

Lectures 18 & 19: Generation of Force by Muscles, Biomechanics.

Force at the Level of Sarcomeres. The force produced by a muscle depends only on:

1. How **many** sarcomeres are involved in a contraction,
2. **How** the sarcomeres contract.

The first point is straightforward - if more myofibers are stimulated simultaneously, a more powerful contraction results. This is why the cross-sectional area of a muscle is the primary determinant of its 'physiological strength'.

The second point is more complex — for a specific amount of shortening, different force can be produced by two different sarcomeres, or by one sarcomere under two different conditions.

Two major variables affect the force produced by a sarcomere - ***length and speed of contraction.***

Force and Length of Sarcomere:

(Overhead: Eckert Fig 10-8)

The tension produced by a sarcomere depends on the number of actin-myosin cross-bridges it forms. The number of cross bridges depends on the length of the sarcomere, because this determines how much overlap between myosin and actin filaments occurs. (The number of cross bridges per μm of overlap is not variable.)

One extreme - sarcomere is stretched so far that A-M overlap falls to zero \Rightarrow no force

Other extreme - sarcomere is compressed so far that Z-disks begin compressing myosin filaments \Rightarrow no force (or even negative force)

Intermediate plateau:

1. Entire length of myosin that bears cross bridges is overlapped by actin filaments
2. Actin filaments from opposite ends of sarcomere do not overlap and interfere with each other

\Rightarrow maximal force produced

Note that there is a range of lengths for which 1 & 2 are true, not just a single length. This is because the central portion of the myosin filament does not have heads. As sarcomere contracts from the length at which actin filaments begin to overlap this zone to the length at which actin filaments from each end of sarcomere overlap, there is no loss

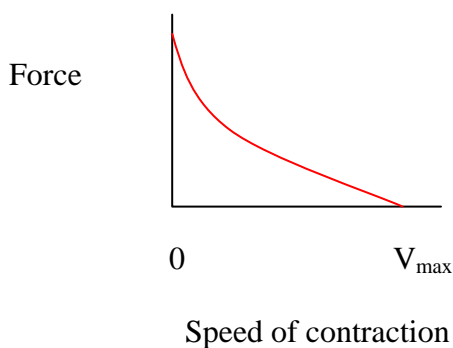
of force (because entire length of myosin with heads is overlapping just one actin filament).

This gives a plateau in the force-length relationship, rather than a distinct peak. Good design, because it allows leeway in the length of the sarcomere that can produce maximal tension \Rightarrow allows muscle to work at peak force over wider range of lengths.

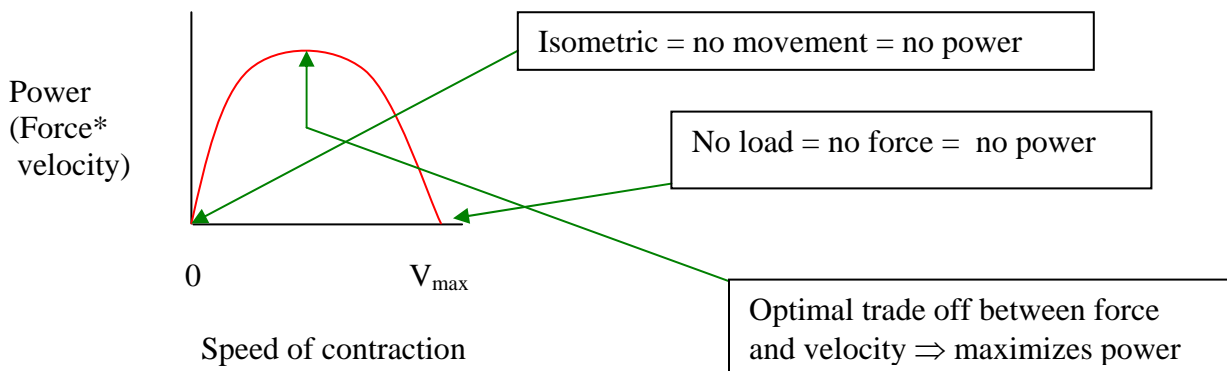
Force and Velocity of Contraction:

(Overhead: Eckert Fig 10-13)

For a given muscle, with A-M overlap held constant, there is an ***inverse relationship*** between velocity of contraction and force produced.



Power = (force * change in length)/time = force * velocity: so an inverse relationship between force and velocity means:



Implications:

1. ***Power is maximized at intermediate speed*** of contraction. Specifically, at $V/V_{max} = 0.15$ to 0.40 .

2. **To \uparrow force that can be produced at given speed of contraction, must $\uparrow V_{max}$.** For a specific muscle fiber, V_{max} is constant. Among muscle types, V_{max} varies, matching muscle physiology to demands placed on that muscle. More on this later.

The inverse force-velocity relationship is due to dynamics of crossbridges forming and breaking.

At any instant, the force produced by a myosin filament depends on two factors:

1. The number of crossbridges attached
2. The average force produced by each cross bridge

As velocity of contraction \uparrow both of these \downarrow .

