Muscle and Limb Mechanics

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ABSTRACT

Understanding of the musculoskeletal system has evolved from the collection of individual phenomena in highly selected experimental preparations under highly controlled and often unphysiological conditions. At the systems level, it is now possible to construct complete and reasonably accurate models of the kinetics and energetics of realistic muscles and to combine them to understand the dynamics of complete musculoskeletal systems performing natural behaviors. At the reductionist level, it is possible to relate most of the individual phenomena to the anatomical structures and biochemical processes that account for them. Two large challenges remain. At a systems level, neuroscience must now account for how the nervous system learns to exploit the many complex features that evolution has incorporated into muscle and limb mechanics. At a reductionist level, medicine must now account for the many forms of pathology and disability that arise from the many diseases and injuries to which this highly evolved system is inevitably prone. © 2017 American Physiological Society. *Compr Physiol* 7:429-462, 2017.

Introduction

Quality of life and reproductive success depend on the ability to execute voluntary movements that are effective, efficient, and safe. Animals learn to move their limbs by coordinating neural commands to skeletal muscles. Although most everyday movements are carried out with little mental effort, their neuromuscular control is difficult to understand. Consequently, many debilitating disorders of mechanics and movement remain poorly diagnosed and treated. This article provides descriptions of the structure and function of muscles and articulated limbs from two perspectives: the muscle physiologist or biomechanician who wants to understand these structures for their own sake, and the sensorimotor neurophysiologist who needs to understand how these structures define the control problems that are solved by the nervous system. Scientific interest in and research on musculoskeletal systems have been longstanding and voluminous and well reviewed (246). It is now possible to replace many of the lumped, phenomenological models of the past with reductive and quantitative models in which observed properties of muscle arise from the properties and functions of individual structures within the system (206). This article presents the most current and widely accepted mechanisms, theories, and models of action and identifies aspects that remain uncertain and even contentious but are probably important for system control, performance, development, and/or dysfunction. Many details regarding the biochemistry and genetic expression of these mechanisms are the subject of much research in muscle physiology, which lies outside the scope of this review.

What Are the Drivers of Musculoskeletal Structure and Function?

Muscles are perhaps the most highly evolved tissues in the body. The basic architecture and biochemistry of the contractile apparatus is highly conserved throughout the animal kingdom (Fig. 1). Nevertheless, because muscles represent the majority of the mass and metabolic demand of most multicellular animals, any opportunity to improve functionality within a particular ecological niche has likely been discovered and exploited (245). This review is focused on mammalian skeletal muscle and particularly human physiology and performance, to the exclusion of many specializations and features well described in other classes and species. The details and specializations of the structure and function of the elements reviewed herein may be easier to appreciate in the context of the attributes that they support.

Strength

The ultimate limit on the contractile force that can be generated by a muscle is the tensile strength of the material from

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Published online, April 2017 (*comprehensivephysiology.com*)
DOI: 10.1002/cphy.c160009

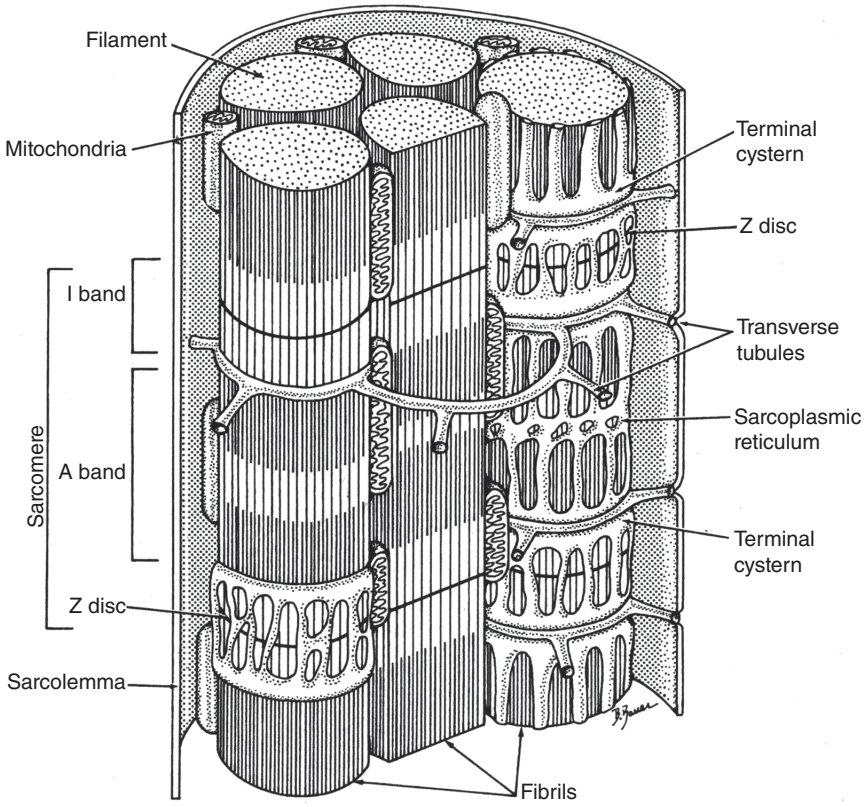

Figure 1 Basic architecture of a mammalian striated skeletal muscle fiber, consisting myofibrillar bundles of paracrystalline myofilaments organized into serially repeating sarcomeres. Action potentials traveling along the sarcolemma and invaginations called transverse tubules activate the contractile state by releasing calcium from terminal cisternae of the sarcoplasmic reticulum; relaxation occurs as calcium is pumped back into the sarcoplasmic reticulum. Varities of recently elucidated scaffold structures (not illustrated) maintain the highly regular alignment of all of these structures across the length and breadth of muscle fibers. Reprinted with permission (207).

which it is made—filamentous proteins composed of peptide linkages. The more tightly such filaments can be packed into a given space, the stronger the material. At the level of the individual muscle fibers, the evolutionary competition for strength results in a paracrystalline packing of myofilaments (124,163) that, nevertheless, must slide freely past each other. Because muscle fibers are filled with an essentially constant volume of incompressible material, any change in length must change the cross-sectional area and hence the lattice spacing of these myofilaments. Many of the length-dependent complexities of force generation arise from these simple physical constraints.

At the level of whole muscles, the evolutionary competition for strength results in arrangements of muscle fibers, tendons, and their arrangement on the bones so as to maximize forces delivered to end effectors such as fingers, claws, and teeth. Features such as pennate muscle architecture, moment arms, and tendons with pulleys and retinacular constraints reflect attempts to optimize strength within constraints on mass and its distribution on the skeleton (120).

Power

Animals convert the chemical energy that they derive from food into mechanical energy that can be used to interact with the world around them. From physics, we know that this requires force to be applied over a distance; the product of force and distance is work. Note that the actual motion of the limb to which the muscle is attached is the result of many different internal and external forces, so may result in shortening (negative length change) or stretching (positive length change) of the muscle, hence positive or negative work, respectively. The rate at which work is accomplished is power, the product of force and velocity (which has a positive or negative sign). If the positive power generating capability of a muscle is bounded (e.g., by its blood supply and the kinetics of crossbridge cycling), then force must decrease as velocity increases. Structural features that optimize strength (e.g., large moment arms or pennate architecture with short fascicles and long aponeuroses) tend to increase the velocities of fascicular and crossbridge motion for a given joint angle velocity, thereby reducing power output (120). Most muscles

are comprised of a mix of fiber types, each of which has crossbridge kinetics that are designed to work best under different kinematic conditions of use.

Efficiency and economy

Perhaps the most important driver of animal evolution is the need to maintain positive energy balance. Growth and reproduction are possible only if the organism obtains more calories from its food than it expends acquiring it. According to thermodynamics, energy consumption is required only when doing positive work, that is, a muscle generating force while shortening. The amount of positive work performed per unit of energy consumed is efficiency. The complex arrangement of multiple muscles crossing multiple joints in various combinations provides opportunities to transfer momentum (i.e., kinetic energy) from one part of the body to another when muscles are isometric or lengthening (273, 340); thermodynamically, this requires no energy consumption. The complex mechanisms for crossbridge binding and release are designed to maximize economy, which is the momentum generated (the product of force and time) per unit of energy consumed. During active lengthening of muscles, crossbridges can reattach rapidly to maintain force production while consuming no energy at all, a huge evolutionary advantage. This allows animals with limbs to consume very little energy when locomoting at constant velocity on level terrain, a condition for which an idealized machine requires zero energy consumption.

Modulation and control

Precise movements are possible only if muscles are organized to permit precisely graded and rapidly modulated force output. This is largely the function of the endoplasmic reticulum, a highly refined set of membrane invaginations, pumps, conduits, and cisterns whereby the state of activation of the muscle can be controlled (Fig. 1). Rapid cyclical movements such as running require muscles to cycle rapidly between freely stretchable and maximal force generating states in response to neural impulses arriving at a single synaptic location that may be centimeters from the distributed sites of force generation throughout the muscle fiber. The signaling and control system for activation consumes a substantial part of the energy budget (see *"Modeling muscle mechanics and energetics—Energetics"*) and tends to be optimized for different types of behaviors in different types of muscle fibers.

Structural stability

A system that is designed to operate near its limits of structural strength and speed will necessarily be particularly vulnerable to damage from unstable states. Muscle fibers contain a variety of internal structural proteins and external connective tissues to mitigate these risks. Disorders and failures of these structures are responsible for the majority of injuries and disabilities treated in the health care system. The notion that muscle fibers and myofibrils should be free to slide past each other without friction or viscosity was based on the observation that little or no heating relatable to mechanical energy dissipated in such friction or viscosity could be detected in thermodynamic experiments (151). A tightly coupled system that prevents most such sliding motion seems more realistic and also satisfies this thermodynamic observation and the associated attribute of efficiency and economy (see earlier).

Self-organization

Like all biological tissues, the structural and contractile elements that comprise a muscle must be constantly replaced. As the animal grows, new material must be added to maintain strength and function. Higher animals with sophisticated nervous systems compete by adapting to ecological niches and learning useful behavioral patterns. The actual conditions and patterns of use of a given muscle cannot be predicted, especially as species evolve through mutations of musculoskeletal structure, so cannot be predetermined genetically. Responding to these conditions of use requires machinery within the individual muscle fibers that can identify wear and usage patterns, direct the resynthesis of the required materials, and insert them into the structure while it is constantly under active use. This is the function of various scaffold proteins and signaling pathways that are just starting to be discovered (124).

How Does Musculoskeletal Structure and Function Affect Motor Behavior?

A plausible scheme for the neural control of any movement must explain how neural commands interact with the intrinsic mechanical properties of muscles and skeletal articulations to produce that movement. A major challenge with identifying such schemes is that the relationship between neural commands and musculoskeletal structure is basically circular: neural activation of a muscle results in contractile forces that result in skeletal motion that changes the kinematics of the muscle and hence its force production. That is to say that skeletal kinetics (forces applied to the system) affect skeletal kinematics (position, velocity, and acceleration) and muscle kinematics (sarcomere length and velocity), which in turn affect muscle kinetics (contractile force). The control schemes are also circular: centrally generated neural commands are deeply modulated by the somatosensory feedback that represents the motion and forces associated with the behavior. Experimental techniques to observe behaving animals usually provide only a tiny subset of the many state variables and neural signals required to understand such a system (Fig. 2). The rest must be inferred from formal or informal models of the components themselves (209).

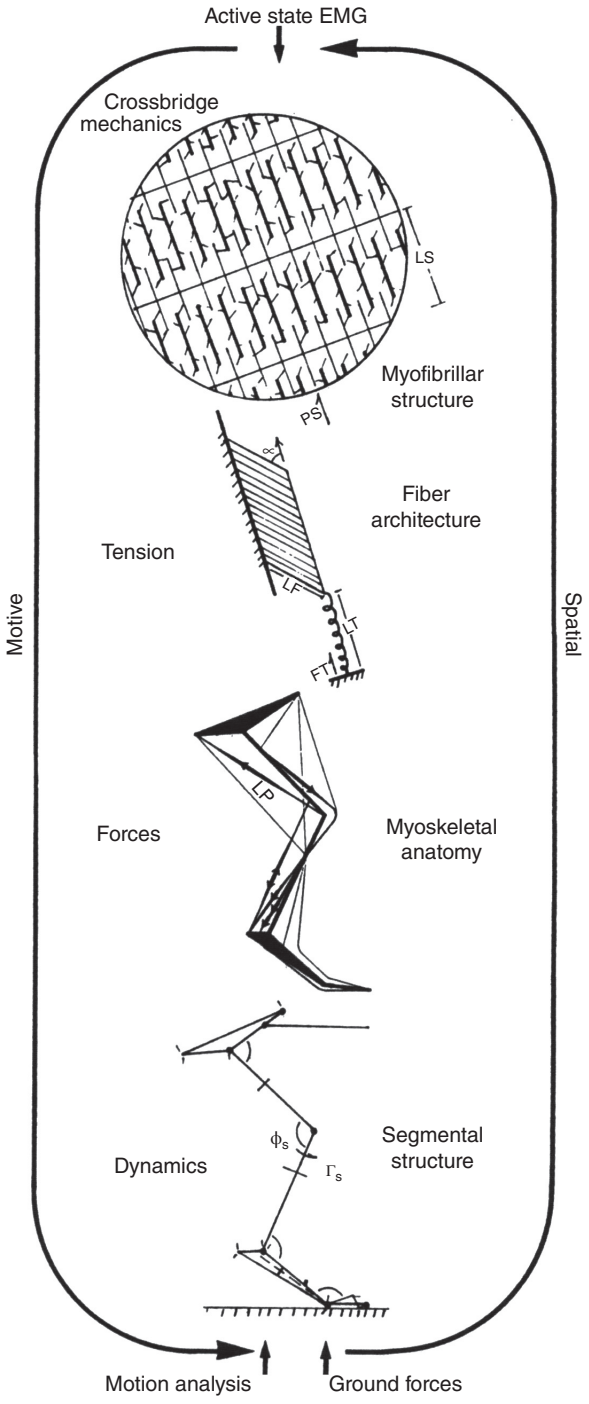

Figure 2 Motor behaviors are the result of many complex physiological and mechanical processes that have limited experimental observability. The state of activation of muscles is often measured by electromyographical signals (EMG) reflecting action potentials along muscle fibers. The consequent kinetic (motive) processes that eventually affect the observable motion of the body and any forces applied to contacting objects depend, in turn, on the architecture, posture, and motion (spatial) of the musculoskeletal system. Reprinted with permission (207).

One engineering strategy for controlling a complex plant is to create an inverse model of the plant's dynamics. Such a model can be used to compute the feed-forward command signals that will result in the desired change of state of the plant. The feasibility of this approach depends on the complexity and stationarity of the plant dynamics. This review describes the many complex features of the musculoskeletal system that contribute to its desirable functional attributes but require extremely complex and generally noninvertible models to describe. To make the problem even worse, muscle mechanics are not stationary. Muscle properties change even during a single movement, which changes the neural commands required for the task and therefore the demands placed on neural structures (e.g., spinal cord and brain) to generate them. The mechanics of skeletal muscle can change from their normal, resting state as a result of potentiation, fatigue, injury, disease as well as longer-term physiological and morphological changes that depend on activation, length, and loading history.

Limb Mechanics

Limb motion results from the combined set of a variety of forces that the limbs experience. These forces can be generated within the limb itself, such as by musculotendons, ligaments, and interaction forces caused by the inertia and rotational acceleration of connected limb segments (see Section "Joint constraints"). Forces exerted on the limb can also originate from outside of the limb and include gravity as well as contact with the environment. The motion that results depends on the magnitude, location, and direction of all of these forces. The motion also depends on the mass and mass distribution of individual limb segments that resist acceleration, as well as how the limb segments are connected by anatomical joints and any constraints on their motion, which define the interaction forces between all connected limb segments.

Force location and direction

The forces exerted by the environment can be applied in theory to any location on the body and in any direction depending on the type of interaction. The force of gravity on the other hand has a virtually constant direction and magnitude, and its location is effectively at the center of mass of each limb segment. The forces that are generated within the limb, for example, the musculotendon forces in particular, have a location and direction that is defined by the anatomy (see Section "Musculotendon path"). The attachment points of the musculotendons on the skeleton define the force location, while the orientation of the tendon at the attachment site defines the pulling direction of the musculotendon force.

The portion of the force that actually contributes torque to rotate a joint depends on the origin and insertion points of the muscle on the skeleton and constraints imposed by anatomical joints. Anatomical joints allow motion of the limb segments in some axes, but not others, and may include anatomical stops in

the allowed axes. The better the alignment between the force direction and the allowable direction of motion of the joint, the more that the force contributes to motion of the joint. For example, a larger portion of the force generated by the biceps contributes to rotation of the elbow than the brachialis muscle, because a relatively larger component of the brachialis force is in the direction that is perpendicular to its allowable motion and hence simply compresses the elbow joint.

Mass

Musculotendon forces accelerate the limb mass, which consists mostly of the mass of the underlying bones and soft tissue including musculotendons themselves, which often account for the majority of the limb mass (73, 113, 116). The mass distribution of the limbs determines the limb's inertial resistance to motion along all possible directions. The mass distribution can change within a movement due to changes of location and shape of underlying muscles that stretch and shorten during movement (243). One general design principle for limbs is to minimize the mass of the distalmost parts of the limb that experience the largest accelerations and decelerations. This gives rise to muscles with long distal tendons that commonly insert close to joints resulting in small moment arms. To generate the contractile force and torque required to exert useful forces at the end points of such limbs, such muscles tend to be highly pennate, complicating their dynamics and control.

Joint constraints

Motion of limb segments is coupled through the anatomical joints that join them (154, 257, 258). A force will not only accelerate the limb segment it is applied on but also all other connected segments (194, 252). Imagine, for example, placing your arm in front of you in a horizontal posture and increasing the activation to your monoarticular shoulder flexors. This would not only cause your shoulder joint and upper arm to rotate in the direction of flexion, but it would also pull the lower arm along because it is connected to the upper arm via the elbow joint. The portions of the lower and upper arm closest to elbow joint will move similarly, but the distal portion of the lower arm would lag behind due to the inertia of the segment. The elbow joint and lower arm would, therefore, rotate in the direction of extension. Such interaction forces influence the muscle forces required for a desired movement. If the passive extension of the elbow brings the hand near a desired target, then minimal activation of the elbow musculature would be necessary. If passive extension overshoots the target, the elbow flexors would need to be activated to brake the movement and, conversely, if passive extension undershoots the target, then elbow extensors would need to be activated to increase the amount of the elbow extension.

Biarticular muscles present opportunities to correct for these effects as well as to transfer momentum efficiently between segments (331) but these indirect effects make it impossible to determine the effects of their activation on either limb posture or end-point force without considering the kinematics and kinetics of the whole limb (311). Much recent research in sensorimotor planning and control has been focused on how the CNS anticipates and compensates for these complexities during reaching movements of the arms (126, 192).

These interaction effects (also called Coriolis forces) result in muscles generating accelerations at joints that they do not cross that are both proximal and distal to those on which they exert direct torques (194, 252). For example, during quiet standing in humans, activation of the monoarticular ankle extensor soleus results in extensor accelerations of both the knee and hip as it pulls against the linked masses of the proximal leg and trunk. For the biarticular gastrocnemius muscles, which are anatomical knee flexors as well as ankle extensors, the net acceleration at the knee may be a counterintuitive knee extension for most standing postures (126, 192, 311, 331, 343).

Formal modeling of limb dynamics

Each limb segment moves according to the forces applied on it primarily by the musculotendons, the environment, and the movement constraints imposed on it by connected segments. The complex relationship between limb forces and movement obeys Newton's laws of motion for point masses. In the simplest case, it can be assumed that each limb segment is composed of a collection of point masses that are rigidly connected, formally known as a rigid body. The effect of forces on motion of rigid bodies has been derived from Newton's laws and is formally known as Euler's laws of motion.

Euler's laws of motion for one segment fully define its relationship between forces and motion when it is not connected to any other segment. To account for motion of the entire limb, Euler laws of motion must be applied to all limb segments but the forces applied to a given segment must be supplemented with the forces that are necessary for satisfying the constraints imposed by the anatomical joints. This is a complicated, nonintuitive task and many mathematical formulations have been developed to do it (341). To make matters even more complicated, limb segments deform in reality, for example, via changes in muscle shape resulting from contractions and limb movement, which may have a significant effect on limb mechanics (64). Such deformations can be represented by splitting limb segment representations into multiple rigid bodies that can move relative to each other, storing, releasing, dissipating, and transferring kinetic energy through viscoelastic coupling between them. Characterizing limb motion in this case would involve describing the motion of a larger number of rigid bodies with a larger number of constraints associated with them.

Coupling of muscle and limb mechanics

Limb mechanics are strongly coupled to muscle mechanics (Fig. 3). The force generated by a given muscle is applied indirectly to the limb by stretching the intermediate tendon plus aponeurosis. Furthermore, the musculotendon forces

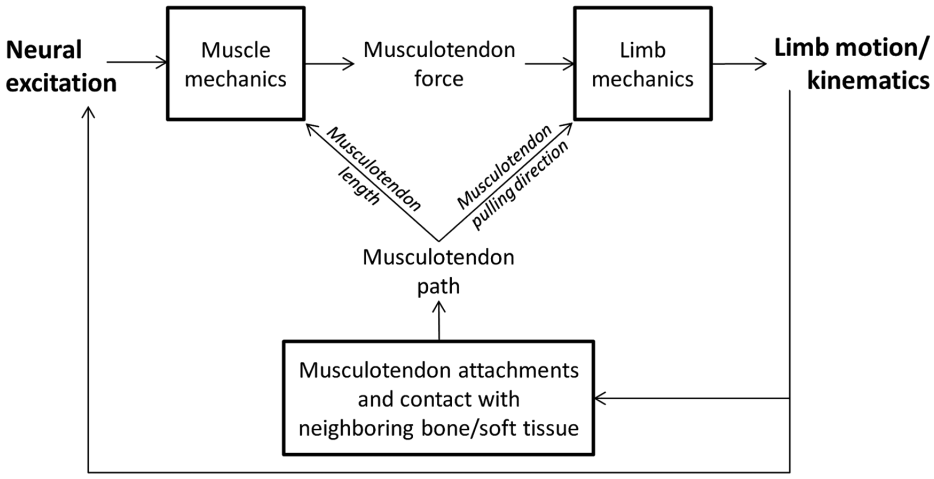

Figure 3 Coupling between muscle and limb mechanics. Neural signals from motoneurons in the spinal cord excite muscles that then generate force depending on the time course of musculotendon length (see Section "Muscle mechanics in the potentiated, nonfatigued state"). The musculotendon force then influences limb motion depending on the mechanics of the limb as well as the location and the pulling direction of the musculotendon force. The limb motion that results changes the musculotendon path depending on the musculoskeletal attachments within the limb and the physical constraints due to contact with neighboring bone/soft tissue. The musculotendon path determines both the musculotendon length, which has substantial effects on muscle mechanics, and musculotendon pulling direction, which has substantial effects on limb mechanics. Moreover, the limb motion, which results largely from musculotendon forces also modulates muscle mechanics through its effects on neural excitation of muscle through proprioceptor mediated input to the spinal cord and brain.

applied to the limb are modulated substantially by the limb motion itself (see Section "Muscle mechanics in the nonfatigued state"). The effects of musculotendon force on limb motion, and vice versa, are defined by the musculotendon path from origin to insertion. Textbook descriptions of muscle mechanics usually illustrate a single muscle attached directly to bones on either side of a single joint with a single hinge-like axis of motion. In fact, the majority of skeletal muscles cross more than one joint and the majority of joints have more than one degree of freedom of motion. The moment arm in one axis of motion may depend on the joint angle in another axis of motion, even reversing sign (336). Tendons are often constrained to follow nonstraight paths by passing over pulleys and through retinacula, which causes them to generate torques at those intermediate points and not just at the origin and insertion. In axial muscles of the neck and trunk, individually innervated neuromuscular compartments are often connected in series with partial attachments to parallel muscles and bones (178, 264). Mathematical models of musculoskeletal mechanics are complex but feasible for most limb systems (given some simplifying assumptions) but have been attempted for only a few axial systems (74, 223, 313). This section provides examples of how various anatomical arrangements can affect the actions of individual muscles.

