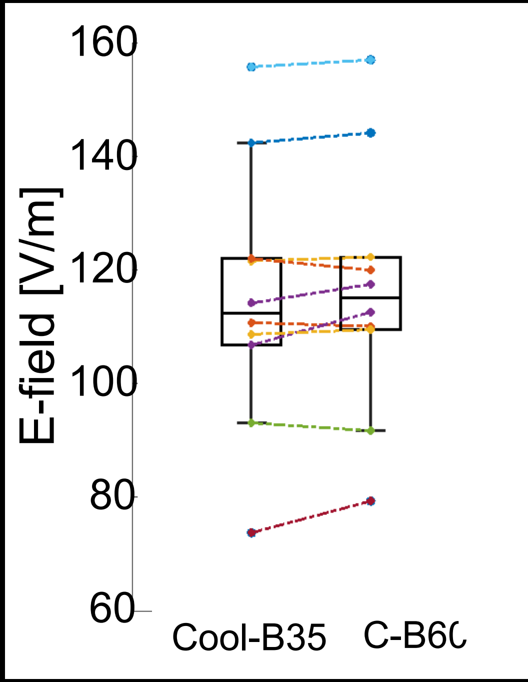
MSO=Maximal Stim. Output



Computed cortical E-field

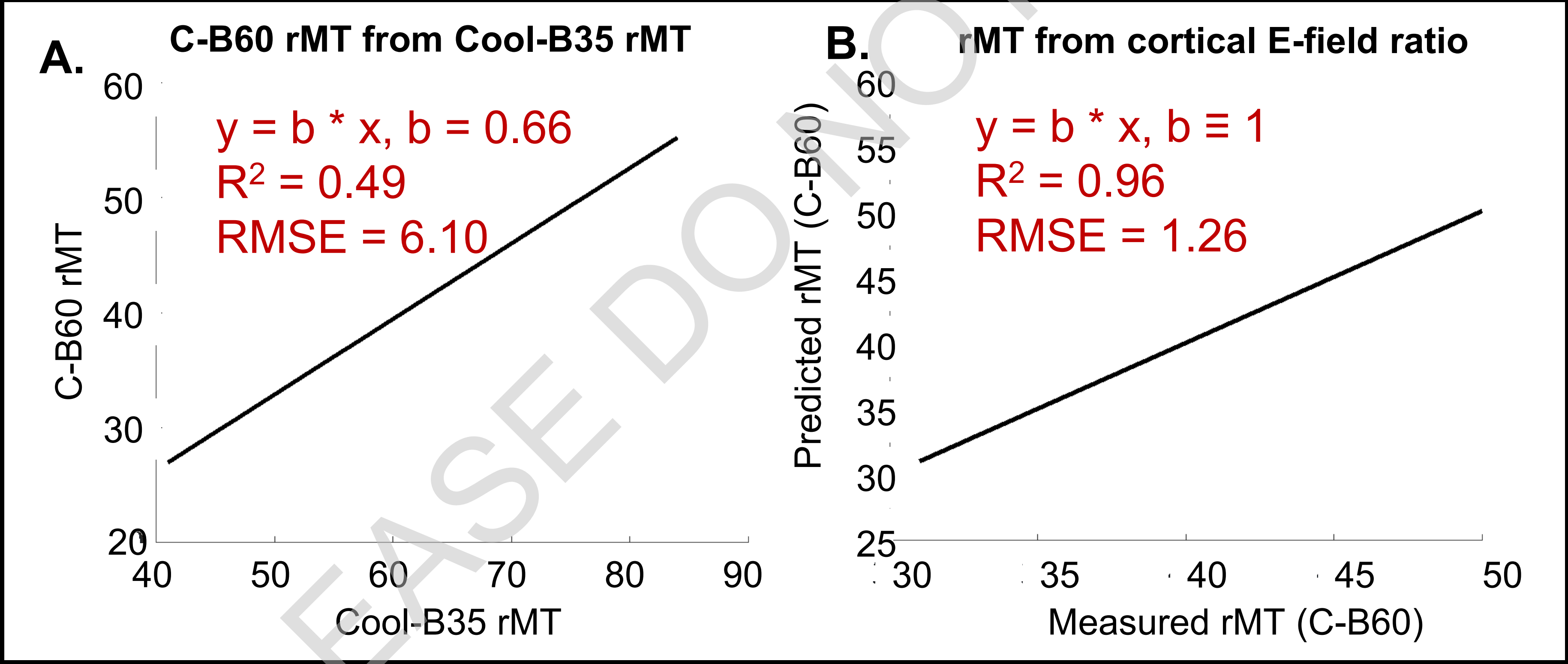


Peak E-field on motor area



Predicting the rMT using E-field modeling

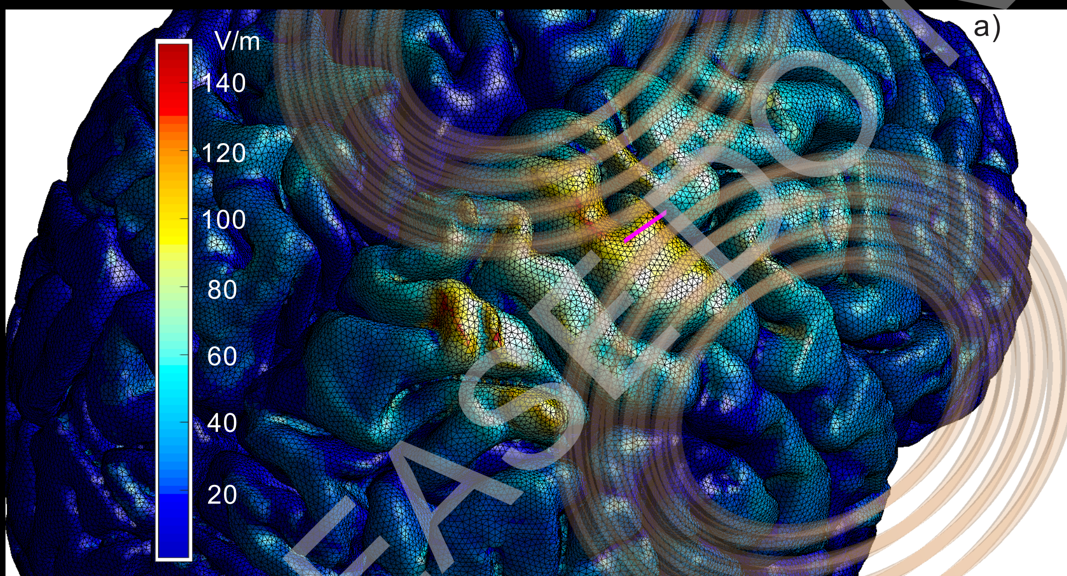
$$E_{th}(r) = \frac{dI_{coil1}}{dt} \times L(r)_{coil1} = \frac{dI_{coil2}}{dt} \times L(r)_{coil2} \text{ and } \frac{dI}{dt} \propto MSO\%$$

