Major mechanistic questions and technology opportunities in Spinal Cord and Deep Brain Stimulation

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The science of invasive neuromodulation is at a stand-still

- Breakthrough have come through fortuitous observations by clinicians
- Technology incremental and adapted from prior applications
- Ad hoc targets and programming
- Burdensome regulatory and reimbursement process

Dr. Alim Louis Benabid
Advancing neuromodulation requires collaboration between physicians and engineers

Proposition: The main hurdle in the creation of brain stimulation technology is how to translate across disciplines
How to optimize neuromodulation

**Patient:** Inclusion, exclusion, medication, therapy and rehabilitation ...

**Technology:** Just Dose

- **What electrodes:** Where and what shape (e.g. 1 mm² at STN)
- **What waveform:** Pulse shape, frequency, burst (e.g. 100 Hz biphasic square wave)

⚠️ Every neuromodulation breakthrough is just “where and waveform”
What is the "dose" of neuromodulation?
Dose is controlled (prescribed)

Drug dose is set by systemic application (tablets...)

Pharmacologic activity (efficacy and safety) is determined by drug concentration at tissue

Physiological and behavioral response

“Electroceutical” dose is set by stimulation parameters (coil/electrode and waveform)

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

Physiological and behavioral response
Neuromodulation dose is defined by all parameters of the stimulation device and software that affect the current flow (electric fields) generated in the body”

1) Stimulation electrode parameters: shape, size, position
2) Current or voltage waveform parameters: pulse amplitude, width, polarity, repetition frequency, train duration, interval
1) A box (can) that generates a electrical waveform

2) Electrodes next to target outside or inside body

Wire (lead)

Electrical current are generated inside the brain leading to neuronal changes

Dose of neuromodulation devices

Only those parameters that influence currents in body
Subject data:
age, sex, MRI, DTI, diagnosis

General knowledge (subject independent):
mechanisms of action, prior clinical experience, etc.

Response measures:
motor threshold, seizure threshold, cognitive, clinical response, side effects, etc.

Dosing decision
Reduced metrics (e.g., electrode current density, total charge, total energy)

Computational models

Stimulation device
Waveform generator
Electrodes/coil

Choice of device type and settings

EM dose
Electrode/coil current/voltage waveform
Electrode/coil configuration

EM dose monitoring/verification

Subject
Induced electric field
Physiological response

Response measures:
motor threshold, seizure threshold, cognitive, clinical response, side effects, etc.
Not Dose
• **Currents generated in the body is NOT dose**
• But critically defines outcomes of stimulation
• Current in body determined by dose and tissue properties
• And so is subject specific
• Can be predicted using models or measured (dosimetry)
Response to stimulation is NOT dose
- But represent outcomes of stimulation
- Can be used to adjust dose
  (rTMS for Depression uses TMS MEP, closed-loop for epilepsy uses EEG, Seizure for ECT)
- Essentially all FDA cleared technologies measure responses to adjust stimulation* (biomarker, sensation, behavior..)
  *And studies / protocols do not report individual dose
• **Device name (brand) is NOT dose**
• Names end with “s” (Stimulation) that typically refer to how current is delivered to body and “intended” target. “Transcranial”, “deep”, “nerve X”
How to optimize neuromodulation

**Patient:** Inclusion, exclusion, medication, therapy and rehabilitation ...

**Technology:**
Just Dose

- **What electrodes:** Where and what shape (e.g. 1 mm$^2$ at STN)
- **What waveform:** Pulse shape, frequency, burst (e.g. 100 Hz biphasic square wave)

Plus safety design

⚠️ Every neuromodulation breakthrough is just “where and waveform”
Device design other than DOSE matter

Safety and convenience: Device physical features (electrode materials) (batteries) (implant tools)
How to optimize neuromodulation

**Patient:** Inclusion, exclusion, medication, therapy and rehabilitation

**Technology:**
Just Dose

- What electrodes:
  Where and what shape (e.g. 1 mm$^2$ at STN)

- What waveform:
  Pulse shape, frequency, burst (e.g. 100 Hz biphasic square wave)

Every neuromodulation breakthrough is just “where and waveform”
Giving everyone the same neuromodulation dose does not work (well)

- Every successful (FDA approved) neuromodulation technique includes subject specific adjustment of dose
- Every attempt without subject specific adjustment as failed (FDA approval)
- Techniques and indications where a **rapid** response in behavior can be used to titrate dose have a higher change of success
- Automatic techniques to limit the dose search space are useful (needed)
Advancing neuromodulation requires collaboration between physicians and engineers.

To integrate new technologies with new protocols to effectively (electrode position) rapidly (waveform) search the dose space.

Proposition: The main hurdle in the creation of brain stimulation technology is how to translate across disciplines.
Image Guided Targeting of Brain Stimulation

MRI, fMRI, EEG, chemical, bio-impedance, biomarkers....

**Offline:** Imaging identifies target then brain stimulation applied to target
- Electrode position (existing leads)

**Online:** Imaging measures target response and brain stimulation changed
- Waveform (existing devices)

Current Limitations

(?): A single target is identified across a patient population, circumscribed by a generic atlas.

(?): Both diagnosis and neuromodulation defined by a sliding-scale of brain function (e.g. dLPFC hypo-function is depression, stimulation dials activity back up to enhance mood).

(?): Protocols empirically determined with limited device innovation and mixed success.
Imaging Anatomical
Functional

Tissue Segmentation
“Universal Solutions” (FEM)

Subject specific, target ambivalent

Computationally costly, technical, and dynamic

Target Selection (GUI)
Optimized Therapy (Stimulation Dose)

Computationally light

(1)
Automated, hypothesis-driven, individualized neuromodulation.

1) New algorithms for segmentation and brain stimulation optimization (Parra, Dmoschowski)

- Segmentation for device modeling
- Linear problems allow for rapid and “true” optimization
Automated, hypothesis-driven, individualized neuromodulation.

1) New algorithms for segmentation and brain stimulation optimization (Parra, Dmoschowski)

2) Computational Neurostimulation (beyond sliding scale)
Automated, hypothesis-driven, individualized neuromodulation.

1) New algorithms for segmentation and brain stimulation optimization (Parra, Dmoschowski)

2) Computational Neurostimulation (beyond sliding scale)

3) Verification and Validation
Automated, hypothesis-driven, individualized neuromodulation.

1) New algorithms for segmentation and brain stimulation optimization (Parra, Dmoschowski)

2) Computational Neurostimulation (beyond sliding scale)

3) Verification and Validation

4) Closed-loop targeting
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Tissue Segmentation

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Target Selection (GUI)

Optimized Therapy (Stimulation Dose)
Imaging Anatomical  Functional

Tissue Segmentation

“Universal Solutions” (FEM)

Subject specific, target ambivalent

“Simple” Closed Loop

Computationally light

Target Selection (GUI)

Optimized Therapy (Stimulation Dose)
Imaging Anatomical Functional

Tissue Segmentation

“Universal Solutions” (FEM)

Computationally costly, technical, and dynamic

Subject specific, target ambivalent

Computationally light

Target Selection (GUI)

Optimized Therapy (Stimulation Dose)

Functional Closed Loop