Considerations on the history dependence of muscle contraction

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Rassier, Dilson E., and Walter Herzog. Considerations on the history dependence of muscle contraction. J Appl Physiol 96: 419–427, 2004; 10.1152/japplphysiol.00653.2003.—When a skeletal muscle that is actively producing force is shortened or stretched, the resulting steady-state isometric force after the dynamic phase is smaller or greater, respectively, than the purely isometric force obtained at the corresponding final length. The cross-bridge model of muscle contraction does not readily explain this history dependence of force production. The most accepted proposal to explain both, force depression after shortening and force enhancement after stretch, is a nonuniform behavior of sarcomeres that develops during and after length changes. This hypothesis is based on the idea of instability of sarcomere lengths on the descending limb of the force-length relationship. However, recent evidence suggests that skeletal muscles may be stable over the entire range of active force production, including the descending limb of the force-length relationship. The purpose of this review was to critically evaluate hypotheses aimed at explaining the history dependence of force production and to provide some novel insight into the possible mechanisms underlying these phenomena. It is concluded that the sarcomere nonuniformity hypothesis cannot always explain the total force enhancement observed after stretch and likely does not cause all of the force depression after shortening. There is evidence that force depression after shortening is associated with a reduction in the proportion of attached cross bridges, which, in turn, might be related to a stress-induced inhibition of cross-bridge attachment in the myofilament overlap zone. Furthermore, we suggest that force enhancement is not associated with instability of sarcomeres on the descending limb of the force-length relationship and that force enhancement has an active and a passive component. Force depression after shortening and force enhancement after stretch are likely to have different origins.

force depression; force enhancement; instability; sarcomere nonuniformity

The cross-bridge model of muscle contraction was proposed by Huxley (38) and was further characterized in experiments conducted in his laboratory (41). Together with the sliding filament theory (39, 40, 42, 43), and strengthened by the description of the sarcomere force-length relationship (27), the cross-bridge model has been accepted to the point that it may be considered a true scientific paradigm. According to Kuhn (48), a scientific paradigm is expected to explain most but not necessarily all experimental observations in a given area of investigation. In the field of muscle mechanics and physiology, most studies are interpreted and explained within the framework of the cross-bridge model.

Abbott and Aubert (1) observed that the steady-state isometric force after active shortening and active stretching of muscles is lower and higher, respectively, than the purely isometric force at the corresponding lengths. These results have been observed consistently for over 50 years in a variety of experimental preparations (e.g., Refs. 19, 21, 30, 50). This history dependence of force production is typically not accounted for in the mathematical formulation of the cross-bridge model of muscle contraction (38, 41) and cannot be explained directly by the degree of myofilament overlap in sarcomeres (27).

In the past two decades, it has been suggested repeatedly that force depression after shortening and force enhancement after stretching are associated with nonuniformity and dispersion of sarcomere lengths (e.g., Refs. 10, 19, 45, 56–58, 73). By using sarcomere length nonuniformity and dispersion, many results could be interpreted without altering the basis of the cross-bridge model of muscle contraction, thereby providing a convincing and simple explanation for experimental findings that had no ready explanation on the molecular level. However, there is mounting evidence that sarcomere length nonuniformities alone cannot explain force depression after shortening and force enhancement after stretch (28, 32, 61, 63, 64). Furthermore, hypotheses based on novel findings have been proposed to explain history-dependent properties of muscle contraction (5, 32, 34).

The purpose of this review is to present key observations associated with force depression after shortening and force enhancement after stretch, to describe the main hypotheses that have been proposed to explain these history-dependent phenomena (including the sarcomere length nonuniformity hypothesis), and to critically interpret the experimental evidence.
Experimental Observations

An example of force depression after active muscle shortening from experiments on a single muscle fiber is shown in Fig. 1. During shortening, force rapidly decreases, and once shortening is completed, force recovers and attains a new steady-state value within a few seconds (19, 30, 33, 58). This steady-state force is lower than the purely isometric force obtained at the corresponding final length.

The amount of force depression has been found to increase with increasing amplitudes of shortening (1, 30, 34, 55, 58), decreasing speeds of shortening (1, 13, 30, 34, 58), and increasing forces for constant speeds during the shortening phase (30). Force depression after shortening appears largely unaffected by previous muscle stretch (31). Absolute force depression in human muscles increases with increasing activation (13).

