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FROM SARCOMERES TO WHOLE MUSCLES

BY D. L. MORGAN

Department of Electrical Engineering, Monash University, Clayton, Victoria 3168, Australia

SUMMARY

The series connection of sarcomeres in a muscle raises the possibility of instabilities due to some sarcomeres being capable of greater isometric tension than others, due to non-uniform activation, cross-sectional area or sarcomere length. Such instabilities are heavily damped by the force-velocity curve and stabilized by passive tension. The variation of active tension with sarcomere length may act to stabilize or destabilize the situation. Such instabilities can affect tension in a complex manner, causing both increases and decreases in different situations. Some examples of situations where sarcomere non-uniformities have been observed or inferred are given, and their mode of action explained.

INTRODUCTION

It is tempting to model a whole muscle simply as a scaled sarcomere, that is, to scale tension and stiffness by the area of the muscle and velocity and compliance by the number of sarcomeres in a fibre, and assume that other properties are unchanged. Clearly, the presence of fibres with a range of sarcomere numbers complicates the situation, as does the extra compliance introduced by tendinous connections. However, the series connection of sarcomeres in a fibre inherently raises the possibility of internal motion if some sarcomeres are capable of exerting greater isometric tensions than others. A length-tension diagram with a region where tension decreases with increasing length means that such motion may be self perpetuating, and a non-linear force-velocity relationship can cause the tension to be significantly different from that appropriate to a 'sarcomere isometric' contraction. The principles of such non-uniformities, some examples of phenomena that can be explained by them, and some indication of their relevance to muscle physiology form the subjects of this paper.

GENERAL PRINCIPLES

Constant overall length

As a simple introduction, consider two sarcomeres with different isometric tensions (for some reason to be considered later). Assuming that their unloaded shortening

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velocities are equal, the two sarcomeres can be represented by the force-velocity curves in Fig. 1. If the sarcomeres are connected in series and inertial forces neglected, the tension in the two sarcomeres must be equal. If, furthermore, the length of the combination is held constant (i.e. the total velocity is zero) then the velocities of the two sarcomeres must be equal in magnitude and opposite in sign. Thus, the tension can be determined from Fig. 1, as shown. If the force-velocity curve had been linear in this region, the tension would have been the mean of the two isometric tensions. However the force-velocity curve is generally found to be distinctly non-linear about zero with the slope changing by a factor of 6 for frog twitch muscle (Katz, 1939) and possibly more for slow or tonic muscle (Lännergren, 1978), being steeper for stretch than release. This means that the 'fibre isometric' or fixed end tension will be greater than the mean of the 'sarcomere isometric' tensions, as shown in Fig. 1.

The steepness of the force-velocity curve ensures that moderate differences in isometric capability lead to quite small velocities, especially for small values of a/P_0, (i.e. large curvature of the force-velocity curve). In fact, it can be shown that the ratio between velocity, normalized to the speed of unloaded shortening (V_{max}), and normalized tension is approximately $[1/(n+1)]\cdot[(a/P_0)/(1+a/P_0)]$, where n is the ratio of slope change at zero velocity and a/P_0 is the parameter of an A. V.

