



EM-Neuro Modeling Across Scales for Bioelectronic Medicine

Lecture 3: Axon Models, Activating Functions, and Electrical Stimulation

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- **Lecture Overview**
- **Axons**
- **Cable Equation and Compartmental Models**
- **Extracellular Stimulation**
- **Activating Function and Generalization**
- **Deep Brain Stimulation**
- **Summary of Today's Lecture & Outlook**

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DATE	LECTURE THEME
19.02	Motivation, logistics & tooling (EN, TNE)
26.02	Ion channels & membranes (EN)
05.03	Axon models, activating functions & electrical stimulation (EN)
12.03	EM field simulation fundamentals & coupled EM-neuro workflows (EN)
19.03	Peripheral nerves & interfaces for bioelectronic medicine (EN)
26.03	Spinal cord stimulation for neuroprosthetics and pain management & low-frequency exposure safety (TNE)
02.04	Morphology, synapses, microcircuits; point vs spiking networks (TNE)
09.04	No class: Easter break
16.04	Neural mass & whole brain models; hybridization (TNE)
23.04	Recording modalities, signal content & the reciprocity theorem (TNE)
30.04	Non invasive brain stimulation & temporal interference (TNE)
07.05	Image based/personalized treatment planning and optimization (EN)
14.05	No class: Ascension Day
21.05	Verification, validation, UQ, and reproducibility (EN)
28.05	Project presentations & synthesis (EN, TNE)

Room: ETZ E7

13:15-14:00 Lecture

14:00-14:15 Break

14:15-15:00 Lecture

14:00-14:15 Break

15:15-16:00 Exercise

**Lecture Recordings
& Slides**[Provided Here](#)

(will successively appear)

DATE	EXERCISE THEME
19.02	"Hello Neuron": integrate-and-fire in Python/NEURON
26.02	Point neuron phase portrait; basic time integration numerics
05.03	Recruitment prediction for myelinated axon using AF/GAF
12.03	EM (FEM) modeling of transcranial brain stimulation
19.03	Stimulation selectivity and signal content modeling for nerve interfaces
26.03	Guest (SCS – NeuroRestore)
02.04	Mini project work
09.04	No class: Easter break
16.04	Guest (Neuromodulation Spin-Off – Z43)
23.04	Mini project work
30.04	Guest (NIBS – Kinderspital)
07.05	Mini project work
14.05	No class: Ascension Day
21.05	Mini project work
28.05	Project presentations

Room: ETZ E7

13:15-14:00 Lecture

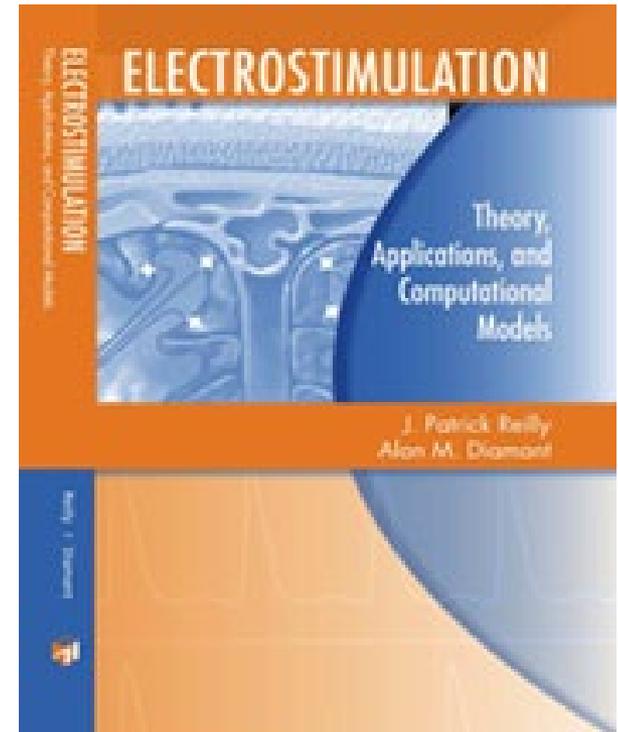
14:00-14:15 Break

14:15-15:00 Lecture

14:00-14:15 Break

15:15-16:00 Exercise

- Reilly, J. Patrick, and Alan M. Diamant. *Electrostimulation: theory, applications, and computational model*. Artech House, 2011



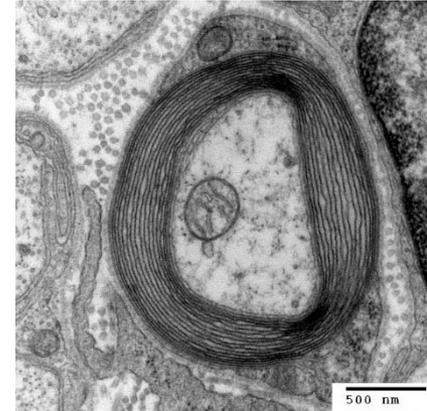
At the end of this lecture, you will have

- improved understanding of axonal electrophysiology and models thereof
- knowledge about neural interfaces for electrical nerve and deep-brain stimulation
- tools for interpreting and predicting neural fibre recruitment and for optimizing effectivity and selectivity
- The exercise will revolve around comparing two methods for predicting axonal stimulation and studying the impact of pulse shape

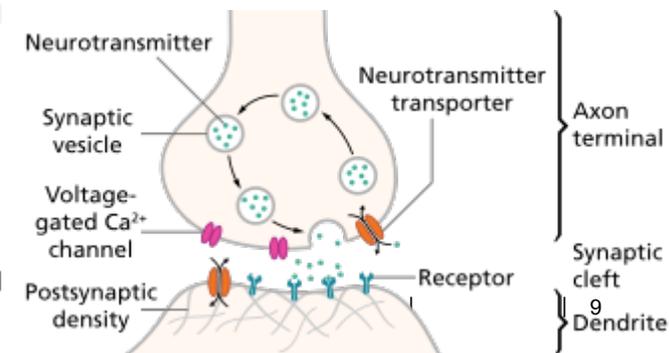
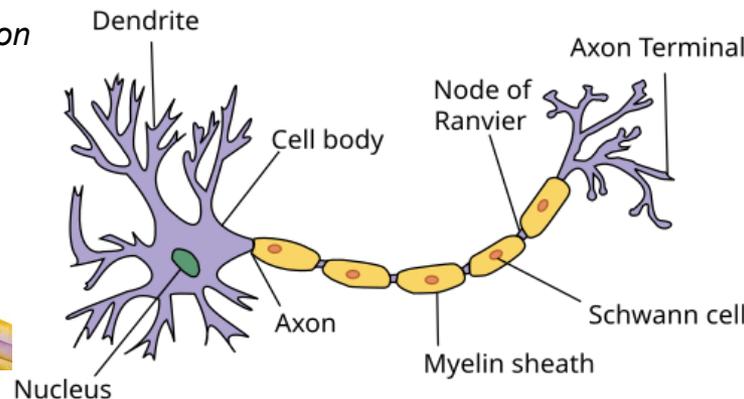
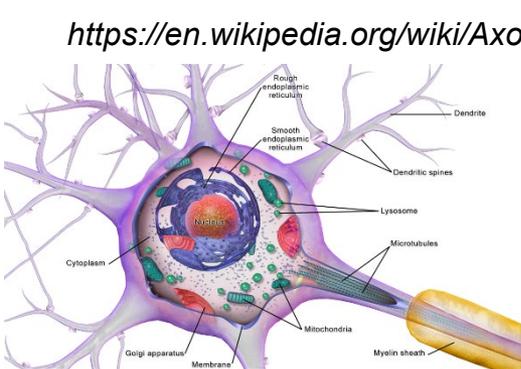
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- long, slender projections of nerve cells that conduct action potentials
 - nerve fibers, spinal cord, white matter, cortex...
 - bundles: fascicles (PNS), tracts (CNS, 200Mio in corpus callosum)
 - largest cells can reach >1m (e.g., sciatic nerve)
- myelin: insulating fatty layer formed by glia cells
 - Schwann cells(PNS), oligodendrocytes (CNS)
- nodes of Ranvier: gaps in myelin sheath
- myelin & nodes of Ranvier give rise to fast saltatory conduction
- axon hillock, initial segment (facilitates AP initiation), boutons (synaptic junctions along axon), axon terminals (synapses, potentially branching telodendron)

<https://de.wikipedia.org/wiki/Myelin>



<https://en.wikipedia.org/wiki/Axon>

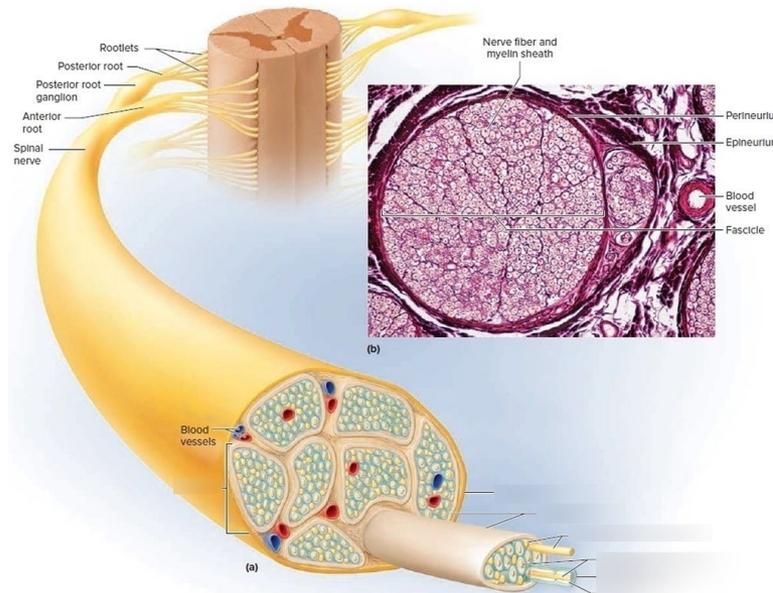


- classification according to diameter, myelination, function...
- we will mostly use thickness and myelination based classification (Erlanger-Gasser), with distinction in PNS of autonomic, motor and sensory, afferent and efferent

