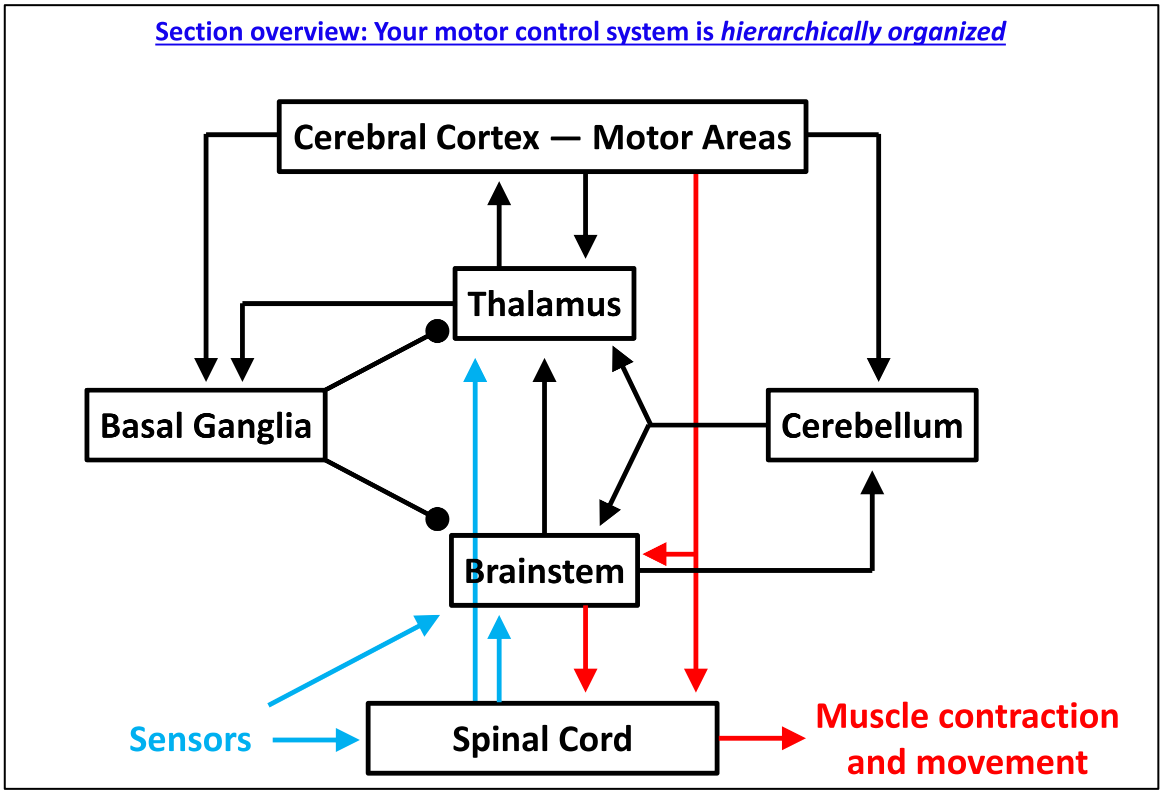
Lecture 22. Spinal Cord and Central Pattern Generation

Dr. Jesse Goldberg



Pre-lecture preparation: (you will be tested on this content)

1. Panopto video on Neuromuscular Junction, motor neurons and motor units
2. Panopto video on spinal reflexes and CPGs

Additional Reading (not required but may be helpful)

1. Wikipedia entry on the Neuromuscular Junction (NMJ), http://en.wikipedia.org/wiki/Neuromuscular_junction

2. Wikipedia entry on the disease of the NMJ, Myasthenia Gravis http://en.wikipedia.org/wiki/Myasthenia_gravis

3. Bear Textbook figures 13.1, 13.4, 13.9, Box 13.2, 13.29

Learning Objectives

A PDF of the PowerPoint slides from this lecture will be made available on the class website and will contain all key figures and concepts you need to know for this unit.

I. Be able to explain to your friends why animals have brains in the first place. (The case of the sea squirt: animals have brains for the purpose of moving)
II. Be able to invoke Marr's three levels to explain what it would mean to understand the neural basis of behavior.
III. Be able to visualize (and actually draw) the basic anatomy of the spinal cord, including (i) Motor neurons that project to muscle; (ii) Intrinsic spinal circuits that implement simple reflexes; and (iii) Spinal central pattern generators (CPGs) emerge from interactions between intrinsic and synaptic conductances.

Lecture Outline

<u>1. Introduction to the motor control section: Why we have brains? What does it mean to understand the link between brain and behavior?</u>

A. Organisms that move in a goal-directed fashion need nervous systems (trees don't think). The case of the sea squirt. They are mobile as larvae and at this stage they have a nervous system. Then they settle down and become sessile, and they digest their own brains!

Cortex
↓
basal ganglia
↓
Cerebellum
↓
brainstem
↓
Spinal cord
↓
neuromuscular junction

B. The motor system is hierarchically organized. From 'low' to 'high' in the hierarchy: neuromuscular junction, spinal cord, brainstem, cerebellum, basal ganglia, cortex.

C. What does it mean to understand the neural basis of behavior?

<u>Marr's Three levels of analysis:</u>

(1) Computational level: what does the system do (e.g.: what problems does it solve or overcome) and, equally importantly, why does it do these things.

(2) Algorithmic/representational level: How does the system do what it does, specifically, what representations does it use and what processes does it employ to build and manipulate the representations.

(3) Physical/implementation level: how is the system physically realized (what neural structures and neuronal activities implement the algorithm)

<u>2. Motor Neurons are the final common output of the nervous system</u>.
Neurons that contact muscle are called motoneurons. They are located in the ventral horn of the spinal cord.

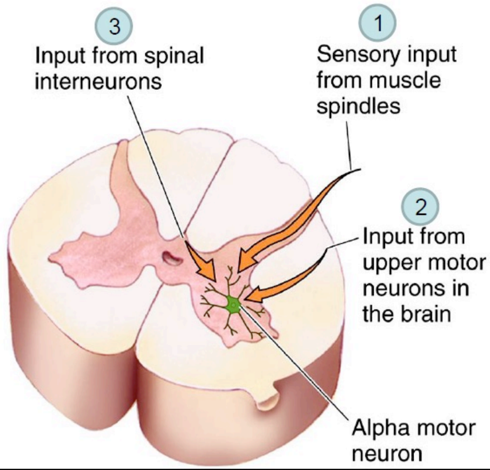
→ motoneurons contact muscles
→ Ventral horn of spinal cord.

