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Skeletal Muscle is a Biological Example of a Linear Electro-Active Actuator

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ABSTRACT

Skeletal muscle represents a classic biological example of a structure-function relationship. This paper reviews basic muscle anatomy and demonstrates how molecular motion on the order of nm distances is converted into the macroscopic movements that are possible with skeletal muscle. Muscle anatomy provides a structural basis for understanding the basic mechanical properties of skeletal muscle—namely, the length-tension relationship and the force-velocity relationships. The length-tension relationship illustrates that muscle force generation is extremely length dependent due to the interdigitation of the contractile filaments. The force-velocity relationship is characterized by a rapid force drop in muscle with increasing shortening velocity and a rapid rise in force when muscles are forced to lengthen. Finally, muscle architecture—the number and arrangement of muscle fibers—has a profound effect on the magnitude of muscle force generated and the magnitude of muscle excursion. These concepts demonstrate the elegant manner in which muscle acts as a biologically regenerating linear motor. These concepts can be used in developing artificial muscles as well as in performing surgical reconstructive procedures with various donor muscles.

1. INTRODUCTION

Skeletal muscle's anatomical and biomechanical properties have been widely studied since the 1600s[1]. Since the primary purpose of skeletal muscle is to generate force and movement and since this function is substituted for by motors, machines and materials, it is first important to understand the mechanical basis of muscle function.

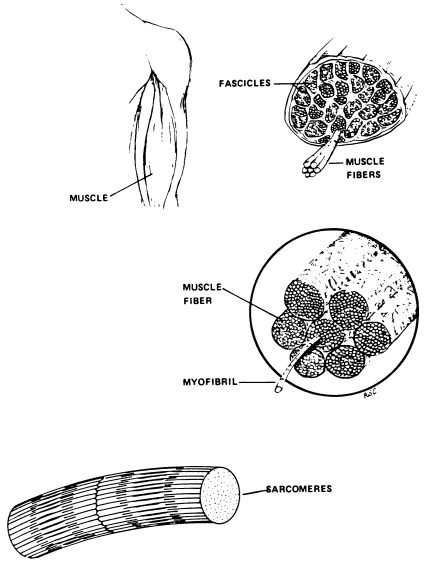


Figure 1: Structural hierarchy of skeletal muscle from muscle to myofibrils.

The largest functional unit of contractile filaments is the myofibril (literally, "muscle thread"). Myofibrils are simply a string of sarcomeres arranged in series. Myofibrillar diameter is about 1 μm, which means that thousands of myofibrils can be packed into a single muscle fiber. Myofibrils are arranged in parallel (side by side) to make up the muscle fiber. Groups of muscle fibers are surrounded by a connective tissue sheath known as perimysium (literally, "around muscle") and arranged in bundles called fascicles. These fascicles are also bundled together, surrounded by more connective tissue (epimysium, literally, "on top of muscle") to form the whole muscle, which we can inspect visually. Myofibrils are subdivided into their component units known as sarcomeres (Figure 1), the functional unit of muscle contraction. A myofibril is therefore a number of sarcomeres (literally, "muscle segment") arranged in series. The total number of sarcomeres within a fiber depends on the muscle fiber length and diameter. Because of the series arrangement of sarcomeres within a myofibril, the total distance of myofibrillar shortening is equal to the sum of the individual shortening distances of the individual sarcomeres. This is why a whole muscle may shorten several centimeters even though each sarcomere can only shorten about 1 μm. It should also be stated that the number of sarcomeres in a mature muscle can change given the appropriate stimulus. This gives skeletal muscle a tremendous ability to adapt.

Ideally, muscle contraction would be studied during normal movement--that is, under conditions of physiological activation, experiencing physiological loads, and contracting at physiological velocities. Clearly, this is technically not possible in humans. Thus, descriptions of muscle biomechanical properties have relied on experimental studies in model systems where muscle is highly accessible (*i.e.* animal model systems) and where the mechanical environment is highly controlled (*i.e.* length or velocity is held constant). In this paper, we will review the basic structure and mechanical properties of skeletal muscle in order to provide a reasonable comparison to materials and machines designed to mimic muscle function.

