Spinal Circuits for the Control of Dexterous Movement

NINDS/NIH U19 funded through the BRAIN Initiative

Spinal Circuits

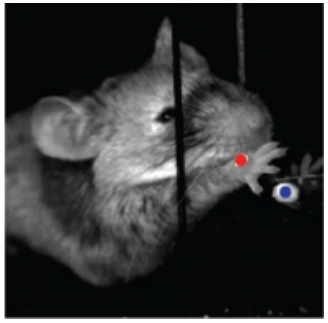
Limb Mechanics

Behavior

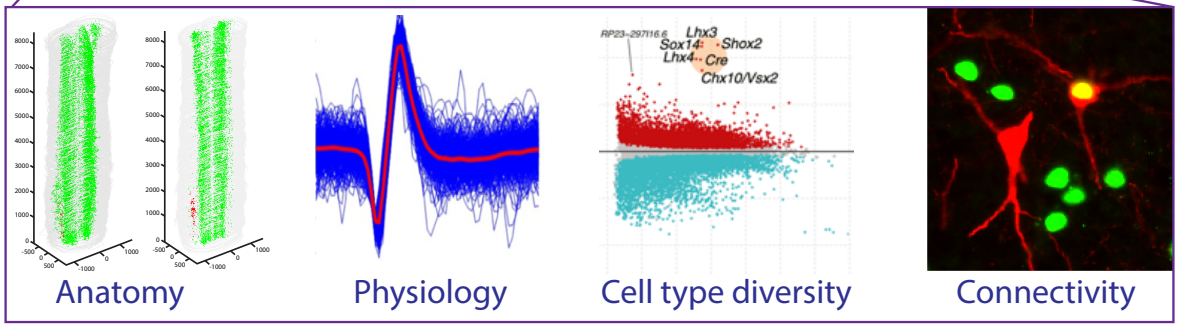
Cervical Spinal Cord

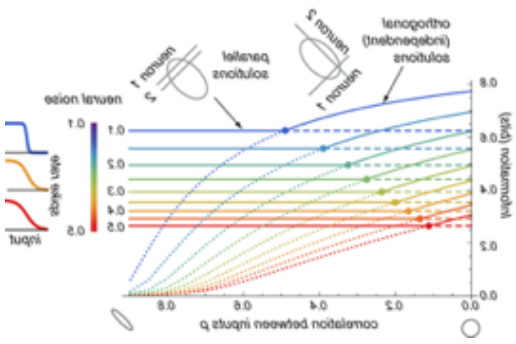
Forelimb Muscles

Rhythmic Movement Locomotion

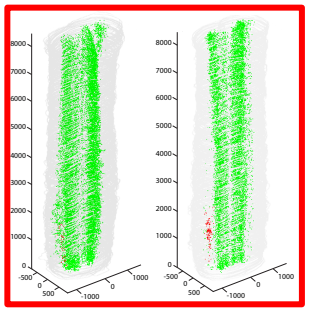


Non-Rhythmic Movement Reaching/Grasping





Modeling



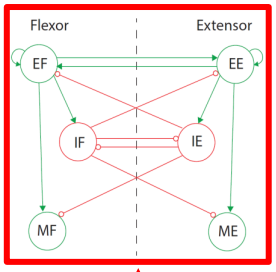
Anatomy

Reference

Atlas

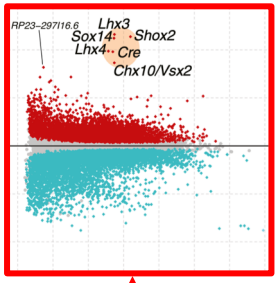
Modeling

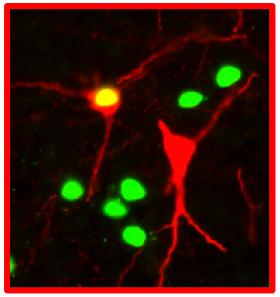
Golomb/Sharpee



Cell Phenotyping

Pfaff





Connectivity/
Physiology

Goulding

Behavior/
***In vivo* Physiology**

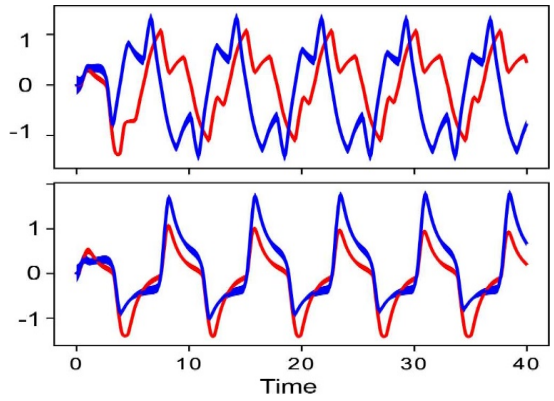
Azim/Nimmerjahn

DataCore

Sharpee

MetaCell