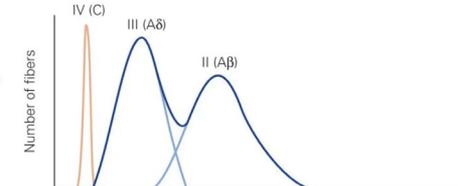
https://www.researchgate.net/figure/Mixed-nerve-containing-both-myelinated-motor-fibers-and-unmyelinated-sensory-fibers-Each_fig3_367795444

<https://neupsykey.com/the-somatosensory-system-receptors-and-central-pathways>

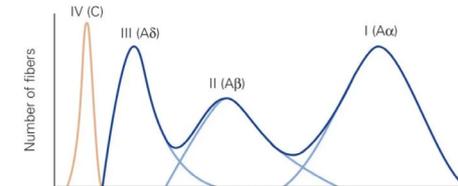
	A α	A β	A δ	C
Axons from skin				
Axons from muscles	Group I	II	III	IV
Diameter (μ m)	13–20	6–12	1–5	0.2–1.5
Speed (m/sec)	80–120 270 mph	35–75 80–170 mph	5–30 10–70 mph	0.5–2 1 mph
Sensory receptors	Skeletal muscle proprioceptors	Skin mechanoreceptors	Nociceptors, thermoreceptors	
Motor	Fast twitch Skeletal muscle	Slow twitch Skeletal muscle	ANS preganglionic	ANS postganglionic



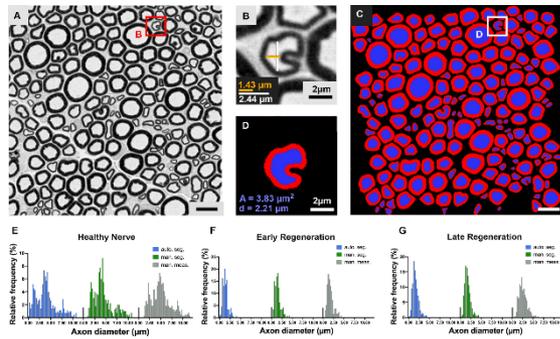
Cutaneous nerve



Muscle nerve



- classification according to diameter, myelination, function...
- we will mostly use thickness and myelination based classification (Erlanger-Gasser), with distinction in PNS of autonomic, motor and sensory, afferent and efferent



<https://www.nature.com/articles/s41598-022-10066-6>

Motor fiber types

Type	Erlanger-Gasser Classification	Diameter (μm)	Myelin	Conduction velocity (meters/second)	Associated muscle fibers
Alpha (α) motor neuron	Aα	13–20	Yes	80–120	Extrafusal muscle fibers
Beta (β) motor neuron	Aβ				
Gamma (γ) motor neuron	Aγ	5-8	Yes	4–24 ^{[50][51]}	Intrafusal muscle fibers

Autonomic Fiber types

Type	Erlanger-Gasser Classification	Diameter ^[52] (μm)	Myelin ^[53]	Conduction velocity (m/s)
preganglionic fibers	B	0.5–3	Yes	3–15
postganglionic fibers	C	0.2–1.4	No	0.5–2.0

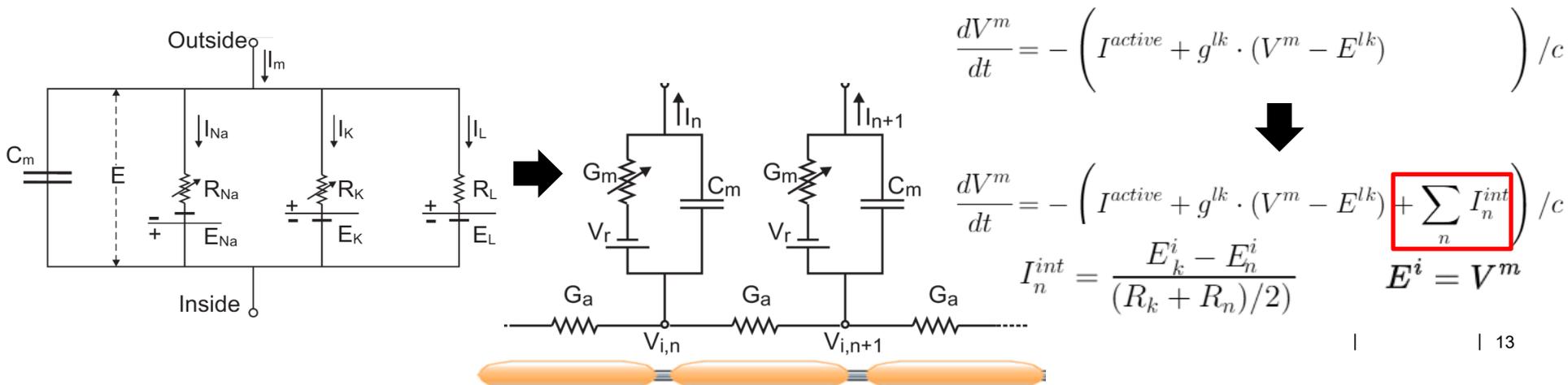
<https://en.wikipedia.org/wiki/Axon>

Sensory fiber types

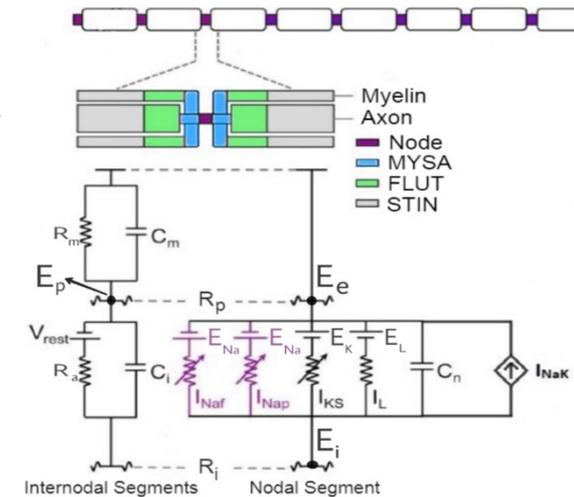
Type	Erlanger-Gasser Classification	Diameter (μm)	Myelin	Conduction velocity (m/s)	Associated sensory receptors	Proprioceptors	Mechanoceptors	Nociceptors and thermoreceptors
Ia	Aα	13–20	Yes	80–120	Primary receptors of muscle spindle (annulospiral ending)			
Ib	Aα	13–20	Yes	80–120	Golgi tendon organ			
II	Aβ	6–12	Yes	33–75	Secondary receptors of muscle spindle (flower-spray ending). All cutaneous mechanoreceptors	✓		
III	Aδ	1–5	Thin	3–30	Free nerve endings of touch and pressure Nociceptors of lateral spinothalamic tract Cold thermoreceptors		✓	
IV	C	0.2–1.5	No	0.5–2.0	Nociceptors of anterior spinothalamic tract Warmth receptors			✓

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- $$I = C_m \frac{dV_m}{dt} + g_K (V_m - V_K) + g_{Na} (V_m - V_{Na}) + g_l (V_m - V_l)$$
- following *Danner, Simon & Wenger, Cornelia & Rattay, Frank. (2011). Electrical stimulation of myelinated axons: An interactive tutorial supported by computer simulation*
- McNeal:
 - compartmental model
 - connect HH-like nodes of Ranvier by perfectly insulated, resistive myelinated segments
 - consider axial currents

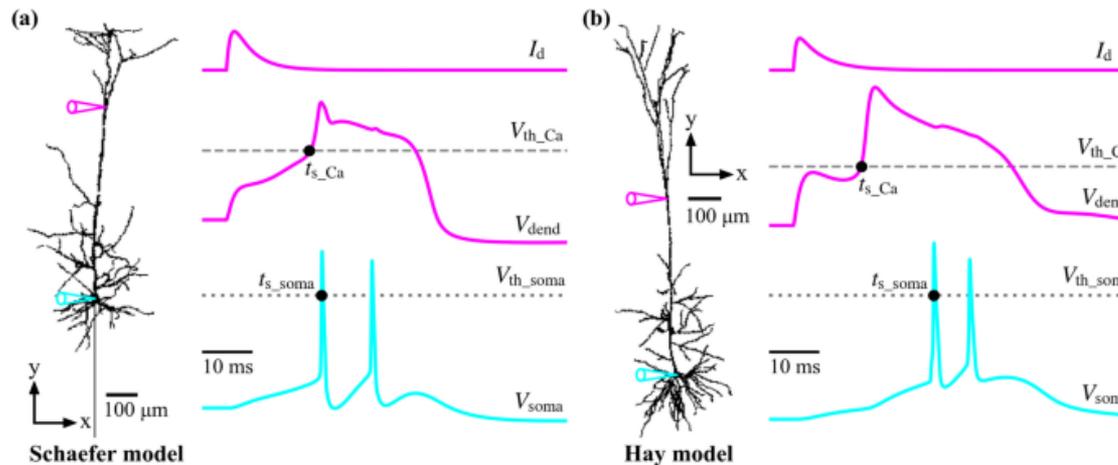


- “MRG”
 - McIntyre, Richardson, Grill. *J Neurophysiol.* 2002 Feb;87(2)
 - more realistic model(s) of mammalian fibers
 - periaxonal spaces (double cable equation)
 - paranodal elements
 - finite myeline resistance
 - extended & modified ion channels



Kamelian Rad, et al. (2022). *Journal of Mathematical Biology.* 86.

