

# BIOMECHANICS OF MUSCULOSKELETAL SOFT TISSUES

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## Summary

The musculoskeletal system has four primary soft tissues: skeletal muscles, tendons, ligaments and articular cartilages. Skeletal muscles are contractile, and their primary function is to shorten and produce force and so cause movements at joints. Muscle contraction occurs through cyclic interactions of myosin-based cross-bridges with actin. Contractions are fuelled by the hydrolysis of adenosine triphosphate (ATP). Tendons connect muscles to bones. Because of their nearly elastic properties, they are excellent for storing and releasing energy during cyclic movements and they affect the contractile conditions, and thus the properties of muscles in the human body. Ligaments connect bones across joints. Ligaments guide the movements of joints, they keep the articulating surfaces aligned for optimal congruence and they are associated with providing feedback about the orientation of the bones that make up a joint. Articular cartilage is a thin, avascular, aneural, layer of connective tissue covering the surfaces of bones in synovial joints. The primary functions of cartilage include the transmission of forces across joints, the distribution of forces across the joint surfaces, and the provision of smooth surfaces for optimal joint function.

## 1. Introduction

The musculoskeletal system of the human body consists of hard and soft tissues. The hard tissues are the bones that provide the skeleton for attachment of the soft tissues. The soft tissues can be divided into contractile tissues and non-contractile tissues. The contractile tissues are the muscles, while the non-contractile soft tissues consist of cartilage, ligaments and tendons.

The contractile tissues of the musculoskeletal system are referred to as skeletal muscles to distinguish them from the heart (cardiac muscle) and the smooth involuntary muscles that are found, for example, in the gastrointestinal system and the walls of blood vessels. Here, we deal exclusively with skeletal muscles. Skeletal muscles are the muscles that are under voluntary control and allow for directed movement. They have a typical striation pattern that has been observed by anatomists in the 19<sup>th</sup> century, and that is caused by the contractile proteins, actin and myosin, that are arranged in a highly organized manner. Contraction of muscles is initiated by nerve signals that arrive at the so-called neuromuscular junction, the place where the end of a nerve meets the muscle. At the neuromuscular junction, the nerve releases a neurotransmitter, acetylcholine, which crosses the synaptic cleft, binds to receptor molecules on the muscle fiber membranes and causes a depolarization of the fiber membrane that leads to a cascade of events culminating in muscle contraction and force production. When activated, the mechanical properties of skeletal muscles change dramatically, thus it is virtually impossible to describe them with a consistent set of constitutive equations. The major function of muscles is to contract and produce force, thereby creating movements.

The non-contractile soft tissues of the musculoskeletal system are cartilage, ligaments and tendons. Cartilage, or more precisely articular cartilage, is a thin layer of fibrous connective tissue on the articular surfaces of bones in synovial joints. Articular cartilage consists of cells (~5% in terms of volumetric fraction), and an intercellular matrix (~95%) which consists primarily of water (65-80%). Articular cartilage behaves visco-elastically, and in conjunction with the synovial fluid, provides for extremely low friction (~0.0025) in healthy joints. The major functions of articular cartilage are to transfer forces between articulating bones, to distribute the forces in joints, and to allow for relative movements of articular surfaces with minimal friction.

Ligaments take their name from the Latin word “ligare” to bind, and are connective tissues consisting of elastin and collagen fibers. Collagen is the main protein in ligaments and is typically found in fibrillar form oriented between the insertion sites so as to resist tensile forces. The major functions of ligaments are to attach articulating bones across a joint, to guide the movement of joints, to maintain joint congruency, and to act as position and strain sensors for the joint.

Finally, tendons are dense fibrous tissues that connect muscles to bones. Tendons appear in a variety of shapes and sizes, depending on the morphological, physiological and mechanical characteristics of the muscle to which the tendon is attached. Typically, tendons are glistening and pearly white. They may take the shape of a thin cord or a broad sheet. The primary function of tendons is to transmit the forces generated by muscles to the bones and so produce movements. Further functions include the regulation of contractile conditions in the muscle, enhancement of force and power output, and the storage of elastic energy.

