Chapter 6
A Molecular Basis for Intrinsic Muscle Properties: Implications for Motor Control

Kiisa C. Nishikawa, Jenna A. Monroy, Krysta L. Powers, Leslie A. Gilmore, Theodore A. Uyeno and Stan L. Lindstedt

Contributions of Muscle to Motor Control

Muscles serve a variety of functions during movement, not only shortening to provide actuation but also stabilizing joints, storing and recovering elasticpotential energy, and even absorbing energy (Full and Koditschek 1999; Dickinson et al. 2000; Roberts and Azizi 2011). Over the past 20 years, the idea that muscles not only produce movement but also contribute to control of movement has become well established (Chiel and Beer 1997; Loeb et al. 1999; Nichols et al. 1999; Wagner and Blickhan 1999). Motor control thus comprises not only descending input from the nervous system and proprioceptive feedback, but also muscle viscoelastic properties, body dynamics and interactions with the environment (Hogan 1985; Chiel and Beer 1997; Wagner and Blickhan 1999; Monroy et al. 2007).

Dynamic regulation of muscle stiffness during perturbations is a long known function of proprioceptive sense organs (i.e., muscle spindles and Golgi tendon organs) and spinal reflexes (Matthews 1959). If muscles could also regulate stiffness dynamically, then they would play an important role in motor control. In fact, the nonlinear, viscoelastic behavior of muscles provides instantaneous dynamic tuning of stiffness during load perturbations (Slager et al. 1998). In classic experiments on soleus muscles of decerebrate cats, Nichols and Houk (1976) demonstrated that both sensory reflexes and muscle intrinsic properties regulate muscle stiffness in response to load perturbations. They found that denervated muscles respond instantaneously to perturbations, becoming stiffer during stretch and more compliant during unloading. After a delay of ~20 in cat soleus, the slower acting reflexes blend seamlessly with intrinsic muscle properties by adjusting muscle firing rates and recruiting additional motor units to match the altered load (Matthews 1959). These classic experiments

K. C. Nishikawa (✉) · J. A. Monroy · K. L. Powers · L. A. Gilmore · S. L. Lindstedt
Department of Biological Sciences, Northern Arizona University,
Flagstaff, AZ 86011-5640, USA
e-mail: Kiisa.Nishikawa@nau.edu

T. A. Uyeno
Department of Biology, Valdosta State University, Valdosta, GA 31698-0015, USA

M. Riley et al. (eds.), *Advances in Motor Control,*
Advances in Experimental Medicine and Biology,
DOI 10.1007/978-1-4614-5465-6_6, © Springer Science+Business Media New York 2012

Book ID: 270618_1_En ChapterID: 6 Dispatch Date: 16-10-2012 Proof No: 1

thus demonstrated that the intrinsic viscoelastic properties of muscle are critically important in stabilizing perturbed movements during the ~20 ms prior to the arrival of sensory feedback, and also at the limits of muscle recruitment when muscle force is near its minimum or maximum values and reflexes are least effective at modulating force output (Nichols and Houk 1976). The importance of muscle's instantaneous contributions to motor control is vividly illustrated by imagining an antelope attempting to outrun a lioness, when the pace is fast and any misstep, however small, is fatal.

Since this pioneering work, numerous examples have demonstrated a role for muscle intrinsic properties in stabilizing movement. In spinal frogs, perturbations applied during hindlimb wiping movements are compensated, so that the limb reaches the target in spite of the perturbation. In both intact and deafferented frogs, the hindlimb path after perturbation converges with the unperturbed path, such that the final position is always the same (Richardson et al. 2005). When guinea fowl run over rough terrain, they maintain stability by changing their posture to control velocity. Rapid changes in posture are due to muscle intrinsic properties. This simple mechanism allows for guinea fowl to absorb energy and slow down in response to a drop in terrain (Daley and Biewener 2006; Daley et al. 2009). These results suggest that compensation for perturbations is accomplished by muscle intrinsic properties.

During feeding in frogs, the mouth-opening muscles are pre-loaded prior to movement. During ballistic prey capture, recovery of elastic energy from the muscles and tendons, stored during pre-loading, determines the amplitude and speed of mouth opening (Lappin et al. 2006). These results suggest that intrinsic muscle properties not only provide stability during perturbations, but also determine the amplitude and velocity of ballistic movements.

The nonlinear, intrinsic viscoelastic properties of active muscle are best illustrated in isolated muscles as they are stretched and shortened at constant velocity (e.g., isovelocity experiments, Sandercock and Heckman 1997; Fig. 6.1). During constant velocity stretch, muscle force increases faster in the first 20 ms than during the next 50 ms of the stretch. Likewise, muscle force decreases faster initially during shortening (Fig. 6.1). Rack and Westbury (1974) were among the first to describe this time- and velocity-dependent viscoelastic behavior of muscles, in which stiffness is high initially, followed by yielding. As there were, at the time, no other candidates to whom this behavior could be attributed, they viewed it as a property of the cross-bridges and termed it the *short-range stiffness*.

In addition to this rapid response, there are also longer-lasting changes in the force output of a muscle following stretch or shortening. After stretch, muscles exhibit "force enhancement", an increase in force that persists after stretching has stopped. Likewise, "force depression" is a decrease in force that persists after shortening has stopped (Fig. 6.1). These isovelocity experiments and others like them demonstrate that the force output of muscle depends not only on the activation history of a muscle, but also its movement history and ongoing interactions with the environment. Due to the history dependence of force output, the traditional isometric length–tension and force–velocity relationships are insufficient to predict muscle force output during actual movements (Sandercock and Heckman 1997; Nichols and Cope 2004).

