FMR
Physiology

SKELETAL, CARDIAC, AND SMOOTH MUSCLE

BY TYLER BLAND[1] AND MEIZE GUO[2]
UNIVERSITY OF IDAHO[1] AND UNIVERSITY OF FLORIDA[2]

Session Learning Objectives

SLO1. Explain how muscle contracts, outlining how sliding of actin filaments in sarcomeres is driven by ATP-dependent cycling of myosin motor proteins.

SLO 2. Explain excitation-contraction coupling and relaxation in skeletal muscle by identifying the roles of t-tubules, calcium channels (Cav1.1 and the ryanodine receptor), thin filament regulators (troponin and tropomyosin), and ATP-dependent calcium pumps.

SLO3. Compare twitch contractions for slow/type 1 and fast/type 2 skeletal muscle fibers and explain the molecular bases for the differences in behavior. Define isometric and isotonic contractions.

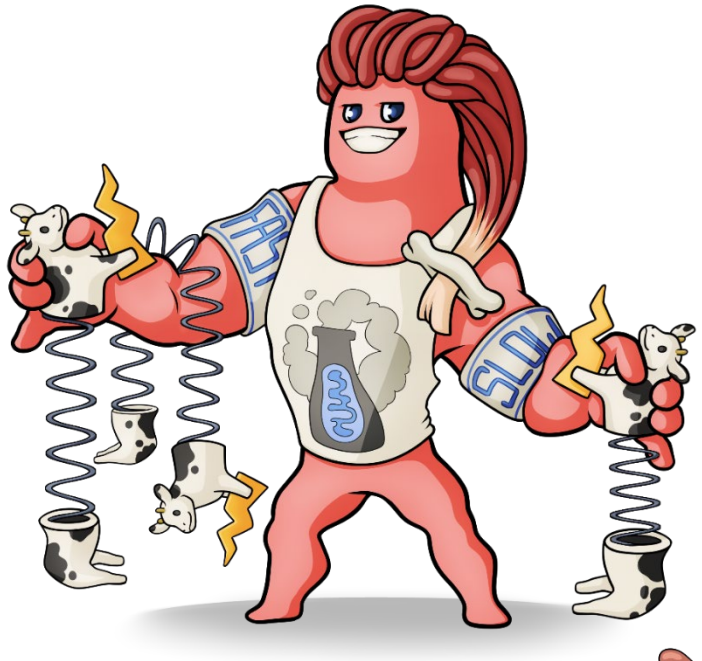
SLO4. Explain how smooth, graded contractions of a skeletal muscle are produced by changes in stimulus intensity and the size principle of motor unit recruitment.

SLO5. Understand the differences in excitation-contraction coupling between skeletal, cardiac, and smooth muscle. Describe the two-stage phospho-regulatory cascade that initiates smooth muscle contraction.

SLO6. Compare and contrast how skeletal, cardiac, and smooth muscle are controlled by the nervous system. Define single-unit vs. multi-unit smooth muscle types.

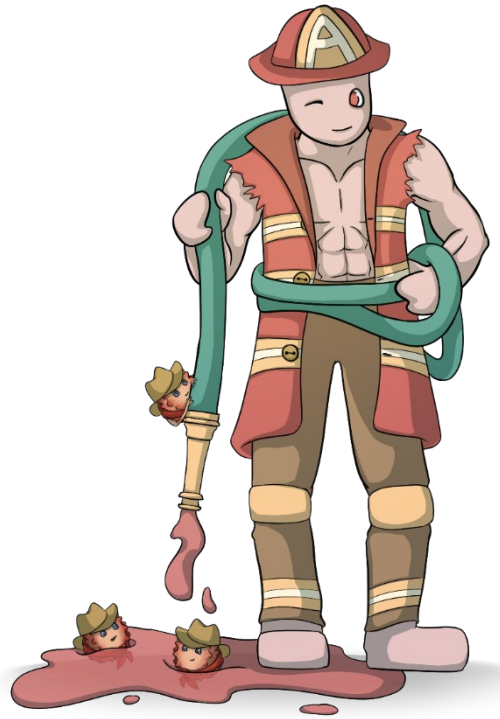
MEDIMON

A GAME OF MEDICAL MONSTERS



SKELETAL MUSCLE

HEART

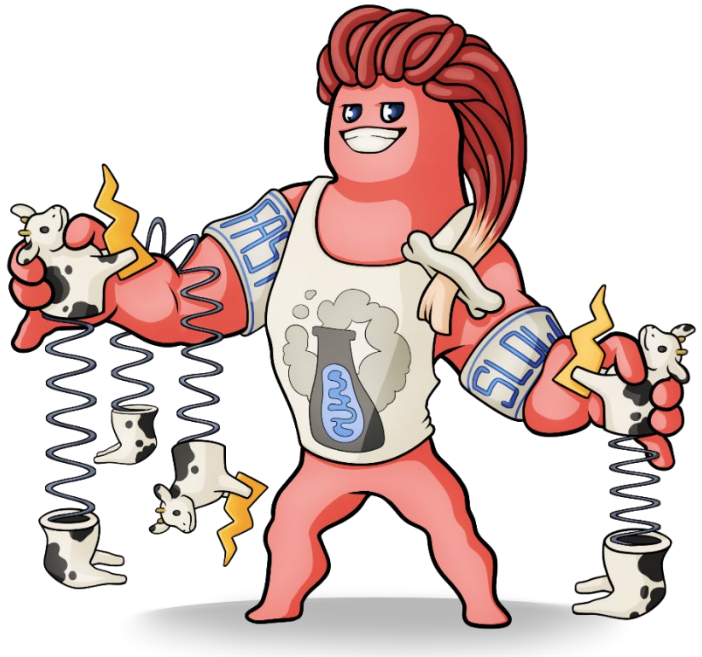


ARTERY

BRONCHIAL TREE

MEDIMON

A GAME OF MEDICAL MONSTERS

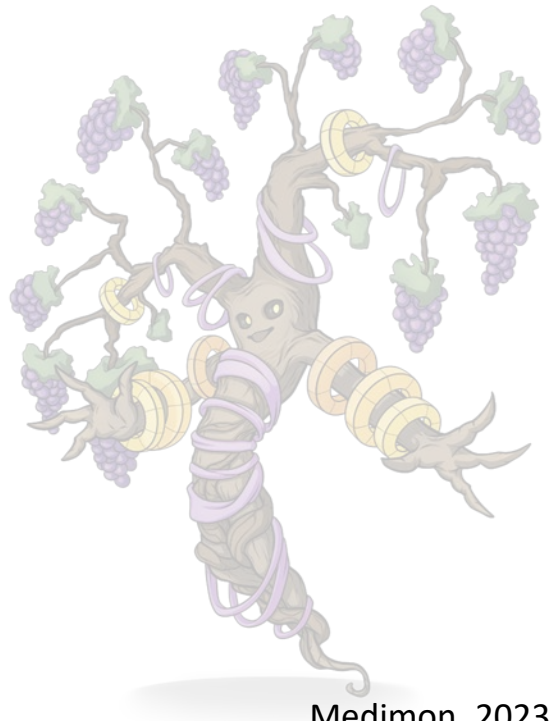


SKELETAL MUSCLE

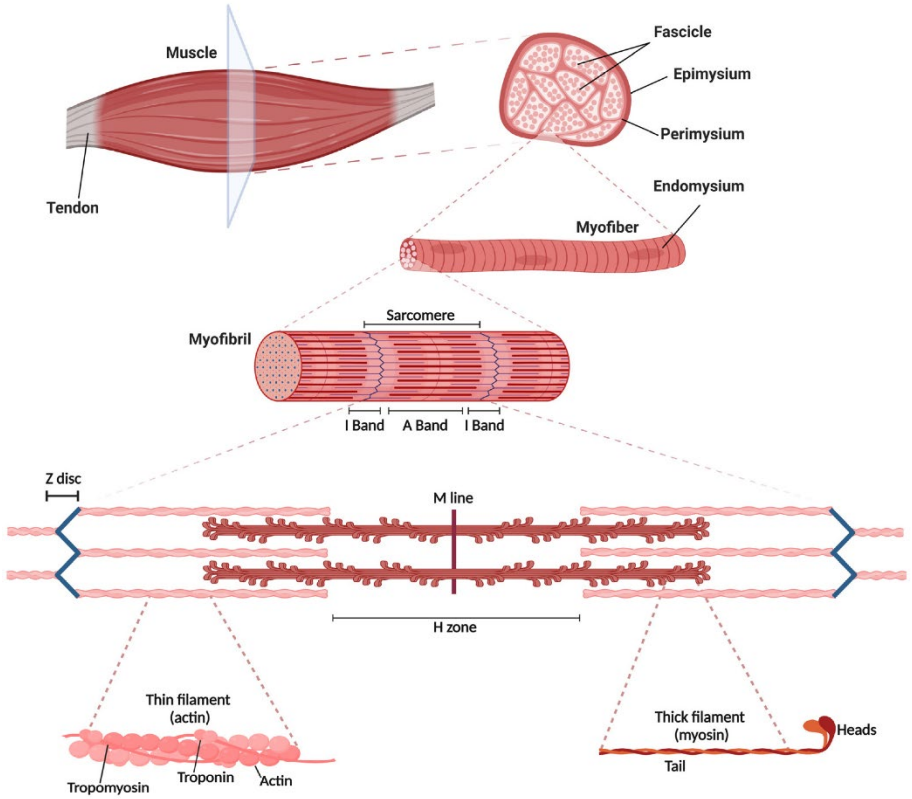
HEART

ARTERY

BRONCHIAL TREE

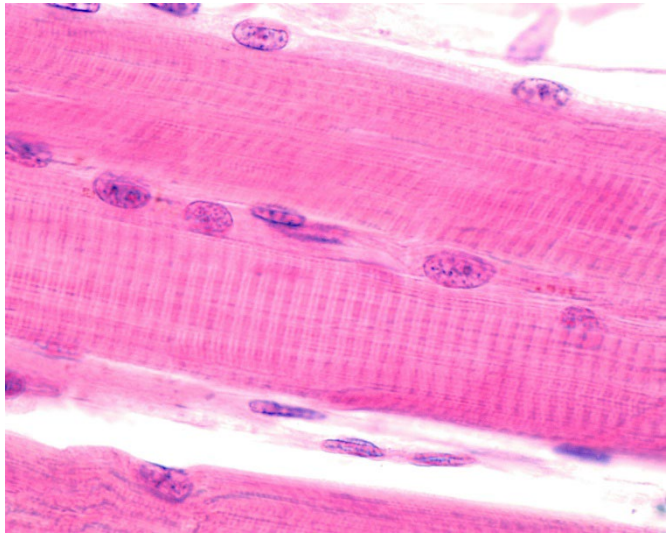


Skeletal muscle
(hierarchical organization)



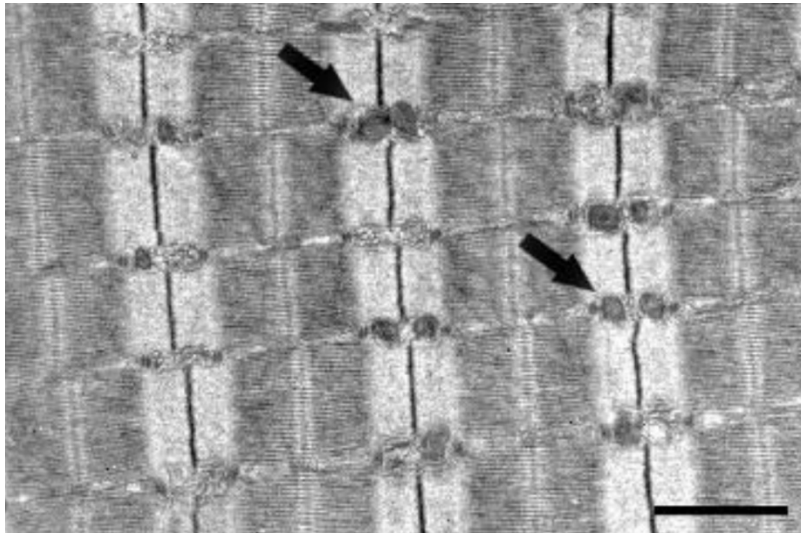
Zuccaro et al, 2023

muscle fibers
(by light microscopy)



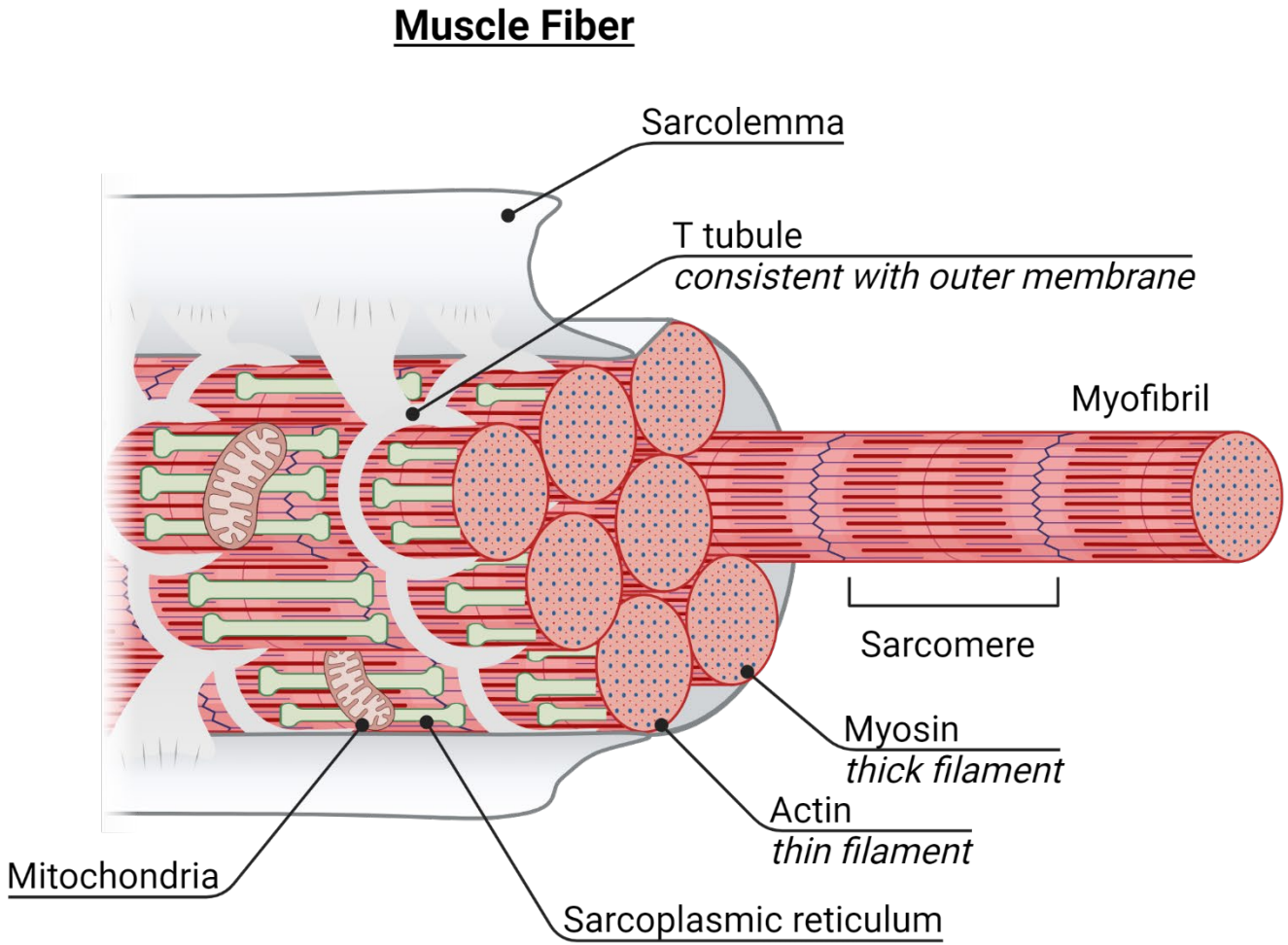
JosLuis, stock.adobe.com

Myofibrils
(electron microscopy)