Tendon and aponeurosis

Muscles do not exert forces on bones directly. Muscles are joined with bones through elastic connective tissue such as tendons, which may be longer than the muscles or almost nonexistent. In pennate muscle, muscle fascicles are oriented obliquely with respect to the line of pull of the whole muscle and terminate on thin fibrous aponeurotic sheets on the surface or within the muscle that then converge to tendons (119). It has been shown that stresses and strains, hence stiffness, are the same for aponeuroses and tendons across a wide range of forces generated by a given muscle (216, 279). Stiffness is low near the slack length of the tendon/aponeurosis and increases exponentially with strain until about 2% to 3% strain and remains constant across higher strains that are within the damaging limit of about 5% strain [Fig. 4 (1, 28, 265, 279)]. The length and stiffness of the aponeurosis plus tendon determine the dynamics of force transmission. The more compliant the tendon, the more strain it would have to undergo to generate a given level of force and the more mechanical energy it can store as a stretched spring (see later). Strain of the tendon/aponeurosis also determines the relative length changes experienced by muscle fascicles and tendon for a given level of activation. Upon activating a musculotendon isometrically, for example, a relatively long and compliant tendon would cause a large decrease in muscle fascicle length and a high shortening velocity, both of which have strong influences on muscle force generation (see Section "Muscle mechanics in the nonfatigued state").

The changes in fascicle length, velocity, and force also lead to changes in muscle spindle and Golgi tendon organ afferent signals that contribute to the sense of proprioception and to motoneuron activity generated via spinal and supraspinal pathways. The muscle spindle afferent signals that depend on length and velocity of muscle fascicles are thought

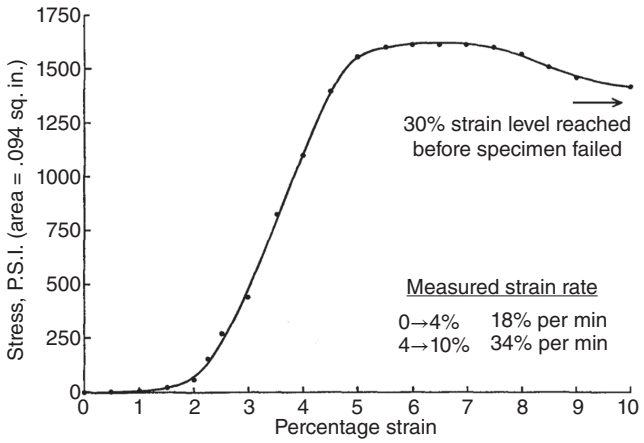

Figure 4 Tendon stiffness. The stress strain curve of a tendon is shown over a wide range of strains. As strain is increased past the slack length of the tendon, tensile stress begins to build in the tendon. As strain increases tendon stiffness increases so the effects of strain on stress grow stronger up until a point where stiffness plateaus (2%-3%) and the sensitivity of stress to strain becomes maximal. Further increases in strain result in linear increases in stress up to a point (5%-6%) where the tendon starts to experience irreversible damage and stress abruptly stops increasing in response to further strain and even starts decreasing for strains greater than about 7%. The experiment was performed on fresh cadaveric Achilles tendon from a 54 year woman at 37°C. Reprinted with permission (1).

to be integrated by the nervous system to sense body posture and motion (278). The elasticity of the tendon/aponeurosis makes such process more challenging because it complicates the relationship between muscle fascicle motion and whole musculotendon motion (153). For example, if a muscle is activated while the musculotendon is stretched due to an external load, the muscle fascicles may shorten and therefore experience temporarily an opposite displacement than the whole musculotendon (344).

The elastic connective tissue also enables storing and releasing of mechanical energy for economical use of metabolic energy (6, 7, 65, 169). For example, a muscle with elastic connective tissue that is first lengthened and then shortened (as in jumping, running, etc.) would be able store elastic energy during the lengthening phase and apply some of that energy during the shortening phase as positive work (244,344). Furthermore, because lengthening contractions are much more economical than shortening contractions (generating higher force with little ATP consumption), the muscle can be activated during the lengthening phase to increase the strain and energy stored in the series elastic element, thus reducing the amount of positive work that would have to be supplied through the relatively uneconomical shortening contractions (342, 344). Proper understanding of in-series elasticity is important when interpreting whole musculotendon mechanics, but it is often done in error. If the tendon is short, the model may omit in-series elasticity, overlooking the similarly elastic aponeurosis, which may be longer than the muscle fascicles in a pennate muscle. To simplify dynamical models of musculoskeletal systems, the series elasticity is often modeled as a linear spring. Because most of the compliance of the tendon+aponeurosis occurs at the relatively low forces associated with phasic muscle activities such as walking, the errors can be substantial. For example, consider a pennate muscle with a nominal 10 cm fascicle length in series with 10 cm of tendon plus 20 cm of aponeurosis. If the nervous system suddenly activates the muscle to produce about 20% force under isometric conditions, the tendon+aponeurosis will experience about 3% or 0.9 cm of strain during the 100 ms rise time of force, resulting in a velocity of shortening of the fascicle of about 0.9 L_0/s. When the muscle is deactivated, the stored energy in the tendon+aponeurosis spring will stretch the relaxing muscle, delaying the decrease in force in the system. A forward dynamics model that neglected these effects would generate a substantially different trajectory of motion than one that modeled them correctly.

Musculotendon path

The musculotendon path determines both the musculotendon length, which modulates force as well as the location and pulling direction of the musculotendon force that influences movement. The musculotendon path is defined by the attachment locations of the musculotendon on the skeleton, the posture of the body, and the interactions with neighboring bone and soft tissue.

Contact between musculotendons and bone has a large influence on muscle path. For example, when the elbow is fully extended, the musculotendon of the medial triceps brachii forms a nearly straight line from its origin on the humerus to its insertion on the ulna (234). At more flexed postures, however, the triceps musculotendon path must wrap around the elbow, which causes the musculotendon path and the moment arm at the elbow to be substantially longer than if it followed a straight line from origin to insertion.

Contact between musculotendons and fascial tissue also has a large influence on musculotendon path. For example, the tibialis anterior musculotendon is constrained by a dense band of fascial tissue known as a retinaculum that wraps tightly around the tendon near the distal end of the shank (27). At highly plantarflexed postures of the ankle, the tibialis anterior muscle follows nearly a straight line from its origin on the tibia to its insertion on the medial cuneiform bone. At highly dorsiflexed postures, however, the musculotendon path wraps around the inside surface of the retinaculum. The presence of the retinaculum, therefore, leads to relatively longer musculotendon lengths but a smaller moment arm than if it were not there and the musculotendon path were allowed to follow a straight line.

Contact among musculotendons themselves can also influence the musculotendon path and their effects are much more complex (32). Musculotendons are tightly packed around bones and are often in contact with each other. Limb posture and muscle activation have a large influence on muscle shape, for example, a large amount of bulging can occur if muscle becomes shorter due to strong contractions and limb

postures that shorten the musculotendon. Such change in muscle shape can displace adjacent muscles that are in contact, thus leading to changes in their overall musculotendon path and, hence, their moment arms at the joints that they cross. This effect is especially pronounced in gluteal muscles where the gluteus maximus wraps around the gluteus medius and minimus. Shortening of muscle gluteus medius and minimus due to strong contractions can lead to large displacements of the gluteus maximus leading to a more curved and longer musculotendon path than if no bulging occurred (32). Furthermore, individual muscles or separately innervated neuromuscular compartments may not be free to slide past each other and may instead be partially coupled mechanically as a result of shared or bridging connective tissue structures (35, 274, 284, 337). Such changes in musculotendon length can happen rather quickly due to rapid changes in muscle activation and limb postures that occur during rapid movements. Therefore, muscle-muscle interactions may also have a particularly large and complex influence on musculotendon length and velocity and therefore also have strong effects on muscle mechanics.

Changes in musculotendon path due to changes in posture not only lead to changes in musculotendon length, but also to changes in pulling direction (2-4, 54, 101, 276). If a muscle's pulling direction is aligned with the direction of a desired movement initially, it may become misaligned during the movement due to the effects of postural changes on its musculotendon path. For example, the anterior deltoid, which wraps around the anterior part of the shoulder in the neutral anatomical posture (i.e., with the upper arm lying against the side of the body with the palms facing anteriorly), experiences large changes in pulling direction with changes in posture. At neutral posture, the anterior deltoid is a strong shoulder flexor (2, 276), but a weak shoulder adductor/abductor (2, 276) and weak internal rotator (4, 276). External rotation of the shoulder, however, shifts the position of the anterior deltoid posteriorly toward the top of the shoulder, thus making it a stronger abductor (276).

Musculotendons can cross one or more joints so their path from origin to insertion and their force generating capacity depends on the posture of all these joints. The rectus femoris, for example, crosses both the knee and hip so the more extended the knee and the more flexed the hip, the shorter the musculotendon length. Thus, the capacity of such muscles to cause motion at one joint depends on the posture of all of the joints that they cross. The hamstring muscles extend the hip and flex the knee, so become highly stretched and generate passive tension that limits the range of motion in postures that combine hip flexion and knee extension.

Force transmission from muscles to limbs

In the simplest case, muscles are parallel fibered and connect from origin to insertion in a roughly straight line. The forces exerted by these muscles and transmitted to the limbs can be represented with two vectors with points of application at the centroid of the origin and insertion, respectively, and a pulling direction along the line connecting the centroids of the origin and insertion. Although this is a good representation for several muscles in the human body (e.g., brachialis and sartorius), there are many musculotendons with different architectural properties that must be modeled differently, including muscles that are eponymous but not homologous among species.

1. *Muscle fibers are aligned obliquely with respect to the pulling direction of the musculotendon.* The larger the angle between the muscle pulling direction and the longitudinal axis of the muscle fibers, that is, the pennation angle, the smaller the fraction of tensile force in the muscle fibers that is transmitted through the tendon to the attachment sites. Similarly, the larger the pennation angle, the smaller the change in muscle fiber length for a given change in musculotendon length. These effects are considered to be small for most pennate muscles (281). However, rotation of the muscle fascicles is inevitable geometrically and has been observed directly for some muscles during muscle contractions *in vivo* (13), indicating that large changes in pennation angles may have a strong influence on fascicle velocity, hence the overall mechanics of the musculotendon. It should be noted that the component of fascicular tension that is not directed to the tendon results in increases in hydrostatic pressure within the muscle, which actually results in complex curvatures of both fascicles and aponeuroses that are implicit in the bulging shape of active pennate muscles (242).

2. *Constituent muscle fibers are not parallel to each other.* Multipennate muscles like the deltoid and fan-shaped muscles like the pectoralis major have muscle fibers with substantially different pulling directions and terminations on aponeuroses. The distribution of fiber pulling directions and locations of these fibers determines the net effect of muscle activation on limb movement as well as the effect of postural changes on the forces generated by the constituent muscle fascicles.

3. *Broad origins and insertions.* Given the complexity of musculotendon architecture and broad attachments of many muscles, the centroid of a musculotendon attachment region may differ substantially from the center of tensile force exerted by the musculotendon and the center of force may vary significantly depending on which regions of the muscle are activated.

4. *Multiple neuromuscular compartments.* Different regions of some muscles such as the trapezius (156) and several shoulder muscles (189) in humans and hindlimb muscles in the cat (63,68,253,254) can be controlled independently by the nervous system. The forces generated by each of these neuromuscular compartments can affect limb motion differently (63) due to differences in their muscle fascicle

configuration that affects both the point of application and pulling direction of the force.

5. *Multiple muscles share a tendon*. Some groups of muscles such as the biceps brachii (short and long head), triceps brachii (medial, lateral, and long heads), triceps surae (soleus, medial gastrocnemius, and lateral gastrocnemius) and femoral quadriceps (vastus medius, intermedius and lateralis plus rectus femoris) have a common tendon of insertion. When one muscle is activated and pulls on the tendon, the tendon becomes stiffer (see Section "Tendon and aponeurosis"). Changing the stiffness of the common tendon affects the length and velocity of the rest of the muscles in the group (271), which affects the dynamics of force generation and transmission and energy storage.

6. *Tendon complex crosses multiple parallel joints*. Some muscles, for example, the extensor digitorum communis that extends the fingers (138), attach to tendon complexes that partially couple the motion of one set of distal joints to another set (275, 284). Tendon strain and stiffness and relative motion of the neuromuscular compartments depends on the posture of all of the joints; activation of these muscles exerts a complex influence on all of these joints depending on their posture. These tendon complexes may be connected to multiple muscles or separately controllable neuromuscular compartments (138, 275) so that activation of the other muscles may also affect the stiffness of the tendon complex.

Muscle Mechanics in the Nonfatigued State

The remainder of this article deals with the properties of individual muscles and their underlying physiological mechanisms. We start with the most general properties and mechanisms representing an archetypal mammalian skeletal muscle and then consider various specializations and modulations of that base condition. Much muscle physiology has been performed on slow-twitch muscle fibers, which are first recruited in mixed muscle and can generate many contractions without changing their performance as a result of fatigue or potentiation. Potentiation involves mainly an increase in fast-twitch muscle force at submaximal activation levels (41, 46, 47, 78). The process occurs rapidly in response to moderate to high levels of activation and reverses slowly so that muscles mostly operate in a potentiated state during everyday activities (46). Potentiated fast-twitch muscle is qualitatively more similar to slow-twitch muscle than dispotentiated fast-twitch muscle (e.g., in terms of the active force-length relationship at submaximal activation), providing a useful common starting point for quantitative modeling (308), to which the effects of fatigue, injury, disease, and adaptation due to exercise can then be added. Determining how muscle mechanics are influenced by these different phenomena requires an understanding of crossbridge dynamics, metabolism, and the structures involved in active force transmission from muscle fibers to the tendon.

Crossbridge: The origin of active muscle force

Whole muscle mechanics emerge largely from the average behavior of the underlying crossbridges, which are the source of active force generation. The following section explains how crossbridges are formed and the major factors that affect their formation and the force that they generate. Such knowledge is essential for understanding the mechanism of muscle contraction and for developing predictive models.

The crossbridge is the site of active muscle force production. A crossbridge is formed when a bond is made between the globular head of a myosin molecule projecting from a thick filament and a specialized binding site on each of the actin monomers in the thin filament. Formation of the bond converts strain energy stored within the activated myosin head into torque that pulls the thin filament toward the middle of the sarcomere, that is, in the direction of muscle shortening. If the pulling force is greater than the external load on the thin filament, then the sarcomere will shorten. As the crossbridge pulls on the actin, the strain and therefore force of the crossbridge progressively decreases, the probability of detachment increases, and the crossbridge will detach if and when an ATP molecule is available to restore the strained configuration of the myosin head. If the pulling force is less than the external load, then the sarcomere will stretch and the crossbridge will be pulled apart without losing its stored strain energy or bound ADP, after which the myosin head can rebind with an actin site faster than if the crossbridge had completed the cycle. Muscle mechanics and energetics arise largely from the effects of muscle activation, kinematic state, and external loads on the number of crossbridges formed and the distribution of their configurations. The following are the primary factors that influence the number of crossbridges formed:

1. *Myofilament overlap*. Myofilament overlap determines the total number of myosin heads that are located adjacent to actin sites. The more overlap between actin and myosin, the higher the number of myosin heads that sit near an actin-binding site.

2. *Number of available actin binding sites*. The thin filament consists of a double helix of polymerized actin wrapped with two helical molecules of tropomyosin that include multiple binding sites for calcium on attached troponin molecules. In the resting state of muscle with low calcium in the sarcoplasm, the tropomyosin is positioned to block the myosin heads from forming crossbridges. Muscle activation consists of release of calcium into the sarcoplasm, which binds to troponin and changes the orientation of tropomyosin, exposing the actin binding sites. The actual availability of binding sites depends on the complex diffusion and reuptake kinetics for sarcoplasmic calcium and

various types of cooperativity among the troponin binding sites and the effects of currently attached crossbridges.

3. *The kinetics of crossbridge formation*. The longer that a cocked myosin head and an actin binding site are within the critical distance for binding, the higher the probability that a crossbridge will form. This apposition is affected primarily by the velocity of the contraction as well as the squirming motion of myofilaments due to myofilament compliance, thermal vibrations, and asynchronous formation of neighboring crossbridges.

4. *Transverse distance between myosin heads and actin-binding sites*. The smaller the transverse distance between myosin heads and actin-binding sites, the higher the probability that they will bind to form a crossbridge. At longer fiber lengths, the myofilament lattice is more tightly packed, which decreases the transverse distance. Phosphorylation of the myosin regulatory light chain, for example, occurring during potentiation, also decreases the transverse distance by canting the lever arm on the myosin head (the myosin light chain) further from the thick filament.

5. *Steric effects*. The thick filament of the sarcomere is shorter than the sum of the thin filaments extending from each delimiting Z-plate, so at short sarcomere lengths, the thin filaments from opposite ends of the sarcomere overlap and sterically hinder formation of crossbridges within this region of overlap.

Active muscle force depends not only on the number of crossbridges formed, but also on their configuration or strain. It is often assumed that the force generated by the crossbridge is linearly related to its strain (23, 177), but recent observations show that the relationship between crossbridge force and strain is highly nonlinear (182, 240). This nonlinear property has important implications for interpreting observed muscle mechanics from the sarcomere level up to the muscle level. The release of the crossbridge as its strain goes to zero has its own kinetics, which depend on the availability of an ATP molecule to displace bound ADP. At high shortening velocities or in fatigued muscles, the crossbridge may remain attached past the point of zero strain, in which case it starts to generate negative forces that oppose the contractile forces being generated by other crossbridges. The velocity at which the positive and negative forces in all of the crossbridges in their time-varying states sum to zero is V_{max}, the velocity at which a muscle can contract under zero load.

Force-length relationship

The force delivered to the end of a muscle consists of two length-dependent terms known as passive force and active force. Passive force arises from various springlike materials both within and between the muscle fibers that are required for mechanical stability. It gives rise to a nonlinear stress-strain relationship that starts to rise exponentially at fiber lengths near the middle of the range of motion of most muscles and then continues in a steep, linear relationship up to the limits of range of motion. Active force depends on both the level of activation of the muscle fiber and the length and velocity at which it is operating. Under isometric conditions, the active component of force reaches a maximum near the middle of the range of motion of most muscles and declines on either side. The structures that give rise to passive and active force are separate and subject to independent trophic factors in their development, so the shape of the total force-length relationship is complex and varies from muscle to muscle (45) and for different levels of activation.

Active

Active muscle force at tetanic stimulation frequencies is maximal at an intermediate length (known as "optimal length" or L_0) and declines at either shorter or longer lengths (133,277,314). The classical relationship between maximally active muscle force and muscle length (shown in Fig. 5) is thought to arise from several independent mechanisms. Active muscle force declines at lengths longer than optimal because at longer muscle lengths, the underlying sarcomeres lengthen and the overlap between thick and thin filaments decreases. Reduced overlap reduces the number of actin binding sites that sit across the myosin heads, hence the number of crossbridges that can form. At muscle lengths that are shorter than optimal, the thin filaments from one end of the sarcomere start to interdigitate with those from the other end (known as "double overlap"), where they sterically hinder myosin heads from binding to the appropriate actin filament. The further reduction in active force that occurs at sarcomere lengths shorter than the thick filament is properly modeled as an opposing passive force; see next section.

At submaximal (hence more physiological) activation in mammalian muscle, the length at which active force is maximal shifts toward longer sarcomere lengths (Fig. 6), at which filament overlap is actually suboptimal (40). At submaximal activation, the amount of calcium released into the sarcoplasm is much less than needed to saturate troponin everywhere along the thin filaments. Many of the myosin heads lie adjacent to actin-binding sites that are not available or only partially exposed but they are more likely to reach and bind to nearby available sites when the lattice spacing between filaments is smaller at the longer sarcomere lengths (see Section "Activation-frequency relationship"). These two different effects may be further influenced by the dynamics of activation and deactivation and externally imposed length changes (see Section "Activation/deactivation dynamics") and by phenomena such as potentiation, all of which have powerful effects under physiological conditions of muscle use.

Passive

The other major mechanisms that underlie the force-length relationship involve passive forces arising from extension and

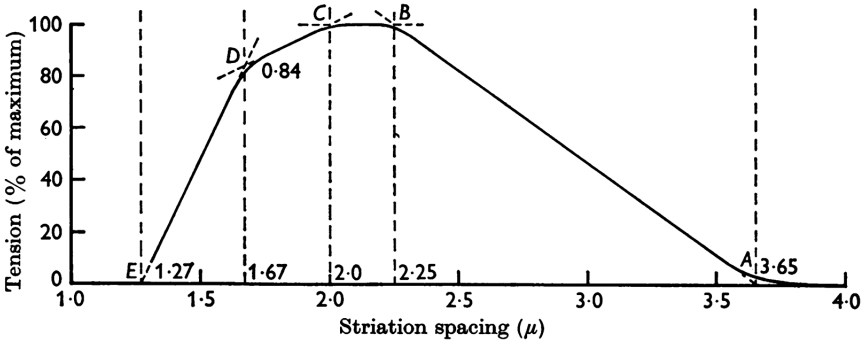

Figure 5 Tetanic force-length relationship. Muscle fiber tension as a function of sarcomere length is shown. When the muscle is stretched beyond the point of no overlap between thick and thin filaments (point A), tension is zero. As sarcomere length decreases, tension increases in proportion to the amount of myofilament overlap until it becomes maximal (point B). As sarcomere length decreases further (until point C), myofilament overlap increases but the number of crossbridges stay the same so tension does not change. Decreasing sarcomere length from this point leads to overlap of actin filaments from opposite sides of the sarcomere and tension decreases in proportion of this overlap until point D, where the force starts to decrease more steeply due to contact of the thick filament with the z discs and a passive restoring force in the opposite direction of active tension. This experiment was performed on intact single fibers from the semitendinosus muscle of the frog (Rana temporaria) at 4°C (132). Reprinted with permission (133).

compression of elastic structures located within the muscle. At short muscle lengths, passive forces are generated that oppose contraction and are largely attributed to compression of the thick filament. When the sarcomere length becomes shorter than the thick filament, the thick filaments will be compressed against the z discs, which leads to a restoring force in the direction of sarcomere lengthening, thus opposing the contractile force generated by crossbridges. This effect was originally bundled into the active force-length relationship, giving rise to a secondary and steeper slope at the shortest

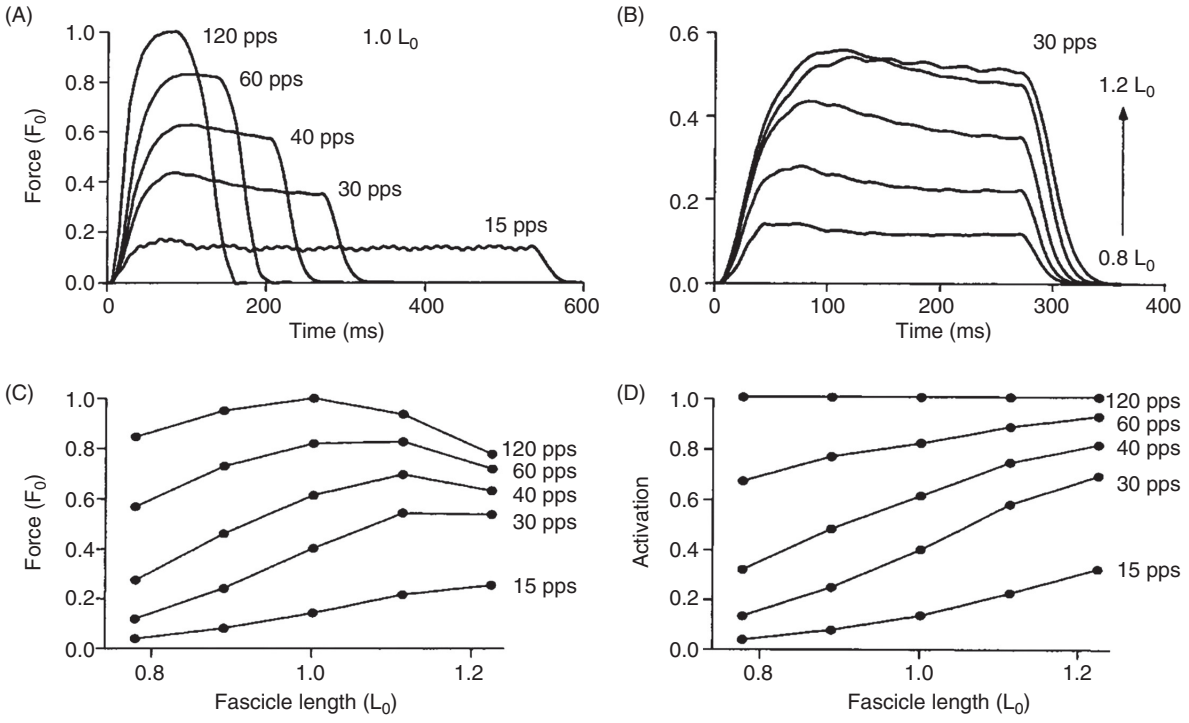

Figure 6 Force-length relationship at physiological firing rates (15, 30 pps) compared to tetanic (120 pps) in feline fast-twitch muscle. (A and B) Typical isometric contractions. (C) Optimal length at physiological frequencies is substantially longer than the classical L_0 defined at maximal tetanic activation when filament overlap is the only effect. (D) Effects of filament overlap were removed by normalizing curves to maximal activation at 120 pps, revealing dependence of activation on filament length as a result of unsaturated calcium diffusion kinetics. Reprinted with permission (40).

sarcomere lengths, but modeling it in this way gives rise to errors when trying to account for the force and stiffness of muscles under dynamic conditions of use (40, 133, 277). At the shortest lengths, thick filament compression and restoring force will increase until the point where contractile force generated by the crossbridges equals the restoring force and net force then becomes zero. But the contractile force and muscle stiffness generated by crossbridges depends on the level of activation of the muscle and its velocity of motion as well as length, so the sarcomere length at which total force measured at the ends of the muscle goes to zero is not a simple value.