A. The neuromuscular junction – Motoneurons release acetylcholine. Acetycholine receptors are clustered at the junction postsynaptically. They are calcium permeable and when the receptor open, calcium rushes in and depolarizes the muscle, causing a muscle action potential calcium-induced contraction. Note that CALCIUM IS THE ION THAT CONNECTS THE ELECTRICAL AND ORGANIC WORLDS – This is why it is the second messenger that links action potentials to downstream effector actions (such as muscle contraction in this case).

acH release → Ca^{2+} rushes in depolarizing muscle → AP Ca^{2+}-induced contraction

B. Definition of motor unit: the motoneuron and all of the muscle fibers it innervates. These behave as a functional unit in mammals because when the motoneuron fires an action potential, so do all of the muscle fibers it innervates.

Three inputs to spinal motor neurons



1. **Sensory input from muscle spindles (with information about the length of the muscle)**
2. **Inputs from upper motor neurons (e.g. in brainstem and cortex)**
3. ****Spinal interneurons (e.g. within the spinal microcircuit)**

<u>**3. Reflexes and Central Pattern Generators (CPGs).**</u>

A. Reflex. When you go to the doctor and he strikes your patella tendon on your knee,

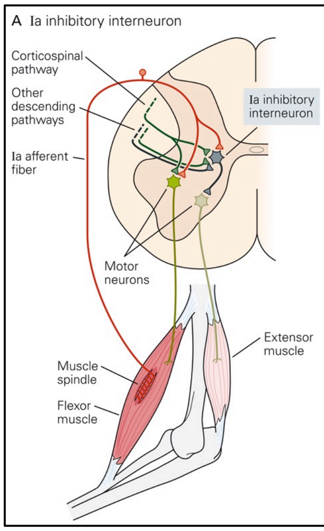


Figure 35–5 Inhibitory spinal interneurons coordinate reflex actions.

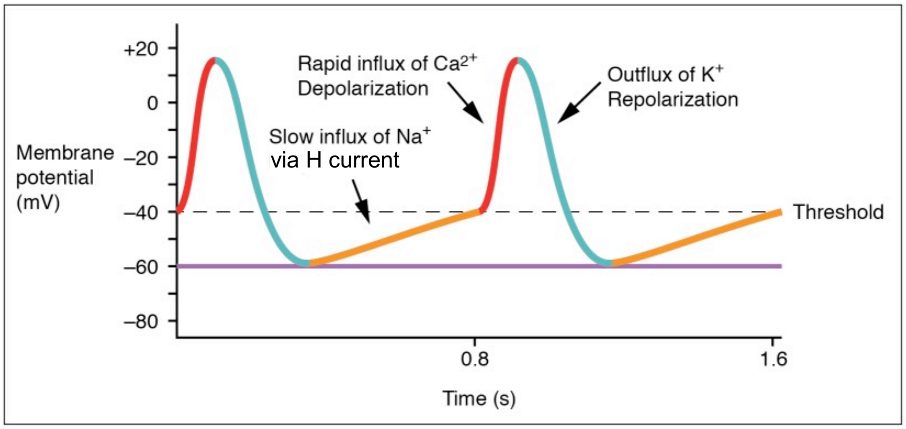
A. The Ia inhibitory interneuron regulates contraction in antagonist muscles in stretch-reflex circuits through its divergent contacts with motor neurons. In addition, the interneuron receives excitatory and inhibitory inputs from corticospinal and other descending pathways. A change in the balance of these supraspinal signals allows the interneuron to coordinate co-contractions in antagonist muscles at a joint.

you reflexively jerk your leg. It's like a chain of dominoes.

B. Central Pattern Generator: Many movements are rhythmic: the same movement is made over and over again (like when we breathe, walk, run, swim, chew etc).Neural circuits produce rhythmic action potential firing that, in turn, produce rhythmic behaviors.

Two main circuit mechanisms can create rhythmic output:
1. Intrinsic conductances in a cell:

Intrinsic conductances in a cell can create rhythmic output



An example of this is rhythmogenesis in the sinoatrial node of the heart. Intrinsic conductances of a single neuron can generate oscillations that drive rhythmic output (in this case the heart beat), as follows (see figure below).
1) There is no resting state – there is always an oscillation. But let's start with the rapid depolarization triggered by T-type calcium channels, which are activated at a low threshold (-40 mV). This depolarization activates voltage sensitive potassium channels, which re-polarize the membrane (to -60mV). This triggers the hyperpolarization activated current (the H current), which causes a slow depolarization until threshold for the calcium action potential is reached – A CYCLE!

2. Synaptic conductances in a network

CPGs get more interesting when the rhythm emerges from circuit interactions – that is, synaptic connectivity in a network. For example mutual synaptic inhibition between two neurons (half-center organization, see Kandel Figure 36-4b) that express the right repertoire of ion channels can comprise a simple oscillator – as follows:

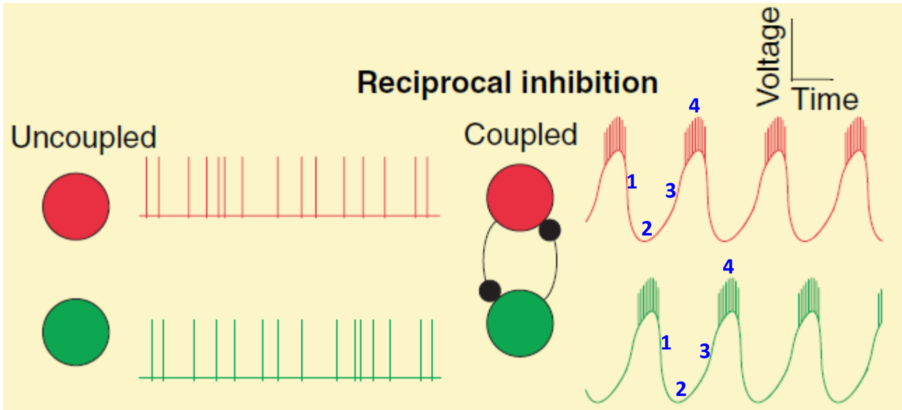
(≃ +20mV) (-60mV)

influx of Ca^{2+} → Depolarization → K^+ Voltage gated channels open → Cell hyperpolarizes

↓

I_h current activates causing **slow** depolarization until Ca^{2+} threshold is reached

A cycle!



When the two cells are disconnected (left) there is no rhythm (left).