Stevens et al, 2022

Skeletal muscle
(hierarchical organization)

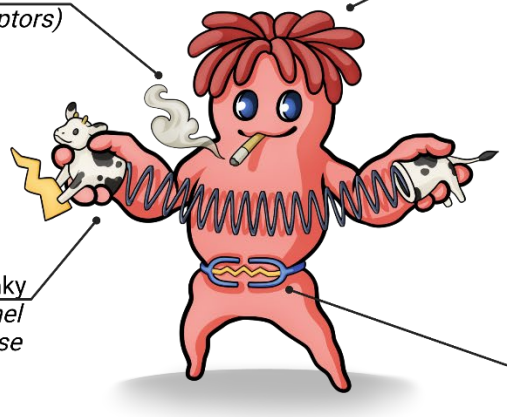


- Excitation travels deep into muscle fiber through **T-tubules**
- **T-tubules** pass very near the **sarcoplasmic reticulum**

MEDIMON

A GAME OF MEDICAL MONSTERS

MYOFIBRIL



Cigarette
(nicotinic receptors)

Dreadlocks
(bundle of actin/myosin filaments)

Cow holding lightning bolt slinky
- *lightning bolt: voltage gated Ca^{2+} channel*
- *slinky: calcium mediated Ca^{2+} release*

Squeezing belt
(sarcomere - contracts)

MUSCLE FIBER

Dreadlocks
(made of bundle of myofibrils)

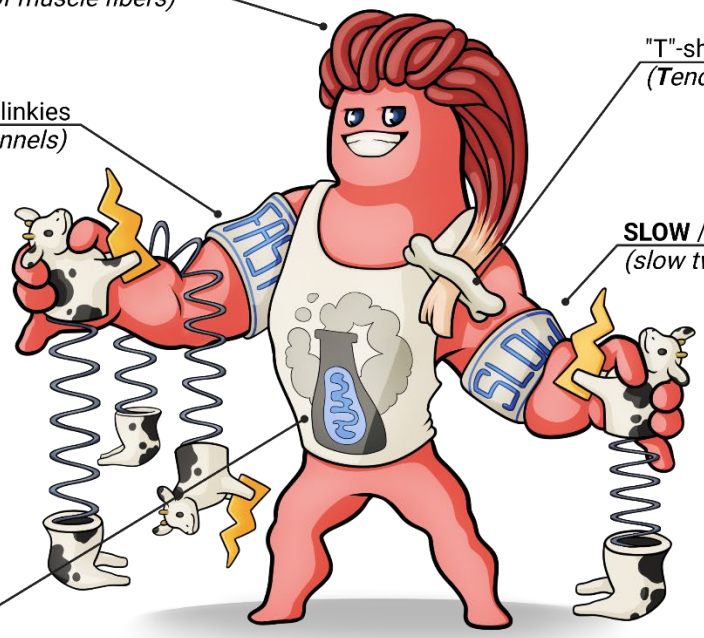
Sarc lama head band
(sarcolemma surrounds fiber)

T-shirt
(t-tubule)

Lightning bolt down to cow belt
(electric signal from t-tubule activates calcium release)

Cow **Ca**lcium belt
(calcium causes cell to constrict)

MUSCLE



Dreadlocks
(made of bundle of muscle fibers)

"T"-shaped bone hair band
*(**T**endons connect muscle - bone)*

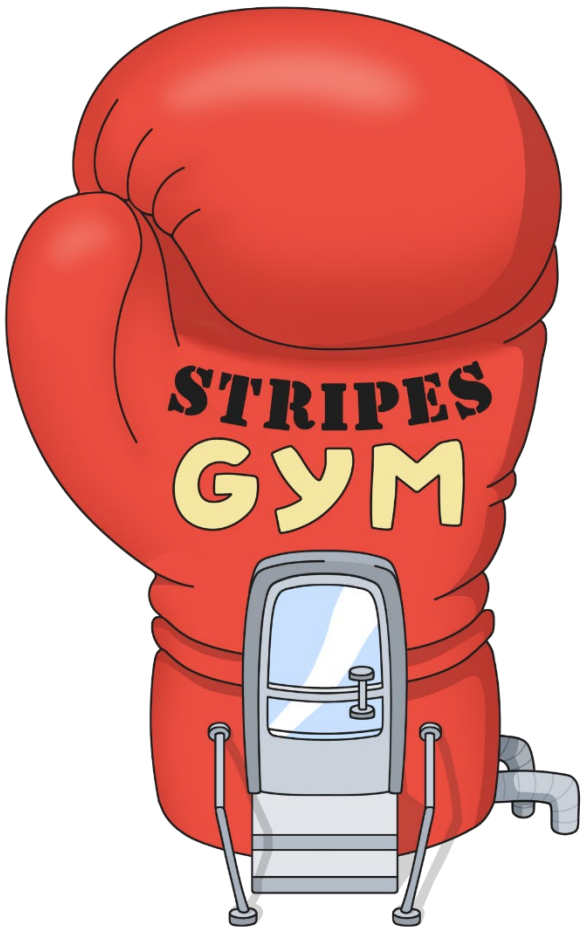
FAST / multiple slinkies
(fast twitch have more Ca_{2+} channels)

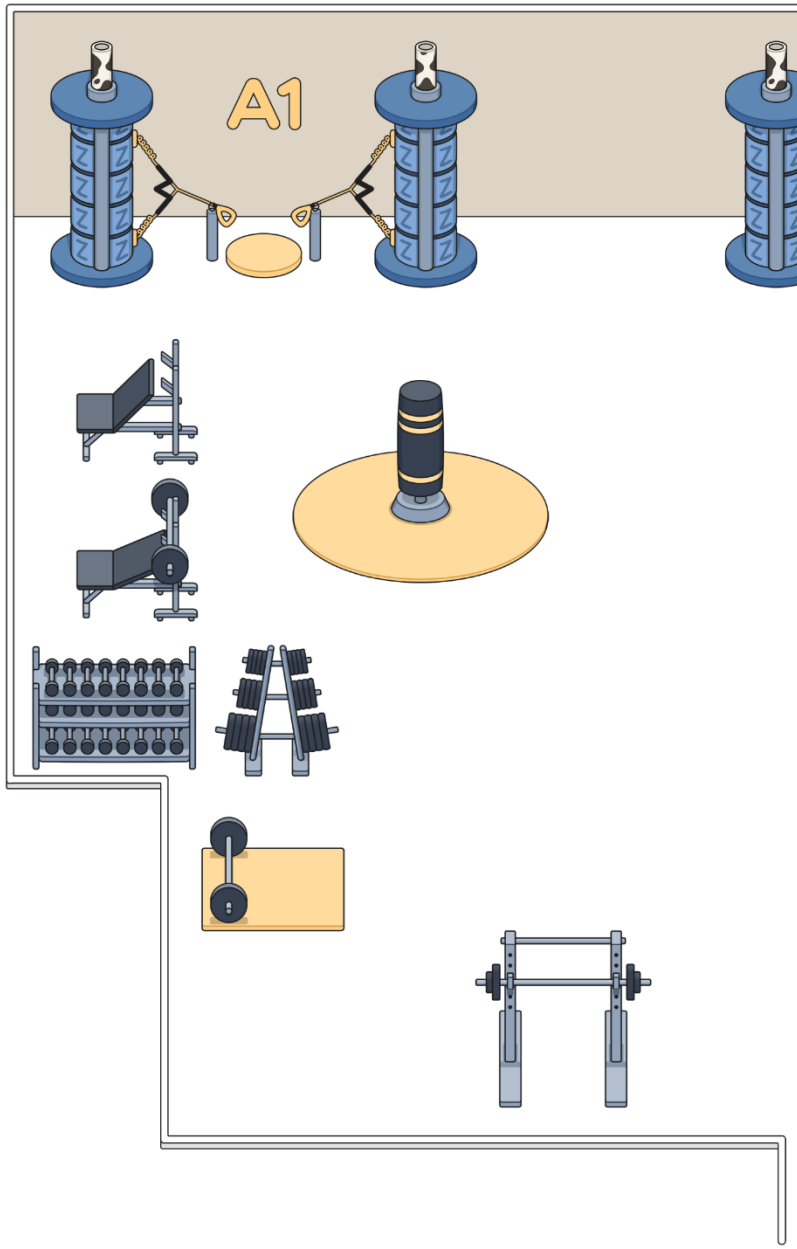
SLOW / single slinky
(slow twitch have fewer Ca_{2+} channels)

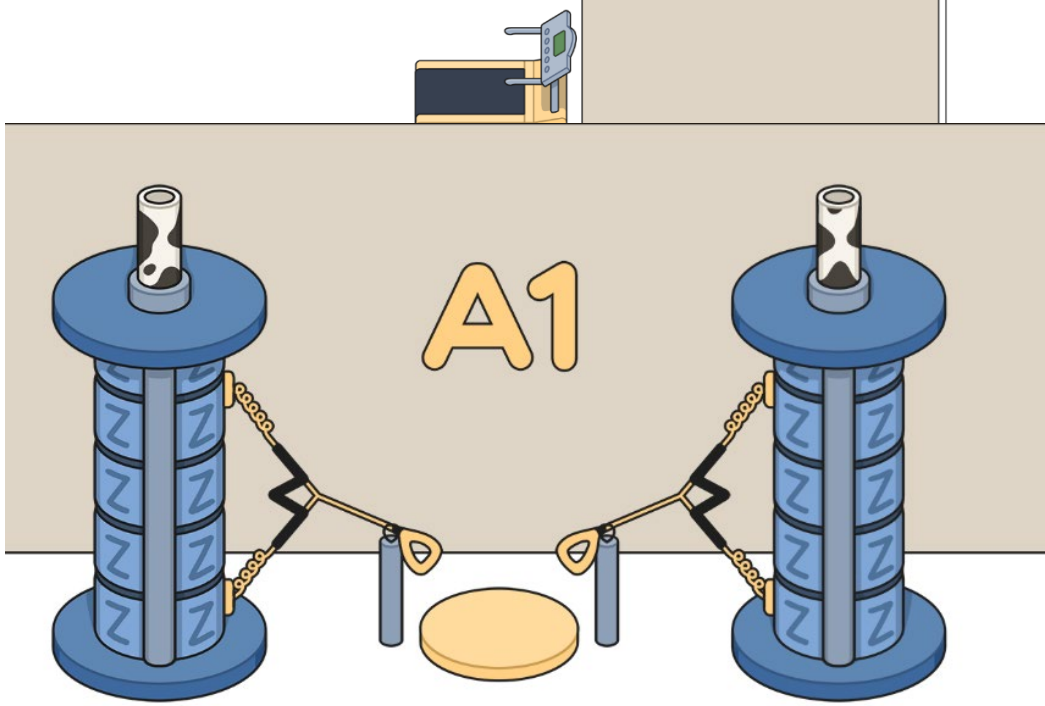
Mitochondria factory
(high energy production)