At long muscle lengths, many elastic structures undergo tensile strain and contribute to springlike forces that oppose further elongation. Inside the sarcomere, a highly elastic protein known as titin runs along the length of the thick filaments and extends across the sarcomere to connect to the z discs at either end. It keeps the thick filaments centered in the sarcomere so that slight imbalances in crossbridges at either end do not cause it to walk toward one end of the sarcomere. It also maintains the alignment of the lattice of thick and thin filaments at long sarcomere lengths where they no longer overlap (157, 316).

Muscle includes also an elaborate network of elastic structures that help stabilize and transmit active forces from the sarcomere to the tendon (see Fig. 7). Force is transmitted from the muscle fibers to the tendon through the complex extracellular matrix that links them. The extracellular matrix is comprised primarily of a network of collagen fibers that is continuous with the collagenous network of the tendon (127). The collagenous network has particularly dense regions surrounding the entire muscle [i.e., the epimysium, (121)], single fibers [i.e., endomysium, (305)], and, most pronouncedly, bundles of muscle fibers known as fascicles [i.e., perimysium, (36, 255)]. This collagenous network that surrounds muscle fibers is linked with other elastic structures within the muscle fibers that help transmit muscle fiber force to the extracellular matrix. The extracellular matrix is linked to myofibrils through protein assemblies known as costameres that connect sarcomere z discs to the extracellular matrix through the sarcolemma (248). One of these transmembrane proteins is dystrophin, which can be weakened by various mutations that result in muscular dystrophy (31). Myofibrils are linked to each other mainly through proteins called desmin that connect their z discs transversely and longitudinally (199, 286, 317). Z discs of the same myofibril are also connected to each other through longitudinal connections (317). At short muscle lengths, the collagen fibers are in a crimped configuration and oriented obliquely relative to the longitudinal axis (256), and therefore not in tension, but at larger lengths the surrounding collagen stretches along with the muscle and generates tension (268). The tension increases nonlinearly with stretch (45), which is consistent with the material properties of collagen (201,279). When muscle and the connective tissue surrounding the muscle fibers stretch, the underlying elastic structures that link the extracellular matrix to the sarcomeres also stretch, each of which can contribute to the passive restoring force depending on their stiffness (287). Stretching of the sarcomeres by tension transmitted through the extrasarcomeric elastic structures pulls apart the myosin filaments from the z discs and therefore stretches the titin proteins that also can contribute to passive force depending on their stiffness.

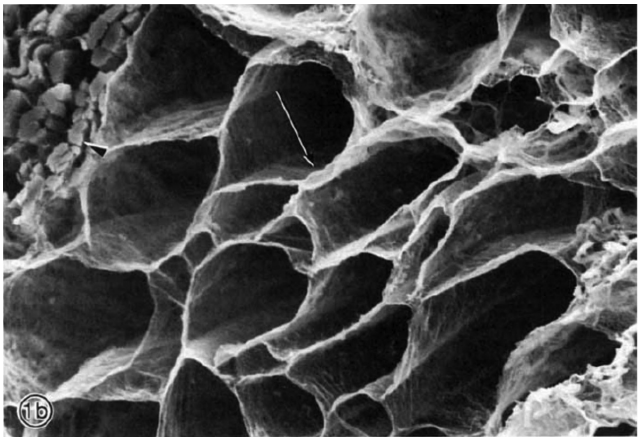

Figure 7 Scanning electron micrograph of the collagenous stroma that surrounds individual muscle fibers (long arrow), here removed by NaOH digestion; arrowhead points to perimysial bundles of thick collagen fibers that separate muscle fascicles. Reprinted with permission (305).

Magid and Law (215) reported that mechanically skinned frog muscle fibers generate similar passive tension as the whole muscle from which they were dissected, which has prompted many to conclude that the primary mechanism of passive force generation is stretching of the titin molecules. More recently, the existence and possible contributions of desmin (123,287) and costameres (122,287) have been recognized. All of these components, however, might be expected to scale with sarcomere length and cross-sectional area. In cat (and probably other mammals), passive tension of intact whole muscles is considerably higher and does not scale simply with sarcomere dimensions (45). The much denser extracellular collagen matrix of mammalian fibers (304) probably plays a dominant role that can be modified independently of sarcomere dimensions. Passive stiffness depends on the patterns of muscle use in humans [(118); see Section "Adaptation to conditions of use"]. In particular, passive stiffness increases with immobilization at short lengths and decreases with immobilization at long lengths. This would explain the variability observed in passive stiffness across muscles with different anatomical ranges of motion as well as the (relatively smaller) variability across subjects due to different operating ranges of motion (45). In fact, the passive force-length relationship of muscles is best predicted by scaling a generic relationship by the maximum anatomical fascicle length (45). This could occur from adaptation of any one or all of the elastic structures involved (134, 330).

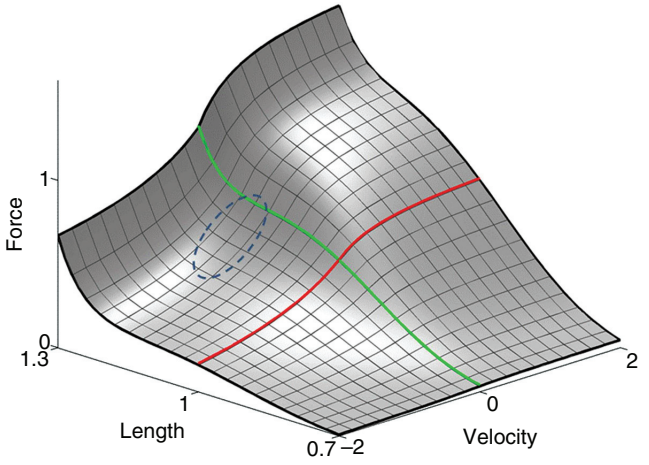

Figure 8 The total force (active plus passive) produced by a muscle depends on both its length (green line shows isometric force-length relationship at velocity = 0) and velocity (red line shows force-velocity relationship at optimal length = L_0). For a supramaximally activated slow-twitch muscle like feline soleus, this results in a complex surface that includes a negative slope region for a small range of muscle lengths above L_0 (dashed circle).

Stability

There is a long-standing controversy regarding the homogeneity of sarcomere lengths in an active muscle. Under some circumstances, the total force-length relationship may become nonmonotonic (with a negative slope region as illustrated in Fig. 8), which suggests that the muscle fiber could become unstable. The tension everywhere in a ropelike structure must be equal but a given submaximal tension in a nonmonotonic system could be achieved with different sarcomere lengths in different regions of the muscle fiber. During activation of an isometric muscle at homogeneous optimal sarcomere length L_0, some sarcomeres could start to lengthen past L_0 and others in-series with them would then shorten below L_0. Because of the shape of the force-length relationship, both populations of sarcomeres could be generating the same force, satisfying the basic physical constraint of a rope under tension. The situation is unstable, however, because the lengthening sarcomeres will continue to lengthen until their increasing passive tension results in a positive slope of the total force-length relationship (229). Effects consistent with such "sarcomere popping" have been observed in reduced preparations and may account for some forms of muscle injury (see later), but the notion that muscles behave this way normally remains controversial. There are several reasons to suggest that such sarcomere heterogeneity does not normally occur:

- Contrary to previous conceptions, it is now appreciated that muscle fibers and the sarcomeres within them are not free to slide in a frictionless environment. They are tightly coupled laterally by means of intracellular scaffolds, an extracellular collagen matrix, and transmembrane proteins. All of these structures and the sarcomeres themselves appear to develop in response to mechanical trophisms that tend to result in homogeneous stresses and strains throughout the muscle, as might be expected for a system attempting to operate optimally.

- The peak of the active force-length relationship appears to be located at sarcomere lengths that are near the middle of the operating range of most muscles but only for tetanic stimulation frequencies (59). As shown in Figure 6, the peak of the active force-length relationship at physiological frequencies of motoneuron firing is shifted to much longer lengths (40, 259) at which the passive force-length relationship is much steeper. A negative slope region in the total force-length relationship is much less likely to occur.

- The negative slope region of the total force-length curve depends on the relative contribution of the active versus passive force-length relationships that sum to create it. Under all but the maximal activation conditions illustrated in Figure 8, the active force-length curve is scaled to much smaller values compared to the passive force-length curve, which is unaffected by activation and which always has a monotonic positive slope. Because of the lateral coupling mechanisms listed earlier, passive forces in inactive muscle fibers will tend to stabilize a subpopulation of active muscle fibers.

- Even if there is a net negative slope region in the highly activated muscle, the sarcomeres have to change length in different directions to become heterogeneous. As described in the next section, the force generated by a lengthening (i.e., "popping") sarcomere will actually be much higher than the isometric force predicted by its current length; conversely, the destabilizing force generated by the shortening sarcomeres will be much lower. Because maximal activation of muscles is rare and usually transient, the system may not have time to get into the theoretically unstable steady state.

Rather than a population of independently functioning muscle fibers and motor units, it may be more useful to think of muscle as a composite material—muscle fibers embedded in and adherent to a continuous matrix of collagen (Fig. 7). The bulk properties of the composite are modulated by neuromuscular activation (306). Tension in any single muscle fiber is more likely to be transferred as shear forces into the surrounding endomysial collagen matrix and adjacent muscle fibers (which may be active or passive) than to be conveyed to the distant ends. This is particularly important in muscles with long fascicles, which are generally composed of muscle fibers that are shorter than the fascicles and terminate at one or both ends in elongated tapers rather than as the specialized myotendinous structures required to transfer tensile force abruptly into tendons. If long fascicles were composed entirely of equally long muscle fibers that were all innervated near the middle

of each fiber, the distribution of activation, stress, and strain in the muscle at the onset of activation would be uneven and unstable because the electrical conduction delays along the sarcolemma would be comparable to the rise time of contractile force (208). For example, a 20 cm muscle fiber innervated at its midpoint and conducting at a typical 3 m/s results in a 33 ms delay, which is a substantial fraction of the rise time of activation. The midregion of the muscle would be generating active force while the ends were not yet activated. This might lead to an extreme form of sarcomere popping in which the sarcomeres at the ends of the fibers were lengthened past optimal overlap of the myofilaments and the sarcomeres at the middle shortened until their active force dropped to the same submaximal value. This condition appears to be avoided in most large animals by the in-series fiber architecture in which relatively short and presumably stable muscle fibers are distributed throughout the length of the fascicle, with multiple bands of neuromuscular synapses corresponding to the midpoints of the various fibers. Humans, however, appear to utilize a different solution to this problem in which individual muscle fibers may be >20 cm but they and their individual neuromuscular synapses are staggered along even longer fascicles (147). Because the motor axons conduct much faster (~80 m/s in humans), all of the muscle fibers of a given motor unit will start to be activated at the same time. As long as the cross-sectional area of activated sarcomeres is more or less equal throughout the muscle as the effects of activation spread among the interdigitated muscle fibers, the system should be grossly stable. This places a particular burden on the endomysial connective matrix, which must distribute dynamically changing shear forces equally to avoid transient local stresses that might damage the matrix. This may be related to the apparently unique susceptibility of humans to hamstring pull injuries, which tend to occur under conditions of submaximal but rapidly modulated activation (143).

Force-velocity relationship

At tetanic frequencies of muscle stimulation at a particular length, muscle force decreases relative to isometric if the muscle is shortening and increases relative to isometric if the muscle is lengthening [(40, 277); Figs. 8 and 9]. The slope of these force changes is most steep around isometric and the force changes occur virtually instantaneously when velocity changes, resulting in large, rapid and generally stabilizing effects on limb posture that have been called "preflexes" (206). The mechanism of this effect remains controversial because the experimental techniques used to date to observe crossbridge behavior are largely indirect. Active force must be the sum of forces being produced by all attached crossbridges, but the numbers of crossbridges and their various states of strain reflect a probability density distribution that depends on the kinematics and kinetics of crossbridge cycling.

Experiments where muscle fiber length is decreased over a brief time period (that is, faster than the time it takes for crossbridges to form) have been used to measure the crossbridge

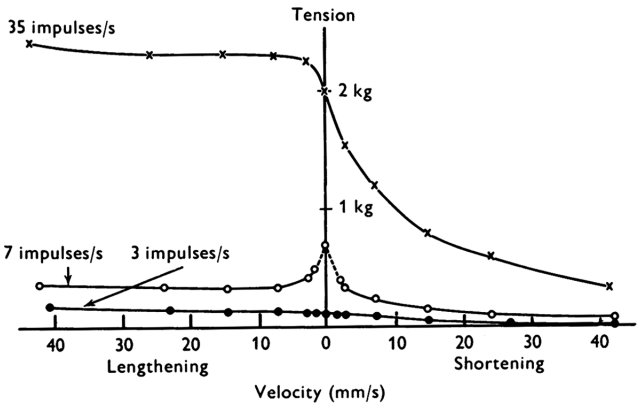

Figure 9 Force-velocity relationship/yield. At stimulation frequencies that generate near maximal isometric force (35 Hz), slow-twitch muscle generates higher forces while lengthening and lower forces while shortening. For moderate stimulation frequencies (7 Hz), force decreases relative to isometric for both the lengthening and shortening conditions. For low frequencies (3 Hz), the lengthening muscle produces slightly higher forces than the isometric condition and shortening muscle produces slightly lower forces. The experiment was performed on feline soleus muscle at 37°C with intact nerve and blood supply. Groups of motoneurons were stimulated asynchronously to reproduce the smooth contractions observed *in vivo* for low frequencies of stimulation. Reprinted with permission (176).

strain by measuring the smallest muscle fiber length decrease that reduces force to zero (165), which is the point at which all crossbridges reach the critical strain for detachment, or the end of their powerstroke (79). Smaller length changes are required to reduce muscle force to zero during shortening (114) and larger length changes are required to reduce force to zero during lengthening (251) relative to isometric. This indicates that mean crossbridge strain is smaller in shortening muscle and larger in lengthening muscle relative to the isometric condition. Quantifying the amount of strain, however, is difficult because muscle fiber strain is not only taken up by crossbridges but also by other elastic structures that are arranged in series such as thin filaments (149, 166, 168, 187, 204, 315) and thick filaments (167). Quantification would be possible if the compliance of crossbridges relative to all structures in series was known, but it has not yet been characterized accurately (241).

The contribution of the crossbridge number to the force-velocity relationship has been assessed by measuring muscle stiffness, which is thought to be proportional to the number of crossbridges formed at any given time (23). If the crossbridges were the only elastic structures in muscle and their stiffness did not depend on strain, then muscle fiber stiffness would be linearly related to crossbridge number. However, as mentioned earlier, there are other elastic structures in series with crossbridges that make the relationship between fiber stiffness and crossbridge stiffness nonlinear even if their stiffnesses were linear. In fact, both myofilament (105, 167) and crossbridge stiffness (182, 240) are highly nonlinear and not well characterized. For example, if crossbridge stiffness is substantially lower at smaller strains, then small changes in

crossbridge strain may explain both the lower force and lower muscle fiber stiffness observed during rapidly shortening contractions, when many of the crossbridges will be near the end of their cycle. These uncertainties give rise to a variety of plausible explanations for the complex shape of the force-velocity relationship:

- The reduction in contractile force during shortening could occur without a reduction in crossbridge number if the release of the crossbridge (which requires ATP binding) requires sufficient time that the still-attached crossbridge is carried to a position where it exerts negative (pushing) force on the thin filament.
  - A reduction of crossbridge number can result during shortening if the time required for a myosin head to bind to an actin site is greater than the time available as the filaments slide rapidly past each other.
- The increase in the contractile force during lengthening could occur without an increase in crossbridge number if the existing crossbridges were pulled into an excessively strained condition before detaching (and they could reattach almost immediately to the next available actin site).
  - An increase in the number of crossbridges during a lengthening contraction can result, in theory, from binding of myosin heads whose neighboring myosin head in the dimer is already attached in the isometric condition (52, 117). Tensile strain of the attached myosin head during lengthening may bring the adjacent myosin head to a more favorable conformation for binding. This would provide a role for the double-headed myosin architecture, which otherwise seems like unnecessary clutter in the densely packed myofilament lattice.

The aforementioned various mechanisms have different implications for the rate of metabolic energy consumption. If completion of each crossbridge cycle is tightly coupled with dephosphorylation of one ATP molecule, and crossbridge number is not altered by shortening, then the rate of metabolic energy consumption should increase linearly with shortening velocity. What has been observed instead is that the slope of the energy rate versus velocity relation gradually decreases with velocity and has been shown even to become negative at high velocities (18, 24, 152). This may indicate either that crossbridge number decreases at high velocities (23) or that multiple crossbridge cycles can be fueled by a single ATP molecule (139, 148, 184, 335).

Crossbridges in slow-twitch muscle attach and detach slower than in fast-twitch muscle, presumably because they employ a different isoform in the myosin head (137, 322). The slower crossbridge attachment rate of slow-twitch muscle limits force generation when the muscle is either shortening or lengthening at subtetanic frequencies (see Section "Yield" section) so it is possible that it also limits force generation when the muscle is shortening/stretching during tetanic activation as well. Thus, a decrease in the number of crossbridges may explain a significant part of the reduction of slow muscle force while shortening at high speeds. In fact, slow-twitch muscle force decreases to a substantially larger extent than fast muscle for the same, relatively modest shortening speeds [see Fig. 10 in (47)]. If crossbridge attachment were slower for slow-twitch muscle, then it would seem likely that force for slow muscle would increase less than fast muscle, particularly at high lengthening velocity, because the number of crossbridges present during lengthening would be relatively smaller for slow muscle due to the slower rate of crossbridge reattachment after detachment during a stretch. However, it has been observed that slow muscle force increases substantially more than fast muscle for the same velocity of stretch (47). This can be explained if the mean force generated by slow crossbridges is greater than that generated by fast crossbridges. If the slow crossbridges detach during lengthening at a slower rate relative to fast crossbridges, they will reach larger strains and hence larger forces before they detach. Similarly for shortening contractions, slow-twitch crossbridges will reach smaller (even negative) strains and forces before they detach. All of this could be further complicated by the unknown (if any) role of the second head of the myosin dimer, which may be different in slow- versus fast-twitch muscle.

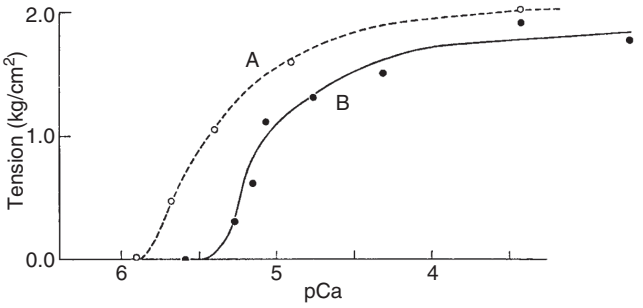

Figure 10 Ca^{2+} activation of muscle. The effects of calcium concentration ($[Ca^{2+}]$; $pCa = -\log([Ca^{2+}])$ on muscle fiber tension is shown. Force is generated once Ca exceeds some threshold. As Ca increases, its effects on tension become stronger up until a level of calcium that generates a moderate level of tension. Increasing Ca further leads to smaller effects of Ca on tension up until the point where tension saturates at high levels of Ca. Curve A and B were obtained using data from fibers in a different chemical environment [see (104) for more details]. The experiments were performed on single skinned muscle fibers from the frog at 0°C. Reprinted with permission (104).

Activation-frequency relationship

As described earlier, the availability of crossbridge binding sites on the thin filaments depends on their binding of calcium from the sarcoplasm (Fig. 10). In a relaxed muscle, the sarcoplasmic calcium concentration is maintained close to zero by metabolically active pumps that collect and concentrate the calcium into the vesicular endoplasmic reticulum. Muscle activation requires release of that calcium; relaxation requires its reuptake. The design goals of control, speed, and stability all lead to complex mechanisms and trade-offs to propagate,

amplify, and synchronize these electrical and chemical processes over muscle fibers that may be many centimeters long.

Each mammalian skeletal muscle is typically innervated by a hundred or so motoneurons whose cell bodies are located in the ventral horn of the spinal cord or in motor nuclei of the brainstem. When an action potential in the motoneuron travels along its motor axon to the muscle, it triggers the release of large amounts of acetylcholine at specialized synapses onto each of the typically hundreds of muscle fibers that the axon branches to innervate (the motor unit). In a healthy muscle, each such action potential in the motoneuron gives rise to an action potential that propagates along the sarcolemma of each muscle fiber and into the depths of the muscle fiber via invaginations of the sarcolemma called transverse tubules. Individual t-tubules run between a pair of terminal cisternae regions of the sarcoplasmic reticulum (the t-tubule and two adjacent terminal cisternae are known collectively as the triad). The action potentials that travel through the transverse tubules activate voltage-sensitive proteins along the t-tubule membrane, known as dihydropyridine receptors [DHPR; (195)] that are mechanically coupled to Ca^{2+} release channels on the terminal cisternae membranes of the sarcoplasmic reticulum (102, 196, 224), known as the ryanodine receptors [RYR; (111)]. The brief opening of the Ca^{2+} release channels in response to an action potential causes Ca^{2+} to diffuse passively into the sarcoplasm. Most of the released Ca^{2+} binds to troponin molecules on the thin filaments to activate crossbridge binding sites (26), ATP (26, 180), or parvalbumin protein [present in significant amounts in fast-twitch muscle of small mammals and amphibians (29, 145)], and eventually to Ca^{2+} pumps located on the sarcoplasmic reticulum membrane [SERCA pumps; (26, 212)] that reuptake Ca^{2+} to restore the concentration gradient between sarcoplasmic reticulum and the sarcoplasm.

The availability of calcium to bind to the troponin control sites on the thin filaments depends on the details of the kinetics of its release, diffusion, binding, and reuptake. The small amount of calcium released by a single action potential will tend to be taken up rapidly by the SERCA pumps, so will not have time to diffuse to most troponin binding sites. The result is a brief, weak contraction called a twitch. If another action potential arrives before the calcium released by the first has been pumped back, the calcium that it releases will add and diffuse further, activating more crossbridge binding sites. As successive action potentials arrive at an increasing rate, the mean force produced by the muscle fiber increases nonlinearly and the fluctuations from each individual action potential become smaller. This nonlinear summation may be enhanced by the finite number of SERCA pumps and their finite cycling time; it may be counteracted by depletion of the calcium that is available to be released from the cisterns. At some frequency known as tetanic contraction, the sarcoplasmic calcium levels and the extent of calcium diffusion result in binding to all troponin molecules and complete availability of the crossbridge binding sites, so force no longer increases or fluctuates. When action potentials and calcium release cease, the timing of relaxation will depend on the kinetics of calcium release from troponin and other buffering proteins such as parvalbumin, crossbridge detachment kinetics, and binding and uptake by the SERCA pumps.

