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OPTIMAL SYSTEMS: III. MUSCLE

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The optimal systems approach to the muscular system leads to difficulties since the properties of the muscular system are determined to a great extent by the nature of the contractile unit or molecule. This unit has determined the morphology and dynamic characteristics of muscle, and only smaller order alterations are then possible to adapt muscle to its several functions.

A model of the contractile unit is developed that shows agreement with experimental findings with respect to the velocity-load relation, heat effects, and several aspects of knowledge of the structure of the contractile proteins.

In the first two papers of this series (Cohn, 1954; 1955), emphasis has been placed on mathematical aspects of the optimal system approach to a problem of biological importance, the form of the vascular tree. Physicomathematical methods could be applied in detail to this problem only because we could analyze the vascular tree form in terms of a simple condition known to be of survival value to the organism. This condition is that the vascular tree shall have a minimum resistance to fluid flow. We were able to find the conditions which minimize the flow resistance of a branching system of vessels such as the vascular tree by well-known mathematical methods. From such basic considerations a system was then constructed very similar in form to the actual vascular tree.

In the above papers emphasis was placed on engineering aspects of the constructed system. There was also a discussion of the biological significance of organic system construction based on engineering principles. It was stated that, in the case of a highly evolved organ system, the system actually developed will probably have greater survival value for the organism. This fact may then be used when considering why the system developed the way it did. That is, we first determine the factors influencing survival value and then construct a form utilizing available materials to perform the required function, a procedure that was discussed in great detail in the first paper of this series.

The choice of the vascular system was fortuitous in that survival value could be correlated with a well-defined physical concept, the resistance of the system to fluid flow. Then the *biological* problem of maximizing survival value was analogous to the *mathematical* problem of minimizing the flow resistance of the system. The success of the analysis applied to this one simple example gives us hope that we have come a little closer to stating in mathematical form one of the well-known basic laws of life—the survival of the fittest. This in turn is an important determiner of the nature of organic form.

The approach described above may, we believe, be successfully extended to organic systems other than the vascular tree. However, it was not our intention to convey the idea that all systems could be so simply analyzed in terms of a single explicit factor (flow resistance in the above example). The present paper will be an extension of the "optimal systems" approach to a more complex problem.

Implicit in the solution of the problem of the form of the vascular tree were limiting conditions placed on certain factors that might affect the final solution. For example, we assumed the physical characteristics of the blood could be treated as constant, and the form of the vascular tree could be altered independently of these. However, the physical characteristics of the blood also placed limits on possible variations of the form of the vessels. An obvious extension of the method is then the consideration of several factors affecting the survival value of the organ system.

One problem that will illustrate the intended broad approach of the optimal systems analysis is that of general considerations on muscle. The mammalian muscular system is very complex, and represents a large part of the mass of the mammalian body. Considerations on the "optimal" aspects of the muscle system immediately lead the reader to expect speculations on why we have as many muscles as we do, the economy of the mass of the muscular system relative to the rest of the body, etc. Important as these questions are, there is one basic consideration whose understanding is necessary for an answer to the type of question mentioned above. This is an understanding of the nature of the contractile mechanism itself. Only when we understand this can we speculate concerning its possible variations to suit different functions in the body. However, before considering the contractile mechanism in detail we shall briefly summarize the many possible factors affecting the form of the muscular system. The following is one list of possible regions of variation for the type of factor that we will consider. With each region examples of possible variations within the region have been listed as illustrations.

Intra-cellular factors:

1. Basic chemistry of the cell. The possibility of contractile tissue existing as we know it is due to the fact that the main structural material of plants, cellulose, is replaced by the more labile proteins of the keratin group in the animal cell.

2. The specific biochemistry of muscle. The actin-myosin protein system is very specific and does not allow for any variation among organisms. The metabolic phosphate transport system involving creatine in the vertebrates and arginine in the invertebrates illustrates adaptation to different modes of life.

3. The organization of the muscle cell. Localization of function is the most important phenomenon, which is particularly important in the differences between smooth and striated muscle. This is an adaptation to a speeding up of the molecular machinery of muscle.

Inter-cellular factors:

4. The organization of cells to form muscle. This is illustrated by the difference between skeletal striated muscle (in general parallel muscle cells), and cardiac muscle (a syncytium of cells).

5. The organization of muscles within the body to form the complete muscular system. Under this heading we would consider partitioning of different relative amounts of muscle to different functions in different organisms.

