SCS: Neurovascular Modulation and Heating

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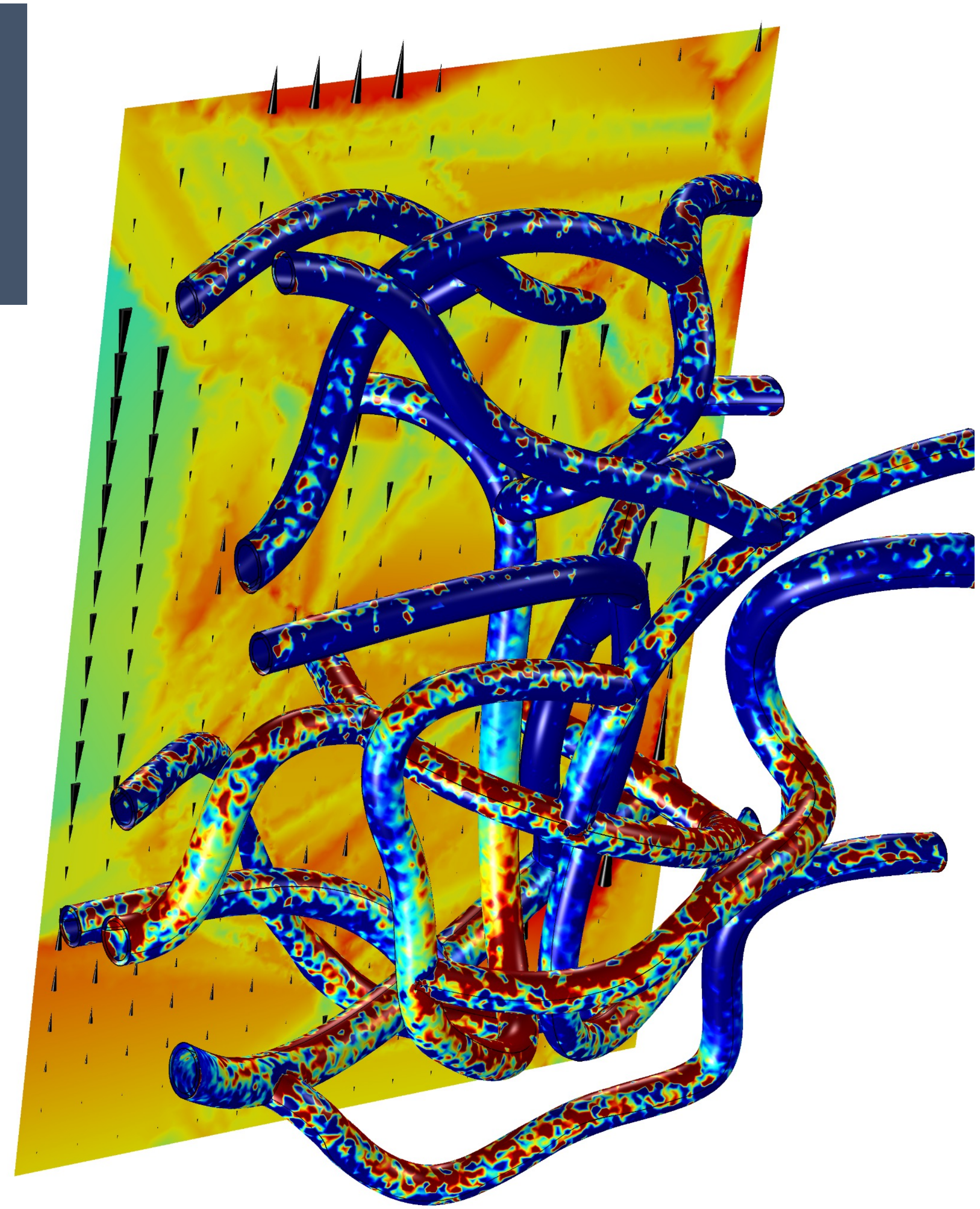
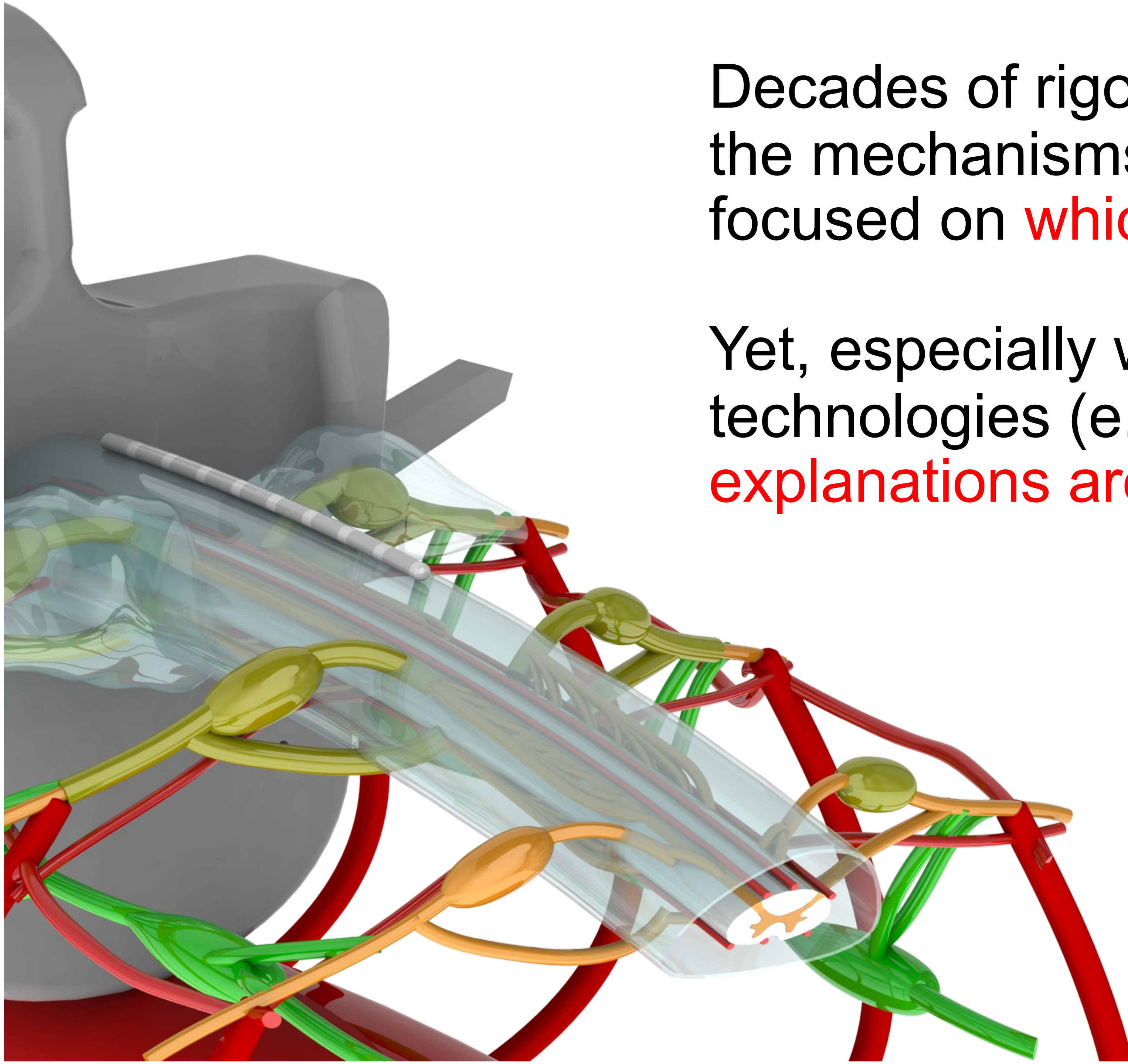