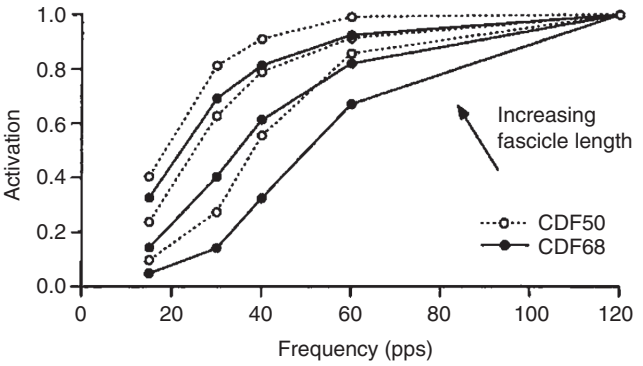

Figure 11 Force-frequency relationship at fascicle lengths from 0.8 to 1.2 L_0 in feline fast-twitch muscle. Naturally occurring firing rates are in the range 20 to 40 pps where the slope is steep. Reprinted with permission (40).

Under physiological conditions of synaptic recruitment, motoneurons are modulated over a limited range of firing rates where the slope of the activation curve is steepest (40, 100, 104, 176, 323), as shown by the sigmoidal curves in Figure 11. Thus both motoneuron recruitment and motoneuron frequency modulation contribute substantially to the fine control of force. This strategy also minimizes wasted metabolic energy that would be associated with low firing rates, in which most of the released calcium is pumped back up before it gets to troponin binding sites, and high firing rates, in which all troponin binding sites are occupied and the excess calcium has to be pumped up before relaxation can occur.

The troponin-tropomyosin mechanism has some complex features that cause the effective level of muscle activation to depend on motion as well as neural excitation. Because the tropomyosin strands extend continuously along the creases in the actin double helix, the relatively small positional changes caused by Ca^{2+} binding at one troponin site and/or the presence of myosin heads already bound as crossbridges change the effectiveness of Ca^{2+}binding to adjacent sites (262); see (131) for review. This effect is known as cooperativity. One manifestation is the tendency for relaxation to occur more slowly when the sarcomeres are isometric than when they are moving in either direction and the crossbridges are cycling rapidly (49). This may contribute to the economical use of isometric muscles to maintain steady posture.

The activation-frequency relationship is often assumed to be independent of the length and velocity of the muscle fiber, allowing active force to be computed as the product of three independent functions (activation frequency, force length, and force velocity. At physiological subtetanic frequencies of stimulation (40, 259) and calcium levels (108, 109, 218, 228, 231, 293, 294), the effective activation depends also on crossbridge kinetics (Fig. 12). This

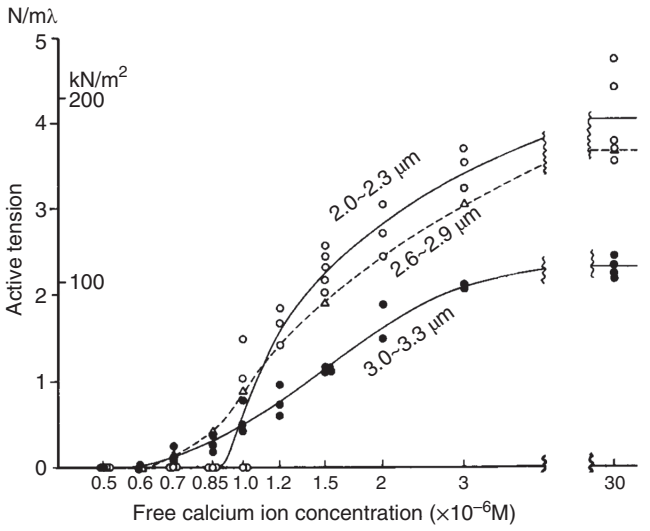

Figure 12 Effects of length on Ca^{2+} induced muscle activation. The active tension-Ca^{2+} relationship is shown for different sarcomere lengths. If the only effect of length on tension is due to its effects on myofilament overlap then the tension-Ca^{2+} relationship should scale similarly across all Ca^{2+} levels. This classical study shows, however, that as Ca^{2+} decreases from levels near maximal tension, tension at longer lengths decreases less than tension at shorter lengths, having near optimal overlap, and for low enough Ca^{2+} tension at suboptimal myofilament overlap even exceeds tension generated at optimal overlap. This indicates that stretching the muscle fiber facilitates muscle activation independent of the effects of myofilament overlap. The experiment was performed on single skinned muscle fibers from the toad (Xenopus laevis) at 0°C. Reprinted with permission (108).

is thought to occur because muscle fibers and underlying myofilament lattice have a constant volume (219) so myofilament lattice spacing decreases as muscle length increases (107,161,219,266). This reduces the spacing between myosin heads and actin binding sites, which is thought to speed up crossbridge attachment rate and increase the number of crossbridges formed (128).

Activation/deactivation dynamics

The time it takes from the onset of Ca^{2+} release to reach a steady state of crossbridge formation (see Fig. 13) depends on factors that change with contractile conditions. This delay depends mainly on diffusion distances between Ca^{2+} release sites and troponin, the attachment rate of crossbridges as well as the degree of cooperativity of actin binding sites. At low firing rates, rise time increases with fascicle length (49). For mammalian muscle, the location of the triads, hence Ca^{2+} release sites, has been shown to be fixed with respect to the actin filaments near their midpoint (44) so increasing muscle length increases the average diffusion distance between Ca^{2+} release sites and actin binding sites in the overlap region. Diffusion has been shown to be a significant contributor to rise time (26, 62). The reverse has been observed for high firing rates, where rise time decreases with length [Fig. 13; (49)]. Increasing length also increases the rate of crossbridge attachment (128), thus decreasing rise time (222). For higher firing rates, this effect appears to outweigh the effect of increased diffusion distances. This is likely because more calcium is released at higher firing rates, which increases its diffusion extent and would thus weaken the effect of length on diffusion distances. Furthermore, at higher firing rates and widespread actin activation, myosin heads are more likely to be optimally oriented with respect to actin binding sites and therefore would benefit more from a reduced myofilament lattice spacing and distance between myosin heads and active actin sites that increases the crossbridge rate of attachment. Rise times are slowest at intermediate firing rates, where cooperativity

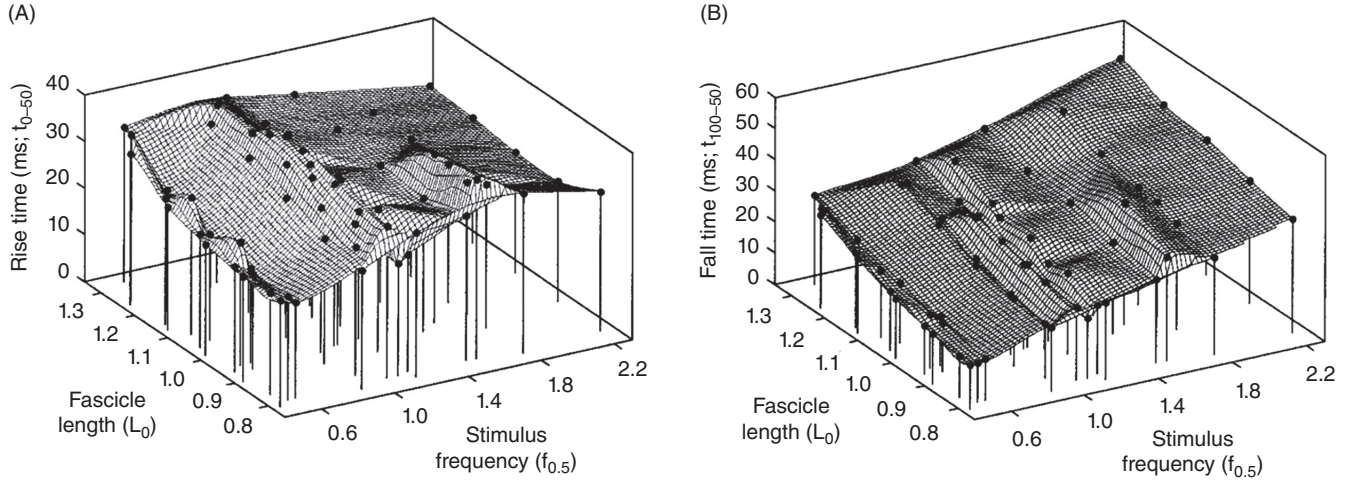

Figure 13 Activation rise and fall times. (A) Rise times to half of the maximal force are shown for a wide range of muscle fascicle lengths and frequencies of stimulation. At low stimulus frequencies, rise time decreases with fascicle length and at high stimulus frequencies, the relationship is reversed. (B) Fall times from the end of stimulation after reaching a steady state force to the time at which force drops to half of the steady state value. Fall time increases with both fascicle length and stimulus frequency. The experiments were performed on feline caudofemoralis at 37°C with intact nerve and blood supply. Groups of motoneurons were stimulated asynchronously to reproduce the smooth contractions observed *in vivo* for low frequencies of stimulation. Reprinted with permission (49).

is maximal (see Section "Activation-frequency relationship"). Cooperativity increases rise time because force will continue to increase after initial crossbridges form until all additional crossbridges are enabled by the cooperativity. Because there are various competing processes, the shape of the force waveform is not well described by a single time constant for either rising or falling conditions, which complicates the comparison of experimental reports and computational models.

The time from the last pulse of Ca^{2+} release, when force is maximal, to returning to resting Ca^{2+} levels and resting tension depends mainly on diffusion of Ca^{2+} to sarcoplasmic reticulum SERCA pumps, Ca^{2+} pumping rate, and the rate of crossbridge detachment. The fall time of contractile force from a steady-state level has been shown to increase both with firing rate (or activation level) (49, 324) and with length [(47, 49, 77, 140, 172, 333); Fig. 13]. Increased length leads to a decrease in lattice spacing of myofilaments in the sarcomere and brings myosin heads and actin binding sites closer, leading to stronger bonds between them and a lower rate of detachment (see Section "Activation-frequency relationship"). The rate of crossbridge detachment limits the final phase of the force fall time (61, 76, 164). Such mechanism would therefore be consistent with a prolonged final phase of force fall time. Indeed, it has been shown that for twitch contractions, increasing muscle length prolongs the final phase of twitch fall time while not significantly affecting the initial phase of the fall time (47). Fall time could increase with activation level because as Ca^{2+} is being pumped out of the sarcoplasm, and as more Ca^{2+}ions are detaching from troponin, the corresponding actin binding sites would remain active for a relatively longer period of time due to cooperativity mechanisms. This is also consistent with the relatively prolonged final phase of fall time observed for high levels of activation (324). Fall times are also longest for isometric conditions and decrease for both positive and negative velocities when more rapid crossbridge cycling is likely to reduce cooperativity effects (49).

Yield

Yield refers to a phenomenon that occurs in slow-twitch muscle fibers at submaximal frequencies of stimulation (84, 176, 239, 296). In slow-twitch muscle, the effects of shortening/lengthening velocity on force depend on firing rate. At submaximal activation, the percent decrease in force due to a particular shortening velocity relative to isometric is larger than at maximal activation (Fig. 9). Furthermore, the percentage increase in force due to lengthening is smaller at submaximal activations and force even decreases substantially relative to isometric for a range of moderate levels of activation. These features have been incorporated into computational models of muscle force (70) but the underlying mechanisms remain unclear.

Investigations of muscle fiber mechanics have identified that the amount of yield exhibited by muscle fibers correlates with stiffness (217). Changes in stiffness can result from changes in crossbridge number, but can also result from changes in crossbridge strain due to the nonlinear stiffness of crossbridges, i.e., the increase in crossbridge stiffness with strain (see Section "Force-velocity relationship"). Changes in crossbridge strain, or force per crossbridge, is unlikely the cause of yield because crossbridges of lengthening muscle are more strained and therefore more stiff relative to isometric, but an overall decrease in stiffness for lengthening contractions relative to isometric has been observed instead (217). The more likely cause is therefore a reduction in crossbridge number that can result from the following mechanism. At low activations, fewer of the available actin sites are optimally oriented, thus it could take longer for the myosin heads to bind to actin after being detached during relative myofilament motion. The attachment rate and/or mobility of the slow myosin head is low (lower than fast-twitch myosin) and it could limit its ability to bind to suboptimally oriented actin sites during relative motion between actin and myosin filaments that reduces the time that myosin heads spend near active actin sites (112). This is consistent with the observation that the yielding effect increases with contractile velocity (176). The low crossbridge attachment rate of slow relative to fast myosin (226) is consistent with the fact that under physiological muscle shortening/stretching yield is observed in slow but not fast-twitch muscle.

Sag

Sag is a phenomenon observed in fast-twitch muscle (49, 57, 83, 312), particularly at subtetanic, physiological firing rates (Fig. 14). In response to constant frequency of stimulation, muscle force declines slowly after reaching a maximal value [with a time constant of about 40 ms for feline caudofemoralis muscle; (49)] and recovers after stimulation ceases with a longer time constant (about 80 ms for feline caudofemoralis). These features have been incorporated into computational models of muscle force (49, 70) but the underlying mechanisms remain unclear.

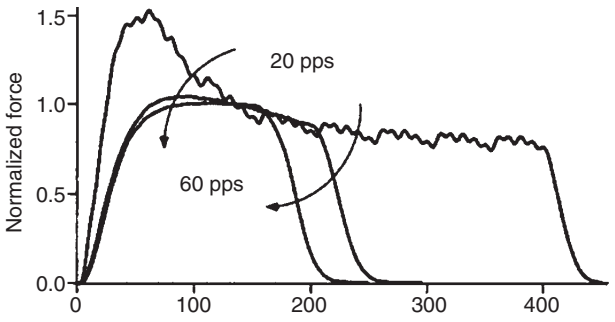

Figure 14 Sag. During constant frequency electrical stimulation of the fast-twitch feline caudofemoralis muscle under isometric conditions at optimal length L_0 *in situ*, force decreases substantially at 20 pps, less at 40 pps and not at all at the 60 pps tetanic frequency (timebase in ms; forces normalized to values at 133 ms for comparison of time course). Reprinted with permission (49).

Sag can occur theoretically due to a decrease in the number of crossbridges or a decrease in force per crossbridge. The mechanism of sag has been investigated by comparing muscle twitches elicited before sag commenced and during the presence of sag (49). If a decrease in force per crossbridge underlies sag, then twitch force during sag should be less than twitch force before sag over the entire duration of the twitches. It has been shown, however, that twitch force is the same before and during sag for the majority of the rise phase of the twitch. Sag, therefore, likely results from a decrease in crossbridge number, which can occur due to a decrease in crossbridge attachment rate, an increase in detachment rate of crossbridges, or a decrease in Ca^{2+} in the sarcoplasm via reduced Ca^{2+} released by the sarcoplasmic reticulum in response to an action potential or via an increase in Ca^{2+} removal by SERCA Ca^{2+} pumps. The fact that the beginning of the rise phase of twitch force does not change during sag also suggests that a change in attachment rate of crossbridges and calcium release are not causes of sag. The rate of force decline during the end of the fall phase of the twitch is thought to be limited by the detachment rate of crossbridges. During sag, this quantity does not change, which implies that changes in crossbridge detachment rate are also not a cause of Sag. An increase in the rate of Ca^{2+} removal from the sarcoplasm is therefore the most likely cause of sag; Ca^{2+} potentiation of the SERCA pumps would be a plausible mechanism. This would cause a more rapid decline of sarcoplasmic Ca^{2+}, which would reduce the time it would take for the twitch response to reach maximal force (i.e. overall rise time would decrease) as well as the maximal twitch force itself; it would also cause a decrease in overall fall time, particularly the initial phase that is limited by the rate of Ca^{2+} removal. All of these effects of an increase of Ca^{2+}reuptake on twitch force are consistent with the observed effects of sag on twitch force (49).

Effects on muscle mechanics due to fatigue, conditions of use, and injury

Fatigue

Muscle fatigue is the reversible change in resting muscle mechanics that occurs after repeated muscle activation. As explained in Section "Muscle mechanics in the nonfatigued state," muscle is typically in a potentiated state so changes in muscle mechanics will be discussed relative to the nonfatigued, potentiated state. After repeated muscle activation, force generating capacity declines, activation and deactivation slow down, and maximal velocity of contraction decreases. Force decline can occur theoretically due to a shortage of ATP supply that fuels contraction or changes in the chain of events whereby muscle is activated and crossbridges form and generate force. ATP supply does not appear to be the primary factor, as ATP concentration in the muscle fiber has been shown to remain high despite large declines in force generating capacity (90,198,292). Furthermore, the concentrations of nutrients from which ATP is derived, for example, glycogen, have been shown to be dissociated from fatigue (60, 72, 146). Changes in biochemical state must therefore be the primary cause of fatigue. Impairment of one of many different biochemical reactions and associated physiological processes may lead to fatigue because force results after a sequence of several major events.

1. Action potentials from the motoneuron are transmitted throughout the muscle fibers via the neuromuscular synapses and sarcolemma.

2. The action potentials that reach the terminal cisternae of the SR trigger the release of Ca^{2+} to the sarcoplasm.

3. Ca^{2+} diffuses to troponin on the thin filaments to expose crossbridge binding sites on the actin.

4. Myosin heads from the thick filaments bind to exposed sites on actin to generate force.

In theory, a decline in force-generating capacity can result from impairment of any one of these steps. It has been shown, however, that under physiological conditions in otherwise healthy muscles, fatigue is not caused by impairment of the transmission of action potentials to or throughout the muscle fibers [(15, 30, 272, 290, 320); see (9) for review]. Fatigue conditions also do not seem to impair calcium activation of troponin-tropomyosin (9, 131), which leaves impairment of steps 2 and 4 as the strongest contributors to muscle fatigue.

Possible reasons for impaired Ca^{2+} release (step 2) include increases in Mg^{2+} and decreases in ATP (for severe fatigue) that interfere with the normal interaction between the DHPR receptor that detects the action potential traveling through the t-tubule and the RYR Ca^{2+} channel that is triggered by the DHPR receptor (8). Reduced Ca^{2+} release may also occur due to an increase in inorganic phosphate (P_i) that is thought to enter the SR and precipitate with Ca^{2+}, thus reducing the amount of free Ca^{2+} in the SR and the amount of Ca^{2+} that diffuses into the sarcoplasm during the brief period when the RYR Ca^{2+} channels open in response to an action potential.

There are also a few different mechanisms that contribute to crossbridge formation during fatigue (step 4). The normal crossbridge cycle (125), starting from the rigor state where the myosin head is strongly bound to an actin binding site (A-M), begins by binding of ATP to the myosin head and subsequent release of the myosin head from actin (M-ATP). ATP is then hydrolyzed to ADP and P_i that remain attached on the myosin head (M-ADP-P_i). This causes a conformational change of the myosin head that stores mechanical energy and enables it to bind to actin. M-ADP-P_i attaches to actin weakly and then more strongly (A-M-ADP-P_i). Strong binding and the subsequent release of the mechanical energy to power the crossbridge rotation is thought to be facilitated by the release of P_i (A-M-ADP). ADP is subsequently released to return the crossbridge to the original rigor state (A-M).

Increases in muscle fiber P_i have been shown to depress force generating capacity (81,82), which could be due to hindering the release of P_i from the crossbridge. Increases in P_i have also been shown to slow muscle deactivation (88, 232), which could also result from slowed release of P_i from the crossbridges (325). P_i release facilitates the normal progression of the crossbridge cycle, thus slowed release would prolong the duration of the cycle and lead to slower crossbridge detachment and force decline upon cessation of muscle excitation. Pushing force from crossbridges that complete their cycle but fail to detach promptly would reduce V_{max}, the maximal shortening velocity that the muscle can generate as load goes to zero. Slow crossbridge detachment would also lead to higher crossbridge strain and force per crossbridge during lengthening contractions. This is consistent with fatigued human muscle showing a steeper force decline relative to isometric for concentric (shortening) activation and a steep force rise for eccentric (lengthening) activation (92). Such difference in force-velocity relationship between fresh and fatigued muscle has also been observed between fast and slow-twitch muscle [(47); see Section "Force-Velocity relationship"].

Low pH from the accumulation of acidic metabolic products such as lactic acid has also been thought to contribute to muscle fatigue because it has been shown to depress both force and maximal contractile velocity (81, 225) as well as to slow down deactivation. pH can affect every step in the crossbridge cycle, but the extent and mechanisms are poorly understood (80, 95).

Classical experiments on the effects of metabolites on muscle fatigue have shown large effects of pH and P_i on fatigue (81, 82, 225). These experiments, however, were performed at unphysiologically low temperatures; recent experiments at higher temperatures showed that fatigue effects of these metabolites are insignificant (96, 186, 321). Even more recently, however, it was shown that these metabolites have interactive effects on fatigue that are much larger than their independent effects, leading up to about a 50% reduction in peak isometric force (179, 237, 238).

The link between metabolite buildup and fatigue implies an important role of the contractile and metabolic processes that generate these metabolites. P_i accumulates faster, for example, when the rate of ATP hydrolyzed for contraction is high, which is the case for strong and rapid contractions in fast-twitch fibers, which are known to be associated with higher fatigue rates. Fatigue rates are especially high when the rate at which ATP is replenished (and P_i accumulation is reversed) is low, which is the case when nutrient catabolism is slow. This is consistent with the fact that muscle fibers classified as fast fatigable have low oxidative capacity and fatigue quickly while fast fatigue-resistant fibers have high oxidative capacity and fatigue more slowly (55). Slow-twitch fibers fatigue even more slowly because they hydrolyze ATP at a slower rate and also have a high oxidative capacity that together contribute to less metabolite buildup.

Catabolic pathways can effectively reverse ATP breakdown and P_i accumulation over long durations of muscle activity as long as blood flow to the muscle fibers is sufficient for maintaining an adequate supply of the necessary substrates such as glucose for glycolysis, and glucose/fatty acids, and oxygen for oxidative phosphorylation. High blood flow is also important for removing metabolites from muscle that cause fatigue such as H^+, which is a byproduct of ATP hydrolysis, glycolysis and, to a lesser extent, oxidative phosphorylation (183). Blood flow capacity for a given muscle fiber depends primarily on its density of capillaries, that is, capillarization as well the surrounding hydrostatic pressure that can occlude blood flow. Blood flow can become completely occluded even when contractile force is as low as about 30% maximum voluntary contraction (MVC) (93), particularly in pennate muscles in which a substantial fraction of the contractile force vector of the muscle fascicles results in compression of the muscle rather than contractile force at the tendon (171).

Adaptation to conditions of use

Muscle structure adapts so as to optimize function for its conditions of use. Conditions of use change mainly in terms of load magnitude and duration, as well as the operating length of the muscle. If muscles experience relatively larger loads than usual, they adapt so as to be able to generate higher forces by undergoing an increase in their number of sarcomeres arranged in parallel. This usually occurs via an increase in muscle fiber size (i.e., an increase in myofibril size and number; known as hypertrophy) rather than an increase in the number of muscle fibers (known as hyperplasia) (129, 130, 214, 221). Substantial adaptation can occur after 3 weeks of high resistance training in humans (97, 285). Tendon also adapts to overload conditions, as it undergoes an increase in stiffness, which reduces the larger and potentially damaging strains that the tendon would experience at the larger muscle forces. Theoretically, tendon stiffness can increase via an increase in collagen fibers in parallel, an increase in the crosslinks between collagen fibers, changes in collagen isoforms as well as a decrease in overall collagen fiber length. Tendon stiffness has been shown to increase in humans *in vivo* in response to overload primarily due to changes in its internal structure and composition rather than changes in size [see (34) for review]. Such adaptation occurs roughly after 8 weeks of high resistance training (190, 191), which suggests some vulnerability to injury if recent training has increased muscle strength more rapidly. If muscle experiences only reduced loads, the reverse occurs: myofibrils decrease in size and number (129, 158, 303), and tendon stiffness decreases (220). These changes have been shown to occur at a similar (37, 89, 235) or faster time scale (110, 136) than during overload conditions.