- L5 pyramidal neurons: examples of complex multicompartmental model



Huang, et al. *J Comput Neurosci* 53, 25–36 (2025).

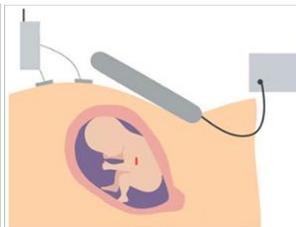
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- desired fiber activation by exposure to electric potential
 - PNS implants: electroceuticals, neuroprosthetics
 - CNS implants: deep brain stimulators, spinal cord stimulators, brain-machine/computer-interfaces
 - transcranial brain stimulation
 - transcutaneous nerve / spinal-cord stimulation
- unwanted LF stimulation (e.g., MRI)



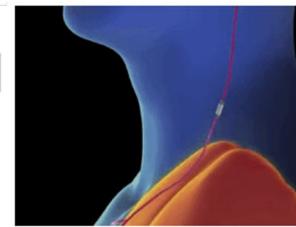
Brain and Spine Implants Let a Paralyzed Monkey Walk Again

10 Nov 2016



Fetal Pacemaker Ready for Human Trial

11 May



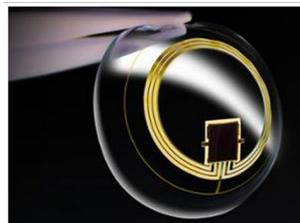
Vagus Nerve Stimulation Fights Rheumatoid Arthritis

25 Jul 2016



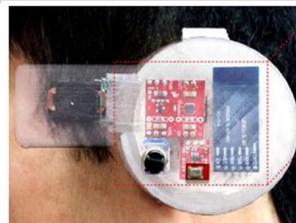
AI Can Help Patients Recover Ability to Stand and Walk

19 Jul



Smart Contact Lenses and Eye Implants Will Give Doctors Medical Insights

25 Jul



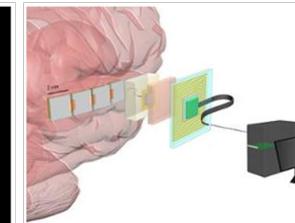
3D-Printed "Earable" Sensor Monitors Vital Signs

27 Jul



Wearable Sensors Give Skin Space to Breathe

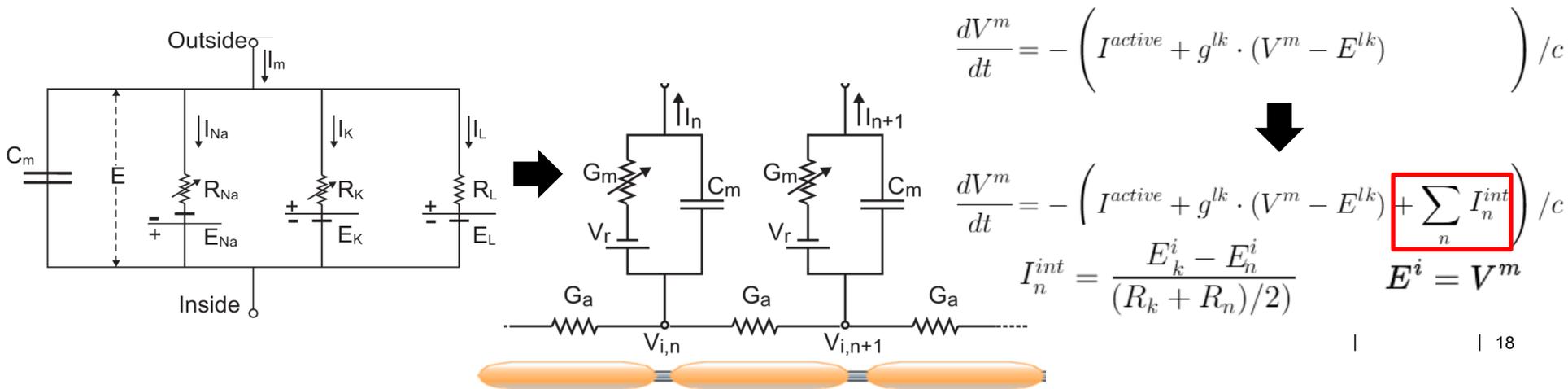
20 Jul

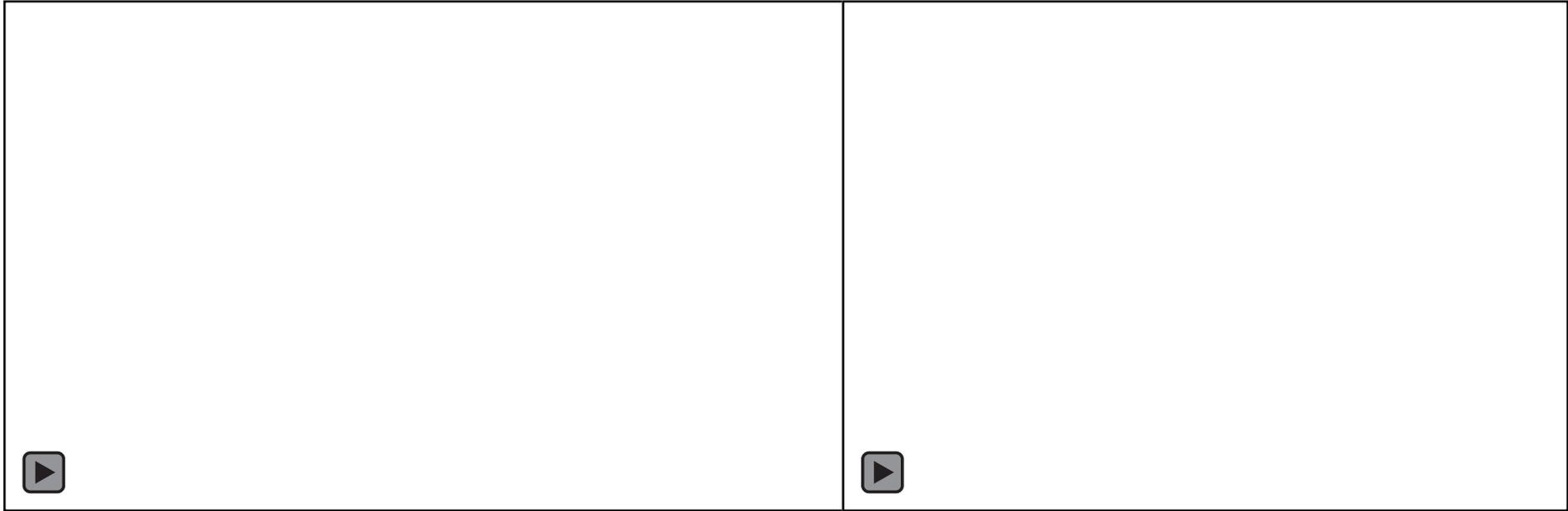


DARPA Wants Brain Implants That Record From 1 Million Neurons

10 Jul

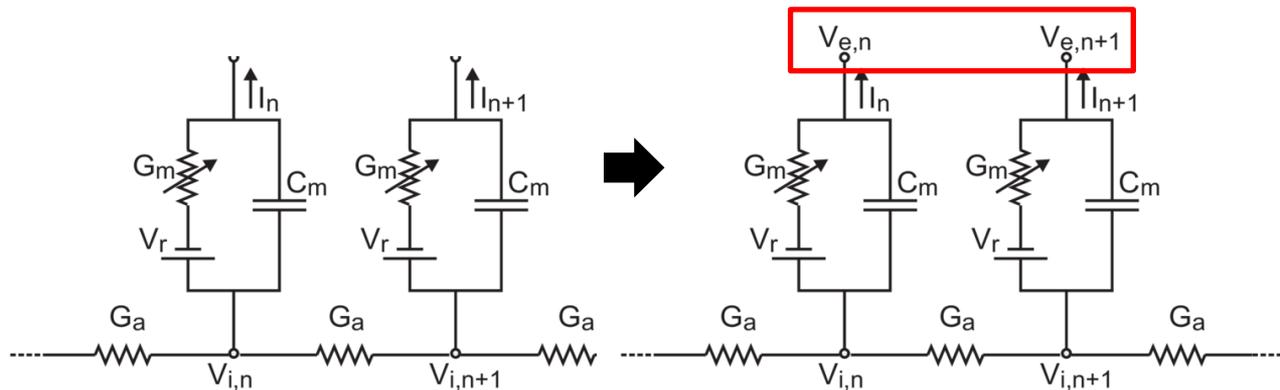
- $$I = C_m \frac{dV_m}{dt} + g_K (V_m - V_K) + g_{Na} (V_m - V_{Na}) + g_l (V_m - V_l)$$
- following *Danner, Simon & Wenger, Cornelia & Rattay, Frank. (2011). Electrical stimulation of myelinated axons: An interactive tutorial supported by computer simulation*
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$$\frac{dV^m}{dt} = - \left(I^{active} + g^{lk} \cdot (V^m - E^{lk}) + \sum_n I_n^{int} \right) / c$$

$$I_n^{int} = \frac{E_k^i - E_n^i}{(R_k + R_n)/2} \quad \boxed{E^i = V^m}$$



↓

$$\left(I^{active} + g^{lk} \cdot (V^m - E^{lk}) + \sum_n I_n^{int} \right) / c$$

$$= \frac{E_k^i - E_n^i}{(R_k + R_n)/2} \quad \boxed{E^i = V^m + V^e}$$

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- $\frac{dV^m}{dt} = - \left(I^{active} + g^{lk} \cdot (V^m - E^{lk}) + \sum_n I_n^{int} \right) / c$ $I_n^{int} = \frac{E_k^i - E_n^i}{(R_k + R_n)/2}$ $E^i = V^m + V^e$
- extract terms related to external potential – the “activating function”:

$$f_n = 1/c \left(\frac{V_{n-1}^e - V_n^e}{R_{n-1}/2 + R_n/2} + \frac{V_{n+1}^e - V_n^e}{R_{n+1}/2 + R_n/2} + \dots \right)$$

