



# EM-Neuro Modeling Across Scales for Bioelectronic Medicine

## Lecture 5: Hybrid EM-Neuro Modeling of Nerve Interfaces for Bioelectronic Medicine

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- **Lecture Overview**
- **The PNS, Bioelectronic Medicine, and the Role for Modeling**
- **Creating and Functionalizing Nerve Models**
- **Predicting Recruitment and Selectivity**
- **Balancing Safety, Effectivity, and Efficiency**
- **Summary of Today's Lecture & Outlook**

- **Lecture Overview**

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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

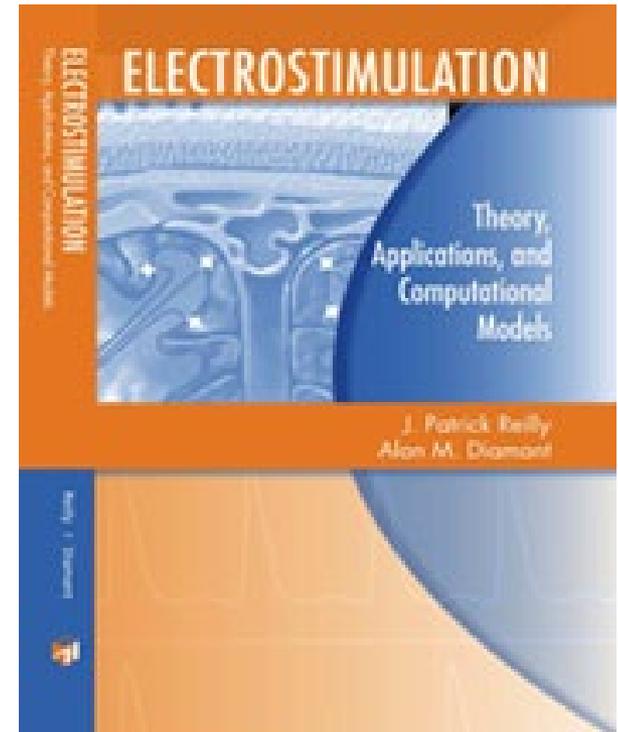
14:00-14:15 Break

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

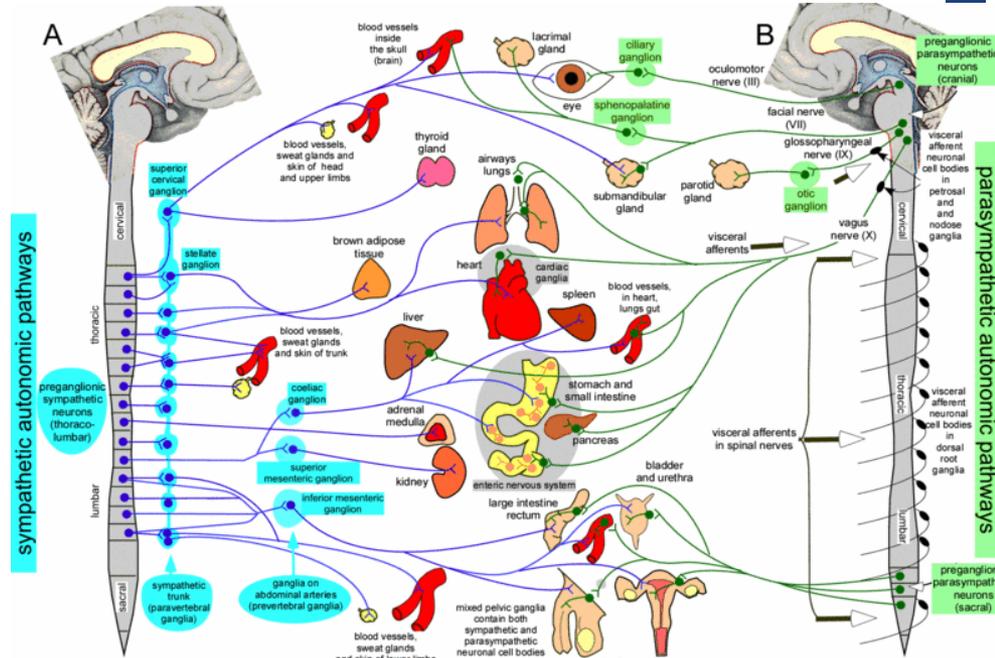


## At the end of this lecture, you will have

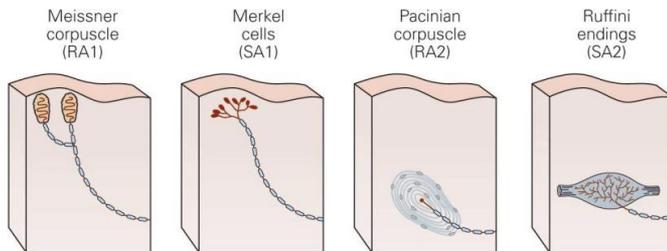
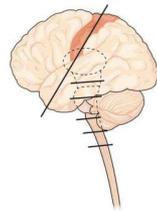
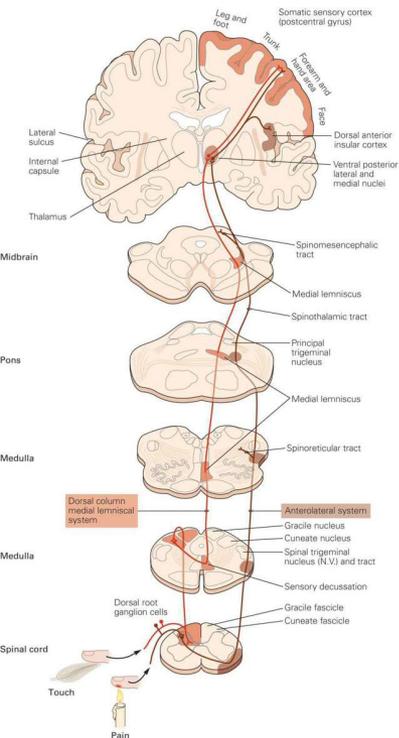
- knowledge about the peripheral nervous system and how it is leveraged in bioelectronic medicine to compensate for lost sensorimotor function, or regulate organ function
- understand how to create EM-electrophysiological nerve models for safety, effectivity, and efficiency assessment and optimization
- The exercise will revolve around modeling nerve recruitment and assessing selectivity and recording sensitivity

- Lecture Overview
- **The PNS, Bioelectronic Medicine, and the Role for Modeling**
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- Predicting Recruitment and Selectivity
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- Summary of Today's Lecture & Outlook

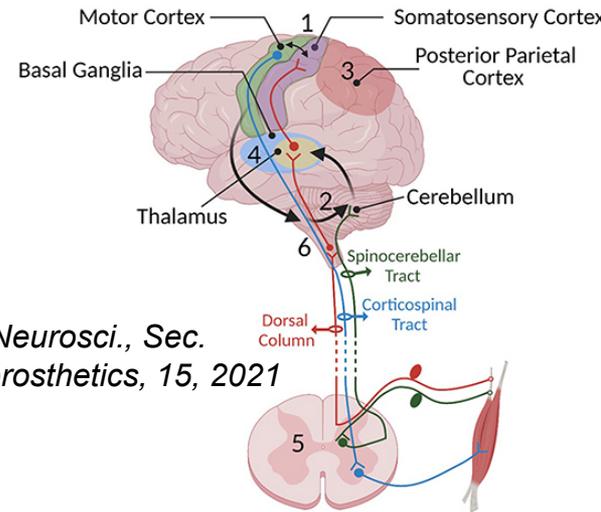
- autonomic PNS
  - regulate organ function
- sensorimotor PNS
  - somatosensory: exteroception, proprioception, (interoception)
  - motoric



[http://www.scholarpedia.org/article/File:Autonomic\\_nervous\\_system\\_main\\_figure\\_Blessing.gif](http://www.scholarpedia.org/article/File:Autonomic_nervous_system_main_figure_Blessing.gif)



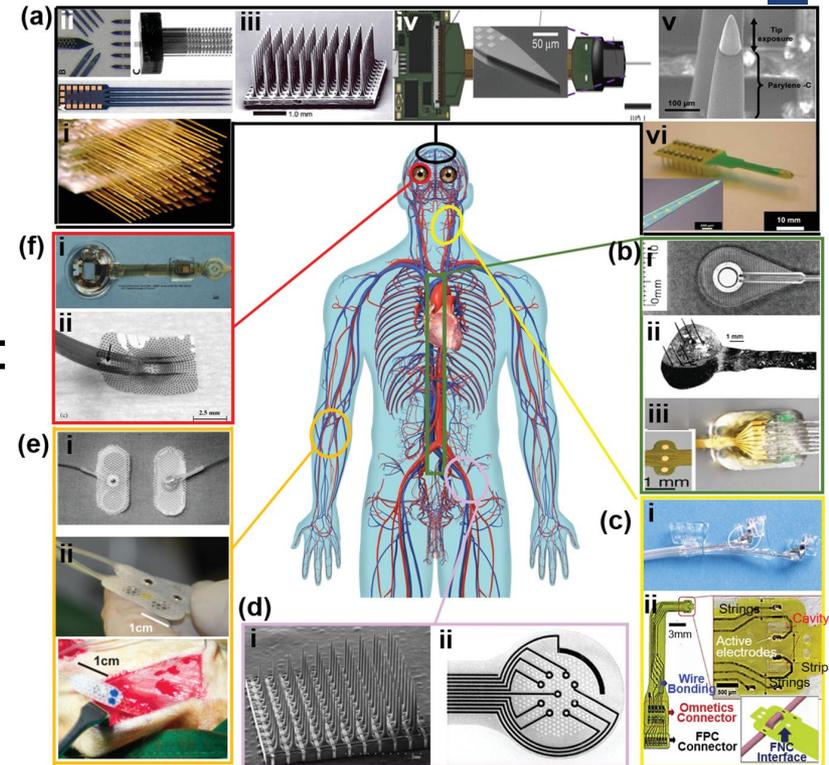
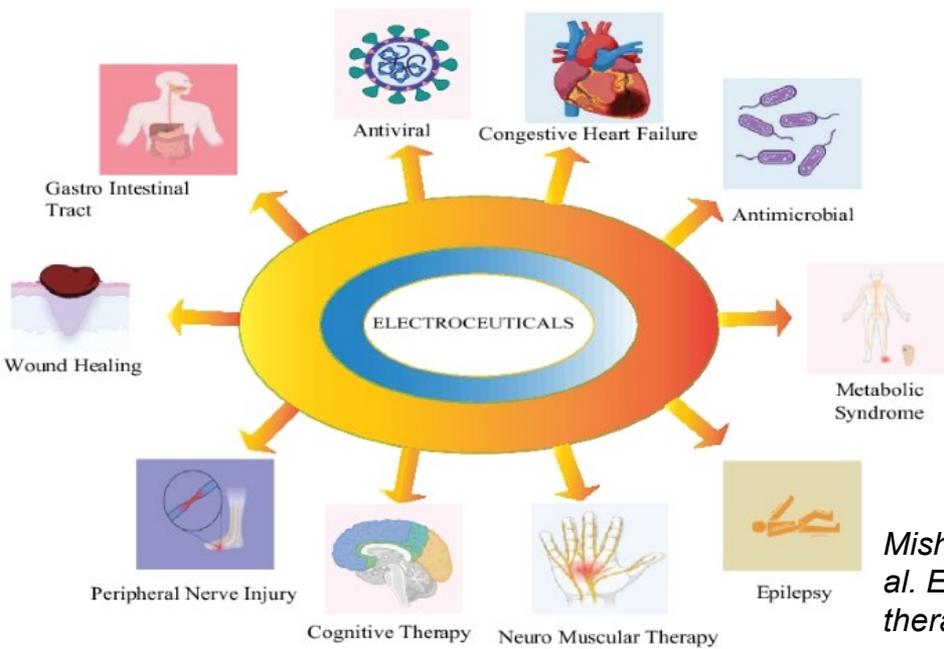
<https://neupsykey.com/the-somatosensory-system-receptors-and-central-pathways/>



Front. Neurosci., Sec. Neuroprosthetics, 15, 2021

interface with the

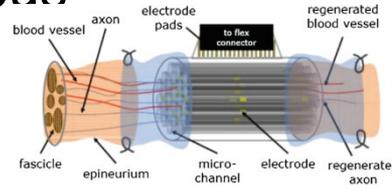
- autonomic PNS (electroceuticals):
  - for organ control: heart rate, diabetes, bladder control, inflammation...
- sensorimotor PNS (neuroprosthetics):
  - to replace lost sensory function: vision, audition, touch...
  - for motor control: locomotion...



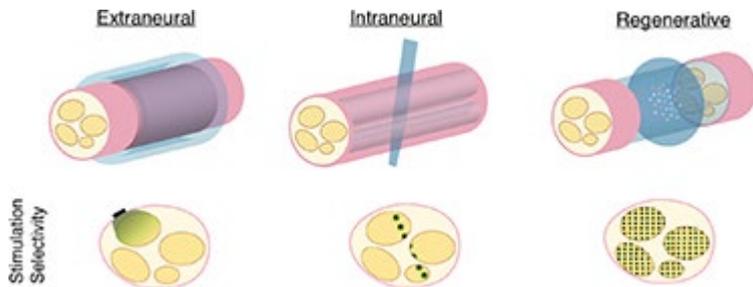
<https://advanced.onlinelibrary.wiley.com/doi/10.1002/adv.202004023>

Mishra, I., Chaudhary, K., Sharma, V. et al. Electroceuticals: Unlocking the promise of therapies. *DARU J Pharm Sci* 33, 7 (2025).

