New insights into the behavior of muscle during active lengthening

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ABSTRACT A muscle fiber was modeled as a series-connected string of sarcomeres, using an A. V. Hill type model for each sarcomere and allowing for some random variation in the properties of the sarcomeres. Applying stretches to this model led to the prediction that lengthening of active muscle on or beyond the plateau of the length tension curve will take place very nonuniformly, essentially by rapid, uncontrolled elongation of individual sarcomeres, one at a time, in order from the weakest toward the strongest. Such a "popped" sarcomere, at least in a single fiber, will be stretched to a length where there is no overlap between thick and thin filaments, and the tension is borne by passive components. This prediction allows modeling of many results that have previously been inexplicable, notably the permanent extra tension after stretch on the descending limb of the length tension curve, and the continued rise of tension during a continued stretch.

INTRODUCTION

It is a common observation that lengthening of muscles produces results that are not as consistent or as easy to interpret as those produced from experiments in which the muscles shorten. While it is not practical to reproduce examples of all of them, many of them are apparent in Fig. 1.

Rising tension during stretch

When a muscle or muscle fiber is shortened at constant velocity within the plateau region of the length tension curve, the tension initially falls, but quickly reaches a very nearly constant value. However, constant velocity lengthening produces a much more complex tension record, consisting of an initial steep rise sometimes followed by a brief fall, giving way usually to a continued rise in tension throughout the movement. This has been clearly documented for whole muscles in the preceding paper (Harry et al., 1990) and can be seen in published single fiber records both near optimum length (Morgan et al., 1982) and on the descending limb of the length tension relation. Note that some records, particularly of long stretches, do show regions of decreasing tension during stretch (e.g., Edman et al., 1978; Fig. 2 *B*), though these usually occur only in long stretches and are often not reproducible (personal observations). Even when lengthening is done at velocities sufficiently high so that further increases in velocity produce no further increases in tension, the tension continues to rise as the stretch continues. This phenomenon on a sarcomere scale is incompatible with independent crossbridge models. When the amplitude of a constant velocity movement is large compared with the crossbridge stroke, the crossbridge distribution and hence the tension of the model will reach a steady state.

The converse of this is the slowing of stretch at constant tension, particularly for tensions in excess of the so-called yield point. When such a tension is applied to an isometric muscle, it lengthens rapidly, but under constant load, the rate of elongation decreases with the extent of the stretch.

A further variant is the phenomenon that Katz (1939) noted and that Huxley (1971) addressed. This is the experiment in which a tension equal to isometric capability is applied to a shortening muscle. This causes a yield, consistent with the crossbridge theory prediction that the number of crossbridges is reduced during shortening. However, the yield quickly comes to an end. It is difficult to see how sufficient bridges could attach during the rapid lengthening to bring that lengthening to a halt (Huxley, 1980, p. 84).

Permanent extra tension

Perhaps the most studied subject to be dealt with here is the "permanent extra tension". This is the name given to the observation that the tension, after an active lengthening along the descending limb of the length tension relationship, does not tend toward the tension appropriate to the longer final length, but stays above that as long as stimulation continues (Julian and Morgan, 1979*b*; Edman et al., 1982; Woledge et al., 1985, p. 75). Careful observation with single fibers and long enough tetani to

show a truly steady tension (Julian and Morgan, 1979*b*) showed that it tends toward a value close to the isometric tension at the original shorter length. Sarcomere nonuniformities were implicated, in that the pattern of internal motion within a fiber contracting at long length was shown to be changed by stretch, and the "extra tension" was quickly abolished by sufficient relaxation to be associated with sarcomere length redistribution. However, the stretch appeared to be distributed fairly evenly over most of the fiber, and no clear picture emerged of what the pattern of nonuniformities might have been, nor of why the tension took up the value that it did.

Maintained tension during fast stretch

The preceding paper (Harry et al., 1990) has shown both that the tension in a whole muscle does not fall significantly with increasing velocity up to quite large velocities, and that such a maintained tension at high velocity is not compatible with crossbridge models of contraction under reasonable assumptions. Although the model of A. F. Huxley (1957) did give an asymptote of tension for large lengthening velocities, the asymptote was much higher than that found experimentally. Furthermore, the model assumed no limit to the possible extension of a crossbridge. Harry et al. (1990) showed that attempts to incorporate a limit on the maximum extension of a crossbridge invariably lead to a force velocity curve that falls at high velocities, both for the original Huxley model and for models with the rate constants modified to produce more realistic tensions during lengthening. Even a limit of five times the maximum isometric extension produces a decrease much greater than seen experimentally. Basically this is because the number of bridges formed continues to fall as velocity increases. Only if the average force and hence extension of a bridge continues to rise can a fall in tension be avoided. Even allowing the force extension characteristic of the crossbridges to be nonlinear did not produce a satisfactory fit to experimental results with a limited crossbridge extension.

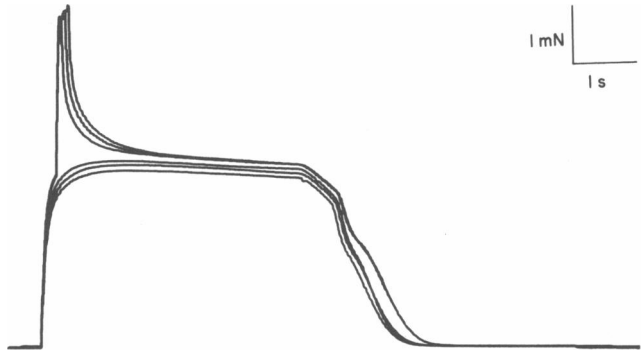

FIGURE 1. Experimental records showing permanent extra tension. Stretches of 3, 5, and 7% of just taut length were applied before and during tetani on the descending limb of the length tension curve. The stretches applied before the commencement of stimulation (*lower three traces*) produced a decreased tension with increased length, but the stretches during stimulation (*upper three traces*) all produced the same final tension. Note also the continued rise of tension throughout the stretches. Stimulation frequency of 16 pulses/s, temperature of 4°C, initial sarcomere length 2.5 μm, and ramp speed of 0.3 muscle lengths/s. Reproduced from Julian and Morgan (1979*b*), with permission of the authors.

Damage from eccentric contractions

Another peculiarity of muscle being stretched rather than shortening is its propensity to damage. Stretches, particularly long and fast ones, commonly damage single fibers that have withstood many isometric or shortening contractions at the same lengths (personal observations). In intact animals and humans, lengthening contractions have been shown to lead to damage in the muscle, typically pain and stiffness a day or two later, accompanied by histological observations of massive degeneration and replacement of muscle fibers. Shortening contractions of the same tension, duration, and speed caused little or no damage (Armstrong et al., 1983; Newham et al., 1983; McCully and Faulkner, 1985).

Variability of measurements

Many parameters used to describe the behavior of lengthening muscle show considerable variability between experiments and between experiments. Perhaps the most obvious example of this is measurement of the force velocity curve for lengthening. Woledge et al. (1985) have reviewed the various published measurements of this, and discussed at some length the variability of the results reported. The slope of the curve for slow lengthening is usually found to be greater than for slow shortening, but the difference varies greatly. As the lengthening velocity becomes large, the tension has been reported to decrease slightly, show a continuing increase, or to tend to an asymptote as described by Katz (1939). Even when an asymptote is seen, the range of reported values is large. This applies for both whole muscles and single fibers.

