

## **Mechanics and models of the myosin motor**

A. F. Huxley

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# **Measurement of the myosin motor**<br> **Mechanics and models of the myosin motor**

**A. F. Huxley**\*

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In striated muscles, shortening comes about by the sliding movement of thick filaments, composed mostly In striated muscles, shortening comes about by the sliding movement of thick filaments, composed mostly<br>of myosin, relative to thin filaments, composed mostly of actin. This is brought about by cyclic action of<br>'cross-brid In striated muscles, shortening comes about by the sliding movement of thick filaments, composed mostly of myosin, relative to thin filaments, composed mostly of actin. This is brought about by cyclic action of 'cross-brid of myosin, relative to thin filaments, composed mostly of actin. This is brought about by cyclic action of 'cross-bridges' composed of the heads of myosin molecules projecting from a thick filament, which attach to an adja 'cross-bridges' composed of the heads of myosin molecules projecting from a thick filament, which attach<br>to an adjacent thin filament, exert force for a limited time and detach, and then repeat this cycle further<br>along the phate to the diphosphate and inorganic phosphate, the steps of this reaction being coupled to mechanical along the filament. The requisite energy is provided by the hydrolysis of a molecule of adenosine triphos-<br>phate to the diphosphate and inorganic phosphate, the steps of this reaction being coupled to mechanical<br>events wit phate to the diphosphate and inorganic phosphate, the steps of this reaction being coupled to mechanical<br>events within the cross-bridge. The nature of these events is discussed. There is good evidence that one of<br>them is a events within the cross-bridge. The nature of these events is discussed. There is good evidence that one of<br>them is a change in the angle of tilt of a 'lever arm' relative to the 'catalytic domain' of the myosin head<br>which them is a change in the angle of tilt of a 'lever arm' relative to the 'catalytic domain' of the myosin head<br>which binds to the actin filament. It is suggested here that this event is superposed on a slower, tempera-<br>tureremain.

**Keywords:** muscle contraction mechanism; myosin; molecular motors; motor proteins

#### **1. GENERAL FEATURES**

Most of what is now known about the physical processes involved in generation of tension or shortening of muscle has been deduced from experiments on two types of as been deduced from experiments on two types of wolved in generation of tension or shortening of muscle<br>as been deduced from experiments on two types of<br>nuscle, the skeletal muscles of vertebrates (mostly frog<br>nd rabbit) and to a lesser extent the bigbly specialized as been deduced from experiments on two types of<br>nuscle, the skeletal muscles of vertebrates (mostly frog<br>nd rabbit) and to a lesser extent the highly specialized<br>synchronous' flight muscles of certain of the Orders of uscle, the skeletal muscles of vertebrates (mostly frog<br>nd rabbit) and to a lesser extent the highly specialized<br>isynchronous' flight muscles of certain of the Orders of<br>sects which are exceptionally regular in structure. nd rabbit) and to a lesser extent the highly specialized<br>isynchronous' flight muscles of certain of the Orders of<br>isects, which are exceptionally regular in structure. Both isynchronous' flight muscles of certain of the Orders of<br>isects, which are exceptionally regular in structure. Both<br>f these are types of striated muscle, i.e. their fibres are<br>rossed at intervals of a few micrometres by al is sects, which are exceptionally regular in structure. Both<br>f these are types of striated muscle, i.e. their fibres are<br>rossed at intervals of a few micrometres by alternate<br>ands of higher and lower refractive index refle f these are types of striated muscle, i.e. their fibres are<br>rossed at intervals of a few micrometres by alternate<br>ands of higher and lower refractive index, reflecting<br>igher and lower total concentrations of protein. The rossed at intervals of a few micrometres by alternate<br>ands of higher and lower refractive index, reflecting<br>igher and lower total concentrations of protein. The<br>ands with higher refractive index are known as the ands of higher and lower refractive index, reflecting A bands because they are optically anisotropic, i.e. they ands with higher refractive index are known as the<br>  $\therefore$  bands because they are optically anisotropic, i.e. they<br>
re birefringent, with the slow direction along the long<br>
vis of the fibre, the intervening low-refractive-A bands because they are optically anisotropic, i.e. they<br>intervening the long<br> $\begin{cases} x_i$  is of the fibre, the intervening low-refractive-index<br>ands being nearly isotropic and therefore known as the re birefringent, with the slow direction along the long<br>
xis of the fibre, the intervening low-refractive-index<br>
ands being nearly isotropic and therefore known as the<br>
hands It is natural to suppose that the mechanism of xis of the fibre, the intervening low-refractive-index<br>ands being nearly isotropic and therefore known as the<br>bands. It is natural to suppose that the mechanism of nooth (unstriated) muscles, and of other forms of movement driven by other types of myosin, is essentially shooth (unstriated) muscles, and of other forms of move-<br>ent driven by other types of myosin, is essentially<br>milar, but any such phrase serves chiefly to conceal our<br>programs of the extent of the differences The diven by other types of myosin,<br>milar, but any such phrase serves chiefly<br>prorance of the extent of the differences.<br>It was shown in  $1953-1954$  (H E Huy) milar, but any such phrase serves chiefly to conceal our<br>norance of the extent of the differences.<br>It was shown in 1953–1954 (H. E. Huxley 1953; H. E.<br>1954: A. E. Huxley & Niedergerke

Frame of the extent of the differences.<br>
I twas shown in 1953–1954 (H. E. Huxley 1953; H. E.<br>
Huxley & Hanson 1954; A. F. Huxley & Niedergerke<br>
1954) that shortening of the muscle fibre takes place by It was shown in 1953–1954 (H. E. Huxley 1953; H. E.<br>Suxley & Hanson 1954; A. F. Huxley & Niedergerke<br>(1954) that shortening of the muscle fibre takes place by<br>elative sliding movement of two sets of filaments whose Juxley & Hanson 1954; A. F. Huxley & Niedergerke<br>  $2^{954}$ ) that shortening of the muscle fibre takes place by<br>
elative sliding movement of two sets of filaments whose<br>
relative sure the high refractive index and higher f Guxley & Hanson 1954; A. F. Huxley & Niedergerke<br>954) that shortening of the muscle fibre takes place by<br>elative sliding movement of two sets of filaments whose<br> $\cdot$  and birefringence elative sliding movement of two sets of filaments whose<br>nds overlap, the high refractive index and birefringence<br>f the A bands being due to the presence there of `thick<br>laments', composed, mostly, of the protein, myosin nds overlap, the high refractive index and birefringence<br>f the A bands being due to the presence there of 'thick<br>laments', composed mostly of the protein myosin<br>Hasselbach 1953: Hanson & H E Huyley 1953) that f the A bands being due to the presence there of 'thick laments', composed mostly of the protein myosin Hasselbach 1953; Hanson & H. E. Huxley 1953), that  $\lambda$  beredigitate with 'thin filaments' composed mostly of laments', composed mostly of the protein myosin<br>Hasselbach 1953; Hanson & H. E. Huxley 1953), that<br> $\Omega$  iterdigitate with 'thin filaments' composed mostly of<br>tin Tension is developed if shortening is prevented Hasselbach 1953; Hanson & H. E. Huxley 1953), that<br>Diterdigitate with 'thin filaments' composed mostly of<br>ctin. Tension is developed if shortening is prevented<br>signetric contraction'. The intervalse in the set of the field of the contraction').<br>
Sometric contraction').

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Two very general features of the mechanism of muscle Two very general features of the mechanism of muscle<br>contraction that are now almost universally accepted<br>were suggested by observations that had been made long Two very general features of the mechanism of muscle<br>contraction that are now almost universally accepted<br>were suggested by observations that had been made long<br>before the advent of the sliding-filament theory contraction that are now almost universally accepted<br>were suggested by observations that had been made long<br>before the advent of the sliding-filament theory, as<br>follows follows.

#### **2. INDEPENDENT FORCE GENERATORS**

Experiments by Ramsey & Street (1940), in which **EXECUTE CONCE GENERATORS**<br>
Experiments by Ramsey & Street (1940), in which<br>
intact isolated muscle fibres from the frog were stretched<br>
to various lengths and then stimulated showed a roughly Experiments by Ramsey & Street (1940), in which<br>intact isolated muscle fibres from the frog were stretched<br>to various lengths and then stimulated, showed a roughly<br>linear decline of active force with extension of the fibre intact isolated muscle fibres from the frog were stretched<br>to various lengths and then stimulated, showed a roughly<br>linear decline of active force with extension of the fibre<br>beyond the length at which it gave maximum forc to various lengths and then stimulated, showed a roughly<br>linear decline of active force with extension of the fibre<br>beyond the length at which it gave maximum force<br>(figure 1). This received a simple explanation on the linear decline of active force with extension of the fibre sliding-filament theory, namely that contributions to force (figure 1). This received a simple explanation on the sliding-filament theory, namely that contributions to force were provided by active sites, uniformly spaced along each zone where myosin and actin filaments overlap and sliding-filament theory, namely that contributions to force<br>were provided by active sites, uniformly spaced along<br>each zone where myosin and actin filaments overlap, and<br>acting more or less independently so that total forc were provided by active sites, uniformly spaced along<br>each zone where myosin and actin filaments overlap, and<br>acting more or less independently, so that total force<br>would be proportional to the extent of overlap (A F each zone where myosin and actin filaments overlap, and<br>acting more or less independently, so that total force<br>would be proportional to the extent of overlap (A. F.<br>Huyley & Niedergerke 1954). The agreement with the acting more or less independently, so that total force<br>would be proportional to the extent of overlap (A. F.<br>Huxley & Niedergerke 1954). The agreement with the<br>relation expected from the lengths of the filaments was would be proportional to the extent of overlap (A. F.<br>Huxley & Niedergerke 1954). The agreement with the<br>relation expected from the lengths of the filaments was<br>shown to be quantitative when precautions were taken to Huxley & Niedergerke 1954). The agreement with the relation expected from the lengths of the filaments was shown to be quantitative when precautions were taken to avoid complications due to pop-uniformity of the relation expected from the lengths of the filaments was<br>shown to be quantitative when precautions were taken to<br>avoid complications due to non-uniformity of the<br>stretching of a fibre (Gordon et al. 1966) Meanwhile shown to be quantitative when precautions were taken to avoid complications due to non-uniformity of the stretching of a fibre (Gordon *et al.* 1966). Meanwhile, avoid complications due to non-uniformity of the stretching of a fibre (Gordon *et al.* 1966). Meanwhile, these active sites were identified, by electron microscopy, with 'cross-bridges' extending from the myosin filament stretching of a fibre (Gordon *et al.* 1966). Meanwhile, these active sites were identified, by electron microscopy, with 'cross-bridges' extending from the myosin filament to the actin filament in each zone where they ov these active sites were identified, by electron microscopy,<br>with 'cross-bridges' extending from the myosin filament to<br>the actin filament in each zone where they overlap (H. E.<br>Huyley 1957) with 'cross-bridges' extending from the myosin filament to<br>the actin filament in each zone where they overlap (H. E.<br>Huxley 1957).