When they are connected, a rhythm emerges by the following sequence, which repeats itself on each cycle

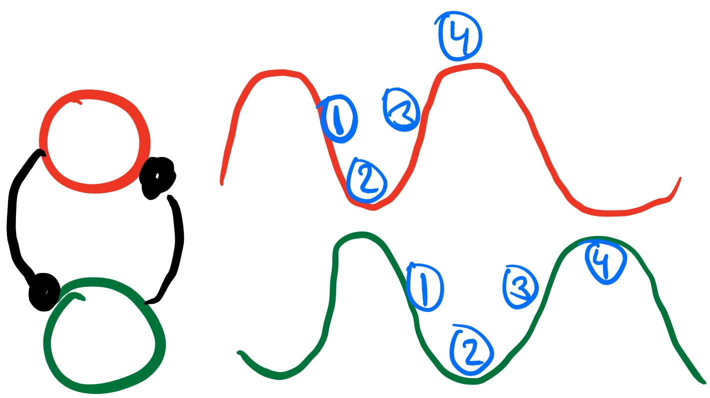
(1) Synaptic hyperpolarization → (2) Ih mediated slow depolarization → (3) Low threshold calcium channel fast depolarization → (4) Sodium action potentials (spikes)

There are two key rhythms for locomotion: Flexor – extensor alternation, and Left – right alternation.

Descending inputs from the brainstem 'turn on' spinal rhythms:

Rhythm generating circuits of the spinal cord are activated by descending inputs from the brainstem.

The MIDBRAIN LOCOMOTOR REGION sends axons to spinal CPGS to initiate locomotion.



Rhythms

- Left/Right Alternation
- Flexor/Extensor Alternation

(1) Synaptic hyperpolarization → (2) I_h mediated slow depolarization → (3) Low threshold Ca^{2+} channel fast depolarization → (4) Na^+ AP Spikes

- inputs from brainstem activate the rhythym generating circuits of spinal cord
- MIDBRAIN LOCOMOTOR REGION initiates locomotion by sending axons to spinal CPGS

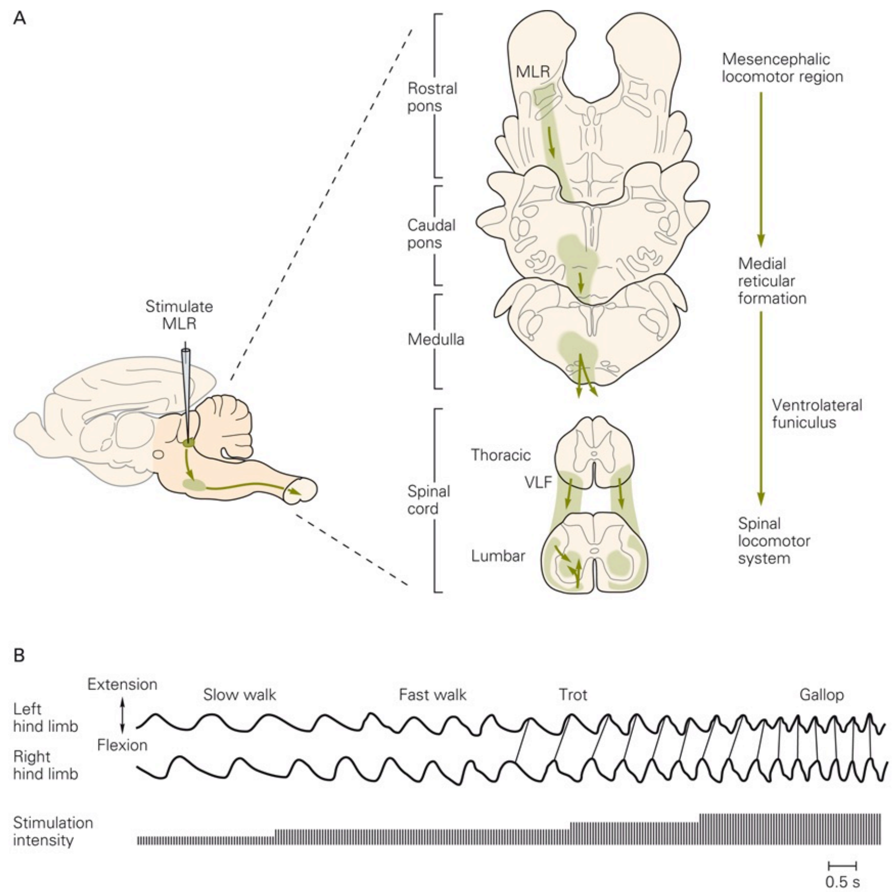


Figure 36–11 The mesencephalic locomotor region modifies stepping patterns.

A. Stimulation of the mesencephalic locomotor region (**MLR**) excites interneurons in the medial reticular formation whose axons descend in the ventrolateral funiculus (**VLF**) to the spinal locomotor system. (Adapted, with permission, from Mori et al. 1992.)

B. When the strength of stimulation of the mesencephalic locomotor region in a decerebrate cat walking on a treadmill is gradually increased, the gait and rate of stepping change from slow walking to trotting and finally to galloping. As the cat progresses from trotting to galloping, the hind limbs shift from alternating to simultaneous flexion and extension.

Study Questions

1. How could you slow down or speed up the cardiac rhythm? How about a locomotor rhythm?
2. How might increased MLR stimulation accelerate the locomotor rhythm?
3. Explain locomotion at each of Marr's three levels.
4. Devise an experiment to test if the rhythm generation in a CPG relies on the intrinsic conductances of a single neuron or if it instead results from synaptic interactions between multiple neurons.