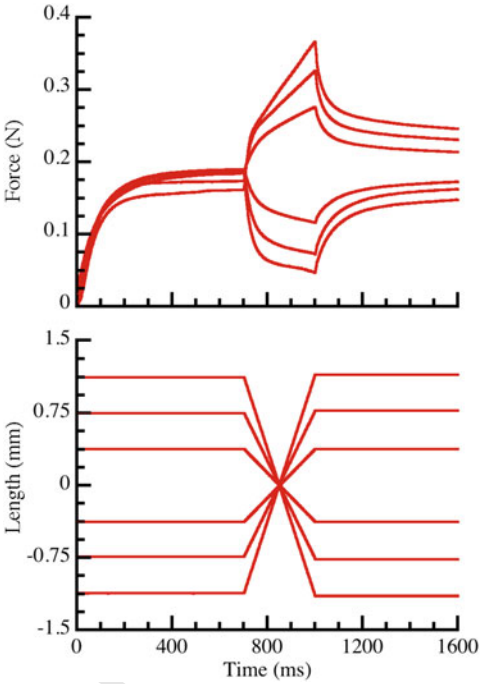

Fig. 6.1 Force (*above*) and length (*below*) data recorded during an isovelocity experiment on a single mouse soleus muscle. The muscle was first stimulated isometrically for 700 ms then stretched or shortened for 300 ms. Traces illustrate the nonlinear, time-dependent and history-dependent viscoelastic behavior of the active muscle

Not only extrafusal muscle fibers, but also the intrafusal fibers of the muscle spindle apparatus exhibit nonlinear, viscoelastic and history-dependent behavior and thus contribute to motor control (Nichols et al. 1999; Huyghues-Despointes et al. 2003a, b; Haftel et al. 2004). Whereas history-dependent behavior affects force output of extrafusal fibers, it appears that the reflex gain of spindle afferents is graded by the amplitude of prior movements in intrafusal fibers (Nichols et al. 1999).

The ability of muscles to adjust their stiffness to changes in load is important for several reasons. First, loads are imposed on a muscle by its environment, not only including reaction forces that result from interactions with external objects, but also loading imposed by the activation of antagonistic muscles as well as inertial and even coriolis forces from the musculoskeletal system. The muscles manage interactions with the environment by virtue of their nonlinear viscoelastic properties.

The fact that a mathematical representation of these interaction forces is complex (Hogan 1985) suggests that the responses of muscles to changing loads may be learned, rather than computed, and in fact in the fastest moving robots, the tuning of feedforward control to emergent body dynamics can sometimes be accomplished only by trial and error (Koditschek et al. 2004).

Despite recognition of the importance of muscle intrinsic properties to motor control, a theoretical framework that accounts for these muscle properties remains largely undeveloped. The widely accepted theory of muscle contraction, the "sliding-filament–swinging cross-bridge" theory, explains muscle contraction as resulting

from the interaction between two motor proteins, myosin and actin, which are arrayed in thick and thin filaments within muscle sarcomeres (Fig. 6.2). Briefly, in this theory, overlap between the sliding filaments determines the active muscle force (Gordon et al. 1966). When a muscle is activated, myosin cross-bridges bind to actin, hydrolyze ATP, and undergo a deformation (swinging) that translates the thin filaments (Huxley 2004), producing muscle force.

However, the sliding-filament–swinging cross-bridge theory and the muscle models derived from it (i.e., Hill-Zajac, length–tension and force–velocity based models; commonly used in muscle simulations) fail to account for history dependent behavior (Sandercock and Heckman 1997; Herzog et al. 2008). Despite decades of intensive research, the molecular basis for these intrinsic properties of muscle has eluded explanation since their original observation in the early 1950s (Abbott and Aubert 1952; Herzog et al. 2008). In the absence of a plausible mechanism, phenomenological models have been used to describe the nonlinear viscoelastic behavior of muscle (Forcinito et al. 1998; Cheng et al. 2000; Lin and Crago 2002). However, these are poor substitutes for a deeper understanding of the underlying mechanisms.

We recently proposed a novel molecular mechanism, the "winding filament" hypothesis that accounts for the viscoelastic properties of active muscle (Nishikawa et al. 2011). Here, we explore the implications of the winding filament hypothesis for informing our understanding of the contributions of muscle intrinsic properties to motor control. We first review the structure and function of titin within muscle sarcomeres. Next, we describe the details of the winding filament hypothesis. Finally, we end by discussing the implications of this hypothesis for understanding the muscle's contributions to motor control.

Titin Structure and Function

The largest known protein, titin (also known as connectin), was also one of the last muscle proteins to be discovered (Maruyama et al. 1976), despite the fact that it is the third-most abundant protein in striated muscle. Although the existence of titin-like fibers was inferred in early structural studies (Huxley and Hanson 1954), titin was discovered more than 20 years after development of the sliding filament theory (Maruyama et al. 1976). For this reason, the development of the sliding-filament–swinging cross-bridge theory proceeded without considering titin.

Titin spans an entire half-sarcomere (~1 mm) from Z-disk to M-line (Gregorio et al. 1999). The overlap of titin molecules in both Z-disks and M-lines produces a titin filament system that is continuous among the entire length of a muscle fiber. Early studies of titin established its roles in maintaining sarcomere integrity (Horowitz et al. 1987) and contributing to passive tension (Linke et al. 1998). Current work focuses on titin's roles in regulating myofibrillar assembly (Gregorio et al. 1999) and cell signaling (e.g., Krüger and Linke 2011).