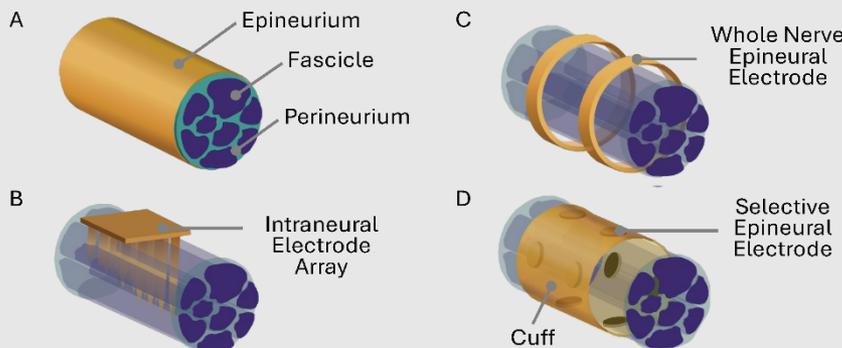
- Varying degrees of invasiveness
  - transcutaneous
  - epineural
  - intraneural
  - regenerative



- We'll talk another time about sensing

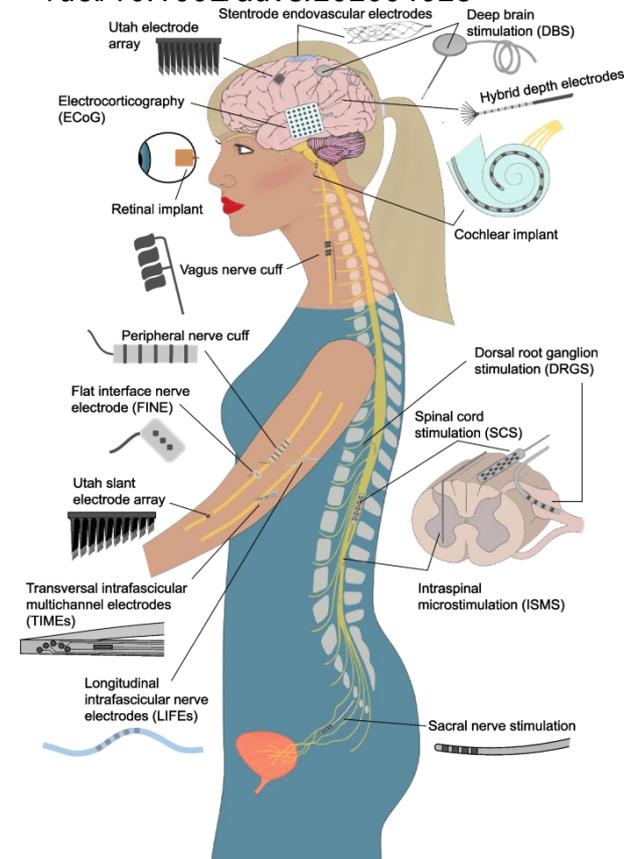


Valentina Paggi et al 2021 J. Neural Eng. 18 031001



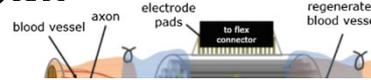
Riley, et al.. Micromachines 2024, 15, 1036

<https://advanced.onlinelibrary.wiley.com/doi/10.1002/adv.202004023>



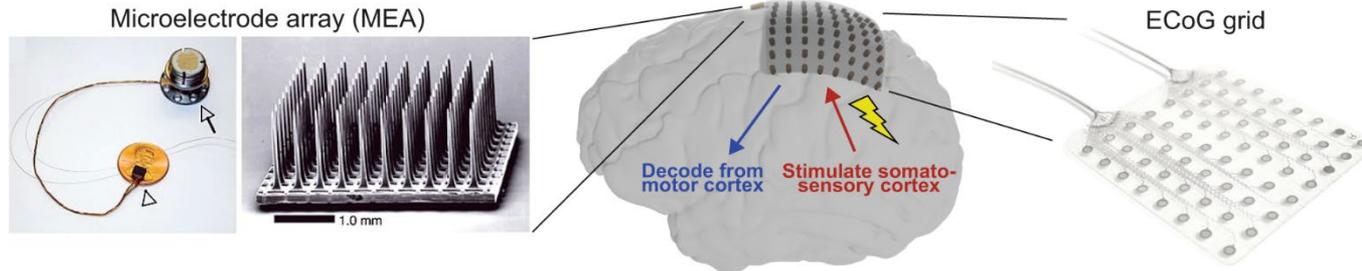
- Varying degrees of invasiveness

- transcutaneous
- epineural



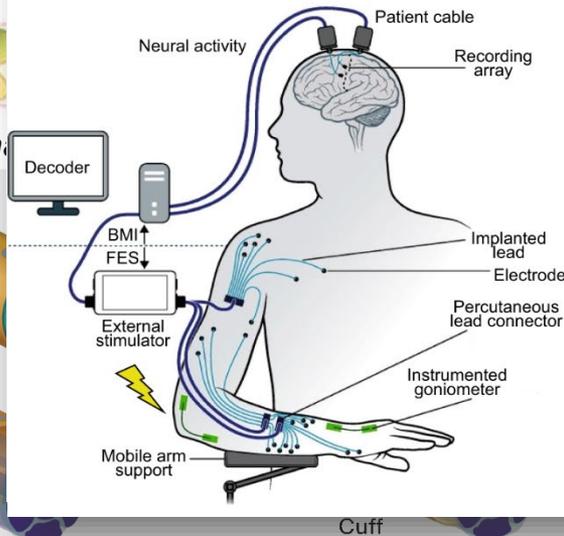
- Gupta, A., et al. *Neuroprosthetics: from sensorimotor to cognitive disorders. Comm Biol* 6, 14 (2023).

- a) Cortical implants for sensorimotor neuroprostheses

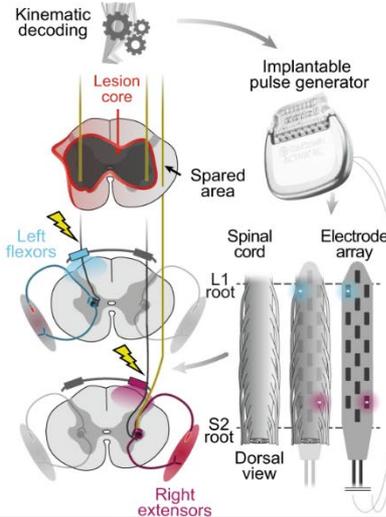


- b) Peripheral and spinal implants for sensorimotor neuroprostheses

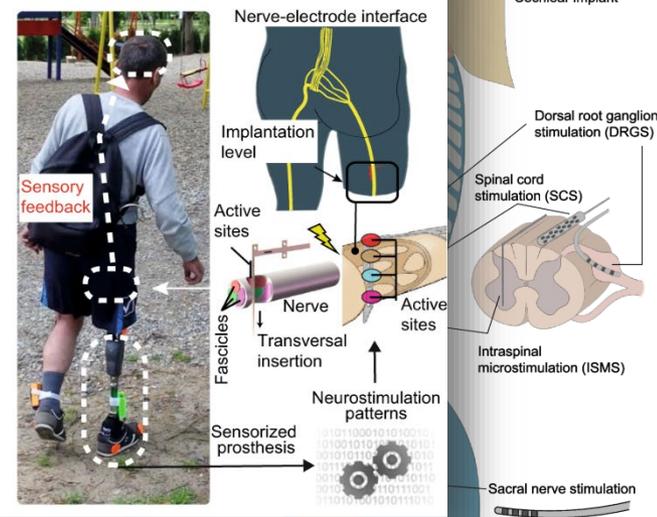
Functional Electrical Stimulation (FES)



Spinal Cord Stimulation (SCS)

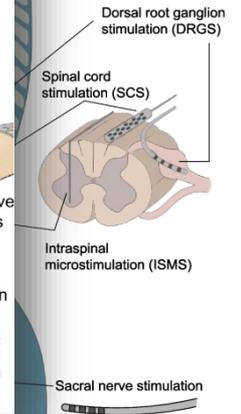
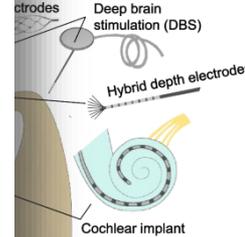


Peripheral Nerve Stimulation (PNS)



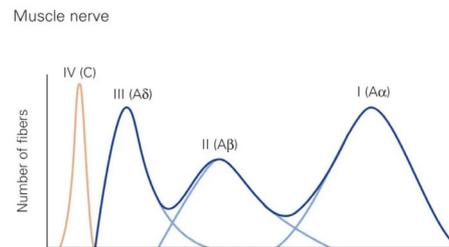
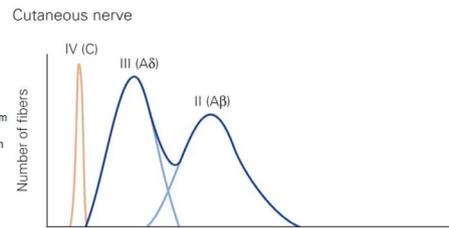
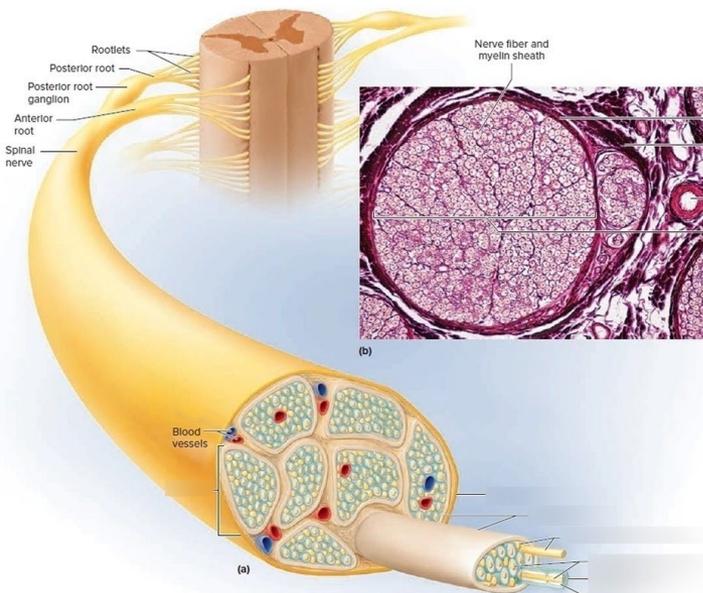
library.wiley.com

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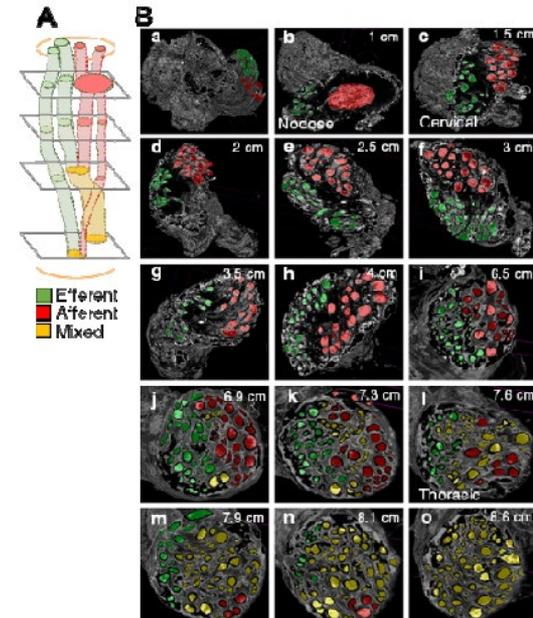


- complex nerves / neurovascular bundles combine fiber subpopulations with diverse function
  - closer to the muscle / end-organ, the organization get's simpler
  - fascicles merge and split
- nevertheless, there is topographic organization that can be elucidated (e.g., using viral tracing)

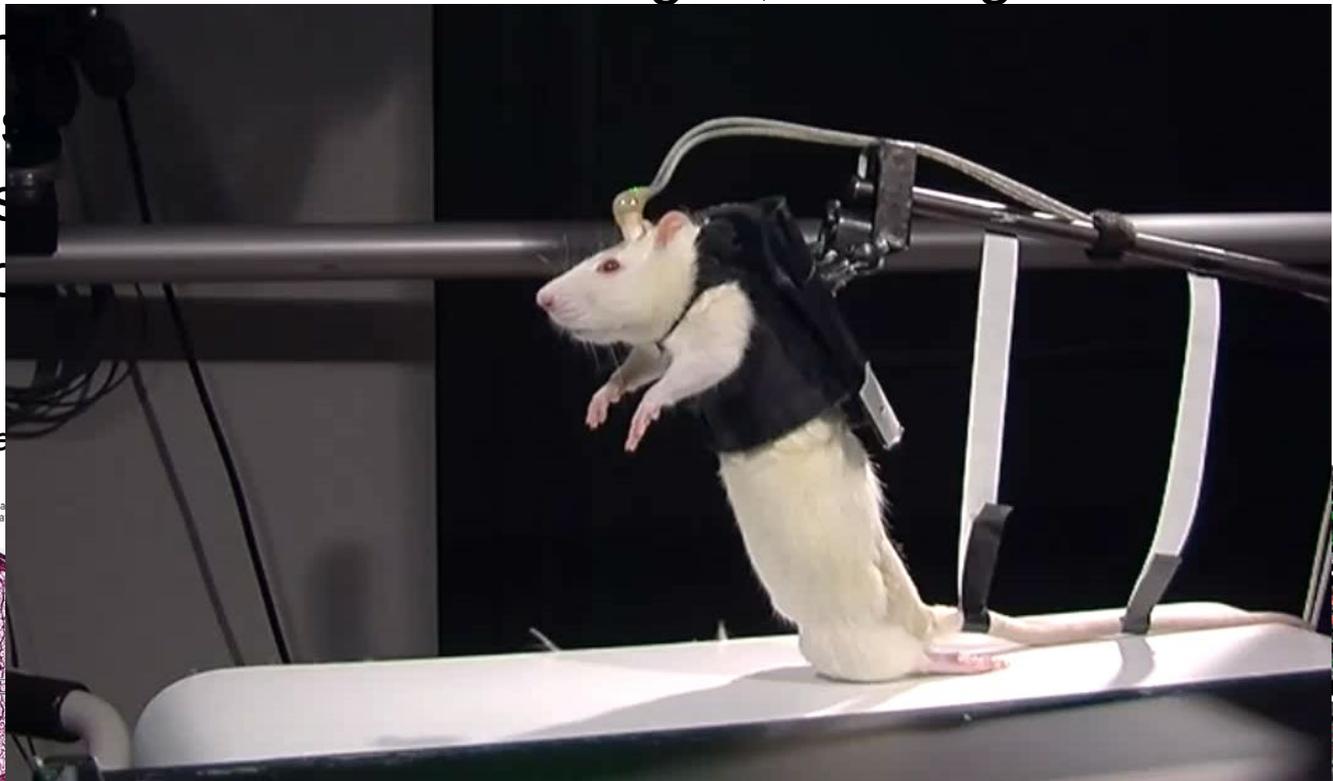
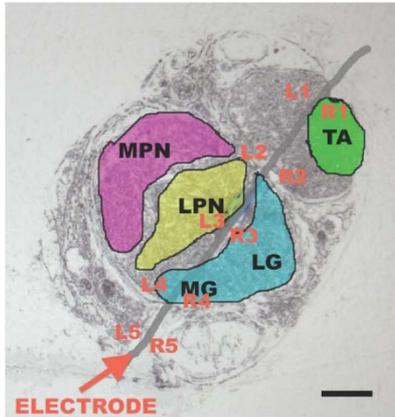
<https://neupsykey.com/the-somatosensory-system-receptors-and-central-pathways>



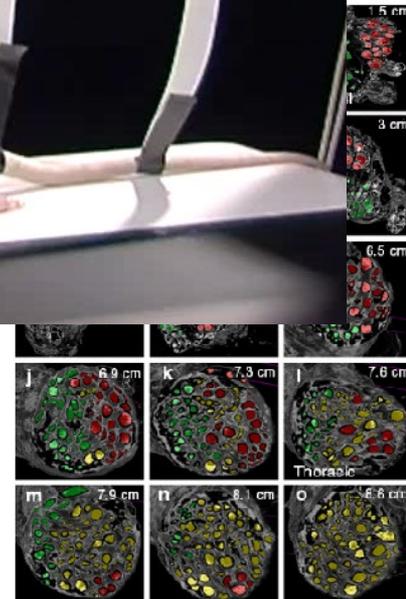
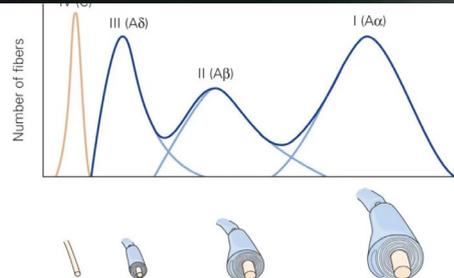
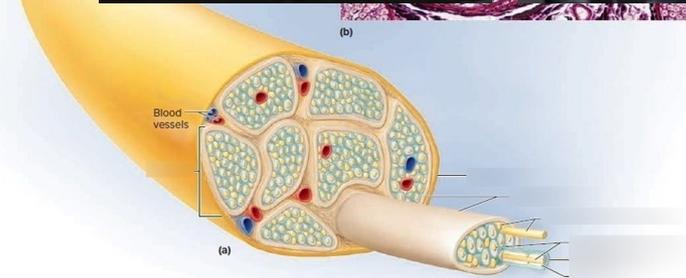
Jayaprakash, Naveen, et al.  
BioRxiv (2022): 2022-03.