The behavior not represented by the force velocity curve is also very variable. The slope of the continued rise in tension referred to above is very variable, as is the existence and size of the falling phase immediately after the initial rise.

Huxley (1971) investigated the "pullout" behavior observed when a load equal to isometric capability is applied to a shortening muscle, because it provided sup-

port for the general principles of the crossbridge theory. However, he found the variability so large that he was unable to give "a quantitative account of the phenomenon."

THEORY

Sarcomere length-tension curve

Many muscles, and certainly the single frog fibers commonly used in muscle experiments, show a region of their "isometric" tension versus length relationship where total tension decreases as muscle length increases. In the case of single frog fibers, using contractions in which the sarcomeres were as nearly isometric as possible, Gordon et al. (1966) found a linear decrease in active tension which correlated with decreasing overlap of thick and thin filaments. Even for those whole muscles where total tension does not show a descending limb, the source of the rising passive tension may not be effectively in parallel with individual sarcomeres, so that lengthening of one sarcomere within the muscle, without lengthening of neighboring sarcomeres, may well give decreased total tension in the one lengthening sarcomere.

Instability during fixed end contractions

It has been pointed out before that a series connection of elements whose tension decreases with increasing length must be unstable. Such instabilities are believed to give rise to the internal motion seen in a fiber contracting at fixed overall length, when the length puts sarcomeres on the descending limb of their length tension relation. The force velocity relation provides damping to prevent these instabilities from becoming catastrophic. This internal motion, combined with the discontinuity of slope of the force velocity curve, is thought to be responsible for the creep phase of tension rise (See for example Huxley and Peachey, 1961; Julian and Morgan, 1979*a*; Edman and Regiani, 1984; Altringham and Bottinelli, 1985; Bagni et al., 1988). These phenomena have been extensively studied and debated, and will not be considered further here.

Instability during shortening

If a fiber on the descending limb is allowed to shorten slowly, the strongest sarcomeres (those able to develop the greatest isometric tension) are expected to take up most of the shortening. If they are stronger because they are shorter, then the nonuniform shortening will increase the differences. An explanation based on this idea has been presented before (Julian and Morgan, 1979*b*) to account for the observation that slowly shortening a fiber along the descending limb does not produce the tension appropriate to the final average length. Evidence that such shortening is extremely nonuniform, being almost entirely confined to the end regions, has also been presented. Confirmation of that explanation by modeling is presented here.

Instability during lengthening

Instabilities during lengthening of a fiber have not previously been considered in detail. It is important to note that the existence of a horizontal region of the force velocity curve for lengthening provides the possibility for essentially undamped instabilities, since at high enough lengthening velocities the tension is virtually independent of velocity.

The present modeling depends upon the assumption that the sarcomeres of any real fiber will have some random variation in their strengths, defined here as isometric capability at their current length. This may arise from random variations in sarcomere lengths, in cross-sectional area of contractile material, or as statistical variation between sarcomeres in the number of attached crossbridges, or as a combination of these factors. If we imagine stretching such a fiber, the tension will rise as series elastic structures and crossbridges are stretched and all the sarcomeres lengthen slowly and almost uniformly, until the tension nears the yield tension of the weakest sarcomeres. (At this stage of the discussion, the classic Katz [1939] curve is assumed, and the yield tension is the asymptote. Other cases are considered below.) Under these conditions, small differences in the yield tensions of the various sarcomeres will lead to very large differences in lengthening velocities, with the weakest sarcomeres lengthening rapidly. If they are on the plateau of the length tension curve, this will not change their strength, and hence their yield tension, until they are stretched to the descending limb. Once the weakest sarcomeres are on the descending limb and become weaker with increasing length, they become unable to hold the existing tension at any velocity, and will lengthen ever more rapidly, limited only by inertial or passive viscous forces, until eventually rising passive tension prevents further lengthening. This rapid lengthening of the weakest sarcomere(s) will prevent further tension rise due to the stretching of the whole fiber, and will even cause the tension to fall temporarily, as other parts of the fiber shorten. The process will then be repeated with the next weakest sarcomere.

This, then, is the central mechanism being proposed here; that forced lengthening of a muscle on the plateau or descending limb of the length tension curve must take place essentially by "popping" of sarcomeres, ideally one

at a time, in order from the weakest toward the strongest. The term "popping" is used to describe this uncontrolled, virtually instantaneous lengthening of a sarcomere from a length commensurate with its passive length to a length where passive structures primarily support the tension. If the strength variations are randomly distributed along most of the fiber, active lengthening will involve extreme lengthening of a few randomly distributed sarcomeres, with minimal length changes in most of the sarcomeres. It is proposed that this is an inescapable consequence of a descending limb of the length tension relation and a tension that does not continue to increase with increasing stretch velocity.

If in fact the sarcomere force velocity curve has a peak and decline, as suggested by Harry et al. (1990) from crossbridge modeling, the instabilities will be even greater, and a similar pattern of lengthening will emerge. In this case, though, the force velocity curve is unstable independent of the length tension curve. Because of this, popping would be instantaneous from the plateau as well as from the descending limb. On the ascending limb of the length tension diagram, lengthening will increase the strength of a sarcomere, thereby providing some stabilization of sarcomere lengths. The result would then depend on the actual shape of the force velocity curve, and no experimental simulations have been done on this region.

If on the other hand the force velocity curve continued to rise slowly with increasing lengthening velocity, then any tension could be sustained at a high enough velocity. Hence there would be no instantaneous popping, but rather a rapid lengthening of the weakest sarcomeres. For a small slope, the final result would be essentially the same as for zero slope. If the slope were greater, then the inequality of the distribution of lengthening between sarcomeres would be less; that is, sarcomeres other than the weakest would take up a larger fraction of the movement.

MODELING

The model

The model was closely based on that of Morgan et al. (1982), run on a Macintosh computer (Apple Computer Inc., Cupertino, CA), and was written in Lightspeed Pascal (Think Technologies, Bedford, MA) using the Programmers Extender (Invention Software Corp, Ann Arbor, MI). One half of the muscle fiber was modeled as either 100 or 500 sarcomeres connected in series. In order to accommodate different muscles and temperatures, the unit of time was defined as the time for an unloaded sarcomere to shorten 1 μm. Thus, the unloaded shortening velocity was 1 μm/sarcomere per time unit. For the usual frog single fibers, this means that one time unit corresponds to ~0.5 s at 0°C, and ~50 ms at 20°C. Each sarcomere was represented by a Hill type model, consisting of a contractile component characterized by a force velocity curve, a linear series elastic component, and an exponential parallel elastic component. The force velocity curve was taken as the classic Hill-Katz curve as quantified by Morgan et al. (1982). Constants could be entered for a/P_o, (default:0.25), the change of slope between slow lengthening and slow shortening, (default:6), the asymptote for lengthening, (default:1.8), and a curvature coefficient for the lengthening region. The unloaded shortening velocities of all sarcomeres were the same. For each sarcomere the isometric tension was determined by the length tension curve of Gordon et al. (1966), and by the specified isometric capability at optimum length $P_{o_{opt}}$ of that sarcomere. The distribution of $P_{o_{opt}}$ was specified as an exponential distribution with a random variation added. Values for the end sarcomere, the central sarcomere, the length constant of the exponential distribution, the random component amplitude, and the random number generator seed were all specified by the user. The random component was generated by smoothing a series of pseudo-random numbers generated by the computer, giving an approximately Gaussian distribution. The initial length distribution was very similarly specified. The passive tension curves for the different sarcomeres were all scaled from a basic curve to produce the same passive tension at the beginning of a simulation. The basic curve was exponential, specified by the slack length, a length constant, and the tension at some specified sarcomere length.