## **2. Muscle**

Skeletal muscles can contract and produce force. It is this ability that allows for movement of joints and goal directed motion, such as walking, playing the piano and throw a ball (Figure 1). The importance of muscles has been recognized for centuries,

and was the topic of intense investigation by Renaissance men, such as Leonardo da Vinci, Vesalius and the classic works of Giovanni Borelli summarized in his book *De Motu Animalium*.

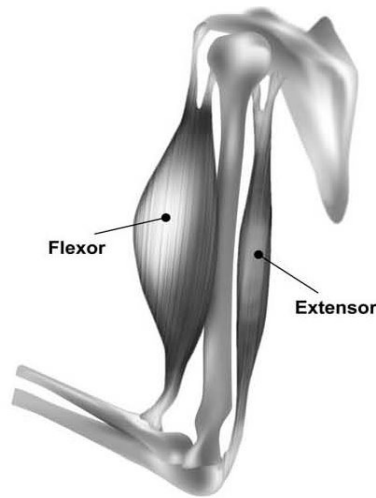


Figure 1. Human elbow flexor and extensor muscles

However, despite centuries of investigation, the detailed molecular mechanism of muscle contraction remain a topic of debate (Pollack, 1983), and many basic properties of skeletal muscle contraction remain without satisfactory explanation (Herzog et al., 2006; Herzog et al., 2012a). As for many biological tissues, much of the function and properties is revealed by the structure and composition of the tissue, and skeletal muscle is no exception. Therefore, a proper understanding of muscle morphology is essential to understanding this most intriguing of all biological tissues.

## 2.1. Morphology

Skeletal muscles may be thought of in structural units of decreasing size. The entire muscle is typically wrapped in various layers of connective tissue connecting one muscle to its synergists, to bones, and to other soft tissue and connective tissue structures. The connective tissue layer closest to the muscle is called the epimysium. It consists of irregularly distributed collagenous, reticular and elastic fibers, connective tissue cells, and fat cells (Figure 2). Muscles are typically sub-divided into muscle bundles (called fascicles) which consist of an assembly of muscle fibers. Fascicles are separated from other fascicles by a layer of connective tissue; the perimysium. Each fascicle consists of fibers, which are the multinucleated, long cells of skeletal muscle tissue. Each fiber is surrounded by a thin connective tissue sheath (endomysium) that principally consists of reticular fibers that bind adjacent cells. Each cell, or muscle fiber, has a delicate membrane called the sarcolemma which is designed to receive and conduct stimuli.

Muscle fibers, in turn, are made up of myofibrils. Myofibrils are strands of tissue that contain the smallest structurally intact contractile elements of skeletal muscles, the sarcomeres. Sarcomeres in a myofibril are arranged in series. Myofibrils are approximately 0.5-1.0 $\mu$ m in diameter, and thus a typical skeletal muscle fiber contains

approximately 1,000-10,000 myofibrils. Each sarcomere within a mammalian myofibril is approximately 2.0-2.8 $\mu\text{m}$  long at the so-called optimal length, depending on species, but they can be substantially longer for non-mammalian species. Sarcomeres are bordered by the so called z-line (z = stands for the German word *Zwischenscheibe*, or separating plate) and contain the contractile proteins actin and myosin (Figure 3). Sarcomeres also contain a vast number of structural proteins (many of them have not been identified), with the most important of them being titin, desmin, nebulin and dystrophin. These structural proteins have passive functions but at least in one case (titin) might also regulate active force production (Herzog et al., 2012b).