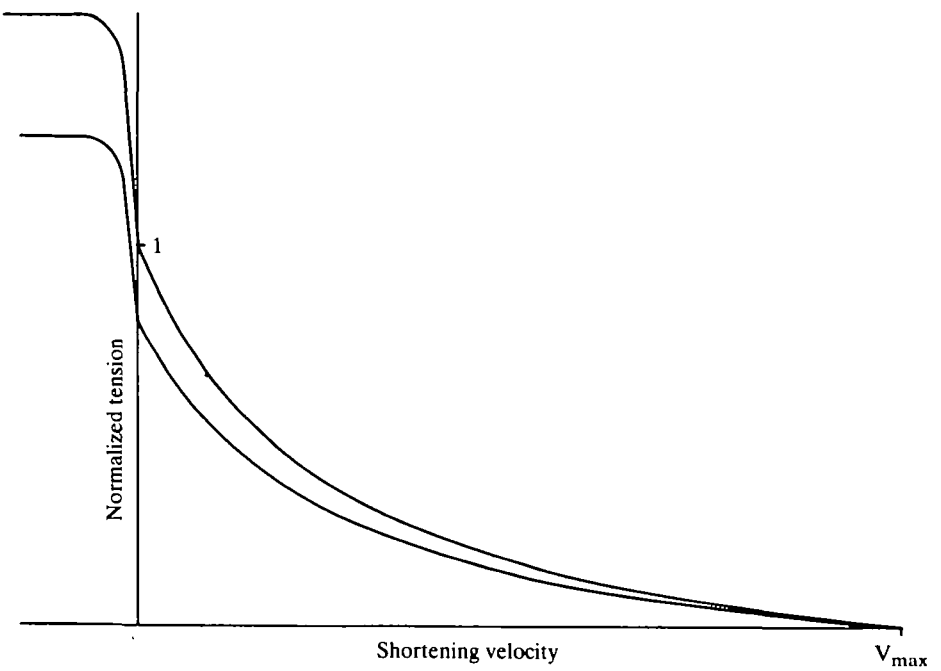

Fig. 1. Force-velocity curves for two sarcomeres with isometric tensions of 1 and 0·8, $a/P_0 = 0{\cdot}25$, ratio of slopes for slow lengthening and slow shortening (slope changes at origin) = 6, and yield point = 1·6 × isometric tension. Sarcomere velocities are equal and opposite for a tension of 0·97 where the magnitude of each velocity is 0·0058 V_{max}. Only if the strong sarcomere is shortening more quickly than 0·04 V_{max}, causing the tension to fall below 0·8, will the weak sarcomere shorten.

Hill hyperbola. For $n = 6$, and $a/P_0 = 0{\cdot}25$ (Hill, 1938) this evaluates to 1/35, so that a tension difference of 20% would correspond to velocities of only 0·58% of the unloaded shortening speed. Furthermore the tension will be below the isometric value of the stronger sarcomere by only $1/(n+1)$ of the difference between isometric values. Using the numbers above, two sarcomeres with isometric tensions of 1 and 0·80 would produce a 'fibre isometric' tension of 0·97 and velocities of $0{\cdot}0058\,V_{max}$.

It is clear then that the fibres will not fly apart, but will slowly change their sarcomere length distribution. This will change the passive tension in the various sarcomeres, always in such a direction as to stabilize the distribution and reduce the internal motion.

As well as changing passive forces, the internal motion will in some circumstances change the active tension generated. If the active tension increases with increasing sarcomere length this will be a further stabilizing influence. If, however, the isometric tension falls with increasing length, then the internal motion will increase the non-uniformity of isometric sarcomere tensions, providing a destabilizing effect as the weaker sarcomere slowly lengthens and becomes even weaker. If the sarcomere length-tension curve has a maximum near the average length, then non-uniformity may reduce the isometric tension capabilities of both sarcomeres, one becoming shorter than optimum and the other longer. The actual motion always increases the tension, due to the force-velocity curve, but the resulting changes in length distribution may decrease the tension depending on the length-tension curve.

Overall movement

If the series connection of the two sarcomeres is allowed to shorten at constant velocity the force-velocity curves of Fig. 1 still apply, the tensions must still be equal but now the individual sarcomere velocities must add to equal the imposed overall velocity. It can be seen from Fig. 1 that the shortening velocities of the two sarcomeres will be very different for small total velocities. In particular, if the velocity is not sufficient to cause the tension to fall below the isometric capability of the weaker sarcomere, then the weaker sarcomere will in fact continue to lengthen. In our numerical example, this requires a shortening speed of 4% V_{max} for the stronger sarcomere. Anything less than this will be entirely absorbed by the stronger sarcomere. As the overall velocity is increased above this, it will be shared more evenly between the two sarcomeres until at zero tension, the speeds will be equal. The much larger sarcomere velocities involved here will cause much greater changes in sarcomere length during a contraction, so that the effect of sarcomere length on sarcomere isometric tension is much more important. This is particularly so if it is a destabilizing influence, as the stabilizing effect of passive tension will be small during shortening.