Model motoneuron and muscle recruitment during motor behaviors



Flexor

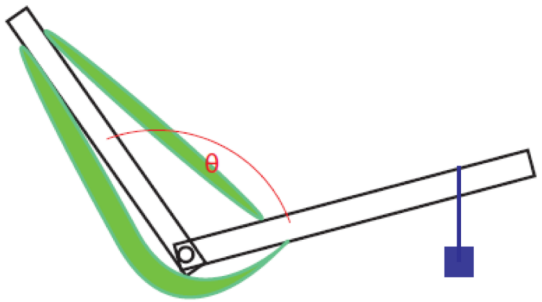
Extensor

Conductance-based model $C\frac{dV}{dt} = -\sum_{\text{ions}} I_{\text{ions}} - \sum_{\text{syn}} I_{\text{syn}}$

Develop models of single neurons and synaptic connections

These models will be incorporated into network models and will be used to evaluate the roles of intrinsic neuronal properties in network dynamics.

Model mechanical forelimb responses

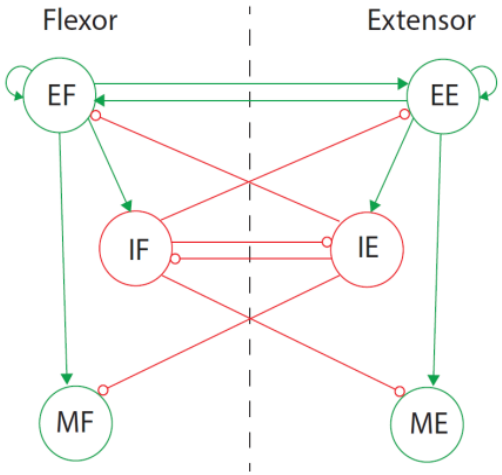


Newtonian mechanics, model for muscle contraction

Constructing simple mechanical models of the elbow and wrist joints

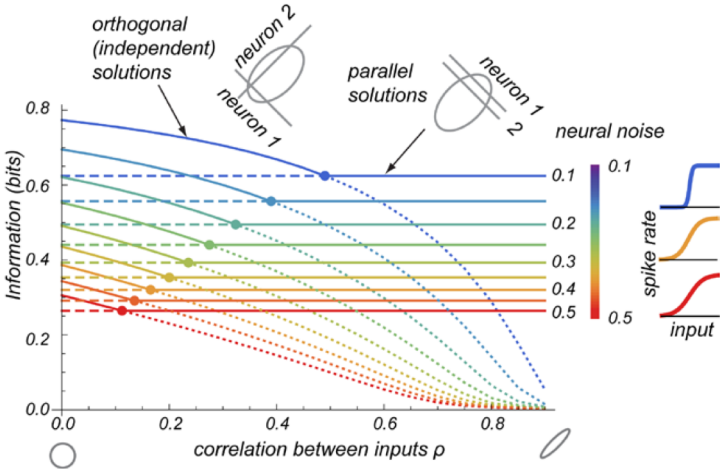
The mechanical models will be combined with the network models to demonstrate how the neuronal circuits control elbow and wrist movements.