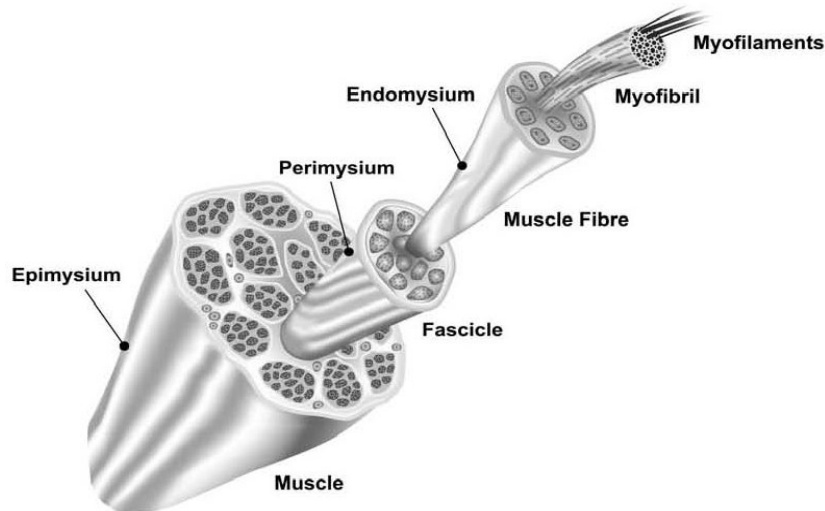


Figure 2. Schematic illustration of the different structures of skeletal muscle

Serially arranged sarcomeres in a myofibril exhibit a typical striation pattern under the light microscope that is associated with the repeat arrangement of actin (thin) and myosin (thick) filaments. The dark regions (A- or anisotropic bands) are formed by the thick filaments, while the light regions (I- or isotropic bands) are associated with regions of the thin filaments. Each I-band region is divided by a small dark region that is caused by the dense z-lines (Figure 3). This arrangement of dark and light regions has led to the name striated muscles.

The contractile proteins actin and myosin are thought to be responsible for the contraction and force production in skeletal muscle (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). Actin, or thin filaments, are located on either side of the sarcomere and insert into the z-line from where they protrude towards the centre of the sarcomere (Figure 3). The backbone of thin filaments is composed of two chains of serially linked actin globules (Figure 4) that wrap around each other to give the appearance of a double helix with the loop of the helix repeating approximately every 36-39nm. Thin filaments further contain the regulatory proteins tropomyosin and troponin. Tropomyosin is a long fibrous protein that lies in the groove formed by the actin chains of the thin filament. In the resting muscle, tropomyosin blocks the cross-bridge attachment site on actin, thereby preventing contraction and force production. Troponin is composed of three sub-units, troponin C, T, and I. In the resting muscle, troponin T, is bound to tropomyosin and locks it down in its position on actin together with troponin I. Upon muscle activation, calcium is released from the sarcoplasmic

reticulum and binds to troponin C. This unlocks the binding of tropomyosin from the cross-bridge attachment site on actin, and allows for attachment of the myosin head (cross-bridge) to actin and so produce contraction and force.

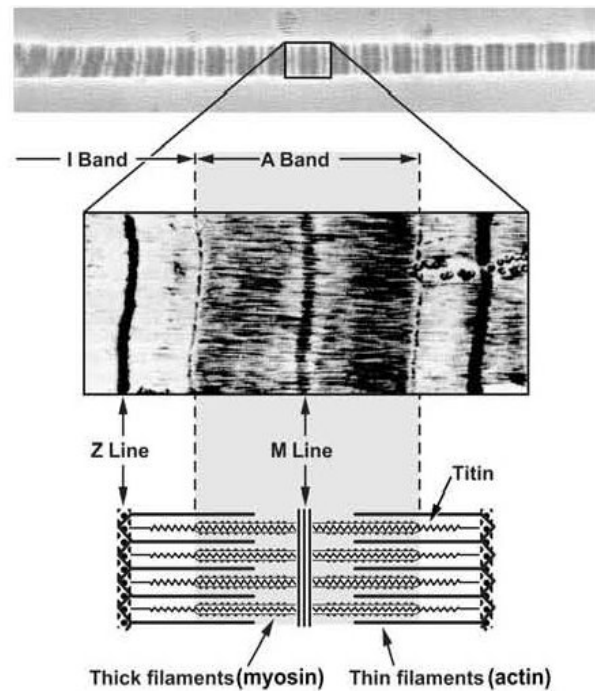


Figure 3. Light microscope picture of sarcomeres within a myofibril (top panel), electron-micrograph of a single sarcomere (mid-panel), and the corresponding schematic illustration of a sarcomere with z-lines, contractile proteins (actin and myosin), and the structural protein titin.