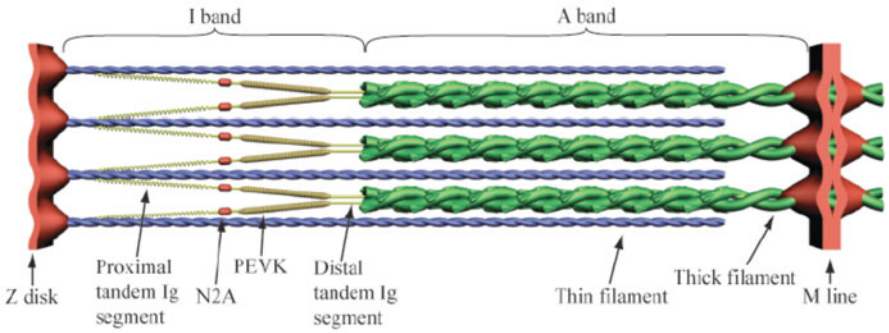

Fig. 6.2 Schematic diagram of a skeletal muscle half-sarcomere, illustrating the layout of titin (*yellow* with *red* N2A segment). Each titin molecule is bound to the thin filaments (*blue*) in the I-band, and to the thick filaments (*green*) in the A-band. For simplicity, thick filaments are illustrated as double-stranded, whereas in vertebrate skeletal muscle, they appear to be triple-stranded. The N2A region is located between the proximal tandem Ig segment and the PEVK segment. (Reprinted from Nishikawa et al. 2011)

Titin's Role in Muscle Passive Tension

The I-band region of titin (Fig. 6.2) is elastic and extends when the sarcomere is stretched, giving rise to passive muscle force (Labeit et al. 2003; Linke et al. 1998). In skeletal muscle, the I-band region of titin is composed of two serially linked spring elements: tandem immunoglobulin (Ig) domains and the PEVK segment (named for its most common amino acids). At relatively short sarcomere lengths, passive stretch straightens the folded tandem Ig domains with little change in passive tension. At longer sarcomere lengths, the PEVK segment elongates and passive tension increases steeply. Within the physiological range of sarcomere lengths, elongation of the PEVK segment largely determines the passive elasticity of skeletal muscle fibers (Linke et al. 1998).

Is There a Role for Titin in Active Muscle?

It has frequently been suggested that titin could function as a spring not only in resting muscles but also in active muscles (Bagni et al. 2002, 2004; Labeit et al. 2003; Reich et al. 2000). As yet, no compelling mechanism has been offered for how titin could play such a role. In resting muscle, titin is far too compliant to contribute significantly to active muscle force (Campbell and Moss 2002). However, several studies have demonstrated that titin stiffness increases in the presence of Ca^{2+}. In active muscle fibers, Ca^{2+} influx increases the tension and stiffness of a non-cross-bridge structure, possibly titin (Bagni et al. 2002, 2004). Ca^{2+} influx increases the stiffness of PEVK fragments as well as muscle fibers (Labeit et al. 2003). Nevertheless, the effects of Ca^{2+} on titin stiffness observed in these studies are ~10 times too small to account for the observed increase in stiffness of muscle fibers upon calcium activation.

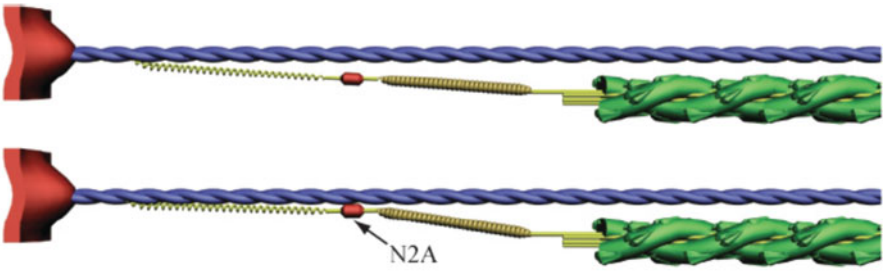

Fig. 6.3 Schematic diagram illustrating the hypothesis that titin is engaged mechanically with Ca^{2+} influx upon muscle activation. (*Above*) resting sarcomere at slack length at low Ca^{2+} concentration (pCa = 9). Titin binds to the thin filaments only near the Z-disk. (*Below*) Upon Ca^{2+} influx (pCa = 4.5), N2A binds to the thin filaments (*blue*) in the I-band, which shortens and stiffens the titin spring in active sarcomeres. (Reprinted from Nishikawa et al. 2011)

Titin has also been implicated in the increase of passive force following deactivation of actively stretched muscle fibers. In myofibrils in which active force production was prevented by removal of troponin C, a Ca^{2+} induced increase in titin-based stiffness was observed, but the increase was also too small to account for passive force enhancement (Joumaa et al. 2008). The results suggest that passive force enhancement requires not only Ca^{2+} influx, but also active force production.

In an innovative series of experiments, Leonard and Herzog (2010) stretched myofibrils, both passive and active, far beyond overlap (i.e., sarcomere lengths up to 6 μm) of the thick and thin filaments (Leonard and Herzog 2010). In these experiments, they found evidence for both an activation-dependent and a force-dependent increase in titin stiffness. At the longest lengths, the difference in stiffness between active vs. passive myofibrils was substantial. Taken together, *these experiments demonstrate that, in active muscle, titin stiffness is increased by Ca^{2+} influx and force development*.

The Winding Filament Hypothesis

Our recent "winding filament" hypothesis (Nishikawa et al. 2011) proposes that the giant, elastic titin protein is first engaged mechanically during Ca^{2+} activation in skeletal muscle, and the cross-bridges then wind titin on the thin filaments, storing elastic potential energy during force development. Storage and recovery of elastic energy in titin accounts for the time- and history-dependent behavior of active muscles.