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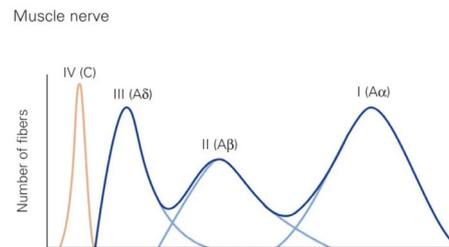
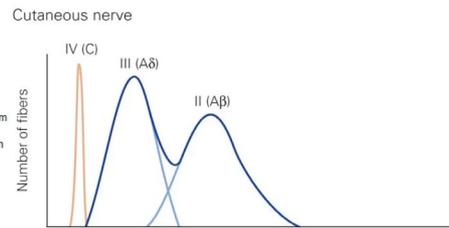
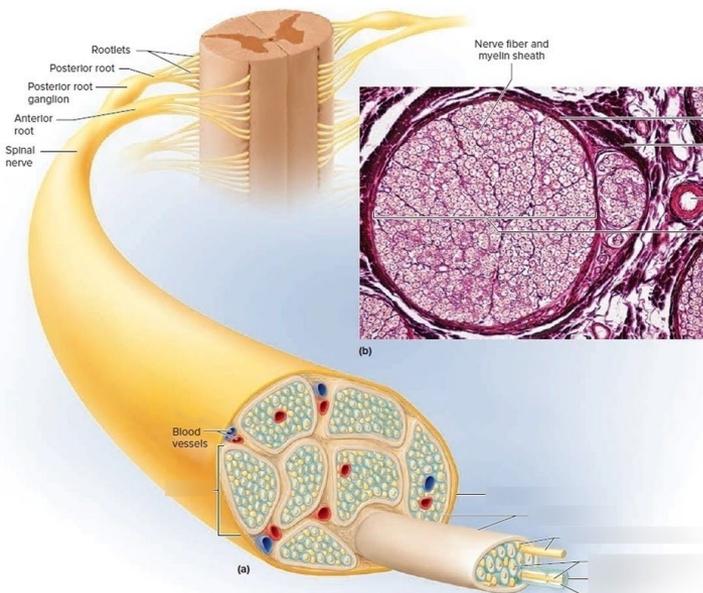


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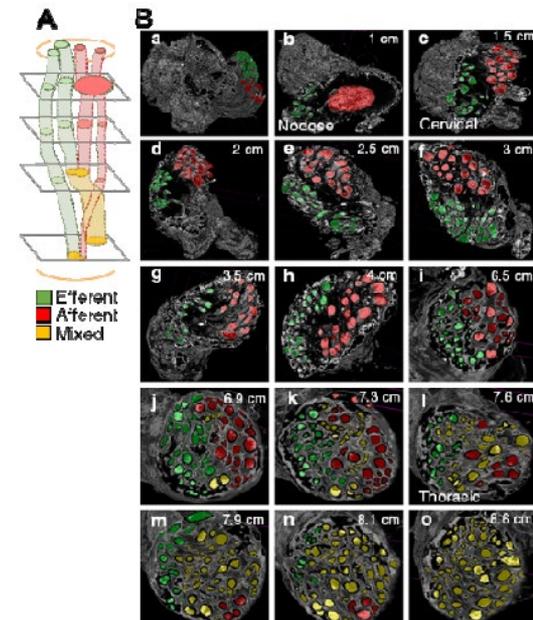


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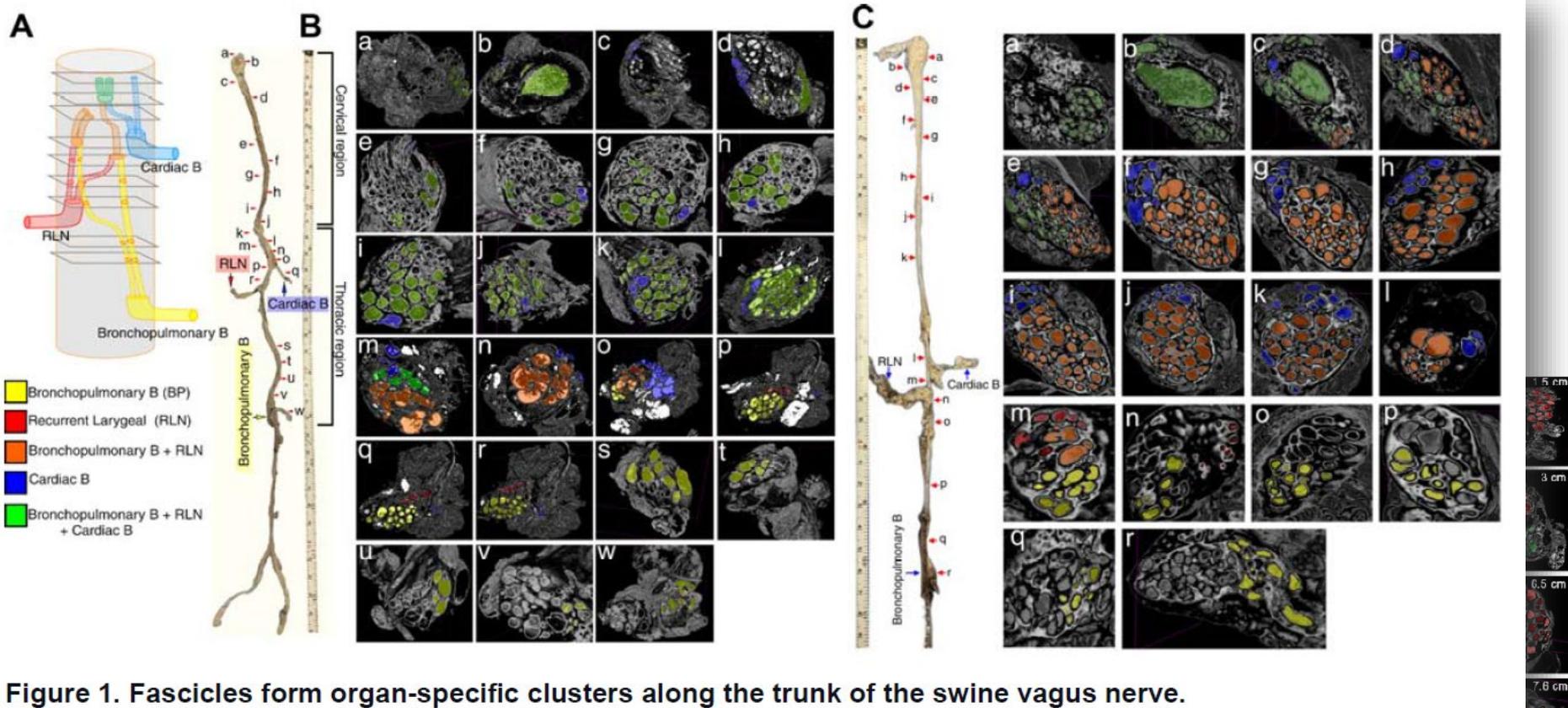
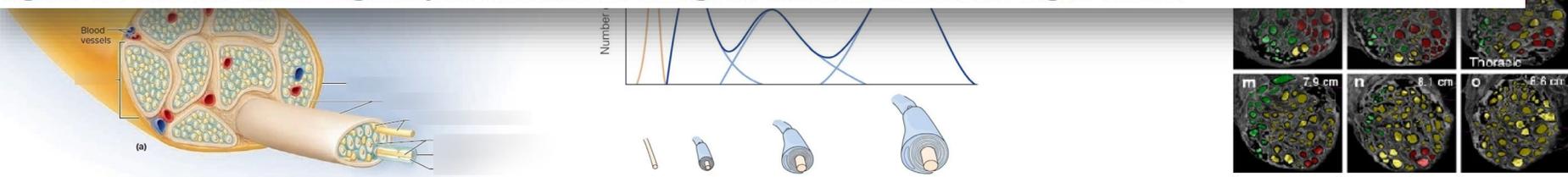


Figure 1. Fascicles form organ-specific clusters along the trunk of the swine vagus nerve.



- complex nerves / neurovascular bundles combine fiber

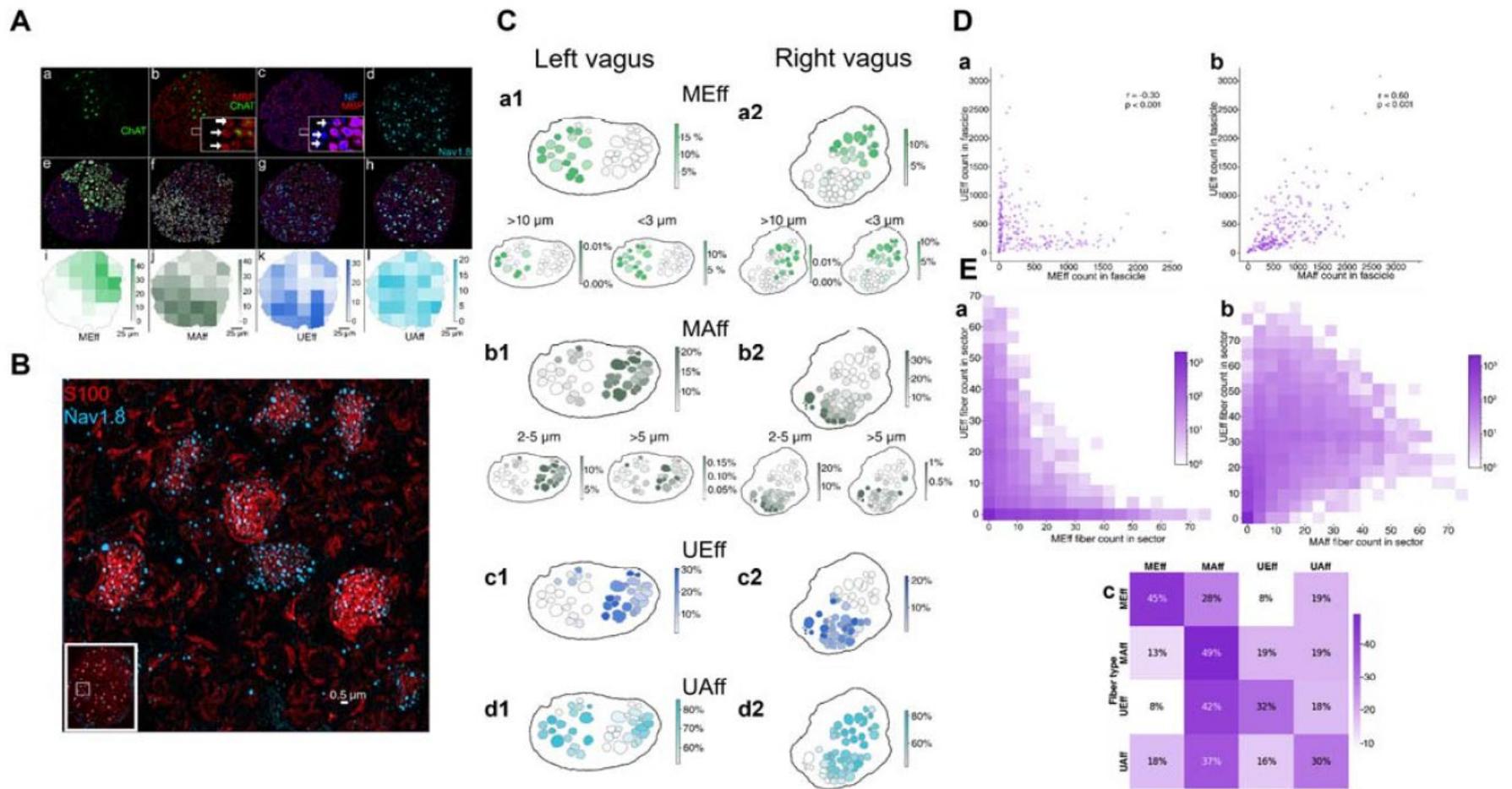
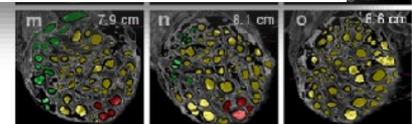


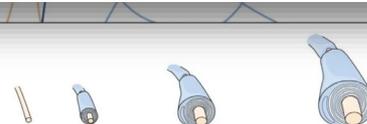
Figure 3. Morphologically distinct fiber types are organized across and within fascicles in the cervical vagus nerve of the swine in a specific, nonuniform pattern.