If muscle is active for sustained periods as in marathon running, then muscle structure adapts so as to reduce fatigability. As discussed in Section "Fatigue," fatigability can improve via more economical use of ATP (i.e., a decrease in ATP needed per unit momentum generated), increased rate of ATP replenishment, and increased rate of removal of

metabolites that interfere with muscle contraction. The economy of force production increases via transformation of myosin isoforms from fast (type II) to slow (type I) (155,170) that cycle slower and therefore consume ATP at a slower rate for the same level of whole muscle force generated (18). Economy also increases via a decrease in the density of SERCA pumps that actively pump Ca^{2+} back into the sarcoplasmic reticulum (144,185). The adapted myofibrils pump Ca^{2+} back to the sarcoplasmic reticulum slower, so the relaxation rate is slower and motoneurons can fire at a lower rate to produce a given force, releasing less Ca^{2+} to be pumped back. Muscle structure changes also increase the rate at which ATP is replenished, primarily by increasing the volume fraction of mitochondria and oxidative enzymes (155), myoglobin concentration (99), and capillarization (10,98). Muscle fibers have also been shown to reduce in size (98), which reduces the diffusion distances between the capillaries and mitochondria, thus increasing oxygen availability for long duration contractions. Increased capillarization and smaller fiber size also increases the clearance rate of metabolic byproducts that cause fatigue such as H^+ (see Section "Fatigue"). If a muscle becomes less active than usual, then the reverse transformations have been shown to occur. Interestingly, the transformations have also been shown to occur in a different order. For example, myosin isoform change is one of the last adaptations in response to increased use (160,250) and one of the earliest adaptations in response to decreased use (42). The trophic signal that maintains the PCSA of regularly activated muscles appears to be a kinase activated by sarcoplasmic Ca^{2+} associated with the activation process itself rather than the force generated by the muscle fibers (25). Low-frequency electrical stimulation of twitches in otherwise paralyzed muscles is just as effective at preventing disuse atrophy as more physiological firing rates that produce much higher forces (103). The trophic signals for hypertrophy resulting from intensive training, however, may include other factors such as mechanical stress, metabolic products, and hormones.

If muscle operating length increases, the number of sarcomeres in series increases (33, 297, 298), which helps maintain a high force-generating capacity and good stability over the new operating range of the muscle lengths. The new sarcomeres have been shown to be added near the musculotendon junction (328). By contrast, if muscle operating length decreases, then the number of sarcomeres in series decreases (86, 297). The maximum length experienced by muscle has also been shown to influence its passive stiffness. Muscles experiencing shorter lengths have a higher passive stiffness while muscles experiencing longer lengths have a lower passive stiffness (45). Muscles that are chronically shortened below their anatomical maximum length experience an increase in passive stiffness (297, 329, 332), which is reversed if the muscle is relengthened to its original anatomical maximum and partly reversed if the muscle is lengthened to an intermediate length (297). This is consistent with the finding that feline muscles with larger maximum anatomical lengths are less stiff than muscles with shorter maximum anatomical lengths (45). Changes in passive stiffness arise largely from changes in collagen amount (330) and arrangement in the extracellular matrix (330), serial sarcomere number (332), and titin isoform (134).

For human muscles *in vivo*, the conditions of use vary not only across muscles, but also within muscles. This is consistent with the fact that muscle fibers across and within muscles have varying contractile, metabolic, and morphometric characteristics (173, 302). It is also consistent with the fact that individuals engaging in similar activity have similar muscle fiber characteristics [e.g., weight lifters (115), long distance runners (170), sprinters (85)]. A given human skeletal muscle *in vivo* experiences many different combinations of the aforementioned conditions of use whose aggregate effect on muscle structure and function is usually complex. The effects of various conditions on muscle structure and function are often interactive and nonlinear. For example, it has been shown that a combination of strength and endurance training lead to less muscle fiber hypertrophy than strength training alone (188), and a smaller increase in oxidative capacity than endurance training alone (236). Moreover, it has been shown that a decrease in serial sarcomere number resulting from a mouse soleus muscle being immobilized in a shortened position for 2 weeks can be avoided if the muscle is passively stretched for only about 30 min a day (327). Complete identification and quantification of these interactive mechanisms remain to be determined.

Injury

Musculotendon injury can occur suddenly or gradually and induces long-term changes in muscle mechanics. The nature of the injury and effects on muscle mechanics depend on the type of insult as well as the physiological state of the musculotendon. Injury causes immediate changes to muscle mechanics, which continue to evolve during the degeneration and replacement/regeneration of damaged structures. Changes in muscle mechanics are assumed to correlate with changes in force generating capacity, which decreases abruptly after an insult, then decreases gradually during the degeneration phase and finally starts to recover even more gradually during the regeneration phase (319). Injury due to strain of underlying structures of the musculotendon is by far the most common injury observed for humans *in vivo*, followed by contusion resulting from impact with blunt objects. Contusion typically affects muscles located near the skin surface (e.g., rectus femoris of the quadriceps) and damages a region of muscle fibers and blood vessels, depending on the intensity and contact area of the collision. The effects of muscle contusions on muscle mechanics have not been investigated systematically, but major consequences are a decrease in muscle force generating capacity due to damaged muscle fibers as well as an increase in fatigability due to the damage in blood vessels that supply nutrients for contraction and clear metabolites that interfere with contraction. The effects of contusion on muscle

mechanics are typically reversed faster than musculotendon strain injuries (301).

Musculotendon strain injuries can occur at different locations along the musculotendon, which are typically associated with distinct effects on muscle mechanics and recovery times. High tendon strains and stresses can lead to partial tears and avulsion of tendons. Such injury is associated with the longest healing time, ranging from 3 to 18 months (269,270,334). Partial tendon tears reduce the effective cross-sectional area of the remaining tendon, increasing its stress and strain. This would effectively shorten the muscle for a given musculotendon length or posture, which can alter muscle mechanics substantially, as explained in Section "Muscle mechanics in the nonfatigued state." Such increase in tendon strain and especially high and uneven stresses near the affected region can lead to further damage of the tendon.

The myotendinous junction is even more susceptible to injury than the osteotendon junction and results in detachment of muscle fibers from the tendon/aponeurosis. This decreases the number of fibers that transmit force to the tendon and therefore reduces the force generating capacity of the musculotendon. The weaker attachment of muscle fibers to the tendon decreases the overall stiffness of the muscle and, therefore, increases the amount of strain taken up by the attached muscle fibers for a given musculotendon force. Increases in muscle fiber strain may lead to detachment of additional muscle fibers and exacerbate damage in the myotendinous junction. Recovery ranges roughly from 1 to 3 months (12).

Strain injury can also occur within muscle fibers at musculotendon stresses that are lower than the threshold for causing myotendinous, tendon, and osteotendinous injury. The likelihood and extent of this type of injury has been shown to increase with force, length, and lengthening velocity of contraction (39, 202, 230, 247, 318). It is thought to occur due to overstretching of a large number of underlying sarcomeres (203, 229). At any given muscle length, the length of all sarcomeres is not the same. For long muscle lengths in particular (i.e., greater than optimal length), the differences in sarcomere length cause some sarcomeres to operate in the ascending portion of the active force-length curve and others to operate in the descending portion. As muscle stretches, contractile force of the shorter sarcomeres will increase while contractile force of the longer sarcomeres will decrease. This shortens the shorter sarcomeres and lengthens the longer sarcomeres, which under extreme conditions (see Section "Force-length relationship/stability") can lead to a number of "popped" sarcomeres that irreversibly stretch beyond the point of no myofilament overlap (43, 203). These sarcomeres can no longer contribute to active force, but add to the in-series elasticity of the muscle fiber. The likelihood and extent of injury may increase at long lengths, because more sarcomeres operate in the descending portion of the force-length curve. Injury susceptibility increases for higher levels of muscle activation, because higher forces stretch the underlying sarcomeres at a faster rate. Injury susceptibility is higher during active stretching (eccentric work) possibly because sarcomeres stretch at a higher rate on average and forces are higher as a result of the force-velocity relationship. Overstretched sarcomeres lead to less sarcomeres contributing to active force, hence a reduction in force generating capacity. Overstretched sarcomeres also lead to a decrease in length of the remaining functional sarcomeres. Decreased sarcomere length can have substantial effects on muscle mechanics, as explained in Section "Muscle mechanics in the nonfatigued state." Out of all types of musculotendon strain injuries, changes in muscle mechanics due to injury within the muscle takes the shortest time to recover and occurs roughly within 1 month (38, 75, 319).

Strain injuries may also begin in the connective tissue matrix between muscle fibers, particularly if the pattern of activation of the muscle fibers results in the generation of shear forces between them. Muscles with long fascicles often have a substantial number of muscle fibers that end as free tapers within this matrix rather than projecting to a myotendinous attachment (306). All of their contractile force must be distributed as shear into and through the matrix to adjacent muscle fibers, which are likely to be from other muscle units and may not be activated. As individual muscle fibers become longer, the time required for action potentials to propagate from neuromuscular endplates near their middle to activate the ends of the fiber may become a substantial portion of the rise time of active force generation, producing longitudinal imbalances that result in shear of the matrix (208). Human hamstring muscles appear to have unusually long muscle fibers and many with tapered intramuscular ends (147). This may contribute to their predisposition to "pulled hamstring" strain injuries that appear to occur during brief, active-lengthening contractions at the end of the swing phase of sprinting (300).

Modeling Muscle Mechanics and Energetics

Mechanics

Computational models of muscle and limb mechanics are useful for testing whether theories of movement control are compatible with the known properties of muscle and limb mechanics. Conversely, models can be used to investigate emergent properties of muscle and limb mechanics to gain insight into the control problem faced by the central nervous system. Mechanistic models in particular provide the opportunity to investigate the influence of individual properties of muscles and limbs on movement by selectively manipulating model components. If the data that define the properties that are highly influential are missing or inaccurate, then this would warrant further experimentation to improve the model. Limb mechanics have been modeled reasonably well by representing each limb as a set of rigid body segments constrained by mechanical joints representing the anatomy.

Muscle mechanics have been less well characterized and their underlying mechanisms remain contentious, as

reviewed herein. One approach generally known as "Hill-type modeling" creates arbitrary mathematical functions that fit measured force to the effects of length and velocity on maximally activated muscle (151, 299, 339). These tend to be inaccurate when extrapolated to more physiological, subtetanic conditions that interact nonlinearly to modulate these effects. Another approach generally known as "Huxley-type modeling" starts with a detailed model of cross-bridge kinetics and dynamics and synthesizes population effects to account for observable phenomena in whole muscles (141, 162, 213, 338). These tend to be complex and computationally expensive and require *ad hoc* additions to account for other elements of force generation such as activation dynamics and passive force. As more data become available from more muscles studied under a wider range of physiological conditions, it becomes feasible to design hybrid models whose individual functions reflect known anatomical components and their presumed physiological mechanisms (308); see (308, 309) for history and comparison of muscle models. These muscle models account well for both slow and fast-twitch muscle mechanics in the potentiated, nonfatigued state. Such mechanistic models are a good starting point for accounting for the effects of fatigue, adaptation to exercise, and various types of diseases and injuries.

The predictive ability of any model depends on the data driving it. Most of the early studies on muscle mechanics were performed on isolated amphibian muscle under unphysiological conditions (e.g., low temperature, removed blood circulation) to facilitate control and measurement of muscle fiber mechanics while preserving the biochemical/mechanical stability of the preparation (150, 197, 282, 295). Although these types of preparations provided insight into the qualitative behavior and mechanisms of muscle contraction, they are not a good quantitative representation of muscle mechanics *in vivo*, because temperature (24, 91, 94, 260, 261, 263) and the chemical environment of the contractile apparatus (9) are known to have strong and complex interactive effects (96, 179, 186, 237, 238) on muscle mechanics. Furthermore, until recently, muscle mechanics were investigated mostly under tetanic or twitch stimulation and isometric or isotonic loads, conditions under which muscles seldom operate *in vivo*. As noted earlier, motoneurons fire only at intermediate rates that correspond to those for which the activation-rate relationship is most steep. Lengthening contractions occur frequently, particularly in antigravity muscles, but were rarely investigated and only for relatively low velocities (175) due to substantial muscle fiber damage that would often result under the unphysiological conditions of the experiments (106, 181, 211). The interactive effects of motor unit firing rate, length, and velocity of contraction on muscle force were not systematically investigated until recently, although known to be strong and complex (16, 175, 259, 267, 289, 293).

A complete understanding of muscle mechanics should account for the interactive effects of muscle length, velocity, and activation on force across the full range of physiological conditions. In one study, the interactive effects of muscle length and velocity on muscle force generation have been measured and characterized mathematically for the predominately slow-twitch soleus muscle at a subtetanic stimulation frequency of 12.5 Hz (288). Additional data have been collected from another series of studies on feline muscle that also included fast-twitch muscle and the full physiological range of firing rates. In this series of experiments, length, velocity, and firing rate of motor units were systematically varied while measuring the force generated (40, 47-49, 51, 175, 259, 277). The following experimental design principles were implemented to ensure that the neuromuscular preparation was kept as close as possible to its physiological state:

- These mammalian muscles were maintained at their physiological temperature of 37°C and blood circulation was kept intact to preserve their physiological chemical environment.

- Whole muscles with intact muscle fibers and extracellular matrix were used to ensure physiological force transmission from the muscle fibers to the tendon.

- Separate bundles of neurons from the ventral roots were stimulated at the same desired frequency but asynchronously to replicate the asynchronous firing of motor units that occurs in physiological behavior (259). If the twitch-eliciting action potentials arrive at the muscle fibers of all motor units synchronously, then the whole muscle behaves like a single muscle fiber and exhibits unfused contractions. Large oscillations of force produce oscillations in the stretch of series-elastic elements and in the length and velocity of the sarcomeres, which in turn results in oscillations of force generation by crossbridges. With physiological recruitment to achieve low forces, motoneurons may fire at low firing rates but muscle contractions are relatively smooth (174) because motor units fire asynchronously (176, 259, 283).

The muscles investigated in these studies, feline soleus (51, 175, 259, 277) and caudofemoralis (40, 47-49), were specifically chosen because they have a relatively simple uniform architecture, which allows for more direct control and assessment of muscle fiber mechanics (50, 233). Caudofemoralis in particular has parallel fibers with essentially no aponeurosis; it can be connected to a muscle puller with essentially no in-series elasticity (50). These muscles were chosen also because they are almost entirely homogeneous in histological fiber type (feline soleus is 100% slow-twitch, type I (11) and caudofemoralis is 100% fast twitch, ~95% type IIb (50). It is important to understand the differences in the mechanics of fiber types because they are substantially different and because most muscles contain a mix of fiber types that could vary to a large extent across different muscles in the body as well as across individuals (173, 227). The data obtained from these studies were used to create a model of muscle mechanics for slow and fast-twitch muscle that has been validated across a wide range of physiological

conditions (49). The model was then extended to model muscles of other mammalian species, including humans (70).

The mechanics of individual fiber types can be investigated in other ways as well, but the associated experimental preparations lead to artifacts that make the data invalid for physiological conditions. One way is to dissect individual muscle fibers from bundles of one fiber type but, as mentioned in this section earlier, these preparations commonly exhibit unphysiological behavior as a result of damage to blood supply and endomysial connective tissue. Another way is to selectively stimulate one motor unit (all of whose fibers will have the same histological and physiological type) in an intact whole muscle and investigate its effects on whole muscle mechanics (53, 291). Although this type of experiment is typically performed on intact muscle and at physiological temperatures, the relatively weak forces measured at the tendon in response to stimulation of only one motor unit may be distorted by inertia and compliance of the large mass of inactive muscle and connective tissue (142).

Energetics

More recently, the model of muscle mechanics mentioned earlier was extended and validated using data from thermodynamic experiments to predict the energetics of contractions (310). When a muscle is activated from its resting state, the primary contributors to muscle energy consumption during the first few seconds are the cycling crossbridges that generate force and the SERCA Ca^{2+} pumps that help regulate calcium flux in the sarcoplasm (19, 20, 22). These processes consume metabolic fuel in the form of ATP, which is completely replenished within a few minutes after deactivation by the catabolic pathways of glycolysis and oxidative phosphorylation [when perfusion is not limiting; (198, 200)]. These catabolic pathways are not perfectly efficient; in fact, the amount of energy required to replenish the ATP that drives contraction is generally at least as high as the energy that directly drives the contraction (21, 200). To understand and quantitatively predict muscle energetics across a wide range of conditions, it is important to account for each of these active processes, because they depend strongly on the contractile conditions. For shortening (i.e., concentric) contractions, crossbridges complete their cycle and consume ATP at an even higher rate; however, for lengthening contractions (i.e., eccentric), crossbridges generally do not complete their cycle and energy related to crossbridges is nearly zero, so Ca^{2+} pumping energy accounts for most of the energy consumed in this condition (87). For isometric contractions, crossbridges consume about 2/3 of the energy required and SERCA Ca^{2+} pumps consume the remaining 1/3 (18, 20, 22). Although there is nominally no myofilament sliding under isometric conditions, there is sufficient thermodynamic motion that crossbridges cycle at modest rates. The energy required to replenish the ATP consumed depends on the metabolic pathways used and the contractile conditions that determine the amount of ATP that must be replenished (200). The model relates muscle mechanics to metabolic energy consumed by each one of these processes, which enables predictions of metabolic energy consumption across a wide range of physiological conditions (310).

A plausible mechanism for the neural control of movement must explain how neural commands to the muscles are generated to produce movement. A major challenge with identifying such mechanism is that neural commands to muscles are often nonintuitive and difficult to measure. Accurate predictions of muscle energy consumption are important for predicting muscle recruitment strategies that underlie movement because subjects typically adopt muscle recruitment strategies that minimize metabolic energy consumption (66, 159), presumably to avoid fatigue and conserve energy for all other active processes in the body. Researchers have traditionally assumed that minimizing energy is equivalent to minimizing force or related quantities such as stress, work, activation (or arbitrary mathematical functions of these quantities), but it has been shown that such quantities relate poorly to actual energy cost and are even inversely related for some conditions (310). For example, when a muscle is activated isometrically and then is allowed to shorten, the rate of energy consumption will increase because crossbridges will complete their cycle at a faster rate while force output will decrease due to decreases in crossbridge strain and possibly crossbridge number, as explained in Section "Muscle mechanics in the nonfatigued state/Force-velocity relationship." The validated energetics model (309,310) enables prediction of recruitment strategies by minimizing actual metabolic cost and has been employed to investigate the role of muscle physiology and spinal circuitry in generating metabolically efficient voluntary movement (307).

Accounting for contraction energetics is necessary for modeling the changes in muscle mechanics that result from fatigue, because energetics drive contractile fuel consumption and metabolism (193) that alter the biochemical state of the muscle and cause fatigue (9). Because the model accounts for the complex muscle fiber mechanics/energetics and for the recruitment of multiple motor units, computing its dynamics requires integrating a large number of coupled state equations, which is computationally intensive and impractical for simulating large-scale musculoskeletal systems. To overcome this, a computationally efficient algorithm was developed that mathematically lumped all motor units within a given fiber type into one effective motor unit that represented the population (310).

Muscle Recruitment and Its Measurement

Fiber types

Most of the muscle physiology presented earlier reflects either the generic mechanisms common to virtually all skeletal muscles or features that are specific to one particular fiber type (e.g., sag and yield). Most mammalian skeletal muscles are mixtures or two or more fiber types that differ in the parameters of their various mechanisms. These give rise to observable

physiological and histochemical properties that have been used in various combinations to identify and classify fiber types (55):

- Fiber diameter. Fast-twitch fibers tend to have substantially larger diameter (~1.5-2×) and cross-sectional area (2-4×) than slow-twitch fibers in the same muscle, but the specific active tension tends to be similar [~31 N/cm^2; (210)].

- Myoglobin concentration. High levels give slow-twitch fibers their darker red color and facilitate their oxidative metabolism by enhancing the diffusion of oxygen from the capillary circulation.

- Myosin isoforms. These were traditionally identified by differences in ATPase activity as revealed by histological staining under different pH condition; now usually identified by monoclonal antibodies to a specific isoform.

- Speed of shortening (V_{max}). The myosin isoforms have different crossbridge attachment and detachment kinetics; fast-twitch myosin kinetics result in higher maximal velocity of unloaded shortening.

- Speed of activation (T_{rise}) and deactivation (T_{fall}). The sarcoplasmic reticulum of fast-twitch muscle fibers both releases and reuptakes calcium more rapidly, resulting in faster rise and fall of twitch tension; this manifests also as requiring a higher firing rate to reach maximal tetanic activation.

- Glycogen concentration in the cytoplasm. High levels are generally a feature of fast-twitch fibers that can break down glycogen into a plentiful supply of glucose to supply rapid but inefficient glycolytic metabolism.

- Oxidative enzyme concentration. High levels are associated with higher density of the mitochondria supporting oxidative metabolism in slow-twitch fibers.

- Fatigability. Slow-twitch muscles with high oxidative capacity can be activated repeatedly and almost indefinitely as long as they are supplied with glucose and oxygen and cleared of carbon dioxide via capillary circulation; fast-twitch muscles tend to fatigue after repeated activation, but with a very wide range from less than a minute to an hour.

Muscle fibers vary in terms of each of the aforementioned subcellular features that tend to covary in normal muscle. Generally, muscle that activates and deactivates slowly in response to neural excitation (i.e., slow-twitch muscle that has long rise and fall times) also has a relatively low V_{max} and generates force more economically, has higher oxidative capacity, and has lower fatigue susceptibility. Conversely, muscle that activates and deactivates quickly (i.e., fast-twitch muscle) also has a relatively high V_{max} and generates force less economically, has a higher glycolytic capacity, and higher fatigue susceptibility. The feline soleus muscle fibers represent the slow extreme of muscle fibers across muscles in the cat (55, 56) as well as across many other species such as humans (17, 70), while the feline caudofemoralis muscle fibers represent the fast extreme for the cat (50) as well as across species (70). Most whole muscles are composed of a mix of fiber types. The mean attributes that are observed depend on the relative recruitment of the various motor units and their state of fatigue and potentiation.

It is important to note that each of these functional attributes of muscle is the product of a different anatomical structure with its own genetic specification and trophic modification mechanisms, so their actual quantitative values may vary among species and muscles and may not covary in the usual pattern, particularly in muscles that have been subjected to unusual patterns of use, disuse, or disease. For example, the susceptibility and effects of fatigue may manifest differently in the same histochemical fiber type depending on the muscle in which it is located and its exercise history. The caudofemoralis muscle, in particular, exhibits one of the fastest twitch contraction times, but it fatigues slower than other muscles such as the medial gastrocnemius of the cat (50) that have a substantially lower percentage of fast-twitch fibers [~60% Type IIb (58) vs. 95% Type IIb (50)]. The caudofemoralis mechanics during the fatigued state may not reflect the fatigued mechanics of other muscle fibers or whole muscles that fatigue faster. To model whole muscle mechanics during fatigue, it is also important to account for the metabolic profile of the constituent fibers (see Section "Fatigue").

The mixture of types that are present in a given muscle appears to be determined genetically but the prevalence of fibers of a given type can be substantially modified by patterns of use. In fact, the exact number of distinct fiber types is often uncertain, particularly in animals living under uncontrolled natural conditions, because many of the structures that give rise to the distinguishing parameters for a given fiber type are subject to trophic effects that are driven by different aspects of patterns of muscle use, as described under Section "Adaptation to conditions of use." This may result in intermediate fiber types that are mixes of characteristics of the predominant fiber types and may be in transition between them as a result of changes in behavior.

Muscle unit architecture

The number of muscle fibers innervated by a single motoneuron varies hugely from muscle to muscle but the fibers innervated by a given motoneuron (the muscle unit) are usually homogeneous in their parameters, at least in part because all muscle fibers of a given muscle unit will have had identical patterns of usage. In a healthy muscle, the fibers of a given muscle unit tend to be scattered through a substantial percentage of the cross-sectional area of the muscle (see later) and, hence, to be surrounded primarily by fibers of other muscle units. The slow-twitch muscle units are innervated by the

smaller alpha motoneurons and are generally comprised of smaller numbers of fibers than the fast-twitch muscle units. The distribution of slow and fast-twitch fiber types is often skewed, with the deeper layers populated predominantly by slow-twitch fibers and the superficial layers by fast-twitch fibers. This may provide thermal benefits, with the usually inactive fast muscle layers providing insulation from the cold for the deeper slow muscle and then dissipating their higher heat production more efficiently to the overlying skin when the fast muscle is recruited during intensive physical activities (55).

