Neuromuscular Stimulation

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ABSTRACT

This contribution describes electrical activation of the neuromuscular system with electrodes positioned in or on skeletal muscle. The mechanisms of neuromuscular stimulation are described, with reference to transmission at the neuromuscular junction, to illustrate that it is the motor nerve, rather than the muscle, that is stimulated. The two methods to modulate muscle force, recruitment and rate modulation, are reviewed with reference to their basis in the properties of the neuromuscular system including the force frequency relationship of skeletal muscle and the strength-duration, current-distance and current-diameter relationships for excitation of motor nerve fibers. The elements that impact the shape of the input-output (recruitment) curve of muscle force as a function of stimulation intensity are presented, including a description of position-dependent recruitment. In addition the biomechanical impacts on motor output including the length-tension properties of skeletal muscle and the transformation of muscle force to joint moment are reviewed. This contribution serves as a comprehensive review of the fundamental aspects of neuromuscular stimulation.

INTRODUCTION

Electrical stimulation can be used to generate muscular contraction, and neuromuscular excitation was one of the earliest documented interactions of electricity and a living organism (McNeal, 1977). An understanding of neuromuscular excitation and the properties of activated muscle are relevant for understanding natural neural control of movement as well as the restoration of movement using artificial electrical activation of the neuromuscular system (Solomonow, 1984). Electrical activation of the

nervous system can be used to restore function and is referred to as functional electrical stimulation (FES) (Vodovnik et al., 1981, Kralj and Bajd, 1989, Stein et al., 1992). In the instance that electrical stimulation is applied to the neuromuscular system for restoration of motor function (Kralj et al., 1980) it is referred to as functional neuromuscular stimulation (FNS).

This contribution describes electrical activation of the neuromuscular system with electrodes positioned in or on the skeletal muscle (muscle-based electrode). The neuromuscular system can also be activated using electrodes placed on peripheral nerves or within the central nervous system (Grill, 2001). These electrode locations will not be considered directly in this contribution, but the properties of electrically activated muscle are similar irrespective of electrode location.

The focus of the material presented is on the fundamental properties of neuromuscular stimulation, rather than its applications to restore function. For the latter the reader is referred to (Grill and Kirsch, 2000). First, the mechanism of neuromuscular activation is described with reference to neuromuscular transmission, and the block of transmission under experimental conditions reveals that it is the nerve, rather than the muscle, that is stimulated by muscle-based electrodes. Next, the two principal methods to control muscle force – recruitment and rate modulation – are considered. The temporal properties of the muscle twitch response, temporal summation, and the force-frequency relationship are described to form the basis for control of force with rate modulation. The excitation properties of motor nerve fibers including the strength-duration relationship, the current-distance relationship, and the current-diameter relationship are then described to provide the basis for control of muscle force via recruitment. Finally, the

biomechanical factors that impact the motor response are considered including the length-tension properties of skeletal muscle, position-dependent recruitment properties of muscle-based electrodes, and the conversion of muscle force to joint moment.

NEUROMUSCULAR EXCITATION

Neuromuscular excitation is effected by applying a short (typically 100-200 μs) pulse of current to the tissue through a pair of electrodes - a source (anode) and sink (cathode) of current. Electrical current pulses create extracellular potentials in the tissue that in turn lead to the generation of neural excitation (see 0825, Nerve Stimulation). Neurons in the vicinity of a cathodic electrode will be depolarized, and if the current amplitude is large enough to bring the depolarized portion of the membrane to threshold then the nerve will be stimulated. In contrast, neurons in the vicinity of the anodic electrode will be hyperpolarized, and although anodic stimuli can also generate excitation, the anodic stimulus amplitudes required for excitation are generally larger than those required with cathodic stimuli (see 0825, Nerve Stimulation).

