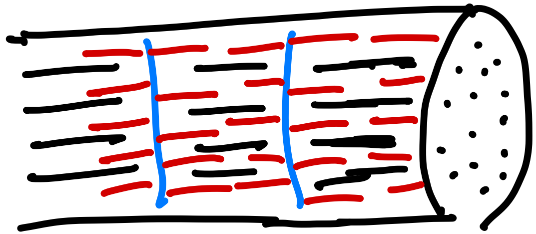
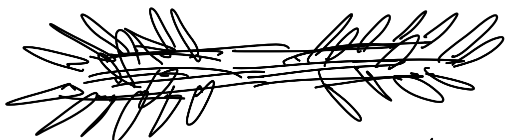
Muscle Fiber – Subcellular anatomy I : myofibrils



- Composed of highly organized bundles of proteins known as

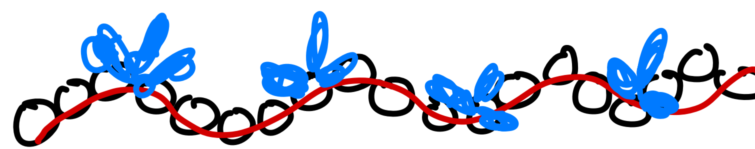
Thick filaments and

Thin filaments



Thick filament

- a bundle of ~300 myosin proteins (a <u>motor</u> protein)