Disclosure

The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple

Support

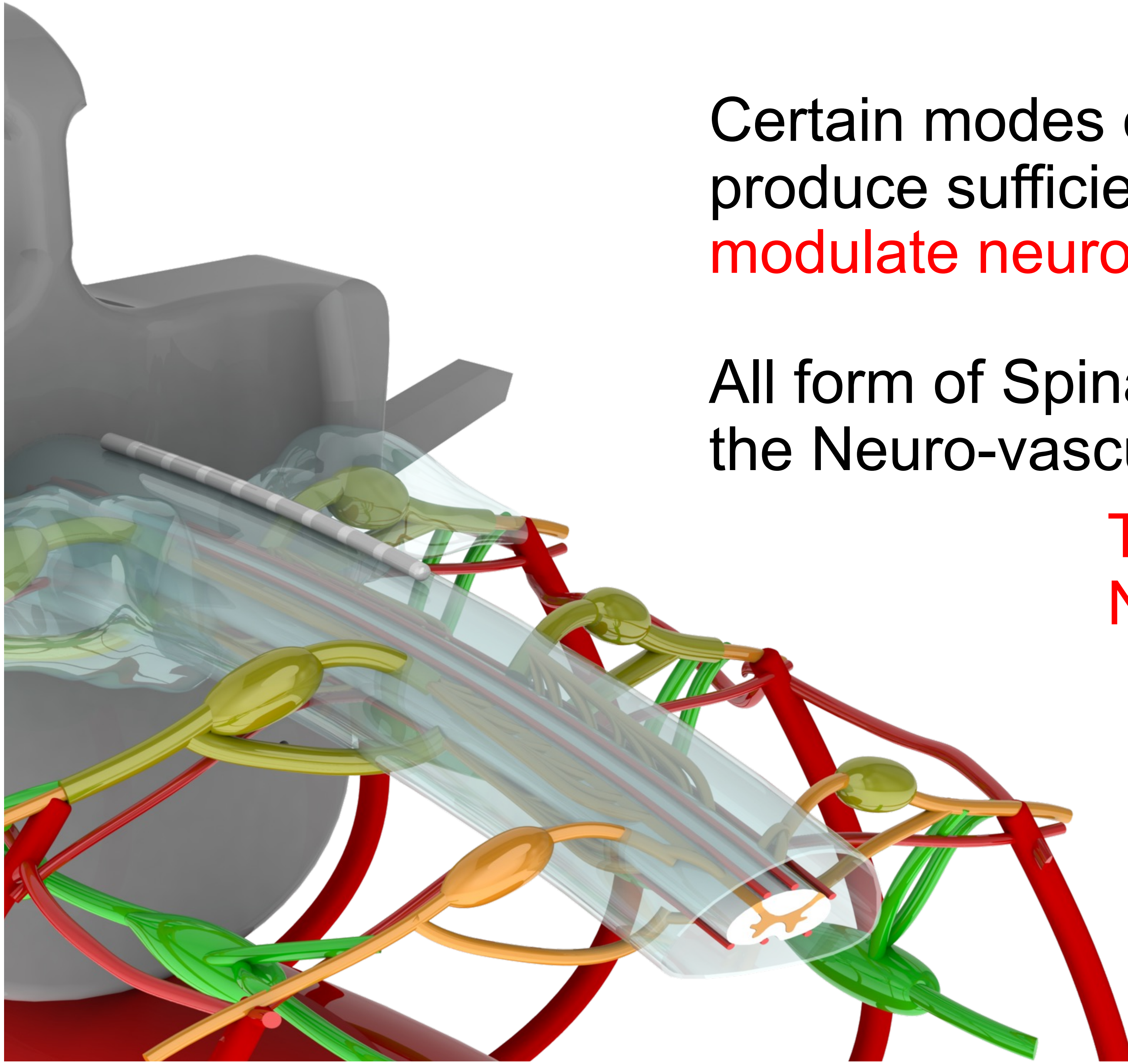
NYS DOH, NIH (NIMH, NINDS) – *BRAIN Initiative*, NSF, Grove Foundation, Harold Shames, CCNY Fund, 21st Century Fund



Decades of rigorous efforts to understand the mechanisms of Spinal Cord Stimulation focused on which neurons are zapped.

Yet, especially with introduction of new technologies (e.g., waveforms) new explanations are needed.

Khadka et al. Realistic anatomically detailed open-source spinal cord stimulation (RADO-SCS) model. *J Neural Engr* 2020



Certain modes of Spinal Cord Stimulation produce sufficient (joule) heating to modulate neurons.

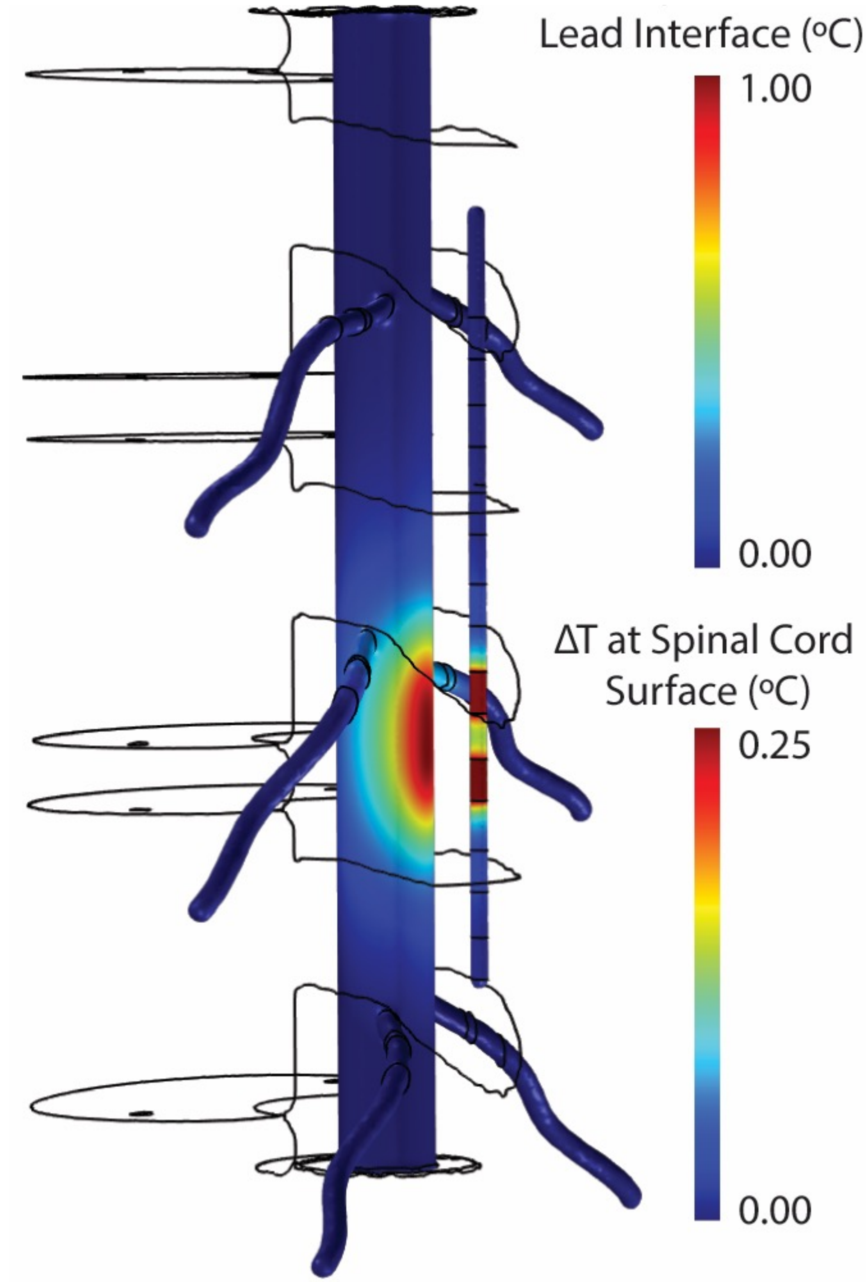
All form of Spinal Cord Stimulation engage the Neuro-vascular Unit.

Three-aspect theory of Neurovascular Modulation.

When SCS electrical current flows through tissue, joule heating will increase tissue temperature.

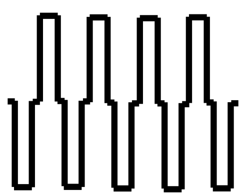
How much and how the body (neurons) responds depends on the SCS technology and properties of the body.

We developed bioheat computational models of SCS to predict temperature increase.



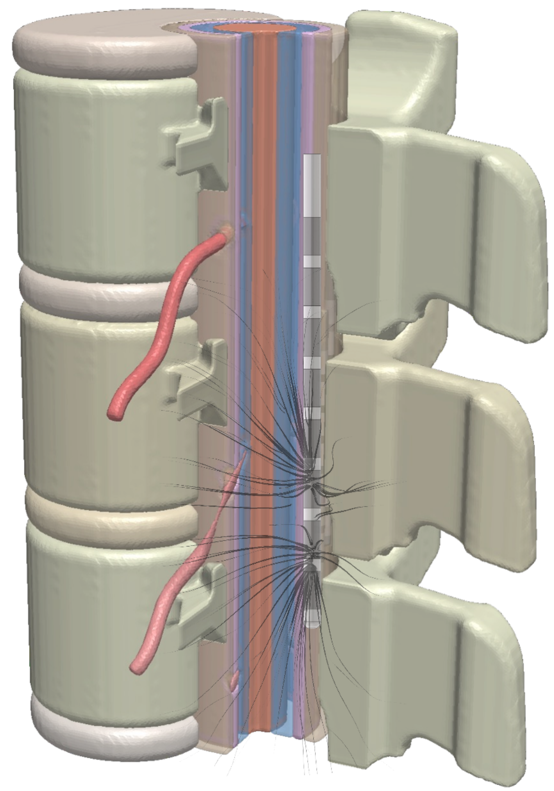
Spinal Cord Stimulation bio-heat model pipeline