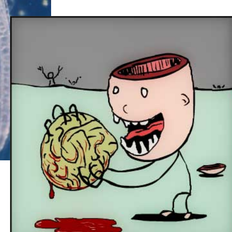
Movement is why we have brains

A tree

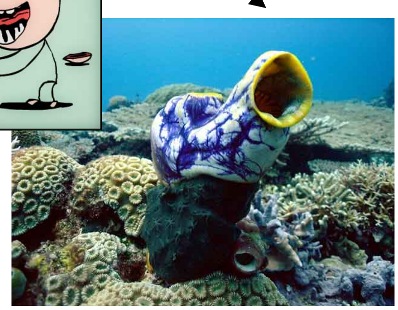
A fish

Some Tunicates (Sea squirts) digest their own brain after they settle down

Mobile larval stage

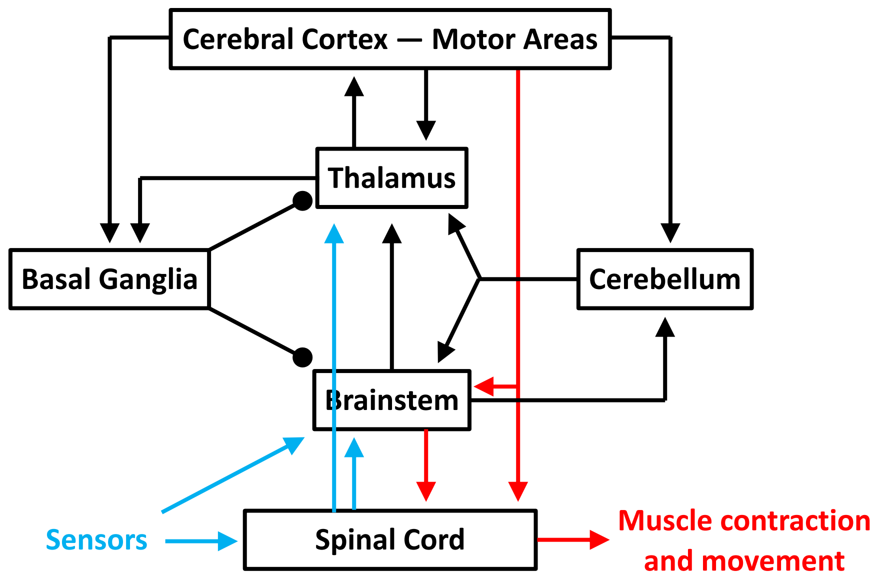


Sessile adult stage



If we can't move in response to our world, why have a brain at all?

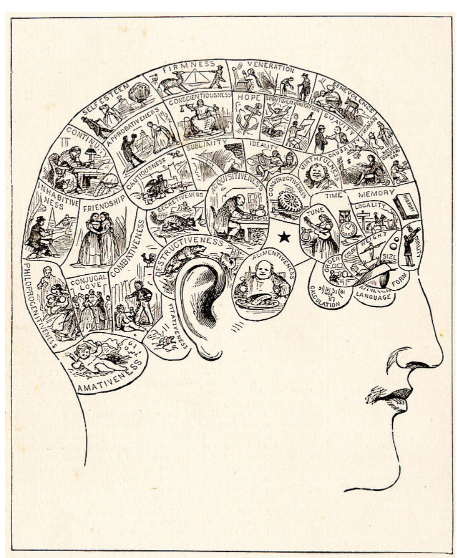
Your motor system is hierarchically organized



'Systems' neuroscience, a microcircuit-level understanding, and disease pathogenesis

What does it mean to understand the brain basis of behavior?

Phrenological chart, 1883

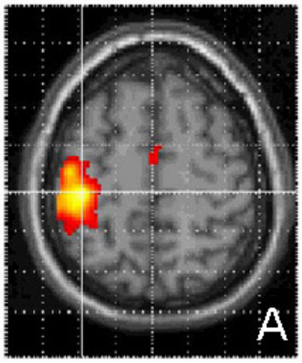


Phrenological Chart of the Faculties.

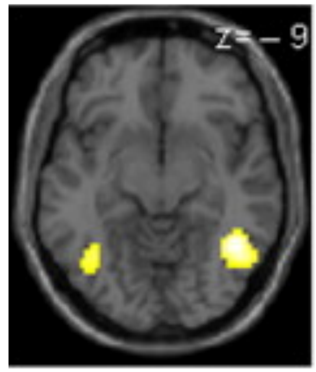
What does it mean to understand the neural basis of behavior?

<u>Functional magnetic resonance imaging (fMRI) allows us to peer inside the human brain in action</u>

"Tap your finger"



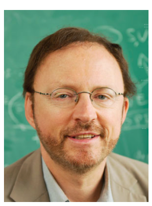
"Multiply 9 x 9"

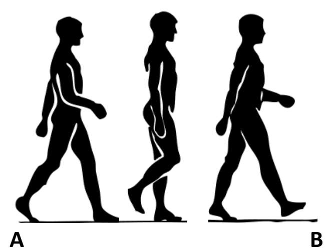


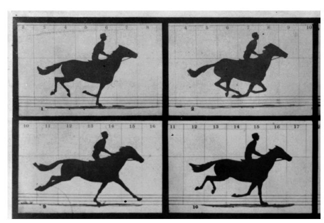
Localization of function is not sufficient…we aspire to understand what is *computed*

What does it mean to understand the neural basis of behavior?

David Marr 1945-1980







Marr's Three levels of analysis

1. Behavioral level: What does it do? Why?

Move from location 'A' to location 'B' (Locomotion)

2. Algorithmic level: What is the strategy? What representations are used?

WALKING: Rhythmic Left/Right and Flexor/Extensor Alternation

GALLOPING: Rhythmic Anterior/Posterior and Flexor/Extensor Alternation

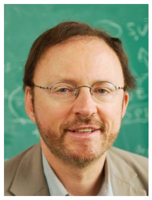
3. Implementation level: How is the algorithm *implemented* in physical reality

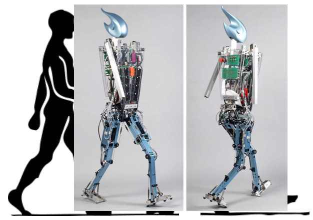
Neuronal networks that give rise to oscillations

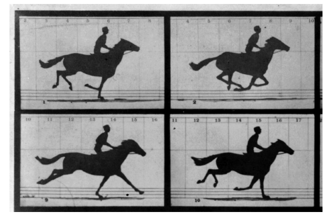
Synaptic inhibition between Left – Right Motor Outputs

What does it mean to understand the neural basis of behavior?

David Marr 1945-1980







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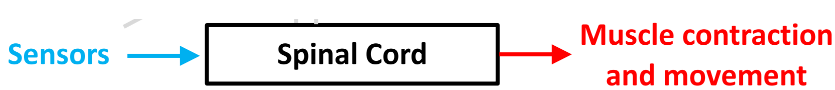
Boston Dynamics robots