#### **3. CYCLIC ACTION**

Most, if not all, theories of muscle contraction before S. CYCLIC ACTION<br>Most, if not all, theories of muscle contraction before<br>the advent of sliding filaments, and many since then,<br>assumed that shortening was due to a progressive change Most, if not all, theories of muscle contraction before<br>the advent of sliding filaments, and many since then,<br>assumed that shortening was due to a progressive change<br>from a long to a short state in the contractile material the advent of sliding filaments, and many since then,<br>assumed that shortening was due to a progressive change<br>from a long to a short state in the contractile material. As<br>far as I know the first suggestion of a cyclic as o assumed that shortening was due to a progressive change<br>from a long to a short state in the contractile material. As<br>far as I know, the first suggestion of a cyclic, as opposed<br>to progressive, mechanism was made by Dorothy from a long to a short state in the contractile material. As

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overlapping; B, all myosin heads overlapped by actin filament; C, actin filaments. Frog muscle: A, filaments just not<br>perlapping; B, all myosin heads overlapped by actin filament; C, actin filaments collide at centre of A (a) igure 1. Variation of active tension with overlap between myosin and actin filaments. Frog muscle: A, filaments just not<br>experiment in the point of I band. From Gordon *et al.* (1966). The point E where active tension verlapping; B, all myosin heads overlapped by actin filament; C, actin filaments collide at centre of A band: D, myosin<br>laments collide at centre of I band. From Gordon *et al.* (1966). The point E where active tension is not well defined because, even at shorter lengths some tension does develop extremely slowly and the shortening is then<br>reversible ('delta state', Ramsey & Street 1940).



igure 2. Rate of energy liberation above isometric rate, as a fugure 2. Rate of energy liberation above isometric rate, as a<br>function of shortening speed. Solid line: rectangular hyperbola<br>from Hill (1938). Broken line: revised formula of Hill (1964) from Hill (1938). Broken line: rectangular hyperbolarity of shortening speed. Solid line: rectangular hyperbolarity on Hill (1938). Broken line: revised formula of Hill (1964).  $\Box$  om Hill (1938). Broken line: revised formula of Hill (1964).<br> $\Box$  rom A. F. Huxley (1974).

O<br>Seedham (1950, p. 48), on the basis of the relationships between load, speed of shortening and rate of heat From (1950, p. 48), on the basis of the relationships<br>etween load, speed of shortening and rate of heat<br>roduction found by Hill (1938) in intact frog muscles,<br>nd formulated by him in simple mathematical expresetween load, speed of shortening and rate of heat<br>roduction found by Hill (1938) in intact frog muscles,<br>nd formulated by him in simple mathematical expres-<br>ons. More explicitly I remember her pointing out the roduction found by Hill (1938) in intact frog muscles,<br>nd formulated by him in simple mathematical expres-<br>ions. More explicitly, I remember her pointing out the<br>analogy between Hill's hyperbolic dependence of rate of In different formulated by him in simple mathematical expresions. More explicitly, I remember her pointing out the  $\overline{O}$  nalogy between Hill's hyperbolic dependence of rate of ions. More explicitly, I remember her pointing out the<br>
palogy between Hill's hyperbolic dependence of rate of<br>
nergy liberation (heat + work) on speed of shortening<br>
figure 2) on the one hand and on the other the hyper-) nalogy between Hill's hyperbolic dependence of rate of nergy liberation (heat + work) on speed of shortening figure 2) on the one hand, and on the other the hyper-olic Michaelis-Menten dependence of the rate of an holds are dependence of shortening figure 2) on the one hand, and on the other the hyper-<br>olic Michaelis-Menten dependence of the rate of an<br>azymic reaction on substrate concentration (More figure 2) on the one hand, and on the other the hyper-<br>olic Michaelis-Menten dependence of the rate of an<br>nzymic reaction on substrate concentration. (More<br>ecent work has modified Hill's (1938) relationship.) olic Michaelis-Menten dependence of the rate of an

Such ideas, involving repeated operation of each active site during a single contraction, are incompatible with the Such ideas, involving repeated operation of each active<br>site during a single contraction, are incompatible with the<br>notion, generally accepted at that time, that the active<br>sites in a protein chain switch successively from site during a single contraction, are incompatible with the notion, generally accepted at that time, that the active<br>sites in a protein chain switch successively from a long to<br>a short state during muscle contraction. On t notion, generally accepted at that time, that the active<br>sites in a protein chain switch successively from a long to<br>a short state during muscle contraction. On the other<br>hand they fit naturally with sliding filaments: the sites in a protein chain switch successively from a long to<br>a short state during muscle contraction. On the other<br>hand, they fit naturally with sliding filaments: the a short state during muscle contraction. On the other<br>hand, they fit naturally with sliding filaments: the<br>frequency with which a site on the myosin filament<br>approaches a site on the actin filament with which it may hand, they fit naturally with sliding filaments: the<br>frequency with which a site on the myosin filament<br>approaches a site on the actin filament with which it may<br>interact is proportional to the speed with which the frequency with which a site on the myosin filament<br>approaches a site on the actin filament with which it may<br>interact is proportional to the speed with which the<br>filaments slide past one another i.e. to the speed of shortapproaches a site on the actin filament with which it may<br>interact is proportional to the speed with which the<br>filaments slide past one another, i.e. to the speed of short-<br>enjng just as in an enzymic reaction the frequenc interact is proportional to the speed with which the filaments slide past one another, i.e. to the speed of shortening, just as in an enzymic reaction the frequency with which substrate molecules approach the enzyme is filaments slide past one another, i.e. to the speed of shortening, just as in an enzymic reaction the frequency with which substrate molecules approach the enzyme is proportional to substrate concentration. Practically all ening, just as in an enzymic reaction the frequency with<br>which substrate molecules approach the enzyme is<br>proportional to substrate concentration. Practically all<br>current theories of contraction that have been developed which substrate molecules approach the enzyme is<br>proportional to substrate concentration. Practically all<br>current theories of contraction that have been developed<br>to a quantitative level are cyclic in this sense proportional to substrate concentration. Practically all current theories of contraction that have been developed to a quantitative level are cyclic in this sense.

#### **4. A. F. HUXLEY'S 1957 THEORY**

**4. A. F. HUXLEY'S 1957 THEORY**<br>I developed the idea of cyclic interactions in a theory<br>at provided an adequate fit to Hill's equations (A F 4. **A. F. HUXLET S 1957 THEORT**<br>I developed the idea of cyclic interactions in a theory<br>that provided an adequate fit to Hill's equations (A. F.<br>Huyley 1957). It was purely kinetic in character i.e. it I developed the idea of cyclic interactions in a theory<br>that provided an adequate fit to Hill's equations (A. F.<br>Huxley 1957). It was purely kinetic in character, i.e. it<br>did not make specific postulates about the structur that provided an adequate fit to Hill's equations (A. F. Huxley 1957). It was purely kinetic in character, i.e. it did not make specific postulates about the structural and Huxley 1957). It was purely kinetic in character, i.e. it<br>did not make specific postulates about the structural and<br>biochemical events underlying the interactions between<br>muosin and actin sites. Its essential features are did not make specific postulates about the structural and<br>biochemical events underlying the interactions between<br>myosin and actin sites. Its essential features are as<br>follows follows.

- 1. Each cross-bridge formed by an interaction between<br>myosin and actin contains an elastic element, allowing Each cross-bridge formed by an interaction between<br>myosin and actin contains an elastic element, allowing<br>Brownian movement before an interaction occurs and Each cross-bridge formed by an interaction between<br>myosin and actin contains an elastic element, allowing<br>Brownian movement before an interaction occurs and<br>causing force to be produced when the cross-bridge is myosin and actin contains an elastic element, allowing<br>Brownian movement before an interaction occurs and<br>causing force to be produced when the cross-bridge is strained. 2. The rate constant for attachment is moderate when the separation between the two sites is within a certain
- strained.<br>The rate constant for attachment is moderate when the<br>separation between the two sites is within a certain<br>range where attachment will cause positive tension but The rate constant for attachment is moderate when the<br>separation between the two sites is within a certain<br>range where attachment will cause positive tension but<br>zero if attachment would cause perative tension separation between the two sites is within a certain<br>range where attachment will cause positive tension but<br>zero if attachment would cause negative tension. range where attachment will cause positive tension but<br>zero if attachment would cause negative tension.<br>3. The rate constant for detachment is small as long as<br>the cross-bridge is exerting positive tension but
- Exero if attachment would cause negative tension.<br>The rate constant for detachment is small as long as<br>the cross-bridge is exerting positive tension but<br>becomes large as soon as shortening has brought the The rate constant for detachment is small as long as<br>the cross-bridge is exerting positive tension but<br>becomes large as soon as shortening has brought the<br>cross-bridge past the position where the force it exerts the cross-bridge is exerting positive tension but<br>becomes large as soon as shortening has brought the<br>cross-bridge past the position where the force it exerts<br>is zero. becomes<br>cross-brie<br>is zero.



to a sudden shortening of 4.5 nm in each overlap zone (frog, igure 3. (a) Early part of tension response of a muscle fibre<br>  $\alpha$  a sudden shortening of 4.5 nm in each overlap zone (frog,<br>
bout 1 °C). Phase 1: initial drop. Phase 2: early tension<br>  $\alpha$ between a shortening of 4.5 nm in each overlap zone (frog, bout 1 °C). Phase 1: initial drop. Phase 2: early tension ecovery, complete in about 2 ms. Phase 3: slowing (sometimes eversal) of tension recovery. Phase 4: the f bout  $1^{\circ}$ C). Phase 1: initial drop. Phase 2: early tension covery, complete in about 2 ms. Phase 3: slowing (sometiversal) of tension recovery. Phase 4: the final roughly represential approach to the original tension, export exponential approach to the original tension, takes about x<br>ponential approach to the original tension, takes about eversal) of tension recovery. Phase 4: the final roughly<br>xponential approach to the original tension, takes about<br>00 ms and is not seen in this record. Adapted from A. F.<br>Iuvley (1974), fig. 8, (b, c) Contrast between osc xponential approach to the original tension, takes about 00 ms and is not seen in this record. Adapted from A. F. Iuxley (1974), fig. 8.  $(b, c)$  Contrast between oscillatory with change in response to load step  $(b)$  load i luxley (1974), fig. 8.  $(b, c)$  Contrast between oscillatory ingth change in response to load step  $(b, \text{load increase}$  from .9  $T_0$  to  $T_0$  between arrows) and limited sequence of phases ingth change in response to load step (*b*, load increased from<br>
.9  $T_0$  to  $T_0$  between arrows) and limited sequence of phases<br>
1 tension response to length step (*c*, stretch by 4.8 nm in each<br>
verlan zone, at first a .9  $T_0$  to  $T_0$  between arrows) and limited sequence of phases<br>1 tension response to length step (*c*, stretch by 4.8 nm in each<br>verlap zone, at first arrow). Phase 3 after a stretch shows up<br>5 a delayed rise of tension a tension response to length step  $(c,$  stretch by 4.8 nm in each verlap zone, at first arrow). Phase 3 after a stretch shows up s a delayed rise of tension  $(D)$ .  $(b)$  and  $(c)$  from Armstrong  $et$ verlap zone, at first arrow). Phase 3 after a stretch shows up s a delayed rise of tension  $(D)$ .  $(b)$  and  $(c)$  from Armstrong *et l*. (1966).