Lead model and electrode selection

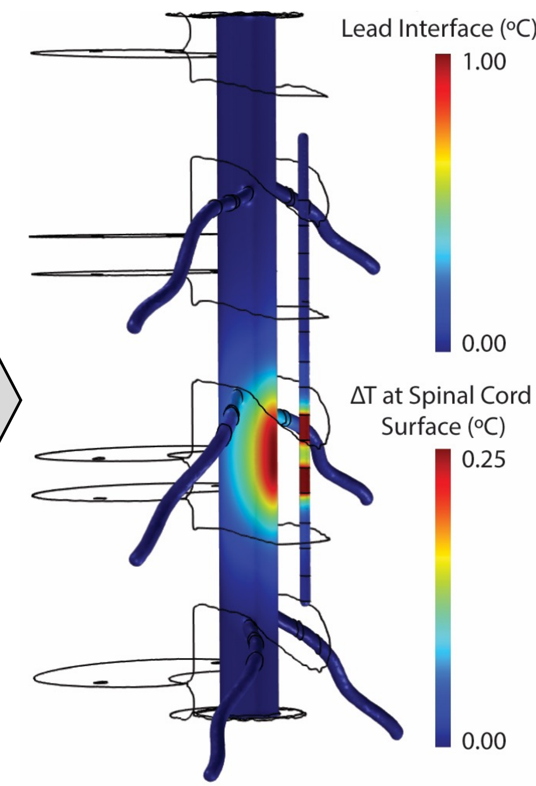


SCS waveform (Frequency, pulse width) and amplitude

Spinal column anatomy and tissue properties (resistivity, blood flow…)

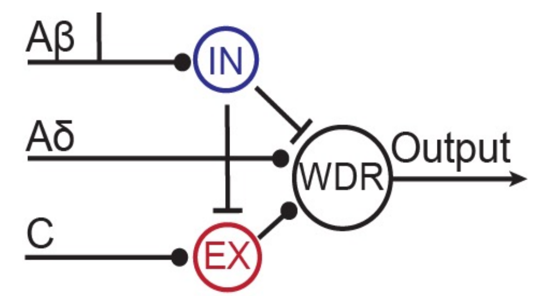


Bioheat transfer model



Network model

Role in Analgesia



IN: Inhibitory Interneurons
EX: Excitatory Interneurons

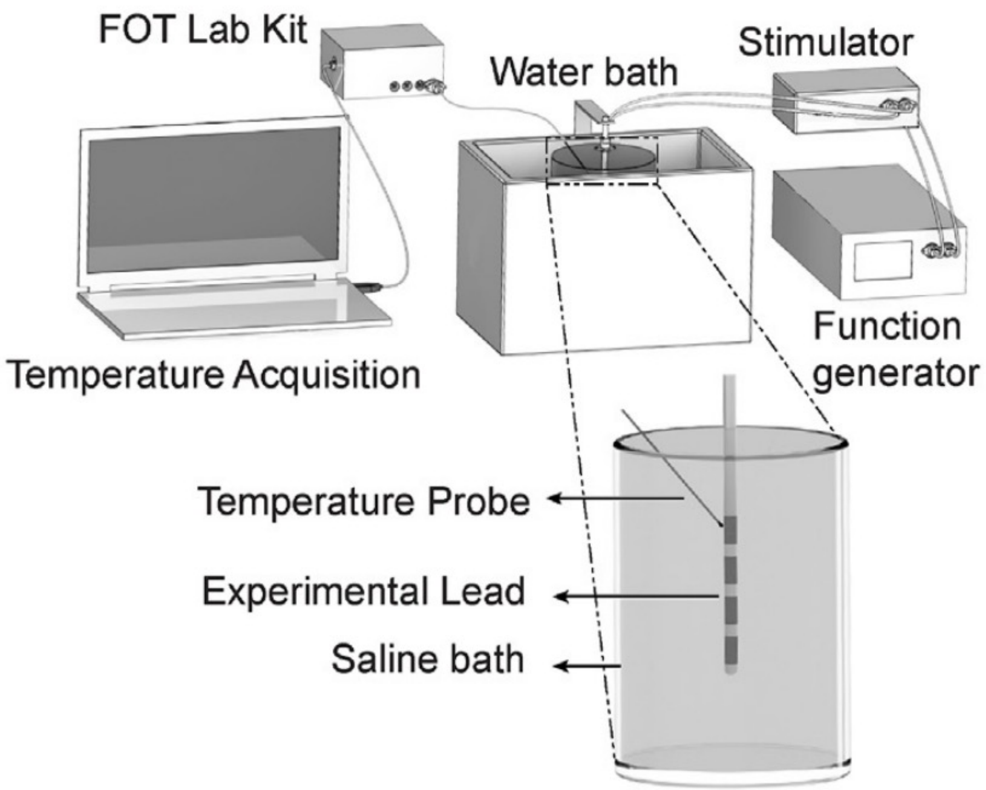
Essential question for the heating-based mechanisms of SCS is how much does temperature increases?

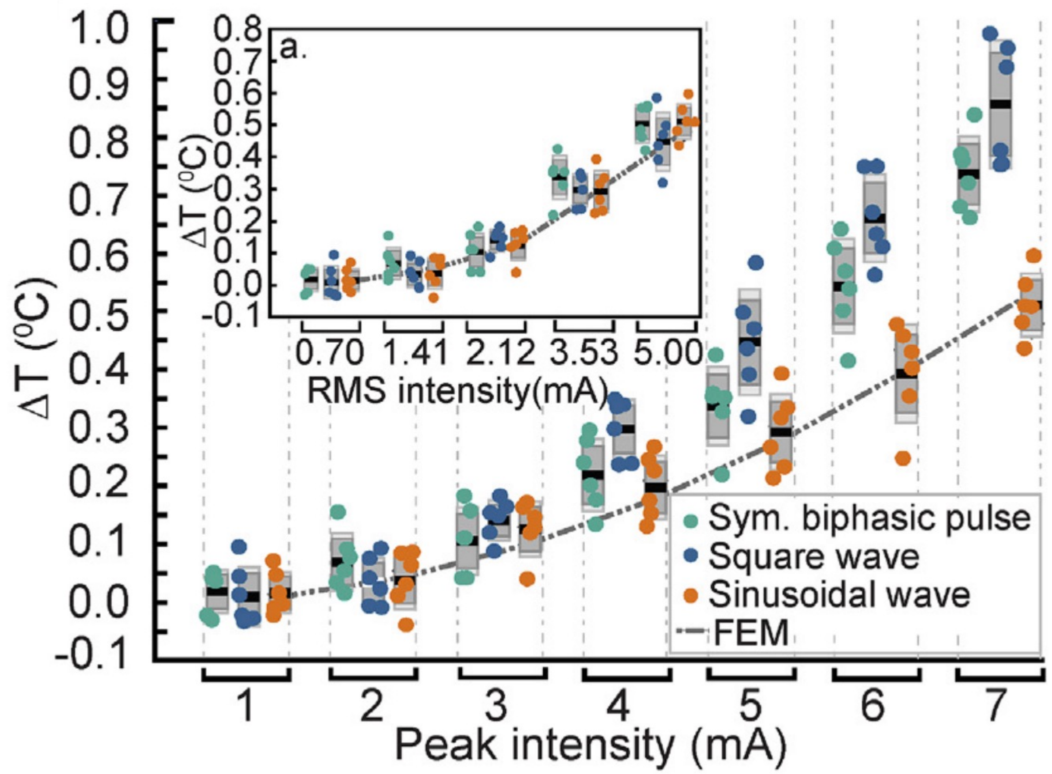
Zannou, Khadka, Truong, Zhang, Esteller, Hershey, Bikson. Temperature increases by kilohertz frequency spinal cord stimulation. *Brain Stimulation.* 2019

Heating by SCS depends on the power (RMS) of the stimulation.

I_{RMS} = **Peak Current** (mA) * (**Duty Cycle**)$^{1/2}$

Phantom bath measurements show temperature increase the RMS of the waveform irrespective of its other parameters.