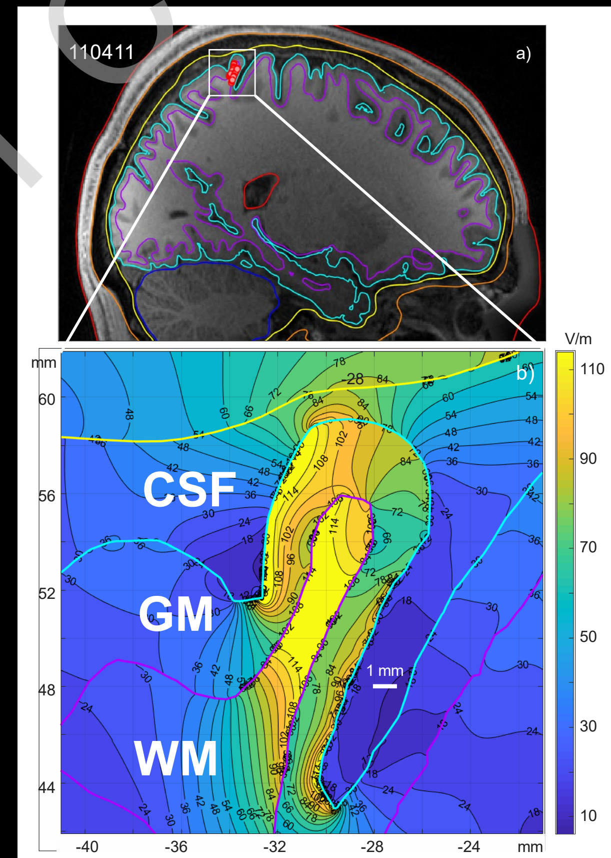


Fast high-resolution TMS modeling with MATLAB

https://tmscorelab.github.io/TMS-Modeling-Website/

- The BEM-FMM TMS toolkit has been implemented and prepared for dissemination
- MATLAB package freely available for download
- Flexible coil modeling approaches implemented



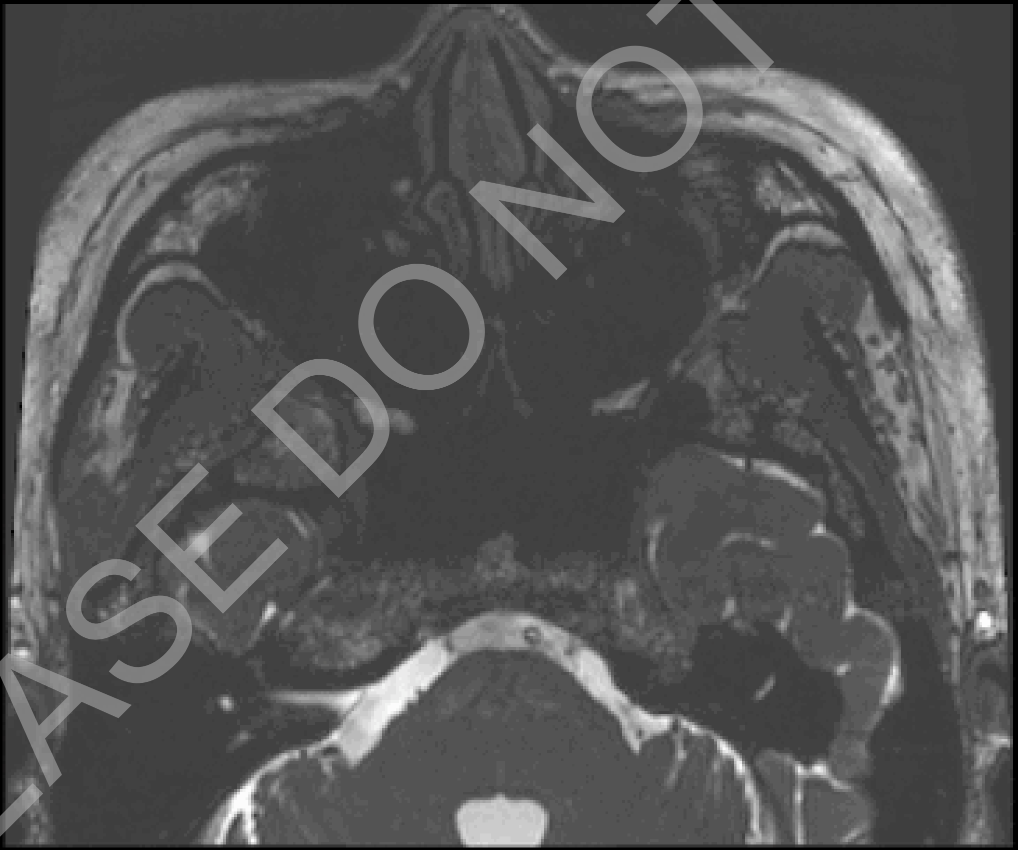


Makarov SN, Wartman WA, Daneshzand M, Fujimoto K, Raij T, Nummenmaa A. J. Neural Eng. 2020

Modeling assumptions: What IS the CSF thickness?