Model optimal circuit configurations



Rate model $\frac{ds}{dt} = -\frac{s}{\tau_s} M \quad M = \beta[\sum_{\alpha} J_\alpha s_\alpha - a - \theta]_+$

Predict cell types



Control theory, Information theory

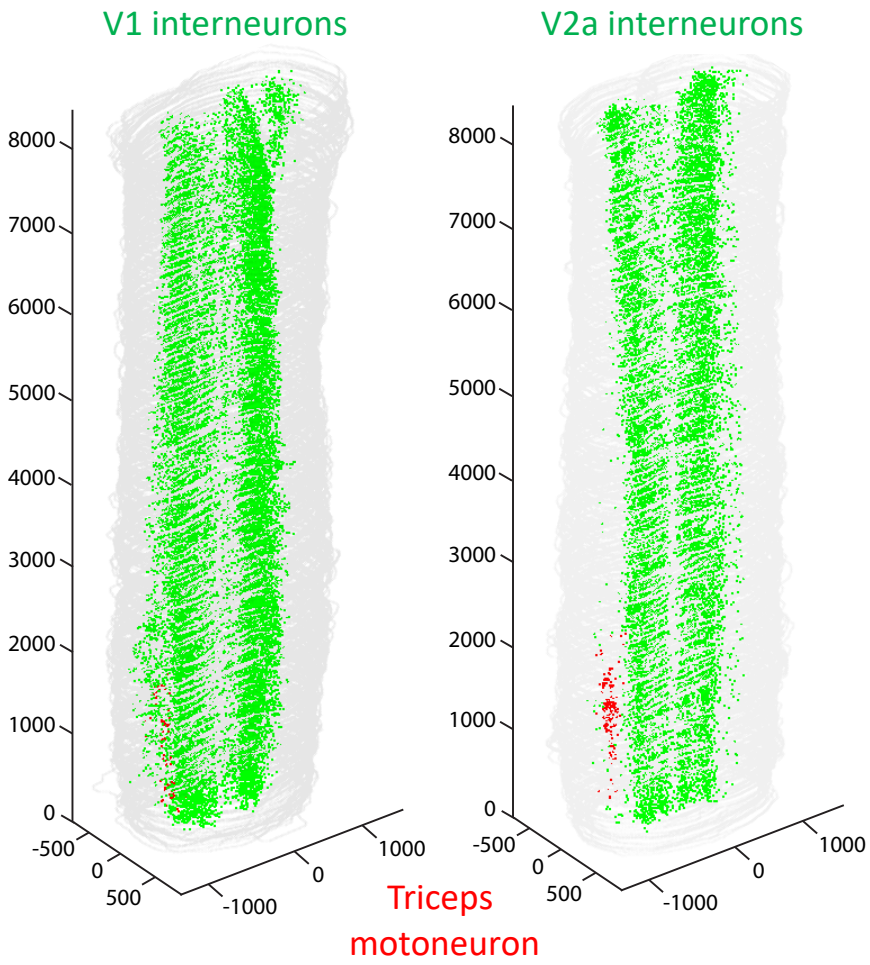
Building and analyzing models spinal cord circuits

The circuits models account for rhythm generation as well as transition to steady states. Conductance-based models are mapped to rate models that are amenable for analytical treatment.

Anatomical Scaffold for Modeling and Experimental Studies

Annotated Atlas of the cardinal premotor interneuron classes

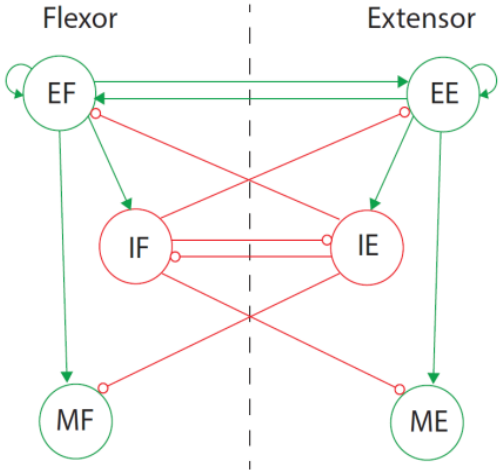
3D rendering of the spatial distribution of cardinal pre-motor interneurons and reference motoneurons