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Simple functions leading to an explicit solution of the<br>ustions were chosen for the dependence of the rates of Simple functions leading to an explicit solution of the quations were chosen for the dependence of the rates of the cross-Simple functions leading to an explicit solution of the quations were chosen for the dependence of the rates of the cross-<br>tidre and the parameters were adjusted by trial and quations were chosen for the dependence of the rates of<br>trachment and detachment on extension of the cross-<br>ridge, and the parameters were adjusted by trial and<br>ror so as to obtain an adequate match to Hill's tachment and detachment on extension of the cross-<br>ridge, and the parameters were adjusted by trial and<br>rror so as to obtain an adequate match to Hill's<br>quations quations. rror so as to obtain an adequate match to Hill's quations.<br>The theory is certainly incomplete. For example, it

quations.<br>The theory is certainly incomplete. For example, it<br>sumes that force generation occurs instantaneously<br>then a cross-bridge is formed, and it therefore fails to The theory is certainly incomplete. For example, it<br>sumes that force generation occurs instantaneously<br>then a cross-bridge is formed, and it therefore fails to<br>via the rapid changes of tension that were subsumes that force generation occurs instantaneously<br>then a cross-bridge is formed, and it therefore fails to<br>xplain the rapid changes of tension that were sub-<br>equently found to follow when the length of a muscle then a cross-bridge is formed, and it therefore fails to  $\chi$  plain the rapid changes of tension that were sub-<br>
sequently found to follow when the length of a muscle<br>
here is suddenly changed during contraction. Some of xplain the rapid changes of tension that were sub-<br>
acquently found to follow when the length of a muscle<br>
bre is suddenly changed during contraction. Some of its<br>
partitative features are also wrong: for example the equently found to follow when the length of a muscle<br>bre is suddenly changed during contraction. Some of its<br>uantitative features are also wrong; for example, the<br>etachment rate while a cross-bridge is everting positive be is suddenly changed during contraction. Some of its<br>uantitative features are also wrong; for example, the<br>etachment rate while a cross-bridge is exerting positive<br>are was chosen to match the rapid exponential phase of uantitative features are also wrong; for example, the etachment rate while a cross-bridge is exerting positive orce was chosen to match the rapid exponential phase of elaxation at the end of a neriod of stimulation, wherea etachment rate while a cross-bridge is exerting positive<br>orce was chosen to match the rapid exponential phase of<br>elaxation at the end of a period of stimulation, whereas<br>is now known that this phase is due to rapid elongat is the set of elaxation at the end of a period of stimulation, whereas<br>is now known that this phase is due to rapid elongation<br>of particular parts of the muscle fibre, usually near its elaxation at the end of a period of stimulation, whereas<br>  $\therefore$  is now known that this phase is due to rapid elongation<br>  $\int$ f particular parts of the muscle fibre, usually near its<br>
nds I ater work by Hill (1964) showed It is now known that this phase is due to rapid elongation<br>Of particular parts of the muscle fibre, usually near its<br>nds. Later work by Hill (1964) showed that the rate of<br>nergy liberation did not continue to increase wit If particular parts of the muscle fibre, usually near its<br>nds. Later work by Hill (1964) showed that the rate of<br>nergy liberation did not continue to increase with short-<br>ning speed throughout the range but declined when t nds. Later work by Hill (1964) showed that the rate of nergy liberation did not continue to increase with shortning speed throughout the range but declined when the naximum velocity was approached (figure 2); explananergy liberation did not continue to increase with shortlons for this have been suggested (A. F. Huxley 1973;

Barclay 1999) but remain speculative. On the other hand,<br>the 1957 theory was successful in predicting the depen-Barclay 1999) but remain speculative. On the other hand,<br>the 1957 theory was successful in predicting the depen-<br>dence of longitudinal stiffness on speed of shortening Barclay 1999) but remain speculative. On the other hand,<br>the 1957 theory was successful in predicting the depen-<br>dence of longitudinal stiffness on speed of shortening,<br>which had not previously been measured. Most if not a the 1957 theory was successful in predicting the dependence of longitudinal stiffness on speed of shortening, which had not previously been measured. Most, if not all, current cross-bridge theories have features qualitativ dence of longitudinal stiffness on speed of shortening,<br>which had not previously been measured. Most, if not all,<br>current cross-bridge theories have features qualitatively<br>similar to those numbered  $1-3$  above which had not previously been measure<br>current cross-bridge theories have fea<br>similar to those numbered 1–3 above.<br>It is nowadays supposed that most or Frent cross-bridge theories have features qualitatively<br>
indiar to those numbered  $1-3$  above.<br>
It is nowadays supposed that most or perhaps all of the<br>
is now a cross-bridge is generated by

similar to those numbered  $1-3$  above.<br>It is nowadays supposed that most or perhaps all of the<br>tension produced by a cross-bridge is generated by<br>transitions that occur after attachment. It is however tension produced by a cross-bridge is generated by transitions that occur after attachment. It is, however, tension produced by a cross-bridge is generated by<br>transitions that occur after attachment. It is, however,<br>uncertain whether the first attached state rigid enough to<br>transmit force does exert force and if so whether its transitions that occur after attachment. It is, however,<br>uncertain whether the first attached state rigid enough to<br>transmit force does exert force and if so whether its<br>contribution is positive or pecative. A small pecati uncertain whether the first attached state rigid enough to<br>transmit force does exert force and if so whether its<br>contribution is positive or negative. A small negative<br>contribution might be the origin of the 'latency relax transmit force does exert force and if so whether its contribution is positive or negative. A small negative contribution might be the origin of the 'latency relaxation', the small drop in tension after a stimulus before tension begins to rise. tion', the small drop in tension after a stimulus before

#### **5. MECHANICAL TRANSIENT RESPONSES**

Attempts at measuring the responses of muscle to S. MECHANICAL TRANSIENT RESPONSES<br>Attempts at measuring the responses of muscle to<br>sudden changes of load or length during contraction had<br>heen made before the Second World War (e.g. Gasser & Attempts at measuring the responses of muscle to<br>sudden changes of load or length during contraction had<br>been made before the Second World War (e.g. Gasser &<br>Hill 1994) but had been inconclusive largely because sudden changes of load or length during contraction had<br>been made before the Second World War (e.g. Gasser &<br>Hill 1924), but had been inconclusive, largely because<br>the recording instruments were not fast enough. The first been made before the Second World War (e.g. Gasser & Hill 1924), but had been inconclusive, largely because the recording instruments were not fast enough. The first Hill 1924), but had been inconclusive, largely because<br>the recording instruments were not fast enough. The first<br>useful measurements were made by Podolsky (1960) on a<br>small from muscle: he recorded the time-course of the the recording instruments were not fast enough. The first<br>useful measurements were made by Podolsky (1960) on a<br>small frog muscle; he recorded the time-course of the<br>length changes that followed when the load on the useful measurements were made by Podolsky (1960) on a<br>small frog muscle; he recorded the time-course of the<br>length changes that followed when the load on the<br>muscle was suddenly reduced and found that the steady small frog muscle; he recorded the time-course of the length changes that followed when the load on the muscle was suddenly reduced, and found that the steady length changes that followed when the load on the<br>muscle was suddenly reduced, and found that the steady<br>speed of shortening was approached through a damped<br>oscillation. Almost all the experiments on transient muscle was suddenly reduced, and found that the steady<br>speed of shortening was approached through a damped<br>oscillation. Almost all the experiments on transient<br>responses in my laboratory have used the converse type speed of shortening was approached through a damped<br>oscillation. Almost all the experiments on transient<br>responses in my laboratory have used the converse type<br>of experiment in which length, not load, is altered oscillation. Almost all the experiments on transient responses in my laboratory have used the converse type of experiment in which length, not load, is altered responses in my laboratory have used the converse type<br>of experiment in which length, not load, is altered<br>suddenly. In this case (figure 3*a*), there is a simultaneous<br>change of tension (phase 1) followed by approach to t of experiment in which length, not load, is altered<br>suddenly. In this case (figure 3*a*), there is a simultaneous<br>change of tension (phase 1) followed by approach to the<br>original tension, through a sequence of three more suddenly. In this case (figure 3*a*), there is a simultaneous<br>change of tension (phase 1) followed by approach to the<br>original tension through a sequence of three more<br>phases each with a roughly exponential decline. Phase change of tension (phase 1) followed by approach to the original tension through a sequence of three more phases, each with a roughly exponential decline. Phase 2 original tension through a sequence of three more<br>phases, each with a roughly exponential decline. Phase 2<br>is a rapid (of the order of 1ms in frog muscle near  $0^{\circ}C$ )<br>recovery towards the initial tension: during phase 3 phases, each with a roughly exponential decline. Phase 2<br>is a rapid (of the order of 1 ms in frog muscle near  $0^{\circ}C$ )<br>recovery towards the initial tension; during phase 3 the<br>rate of recovery is greatly reduced or actua is a rapid (of the order of 1 ms in frog muscle near  $0^{\circ}C$ )<br>recovery towards the initial tension; during phase 3 the<br>rate of recovery is greatly reduced or actually reversed<br>(of the order of  $10 \text{ ms}$ ); and in phase 4 recovery towards the initial tension; during phase 3 the<br>rate of recovery is greatly reduced or actually reversed<br>(of the order of 10 ms); and in phase 4 there is a roughly<br>exponential recovery to the original tension (of rate of recovery is greatly reduced or actually reversed<br>(of the order of 10 ms); and in phase 4 there is a roughly<br>exponential recovery to the original tension (of the order<br>of  $50 \text{ ms}$ ). The contrast between the oscill (of the order of  $10 \text{ ms}$ ); and in phase 4 there is a roughly<br>exponential recovery to the original tension (of the order<br>of  $50 \text{ ms}$ ). The contrast between the oscillatory response<br>to load change and the small number of exponential recovery to the original tension (of the order<br>of 50 ms). The contrast between the oscillatory response<br>to load change and the small number of exponentially<br>decaying phases in response to length change is broug of 50 ms). The contrast between the oscillatory response<br>to load change and the small number of exponentially<br>decaying phases in response to length change is brought<br>out in figure 3*bc* reproduced from Armstrong *et al* to load change and the small number of exponentially decaying phases in response to length change is brought out in figure  $3b$ ,*c*, reproduced from Armstrong *et al.* (1966). I did in fact show (unpublished data) that th out in figure  $3b$ , $c$ , reproduced from Armstrong *et al.* (1966). I did in fact show (unpublished data) that these are two different expressions of the same properties, by  $(1966)$ . I did in fact show (unpublished data) that these are two different expressions of the same properties, by superposing numerically the tension responses to a sequence of small length steps whose amplitude and are two different expressions of the same properties, by<br>superposing numerically the tension responses to a<br>sequence of small length steps whose amplitude and<br>direction were chosen so that the overall tension change superposing numerically the tension responses to a<br>sequence of small length steps whose amplitude and<br>direction were chosen so that the overall tension change<br>was a step and found that the length steps added up to sequence of small length steps whose amplitude and<br>direction were chosen so that the overall tension change<br>was a step, and found that the length steps added up to direction were chosen so that the overall tension change<br>was a step, and found that the length steps added up to<br>an oscillatory change indistinguishable from the experi-<br>mental length change following a small step change o was a step, and found that the length steps added up to<br>an oscillatory change indistinguishable from the experi-<br>mental length change following a small step change of<br>load. The fact that the response to length change is an oscillatory change indistinguishable from the experimental length change following a small step change of load. The fact that the response to length change is composed of first-order delays while that to load change is mental length change following a small step change of<br>load. The fact that the response to length change is<br>composed of first-order delays while that to load change is load. The fact that the response to length change is<br>composed of first-order delays while that to load change is<br>oscillatory implies that the molecular events are directly<br>affected by longitudinal displacement of the filam composed of first-order delays while that to load change is<br>oscillatory implies that the molecular events are directly<br>affected by longitudinal displacement of the filaments<br>rather than by the tension in them oscillatory implies that the molecula<br>affected by longitudinal displacement<br>rather than by the tension in them.<br>Over most of the range where it of affected by longitudinal displacement of the filaments<br>rather than by the tension in them.<br>Over most of the range where it can be measured, the

rather than by the tension in them.<br>Over most of the range where it can be measured, the<br>tension change during phase 1 is nearly proportional to<br>the imposed length change, implying a roughly linear Over most of the range where it can be measured, the<br>tension change during phase 1 is nearly proportional to<br>the imposed length change, implying a roughly linear<br>compliance in the muscle structure. On present evidence tension change during phase 1 is nearly proportional to<br>the imposed length change, implying a roughly linear<br>compliance in the muscle structure. On present evidence,<br>about half of this appears to be actually within the cro the imposed length change, implying a roughly linear<br>compliance in the muscle structure. On present evidence,<br>about half of this appears to be actually within the crossbridges and half in the ¢laments. It is still uncertain to