The length changes to be applied were specified by the times of beginning and ending the ramp, and the final average sarcomere length. The initial length was calculated from the initial sarcomere length distribution. The program included facilities to display, save, and print the length tension relation, the force velocity relation, the passive curve for any sarcomere, the movement being applied, and the distributions of $P_{o_{opt}}$, strength, and of sarcomere length, as well as the tension-time record being produced. Sarcomere length, $P_{o_{opt}}$, and strength could also be displayed as histograms. In addition, a "segment length" record was obtained by adding the sarcomere lengths of the "central" half of the fiber. The simulation could be stopped at any time to examine these curves and then resumed.

The solution proceeded iteratively as before. The time intervals for the calculation were not equal, but varied automatically to accommodate the rate of change of tension. No interval >0.0001 time units (or less during very rapid ramps) was accepted if tension changed more than 2% of isometric tension of if the length of any sarcomere changed more than 0.2 μm. An option allowed the fiber to be replaced by a single sarcomere, with

parameters equal to the average of those for the fiber. Tension was plotted on the screen as a simulation progressed.

Shortening

As a preliminary example of an experiment in which sarcomere nonuniformities are thought to be important, simulations were run of the slow shortening experiments of Julian and Morgan (1979*b*) (their Figs. 1 and 2) and the results are shown in Fig. 2. The 100-sarcomere fiber shortens nonuniformly, and consequently does not produce the tension that it would if stimulated at the final length. The single sarcomere, on the other hand, increased its tension at constant velocity in proportion to its isometric capability, as expected. The simulated central segment length record shows very little movement, as shown experimentally by Julian and Morgan, and recently confirmed by Tsuchiya and Sugi (1988), Fig. 5.

Lengthening

Existence of popping

Attempting to simulate a lengthening fiber quickly brought home the truth of the assertion above, that lengthening must be extremely nonuniform. When inertial and passive viscous forces are ignored, as in this model, finding a solution as the tension approaches the yield point of the weakest sarcomere is extremely difficult. Very small changes in the tension produce much larger changes in the velocity of some sarcomeres and hence of the fiber. Besides the problems of stability and numerical accuracy, it is not clear that a solution actually exists during the rapid lengthening of a sarcomere. This depends on whether the lengthening of the sarcomere reduces its tension-generating capacity due to reduced overlap more rapidly or less rapidly (giving a solution) than it reduces the tension of the rest of the fiber, due to its elasticity. This in turn depends on the number of sarcomeres and the series compliance. More sarcomeres make instability more probable, and for any physiological number, there is no solution. Adding a small parallel damper to the series elastic element ensured that the fall in tension in the rest of the fiber could be greater at sufficient velocity. Using this it was possible to trace the stretch of a fiber, seeing the popping of each sarcomere. This did, however, produce a large number of very small time intervals for each pop, and was not a practical method for simulating the 500-sarcomere fiber needed to reduce the effect on the tension of each sarcomere popping.

Consequently a "quick pop" option was added. With this option enabled, no attempt was made to track a sarcomere through popping. After solving for the tension

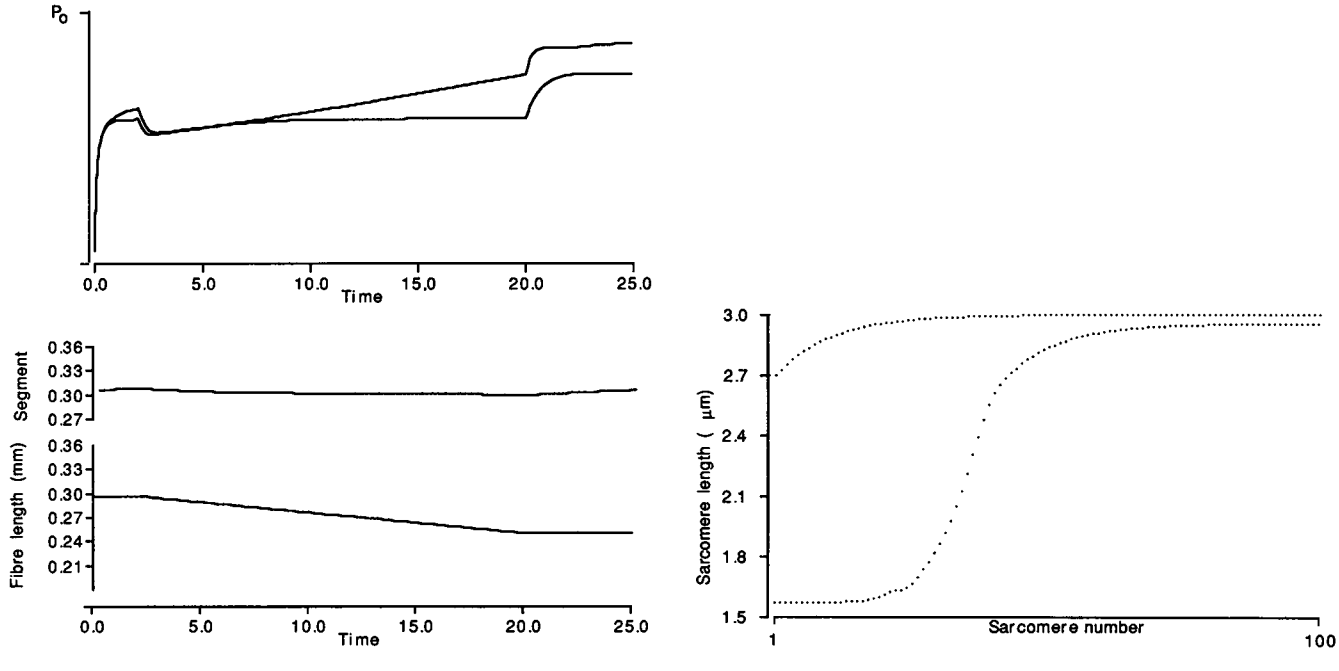

FIGURE 2 Model records for slow shortening. The upper left panel shows the tension produced during shortening of a single sarcomere (*upper trace*) and of a 100-sarcomere half fiber. The traces below show the sum of the sarcomere lengths (*bottom*), and (twice) the sum of the central 50 sarcomeres, representing a segment length record. The right-hand traces show the initial and final sarcomere length distributions.