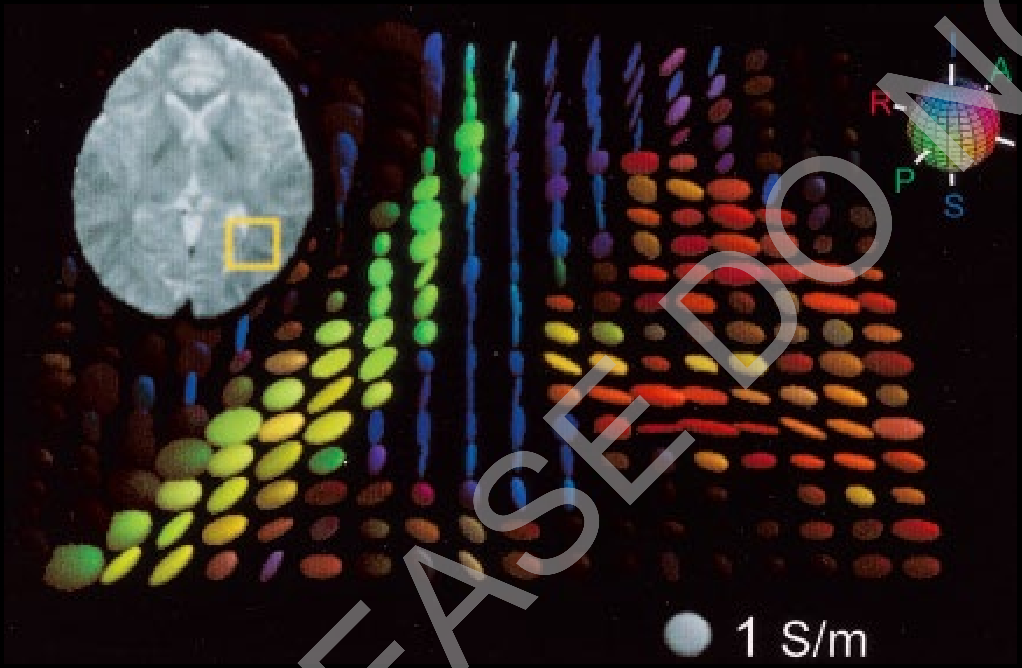
CISS (Constructive Interference In Steady State) MRI:

Spatial resolution = 0.6 mm = 600 micrometer



How about conductivity anisotropy?

Diffusion Tensor Imaging (DTI) can be used in FEM to measure anisotropy of water diffusion in the human brain non-invasively.



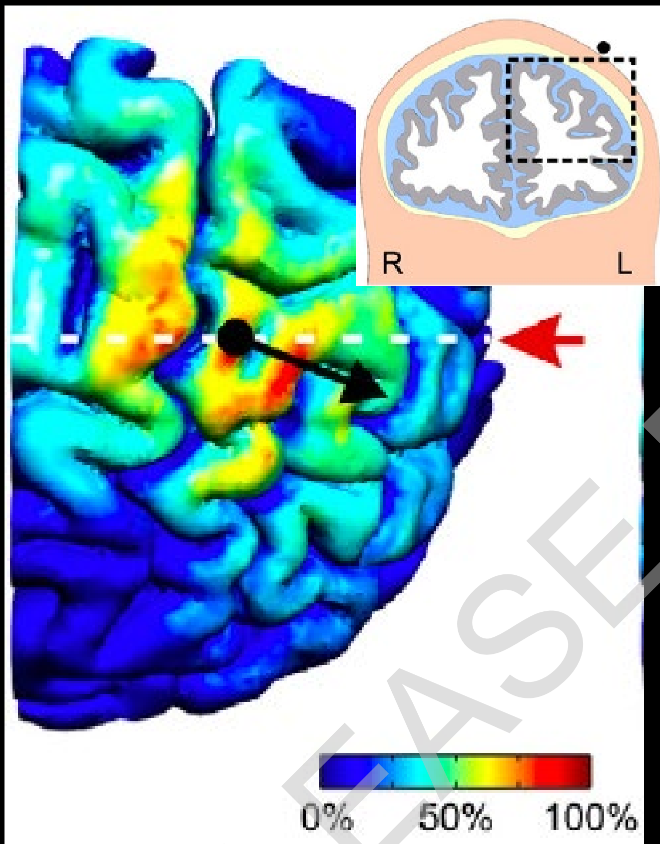
From Tuch et al. PNAS 2001

Making some assumptions about cross-property relationship between diffusion and conductivity, anisotropic conductivity can be incorporated into TMS E-field models.

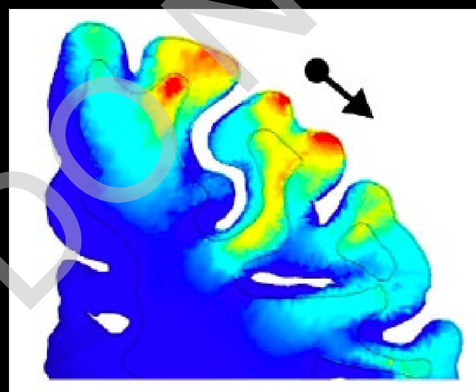
Effects of anisotropy to TMS E-fields

E-field estimates with and without anisotropic conductivities

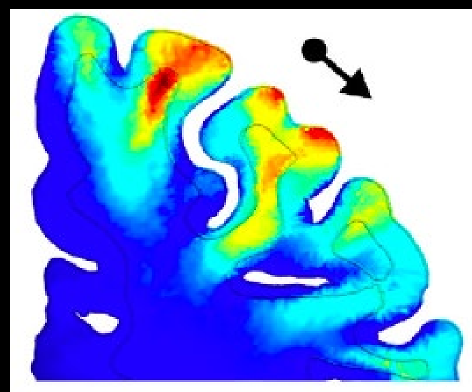
(From Opitz *et al.* NeuroImage 2010)



WM conductivity
isotropic



WM conductivity
anisotropic

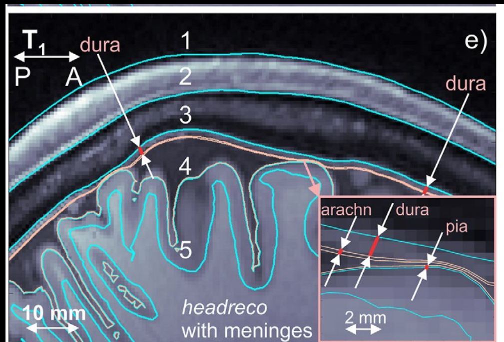


Anisotropy seems to further influence the E-field.