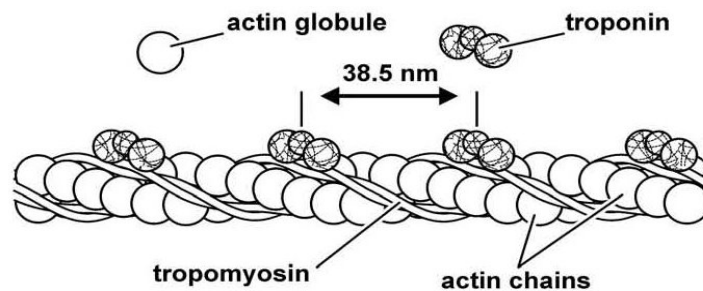


Figure 4. Schematic illustration of the thin (actin) myofilament composed of two chains of serially-linked actin globules and associated regulatory proteins, tropomyosin and troponin.

Myosin, or the thick filament, is located in the centre of the sarcomere and is thought to be held in place by the structural protein titin (Figure 3). Thick filaments are composed of myosin molecules. A myosin molecule contains a long tail portion, which is composed of light meromyosin, and two globular heads, containing heavy meromyosin (Figure 5). The head portion extends outward from the thick filaments. It contains a binding site for actin and an enzymatic site that catalyzes the hydrolysis of ATP

(adenosine triphosphate) which releases the energy needed for muscular contraction. The myosin molecules in each half sarcomere are arranged so that their tail ends are directed towards the centre of the filament allowing the head portion (the cross-bridge) to pull the thin filaments towards the centre of the sarcomere upon contraction.

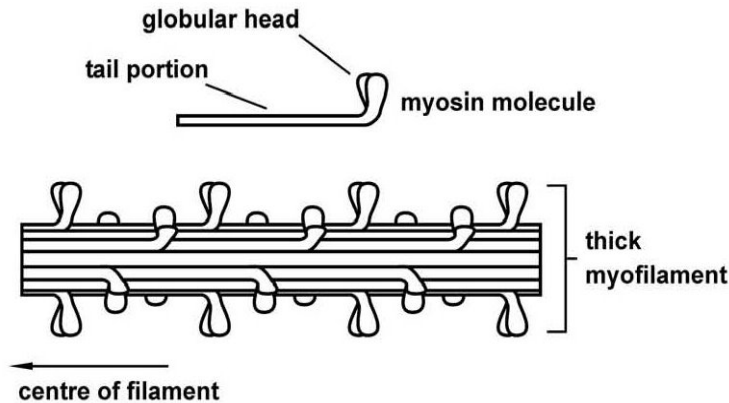


Figure 5. Schematic illustration of the thick (myosin) myofilament with cross-bridges (globular heads) protruding from the body of the filament.

The cross-bridges on the thick filament are offset by 14.3nm in the axial direction and by 60° in the radial direction (Figure 6). Since cross-bridges are thought to come in pairs offset by 180°, two cross-bridges with identical orientation, interacting with the same thin filament, are about 42.9nm apart.

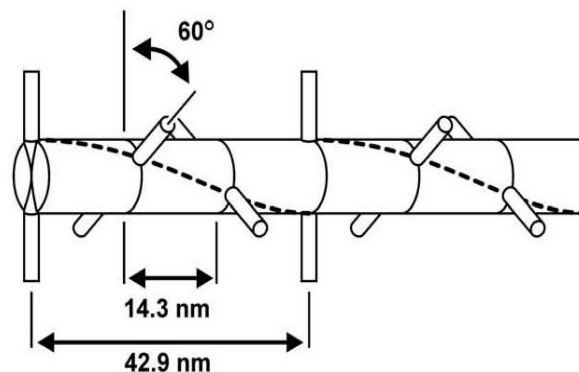


Figure 6. Schematic illustration of the cross-bridges on the thick myofilament (from Pollack, 1990) with permission)

Thick filament lengths appear to be remarkably constant among vertebrates (about 1.63µm), while thin filament lengths vary from 0.925µm in frogs to 1.27µm in humans. These lengths correspond to 24 and 33 periodicities of actin binding proteins (spaced about 38.5nm) on the thin filament.