The intramuscular branching patterns of muscle nerves and their motor axons are complex and variable, depending on the architecture and function of the muscle as a whole. In a relatively simple parallel-fibered muscle with a single, localized origin and insertion, all of the neuromuscular synapses will generally be in a single band of endplates extending across the width of the muscle near its midpoint. Individual motor axons branch to innervate their muscle fibers in a widely distributed pattern. Parallel-fibered muscles with broad origins or insertions tend to be divided into more than one neuromuscular compartment, each of which functions like a separate and more mechanically homogeneous muscle with its unique population of muscle units that may be recruited independently of the other compartments (253). In at least one case (feline anterior sartorius), a single neuromuscular compartment was found to be innervated by two, separately recruited populations of motoneurons that were related to different phases of muscle work (205, 254). Some long muscles are divided into anatomically separate neuromuscular compartments in series, separated by myotendinous inscriptions; examples include semitendinosus in the leg, digastric in the jaw and many axial muscles of the neck and back. Many long muscles with long, parallel fascicles have no discrete inscriptions but are instead composed of shorter, interdigitated muscle fibers; their neuromuscular architecture has been studied in only a few cases (5, 208). In some cases, individual motor units are distributed equally over the length of the fascicles; in others, the cross-sectional area of individual motor units may be highly asymmetrically distributed, which could result in instability if their contractile forces were not offset by other muscle units with inverse distributions (280).

Electromyography, force, and energetics

The electrical signals produced by active muscles are relatively easy to record by electromyography [EMG; (207)]. A single action potential in a single motoneuron gives rise to simultaneous action potentials in perhaps hundreds of muscle fibers comprising a muscle unit. The action potentials in each muscle fiber must be sustained by large action currents flowing across the large, bare sarcolemma, which is electrically similar to a large, unmyelinated axon but with even more current associated with the large network of electrically active transverse tubules. To a first approximation, the total action current produced by a given muscle unit is probably fairly linearly related to its physiological cross-sectional area, hence its force generating capacity. In simple parallel-fibered muscles, the action currents from all of the fibers of a given muscle unit tend to add in phase. When recorded by relatively large electrodes on the skin surface or in the muscle (gross EMG), this results in large, extracellularly recordable field potentials with a fairly simple, approximately biphasic waveform. At low levels of recruitment with little overlapping activity from multiple units, it is even possible to record discriminable unitary potentials from skin surface electrodes, but such records are usually obtained from intramuscular microelectrodes that record large unitary potentials from a small number of immediately adjacent, individual muscle fibers. In pennate muscles, the shorter muscle fibers and their endplates tend to be staggered across the length of the muscle belly, resulting in more complex, polyphasic potentials as the action currents pass gross EMG electrodes at a given recording site with different time lags from conduction along the muscle fibers. Those time lags will increase when the muscle is stretched, changing the shape and amplitude of the local EMG signatures. Muscles with multiple endplate zones innervating short fibers that are scattered over the length of long fascicles result in highly complex and labile waveforms as action potentials conducting in different directions along muscle fibers pass each other. By recording the waveforms at a large number of points along the muscle, it is possible to identify systematic changes in the latency and shape of these waveforms to make inferences about the distribution of muscle fibers and endplates constituting single muscle units (67).

When multiple muscle units are recruited normally, they tend to fire asynchronously at different frequencies, which contributes to the smoothness of the overall force production at physiological firing rates for which contractions are metabolically efficient but unfused in the force output of individual muscle units. The resulting stochastic summation of biphasic action currents results, however, in a waveform that is inherently noisy. Perhaps the most common use of gross EMG signals is to infer relative magnitude of muscle activity, force and energy consumption, which then requires signal-processing techniques to average out the stochastic fluctuations over time. The native rise and fall times of the activation process itself (typically 50-200 ms) provides a useful window over which to smooth EMG signals (14, 135).

Many different parameters of the gross EMG signal can be measured (peak amplitude, mean rectified amplitude, mean power, number of peaks, number of zero crossings, power in a given frequency band, etc.). There are long-standing controversies regarding whether each of these measures is related linearly, logarithmically, or exponentially to muscle activation, force or energy consumption (207). Given the variety of muscle fiber architectures, tasks and EMG electrode designs, it is not surprising that almost any result might be obtained. One of the largest confounding factors arises from the asymmetrical distribution of muscle fiber types in many muscles. The amplitude of the EMG signal generated by action currents of a given muscle unit tends to decay rapidly with distance

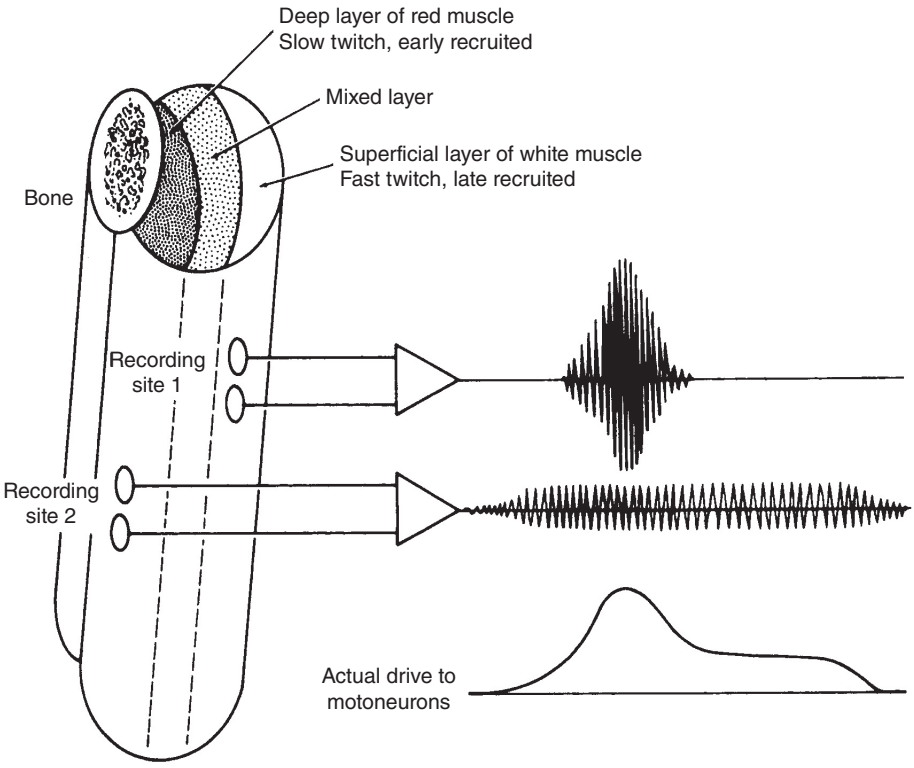

Figure 15 Typical bipolar EMG recording configurations from a mixed muscle with regional stratification of early recruited, slow-twitch muscle fibers versus late recruited, fast-twitch muscle fibers. Reprinted with permission (207).

from the source muscle fibers of the unit (theoretically as distance squared for distances greater than the ~10 mm wavelength of action potentials along muscle fibers). Because of the orderly recruitment of muscle units starting with slow-twitch units at low forces and then fast-twitch units at high forces, the rate of growth of a local EMG signal recorded with macroelectrodes on or within a muscle during progressive muscle recruitment depends on the density of active muscle fibers locally. In a region of the muscle that has predominantly slow fibers, the rate of growth of amplitude of the gross EMG signal will be high at low recruitment and force levels and then tend to saturate after all of the local slow fibers have already been recruited. In a region with predominantly fast fibers, very little EMG may be recorded at low recruitment and force levels, followed by rapid increases at higher levels when the local fast-twitch units start to become active (Fig. 15). In one example, the two series-inscripted and separately innervated heads of the feline semitendinosus muscle are necessarily recruited simultaneously but may appear to work asymmetrically if the EMG recorded from the deep (slow) surface of one head is compared with the superficial (fast) surface of the other head (69).

Obviously, EMG is most directly related to the activation process, although the absolute amplitude of the EMG signal will depend strongly on the design and placement of the EMG electrode. Any quantitative relationship to force or energy consumption will depend highly on kinematic conditions of muscle work. As described earlier, the active force-generating capability of a muscle fiber depends moderately on its length for physiological conditions around its optimal length but changes greatly and rapidly for small fluctuations in velocity around isometric. Energy consumption is even more complexly related to kinematics and also to level of recruitment in mixed muscles because of the different metabolic pathways that tend to be utilized by slow- versus fast-twitch fibers. Both problems are compounded under dynamic conditions of recruitment because the stretching and release of series-elastic tendon+aponeurosis makes it difficult to infer the kinematics of the muscle fascicles from the more observable kinematics of the limb. Given sufficient kinematic as well as EMG data, it is theoretically possible to construct quantitative models to correct for these effects, but this has been attempted only rarely (71).

Conclusion

Most of the observable phenomena of normal skeletal muscles are now well accounted by structure-function relationships that have been identified, measured, and modeled, at least individually. The biochemical details and self-organizing mechanisms of those structures are yielding rapidly to ultrastructural, genomic and proteomic analysis. This can be expected to provide insights into the trophic and pathological

mechanisms whereby the properties of muscles change in ways that are clinically important but still largely unaccounted. For example, we are just beginning to understand how the transmembrane protein dystrophin interacts with the many other structural elements that protect muscle fibers from the types of progressive damage that are associated with various forms of muscular dystrophy (249).

Integrating the structure-function relationships of individual muscle fibers into models of complete musculoskeletal systems is now feasible but remains daunting because of the large number of morphometric and physiological parameters that are required to properly define such systems. The mix of muscle fiber types and physiological properties and their mechanical integration with connective tissue results in a wide range of composite materials to which we give individual anatomical names as muscles. Each muscle has properties that tend to suit it uniquely to the functional requirements imposed by patterns of behavior and musculoskeletal mechanics. Disorders of the nervous system such as cerebral palsy lead to a variety of chronic maladaptations of the musculoskeletal system (326). As the genetic instructions and trophic mechanisms that govern these adaptive changes are unraveled, it will lead inevitably to an understanding of and new treatments for many clinical disorders.

References

1. Abrahams M. Mechanical behavior of tendon in vitro. *Med & Biol Engng* 5: 433-443, 1967.
2. Ackland DC, Pak P, Richardson M, Pandy MG. Moment arms of the muscles crossing the anatomical shoulder. *J Anat* 213: 383-390, 2008.
3. Ackland DC, Pandy MG. Lines of action and stabilizing potential of the shoulder musculature. *J Anat* 215: 184-197, 2009.
4. Ackland DC, Pandy MG. Moment arms of the shoulder muscles during axial rotation. *J Orthop Res* 29: 658-667, 2011.
5. Adrian ED. The spread of activity in the tenuissimus muscle of the cat and in other complex muscles. *J Physiol* 60: 301-315, 1925.
6. Alexander RM. Tendon elasticity and muscle function. *Comp Biochem Physiol Part A* 133: 1001-1011, 2002.
7. Alexander RM, Vernon A. The mechanics of hopping kangaroos (Macropodidae). *J Zool* 177: 265-303, 1975.
8. Allen DG, Lamb GD, Westerblad H. Impaired calcium release during fatigue. *J Appl Physiol* 104: 296-305, 2008.
9. Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: Cellular mechanisms. *Physiol Rev* 88: 287-332, 2008.
10. Andersen P, Henriksson J. Capillary supply of the quadriceps femoris muscle of man: Adaptive response to exercise. *J Physiol* 270: 677-690, 1977.
11. Ariano MA, Armstrong RB, Edgerton VR. Hind limb muscle fiber populations of five mammals. *J Histochem Cytochem* 21: 51-55, 1973.
12. Askling CM, Tengvar M, Saartok T, Thorstensson A. Proximal hamstring strains of stretching type in different sports: Injury situations, clinical and magnetic resonance imaging characteristics, and return to sport. *Am J Sports Med* 36: 1799-1804, 2008.
13. Azizi E, Brainerd EL, Roberts TJ. Variable gearing in pennate muscles. *PNAS* 105: 1745-1750, 2008.
14. Bak MJ, Loeb GE. A pulsed integrator for EMG analysis. *Electroencephalogr Clin Neurophysiol* 47: 738-741, 1979.
15. Baker AJ, Kostov KG, Miller RG, Weiner MW. Slow force recovery after long-duration exercise: Metabolic and activation factors in muscle fatigue. *J Appl Physiol* 74: 2294-2300, 1993.
16. Balnave CD, Allen DG. The effect of muscle length on intracellular calcium and force in single fibres from mouse skeletal muscle. *J Physiol* 492: 705-713, 1996.
17. Barany M. ATPase activity of myosin correlated with speed of muscle shortening. *J Gen Physiol* 50: 197-218, 1967.
18. Barclay CJ. Mechanical efficiency and fatigue of fast and slow muscles of the mouse. *J Physiol* 497: 781-794, 1996.
19. Barclay CJ. Energetics of contraction. *Compr Physiol* 5: 961-995, 2015.
20. Barclay CJ, Lichtwark GA, Curtin NA. The energetic cost of activation in mouse fast-twitch muscle is the same whether measured using reduced filament overlap or N-benzyl-p-toluenesulphonamide. *Acta Physiol* 193: 381-391, 2008.
21. Barclay CJ, Weber CL. Slow skeletal muscles of the mouse have greater initial efficiency than fast muscles. *J Physiol* 559: 519-533, 2004.
22. Barclay CJ, Woledge RC, Curtin NA. Energy turnover for Ca^{2+} cycling in skeletal muscle. *J Muscle Res Cell Motil* 28: 259-274, 2007.
23. Barclay CJ, Woledge RC, Curtin NA. Inferring crossbridge properties from skeletal muscle energetics. *Prog Biophys Mol Biol* 102: 53-71, 2010.
24. Barclay CJ, Woledge RC, Curtin NA. Is the efficiency of mammalian (mouse) skeletal muscle temperature dependent? *J Physiol* 588: 3819-3831, 2010.
25. Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling. *Annu Rev Biochem* 75: 19-37, 2006.
26. Baylor SM, Hollingworth S. Model of sarcomeric Ca^{2+} movements, including ATP Ca^{2+} binding and diffusion, during activation of frog skeletal muscle. *J Gen Physiol* 112: 297-316, 1998.
27. Benjamin M. The fascia of the limbs and back - a review. *J Anat* 214: 1-18, 2009.
28. Bennett MB, Ker RF, Dimery NJ, Alexander RM. Mechanical properties of various mammalian tendons. *J Zool Lond* 209: 537-548, 1986.
29. Berchtold MW, Brinkmeier H, Muntener M. Calcium ion in skeletal muscle: Its crucial role for muscle function, plasticity, and disease. *Physiol Rev* 80: 1215-1265, 2000.
30. Bigland-Ritchie B, Johansson R, Lippold OC, Smith S, Woods JJ. Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *J Neurophysiol* 50: 313-324, 1983.
31. Blake DJ, Weir A, Newey SE, Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiol Rev* 82: 291-329, 2002.
32. Blemker SS, Delp SL. Three-dimensional representation of complex muscle architectures and geometries. *Ann Biomed Eng* 33: 661-673, 2005.
33. Boakes J, Foran J, Ward S, Lieber RL. Muscle adaptation by serial sarcomere addition 1 year after femoral lengthening. *Clin Orthop Relat Res* 456: 250-253, 2007.
34. Bohm S, Mersmann F, Arampatzis A. Human tendon adaptation in response to mechanical loading: A systematic review and meta-analysis of exercise intervention studies on healthy adults. *Sports Med* 1: 7, 2015.
35. Bojsen-Møller J, Schwartz S, Kalliokoski KK, Finni T, Magnusson SP. Intermuscular force transmission between human plantarflexor muscles in vivo. *J Appl Physiol* 109: 1608-1618, 2010.
36. Borg TK, Caulfield JB. Morphology of perimysial and endomysial connective tissue in skeletal muscle. *Tissue Cell* 12: 197-207, 1980.
37. Brocca L, Cannavino J, Coletto L, Biolo G, Sandri M, Bottinelli R, Pellegrino MA. The time course of the adaptations of human muscle proteome to bed rest and the underlying mechanisms. *J Physiol* 590: 5211-5230, 2012.
38. Brooks SV, Faulkner JA. Contraction-induced injury: Recovery of skeletal muscles in young and old mice. *Am J Physiol Cell Physiol* 258: C436-C442, 1990.
39. Brooks SV, Zerba E, Faulkner JA. Injury to muscle fibres after single stretches of passive and maximally stimulated muscles in mice. *J Physiol* 488: 459-469, 1995.
40. Brown IE, Cheng EJ, Loeb GE. Measured and modeled properties of mammalian skeletal muscle. II. The effects of stimulus frequency on force-length and force-velocity relationships. *J Muscle Res Cell Motil* 20: 627-643, 1999.
41. Brown GL, Euler US. The after effects of a tetanus on mammalian muscle. *J Physiol* 93: 39-60, 1938.
42. Brown JMC, Henriksson J, Salmons S. Restoration of fast muscle characteristics following cessation of chronic stimulation: Physiological, histochemical and metabolic changes during slow-to-fast transformation. *Proc R Soc Lond B Biol Sci* 235: 321-346, 1989.
43. Brown LM, Hill L. Some observations on variations in filament overlap in tetanized muscle fibres and fibres stretched during a tetanus, detected in the electron microscope after rapid fixation. *J Muscle Res Cell Motil* 12: 171-182, 1991.
44. Brown IE, Kim DH, Loeb GE. The effect of sarcomere length on triad location in intact feline caudofemoralis muscle fibres. *J Muscle Res Cell Motil* 19: 473-477, 1998.
45. Brown IE, Liinamaa TL, Loeb GE. Relationships between range of motion, Lo, and passive force in five strap-like muscles of the feline hind limb. *J Morphol* 230: 69-77, 1996.

46. Brown IE, Loeb GE. Post-activation potentiation - a clue for simplifying models of muscle dynamics. *Amer Zool* 38: 743-754, 1998.
47. Brown IE, Loeb GE. Measured and modeled properties of mammalian skeletal muscle: I. The effects of post-activation potentiation on the time-course and velocity dependencies of force production. *J Muscle Res Cell Motil* 20: 443-456, 1999.
48. Brown IE, Loeb GE. Measured and modeled properties of mammalian skeletal muscle: III. The effects of stimulus frequency on stretch-induced force enhancement and shortening-induced force depression. *J Muscle Res Cell Motil* 21: 21-31, 2000.
49. Brown IE, Loeb GE. Measured and modeled properties of mammalian skeletal muscle: IV. Dynamics of activation and deactivation. *J Muscle Res Cell Motil* 21: 33-47, 2000.
50. Brown IE, Satoda T, Richmond FJR, Loeb GE. Feline caudofemoralis muscle: Muscle fiber properties, architecture and motor innervation. *Exp Brain Res* 121: 76-91, 1998.
51. Brown IE, Scott SH, Loeb GE. Mechanics of feline soleus: II. Design and validation of a mathematical model. *J Muscle Res Cell Motil* 17: 221-233, 1996.
52. Brunello E, Reconditi M, Elangovan R, Linari M, Sun Y, Narayanan T, Panine PP, Piazzesi G, Irving M, Lombardi V. Skeletal muscle resists stretch by rapid binding of the second motor domain of myosin to actin. *PNAS* 104: 20114-20119, 2007.
53. Buchthal F, Schmalbruch H. Contraction times and fibre types in intact human muscle. *Acta Physiol Scand* 79: 435-352, 1970.
54. Buneo CA, Soechting JF, Flanders M. Postural dependence of muscle actions: Implications for neural control. *J Neurosci* 17: 2128-2142, 1997.
55. Burke RE. Motor units: Anatomy, physiology, and functional organization. In: Brooks VB, editor. *Motor Control (Handbook of Physiology, Sect 1, The Nervous System)*. Bethesda, MD: Am Physiol Soc, 1981.
56. Burke RE, Levine DN, Salcman M, Tsairis P. Motor units in cat soleus muscle: Physiological, histochemical and morphological characteristics. *J Physiol* 238: 503-514, 1974.
57. Burke RE, Levine DN, Tsairis P, Zajac FE. Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J Physiol* 234: 723-748, 1973.
58. Burke RE, Tsairis P. Anatomy and innervation ratios in motor units of cat gastrocnemius. *J Physiol (London)* 234: 749-765, 1973.
59. Burkholder TJ, Lieber RL. Sarcomere length operating range of vertebrate muscles during movement. *J Exp Biol* 204: 1529-1536, 2001.
60. Cady EB, Jones DA, Lynn J, Newham DJ. Changes in force and intracellular metabolites during fatigue of human skeletal muscle. *J Physiol* 418: 311-325, 1989.
61. Cannell MB. Effect of tetanus duration on the free calcium during the relaxation of frog skeletal muscle fibres. *J Physiol* 376: 203-218, 1986.
62. Cannell MB, Allen DG. Model of calcium movements during activation in the sarcomere of frog skeletal muscle. *Biophys J* 45: 913-925, 1984.
63. Carrasco DI, Lawerence J, English AW. Neuromuscular compartments of cat lateral gastrocnemius produce different torques about the ankle joint. *Motor Control* 3: 436-446, 1999.
64. Cavagna GA. Elastic bounce of the body. *J Appl Physiol* 29: 279-282, 1970.
65. Cavagna GA. Storage and utilization of elastic energy in skeletal muscle. *Exerc Sport Sci Rev* 5: 89-129, 1977.
66. Cavanagh PR, Williams KR. The effect of stride length variation on oxygen uptake during distance running. *Med Sci Sports Exerc* 14: 30-35, 1982.
67. Chanaud CM, Pratt CA, Loeb GE. A multiple-contact EMG recording array for mapping single muscle unit territories. *J Neurosci Methods* 21: 105-112, 1987.
68. Chanaud CM, Pratt CA, Loeb GE. Functionally complex muscles of the cat hindlimb. II. Mechanical and architectural heterogenity within the biceps femoris. *Exp Brain Res* 85: 257-270, 1991.
69. Chanaud CM, Pratt CA, Loeb GE. Functionally complex muscles of the cat hindlimb. V. The roles of histochemical fiber-type regionalization and mechanical heterogeneity in differential muscle activation. *ExpBrain Res* 85: 300-313, 1991.
70. Cheng EJ, Brown IE, Loeb GE. Virtual muscle: A computational approach to understanding the effects of muscle properties on motor control. *J Neurosci Methods* 101: 117-130, 2000.
71. Cheng EJ, Loeb GE. On the use of musculoskeletal models to interpret motor control strategies from performance data. *J Neural Eng* 5: 232-253, 2008.
72. Chin ER, Allen DG. Effects of reduced muscle glycogen concentration on force, Ca2 release and contractile protein function in intact mouse skeletal muscle. *J Physiol* 498: 17-29, 1997.
73. Chowdhury B, Sjostrom L, Alpsten M, Konstanty J, Kvist H, Lofgren R. A multicompartment body composition technique based on computerized tomography. *Int J Obes Relat Metab Disord* 18: 219-234, 1994.
74. Christophy M, Senan NAF, Lotz JC, O'Reilly OM. A musculoskeletal model for the lumbar spine. *Biomech Model Mechanobiol* 11: 19-34, 2012.
75. Clarkson PM, Nosaka K, Braun B. Muscle function after exercise induced muscle damage and rapid adaptation. *Med Sci Sports Exerc* 24: 512-520, 1992.
76. Cleworth DR, Edman KAP. Changes in sarcomere length during isometric tension development in frog skeletal muscle. *J Physiol* 227: 1-17, 1972.
77. Close RI. The relations between sarcomere length and characteristics of isometric twitch contractions of frog sartorius muscle. *J Physiol* 220: 745-762, 1972.
78. Close R, Hoh JFY. Post-tetanic potentiation of twitch contractions of cross-innervated rat fast and slow muscles. *Nature* 221: 179-181, 1969.
79. Cooke R. Actomyosin interaction in striated muscle. *Physiol Rev* 77: 671-697, 1997.
80. Cooke R. Modulation of the actomyosin interaction during fatigue of skeletal muscle. *Muscle Nerve* 36: 756-777, 2007.
81. Cooke R, Franks K, Luciani GB, Pate E. The inhibition of rabbit skeletal muscle contraction by hydrogen ions and phosphate. *J Physiol* 395: 77-97, 1988.
82. Cooke R, Pate E. The effects of ADP and phosphate on the contraction of muscle fibers. *Biophys J* 48: 789-798, 1985.
83. Cooper S, Eccles JC. The isometric responses of mammalian muscles. *J Physiol* 69: 377-385, 1930.
84. Cordo PJ, Rymer WZ. Contributions of motor-unit recruitment and rate modulation of compensation for muscle yielding. *J Neurophysiol* 47: 797-809, 1982.
85. Costill DL, Daniels J, Evans WF, Fink W, Krahenbuhl G, Saltin B. Skeletal muscle enzymes and fiber composition in male and female track athletes. *J Appl Physiol* 40: 149-154, 1976.
86. Csapo R, Maganaris CN, Seynnes OR, Narici MV. On muscle, tendon and high heels. *J Exp Biol* 213: 2582-2588, 2010.
87. Curtin NA, Davies RE. Very high tension with very little ATP breakdown by active skeletal muscle. *J Mechanochem Cell Motil* 3: 147-154, 1975.
88. Dahlstedt AJ, Katz A, Westerblad H. Role of myoplasmic phosphate in contractile function of skeletal muscle: Studies on creatine kinase-deficient mice. *J Physiol* 533: 379-388, 2001.
89. Dalla Libera L, Ravara B, Gobbo V, Tarricone E, Vitadello M, Biolo G, Vescovo G, Gorza L. A transient antioxidant stress response accompanies the onset of disuse atrophy in human skeletal muscle. *J Appl Physiol* 107: 549-557, 2009.
90. Dawson MJ, Gadian DG, Wilkie DR. Muscular fatigue investigated by phosphorus nuclear magnetic resonance. *Nature* 274: 861-866, 1978.
91. De Ruiter CJ, De Haan A. Temperature effect on the force/velocity relationship of the fresh and fatigued human adductor pollicis muscle. *Pflugers Arch, EJP* 440: 163-170, 2000.
92. De Ruiter CJ, Didden WJM, Jones DA, De Haan A. The force-velocity relationship of human adductor pollicis muscle during stretch and the effects of fatigue. *J Physiol* 526: 671-681, 2000.
93. De Ruiter CJ, Goudsmit JF, Van Tricht JA, De Haan A. The isometric torque at which knee-extensor muslce reoxygenation stops. *Med Sci Sports Exerc* 39: 443-453, 2007.
94. De Ruiter CJ, Jones DA, Sargeant AJ, De Haan A. Temperature effect on the rates of isometric force development and relaxation in the fresh and fatigued human adductor pollicis muscle. *Exp Physiol* 84: 1137-1150, 1999.
95. Debold EP. Recent insights into muscle fatigue at the cross-bridge level. *Frontiers in Physiology* 3: 00151, 2012.
96. Debold EP, Dave H, Fitts RH. Fiber type and temperature dependence of inorganic phosphate: Implications for fatigue. *Am J Physiol Cell Physiol* 287: C673-C681, 2004.
97. DeFreitas JM, Beck TW, Stock MS, Dillon MA, Kasishke PR. An examination of the time course of training-induced skeletal muscle hypertrophy. *Eur J Appl Physiol* 111: 2785-2790, 2011.
98. Denis C, Chatard JC, Dormois D, Linossier MT, Geyssant A, Lacour JR. Effects of endurance training on capillary supply of human skeletal muscle on two age groups (20 and 60 years). *J Physiol (Paris)* 81: 379-383, 1986.
99. Donaghue P, Doran P, Dowling P, Ohlendieck K. Differential expression of the fast skeletal muscle proteome following chronic low-frequency stimulation. *BBA - Protein Proteom* 1752: 166-176, 2005.
100. Donaldson SKB, Kerrick WGL. Characterization of the effects of Mg^{2+} on Ca^{2+} and Sr^{2+}-activated tension generation of skinned skeletal muscle fibers. *J Gen Physiol* 66: 427-444, 1975.
101. Dostal WF, Soderberg GL, Andrews JG. Actions of hip muscles. *Phys Ther* 66: 351-359, 1986.
102. Dulhunty AF. Excitation-contraction coupling from the 1950s into the new millennium. *Clin Exp Pharmacol Physiol* 33: 763-762, 2006.