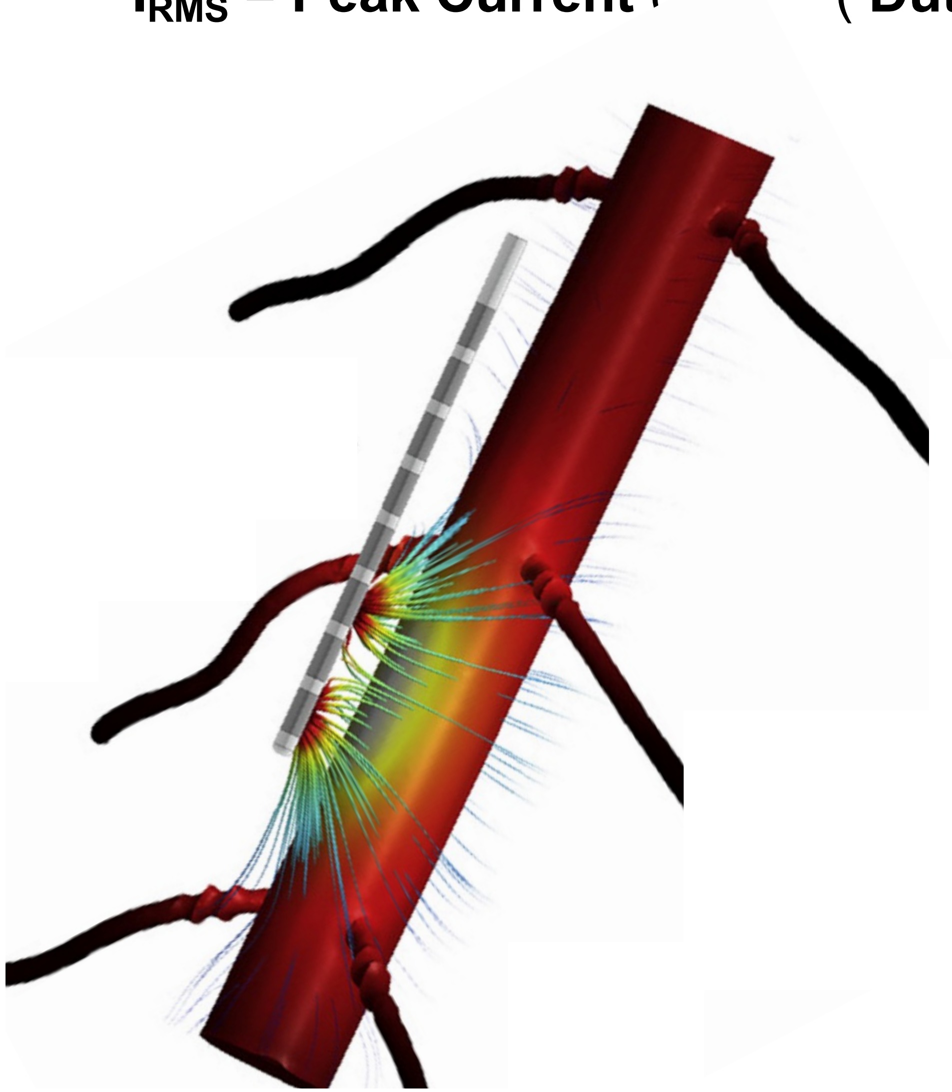
Zannou, Khadka, Truong, Zhang, Esteller, Hershey, Bikson. Temperature increases by kilohertz frequency spinal cord stimulation. *Brain Stimulation.* 2019

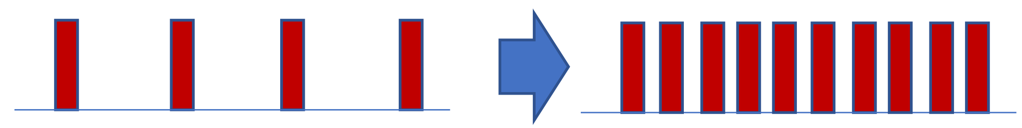
Heating by SCS depends on the power (RMS) of the stimulation.

~0.8° C at 10 kHz

I_{RMS} = **Peak Current** (r) * (**Duty Cycle**)$^{1/2}$

Higher SCS frequencies (kHz) “squeeze” pulses closer together, increasing Duty Cycle (Pulse Density)





	10 KHz (40-10-40 μs)				1 KHz (100-100-100 μs)				100 Hz (200-100-200 μs)			
Pulse Density	6.32				2.00				1.41			
I (mA)	ΔT (°C)				ΔT (°C)				ΔT (°C)			
Peak	*RMS*	Lead	SC	Root	*RMS*	Lead	SC	Root	*RMS*	Lead	SC	Root
1.0	0.89	0.30	0.02	0.01	0.47	0.08	0.00	0.00	0.20	0.02	0.00	0.00
2.0	1.78	1.19	0.12	0.03	0.89	0.31	0.02	0.01	0.40	0.06	0.00	0.00
3.0	2.68	2.69	0.27	0.06	1.34	0.68	0.07	0.02	0.60	0.13	0.01	0.01
3.5	3.13	3.60	0.37	0.08	1.57	0.92	0.09	0.02	0.70	0.19	0.01	0.01
4.0	3.57	4.71	0.49	0.10	1.79	1.21	0.12	0.03	0.80	0.24	0.02	0.01
5.0	4.47	7.25	0.77	0.16	2.24	1.89	0.19	0.04	1.00	0.39	0.03	0.01

Zannou, Khadka, Truong, Zhang, Esteller, Hershey, Bikson. Temperature increases by kilohertz frequency spinal cord stimulation. *Brain Stimulation.* 2019

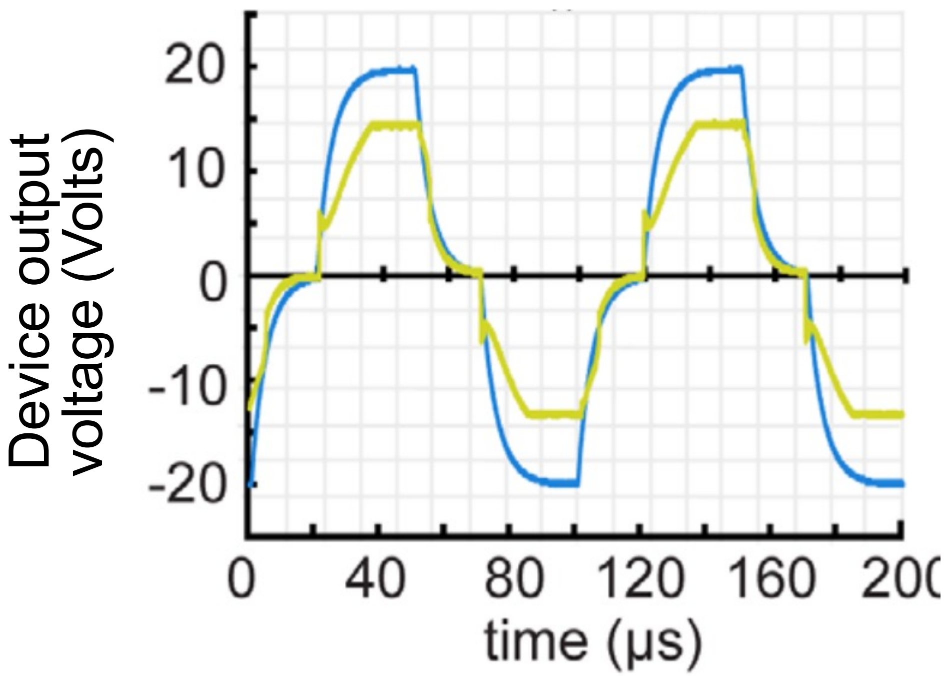
~0.8^{o} C at 10 kHz

Heating by SCS depends on the power (RMS) of the stimulation.

I_{RMS} = **Peak Current** (mA) * (**Duty Cycle**)$^{1/2}$

Zannou, Khadka, FallahRad, Truong, Kopell, Bikson. Tissue temperature increases by a 10 kHz spinal cord stimulation system: Phantom and bioheat model. *Neuromodulation*. 2019

~0.4^{o} C at 10 kHz

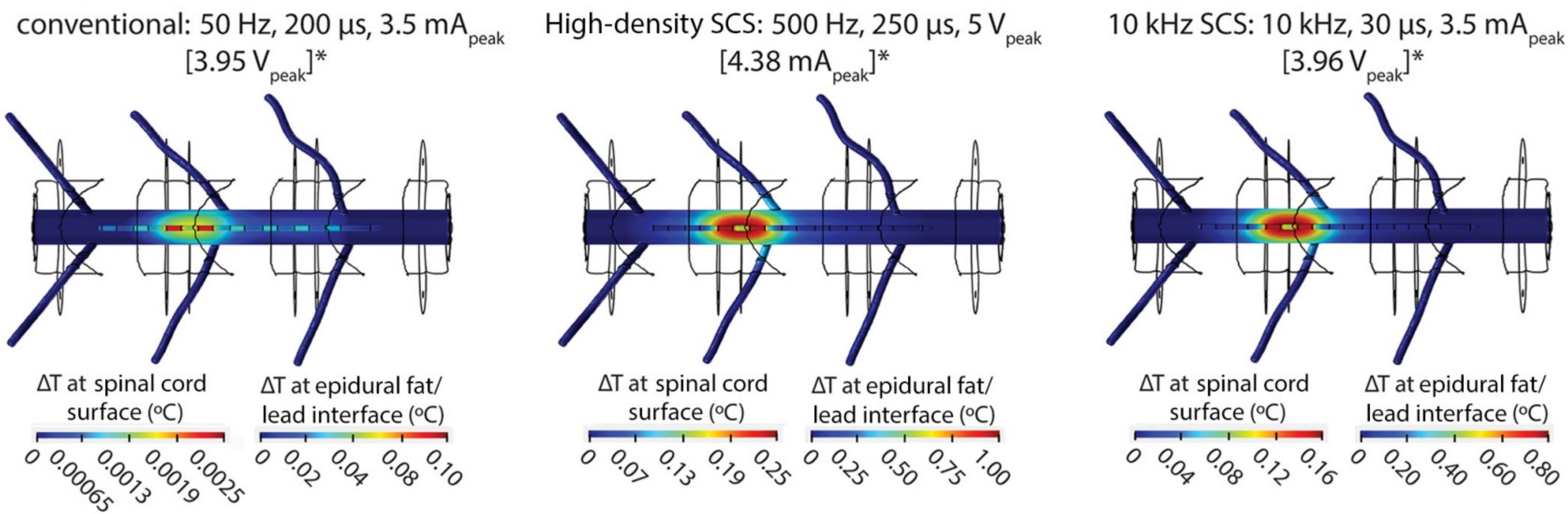


10 kHz, 4 mA: Ideal current-controlled stimulator (bench-top device)

10 kHz, level 4, commercial SCS IPG

At 10 kHz with increasing outputs level (and impedance), commercial IPG “naturally” throttles output, so limits heating.