The applied stimulus may be either a constant (regulated) voltage pulse or a constant (regulated) current pulse, and the type of pulse that is used will impact the properties of neural stimulation. Electrical stimulation of neurons is mediated by the electric field is the tissue, and regulated current pulses produce the same current flow through the tissue, and thus the same electric field, independent of impedance of the electrode tissue interface. However, with regulated voltage pulses, the current flow through the tissue, and thus neuronal excitation, is dependent on the impedance of the electrode-tissue interface. Constant current stimulation maintains the same current,

independent of the load impedance, and thus enables direct control over neuronal excitation. However, when using surface electrodes, constant current pulses can pose a risk for discomfort or tissue injury. If the surface electrode were to become partially dislodged, the impedance of the electrode tissue will increase. A regulated current pulse will then deliver the same current into a smaller area resulting in an increase in current density that could cause pain or skin damage. A regulated voltage pulse will deliver less current if the impedance of the electrode-tissue interface increases.

THE RESPONSE TO STIMULATION

The application of a single brief pulse of current of sufficient amplitude will produce a twitch response from the muscle (Figure 1). The amplitude and time-course of the force twitch are dependent on the type of muscle fibers, the muscle length, as well as the intensity (amplitude and duration) of the stimulus pulse.

Muscle Fibers and Motor Units

Skeletal muscle is composed of bundles of individual cells or muscle fibers. The muscle fibers are the contractile units of the muscle and there are two general types of muscle fibers. Fast muscle fibers (also called pale or white muscle as a result of low myoglobin levels and sparse vascularization) contract and relax rapidly (Figure 1B) and generate large forces. Fast muscle fibers lose their force generating capacity rather quickly after repeated contractions (fatigue), although there is also a class of fatigue resistant "fast" muscle fibers. Slow muscle fibers (also called red muscle as a result of high myoglobin levels and rich vascularization), contract and relax slowly, generate smaller forces, but are fatigue resistant. Most muscles consist of a mixture of these fiber

types and thus produce intermediate contractions, and different types of muscle fibers within a muscle may be activated as appropriate for different tasks.

Motor units are the fundamental unit of neuromuscular activation. They consist of a motor neuron and the group of muscle fibers that it innervates. The cell body of the motor neuron resides in the ventral horn of the spinal cord and its axon extends into the periphery to contact the muscle fibers. In general the muscle fibers within a motor unit are all of one type.

What is Stimulated?

Passage of current with electrodes placed in or on a muscle will cause depolarization of both nerve and muscle fibers and thus both motor nerve fibers and skeletal muscle fibers can be excited by an extracellular electric field. With an electrode placed in, on, or near a skeletal muscle, it is unclear what is being stimulated. Either the muscle may be activated directly or the motor nerve may be stimulated as it enters the muscle, and the ensuing muscle contraction is activated indirectly as a result of neuromuscular transmission. Before considering this issue further a brief review of neuromuscular transmission is presented.

Action potentials in motor nerve fibers lead to muscle contraction by synaptic transmission across the neuromuscular junction (Figure 2). Depolarization of the motor nerve terminal by the action potential leads to influx of calcium and subsequent release of the neurotransmitter acetylcholine (ACh) (Figure 2B). The binding of Ach to ACh receptors present on the postsynaptic (muscle) membrane causes them to open and enable the influx of sodium, which is in higher concentration outside the cell than inside the cell.

The influx of sodium depolarizes the muscle membrane potential, leading to calcium release, and subsequent contraction of the muscle.

Block of neuromuscular transmission has been used to determine whether electrical stimulation of the muscle excites the presynaptic motor nerve fiber or the postsynaptic muscle fibers (Crago et al., 1974). The muscle was activated with an electrode inserted into the muscle belly and the evoked force, F, was measured. Neuromuscular transmission was then block by application of a competitive antagonist that binds to the acetylcholine receptor, such as curare. This prevents the ACh that is released from the nerve terminal from binding to the ACh receptors on the muscle membrane and initiating muscular contraction (Figure 2C). Following blockade, electrical stimulation was again applied and the evoked force, F', was measured. If intramuscular stimulation evoked muscle force by direct activation of the skeletal muscle, then neuromuscular transmission would not be required, and the same force would be evoked in the blocked and unblocked condition (F'/F=1). The ratio of F'/F measured in these experiments was 0. 04 indicating that neuromuscular transmission was required to evoke force by intramuscular stimulation (Crago et al., 1974).