MEDIMON

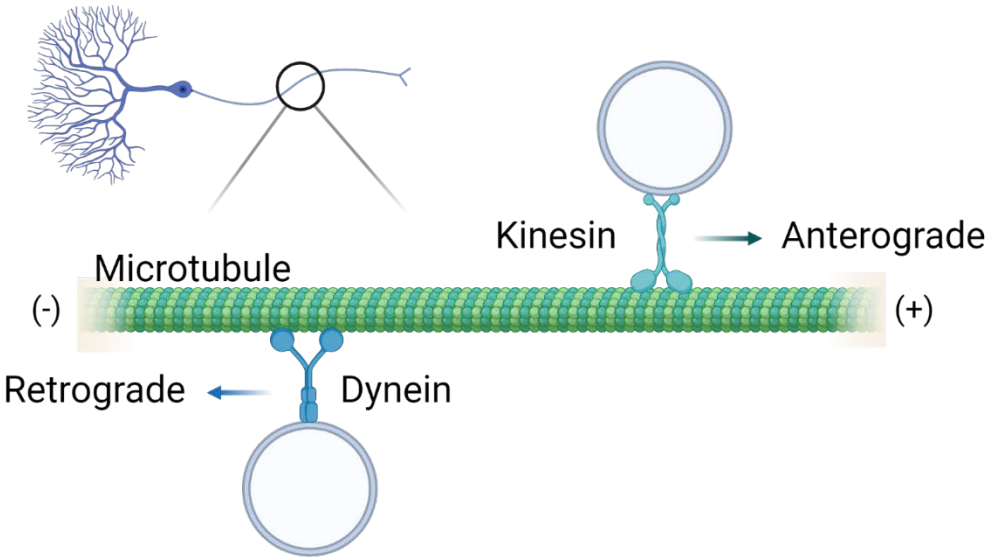
A GAME OF MEDICAL MONSTERS

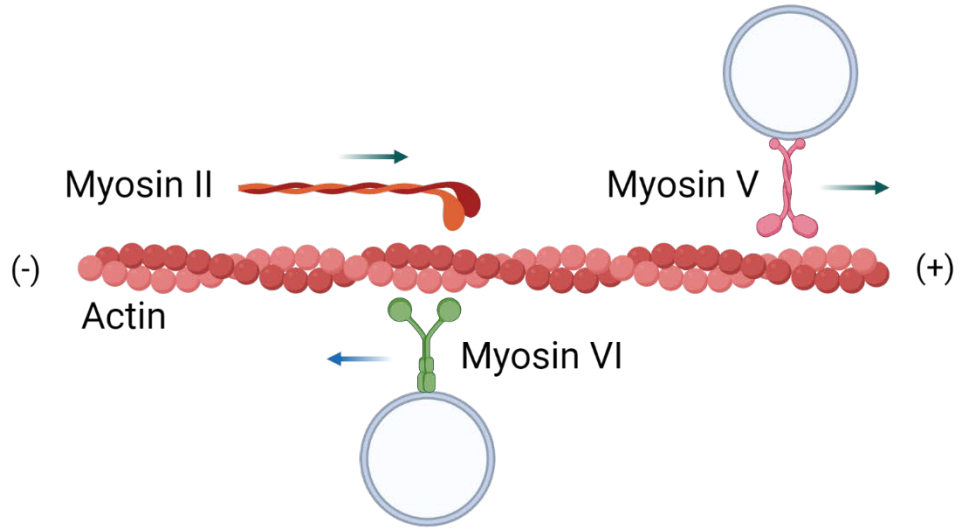






Molecular motors



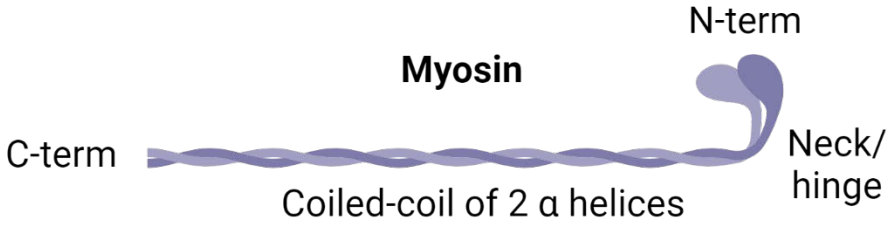


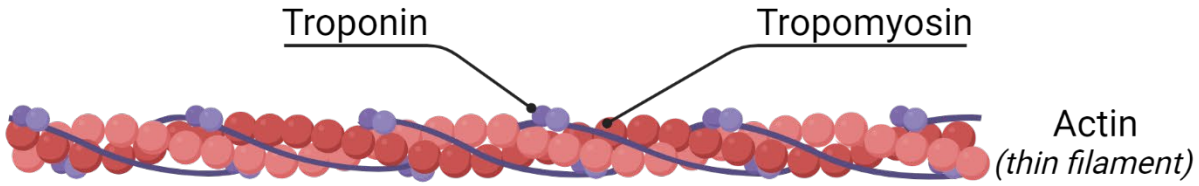
Motor	Track & direction	Examples of cellular function
Kinesin 1	microtubules, to ***plus*** end	vesicle transport in neurons
Kinesin 2	microtubules, to ***plus*** end	axoneme assembly
Kinesin 5 ("Eg5")	microtubules, to ***plus*** end	mitotic spindle assembly
Kinesin 14 ("Ncd")	microtubules, to ***minus*** end	meiotic spindle assembly
Dynein, Axonemal	microtubules, to ***minus*** end	beating of cilia, flagella
Dynein, Cytoplasmic	microtubules, to ***minus*** end	vesicle transport
Myosin II	F-actin, to ***plus*** end	muscle contraction
Myosin V	F-actin, to ***plus*** end	vesicle transport
Myosin VI	F-actin, to ***minus*** end	stereocilia (ear) development

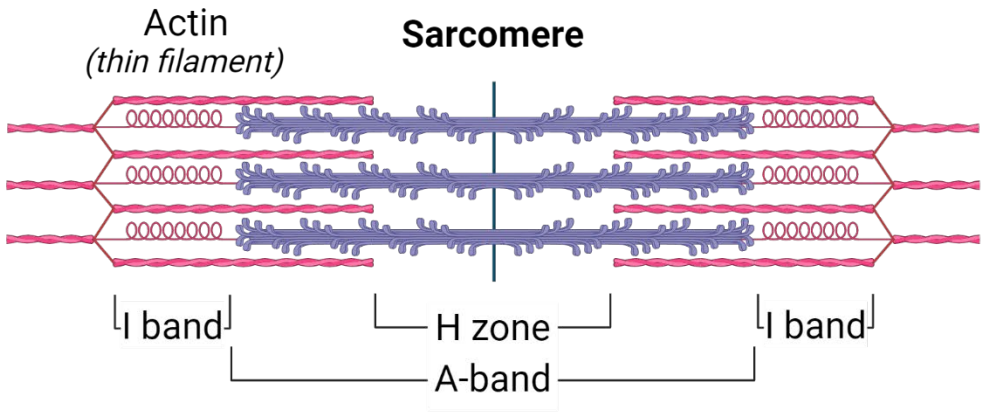
Bland, 2023; Chip Asbury, 2023

Sarcomeres

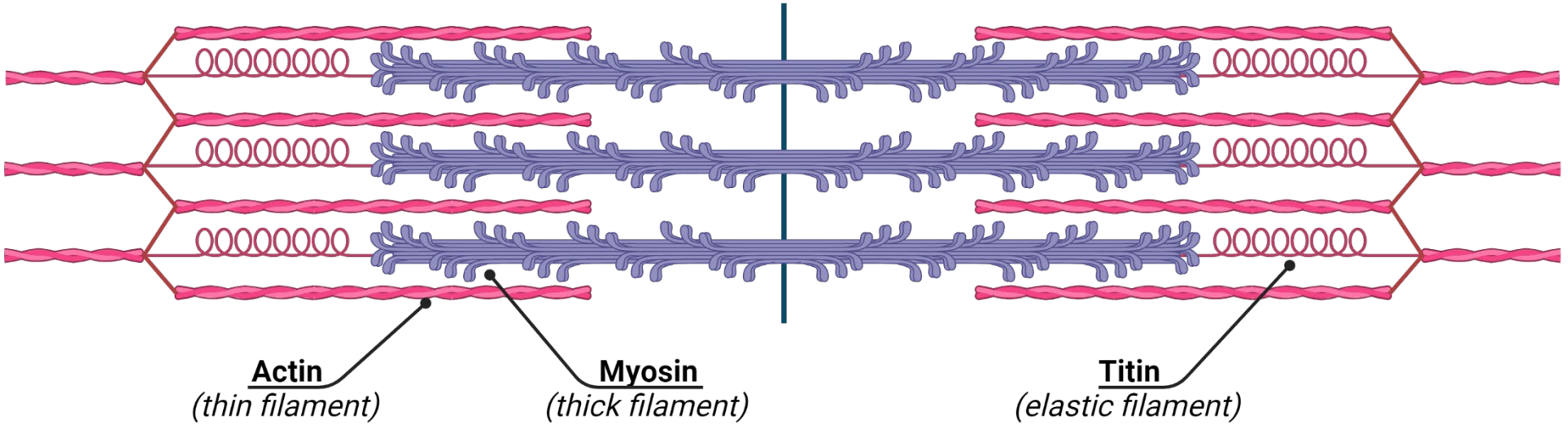
- Hundreds of myosins assemble to form the thick filaments
- Actin polymers form the thin filaments
- Interaction between the thick (myosin) and thin (actin) is blocked by tropomyosin and troponin







Sarcomeres



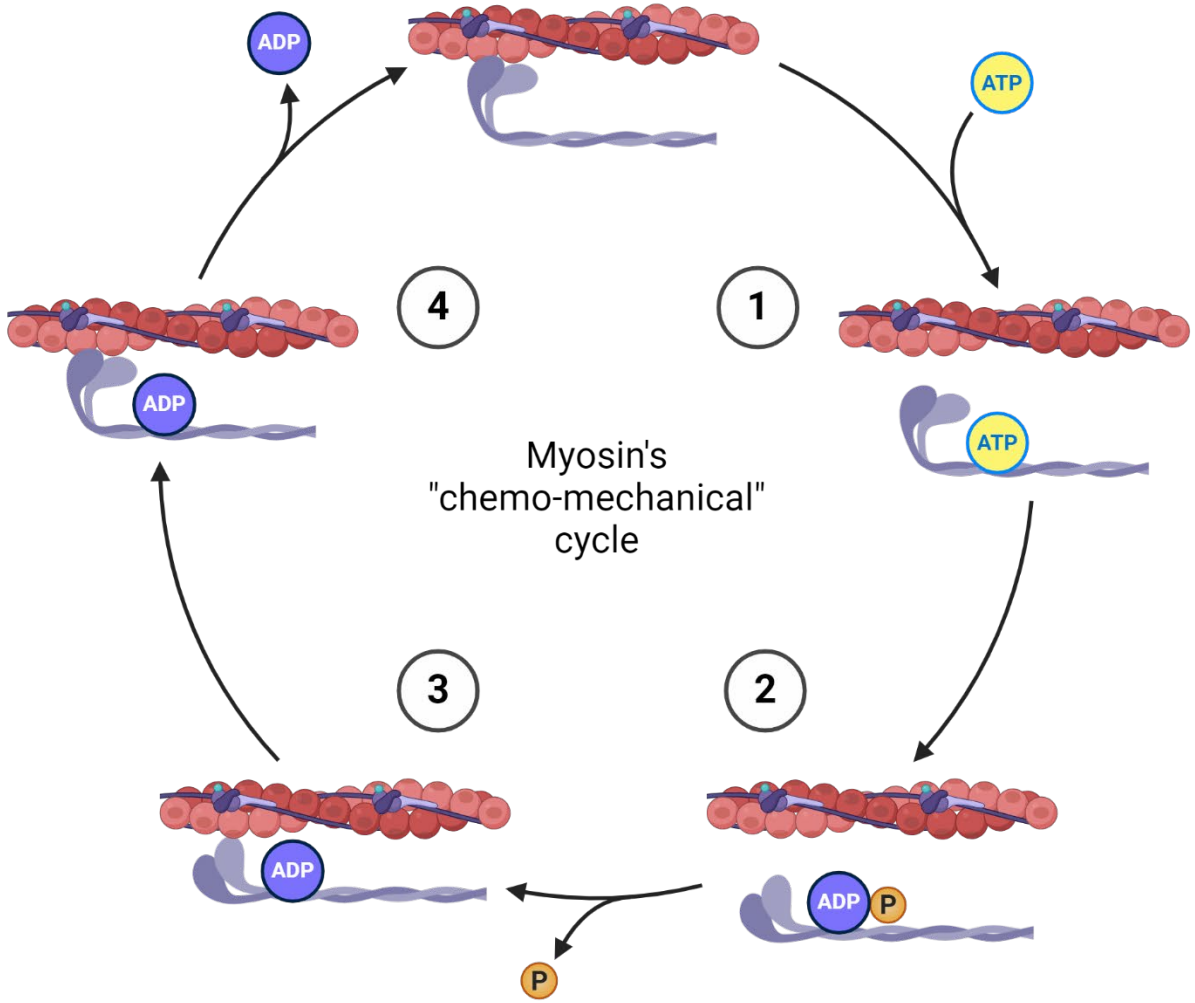
- **Active contractile elements:** interacting thick & thin filaments convert ATP into mechanical work, defined as force acting through distance

- **Passive elastic elements:** titin filaments (etc) only become tense when stretched, essentially behave like rubber bands

Myosin’s chemo-mechanical cycle

- Lever-arm rotation is coupled to ATP hydrolysis

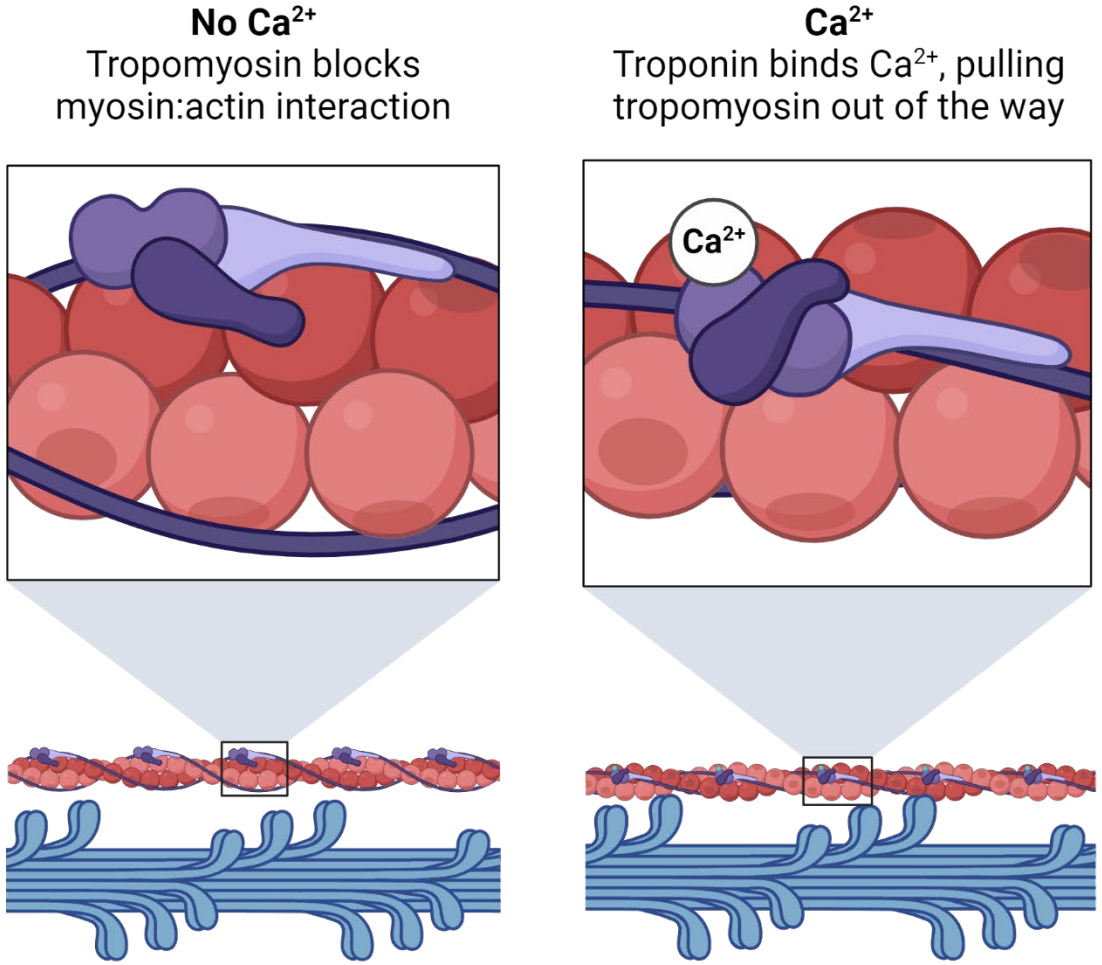
1. Binding of ATP detaches myosin from actin
2. Hydrolysis of ATP cocks the myosin head
3. Binding of myosin-ADP to actin
4. Power stroke and release of ADP



Sarcomeres

- Calcium stimulates contraction

1. Calcium binds to troponin which pulls tropomyosin out of the way
2. Myosin can interaction with the thin filament (actin)
3. Repeated power strokes contract the sarcomere