6. The determination of the form of the entire organism by the above factors.

The intra-cellular factors will be treated in this paper. It is planned to treat the inter-cellular factors in a future paper. The following is an example of the type of treatment planned. This example relates to the last of the factors mentioned above.

Determination of the optimum size of an organism considering the limitations placed on it by its muscular system.

Given an organism of mass M, and specific gravity σ; then the volume of the organism will be M/σ. A typical linear dimension L_T we define as a length such as an average diameter for a simple organism, or the length of an appendage or trunk, etc., for a more complex organism. Then

$$L_T = \sqrt[3]{\frac{M}{\sigma}} \tag{1}$$

is a typical linear dimension.

We desire the contractile system to move the body of mass M through a distance L_T. Thus the work, W, that we expect of the contractile system per contraction is

$$W = MgL_T \,, \tag{2}$$

in which g is the gravity constant.

If we call m the mass of the contractile unit, then W_{cu}, the work we can expect of the contractile unit per unit weight per contraction, is

$$W_{cu} = \frac{W}{m} = \frac{MgL_T}{m}. \tag{3}$$

Let us define the contractile substance as the specific molecule or molecules able to contract and change linear dimension. Then not all the contractile unit will be contractile substance. Call the fraction of the contractile unit that is contractile substance γ, and assume this fraction to be independent of body mass. Then we see that the work expected per unit weight of contractile substance is

$$W_{cs} = \frac{W}{\gamma m} = \frac{MgL_T}{\gamma m}. \tag{4}$$

Substituting (1) in (4) and noting that m is proportional to M we obtain

$$W_{cs} = KM^{1/3} \,. \tag{5}$$

Since the work obtainable from a single contractile unit is constant, the above equation implies an upper limit to the size of organisms if the relative size of the muscle and the variety of movements are kept constant. To exceed this size would mean increased sluggishness or loss of variety of movement. This may help explain the fact that animals in the weight region of several hundred pounds are the most successful land predators (i.e., the lion and tiger and other large members of the cat family), as well as the fastest land animals.

Another topic to be considered would be the possible modes of organization of cells to form muscle. Different length-tension diagrams are possible with different structural patterns. The increased possible tension of heart muscle at greater than rest length is an interesting adaptation of the normal length-tension diagram of muscle (maximum tension at near rest length) to a situation in which the increased tension at great lengths is necessary.

However, before considering these special situations it is necessary to consider the intra-cellular limitations placed on the muscular system. This will be done in the present paper where we will deal mainly with consider-

ations on the contractile system of muscle, which we will later utilize in further work on more general aspects of the muscular system (which approach has been outlined above). The present work is then a necessary aside to the main theme of the series.

Present state of theory construction concerning muscle. There is a large spectrum of experimental approaches to the study of muscle as well as many levels of theorizing concerning the nature of the contractile mechanism. In this paper we will be concerned with a theoretical approach to the subject. Naturally, the motivation as well as validation of any such approach is dependent on the accumulated experimental data in the field. This data has been adequately reviewed recently and for this the reader is referred to M. Dubuisson (1954), A. Szent-Gyorgyi (1951), W. F. H. M. Mommaerts (1950), and D. R. Wilkie (1954).

Even a casual study of the experimental data will convince the reader that a great deal of time and effort has been devoted to studies of the contractile mechanism. However, the uncertain state of knowledge and theorizing concerning the contractile mechanism is illustrated by the present conflict of views concerning very fundamental questions. For example, the still undecided question of whether contraction or relaxation is the "active" part of the contractile cycle; and the question of whether contraction is entropic or due to internal changes.

Considering the difference between the many experimental facts obtained and the lack of an adequate theoretical explanation of the physiological phenomena it might be useful to investigate the nature of theory construction in this field in the hope of throwing light on its inadequacies.

Most theoretical attempts to explain muscle action have been based on some known molecular physicochemical mechanism. Then the observed action has been interpreted as a macroscopic manifestation of the microscopic phenomena. Wherever the model contradicted observed properties of muscle it was altered. However, the emphasis has been on the molecular interpretation. This approach is typical of recent physicochemical approaches to biological problems.

In the specific case at hand we have many physicochemical observations available. While a good theory must ultimately explain as many experimental facts as possible, because of the complexity of the present picture it is difficult to build a theory from some specific facts. Our efforts will be better directed if we consider the large-scale picture and the consequences of present knowledge concerning the general molecular structure of organic molecules; in the case of muscle particular emphasis will be placed on the protein molecule.