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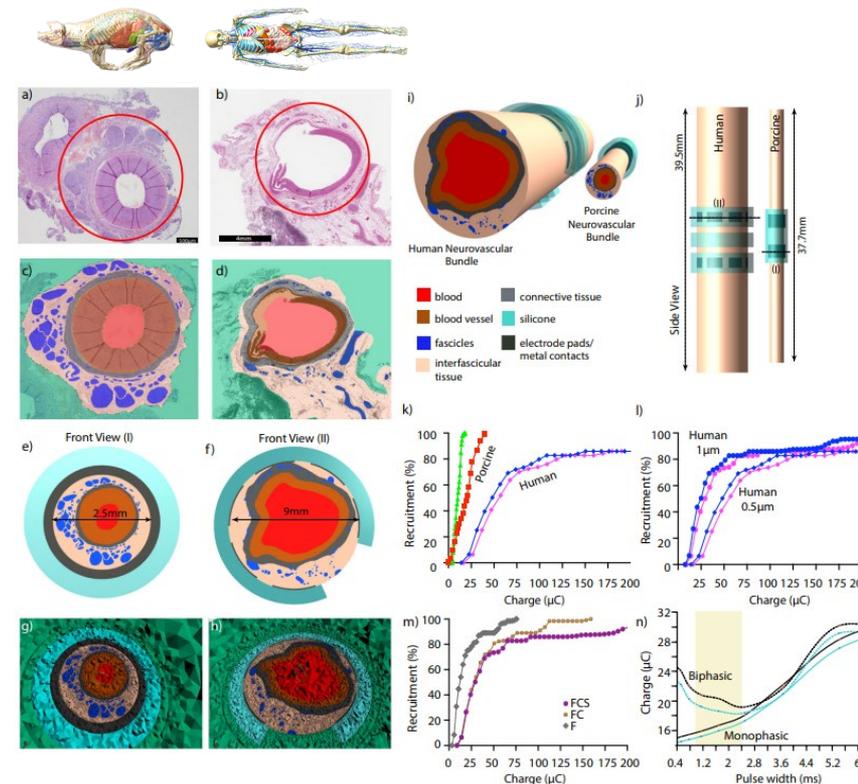
Poste gang  
Anterior root  
Spinal nerve



(a)



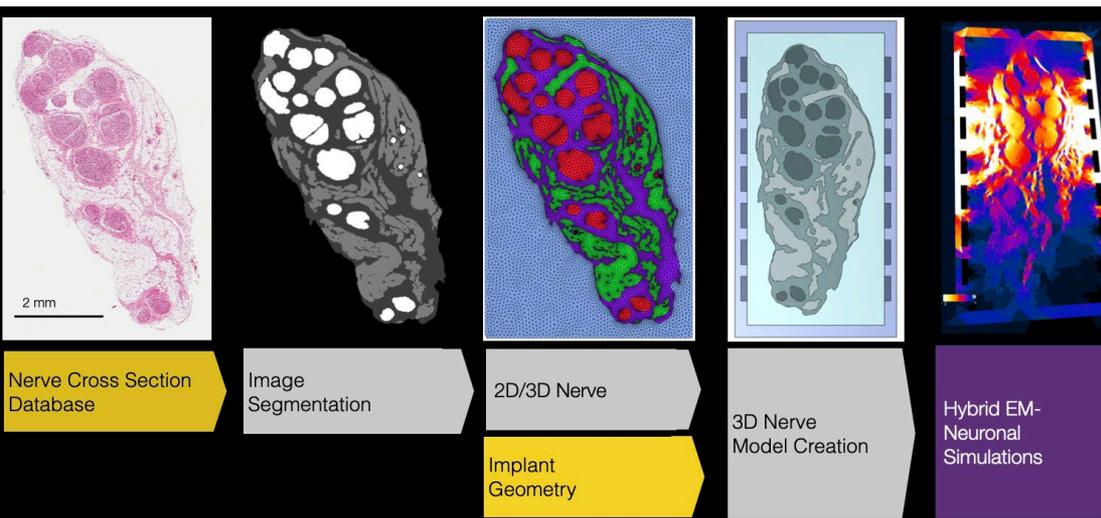
- analyse
  - insight beyond experimentally accessible, well controlled, dense information, visualization
- optimize
  - device design, performance, safety
- understand & troubleshoot
  - mechanism elucidation, problem identification
- reduce time-to-market
  - in silico* prototyping & testing
- perform trials
  - in silico* trials, reduce bench/animal/human trials
- personalize
  - image-based anatomy, patient specific properties/processes, treatment planning



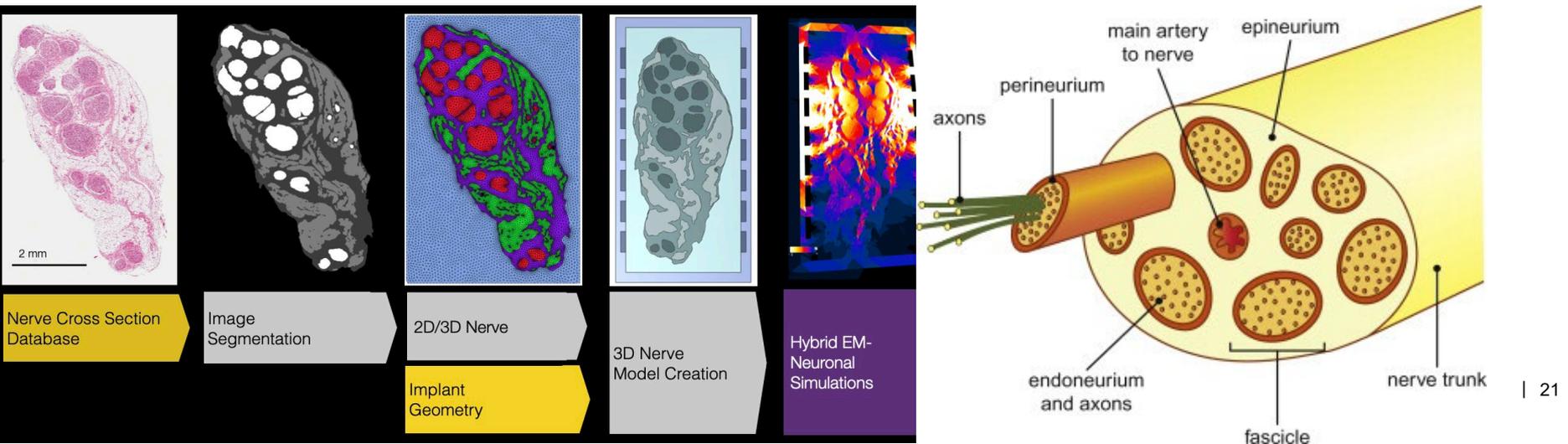
Gupta, Isha, et al. "Quantification of clinically applicable stimulation parameters for precision near-organ neuromodulation of human splenic nerves." *Communications biology* 3.1 (2020): 577.

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1. Segment histological image
2. 2D mesh
3. extrude
4. (integrate virtual perineurium as thin resistive layer)
5. integrate neural interface



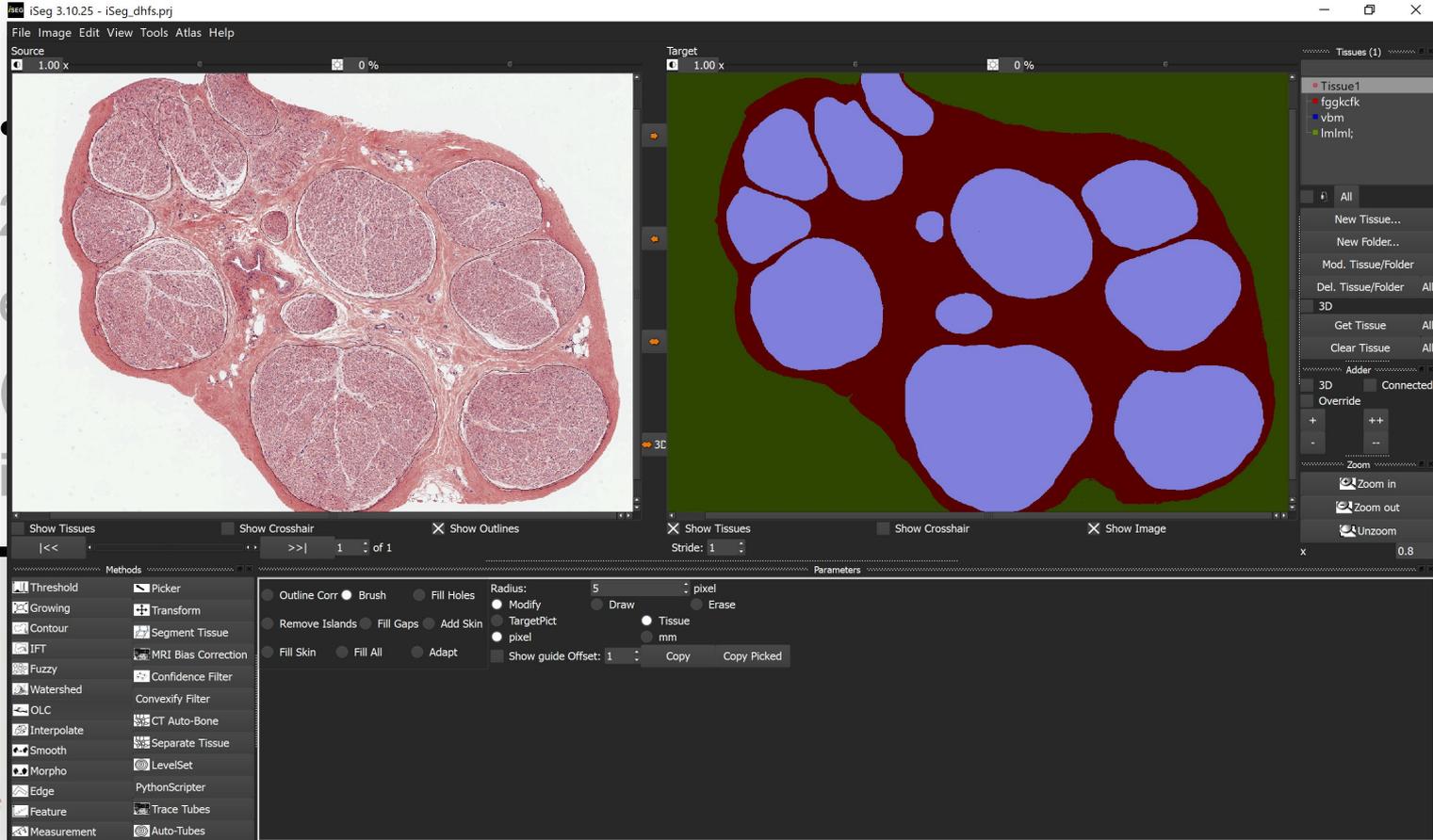
1. Segment histological image
  - fascicles, endoneurium, connective tissue, (perineurium), (vasculature)
  - general purpose segmentation tool or specialized AI
2. 2D mesh
3. extrude
4. (integrate virtual perineurium as thin resistive layer)
5. integrate neural interface



# 1. Segment histological image

- fascicles, endoneurium, connective tissue,

2.  
3.  
4.  
5.



Nerve Cross Section Database

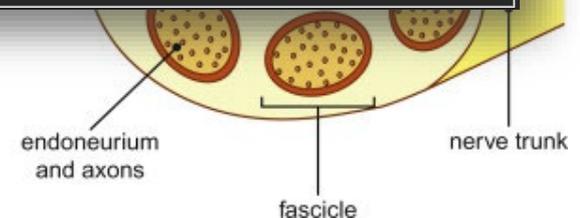
Image Segmentation

2D/3D Nerve

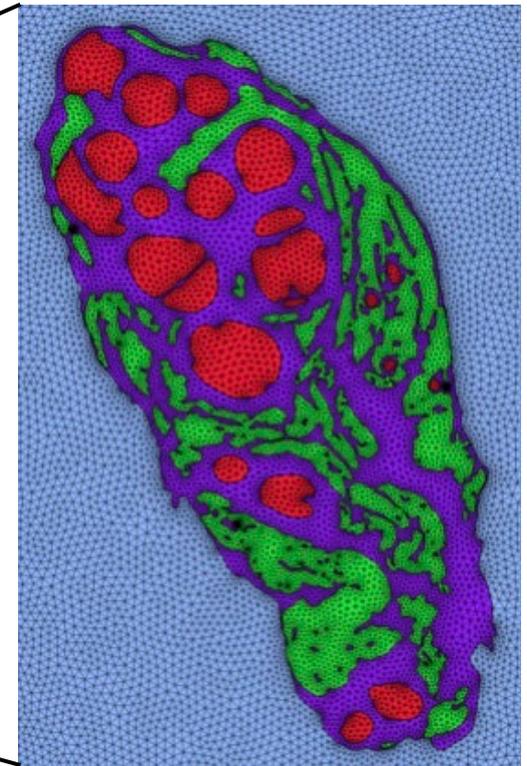
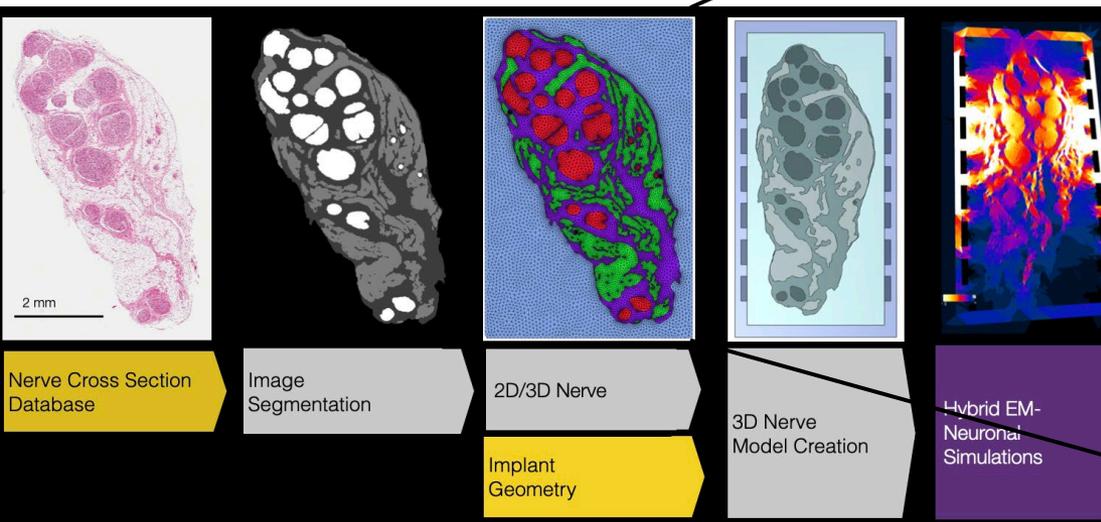
Implant Geometry