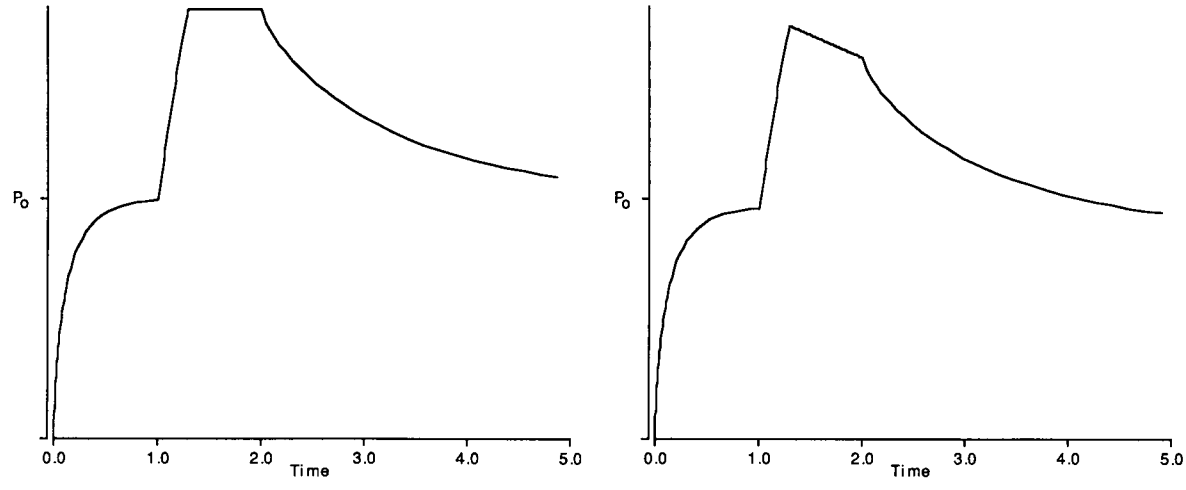

FIGURE 3 Model records for a single sarcomere subjected to a stretch. On the left, the stretch began at 2.05 μm and ended at 2.2 μm, that is, within the plateau of the length tension relation. One the right, the stretch was from 2.35 to 2.5 μm, that is, of the same amplitude but on the descending limb of the length tension curve.

in each time interval, but before updating the sarcomere lengths, a check of the weakest sarcomere was made to see if its updated yield point would be less than the existing tension, that is, whether the tension would need to be reduced in the next time interval. If so, the present time step was repeated with half the interval. When a tension decrease would be required and the time interval was at the minimum allowed (0.0001 time units), then the sarcomere would be popped by setting its isometric capability to zero. This ensured that only its passive tension would be used from then on, and that during the next time interval, it would be stretched appropriately. This led to an instantaneous fall in tension, as the other sarcomeres shortened. This option reduced the calculations considerably, but was shown not to affect the results preceptibly other than during the pop.

Stretches on and off the plateau

Figs. 3–6 show some simulated stretches using the model with 1 and 100 sarcomeres. With only 100 sarcomeres, the popping of each sarcomere produces a clear drop in tension. Although this produces rather unrealistic tension traces, it does aid in seeing the results of varying the other parameters. In each case, the left panel is for a stretch entirely within the plateau region of the length tension curve (2.05–2.2 μm average sarcomere length), and the

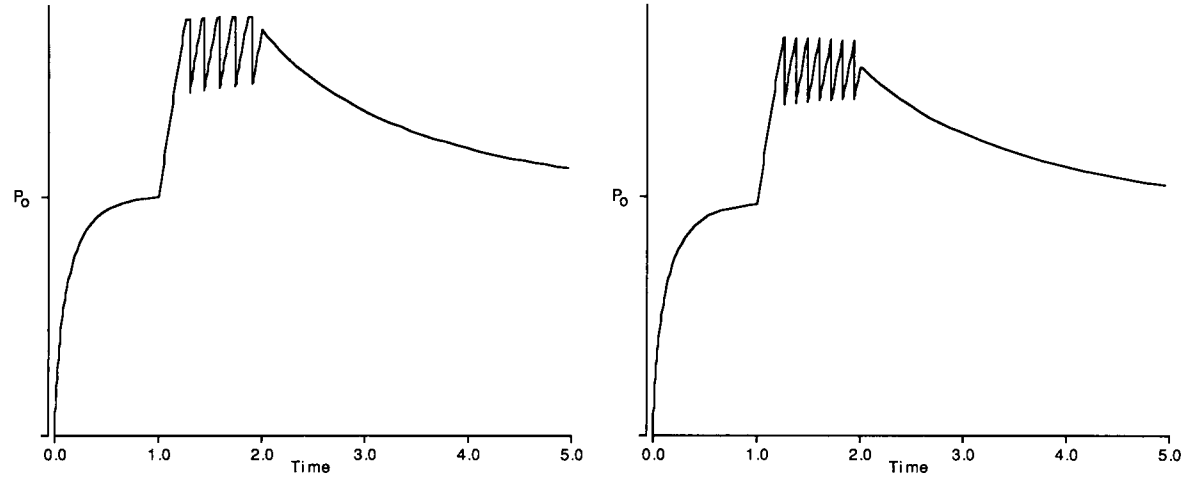

FIGURE 4 Model records for a fiber of 100 sarcomeres stretched over the same sarcomere length ranges as for Fig. 3. For these records, all the sarcomeres began at the same length, but isometric capability had a 2% rms random variation.

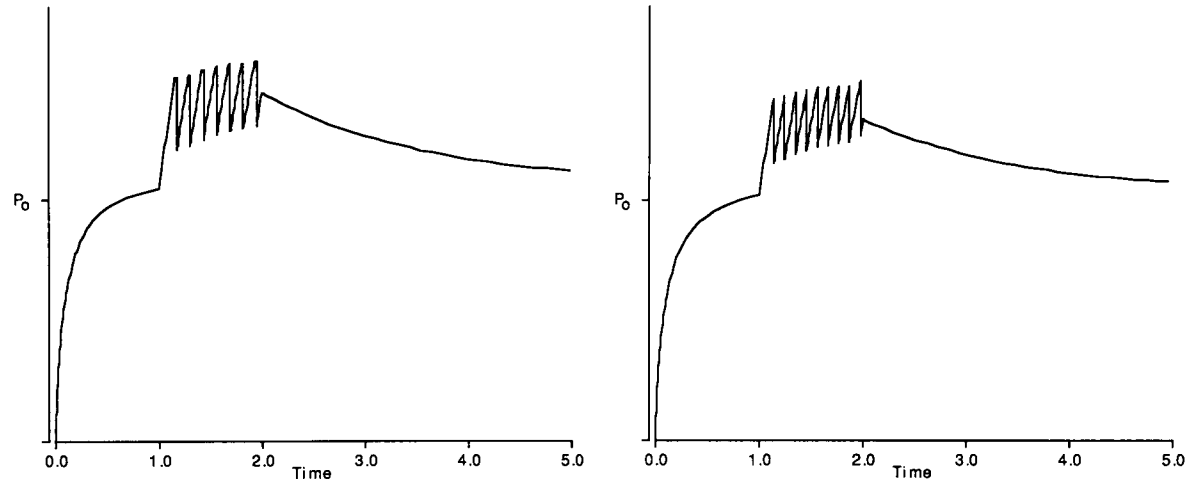

FIGURE 5 Model records for a fiber of 100 sarcomeres stretched over the same sarcomere length ranges as for Fig. 3. For these records, the random variation in isometric capability has been increased to 10%, but the initial sarcomere lengths were still uniform.

right panel represents the same fiber being stretched along the descending limb (2.35–2.5 μm average sarcomere length). In each case the stretch is completed in 1 time unit, giving a velocity of -0.15 times the unloaded shortening velocity.

Fig. 3 shows a single sarcomere. In this case the stretch across the plateau shows a constant tension, and the stretch on the descending limb shows a tension decreasing as the sarcomere is lengthened. This is the behavior expected of a single sarcomere or a perfectly uniform fiber, but is not typical of real muscle.