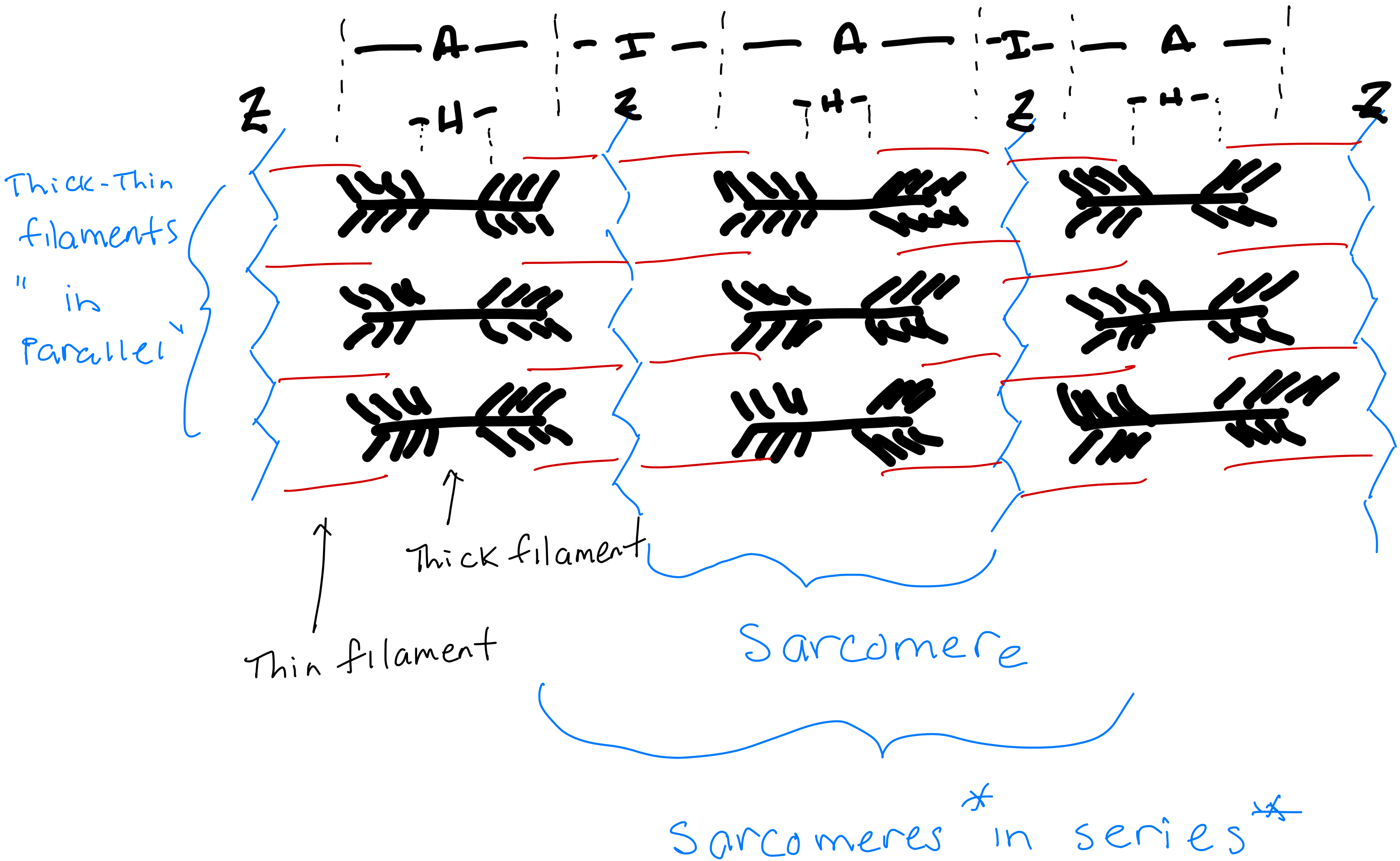


Thin filament:

Actin – myosin binding sites

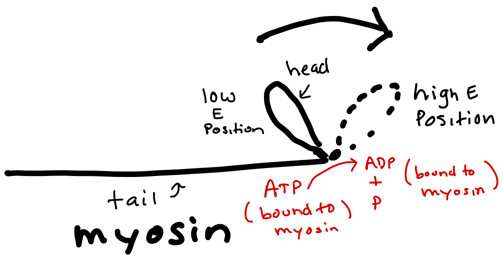
Tropomyosin – regulates Actin-myosin binding

Troponin – regulates Tropomyosin (ultimately actin/myosin)


A
I
A
I
A
Z
H
Z
H
Z
H
Z
Thick-Thin filaments " in Parallel"
Thick filament
Thin filament
Sarcomere
Sarcomeres* in series*

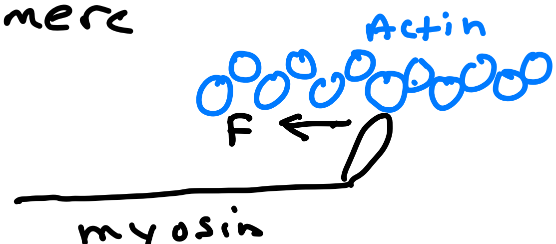
Sliding Filament Model

1. head in low E position unbinds actin
2. myosin hydrolyzes ATP and head pivots to high E position

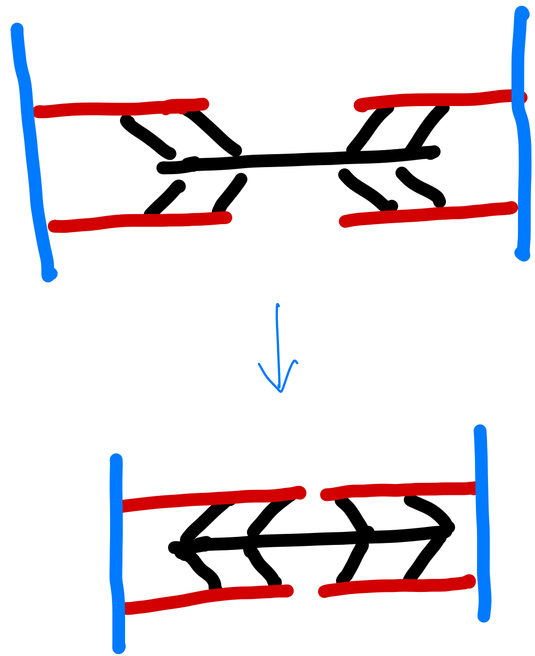


ATP hydrolysis by myosin transfers Chemical Energy in ATP to Elastic Strain Energy in pivoted myosin head

3. myosin head binds to actin and pulls thin filament with force directed to center of sarcomere



Sliding Filament Model



myosin heads bind to actin and pull thin filament + Z-disc toward center of sarcomere. The thin filaments slide past the thick filaments

Simplifications:

1) sarcomeres shorten only in concentric contraction

2) myosin heads* do Not* work in synchrony as illustrated here!

