Towards a spinal cord model to produce experimental protocols

A Feinberg Argonne collaboration

Matthieu K Chardon

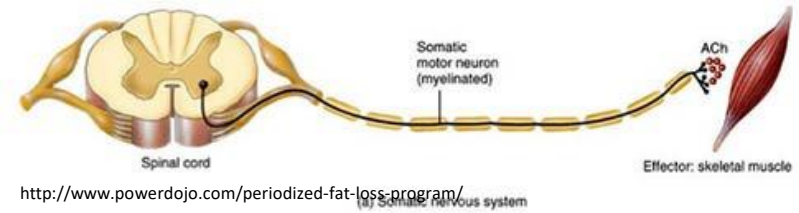
Northwestern and Argonne Workshop on Computational Neuroscience

August 31, 2018

Heckman Lab & Spinal Cord Research

Johnson, M. D., Kajtaz, E., Cain, C. M., & Heckman, C. J. (2013). Motoneuron intrinsic properties, but not their receptive fields, recover in chronic spinal injury. *The Journal of Neuroscience*, *33*(48), 18806–18813.

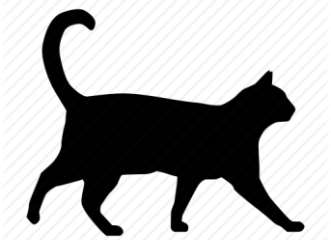
Motoneuron



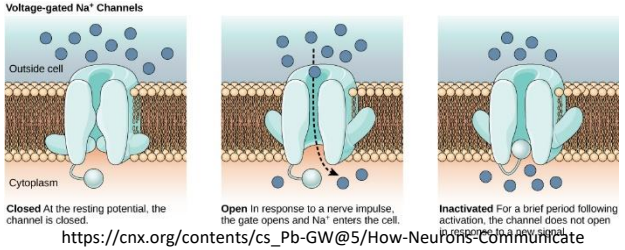
http://www.powerdojo.com/periodized-fat-loss-program/

Johnson, M. D., Hyngstrom, a. S., Manuel, M., & Heckman, C. J. (2012). Push-Pull Control of Motor Output. *Journal of Neuroscience*, *32*(13), 4592–4599. http://doi.org/10.1523/JNEUROSCI.4709-11.2012

Motor Control



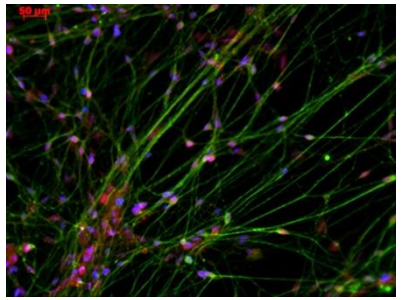
Molecule



https://cnx.org/contents/cs_Pb-GW@5/How-Neurons-Communicate

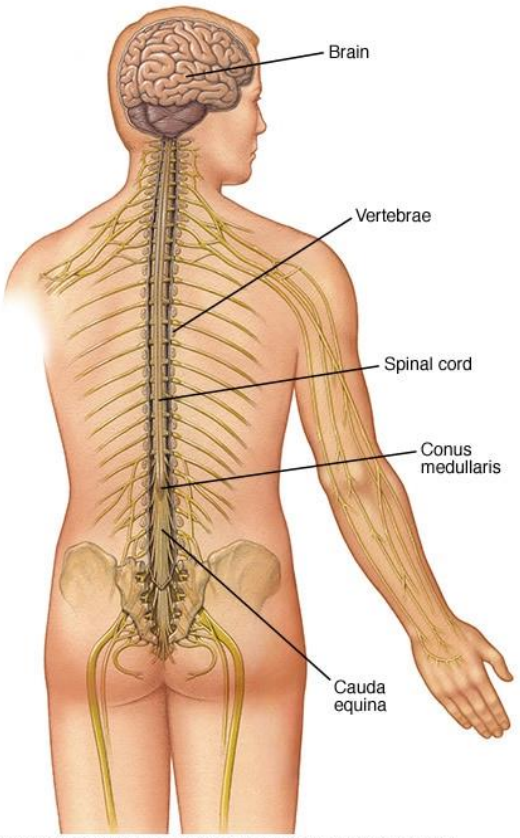
Powers, R. K., & Heckman, C. J. (2017). Synaptic control of the shape of the motoneuron pool input-output function. *Journal of Neurophysiology*, jn.00850.2016. http://doi.org/10.1152/jn.00850.2016

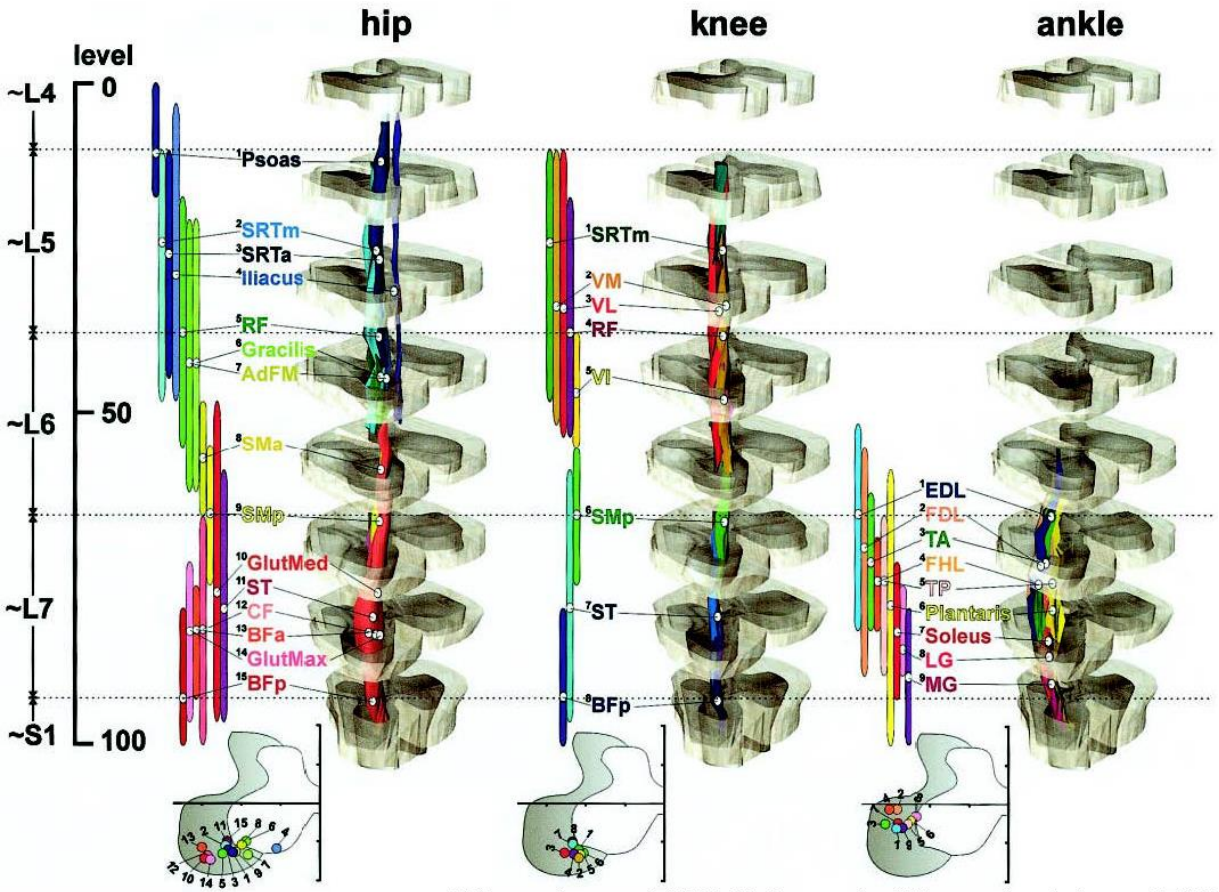
Spinal Circuits



Hyngstrom, A. S., Johnson, M. D., Miller, J. F., & Heckman, C. J. (2007). Intrinsic electrical properties of spinal motoneurons vary with joint angle. *Nature Neuroscience*, *10*(3), 363–369.

What experimental protocol?

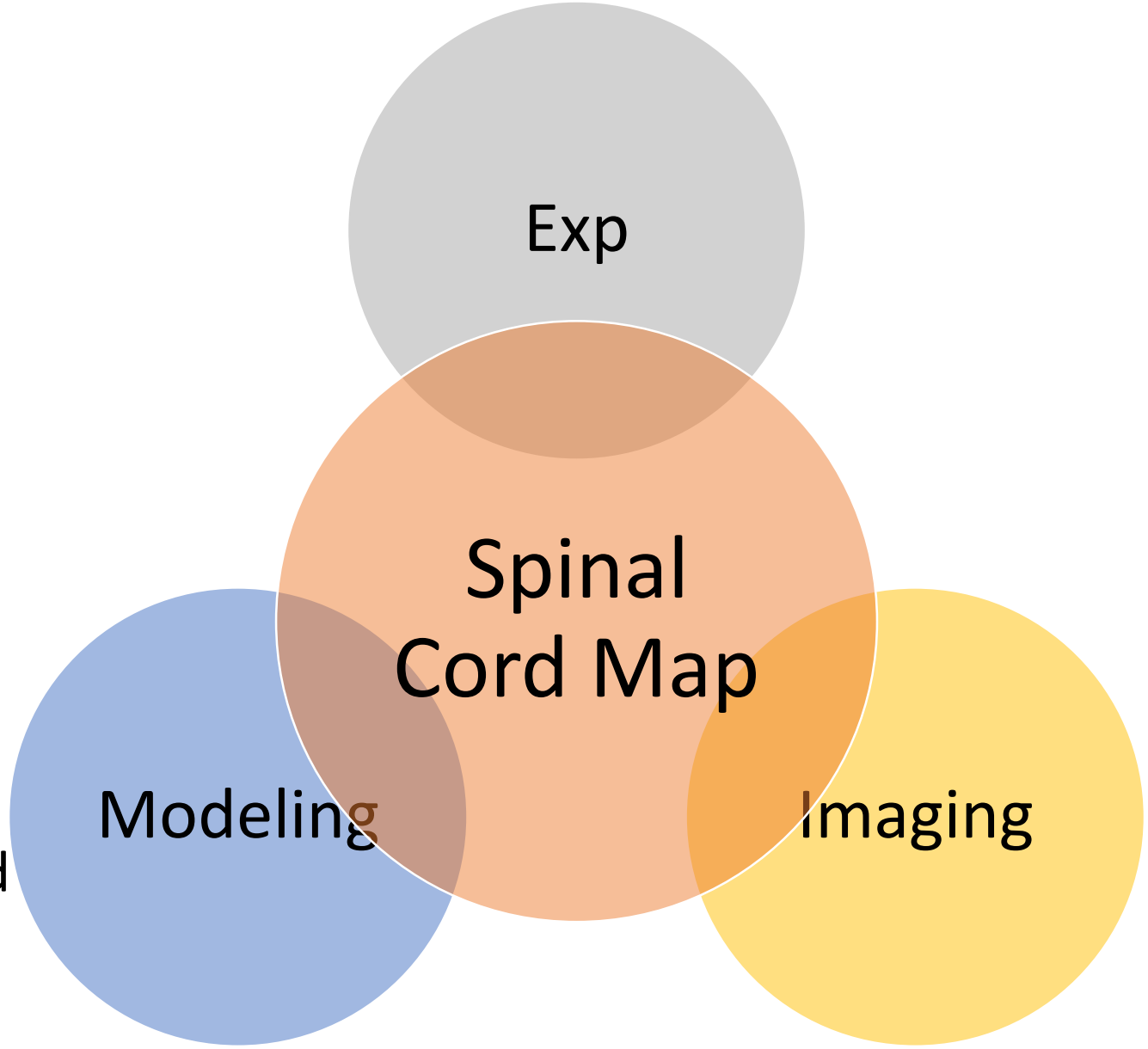




Yakovenko et al (2002). Journal of Neurophysiology, 87(3)

Would it be useful?