**SEP amplitude per half-sarcomere, nm**<br>igure 4. Nonlinearities in (*a*) extent, and (*b*) rate, of early<br>argion recovery (phase 2) ofter a step change of length tension recovery (phase 2) after a step change of length.<br>these summary of experimental results of Eord *et al.* (197) Lines: summary of experimental results of Ford *et al*. (1977). <sup>2</sup> in the except tended in the set of Ford *et al.* (1977).<br> *T*<sub>0</sub>, *T*<sub>1</sub> and *T*<sub>2</sub> defined in figure 3*a*. Symbols: simulation based by an undeted version of the theory of A F. Huyley & ines: summary of experimental results of Ford *et al.* (1977).<br>  $\tilde{v}_0$ ,  $T_1$  and  $T_2$  defined in figure 3*a*. Symbols: simulation base<br>
n an updated version of the theory of A. F. Huxley &<br>  $\tilde{v}_1$  immons (1971): f  $\tilde{L}_0$ ,  $T_1$  and  $T_2$  defined in figure 3*a*. Symbols: simulation based<br>n an updated version of the theory of A. F. Huxley &<br>immons (1971); filled symbols taking account, and open<br>ambols not taking account of detachm n an updated version of the theory of A. F. Huxley &<br>
immons (1971); filled symbols taking account, and open<br>
whols not taking account, of detachment of cross-bridges.<br>
rom A. F. Huxley & Tideswell (1996). From A. (1971); filled symbols taking accept and provided a count, of detachment compared at  $\mathbb{R}$  rom A. F. Huxley & Tideswell (1996).

what extent the cross-bridges can exert negative tension when relatively large shortening is imposed. nat extent the cross-bridges can exert negative tension<br>hen relatively large shortening is imposed.<br>During phase 2, there is little change in stiffness of the<br>uscle, suggesting that few cross-bridges detach or attach

During phase 2, there is little change in stiffness of the puscle, suggesting that few cross-bridges detach or attach  $\mu$  uring this phase. The tension change is therefore usually The use of events happening that few cross-bridges detach or attach<br>a puring this phase. The tension change is therefore usually<br>attributed to events happening in cross-bridges that were<br>a leady attached before the length uring this phase. The tension change is therefore usually<br>ttributed to events happening in cross-bridges that were<br>lready attached before the length step was imposed, i.e.<br>his phase is thought to represent the actual 'work tributed to events happening in cross-bridges that were<br>lready attached before the length step was imposed, i.e.<br>his phase is thought to represent the actual 'working<br>roke' of attached cross-bridges. lready attached before the length step was imposed, i.e. his phase is thought to represent the actual 'working<br>
roke' of attached cross-bridges.<br>
Phase 3 is not well understood. In small releases,<br>
phase 3 is not well understood. In small releases,<br>
phase at cross-

Phase 3 is not well understood. In small releases,<br>  $\frac{1}{2}$  ension actually falls, so it is natural to suppose that cross-<br>  $\frac{1}{2}$  oridges are detaching. In a small stretch, this phase shows Phase 3 is not well understood. In small releases,<br>
consider a small stretch, this phase shows<br>
cridges are detaching. In a small stretch, this phase shows<br>
in as a delayed rise in tension as in figure 3c; it may be exteed in a delayed rise in tension, as in figure 3*c*; it may be put a delayed rise in tension, as in figure  $3c$ ; it may be put  $e^{i\theta}$  in tension, as in figure  $\theta$ ; it may be put  $e^{i\theta}$  is the  $\theta$  and increase in If it is phase shows<br>p as a delayed rise in tension, as in figure  $3c$ ; it may be<br>ue either to an increase in the rate of attachment of<br>worin heads previously free or a decrease in the rate of p as a delayed rise in tension, as in figure  $3c$ ; it may be<br>ue either to an increase in the rate of attachment of<br>nyosin heads previously free or a decrease in the rate of<br>etachment of heads previously attached (or both) we either to an increase in the rate of attachment of<br>hyosin heads previously free or a decrease in the rate of<br>etachment of heads previously attached (or both).<br>Nuring this phase the events underlying the ranid



Figure 5. Schematic representation of theory of A. F. Hu & Simmons (1971). Tension is generated by clockwise rotation of the myosin head, stretching the spring in the Figure 5. Schematic representation of theory of A. F. Huxl<br>& Simmons (1971). Tension is generated by clockwise<br>rotation of the myosin head, stretching the spring in the<br>connection to the myosin filament. This rotation goes & Simmons (1971). Tension is generated by clockwise<br>rotation of the myosin head, stretching the spring in the<br>connection to the myosin filament. This rotation goes in a<br>small number of steps. In going from state  $A1(a)$  to rotation of the myosin head, stretching the spring in the<br>connection to the myosin filament. This rotation goes in a<br>small number of steps. In going from state A1  $(a)$  to A2  $(b)$ ,<br>the bond that is formed is stronger than small number of steps. In going from state A1  $(a)$  to A2  $(b)$ , the bond that is formed is stronger than the one that is broken. The diagram is not meant to imply anything more than the stepwise progression and the presence of an elastic broken. The diagram is not meant to imply anything more<br>than the stepwise progression and the presence of an elastic<br>element within the cross-bridge, e.g. the stepwise change may<br>occur at a hinge where a 'lever arm' is att than the stepwise progression and the presence of an elastic<br>element within the cross-bridge, e.g. the stepwise change may<br>occur at a hinge where a 'lever arm' is attached to the part<br>hound to actin (as in figure 6) and th element within the cross-bridge, e.g. the stepwise change may<br>occur at a hinge where a 'lever arm' is attached to the part<br>bound to actin (as in figure 6) and the elastic element may<br>reside in bending of this lever arm. A occur at a hinge where a 'lever arm' is attached to the part<br>bound to actin (as in figure 6) and the elastic element may<br>reside in bending of this lever arm. Adapted from A. F.<br>Huxley (1974). reside in bending of this lever arm. Adapted from A. F.

Huxley (1974).<br>regeneration of the power stroke (Lombardi *et al.* 1992;<br>see n 439) take place regeneration of the posee p. 439) take place.<br>During Phase 4 pres generation of the power stroke (Lombardi *et al.* 1992;<br>
a p. 439) take place.<br>
During Phase 4, presumably bridges are detaching and<br>
attaching further along the actin filament

see p. 439) take place.<br>During Phase 4, presumably bridges are de<br>reattaching further along the actin filament.<br>As regards the origin of the force gene During Phase 4, presumably bridges are detaching and<br>attaching further along the actin filament.<br>As regards the origin of the force generated by a<br>uscle, phase 2 is the most informative. It shows two

During phase 2, there is little change in stiffness of the an equilibrium in which the bridge switched from one to uscle, suggesting that few cross-bridges detach or attach another of these states at intervals of time comp nyosin heads previously free or a decrease in the rate of transient represents the re-establishment of equilibrium.<br>
etachment of heads previously attached (or both). At any instant, the total tension depends on the relati reattaching further along the actin filament.<br>As regards the origin of the force generated by a<br>muscle, phase 2 is the most informative. It shows two<br>striking poplinearities respectively in the extent As regards the origin of the force generated by a muscle, phase 2 is the most informative. It shows two striking nonlinearities, respectively in the extent (figure 4a) and in the speed (figure 4b) with which muscle, phase 2 is the most informative. It shows two<br>striking nonlinearities, respectively in the extent<br>(figure 4*a*) and in the speed (figure 4*b*) with which<br>tension approaches the value before the imposed step A striking nonlinearities, respectively in the extent (figure  $4a$ ) and in the speed (figure  $4b$ ) with which tension approaches the value before the imposed step. A semi-quantitative explanation for both these nonlineari-(figure 4*a*) and in the speed (figure 4*b*) with which<br>tension approaches the value before the imposed step. A<br>semi-quantitative explanation for both these nonlineari-<br>ties was given (A E Huyley & Simmons 1971) by tension approaches the value before the imposed step. A semi-quantitative explanation for both these nonlineari-<br>ties was given (A. F. Huxley & Simmons 1971) by assuming that during steady contraction, each crossties was given (A. F. Huxley & Simmons 1971) by<br>assuming that during steady contraction, each cross-<br>bridge could exist in one or other of two (or more) states<br>(as shown schematically in figure 5) and that there was assuming that during steady contraction, each cross-<br>bridge could exist in one or other of two (or more) states<br>(as shown schematically in figure 5), and that there was<br>an equilibrium in which the bridge switched from one bridge could exist in one or other of two (or more) states<br>(as shown schematically in figure 5), and that there was<br>an equilibrium in which the bridge switched from one to<br>another of these states at intervals of time compa (as shown schematically in figure 5), and that there was an equilibrium in which the bridge switched from one to<br>another of these states at intervals of time comparable to<br>the duration of phase 2 (of the order of 1ms). Denoting<br>these attached states by  $\Delta 1$ ,  $\Delta 2$ , etc., the another of these states at intervals of time comparable to<br>the duration of phase 2 (of the order of 1 ms). Denoting<br>these attached states by A1, A2, etc., the bonds holding<br>the bridge in state A2 would be stronger than th the duration of phase 2 (of the order of  $1 \text{ ms}$ ). Denoting<br>these attached states by A1, A2, etc., the bonds holding<br>the bridge in state A2 would be stronger than those<br>holding it in state A1 creating a tendency to switc these attached states by A1, A2, etc., the bonds holding the bridge in state  $A2$  would be stronger than those the bridge in state A2 would be stronger than those<br>holding it in state Al, creating a tendency to switch from<br>state Al to A2, stretching the elastic element and therefore<br>causing an increase in tension. This increase in t holding it in state Al, creating a tendency to switch from<br>state Al to A2, stretching the elastic element and therefore<br>causing an increase in tension. This increase in tension<br>creates a tendency for the cross-bridge to re state Al to A2, stretching the elastic element and therefore<br>causing an increase in tension. This increase in tension<br>creates a tendency for the cross-bridge to revert to state causing an increase in tension. This increase in tension<br>creates a tendency for the cross-bridge to revert to state<br>A1, leading to an equilibrium that would be disturbed<br>when the muscle fibre is stretched or released becau creates a tendency for the cross-bridge to revert to state<br>Al, leading to an equilibrium that would be disturbed<br>when the muscle fibre is stretched or released because this<br>would alter the force on the cross-bridge: phase Al, leading to an equilibrium that would be disturbed<br>when the muscle fibre is stretched or released because this<br>would alter the force on the cross-bridge; phase 2 of the<br>transient represents the re-establishment of equil when the muscle fibre is stretched or released because this<br>would alter the force on the cross-bridge; phase 2 of the would alter the force on the cross-bridge; phase 2 of the<br>transient represents the re-establishment of equilibrium.<br>At any instant, the total tension depends on the relative<br>numbers of cross-bridges in states Al and A2. Th transient represents the re-establishment of equilibrium.<br>At any instant, the total tension depends on the relative<br>numbers of cross-bridges in states A1 and A2. The range