Intrinsic circuits of the spinal cord: Simple reflexes and pattern generators

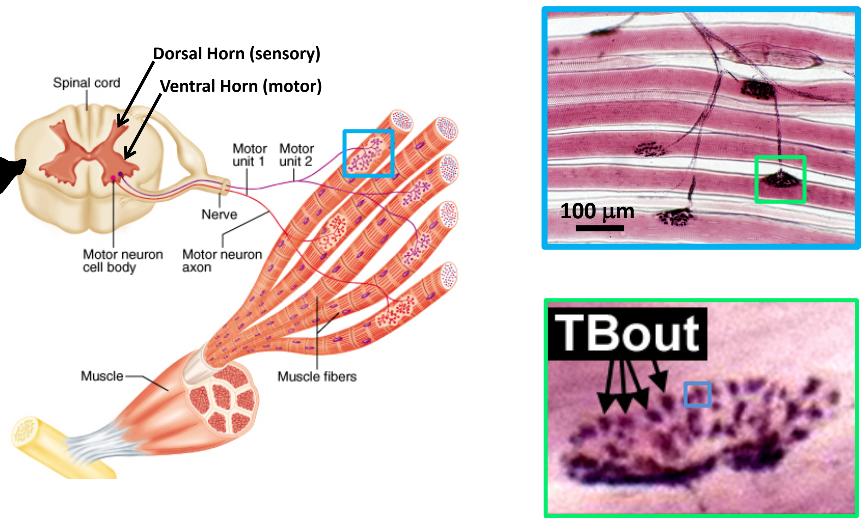
Goals of today's lecture

1. Neuromuscular Junction
2. Motor neurons and motor units
3. Simple Reflexes
4. Central Pattern Generators (CPGs)



Motor neurons terminate at the NEUROMUSCULAR JUNCTION

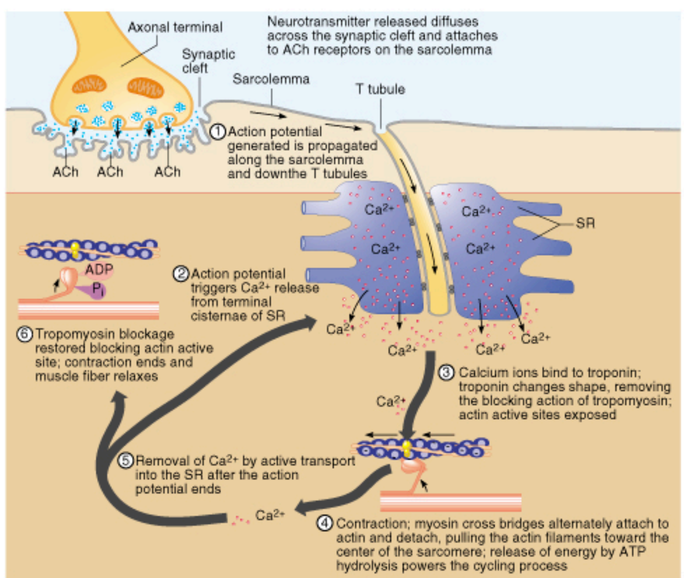
where white matter is



The motor unit: A motor neuron and all of the muscle fibers it targets

ach released @ neuromuscular junction

EXCITATION-CONTRACTION COUPLING at the neuromuscular junction



how action potential causes muscle contraction

Ach Release from terminal → Bind nAchRs → Muscle Na action potential → Calcium influx from intracellular stores (sarcoplasmic reticulum) → Muscle contraction

CLICKER QUESTION: Which of the following would cause a muscle weakness and / or paralysis?

A. An circulating antibody that destroys acetylcholine receptors at the neuromuscular junction (NMJ)

B. Ingestion of a drug that blocks cholinesterase, the enzyme that clears acetylcholine from the synaptic cleft at the NMJ More acH

C. Activation of excitatory inputs to motor neuron

D. Cancerous metastases that specifically lesioned the dorsal roots along several segment of the spinal cord

E. None of the above.

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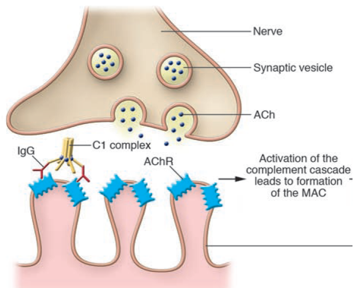
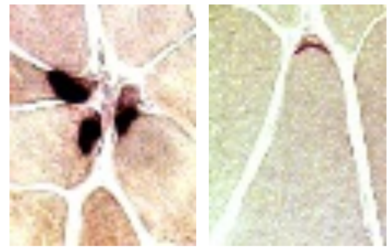
E. None of the above.

Myasthenia Gravis: A disease of the neuromuscular junction:
Antibodies against the nAch receptor on muscle attack the NMJ



Normal | Myasthenia Gravis

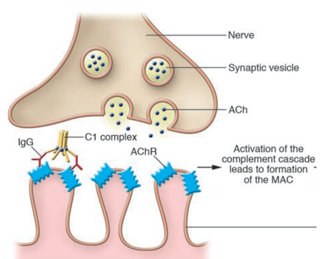


Myasthenia Gravis results in INTENSE muscle weakness and fatigue

0 sec | **+ 10 sec upward gaze (Simpson)** | **+ 30 sec upward gaze (Simpson)**

[Young woman with myasthenia gravis]

CLICKER QUESTION: What treatment might help a patient with myasthenia gravis?



A. An acetylcholine receptor antagonist

B. A calcium channel antagonist

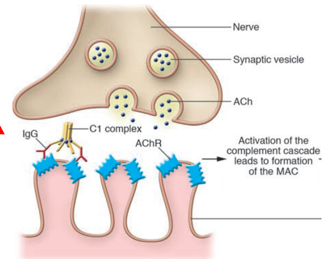
C. A cholinesterase antagonist that increases Ach levels in the synaptic cleft

D. An infusion of antibodies against the Ach receptor

E. Sodium channel antagonist

CLICKER QUESTION: What treatment might help a patient with myasthenia gravis?

In MG, nAChRs are blocked, so one treatment option is to increase Ach levels at the synapse by blocking Ach breakdown



A. **An acetylcholine receptor antagonist**

B. **A calcium channel antagonist**

C. **A cholinesterase inhibitor that increases Ach levels in the synaptic cleft**

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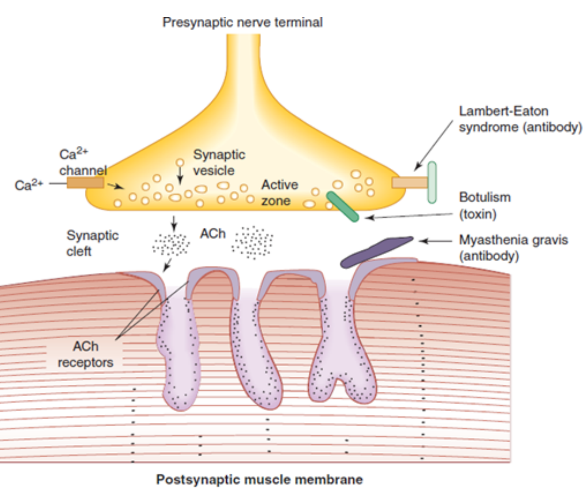
Other diseases of the neuromuscular junction



Lambert Eaton: Antibodies against Ca channels necessary for Ach vesicle release
Botulism Toxin: Blocks vesicle release
Myasthenia gravis: Antibodies against Ach Receptor

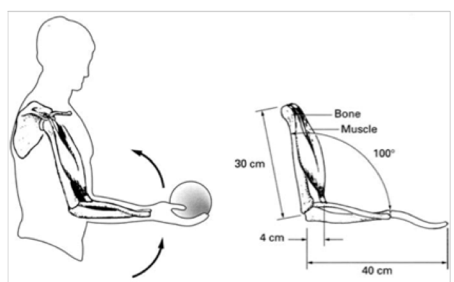
Intrinsic circuits of the spinal cord: Simple reflexes and pattern generators