(Overhead: Eckert Fig 10-11B)

1. Number of crossbridges \downarrow because myosin heads can only bind when site M1 contacts a G-actin binding site - if actin filament is sliding past quickly, this alignment becomes more unlikely.

(Overhead: Eckert Fig 10-14A & 10-14B)

2. Average force per crossbridge \downarrow because force generated by a bridge depends on its displacement, and:
 - a. average displacement of heads decreases
 - b. more heads are slid into positions of negative force before they can detach

(Overhead: Eckert Fig 10-14C)

V_{max} of a muscle fiber is reached when the negative force due to crossbridges displaced in the 'wrong' direction exactly balances positive force due to other crossbridges. Critical variable is **how quickly myosin heads can detach**.

- Detachments of heads depends on ATP attaching to myosin, then being hydrolyzed to ADP & P_i .
- As ADP and phosphate unbind from myosin, head rocks and detaches.
- The rate of detachment is altered by altering the speed at which ADP and P_i split from myosin heads.
- myosin-ATP-ase enzyme activity determines this rate

The above applies to **at the level of sarcomeres**. The maximal rate of contraction of an **entire myofiber** can be affected by additional variables (e.g rate at which Ca^{2+} is released by sarcoplasmic reticulum, which depends on density of pores in SR membrane.) More on this later.

Contraction at Level of Entire Muscle: rest of lecture focuses on entire muscle, not individual sarcomere or myofiber.

(Overhead: Eckert Fig 10-12)

Two main types of contraction:

Isometric - no change in length

Isotonic - shortens during contraction

(Overhead: Eckert Fig 10-26)

Monitoring forces becomes complicated \Rightarrow entire muscle might be producing little or no contraction or force, even though cross bridges are working maximally. The muscle is composed of:

Contractile component: produces force, composed of myofibers

Elastic component: absorbs some of muscle's force by stretching. Has two subsets:

Parallel elastic component: membranes running along myofibers (e.g. plasma membrane, sarcoplasmic reticulum)

Series elastic component: tendons and fascia that binds muscle to insertion on bone.

(parallel and series borrowed from circuit terminology)

(Overhead: Eckert Fig 10-27)

Elastic components can create **slack**, depending on the degree of stretch. If no slack in elastic component, then force at level of fibers is registered as force at level of muscle.

Consequence: Latent period, between arrival of AP and production of force at level of myofibers (cross bridge formation) is only about 2 μ s. Once force is being produced at level of myofibers, the muscle is in **active state**, whether or not external tension is produced. The delay before external force is produced by muscle itself is longer, 10 to 200 μ s, depending on the configuration of elastic components.

Inactive \rightarrow	Latent \rightarrow	Active \rightarrow	Active with external force
Membrane at Resting potential \rightarrow	AP arrives \rightarrow	Crossbridges formed \rightarrow	Elastic slack has been taken up

Quick stretch experiments can measure internal tension of a muscle, to **distinguish active state** from inactive and latent state. Measures the resistance a

muscle has to quick stretch, even when it is not producing external tension. Takes slack out of elastic components, isolating contractile component.

Twitch Force and Maximum (tetanic) Force

(Overhead: Eckert Fig 10-27A and 10-28)

External force of normal twitch \ll maximal external force muscle can produce

Why?

1. Ca^{2+} pumps begin resequestering calcium as soon as it is released by depolarization.
2. Ca^{2+} in myoplasm falls below 10^{-7} M before elastic component is fully stretched.
3. If AP's arrive in slow succession, Ca^{2+} doesn't drop below threshold for contraction
4. Muscle stays in active state continuously, contractions begin to sum because elastic slack doesn't fully return between AP's.
5. If AP's arrive in rapid succession, all elastic slack is taken up, maximal force is produced \Rightarrow ***tetanus***.

Elastic component involves constraints and trade-offs in muscle performance.

Constraint: skeletal muscle must insert on bone to be useful. Connection has to be made of something flexible, because angles of insertion change as joints move. Providing flexibility inherently constrains the connections to be elastic to some degree.

Trade-off: Elastic component means that muscle produces less than maximal tension (cost), but provides benefit because movements become less jerky. Coordinating movements produced by tetanic contractions would be difficult.

Energetics of Contraction

ATP is used to provide energy for contraction. Energy is required for

1. Cross bridge movements (70% - 75%)
2. Calcium pumps (25% - 30%)

However, experiments have shown that ATP concentration in a muscle cell does not decline as the muscle works. How is ATP held constant, while being consumed?

(Overhead: Eckert Fig 10-29)

In long term, ATP is regenerated by ***oxidative phosphorylation*** (via the Krebs cycle and electron transport chain, in mitochondria, when oxygen is available).

In the medium-term, ATP can also be regenerated by *anaerobic glycolysis*. Recall that anaerobic metabolism is 20 times less efficient than oxidative phosphorylation. Because it is much less efficient, glycolysis cannot be used to restore ATP for long periods.

Intense short-term activity burns ATP faster than it can be regenerated by cellular respiration and anaerobic glycolysis. In this case, ATP is regenerated by *direct phosphorylation*. *Creatine phosphate* has a phosphate bond that, when broken, yields more energy than is needed to synthesize ATP from ADP, in a coupled reaction promoted by the enzyme *creatine phosphokinase*.

