Using computational models in tDCS research and clinical trials

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Hypothesis: Appropriately applied computational models are pivotal for rational tDCS dose selection.

As a clinician:
How do you leverage computational models in the design of a clinical trial?
Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic electrodes
*Clinical Neurophysiology 2010 121:2165-71*
Moliadze V, Antal A, Paulus W

Electrode montages for tDCS and weak transcranial electrical stimulation: Role of “return” electrode’s position and size
*Clinical Neurophysiology 2010 121:1976-8*
Datta A, Rahman A, Scaturro J, Bikson M

M1-SO Montage  M1-Extracephalic montage

< A priori assumption: **Increased** current delivered to brain (decrease scalp shunt)
> **Clinical neurophysiological**: **Decreased** motor-cortex modulation (TMS-MEP)
> **Model prediction**: Temporal current “slip”- **reducing** intensity at motor cortex.
> **Clinical trial**: **Decreased** analgesic effect

Transcranial DC stimulation in fibromyalgia: optimized cortical target supported by high-resolution computational models
*J Pain 2011 12:610-7*
Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, Araujo CP
Hypothesis: Appropriately applied computational models are pivotal for rational tDCS dose selection.

Why should clinicians use models?

- You control the tDCS dose applied (electrode position, number, shape, current).
- But need to know which brain regions are stimulated.
- Computational models relate tDCS dose to brain stimulation.
Pharmacologic activity (efficacy and safety) is determined by drug concentration at tissue

Clinical dose is set by systemic application (tablets…)

Electrical activity (efficacy and safety) is determined by electric fields at tissue

tDCS dose is set by surface application (electrodes)

Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices Brain Stimulation 2012 5:435-53
Peterchev AV, Wagner TN, Miranda PC, Nitsche MA, Paulus W, Lisanby SG, Pascual-Leone A, Bikson M.
tDCS and High-Definition tDCS (HD-tDCS)

- Conventional electrodes: large pads, saline or gel
- HD-electrodes: small and gel based

(!) tDCS and HD electrode design is not trivial. Electrode design determines skin tolerability and sensation. When changing electrode design or dose, results cannot be extrapolated across safety and sham studies.

Electrodes for high-definition transcutaneous DC stimulation for applications in drug-delivery and electrotherapy including tDCS. *J Neuroscience Methods* 2010 190:188-97
Minhas P, Patel J, Bansal V, Ho J, Datta A, Bikson M.
Hypothesis: Appropriately applied computational models are pivotal for rational tDCS dose selection.

How should clinicians use models?
• Decide on brain regions of interest and other criterion.
• Use computational models to determine optimized dose.
1. **Hardware**: Array of possible HD electrodes and related safety constraints (e.g. maximum current per electrode).

2. **Criterion (goal)**: Target brain region(s) is selected and optimization criterion (e.g. maximum focality or intensity).

3. **Dose**: Use computational models to optimize current applied to select HD electrodes.

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*Optimized multi-electrode stimulation increases focality and intensity at target*

*J Neural Engineering* 2011 8(4)

Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC
1. **Hardware:** Minimize number of electrodes, 2 mA maximum per HD electrode (20 minutes)

2. **Criterion (goal):** Target cortical brain region with controlled focality and “conventional” peak intensity. Unidirectional modulation.

3. **Dose:**

   4x1-Ring HD-tDCS Montage (total 5 electrodes)
   - Center active electrode (2 mA) over cortical target
   - Four surround return electrodes (0.5 mA each)
   - Ring radius circumscribes underlying cortical region of interest

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Gyri-precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad *Brain Stimulation* 2009 2(4):201-207
Datta A, Bansal V, Diaz J, Patel D, Reato M, Bikson M.
High-Definition tDCS 4x1-Ring Montage

- Center electrode determines polarity (anode, cathode)
- Ring radius determines modulation area

Focal Modulation of the Primary Motor Cortex in Fibromyalgia Using 4x1-Ring HD-tDCS: Immediate and Delayed Analgesic Effects of Cathodal and Anodal Stimulation

*J Pain* 2013

Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, Fregni F
High-Definition tDCS 4x1-Ring Montage

- 10 minutes of 2 mA 4x1 HD-tDCS produces >2 hour of after-effects

Comparing cortical plasticity induced by conventional and high-definition 4x1 ring tDCS: a neurophysiological study

*Brain Stimulation* 2012
Kuo HI, Datta M, Bikson M, Minhas P, Paulus W, Kuo MF, Nitsche MA
High-Definition tDCS 4x1-Ring Montage

Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS

*NeuroImage* 2012
Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M

Transcranial Electrical Stimulation (TES) – short high-intensity pulse that triggers motor response (MEP)

- Comparable focality to TMS
Subject specific modeling and experiments
Inter-subject variation in susceptibility >2x

- Change TES intensity to give same MEP response (left)
- Same TES intensity giving different MEP responses (right)
Hypothesis: Appropriately applied computational models are pivotal for rational tDCS dose selection.