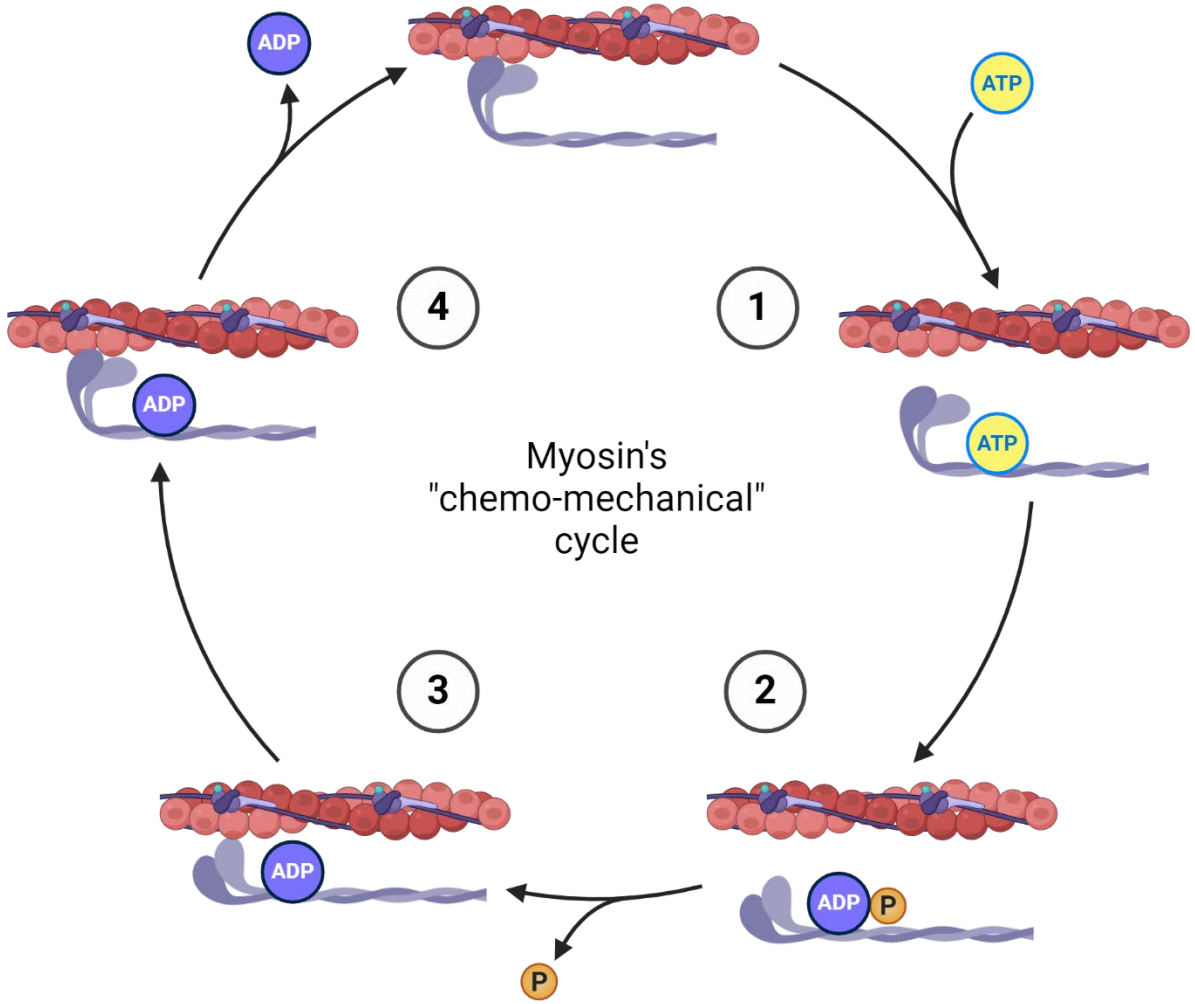


Rigor mortis

- Rigor mortis: postmortem, muscles get stiff and difficult to manipulate
  - onset ~3 hrs post mortem
  - peaks after ~12 hrs
  - then dissipates over ~3 days

Why do limbs become stiff after death?

Lack of ATP binding prevents the detachment of myosin from actin



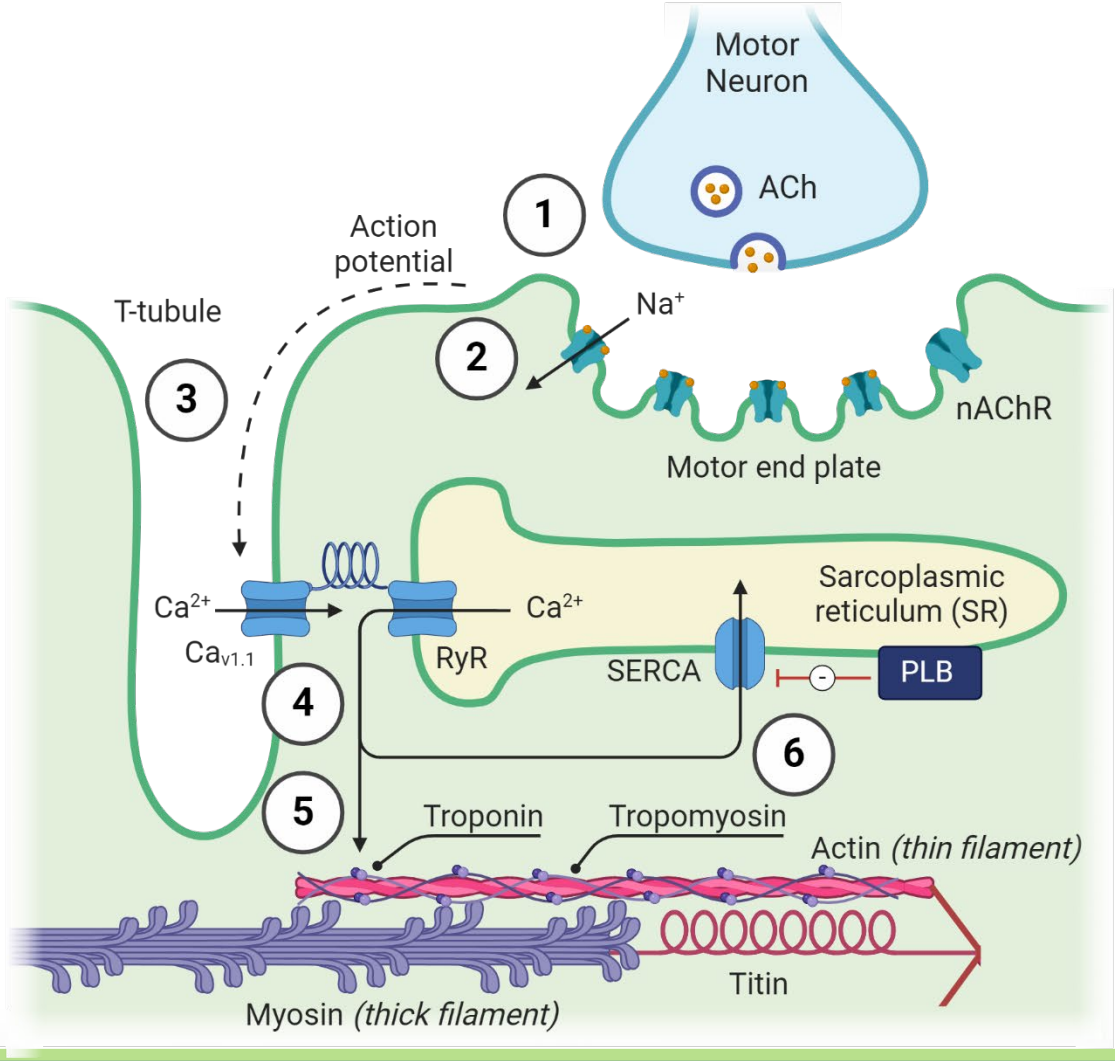
Meat tenderness

- After slaughter, carcasses are typically hung from their hind legs – this causes stretch in some muscles (e.g., in loin), while others remain unstretched (e.g., rump).
- As **rigor mortis** develops, muscles with less stretch become tougher due to **greater overlap between thick and thin filaments.** Conversely, muscles that are more stretched produce more tender, more palatable meat.
- This is a major reason why tenderloin is the most tender cut of beef.
- Hanging carcasses from pelvic bone increases stretch of rump muscles, making them more tender (but this method produces a tougher loin).

Skeletal muscle

(excitation-contraction coupling)

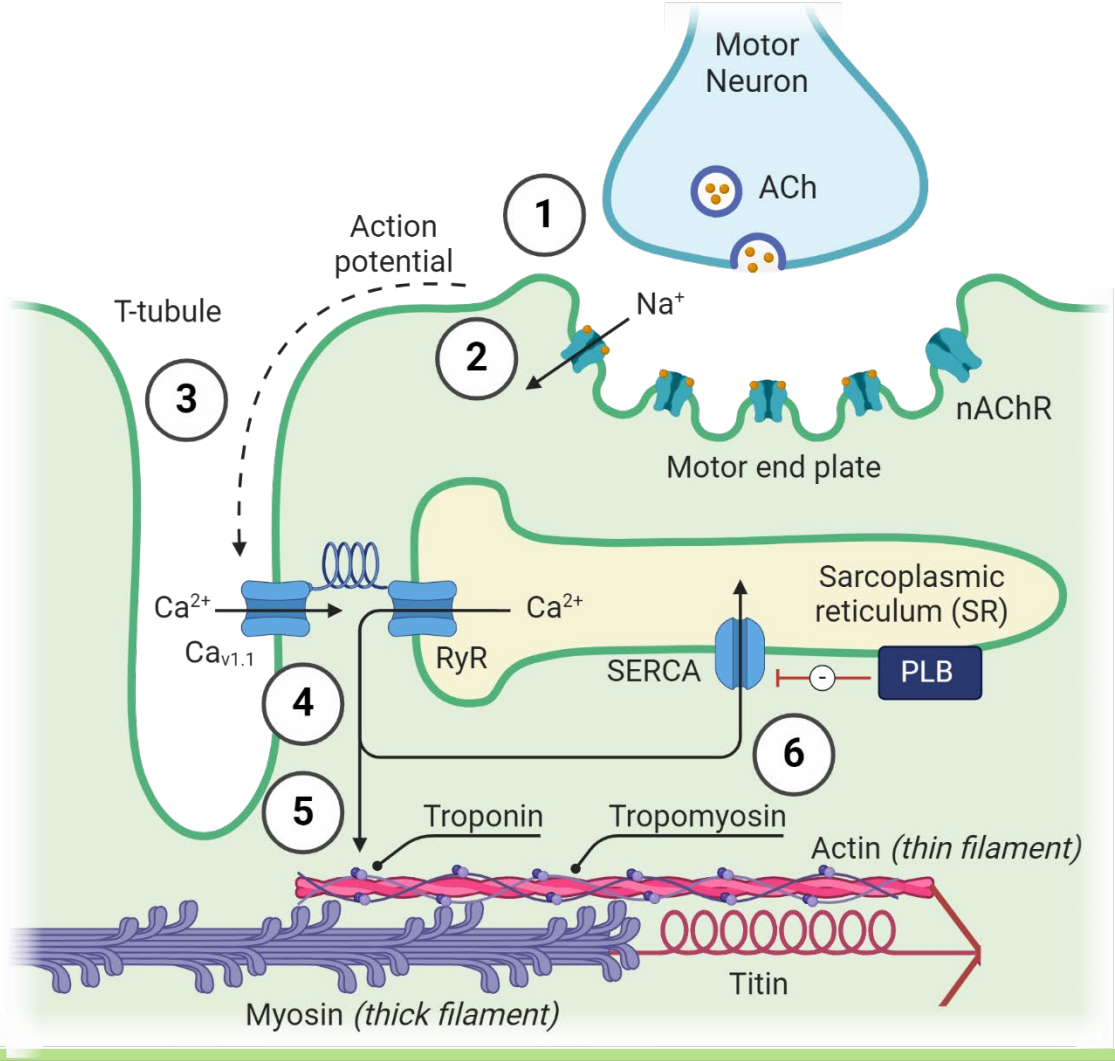
1. **Motor neuron** releases ACh into NMJ
2. Activation of **nAChR** in the motor end plate initiate action potential
3. Action potential travels down **T-tubule**
4. Voltage-gated Ca^{2+} channels open and promote opening of RyR receptors in the SR **(CICR)**
5. Calcium binds **troponin** which pulls **tropomyosin** out of the way. Myosin binds to actin and the muscle contracts
6. **SERCA** pumps Ca^{2+} back into SR, sequestering Ca^{2+} and the muscle relaxes.