- these are sources of depolarization / hyperpolarization
- help predict location and likelihood of action potential initiation

- $f_n = \frac{d\Delta x}{4\rho_i Lc} \frac{V_{n-1}^e - 2V_n^e + V_{n+1}^e}{\Delta x^2}$

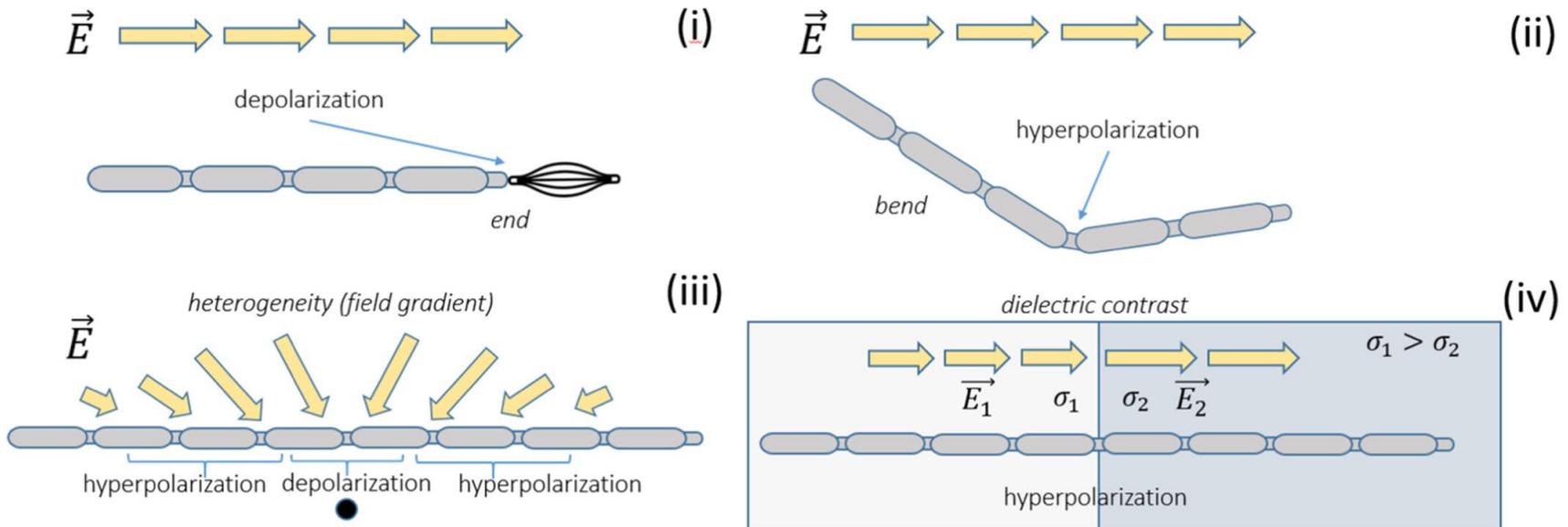
where d is the constant fiber diameter, Δx the node-to-node distance, L the node length ρ_i the axoplasmatic resistivity, c the capacity and i_{ion} the ionic currents.

- this has the form of a finite-difference 2nd derivative
- for unmyelinated fibers: continuum limit, with vanishing myelin

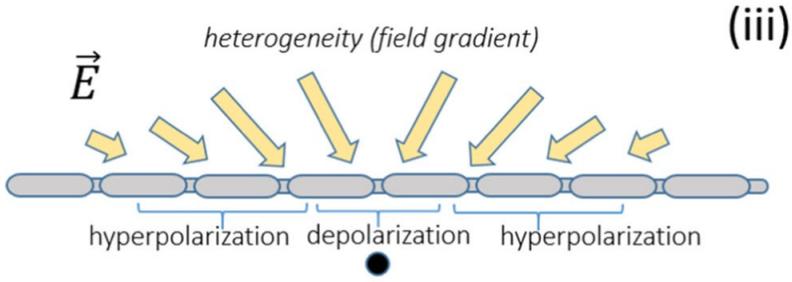
$$f = \frac{d}{4\rho_i c} \cdot \frac{\delta^2 V^e}{\delta x^2}$$

$$f_n = \frac{d\Delta x}{4\rho_i Lc} \frac{V_{n-1}^e - 2V_n^e + V_{n+1}^e}{\Delta x^2}$$

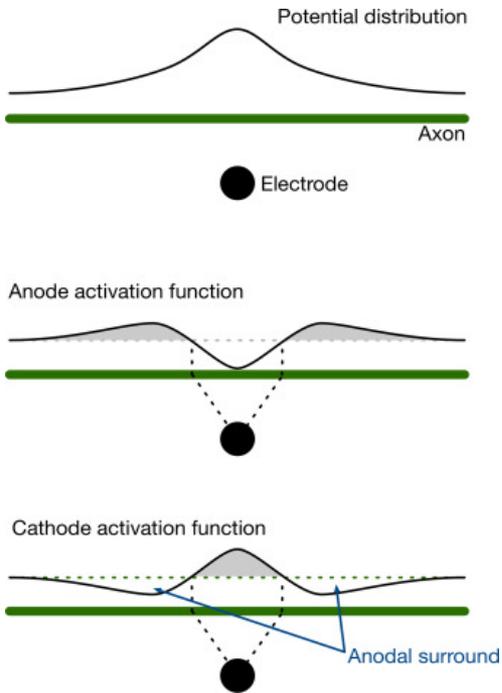
- interpretation: imbalance between incoming and outgoing axial currents leads to charge build up and membrane polarization
- center-node (activating function): bending, field heterogeneity, dielectric contrast at tissue interfaces
- end-node: proportional to tangential E-field



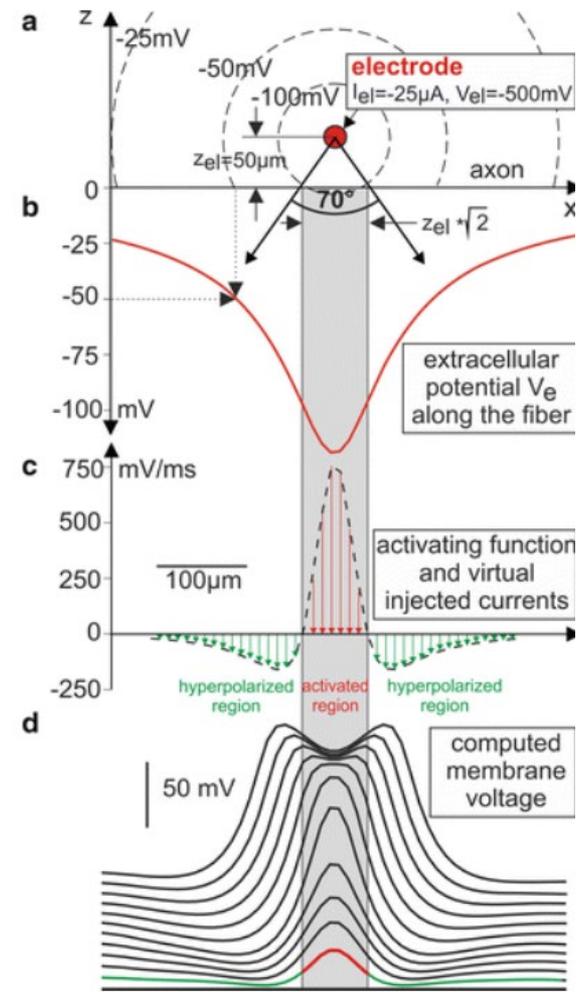
$$f_n = \frac{d\Delta x}{4\rho_i Lc} \frac{V_{n-1}^e - 2V_n^e + V_{n+1}^e}{\Delta x^2}$$



