Muscle Physiology and Contraction Theories

By Richard J. Podolsky, Ph.D.

The structural basis of current contraction theories is the double array of thick and thin myofilaments revealed by the electron microscope. The physiologic properties that characterize the contractile process are natural consequences of this structure if (a) during shortening the 2 sets of filaments move relative to each other and (b) the flux of chemical energy through the contractile mechanism is limited by interaction between complementary sites distributed along the 2 sets of filaments. Contraction models fitted to these ideas differ largely in the mechanism by which force is generated. In the sliding model, force is developed by mechanical interaction between the thick and thin filaments, and filament length remains constant during contraction. In the folding model, force is developed in the thin filament, which shortens during contraction. Both models quantitatively account for the force-velocity relation and the Fenn effect. They also accommodate the quick-release phenomenon and predict, at least qualitatively, the isotonic velocity transients that can be seen after quick release from tetanic tension.

Biochemical processes in muscle cells have 2 exceptional characteristics. The first, of course, is that they generate large forces. The second, which is not quite so obvious, is that they proceed at a rate which depends on the motion of the cell. Many properties of contracting muscle can be traced back to the influence of the motion of the cell on the chemical processes driving the contractile mechanism, an idea first proposed by Fenn.1

It seems very natural that a muscle should lift a light load more rapidly than a heavier load. However, as Fenn wrote some years ago, "the more one tries to explain these simple facts, the less obvious do they seem to be."2

The "simple" fact is shown in figure 1, the force-velocity curve for the classical striated muscle, the frog sartorius. The circles are data from an experiment we shall discuss later. The smooth curve is A. V. Hill's force-velocity relation.3 The question is: Why does the contractile force fall with the velocity?

In the early twenties, the force-velocity relation was explained with a viscoelastic model4 along the following lines: Upon activation, muscle becomes an elastic filament, like a spring. The spring is immersed in a viscous fluid. When the muscle shortens a given distance, the available potential energy appears either as work or as heat. The more quickly the muscle moves, the greater the viscous force, the greater the heat production, and the smaller will be the energy available for work. Thus the fall in force with speed.

The essential part of the viscoelastic model is that, in shortening a given distance, the available energy is independent of the mechanical conditions of contraction. The corollary, that the amount of heat produced in a contraction increases with the speed, was doubted as long ago as 1864.5 The unambiguous experiments of A. V. Hill confirmed these doubts.

Figure 2, taken from Hill's classical 1938 paper,3 shows the critical experiment.6 Curve E is the total heat produced as a function of time when the frog sartorius is tetanized isometrically. Curves F, G, H, and J show the heat liberated when the muscle is released, at the time indicated by the first arrow, and allowed to shorten a given distance. Although the speed of contraction in J, say, is 5 times greater than in F, the total extra heat due to shortening does not change. Since it was clear that heat production did not increase with speed, the viscoelastic theory was demolished.

The error, of course, is that the energy available during contraction is not constant. The flux of chemical energy into the muscle is somehow affected by the motion itself. In other words, some kind of mechanochemical control is built into the contractile mechanism. The force-velocity relation might be a reflection of this mechanochemical control if the tension generating process were continuously opposed, or inactivated, by the mechanical motion.

This idea is schematized in figure 3. We assume that a sequence of chemical reactions drives the contractile mechanism. One of these reactions, $M$, is closely linked to the contractile mechanism. Since the chemical reactions are themselves linked like a train of gears, the extent of the reaction during a contraction is limited by the turnover of $M$, which, in turn, is some function of the shortening velocity. The total energy produced during contraction depends on the extent of the reaction $A + M$. This chemical energy\footnote{In this paper, "energy" denotes the enthalpy of reaction, $\Delta H = \Delta U + P \Delta V$. The energy available for mechanical work is the free energy, $\Delta H - T \Delta S$. In these expressions, $U$ is internal energy, $P$ is pressure, $V$ is volume, $T$ is temperature, and $S$ is entropy.}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{frog_sartorius.png}
\caption{Relation between force, $P$, and velocity, $V$, in living muscle. Experimental points are calculated from data of figure 12; smooth curve is the force-velocity equation of A. V. Hill.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Heat production of living muscle. Tetanically stimulated frog sartorius at 0 C. (a) $A$: isometric contraction. $B$, $C$, $D$: 1.2 sec. after start of stimulus, muscle is released and allowed to shorten various distances ($B < C < D$) under constant load. (b) $E$: isometric contraction. $F$, $G$, $H$, $J$: muscle is allowed to shorten the same distance under various loads ($F > G > H > J$). (From Hill.\textsuperscript{3})}
\end{figure}

is partitioned between work and heat. Conversely, the rate of chemical reaction can be inferred from the rate of total energy production. The trick in devising contraction theories is to make the link between mechanical and chemical processes such that both the total energy production and its partition into work and heat depend on mechanical motion in just the right way. We shall first show what the "right way" is, and then describe how several models manage to do this.