Goals of today's lecture

1. Neuromuscular Junction
2. Motor neurons and motor units
3. Simple Reflexes
4. Central Pattern Generators (CPGs)

Sensors → Spinal Cord → Muscle contraction and movement

Three levels of the spinal STRETCH reflex



***1. Computational/Behavioral Level*: What does it do?**

Maintain limb stability – maintain joint angle stability

2. Algorithmic Level: What is the strategy? What representations are used?

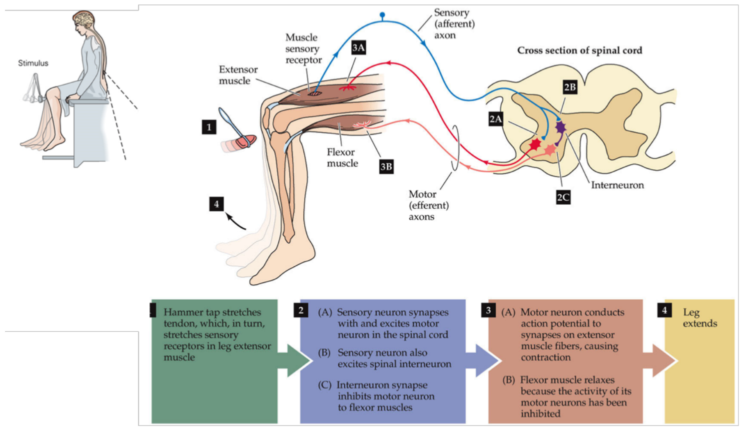
Counteract unexpected change to joint angle

If a muscle is stretched – then contract it

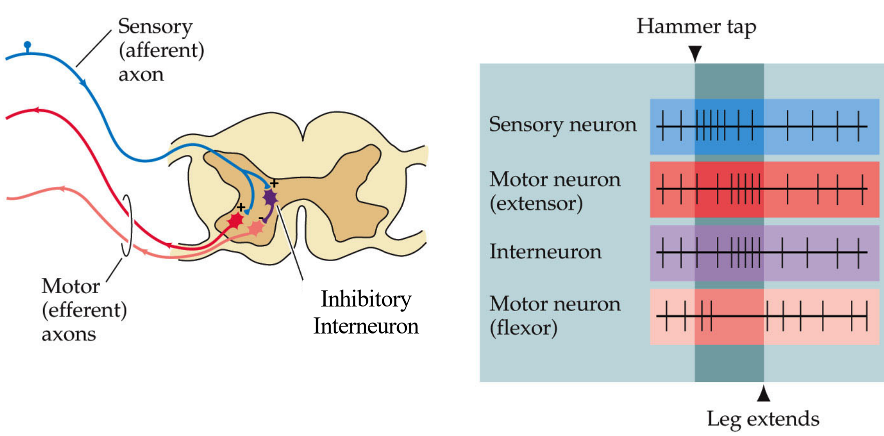
3. Implementation level: How is the algorithm implemented in physical reality

A spinal microcircuit links a STRETCH RECEPTOR to a MUSCLE CONTRACTOR

The stretch reflex relies on a relatively simple spinal circuit



Signal propagation through spinal circuit controlling the knee jerk reflex



Intrinsic circuits of the spinal cord: Simple reflexes and pattern generators

Goals of today's lecture

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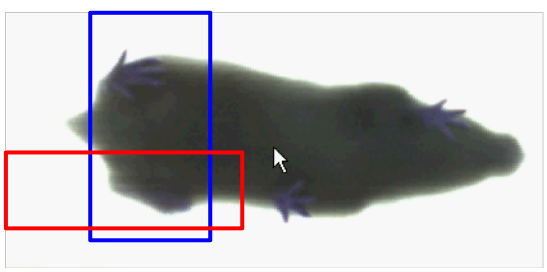
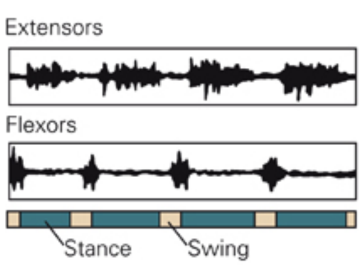
Sensors → Spinal Cord → Muscle contraction and movement

Many behaviors are rhythmic and internally generated





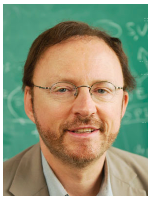
Flexor – Extensor Alternation

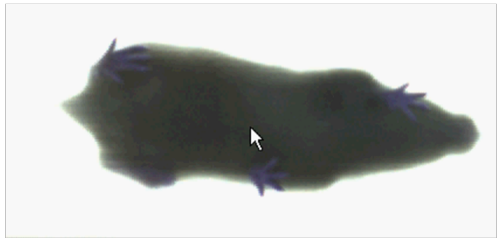
Left – Right Alternation

All you need to implement this is a rhythmogenic circuit (a CPG)!

What does it mean to understand the neural basis of behavior?

David Marr 1945-1980





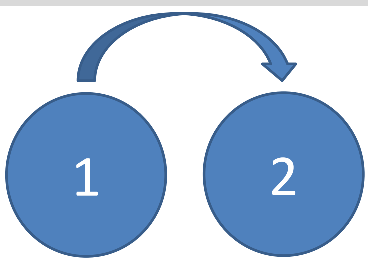
Marr's Three levels of analysis

1. ***Behavioral level***: What does it do?
   Move from location 'A' to location 'B' (Locomotion)

2. ***Algorithmic level: What is the strategy? What representations are used?***
   WALKING: Rhythmic Left/Right and Flexor/Extensor Alternation

3. ***Implementation level***: How is the algorithm *implemented* in physical reality
   Neuronal networks that give rise to oscillations
   Synaptic inhibition between Left – Right Motor Outputs

CLICKER QUESTION: A small circuit consists of an intrinsically bursting neuron 1 which synapses on neuron 2. If you break the synaptic connection between neurons 1 and 2, what would happen to the firing pattern of neuron 1?