2. SKELETAL MUSCLE ANATOMY

Perhaps the most distinctive feature of the muscle cell is the ordered array of contractile filaments that are arranged throughout the cell (Figure 1). Sarcomeres are composed of contractile filaments termed "myofilaments." Two major sets of contractile filaments exist in the sarcomere: One set is relatively thick, and the other set is relatively thin (Figure 2). These thick and thin filaments represent large polymers of the proteins myosin and actin, respectively. It is the active interdigitation of these microscopic filaments that produces muscle shortening. It is also this interdigitated pattern that gives the muscle its striated or striped appearance that is observable microscopically (Figure 3) either at the light or electron microscopic level. Figure 3 represents a longitudinal electron micrograph in which the muscle was cut parallel to the force-generating axis.

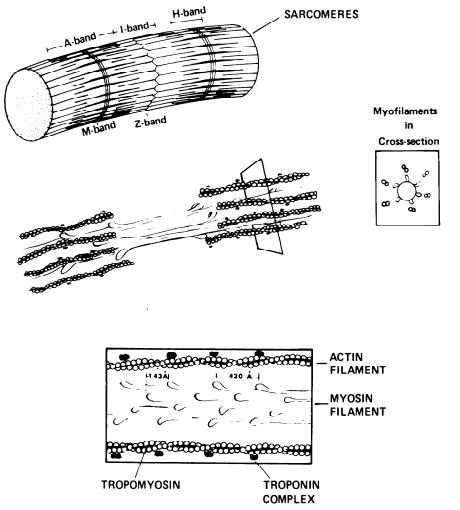


Figure 2: Hierarchy of skeletal muscle from myofibrils to myofilaments.

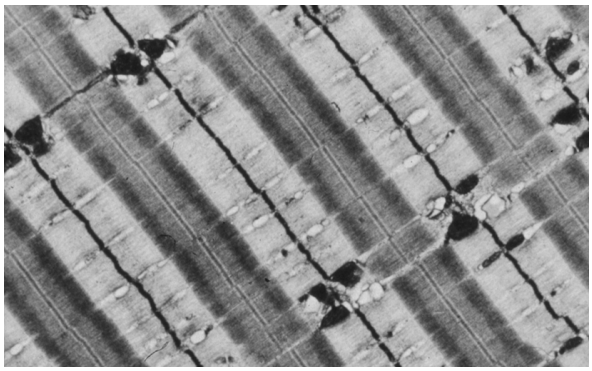


Figure 3: Longitudinal electron micrograph of a human thigh muscle biopsy specimen that was chemically-fixed, embedded in plastic, sectioned thickness and stained with heavy metals for contrast. The alternating light and dark wide regions correspond to the sarcomere A- and I-bands, while the thin, dark bands correspond to the sarcomere Z-bands. Only a portion of a single fiber is shown in this section (magnification approximately 20,000 X)

3. SKELETAL MUSCLE MECHANICAL PROPERTIES

3.1 Isometric Active Length-Tension Properties:

The original biological experiments performed by Blix[1] demonstrated that the force developed by a muscle during isometric contraction (i.e., when the muscle is not allowed to shorten) varies with its length. Experimentally, isometric contractions are performed at different lengths and peak isometric tension is measured at each length. These tensions are then plotted against length and a relationship such as that shown in Figure 4 is obtained. It has thus been demonstrated that at very long and very short lengths, muscle generate low force while at intermediate or "optimal" lengths, muscle generate higher force. While a general description of this relationship was presented in the 1800s, the precise structural basis for the length-tension relationship in skeletal muscle was not elucidated until the sophisticated mechanical experiments of the early 1960s were performed[2, 3]. It was these experiments that defined the precise relationship between myofilament overlap and tension generation, which we refer to today as the sarcomere length-tension relationship.