Mechanical Engagement of Titin Upon Ca^{2+} Activation

Titin is a huge, multidomain protein that corresponds roughly in size to a thousand average-sized protein. Within this giant protein, the N2A region of titin (Fig. 6.3) is in an ideal position to modulate titin stiffness through Ca^{2+} dependent binding to

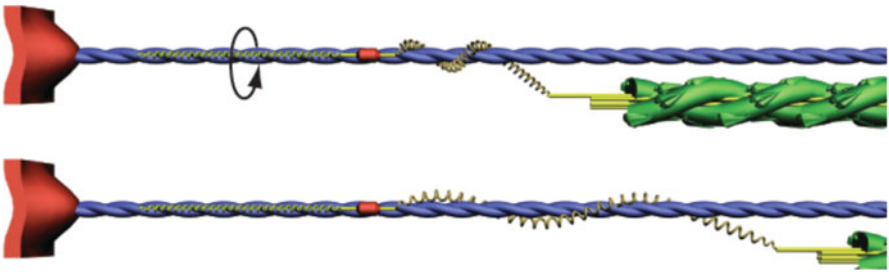

Fig. 6.4 Schematic diagram illustrating how cross-bridge cycling results in titin winding. (*Above*) Cycling of the cross-bridges winds PEVK on the thin filaments (*arrow* indicates direction of rotation). The winding angle depends only on sarcomere geometry. (*Below*) Stretch of an active sarcomere extends the PEVK segment and enhances the active force. (Reprinted from Nishikawa et al. 2011)

thin filaments. Binding of titin to actin at this location would eliminate low-force straightening of proximal tandem Ig domains in the I-band that normally occurs upon passive stretch of myofibrils at slack length (Linke et al. 1998). Furthermore, when Ca^{2+} activated sarcomeres are stretched, the PEVK segment of titin (Fig. 6.3) will elongate at high force. If Ca^{2+} dependent binding between N2A titin and thin filaments could be prevented, then active force production should decrease at short sarcomere lengths because any strain that developed in titin would straighten the tandem Ig segments at low force rather than extend the PEVK segment at higher force. Thus, the contribution of titin to the total active force would be reduced.

Thin Filament Rotation and Titin Winding

In active muscle sarcomeres, cross-bridges likely rotate as well as translate the thin filaments (Nishikawa et al. 2011; Fig. 6.4). Given the structure of the thick and thin filaments, maintenance of stereo specific binding between an actin monomer and its three neighboring thick filaments requires the thin filaments to rotate as the myosin heads translate the thin filaments toward the M-line (Morgan 1977).

As titin is bound to thick filaments in the A-band and to thin filaments in the Z-disk (Funatsu et al. 1993), rotation of thin filaments by the cross-bridges must inevitably lead to winding of titin upon them. Rotation of the thin filaments by the cross-bridges would also produce a torque in alpha-actinin in the Z-disk. Winding of titin on the thin filaments is predicted to change the length and stiffness of PEVK, storing elastic potential energy during isometric force development and active stretch. This energy could be recovered during active shortening.

Unwinding of titin from the thin filaments could be prevented by electrostatic interactions between titin's PEVK segment and the thin filaments (Bianco et al. 2007). Spontaneous dissociation rates of PEVK bound to actin are low, and the force required to break the bonds is approximately equal to the force required to break an actomyosin cross-bridge. Unwinding of PEVK from the thin filaments is

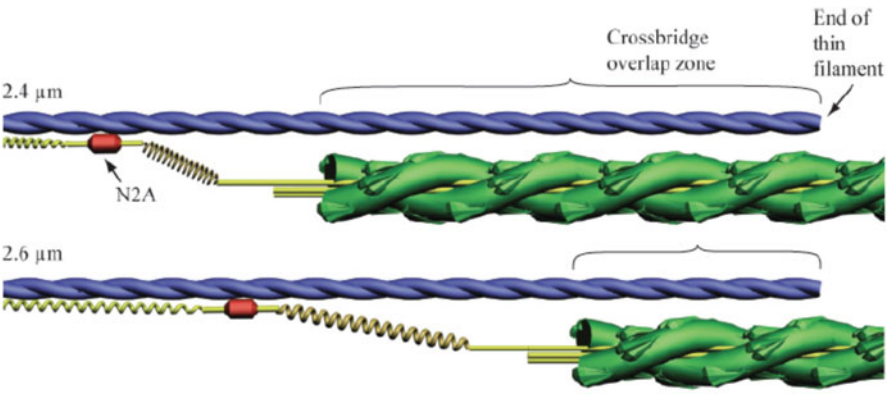

Fig. 6.5 Schematic diagram illustrating the contribution of titin to the force–length relationship. Imagine a muscle or muscle fiber that is stretched passively, and then activated at different lengths. Upon calcium influx, N2A titin (*red*) will bind to the nearest actin monomer in the thin filament (*blue*). Once N2A binds, the active elastic properties will be determined by PEVK titin and will be invariant across a range of lengths until a length is reached at which PEVK titin is extended passively before activation. As long as the binding site for N2A titin depends only on the sarcomere length at the time of activation, then a plateau is predicted in active force. For example, in rabbit psoas muscle a plateau is predicted at sarcomere lengths between 2.4 μm (*above*) and 2.6 μm (*below*). (Reprinted from Nishikawa et al. 2011)

hypothesized to occur during active shortening at low loads when the combined PEVK-actin and cross-bridge forces are too low to hold the torques in titin and alpha-actinin, as well as during muscle relaxation.

Implications For Understanding Motor Control

Here, we address implications of the winding filament hypothesis for understanding motor control. First, we discuss how mechanical engagement of the titin spring upon Ca^{2+} activation provides a mechanism by which nearly invariant contractile and viscoelastic properties can be produced regardless of the initial sarcomere length at which the muscles are activated. Next, we discuss how winding of titin on the thin filaments upon activation changes a muscle's equilibrium position and stiffness as a function of muscle recruitment. These changes, in turn, produce forces that move the limbs to their final position regardless of unexpected perturbations.