The conclusion that electrical stimulation of the muscle excites the presynaptic motor nerve fiber is important for two principal reasons. First, it means that electrical activation of skeletal muscle requires the presence of a motor neuron- that is, the muscle must not be denervated. While it is possible to stimulate denervated muscle, the stimulus intensities required to do so are substantially (and in some cases prohibitively) higher than those required to activate innervated muscle. Second, it means that the properties of

neuromuscular excitation are those of exciting the motor nerve fibers (see 0825 Nerve Stimulation) rather than those of the muscle fibers.

MODULATION OF MOTOR OUTPUT

The nervous system uses two mechanisms to modulate muscle force: recruitment and rate modulation (or rate coding) (Zhou et al., 1987). Recruitment refers to the number of motor units that are activated, where a motor unit is defined as a motor neuron and the muscle fibers that it innervates. The more motor units that are activated the greater the force that is produced. Rate modulation refers to how frequently motor units are activated. The more frequently motor units are activated the greater force that they produce. These same two mechanisms are available to regulate muscle force when using electrical stimulation.

Force Frequency Relationship

Single stimuli evoke twitch contractions from skeletal muscle (Figure 1B). However, when the interpulse interval (reciprocal of the stimulation frequency) in a train of repeated pulses is less than the twitch duration, the force responses to each stimulus overlap and add together (Figure 1C). As the stimulus frequency is further increased the twitch continue to add together, the force generated increases, and the force ripple decreases (ripple is defined as the difference between the force at the peaks and force in the valleys during the stimulus train). This process of force addition due to overlap of individual responses is termed temporal summation and results in sigmoidal relationship between the evoked force and the stimulus frequency (Figure 1D) termed the force-frequency relationship.

The stimulation frequency at which individual muscle twitches add together is dependent on their durations. Recall that different muscle fiber types have different duration twitches (Figure 1B), and thus different muscle fiber types (motor units) will fuse to form a contraction with very little ripple at different frequencies. For example the fusion frequency of a slow twitch motor unit may be as low as 10 Hz, while that of a fast motor unit may be as high as 50 Hz.

During a voluntary muscle contraction the firing times of individual motor units are asynchronous. In contrast, each current pulse in a train of artificial stimuli produces synchronous activation of all excited motor units. This synchronous activation requires a higher average activation frequency to produce a fused contraction than the asynchronous firing during a voluntary contraction, and the higher activation frequency may contribute to the onset of fatigue (see below).

Recruitment

The second means to control muscle force is through the use of stimulation intensity to alter the number of motor units that are activated. The nervous system modulates the number and distribution of active synapses on motor neurons to control the number of active motor units. Using artificial electrical stimulation the number of active motor units (recruitment) is controlled through the intensity of the stimulation that determines the number of nerve fibers that are stimulated.

The stimulation intensity can be modulated by alterations in either the duration or amplitude of the stimulus pulses according to the strength-duration property of stimulated nerve fibers (Figure 3A). For a fixed stimulus pulse duration, increases in the amplitude of the stimulus will activate more nerve fibers (motor units) and generate more force.

Similarly, for a fixed stimulus pulse amplitude, increases in the duration of the stimulus pulse will activate more motor units and generate more muscle force.

The stimulation intensity required to activate a given nerve fiber is dependent on the size of the nerve fiber (diameter) and its distance from the electrode (Figure 3B). The stimulation intensity is approximately inversely proportional to the square root of the fiber diameter, such that larger diameter nerve fibers require less intense stimuli for excitation. Similarly, threshold stimulation intensity is approximately proportional to the square of the distance between the electrode and the nerve fiber, such that more intense stimuli are required to activate nerve fibers farther from the electrode.

These factors result in a distribution of threshold stimulation intensities related to the size of the motor nerve fibers and the position of the nerve fibers relative to the electrode (Figure 3C). Recruitment is achieved by activation of different numbers of motor units from this distribution. This must necessarily occur from left to right along the stimulation intensity axis, i.e., nerve fibers with lower intensity thresholds are recruited before nerve fibers with higher intensity thresholds. Thus, increasing stimulus intensity is analogous to cumulative summation (integration) of the distribution of stimulation thresholds. The cumulative probability distribution describes the muscle force as a function of stimulation intensity, and under simple circumstances force muscle force is a sigmoidal function of stimulation intensity (Figure 3D).