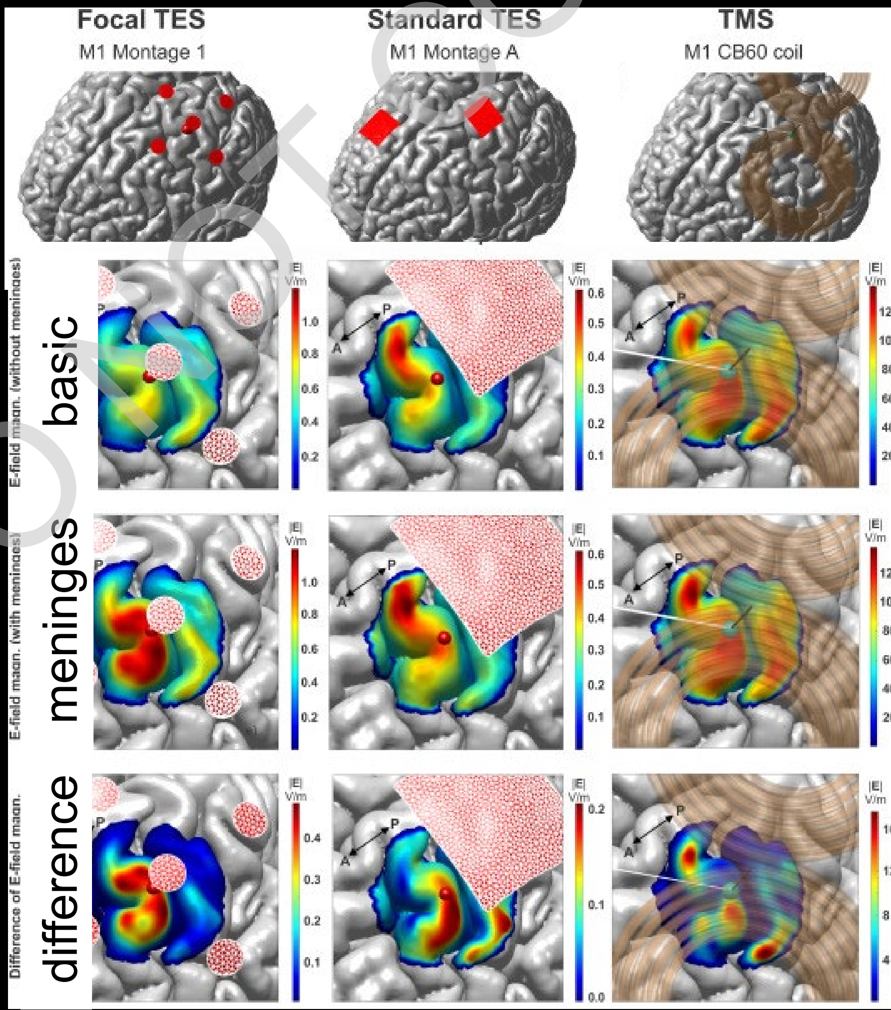
Further studies needed to validate the diffusion vs. conductivity mapping.

Advanced topics

TMS vs. TES



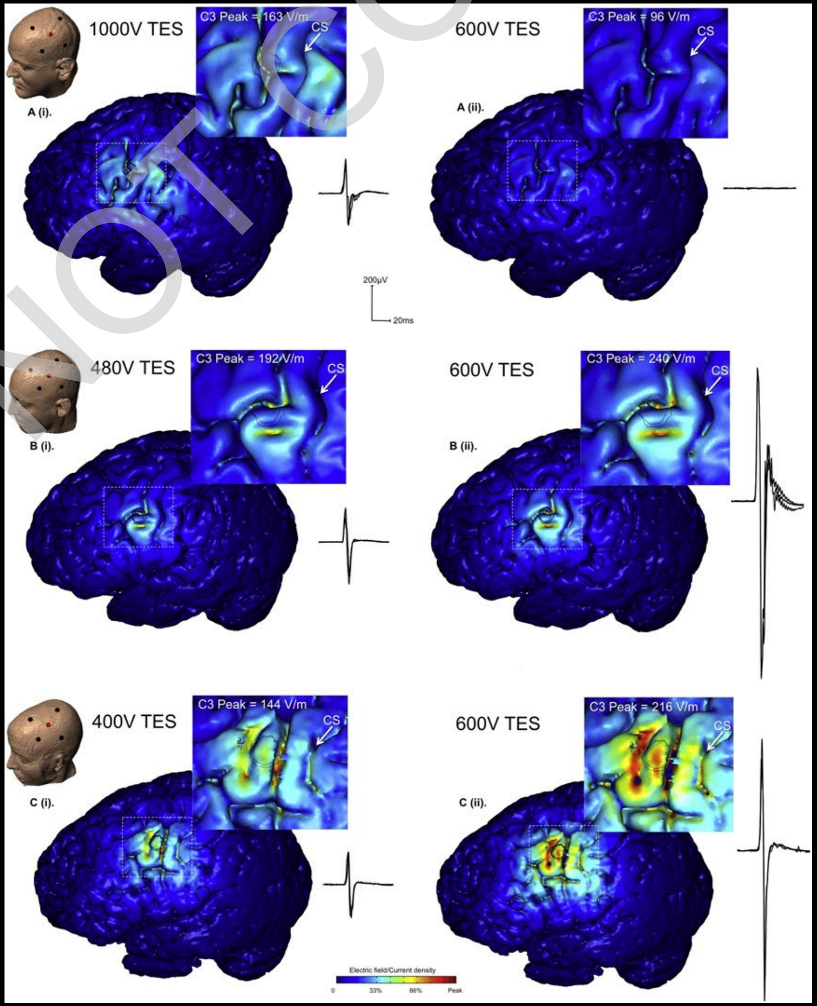
- In TES the current has to go through electrically insulating skull
- The current goes through the path of least resistance & tissue composition of skull & dura etc. plays an important role
- The TES E- fields are typically << TMS fields