Fig. 4 shows results for a simulated fiber with 2% variation in $P_{0_{opt}}$ (isometric capability at optimum length), but with initially uniform sarcomere lengths. Popping of sarcomeres occurs in both traces, but with some differences. On the plateau each pop was preceded by a brief period of constant tension as the current weakest sarcomere was stretched from near 2.05 μm to 2.25 μm, where its strength began to fall. When the stretch began on the descending limb, such pauses were not evident. Note that, although no clear rise in tension during the stretch is apparent with this degree of nonuniformity, the decrease during stretch at long lengths has been virtually abolished.

Fig. 5 shows a fiber with 10% variation in $P_{0_{opt}}$, but still initially uniform sarcomeres. The continued rise in ten-

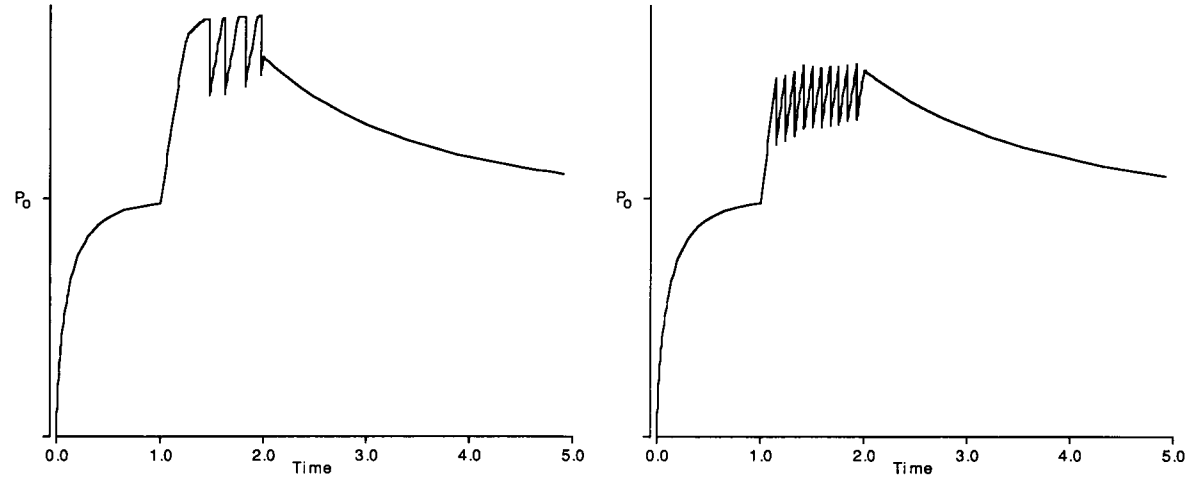

FIGURE 6 Model records for a fiber of 100 sarcomeres stretched over the same sarcomere length ranges as for Fig. 3. For these records, the isometric capability again had a 2% rms random variation, but, in addition, the initial sarcomere lengths had a random variation of 0.1 μm rms.

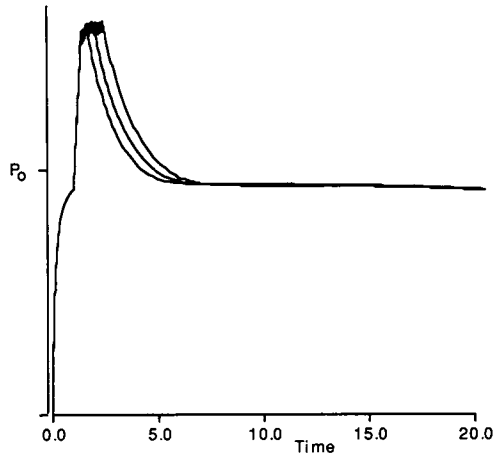

FIGURE 7 Model records for a half fiber of 500 sarcomeres during stretches similar to those used in Fig. 1. The isometric capability distribution was random with an amplitude of 3% of optimum tension. The initial sarcomere length distribution is shown in Fig. 8. The yield point of the force velocity curve has been increased from the usual 1.8 to 2.2 times isometric, as the present theory suggests that the true value for a sarcomere is higher than ever seen for a fiber (see Predictions).

sion throughout the stretch (each pop occurs at a greater tension than the previous one) is more pronounced at both lengths, due to the greater differences in isometric capabilities. The slopes of the curves during the stretch are approximately equal, independent of initial length.

In Fig. 6, the variation in $P_{o_{opt}}$ has been returned to 2%, but a random dispersion of initial sarcomere lengths with an amplitude of 0.1 μm has been added. As might be expected, this made very little difference in the result near optimum length, but increased the slope of the tension time trace beyond the plateau. Most experimenters agree that this slope is experimentally greater at longer initial lengths than on the plateau, suggesting that dispersion of sarcomere lengths is probably an important source of strength dispersion. Note that the record at optimum length shows considerable lengthening before the first pop. Examination of the progress of the contraction showed that the weakest sarcomere happened to have a very short initial length, so that it lengthened quite a way up the ascending limb and across the plateau before reaching the end of the plateau and popping. When the initial lengths are on the descending limb, sarcomeres pop