103. Dupont Salter AC, Richmond FJ, Loeb GE. Prevention of muscle disuse atrophy by low-frequency electrical stimulation in rats. *IEEE Trans Neural Syst Rehabil Eng* 11: 218-226, 2003.
104. Ebashi S, Endo M. Calcium ion and muscle contraction. *Prog Biophys Mol Biol* 18: 123-183, 1968.
105. Edman KAP. Non-linear myofilament elasticity in frog intact muscle fibres. *J Exp Biol* 212: 1115-1119, 2009.
106. Edman KAP, Elzinga G, Noble MIM. Enhancement of mechanical performance by stretch during tetanic contractions of vertebrate skeletal muscle fibres. *J Physiol* 281: 139-155, 1978.
107. Elliott GF, Lowy J, Worthington CR. An X-ray and light-diffraction study of the filament lattice of striated muscle in the living state and in rigor. *J Mol Biol* 25: 295-305, 1963.
108. Endo M. Stretch-induced increase in activation of skinned muscle fibres by calcium. *Nature* 237: 211-213, 1972.
109. Endo M. Length dependence of activation of skinned muscle fibers by calcium. *Cold Spring Harb Symp Quant* 37: 505-510, 1973.
110. Ferrando AA, Stuart CA, Brunder DG, Hillman GR. Magnetic resonance imaging quantitation of changes in muscle volume during 7 days of strict bed rest. *Aviat Space Eviron Med* 66: 976-981, 1995.
111. Fill M, Copello JA. Ryanodine receptor calcium release channels. *Physiol Rev* 82: 893-922, 2002.
112. Flitney FW, Hirst DG. Cross-bridge detachment and sarcomere 'give' during stretch of active frog's muscle. *J Physiol* 276: 449-465, 1978.
113. Forbes RM, Cooper AR, Mitchell HH. The composition of the adult human body as determined by chemical analysis. *J Biol Chem* 203: 359-366, 1953.
114. Ford LE, Huxley AF, Simmons RM. Tension transients during steady shortening of frog muscle fibres. *J Physiol* 361: 131-150, 1985.
115. Fry AC, Schilling BK, Staron RS, Hagerman FC, Hikida RS, Thrush JT. Muscle fiber characteristics and performance correlates of male Olympic-style weightlifters. *J Strength Cond Res* 17: 746-754, 2003.
116. Fuller NJ, Hardingham CR, Graves M, Screaton N, Dixon AK, Ward LC, Elia M. Assessment of limb muscle and adipose tissue by dual-energy X-ray absorptiometry using magnetic resonance imaging for comparison. *Int J Obesity* 23: 1295-1302, 1999.
117. Fusi L, Reconditi M, Linari M, Brunello E, Elangovan R, Lombardi V, Piazzesi G. The mechanism of the resistance to stretch of isometrically contracting single muscle fibres. *J Physiol* 588: 495-510, 2010.
118. Gajdosik RL. Passive extensibility of skeletal muscle: Review of the literature with clinical implications. *Clin Biomech* 16: 87-101, 2001.
119. Gans C, Bock WJ. The functional significance of muscle architecture–a theoretical analysis. *Ergeb Anat Entwicklungsgesch* 38: 115-142, 1965.
120. Gans C, Gaunt AS. Muscle architecture in relation to function. *J Biomech* 24: 53-65, 1991.
121. Gao Y, Kostrominova TY, Faulkner JA, Wineman AS. Age-related changes in the mechanical properties of the epimysium in skeletal muscles of rats. *J Biomech* 41: 465-469, 2008.
122. Garcia-Pelagio KP, Bloch RJ, Ortega A, Gonzales-Serratos H. Biomechanics of the sarcolemma and costameres in single skeletal muscle fibers from normal and dystrophin-null mice. *J Muscle Res Cell Motil* 31: 323-336, 2011.
123. Garcia-Pelagio KP, Bloch RJ, Wimmer R, Gonzales-Serratos H. Mechanical properties of desmin in skinned fibers from normal and desmin-null mice. *Biophys J* 98: 406a-407a, 2010.
124. Gautel M, Djinović-Carugo K. The sarcomeric cytoskeleton: From molecules to motion. *J Exp Biol* 219: 135-145, 2016.
125. Geeves MA, Holmes KC. The molecular mechanism of muscle contraction. *Adv Protein Chem* 71: 161-193, 2005.
126. Ghez C, Krakauer J, Sainburg R, Ghilardi M. Spatial representations and internal models of limb dynamics in motor learning. *New Cogn Neurosci* 2: 501-514, 2000.
127. Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. *Muscle Nerve* 44: 318-331, 2011.
128. Godt RE, Maughan DW. Influence of osmotic compression on calcium activation and tension in skinned muscle fibers of the rabbit. *Pflugers Arch* 391: 334-337, 1981.
129. Goldspink G. Cytological basis of decrease in muscle strength during starvation. *Am J Physiol* 209: 100-104, 1965.
130. Goldspink G, Howells KF. Work-induced hypertrophy in exercised normal muscles of different ages and the reversibility of hypertrophy after cessation of exercise. *J Physiol* 239: 179-193, 1974.
131. Gordon AM, Homsher E, Regnier M. Regulation of contraction in striated muscle. *Physiol Rev* 80: 853-924, 2000.
132. Gordon AM, Huxley AF, Julian FJ. Tension development in highly stretched vertebrate muscle fibres. *J Physiol* 184: 143-169, 1966.
133. Gordon AM, Huxley AF, Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J Physiol* 184: 170-192, 1966.
134. Goto K, Okuyama R, Honda M, Uchida H, Akema T, Ohira Y, Yoshioka T. Profiles of connectin (titin) in atrophied soleus muscle induced by unloading of rats. *J Appl Physiol* 94: 897-902, 2003.
135. Gottlieb G, Agarwal G. Filtering of electromyographic signals. *Am J Phys Med Rehabil* 49: 142-146, 1970.
136. Gruther W, Benesch T, Zorn C, Paternostro-Slugo T, Quittan M, Fialka-Moser V, Spiss C, Kainberger F, Crevenna R. Muscle wasting in intensive care patients: Ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med* 40: 185-190, 2008.
137. Guth L, Samaha FJ. Qualitative differences between actomyosin ATPase of slow and fast mammalian muscle. *Exp Neurol* 25: 138-152, 1969.
138. Haines RW. The extensor apparatus of the finger. *J Anat* 85: 251-259, 1951.
139. Harada Y, Sakurada K, Aoki T, Thomas DD, Yanagida T. Mechanochemical coupling in actomyosin energy transduction studied by in vitro movement assay. *J Mol Biol* 216: 49-68, 1990.
140. Hartree W, Hill AV. The nature of the isometric twitch. *J Physiol* 55: 389-411, 1921.
141. Hatze H. Dynamics of the musculoskeletal system. *J Biomech* 18: 515-515, 1985.
142. Heckman CJ, Weytjens JL, Loeb GE. Effect of velocity and mechanical history on the forces of motor units in the cat medial gastrocnemius muscle. *J Neurophysiol* 68: 1503-1515, 1992.
143. Heiderscheit BC, Hoerth DM, Chumanov ES, Swanson SCT, Thelen BG, Thelen DG. Identifying the time of occurrence of a hamstring strain injury during treadmill running: A case study. *Clin Biomech* 20: 1072-1078, 2005.
144. Heilmann C, Muller W, Pette D. Correlation between ultrastructural and functional changes in sarcoplasmic reticulum during chronic stimulation of fast muscle. *J Membr Biol* 59: 143-149, 1981.
145. Heizmann CW, Berchtold MW, Rowlerson AM. Correlation of parvalbumin concentration with relaxation speed in mammalian muscles. *PNAS* 79: 7243-7247, 1982.
146. Helander I, Westerblad H, Katz A. Effects of glucose on contractile function, [Ca2+]i and glycogen in isolated mouse skeletal muscle. *Am J Physiol Cell Physiol* 282: C1306-C1312, 2002.
147. Heron MI, Richmond FJR. In-series fiber architecture in long human muscles. *J Morphol* 216: 35-45, 1993.
148. Higuchi H, Goldman YE. Sliding distance per ATP molecule hydrolysed by myosin heads during isotonic shortening of skinned muscle fibers. *Biophys J* 69: 1491-1507, 1995.
149. Higuchi H, Yanagida T, Goldman YE. Compliance of thin filaments in skinned fibers of rabbit skeletal muscle. *Biophys J* 69: 1000-1010, 1995.
150. Hilber K, Tefan Galler S. Improvement of the measurements on skinned muscle fibres by fixation of the fibre ends with glutaraldehyde. *J Muscle Res Cell Motil* 19: 365-372, 1998.
151. Hill AV. The heat of shortening and the dynamic constants of muscle. *Proc R Soc Lond* 126: 136-195, 1938.
152. Hill AV. The effect of load on the heat of shortening of muscle. *Proc R Soc B* 159: 297-318, 1964.
153. Hoffer JAC, Caputi AA, Pose IE, Griffiths RI. Roles of muscle activity and load on the relationship between muscle spindle length and whole muscle length in the freely walking cat. *Prog Brain Res* 80: 75-85, 1989.
154. Hollerbach MJ, Flash T. Dynamic interactions between limb segments during planar arm movement. *Biol Cybern* 44: 67-77, 1982.
155. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol* 56: 831-838, 1984.
156. Holtermann A, Roeleveld K, Mork PJ, Gronlund C, Karlsson JS, Andersen LL, Olsen HB, Zebis MK, Sjogaard G, Sogaard K. Selective activation of neuromuscular compartments within the human trapezius muscle. *J Electromyogr Kinesiol* 19: 896-902, 2009.
157. Horowits R, Kempner ES, Bisher ME, Podolsky RJ. The physiological role of titin and nebulin in striated muscle. *Nature* 323: 160-164, 1986.
158. Hortobagyi T, Dempsey L, Fraser D, Zheng D, Hamilton G, Lambert J, Dohm L. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. *J Physiol* 524: 293-304, 2000.
159. Huang HJ, Kram R, Ahmed AA. Reduction of metabolic cost during motor learning of arm reaching dynamics. *J Neurosci* 32: 2182-2190, 2012.
160. Hudlicka O, Tyler KR, Srihari T, Heilig A, Pette D. The effect of different patterns of long-term stimulation on contractile properties and myosin light chains in rabbit fast muscles. *Pflugers Arch* 393: 164-170, 1982.
161. Huxley HE. X-ray analysis and the problem of muscle. *Proc R Soc Lond (Biol)* 141: 59-62, 1953.
162. Huxley AF. Muscle structure and theories of contraction. *Prog Biophys Mol Biol* 7: 255-318, 1957.
163. Huxley HE, Brown W. The low angle X-ray diagram of vertebrate striated muscle and its behavior during contraction and rigor. *J Mol Biol* 30: 383-434, 1967.

164. Huxley AF, Simmons RM. Rapid 'give' and the tension 'shoulder' in the relaxation of frog muscle fibres. *J Physiol* 210: 32P-33P, 1970.
165. Huxley AF, Simmons RM. Proposed mechanism of force generation in striated muscle. *Nature Lond* 233: 533-538, 1971.
166. Huxley HE, Stewart A, Sosa H, Irving T. X-ray diffraction measurements of the extensibility of actin and myosin filaments in contracting muscle. *Biophys J* 67: 2411-2421, 1994.
167. Irving T, Wu Y, Bekyarova T, Farman GP, Fukuda N, Granzier H. Thick-filament strain and interfilament spacing in passive muscle: Effect of titin-based passive tension. *Biophys J* 100: 1499-1508, 2011.
168. Isambert H, Venier P, Maggs AC, Fattoum A, Kassab R, Pantolani D, Carlier MF. Flexibility of actin filaments derived from thermal fluctuations: Effect of bound nucleotide, phalloidin, and muscle regulatory proteins. *J Biol Chem* 270: 11437-11444, 1995.
169. Ishikawa M, Komi PV, Grey MJ, Lepola V, Bruggemann GP. Muscle-tendon interaction and elastic energy usage in human walking. *J Appl Physiol* 99: 603-608, 2005.
170. Jansson E, Kaijser L. Muscle adaptation to extreme endurance training in man. *Acta Physiol Scand* 100: 315-324, 1977.
171. Jenkyn TR, Koopman B, Huijing P, Lieber RL, Kaufman KR. Finite element model of intramuscular pressure during isometric contraction of skeletal muscle. *Phys Med Biol* 47: 4043-4061, 2002.
172. Jewell BR, Wilkie DR. The mechanical properties of relaxing muscle. *J Physiol* 152: 30-47, 1960.
173. Johnson MA, Polgar J, Weightman D, Appleton D. Data on the distribution of fibre types in thirty-six human muscles. An autopsy study. *J Neurol Sci* 18: 111-129, 1973.
174. Jones KE, Hamilton AF, Wolpert DM. Sources of signal-dependent noise during isometric force production. *J Neurophysiol* 88: 1533-1544, 2002.
175. Joyce GC, Rack PMH. Isotonic lengthening and shortening movements of cat soleus muscle. *J Physiol* 204: 475-491, 1969.
176. Joyce GC, Rack PMH, Westbury DR. The mechanical properties of cat soleus muscle during controlled lengthening and shortening movements. *J Physiol* 204: 461-474, 1969.
177. Julian FJ, Sollins MR. Variation of muscle stiffness with force at increasing speeds of shortening. *J Gen Physiol* 66: 287-302, 1975.
178. Kamibayashi LK, Richmond FJR. Morphometry of human neck muscles. *Spine* 23: 1314-1323, 1998.
179. Karatzaferi C, Franks-Skiba K, Cooke R. Inhibition of shortening velocity of skinned skeletal muscle fibers in conditions that mimic fatigue. *Am J Physiol Regul Integr Comp Physiol* 294: R948-R955, 2008.
180. Kargacin ME, Kargacin GJ. Predicted changes in concentrations of free and bound ATP and ADP during intracellular Ca^{2+} signaling. *Am J Physiol* 273: C1416-C1426, 1997.
181. Katz B. The relation between force and speed in muscular contraction. *J Physiol* 96: 45-64, 1939.
182. Kaya M, Higuchi H. Nonlinear elasticity and an 8-nm working stroke of single myosin molecules in myofilaments. *Science* 329: 686-689, 2010.
183. Kemp GJ, Taylor DJ, Styles P, Radda GK. The production, buffering and efflux of protons in human skeletal muscle during exercise and recovery. *NMR Biomed* 6: 73-83, 1993.
184. Kitamura K, Tokunaga M, Iwane AH, Yanagida T. A single myosin head moves along an actin element with regular steps of 5.3 nanometres. *Nature* 397: 129-134, 1999.
185. Klug G, Wiehrer W, Reichmann H, Leberer E, Pette D. Relationships between early alterations in parvalbumins, sarcoplasmic reticulum and metabolic enzymes in chronically stimulated fast twitch muscle. *Plfugers Arch* 399: 280-284, 1983.
186. Knuth ST, Dave H, Peters JR, Fitts RH. Low cell pH depresses peak power in rat skeletal muscle fibres at both 30C and 15C: Implications for muscle fatigue. *J Physiol* 575: 887-899, 2006.
187. Kojima H, Ishihima A, Yanagida T. Direct measurement of stiffness of single actin filaments with and without tropomyosin by in vitro nanomanipulandum. *PNAS* 91: 12962-12966, 1994.
188. Kraemer WJ, Patton JF, Gordon SE, Harman EA, Deschenes MR, Reynolds K, Newton RU, Triplett NT, Dziados JE. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J Appl Physiol* 78: 976-989, 1995.
189. Kronberg M, Nemeth G, Brostrom LA. Muscle activity and coordination in the normal shoulder. An electromyographic study. *Clin Orthop Relat Res* 257: 76-85, 1990.
190. Kubo K, Ikebukuro T, Maki A, Yata H, Tsunoda N. Time course of changes in the human Achilles tendon properties and metabolism during training and detraining in vivo. *Eur J Appl Physiol* 112: 2679-2691, 2012.
191. Kubo K, Ikebukuro T, Yata H, Tsunoda N, Kanehisa H. Time course of changes in muscle and tendon properties during strength training and detraining. *J Strength Cond Res* 24: 322-331, 2010.
192. Kurtzer IL, Pruszynski JA, Scott SH. Long-latency reflexes of the human arm reflect an internal model of limb dynamics. *Curr Biol* 18: 449-453, 2008.
193. Kushmerick MJ. From crossbridges to metabolism: System biology for energetics. *Adv Exp Med Biol* 565: 171-180, 2005.
194. Lackner JR, DiZio P. Rapid adaptation to Coriolis foce perturbations of arm trajectory. *J Neurophysiol* 72: 299-313, 1994.
195. Lamb GD. DHP receptors and excitation-contraction coupling. *J Muscle Res Cell Motil* 13: 394-405, 1992.
196. Lamb GD. Excitation–contraction coupling and fatigue mechanisms in skeletal muscle: Studies with mechanically skinned fibres. *J Muscle Res Cell Motil* 23: 81-91, 2002.
197. Lannergren J, Westerblad H. The temperature dependence of isometric contractions of single, intact fibres dissected from a mouse foot muscle. *J Physiol* 390: 285-293, 1987.
198. Lanza IR, Wigmore DM, Befroy DE, Kent-Braun JA. In vivo ATP production during free-flow and ischaemic muscle contractions in humans. *J Physiol* 577: 353-367, 2006.
199. Lazarides E. Intermediate filaments as mechanical integrators of cellular space. *Nature* 283: 249-256, 1980.
200. Leijendekker WJ, Elzinga G. Metabolic recovery of mouse extensor digitorum longus and soleus muscle. *Pflugers Arch* 416: 22-27, 1990.
201. Licup AJ, Munster S, Sharma A, Sheinman M, Jawerth LM, Fabry B, Weitz DA, MacKintosh FC. Stress controls the mechanics of collagen networks. *PNAS* 112: 9573-9578, 2015.
202. Lieber RL, Friden J. Muscle damage is not a function of muscle force but active muscle strain. *J Appl Physiol* 74: 520-526, 1993.
203. Lieber RL, Woodburn TM, Friden J. Muscle damage induced by eccentric contractions of 25% strain. *J Appl Physiol* 70: 2498-2507, 1991.
204. Linari M, Dobbie I, Reconditi M, Koubassova N, Irving M, Piazzesi G, Lombardi V. The stiffness of skeletal muscle in isometric contraction and rigor: The fraction of myosin heads bound to actin. *Biophys J* 74: 2459-2473, 1998.
205. Loeb GE. Motoneuron task groups—coping with kinematic heterogeneity. *J Exp Biol* 115: 137-146, 1985.
206. Loeb GE, Brown IE, Cheng EJ. A hierarchical foundation for models of sensorimotor control. *ExpBrain Res* 126: 1-18, 1999.
207. Loeb GE, Gans C. *Electromyography for Experimentalists*. Chicago: University of Chicago Press, 1986.
208. Loeb GE, Pratt CA, Chanaud CM, Richmond FJR. Distribution and innervation of short, interdigitated muscle fibers in parallel-fibered muscles of the cat hindlimb. *J Morphol* 191: 1-15, 1987.
209. Loeb GE, Tsianos GA. Major remaining gaps in models of sensorimotor systems. *Front Comput Neurosci* 9: 70, 2015.
210. Lucas SM, Ruff RL, Binder MD. Specific tension measurements in single soleus and medial gastrocnemius muscle fibres of the cat. *Exp Neurol* 95: 142-154, 1987.
211. Lynch GS, Rafael JA, Chamberlain JS, Faulkner JA. Contraction-induced injury to single permeabilized muscle fibers from mdx, transgenic mdx, and control mice. *Am J Physiol Cell Physiol* 279: C1290-C1294, 2000.
212. Lytton J, Westlin M, Burk SE, Shull GE, MacLennan DH. Functional comparisons between isoforms of the sarcoplasmic or endoplasmic reticulum family of calcium pumps. *J Biol Chem* 267: 14483-14489, 1992.
213. Ma S, Zahalak GI. A distribution-moment model of energetics in skeletal muscle. *J Biomech* 24: 21-35, 1991.
214. MacDougall JD, Elder GC, Sale DG, Moroz JR, Sutton JR. Effects of strength training and immobilization on human muscle fibres. *Eur J Appl Physiol Occup Physiol* 43: 25-34, 1980.
215. Magid A, Law DJ. Myofibrils bear most of the resting tension in frog skeletal muscle. *Science* 230: 1280-1282, 1985.
216. Magnusson SP, Aagaard P, Rosager S, Dyhre-Poulsen P, Kjaer M. Load-displacement properties of the human triceps surae aponeurosis in vivo. *J Physiol* 531: 277-288, 2001.
217. Malamud JG, Godt RE, Nichols TR. Relationship between short-range stiffness and yielding in type-identified, chemically skinned muscle fibers from the cat triceps surae muscles. *J Neurophysiol* 76: 2280-2289, 1996.
218. Martyn DA, Gordon AM. Length and myofilament spacing dependent changes in calcium sensitivity of skeletal fibres: Effects of pH and ionic strength. *J Muscle Res Cell Motil* 9: 428-445, 1988.
219. Matsubara I, Elliott GF. X-ray diffraction studies on skinned single fibres of frog skeletal muscle. *J Mol Biol* 72: 657-669, 1972.
220. Matsumoto F, Trudel G, Uhthoff HK, Backman DS. Mechanical effects of immobilization on the Achilles' tendon. *Arch Phys Med Rehabil* 84: 662-667, 2003.
221. McCall GE, Byrnes WC, Dickinson A, Pattany PM, Fleck SJ. Muscle fiber hypertrophy, hyperplasia, and capillary density in college men after resistance training. *J Appl Physiol* 81: 2004-2012, 1996.
222. McDonald KS, Wolff MR, Moss RL. Sarcomere length dependence of the rate of tension redevelopment and submaximal tension in rat and rabbit skinned skeletal muscle fibres. *J Physiol* 501: 607-621, 1997.