Weise K et al., Brain Stim. (2022): 15(3):654-663

TES vs. tDCS

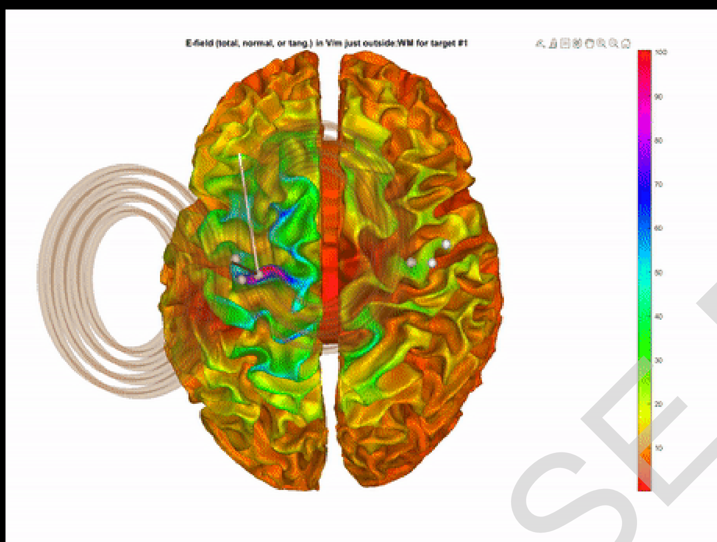
- TES typically uses brief (~50 μs) voltage-controlled (>200 V) pulses
- tDCS is low voltage (~10–20 V) and current-controlled (~1–2 mA), applied for several minutes.
- TES can activate the corticospinal tract leading to a muscle twitch
- tDCS does not evoke overt neurophysiological responses but rather is thought to alter the tone of neuronal excitability
- The scalp E-fields for TES are very strong → subject discomfort!

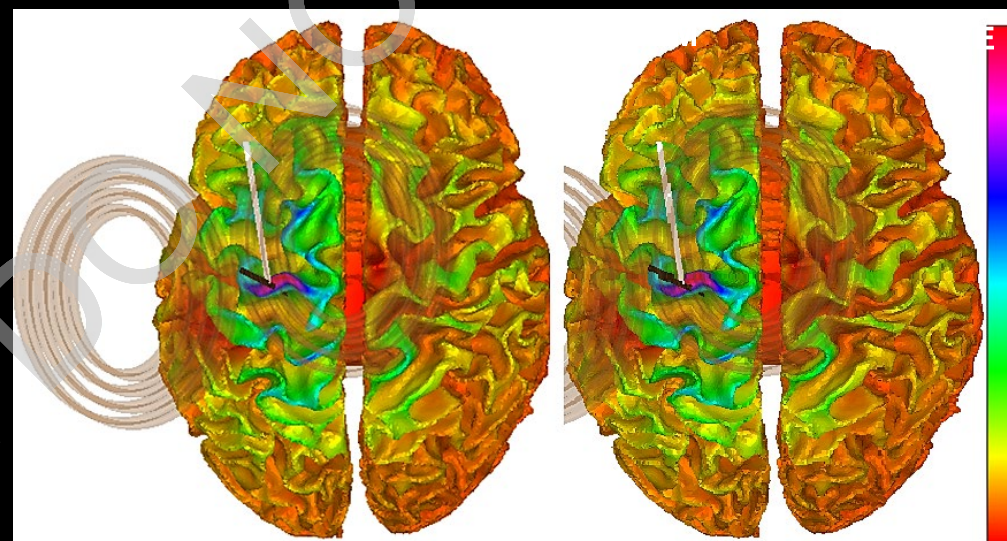


Edwards D et al., NeuroImage (2013): 74:266-275

Near real-time TMS E-field computation

- Fast precomputation or the system matrix with Fast Multipole Method
- A *numerically exact direct E-field solver* for ”mapping speed” applications
- Pre-computation 40 mins / computation per coil position ~3 sec

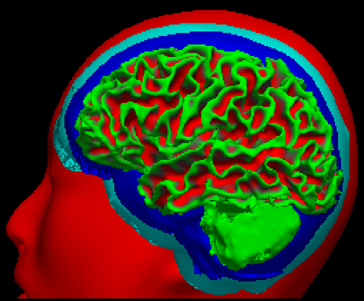


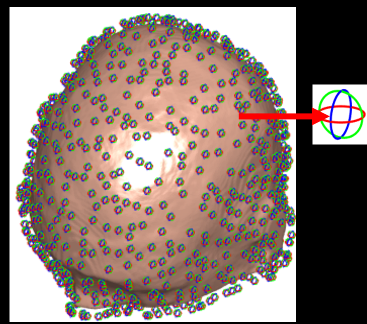


- For real-time TMS guiding frame rates of 5-15 Hz needed
- Further pre-computation necessary!

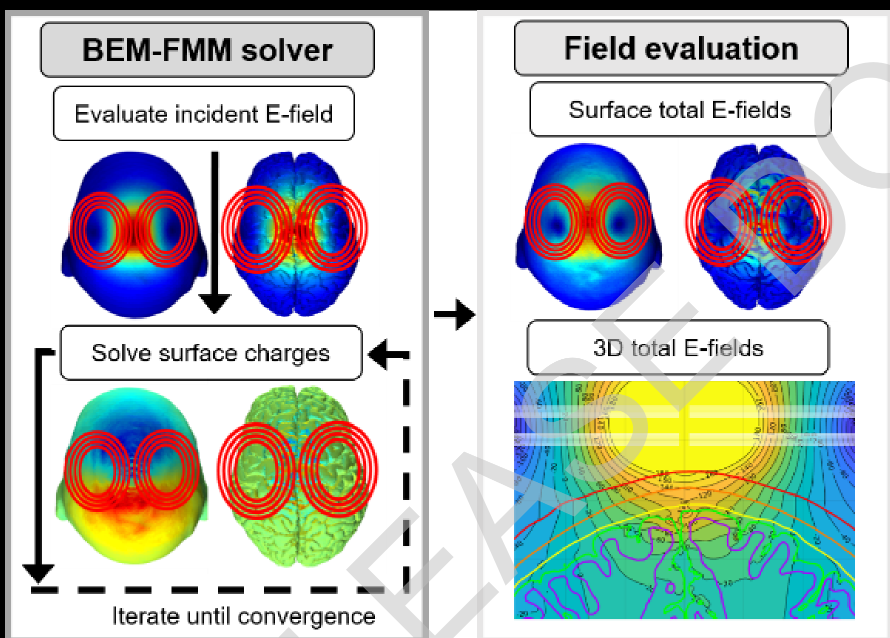
Makaroff SN, et al. Sci Rep. 2023 Oct 31;13(1)

Dipole basis function approximation





- Covering the head surface with a set of stationary dipoles
- E-fields of arbitrary moving coil can be approximated (cf. Huygens' Principle)



- BEM formulation: The incident field in free space & conductivity boundaries determine the full solution