Length Invariance of Muscle Contractile and Elastic Properties

The idea that titin is engaged mechanically when N2A binds to the thin filaments upon Ca^{2+} activation has several important implications for understanding the contribution of muscle to motor control. If N2A titin can bind to a thin filament at multiple locations along its length (Fig. 6.5), then muscle contractile (e.g., force, velocity) and

viscoelastic properties will remain relatively constant despite increases in sarcomere length (Edman 1979). The relative constancy of these properties with muscle length has important implications for control of movement. For example, Asatryan and Feldman (1965) demonstrated that, during involuntary arm movements elicited by unloading, as well as voluntary arm movements produced intentionally, the final position of the human arm is controlled by varying the position at which the muscles are activated. Once activated, the nonlinear viscoelastic properties of the muscles move the arm to the final position. The relative constancy of muscle viscoelastic properties across a range of muscle lengths ensures that the passive dynamics are predictable, as well as independent of the joint angle (Feldman and Levin 2009).

Motors vs. Springs: Time- and History-Dependent Properties of Active Muscle

The history-dependent properties of active extrafusal and intrafusal muscle fibers are exactly those expected of nonlinear, time-dependent springs, which produce greater tensile force when stretched and less tensile force when shortened, in proportion to the change and rate of change in length. However, within the framework of the sliding-filament theory, muscles are viewed primarily as motors. Hence, few of the ideas that have been proposed to explain the history-dependent effects deal explicitly with spring properties (see e.g., Rassier and Herzog 2004). Mechanisms of force enhancement during active stretch as well as mechanisms of force depression during shortening have invoked processes that affect the internal work done by the myosin heads during cross bridge cycling (Herzog 1998; Nichols and Cope 2004). These ideas share the common theme that the proposed mechanism interferes with the ability of the cross-bridges to produce force.

In the winding filament hypothesis, both the time dependence and history-dependence of muscle force are viewed as viscoelastic properties associated with the titin spring in muscle sarcomeres. During active stretch, muscle force increases rapidly to values up to nearly twice the maximum isometric force. The force then decays rapidly to a steady state value that increases with the amplitude of the stretch and with sarcomere length. In the winding filament hypothesis, the work done in stretching a muscle will extend titin, storing elastic strain energy. This added force increases with the distance stretched (Nishikawa et al. 2011).

During active shortening, muscle force decreases rapidly and then returns more slowly to a steady state level that depends upon both the amplitude and velocity of shortening. In the winding filament hypothesis, energy stored in titin during isometric force development will be converted to kinetic energy during shortening, and the muscle force will decrease in direct proportion to the distance shortened. The velocity dependence of force depression results from the velocity-dependent unwinding of titin from the thin filaments (Nishikawa et al. 2011).

To demonstrate how the winding filament model accounts for history dependent properties of active muscle, we developed a kinematic model (Fig. 6.6) to quantify the effects of thin filament rotation on titin during isometric force development and

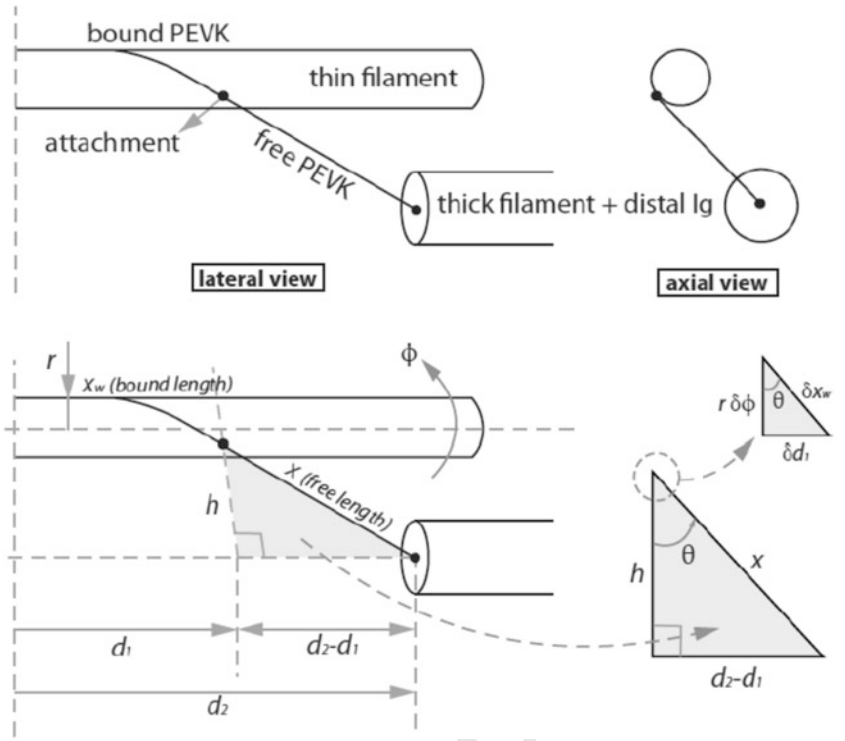

Fig. 6.6 Kinematics of titin winding. Winding angle (θ) is the angle formed between the titin filament and a line (h) parallel to the Z-disk. In the model, the winding angle is determined by sarcomere geometry and increases with sarcomere length. As the winding angle (θ) increases, the length of free titin (x) will decrease for a given angle of thin filament rotation (ϕ). d_1 distance from Z-disk to the point at which bound PEVK becomes free, d_2 distance from Z-disk to distal (C-terminal) end of PEVK, r radius. (Reprinted from Nishikawa et al. [2011])

active stretch. The model is based on a sarcomere structure similar to rabbit psoas muscle (Nishikawa et al. 2011). The model assumes that winding of titin on the thin filaments proceeds until the radial component of the cross-bridge force is equal to the sum of the radial forces in titin and alpha-actinin. As the force develops, the length of bound titin that is wound upon the thin filaments increases, increasing strain and stiffness in the free portion of titin (Fig. 6.6). When active sarcomeres are lengthened by the application of an external force, the work done in elongating free titin is stored as elastic potential energy, resulting in force enhancement at low energy cost.