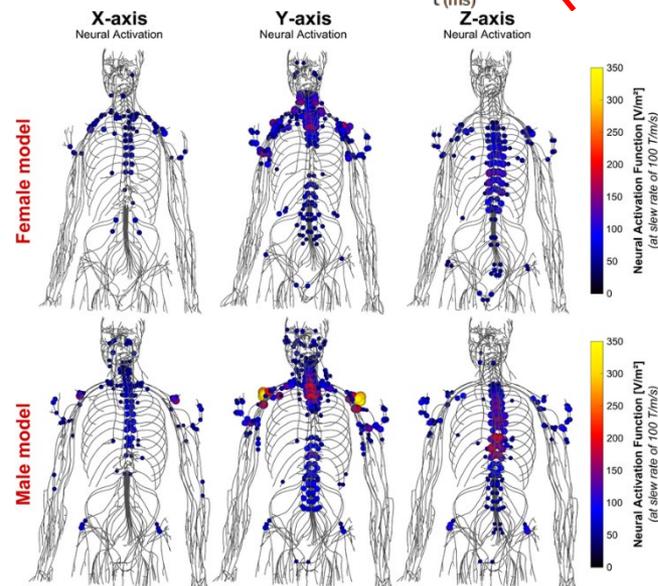
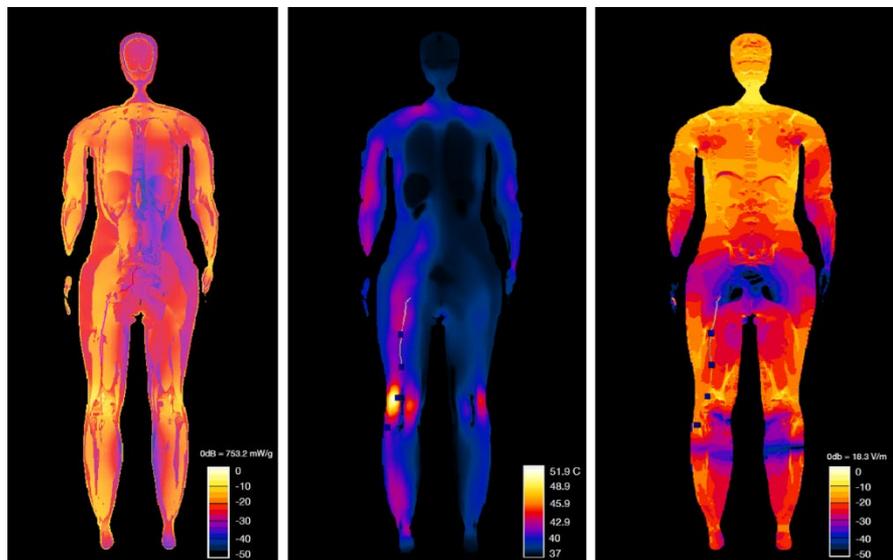
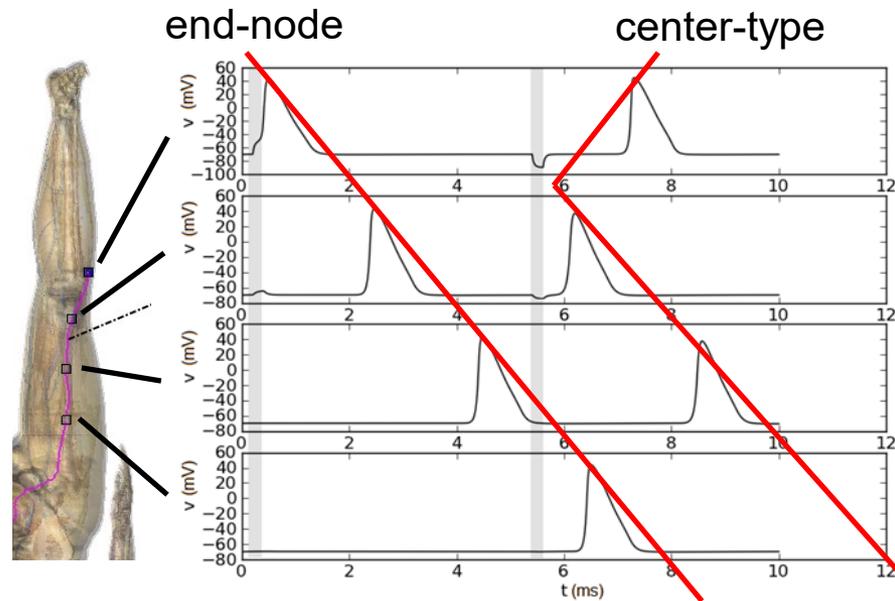
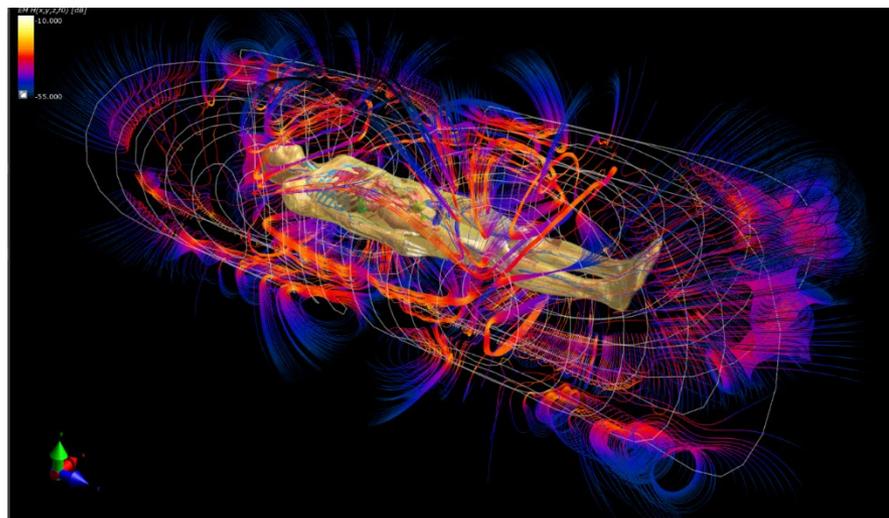
<https://www.sciencedirect.com/topics/engineering/stimulating-electrode>



Rattay et al. (2014). *Finite Element Modeling for Extracellular Stimulation*. 10.1007/978-1-4614-7320-6 593-5.



... and for Safety Assessment (e.g., MRI LF Exposure)



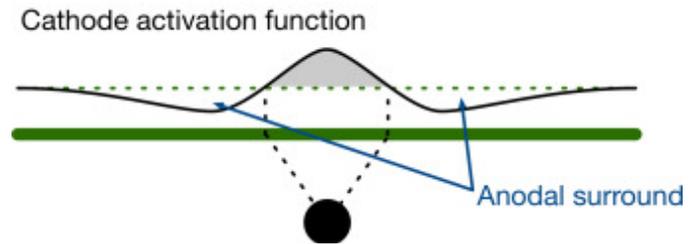
strengths

- very cheap to compute
- amenable to superposition principle
 - valuable when studying multi-contact electrodes
- often offers good relative assessment of stimulability

$$f_n = \frac{d\Delta x}{4\rho_i Lc} \frac{V_{n-1}^e - 2V_n^e + V_{n+1}^e}{\Delta x^2}$$

weaknesses

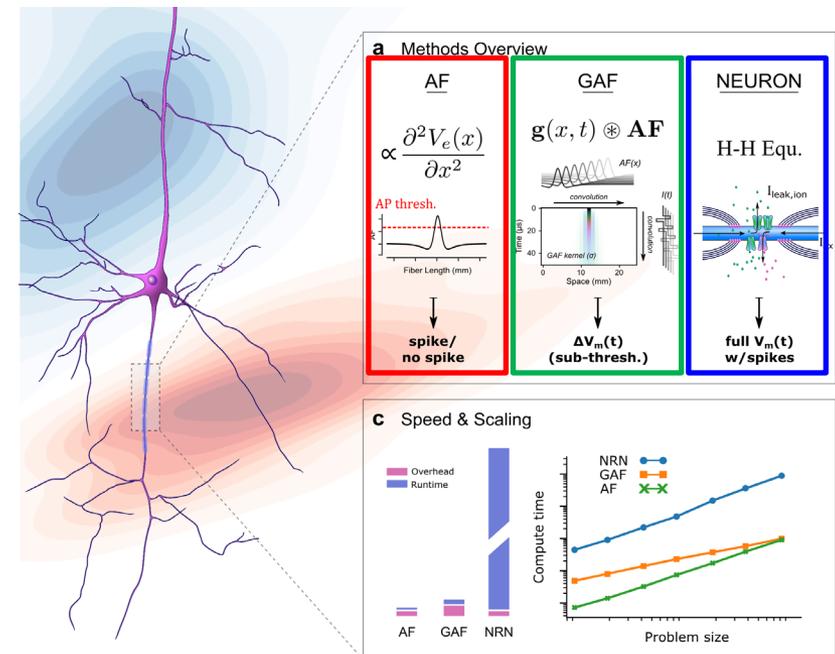
- neglects axial diffusion
 - remember the “*virtual anodes*”
- neglects leakage currents
- no absolute predictions of membrane dynamics
- no transient dynamics
 - e.g., not suitable for comparing pulse shapes



- **Activating Function**
 - cheap, but...
 - **NEURON**
 - expensive, but comprehensive
 - **Generalized Activating Function**
 - neglect active channel dynamics to keep ODE linear
 - appropriate for predicting subthreshold dynamics up to crossing of stimulation threshold
 - linear and translation invariant
- => Green's function

$$C \frac{dV_n}{dt} = I_{ion} + \frac{V_{n+1} - V_n}{R_a} - \frac{V_n - V_{n-1}}{R_a} + \frac{V_{n+1}^e - V_n^e}{R_a} - \frac{V_n^e - V_{n-1}^e}{R_a}$$

Rate of change Ion Lateral displacement (propagation) Lateral displacement (due to external potential)



- For a linear differential operator $\mathcal{L}_{x,t}$
- Green's function:

$$\mathcal{L}_{x,t} G(x, t; x', t') = \delta(x - x', t - t')$$

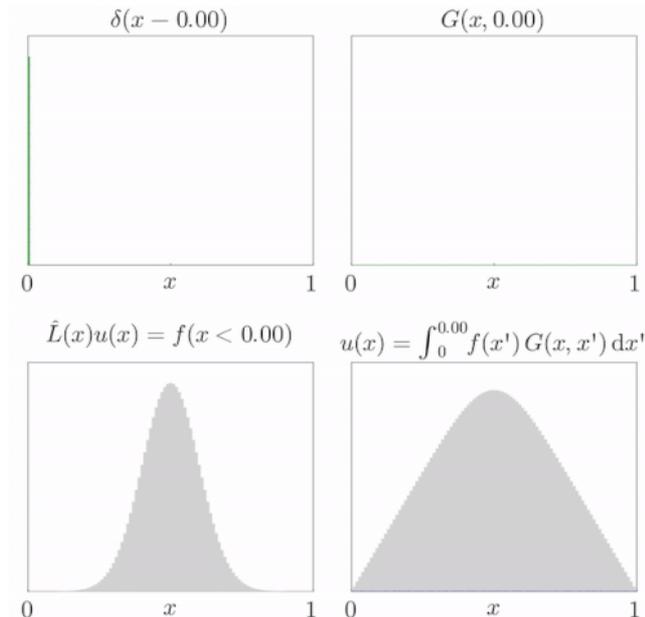
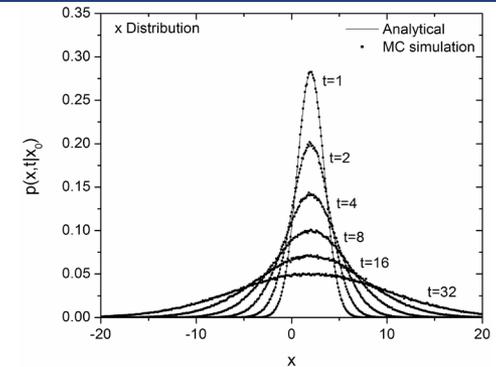
- Then the solution to $\mathcal{L}_{x,t} T(x, t) = f(x, t)$ is:

$$T(x, t) = \int G(x, t; x', t') f(x', t') dx dt$$

$$\begin{aligned} \mathcal{L}_{x,t} \int G(x, t; x', t') f(x', t') dx dt &= \int \mathcal{L}_{x,t} G(x, t; x', t') f(x', t') dx dt = \\ &= \int \delta(x - x', t - t') f(x', t') dx dt = f(x, t) \end{aligned}$$