Match the incident E-field with dipoles

⬇

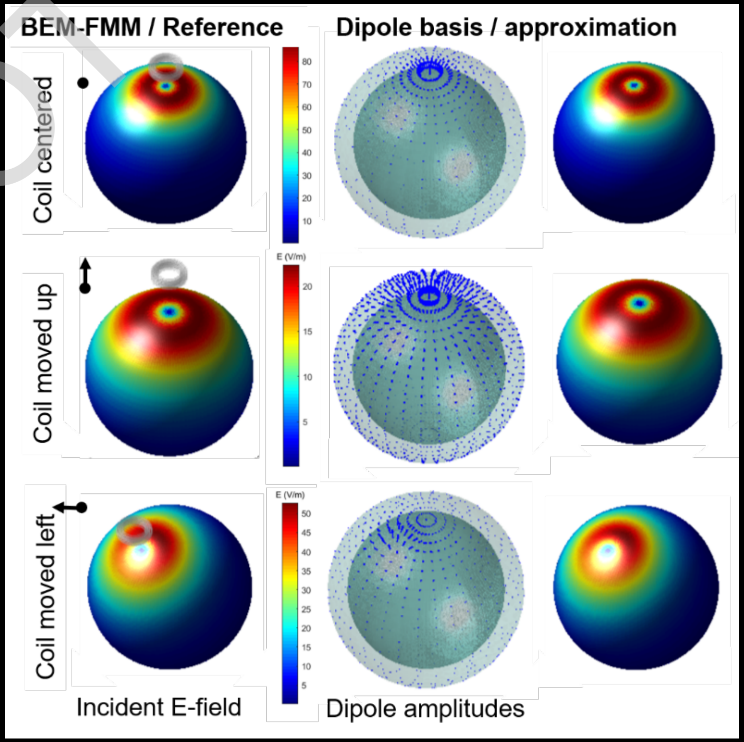
Total E-fields will also match by superposition

Daneshzand M et al. 2021 NeuroImage

Dipole basis function approximation (cont)

How to choose the dipole basis set → In theory radial dipoles are enough

- 3x orthogonal dipoles at each location sufficient
  → added flexibility to model non-tangential coils



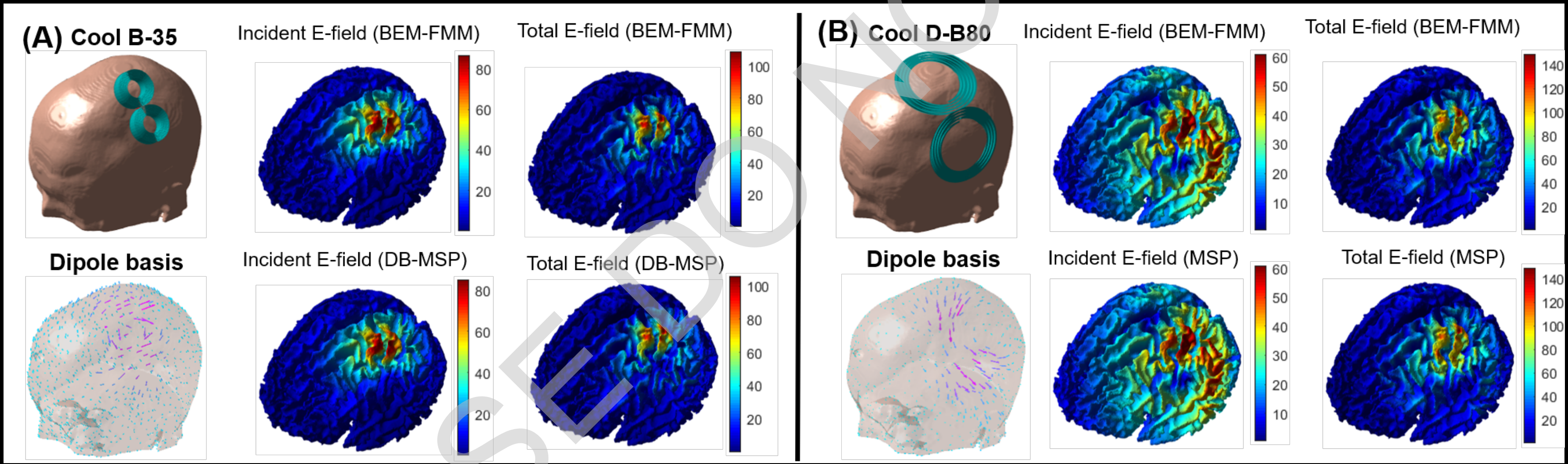
- Around 1000 locations & 3 orientations
  → 3000 dipoles need to be pre-computed

- 3 seconds x 3k dipoles = 9000 s = 2.5 hours
  → exhaustive computation remains tractable!