Increasing strain and stiffness of titin due to thin filament rotation depends on the winding angle of titin upon the thin filament (Fig. 6.6). The winding angle (θ) is defined as the angle formed between the titin filament and a line (h) parallel to the Z-disk. In the model, the winding angle is determined by sarcomere geometry, and increases with sarcomere length. As the thin filament rotation angle (ϕ) increases, the length of the free titin segment decreases and the stress in this segment increases, thereby increasing its effective stiffness. The edge between free and bound titin will also advance toward the m-line, reducing the titin strain.

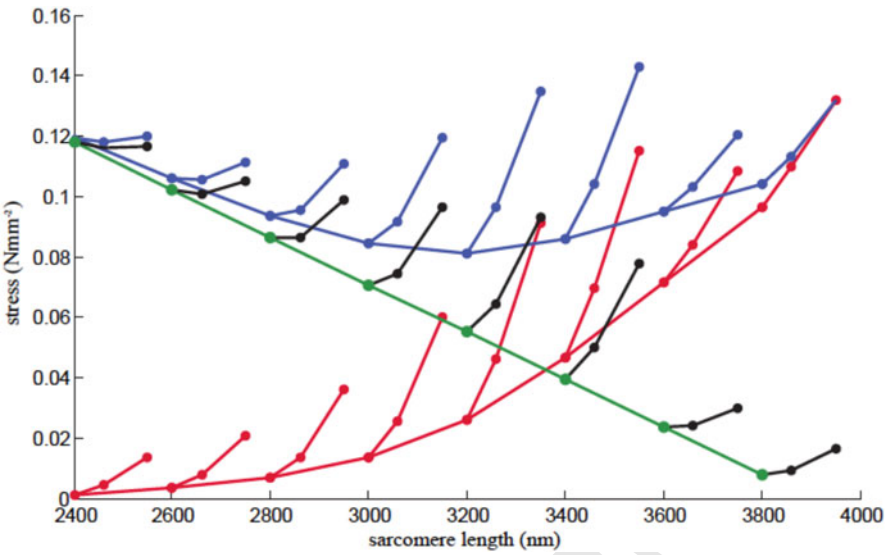

Fig. 6.7 Simulation of residual force enhancement on the descending limb of the force-length relationship. Predicted axial stress due to cross-bridges (*green*) and titin (*red*). Total axial stress (*blue*) is the sum of axial stress due to cross-bridges and titin. Baselines show steady state isometric stress. Branches show increased stress due to stretch. Residual force enhancement (*black*) is the increase in force due to active stretching above the isometric force at the corresponding length. (Reprinted from Nishikawa et al. 2011)

A nonlinear ordinary differential equation (ODE) was used to simulate the kinematics of titin winding and the resulting axial forces for a given profile of thin filament rotation $\phi(t)$ and sarcomere geometry. In the axial direction, the total force is the sum of the axial forces produced by titin and the cross-bridges. In the axial plane, the sum of the torques due to radial forces produced by titin in the I-band and alpha-actinin in the Z-disk are equal and opposite to the torque produced by the cross-bridges (Nishikawa et al. 2011).

Using this model, we simulated the force enhancement on the descending limb of the force–length relationship by alculating the axial forces produced by the cross-bridges and titin in sarcomeres activated at different initial lengths, and then stretched while active (Fig. 6.7). The results are qualitatively similar to experimental observations (Edman et al. 1982). These results demonstrate that the winding filament hypothesis accounts for the observed pattern of force enhancement in actively stretched muscles.

Motor Control and Higher Brain Centers

Theories of motor control abound and no clear consensus has emerged (Ajemian and Hogan 2010). Some workers adopt a hierarchical view of motor control (Cheng et al. 2000), in which higher brain centers (e.g., motor cortex) encode intended

movements at a more abstract level (e.g., intended movement direction) and in a retinocentric coordinate frame (Georgopoulos 1986). At lower levels in the hierarchy (e.g., spinal cord), intended movements are encoded at more concrete levels (e.g., joint torque) and reference frames that are increasingly closer to the muscles that actuate the movements (see e.g., Flanders et al. 1992). Other workers have noted that feedforward control is actually simplified when the nonlinear properties of multijoint systems and intrinsic viscoelastic properties of muscle are taken into account (Hogan 1985; Todorov 2000).

A common theme of all current theories of motor control is that the feedforward controller must anticipate the nonlinear viscoelastic properties of the actuators in order to produce an intended movement. In fact, several recent neurophysiological studies suggest that the human brain anticipates the nonlinear viscoelastic properties of its muscle actuators in the neurally encoded control signals that produce voluntary movements (Feldman and Levin 2009).

The equilibrium point hypothesis (Feldman and Levin 2009) is a case in point. Asatryan and Feldman (1965) demonstrated that, the final position of the human arm during involuntary arm movements elicited by unloading and voluntary arm movements produced intentionally, is controlled by varying the initial position at which the muscles are activated. Once activated, the nonlinear viscoelastic properties of the muscles interact with length feedback to move the arm to the final position. Using transcranial magnetic stimulation to measure motor-evoked potentials, Raptis et al. (2010) and Sangani et al. (2011) showed that the human motor cortex participates in specifying the initial arm position at which the muscles are activated.

The winding filament hypothesis provides realistic biological mechanisms for implementing this simple control strategy. The engagement of the titin spring upon muscle activation provides a mechanism by which nearly invariant muscle force output can be produced when the muscles are activated at varying initial positions. The winding of titin on the thin filaments upon activation provides for changes in a muscle's characteristic length and stiffness as a function of muscle recruitment, which in turn provides the forces that move the limbs to their final positions regardless of unexpected perturbations.