The situation for lengthening movements is rather more complicated as the force-velocity curve is less well defined, and more slowly attained. That is, the force-velocity curve represents the constant force at constant velocity, and during stretch, a longer time is taken for the values to become nearly constant. However, it is clear that a

lengthening movement will be unequally distributed, with the weaker sarcomere lengthening most, particularly for velocities sufficient to raise the tension to the yield point. Passive tension may be an important stabilizer in this situation.

EXPERIMENTAL EXAMPLES

Maximum length for contraction

The first example of significant effects of sarcomere non-uniformities came in the work of Huxley & Peachy (1961). They found that when a single frog twitch fibre was stretched to a mean sarcomere length of more than 3·7 μm, where sarcomeres were expected to develop no tension, some sarcomeres, principally near the ends, were significantly shorter than average. On stimulation, these sarcomeres contracted against the passive viscoelasticity of the long sarcomeres, causing the fibre slowly to develop some tension. The situation was stabilized by the passive length-tension relationship, and destabilized by the active length-tension relation. (Those sarcomeres that shortened became stronger and so more able to shorten.)

Isometric tetani at long length

When Gordon, Huxley & Julian (1966*a*,*b*) set out to measure the isometric sarcomere length-tension relationship, they were aware of non-uniformities. They provided a brief description of short-duration, fixed-end tetani, before proceeding to avoid most of the problem by controlling the length of a nearly uniform central segment. Further descriptions of longer duration, fixed-end tetani have been provided by Julian & Morgan (1979*a*).

When the muscle was stimulated, the tension rose rapidly at first and then more slowly ; the so-called 'creep phase'. Microscopic observation and the use of attached markers showed that the slow rise was accompanied by shortening of small regions usually near the ends of the fibres and slow stretching of most of the fibre. When a central, near uniform, segment of the fibre was held constant, by controlled shortening of the overall fibre during the contraction, the creep phase was much slower.

These observations were explained as developing non-uniformities with the initial differences in isometric tension caused by differences in sarcomere length on the descending limb of the length-tension curve. Small numbers of initially shorter and hence stronger sarcomeres shorten, stretch most of the sarcomeres, raise the tension and increase their force capability, leading to further increases in dispersion and tension. The process is damped by the force-velocity curve and stabilized to some degree by the passive length-tension curve.

If the contraction continues long enough, some sarcomeres shorten below their optimum length, so that their isometric tension ceases to rise and then actually falls. However, between these very short sarcomeres and the long sarcomeres in the centre of the fibre is a transition zone of sarcomeres of intermediate length (Lieber & Baskin, 1983, Fig. 7). As these sarcomeres become shorter, more sarcomeres pass from the

lengthening zone into the transition zone and on into the 'shortened' zone. (It is proposed that this transition zone is maintained by local passive forces. A sudden change in sarcomere length along the fibre would necessitate a sudden change in diameter, which would be resisted by the cytoskeleton.)

About the time that the initial shortening patch passes the optimum length, the rate of central stretch slows down, and the tension ceases to rise, and usually begins to decline slowly. Modelling suggests that this is not some kind of fatigue, but is due to the declining isometric capability of the central sarcomeres (Morgan, Mochon & Julian, 1982). Throughout the tetanus the central sarcomeres are stretched by the ends, maintaining tension above their isometric value according to the force-velocity curve. However the resultant lengthening decreases that isometric value (in the absence of significant passive tension) so that the tension slowly falls. Internal motion then is probably responsible for the slow fall in tension as well as the creep phase of rise. It is certain that the central region continues to stretch as monitored by a spot follower (Julian & Morgan, 1979*a*), by photography (Julian, Sollins & Moss, 1978), by laser diffraction (Lieber & Baskin, 1983) and by ciné film (F. J. Julian & D. L. Morgan, unpublished observations).