From Daneshzand M et al. 2021 NeuroImage

The magnetic stimulation profile

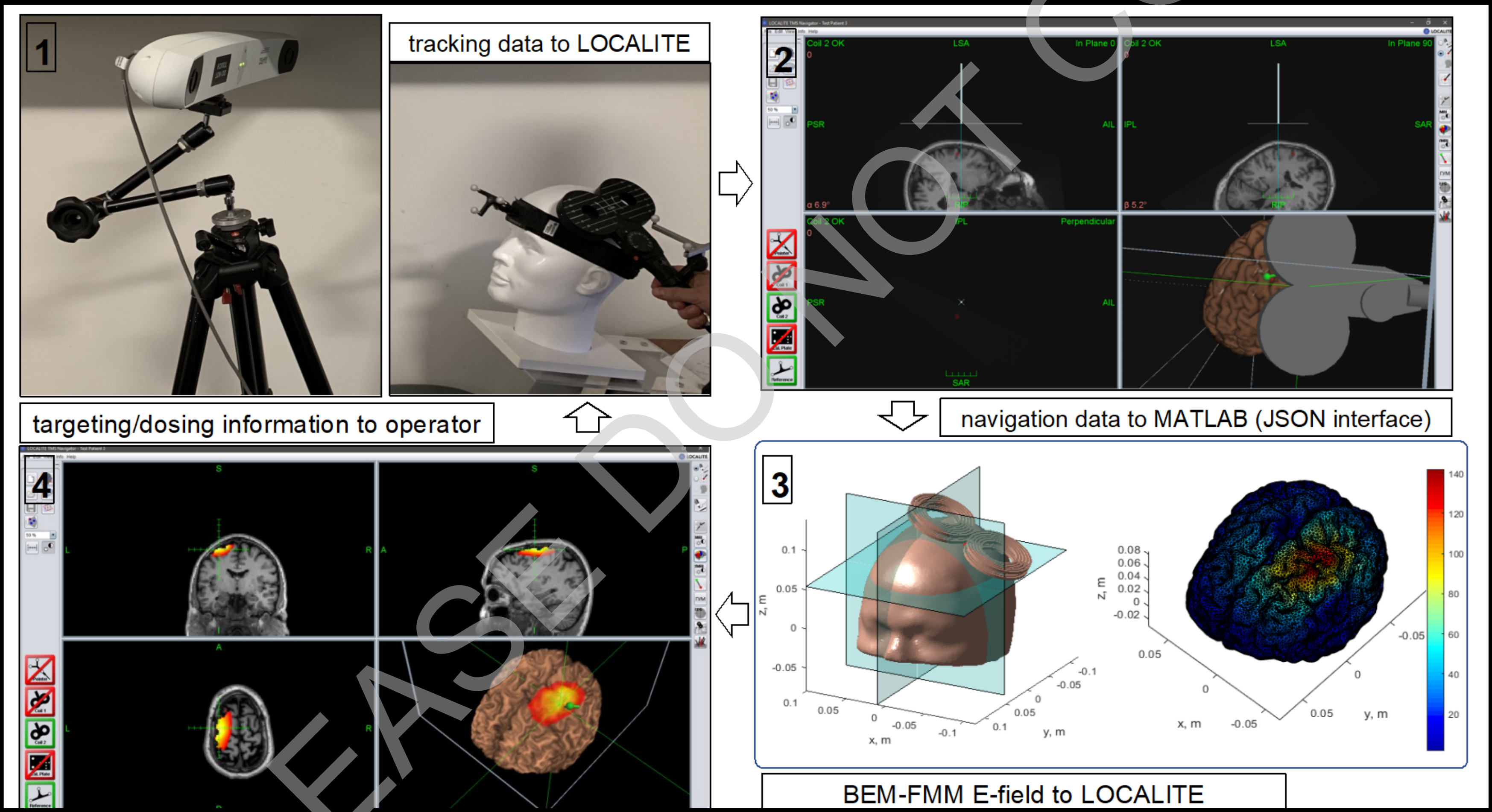
The fundamental dipole basis solution is termed ‘Magnetic Stimulation Profile” (MSP)
→ Depends solely on the head conductivity geometry



The MSP can be used to model fields of ANY TMS coil!

Daneshzand M et al. 2021 NeuroImage

Prototype – Interfacing with Localite neuronavigation

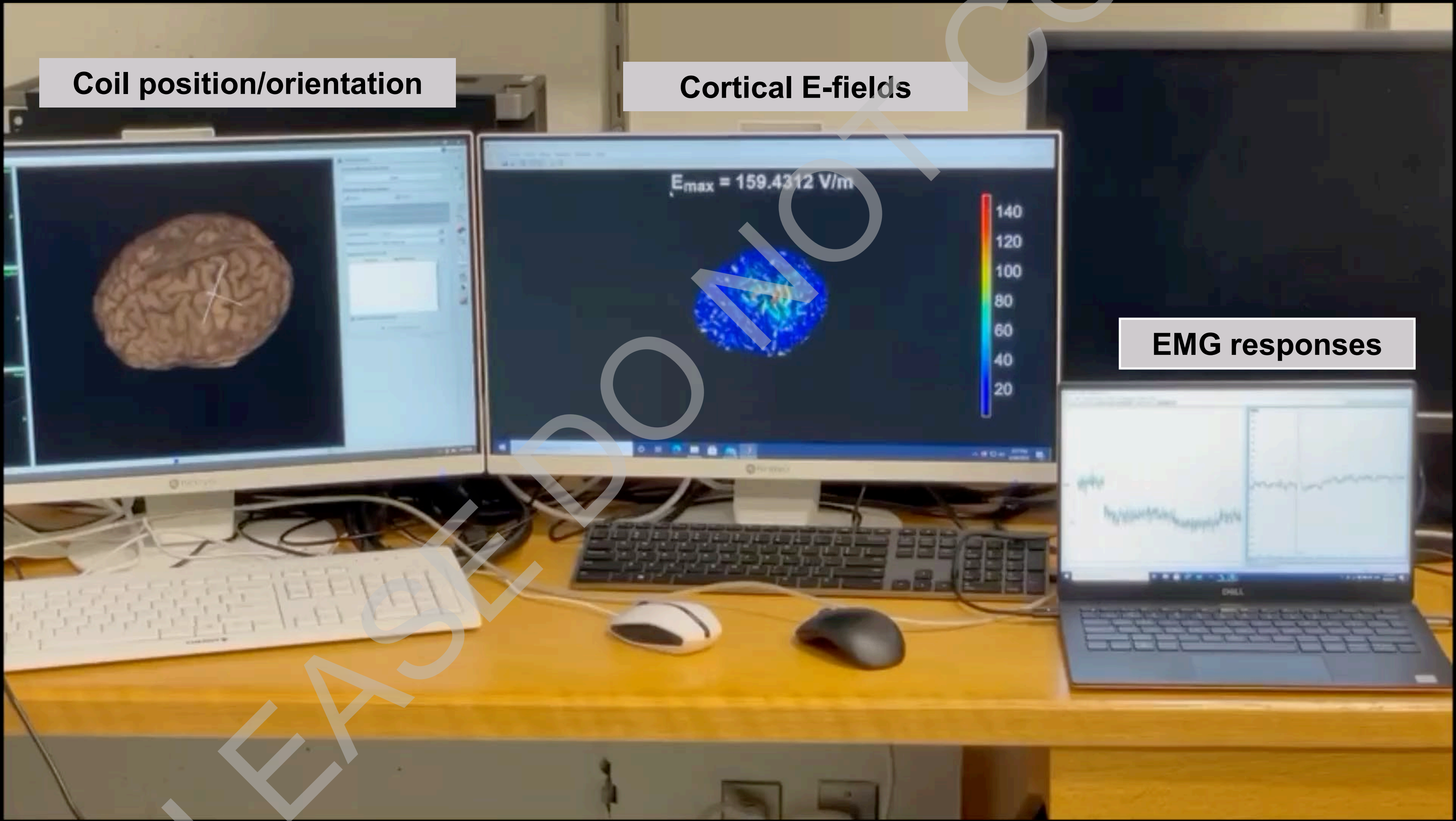


MSP approach combined with neuronavigation

E-field display frame rate = 6Hz (including **data streaming delay**, **calculations** & **rendering**)