Zannou, Khadka, Bikson. Bioheat Model of Spinal Column Heating During High-Density Spinal Cord Stimulation. *Neuromodulation.* 2022

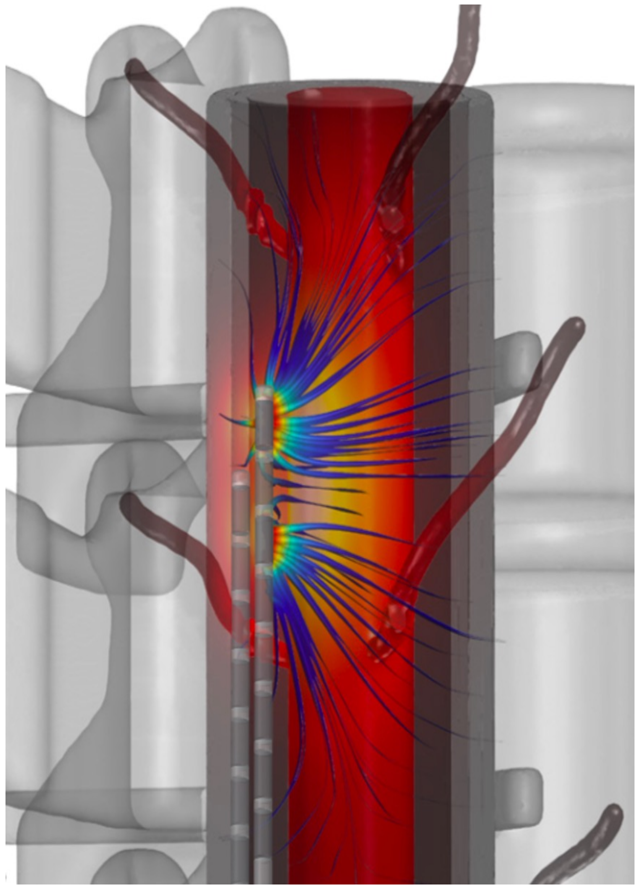


High-Density (500 Hz, 250 us pulse width) stimulation under **voltage control** can exceed 10 kHz heating under specific conditions (encapsulation layer, guarded tripole).

Bioheat Model of Spinal Column Heating During High-Density Spinal Cord Stimulation. *Neuromodulation.* 2022

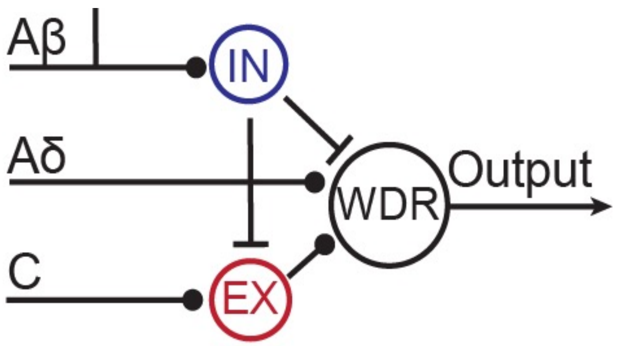
Tissue temperature increases by a 10 kHz spinal cord stimulation system: Phantom & bioheat model. *Neuromodulation*. 2019

Temperature increases by kilohertz frequency spinal cord stimulation. *Brain Stimulation.* 2019



Subject to assumptions* and experimental validation: High-kHz and High-Density SCS increase spinal cord temperature 0.5-1^{o}C (more near lead), enough to modulate but not injure neural tissue.

*Does increased metabolic activity during SCS further increase heating? Does blood flow increase in response, decease heating…



IN: Inhibitory Interneurons increase activity with temperature

EX: Excitatory Interneurons decrease activity with temperature

Spinal Cord Stimulation of the neuro-vascular unit (Neurovascular-modulation)

FIRST ASPECT:

SECOND ASPECT:

THIRD ASPECT:

Spinal Cord Stimulation of the neuro-vascular unit (Neurovascular-modulation)

FIRST ASPECT: SCS of neuro-vascular coupling.

SECOND ASPECT:

THIRD ASPECT:

Spinal Cord Stimulation of the neuro-vascular unit (Neurovascular-modulation)

FIRST ASPECT: SCS of neuro-vascular coupling.

SECOND ASPECT: Direct stimulation of brain vascular/ blood-brain-barrier function.

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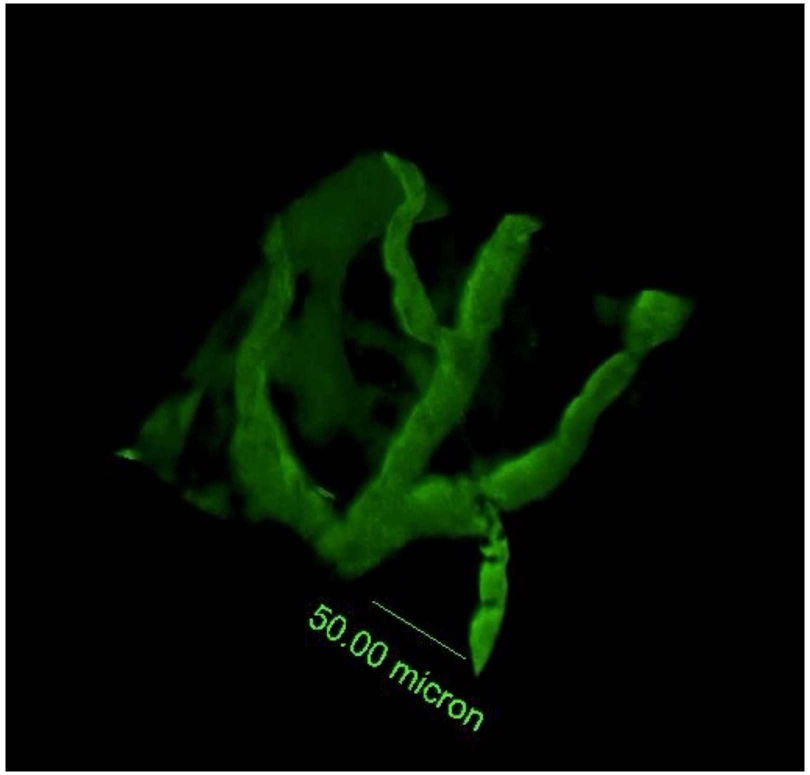
Spinal Cord Stimulation of the neuro-vascular unit (Neurovascular-modulation)

FIRST ASPECT: SCS of neuro-vascular coupling.

SECOND ASPECT: Direct stimulation of brain vascular/ blood-brain-barrier function.

THIRD ASPECT: Capillaries distort current flow, changing neuronal stimulation.

- **Neurovascular coupling (unit):** Coupling between neuronal activity, vascular flow and blood-brain barrier (BBB) permeability, and glia.
- **Two-way interaction**. Neuronal activity activates vascular (eg. fMRI), Transport across BBB tightly controlled to regulate brain function.



Stimulation of neurovascular unit:

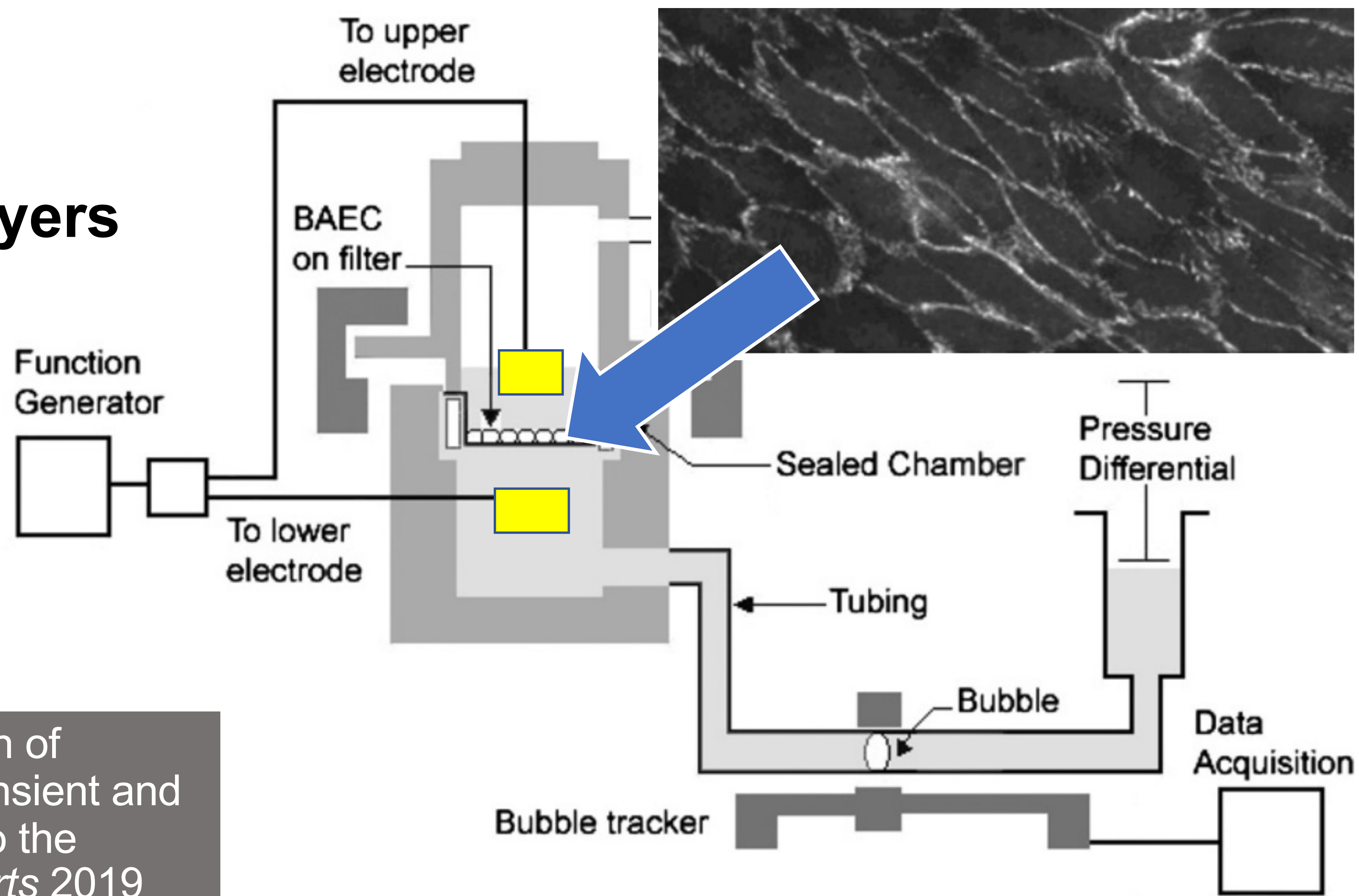
FIRST ASPECT: Brain vasculature changes inevitable **secondary** to neuronal stimulation (eg. fMRI changes after brain stimulation).

SECOND ASPECT: Can neuromodulation **directly** activate endothelial cells of the BBB, leading to secondary neuronal changes.

“Primacy” of neurons as targets of neuromodulation means any changes in vascular function assumed secondary to neuron stimulation.

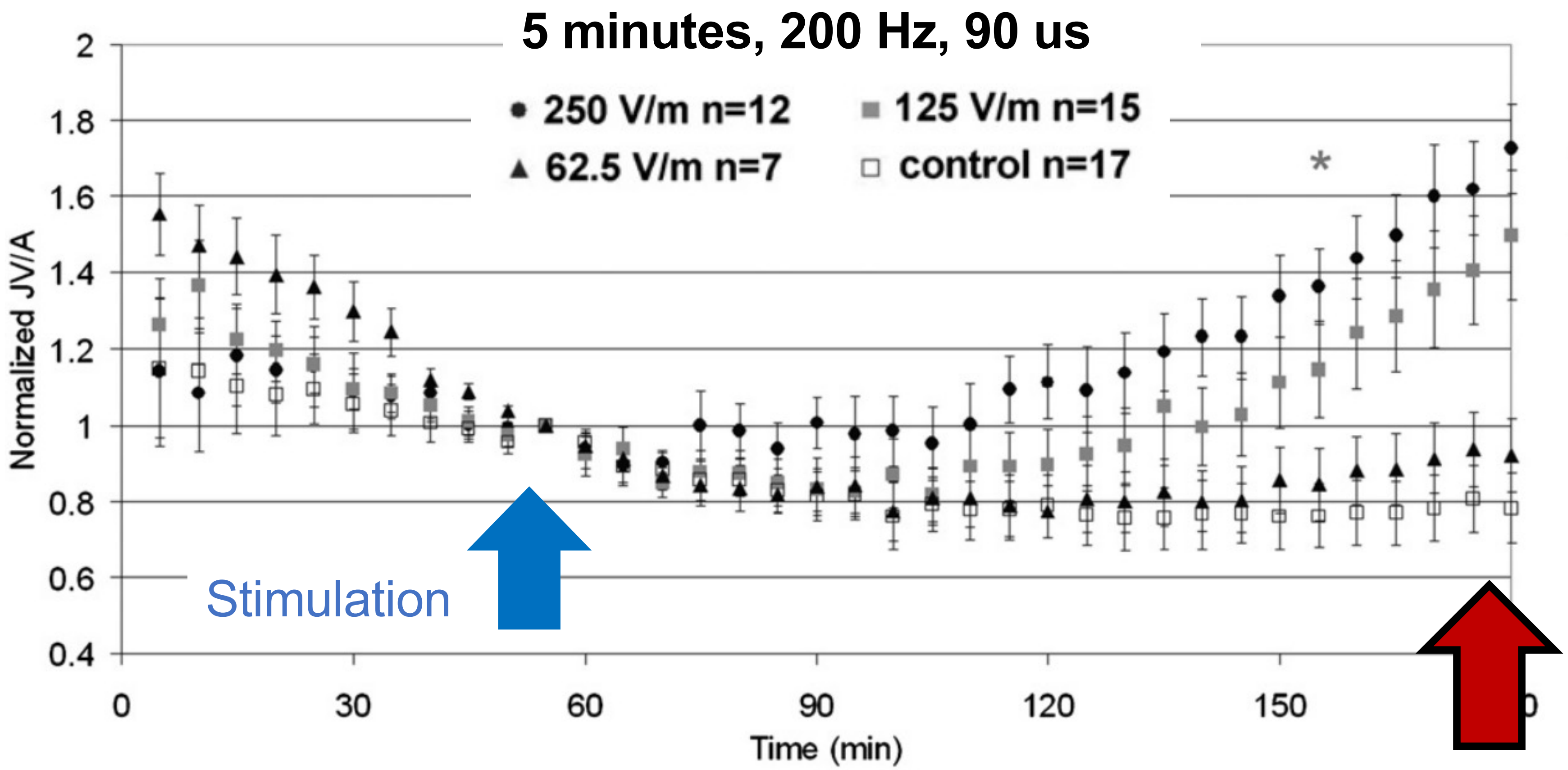
Isolated BBB stimulation established direct neuromodulation.

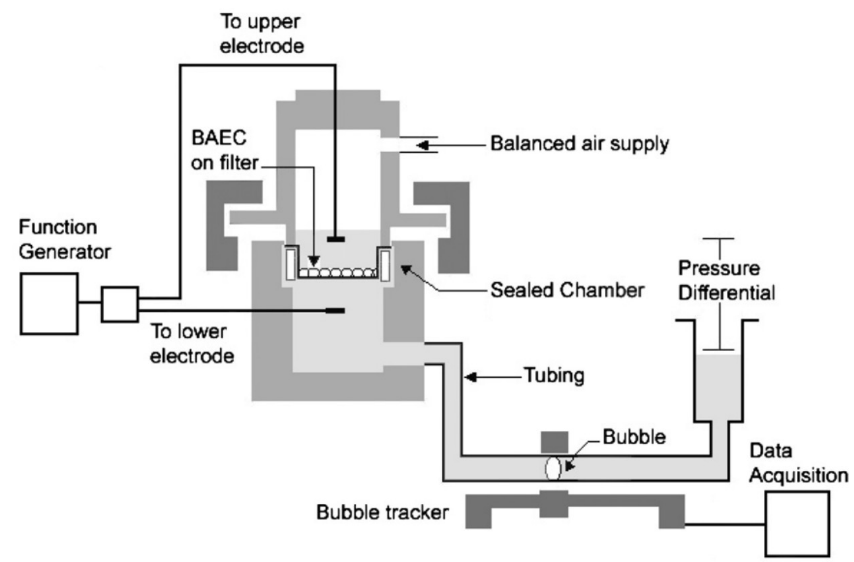
BBB model: **cultured endothelium monolayers**



Cancel et al. Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. *Scientific Reports* 2019

High-intensity pulsed electric fields (SCS like) modulate isolated endothelial cells (BBB) including water and transport flux.