Mechanisms of Force Depression After Shortening

There are a number of hypotheses that have been proposed in the literature to explain force depression. The following hypotheses are the most prominent in our view: 1) sarcomere length nonuniformity (19, 45, 58), 2) accumulation of fatigue products (28), and 3) stress-induced inhibition of cross-bridge attachment (55).

Sarcomere length nonuniformity hypothesis. The sarcomere length nonuniformity hypothesis may be explained as follows (45, 58). During shortening of a muscle (fiber) on the descending limb of the force-length relationship, sarcomeres are assumed to shorten by different amounts because of instability. Some sarcomeres shorten more than average; these sarcomeres may shorten to a degree that places them on the ascending limb of the force-length relationship (58). This nonuniform behavior leads to a situation in which these two groups of sarcomeres, after attaining force equilibrium, produce tension that is smaller than that produced at the corresponding length obtained during an isometric contraction in which sarcomeres are assumed to be at relatively uniform lengths (Fig. 2).

The sarcomere length nonuniformity hypothesis provides the following testable predictions: 1) force depression should be abolished when sarcomere lengths are kept uniform during and after shortening; 2) force depression should not be ob-
served on the stable ascending limb of the force-length relationship, because large sarcomere length nonuniformities are not supposed to happen in this region; and 3) force depression should be associated with a slight increase in stiffness, because after muscle (fiber) shortening some sarcomeres are assumed to be on the ascending limb (or plateau) of the force-length relationship.

Regarding prediction 1, Edman et al. (19) investigated force depression with and without control of sarcomere length, by using the segment length clamping technique (27). Force depression was observed when sarcomere lengths were not controlled, but force depression was eliminated when sarcomere lengths were kept uniform, suggesting that force depression was associated with the development of sarcomere length nonuniformity. However, Granzier and Pollack (28) performed essentially the same experiments as Edman et al. (19) but observed opposite results, reaching opposite conclusions. They found that force depression was similar in single fibers undergoing active shortening with and without segment length control, therefore concluding that force depression occurred even in the absence of sarcomere length nonuniformities. Naturally, Granzier and Pollack (28) may have been unable to detect small sarcomere length nonuniformities in their system and so may have missed the positive result observed by Edman et al. (19). However, for lack of further evidence, the results of these two studies remain inconclusive.

Regarding prediction 2, small levels of force depression have been observed on the stable ascending limb of the force-length relationship in different preparations (13, 28, 30, 33). Regarding prediction 3, there are few studies that investigated systematically the relationship between force depression and stiffness. Interpretation of these studies is complicated by the fact that fiber or muscle stiffness is not linearly related to the proportion of attached cross bridges, because of the well-known compliance of the myofilaments and other structures that influence fiber and muscle stiffness measurements. Nevertheless, Sugi and Tsuchiya (69) observed that force depression is associated with a decreased stiffness after shortening in single fibers, compared with the stiffness obtained during isometric contractions at the corresponding final length. Similar results were observed by Lee and Herzog (49) using the adductor pollicis muscle stimulated artifically. These two results suggest, but do not prove, that force depression may be associated with a decrease in the proportion of attached cross bridges.

Summarizing, some of the specific predictions arising from the sarcomere length nonuniformity theory are not always satisfied in experimental studies, and, therefore, it seems unlikely that it can account for the experimentally observed force depression after active muscle shortening.

Accumulation of fatigue products hypothesis. Granzier and Pollack (28) suggested that an increase in protons (H⁺) and inorganic phosphate (Pᵢ) resulting from shortening could be responsible for force depression. It has been shown that an accumulation of H⁺ and Pᵢ during repetitive stimulation causes muscle fatigue (77, 78). ATP consumption increases steeply with the amount of work, consequently increasing H⁺ and Pᵢ; therefore, one might expect a great increase in H⁺ and Pᵢ when mechanical work is performed during shortening compared with an isometric contraction. Because H⁺ and Pᵢ accumulations cannot be removed quickly (<1 s), but rather take minutes to regain resting levels, this hypothesis allows for the following testable predictions: 1) force depression should be long lasting, and 2) force depression should not be abolished by short deactivation of the muscle.