Cross-bridge cycling -- In muscle contraction, myosin goes through many rounds of

1. hydrolyze ATP
2. Pivot to high Energy position *
3. bind to actin
4. Pivot to low E position, which pulls thin filament and generates active contractile force
5. Unbind
6. repeat

Consequently contracting muscle is a Big consumer of ATP!

* The cycle starts here because the heads are in high E position in relaxed muscle

Physics of Muscle Performance

$V = \frac{d}{t}$ ← displacement - The change in position of an object
← time

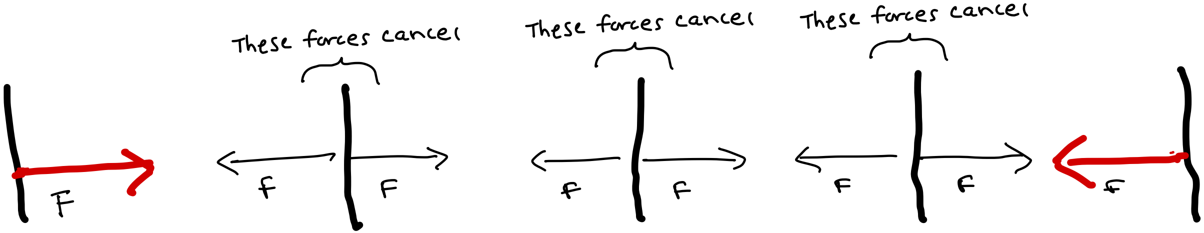
$F = ma$
$F/m = a$

an unbalanced F applied to an object causes an acceleration that is inversely proportional to the object's mass. mass is the property of an object that resists acceleration.

$W = F \cdot d$ W (work) is mechanical Energy work "is done" on an object when it moves d in response to F

$P = \frac{W}{t} = \frac{F \cdot d}{t} = F \cdot \frac{d}{t} = F \cdot V$ Power (P) is the rate of doing work

muscle Performance



Sarcomeres in Series

Note that all the forces effectively cancel except the two at the ends. Consequently, the max force able to be generated by the myofibril is simply the max force generated by a single sarcomere!

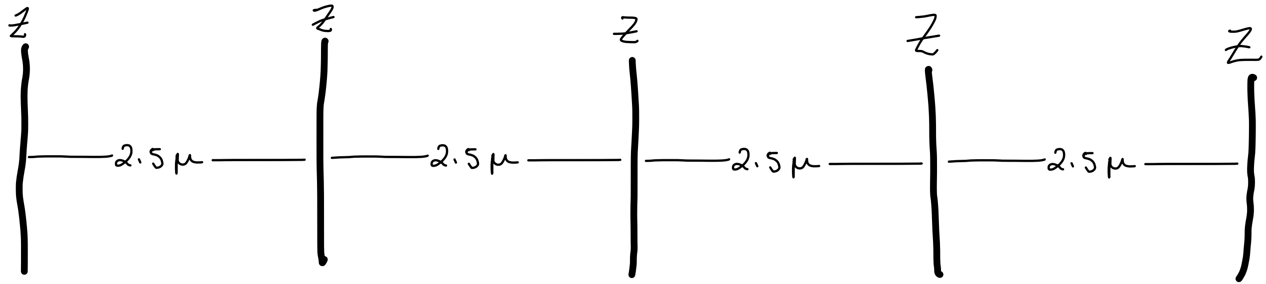
consequently...

rule #1 $F_{max} \propto$ **cross-sectional area**

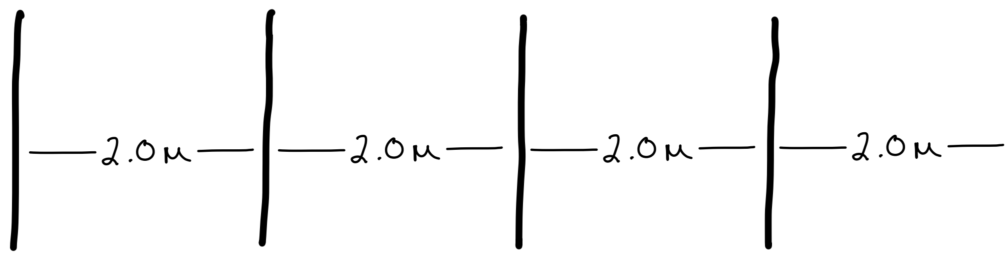
and not length. This is true at the level of the myofibril, the muscle fiber, and the whole muscle

muscle performance

sarcomeres in series



↓ each sarcomere shortens .5 μ ↓



rule # 2 - $V_s \propto$ length

V_s is shortening velocity. If each sarcomere shortens .5 μ in 1 s then then the myofibril shortens $n \cdot .5$ μ in 1 s.