- Well established market for pain
  - 30,000 implants/year
  - 1.8 Billion USD
  - 50% do not work
  - No placebo studies
  - Hard to measure
- SCI Autonomic system: bladder control, blood pressure, sexual arousal, etc.
- SCI Motor system: believe to be best model as it is can be measured in animal models easily.

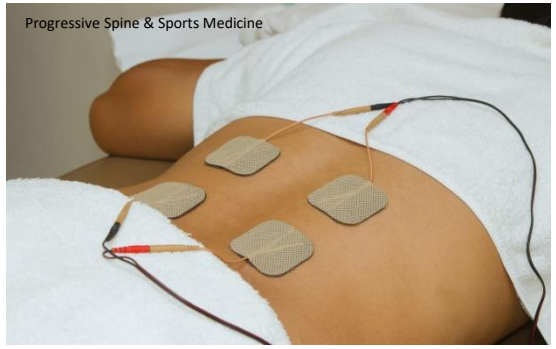


Background

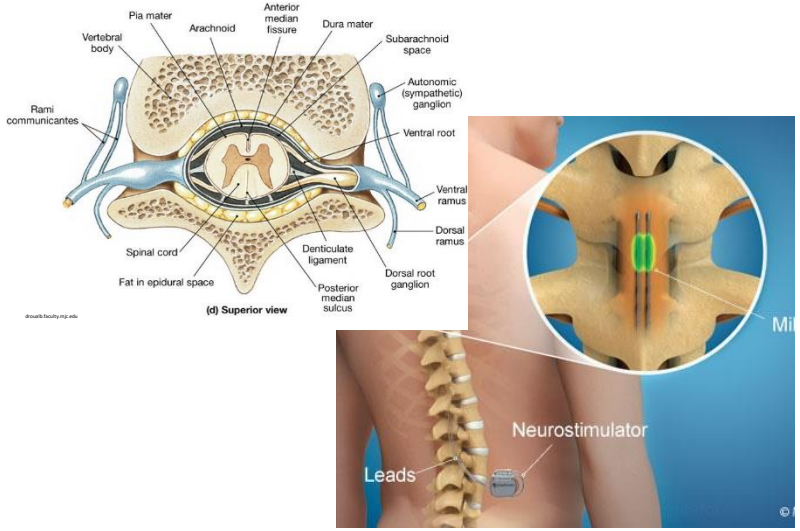
Common Stimulation Types

More Invasive

Transcutaneous



Epidural



Intraspinal microstimulation

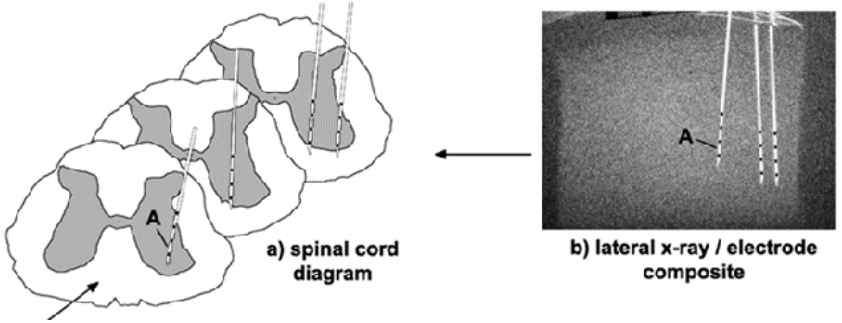


Fig.1. Snow, S. et al (2006). IEEE Transactions on Biomedical Engineering, 53(2), 311–319.

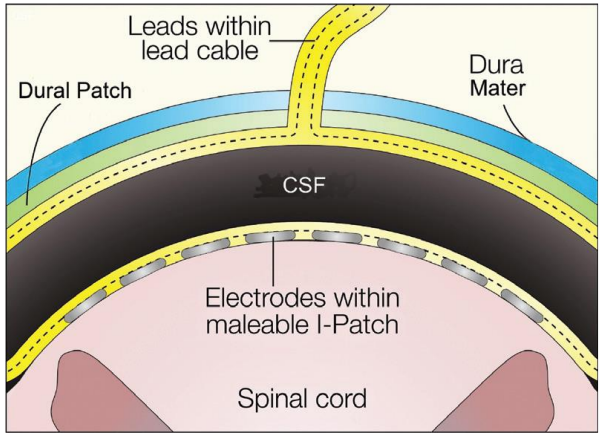
Less specific

Direct Electrical Stimulation (DES)

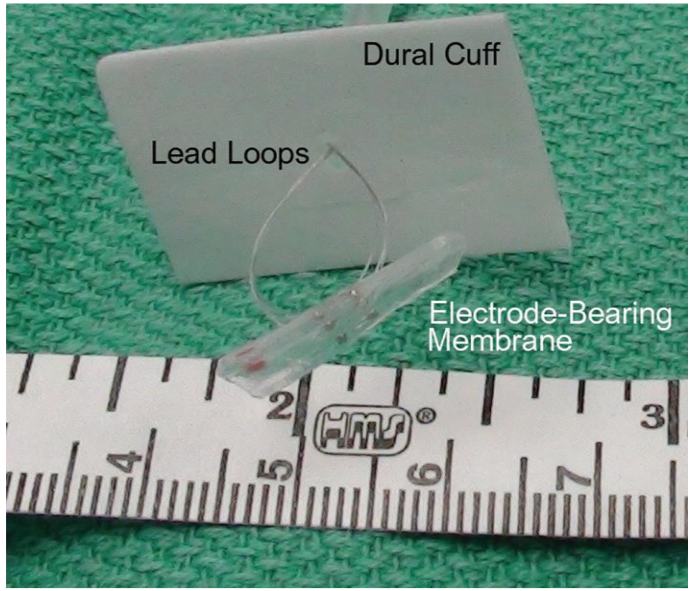
Subdural space

More Invasive

Epidural



Dalm, B. D. et al. (2014). Innovative Neurosurgery, 2(1–4), 13–20.



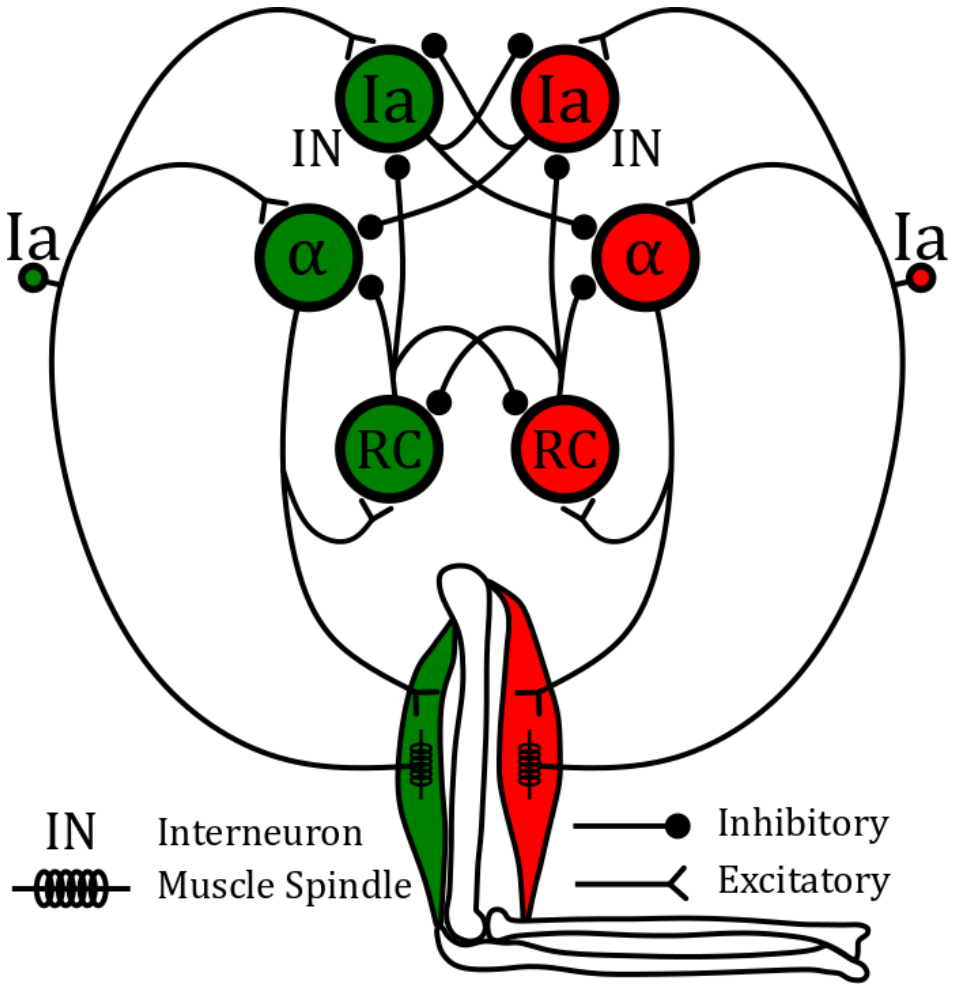
Intraspinal microstimulation

Less specific

Canonical Motor Microcircuit (CMM)