The relationship between the force (number of active motor units) and the stimulation intensity is referred to as a recruitment curve, and in practice, muscle-based electrodes often have complex recruitment characteristics (Crago et al., 1980, Popovic et al., 1991). Deviations from a simple sigmoid curve are caused by the non-uniform

distribution of terminal motor nerve fibers in the muscle that lie at different distances from the electrode, and create regions of variable recruitment slope or gain. In the example of Figure 4B the motor nerve branches near the electrode (Figure 4C) and thus two populations of motor nerve fibers lie at two different distances from the electrode resulting in a recruitment curve appearing as the sum of two sigmoids. In regions of low gain, large changes in the stimulus amplitude or pulsewidth generate only small changes in force, while in regions of high gain small changes in stimulus intensity generate large changes in force. In cases where the user voluntarily grades the stimulus parameters, the changes in gain produce poor control characterized by deadbands, overshoot, and hunting behavior (Hines et al., 1992).

Fatigue

Fatigue refers to a reduction in force generating capacity following repeated or prolonged contraction, and will diminish the force evoked by neuromuscular stimulation. This problem is particularly acute in paralyzed muscle that loses mass and force generating capacity and becomes more susceptible to fatigue as a result of disuse atrophy (Gordon and Mao, 1994). Chronic activation of paralyzed muscle (electrically-induced exercise) can reverse some of the effects of disuse atrophy and result in increases in force generating capacity and fatigue resistance (Peckham et al., 1976, Stein et al., 1992). This occurs through activity-dependent increases in muscle mass and muscle fiber-type conversion (Salmons and Vrbova, 1969, Peckham et al., 1973).

Length Force Relationship

The muscle force, or tension, consists of an active component that results from the contraction of the active muscle fibers, and a passive component that results from

stretching tissues that exhibit a spring-like property. Recall that the force generated by a spring, F, is proportion to the change in length, Δx, ($F=k\cdot\Delta x$, where k is the spring constant). The active force generation capacity of skeletal muscle is a function of the muscle length (Figure 4A) (Rack and Westbury, 1969, Baratta et al., 1993). At a constant level of activation, the active force increases as the muscle length increases up to a limit known as the optimal length. As the length is increased beyond the optimal length the active force decreases. The passive force is close to zero at lengths less than the optimal length, but as the length approaches the optimal length passive force increases with further increases in length. Cumulatively, the sum of the active force and passive force is referred to as the total force and it varies with muscle length (Figure 4A). Thus, when considering control of the neuromuscular system, either by the nervous system or by electrical stimulation, one must be aware of not only the changes in force that result from recruitment and rate modulation, but also the changes in force that result from the inherent length-tension properties of the muscle.

Length-Dependent Recruitment

The force produced by neuromuscular stimulation with a muscle-based electrode can be strongly dependent on muscle length, which in turn is determined by the position of the limb (Figure 4B). This effect, termed length-dependent recruitment, results from position-dependent changes in the relative locations of the electrode (placed in or on the muscle) and the motor nerve fibers innervating the muscle (Crago et al., 1980, Grandjean and Mortimer, 1986). At one limb position (muscle length) the electrode may by closer to or more distant from the nerve fibers that at another limb position (Figure 4C). This can affect the threshold for activation, the relationship between stimulation intensity and

muscle force (recruitment curve), and, due to the muscle length tension properties, the maximum force that can be generated. This makes recruitment a non-unique function of the stimulus parameters. Thus, not only does the force generation of muscle depend on its length, but the level of activation (effective intensity of stimulation) can also depend on the muscle length (limb position).

From Force to Movement

The forces generated by contracting muscles create movements by generating moments about joints. The joint moment is equal to the product of the muscle force, F, and the moment arm, d, between the location of the muscle insertion and the joint rotation center (Figure 4D). Thus, all the descriptions above of the characteristics of muscle force (modulation, length-dependence), also apply to the joint moment. This assumes that the moment arm, d, is constant, but in fact d is a function of the joint angle. Thus, muscle force goes through an additional position dependent transformation at the joint.