It has been shown repeatedly that force depression is long lasting (1, 18, 30, 33, 34, 45, 58). However, several studies have shown that sufficiently long (~0.5–1.0 s) periods of force release produced by deactivation of muscles abolishes force depression instantaneously (1, 30, 45, 58), suggesting that this hypothesis is not correct.

Stress-induced inhibition of cross-bridge attachment hypothesis. Maréchal and Plaghki (55) suggested that force depression may be related to a stress-induced inhibition of cross-bridge attachments in the myofilament overlap zone that is newly formed during shortening. When muscle is activated, stress causes a small elongation of the thin and thick filaments (thick and thin filaments are slightly compliant within the physiological load range) (26, 44, 47, 59, 76), possibly resulting in angular distortions of the myosin binding sites (12). The greater the stress during activation, the greater the angular distortions that may cause inhibition of cross-bridge attachments. When the muscle is then shortened, but the stress in the thin filaments is maintained, the probability of cross-bridge attachment in the newly formed overlap zone may be reduced (Fig. 3).

![Fig. 3. Schematic representation of the idea that FD is caused by a stress-induced inhibition of cross-bridge attachment in the overlap zone formed by muscle shortening. Imagine that the muscle is isometrically activated at an average sarcomere length (A). The actin filament is stretched because of its compliant nature. While shortening to the new length (B), stretched parts of the actin filament enter the overlap zone. It is assumed that attachment of cross bridges to the stretched parts of actin is inhibited in a stress-dependent way; therefore, the amount of force and the magnitude of shortening will influence the magnitude of force depression in this theory.](http://jap.physiology.org/)
This mechanism of force depression provides the following testable predictions: 1) force depression should be long lasting if myofilament stress is maintained but should be abolished instantaneously on full stress release, 2) force depression should be associated with a decreased stiffness, and 3) force depression should increase with increasing shortening distances, and with increasing forces during shortening, and, therefore, force depression should be directly related to the mechanical work produced during shortening.

All these predictions have been supported by experimental results. Force depression is long lasting (1, 28, 30, 33, 34, 45, 58), but when the stress from muscle or fiber preparations is released for brief moments (by deactivation), such that force will not go to zero, there is a loss of force depression that is directly proportional to the decrease in force during stress release (34). If deactivation is long enough, so that force goes to zero, all force depression is abolished on reactivation (1, 34). Force depression and stiffness are closely correlated; i.e., the greater the force depression, the smaller the muscle or fiber stiffness (49, 69). Finally, it has been shown that force depression increases with the mechanical work produced during shortening (1, 30, 33, 34, 55, 58).

On the basis of the evidence presented above, and until experiments have been conducted to disprove directly the hypothesis of stress-induced cross-bridge inhibition, it should be considered as a potential candidate to explain force depression after shortening.

Summary. Although in some circumstances the sarcomere length nonuniformity theory relates well to force depression, specific predictions from the hypothesis have been rejected in different experiments. There is agreement that force depression is 1) directly associated with a decrease in stiffness (49, 69) and 2) directly related to the magnitude of mechanical work produced during the shortening phase (34). If we assume that stiffness from non-cross-bridge-related structures is constant, and that cross-bridge attachments along the myofilaments are random for the isometric reference and the force-depression states, then changes in stiffness reflect changes in the proportion of attached cross bridges (25), albeit not in a linear proportional way. Therefore, it appears that force depression is caused by a decrease in the proportion of attached cross bridges and not by a decrease in the average force per cross bridge.

If so, the question arises: How does the proportion of attached cross bridges decrease with the magnitude and force during shortening? One possibility is that there is a stress-induced inhibition of cross-bridge attachment in the myofilament overlap zone that is newly formed during active muscle shortening, as proposed by Maréchal and Plaghki (55). When stress is released completely from a muscle or fiber, force depression is abolished instantaneously (1, 34), and when stress is released incompletely, force depression decreases with increasing amounts of stress release (34). The detailed mechanism of force depression caused by a shortening-induced decrease in the proportion of attached cross bridges is not known and will require further research.

**FORCE ENHANCEMENT AFTER MUSCLE STRETCH**

**Experimental Observations**

Typical tracings of force enhancement after active stretch in experiments conducted with single muscle fibers are shown in Fig. 4. During active stretch, force rapidly increases (20, 21, 23, 32, 35, 64). After the stretch is completed, force decreases and reaches a steady state until the end of activation (21, 23, 32, 35, 64). This steady-state force is higher than the purely isometric force observed at the corresponding final length.