In its most basic form, the length-tension relationship illustrates that tension generation in skeletal muscle is a direct function of the magnitude of overlap between the actin and myosin filaments. As a muscle was highly stretched to a sarcomere length of 3.65 μm, the muscle developed no active tension. This was due to the fact that, since the myosin

filament is 1.65 µm long and the actin filament is 2.0 µm in length, at a sarcomere length of 3.65 µm, there is no overlap (interdigitation) between actin and myosin filaments. Therefore, although fiber excitation might permit actin-myosin interaction by removing the inhibition of the actin filament, because no myosin cross-bridges are in the vicinity of the actin active sites, no tension generation occurs. As muscle length decreases, overlap between actin and myosin is possible, and the amount of tension generated by the muscle increases as sarcomere length decreases.

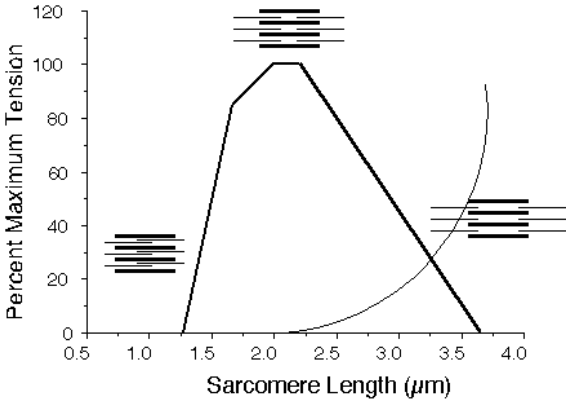


Figure 4: Sarcomere length-tension relationship demonstrating active force (heavy line) and passive force (thin line) developed by muscle sarcomeres.

Increasing tension with decreasing sarcomere length occurs until the muscle reached a sarcomere length of 2.2 µm. As sarcomere length changed between 2.0 µm and 2.2 µm, muscle tension remaines constant. This is a direct result of thick filament structure. Since the myosin filament is a polymeric arrangement of myosin molecules arranged in an antiparallel fashion, many myosin "backbones" come together in the center of the myosin filament. Thus, there exists a bare region of the myosin molecule that is devoid of cross-bridges. The length of this bare region was 0.2 µm. Even though sarcomere shortening over the range 2.2-2.0 µm results in greater filament overlap, it does not result in increased tension generation since no additional cross-bridge connections are made. The region of the length-tension curve over which length change results in no change in tension is known as the plateau region. The maximum tetanic tension of the muscle in this region is abbreviated P_O. The muscle length at which P_O is attained is known as optimal length (L_O).

At a sarcomere length of 2.0 µm, the actin filaments from one side of the sarcomere juxtapose the actin filaments from the opposite side of the sarcomere. It might be predicted that shortening past this point would be impossible. However, as sarcomere length decreases below the plateau region, actin filaments from one side of the sarcomere overlap with the actin filaments on the opposite side of the sarcomere. That is, at these lengths, actin filaments overlap both with the opposing actin filament and with the myosin filament. Under these conditions, the actin filament from one side of the sarcomere interferes with cross-bridge formation on the other side of the sarcomere, and this results in decreased muscle force output.

3.2 Passive Length-Tension Properties:

The thin line in Figure 4 represents the tension recorded if a muscle is stretched to various lengths without stimulation. Note that near the optimal length, passive tension is almost zero. However, as the muscle is stretched to longer lengths, passive tension increases dramatically. These relatively long lengths can be attained physiologically, and therefore, passive tension can play a role in providing resistive force even in the absence of muscle activation. The structure(s) responsible for passive tension are obviously outside of the cross-bridge itself since muscle activation is not required. Recent studies have shown that the origin of passive muscle tension is actually within the myofibrils themselves[4, 5]. Interestingly, a new structural protein has been identified, which is the source of this passive tension. The very large protein, creatively named "titin" (and formerly termed "connectin") connects the thick myosin filaments end to end.

3.3 Isotonic Active Force-Velocity Properties:

In contrast to the sarcomere length-tension relationship, the force-velocity relationship does not have a precise, anatomically identifiable basis. The force-velocity relationship illustrates that the maximum force generated by a muscle is a very strong function of its velocity. It can also be stated in the reverse, such that muscle contraction velocity is dependent on the force resisting the muscle. Historically, the force-velocity relationship was used to define the kinetic properties of the cross-bridges as well as the precise form of the force-velocity relationship itself. The form of this relationship has been shown to explain the behavior of whole muscle[6, 7] and isolated single muscle fibers[8, 9].