With the previous pages providing a background for our approach we will now give a detailed presentation.

The general structure of striated muscle:

Striated muscle is composed of many long cells held together by connective tissue. The cells are passively bound together and we may consider as the anatomical unit of function a single one of these cells. Thus we may limit ourselves at present to considerations of the single cell. The muscle cell must consist of the following components.

1. A structure to keep the cell localized. This is necessary because of the fluid nature of most of the cell. This structure is the sarcolemma. Anatomically it helps maintain the integrity of the cell by inhibiting long extensions.

2. A matrix to support the functional components of the contractile system within the cell. This matrix will be fluid in nature.

3. A metabolic system to supply energy.

4. A contractile system which converts metabolic chemical potential energy into mechanical energy.

5. A trigger mechanism to activate the cell. This is the mechanism of membrane stimulation and possibly the reactions of the muscle cell to varying amounts of tension.

The contractile mechanism. Of the above listed components the one that most distinguishes the muscle cell from other cells is the contractile mechanism. Since we are not here concerned with theories of general cellular function, we will limit our speculations to this contractile component of the muscle cell.

There are in existence several kinetic theories of this unit. The most complete exposition is found in M. J. Polissar (1951) and essentially similar ideas are investigated by F. Buchtal and E. Kaiser (1951). Their models involve units capable of existing in two forms, which for convenience we may call long and short. A single muscle fiber is then considered to be made of many such units strung together in series. The kinetics for the transition of a single unit from the long to short and from the short to long form are considered and the state of the fiber is then obtained as a thermodynamic equilibrium of short and long forms.

Subdivision of the contractile mechanism. Our model will start with one basic assumption similar to the above. This is that the contractile units can exist in one of two states, a long or short configuration. However, we assume that the fiber consists of another element which we call the transmissive element. This transmissive element functions in a passive role and serves simply to maintain the contracted muscle in a certain state.

Justification for introducing idea of transmissive unit. Since the introduction of a new element into the muscle mechanism introduces a complexity not found in simpler models, we feel there should be an adequate justification for this step. The main justification comes from considerations on the dimensional changes possible to a contracting fiber. The stretched stimulated fiber may contract from 200% rest length to less than 60% rest length (Davson, 1952, p. 491). If the fiber were to consist of contractile units arranged in series, since the contraction of the fiber is the sum of the contractions of the units of which it is composed, a single unit must be able to reversibly shorten over a range of at least three times its shortest length. However, the best evidence available today concerning the structural chemistry of muscle proteins indicates a much smaller magnitude of reversible contraction [see transformations from pleated sheet configuration (β) to folded (α) chain of keratin-like proteins in Pauling and Corey (1951a, b) and Pauling, Corey, and Bramson (1951)].

A model of the contractile mechanism. We assume that the muscle contractive mechanism consists basically of two parts as outlined above: one, a so-called *active unit*, which shortens relatively little and which also provides the energy of contraction; the other we call the *passive unit* (Fig. 1). The latter may be conceived as a long-chain molecule, which can fold into a much shorter one. Before the active unit contracts, it is assumed to become rigidly linked to the passive unit. Therefore its contraction results in a shortening of the passive unit also. We assume, moreover, that the rate of return of the active unit to its original length is much faster than the rate of return of the passive unit. During the return the two parts are assumed to be disconnected. We then have the following chain of events.

When relaxed the muscle may be freely moved or stretched within limits imposed by the elasticity of the sarcolemma (Fig. 1A). Thus we assume very weak or no binding together of the component parts of the contractile mechanism. Since very little heat is generated, we also assume no chemical reactions other than the normal non-contractile metabolic reactions.

When stimulated, the following is postulated:

1. Electrical and consequent ionic changes in and around the sarcolemma and possibly throughout the fiber induce a changed internal state of the fiber.

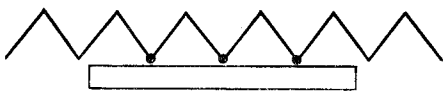
2. The changed internal state of the fiber causes a binding together of the passive unit as well as a binding of the active to the passive units (Fig. 1B; see below for details of these two processes).

3. The active units are now able to contract, supplying mechanical

energy to the passive units (the source of this energy being the metabolic system; Fig. 1C).