- When shift invariant: convolution
 - can be efficiently evaluated in Fourier space

$$f * g = \mathcal{F}^{-1} \{ \mathcal{F}\{f\} \cdot \mathcal{F}\{g\} \}$$



- continuum variant (cable equation, unmyelinated)

$$\frac{\partial V(x, t)}{\partial t} = \frac{d}{4\rho_a c_m} \left[\frac{\partial^2 V_e(x, t)}{\partial x^2} + \frac{\partial^2 V(x, t)}{\partial x^2} \right] - \frac{g_l}{c_m} V(x, t)$$

- equivalent to classic cable equation: $\frac{1}{r_l} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m}$
- characteristic time scale: $\tau_m = c_m / g_l$

- continuum variant (cable equation, unmyelinated)

$$\frac{\partial V(x, t)}{\partial t} = \frac{d}{4\rho_a c_m} \left[\frac{\partial^2 V_e(x, t)}{\partial x^2} + \frac{\partial^2 V(x, t)}{\partial x^2} \right] - \frac{g_l}{c_m} V(x, t)$$

$$G(x, t) = H(t) \frac{1}{2} e^{-t/\tau_m} \frac{1}{\sqrt{4\pi\kappa t}} \left(\frac{x^2}{2\kappa t} - 1 \right) \exp\left[-\frac{x^2}{4\kappa t} \right] \quad \kappa \equiv \frac{d}{4\rho_a c_m}$$

$$V(x, t) = G(x, t) \otimes_{x,t} V_e(x, t)$$

- discrete variant (nodes of Ranvier)

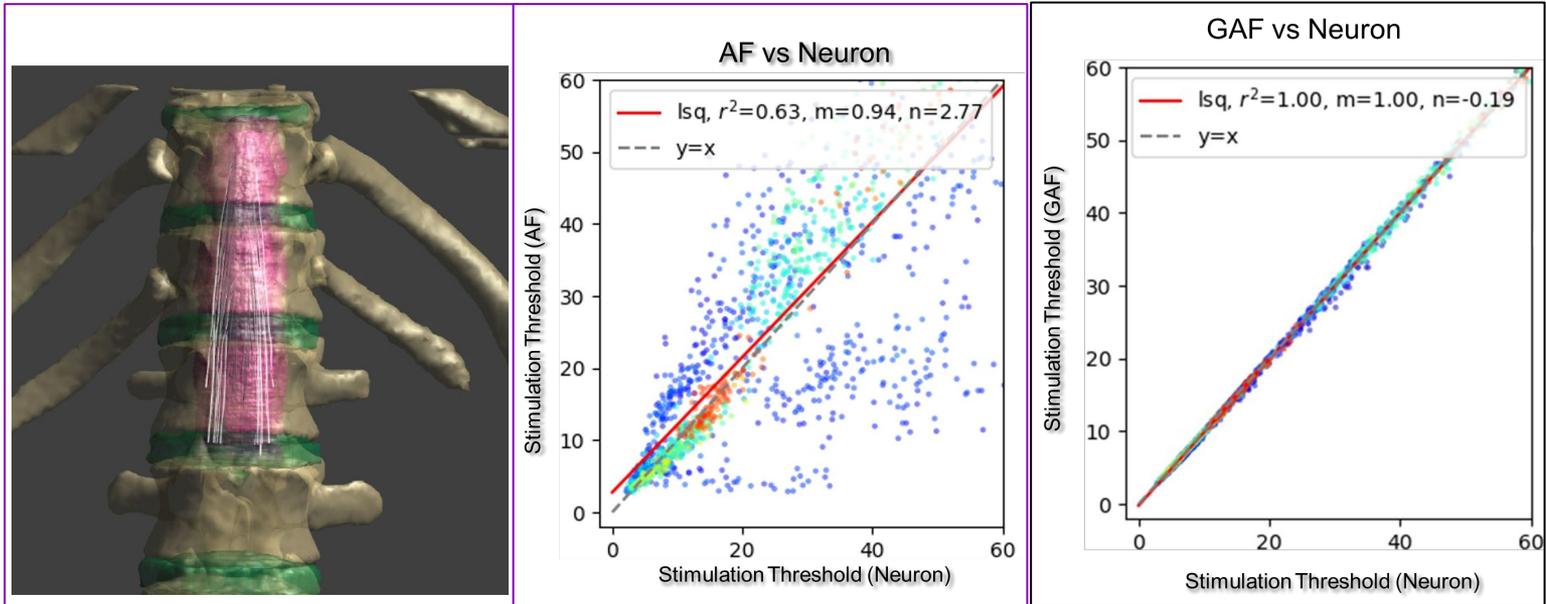
$$\frac{dV_n}{dt} = \frac{G_a}{C_m} [V_{e,n-1} - 2V_{e,n} + V_{e,n+1}] + \frac{G_a}{C_m} [V_{n-1} - 2V_n + V_{n+1}] - \frac{G_l}{C_m} V_n$$

$$\frac{d\mathbf{V}(t)}{dt} = \mathbf{A}\mathbf{V}_e(t) + \tilde{\mathbf{A}}\mathbf{V}(t) \quad (\text{circulant matrices; diagonalize in Fourier basis } \tilde{\mathbf{A}} = \mathbf{F}^* \mathbf{\Lambda} \mathbf{F})$$

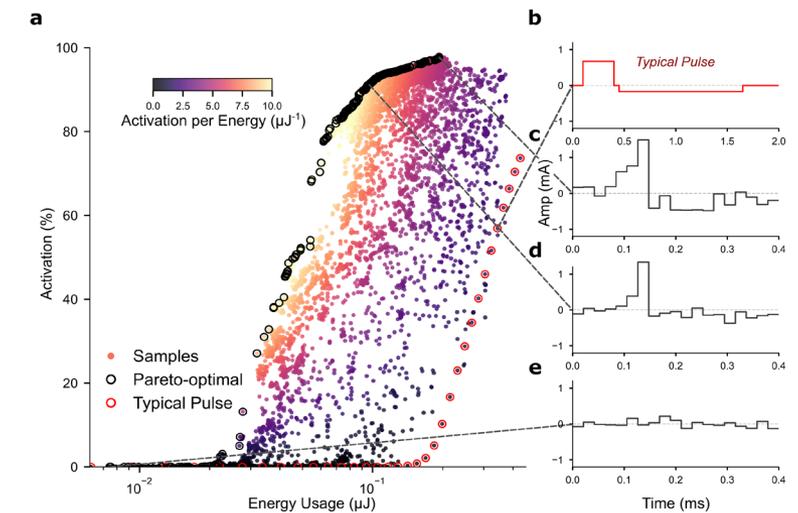
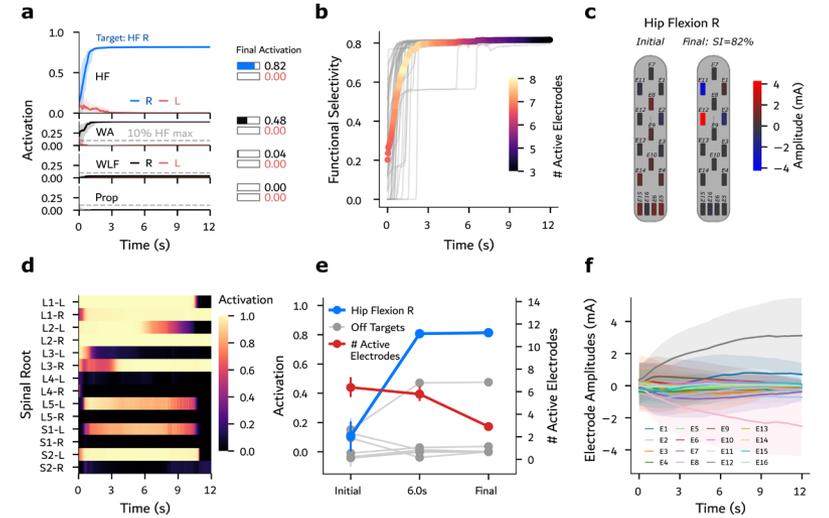
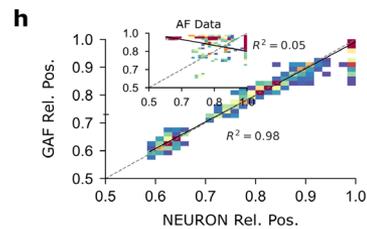
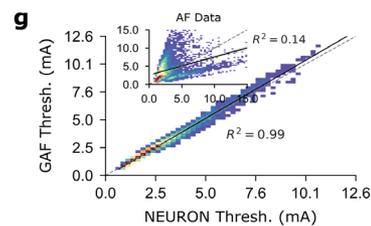
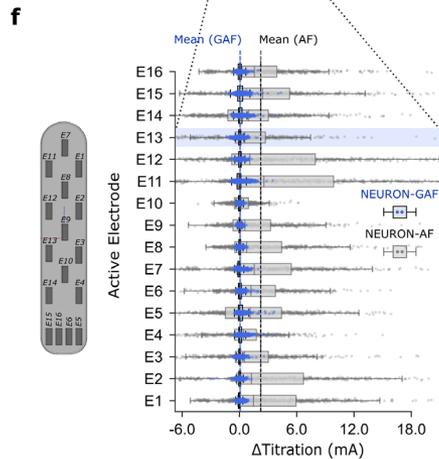
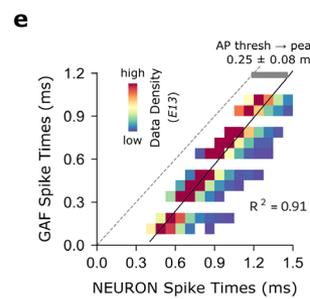
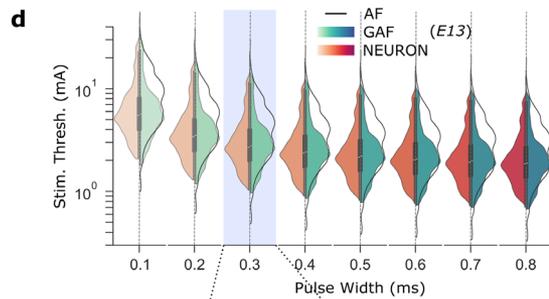
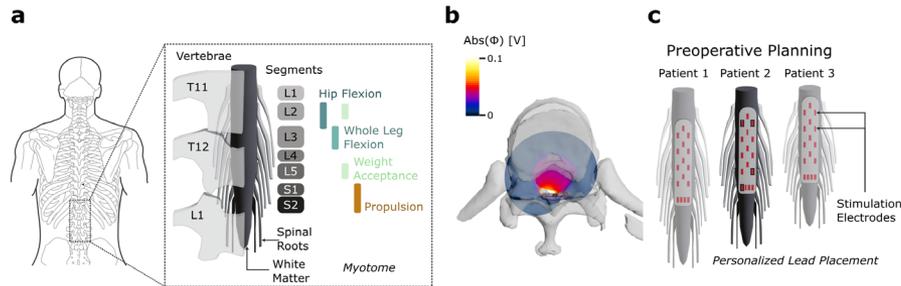
$$\mathbf{G}(t) = e^{\tilde{\mathbf{A}}t} \mathbf{A} H(t) \quad e^{\tilde{\mathbf{A}}t} = \mathbf{F}^* e^{\mathbf{\Lambda}t} \mathbf{F}$$