Creatine phosphate is 4x to 8x more concentrated than ATP in muscle cells, so it provides a strong *buffer against ATP depletion*, but prolonged, intense activity can cause depletion. Muscles lock up in rigor, so activity is stopped, and aerobic respiration restores ATP, removes lactic acid from cells.

A good example is a mile race. Feel pretty good at first (oxidative phosphorylation). Muscles start to hurt (lactic acid from anaerobic glycolysis accumulating), and ultimately start to lock up (ATP depletion prevents crossbridges from detaching).

Matching of Muscle Physiology to Demands

Vertebrate skeletal myofibers come in four types - *tonic* fibers and 3 types of *twitch fibers*. Each fiber type is suited to different demands.

Tonic fibers are fundamentally different than twitch fibers:

- Do not produce action potentials,
- Thus do not produce all-or-none twitches.
- Instead of a single neuromuscular junction, a motor neuron has many synapses along fiber
- Thus show *graded response* - stronger contraction with more AP's from motor neuron
- Involved in posture - operating continuously
- Very slow, but produce force efficiently (recall inverse force-velocity relationship)

Twitch fibers (3 types):

- Produce AP's
- Contract in an all or none manner.
- Differ in 8 physiological factors that determine the force they can produce, and the energy efficiency with which they produce force.

Table summarizes the differences among twitch fiber types.

<i>Property</i>	<i>Slow Oxidative</i>	<i>Fast Oxidative</i>	<i>Fast Glycolytic</i>	<i>Comment</i>
1. Vmax	Slow	Fast	Fast	
2. Myosin ATPase activity	Low	High	High	determines Vmax
3. Resistance to fatigue	High	Int	Low	
4. Capacity for Oxidative phosphorylation	High	High	Low	affects resistance to fatigue
5. Density of mitochondria	High	High	Low	affects resistance to fatigue
6. Enzymes for anaerobic glycolysis	Low	Int	High	affects short term force
7. Fiber diameter	Low	Int	High	
8. Force/cross sectional area	Low	Int	High	due to all of above

There is a *trade-off between force (power) and energy efficiency*.

(Overhead: Eckert Fig 10-31 A & B)

Recall from sarcomere level that a given myofiber produces less force the faster it contracts, relative to its maximum speed (Force ↓ as V/V_{max} ↑). **So increasing Vmax increases force** that is produced at given velocity of contraction. Power (force/time) is greater for fiber with high V_{max} than for fiber with low V_{max} , at any speed of contraction.

(Overhead: Eckert Fig 10-31 C & D)

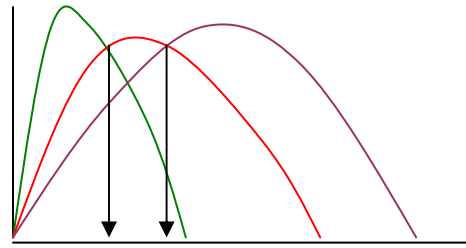
So why not have only very fast fibers (fast glycolytic fibers)? Because a myofiber with high V_{max} uses more energy than a fiber with low V_{max} , if both contract at same speed. Can examine the trade-off between power and energy quantitatively by calculating efficiency:

$$\text{Efficiency} = \frac{\text{Power}}{\text{Energy utilization}}$$

Slow twitch fibers are more efficient than fast twitch fibers, at low velocity of contraction.

Fast twitch fibers are more efficient at high velocity.

Efficiency
(Power/energy use)



Velocity

Slow oxidative fibers
most efficient in this
range of contraction
velocity

Fast oxidative
fibers become
more efficient at
intermediate
speeds

Fast
glycolytic
fibers most
efficient at
top speeds

Because movements of different types require different power, fiber types are matched to the demands placed on a muscle, so that the ***most efficient fiber type capable of producing the required power will be used.***

(Overhead: Eckert Fig 10-30)

A ***muscle contains more than one fiber type*** (there are exceptions to this), to allow fine tuning of muscle physiology to demands.

Examples of matching physiology to demands:

(Overhead: Eckert Figs 10-35, 10-36)

1. Steady swimming vs escape response in fish:

Activity	Movement	Muscle Type	Attachment
Steady swim	Slow, small displacement	red (slow oxidative)	parallel to body
Escape	Fast, large Displacement	white (fast glycolytic)	oblique

3. Sonic muscle in toadfish swimbladder. Produce sound by making air bladder resonate. Must contract and relax at > 100 Hz (cycles/sec).

(Overhead: Figs 10-41, 10-42)

To contract and relax at this very high rate, sonic muscles:

- Release Ca^{2+} quickly (due to high density of Ca^{2+} channels in SR membrane)
- Get Ca^{2+} to actin filament quickly (due to SR being close to filaments)
- Bind Ca^{2+} to actin quickly, exposing myosin binding sites (due to high density of troponin groups along tropomyosin)
- Resequester Ca^{2+} quickly (due to high density of Ca^{2+} pumps in SR membrane, and low affinity for Ca^{2+} of troponin)
- Perhaps also have fast detachment of cross bridges - mechanism not understood.