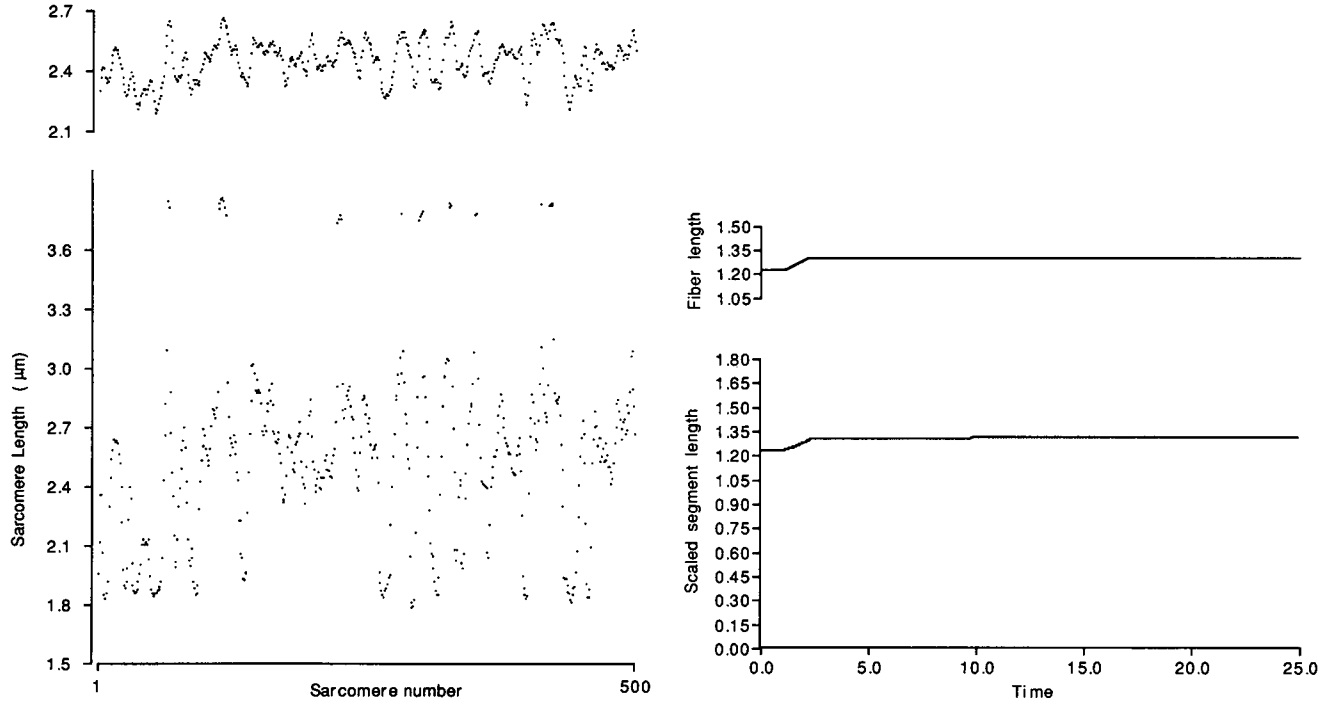

FIGURE 8 Other records from the 7% stretch shown in Fig. 7. The left side shows the initial (*above*) and final (*lower*) sarcomere length distributions. The initial distribution had an exponential component ranging from 2.3 μm at the end to 2.5 μm in the center, and a random component of amplitude 0.1 μm. The large increase in dispersion without any particular areas of long or short sarcomeres is clear, as is the presence of popped sarcomeres with lengths around 3.8 μm. The right-hand side shows the length change for the whole fiber (*upper*) and for the central half scaled to match the whole fiber. It is clear that segment length measurements cannot prove or disprove the model.

as soon as the tension nears their yield point, and they become weaker through lengthening.

Simulation of "permanent extra tension"

Simulations using the model with 500 sarcomeres and extending the duration of the contraction to show permanent extra tension are shown in Fig. 7. The parameters for these simulations have been chosen to match the experimental records reproduced in Fig. 1. The essential features of the experiments that are successfully reproduced by the model include the continued rise of tension throughout the stretch, and a final tension independent of the amount of stretch and nearly equal to the isometric tension at the original length. This contrasts with the tension that results if the stretch is applied before stimulation, which decreases with increasing stretch (not illustrated).

Sarcomere lengths

On the left of Fig. 8, the initial and final sarcomere length distributions of the largest movement of Fig. 7 are shown. The initial distribution includes an exponential and a random component. Even with smoothing of the random component, it is clear that the popped sarcomeres were distributed along much of the fiber. This is confirmed by the comparison of the "segment length" and fiber length traces on the right.

INTERPRETATION

Many of the experimental results duplicated by this modeling can be understood directly from the basic hypothesis enunciated above.

Continued rise during stretch

The continued rise during stretch follows from the "popping one at a time from weakest to strongest" hypothesis. After each sarcomere pops, the tension must reach the slightly higher yield tension of the next weakest sarcomere before another pop occurs. Note that this leads to an increasing tension even when all the sarcomeres are on the plateau of the length tension curve, provided that there is a random variation in their strength.

During the stretch, all the sarcomeres are continually lengthening at a speed less than that required to reach their yield tension. On the descending limb, this will lead to some reduction in their strength. It is interesting to note that periods of decreasing tension are sometimes seen in long stretches. To understand why this only happens for long stretches, we note that the distribution of strengths is likely to be more nearly Gaussian than uniform. At the beginning of a stretch, while popping the sarcomeres in the tail of the strength distribution, the tension rise due to the strength dispersion would be greater than the decrease due to slow lengthening. Late in a long stretch, when a significant number of sarcomeres have been popped, the probability density of the sarcomere strength distribution would be greater, so that the difference between strengths of successively popping sarcomeres could be less than the decrease in strength due to the slow lengthening of the sarcomeres. Records showing such a rise followed by a fall have been produced by the model for appropriate initial strength distributions.

No simulations of isotonic stretches have yet been done. However, it is possible to give at least quantitative explanations of the phenomena seen experimentally. If an isometric muscle was loaded above the yield point of its weakest sarcomeres, they would rapidly extend. After a while, all sarcomeres with yield points below the tension would have popped, and the others would lengthen more slowly, leading to the familiar slowing of an isotonic stretch. The transient behavior of a sarcomere, not included in the Hill model used here, and the ability of the servo system to apply quick tension changes would be important in determining the detailed behavior. If a shortening muscle was loaded above its yield tension (reduced below the isometric value by the shortening), the lengthening would be expected to occur principally in the weakest sarcomeres. This would mean that the others were not lengthening rapidly, and so extra bridges would be able to form in them, and arrest the rapid lengthening of the muscle once the weakest sarcomeres had been popped.

Permanent extra tension

The modeling results can be seen to follow from the basic assumption that lengthening takes place by popping. After a lengthening, most of the sarcomeres have not been lengthened significantly at all, and the few that have been lengthened have been extended to lengths where they support the tension by passive structures. The tension then is expected to be that appropriate to the length of the active sarcomeres, which is unchanged by the stretch. Therefore, the tension also is expected to return to the same value as before the stretch.

Segment length records show near proportional lengthening because the popped sarcomeres are randomly distributed through most of the fiber. The end regions, where the sarcomeres are generally shorter and therefore stronger, will probably contain few, if any, giving the slightly greater than proportional lengthening of a central segment seen in experimental records (Julian and Morgan, 1979*b*). Interruption of stimulation apparently allows the

resting distribution to be restored, so that the resumption of stimulation gives rise to the tension appropriate to the new length.

Crossbridge models

An important result from the modeling is that the tension of a fiber during stretch is independent of the shape of the force velocity curve of its sarcomeres beyond their yield point. Once a sarcomere reaches this point, it will lengthen at a speed limited only by mass or passive viscosity, regardless of the shape of its force velocity curve. If it cannot develop a tension equal to the fiber tension, then the tension that it can develop is essentially irrelevant. The tension during a stretch is determined by the distribution of the yield tensions of the sarcomeres, not by their force velocity curve. This means that the observed force velocity curve for a fiber (with no region of decreasing tension with increasing velocity) can result from a sarcomere force velocity curve that has decreasing tension for lengthening velocities beyond the yield point, that is, a curve consistent with resonable crossbridge model assumptions as shown by Harry et al. (1990). In fact, all the figures shown here were obtained with the instant pop option enabled, equivalent to a force velocity curve that drops immediately to zero whenever large velocities are reached.

Damage

If lengthening involves extreme nonuniformities, as postulated here, then it would not be surprising to find that damage could occur in the regions of extreme stretch. The evidence from the interrupted stimulation after a ramp stretch and hold (Julian and Morgan, 1979*b*, Fig. 6) suggests that popped sarcomeres are not always damaged, that is, they often are able to resume their resting length and then develop tension normally. However, these were relatively small stretches. Perhaps longer and/or repetitive stretches are required to produce actual damage.

The possible sequence of events could run something like this. Lengthening the active muscle causes some sarcomeres in each myofibril to extend to long lengths. Some such sarcomeres do not fully return to the interdigitating pattern on relaxation. Repeated active lengthenings would quickly stretch those sarcomeres, and so place extra tension on neighboring myofibrils at that sarcomere, tending to cause a "tearing" of the sarcomere. If sufficient tearing occurs, the sarcoplasmic reticulum or the sarcolemma could become damaged, leading to intracellular calcium release, contractures, clots, and eventual destruction of the fiber in the days following the exercise, as has been suggested by others.