Model Choice

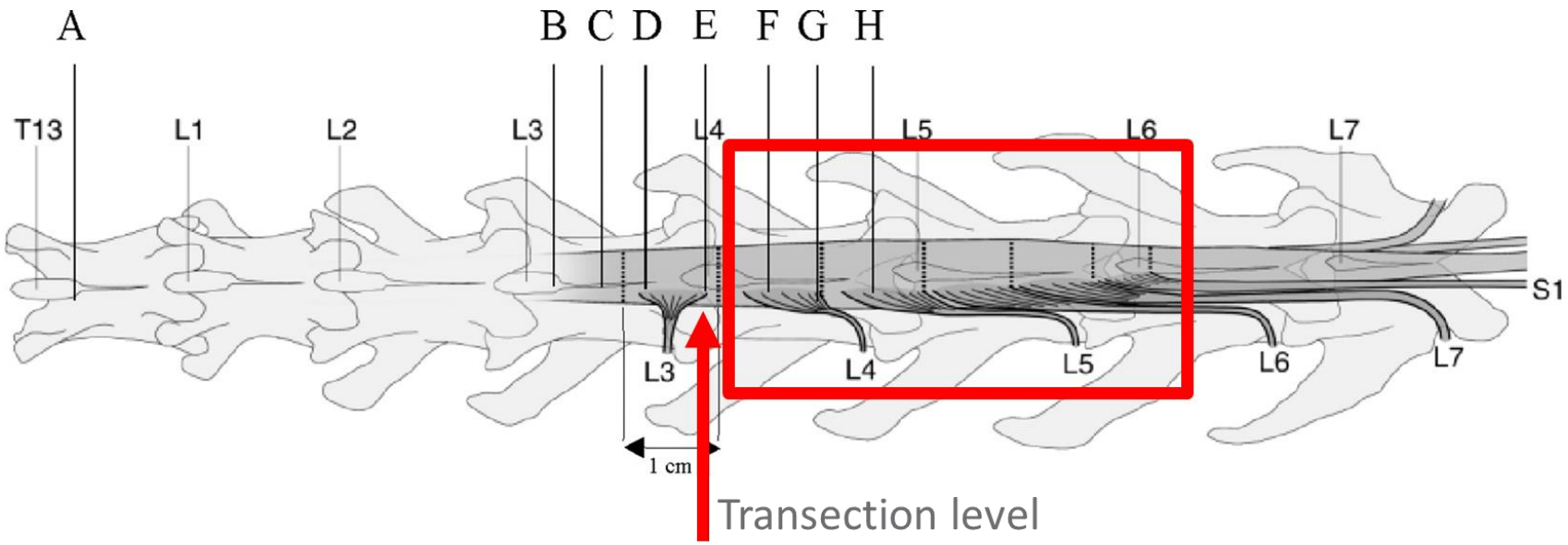
- **Fundamental**: Basis for locomotion (reciprocal inhibition),
- **Understandable:** Large background of its structure (motorpools location),
- **Accessible**: Highest sensitivity to activation by DES are almost certainly the Ia axons arising in muscle spindles (large diam fiber).
- **Generalizable**: Circuit is repeated throughout the spinal cord.



Experimental Data

1. Exp1: General motor pool map with respect to location. Does this map change after full spinal cord transection?
2. Exp2: Map with respect to amplitude and frequency.

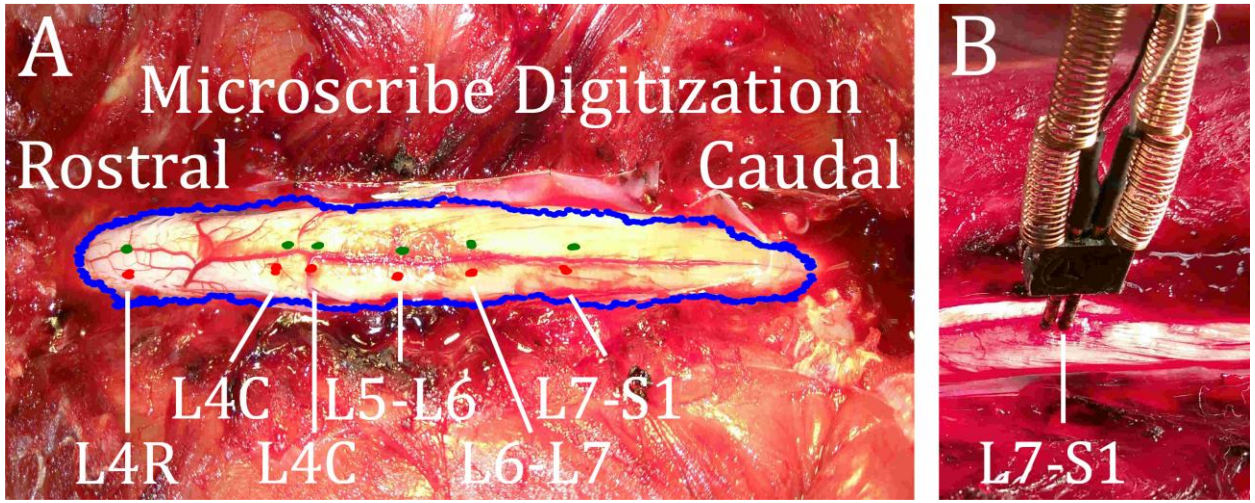
General motorpool map of the lumbar region

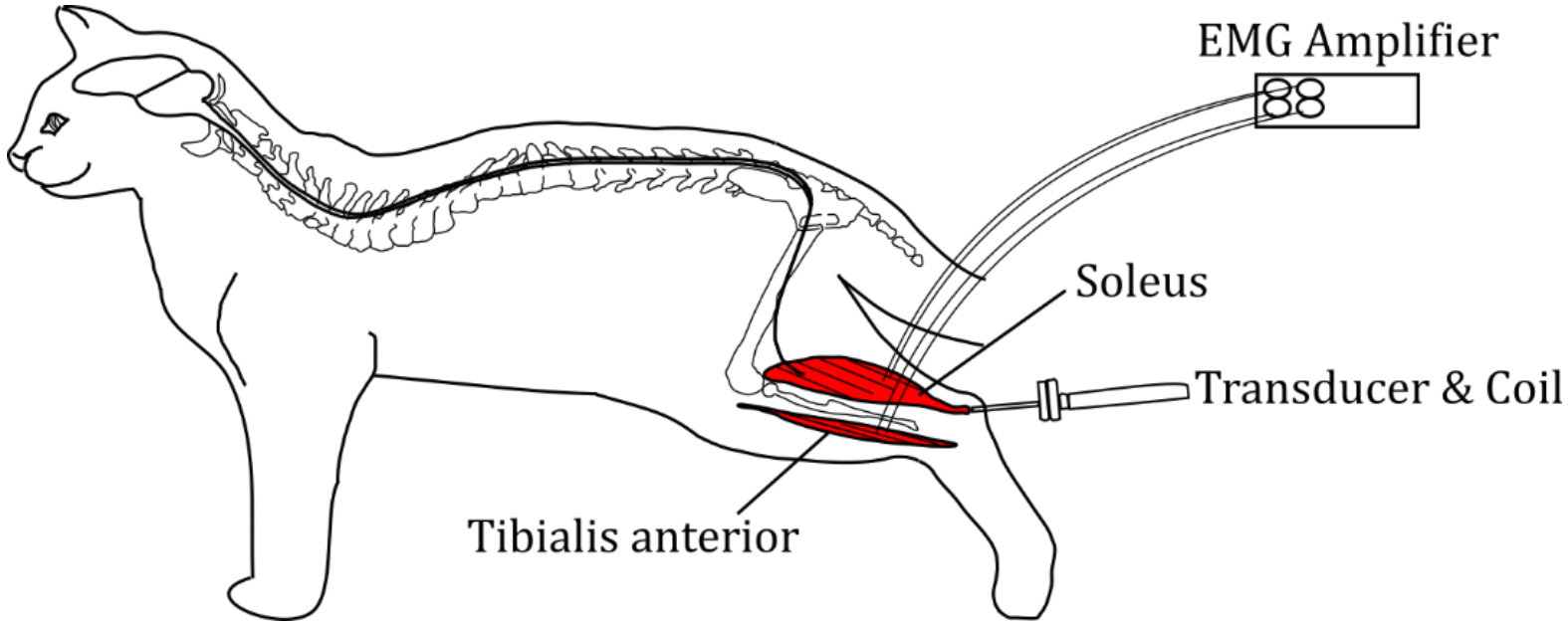


Methods

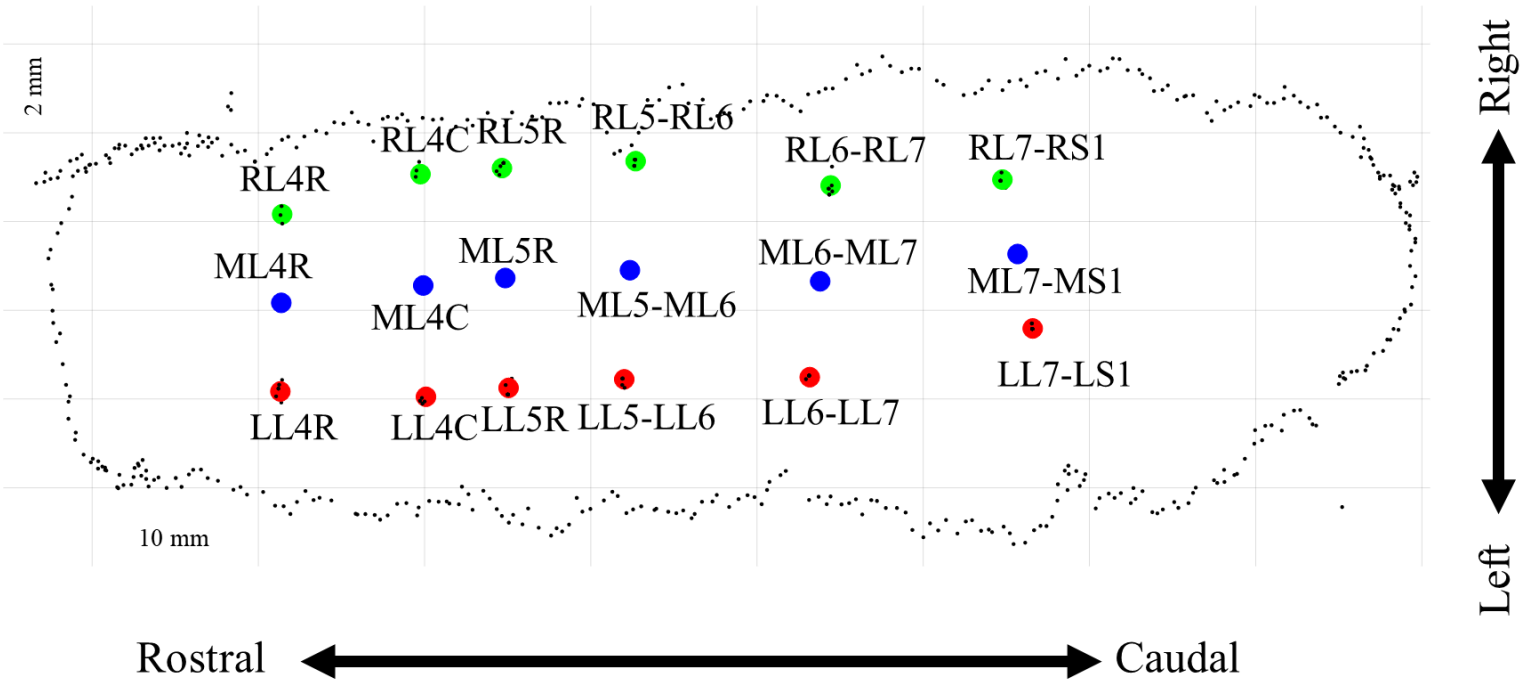
Feline Preparation

- **Lumbar laminectomy**
- **Soleus dissection:** calcaneus attached to vibration coil and transducer