$n = 10^3$ sarcomeres → 500 μ/s
$n = 10^4$ " → 5000 μ/s

* This scales up to level of fiber and whole musc

Q: What do Turkeys do all day?
A: mostly walk slowly around, foraging for food?
Q: what muscles are used for foraging in Turkey?
A: leg muscle (quadruceps, hamstrings, gastrocnemius, etc)
Q: what do we call the leg muscles of Turkey?
A: dark meat
Q: Have you ever seen a Turkey fly?
A: Yes, on occassion when spooked a Turkey will fly across the road or up onto a limb.
Q: What muscle is used to fly?
A: Pectoralis major is the downstroke muscle
Q: What do we call the pec major (breast) in Turkey?
A: White meat

Why?

muscle Performance: **Muscle Fiber Type**

Trait	Type I	Type II b*
myosin isoform	MyHC-β	MyHC-2b
myosin ATPase rate	slow	fast
Twitch rate	slow	fast
mitochondrial density	high	low
Aerobic activity	high	low
Triacylgycerol content	high	low
myoglobin content	high	low
Capillary density	high	low
Color	red	white
glycolytic activity	low	high
creatine phosphate	low	high
glycogen content	low	high
Lactate clearence	low	high
max diameter	small	large
Force	low*	high*
Power	low*	high*
Activity	Endurance	high power

* mammals have multipe type II fiber types, including IIa, which Shares oxidative traits of TI and fast twitch traits of IIb

Trait	Type I	Type IIb
myosin isoform	MyHC-β	MyHC-2b
myosin ATPase rate	slow	fast
Twitch rate	slow	fast

see https://en.wikipedia.org/wiki/Myosin for more on Myosin diversity

MyHC β (myosin heavy chain beta) is expressed in Type I skeletal muscle fibers and cardiac fibers. It's ATPase rate is slow so cross-bridge cycling is slow. Consequently its speed of shortening and twitch development is slow. Note the MyHC β is a myosin Type II isoform so naming is confusing!

MyHC 2b ATPase rate is fast. Consequently

$\uparrow$ ATPase $\longrightarrow$ $\uparrow V_s$ $\longrightarrow$ $\uparrow$ twitch