Only at very long lengths, where passive tension is significant, will the sarcomeres ever be isometric during such a contraction. At moderately long lengths the whole contraction is dynamic. The particular pattern of non-uniformities, and hence the tension that develops depends on the initial pattern of sarcomere lengths, which varies from fibre to fibre and time to time. In particular, a fibre with a smaller range of sarcomere lengths shows a slower creep rise, but often a higher peak tension, as a greater proportion of sarcomeres shorten (see Julian & Morgan 1979*a*, for experimental records, Morgan *et al.* 1982 for modelling). This can lead to a wide variety of length-tension curves when segment clamps are not used (see Pollack, 1983, Fig. 14) particularly when passive stiffness is small (Pollack, 1983, p. 1099).

Shortening up the length-tension curve

If a muscle is stimulated at a long length, then slowly shortened for some distance, and the stimulation continued after movement stops, the tension does not rise to that appropriate to the final length. Correspondingly a muscle allowed to shorten isotonically may not shorten to the length below optimum appropriate to the tension (see Abbott & Aubert, 1952; Délèze, 1961) unless the shortening takes place at light loads (Edman, 1966; Gordon *et al.* 1966*b*).

Other important observations are:

(i) shortening across the plateau does not produce significant depression (Julian & Morgan, 1979*b*, Fig. 1B);

(ii) tension does increase during shortening despite falling passive tension, but decreases again if movement continues long enough (Julian & Morgan, 1979*b*, Fig. 1A);

(iii) if the movement is faster, the final tension depression is less (Fig. 2);

(iv) interruption of stimulation just long enough for tension to fall to zero abolishes the tension depression (Julian & Morgan, 1979*b*, Fig. 2);

(v) spot follower records dramatically show that slow movements are extremely non-uniformly distributed, with the centre region of the fibre showing minimal shortening (Julian & Morgan, 1979*b*, Fig. 1A);

(vi) ciné film observations confirm that the shortening is rapidly absorbed by the end regions.

The extreme non-uniformity developed during such shortening results in sarcomeres in the centre of the fibre near their original lengths, a considerable number of very short sarcomeres near the ends, and the usual transition zone. Hence the tension is near that seen for a fixed-end contraction at the original (longer) length. Slow internal motion continues after the imposed motion stops.

The alternative experiment, of using the spot follower to impose a ramp shortening on the central segment was tried, but always failed. The end shortening required was so large that the segment being controlled translated out of the field of view of the spot follower. This problem also prevents very long duration contractions under constant segment length conditions.

Maintained extra tension after stretch

If a frog single fibre is stretched while active at long lengths, the elevated tension produced decays very slowly (e.g. Edman, Elzinga & Noble, 1982, Figs 4B and 6, where tension tracings are still converging after 5 s at low temperatures), but never meets the tension for a fixed-end contraction at the final length and of the same duration. Instead, it typically comes close to the tension during an isometric contraction at the original length. (Edman *et al.* 1982 reported tension above this level in about half of their fibres, but they measured tension at a fixed time after the stretch, rather than waiting for parallel traces in each case.)