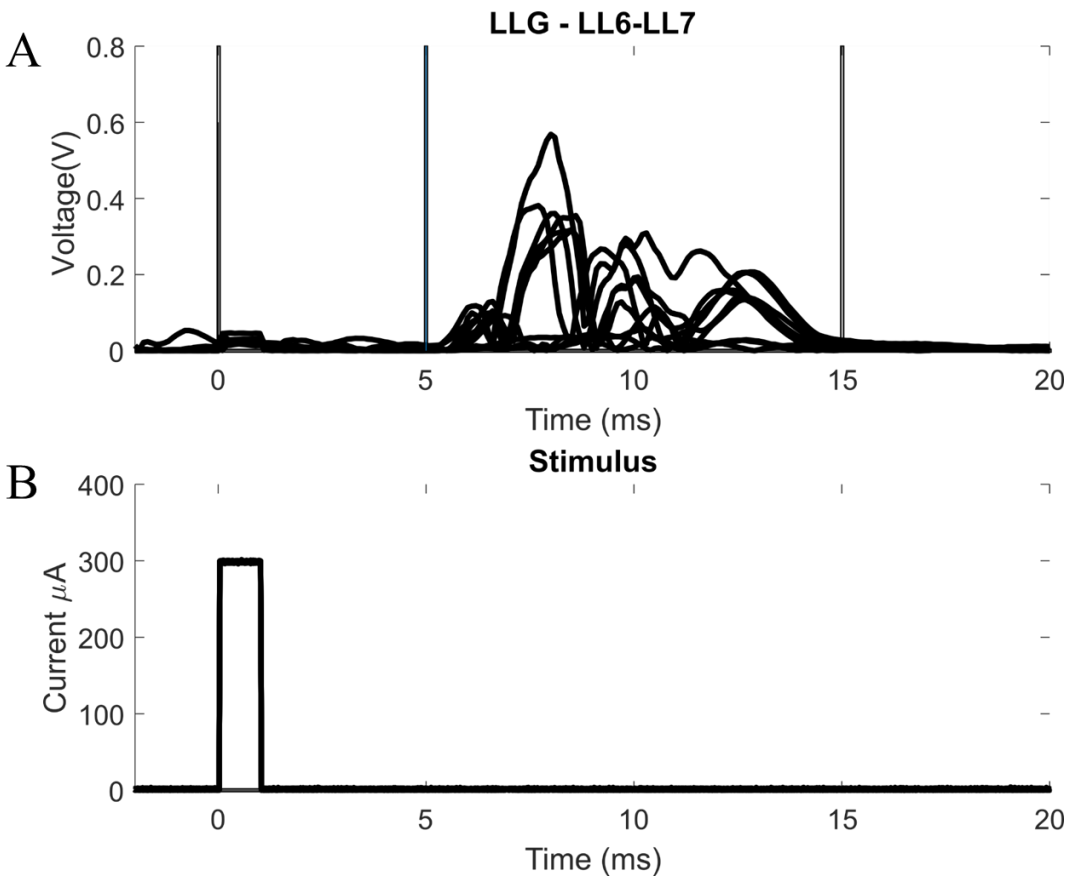
Digitize Location



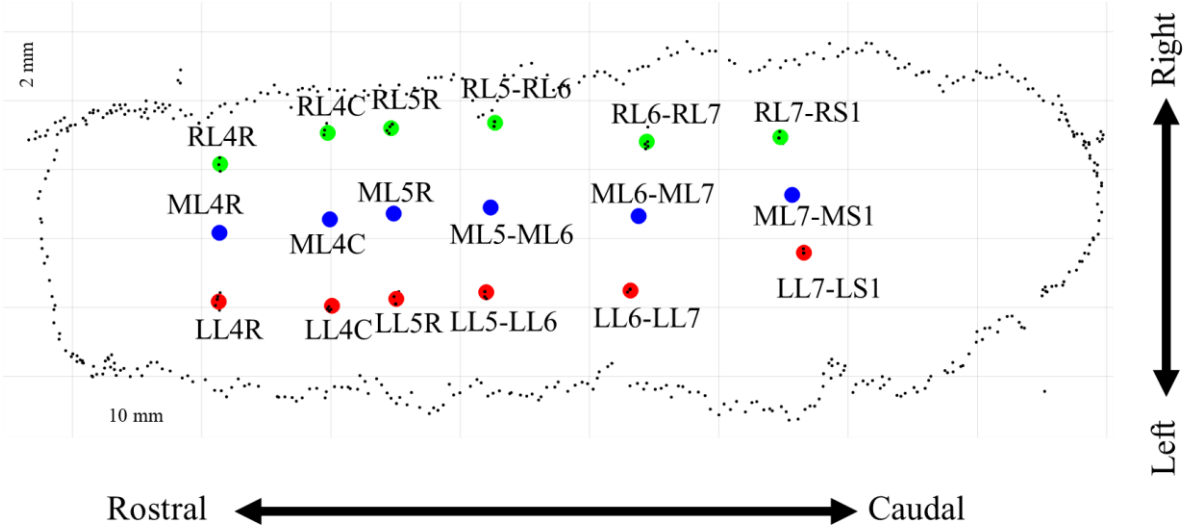
Protocol 1

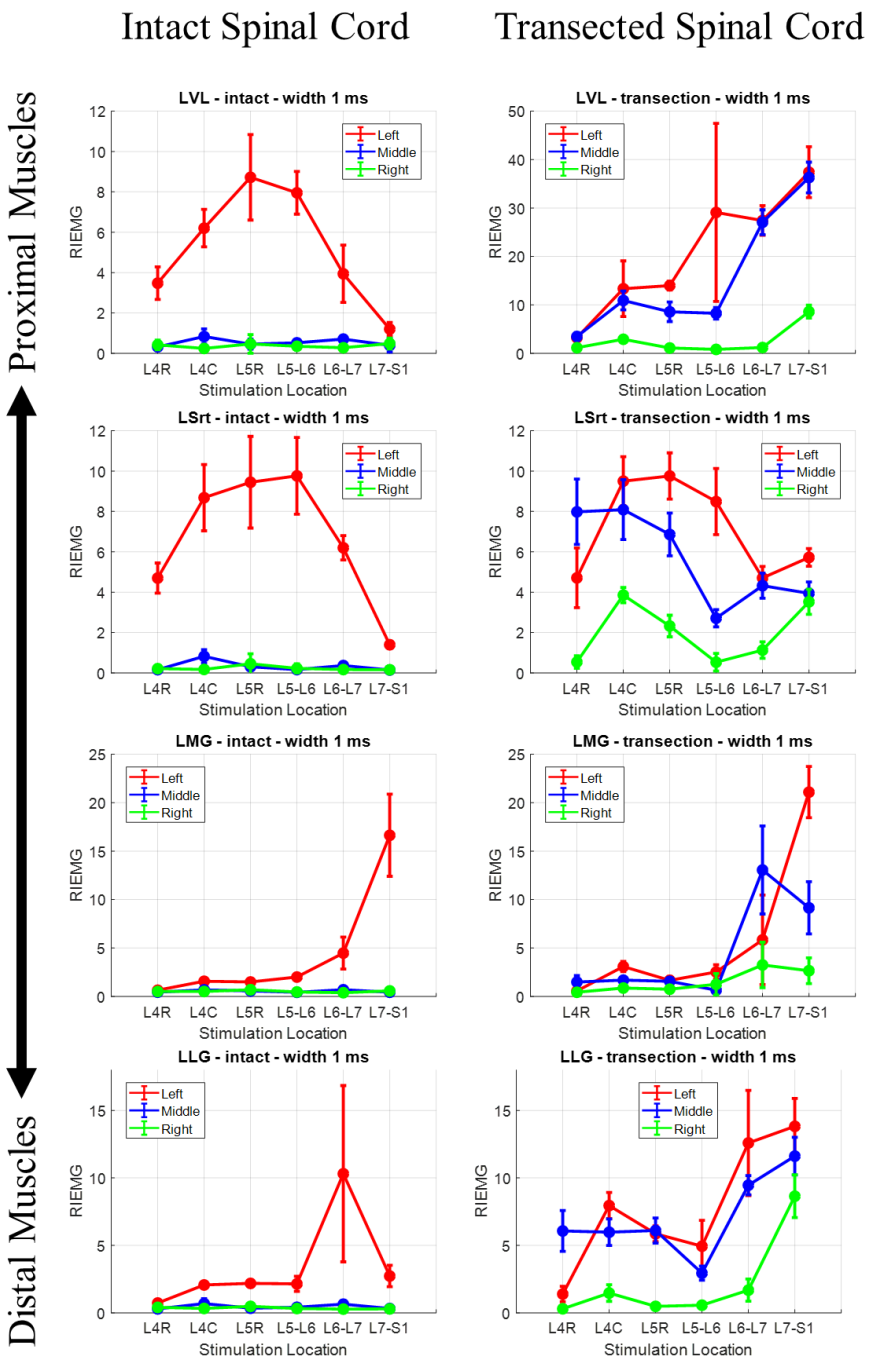
Stimulation & Raw Data

- Measure EMG of VL, Srt, LG and MG
- Stimulation Parameter
  - 300 µA
  - 1 Hz
  - 1 ms width
- Repeat after full transection



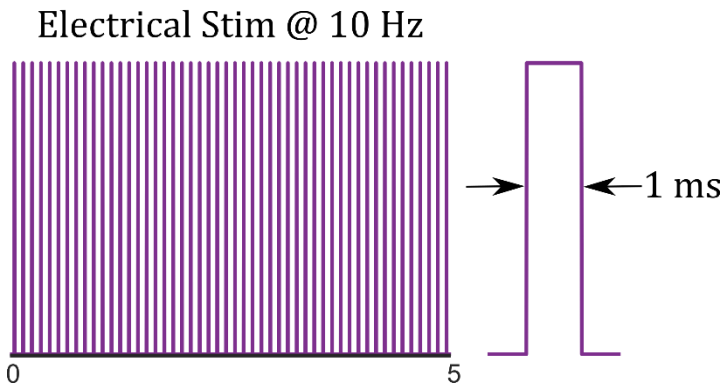
Results


2 mm
RL4R
RL4C
RL5R
RL5-RL6
RL6-RL7
RL7-RS1
ML4R
ML4C
ML5R
ML5-ML6
ML6-ML7
ML7-MS1
LL4R
LL4C
LL5R
LL5-LL6
LL6-LL7
LL7-LS1
10 mm
Rostral
Caudal
Right
Left