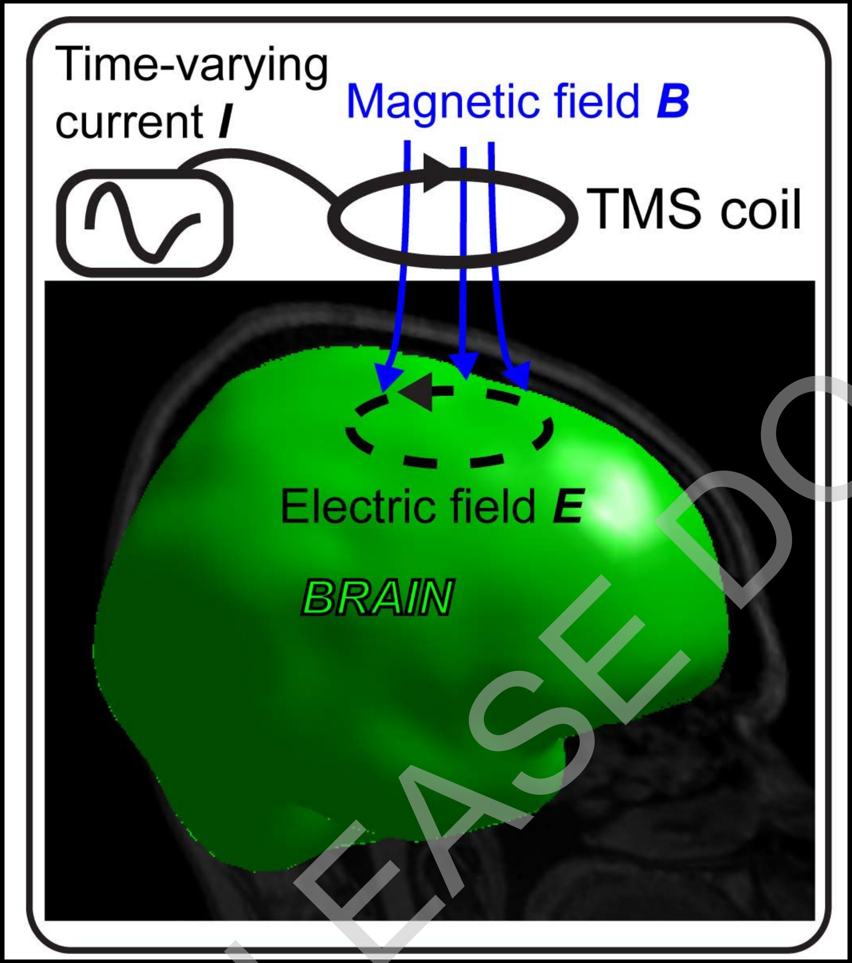
Daneshzand M. et al. 2024 In preparation

Prototype in action!



Summary

TMS physics summary: Time-varying B-field creates E-field!



Maxwell-Faraday equation:

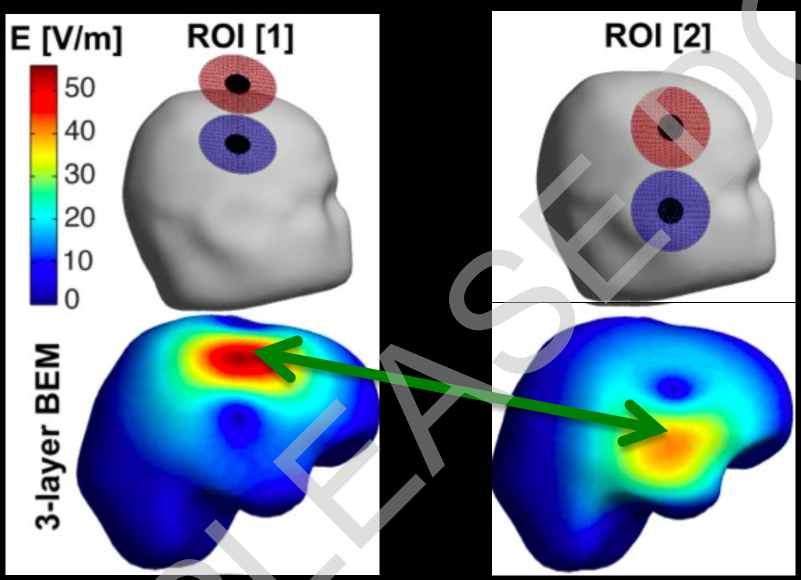
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

$-\dfrac{\partial \mathbf{B}}{\partial t}$ → "E-field opposes the B-field change"

$\nabla \times \mathbf{E}$ → "E-field goes around the B-field"

Potential gains with navigation and modeling

- Navigated targeting with modeling:
  - Consistency of target locations across subjects.
  - Repeatability across pulses, stimulation sessions…
- Navigated dosing with modeling:
  - Equalize stimulation intensity across brain areas.



Navigation + modeling = Better chance of getting a significant & replicable result!

Thanks for your attention!

Martinos TMS Core lab members

- Sergey Makaroff (WPI/MGH)
- Tommi Raij (MGH/Martinos)
- Mohammad Daneshzand (MGH/Martinos)
- Lucia Navarro de Lara (MGH/Martinos)
- Evgenii Kim (MGH/Martinos)
- Yixin Ma (MGH/Martinos)
- Keren Zhu (MGH/Martinos)
- Netri Pajankar (MGH/Martinos)

- Industrial Collaborators
  - Tristan Technologies (San Diego)
  - MagVenture (Denmark)
  - Localite (Germany)

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- R01MH111829,
- P41EB030006,
- R01DC020891, and
- Chernowitz Medical Research Foundation Award

NIH National Institute of Mental Health

CMRF

NIBIB National Institute of Biomedical Imaging and Bioengineering

https://tmslab.martinos.org/

We are hiring (post-docs, RAs)!