Most studies show that the amount of force enhancement increases with increasing amplitudes of stretch (1, 20, 21, 64) and increasing fiber or sarcomere lengths (20, 21, 64) but is independent (or nearly so) of the speed of stretch (1, 21, 64). Recently, it has been shown that, at long muscle lengths, force enhancement is accompanied by a long-lasting increase in the passive force after deactivation of the muscle or fiber (32, 35, 50, 64, 66, 67).

**Mechanisms of Force Enhancement After Stretch**

The following comprise the primary hypotheses that have been proposed to explain force enhancement after stretch: 1) sarcomere length nonuniformity and instability (45, 56–58), 2) increase in the proportion of attached cross bridges (5), and 3) engagement of a passive element (32, 35, 60).

* Sarcomere length nonuniformity and instability hypothesis. Julian and Morgan (45) observed that, during stretch of single fibers on the descending limb of the force-length relationship, sarcomere lengths changed nonuniformly. Sarcomeres near the center of the fibers were observed to stretch more than average, whereas sarcomeres near the end of the fiber stretched less than average, remaining almost isometric. On the basis of such evidence, Morgan (57) suggested that most active force after stretch is produced by the sarcomeres that did not stretch significantly, whereas the sarcomeres that were stretched to a great extent would quickly reach a length at which myofilament overlap was lost. At this point sarcomeres would "pop" (57) and be supported entirely by passive elements. The final force produced by these two populations of sarcomeres would be greater than the force produced during isometric contractions at the corresponding final length, achieved with a relatively uniform distribution of sarcomere lengths (Fig. 5).

![Fig. 4. Force enhancement (FE) after stretch of a single muscle fiber isolated from the lumbrical muscle of frog. In the length traces, 1.0 corresponds to Lø. Starting at a length of 5% greater than Lø, the fiber was stretched by 15% of the fiber length along the descending limb of the force-length relationship, at a speed of 40% fiber length/s. Isometric contractions, performed at Lø, and at the corresponding initial length (L1) and L2 are also shown.](http://jap.physiology.org)
The following testable predictions:

1. Force enhancement should be abolished when sarcomere lengths are kept uniform during and after stretch.
2. Force enhancement should not be observed on the stable ascending limb of the force-length relationship.
3. Force enhancement should not be greater than the isometric force at optimal length.

Edman et al. (21) found that force enhancement was produced not only by a fixed-end muscle fiber but also by individual "clamped" segments of the fiber containing uniform sarcomere lengths. In fact, investigators have failed to find large sarcomere length (37) or fiber segment length (21, 69) nonuniformities after stretch. Therefore, it appears that force enhancement is possible in the absence of gross sarcomere length nonuniformity.

Studies performed in different laboratories have shown a small but consistent force enhancement on the ascending limb of the force-length relationship in experiments conducted with single fibers from frog (61, 68) (Fig. 6), the cat soleus (32), the human adductor pollicis (14, 50), and the human dorsal interosseus (11).

We performed a series of experiments with single muscle fibers aimed at testing the prediction that force after stretch could not be greater than the isometric force produced on the plateau of the force-length relationship. When stretch was initiated at a length slightly longer than optimal length (the length at which active isometric force is greatest), and given the right stretch conditions (amplitude, speed), the steady-state isometric force after stretch exceeded the maximal isometric force produced at optimal length (64) (Fig. 4). This result was confirmed statistically in a study with 28 separate fiber preparations (Fig. 7). A steady-state force enhancement above the plateau of the force-length relationship cannot be caused by nonuniform sarcomere lengths alone.

Studies on the myofibril level. Recently, our laboratory performed a series of active stretch experiments with isolated myofibrils, a preparation in which all sarcomeres (typically

Fig. 5. Schematic representation of the sarcomere length nonuniformity and instability hypothesis for force enhancement. A, Average sarcomere (fiber) length; • different populations of sarcomeres. During stretch of a muscle fiber (from A to B), some sarcomeres are stretched by a small amount (C), whereas other sarcomeres are stretched more than average (D). The overstretched sarcomeres will eventually "pop" and are supported by passive force exclusively (E). At equilibrium, total force is greater than the isometric force at the corresponding Ls, generating FE.