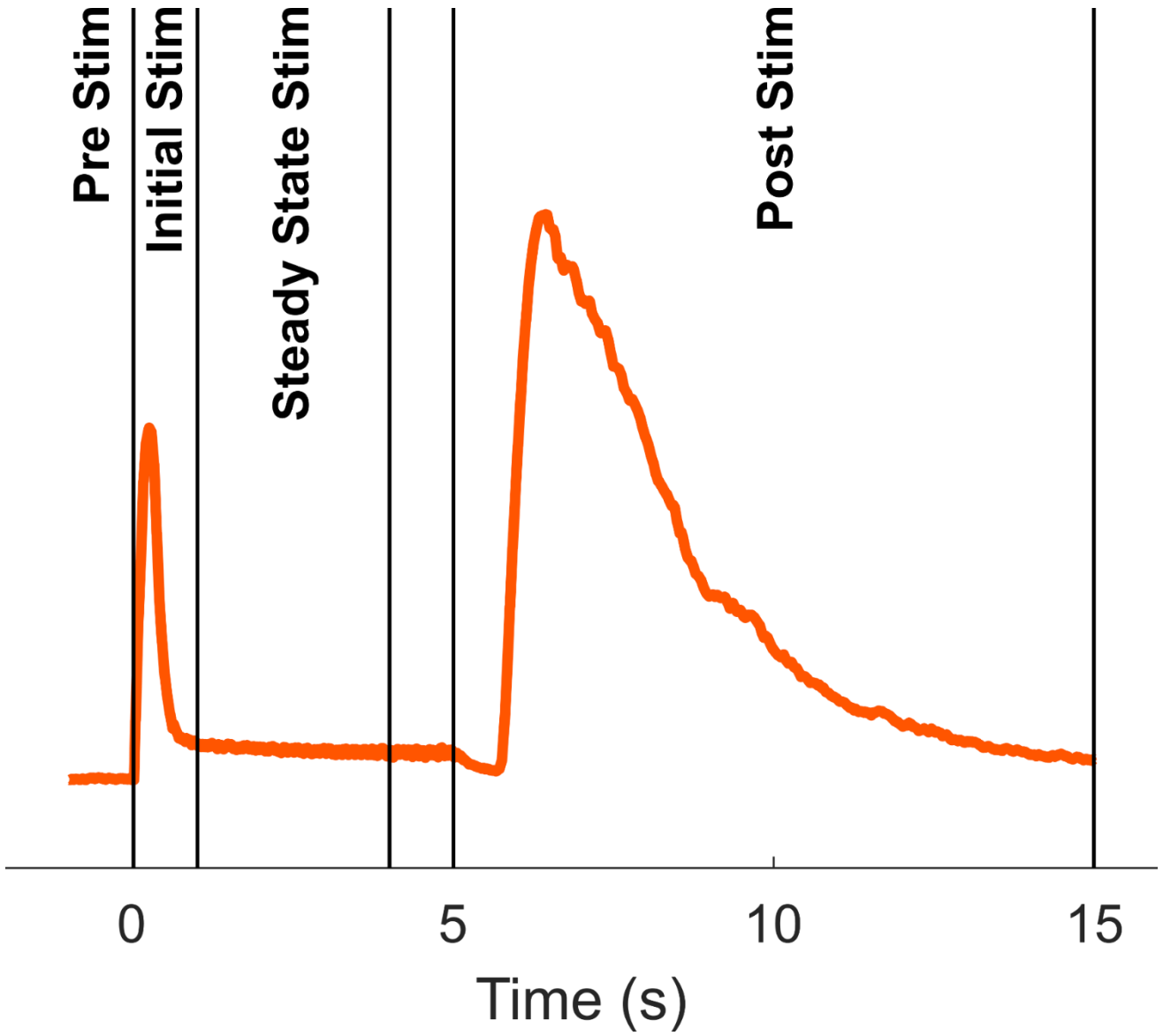

Intact Spinal Cord
Transected Spinal Cord
Proximal Muscles
Distal Muscles
LVL - intact - width 1 ms
LVL - transection - width 1 ms
LSrt - intact - width 1 ms
LSrt - transection - width 1 ms
LMG - intact - width 1 ms
LMG - transection - width 1 ms
LLG - intact - width 1 ms
LLG - transection - width 1 ms
Left
Middle
Right
RIEMG
L4R L4C L5R L5-L6 L6-L7 L7-S1
Stimulation Location

Protocol 2
Location constant but change frequency

- Stimulation Paradigm
  - Amplitude: 100, 200, 300, 400, 500 µA
  - Frequency: 10, 20, 40 Hz
  - Duration 5 s
  - Pulse Width 1 ms



Results


Pre Stim
Initial Stim
Steady State Stim
Post Stim
0
5
10
15
Time (s)

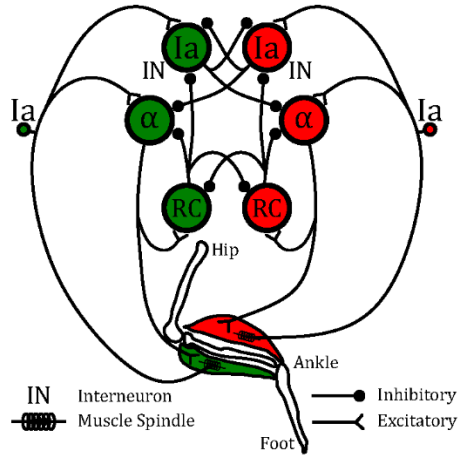
Spinal Cord Computer Modeling

1. Modeling CMM
2. Solving Maxwell Equations – Impedance Measurements
3. Scaling

Goal

Objective 1

Single CMM (8 Neurons)

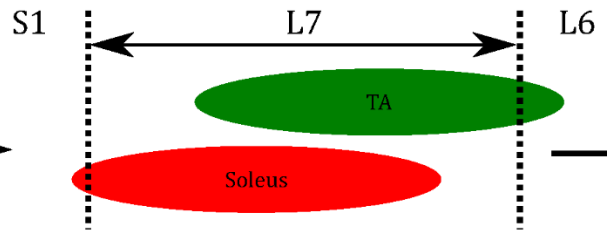


Number of Equations: 172

Neurons = 2 x (MN + RC + Ia + IaIN)

Objective 2

Antogonist Pair CMM (2 x Motorpools)

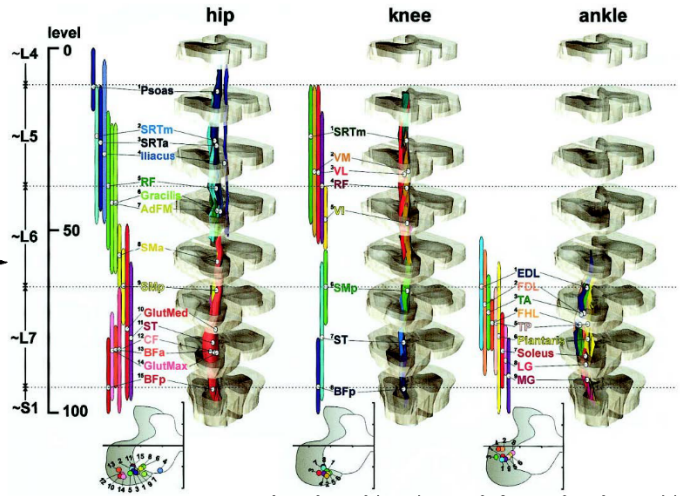


Number of Equations: 103,200

Neurons = 2 x 300 x (MN + RC + Ia + IaIN)

Objective 3

Full Hindlimb CMM (32 x Motorpools)



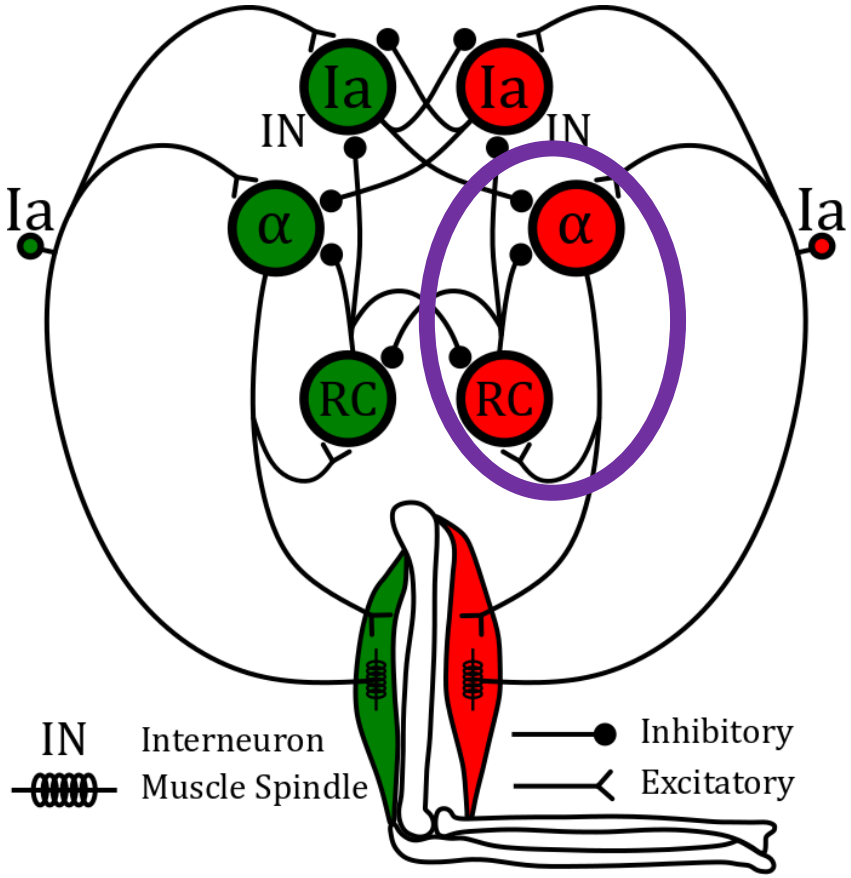
Yakovenko et al (2002). Journal of Neurophysiology, 87(3)

Number of Equations: 3,302,400

Neurons = 2 x 300 x 32 x (MN + RC + Ia + IaIN)

NEURON

Hodgkin-Huckley Model



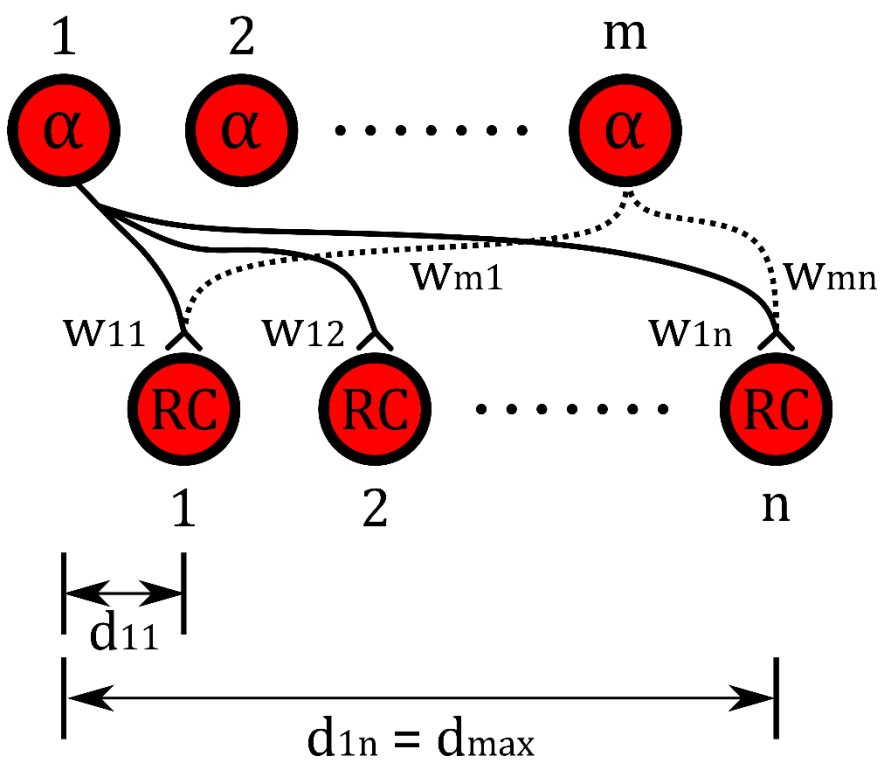
Decorrelating Actions of Renshaw Interneurons on the Firing of Spinal Motoneurons Within a Motor Nucleus: A Simulation Study