ELECTRODES FOR NEUROMUSCULAR STIMULATION

Electrodes placed in or on skeletal muscle are used to excite the terminal endings of motor nerve fibers as they enter the muscle. Muscle-based electrodes, including intramuscular wires and epimysial disks (Figures 4E and 4F), have well-established records of safety and efficacy. Coiled wire intramuscular electrodes that can be placed percutaneously (Caldwell and Reswick, 1975, Knutson et al., 2002) or surgically implanted (Akers et al., 1997, Kilgore et al., 2003) and implanted epimysial electrodes (Grandjean and Mortimer, 1986, Akers et al., 1997, Kilgore et al., 2003) possess the

advantage of good selectivity (recruit force in one muscle, but not others), and have little risk of inducing nerve damage since the electrodes are physically removed from the motor axons. Although percutaneous electrodes can dislodge, fracture, or become infected, the incidence of such complications is very small even when implanted for up to one year (Knutson et al., 2002), and the reliability of surgically-implanted electrodes is outstanding (Kilgore et al., 2003).

An alternative to discrete electrodes connected to a common stimulator package (Bhadra et al., 2001) are individual, self-contained microstimulators (Cameron et al., 1997, Loeb et al., 2004). They are placed in skeletal muscle to excite the motor nerve fibers as they enter the muscle, and have properties similar to conventional muscle-based electrodes. These devices can be powered by either rechargeable batteries or via a radio-frequency (RF) inductive link, and are individually addressable so that multiple stimulators can be implanted and controlled to activate multiple motor nerves. The RF versions may also be used to transmit sensor data out from the implant, such that the devices can be configured to sense position, acceleration, or bioelectric signals (e.g., electromyogram) (Loeb et al., 2004).

The primary method of enhancing the function of motor prostheses is to activate additional muscles. In systems employing muscle-based electrodes or microstimulator the necessity to implant at least one electrode or stimulator per muscle has required that only a subset of muscles be chosen for stimulation, thereby limiting the function of these prostheses. Each additional channel requires an additional device thus increasing system complexity, making implant surgery more difficult and lengthy, and increasing the probability of device failure. In addition, the anatomical location of the motor point of

certain muscles, for example the hamstrings, make repeatable and accurate placement of muscle electrodes difficult. Alternative methods of stimulation are under development including electrode arrays placed in or on peripheral nerves or within the central nervous system (Grill, 2001).

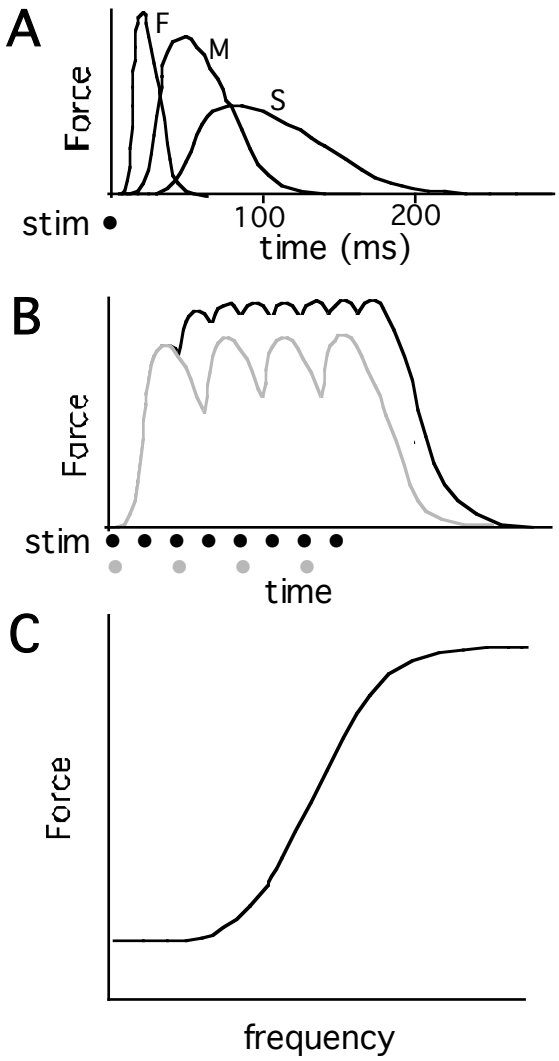

Figure 1 Response of skeletal muscle to electrical stimulation. **A.** Single stimuli result in twitch contractions. The amplitude and time course of the twitch depend on the muscle fiber type (F=fast; M=mixed fast and slow; S=slow). **B.** Repetitive stimuli result in superposition of single twitches. **C.** The force-frequency relationship of skeletal muscle. The force evoked by stimulation increases as the frequency of stimulation increases.