Fig. 6. FE after stretch along the ascending limb of the force-length relationship of a single fiber from the lumbrical muscle of frog. In the length traces, 1.0 corresponds to the L0. Starting at a length of 20% below L0, the fiber was stretched by 10% of the fiber length, at a velocity of 40% fiber length/s. The isometric contraction performed at the corresponding L0 is also shown.

Fig. 7. Steady-state force-length relationship (●) and the steady-state forces obtained after active stretches of different amplitudes starting at 5% (○), 10% (●), and 15% (△) above L0 (1.0 on the length axis). Forces were normalized relative to the maximal isometric force. Note that, for several conditions, the steady-state force after active stretch is greater than the isometric force at L0.
7–30) are arranged in series and can be tracked during activation and stretch (63). On activation on the descending limb of the force-length relationship, sarcomere lengths along the myofibril were nonuniform (Fig. 8). During stretch of the myofibril, all sarcomeres were elongated, albeit by different amounts. Despite length differences after the stretch, sarcomeres remained at a constant length during the isometric phase after myofibril stretching; i.e., they were perfectly stable (63). Therefore, force enhancement of isolated myofibrils occurred in the absence of sarcomere length instability.

The experimental evidence from studies performed on different structural levels contradicts some of the major predictions arising from the sarcomere instability and sarcomere length nonuniformity hypothesis. Although sarcomeres on the descending limb of the force-length relationship of myofibrils were found to be nonuniform on activation and stretch, they seemed to be perfectly stable. Therefore, sarcomere instability and sarcomere length nonuniformity do not appear to be the sole cause of the force enhancement observed experimentally.

Increase in the number of attached cross bridges hypothesis. Force enhancement can be accomplished if, after stretch, there is an increase in the proportion of attached cross bridges to actin (5, 29). If this hypothesis is correct, force enhancement should be accompanied by an increase in muscle or fiber stiffness.

Experiments in which muscle or fiber stiffness was measured in the force-enhanced state as well as in the isometric reference state are inconclusive. In some experiments performed with single fibers, stiffness in the force-enhanced state was found to be the same as that measured during the corresponding isometric reference contractions (45, 69). However, others have reported an increase in stiffness in the steady-state force-enhanced state in cat soleus (31).

Assuming that cross-bridge dynamics play a role in force enhancement, two hypotheses have been suggested to explain how the proportion of attached cross bridges may be increased by active stretch: a reorientation of thin filaments to a position closer to the thick filaments, which would increase the probability of cross-bridge attachment (5), and phosphorylation of the regulatory light chains of myosin (18).

Myosin light chain phosphorylation is believed to move the cross bridges toward the thin filament (54), closer to actin attachment sites, thereby potentially increasing the probability of myosin-actin attachments (71, 72). If stretch induces an increase in myosin phosphorylation, it may produce the observed force enhancement. Because the rate constant for dephosphorylation of the light chains is very slow (70), myosin would likely remain phosphorylated for a long time after stretch, thus producing a long-lasting force enhancement. For this mechanism to work, either some biochemical step along the myosin phosphorylation path would have to be affected by active stretch (e.g., the activity of myosin light chain kinase or phosphatase), or, alternatively, phosphorylation would have to be upregulated by stretch per se. There is no evidence supporting and/or rejecting either possibility.

There is no conclusive evidence to reject the hypothesis that force enhancement is associated with an increase in the proportion of attached cross bridges after stretch. It remains a potential candidate, but additional experiments have to be conducted to clarify the differences in the results regarding stiffness in the enhanced-force state.

Alternatively, force enhancement could be accomplished if the average force were increased in cross bridges after stretch. If, during stretch, cross bridges were brought to a state that facilitates force production, and, furthermore, if they were to stay in that state for subsequent cross-bridge cycles, then a change in cross-bridge force could cause the observed force enhancement. However, there is no direct evidence supporting this idea.

Engagement of a passive-element hypothesis. It has been suggested that force enhancement may be associated with the engagement of a passive element on activation and the extension of this passive element during active stretch (32, 35, 60). This mechanism has been used in models aimed at capturing the history-dependent effects of dynamic muscle contraction (24), and furthermore it provides the following testable predictions: 1) force enhancement should be associated with an increase in the force produced by passive elements after active stretch, and 2) shortening introduced before a given amount of stretching should decrease force enhancement in a dose-dependent manner, because the passive element would be shortened.