Skeletal muscle

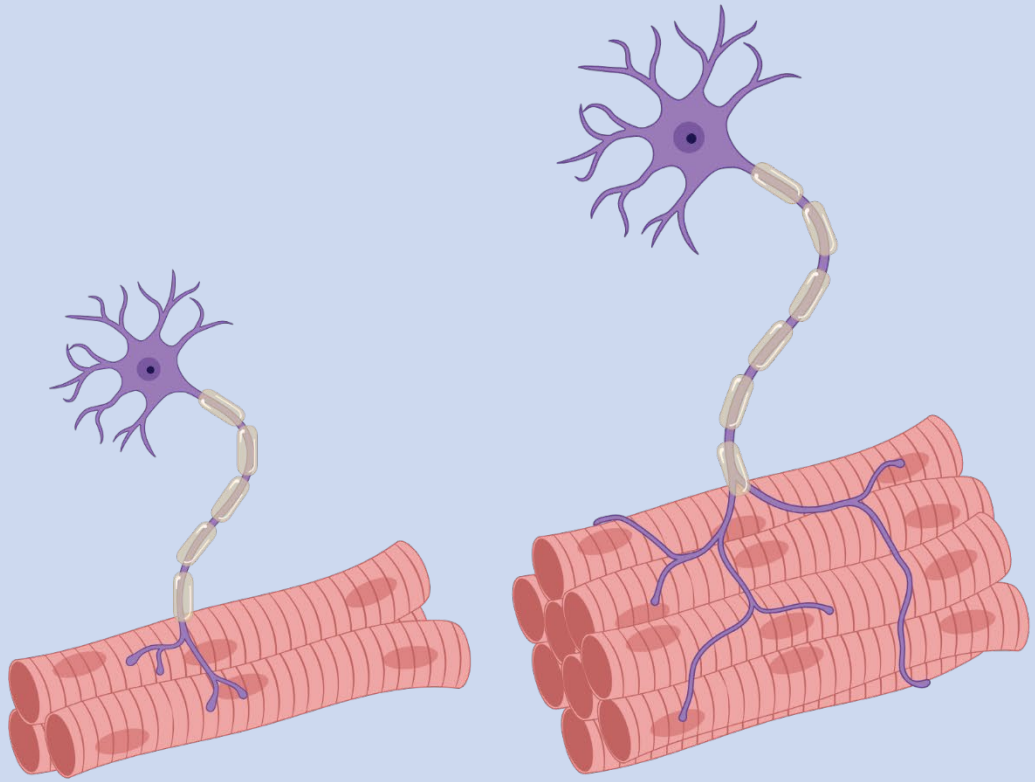
(excitation-contraction coupling)

- **Direct coupling**
  - voltage-dependent conformational changes in Cav1.1 channels directly push RyR open
- **Calcium-induced calcium release (CICR)**
  - calcium in cytosol binds RyR and promotes opening (positive feedback)
- **SERCA** (sarcoplasmic endoplasmic reticulum calcium ATPase)
  - Continuously pumps calcium into sarcoplasmic reticulum using energy from ATP



Skeletal muscle
(motor units)

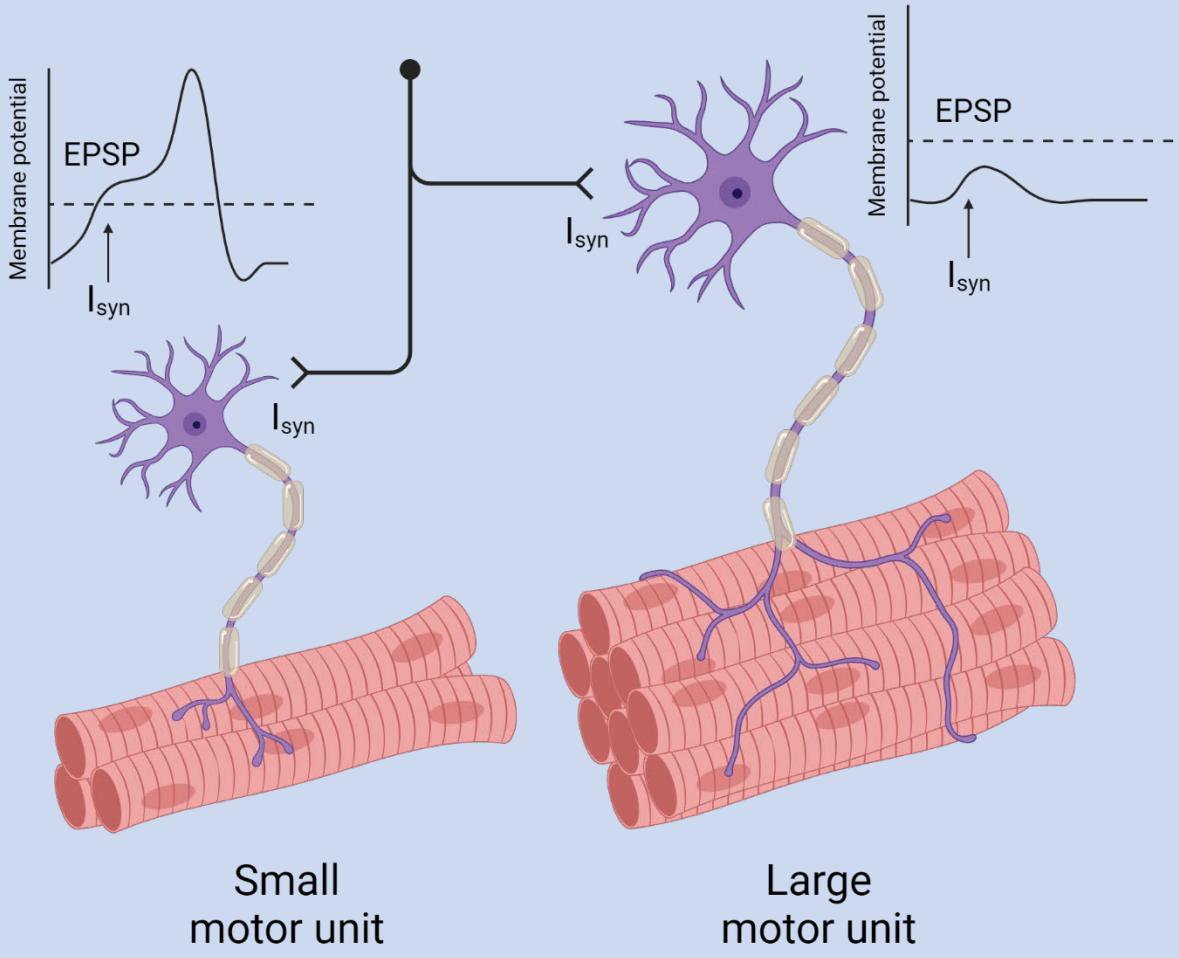
- **Motor unit:** An alpha motor neuron and the group of muscle fibers it innervates.
  - Quantal elements of muscle action.
- **Small motor axons**
  - First motor units activated.
  - Weaker contractile forces.
  - Allow force to be finely graded.
- As more units are recruited, the alpha motor neurons with **progressively larger axons** are activated. These units generate progressively larger amounts of force.



Skeletal muscle

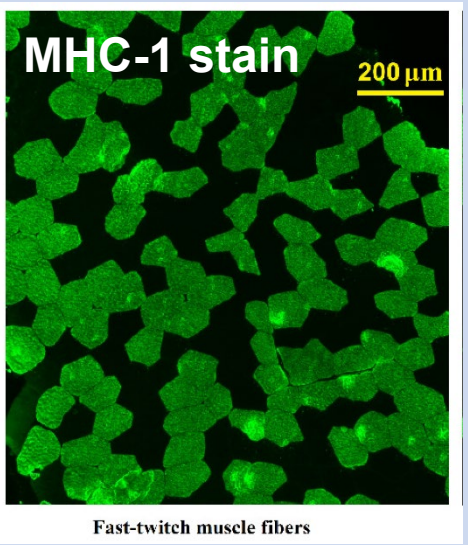
(motor units)

- Smaller motoneurons have fewer parallel ion channels and thus higher electrical resistance (R).
- Synaptic input current (I_{syn}) will generate bigger EPSPs in the smaller motoneurons (by Ohm's Law, E=IR), bringing them to threshold for action potentials sooner than larger motoneurons.
- Smaller motoneurons innervate fewer muscle fibers so they elicit less force.

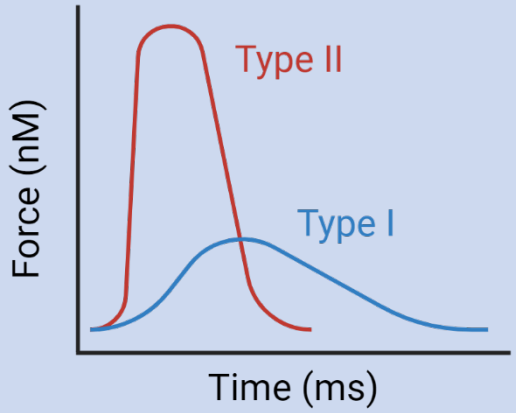


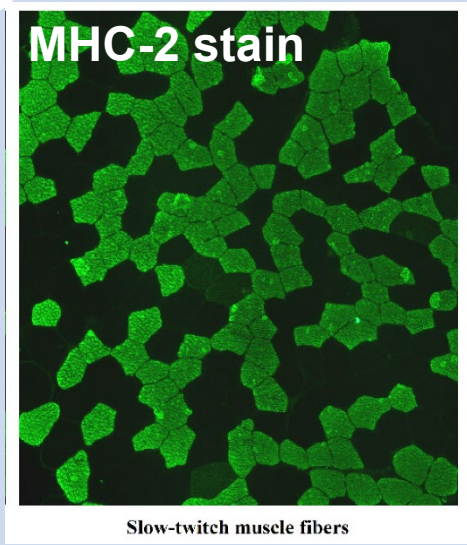
Skeletal muscle

(fiber types)

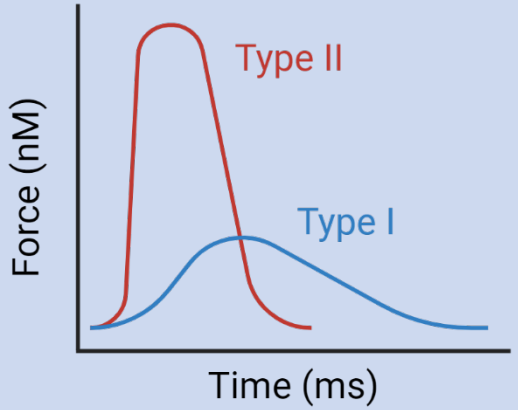


Fast-twitch muscle fibers





Slow-twitch muscle fibers



Type I “slow twitch” fibers

- Lower density of **RyR and Cav1.1**
  - Slower calcium release
  - Slower increase in force
- Lower density of **SERCA**
  - Slower calcium sequestration
  - Slower relaxation of force

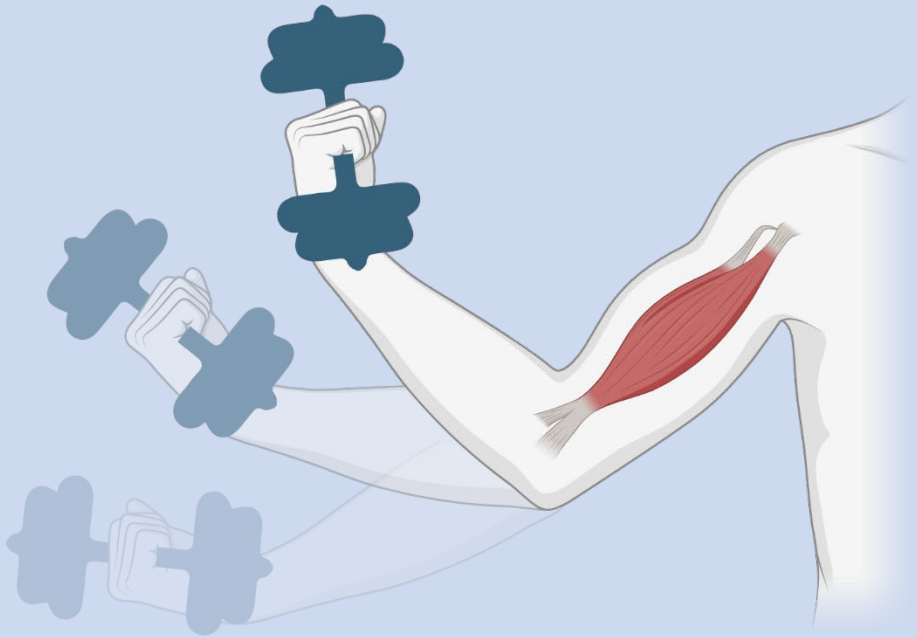
Type II “fast twitch” fibers

- Higher density of **RyR and Cav1.1**
  - Faster calcium release
  - Faster increase in force
- Higher density of **SERCA**
  - Higher calcium sequestration
  - Higher relaxation of force

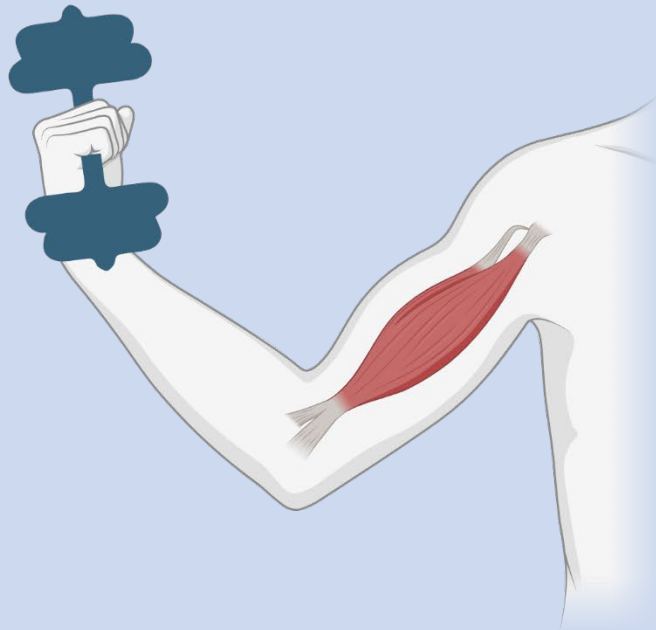
Guilherme et al, 2022; Bland, 2023

Skeletal muscle

(types of muscle contractions)



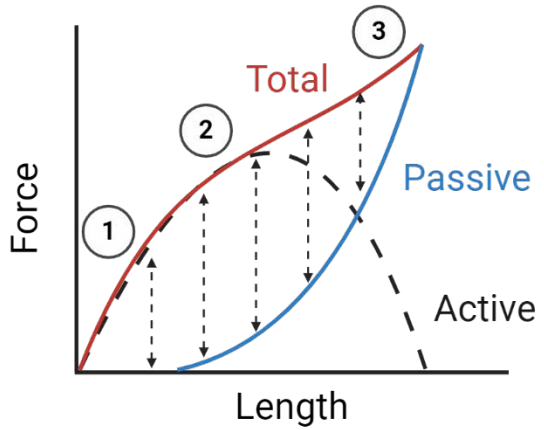
Isotonic: muscle shortens against a constant tension

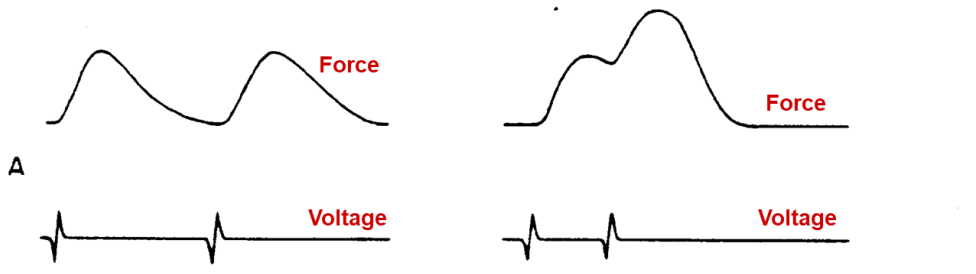


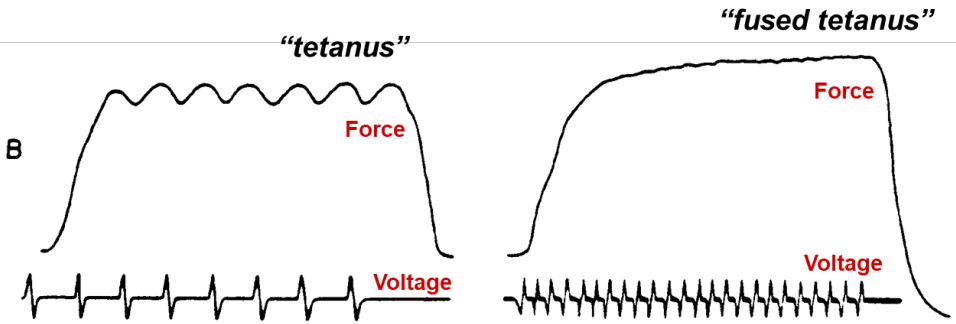
Isometric: muscle does not shorten, but generates tension against a non-moving load