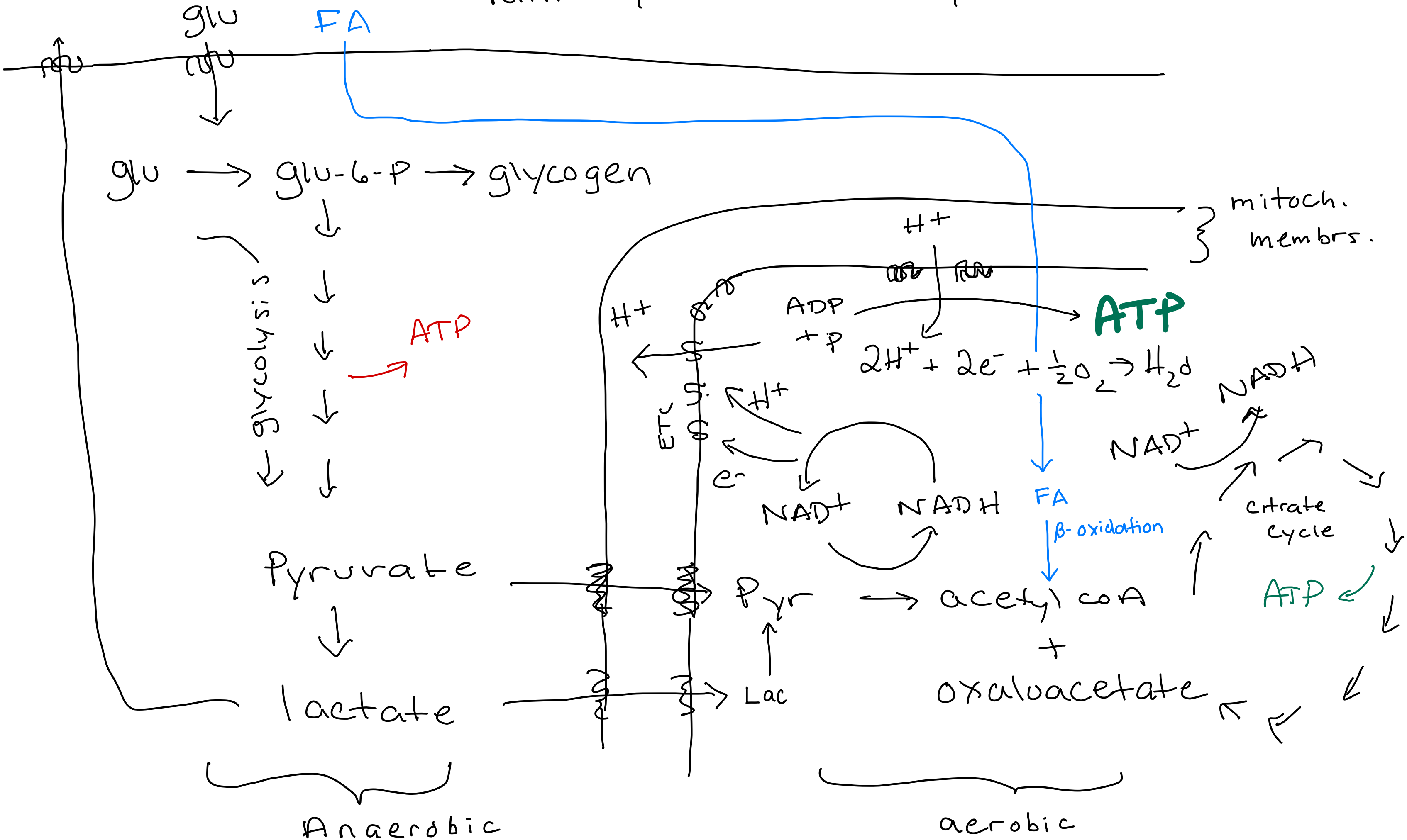
Type I = "slow twitch" fibers, Type II = "fast twitch" fibers

Type I fibers express a slow myosin isoform and so **conserve** ATP; this is the Starting logic for all the other traits of Type 1 fibers as high Endurance fibers

Type IIb fibers express a fast myosin isoform and so generate fast shortening at the cost of **ATP depletion**. This is the Starting logic for all the other traits of Type IIb fibers as high Power fibers.

But, to understand other traits, it's important to know the ...

Pathways for ATP Synthesis



Aerobic pathway –

- in mitochondria, starts w/ Acetyl coA
  - Citrate cycle
    1) generates 1 ATP per "turn",
    * 2) Pass Energy in form of e^- to e^- carriers NADH + $FADH_2$, which pass e^- to
  - Electron Transport Chain (ETC)
    - reactions in chain ("Electron transpor") provide energy to pump H^+ up steep gradient across inner mito membrane. This gradient is a battery, used to
  - Synthesize ATP by oxidative phosphorylation

* Key is Energy flow from Acetyl coA → carriers → ETC → H^+ gradient → ATP

Aerobic Pathway notes

- Called "aerobic" because O_2 is a substrate in the reactions (specifically, it is the "final e⁻ acceptor" in the last reaction

- Generates about

$$\begin{aligned} 3\ NADH \times 2.5\ ATP/NADH &= 7.5\ ATP \\ 1\ FADH_2 \times 1.5\ ATP/NADH &= 1.5\ ATP \\ &\ 1\ ATP \\ \hline &\sim 10\ ATP \end{aligned}$$

- Source of acetyl Co-A is
    - Fatty acids - via β-oxidation. since this occurs in mitochondria, oxidation of FA is entirely aerobic
    - Pyruvate from glycolysis

Anaerobic pathway (glycolysis)

- The first product is Glucose-6-phosphate, whichis a substrate for
    1) **glycogen** synthesis (the P is removed)
    2) glycolysis
- A net 2 ATPs per glucose
- Anaerobic means that O_2 is not a substrate in the reactions. It does **NOT** mean "occurring in the absence of O_2"