Before leaving figure 3, I should like to mention that there is independent evidence, from certain heat measurements, that this representation of the sequence of events is close to the truth.\textsuperscript{6, 7} Perhaps the best justification, though, is that it accommodates the physiology of muscle very comfortably.

**Energy Production**

How does the rate of chemical reaction change with the rate of mechanical contraction in living muscle? This can be inferred from the velocity dependence of the energy flux (fig. 4).

Consider the heat first. You will recall that Hill's heat measurements showed that the heat of shortening is independent of contraction speed (fig. 2). This means that...
the rate of heat production must increase linearly with speed (fig. 4, open region).

The rate of work production also depends on speed: the dependence can be calculated from the force-velocity relation. When the muscle does not move \((V = 0)\) it produces no work. Also, when it is unloaded \((P = 0)\) no work is done. This ties down the ends of the work-flux curve (fig. 4, shaded region). Adding the heat to the work, we see that the total energy flux increases monotonically, but not linearly, with speed. The rate of the rate-limiting chemical reaction, the one linked to the contractile mechanism, must also increase with speed in exactly the same way. To be acceptable, a contraction theory should yield this relation naturally and quantitatively.

Structural Basis of Contraction Theories

What mechanism regulates muscle chemistry according to speed? The double array of filaments revealed in Hugh Huxley’s beautiful electron micrographs provides a clue. Figure 5 shows the characteristic thick and thin filaments. The thick filaments define the A-band. A second set of thinner filaments extend from the Z-line, through the I-band, into the A-band, there interdigitating with the thick filaments. The part of the structure that interests us is diagrammed at the top of figure 6.

Andrew Huxley and Rolf Neidergerke demonstrated that when living muscle shortens, the decrease in length takes place almost entirely in the light I-bands, the width of the dark A-bands remaining constant. There are two obvious ways for this to come about: the filaments could slide along each other or, after anchoring its ends, the thin filament could shorten by folding (fig. 6). In both schemes only the I-band shortens. Also, and this is important in what follows, in both schemes there is relative motion between the 2 sets of filaments. This means that if reactive sites were distributed along both the thick and the thin filaments, and if some kind of interaction between these sites were stochiometrically linked to the driving chemical reaction, the relative motion of the myofilaments—and therefore the sites—would provide a natural basis for introducing velocity as a parameter in the chemical kinetics.

Implications of Relative Motion:

Energy Production

The basic idea is shown in figure 7. Sites
Figure 5

Double array of filaments in striated muscle. Electron micrograph of longitudinal section of saromere (length = 2.5 microns). (From H. E. Huxley.)

D are distributed along the thick filament and complementary sites, K, are distributed along the thin filament. We assume that interaction may take place when these sites pass each other. If interaction does take place, a substrate molecule, M, is used up, and the driving chemical reaction proceeds one step.

Proximity Time Is Rate Limiting

To understand the influence of velocity in the kinetics of such systems, consider first a case in which the probability of interaction depends on the time K spends in the neighborhood of D: the shorter the time, that is, the higher the speed, the lower the probability will be. The interrupted line in figure 8 shows how the probability decreases with speed if the K-D interaction is first order in time. Since at each interaction the driving chemical reaction proceeds 1 step, the interaction probability in a transit of K past D will also be proportional to the energy released for a given amount of shortening. The decrease in this quantity with velocity can be interpreted as the Fenn effect.

To calculate the number of interactions per unit of time, we must remember that the number of chances a given K site will have to interact with D sites—the encounter rate—is proportional to the velocity (dotted line, fig. 8). The number of successful interactions will be the product of the probability and the encounter rate (solid line, fig. 8). Both this function and the rate of the driving chemical reaction in living muscle, calculated from the energetics (fig. 4), depend on velocity in the same way. We conclude, then, that if complementary discrete sites were distributed along the 2 kinds of myofilaments, the rela-

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*In the following, a helpful mnemonic is to read D as 'Dragon,' K as 'Knight,' and M as 'Maiden.'

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Hypothetical mechanisms for muscular contraction. Upper: Configuration of thick and thin filaments in resting muscle (after fig. 5). Lower: Change in filament shape and configuration in sliding and folding contraction models.

**Figure 6**

Distribution of sites along the thick and thin filaments. See text for explanation.