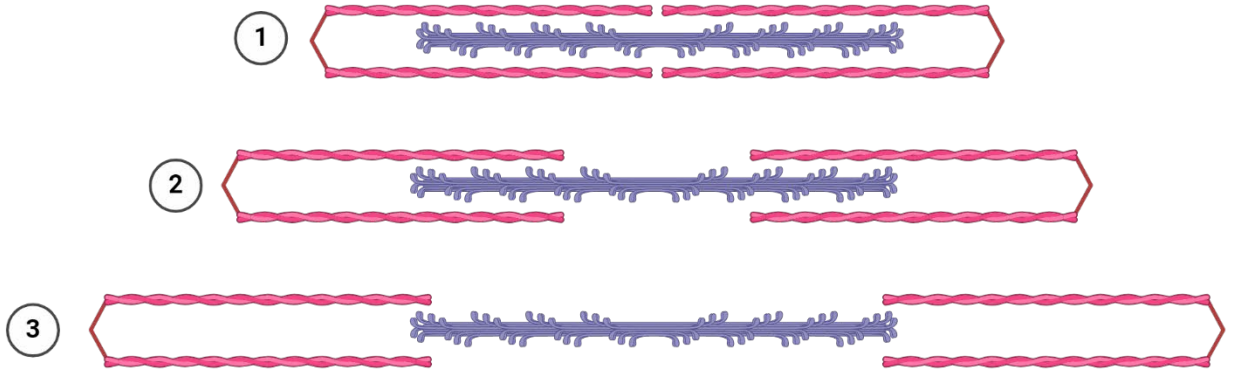
Skeletal muscle
(force production)

- Total force = active + passive
- Active force scales with the amount of overlap
- Repetitive stimulation increases force output
  - force can only increase ~3-fold by this ‘temporal summation’









Chip Asbury, 2023
Bland, 2023

Skeletal muscle

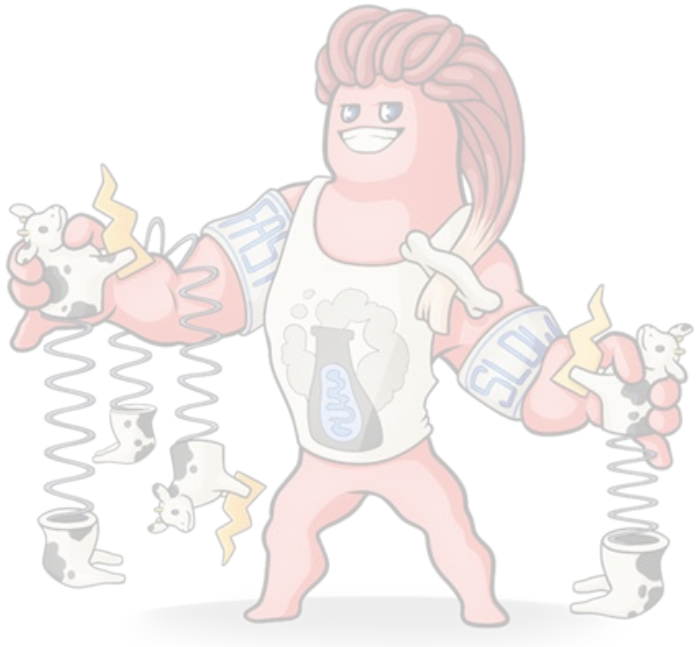
(excitation-contraction coupling)

- Depolarization of a skeletal muscle cell is initiated via neuronal signaling
  - Motor neurons release ACh at the NMJ to activate nAChR and promote depolarization
- T-tubules allow action potentials to travel deep into muscle fiber
  - Electrical signals (which are fast) carried very close to the contractile machinery
- Voltage sensors are directly connected to Ca^{2+} floodgates
  - Floodgates open essentially immediately upon arrival of action potential
- Sarcomeres are surrounded by well-developed sarcoplasmic reticulum
  - Quickly flooded with Ca^{2+} when floodgates open
- Ca2+ sensors are located directly on thin filaments
  - Myosin binding sites uncovered essentially immediately upon arrival of Ca^{2+}
- Myosin cross-bridges and ATP fuel are always ready
  - Built for speed

Single action potential can trigger, at once, much of the contractile machinery in the fiber