3D Nerve Model Creation

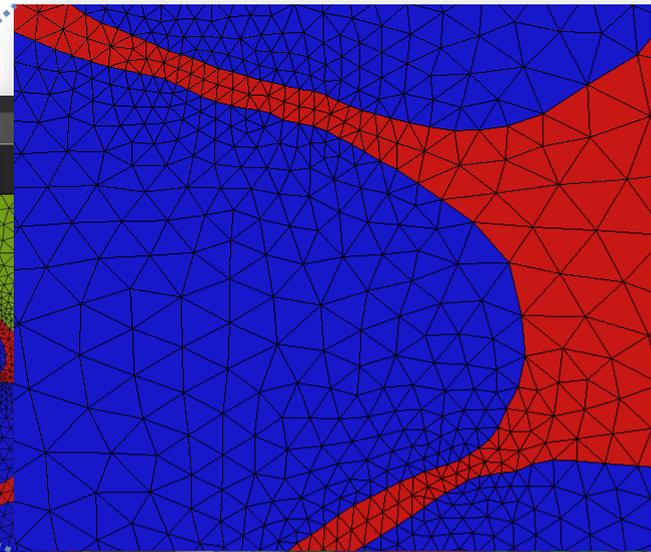
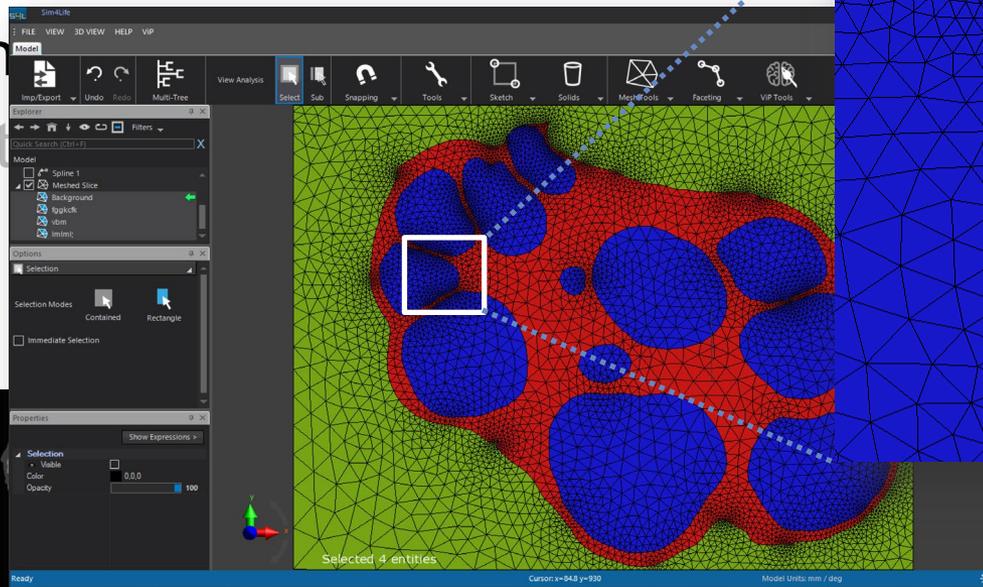
Hybrid EM-Neuronal Simulations



1. Segment histological image
2. 2D mesh
  - refine thin structures / interfaces
3. extrude
4. (integrate virtual perineurium as thin resistive layer)
5. integrate neural interface



1. Segment histological image
2. 2D mesh
  - refine thin structures / interfaces
3. extrude
4. (in)
5. int



Nerve Cross Section Database

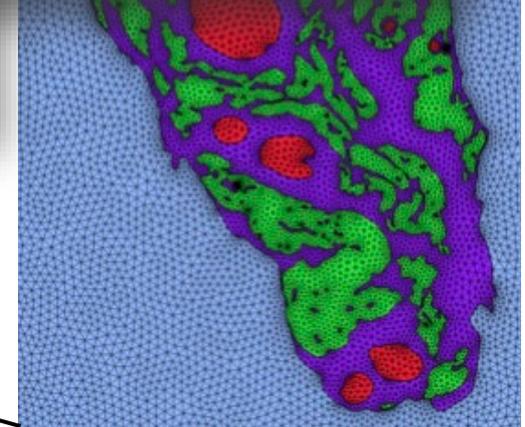
Image Segmentation

2D/3D Nerve

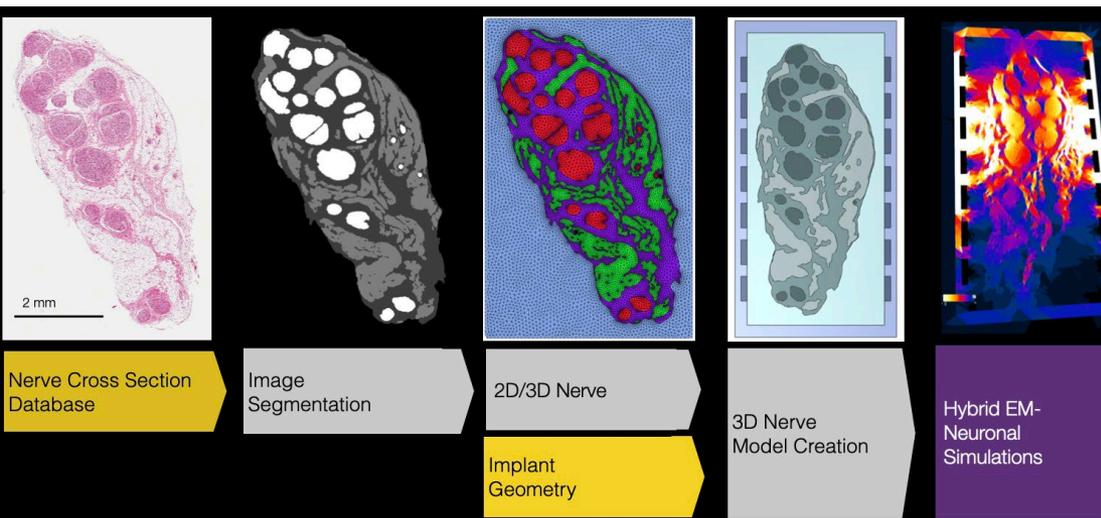
Implant Geometry

3D Nerve Model Creation

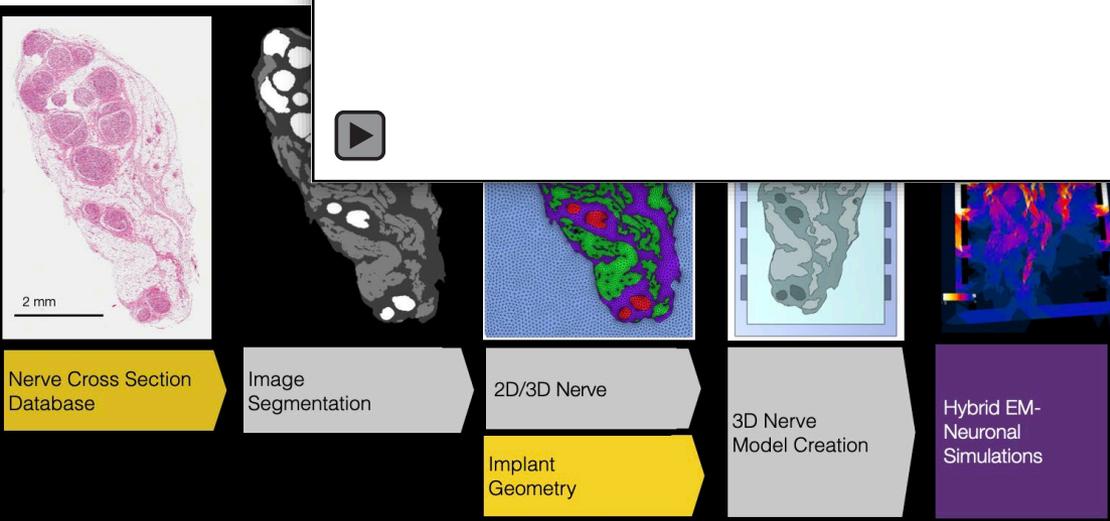
Hybrid EM-Neuronal Simulations



1. Segment histological image
2. 2D mesh
3. extrude
  - 3a. straight on homogeneous background
  - 3b. embed in anatomical environment (can be important current pathway, or affect safety predictions)
4. (integrate virtual perineurium as thin resistive layer)
5. integrate neural interface

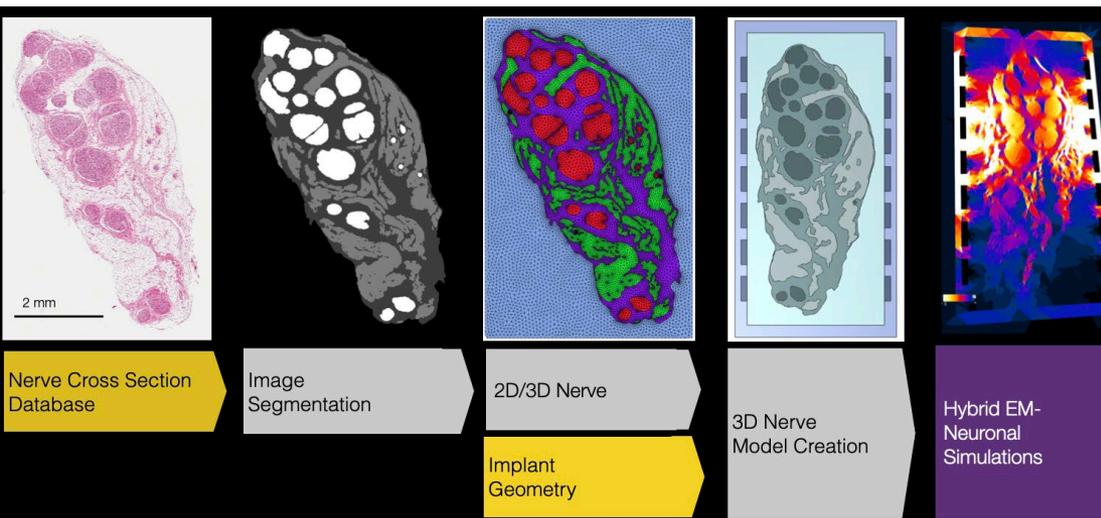


1. Segment histological image
2. 2D mesh
3. extr
  - 3a. s
  - 3b. c
4. (inte
5. inte

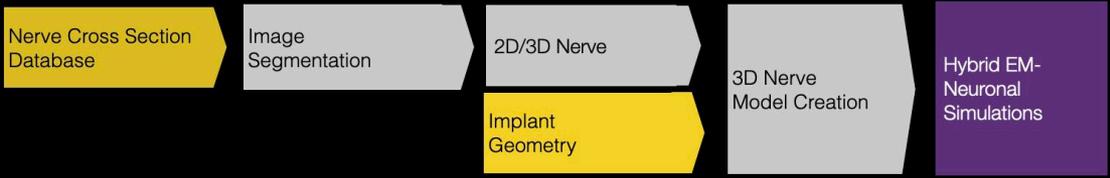
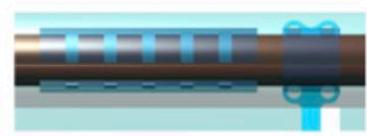
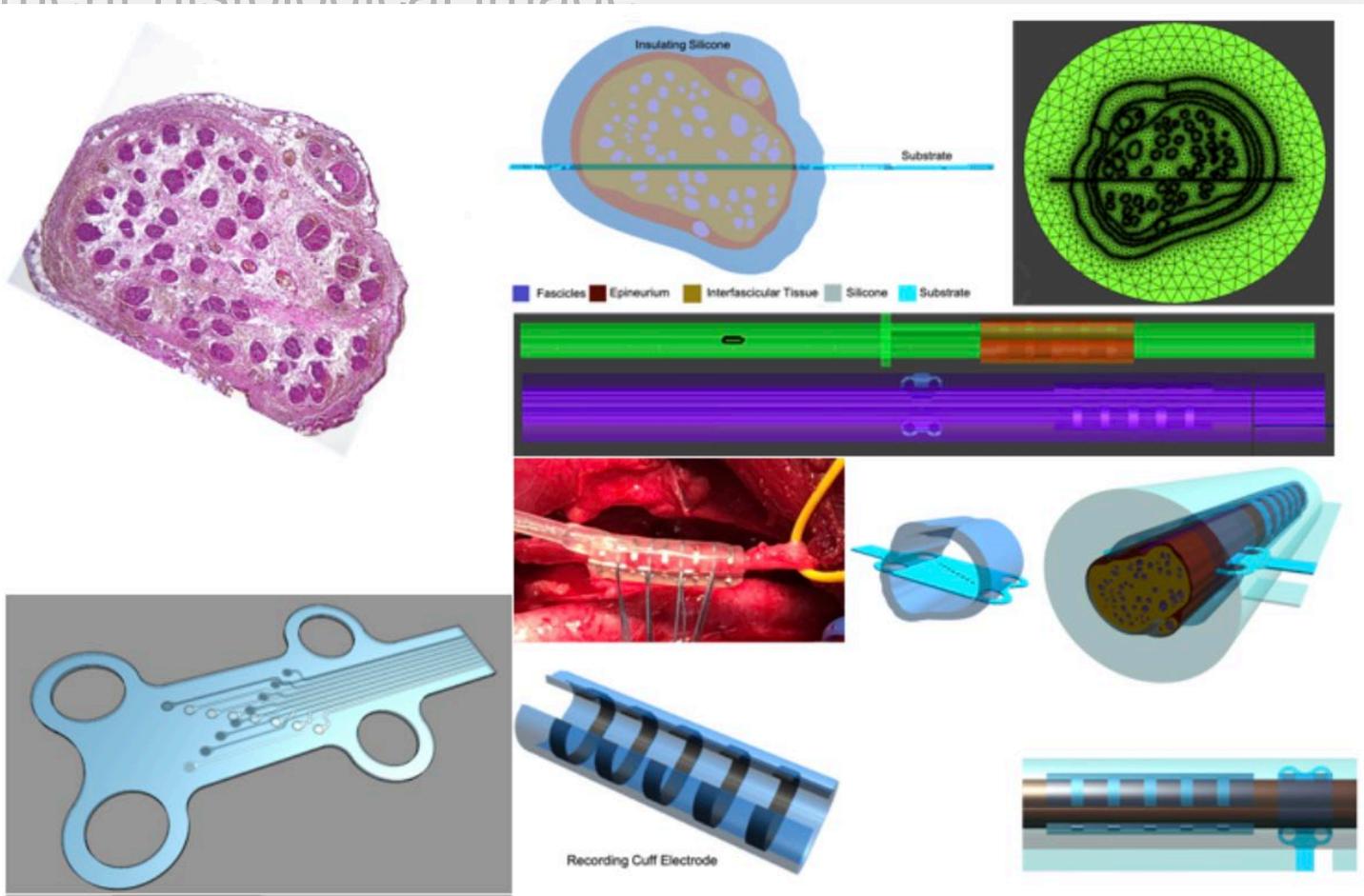


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1. Segment histological image
2. 2D mesh
3. extrude
4. (integrate virtual perineurium as thin resistive layer)
5. integrate neural interface
  - CAD tools: projection, boolean...
  - meshing tools: feature preserving CAD meshing, mesh merging, mesh quality improvement