**Figure 7**

Filling Time Is Rate Limiting

A physically different way of describing interaction between sites on moving filaments focuses on the time spent between, rather than at, encounters. In this case we suppose that the substrate molecule, M, is carried by K past D. If K is loaded with M, an interaction takes place at D, emptying K, regardless of the speed. The rate-limiting step in this scheme is the filling of K with another M after it has been emptied by D. The filling probability will be lower the shorter the time spent between D sites, that is, the higher the speed. It turns out that if the law for filling empty sites is exponential in time, which is not unreasonable, the probability factor will have exactly the same form as in the previous case, in which "proximity time" rather than "filling time" is rate limiting.\(^\text{10}\) This means that there will be no difference in the kinetics of the 2 schemes for steady motions; both explain equally well how motion controls the rate of energy release. The different structure of the schemes will become important, however, when we consider velocity and force transients.

The question of whether the thin filaments fold or slide during shortening has been side-stepped. This could be done because in steady motions the mathematics proves to be substantially the same for both cases.\(^\text{7}\)

**Force**

What generates the contractile force? In a sliding model, since the lengths of both the...
thick and thin filaments remain the same, the contractile force must stem from mechanical interaction between the filaments. In a folding model, however, the contractile force is generated in the thin filament and its length is supposed to decrease during shortening.

A Sliding Model

The mechanical and chemical properties of a sliding mechanism in which the D site on the thick filament has the mechanochemical properties diagrammed in figure 9 was worked out by Andrew Huxley.11 D oscillates back and forth. When the K site passes, it can interact with D to form a mechanical connection. Since the probability of forming a connection in a D-K transit depends on the relative speed, this is a special case of interaction in which "proximity time" is rate limiting. Each connection is, in time, broken. One step of the driving chemical reaction is associated with each connect-disconnect cycle.

If D and K connect, the elastic elements holding D to the thick filament will exert a force on the thin filament that is proportional to the distance of D from O. If the thin filament is moving to the left, connections with D to the right of O will make a positive contribution to the force. Conversely, if motion of the thin filament carries D to the left of O, a force will be developed that retards the motion.

To develop a net positive force—that is, to ensure that there will be a greater number of pulling than retarding connections—Huxley postulates that D can connect to K only when it is to the right of O. The rate constant for breaking a connection also depends on x: it is small when D is to the right of O but large when it is to the left.

The force developed by the model depends on speed because the number of attachments and their distribution about the equilibrium position of the D site depends on speed. This is shown in figure 10, taken from Huxley’s paper.11 The ordinate is the fraction of D sites at a given displacement from the equilibrium position that are connected to K sites. When the filaments do not move, all the connections are on the pulling side of the equilibrium position: links can be made only on this side and there is no motion to carry them to the other side. In steady motion, the number of pulling links decreases; the retarding links tend to increase, and the force drops. At the maximum speed, the pulling and retarding forces balance and there is no net force. Huxley showed that, as the relative speed increases, these shifts in both number and distribution of links between filaments can account quantitatively for the force-velocity relation in living muscle.

The diagram also shows why there must be steady motion for a less-than-maximum force to remain constant. Consider the distribution of connections when the speed say, is one-tenth of the maximum. If the motion should stop, after some time pulling links would form to the right of O, retarding links would open to the left of O, and the net force would increase. The original force could be re-established by relaxing the pulling links.

or stretching the retarding links, that is, by displacing the "connection contour" to the left, which, of course, is what happens when the thin filament slides past the thick filament. A steady force can be set up only when the motion in a given time interval just compensates for the net increase in pulling links formed in that same period.

The diagram also explains what happens if tetanized muscle is quickly released. Before release, the links are all in the pulling position, as shown in the distribution at the top of the figure. If the muscle is moved so quickly that the links do not change their points of attachment, the tension will fail linearly as the links are carried past the equilibrium point and will vanish when the distribution becomes symmetrical about the origin. Thus the model predicts that, if muscle is moved very quickly, the tension will drop to zero with a small displacement, which is what actually happens.12,13 This is a simple mechanical process and is due to the release of strain in the relatively short pulling connections between the thick and thin filaments.

Notice that the distribution of links just after a quick displacement will be rectangular, while the corners are rounded in the steady state. Since, for a given tension, the motion depends on the shape of the "connection contour," this implies that the velocity just after a sudden drop in tension from the maximum to some intermediate value will not be the same as that after the steady state has been established. There should be a velocity transient reflecting the transition of "connection contour" from a rectangle to the steady-state shape. We shall return to this point later.