FA vs glucose oxidation

- one glucose molecule yields 2 ATP in glycolysis
- one glucose molecule yields ~

10 NADH * 2.5 ATP	=	25
2 $FADH_2$ x 1.5	=	3
Gly	=	2
CC	=	2
		32

- 6C equivalent of LCFA (long-chain FA) yields ~

15 NADH x 2.5	=	37.5
3 $FADH_2$ x 1.5	=	4.5
CC	=	3
βox	=	3
		48

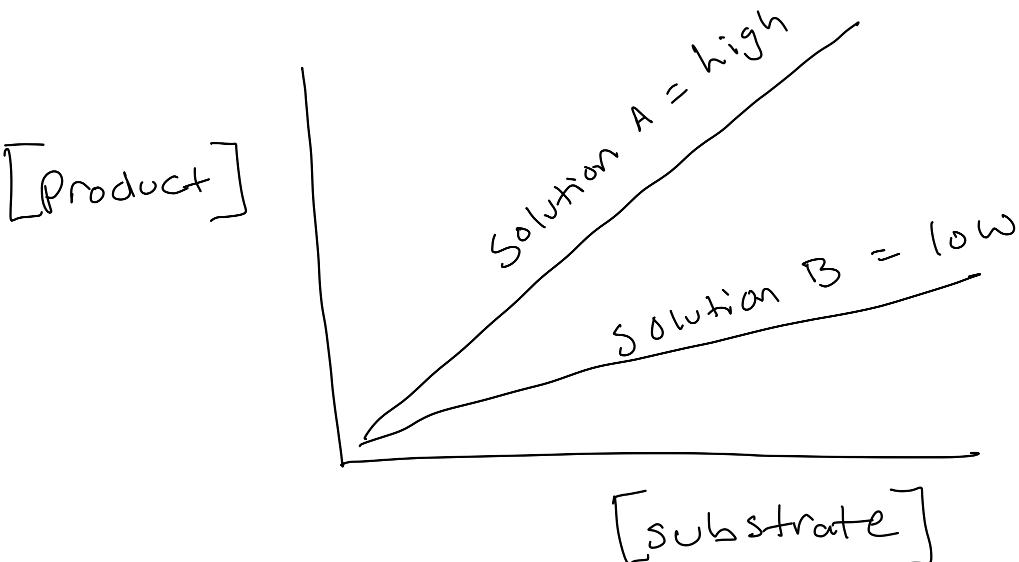
Consequently

1. glycolysis is fast but yields small amount of ATP
2. oxidation of LCFA yields 50% more (1.5 X) ATP per gram than glucose.

SO, for short activities use Anaerobic, for sustained activities use FA

Trait	Type I	Type IIb
mitochondrial density	high	low
Aerobic activity	high	low
Triacylgycerol content	high	low
myoglobin content	high	low
Capillary density	high	low
Color	red	white

what do I mean by aerobic enzyme activity?



Solution A has higher activity than B because more product is made given the same amount of substrate. This could occur because

1) a higher concentration of Enzyme in A

2) an enzyme isoform that has faster kinetics

an example of #2 is myosin ATPase MyHC-β v. MyHC-IIb

Trait	Type I	Type IIb
mitochondrial density	high	low
Aerobic activity	high	low
Triacylgycerol content	high	low
myoglobin content	high	low
Capillary density	high	low
Color	red	white

Type I fibers use predominantly FA for fuel using aerobic pathway. TI fibers have ↑ aerobic activity because of ↑ mitochondrial density. Mitochondrial density is increase by **Mitochondrial biogenesis** -- or mitochondrial division. The process is essentially that of cell fission in bacteria. Increase Endurance stimulus signals ↑ mitochondrial Biogenesis

Trait	Type I	Type IIb
mitochondrial density	high	low
aerobic activity	high	low
Triacylgycerol content	high	low
myoglobin content	high	low
Capillary density	high	low
Color	red	white

↑ Aerobic **Capacity** is increased by

1) increase FA content inside cell, and
2) increased ability to buffer O_2

myoglobin is a protein that is very similar to a subunit of hemoglobin. The protein binds heme, which binds O_2. Binding of O_2 to myoglobin gives TI fibers their red Color

Trait	Type I	Type IIb
mitochondrial density	high	low
aerobic activity	high	low
Triacylgycerol content	high	low
myoglobin content	high	low
Capillary density	high	low
Color	red	white

Type I fibers contract over long periods and need a continuous supply of O_2, TAG, and need to clump CO_2. Consequently Type I fibers are embedded w/in dense capillary networks.