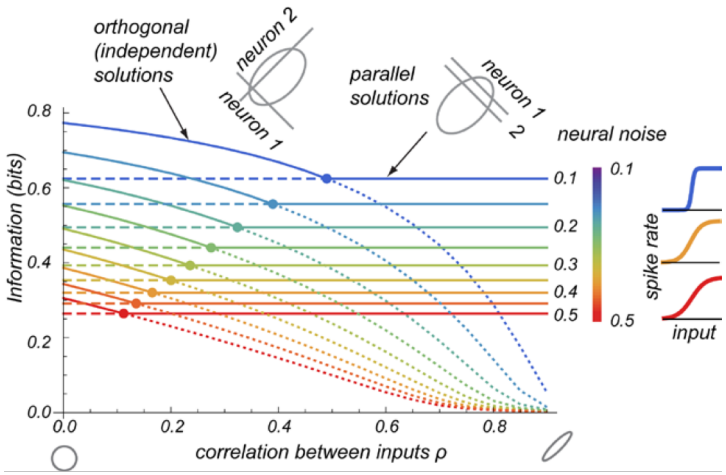
Spatial distribution plotted with Build-a-brain developed by Jeff Moore jemoore@salk.edu
3D rendering with Brainmaker and Neuroinfo from MBF

Modeling Approach

Model optimal circuit configurations



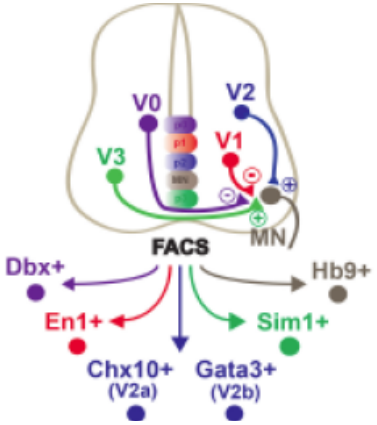
Predict cell types



Experimental Approach to Validate Predictions

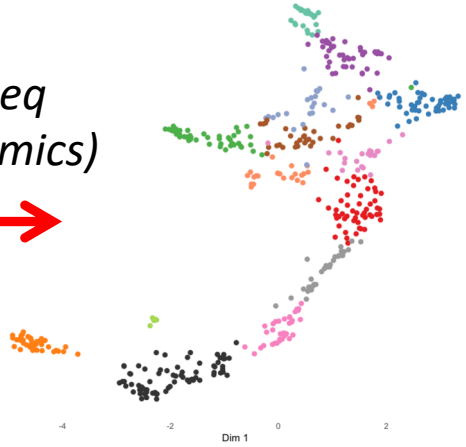
Molecular Heterogeneity

Embryonic (E13.5)
Postnatal (P14)
Adult



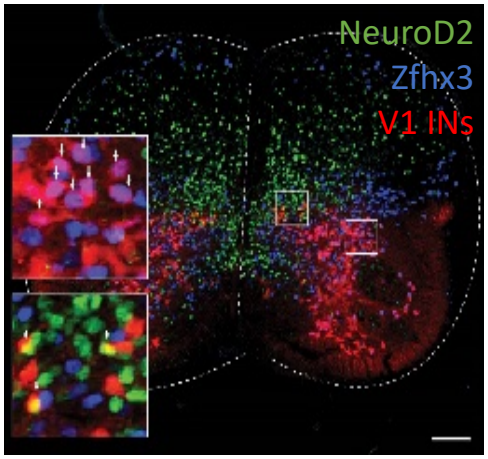
scRNAseq
(10x genomics)