In summary, in the contraction model analyzed by Huxley, the 2 sets of myofilaments slide past each other. The sliding motion arises from mechanical interactions between complementary sites. The chemistry of the system reflects the mechanical motion, since each mechanical interaction is coupled to a chemical reaction. The model explains remarkably well the structural and energetic changes that take place during contraction. The least satisfactory element in it is the rather special nature of the hypothetical mechanochemical sidepieces on the thick filaments, the "pullers." However, "it is not difficult for Nature to do things in ways which seem unduly complicated to physiologists."12

A Folding Model

In a folding model the contractile force arises from a change in state of the thin filaments; the thin filaments become elastic, like a rubber band. To make such a model work, we must assume that force is generated when a substrate molecule, M, binds to (or reacts with) the thin filament at a K site and that the magnitude of the force is proportional to the number of occupied K sites.14 The force could arise from an "electrostatic entropic" process, as has been eloquently argued by Morales and Botts,15 or from a "polymer melting" process, as suggested by Pryor16 and by Flory.17

In an "electrostatic entropic" process, a rubber-like filament is stretched out by the mutual repulsion of distributed, electrically charged groups. At the equilibrium length, the entropic force tending to shorten the filament is just balanced by the electrostatic force tending to extend it. If some of the charged groups were neutralized by the binding of oppositely charged molecules, the net electrostatic force would decrease and the filament would tend to shorten; if length were kept constant, force would be developed.

In a "polymer melting" process, the filament is initially extended by structural forces,
such as those that coordinate a crystalline solid. When a critical temperature is reached, the crystalline structure "melts" and the polymer becomes like rubber. In this state, if kept isometric, the filament will exert considerable force. The dotted line in fig. 11 shows such a phase transition for an ideal crystalline polymer. The melting temperature will be changed if substances bind to (or react with) the polymer; the change will depend on the extent of the binding.

Sharp phase transitions are characteristic of the ideal crystalline polymer. Melting curves or real polymers are often more gradual (solid line, fig. 11); however, in this case too the curve can be shifted by an amount that depends on the extent of binding. Now, if temperature is kept constant (\(T = \tau\)) and the extent of binding varied, the extent of melting will vary. If length is kept constant, the force will increase with binding.

Degree of melting in this process is analogous to charge neutralization in the electrostatic-entropic process; both unlock the rubber-like properties of the polymer. The essential features are that (a) force is generated in a single filament which can shorten by folding and (b) force can change according to the number of small molecules bound to (or reacted with) the filament.

A considerable amount of muscle physiology follows naturally from this hypothesis if we suppose, further, that there are sites on the thick filament that remove the force generating molecules from the thin filament by interacting chemically with them as they move by. In other words, we suppose that there are interactions between the 2 sets of filaments in which "filling time" is rate limiting. We have already shown that this scheme yields up the correct answers for the relation between rate of energy production and speed.*

To explain how the force-velocity curve comes out, consider figure 7 again. Suppose the force is a third of the maximum. Then 1 binding (K) site out of 3 will be filled; 2 out of 3 will be empty. A substrate molecule from the environment will, in time, find its way to one of the empty sites. When the site fills, the force in the filament will rise above that of the load. To re-establish mechanical equilibrium, the filament will shorten by folding until 1 of the filled sites passes a D site, which removes an M so that the force will again be a third of the maximum. The process will be repeated when another binding site is filled. In the steady state, with many sites in the game, the rate of motion will be such that the emptying of full K sites passing D sites is just balanced by filling of empty K sites. The force is the average occupancy of the K

*The energetics of steady motion does not depend on whether "filling time" or "proximity time" is rate limiting. However, in the latter case (as was used in an earlier version of the folding model*), it can be shown that the model does not accommodate the drop in force after quick release from tetanic tension. On the other hand, if "filling time" is rate limiting, the folding model behaves "properly" upon quick release.
sites; the dependence of the average occupancy on velocity is the force-velocity relation. This turns out to be the same as that in living muscle.

What happens when a muscle exerting maximum tension is suddenly released? (You will recall that in the sliding model, because the "pullers" relaxed, the tension dropped linearly with shortening.) In this case, if the motion is quick relative to the filling time, full K sites will be rapidly emptied by reacting chemically with passing D sites, and the tension will drop. The tension will fall linearly with distance only until the force reaches half maximum. Then, because shortening is by folding rather than by sliding, it can be shown that further motion will lead to a proportionately smaller drop in force, which is what happens in living muscle.18

As in the analogous situation in the sliding model, just after a quick drop in force, the distribution of filled sites along the filament is not the same as it will be somewhat later, after the steady state is established. This means that the isotonic velocity after quick release from tetanic tension will generally be different from the later steady velocity. Some time must pass before the velocity settles down to the characteristic steady value.