- Type IIb fibers do not need a rich blood supply because they are less dependent on aerobic pathway

Trait	Type I	Type IIb
glycolytic activity	low	high
creatine phosphate	low	high
glycogen content	low	high
Lactate clearence	low	high
max diameter	small	large

- Type II fibers use glucose/anaerobic path much more than TI fibers, so glycolytic enzyme expression is upregulated (and downregulated in TI fibers)

- CP + ADP $\rightleftharpoons$ C + ATP

This is a very quick reaction for generating ATP!

- glycogen $\rightleftharpoons$ glu-6-P

T2 fibers have ↑ ability to store glucose (as glycogen)

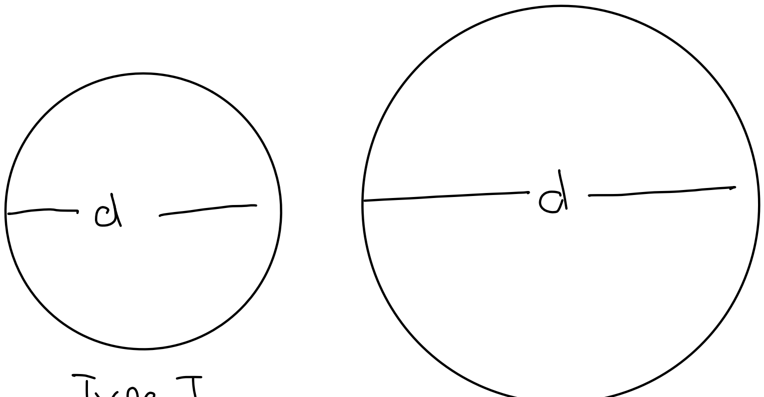
Trait	Type I	Type IIb
Lactate clearence	low	high
max diameter	small	large

- If Aerobic capacity is low (T2 fibers) Lactate builds and cells secrete lactate, which can the be oxidized by other cells or used as substrate to make glucose (gluconeogenesis). In TI fibers, most lactate is shuttle into mitochondria and oxidized
- ↑ F on muscle fibers stimulates ↑ protein synthesis and cell **hypertrophy**. Type I fibers have limited ability to grow as this would come at cost of ability to transport O_2/CO_2

↑ diameter ⟶ ↑ diffusion distance ⟶ ↓ O_2 Consumption

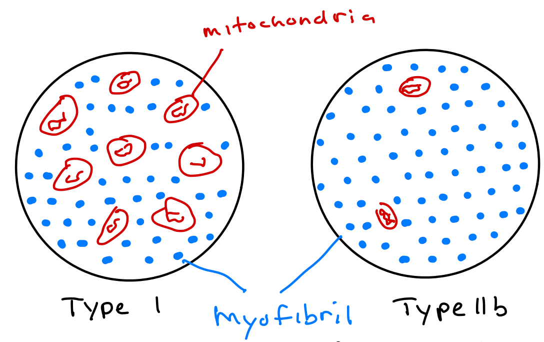
Trait	Type I	Type IIb
Force	low *	high *
Power	low *	high *

- The MyHCβ and MyHC2b isoforms generate Equal Force so all-things-equal we expect T1 and T2 fibers to generate same F, but ...



Type I Type II

Type II fibers tend to be bigger in cross-section, so a Type II fiber tends to generate more force



Type IIb fibers have fewer mitochondria so more space for myofibrils. Consequently, Type IIb fibers have more contractile protein per cross-sectional area, so generate ↑ F per fiber cross-sectional area

$P = F \cdot V$

F — T2 fibers generate more force

V — T2 fibers shorten faster

Q: Why is a Turkey drumstick "dark"?

A: because it is full of Type I fibers that it uses to walk around all day

Q: why is a Turkey breast "white"?

A: because it is full of Type IIb fibers used to generate short, powerful burst that get the bird up onto a tree limb

Q: Why does dark meat taste better than white meat?

A: because all the Fat!