The force-velocity relationship, like the length-tension relationship, is a curve that actually represents the results of many experiments plotted on the same graph. Experimentally, a muscle is stimulated maximally and allowed to shorten (or lengthen) against a constant load. The muscle velocity during shortening (or lengthening) is measured and then plotted against the resistive force. The general form of this relationship is plotted in Figure 5. On the horizontal axis we have

plotted muscle velocity relative to maximum velocity (V_{max}) while on the vertical axis we have plotted muscle force relative to maximum force (P_O).

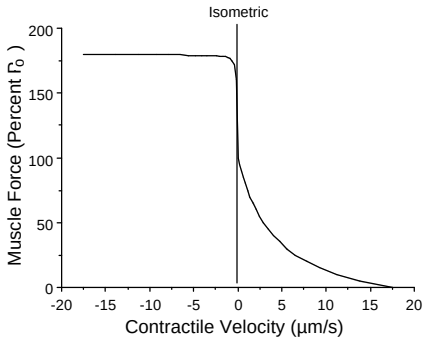


Figure 5: Sarcomere force-velocity relationship.

When a muscle is maximally electrically activated and required to lift a load which is less than its maximum tetanic tension, the muscle begins to shorten. Contractions that permit the muscle to shorten are known as concentric contractions. In concentric contractions, the force generated by the muscle is always less than the muscle's maximum (P_O). As the load the muscle is required to lift decreases, contraction velocity increases. This occurs until the muscle finally reaches its maximum contraction velocity, V_{max} at which force generation = 0. V_{max} is a parameter we can use to characterize muscle, which is related to both fiber type distribution and architecture.

The mathematical form of the force-velocity relationship is a rectangular hyperbola and is given in Equation 1:

$$(P+a)\, v = b\, (P_O - P) \qquad (1)$$

where a and b are constants derived experimentally (usually about 0.25), P is muscle force, P_O is maximum tetanic tension, and v is muscle velocity. This equation can be used to determine the relative muscle force that occurs as a muscle is allowed to shorten. It is important to note that the force-velocity relationship is a steep rectangular hyperbola. In other words, force drops off rapidly as velocity increases. For example, in a muscle that is shortening at only 1% of its maximum contraction velocity (extremely slow), tension drops by 5% relative to maximum isometric tension. Similarly, as contraction velocity increases to only 10% maximum (easily attainable physiologically), muscle force drops by 35%! Note that even when muscle force is only 50% maximum, muscle velocity is only 17% V_{max}. The take-home lesson is that as shortening speed increases, force drops precipitously

As the load imposed on the muscle increases, it reaches a point where the external load is greater than the load which the muscle itself can generate. Thus the muscle is activated, but it is forced to lengthen due to the high external load. This is referred to as an eccentric contraction (contraction in this context does not necessarily imply shortening!). There are two main features to note regarding eccentric contractions. First, the absolute muscle tensions are very high relative to the muscle's maximum tetanic tension. Second, unlike concentric contractions, the absolute tension is relatively independent of lengthening velocity. This suggests that skeletal muscles are very resistant to lengthening, a property which comes in very handy for many normal movement patterns where muscles function as "brakes" to decelerate a limb (for example, the hamstrings "brake" the tibia during the swing phase of gait) or to absorb the momentum of the body during stance (for example, the quadriceps femoris absorb body momentum during heel strike). Eccentric contractions are currently under study for three main reasons: First, much of a muscle's normal activity occurs while it is actively lengthening, so that eccentric contractions are physiologically common. Second, muscle injury and soreness are selectively associated with eccentric contraction. Finally, muscle strengthening is greatest using exercises that involve eccentric contractions[10-12].