Cluster analysis
& subtype identification

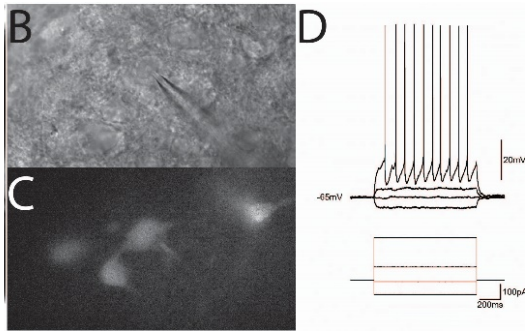


Subtype validation

Molecular identity

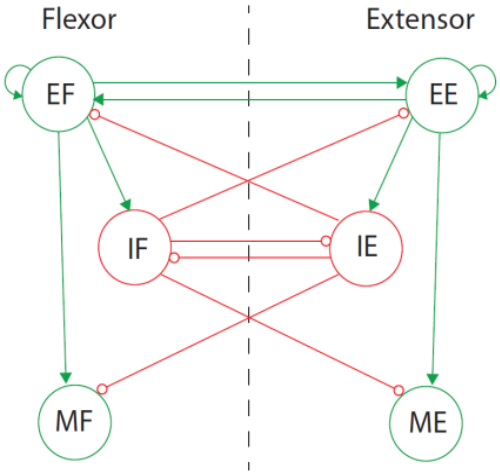


Intrinsic electrophysiological properties

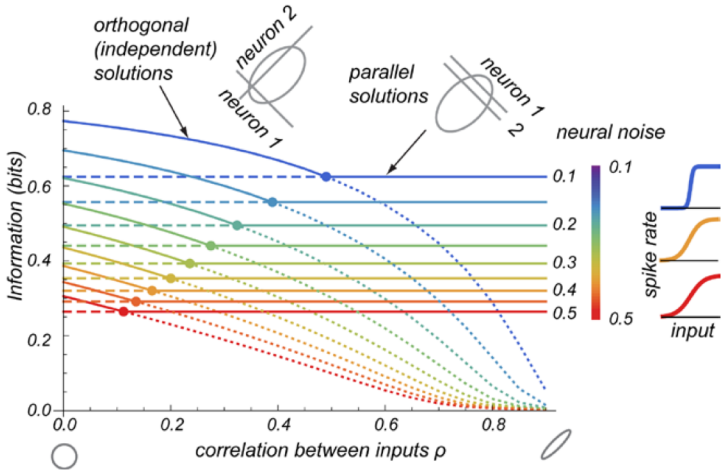


Modeling Approach

Model optimal circuit configurations



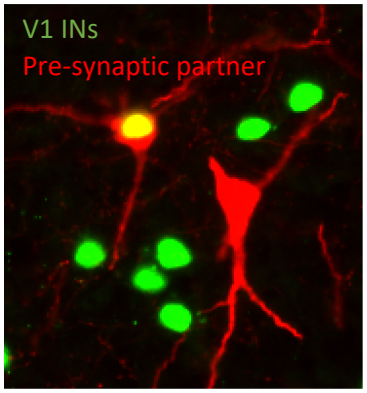
Predict cell types



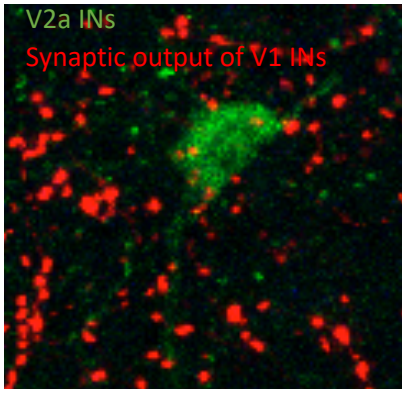
Experimental Approach to Validate Predictions