A. It would stop bursting, and start firing erratically

B. It would start bursting faster

C. It would start bursting slower

D. Nothing.

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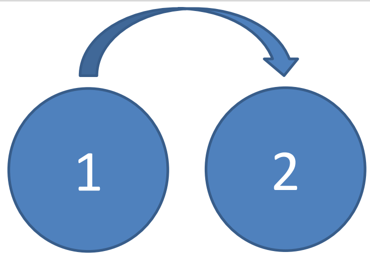

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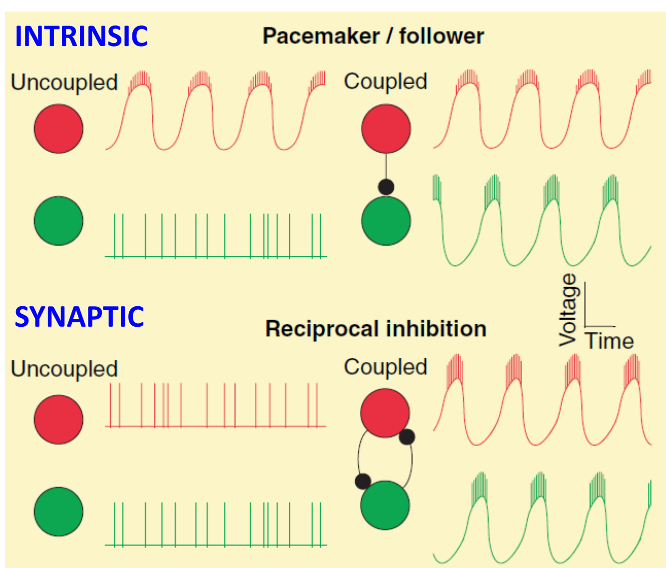
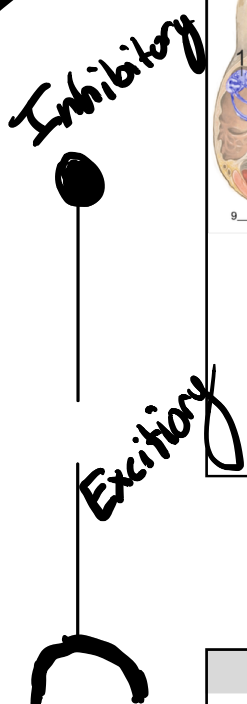
Cellular mechanisms of CPGs: (1) Intrinsic and (2) Synaptic conductances

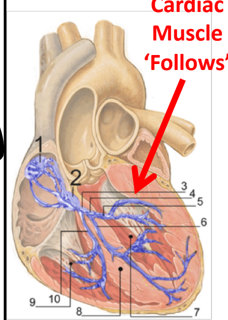


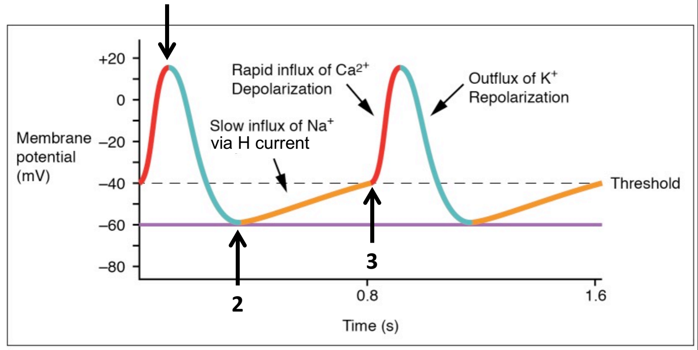
Notation



The Cardiac rhythm is an example of a pacemaker-driven CPG

Cardiac pacemaker cells in the sinoatrial node (SA node)





Pacemaker cells always oscillate

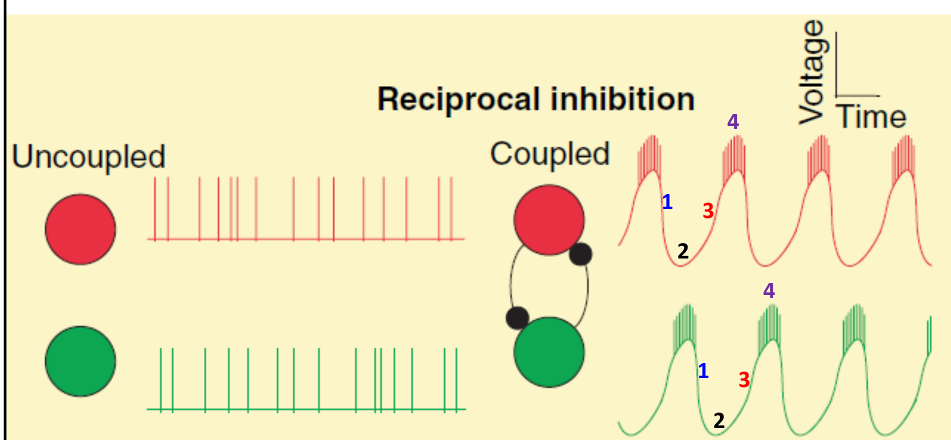
Pacemaker cells have no resting state – when they are ON they are always oscillating!

(1) Potassium current (I_K)-mediated hyperpolarization → (2) H current (I_h) mediated depolarization (slow Na influx) → (3) Calcium Action Potential → Go back to (1)

"inf." rhythym

The H current (also called the hyperpolarization activated cation current)
Facilitates post inhibitory rebound bursting which allows a neuron to be activated once inhibition ends

Half-center oscillator is an example of a network-driven CPG

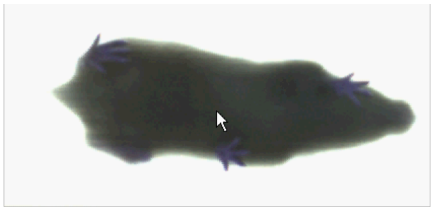


When the two cells are disconnected (left) there is no rhythm (left).

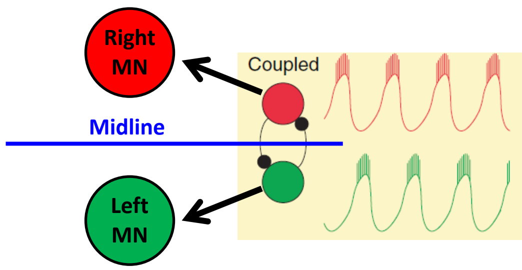
When they are connected, a rhythm emerges by the following sequence, which repeats itself on each cycle:

(1) Synaptic hyperpolarization → (2) I_h mediated slow depolarization→ (3) Calcium channel fast depolarization → (4) Sodium action potentials (spikes) → Go to (1)