Not only is the structure of skeletal muscle highly organized longitudinally, but it is almost crystal like in cross-section. Although several arrangements exist in the packing of thick and thin filaments cross-sectionally, they all involve a greater number of thin compared to thick filaments (Figure 7). The cross-sections of thick and thin filaments

are approximately 12 and 6nm, respectively and the distance between thick and thin filaments varies as a function of sarcomere length, becoming smaller as sarcomere length increases.

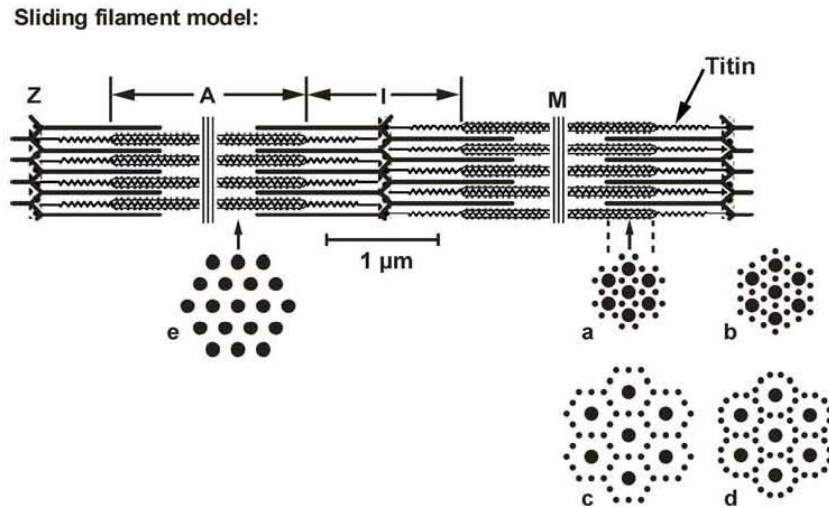


Figure 7. Schematic illustration of thick and thin filament arrangement in a cross-sectional view in an area of thick filaments only (e) and an area of thick-thin myofilament overlap (a-d). (a) vertebrate muscle, (b) insect flight muscle, (c-d) arthropod leg muscles and some synchronous insect flight muscles.

Aside from the contractile proteins, skeletal muscle contains a series of structural proteins. Titin is the largest known protein in the human body (3.0-3.8MDa) and is important in the contraction of striated muscles. It is found in abundance in myofibrils of skeletal muscles and spans from the z-line to the M-band of sarcomeres (Figure 3). Titin is thought to act as a molecular spring that centers the thick filament and prevents instability of the contractile proteins during contraction. Titin has also been shown to change its stiffness in a calcium- (activation-) dependent manner, and thus has been implicated as a regulator of force during muscle stretch. Further evidence for titin as a force regulator through attachment to actin also exists but is not fully understood at this time (Herzog et al., 2012a).

Desmin is another structural protein and is an intermediate filament (52kDa) that is found near the z-lines of sarcomeres. Although little is known about its detailed function, it connects adjacent z-lines and so is thought to keep myofibrils in register. Desmin knockout mice initially develop normally and are fertile, but they develop defects in cardiac and skeletal muscles soon after birth. Muscles become weaker and fatigue easier in the desmin knockout mice compared to control, and injuries to muscle fibers develop easier and are characterized by a “streaming” of the z-lines indicating a lack of structural integrity across z-lines of adjacent sarcomeres.