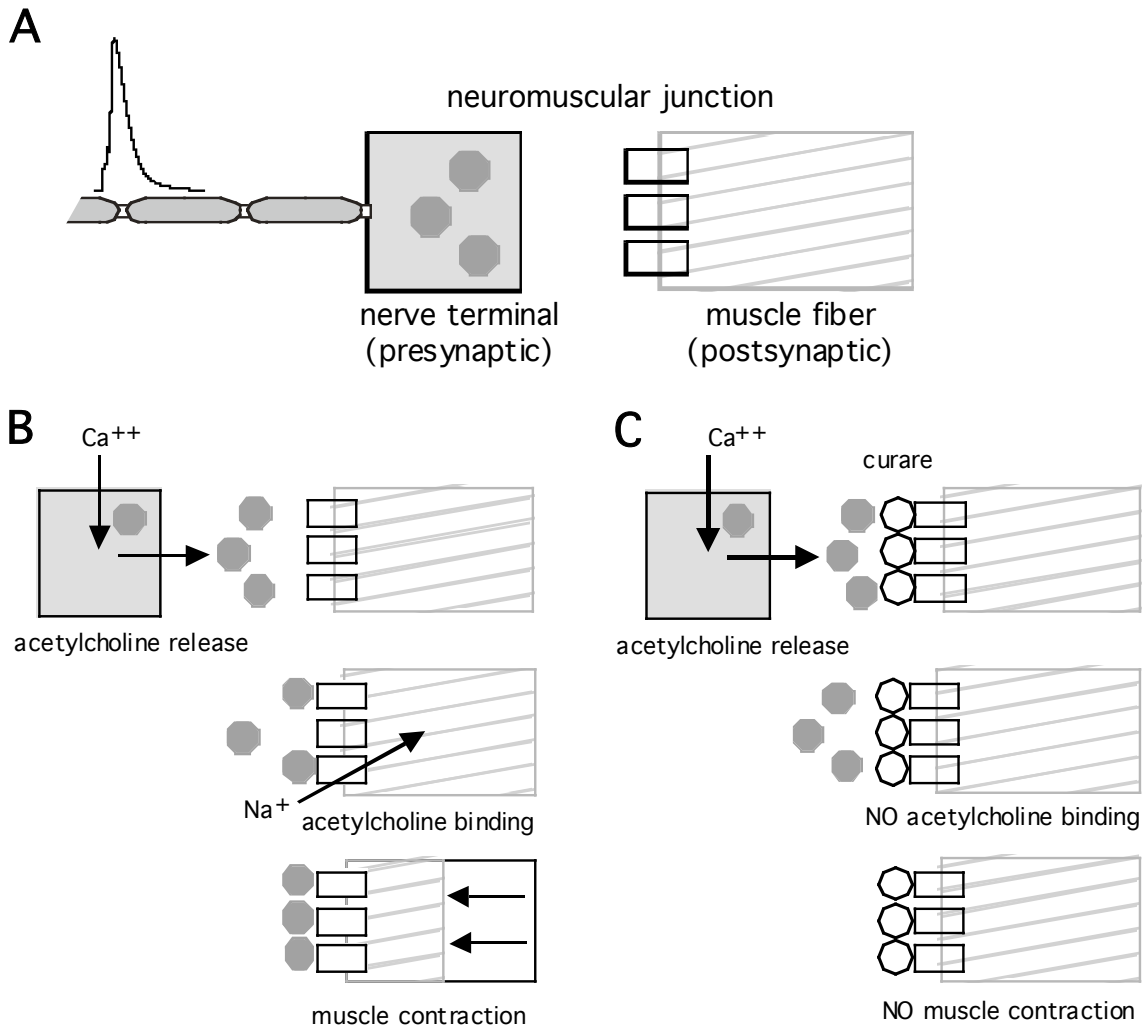

Figure 2 Synaptic transmission and block at the neuromuscular junction. **A.** Neuromuscular stimulation results in generation of an action potential in the presynaptic motor nerve fiber that results in transmission across the neuromuscular junction to effect the postsynaptic muscle fiber. **B.** Calcium influx into the presynaptic terminal results in release of acetylcholine. Acetylcholine binds to postsynaptic acetycholine receptors resulting in depolarization of the muscle cell membrane and subsequent muscle contraction. **C.** Application of a competitive antagonist (curare) blocks the postsynaptic acetylcholine receptors. Although acetylcholine is released as a result of the presynaptic action potential, it cannot bind to the postsynaptic receptors and muscular contraction does not occur.