Why should clinicians use models?

- **Dose Optimization**: Determine best montage given efficacy, safety, and other criterion.
- **Dose normalization**: Determine role of individual variation and predict requisite adjustments in subject specific dose.
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- **Dose Optimization**: Determine best montage given efficacy, safety, and other criterion.
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Inter-individual variation during transcranial Direct Current Stimulation and normalization of dose using MRI-derived computational models. *Frontiers in Neuropsychiatric Imaging and Stimulation 2012*
Datta A, Troung P, Minhas P, Parra LC, Bikson M

Finite Element Study of Skin and Fat Delineation in an Obese Subject for Transcranial Direct Current Stimulation. *IEEE EMBS 2012*
Truong DQ, Magerowski G, Pascual-Leone A, Alonso-Alonso M, Bikson M
Why should clinicians use models?

- **Dose Optimization:** Determine best montage given efficacy, safety, and other criterion.
- **Dose normalization:** Determine role of individual variation and predict requisite adjustments in subject specific dose.
- **Dose design for Susceptible Populations**
  (children, stroke, TBI....)

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Transcranial direct current stimulation in patients with skull defects and skull plates: High-resolution computational FEM study of factors altering current flow.
*NeuroImage* 2010
Datta A, Bikson M, Fregni F.

Individualized model predicts current flow during transcranial direct-current stimulation in responsive stroke patient.
*Brain Stimulation* 2011
Datta A, Baker, J, Bikson M, Fridriksson F.

Transcranial Direct Current Stimulation in Pediatric Brain: A computational modeling study
*IEEE EMBC* 2012
Computational Models of Transcranial Direct Current Stimulation

*Clinical EEG and Neuroscience* 2012; 43(3) 176-183
Bikson M, Rahman A, Datta A
tDCS for stroke rehabilitation

Subject X: Aphasia

Julius Fridriksson
Julie Baker
tDCS for stroke rehabilitation

Brain Electric Field

Brain and CSF Current Density
HD-tDCS for stroke rehabilitation

4x2 HD-tDCS

Prospective Individually Optimized Trial
Targeting of Transcranial Direct Current Stimulation

- Optimization of tDCS based on brain regions of interest.
- Increased degrees of freedom with HD-tDCS (current at every electrode) providing flexibility and specificity.
- Computer modeling tools enhance targeting precision.
- “Best” solution depends on trial objectives including targeting, intensity, tolerability.
- Individual optimization feasible (in cases warranted)
“Deep” tDCS

Alex DaSilva
Felipe Fregni
White matter neuromodulation

Salman Shahid
Conventional and High-Definition Electrodes

Conventional bipolar large electrodes

High-Definition electrodes in “4x1” configuration
Optimized electrotherapy in rehabilitation
Targeting based on functional changes

Vision Rehabilitation
PI: Lotfi Merabet
Targeting and model validation

Post-mortem "fMRI"

Walter Paulus
Andrea Antal
Targeting and model validation

Walter Paulus
Andrea Antal
MRI-derived computational model predict brain current flow during tDCS

Full work-flow developed to preserve accuracy and resolution

MRI sequences optimized for tDCS modeling (3T at 1x1x1 mm)

Special segmentation tools perverse resolution in generation of tissue masks

Mesh includes >10 million elements

Solution provides detail insight into brain modulation

Conjugate gradient solver with <1E-8 tolerance

Model physics/domains include explicit consideration of electrode properties.
Transcranial Direct Current Stimulation (tDCS)

- Two pad electrodes placed on head and connected to DC current stimulator.
- Current passed between ANODE(+) and CATHODE(-)
- DC CURRENT FLOW across cortex.
- Current is INWARD under ANODE and OUTWARD under CATHODE

MRI derived computational model