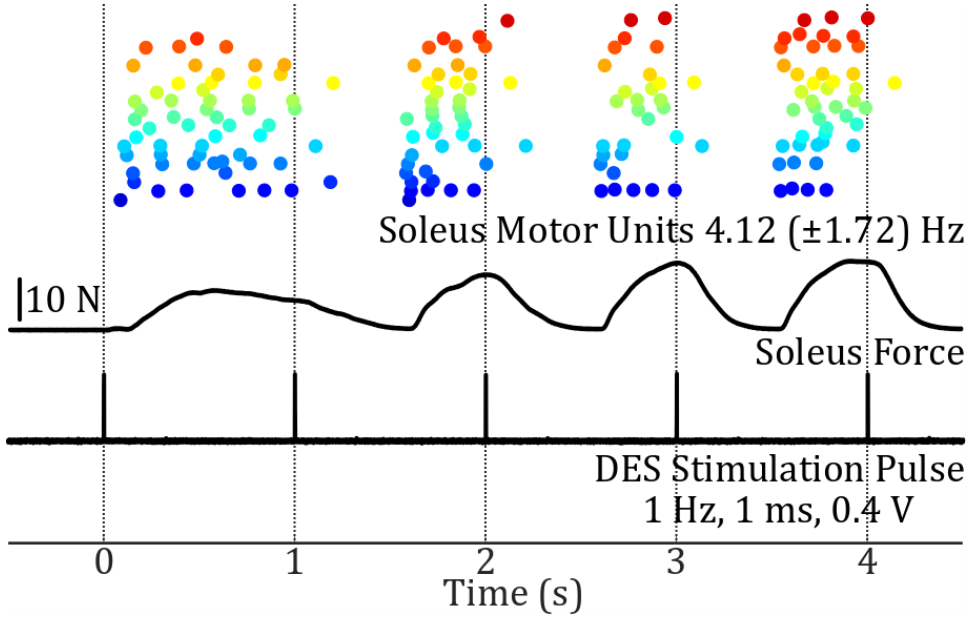
MITCHELL G. MALTENFORT,[1] C. J. HECKMAN,[2] AND W. ZEV RYMER[1]
[1]*Department of Biomedical Engineering, Northwestern University; and* [2]*Department of Physiology, Northwestern University Medical School, Chicago, IL 60611*

Network weights

Example of Network Weight Distribution

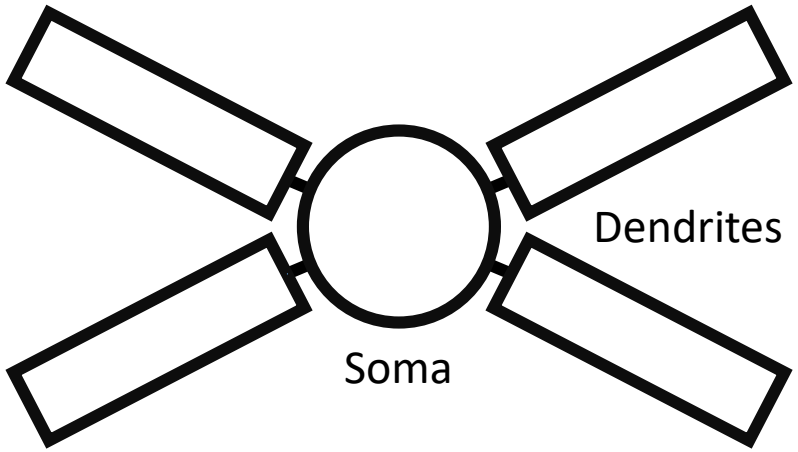
MN (α) to Renshaw Cell (RC) Connection



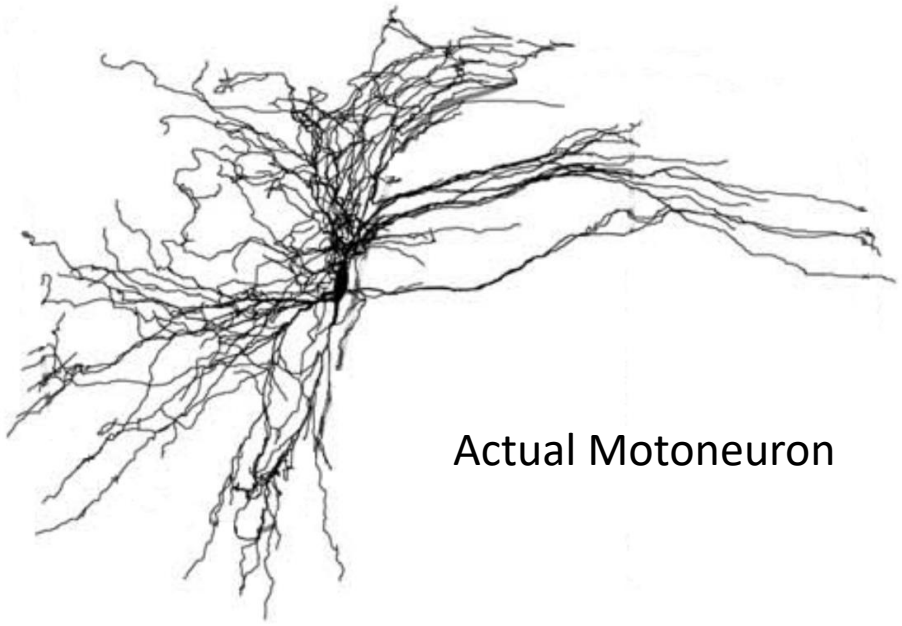


Model

Simple to Complex



Current Motoneuron Model



Actual Motoneuron

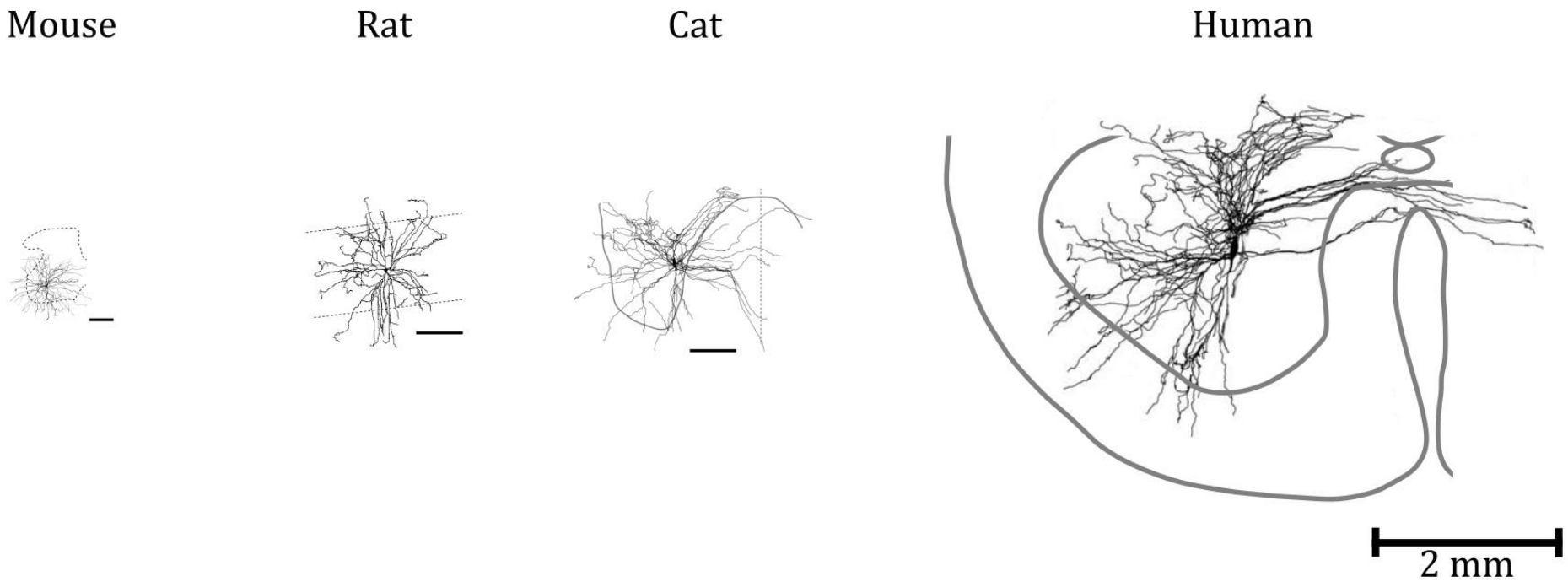
Current Model

- 30 MN
- 50 Ia
- 6 Renshaw

Synaptic control of the shape of the motoneuron pool input-output function

Randall K. Powers[1] and Charles J. Heckman[2]

Scaling the model

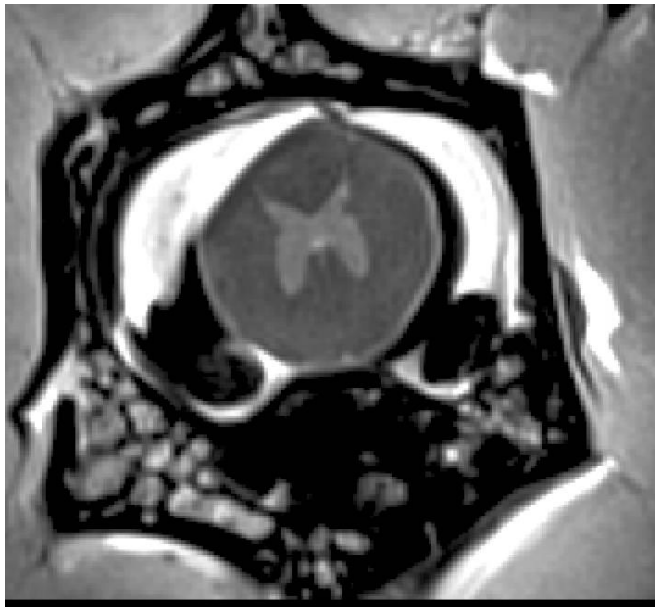


Spinal Cord Imaging

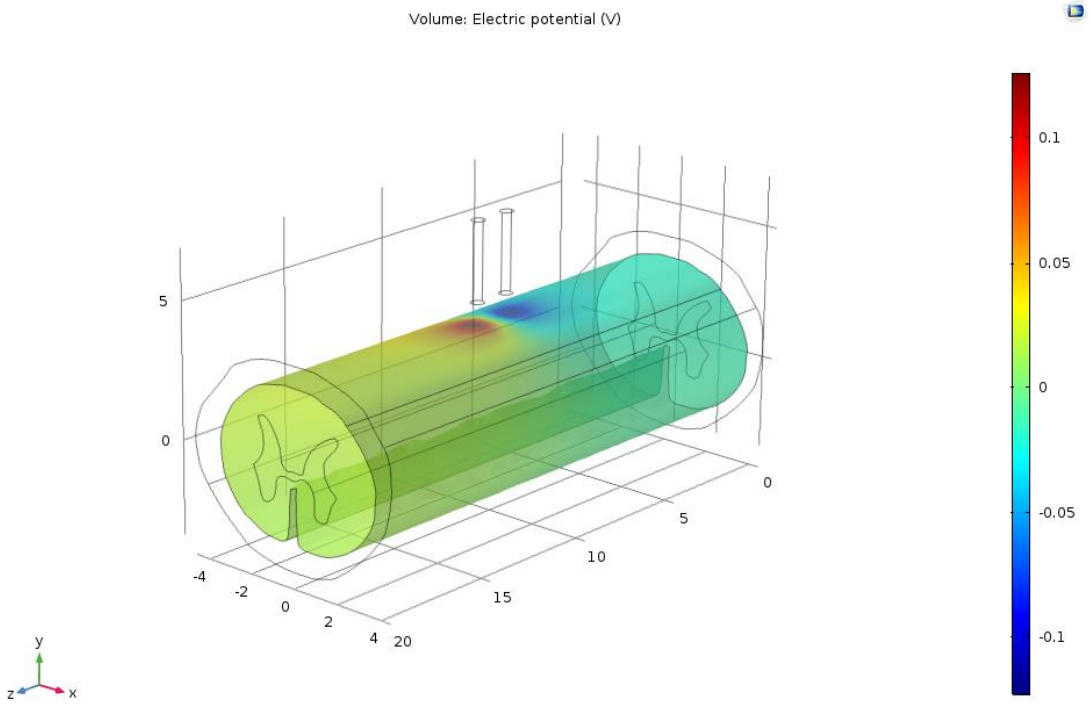
X-Ray microtomography (µCT). Technique provides mesoscale anatomy, of neurons, glial cells and vasculature, at an isometric resolution of ~1μm^3 using large tissue samples (1-2 mm thickness).