Conclusion

The sliding-filament–swinging cross-bridge theory views muscles primarily as motors. Traditional hill-zajac-type muscle models based on this theory emphasize the length–tension and force–velocity properties of muscle. These models fail to predict movement dynamics because they ignore the history dependence of force output. In contrast, muscle fibers, both extrafusal and intrafusal, actually behave as nonlinear, self-stabilizing controllers that become stiffer when the external load increases and more compliant when the load decreases (Lappin et al. 2006; Monroy et al. 2007). When the load changes unexpectedly, muscle stiffness adjusts instantly without requiring neural input (Nichols and Houk 1976). In our winding filament hypothesis,

the nonlinear viscoelastic properties of muscle are due to (1) Ca^{2+} activation of titin, which mechanically engages the titin spring; and (2) cross-bridge winding of titin on the thin filaments, which stores elastic energy in titin and provides viscoelastic forces that set the equilibrium position of the mechanical system.

During perturbations, intrinsic muscle properties provide stability by adjusting their stiffness instantaneously to changes in load. Thus, the muscles themselves are largely responsible for controlling the interaction between the body and the environment, as well as managing interactions between antagonistic muscles that interact via their loads. During planned movements, these intrinsic properties must be anticipated by the central nervous system, so that descending commands result in the intended movements.

It seems doubtful that a cohesive theory of motor control can be developed in the absence of a predictive model of muscle dynamics, since the central nervous system must necessarily take these into account in planning and anticipating movement. Thus, we believe that the winding filament hypothesis can fill existing gaps in our understanding of motor control. Furthermore, by providing a biological mechanism for muscle-intrinsic viscoelastic properties, the winding filament hypothesis holds great promise for inspiring the design of a new generation of actuators and prostheses that, like muscles, will exhibit self-stabilization based on variable, nonlinear compliance.

Acknowledgments We thank Michael Richardson, Michael Riley, and Kevin Shockley for inviting us to participate in the symposium and for editing this book. T. Richard Nichols and Cinnamon Pace provided helpful comments on the manuscript. Our research was supported by grants IOS-0732949, IIS-0827688, and IOS-1025806 from the National Science Foundation, and by TRIF Growing Biotechnology grants from Northern Arizona University.

References

Abbott BC, Aubert XM (1952) The force exerted by active striated muscle during and after change of length. J Physiol 117(1):77–86

Ajemian R, Hogan N (2010) Experimenting with theoretical motor neuroscience. J Motor Behav 42:333–342

Asatryan DG, Feldman AG (1965) Functional tuning of nervous system with control of movement or maintenance of a steady posture—I. Mechanographic analysis of the work of the joint on execution of a postural task. Biofizika 10:837–846

Bagni MA, Cecchi G, Colombini B, Colomo F (2002) A non-cross-bridge stiffness in activated frog muscle fibers. Biophys J 82:3118–3127

Bagni MA, Colombini B, Geiger P, Berlinguer Palmini R, Cecchi G (2004) Non-crossbridge calcium-dependent stiffness in frog muscle fibers. Am J Physiol Cell Physiol 286:C1353–1357

Bianco P, Nagy A, Kengyel A, Szatmari D, Martonfalvi Z, Huber T, Kellermayer MS (2007) Interaction forces between F-actin and titin PEVK domain measured with optical tweezers. Biophys J 93:2102–2109

Campbell KS, Moss RL (2002) History-dependent mechanical properties of permeabilized rat soleus muscle fibers. Biophys J 82:929–943

Cheng EJ, Brown IE, Loeb GE (2000) Virtual muscle: a computational approach to understanding the effects of muscle properties on motor control. J Neurosci Meth 101:117–130

Chiel HJ, Beer RD (1997) The brain has a body: adaptive behavior emerges from interactions of nervous system, body and environment. TINS 20:553–557

Daley MA, Biewener AA (2006) Running over rough terrain reveals limb control for intrinsic stability. Proc Nat Acad Sci 103:15681–15686

Daley MA, Voloshina A, Biewener AA (2009) The role of intrinsic muscle mechanics in the neuromuscular control of stable running in the guinea fowl. J Physiol 587:2693–2707

Dickinson MH, Farley CT, Full RJ, Koehl MAR, Kram R, Lehman S (2000) How animals move: an integrative view. Science 288:100–106

Edman KA (1979) The velocity of unloaded shortening and its relation to sarcomere length and isometric force in vertebrate muscle fibres. J Physiol 291:143–159

Edman KA, Elzinga G, Noble MI (1982) Residual force enhancement after stretch of contracting frog single muscle fibers. J Gen Physiol 80:769–784

Feldman AG, Levin MF (2009) The equilibrium-point hypothesis—past, present and future. Adv Exp Med Biol 629:699–726

Flanders M, Tillery SIH, Soechting JF (1992) Early stages in a sensorimotor transformation. Behav Brain Sci 15:309–362

Forcinito M, Epstein M, Herzog W (1998) Can a rheological muscle model predict force depression/enhancement? J Biomech 31:1093–1099

Full RJ, Koditschek DE,(1999) Templates and anchors—neuromechanical hypotheses of legged locomotion on land. J Exp Biol 202:3325–3332

Funatsu T, Kono E, Higuchi H, Kimura S, Ishiwata S, Yoshioka T, Maruyam K, Tsukita S (1993) Elastic filaments in situ in cardiac muscle: deep-etch replica analysis in combination with selective removal of actin and myosin filaments. J Cell Biol 120:711–724.