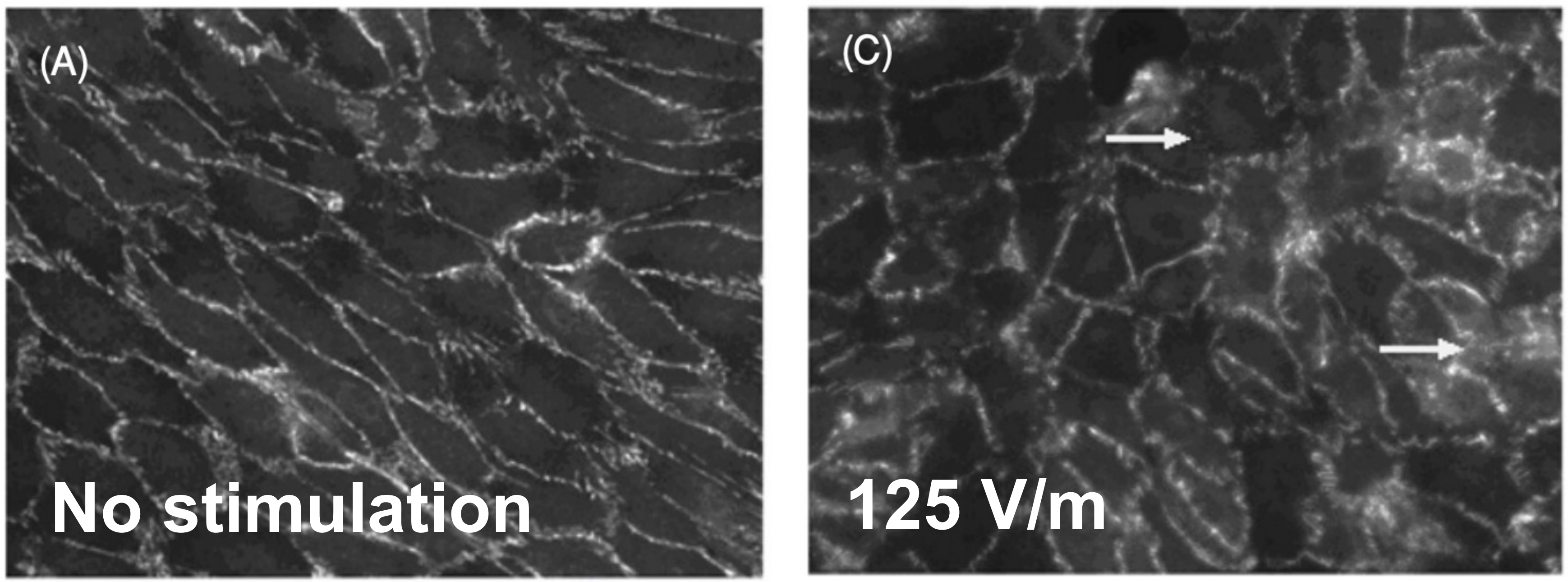




Increased water transport across BBB model following 5 min high-intensity pulsed electric field

Cancel et al. DBS-relevant electric fields increases hydraulic conductivity of in vitro endothelial monolayers. *J Neural Engr* 2010

Lasting (plastic) changes in endothelial cells (BBB) function.



ZO-1 tight-junction protein staining

ZO-1 tight junction protein surrounds endothelial cells in control. Pulsed electric fields modify continuity (arrows).

Cancel et al. DBS-relevant electric fields increases hydraulic conductivity of in vitro endothelial monolayers. *J Neural Engr* 2010

Neurovascular Modulation: Direct effects on brain vasculature suggest unique therapeutic strategies (pathways)

”Boosting” of brain function (transport) / neurorehabilitation efficacy

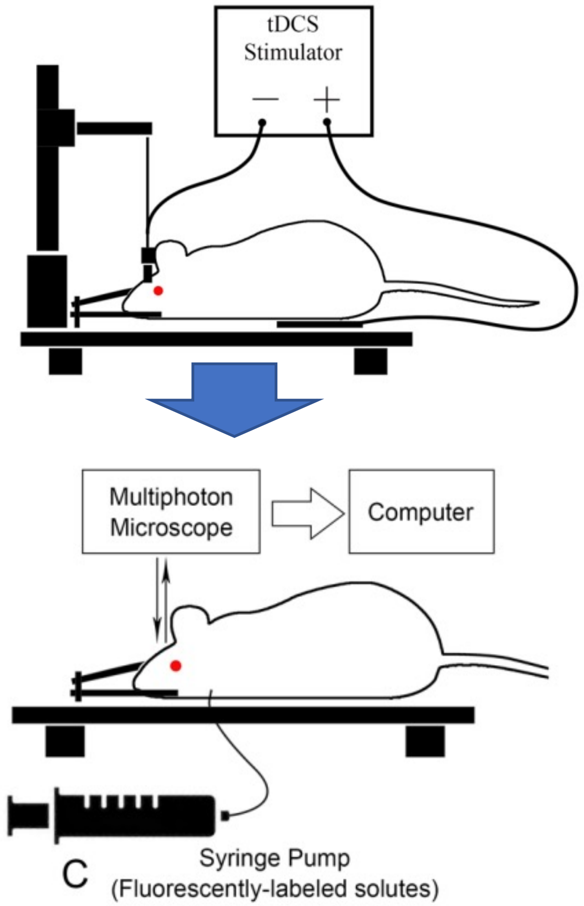
- Cancel et al. DCS of endothelial monolayers induces a transient and reversible increase in transport due to electroosmotic. *Sci Reports* 2019
- Shin et al. In Vivo Modulation of the Blood-Brain Barrier Permeability by tDCS. *Ann Biomed Eng*. 2020

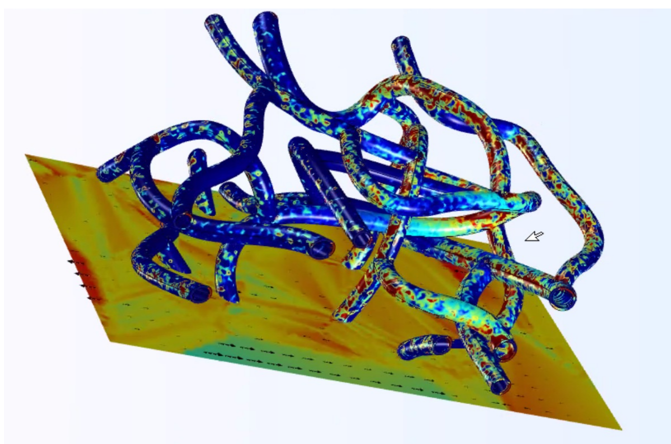
Drive brain clearance (eg. dementia)

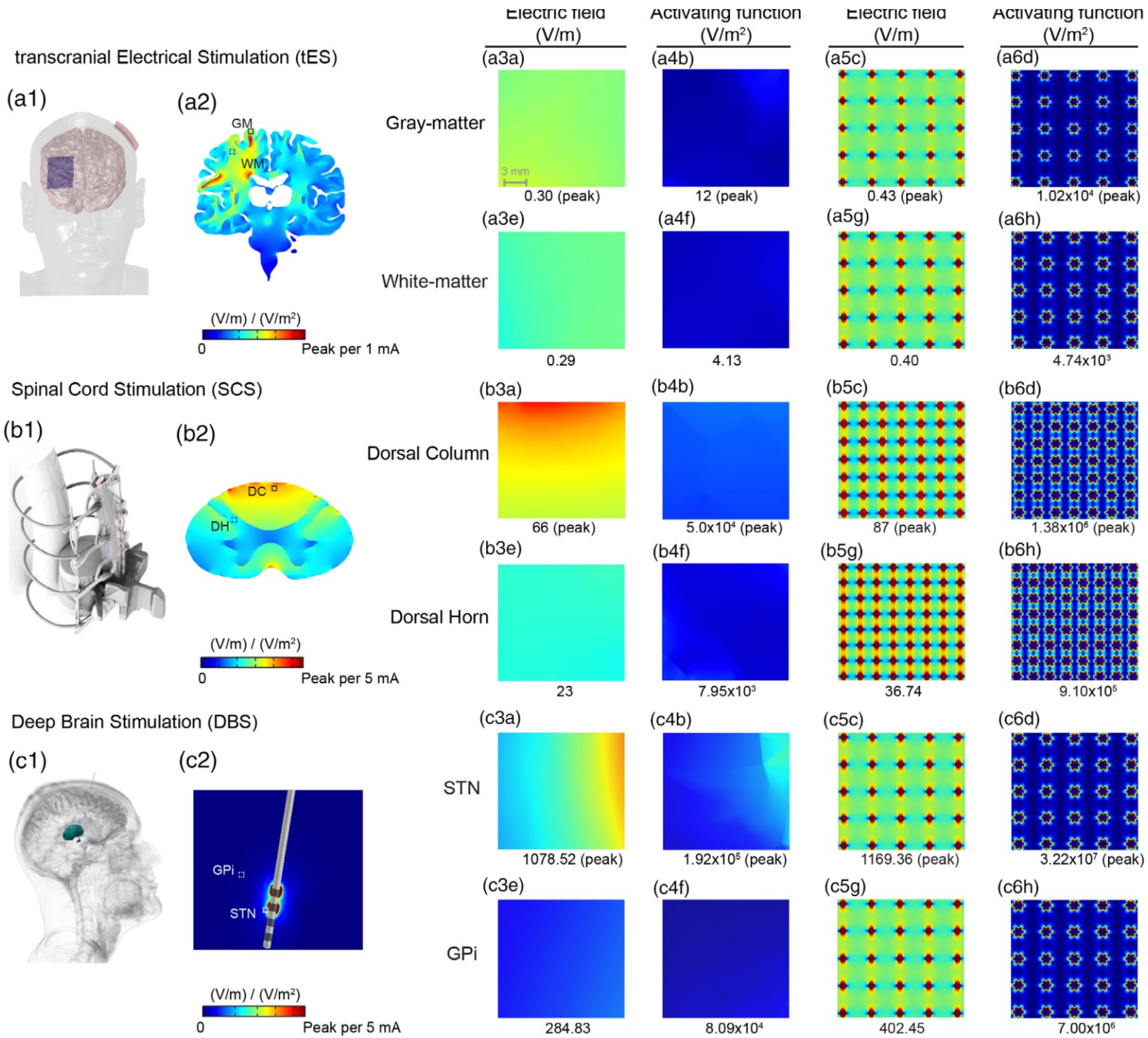
- Khadka et al. Neurocapillary-modulation. *Neuromodulation*. 2020
- Xia et. al Modulation of solute diffusivity in brain tissue as a novel mechanism of transcranial direct current stimulation (tDCS). *Sci Rep* 2020