223. McGill SM. A myoelectrically based dynamic three-dimensional model to predict loads on lumbar spine tissues during lateral bending. *J Biomech* 25: 395-414, 1992.
224. Melzer W, Herrmann-Frank A, Luttgau HC. The role of Ca^{2+} ions in excitation-contraction coupling of skeletal muscle fibres. *Biochim Biophys Acta* 1241: 59-116, 1995.
225. Metzger JM, Moss RL. Greater hydrogen ion-induced depression of tension and velocity in skinned single fibres of rat fast than slow muscles. *J Physiol* 393: 727-742, 1987.
226. Metzger JM, Moss RL. Calcium-sensitive cross-bridge transitions in mammalian fast and slow skeletal muscle fibers. *Science* 247: 1088-1090, 1990.
227. Mizuno M, Secher NH, Quistorff B. ^{31}P-NMR spectroscopy, rsEMG, and histochemical fiber types of human wrist flexor muscles. *J Appl Physiol* 76: 531-538, 1994.
228. Moisescu DG, Thieleczek R. Sarcomere length effects on the Sr^{2+} and Ca^{2+} activation curves in skinned frog muscle fibres. *Biochim Biophys Acta* 546: 64-76, 1979.
229. Morgan DL. New insights into the behavior of muscle during active lengthening. *Biophys J* 57: 209-221, 1990.
230. Morgan DL, Proske U. Sarcomere popping requires stretch over a range where total tension decreases with length. *J Physiol* 574: 627-628, 2006.
231. Moss RL, Swinford A, Greaser ML. Alterations in the Ca^{2+} sensitivity of tension development by single skeletal muscle fibers at stretched lengths. *Biophys J* 43: 115-119, 1983.
232. Mulligan IP, Palmer RE, Lipscomb S, Hoskins BK, Ashley CC. The effect of phosphate on the relaxation of frog skeletal muscle. *Pflugers Arch* 437: 393-399, 1999.
233. Murphy RA, Beardsley AC. Mechanical properties of the cat soleus muscle in situ. *Am J Physiol* 227: 1008-1013, 1974.
234. Murray WM, Delp SL, Buchanan TS. Variation of muscle moment arms with elbow and forearm position. *J Biomech* 28: 513-525, 1995.
235. Narici MV, Roi GS, Landoni LM, Minetti AE, Cerretelli P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *Eur J Appl Physiol Occup Physiol* 59: 310-319, 1989.
236. Nelson AG, Arnall DA, Loy SF, Silvester LJ, Conlee RK. Consequences of combining strength and endurance training regimens. *Phys Ther* 70: 287-294, 1990.
237. Nelson CR, Debold EP, Fitts RH. Phosphate and acidosis act synergistically to depress peak power in rat muscle fibers. *Am J Physiol Cell Physiol* 307: C935-C950, 2014.
238. Nelson CR, Fitts RH. Effects of low cell pH and elevated inorganic phosphate on the pCa-force relationship in single muscle fibers at near-physiological temperatures. *Am J Physiol Cell Physiol* 306: C670-C678, 2014.
239. Nichols TR, Houk JC. Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. *J Neurophysiol* 39: 119-142, 1976.
240. Nocella M, Bagni MA, Cecchi G, Colombini B. Mechanism of force enhancement during stretching of skeletal muscle fibres investigated by high time-resolved stiffness measurements. *J Muscle Res Cell Motil* 34: 71-81, 2013.
241. Offer G, Ranatunga KW. Crossbridge and filament compliance in muscle: Implications for tension generation and lever arm swing. *J Muscle Res Cell Motil* 31: 245-265, 2013.
242. Otten E. Concepts and models of functional architecture in skeletal muscle. *Exerc Sport Sci Rev* 16: 89-137, 1988.
243. Pai DK. Muscle mass in musculoskeletal models. *J Biomech* 43: 2093-2098, 2010.
244. Pandy MG, Zajac FE, Sim E, Levine WS. An optimal control model for maximum-height human jumping. *J Biomech* 23: 1185-1198, 1990.
245. Partridge LD. The good enough calculi of evolving control systems: Evolution is not engineering. *Am J Physiol* 242: R173-R177, 1982.
246. Partridge L, Benton L. Muscle, the motor. *Compr Physiol* 1981.
247. Patel TJ, Das R, Friden J, Lutz GJ, Lieber RL. Sarcomere strain and heterogeneity correlate with injury to frog skeletal muscle fiber bundles. *J Appl Physiol* 97: 1803-1813, 2004.
248. Peter AK, Cheng H, Ross RS, Knowlton KU, Chen J. The costamere bridges sarcomeres to the sarcolemma in striated muscle. *Prog Pediatr Cardiol* 31: 83-88, 2011.
249. Petrof BJ, Shrager JB, Stedman HH, Kelly AM, Sweeney HL. Dystrophin protects the sarcolemma from stresses developed during muscle contraction. *Proc Natl Acad Sci U S A* 90: 3710-3714, 1993.
250. Pette D, Muller W, Leisner E, Vrbova G. Time dependent effects on contractile properties, fibre population, myosin light chains and enzymes of energy metabolism in intermittently and continuously stimulated fast twitch muscles of the rabbit. *Pflugers Arch* 364: 103-112, 1976.
251. Piazzesi G, Francini F, Linari M, Lombardi V. Tension transients during steady lengthening of tetanized muscle fibres of the frog. *J Physiol* 445: 659-711, 1992.
252. Pigeon P, Bortolami SB, DiZio P, Lackner JR. Coordinated turn-and-reach movements. I. Anticipatory compensation for self-generated coriolis and interaction torques. *J Neurophysiol* 89: 276-289, 2003.
253. Pratt CA, Chanaud CM, Loeb GE. Functionally complex muscles of the cat hindlimb. IV. Intramuscular distribution of movement command signals and cutaneous reflexes in broad, bifunctional thigh muscles. *ExpBrain Res* 85: 281-299, 1991.
254. Pratt CA, Loeb GE. Functionally complex muscles of the cat hindlimb. I. Patterns of activation across sartorius. *Exp Brain Res* 85: 243-256, 1991.
255. Purslow PP. Strain-induced reorientation of an intramuscular connective tissue network: Implications for passive muscle elasticity. *J Biomech* 22: 221-312, 1989.
256. Purslow PP, Trotter JA. The morphology and mechanical properties of endomysium in series-fibred muscles: Variations with muscle length. *J Muscle Res Cell Motil* 15: 299-308, 1994.
257. Putnam CA. A segment interaction analysis of proximal-to-distal sequential segment motion patterns. *Med Sci Sports Exerc* 23: 130-144, 1991.
258. Putnam CA. Sequential motions of body segments in striking and throwing skills: Descriptions and explanations. *J Biomech* 26: 125-135, 1993.
259. Rack PMH, Westbury DR. The effects of length and stimulus rate on tension in the isometric cat soleus muscle. *J Physiol* 204: 443-460, 1969.
260. Ranatunga KW. Temperature-dependence of shortening velocity and rate of isometric tension development in rat skeletal muscle. *J Physiol* 329: 465-483, 1982.
261. Ranatunga KW. The force–velocity relation of rat fast and slow-twitch muscles examined at different temperatures. *J Physiol* 351: 517-529, 1984.
262. Regnier M, Rivera AJ, Wang C, Bates MA, Chase PB, Gordon AM. Thin filament near-neighbour regulatory unit interactions affect rabbit skeletal muscle steady-state force-Ca^{2+} relations. *J Physiol* 540: 485-497, 2002.
263. Renaud JM, Stevens ED. Effect of acclimation temperature and pH on contraction of frog sartorius muscle. *Am J PHysiol Regul Integr Comp Physiol* 240: R301-R309, 1981.
264. Richmond FJR, Singh K, Corneil BD. Neck muscles in the rhesus monkey. I. Muscle morphometry and histochemistry. *J Neurophysiol* 86: 1717-1728, 2001.
265. Rigby BJ, Hirai N, Spikes JD, Eyring H. The mechanical properties of rat tail tendon. *J Gen Physiol* 43: 265-283, 1959.
266. Rome E. X-ray diffraction studies on the filament lattice of striated muscle in various bathing media. *J Mol Biol* 37: 331-344, 1968.
267. Roszek B, Baan GC, Huijing PA. Decreasing stimulation frequency-dependent length-force characteristics of rat muscle. *J Appl Physiol* 77: 2115-2124, 1994.
268. Rowe RWD. Collagen fibre arrangement in intramuscular connective tissue. Changes associated with muscle shortening and their possible relevance to raw meat toughness measurements. *J Food Technol* 9: 501-508, 1974.
269. Rubin DA. Imaging diagnosis and prognostication of hamstring injuries. *AJR Am J Roentgenol* 199: 525-533, 2012.
270. Sallay PI, Friedman RL, Coogan PG, Garrett WE. Hamstring muscle injuries among water skiers: Functional outcome and prevention. *Am J Sports Med* 24: 130-136, 1996.
271. Sandercock TG, Maas H. Force summation between muscles: Are muscles independent actuators? *Med Sci Sports Exerc* 41: 184-190, 2009.
272. Sandiford SD, Green HJ, Duhamel TA, Schertzer JD, Perco JD, Ouyang J. Muscle Na-K-pump and fatigue responses to progressive exercise in normoxia and hypoxia. *Am J Physiol Regul Integr Comp Physiol* 289: R441-R449, 2005.
273. Schenau GJVI. From rotation to translation: Constraints on multi-joint movements and the unique action of bi-articular muscles. *Hum Movement Sci* 8: 301-337, 1989.
274. Schieber MH, Chua M, Petit J, Hunt CC. Tension distribution of single motor units in multitendoned muscles: Comparison of a homologous digit muscle in cats and monkeys. *J Neurosci (New York)* 17: 1734-1747, 1997.
275. Schieber MH, Santello M. Hand function: Peripheral and central constraints on performance. *J Appl Physiol* 96: 2293-2300, 2004.
276. Schwartz DG, Kang SH, Lynch TS, Edwards S, Nuber G, Zhang L-Q, Saltzman M. The anterior deltoid's importance in reverse shoulder arthroplasty: A cadaveric biomechanical study. *J Shoulder Elbow Surg* 22: 357-364, 2013.
277. Scott SH, Brown IE, Loeb GE. Mechanics of feline soleus: I. Effect of fascicle length and velocity on force output. *J Muscle Res Cell Motil* 17: 205-218, 1996.
278. Scott SH, Loeb GE. The computation of position sense from spindles in mono-and multiarticular muscles. *JNeurosci* 14: 7529-7540, 1994.

279. Scott SH, Loeb GE. Mechanical properties of aponeurosis and tendon of the cat soleus muscle during whole-muscle isometric contractions. *J Morphol* 224: 73-86, 1995.
280. Scott SH, Thomson DB, Richmond FJ, Loeb GE. Neuromuscular organization of feline anterior sartorius: II. Intramuscular length changes and complex length-tension relationships during stimulation of individual nerve branches. *J Morphol* 213: 171-183, 1992.
281. Scott SH, Winter DA. A comparison of three muscle pennation assumptions and their effect on isometric and isotonic force. *J Biomech* 24: 163-167, 1991.
282. Segal SS, Faulkner JA. Temperature-dependent physiological stability of rat skeletal muscle in vitro. *Am J Physiol Cell Physiol* 248: C265-C270, 1985.
283. Semmler JG, Kornatz KW, Dinenno DV, Zhou S, Enoka RM. Motor unit synchronisation is enhanced during slow lengthening contractions of a hand muscle. *J Physiol* 545: 681-695, 2002.
284. Serlin DM, Schieber MH. Morphologic regions of the multitendoned extrinsic finger muscles in the monkey forearm. *Cells Tissues Organs* 146: 255-266, 1993.
285. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J Appl Physiol* 102: 368-373, 2007.
286. Shah SB, Davis J, Weisleder N, Kostavassili I, McCulloch AD, Ralston E, Capetanaki Y, Lieber RL. Structural and functional roles of desmin in mouse skeletal muscle during passive deformation. *Biophys J* 86: 2993-2008, 2004.
287. Shah SB, Love JM, O'neill A, Lovering RM, Bloch RJ. Influences of desmin and keratin 19 on passive biomechanical properties of mouse skeletal muscle. *J Biomed Biotechnol* 2012: 704061, 2012.
288. Shue G, Crago PE. Muscle–tendon model with length history-dependent activation–velocity coupling. *Ann Biomed Eng* 26: 369-380, 1998.
289. Shue G, Crago PE, Chizeck HJ. Muscle-joint models incorporating activation dynamics, moment-angle, and moment-velocity properties. *IEEE Trans Biomed Eng* 42: 212-223, 1995.
290. Shushakov V, Stubbe C, Peuckert A, Endeward V, Maassen N. The relationships between plasma potassium, muscle excitability and fatigue during voluntary exercise in humans. *Exp Physiol* 92: 705-715, 2007.
291. Sica REP, McComas AJ. Fast and slow twitch units in a human muscle. *J Neurol Neurosurg Psychiatry* 34: 113-120, 1971.
292. Soderlund K, Greenhaff PL, Hultman E. Energy metabolism in type I and type II human muscle fibres during short term electrical stimulation at different frequencies. *Acta Physiol Scand* 144: 15-22, 1992.
293. Stephenson DG, Wendt IR. Length dependence of changes in sarcoplasmic calcium concentration and myofibrillar calcium sensitivity in striated muscle fibres. *J Muscle Res Cell Motil* 5: 243-272, 1984.
294. Stephenson DG, Williams DA. Effects of sarcomere length on the force-pCa relation in fast- and slow-twitch skinned muscle fibres from the rat. *J Physiol* 333: 637-653, 1982.
295. Stephenson DG, Williams DA. Temperature-dependent calcium sensitivity changes in skinned muscle fibres of rat and toad. *J Physiol* 360: 1-12, 1985.
296. Sutarno CG, McGill SM. Isovelocity investigation of the lengthening behaviour of the erector spinae muscles. *Eur J Appl Physiol* 70: 146-153, 1995.
297. Tabary JC, Tabary C, Tardieu C, Tardieu G, Goldsprink G. Physiological and structural changes in the cat's soleus muscle due to immobilization at different lengths by plaster casts. *J Physiol* 224: 231-244, 1972.
298. Takahashi M, Ward SR, Friden J, Lieber RL. Muscle excursion does not correlate with increased serial sarcomere number after muscle adaptation to stretched tendon transfer. *J Orthop Res* 30: 1774-1780, 2012.
299. Thelen DG. Adjustment of muscle mechanics model parameters to simulate dynamic contractions in older adults. *J Biomech Eng-Trans Asme* 125: 70-77, 2003.
300. Thelen DG, Chumanov ES, Sherry MA, Heiderscheit BC. Neuromusculoskeletal models provide insights into the mechanisms and rehabilitation of hamstring strains. *Exerc Sport Sci Rev* 34: 135-141, 2006.
301. Thorsson O, Lilja B, Nilsson P, Westlin N. Immediate external compression in the management of an acute muscle injury. *Scand J Med Sci Sport* 7: 182-190, 1997.
302. Tirrell TF, Cook MS, Carr JA, Lin E, Ward SR, Lieber RL. Human skeletal muscle biochemical diversity. *J Exp Biol* 215: 2551-2559, 2012.
303. Tomanek RJ, Lund DD. Degeneration of different types of skeletal muscle fibres II. Immobilization. *J Anat* 118: 531-541, 1974.
304. Trotter JA. Functional morphology of force transmission in skeletal muscle. *Acta Anatomica* 146: 205-222, 1993.
305. Trotter JA, Purslow PP. Functional morphology of the endomysium in series fibered muscles. *J Morphol* 212: 109-122, 1992.
306. Trotter JA, Richmond FJR, Purslow PP. Functional morphology and motor control of series-fibered muscles. *Exerc Sport Sci Rev* 23: 167-213, 1995.
307. Tsianos GA, Goodner J, Loeb GE. Useful properties of spinal circuits for learning and performing planar reaches. *J Neural Eng* 11: 056006, 2014.
308. Tsianos GA, Loeb GE. Muscle physiology and modeling. *Scholarpedia* 8: 12388, 2013.
309. Tsianos GA, MacFadden LN. Validated predictions of metabolic energy consumption for submaximal effort movement. *PLoS Comput Biol* 12: e1004911, 2015.
310. Tsianos GA, Rustin C, Loeb GE. Mammalian muscle model for predicting force and energetics during physiological behaviors. *IEEE Trans Neural Syst Rehabil Eng* 20: 117-133, 2012.
311. van Ingen Schenau GJ, Boots PJM, De Groot G, Snackers RJ, van Woensel WWLM. The constrained control of force and position in multi-joint movements. *Neuroscience* 46: 197-207, 1992.
312. van Zandwijk JP, Bobbert MF, Harlaar J, Hof AL. From twitch to tetanus for human muscle: Experimental data and model predictions for m-triceps surae. *Biol Cybern* 79: 121-130, 1998.
313. Vasavada AN, Li S, Delp SL. Influence of muscle morphometry and moment arms on the moment-generating capacity of human neck muscles. *Spine* 23: 412-422, 1998.
314. Vaz MA, Freitas CR, Leonard T, Herzog W. The force-length relationship of the cat soleus muscle. *Muscles Ligaments Tendons J* 2: 79-84, 2012.
315. Wakabayashi K, Sugimoto Y, Tanaka H, Ueno Y, Takezawa Y, Amemiya Y. X-ray diffraction evidence for the extensibility of actin and myosin filaments during muscle contraction. *Biophys J* 67: 2422-2435, 1994.
316. Wang K, McCarter R, Wright J, Beverly J, Ramirez-Mitchell R. Viscoelasticity of the sarcomere matrix of skeletal muscles. The titin-myosin composite filament is a dual-stage molecular spring. *Biophys J* 64: 1161-1177, 1993.
317. Wang K, Ramirez-Mitchell R. A network of transverse and longitudinal intermediate filaments is associated with sarcomeres of adult vertebrate skeletal muscle. *J Cell Biol* 96: 562-570, 1983.
318. Warren GL, Hayes DA, Lowe DA, Armstrong RB. Mechanical factors in the initiation of eccentric contraction-induced injury in rat soleus muscle. *J Physiol* 464: 457-475, 1993.
319. Warren GL, Lowe DA, Armstrong RB. Measurement tools used in the study of eccentric contraction-induced injury. *Sports Med* 27: 43-59, 1999.
320. West W, Hicks A, Mckelvie R, O'Brien J. The relationship between plasma potassium, muscle membrane excitability and force following quadriceps fatigue. *Pflugers Arch* 432: 43-49, 1996.
321. Westerblad H, Allen DG, Lannergren J. Muscle fatigue: Lactic acid or inorganic phosphate the major cause? *News Physiol Sci* 17: 17-21, 2002.
322. Westerblad H, Bruton JD, Katz A. Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability. *Exp Cell Res*: 3093-3099, 2010.
323. Westerblad H, Duty S, Allen DG. Intracellular calcium concentration during low-frequency fatigue in isolated single fibers of mouse skeletal muscle. *J Appl Physiol* 75: 382-388, 1993.
324. Westerblad H, Lannergren J. Slowing of relaxation during fatigue in single mouse fibres. *J Physiol* 434: 323-336, 1991.
325. Westerblad H, Lannergren J, Allen DG. Slowed relaxation in fatigued skeletal muscle fibers of Xenopus and mouse contribution of [Ca2+]i and cross-bridges. *J Gen Physiol* 109: 385-399, 1997.
326. Willerslev-Olsen M, Lorentzen J, Sinkjær T, Nielsen JB. Passive muscle properties are altered in children with cerebral palsy before the age of 3 years and are difficult to distinguish clinically from spasticity. *Dev Med Child Neurol* 55: 617-623, 2013.
327. Williams PE. Use of intermittent stretch in the prevention of serial sarcomere loss in immobilised muscle. *Ann Rheum Dis* 49: 316-317, 1990.
328. Williams PE, Goldspink G. Longitudinal growth of striated muscle fibres. *J Cell Science* 9: 751-767, 1971.
329. Williams PE, Goldspink G. Changes in sarcomere length and physiological properties in immobilised muscle. *J Anat* 127: 459-468, 1978.
330. Williams PE, Goldspink G. Connective tissue changes in immobilized muscle. *J Anat (London)* 138: 342-350, 1984.
331. Winter DA. *Biomechanics and Motor Control of Human Movement*. New York, NY: Wiley, 2004.
332. Witzmann FA, Kim DH, Fitts RH. Recovery time course in contractile function of fast and slow skeletal muscle after hindlimb immobilization. *J Appl Physiol* 52: 677-682, 1982.
333. Woittiez RD, Huijing PA, Rozendal RH. Twitch characteristics in relation to muscle architecture and actual muscle length. *Pflugers Arch* 401: 374-379, 1984.
334. Wood DG, Packham I, Trikha SP, Linklater J. Avulsion of the proximal hamstring origin. *J Bone Joint Surg Am* 90: 2365-2374, 2008.

335. Yanagida T, Arata T, Oosawa F. Sliding distance of actin filament induced by a myosin crossbridge during one ATP hydrolysis cycle. *Nature* 316: 366-369, 1985.
336. Young RP, Scott SH, Loeb GE. The distal hindlimb musculature of the cat: Multiaxis moment arms at the ankle joint. *ExpBrain Res* 96: 141-151, 1993.
337. Yucesoy CA, Koopman BH, Baan GC, Grootenboer HJ, Huijing PA. Effects of inter-and extramuscular myofascial force transmission on adjacent synergistic muscles: Assessment by experiments and finite-element modeling. *J Biomech* 36: 1797-1811, 2003.
338. Zahalak GI. A distribution-moment approximation for kinetic theories of muscular contraction. *Math Biosci* 55: 89-114, 1981.
339. Zajac FE. Muscle and tendon: Properties, models, scaling and application to biomechanics and motor control. *Crit Rev Biomed Eng* 17: 359-411, 1989.
340. Zajac FE. Understanding muscle coordination of the human leg with dynamical simulations. *J Biomech* 35: 1011-1018, 2002.
341. Zajac FE, Gordon ME. Determining muscle's force and action in multi-articular movement. *Exerc Sport Sci Rev* 17: 187-230, 1989.
342. Zajac FE, Wicke RW, Levine WS. Dependence of jumping performance on muscle properties when humans use only calf muscles for propulsion. *J Biomech* 17: 513-523, 1984.
343. Zajac FE, Winters JM. Modeling musculoskeletal movement systems: Joint and body segmental dynamics, musculoskeletal actuation, and neuromuscular control. In: Winters JM, Woo SL, editors. *Multiple Muscle Systems*. Springer Verlag, 1990, pp. 121-148.
344. Zajac FE, Zomlefer MR, Levine WS. Hindlimb muscular activity, kinetics and kinematics of cats jumping to their maximum achievable heights. *J Exp Biol* 91: 73-86, 1981.