MEDIMON

A GAME OF MEDICAL MONSTERS



SKELETAL MUSCLE

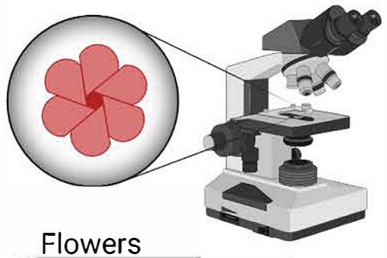
HEART

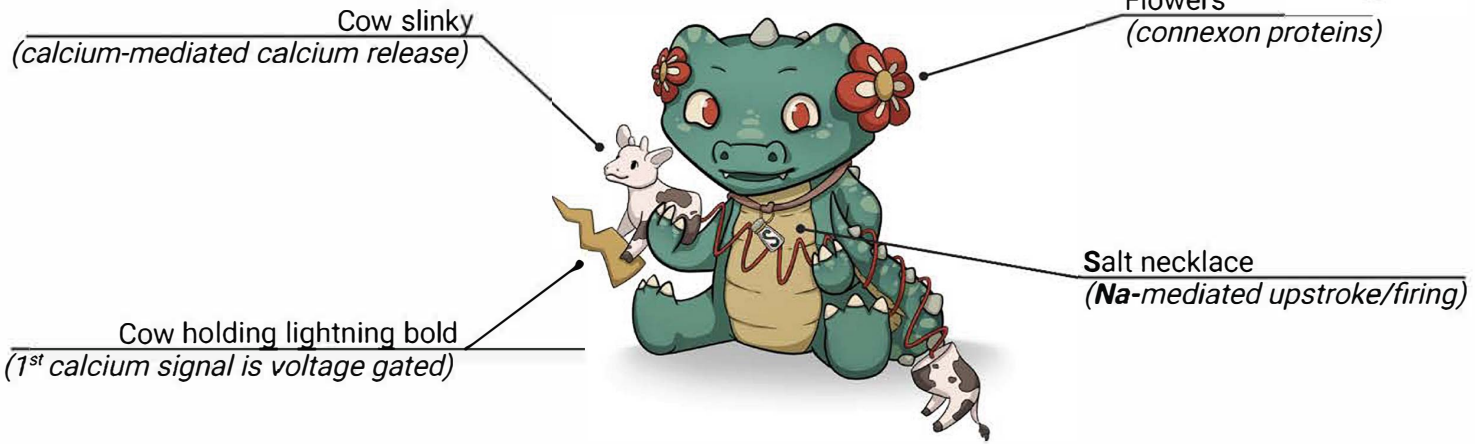
ARTERY

BRONCHIAL TREE

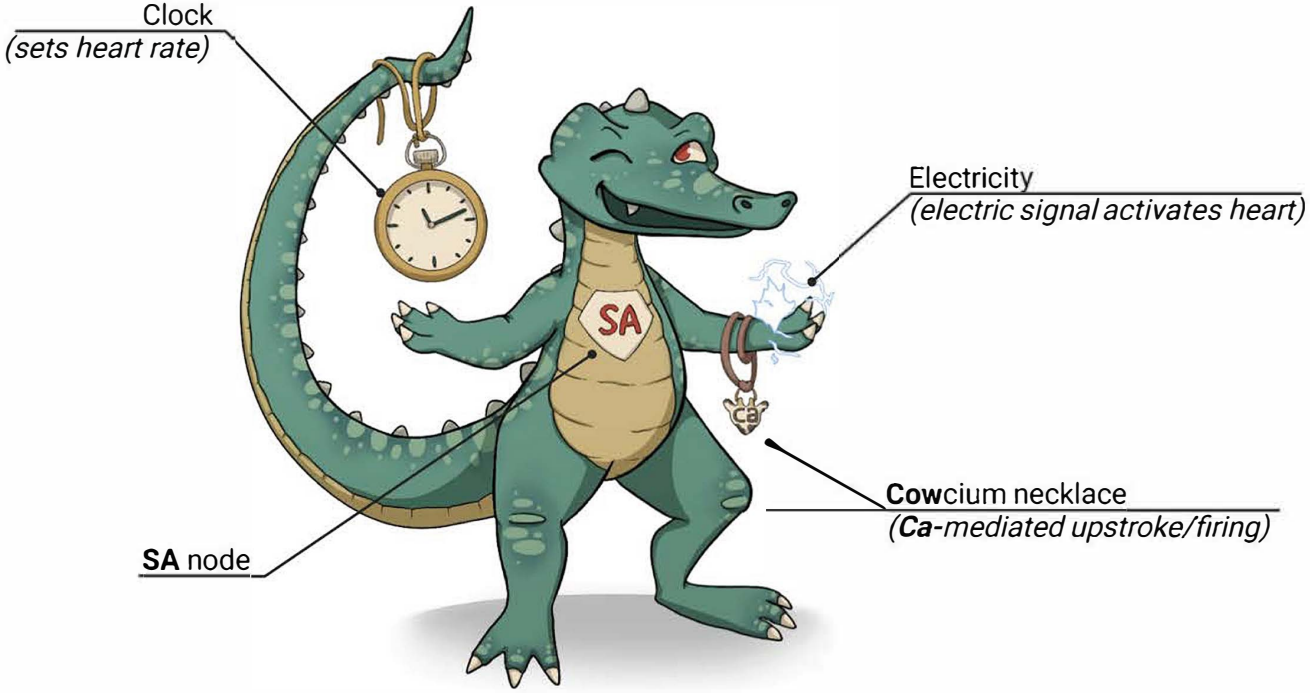
MEDIMON
A GAME OF MEDICAL MONSTERS

CARDIOMYOCYTE

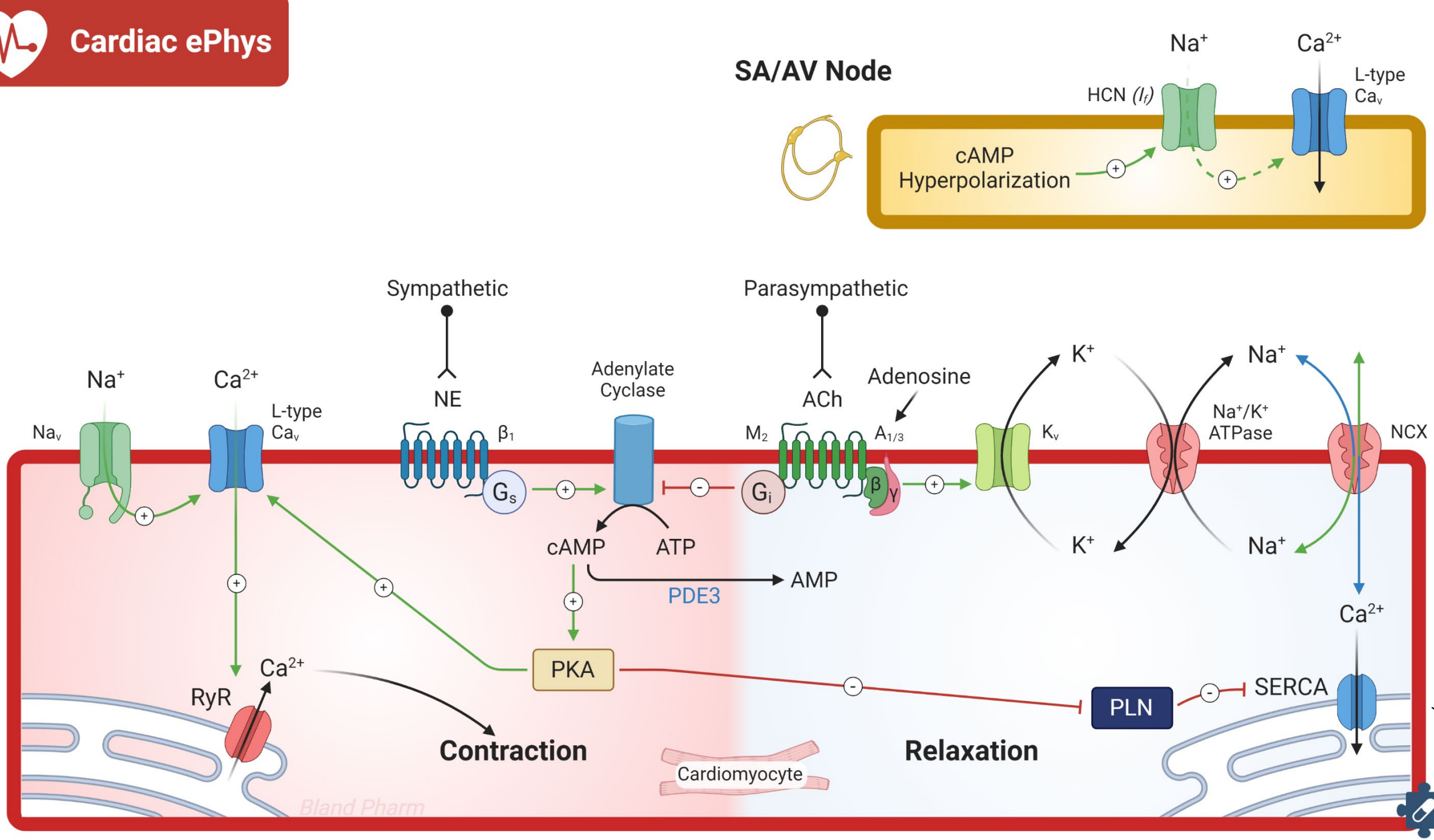




SA NODE



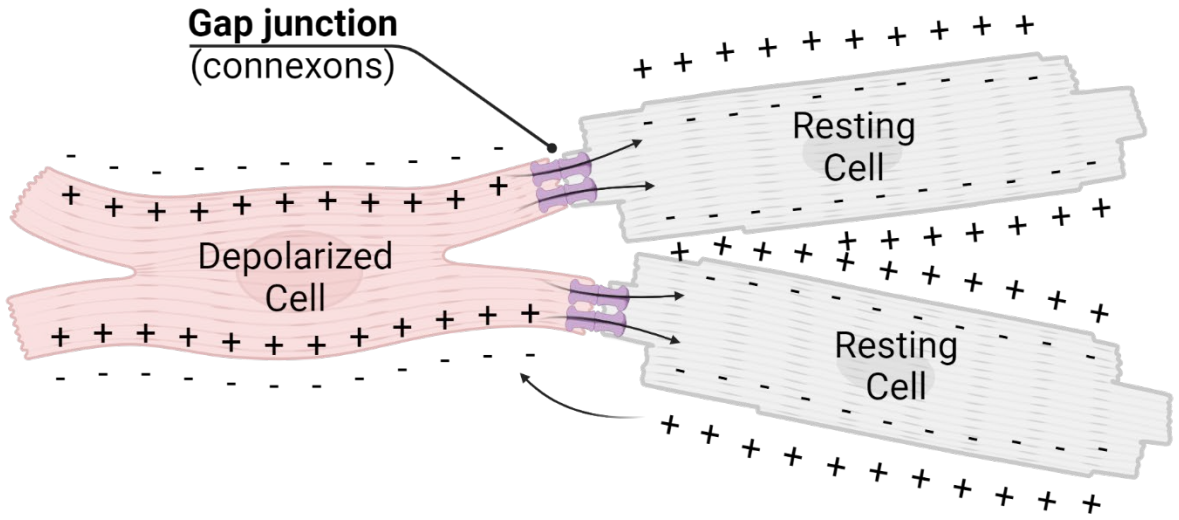
Cardiac ePhys



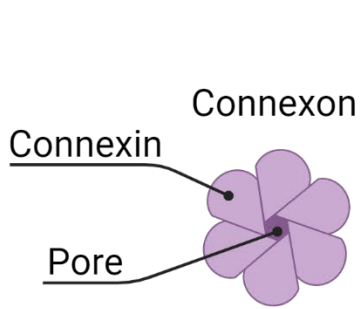
BlandPharm, 2023

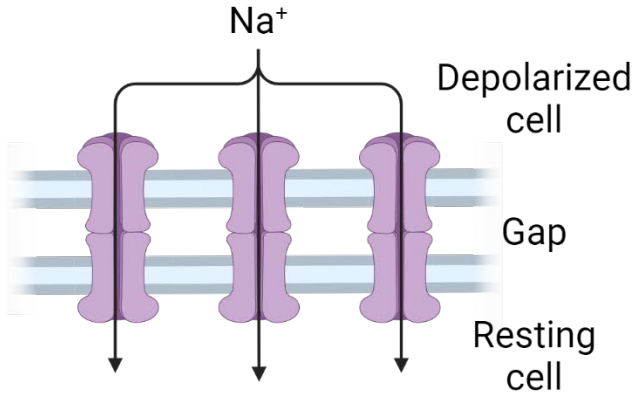
Cardiac muscle

(intercellular electrical conduction)



Gap junctions are hexameric ion channel proteins (connexins) that conduct currents between cells

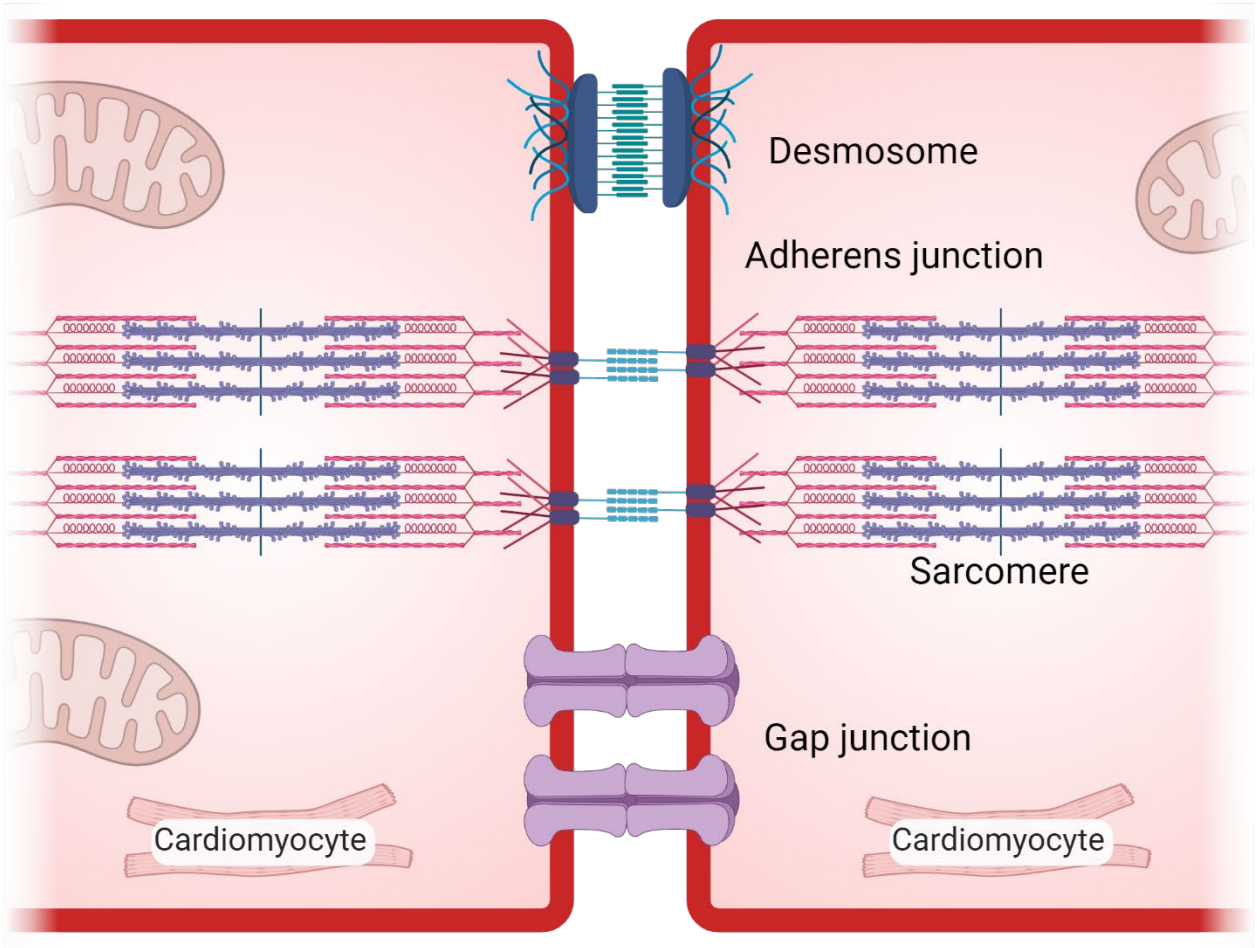




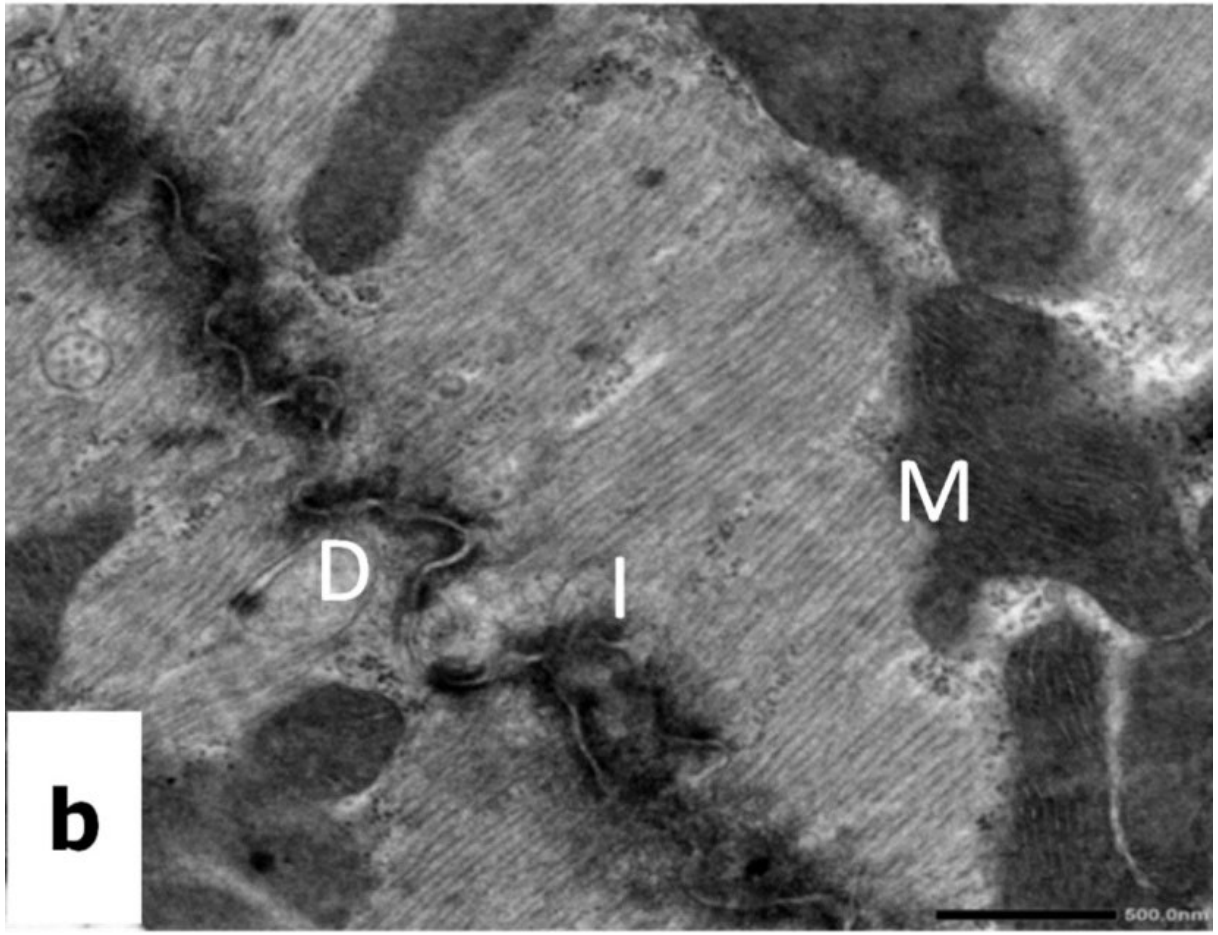
Bland, 2003

Cardiac muscle

(intercellular electrical conduction)



Ultrastructure of an intercalated disk



Cardiac muscle

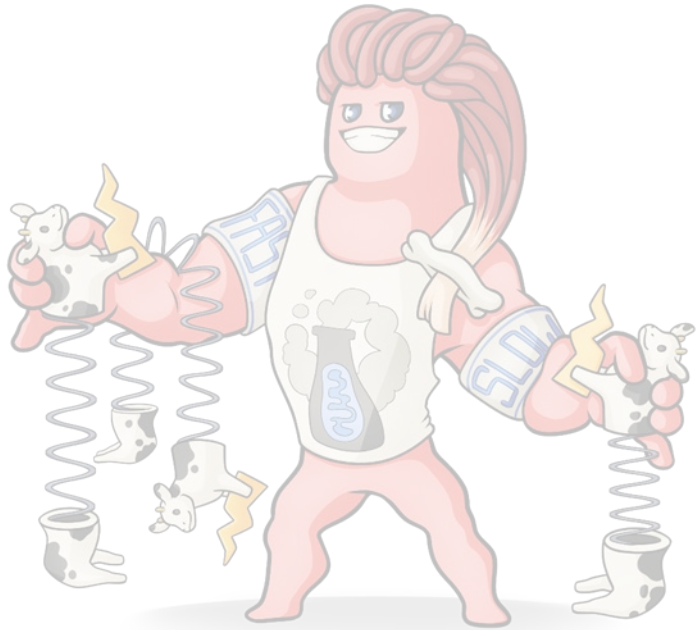
(excitation-contraction coupling)

- Depolarization of a cardiac muscle cell is initiated via gap junctions
  - Wave of electrical activity propagates over heart, beginning at pacemaker cells
- T-tubules allow action potentials to travel deep into muscle fiber
  - Electrical signals (which are fast) carried very close to the contractile machinery
- Voltage sensors are close, but not directly connected to Ca2+ floodgates
  - Floodgates open essentially immediately upon arrival of action potential
- Sarcomeres are surrounded by well-developed sarcoplasmic reticulum
  - Quickly flooded with Ca2+ when floodgates open
- Ca2+ sensors are located directly on thin filaments
  - Myosin binding sites uncovered essentially immediately upon arrival of Ca2+
- Myosin cross-bridges and ATP fuel are always ready
  - Built for speed

Electrical connection through gap junctions allow all connected to cells to fire almost simultaneously.