4. After the active unit has contracted, its binding to the passive unit is broken. Then the active unit returns to its long state very rapidly. During this time of return the passive unit has partly returned to its original long length by the tension existing in the fiber (Fig. 1D). This return,

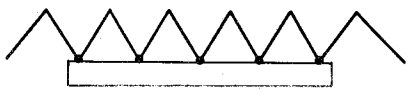
A. Relaxed muscle fiber



B. Stimulated muscle; active and passive units bound

C. Contracted position of active unit; passive unit pulled in with it

D. Relaxation of binding while active unit relaxes and returns to long (L) state; passive unit partly regains original length during this phase



E. Beginning of new cycle with active and passive units again bound together

FIGURE 1. Diagrammatic illustration of the coupling and mode of action of the active and passive units of muscle.

however, is not complete. Therefore, when the extended active unit is again bound to the passive unit, it binds more elements of the passive unit than it bound in the first instance. (In Fig. 1B three elements of the passive unit are bound to the contractile unit. In Fig. 1E five such elements are bound.) Therefore the next contraction of the active unit results in a greater shortening of the passive unit than the preceding contraction gave rise to.

Binding of the passive units. We assume the passive units are long molecules with their long dimension oriented parallel to the long dimension of the fiber. As noted above, since the relaxed muscle can be easily stretched, we assume no strong inter- or intra-molecular binding forces holding the passive units. We might idealize this situation by means of the following simple model. We liken the relaxed passive units to a chain made of freely moving links. During stimulation the internal milieu of the chain is changed and this induces a freezing of the links in position. Now if we assume the muscle passive units to be fixed in position on stimulation, the question arises of how the muscle is able to contract on stimulation. We assume the contraction is due to a continuous working of the active units which act on and contract the passive units. The mechanism of this action will be elaborated in the remainder of this paper.

Mechanism of contraction of the active units. We assume the active units can exist in two states, which we will call long (L) and short (S) states. (We needn't be concerned with the δ state postulated to exist at very short lengths of the fiber; see Ramsey, 1950, for the meaning of this state.) The transition $L \rightarrow S$ is affected by the input of energy from a metabolite, and the transition $S \rightarrow L$ is spontaneous. However, we assume the transition $L \rightarrow S$ takes place in the stimulated muscle fiber only when the active unit is bound to the passive unit. Then the active unit is able to effectively contract the passive unit. The return reaction ($S \rightarrow L$) we assume is preceded by an unbinding of the active and passive units. We further assume that the time of contraction and the time the active unit remains in the contracted (S) state are very short compared with the time of one complete cycle of the active unit. Therefore almost all the time of the cycle is spent by the units bound to each other and not contracted.

All these aspects of the cycle of the active unit are illustrated in Figure 1.

Quantitative aspects of the contractile system model. In the following we will consider observations made on the muscle at or near rest length. For example the isometric tension, referred to as P_{iso}, will always mean the isometric tension at rest length. Later in the paper we will consider possible interpretations of the model by means of which it may be extended to long and short lengths and thus account for the length-tension diagram and other associated experimental findings. The reader should keep this in mind in reading the following.

The active unit has two permissible states. Each state is characterized by a specific length. One associated with its extended (relaxed) and the other with its shortened (contracted) state. The difference between these

two lengths we call Δx_M. Thus Δx_M is the distance through which the active unit contracts. As noted above, we assume that the active unit pulls the passive unit this distance with each contraction. After the contraction the active unit releases the passive unit and they both relax. The active unit then reassumes its original relaxed configuration and is then again bound to the passive unit. During the relaxation time of the active unit, the passive unit is also able to relax. We assume that the return of the passive unit is proportional to the instantaneous tension existing in the muscle. Then we may call the return of the passive unit αP, where P is the instantaneous tension per cross-sectional area existing in the muscle and α is a constant of proportionality.

The quantity Δx_M defined above is the dimensional change of the active unit during contraction. Since the passive unit is pulled through this distance with each contraction of the active unit and then tends to return to its original configuration during the relaxation part of the cycle (when the two units are uncoupled), we may define an effective contraction distance for the passive unit. By this we mean the distance contracted by the active unit (Δx_M) less the return of the passive unit during the relaxation phase. Calling the effective contraction distance Δx, we may define it by the following equation:

$$\Delta x = \Delta x_M - \alpha P \ . \tag{6}$$

We may note that at zero tension ($P = 0$) we find that

$$\Delta x = \Delta x_M \ . \tag{7}$$

This we interpret as follows. With no tension in the passive units there is no return to the pre-contraction length of the transmissive unit during the relaxation phase of the active unit cycle (Fig. 1D). Thus the resultant shortening of the passive units (which is related to the observed shortening) indicates the entire extent of shortening of the active unit.