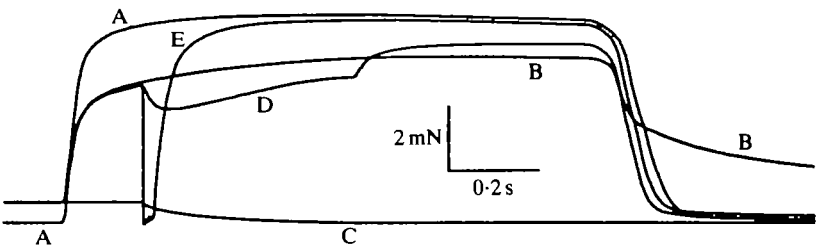

Fig. 2. Shortening at long lengths. Fixed end tetani at two lengths are shown as traces A and B. The corresponding mean sarcomere lengths while passive were 2·6 and 3·0 μm respectively. Slow release while passive, trace C, shows the passive tension differences between the two lengths. The same slow release while active, trace D, caused the tension initially to fall, as predicted by the force-velocity curve, and then to rise slowly. At the end of shortening, the tension recovered to more than that attained at the original length, but substantially less than that appropriate to the new length. However, when the muscle was quickly shortened between the same two lengths, trace E, so that most of the sarcomere shortening was unloaded, the subsequent tension recovery was nearly complete. Single twitch fibre from anterior tibial muscle of *Rana temporaria* at 20 °C, stimulated for 1·2 s at 80 pulses s^{-1}. (Results obtained with Dr F. J. Julian.)

Other important observations are:

(i) lengthening on the ascending limb or near optimum length does not produce maintained extra tension (Julian & Morgan, 1979*b*, Fig. 6; Edman *et al.* 1982, Fig. 1);

(ii) maintained tensions are never above the isometric tension at optimum length (Edman *et al.* 1982, p. 775);

(iii) enhancement is independent of stretch velocity over the explored range, very slow rates being difficult to investigate (Julian & Morgan, 1979*b*, Fig. 3C; Edman *et al.* 1978, Fig. 2B);

(iv) a brief interruption in the stimulation long enough to allow tension to fall to near zero abolishes the enhancement (Julian & Morgan, 1979*b*, Fig. 6);

(v) spot follower records show that the central region stretches slightly more for the same overall length change when active than when passive (Julian & Morgan, 1979*b*, Fig. 3A);

(vi) the pattern of internal movement is quite different after a stretch than at the same time in an isometric contraction (Julian & Morgan, 1979*b*, Figs 3A, 5; Edman *et al.* 1982, Fig. 8; Lieber & Baskin, 1983, Figs 8, 9).

The stretch then changes the sarcomere length distribution late in the tetanus both by being unevenly distributed among the sarcomeres and by altering the pattern of motion, particularly during the time of raised tension. The two contractions (with stretch and isometric at the long length) therefore have quite different patterns of both sarcomere length and velocity, and so must be expected to have different tension time profiles. The tension is usually compared after the same duration of stimulation, but perhaps comparison would be better made at times of equal central sarcomere lengths or equal velocities. Certainly the delayed development of very short sarcomeres at the ends can be expected to raise tension late in the tetanus. (Although the major workers on this problem produce very similar data, the explanation provided here remains somewhat controversial, Edman *et al.* 1982, but no serious alternative has been proposed.)

Non-propagating muscle fibres

In all the examples above, the original non-uniformities in sarcomere isometric tensions have been due to variations in sarcomere length. Variation of activation or cross-sectional area along a fibre could also produce non-uniformities. The greatest opportunities for variable activation occur in the non-propagating slow tonic muscle fibres found in some animals, including anuran skeletal muscle and mammalian extraocular muscles and muscle spindles. The following examples all refer to the tonus bundle of the iliofibularis muscle of toads and frogs, or to single fibres isolated from them. Other examples can be found in Morgan & Proske, 1984*a*,*b*.

Changes in force-velocity curve with contraction duration

Lännergren (1978) found that the ability of an isolated slow fibre to shorten against a load decreased substantially with the duration of activation that preceded the release, even though the isometric tension was well maintained. Furthermore, shortening itself reduced the ability to shorten, and did so more rapidly if imposed late

in a tetanus. Surprisingly, the unloaded shortening velocity did not change. (Sarcomere length was 2·3 μm, just onto the descending limb of the length-tension curve.) An explanation for this result is that gradually developing non-uniformities meant that increasing numbers of sarcomeres were unable to shorten against the imposed load, but all shortened normally in the unloaded case, as the unloaded speed of shortening is independent of sarcomere length, at least for frog twitch muscle over most of the length range (Gordon *et al.* 1966*b*; Edman, 1979; Julian & Morgan, 1981). Furthermore, increased non-uniformity at the beginning of the release would lead to faster increases in non-uniformity and hence slowing of velocity during the release, as fewer sarcomeres participated in the shortening.