Nebulin is an actin-binding protein which is localized in the I-band region of sarcomeres. Nebulin has a molecular weight of about 600-900kDa and its length is approximately proportional to that of actin, thus it is thought to act as a ruler for thin filament lengths. Nebulin knockout mice have reduced thin filament length, impaired

contractile function and they die post-natally suggesting that nebulin is an essential structural protein in skeletal muscle responsible for proper sarcomere and myofibril assembly.

Dystrophin is a protein that connects the cytoskeleton of muscle fibers to the extracellular matrix. Although dystrophin makes up a very small part of muscle (0.002% of total muscle proteins), its absence has severe consequences and causes the class of myopathies collectively referred to as muscular dystrophy. Muscular dystrophy results in pronounced necrosis of myofibrils and fibers and causes impaired contractility and excessive fatigability. Most muscular dystrophy patients become wheel-chair bound early in life and develop fibrosis of the heart which typically leads to premature death.

## 2.2. Molecular Mechanism of Contraction

In the 20<sup>th</sup> century, several mechanisms of muscle contraction were proposed, including contraction and force production through the shortening of the A-band region (thick filament shortening). However, these theories were replaced in the 1950 with the so-called “sliding filament” and “cross bridge theory”. The sliding filament theory states that muscle shortening is accomplished through the relative sliding of the contractile proteins actin and myosin (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954), and the cross-bridge theory asserts that this relative sliding is driven by an ATP-dependent cyclic attachment of myosin “cross-bridges” originating from the thick filament on specialized sites of the thin filament (Huxley, 1957a).

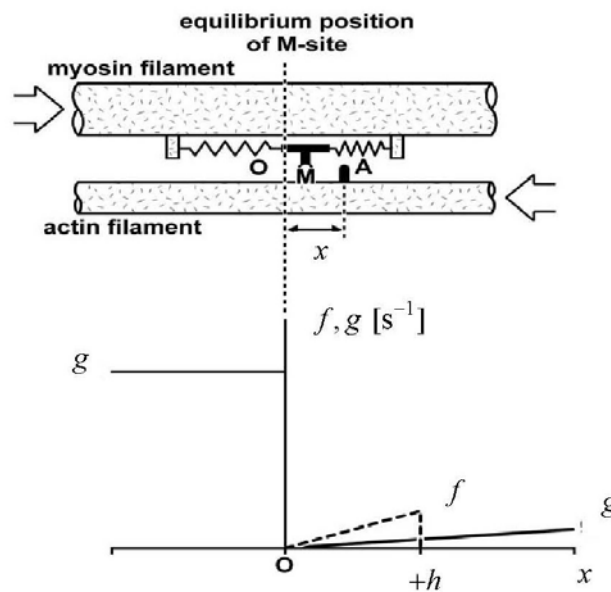


Figure 8. Schematic illustration of Huxley’s 1957 cross-bridge model with the cross-bridge, M, oscillating around its equilibrium position, O, due to thermal agitation (top panel). Rate functions of attachment ( $f$ ) and detachment ( $g$ ) as a function of  $x$ , the distance of the cross-bridge equilibrium position, O, to the nearest actin attachment site (A) (adapted from Huxley, 1957b, with permission).

Andrew Huxley proposed in 1957 that actin filament sliding past the myosin is caused by cyclic interactions of myosin-based cross-bridges with actin (Huxley, 1957a). The



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### **Biographical Sketch**

**Dr. Herzog** received his undergraduate training at the Federal Technical Institute in Zurich, Switzerland (1979), then went to the University of Iowa (USA) for his doctoral research in biomechanics (1985), and completed his training with a postdoctoral fellowship in Neuroscience in Calgary, Canada. He accepted a tenure track position at the University of Calgary in 1990. Presently, Dr. Herzog is a professor in Biomechanics with appointments in Kinesiology, Medicine, Engineering, and Veterinary Medicine. He holds the Canada Research Chair for Cellular and Molecular Biomechanics and The Killam Memorial Chair for Interdisciplinary Research at the University of Calgary. He is an elected fellow of the Royal Society of Canada.