Anatomical Connectivity

Rabies tracings for pre-synaptic input

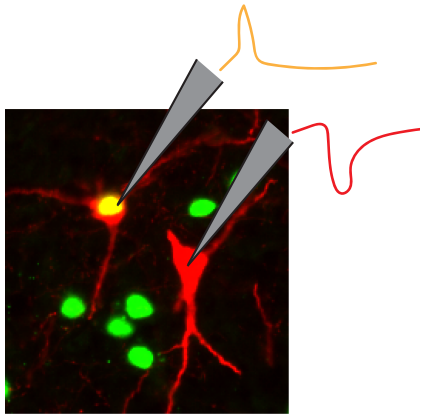


Viral tracings for post-synaptic output

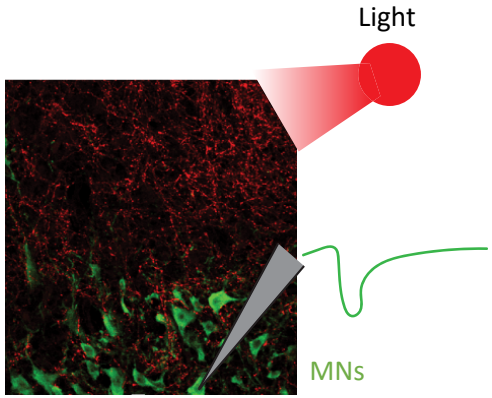


Functional Connectivity

Paired recordings

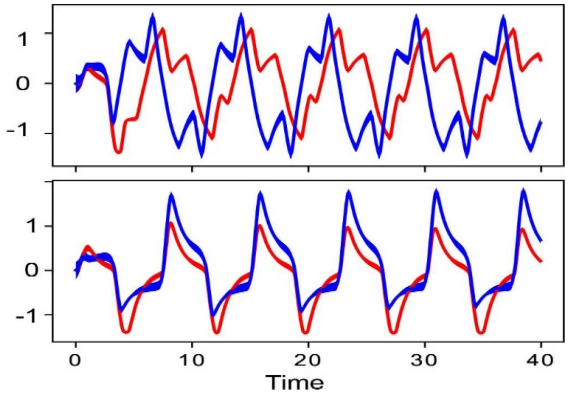


Optogenetic stimulation



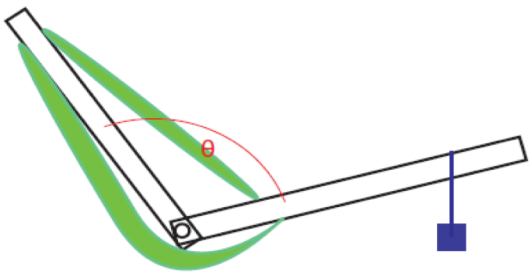
Modeling Approach

Model motoneuron and muscle recruitment during motor behaviors



Conductance-based model $C\frac{dV}{dt} = -\sum_{\text{ions}} I_{\text{ions}} - \sum_{\text{syn}} I_{\text{syn}}$