Georgopoulos AP (1986) On reaching. Ann Rev Neurosci 9:147–170

Gordon AM, Huxley AF, Julian FJ (1966) The variation in isometric tension with sarcomere length in vertebrate muscle fibers. J Physiol (Lond) 184:170–192

Gregorio CC, Granzier H, Sorimachi H, Labeit S (1999) Muscle assembly: a titanic achievement? Curr Opin Cell Biol 1:18–25

Haftel VK, Bichler EK, Nichols TR, Pinter MJ, Cope TC (2004) Movement reduces the dynamic response of muscle spindle afferents and motor neuron synaptic potentials in rat. J Neurophysiol 91:2164–2171

Herzog W (1998) History dependence of force production in skeletal muscle: a proposal for mechanisms. J Electromyogr Kinesiol 8:111–117

Herzog W, Leonard TR, Joumaa V, Mehta A (2008) Mysteries of muscle contraction. J Appl Biomech 24:1–13

Hogan N (1985) The mechanics of multi-joint posture and movement control. Biol Cybern 52: 315–331

Huxley HE (2004) Recent X-ray diffraction studies of muscle contraction and their implications. Phil Trans Roy Soc Lond B. Bio 359:1879–1882

Huxley H, Hanson J (1954) Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. Nature 173:973–976

Huyghues-Despointes CM, Cope TC, Nichols TR (2003a) Intrinsic properties and reflex compensation in reinnervated triceps surae muscles of the cat: effect of activation level. J Neurophysiol 90:1537–1546

Huyghues-Despointes CM, Cope TC, Nichols TR (2003b) Intrinsic properties and reflex compensation in reinnervated triceps surae muscles of the cat: effect movement history. J Neurophysiol 90:1547–1555

Joumaa V, Leonard TR, Herzog W (2008) Residual force enhancement in myofibrils and sarcomeres. Proc Biol Sci 275:1411–1419

Koditschek DE, Full RJ, Buehler M (2004) Mechanical aspects of legged locomotion control. Arthropod Struct Dev 33:251–272

Krüger M, Linke WA (2011) The giant protein titin: a regulatory node that integrates myocyte signaling pathways. J Biol Chem 286:9905–9912

Labeit D, Watanabe K, Witt C, Fijita H, Wu Y, Lahmers S, Funck T, Labeit S, Granzier H (2003) Calcium-dependent molecular spring elements in the giant protein titin. Proc Natl Acad Sci U S A 100:13716–13721

Lappin AK, Monroy JA, Pilarski JQ, Zepnewski ED, Pierotti DJ, Nishikawa KC (2006) Storage and recovery of elastic potential energy powers ballistic prey capture in toads. J Exp Biol 209:2535–2553

Leonard TR, Herzog W (2010) Regulation of muscle force in the absence of actin-myosin-based cross-bridge interaction. Am J Physiol Cell Physiol 299:C14–20

Lin CCK, Crago PE (2002) Neural and mechanical contributions to the stretch reflex: a model synthesis. Ann Biomed Eng 30:54–67

Linke WA, Ivemeyer M, Mundel P, Stockmeier MR, Kolmerer B (1998) Nature of PEVK-titin elasticity in skeletal muscle. Proc Natl Acad Sci U S A 95:8052–8057

Loeb GE, Brown IE, Cheng EJ (1999) A hierarchical foundation for models of sensorimotor control. Exp Brain Res 126:1–18

Maruyama K, Natori R, Nonomura Y (1976) New elastic protein from muscle. Nature 262:58–60

Matthews PBC (1959) The dependence of tension upon extension in the stretch reflex of the soleus muscle of the decerebrate cat. J Physiol 147:521–546

Monroy JA, Lappin AK, Nishikawa KC (2007) Elastic properties of active muscle—on the rebound? Exerc Sport Sci Rev 35:174–179

Monroy JA, Powers KL, Gilmore LA, Uyeno TA, Nishikawa KC (2012) What is the role of titin in active muscle? Exerc Sport Sci Rev. (Epub ahead of print)

Morgan RS (1977) Actin rotates as myosin translates. J Theor Biol 67:769–771

Nichols TR Houk JC (1976) Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. J Neurophysiol 39:119–42

Nichols TR Cope TC (2004) Cross-bridge mechanisms underlying the history-dependent properties of muscle spindles and stretch reflexes. Can J Physiol Pharmacol 82:569–576

Nichols TR, Lin DC, Huyghues-Despointes CM (1999) The role of musculoskeletal mechanics in motor coordination. Prog Brain Res 123:369–378

Nishikawa KC, Monroy JA, Uyeno TE, Yeo SH, Pai DK, Lindstedt SL (2011) Is titin a 'winding filament'? A new twist on muscle contraction. Proc Roy Soc Lond B 279:981–990

Rack PMH, Westbury DR (1974) The short-range stiffness of active mammalian muscle and its effect on mechanical properties. J Physiol 240:331–350

Raptis H, Burtet L, Forget R, Feldman AG (2010) Control of wrist position and muscle relaxation by shifting spatial frames of reference for motoneuronal recruitment: possible involvement of corticospinal pathways. J. Physiol 88:1551–1570

Rassier DE, Herzog W (2004) Considerations on the history dependence of muscle contraction. J Appl Physiol 96:419–427

Reich TE, Lindstedt SL, LaStayo PC, Pierotti DJ (2000) Is the spring quality of muscle plastic? Am J Physiol Regul Integr Comp Physiol 278:R1661–1666

Richardson AG, Slotine JE, Bizzi E, Tresch MC (2005) Intrinsic musculoskeletal properties stabilize wiping movements in the spinalized frog. J Neurosci 25:3181–3191

Roberts TJ, Azizi E (2011) Flexible mechanisms: the diverse roles of biological springs in vertebrate movement. J Exp Biol 214:353–361

Sangani SG, Raptis HA, Feldman AG (2011) Subthreshold corticospinal control of anticipatory actions in humans. Behav Brain Res 224:145–154

Sandercock TG, Heckman CJ (1997) Force from cat soleus muscle during imposed locomotor-like movements: experimental data versus Hill-type muscle predictions. J Neurophysiol 77: 1538–1552

Slager GEC, Otten E, Nagashima T, Van WIlligen JD (1998) The riddle of the large loss in bite force after fast jaw-closing movements. J Dent Res 77:1684–1693

Todorov E (2000) Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3:391–398

Wagner H, Blickhan R (1999) Stabilizing function of skeletal muscles: an analytical investigation. J Theor Biol 199:163–179