Half-center oscillator is an example of a network-driven CPG

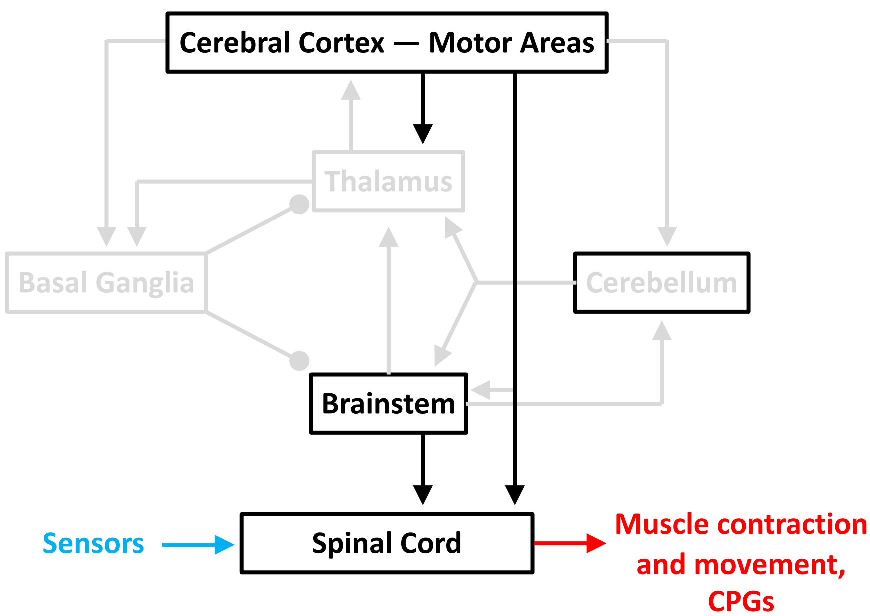


Half-center oscillators can mediate alternation during locomotion



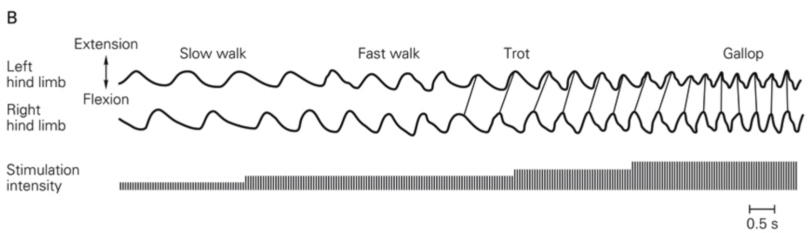
What 'turns on' a CPG in the spinal cord?

Descending inputs to spinal cord can turn on CPGs



Stimulation of the Midbrain locomotor region in the brainstem triggers locomotion

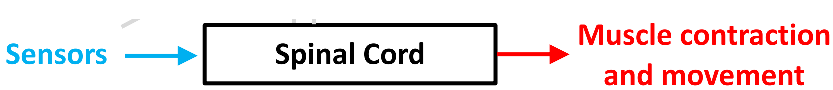
http://www.youtube.com/watch?v=wPiLLplofYw



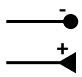
Intrinsic circuits of the spinal cord: Simple reflexes and pattern generators

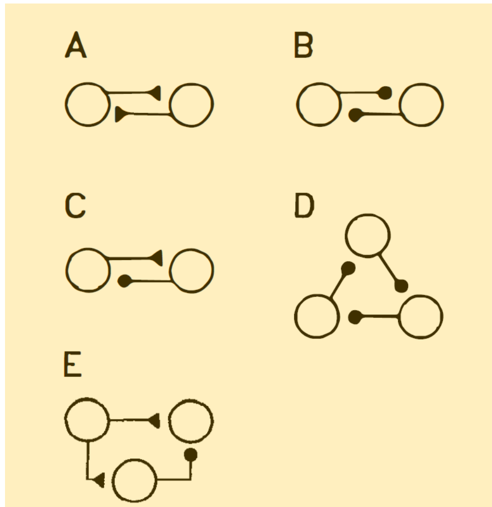
Goals of today's lecture

1. Neuromuscular Junction
2. Motor neurons and motor units
3. Simple Reflexes
4. Central Pattern Generators (CPGs)

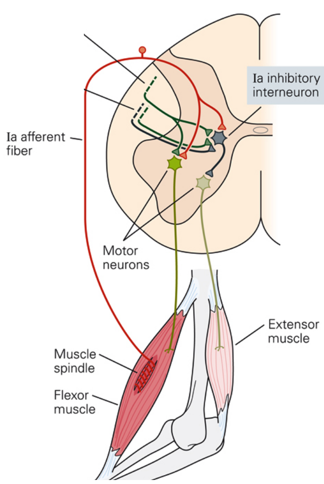


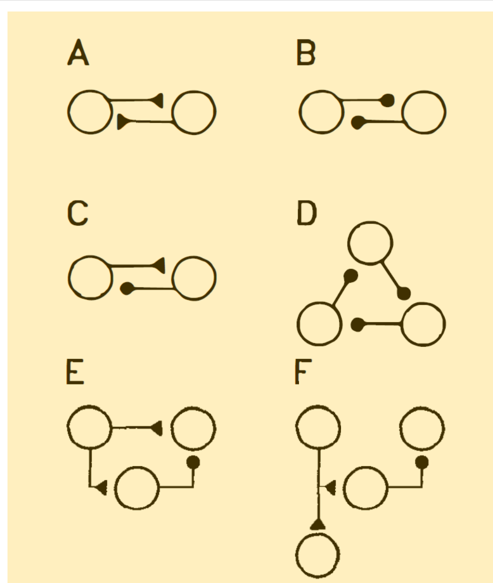
Discussion Question: All neurons in these microcircuits are oscillating. Which microcircuit definitely has an intrinsically bursting neuron driving the rhythm?





Discussion question: Which of these is the spinal microcircuit implementing the stretch reflex?

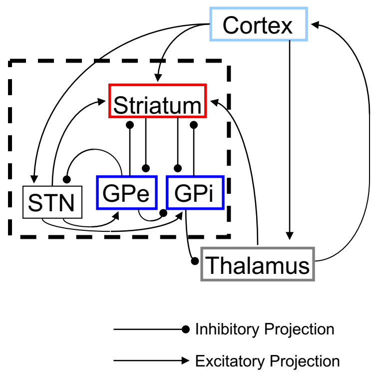




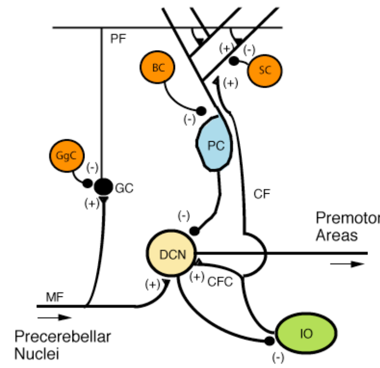
Little microcircuit diagrams…

CPGs provide basic insights into reading wiring diagrams for higher brain circuits

The basal ganglia-thalamocortical circuit



The cerebellar brain circuit



"Half center oscillator."

Lecture this Monday: Motor Cortex and Free Will