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f sliding movement over which this process can occur is<br>mited by the extent of movement corresponding to f sliding movement over which this process can occur is<br>mited by the extent of movement corresponding to<br>witching between the states in question: this would be f sliding movement over which this process can occur is<br>mitted by the extent of movement corresponding to<br>witching between the states in question; this would be<br>a explanation of the poplinearity in the amount of mited by the extent of movement corresponding to<br>witching between the states in question; this would be<br>ne explanation of the nonlinearity in the amount of<br>edevelopment of tension after a sudden length change witching between the states in question; this would be a explanation of the nonlinearity in the amount of edevelopment of tension after a sudden length change. The explanation of the nonlinearity in the amount of edevelopment of tension after a sudden length change.<br>The nonlinearity of the speed of the recovery would arise<br>cause the work done in stretching the elastic element edevelopment of tension after a sudden length change.<br>
The nonlinearity of the speed of the recovery would arise<br>
ecause the work done in stretching the elastic element<br>
constitutes part of the activation energy for the sw The nonlinearity of the speed of the recovery would arise<br>ecause the work done in stretching the elastic element<br>onstitutes part of the activation energy for the switch<br>alom Al to A2 and will vary according to the force i ecause the work done in stretching the elastic element onstitutes part of the activation energy for the switch com A1 to A2 and will vary according to the force in the lastic element. om Al to A2 and will vary according to the force in the

#### **6. NUMBER OF ATTACHED STATES**

**6. NUMBER OF ATTACHED STATES**<br>The number of these attached states, and the amount<br>movement corresponding to each step from one to the **C. NOWBER OF ATTACHED STATES**<br>The number of these attached states, and the amount<br>of movement corresponding to each step from one to the<br>step from the total state are still very uncertain. Estimates of the total In the number of these attached states, and the amount<br>
If movement corresponding to each step from one to the<br>
lext, are still very uncertain. Estimates of the total<br>
mount of movement based on X-ray structures of If movement corresponding to each step from one to the<br>ext, are still very uncertain. Estimates of the total<br>mount of movement based on X-ray structures of<br>provestilized fragments of myosin have ranged between ext, are still very uncertain. Estimates of the total<br>mount of movement based on X-ray structures of<br>rystallized fragments of myosin have ranged between<br>non- $\frac{R}{2}$  are  $\frac{d}{dt}$  (1993) and  $10-12$  nm (Dominguez *et* mount of movement based on X-ray structures of<br>
) rystallized fragments of myosin have ranged between<br>  $\Omega$  nm (Rayment *et al.* 1993) and  $10-12$  nm (Dominguez *et*<br>  $\frac{1}{2}$  1998): these structures have given no indica Prystallized fragments of myosin have ranged between<br> **a** nm (Rayment *et al.* 1993) and  $10-12$  nm (Dominguez *et*<br> *l.* 1998); these structures have given no indication<br>
thether there is more than one step. The curve in

a nm (Rayment *et al.* 1993) and 10-12 nm (Dominguez *et l.* 1998); these structures have given no indication hether there is more than one step. The curve in gure 4*a* reaches zero tension with a release of about  $\ell$ . 1998); these structures have given no indication the<br>ther there is more than one step. The curve in gure  $4a$  reaches zero tension with a release of about<br> $\frac{3 \text{ nm}}{2 \text{ nm}}$  but some  $\frac{2 \text{ nm}}{2 \text{ nm}}$  of this is ac hether there is more than one step. The curve in gure  $4a$  reaches zero tension with a release of about  $3 \text{ nm}$  but some  $2 \text{ nm}$  of this is accounted for by the gure 4*a* reaches zero tension with a release of about the 3 nm but some 2 nm of this is accounted for by the *al*.<br>Salment compliance; simulations (A. F. Huxley & is ideasyell 1996) required two steps with a total moveme 3 nm but some 2 nm of this is accounted for by the<br>fall 1996) required two steps with a total movement<br>fabout 10 nm. The reason we assumed two steps is that Frament compliance; simulations (A. F. Huxley & ideswell 1996) required two steps with a total movement f about 10 nm. The reason we assumed two steps is that as theory of A. F. Huxley & Simmons (1971) leads to an f about 10 nm. The reason we assumed two steps is that<br>in the extent of the step from A1 to A2 is<br>reater than the interval between sites on the actin filae theory of A. F. Huxley & Simmons (1971) leads to an istability if the extent of the step from Al to A2 is reater than the interval between sites on the actin filais intability if the extent of the step from Al to A2 is<br>reater than the interval between sites on the actin fila-<br>net where a myosin may attach (presumably  $5.5 \text{ nm}$ ,<br>ne spacing between actin monomers in each of the reater than the interval between sites on the actin fila-<br>net where a myosin may attach (presumably 5.5 nm,<br>ne spacing between actin monomers in each of the ent where a myosin may attach (presumably 5.5 nm,<br>ne spacing between actin monomers in each of the<br>rands of the filament). However, this argument has<br>een undermined by a simulation by Duke (1999) with a are spacing between actin monomers in each of the rands of the filament). However, this argument has een undermined by a simulation by Duke (1999), with a nole step of  $11 \text{ nm}$ ; instability is present but results only rands of the filament). However, this argument has<br>een undermined by a simulation by Duke (1999), with a<br>ngle step of 11 nm; instability is present but results only<br>alow asynchronous relative movements of adiacent een undermined by a simulation by Duke (1999), with a ngle step of 11 nm; instability is present but results only a slow asynchronous relative movements of adjacent ngle step of 11 nm; instability is present but results only<br>
1 slow asynchronous relative movements of adjacent<br>
laments and the overall shortening of the fibre does not<br>
10W any instability is show asynchronous<br>laments and the over-<br>now any instability.

aments and the overall shortening of the fibre does not<br>bw any instability.<br>Using a single-molecule technique, Veigel *et al.* (1999)<br>we recently found that the working stroke of certain have any instability.<br>
Using a single-molecule technique, Veigel *et al.* (1999)<br>
ave recently found that the working stroke of certain<br>
ow non-muscle myosins consists of two well-separated Using a single-molecule technique, Veigel *et al.* (1999) ave recently found that the working stroke of certain ow, non-muscle myosins consists of two well-separated and can each of about 5 nm. When they used subframent ave recently found that the working stroke of certain<br>ow, non-muscle myosins consists of two well-separated<br>eps, each of about 5 nm. When they used subfragment ow, non-muscle myosins consists of two well-separated<br>
reps, each of about 5 nm. When they used subfragment<br>
I of skeletal muscle, they could not fully resolve two<br>
reps in the attachment but showed that it occupied some Teps, each of about 5 nm. When they used subfragment<br>  $\begin{bmatrix} 1 & \text{of} \end{bmatrix}$  of skeletal muscle, they could not fully resolve two<br>  $\begin{bmatrix} \text{c} \text{es} \\ \text{c} \text{es} \end{bmatrix}$  in the attachment but showed that it occupied some<br>
ms I of skeletal muscle, they could not fully resolve two<br>reps in the attachment but showed that it occupied some<br>ms as against 1ms for detachment, suggesting strongly<br>at it too consists of more than one step. There is no the seps in the attachment but showed that it occupied some ms as against 1ms for detachment, suggesting strongly at it too consists of more than one step. There is no vidence yet to show whether these represent two events while the myosin is attached to a particular actin vidence yet to show whether these represent two events<br>hile the myosin is attached to a particular actin<br>abonomer or whether the second step is due to detach-<br>next with immediate attachment at the next actin while the myosin is attached to a particular actin<br>nonomer or whether the second step is due to detach-<br>next with immediate attachment at the next actin, as<br>lems to be the case in another type of experiment show to detach-<br>seems to be the case in another type of experiment<br>Kitamura et al. 1999) Thent with immediate attachment at the next actin, as<br>
U cems to be the case in another type of experiment<br>
O Kitamura *et al.* 1999).

#### **7. STRUCTURAL CHANGES**

**7. STRUCTURAL CHANGES**<br>The first indication of a structural change underlying<br>a working stroke was given by Reedy et al. (1965) Their T. STRUCTURAL CHANGES<br>The first indication of a structural change underlying<br>a working stroke was given by Reedy *et al.* (1965). Their<br>lectron micrographs of asynchronous insect flight muscle The first indication of a structural change underlying<br>ne working stroke was given by Reedy *et al.* (1965). Their<br>lectron micrographs of asynchronous insect flight muscle<br>lawed that the long axes of the cross-bridges wer showed that the long axes of the cross-bridges were<br>proved that the long axes of the cross-bridges were<br>proved that the long axes of the cross-bridges were<br>proved that the long axes of the cross-bridges were lectron micrographs of asynchronous insect flight muscle<br>Dowed that the long axes of the cross-bridges were<br>oughly perpendicular to the fibre axis in resting muscle<br>ut at about  $45^\circ$  in rigor. This difference was in the but at the long axes of the cross-bridges were<br>oughly perpendicular to the fibre axis in resting muscle<br>ut at about  $45^\circ$  in rigor. This difference was in the direc-<br>on that would correspond to shortening of the fibre if bughly perpendicular to the fibre axis in resting muscle<br>ut at about  $45^{\circ}$  in rigor. This difference was in the direc-<br>on that would correspond to shortening of the fibre if, as is to be expected, the resting state resembles that at the art of the working stroke and rigor resembles that at

the end. The idea that this change of orientation was the the end. The idea that this change of orientation was the event which caused shortening or production of force was developed by H. E. Huxley (1969) and has long been the end. The idea that this change of orientation was the<br>event which caused shortening or production of force was<br>developed by H. E. Huxley (1969) and has long been<br>generally accepted. It was supposed at first that the cr event which caused shortening or production of force was<br>developed by H. E. Huxley (1969) and has long been<br>generally accepted. It was supposed at first that the cross-<br>bridge tilted as a whole-driven by a change in the an developed by H. E. Huxley (1969) and has long been<br>generally accepted. It was supposed at first that the cross-<br>bridge tilted as a whole, driven by a change in the angle<br>at which it is attached to the actin filament, but t generally accepted. It was supposed at first that the cross-<br>bridge tilted as a whole, driven by a change in the angle<br>at which it is attached to the actin filament, but the<br>atomic structure of the myosin head (SI fragment bridge tilted as a whole, driven by a change in the angle<br>at which it is attached to the actin filament, but the<br>atomic structure of the myosin head (S1 fragment) has<br>shown a probable hinge between the catalytic domain at which it is attached to the actin filament, but the atomic structure of the myosin head (SI fragment) has shown a probable hinge between the catalytic domain atomic structure of the myosin head (SI fragment) has<br>shown a probable hinge between the catalytic domain<br>(which binds to the actin filament) and the long  $\alpha$ -helix<br>to which the light chains are attached and it is now shown a probable hinge between the catalytic domain<br>(which binds to the actin filament) and the long  $\alpha$ -helix<br>to which the light chains are attached, and it is now<br>usually supposed that the latter part of SI is a 'lever (which binds to the actin filament) and the long  $\alpha$ -helix<br>to which the light chains are attached, and it is now<br>usually supposed that the latter part of S1 is a 'lever arm'<br>which tilts relative to the catalytic domain ( to which the light chains are attached, and it is now<br>usually supposed that the latter part of SI is a 'lever arm'<br>which tilts relative to the catalytic domain (Rayment *et al*. 1993; Holmes 1997). It is now clear, from measurewhich tilts relative to the catalytic domain (Rayment *et al.* 1993; Holmes 1997). It is now clear, from measurements by resonance energy transfer between luminescent or fluorescent probes attached on either side of the b al. 1993; Holmes 1997). It is now clear, from measure-<br>ments by resonance energy transfer between luminescent<br>or fluorescent probes attached on either side of the hinge,<br>that adding ATP to an appropriate myosin fragment ments by resonance energy transfer between luminescent<br>or fluorescent probes attached on either side of the hinge,<br>that adding ATP to an appropriate myosin fragment<br>causes a bend at the hinge in the direction corresponding or fluorescent probes attached on either side of the hinge,<br>that adding ATP to an appropriate myosin fragment<br>causes a bend at the hinge in the direction corresponding that adding ATP to an appropriate myosin fragment causes a bend at the hinge in the direction corresponding to reversal of the working stroke (Getz *et al.* 1998; Suzuki  $_{et}$  al. 1998) *et al.* 1998).<br>*et al.* 1998).<br>**It** is not b reversal of the working stroke (Getz *et al.* 1998; Suzuki<br>*al.* 1998).<br>It is not, however, excluded that tilt may occur at both<br>accs i.e. at the attachment of the catalytic domain to