4. SKELETAL MUSCLE CONSTITUITIVE PROPERTIES

Whole skeletal muscles are organized arrays of individual myofibers as described above. The mechanical properties of a whole skeletal muscle depend strongly on both the intrinsic properties of the fibers and their extrinsic arrangement, or architecture. Muscle architecture is typically described in terms of muscle length, mass, myofiber length, pennation angle (the angle between the line of action and the myofiber long axis) and physiological cross sectional area (PCSA). PCSA is an approximation of the total cross-sectional area of all muscle fibers, projected along the muscle's line of action, and is calculated using equation 2 shown below, where M = muscle mass, ρ = muscle density (1.056 g/cm^3 in fresh tissue), θ = surface pennation angle, and L_f = myofiber length. This formulation provides a good estimate of experimentally measured isometric muscle force output [13]. In practice, muscle fiber length is measured and then normalized to a constant sarcomere

length. In this way, it is possible to compare fiber lengths between muscles without regard to the actual length of the muscle at the time the measurements were made.

$$\text{PCSA}\ (\text{mm}^2) = \frac{\text{M}\ (\text{g}) \bullet \cos\ \theta}{\text{r}\ (\text{g/mm}^3) \bullet \text{L}_{\text{f}}\ (\text{mm})} \tag{2}$$

Maximum active stress (often termed specific tension) varies somewhat among fiber types and species around a typical value of 250 kPa. Specific tension can be determined in any system in which it is possible to measure force and estimate the area of contractile material. In practice area measurements may be difficult to make giving rise to the large variability of reported values. Given muscle PCSA, the maximum force produced by a muscle can be predicted by multiplying this PCSA by specific tension. Specific tension can also be calculated for isolated muscle fibers or motor units in which estimates of cross-sectional area have been made.

As would be expected based on understanding muscle anatomy, muscle maximum contraction velocity is primarily dependent on the type and number of sarcomeres in series along the muscle fiber length[14]. This number has been experimentally determined for a number of skeletal muscles. Maximum contraction velocity of a given muscle can thus be calculated based on a knowledge of the number of serial sarcomeres along the muscle length multiplied by the maximum contraction velocity of an individual sarcomere. Sarcomere shortening velocity varies widely among species and fiber types.

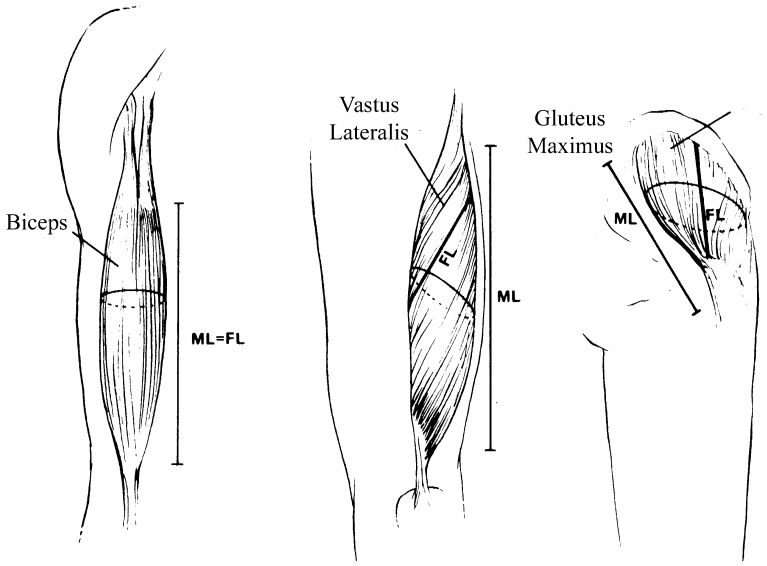
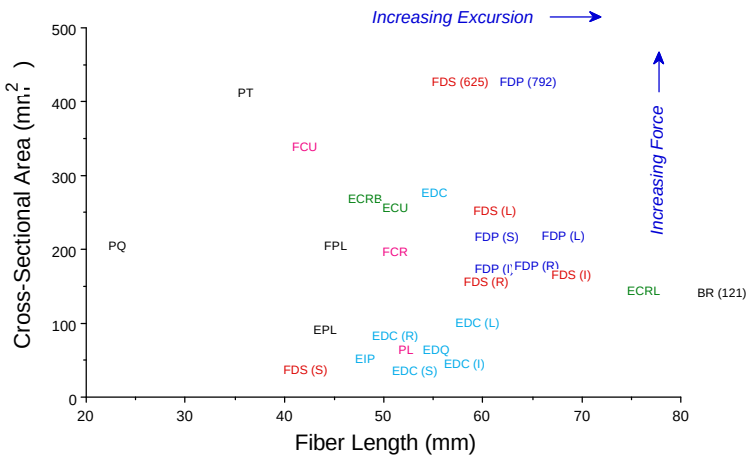