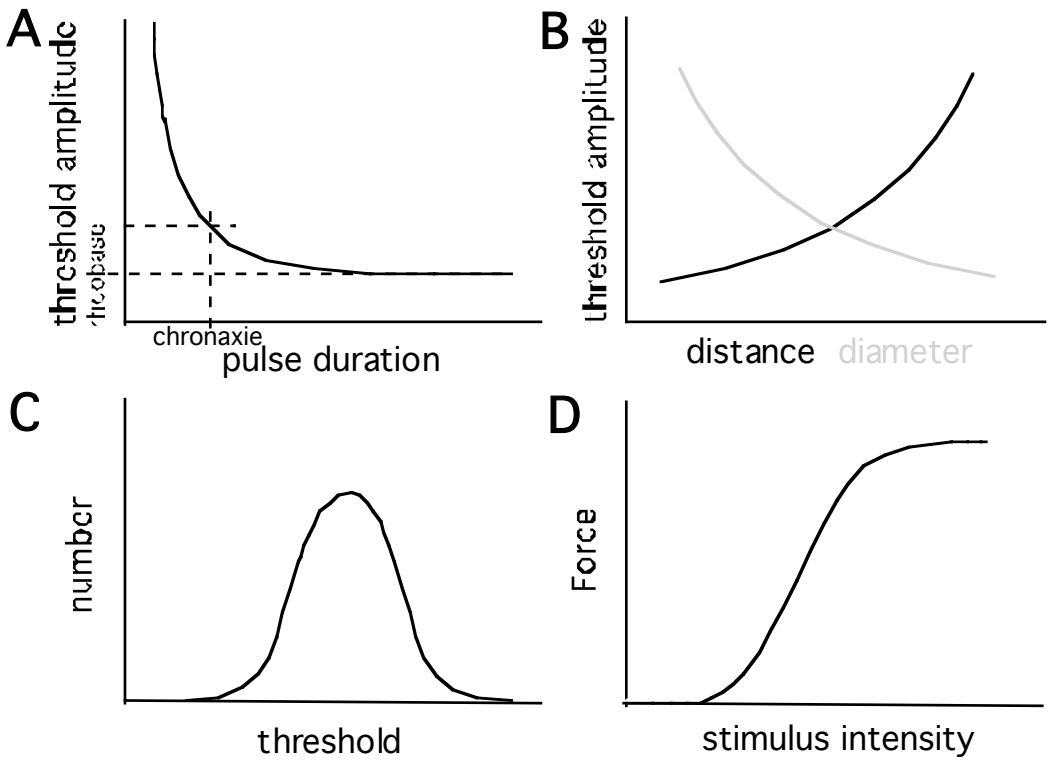

Figure 3 Properties of neuromuscular stimulation. **A.** The strength-duration curve of neural excitation relates the stimulation pulse amplitude to the stimulation pulse duration. The rheobase is the stimulation intensity required for excitation with a stimulus pulse of infinite duration, and the chronaxie is the minimum pulse duration required for excitation when the stimulus amplitude is equal to twice the rheobase intensity. **B.** The threshold intensity required for nerve stimulation varies directly with the distance between the electrode and the nerve fiber and inversely with the diameter of the nerve fiber. **C.** The dependence of excitation threshold on diameter and distance results in a distribution of single nerve fiber thresholds in a motor nerve. **D.** The recruitment curve describes the force (or number of motor units activated) as a function of the stimulus intensity and can be thought of as the cumulative integral of the distribution in **C**.