The theory of A. F. Huxley & Simmons (1971) leads to an atalytic domain along the actin filament might be one of the netheory of A. F. Huxley & Simmons (1971) leads to an atalytic domain along the actin filament might be o *et al.* 1998).<br>It is not, however, excluded that tilt may occur at both<br>places, i.e at the attachment of the catalytic domain to<br>the actin filament as well as at the hinge and Schmitz *et* It is not, however, excluded that tilt may occur at both places, i.e at the attachment of the catalytic domain to the actin filament as well as at the hinge, and Schmitz  $et$   $dt$  (1997) and Taylor  $et$   $dt$  (1999) have propo places, i.e at the attachment of the catalytic domain to<br>the actin filament as well as at the hinge, and Schmitz *et*<br>*al.* (1997) and Taylor *et al.* (1999) have proposed that this<br>is likely on the basis of three-dimensio the actin filament as well as at the hinge, and Schmitz *et al.* (1997) and Taylor *et al.* (1999) have proposed that this is likely on the basis of three-dimensional reconstructions from electron micrographs of cross-bri *al.* (1997) and Taylor *et al.* (1999) have proposed that this<br>is likely on the basis of three-dimensional reconstructions<br>from electron micrographs of cross-bridges in asynchro-<br>nous insect flight muscle. Such a rolling is likely on the basis of three-dimensional reconstructions catalytic domain along the actin ¢lament might be one of nous insect flight muscle. Such a rolling movement of the catalytic domain along the actin filament might be one of the steps proposed by Diaz Baños *et al.* (1996) on the basis of detailed calculations of the forces betwe catalytic domain along the actin filament might be one of<br>the steps proposed by Diaz Baños *et al.* (1996) on the<br>basis of detailed calculations of the forces between atoms<br>in the muosin head and in actin monomers the steps proposed by Diaz Baños *et al.* (1) basis of detailed calculations of the forces be in the myosin head and in actin monomers. in the myosin head and in actin monomers.<br>**8. TEMPERATURE JUMP EXPERIMENTS** 

A recent observation of a quite different kind has also 6. TEMPERATURE JUMP EXPERIMENTS<br>A recent observation of a quite different kind has also<br>given support to this idea. When the temperature of a<br>fibre during active contraction is raised within a fraction A recent observation of a quite different kind has also<br>given support to this idea. When the temperature of a<br>fibre during active contraction is raised within a fraction<br>of a millisecond tension rises relatively slowly (of given support to this idea. When the temperature of a<br>fibre during active contraction is raised within a fraction<br>of a millisecond, tension rises relatively slowly (of the<br>order of  $1-100 \text{ ms}$  depending on the initial and fibre during active contraction is raised within a fraction of a millisecond, tension rises relatively slowly (of the order of  $1-100 \text{ ms}$  depending on the initial and final temperatures). Bershitsky & Tsaturyan (1989) showed that there is no accompanying increase of stiffness, indicating that the tension change is not due to an increas temperatures). Bershitsky & Tsaturyan (1989) showed that there is no accompanying increase of stiffness, indicating that the tension change is not due to an increase in<br>the number of bridges attached and contributing to<br>tension. It might be supposed that this tension rise is due<br>to a shift in the equilibrium between two of the at the number of bridges attached and contributing to<br>tension. It might be supposed that this tension rise is due<br>to a shift in the equilibrium between two of the attached<br>states postulated to explain phase 2 of the tension t tension. It might be supposed that this tension rise is due<br>to a shift in the equilibrium between two of the attached<br>states postulated to explain phase 2 of the tension transient, but Bershitsky & Tsaturyan (1992) and Davis & states postulated to explain phase 2 of the tension transient, but Bershitsky & Tsaturyan (1992) and Davis & Harrington (1993) showed that there is no component with a time-course similar to the early part of phase 2 at sient, but Bershitsky & Tsaturyan (1992) and Davis &<br>Harrington (1993) showed that there is no component<br>with a time-course similar to the early part of phase 2 at<br>the temperature reached in the iumn though the later Harrington (1993) showed that there is no component<br>with a time-course similar to the early part of phase 2 at<br>the temperature reached in the jump, though the later<br>part of phase 2 may well be due to the same event as the with a time-course similar to the early part of phase 2 at<br>the temperature reached in the jump, though the later<br>part of phase 2 may well be due to the same event as the the temperature reached in the jump, though the later<br>part of phase 2 may well be due to the same event as the<br>tension rise after a temperature jump. These observations<br>show that different transitions must be involved in t part of phase 2 may well be due to the same event as the<br>tension rise after a temperature jump. These observations<br>show that different transitions must be involved in the<br>two cases. Further Bershitsky et al. (1997) and Tea tension rise after a temperature jump. These observations<br>show that different transitions must be involved in the<br>two cases. Further, Bershitsky *et al.* (1997) and Tsaturyan<br>*et al.* (1999) have shown that the slow rise o show that different transitions must be involved in the two cases. Further, Bershitsky *et al.* (1997) and Tsaturyan *et al.* (1999) have shown that the slow rise of tension after two cases. Further, Bershitsky *et al.* (1997) and Tsaturyan *et al.* (1999) have shown that the slow rise of tension after a temperature jump is accompanied by a striking change in the  $X$ -ray diffraction pattern. It was *et al.* (1999) have shown that the slow rise of tension after<br>a temperature jump is accompanied by a striking change<br>in the X-ray diffraction pattern. It was already well<br>known that the first layer line related to the lon a temperature jump is accompanied by a striking change<br>in the X-ray diffraction pattern. It was already well<br>known that the first layer line related to the long actin<br>helix (spacing 36 pm) becomes strong when a muscle goes in the X-ray diffraction pattern. It was already well<br>known that the first layer line related to the long actin known that the first layer line related to the long actin<br>helix (spacing 36 nm) becomes strong when a muscle goes<br>into rigor, but during contraction at low temperature it is<br>hardly stronger than at rest (H E Huyley et al. helix (spacing 36 nm) becomes strong when a muscle goes<br>into rigor, but during contraction at low temperature it is<br>hardly stronger than at rest (H. E. Huxley *et al.* 1982).<br>Bershitsky *et al.* (1997) however found that d into rigor, but during contraction at low temperature it is<br>hardly stronger than at rest (H. E. Huxley *et al.* 1982).<br>Bershitsky *et al.* (1997), however, found that during the hardly stronger than at rest (H. E. Huxley *et al.* 1982).<br>Bershitsky *et al.* (1997), however, found that during the rise of tension following a temperature jump, this actin<br>layer line becomes stronger implying that the Bershitsky *et al.* (1997), however, found that during the rise of tension following a temperature jump, this actin layer line becomes stronger, implying that the azimuthal



igure 6. Schematic diagram illustrating possible superposition of two different force-generating transitions. Rapid regeneration<br>f tension after sudden shortening would be the result of transition from A1 to A2 or from B1 igure 6. Schematic diagram illustrating possible superposition of two different force-generating transitions. Rapid regeneration<br>f tension after sudden shortening would be the result of transition from A1 to A2 or from B1 igure 6. Schematic diagram illustrating possible superposition of two different force-generating transitions. Rapid regeneration<br>f tension after sudden shortening would be the result of transition from A1 to A2 or from B1 f tension after sudden shortening would be the result of transition from A1 to A2 or from B1 to B2 (tilting of the light-chain<br>
smain (the lever arm) relative to the catalytic domain) while the rise of tension following a the catalytic domain) while the rise of tension following a temperature jump would be the<br>sult of transition from A1 to B1 and/or from A2 to B2 (rocking of the catalytic domain on the actin filament). In the A-states<br>is e sult of transition from A1 to B1 and/or from A2 to B2 (rocking of the catalytic domain on the actin filament). In the A-states is catalytic domain is free to rotate about the fibre axis but in the B-states it is not, i.e. the direction from ain is free to rotate about the film inding while the A-states do not. The rise of tens<br>the direction from A2 to A1 and from B2 to B1.

e direction from A2 to A1 and from B2 to B1.<br>
rientation of the myosin heads attached to actin comes<br>
comes a follow the long helix of the thin filament. Furthermore rientation of the myosin heads attached to actin comes<br>b follow the long helix of the thin filament. Furthermore,<br>haturyan et al. (1999) estimate that the fraction of crossrientation of the myosin heads attached to actin comes<br>
b follow the long helix of the thin filament. Furthermore,<br>
saturyan *et al.* (1999) estimate that the fraction of cross-<br>
ridges labelling the actin helix increases b follow the long helix of the thin filament. Furthermore, saturyan *et al.* (1999) estimate that the fraction of cross-<br>ridges labelling the actin helix increases from about ridges labelling the actin helix increases from about 5% at 5–6 °C to about 60% at 30 °C (permeabilized og fibres). The absence of an increase of stiffness allowing the temperature iump shows that the heads 5% at 5–6 $\degree$ C to about 60% at 30 $\degree$ C (permeabilized og fibres). The absence of an increase of stiffness pllowing the temperature jump shows that the heads ust have been already attached to actin but discrient. og fibres). The absence of an increase of stiffness<br>pllowing the temperature jump shows that the heads<br>ust have been already attached to actin but disorient-<br>ted in azimuth. An increase in the intensity of the sixth be all the temperature iump shows that the heads<br>in a sust have been already attached to actin but disorient-<br>ted in azimuth. An increase in the intensity of the sixth<br>ind seventh actin layer lines  $(5.9 \text{ and } 5.1 \text{ nm})$  ha nust have been already attached to actin but disorient-<br>ted in azimuth. An increase in the intensity of the sixth<br>nd seventh actin layer lines  $(5.9 \text{ and } 5.1 \text{ nm})$  had been<br>been well during the rise of tension when muscle ted in azimuth. An increase in the intensity of the sixth<br>nd seventh actin layer lines (5.9 and 5.1 nm) had been<br>bserved during the rise of tension when muscle in rigor nd seventh actin layer lines (5.9 and 5.1 nm) had been<br>bserved during the rise of tension when muscle in rigor<br>is heated to about 50 °C (Rapp & Davis 1996), again<br>dicating an increase in stereospecific binding with bserved during the rise of tension when muscle in rigor<br>
i heated to about 50 °C (Rapp & Davis 1996), again<br>
idicating an increase in stereospecific binding with<br>
imperature emperature. It is easiest to imagine that this change takes place at It is easiest to imagine that this change takes place at