Figure 6: Examples of muscle architecture types present in different portions of the human body.

Muscles with fibers that extend parallel to the muscle force-generating axis are termed parallel or longitudinally arranged muscles (Fig. 6, left). While the fibers extend parallel to the force-generating axis, they never extend the entire muscle length. Muscles with fibers that are oriented at a single angle relative to the force generating axis are termed unipennate muscles (Fig. 6, middle). The angle between the fiber and the force-generating axis generally varies from 0° to 30°. It is obvious when preparing muscle dissections that most muscles fall into the final and most general category, multipennate muscles--muscles composed of fibers that are oriented at several angles relative to the axis of force generation (Fig. 6, right). An understanding of muscle architecture is critical to understanding the functional properties of different sized muscles.

5. IMPLICATIONS FOR SURGERY

In addition to improving our understanding of muscle anatomy and function, elucidation of muscle architecture may ultimately provide information useful for selection of muscles used in tendon transfers. To substitute a lost muscle function, it would seem reasonable to select a donor muscle with similar architectural properties as the original muscle. (Of course numerous other factors influence donor selection including donor muscle availability, donor muscle morbidity, preoperative strength, integrity, expendability, synergism, transfer route and direction, and surgeon experience and preference.) These architectural properties have been determined for numerous muscles in the upper extremity and are presented as a summary graph in Figure 7.



Abbreviations of upper extremity muscles used in Figure 7: BR: brachioradialis; EDC I, EDC M, EDC R, and EDC S: extensor digitorum communis to the index, middle, ring and small fingers, respectively; EDQ: extensor digiti quinti; EIP: extensor indicis proprious; EPL: extensor pollicis longus; FDP I, FDP M, FDP R, and FDP S: flexor digitorum profundus muscles; FDS I, FDS M, FDS R, and FDS S: flexor digitorum superficialis muscles; FDS I (P) and FDS I (D): proximal and distal bellies of the FDS I; FDS I (C): the combined properties of the two bellies as if they were a single muscle; FPL: flexor pollicis longus; PQ: pronator quadratus; PS: palmaris longus; PT: pronator teres

Figure 7: Scatter graph of the fiber length and cross-sectional areas of muscles in the human arm. Fiber length is proportional to muscle excursion, and cross-sectional area is proportional to maximum muscle force.

5.1 Surgical restoration of digital extension:

We envision that the difference index might be useful in tendon transfer when a making choice involving multiple donors or when a combination of transfers is available for selection. For example, in the surgical restoration of digital extension following high radial nerve palsy described and accepted potential donor muscles (which are transferred to the EDC) include the FCR, the FCU, the FDS to the middle finger, and the FDS to the ring finger described by Beasley. From the standpoint of architecture *alone*, the FDS M most closely resembles the EDC in terms of force generation (*i.e.* cross sectional area) and excursion (*i.e.* fiber length). If one were to compare individual architectural properties, it is clear that the FDS (M) has more than enough excursion compared to the EDC while the FCU has sufficient force-generating potential. Thus, if the concern were sufficient force, the FCU might be chosen while if the concern were excursion, the FDS (M) might be chosen. Either way, a knowledge of muscle architecture permits the informed decision to be made.