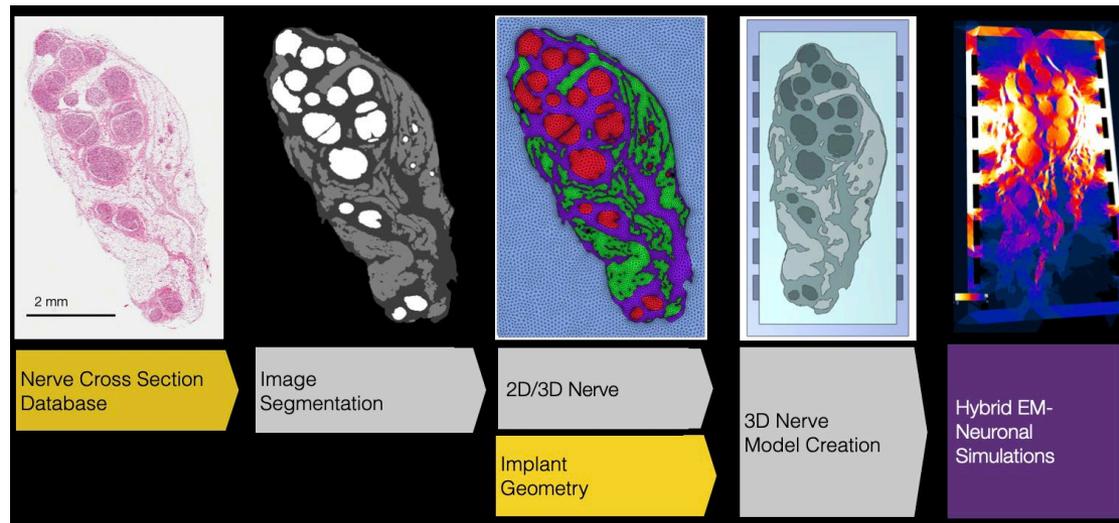


1. Segment histological image
2. 2D
3. extr
4. (inte
5. inte



1. assign tissue properties
    - IT'IS Tissue Properties DB
  2. assign boundary conditions
    - Dirichlet followed by current normalization
    - electrode tissue interface impact on waveform
  3. solve EQS
    - perform convergence analysis (solver, meshing)
- (see last week's lecture about the above)

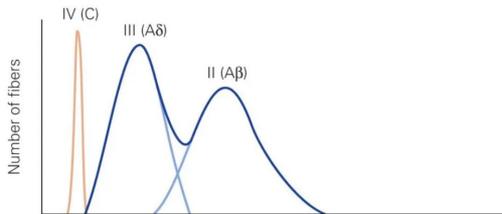
1. quantify uncertainty
  - see later lecture



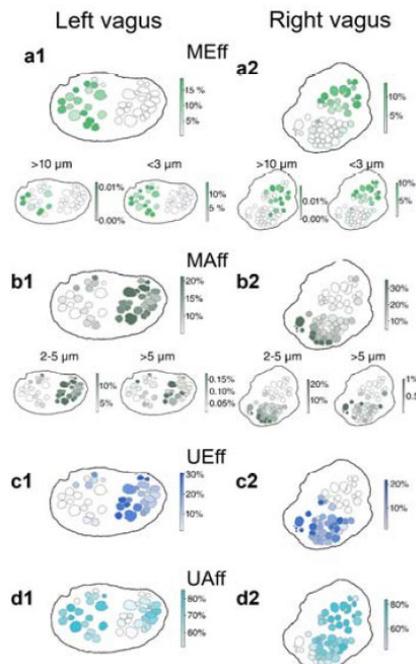
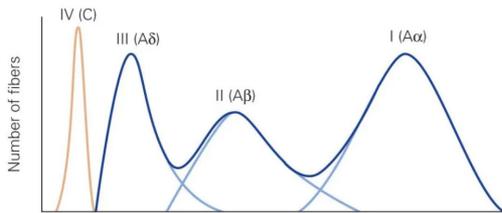
1. determine fiber population statistics
2. insert spline trajectories
3. assign electrophysiological fiber models (compartment discretization & electrophysiology)
4. couple with EM
5. solve differential equations

- determine fiber population statistics
  - histology, tracing...
- insert spline trajectories
- assign electrophysiological fiber models (compartment discretization & electrophysiology)
- couple with EM
- solve differential equations

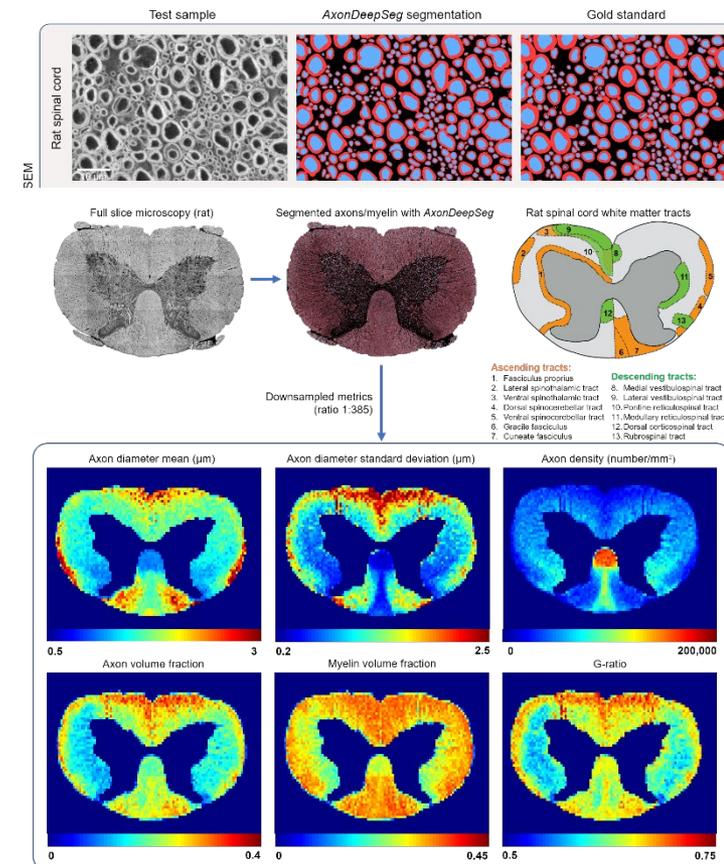
Cutaneous nerve



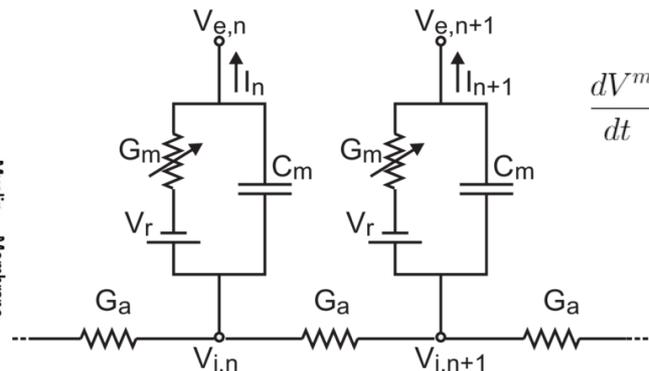
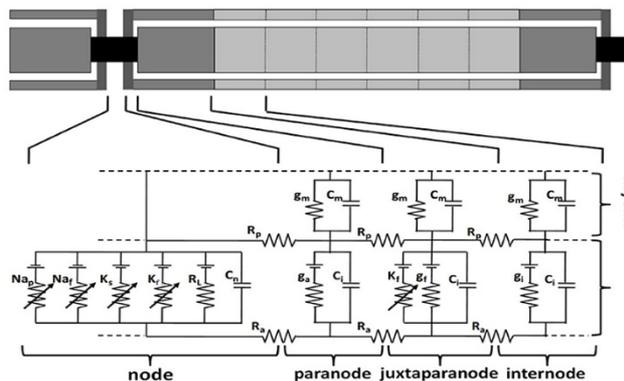
Muscle nerve



<https://axondeepseg.readthedocs.io/en/latest/>



1. determine fiber population statistics
2. insert spline trajectories
  - extrusion of AxonSeg / sampled locations
3. assign electrophysiological fiber models (compartment discretization & electrophysiology)
4. couple with EM
  - ensure interpolation is smooth to avoid EM discretization related AF peaks
5. solve differential equations



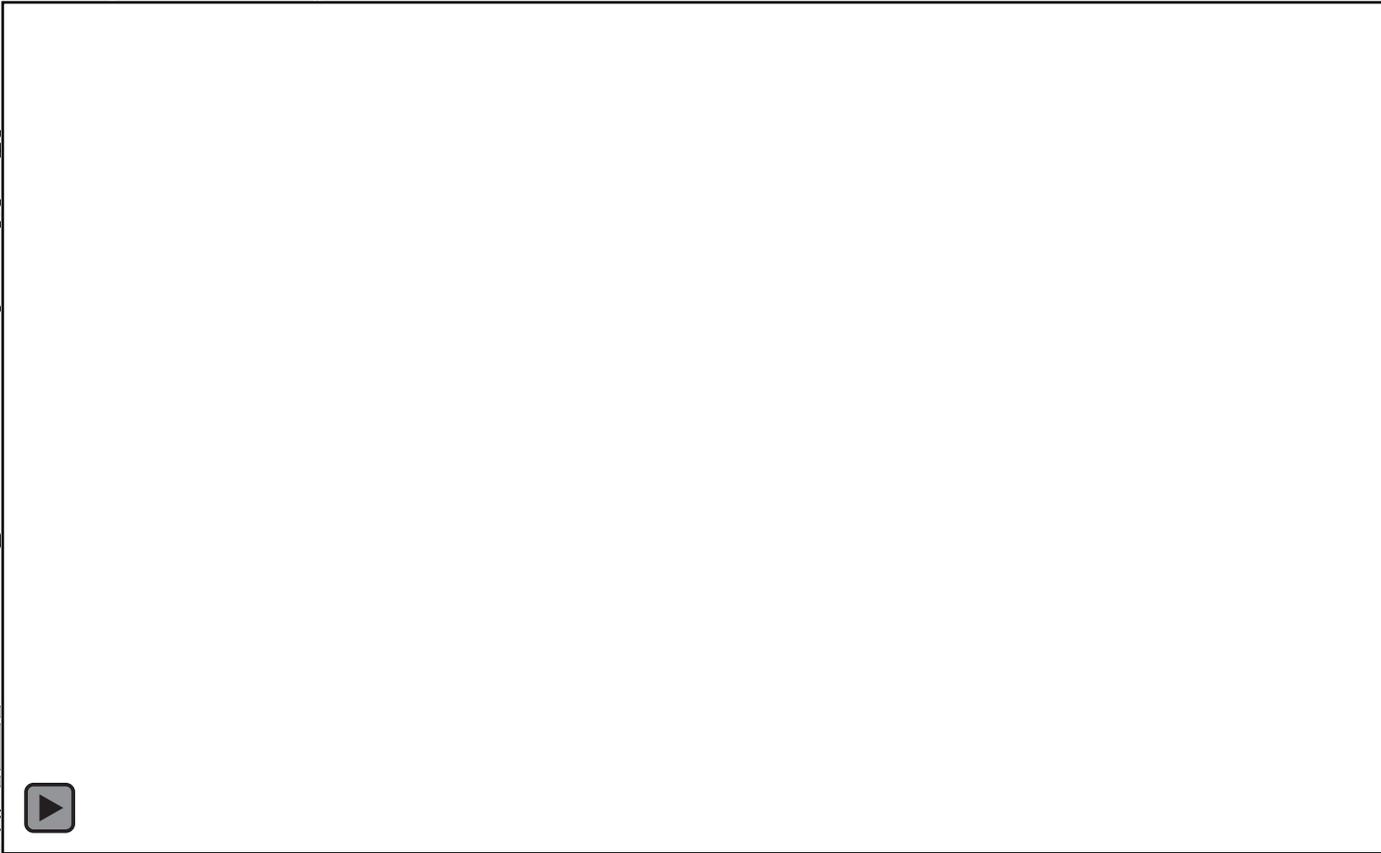
$$\frac{dV^m}{dt} = - \left( I^{active} + g^{lk} \cdot (V^m - E^{lk}) + \sum_n I_n^{int} \right) / c$$

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

$$E^i = V^m + V^e$$

1. determine fiber population statistics
2. insert spline trajectories

- 
- 3. assign
- diso
- 4. cou
- 
- 5. solve

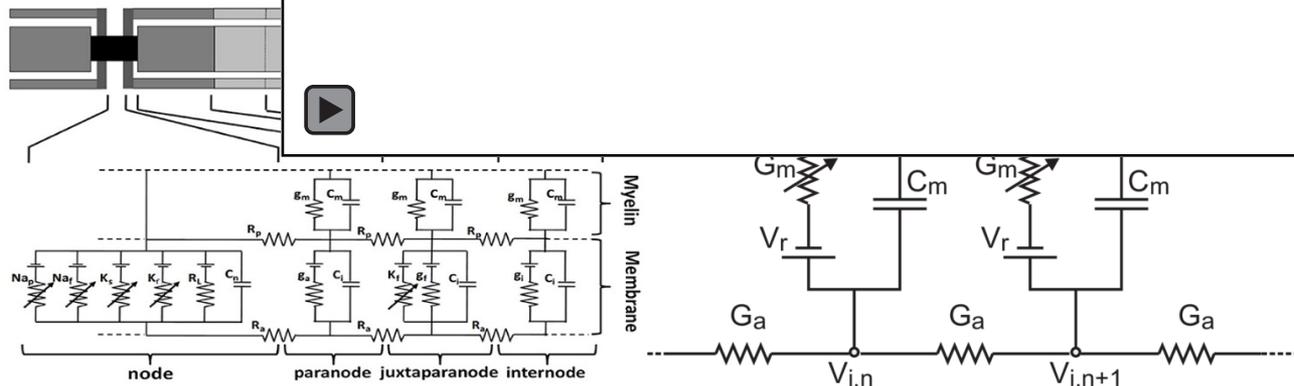


tion

$$\left( E^{lk} + \sum_n I_n^{int} \right) / c$$

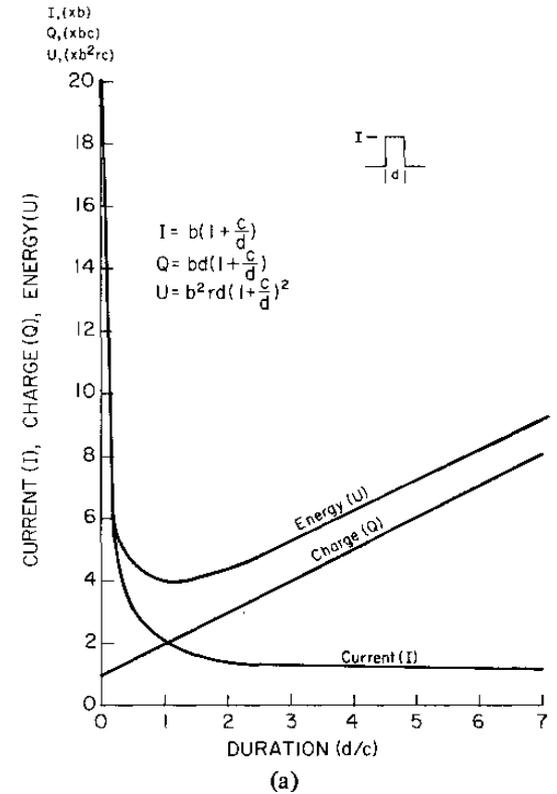
$$I_n^{int} = \frac{E_k^i - E_n^i}{(R_k + R_n)/2}$$