Electromagnetic Modeling

COMSOL

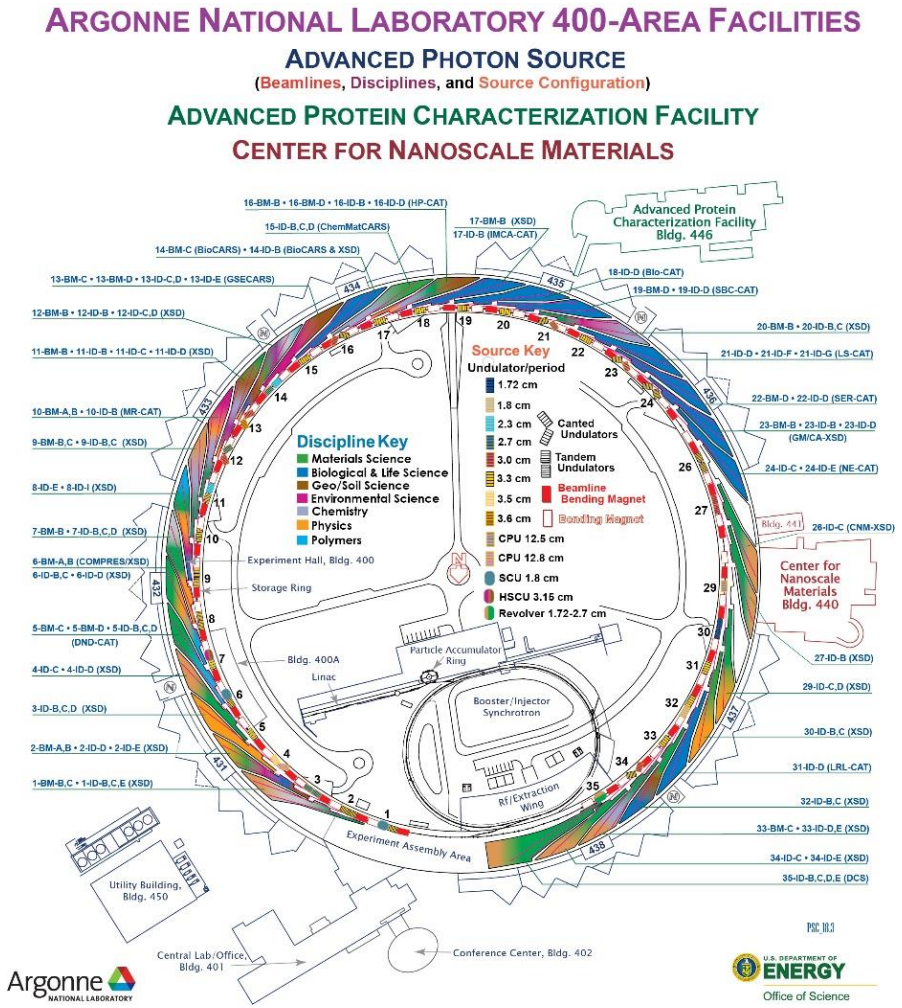


7T MRI Image of Cat Lumbar Spinal Cord

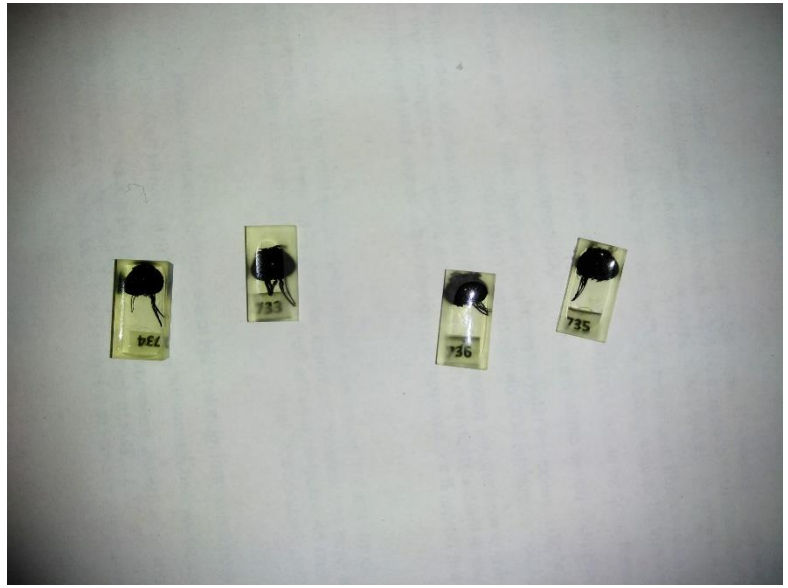


Advance Photon Source (APS)