**Mechanical Transients**

We made a series of experiments to look for this transition phase.18 The study was made with tetanically stimulated frog sartorius at 0 C, (fig. 12).* The upper trace is displacement of one end of the muscle and the lower trace is force at the other end. After full tension was developed, the force on the muscle was suddenly lowered to, and then maintained at, a given value. Each set of traces is for a different final value of the force. The insert (fig. 12g) is a control with the muscle replaced by a simple spring.

Three regions are of interest. To the left of the vertical line we see the quick release phenomenon. The muscle is 35 mm. long; the tension drops to nearly zero when the end moves less than 2 per cent of this length (fig. 12f). Depending on which model we favor, this could be either relaxation of pulling links or emptying of binding sites. Hill found a burst of heat during the quick release, which he attributed to a high thermoelastic coefficient of what in the sliding model corresponds to the pulling spring.19 An alternative interpretation is that a chemical rather than a physical process is associated with the loss of tension, as is the case in the folding model. This interpretation also agrees with the studies of the insect physiologists, who invoke "inactivation by release"—as opposed to "relaxation by release"—to explain the very high frequency movements of certain insect muscles, such as those driving the noisemaker of the locust.20

At each force, the velocity ultimately settles down to the characteristic steady value: the lower the force, the more rapid the motion. (The force-velocity curve in figure 1 was drawn from these data.) The remarkable linearity of the displacement traces supports the idea that the motion is controlled by a feedback mechanism.

The interesting findings in these experiments are the variations in speed (to the right of the vertical line) before the velocity settles down to the steady value; there is a

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*Figure 12 reproduced from Podolsky: Nature 188: 666, 1960. By permission of Nature.

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characteristic isotonic velocity transient for each tension step. One contribution to these transients is the variation in velocity corresponding to the setting up of the steady state of motion in the contraction models we have discussed. However, since the experiments were made with the whole sartorius muscle, there is also a contribution due to the interaction of muscle fibers of different lengths. To sort out these 2 components of the transient seen in the intact muscle, we are repeating these experiments with preparations containing only a few fibers; this should reduce the contribution of fiber interaction. We are also calculating the transients predicted by the sliding and folding contraction models, to see which model accommodates the experimental data better. In these studies attention is focused on the approach to the steady state of motion rather than on the steady state per se; then the contraction kinetics of the 2 models can be distinguished.

Conclusion

In summing up, I should like to point out that the contraction theories work because of 2 basic assumptions. The first—and this can really be elevated to the status of fact rather than assumption—is that the 2 sets of myofilaments move relative to each other in shortening. The second is that the flux of chemical energy through the contractile mechanism is limited by interactions between complementary sites distributed along the 2 sets of filaments.

Two models were fitted to these ideas. They differ largely in the mechanism by which force is generated. In the sliding model, force is developed by mechanical interaction between filaments and there is no change in filament length during shortening. In the folding model, force is developed in a single filament, which shortens during contraction. In both models there is interaction between the mechanical motion and the force-generating mechanism. Chemical processes tend to increase the mechanical force; in the sliding model, pulling connections are made; in the folding model, binding sites, which generate force if filled, become filled. If the load is constant, these processes tend to create a mechanical imbalance which, however, can be righted by shortening: in the sliding model, pulling connections become weaker; in the folding model, binding sites are emptied. Chemical and mechanical equilibrium are incompatible for forces less than full tension. However, since shortening tends to inactivate the force generator, a less-than-maximum force can be maintained if there is steady motion. Conversely, if the load is less than

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Figure 12

Response of muscle to a sudden change in force. Upper trace: displacement; lower trace: tension; frog sartorius, standard length = 35 mm., 0 C. Muscle is initially at the standard length and the record is started after full tetanic force, \( F_{\text{max}} \), has developed. \( P/P_{\text{max}} \): (a) 0.84 (b) 0.69 (c) 0.55 (d) 0.40 (e) 0.26 (f) 0.10. In (g) the muscle is replaced by a simple spring. (From Podolsky, 19)

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*This study is being made in collaboration with Dr. N. Z. Shapiro of the National Institutes of Health.
the maximum force that can be generated, there will be steady shortening. This is the force-velocity relation.

Comparing the models with living muscle, both of them quantitatively account for the changes in force and energy flux with velocity. The quick-release phenomenon is also accommodated: mechanically in the sliding model and chemically in the folding model. Both predict, at least qualitatively, the isotonic velocity transients that can be seen after quick release from tetanic tension.

This list of accomplishments suggests that some of the devices used to get them might actually be built into living muscle.

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