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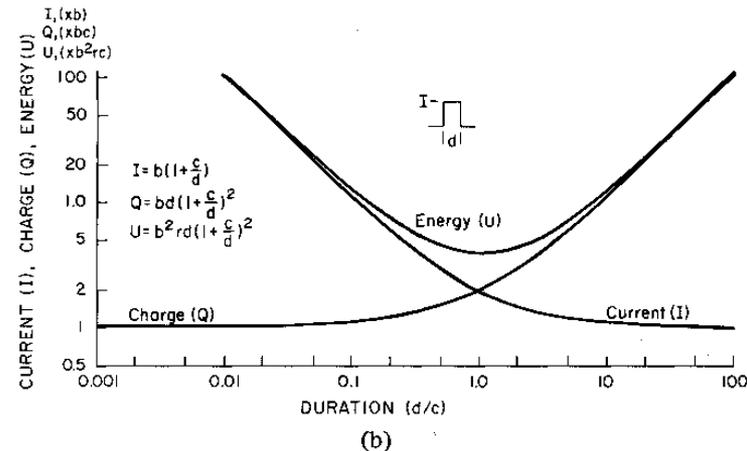
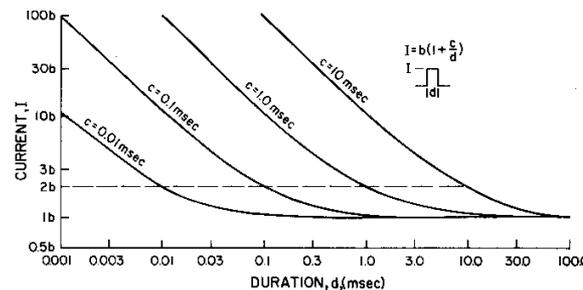
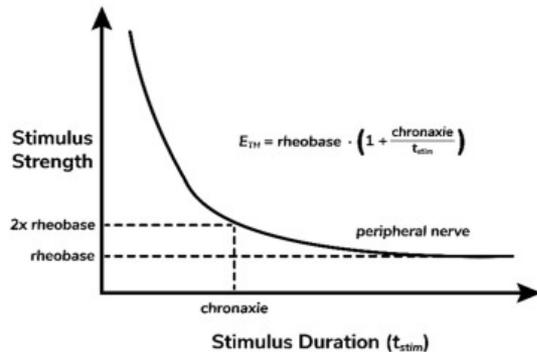


- Lecture Overview
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- **Predicting Recruitment and Selectivity**
- Balancing Safety, Effectivity, and Efficiency
- Summary of Today's Lecture & Outlook

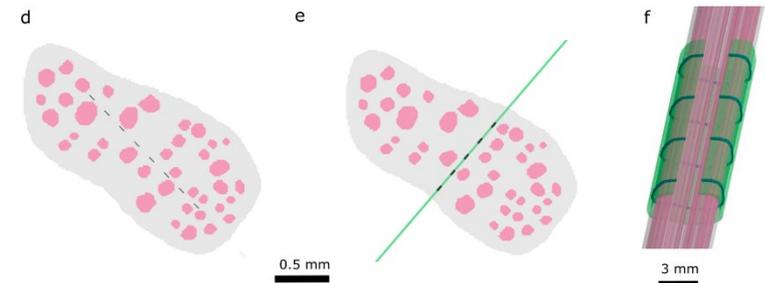
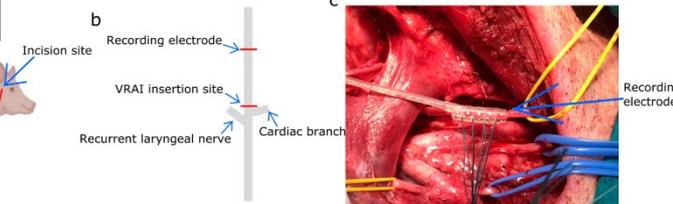
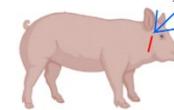
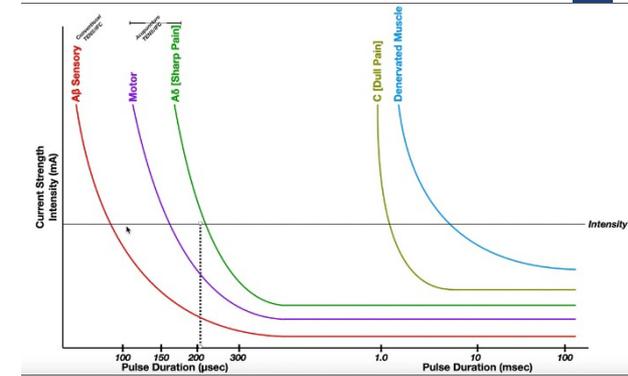
- pulse duration dependence of stimulation threshold
  - short pulses: charge limited
  - long pulses: leakage limited
  - transition: membrane time constant
- terminology: chronaxie, rheobase
- titration to determine threshold



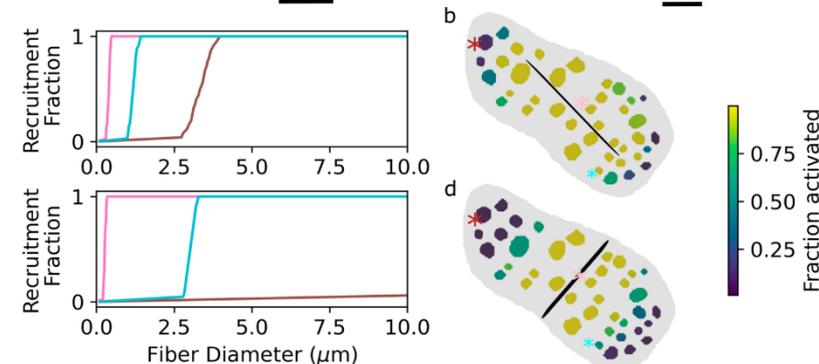
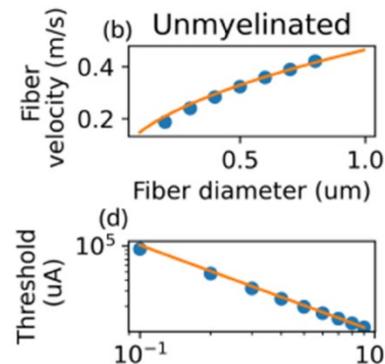
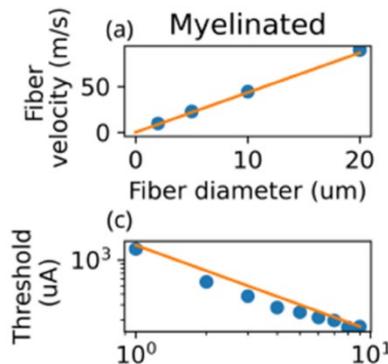
Geddes, Bourland. "The Strength-Duration Curve." IEEE Trans. Biomed. Eng. 32 (1985)



- factors affecting threshold
  - perineurium thickness (fascicle size; AF reduction through insulation & potential smoothing)
  - electrode distance (field magnitude)
  - fiber diameter (stimulability)

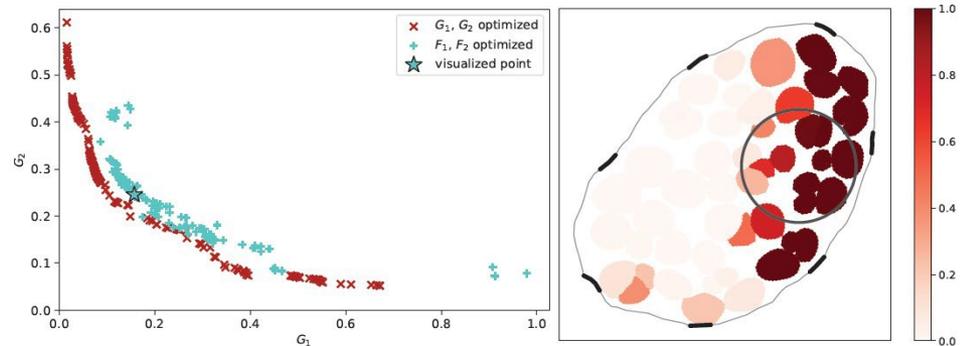
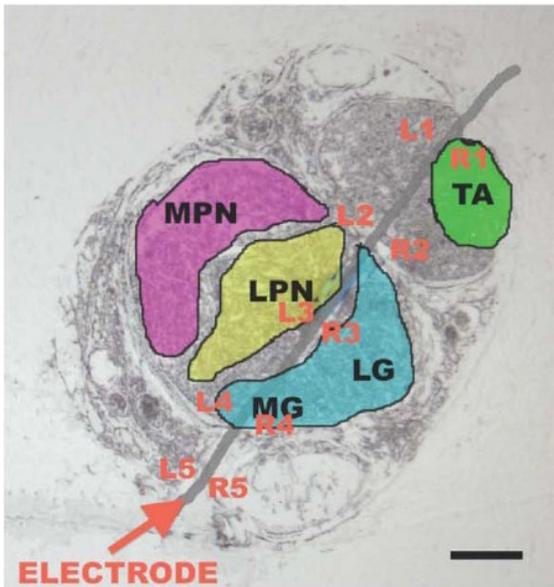
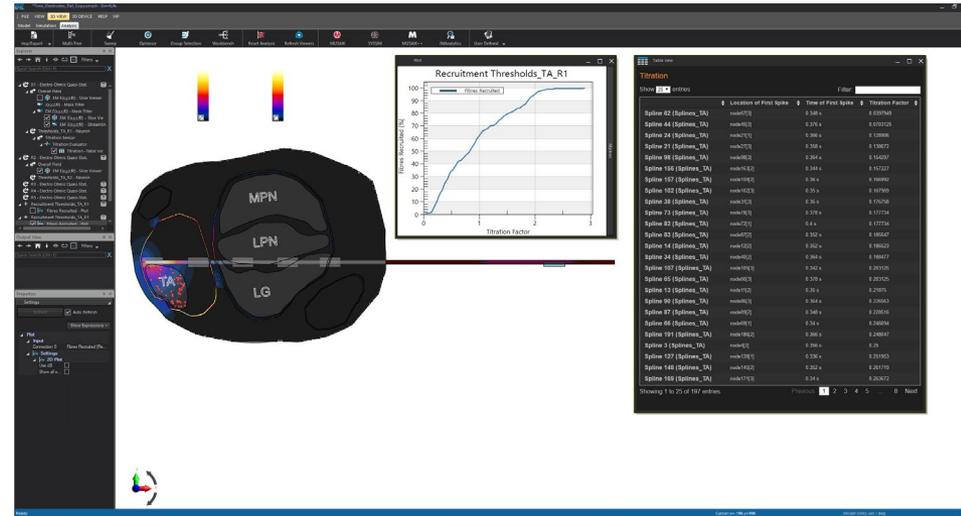


Tharayil, et al. "Simulation insights on the compound action potential in multifascicular nerves." *PLoS Computational Biology* 21.9 (2025)



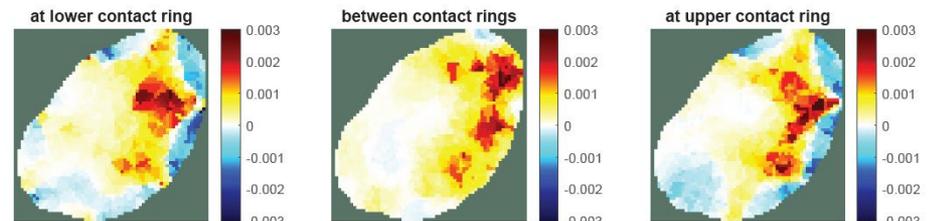
- optimize stimulation selectivity to
  - maximize effectivity
  - minimize off-target stimulation

$$Sel_i = \mu_i - \frac{1}{m-1} \sum_{j=1, j \neq i}^m \mu_j$$



(a) Pareto Fronts

(b) Fascicle Activation Levels

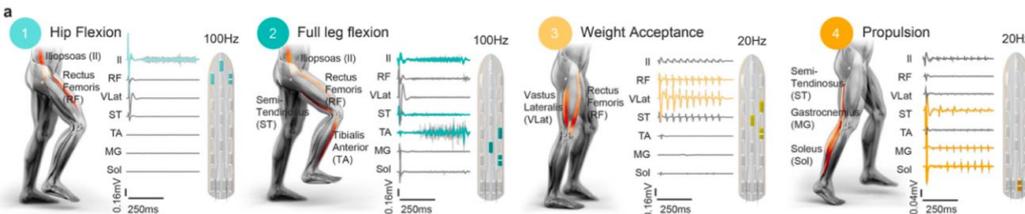


(c) EIT reconstruction of conductivity change (in S/m)

Raspopovic, et. al. *IEEE Trans. Neural Systems and Rehabilitation Engineering* 19.4 (2011): 333-344.