- subtleties: BC and cyclic closure
- for piece-wise constant pulse shapes: step function instead of impulse function

- optimizing spinal cord stimulation to restore locomotion



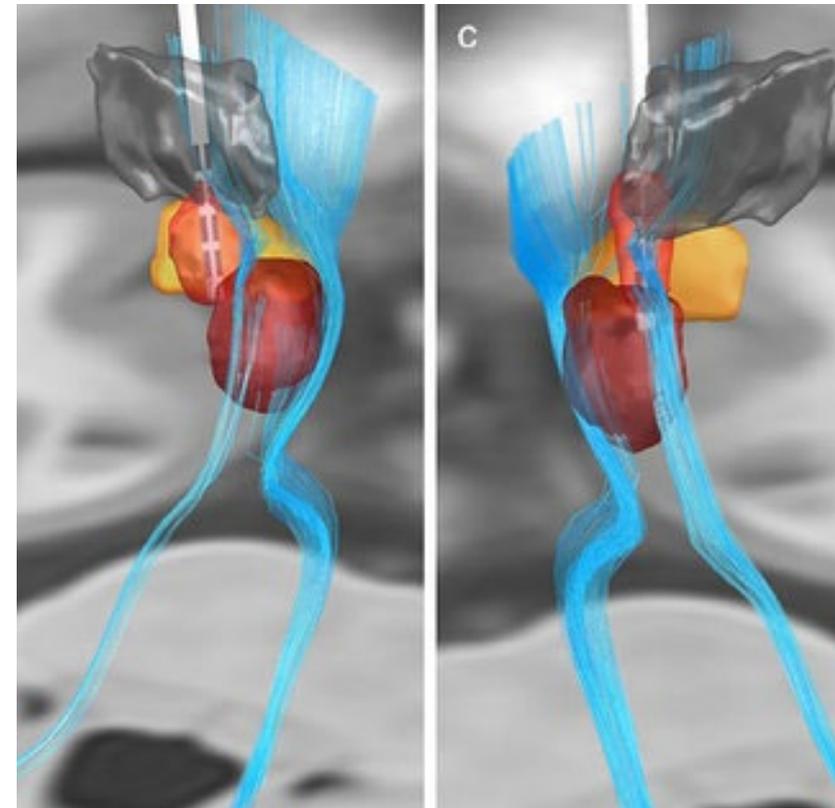
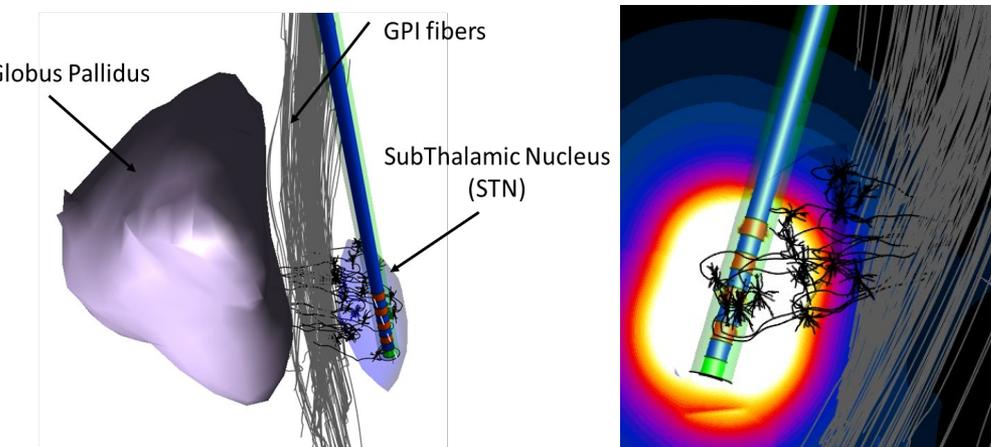
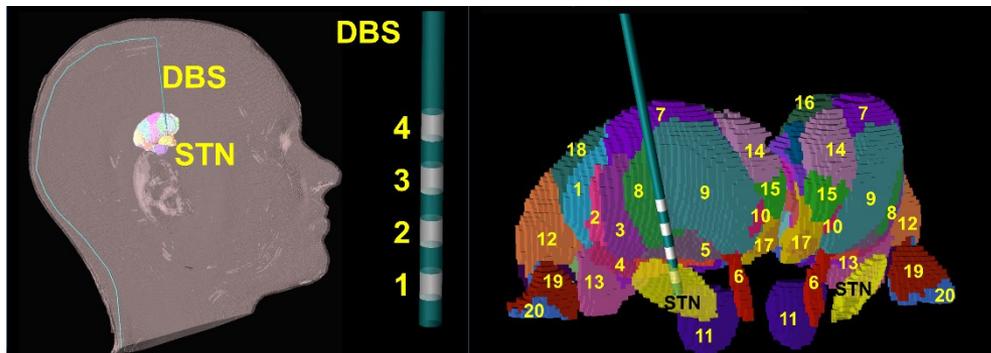
- optimizing spinal cord stimulation to restore locomotion