5.2 Surgical restoration of thumb extension:

To restore EPL function in high radial nerve palsy, potential donors include the FDS to the middle finger, the FDS to the small finger, and the PL. Again, in terms of architecture, the FDS to the small finger and the PL are more similar to the EPL, and therefore should provide the force generation and excursion required to restore lost function.

5.3 Surgical restoration of thumb flexion:

As a final example, following high median nerve palsy, anterior interosseus nerve injury, or isolated, irreparable FPL muscle injury, multiple potential donors for transfer to restore thumb flexion are available. These donors include the BR, the ECRL, the ECRB, the ECU, the EDQ or the FDS to the ring finger. From an architectural standpoint, the ECRB, the FDS R and ECU are most similar to the FPL.

To summarize, although the importance of architecture has been emphasized by Brand *et al* [15]and Smith and Hastings [16], often little attention has been given to this fundamental muscle property. However, when one considers the profound influence of architecture on muscle function, it would seem that architecture deserves further emphasis to provide additional information which may be relevant to extremity function and restoration.

6. REFERENCES

1. M. Blix. "Die lange und die spannung des muskels." *Skand. Arch. Physiol.* **5**, pp. 150-172, 1895.

2. A.M. Gordon, A.F. Huxley, and F.J. Julian. "The variation in isometric tension with sarcomere length in vertebrate muscle fibres." *J. Physiol. (Lond.)***. 184**, pp. 170-192, 1966.

3. A.M. Gordon, A.F. Huxley, and F.J. Julian. "Tension development in highly stretched vertebrate muscle fibres." *J. Physiol. (Lond.)***. 184**, pp. 143-169, 1966.

4. A. Magid, and M.K. Reedy. "X-ray diffraction observations of chemically skinned frog skeletal muscle processed by an improved method." *Biophys. J.* **30**, pp. 27-40, 1980.

5. S. Labeit, and B. Kolmerer. "Titins: Giant proteins in charge of muscle ultrastructure and elasticity." *Science***. 270**, pp. 293-296, 1995.

6. B. Katz. "The relation between force and speed in muscular contraction." *J. Physiol. (Lond.)***. 96**, pp. 45-64, 1939.

7. A.V. Hill. "The mechanics of active muscle." *Proceedings of the Royal Society of London. Series B: Biological Sciences (London)***. 141**, pp. 104-117, 1953.

8. K. Edman, L.A. Mulieri, and M.B. Scubon. "Non-hyperbolic force-velocity relationship in single muscle fibres." *Acta Physiol. Scand.* **98**, pp. 143-156, 1976.

9. K.A.P. Edman. *The velocity of shortening at zero load: Its relation to sarcomere length and degree of activation of vertebrate muscle fibers*. In The cross-bridge mechanism in muscle contraction. University Park Press, Baltimore. 1978.

10. J. Fridén, and R.L. Lieber. "Structural and mechanical basis of exercise-induced muscle injury." *Med. Sci. Sports Exerc.* **24**, pp. 521-530, 1992.

11. R.B. Armstrong. "Mechanism of exercise-induced delayed onset muscular soreness: a brief review." *Med. Sci. Sports Exerc.* **16**, pp. 529-538, 1984.

12. W.T. Stauber. "Eccentric action of muscles: physiology, injury, and adaptation." *Ex. Sport Sci. Rev.* **17**, pp. 157-185, 1989.

13. P.L. Powell, R.R. Roy, P. Kanim, M. Bello, and V.R. Edgerton. "Predictability of skeletal muscle tension from architectural determinations in guinea pig hindlimbs." *J. Appl. Physiol.* **57**, pp. 1715-1721, 1984.

14. C. Gans. *Fiber architecture and muscle function*. In Exercise and Sport Science Reviews. Vol. 10. Franklin University Press, Lexington, MA. 1982.

15. P.W. Brand, R.B. Beach, and D.E. Thompson. "Relative tension and potential excursion of muscles in the forearm and hand." *J. Hand Surg. (Am.)***. 3A**, pp. 209-219, 1981.

16. R.J. Smith, and H. Hastings. "Principles of tendon transfers to the hand." *A.A.O.S International Course Lectures***. 21**, pp. 129-149, 1993.