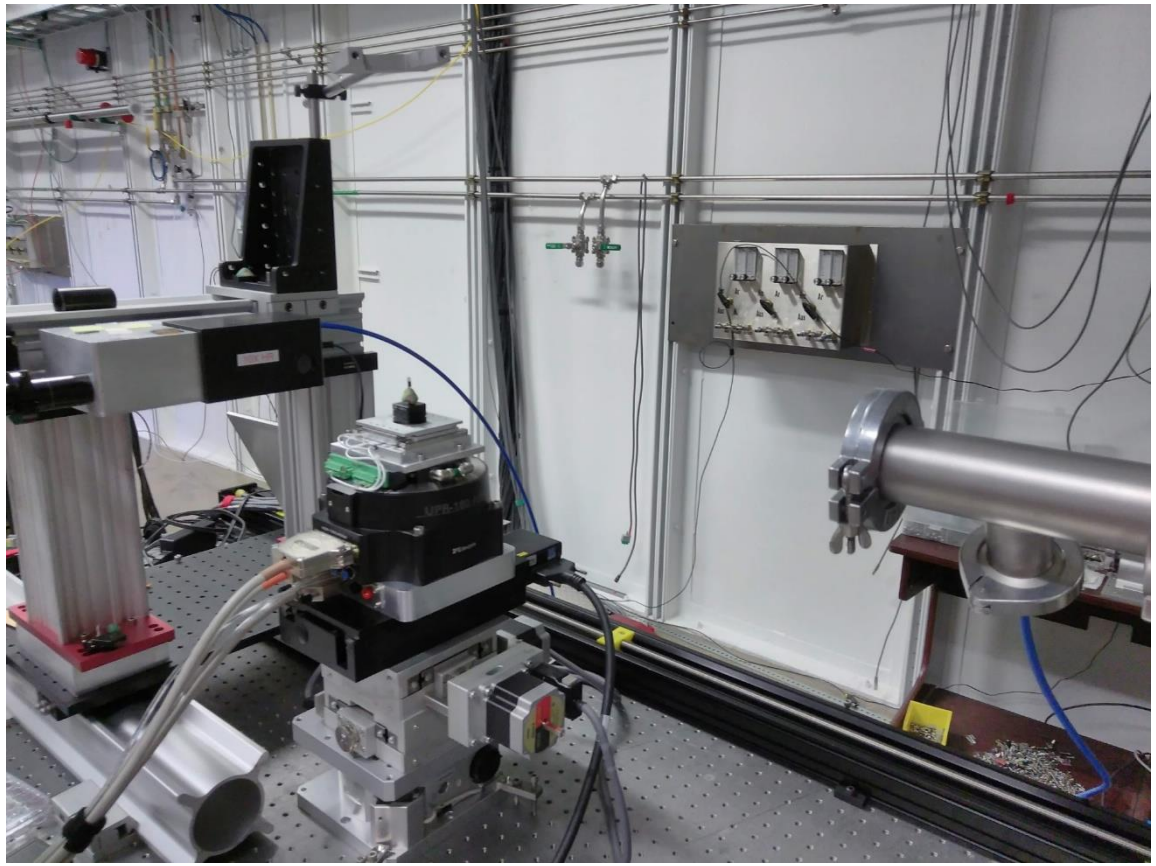
Argonne National Lab



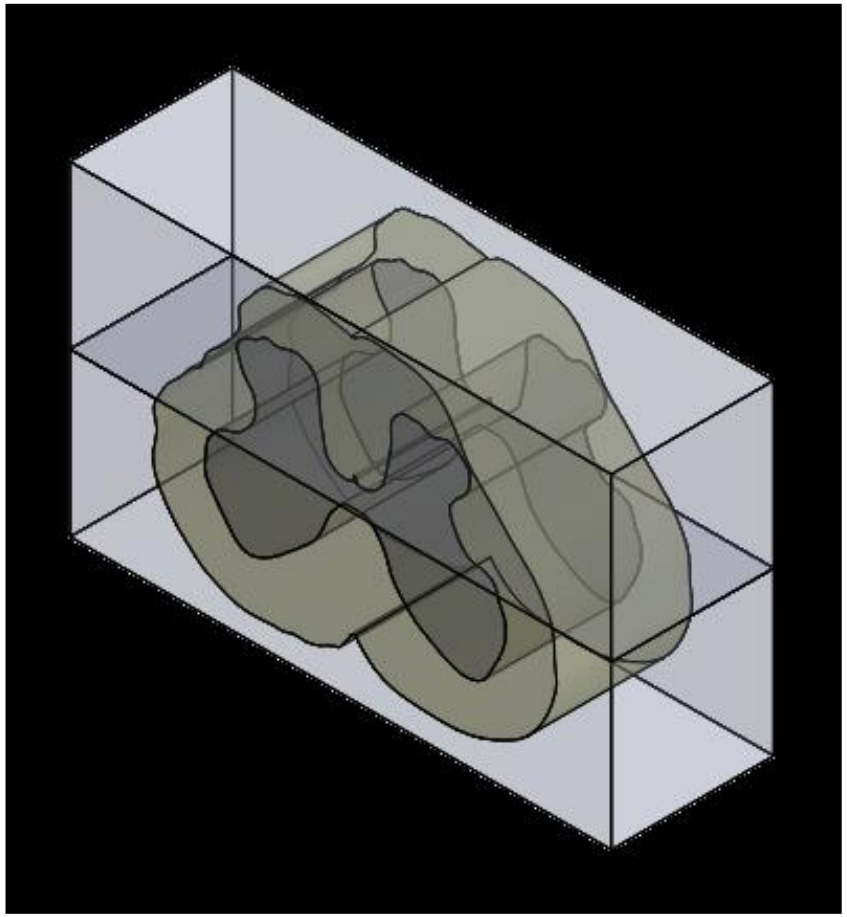
Spinal Cord Sample

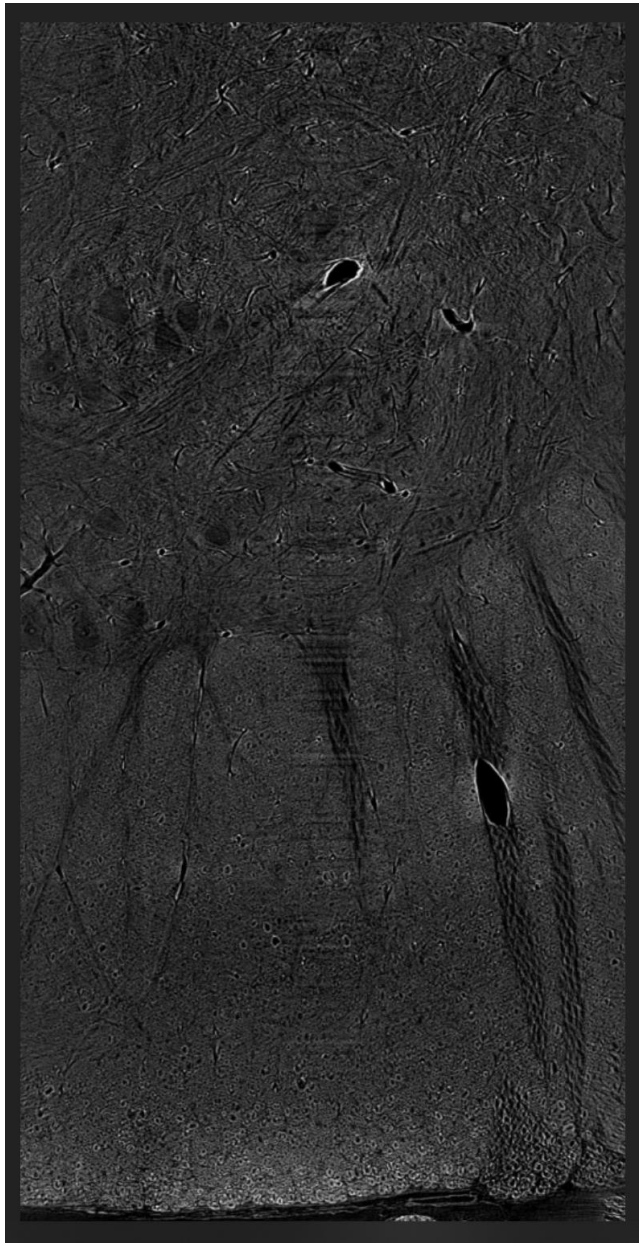


ID-32 Setup

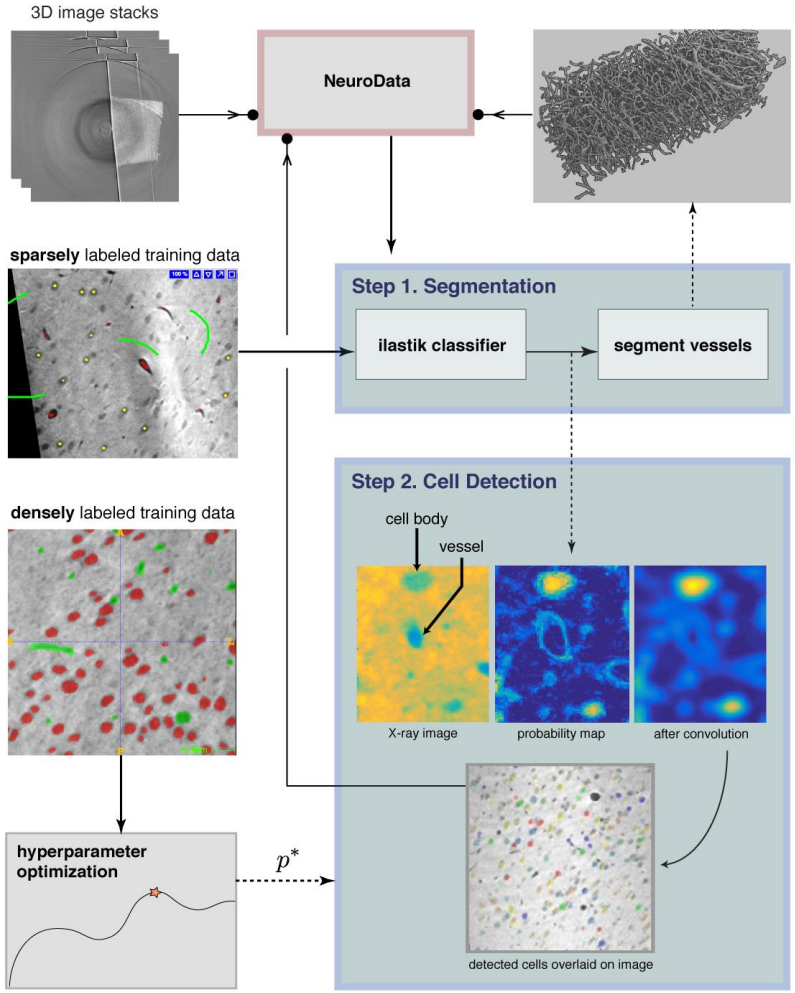


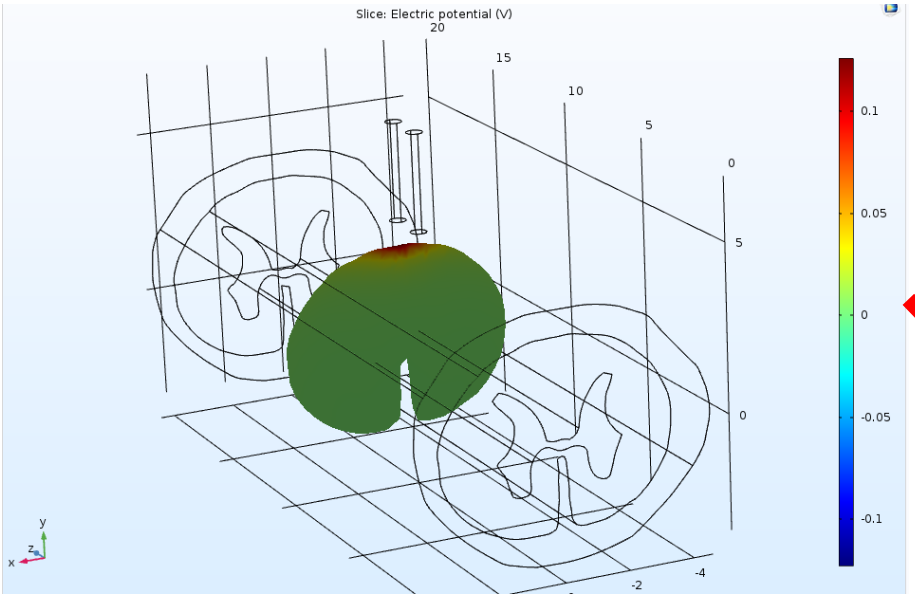
Preliminary Image

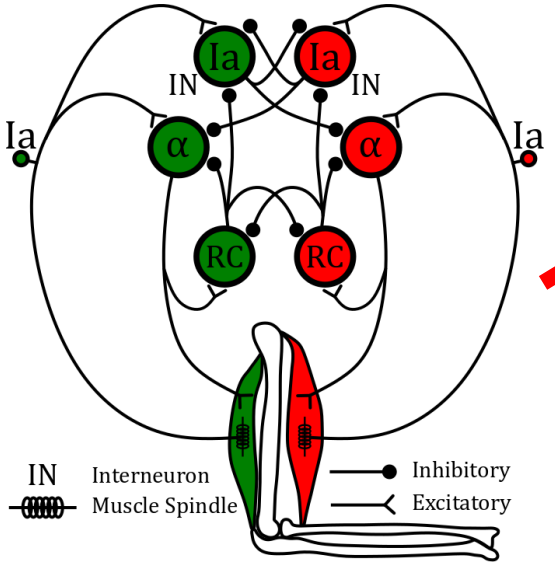


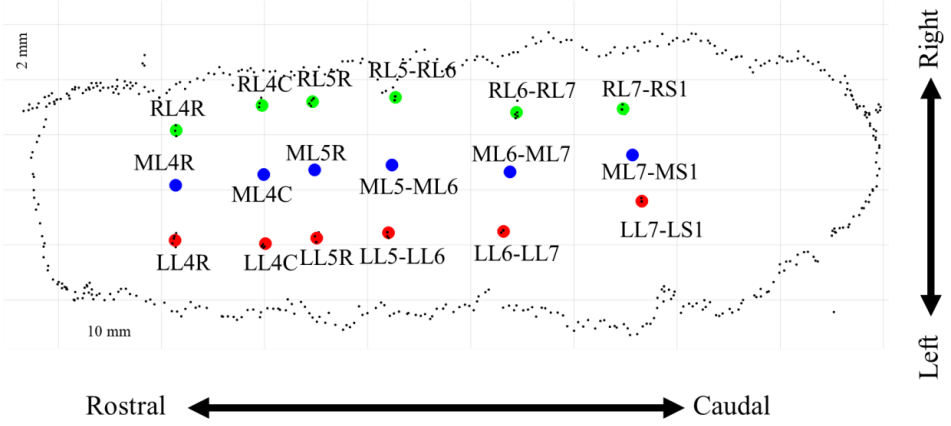


3D Reconstruction – Dr. Kasthuri at UoC



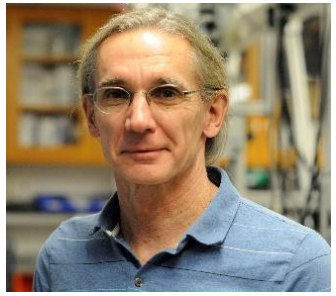

Slice: Electric potential (V)
20
15
10
5
0
5
0
-2
-4
0.1
0.05
0
-0.05
-0.1
y
z
x


Ia
Ia
IN
IN
Ia
Ia
α
α
RC
RC
IN
Interneuron
Muscle Spindle
Inhibitory
Excitatory


2 mm
10 mm
RL4R
RL4C
RL5R
RL5-RL6
RL6-RL7
RL7-RS1
ML4R
ML4C
ML5R
ML5-ML6
ML6-ML7
ML7-MS1
LL4R
LL4C
LL5R
LL5-LL6
LL6-LL7
LL7-LS1
Rostral
Caudal
Right
Left

Many Thanks

Northwestern Medicine
Feinberg School of Medicine



Michael D'Mello

Roberto Paoli

THE UNIVERSITY OF CHICAGO

Rafael Vescovi

Vandana Sampathkumar