It is easiest to imagine that this change takes place at<br>he attachment of the catalytic domain of the myosin<br>ead to the actin filament, as shown schematically in<br>give 6. Since the change is accompanied by a rise in the attachment of the catalytic domain of the myosin<br>read to the actin filament, as shown schematically in<br>gure 6. Since the change is accompanied by a rise in<br>reading it must involve tilting of the whole myosin head ead to the actin filament, as shown schematically in<br>gure 6. Since the change is accompanied by a rise in<br>mision, it must involve tilting of the whole myosin head<br>and a sample in the contrary of the whole myosin head gure 6. Since the change is accompanied by a rise in ension, it must involve tilting of the whole myosin head  $\sigma$  as to increase the force transmitted by the elastic ension, it must involve tilting of the whole myosin head<br>  $\begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}$  as to increase the force transmitted by the elastic<br>
lement, and it must be a change from a state free to<br>  $\begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}$  a sta It as to increase the force transmitted by the elastic<br>plement, and it must be a change from a state free to<br>potate in azimuth to one that is rigid in that direction.<br>his would be the situation if for example the attachmen The situation is a change from a state free to the situation is rigid in that direction.<br>This would be the situation if, for example, the attachment<br>onts shown in figure 6 are all simple-point attachments This would be the situation if, for example, the attachment<br>oints shown in figure 6 are all single-point attachments<br>while in the B-states there is also an attachment displaced

This would be the situation if, for example, the attachment<br>oints shown in figure 6 are all single-point attachments<br>hile in the B-states there is also an attachment displaced<br>at the discrimed perpendicular to the discram in the direction perpendicular to the diagram. The fact and the direction perpendicular to the diagram. The fact and the R-states are favoured by a rise in temperature hile in the B-states there is also an attachment displaced<br>a the direction perpendicular to the diagram. The fact<br>hat the B-states are favoured by a rise in temperature<br>are algests that one of the attachments in the B- bu 1 the direction perpendicular to the diagram. The fact<br>hat the B-states are favoured by a rise in temperature<br>largests that one of the attachments in the B- but not the<br>lastes is the hydrophobic link as in the change from hat the B-states are favoured by a rise in temperature<br>1995 uses that one of the attachments in the B- but not the<br>2.1-states is the hydrophobic link, as in the change from (e<br>1996) state at the form of  $\frac{7 \text{ of } \text{Diag}}{\text$ states is that one of the attachments in the B- but r<br>
D<sub>1</sub>-states is the hydrophobic link, as in the change<br>
cate 3 to state 4 in fig. 7 of Diaz Baños *et al.* (1996).<br>
The change in orientation of the lever arm sho states is the hydrophobic link, as in the change from<br>te 3 to state 4 in fig. 7 of Diaz Baños *et al.* (1996).<br>The change in orientation of the lever arm shown in<br>ure 6 on going from Al to A2 or Bl to B2 would not

the 3 to state 4 in fig. 7 of Diaz Baños *et al.* (1996).<br>The change in orientation of the lever arm shown in gure 6 on going from A1 to A2 or B1 to B2 would not rise if the elastic element resides in bending of the lever The change in orientation of the lever arm shown in gure 6 on going from Al to A2 or Bl to B2 would not rise if the elastic element resides in bending of the lever rm. *Phil. Trans. R. Soc. Lond.* B (2000)

ridges labelling the actin helix increases from about stepwise release and after a temperature jump should be  $5\%$  at  $5^{\circ}$ C to about 60% at  $30^{\circ}$ C (permeabilized different, as is found even when the step is applied emperature.<br>It is easiest to imagine that this change takes place at of sliding force, equal to the tension transmitted by the<br>he attachment of the catalytic domain of the myosin elastic element of the cross-bridge. The eq In any case, it is necessary to suppose that the two In any case, it is necessary to suppose that the two<br>steps can occur more or less independently of one another<br>in order that the time-constants of early recovery after a In any case, it is necessary to suppose that the two<br>steps can occur more or less independently of one another<br>in order that the time-constants of early recovery after a<br>stepwise release and after a temperature jump should steps can occur more or less independently of one another<br>in order that the time-constants of early recovery after a<br>stepwise release and after a temperature jump should be<br>different as is found even when the step is appli in order that the time-constants of early recovery after a stepwise release and after a temperature jump should be different, as is found even when the step is applied during the tension rise following a temperature jump ( stepwise release and after a temperature jump should be<br>different, as is found even when the step is applied during<br>the tension rise following a temperature jump (S. Y.<br>Rershitsky and A. K. Tsaturyan, personal communicadifferent, as is found even when the step is applied during<br>the tension rise following a temperature jump (S. Y.<br>Bershitsky and A. K. Tsaturyan, personal communica-<br>tion). Changes in attitude at the two binges would the tension rise following a temperature jump (S. Y.<br>Bershitsky and A. K. Tsaturyan, personal communica-<br>tion). Changes in attitude at the two hinges would,<br>however, interact, with one another, especially under Bershitsky and A. K. Tsaturyan, personal communication). Changes in attitude at the two hinges would, however, interact with one another, especially under isometric conditions (no relative sliding permitted) since tion). Changes in attitude at the two hinges would,<br>however, interact with one another, especially under<br>isometric conditions (no relative sliding permitted), since<br>any tendency for a change in attitude at one hinge to however, interact with one another, especially under isometric conditions (no relative sliding permitted), since any tendency for a change in attitude at one hinge to isometric conditions (no relative sliding permitted), since<br>any tendency for a change in attitude at one hinge to<br>cause sliding would have to be counteracted by an oppo-<br>site change in attitude at the other. The mean torqu any tendency for a change in attitude at one hinge to<br>cause sliding would have to be counteracted by an oppo-<br>site change in attitude at the other. The mean torques<br>generated at the two binges must produce the same value cause sliding would have to be counteracted by an opposite change in attitude at the other. The mean torques generated at the two hinges must produce the same value of sliding force, equal to the tension transmitted by the site change in attitude at the other. The mean torques generated at the two hinges must produce the same value<br>of sliding force, equal to the tension transmitted by the<br>elastic element of the cross-bridge. The equilibria of both<br>steps would be altered by a change in tension, a of sliding force, equal to the tension transmitted by the elastic element of the cross-bridge. The equilibria of both steps would be altered by a change in tension, as was discussed above in relation to phase 2 of the resp elastic element of the cross-bridge. The equilibria of both<br>steps would be altered by a change in tension, as was<br>discussed above in relation to phase 2 of the response to a<br>length step steps would be altered by a change in tension, as was discussed above in relation to phase 2 of the response to a length step.

## **9. DETACHMENT AND REATTACHMENT WITHIN ONE**<br>9. DETACHMENT AND REATTACHMENT WITHIN ONE **CHMENT AND REATTACHMENT WITHIN**<br>ADENOSINE TRIPHOSPHATE CYCLE

MANI AND REATTACHMENT WITHIN ONE<br>ADENOSINE TRIPHOSPHATE CYCLE<br>Many experiments have suggested that a cross-bridge<br>av remain attached while the filaments slide past one MADENOSINE TRIPHOSPHATE CTCLE<br>Many experiments have suggested that a cross-bridge<br>may remain attached while the filaments slide past one<br>another for distances too long for a particular myosin head Many experiments have suggested that a cross-bridge<br>may remain attached while the filaments slide past one<br>another for distances too long for a particular myosin head<br>to remain attached to the same actin monomer although may remain attached while the filaments slide past one<br>another for distances too long for a particular myosin head<br>to remain attached to the same actin monomer, although only one adenosine triphosphate (ATP) molecule was used to remain attached to the same actin monomer, although<br>only one adenosine triphosphate (ATP) molecule was used<br>(e.g. Higuchi & Goldman 1995; Kitamura *et al.* 1999). The<br>simplest explanation, would be that the cross-bridge only one adenosine triphosphate (ATP) molecule was used<br>(e.g. Higuchi & Goldman 1995; Kitamura *et al.* 1999). The<br>simplest explanation would be that the cross-bridge<br>detaches and reattaches immediately at another site on (e.g. Higuchi & Goldman 1995; Kitamura *et al.* 1999). The simplest explanation would be that the cross-bridge detaches and reattaches immediately at another site on the thin filament. Two situations where there is good e simplest explanation would be that the cross-bridge detaches and reattaches immediately at another site on the thin filament. Two situations where there is good evidence for this are (i) the experiment of Kitamura *et al.* detaches and reattaches immediately at another site on the most of the movement took place in steps closely equal to

he spacing between adjacent monomers in each strand of action in the thin filament, and (ii) stretch of a muscle fibre<br>uring contraction. In the latter case, the tension exerted are spacing between adjacent monomers in each strand of<br>ctin in the thin filament, and (ii) stretch of a muscle fibre<br>uring contraction. In the latter case, the tension exerted<br>v the fibre undergoes a number of striking ch ctin in the thin filament, and (ii) stretch of a muscle fibre event of the undergoes a number of striking changes. A a etailed explanation of these was given by Piazzesi *et al* the th uring contraction. In the latter case, the tension exerted y the fibre undergoes a number of striking changes. A etailed explanation of these was given by Piazzesi *et al*. etailed explanation of these was given by Piazzesi *et al.*<br>1992) on the basis that a cross-bridge torn off by the stress tension imposed by the stretch was in a state capable<br> $\frac{1}{2}$  restraching with a rate constant tw 1992) on the basis that a cross-bridge torn off by the scess tension imposed by the stretch was in a state capable  $f$  reattaching with a rate constant two orders of a ranitude greater than when detached by the normal xcess tension imposed by the stretch was in a state capable<br>f reattaching with a rate constant two orders of<br>nagnitude greater than when detached by the normal Freattaching with a rate constant two orders of<br>agnitude greater than when detached by the normal<br>rocess of binding a fresh ATP molecule. The chemical<br>rate of a muosin head detached in this way is not known agnitude greater than when detached by the normal rocess of binding a fresh ATP molecule. The chemical ate of a myosin head detached in this way is not known, sough it seems likely that it has lost the terminal phos-The chemical ate of a myosin head detached in this way is not known, a lough it seems likely that it has lost the terminal phosate of a myosin head detached in this way is not known, nough it seems likely that it has lost the terminal phos-<br>hate group of the ATP molecule that was bound to it nough it seems likely that it has lost the terminal phos-<br>hate group of the ATP molecule that was bound to it<br>when it attached. Another phenomenon that may be<br>also also detachment during sudden shortening and A hate group of the ATP molecule that was bound to it<br>A then it attached. Another phenomenon that may be<br>A splained by detachment during sudden shortening and<br>A sattachment in a time of the order of 10 ms (Piazzesi & rhen it attached. Another phenomenon that may be<br> **Reattachment** in a time of the order of 10 ms (Piazzesi &<br>
penture in a time of the order of 10 ms (Piazzesi &<br>
penhardi 1995) is 'repriming' the rapid receperation of Explained by detachment during sudden shortening and<br>
eattachment in a time of the order of 10 ms (Piazzesi &<br>
.ombardi 1995) is 'repriming', the rapid regeneration of<br>
the regeneration of extrachment in a time of the order of 10 ms (Piazzesi &<br>
combardi 1995) is 'repriming', the rapid regeneration of<br>
the phenomenon<br>
that for a given total amount of shortening the tension ombardi 1995) is 'repriming', the rapid regeneration of<br>
the power stroke (Lombardi *et al.* 1992). The phenomenon<br>
that, for a given total amount of shortening, the tension<br>  $\begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}$  is a given total amo The power stroke (Lombardi *et al.* 1992). The phenomenon<br>2) that, for a given total amount of shortening, the tension<br> $\begin{bmatrix} 2 \\ 2 \end{bmatrix}$  reached in the early tension recovery is greater if<br>2) a shortening is divided int For shortening, the tension<br>  $\begin{bmatrix} 2 \\ 2 \end{bmatrix}$  reached in the early tension recovery is greater if<br>
a shortening is divided into two steps separated by about<br>  $-20$  ms than if it is applied as a single step or as two st  $\frac{1}{2}$  reached in the early tension recovery is greater if<br>it is applied as a single step or as two steps<br> $-20$  ms than if it is applied as a single step or as two steps<br>encated by less than  $2 \text{ ms}$ . There are however separated by about  $-20 \text{ ms}$  than if it is applied as a single step or as two steps eparated by less than  $2 \text{ ms}$ . There are, however, at least -20 ms than if it is applied as a single step or as two steps<br>
parated by less than 2 ms. There are, however, at least<br>
5 wo other explanations for the phenomenon (A. F. Huxley<br>
7. Tideswell 1997)  $\frac{1}{2}$  wo other explanation.<br>Tideswell 1997).