The converse experiment of examining how well tension is maintained during constant velocity shortening (Morgan & Proske, 1984*b*) of neurally stimulated tonic fibres in a whole muscle confirmed Lännergren's results. The effect was also more prominent in small motor units (believed from other experiments to have a greater proportion of partially activated muscle fibres) but reduced at longer lengths (where passive tension provides more stabilization). It is of interest that the tonic fibres are embedded in much denser connective material than neighbouring twitch fibres.

Combined tension depends on previous stimulation

Another phenomenon explainable in terms of non-uniformities is shown in Fig. 3. More tension was produced by two motor units when the stimulation of the units commenced together than when the stimulation of one began before the other. The proposal is that stimulation of one unit non-uniformly activates some fibres, which then develop sarcomere non-uniformities about the optimum length. Stimulating the second axon makes the activation of these fibres more uniform, stops the internal motion, but the tension is depressed due to the sarcomere length distribution. Stimulating both axons provides a more uniform activation from the beginning, less sarcomere non-uniformity and so a greater tension.

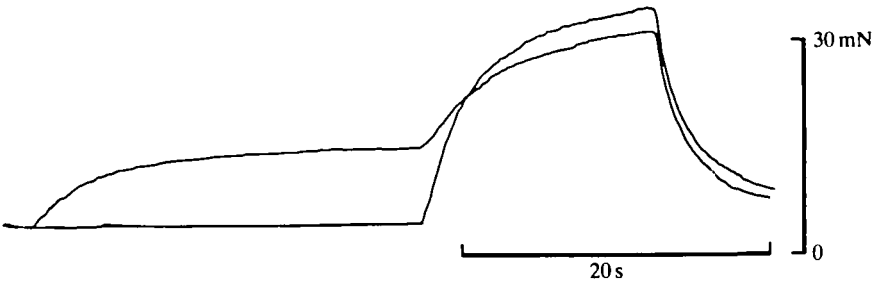

Fig. 3. The tension reached during combined stimulation of two motor units depends on the duration of the preceding period of stimulation. Here two sequences of stimulation have been superimposed. First one unit is stimulated (80 s^{-1}) for a period of 25 s, then a second unit is added to the stimulated bundle and the two are stimulated together for a further 15 s. The tension reached during this final period of combined stimulation is significantly less than when stimulation of the two units is commenced simultaneously. The difference is not due to any kind of fatigue during the longer period of stimulation since tension remains well sustained throughout (Morgan & Proske, 1984*a*).

SIGNIFICANCE

To some extent the phenomena described can be seen as 'artifacts' of using a single fibre with much less stabilizing passive stiffness at long lengths than a whole muscle, and 'curiosities' of unusual fibre types. Measurements of length-tension diagrams of mammalian whole muscles (Close, 1972, p. 142) and bundles (ter Keurs, Luff & Luff, 1983) apparently showed much less creep tension. However there are muscles that show a distinct descending limb of total tension, though they may only be used for impulsive movements, rather than sustained contractions. Care should also be exercised in assuming that all the whole muscle passive stiffness is effectively in parallel with each sarcomere. Sarcomeres at the edge of a fibre are apparently anchored to the sarcolemma, but myofibrils have some freedom to slide past their neighbours, as do fibres. Some of the passive elasticity is effectively in parallel with the fibres, rather than the sarcomeres. The situation that produces the worst non-uniformities in twitch muscle is undoubtedly long, slow shortening of an active muscle from a long length. Any anomalous results from such movements should always be checked for possible sarcomere non-uniformity effects.

As for the non-twitch muscles, perhaps the greatest significance is in muscle spindles. The spindle responds to changes in muscle length transferred to the sensory endings by specialized muscle fibres, some of which do not twitch. Hence the mechanical properties of such fibres play an important role in determining spindle response.

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