Model mechanical forelimb responses

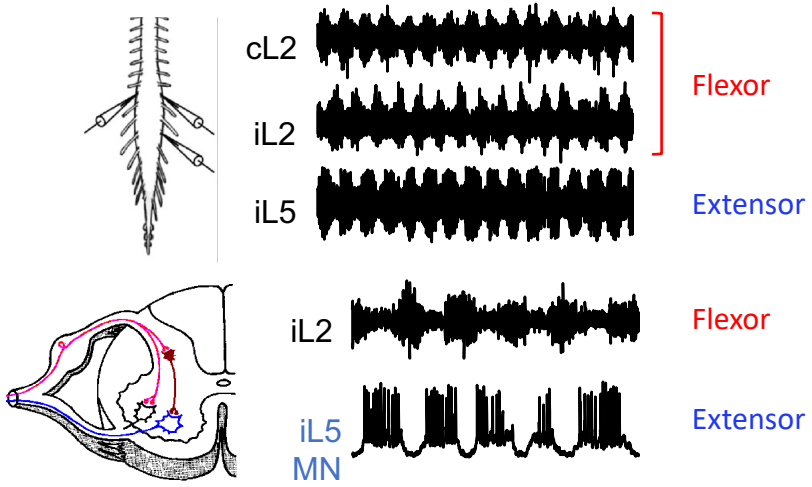


Newtonian mechanics, model for muscle contraction

Experimental Approach to Validate Predictions

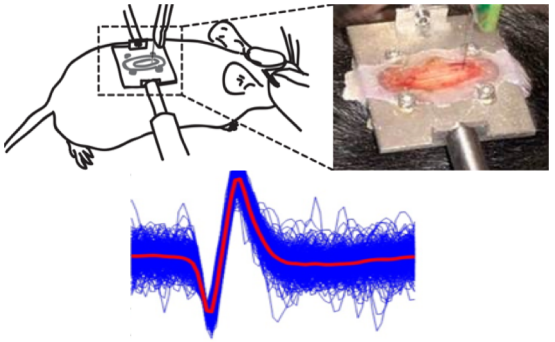
In vitro recordings

Measure changes in motoneuron currents upon modulating the activity of the cardinal pre-motor interneuron classes



In vivo spinal neuron recordings

Analyze the firing pattern of the cardinal pre-motor interneuron classes using opto-tagging in behaving mice



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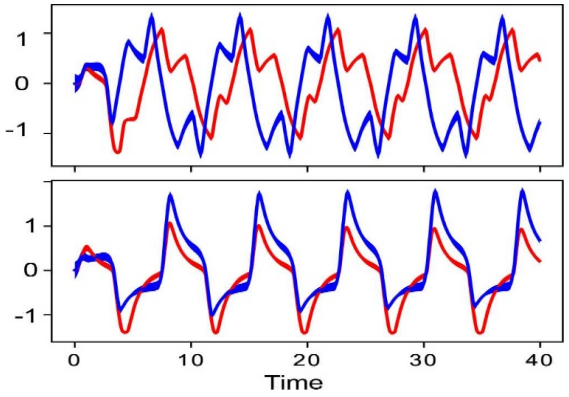

Flexor

Extensor

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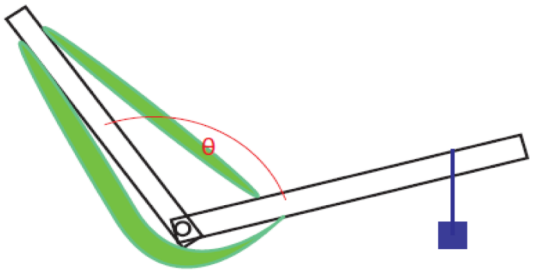
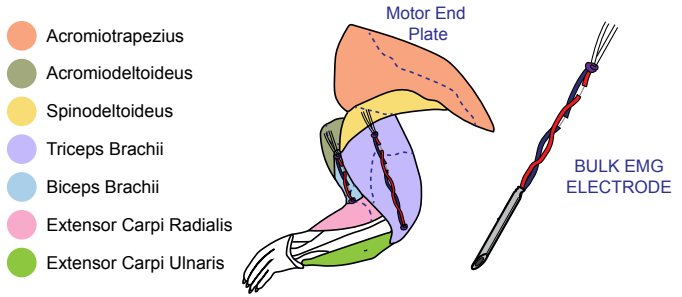
Model mechanical forelimb responses