Variability

If the behavior during stretch is dominated by the nonuniform nature of lengthening as suggested here, then most of the parameters will be affected by the distribution of sarcomere strengths. As this is essentially random, it is likely to vary from fiber to fiber, leading to the variability noted. Furthermore, the previous history of contraction of the fiber is likely to affect the dispersion of sarcomere strengths, either by changing sarcomere length dispersion or by disrupting certain parts of the mucsle.

Since this modeling was done, Colomo et al. (1988) have published experimental evidence that some fibers have clearly identifiable nonuniformities between quite large segments. Where such nonuniformities were seen, the variability in stretch response was large. The present work suggests that, even when nonuniformities are not present on the scale discernible by photography and segment length imaging, they are nonetheless present and important in determining the behavior of the muscle.

EVIDENCE

This model is able to reproduce almost all the essential features of lengthening experiments with an explicitness unmatched by any other proposal. However, that does not conclusively prove that it is correct. Is there any direct evidence to support or contradict it? No photographs of sarcomeres at the end of a stretch showing nonuniformity of the form postulated here are known to the author. However, it is not clear that serious attempts to search for such effects have ever been made. Furthermore, the model assumption of a unique length for each sarcomere that is constant across the fiber is not necessarily true in a real fiber. Perhaps the popping occurs on a myofibrillar basis (see next paragraph), that is, different sarcomeres pop in different myofibrils, so that only increased disorder would be seen. Such increased dispersion, as measured by laser diffraction, has in fact been reported, even for quite small stretches (Altringham and Bottinelli, 1985). It is also possible that popping occurs more commonly in only one half of a sarcomere, again making simple photographic evidence difficult to find.

Damaged sarcomeres after exercise

Published photographs of muscles subjected to eccentric exercise, and then immediately fixed do, however, clearly show small regions of lengthened sarcomeres both from rats on a downhill treadmill (Armstrong et al., 1983) and from needle biopsies of the down-step leg in a step exercise for humans (Newham et al., 1983; Friden et al.,

1983). Indeed this is reported as the only abnormality visible immediately after such exercise. This is certainly consistent with the hypothesis presented here. It is especially interesting to note that some of the damaged regions do not extend all the way across the fiber, and indeed, many are confined to a single half sarcomere of a single myofibril.

Clarkson and Tremblay's (1988) observation of shortening of relaxed muscle immediately after the exercise is consistent with contractures due to increased intracellular calcium in damaged fibers.

Nonuniform stretching in Flitney and Hirst's records

Flitney and Hirst (1978), Fig. 6, published records of tension, muscle length, and sarcomere length as measured by diffraction from a whole muscle. Their records show a phase of very rapid sarcomere lengthening coincident with the yield, i.e., the end of the rapid increase of tension. This lengthening is much faster than appropriate for the rate of lengthening of the whole muscle, and of substantial extent. The authors explained it as being accompanied by shortening of tendons. However, any shortening of tendons should have been accompanied by a fall of tension, which was not seen. Furthermore, examination of the records suggests that, had the observed extension occurred in all sarcomeres, the shortening of the tendon would have been sufficient to drop the tension to zero. The three traces are simply inconsistent with each other. The only available explanation is that the extension was very nonuniformly distributed. Why then did Flitney and Hirst consistently see such lengthening? Possibly the regions sampled were chosen as giving the best diffraction patterns, and contained less connective tissue than the rest of the muscle. This in turn may have led to an unusually high concentration of popping sarcomeres. Alternatively, it may be that the popped sarcomeres contributed to the diffraction pattern more than their number would suggest. The relative contribution of a subpopulation to a diffraction pattern depends on many other factors besides the number of sarcomeres.

The question of why the tension doesn't fall to zero when all the crossbridges are detached after the 12 nm of movement that Flitney and Hirst concluded was the maximum possible, now has a more satisfactory answer than they were able to provide. The yield tension is reached at any time only in the current weakest sarcomere, which does lengthen very rapidly, presumably with very few crossbridges attached. However, the other sarcomeres and the series structures are able to absorb this lengthening of one sarcomere by shortening without significant tension drop. In contrast, the sudden lengthening of all the sarcomeres that Flitney and Hirst postulated could not have been absorbed by the series structures alone without the tension falling to zero.[1]

PREDICTIONS

In addition to predicting that lengthening muscle will have extreme nonuniformity of sarcomere lengths, this work has produced three other predictions.

Decreased stiffness

When modeling a long, slow stretch in a fiber of 100 sarcomeres, where each pop is accompanied by a clearly distinguishable rapid fall in tension, it was noticed that the falls became smaller as the stretch progressed. (This is discernible, for example, in Fig. 4, but was much clearer in other longer stretches.) This was found to be due to an increase in the compliance of the fiber. Each popped sarcomere becomes represented by just its passive stiffness curve, which, for reasonable assumptions, is much less stiff to rapid movement than an active sarcomere. Consequently, more popped sarcomeres means more compliance, or a reduced fiber stiffness. Julian and Morgan (1979*b*), using small stretches, found no significant increase in fiber stiffness, but neither did they see a decrease. Preliminary experiments in collaboration with Drs. Julian and Claflin (unpublished) using longer stretches have shown a decreased stiffness during the stretch, and have also shown that the stiffness change could be permanent. Further investigations are under way. Since those experiments were done, Tsuchiya and Sugi (1988) have reported that they also find that the stiffness decreases during a long stretch. They did not, however, consider the explanation given her.

Yield point and slope

In the model, the yield tension of a fiber is the yield tension of the weakest sarcomere. This implies that the ratio of yield tension to isometric tension (yield ratio) of a sarcomere is always greater than the corresponding ratio for a fiber. Observations of this yield ratio for fibers do show a large spread, often below, but sometimes above, the 1.8 reported by Katz (1939), even when only experiments on frog muscle at low temperature are considered. The theory provides a possible explanation for that varia-

[1]In more recent experiments using single fibers with added series compliance (Bottinelli et al., 1989) the diffraction record does not show this substantial rapid (much greater velocity than proportional to the end movement) lengthening at the yield point, but rather a transition from "less than proportional to movement" to "approximately proportional to movement." (Note the scale change for the diffraction record between the two sides of the figure.)

tion as being due to variability between fibers in the amount of strength dispersion among the sarcomeres, as discussed above. Furthermore, according to the model presented here, the amount by which the fiber yield ratio falls short of the sarcomere yield ratio is some measure of the dispersion of sarcomere strengths in the fiber.

Similarly, the slope of the tension trace during continued stretch is due to the increasing strength of the sarcomeres in the order in which they are popped, and provides another measure of the strength dispersion. Unless some assumptions are made about the shape of the sarcomere strengths distribution, no quantitative connection can be made between the two measures, as one gives information about the extent and the other about the shape of the distribution. However, the model would predict a general correlation between a low fiber yield ratio and a large rate of increase of tension during continued stretch, both being associated with large dispersions. Model runs have confirmed this prediction (compare Figs. 4 and 5) and have also shown that a very large dispersion can also lead to rounding of the tension record.

Examination of the literature seems to provide some support for this hypothesis. It is certainly true that stretches at longer length, where sarcomere length dispersion will contribute to strength dispersion, show a steeper continued rise. Comparisons of yield ratio to slope are hence best made on the plateau. Comparison of Cavagna et al. (1968) Fig. 9, Morgan et al. (1982) Fig. 2 (note that the maximum speed is 5.2% V_{max}, not 5.2 V_{max}), and Julian and Morgan (1979*b*) Fig. 3, shows a trend in the right direction. However, further experiments carefully confined to the plateau region and with the same velocity are required to examine the prediction.