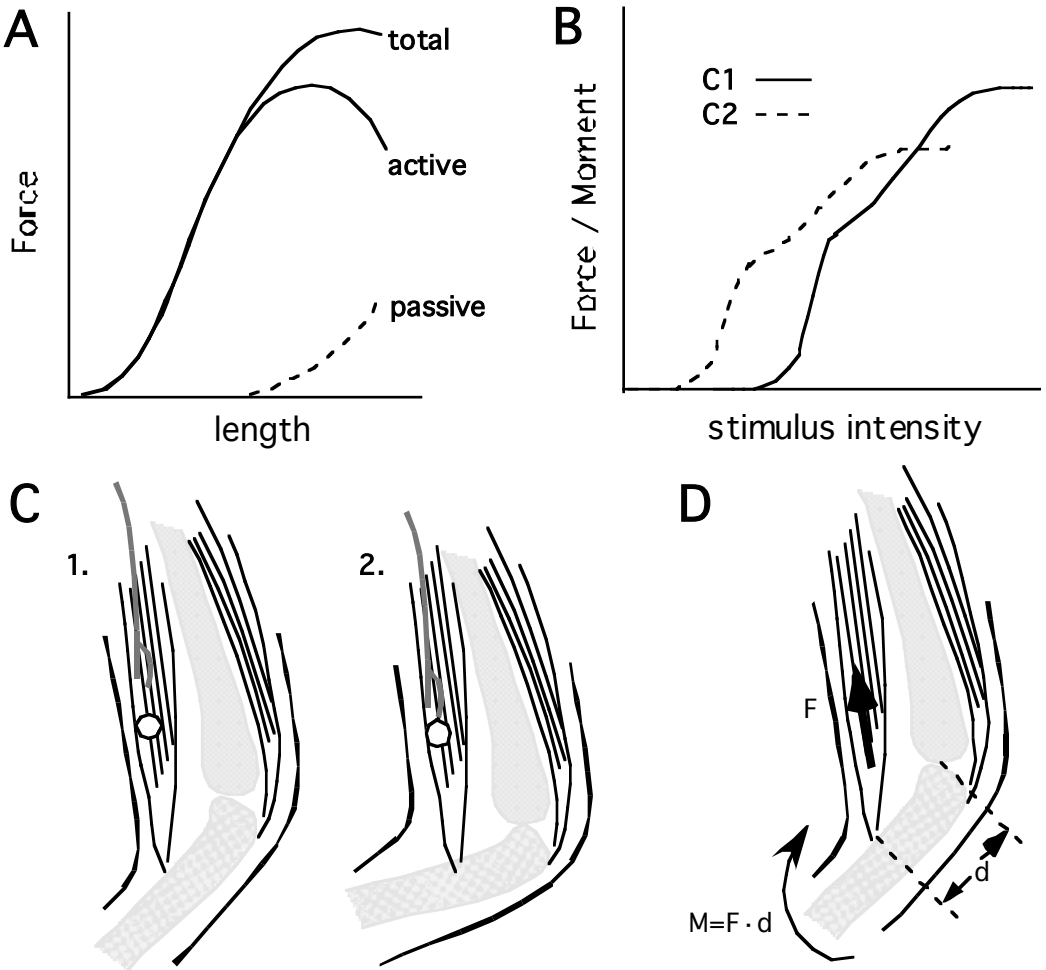

Figure 4 Biomechanical effects on the force / moment produced by neuromuscular stimulation. **A.** The force-length curve of skeletal muscle. The active, passive and total forces produced by a skeletal muscle at a constant level of activation are dependent on the muscle length. **B.** Position dependent recruitment by muscle-based electrodes. Changes in electrode position relative to the motor nerve (shown in C) lead to changes in the relationship between the stimulation intensity and degree of muscle activation. At position C1 the electrode is further from the two branches of the nerve and thus the threshold for activation is higher than in position C2 where the electrode is closer to the two branches of the nerve. The two sections of the sigmoid in each curve represent activation of each of two branches of the motor nerve. The lower maximum force in C2 is a reflection of the length-tension properties of the muscle (shown in A). **C.** Changes in the relative position of the electrode (white disk) relative to the motor nerve (dark gray) occur with changes in joint angle (muscle length). **D.** Muscle force, F, produces movement by generating a moment, M, about a joint equal to the product of F·d, where d is the moment arm between the insertion point of the muscle and the joint rotation center.

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