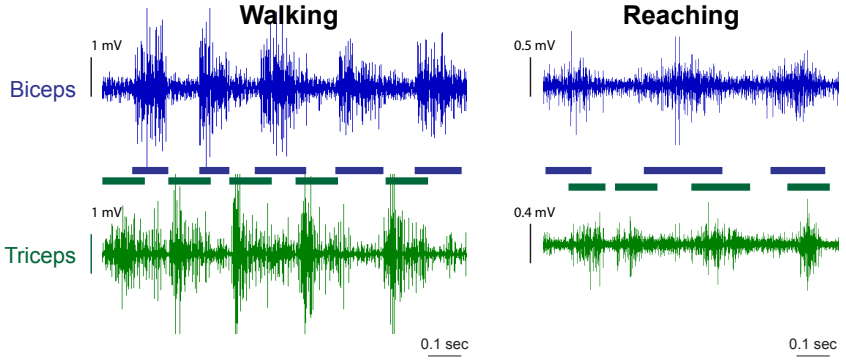


Newtonian mechanics, model for muscle contraction

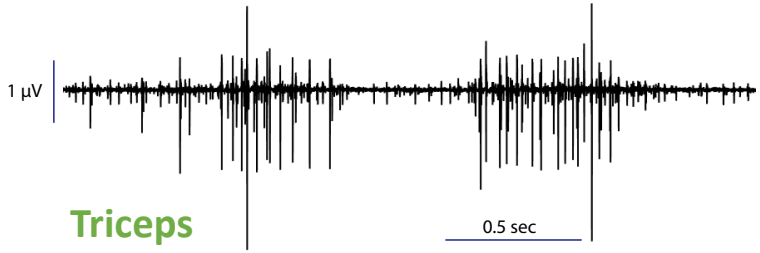
Experimental Approach to Validate Predictions

Bulk EMG Recordings in freely moving mice



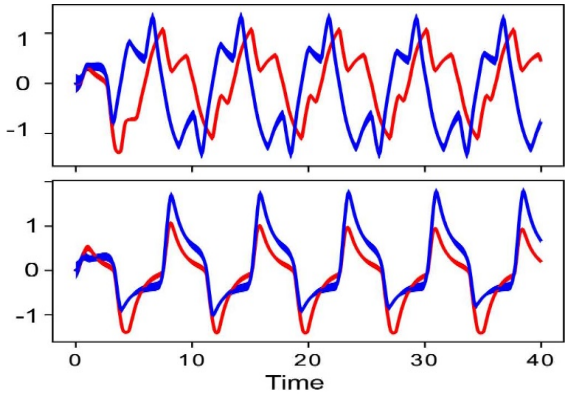


Single Motor Unit EMG Recordings



Modeling Approach

Model motoneuron and muscle recruitment during motor behaviors



Flexor

Extensor

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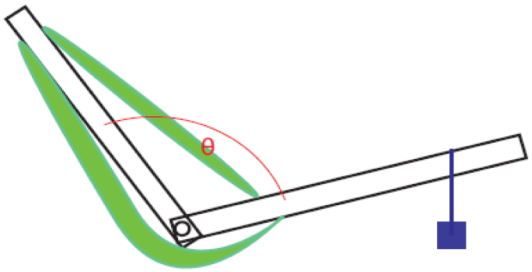
Model mechanical forelimb responses

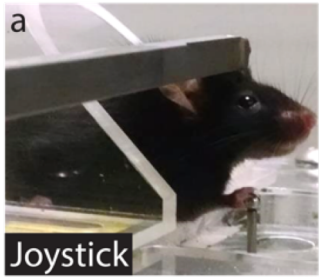


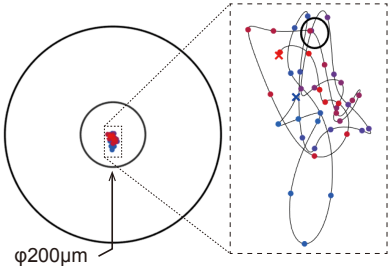
Newtonian mechanics, model for muscle contraction

Experimental Approach to Validate Predictions

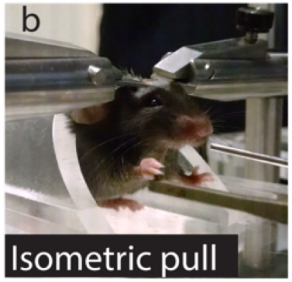
Measure motor behavior changes upon perturbing the function of the cardinal premotor interneuron classes

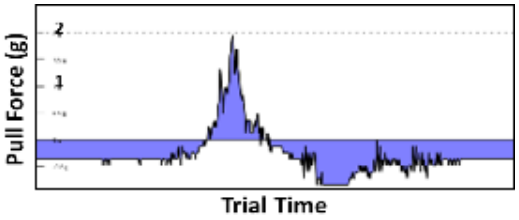
Elbow flexion/extension





Elbow isometric contraction





Wrist abduction/adduction