Extra sarcomeres

It has been shown that repeated downhill running had a specific training effect on certain muscles to prevent damage from a test run downhill (Schwane and Armstrong, 1973). The same regime of uphill running did not prevent damage in the test run. What changed in the downhill trained muscles? One possibility, in light of the current proposals, is that the fibers grew extra sarcomeres so that subsequent active lengthenings occurred on the ascending limb of the length tension curve. Muscles have been shown to change their number of sarcomeres to the extent and on the time scale necessary for this hypothesis in response to other treatments. For a review of this see Goldspink (1985). Clarkson and Tremblay have shown in human forearm flexors that even one bout of mild eccentric exercise was effective in reducing damage and soreness due to a prolonged period of eccentric exercise, an observation consistent with our proposal. This prediction is currently being tested.

CONCLUSIONS

Two accepted properties of muscle sarcomeres are a length tension relationship with a region where isometric tension decreases with increasing length, and a force velocity relationship that does not show a continued rise of tension with increasing lengthening velocity. A series connection of such sarcomeres must be grossly unstable when lengthened at large enough velocities. Any variation in yield tension from sarcomere to sarcomere must lead to grossly nonuniform lengthening. This leads to simple explanations of most of the puzzling features of muscles being forced to lengthen.

Why have these explanations been so long in coming? Nonuniformities have been carefully considered by many experiments since Huxley and Peachey (1961). Previous experiments (Julian and Morgan 1979*b*) have implicated nonuniformities. Yet this suggestion has been repeatedly rejected in the literature (e.g., Tsuchiya and Sugi 1988; Edman et al., 1982) because no regions of different behavior were seen, as during isometric contraction and during shortening. The crucial step was to realize that although the shortest sarcomeres are concentrated at the ends of a fiber, the weakest sarcomeres are scattered throughout most of the length.

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REFERENCES

Altringham, J. D., and R. Bottinelli. 1985. The descending limb of the sarcomere length-force relation in single muscle fibers of the frog. *J. Muscle Res. Cell Motil.* 6:585–600.

Armstrong, R. B., R. W. Ogilvie, and J. A. Schwane. 1983. Eccentric exercise induced injury to rat skeletal muscle. *J. Appl. Physiol. Respir. Environ. Exercise Physiol.* 54:80–93.

Bagni, M. A., G. Cecchi, F. Colomo, and C. Tesi. 1988. Plateau and descending limb of the sarcomere length-tension relation in short

length-clamped segments of frog muscle fibres. *J. Physiol. (Lond.).* 401:581–595.

Bottinelli, R., J. C. Eastwood, and F. W. Flitney. 1989. Sarcomere "give" during stretch of frog single fibres with added series compliance. *Q. J. Exp. Physiol.* 74:215–217.

Cavagna, G. A., B. Dusman, and R. Margaria. 1968. Positive work done by a previously stretched muscle. *J. Appl. Physiol.* 24:21–32.

Clarkson, P. M., and I. Tremblay. 1988. Exercise-induced muscle damage, repair and adaptation in humans. *J. Appl. Physiol.* 65:1–6.

Colomo, F., V. Lombardi, and G. Piazzesi. 1988. The mechanisms of force enhancement during constant velocity lengthening in tetanized single fibers of frog muscle. *Adv. Exp. Med. Biol.* 226:489–500.

Edman, K. A. P., and C. Regiani. 1984. Redistribution of sarcomere length during isometric contraction of frog muscle fibres and its relation to tension creep. *J. Physiol. (Lond.).* 351:169–198.

Edman, K. A. P., G. Elzinga, and M. I. M. Noble. 1978. Enhancement of mechanical performance by stretch during tetanic contractions of vertebrate skeletal muscle fibers. *J. Physiol. (Lond.).* 281:139–155.

Edman, K. A. P., G. Elzinga, and M. I. M. Noble. 1982. Residual force enhancement after stretch of contracting frog single muscle fibers. *J. Gen. Physiol.* 80:769–784.

Flitney F. W., and D. G. Hirst. 1978. Cross-bridge detachment and sarcomere give during stretch of active frog's muscle. *J. Physiol. (Lond.).* 276:449–465.

Friden, J., M. Sjöström, and B. Ekblom. 1983. Myofibrillar damage following intense eccentric exercise in man. *Int. J. Sports Med.* 4:170–176.

Goldspink, G. 1985. Malleability of the motor system: a comparative approach. *J. Exp. Biol.* 115:375–391.

Gordon, A. M., A. F. Huxley, and F. J. Julian. 1966. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J. Physiol. (Lond.).* 184:170–192.

Harry, J. D., A. W. Ward, N. C. Heglund, D. L. Morgan, and T. A. McMahon. 1990. Crossbridge cycling theories cannot explain high-speed lengthening behavior in frog muscle. *Biophys. J.* 57:201–208.

Huxley, A. F. 1957. Muslce structure and theories of contraction. *Prog. Biophys. Biophys. Chem.* 7:255–318.

Huxley, A. F. 1971. The activation of striated muscle and its mechanical response. *Proc. R. Soc. Lond. B. Biol. Sci.* 178:1–27.

Huxley, A. F. 1980. *Reflections on Muscle.* Liverpool University Press, Liverpool. 111 pp.

Huxley, A. F., and L. D. Peachey. 1961. The maximum length for contraction in vertebrate striated muscle. *J. Physiol. (Lond.).* 156:150–165.

Julian, F. J., and D. L. Morgan. 1979*a*. Intersarcomere dynamics during fixed-end tetanic contractions of frog muscle fibers. *J. Physiol. (Lond.).* 293:365-378.

Julian, F. J., and D. L. Morgan. 1979*b*. The effect on tension of non-uniform distribution of length changes applied to frog muscle fibres. *J. Physiol. (Lond.).* 293:379–392.

Katz, B. 1939. The relationship between force and speed in muscular contraction. *J. Physiol. (Lond.).* 96:45–64.

McCully, K. K., and J. A. Faulkner. 1985. Injury to skeletal muscle fibers of mice following lengthening contractions. *J. Appl. Physiol.* 59:119–126.

Morgan, D. L., S. Mochon, and F. J. Julian. 1982. A quantitative model of inter-sarcomere dynamics during fixed end contractions of single frog muscle fibers. *Biophys. J.* 39:189–196.

Newham, D. J., G. McPhail, K. R. Mills, and R. H. T. Edwards. 1983. Ultra-structural changes after concentric and eccentric contractions in human muscle. *J. Neurol. Sci.* 61:109–122.

Schwane J. A., and R. B. Armstrong. 1973. Effect of training on skeletal muscle injury from downhill running in rats. *J. Appl. Physiol. Respir. Environ. Exercise Physiol.* 55:969–975.

Tsuchiya, T., and H. Sugi. 1988. Muscle stiffness changes during enhancement and deficit of isometric force in response to slow length changes. *Adv. Exp. Med. Biol.* 226:503–511.

Woledge, R. C., N. A. Curtin, and E. Homsher. 1985. Energetic aspects of muscle contraction. *Monogr. Physiol. Soc. No. 41.* 359 pp.