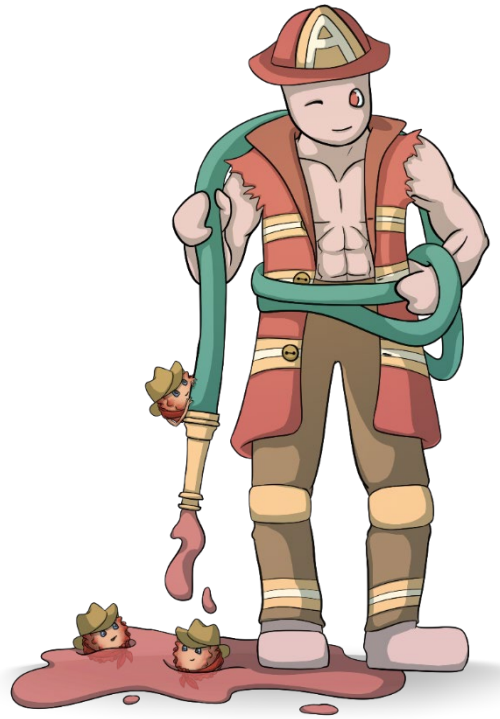
MEDIMON

A GAME OF MEDICAL MONSTERS



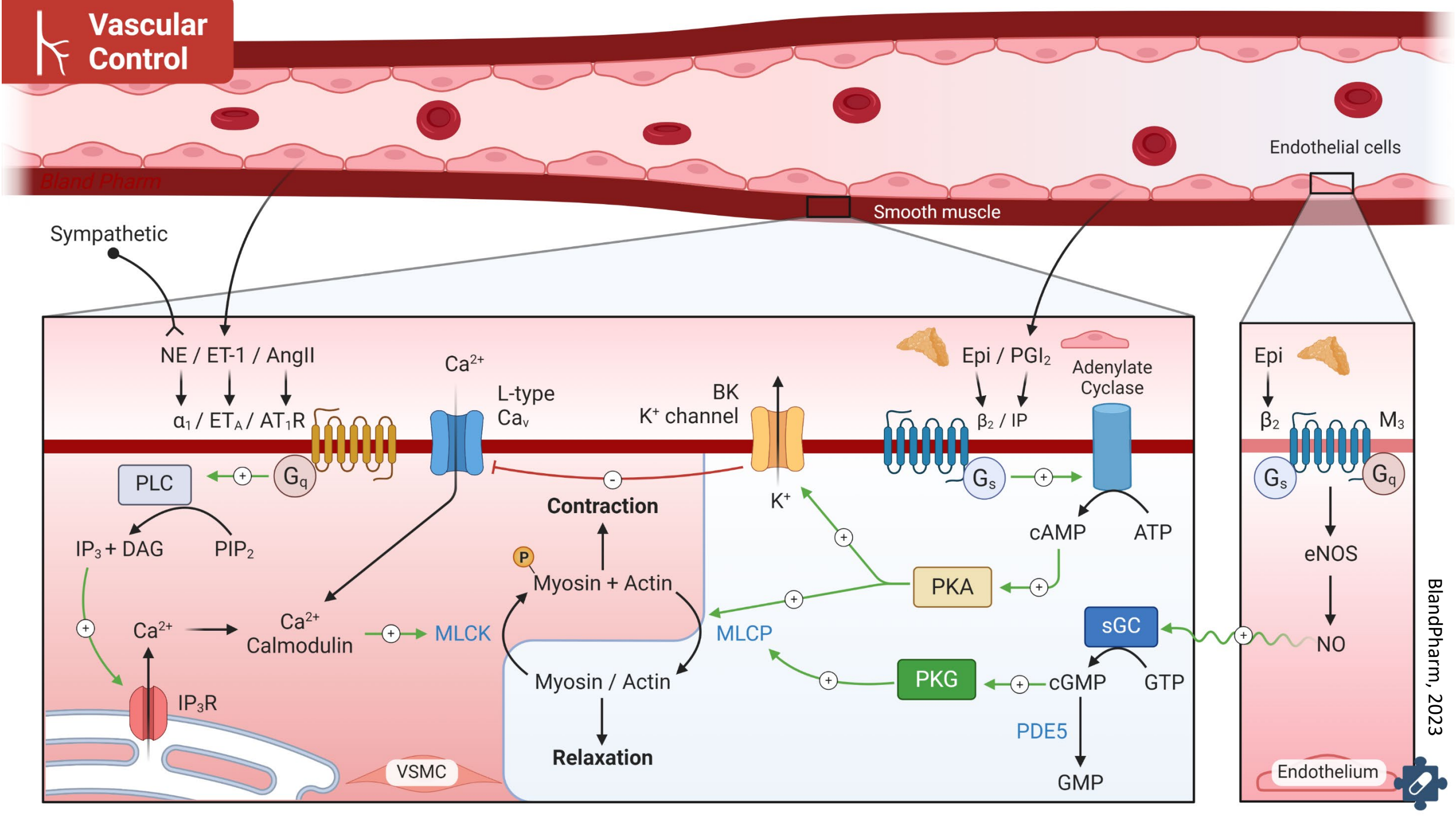
SKELETAL MUSCLE

HEART



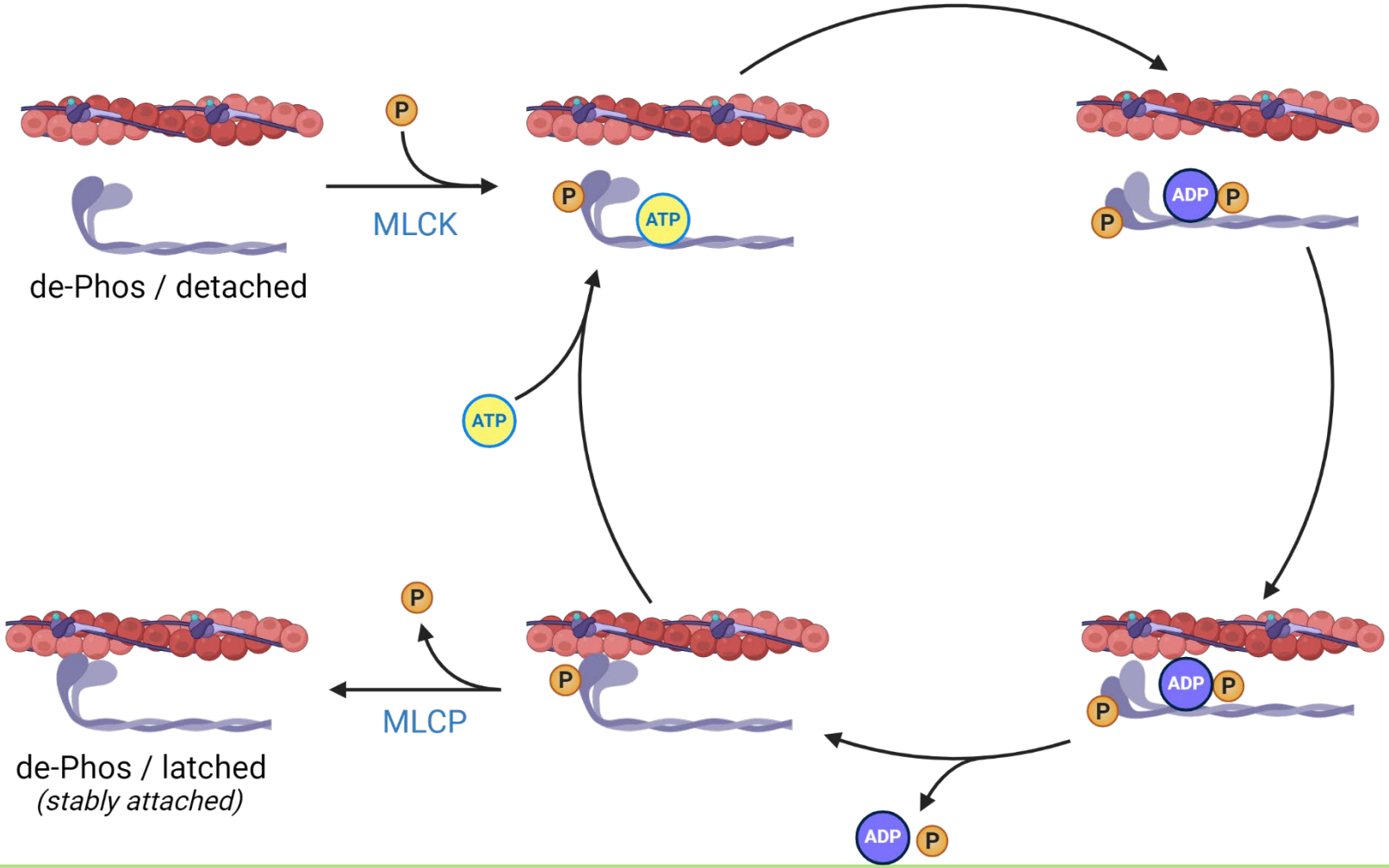
ARTERY

BRONCHIAL TREE


Vascular Control
Endothelial cells
Bland Pharm
Smooth muscle
Sympathetic
NE / ET-1 / AngII
α1 / ETA / AT1R
Ca2+
L-type Cav
BK K+ channel
Epi / PGI2
Adenylate Cyclase
β2 / IP
Gs
Gq
PLC
IP3 + DAG
PIP2
Contraction
K+
cAMP
ATP
PKA
P
Myosin + Actin
Ca2+
Ca2+ Calmodulin
MLCK
MLCP
sGC
NO
Myosin / Actin
PKG
cGMP
GTP
IP3R
PDE5
GMP
Relaxation
VSMC
Epi
β2
M3
eNOS
Endothelium
BlandPharm, 2023

Smooth muscle
('latch' mechanism)

- De-phosphorylation slows the detachment of myosin from actin
- Facilitates long-term control of tension with minimal energy cost (a 'latch' effect).



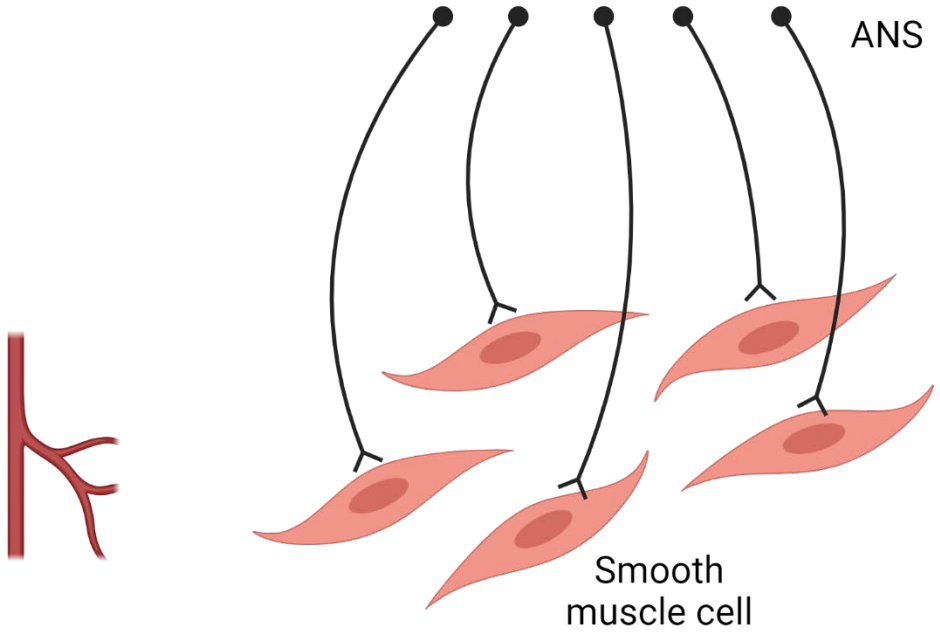
Smooth muscle

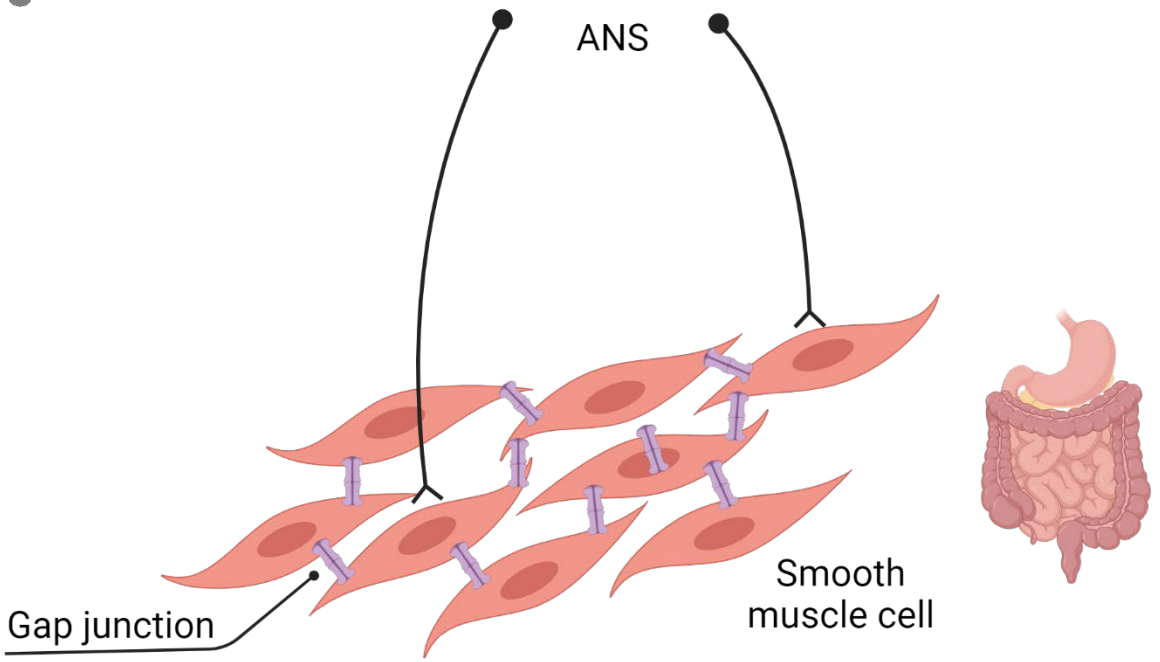
(excitation-contraction coupling)

- No T-tubules, electrical excitation travels only on fiber surface
- Less sarcoplasmic reticulum, reduced Ca^{2+} stores
  - Full contraction requires (slow) diffusion of Ca2+ from the outside deep into the cell
- Ca^{2+} sensors not attached to thin filaments (or to myosin cross-bridges)
  - Contraction initiated by a Ca2+-dependent, 2-stage signaling cascade
- Cross-bridges inactive until Ca^{2+}-dependent phosphorylation of myosin
  - Speed is not critical

Advantage that facilitates long-term control of luminal pressure with minimal energy cost (a 'latch' effect).

Smooth muscle
(innervation types)





Multiunit: capable of sustained "tonic" contraction (e.g., vasculature)

- Electrical isolation of cells allows finer motor control

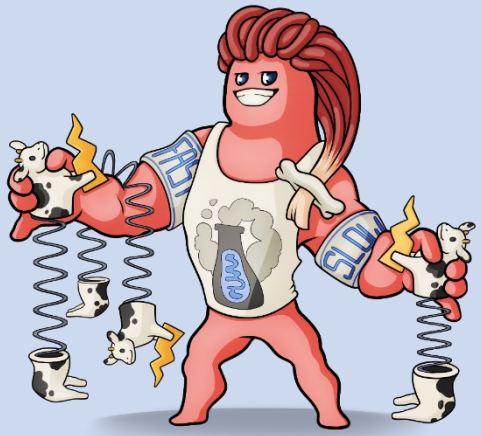
Single-unit: waves of electrical activity generate "phasic" contractions (e.g., peristalsis in GI tract)

- Gap junctions permit coordinated contraction

Contrasting cAMP effects

Happy **cAMP**ers

- Striated and cardiac muscle
- β-receptors increase cAMP levels which activate PKA
- Leads to muscle **contraction** (happy)



Sleepy **cAMP**ers

- Smooth muscle (bronchioles and vasculature)
- β-receptors increase cAMP levels which activate PKA
- Leads to muscle **relaxation** (sleepy)

References

1. Zuccaro, E., Marchioretti, C., Pirazzini, M. & Pennuto, M. Introduction to the Special Issue “Skeletal Muscle Atrophy: Mechanisms at a Cellular Level”. *Cells 2023, Vol. 12, Page 502* **12**, 502 (2023).
2. Stevens, S. *et al.* Skeletal Muscles of Patients Infected with SARS-CoV-2 Develop Severe Myofiber Damage upon One Week of Admission on the Intensive Care Unit. *Applied Sciences 2022, Vol. 12, Page 7310* **12**, 7310 (2022).
3. Guilherme, J. P. L. F. *et al.* Genomic Predictors of Brisk Walking Are Associated with Elite Sprinter Status. *Genes (Basel)* **13**, 1710 (2022).
4. Attia, A. A. *et al.* Biochemical, Histological, and Ultrastructural Studies of the Protective Role of Vitamin E on Cyclophosphamide-Induced Cardiotoxicity in Male Rats. *Biomedicines 2023, Vol. 11, Page 390* **11**, 390 (2023).
5. Asbury, C. Muscle Physiology. UWSOM FMR Pressbook (2023).