- optimize stimulation selectivity to
  - maximize effectivity
  - minimize off-target stimulation

Rowald, Andreas, et al. Nature medicine 28.2 (2022): 260-271



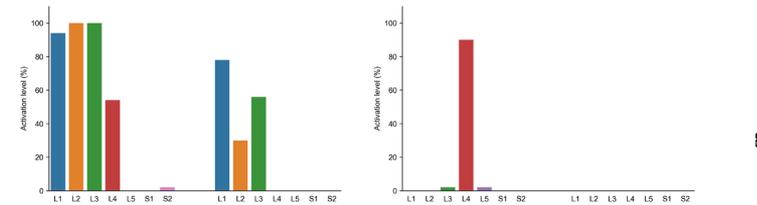
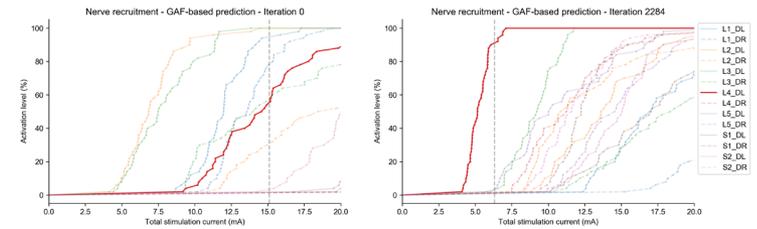
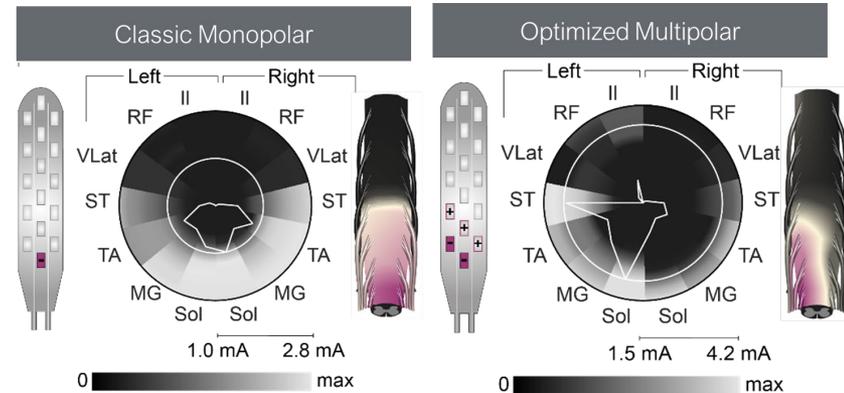
$SI_{computational}(r_i, I)$  for each root  $r_i$  and each stimulation amplitude  $I$ :

$$SI_{computational}(r_i, I) = \frac{A_{r_i}(I)}{1 + \sum_{\text{Other ipsilateral roots}} A_{r_j}(I)} \cdot f_+ \left( \frac{A_{r_i}(I) - A_{r_{contralateral(i)}}(I)}{A_{r_i}(I) + A_{r_{contralateral(i)}}(I)} \right)$$

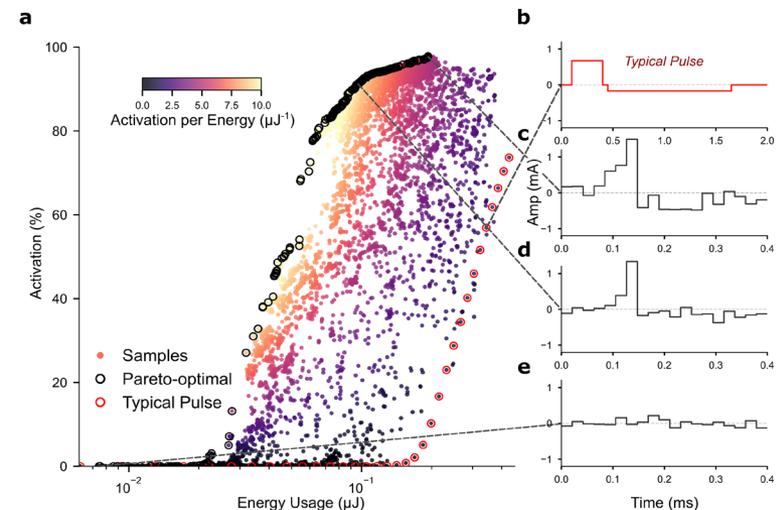
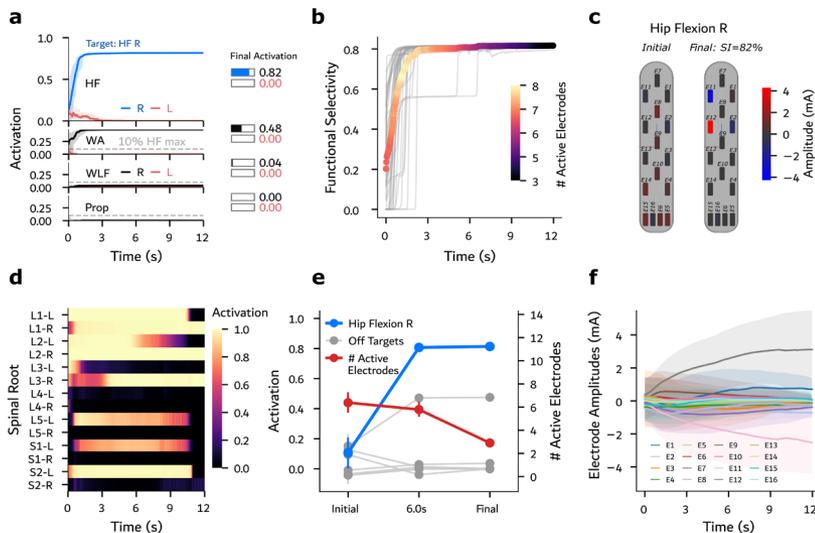
where  $A_{r_i}(I)$  represents the percentage of fibers activated in root  $r_i$ ,  $r_{contralateral(i)}$  is the root contralateral to root  $r_i$ , and  $f_+(x) = \begin{cases} x & \text{if } x > 0 \\ 0 & \text{if } x \leq 0 \end{cases}$ .

$$SI_{functionality}(g_i, I) = SI_{targeted\ muscles}(g_i, I) \cdot SI_{left\ vs\ right}(s_i, I)$$

$$\left\{ \begin{aligned} SI_{targeted\ muscles}(g_i, I) &= f_+ \left( \frac{\sum_{\text{muscles in } g_i} \omega_{i,j} \cdot \log(1 + A_j(I))}{\log 2} \right) \\ SI_{left\ vs\ right}(s_i, I) &= f_+ \left( \frac{\max_{\text{ipsilateral}(s_i)}(A_j(I)) - \max_{\text{contralateral}(s_i)}(A_j(I))}{\max_{\text{ipsilateral}(s_i)}(A_j(I)) + \max_{\text{contralateral}(s_i)}(A_j(I))} \right) \\ f_+(x) &= \begin{cases} x & \text{if } x > 0 \\ 0 & \text{if } x \leq 0 \end{cases} \end{aligned} \right.$$

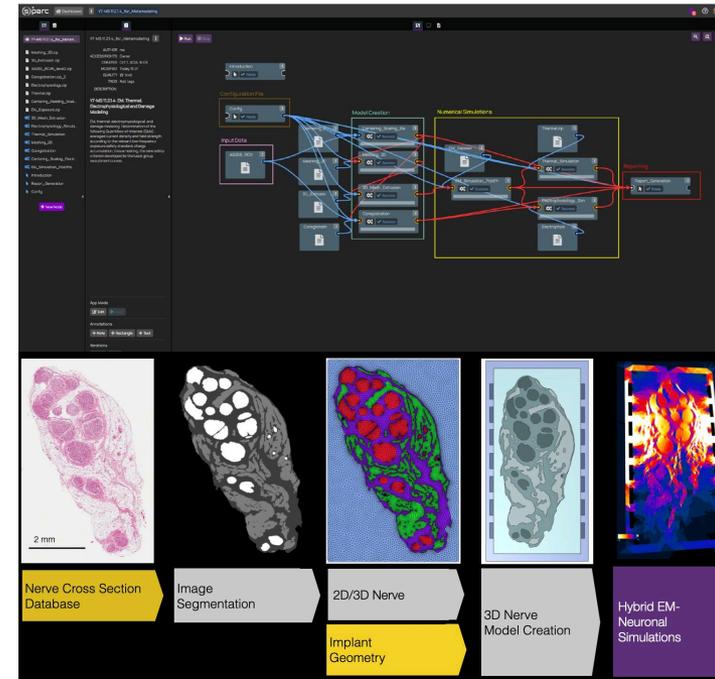


- Remember, how we used the GAF to optimize spinal-cord stimulation selectivity to restore locomotion to paraplegics, and to optimize the pulse shape for efficiency and effectivity”? Let’s revisit...
  - interplay between power ( $J^2$ ) and recruitment ( $J$ )
  - keep current as late as possible (leakage)
  - characteristic time constant

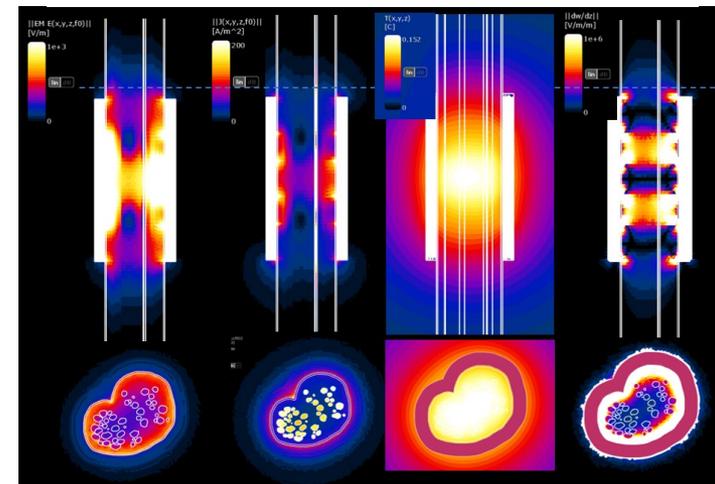


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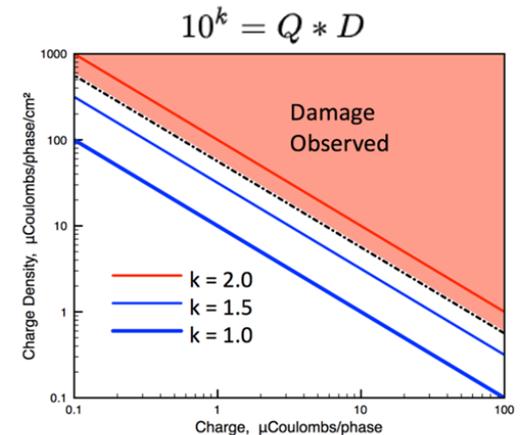
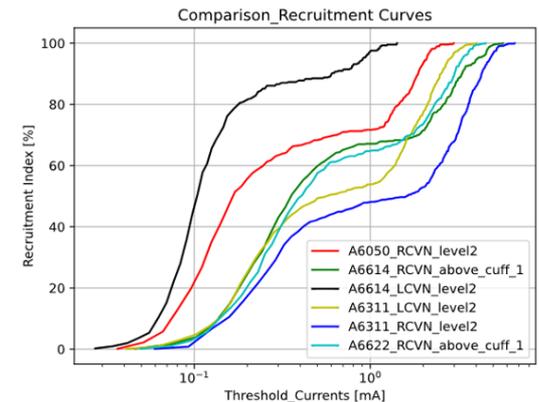
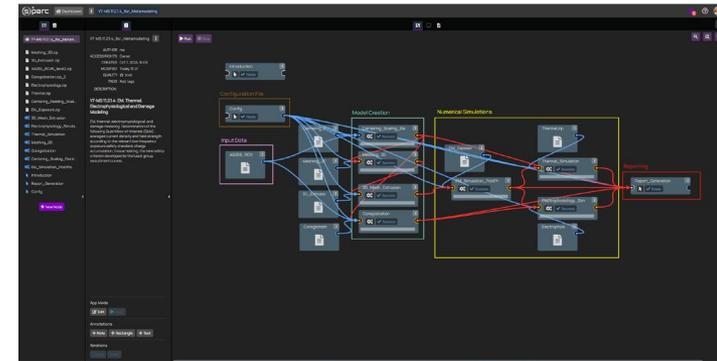
- automatic o<sup>2</sup>S<sup>2</sup>PARC pipeline for neural interface safety and efficacy assessment
- high-throughput screening based on SPARC datasets
- EM, thermal, & electrophysiological simulations (Sim4Life)
  - T: FVM, Pennes Bioheat Equation (incl. perfusion heat transfer)
- extraction of quantities-of-interest
  - averaged current density and field strength according to the relevant low-frequency exposure safety standard (ICNIRP, IEEE)
  - charge accumulation
  - Shannon criterion
  - tissue heating
  - recruitment curves



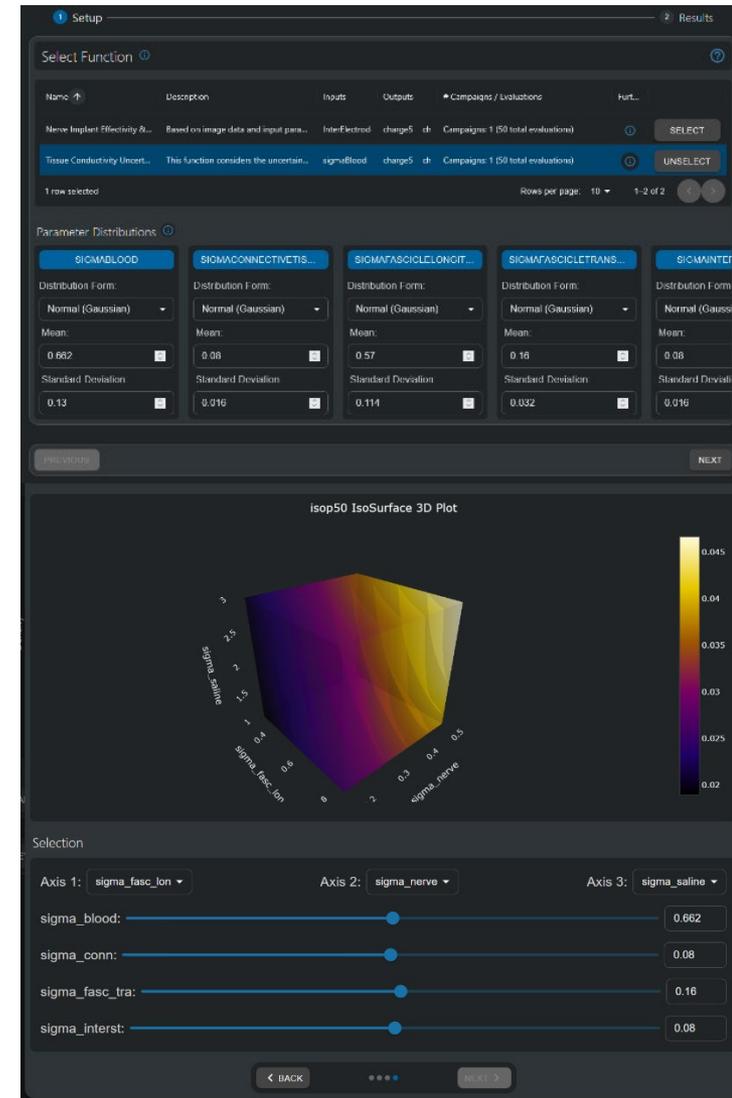
$$\rho C \frac{\partial T}{\partial t} = \nabla k \nabla T + \rho Q + \rho S - \rho_b C_b \rho \omega (T - T_b)$$



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## At the end of this lecture, you will have

- knowledge about the peripheral nervous system and how it is leveraged in bioelectronic medicine to compensate for lost sensorimotor function, or regulate organ function
- understand how to create EM-electrophysiological nerve models for safety, effectivity, and efficiency assessment and optimization

**Next week:** Spinal cord stimulation for neuroprosthetics and pain management & low-frequency exposure safety with Taylor

- The exercise will revolve around modeling nerve recruitment and assessing selectivity and recording sensitivity

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**

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