Neuro-protective role (acute stroke)

- Bahr Hosseini et al. CNS Electrical Stimulation for Neuroprotection in Acute Cerebral Ischemia: Meta-Analysis of Preclinical Studies. *Stoke* 2019







Application of neurocapillary-modulation in tES, DBS, and SCS. Degree and spatial extent of electrical current flow distortion in the brain parenchyma around brain capillaries and the resulting amplification of neuronal polarization, driving factors such as electric field and activating function

See Khadka presentation: Jan 14, S6-Novel indications…

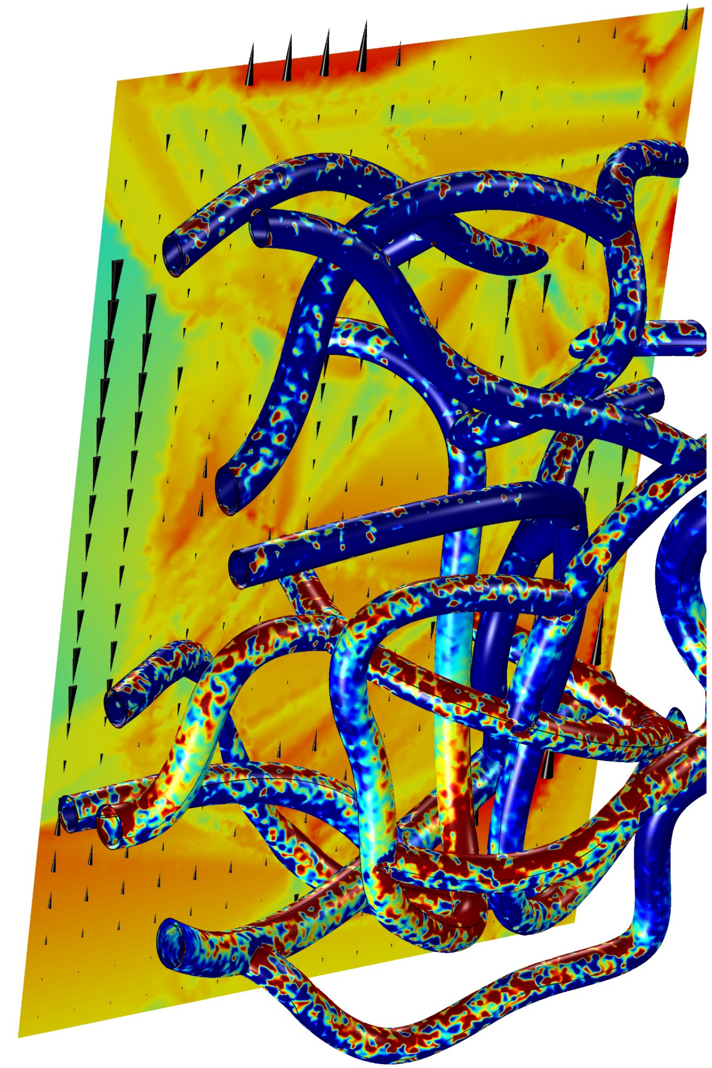
Khadka et al. Neurocapillary-modulation. Neuromodulation: Technology at the Neural Interface. 2020

Things Neuro-vascular Modulation can explain about Spinal Cord Stimulation

First Aspect: SCS cannot significantly modulate neuronal function without engaging neuro-vascular coupling. Imaging by hemodynamic coupling (fMRI…) measure changes in neuro-vascular coupling.

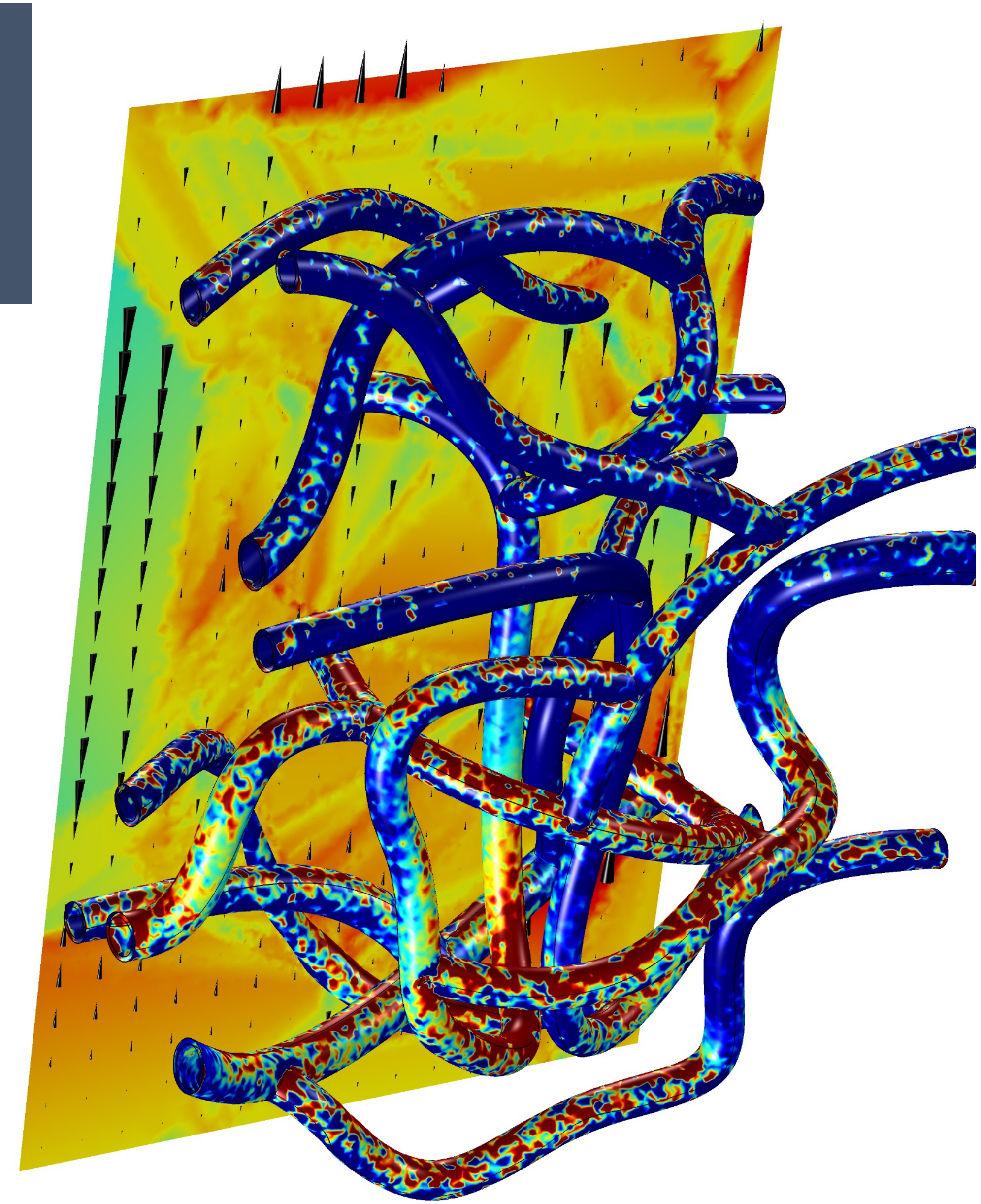
Second Aspect: Direct vascular (BBB) stimulation plausible - in a dose / mechanisms / time-course specific manner. Specific system / behavioral scale outcomes. And suggests unique therapy strategies
(glia activation, brain "flushing..:.)

Third Aspect: Reconsider how neuronal compartments or polarized by SCS. Impacts neuronal sensitivity (can provide "super-sensitivity" above traditional theory) and spatial distribution.



Multi-scale multi-physics model predict fluid "push" around brain during stimulation.

SCS: Neurovascular Modulation and Heating



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