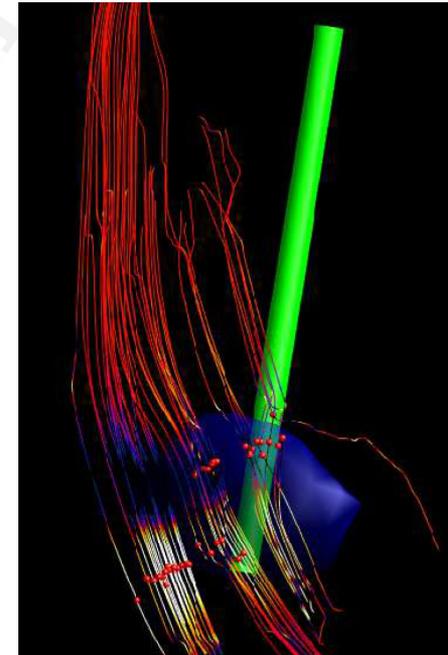
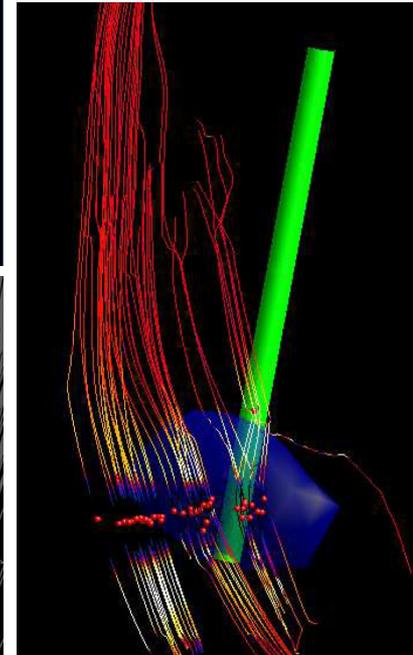
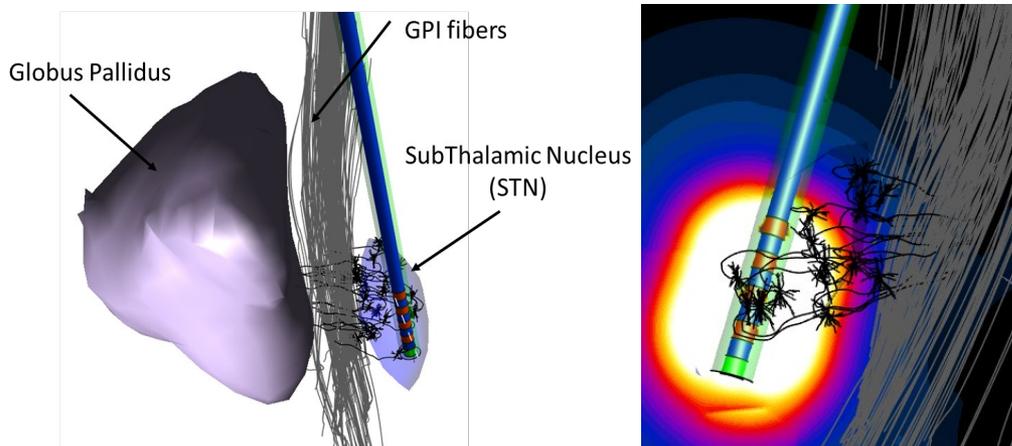
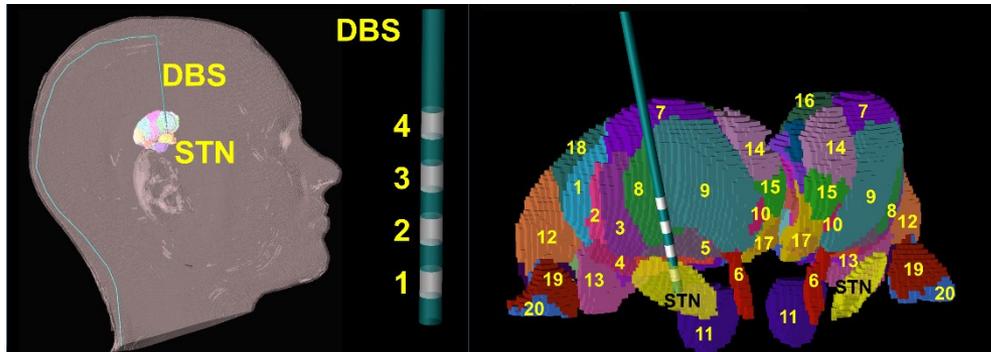
- Lecture Overview
- Axons
- Cable Equation and Compartmental Models
- Extracellular Stimulation
- Activating Function and Generalization
- **Deep Brain Stimulation**
- Summary of Today's Lecture & Outlook

- Volume of Tissue Activation (VTA)
 - initially field magnitude based (e.g., neuron derived)

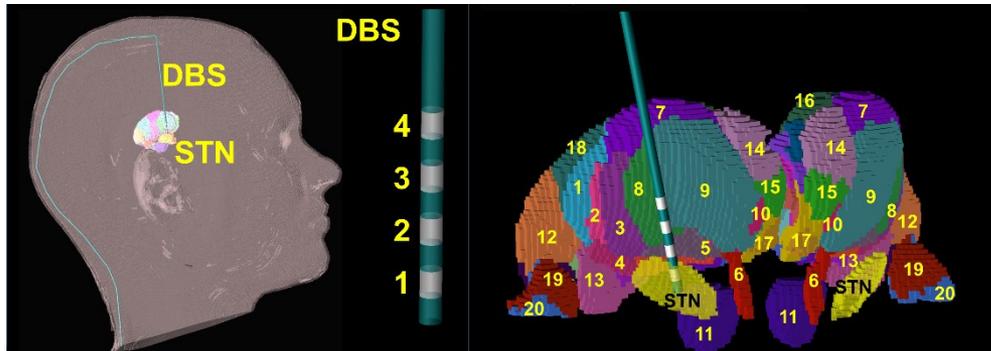
Bargiotas, et al. (2021). Long-Term Outcome and Neuroimaging of Deep Brain Stimulation in Holmes Tremor: A Case Series. *Neuromodulation: Technology at the Neural Interface*. 24. 10.1111/ner.13352.



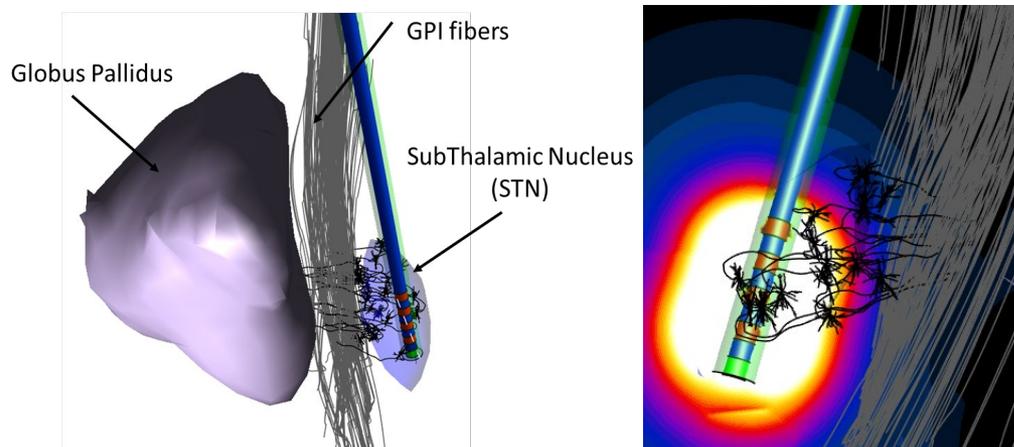
- Volume of Tissue Activation (VTA)
 - initially field magnitude based (e.g., neuron derived)
- GPI fibers of passage: AF or coupling to axon models



- Volume of Tissue Activation (VTA)
 - initially field magnitude based (e.g., neuron derived)
- GPI fibers of passage: AF or coupling to axon models
- without trajectories: Eigenvalues of Hessian
 - but careful with dielectric contrast at interfaces...



$$\bar{\bar{H}} = \begin{bmatrix} \frac{\partial^2 \phi}{\partial x^2} & \frac{\partial^2 \phi}{\partial y \partial x} & \frac{\partial^2 \phi}{\partial z \partial x} \\ \frac{\partial^2 \phi}{\partial x \partial y} & \frac{\partial^2 \phi}{\partial y^2} & \frac{\partial^2 \phi}{\partial z \partial y} \\ \frac{\partial^2 \phi}{\partial x \partial z} & \frac{\partial^2 \phi}{\partial y \partial z} & \frac{\partial^2 \phi}{\partial z^2} \end{bmatrix}$$



$$AF(\vec{n}) = \vec{n} \cdot \bar{\bar{H}} \vec{n}$$

$$\max_{\vec{n}} AF(\vec{n}) = \max_i EV_i(\bar{\bar{H}})$$

- Lecture Overview
- The Hodgkin- Huxley Equation
- Phase Plane Analysis
- Temporal Discretization & Numerical Solving
- NEURON
- **Summary of Today's Lecture & Outlook**

At the end of this lecture, you will have

- improved understanding of axonal electrophysiology and models thereof
- knowledge about neural interfaces for electrical nerve and deep-brain stimulation
- tools for interpreting and predicting neural fibre recruitment and for optimizing effectivity and selectivity

Next week: EM field simulation fundamentals

- The exercise will revolve around comparing two methods for predicting axonal stimulation and studying the impact of pulse shape

DATE	LECTURE THEME
19.02	Motivation, logistics & tooling (EN, TNE)
26.02	Ion channels & membranes (EN)
05.03	Axon models, activating functions & electrical stimulation (EN)
12.03	EM field simulation fundamentals & coupled EM-neuro workflows (EN)
19.03	Peripheral nerves & interfaces for bioelectronic medicine (EN)
26.03	Spinal cord stimulation for neuroprosthetics and pain management & low-frequency exposure safety (TNE)
02.04	Morphology, synapses, microcircuits; point vs spiking networks (TNE)
09.04	No class: Easter break
16.04	Neural mass & whole brain models; hybridization (TNE)
23.04	Recording modalities, signal content & the reciprocity theorem (TNE)
30.04	Non invasive brain stimulation & temporal interference (TNE)
07.05	Image based/personalized treatment planning and optimization (EN)
14.05	No class: Ascension Day
21.05	Verification, validation, UQ, and reproducibility (EN)
28.05	Project presentations & synthesis (EN, TNE)

Room: ETZ E7

13:15-14:00 Lecture

14:00-14:15 Break

14:15-15:00 Lecture

14:00-14:15 Break

15:15-16:00 Exercise

**Lecture Recordings
& Slides**[Provided Here](#)

(will successively appear)

DATE	EXERCISE THEME
19.02	"Hello Neuron": integrate-and-fire in Python/NEURON
26.02	Point neuron phase portrait; basic time integration numerics
05.03	Recruitment prediction for myelinated axon using AF/GAF
12.03	EM (FEM) modeling of transcranial brain stimulation
19.03	Stimulation selectivity and signal content modeling for nerve interfaces
26.03	Guest (SCS – NeuroRestore)
02.04	Mini project work
09.04	No class: Easter break
16.04	Guest (Neuromodulation Spin-Off – Z43)
23.04	Mini project work
30.04	Guest (NIBS – Kinderspital)
07.05	Mini project work
14.05	No class: Ascension Day
21.05	Mini project work
28.05	Project presentations

Room: ETZ E7

13:15-14:00 Lecture

14:00-14:15 Break

14:15-15:00 Lecture

14:00-14:15 Break

15:15-16:00 Exercise