Figure 9. FE in a single muscle fiber isolated from the lumbrical muscle of frog. In the length traces, 1.0 corresponds to Lm. Starting at a length of 5% greater than Lm, the fiber was stretched 15% along the descending limb of the force-length relationship, at a speed of 40% fiber lengths/s. A passive stretch and an isometric contraction performed at the corresponding Ls are also shown. After the active stretch, force is greater than the isometric force recorded at Ls. There is also a passive force enhancement (PFE) after the active but not the passive stretch.
before being stretched and elongation from its initial length would be diminished compared with the case in which stretching was not preceded by shortening.

In a series of recent studies, it has been shown that force enhancement is accompanied by an increase in the passive force after active, but not passive, muscle stretch (32, 35, 50, 64, 67) (Fig. 9). We refer to this phenomenon as “passive force enhancement.” Studies performed in our laboratory have shown that passive force enhancement is long lasting (>25 s) (35), increases with stretch magnitude and initial muscle length, but is independent of the speed of stretch (32, 35, 50). However, passive force enhancement only occurs at long muscle or fiber length at which passive force is naturally occurring.

If a passive element is engaged on activation, and stretching this passive element is responsible for part of force enhancement, then shortening the passive element before stretch should decrease the level of the total and the passive force enhancement. We observed a decrease in total (31, 32, 35, 51, 62) and passive (32, 35, 62) force enhancement that was directly related to the amplitude of shortening preceding the stretch.

There are two independent observations that are consistent with the idea that a passive element may be engaged on activation and may contribute to the total force enhancement. Bagini and colleagues (6, 7) showed that, on activation of muscle fibers, there is an instantaneous increase in stiffness that is not dependent on cross-bridge attachment. This passive fiber stiffness increases with the magnitude of stretch and sarcomere length and is independent of the speed of stretch, properties that agree with the passive force enhancement observed in cat soleus (32, 35).

Edman and Tsuchiya (23) performed experiments in which single fibers were released to shorten against small loads after stretch and after isometric contractions. On release, the length transients after stretch showed a greater and steeper decrease than those obtained during the isometric contractions. This result was attributed to the release of strain from elastic structures that developed during stretch. Such strain was associated with nonuniform distribution of length changes during stretch, inside the fibers (half-sarcomeres being stretched more than others), as well as between myofibrils.

The origin of the passive force enhancement is unknown, but the giant molecular spring titin has been implicated as a possible candidate (32, 60). Titin is responsible for passive force in skeletal and cardiac muscles at long sarcomere lengths (46, 65). If the stiffness of titin is changed on activation and stretch, this protein could be responsible for the passive force enhancement observed experimentally and could contribute to the total force enhancement. Evidence of an increase in titin’s stiffness on active stretching is lacking, but research needs to be performed to elucidate the detailed mechanism underlying passive force enhancement.

**Summary.** The hypothesis that nonuniformity of sarcomere lengths, associated with instability on the descending limb of the force-length relationship, is the exclusive mechanism responsible for force enhancement after stretch cannot be accepted, because specific predictions based on this theory are not satisfied. Sarcomere length nonuniformity may cause part of the observed force enhancement. There is evidence for two additional mechanisms causing force enhancement: an active and a passive mechanism. The active mechanism appears to be associated with an increase in the proportion of attached cross bridges, rather than an increase in average force per cross bridge. However, absolute proof to support this hypothesis is still lacking. The passive mechanism plays a role only when the stretch is initiated at long sarcomere (fiber) lengths and appears to be associated with a structure that is engaged at the onset of muscle or fiber activation.

**CONCLUSIONS**

Force enhancement and force depression may be partially associated with nonuniformity of sarcomere lengths that develop during active shortening and stretch, but sarcomere length nonuniformity seems insufficient to explain the history dependence of force production on its own. On the basis of a review of the literature, and some new evidence, we suggest that the steady-state force depression after active muscle shortening is associated with a stress-induced inhibition of cross-bridge attachment in the myofilament overlap zone that is newly formed during shortening and that force enhancement after active muscle stretch has two components: an active component, likely related to an increase in the proportion of attached cross bridges, and a passive component, possibly related to the molecular spring titin.

**REFERENCES**