#### **10. UNCERTAINTIES**

#### **(a)** *Force generated by one cross-bridge*

It will be evident from what I have said that there are ill great uncertainties in our knowledge of the mechan-It will be evident from what I have said that there are<br>ill great uncertainties in our knowledge of the mechan-<br>cal aspects of the contraction process. For instance, I<br>ave not mentioned a value for the amount of tension ill great uncertainties in our knowledge of the mechan-<br>
ial aspects of the contraction process. For instance, I<br>
ave not mentioned a value for the amount of tension<br>
ontributed by a single cross-bridge: it is clearly of cal aspects of the contraction process. For instance, I<br>ave not mentioned a value for the amount of tension<br>ontributed by a single cross-bridge: it is clearly of the<br>refer of a few piconeutons (I usually assume  $4 \text{ nN}$ ) ave not mentioned a value for the amount of tension<br>ontributed by a single cross-bridge: it is clearly of the<br>rder of a few piconewtons (I usually assume  $4 pN$ ) but ontributed by a single cross-bridge: it is clearly of the rder of a few piconewtons (I usually assume  $4 pN$ ) but II methods of estimating it are subject to uncertainty. My wn work has been entirely on intact isolated musc rder of a few piconewtons (I usually assume  $4 \text{ pN}$ ) but<br>ll methods of estimating it are subject to uncertainty. My<br>wn work has been entirely on intact, isolated muscle<br>hree in which it is reasonable to assume that unli Il methods of estimating it are subject to uncertainty. My<br>wn work has been entirely on intact, isolated muscle<br>bres in which it is reasonable to assume that, unlike in  $\dot{m}$ <br>it is experiments the cross-bridges are in t *vitroria* work has been entirely on intact, isolated muscle bres in which it is reasonable to assume that, unlike in *in itro* experiments, the cross-bridges are in their normal bres in which it is reasonable to assume that, unlike in  $\dot{m}$  *itro* experiments, the cross-bridges are in their normal tuations, but there is much controversy as to the propor-<br>on of the myosin heads that form active tuations, but there is much controversy as to the proportuations, but there is much controversy as to the propor-<br>on of the myosin heads that form active cross-bridges at<br>ny one time (e.g. it is not clear whether both heads of a<br>wosin molecule can contribute to tension, nor how on of the myosin heads that form active cross-bridges at<br>  $\mu$  my one time (e.g. it is not clear whether both heads of a<br>  $\mu$  wosin molecule can contribute to tension, nor how much<br>  $\mu$  the length of each half-turn of t nyosin molecule can contribute to tension, nor how much<br>f the length of each half-turn of the thin-filament helix i available for myosin atachment), and there is considerble variation in the total tension per unit cross-sectional  $\overline{\phantom{a}}$  rea given by different fibres.

Le variation in the total tension per unit cross-sectional<br>ea given by different fibres.<br>Another uncertainty is whether the compliance in a<br>ass-bridge is in the link to the myosin filament as shown rea given by different fibres.<br>Another uncertainty is whether the compliance in a<br>ross-bridge is in the link to the myosin filament as shown<br>beneficially in figures 5, and 6, or in bending of the Another uncertainty is whether the compliance in a<br>ross-bridge is in the link to the myosin filament as shown<br>the shown in figures 5 and 6, or in bending of the<br>external or in flexibility at the hinge I ross-bridge is in the link to the myosin filament as shown<br>Unhematically in figures 5 and 6, or in bending of the<br>extension or in flexibility at the hinge.

#### **(b)** *Single-molecule experiments*

Ideally, the impressive single-molecule experiments (b) **Single-molecule experiments**<br>Ideally, the impressive single-molecule experiments<br>ow being carried out in many laboratories should give a<br>irect answer to questions such as the amount of force per Ideally, the impressive single-molecule experiments<br>ow being carried out in many laboratories should give a<br>irect answer to questions such as the amount of force per<br>ross-bridge but the results from different laboratories ow being carried out in many laboratories should give a<br>irect answer to questions such as the amount of force per<br>ross-bridge, but the results from different laboratories<br>ary widely. There are many sources of possible erro irect answer to questions such as the amount of force per<br>  $\sum_{n=1}^{\infty}$  ross-bridge, but the results from different laboratories<br>  $\sum_{n=1}^{\infty}$  ary widely. There are many sources of possible error,<br>  $\sum_{n=1}^{\infty}$  is ross-bridge, but the results from different laboratories<br>Dary widely. There are many sources of possible error,<br>uch as: most laboratories use myosin molecules, intact or<br>commented stuck down in a layer of nitrocellulose i Fragmented, stuck down in a layer of possible error, ich as: most laboratories use myosin molecules, intact or agmented, stuck down in a layer of nitrocellulose in phonoun orientation (an honourable exception being the uch as: most laboratories use myosin molecules, intact or agmented, stuck down in a layer of nitrocellulose in nknown orientation (an honourable exception being the along the stuck down in a layer of nitrocellulose in<br>nknown orientation (an honourable exception being the<br>aboratory of T. Yanagida, where the usual preparation is<br>synthetic thick filament in which only a few of the nknown orientation (an honourable exception being the iboratory of T. Yanagida, where the usual preparation is synthetic thick filament in which only a few of the *Phil. Trans. R. Soc. Lond.* B (2000)

myosins still have heads capable of attaching to actin);<br>errors are introduced by the compliance of the actin fila-<br>ment and particularly by its attachment to a bead held in myosins still have heads capable of attaching to actin);<br>errors are introduced by the compliance of the actin fila-<br>ment and particularly by its attachment to a bead held in<br>a light trap: much Brownian noise is always pres errors are introduced by the compliance of the actin fila-<br>ment and particularly by its attachment to a bead held in<br>a light trap; much Brownian noise is always present; and<br>the time resolution is not good enough to tell e ment and particularly by its attachment to a bead held in<br>a light trap; much Brownian noise is always present; and<br>the time resolution is not good enough to tell exactly a light trap; much Brownian noise is always present; and<br>the time resolution is not good enough to tell exactly<br>when attachment occurs or to observe transient responses.<br>Skinned or permeabilized fibres, have the immense the time resolution is not good enough to tell exactly<br>when attachment occurs or to observe transient responses.<br>Skinned or permeabilized fibres have the immense<br>advantage over intact fibres that they make it possible to when attachment occurs or to observe transient responses.<br>Skinned or permeabilized fibres have the immense<br>advantage over intact fibres that they make it possible to<br>vary the concentrations of solutes at will but such Skinned or permeabilized fibres have the immense<br>advantage over intact fibres that they make it possible to advantage over intact fibres that they make it possible to<br>vary the concentrations of solutes at will, but such<br>preparations generally give low values for the tension per<br>unit area and show less tension recovery in phase 2 vary the concentrations of solutes at will, but such<br>preparations generally give low values for the tension per<br>unit area and show less tension recovery in phase 2 of the<br>response to sudden shortening than intact fibres: f preparations generally give low values for the tension per<br>unit area and show less tension recovery in phase 2 of the<br>response to sudden shortening than intact fibres; further, unit area and show less tension recovery in phase 2 of the<br>response to sudden shortening than intact fibres; further,<br>the sarcomeres are less regular and it is not clear how<br>much local shortening happens while the total le response to sudden shortening than intact fibres; further,<br>the sarcomeres are less regular and it is not clear how<br>much local shortening happens while the total length is<br>held constant and the preparation is activated the sarcomeres are less regular and it is not a<br>much local shortening happens while the total<br>held constant and the preparation is activated.<br>Apart from such quantitative uncertainties much local shortening happens while the total length is<br>held constant and the preparation is activated.<br>Apart from such quantitative uncertainties, there is

held constant and the preparation is activated.<br>Apart from such quantitative uncertainties, there is<br>always a possibility—indeed, a probability—that our<br>present concents are seriously incomplete or even wrong Apart from such quantitative uncertainties, there is<br>always a possibility—indeed, a probability—that our<br>present concepts are seriously incomplete or even wrong.<br>For example it is still usually assumed that force is generalways a possibility—indeed, a probability—that our<br>present concepts are seriously incomplete or even wrong.<br>For example, it is still usually assumed that force is gener-<br>ated entirely by the lever arm tilting about a sing present concepts are seriously incomplete or even wrong.<br>For example, it is still usually assumed that force is generated entirely by the lever arm tilting about a single axis,<br>whereas it seems to me that there is now a re For example, it is still usually assumed that force is generated entirely by the lever arm tilting about a single axis, whereas it seems to me that there is now a real possibility that tilting can occur at the attachment t ated entirely by the lever arm tilting about a single axis,<br>whereas it seems to me that there is now a real possibility<br>that tilting can occur at the attachment to actin as well as<br>at the hinge. And the suggestion by Harri that tilting can occur at the attachment to actin as well as at the hinge. And the suggestion by Harrington (1979) that tilting can occur at the attachment to actin as well as<br>at the hinge. And the suggestion by Harrington (1979)<br>that contraction may be due to melting of the  $\alpha$ -helix in<br>the S2 portion of myosin has not been excluded at the hinge. And the suggestion by Harringtor<br>that contraction may be due to melting of the  $\alpha$ -<br>the S2 portion of myosin has not been excluded.

The ideas about the events following a temperature jump arose<br>The ideas about the events following a temperature jump arose<br>in conversation with Dr Bershitsky and Dr Tsaturyan. I am also The ideas about the events following a temperature jump arose<br>in conversation with Dr Bershitsky and Dr Tsaturyan. I am also<br>grateful to them and to Dr Vincenzo Lombardi for helpful criti-The ideas about the events following a temperature jump arose<br>in conversation with Dr Bershitsky and Dr Tsaturyan. I am also<br>grateful to them and to Dr Vincenzo Lombardi for helpful criti-<br>cisms of the manuscript in conversation with Dr Bershitsky and Dr Tsaturyan. I am also grateful to them and to Dr Vincenzo Lombardi for helpful criticisms of the manuscript.

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#### *Discussion*

**Discussion**<br>
L. Cruzeiro-Hansson (*Department of Mathematics, Heriot-*<br> *Att University Edinburgh IIK*) I would like to suggest *Discussion*<br>
L. Cruzeiro-Hansson (*Department of Mathematics, Heriot-Watt University, Edinburgh, UK*). I would like to suggest<br>
that there may be no distinction between linear and L. Cruzeiro-Hansson (*Department of Mathematics, Heriot-Watt University, Edinburgh, UK*). I would like to suggest that there may be no distinction between linear and rotary motors in the sense that conformational changes i Watt University, Edinburgh, UK). I would like to suggest that there may be no distinction between linear and rotary motors in the sense that conformational changes in linear motors may also be due to rotation of  $\alpha$ -heli that there may be no distinction between linear and<br>rotary motors in the sense that conformational changes in<br>linear motors may also be due to rotation of  $\alpha$ -helices. In<br>this sense, all motors may be rotary. rotary motors in the sense that conformational changes in

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