Similarly, let us consider the muscle stimulated isometrically. At isometric tension the effective shortening of the muscle is zero ($\Delta x = 0$). Thus at isometric tension (6) becomes

$$\Delta x_M - \alpha P_{iso} = 0 \ .$$

This relation enables us to evaluate α, and we find

$$\alpha = \frac{\Delta x_M}{P_{iso}} . \tag{8}$$

And then (6) may be written as

$$\Delta x = \Delta x_M - \frac{\Delta x_M}{P_{iso}} P$$

or

$$\Delta x = \Delta x_M \left[1 - \frac{P}{P_{iso}}\right]. \tag{9}$$

Next we will consider the rate at which the active units work. During muscular contraction the only factor that we consider as affecting their reaction rate is the tension of the transmissive units. We assume that increasing the tension in the passive units decreases the probability of the active units contracting. In quantitative form, if ν is the average working frequency of the active units (i.e., the average number of cycles described in Fig. 1 per unit time) at any tension P per unit cross-sectional area, and ν_o is the turnover frequency at zero tension (the maximum working frequency), then

$$\nu = \nu_0 e^{-\beta P}, \tag{10}$$

in which β is a constant.

The exponential form of the relation between turnover frequency and tension assumes that there is a one-dimensional barrier to the transition of the active unit into the contracted state. Then the Arrhenius energy of activation is increased by an amount proportional to the observed tension, and this fact is expressed by equation (10).

Equations (6) and (10) are the two important equations of our proposed model. With them we may now proceed to some simple interpretations of experimental findings. Later in this paper, when considering the heat effects of contraction, new assumptions concerning the heat rates of reactions will be necessary. Before complicating our model in that fashion we will consider some simple kinetic results of muscular contraction which may be elaborated with the mechanism now available.

A. The velocity of contraction.

The velocity of contraction, which we call v, may be obtained as the product of the turnover frequency of the active units, the number of contractile units in the muscle, and the distance each contraction of an active unit shortens the muscle, which we call ΔX. Then

$$v = \nu \cdot nlA \cdot \Delta X, \tag{11}$$

in which n is the number of active units per unit volume of muscle and lA is the volume of the muscle.

The quantity ΔX may be related to the Δx of equation (9) in the following way. The Δx we have obtained in (9) represents the distance by which

one working cycle of the active unit shortens the particular passive unit on which it acts. However, a muscle or muscle fiber consists of many passive units in parallel. Assuming muscle tissue to be homogeneous, we may assume that the number of passive units per unit cross-sectional area is constant. Call this number N. Then the total number of passive units in parallel in the muscle is NA, in which A is the cross-sectional area of the muscle. It is then reasonable that with this number of passive units in parallel a contraction of all passive units through a distance Δx will contract the entire muscle the same distance. We may then say that on the average the amount a single contraction of an active unit effectively

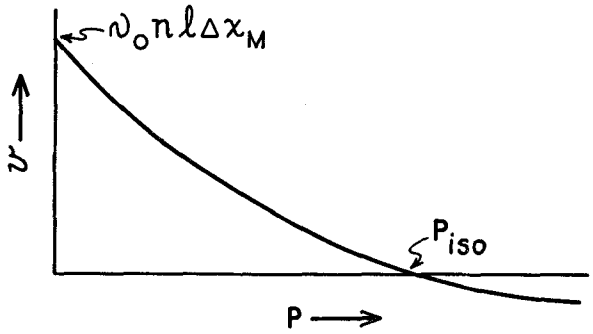


FIGURE 2. Theoretical velocity-tension curve

contracts the muscle is only a small fraction of the amount it contracts the passive unit on which it acts. In particular,

$$\Delta X = \frac{\Delta x}{NA}. \tag{12}$$

Inserting (9) in (12) we obtain

$$\Delta X = \frac{\Delta x_M}{NA}\left[1 - \frac{P}{P_{iso}}\right]. \tag{13}$$

Finally, substituting in (11) expressions (10) and (13) we find

$$v(P) = v_0 \cdot nl \cdot \Delta x_M \, e^{-\beta P}\left[1 - \frac{P}{P_{iso}}\right]. \tag{14}$$

The graphical form of this relation is shown in Figure 2.

The experimentally determined velocity-load relation is similar in form (Buchtal and Kaiser, 1951, p. 150). After considerations of heat evolution during muscular contraction we will be able to consider this relation in greater quantitative detail and make comparisons with experimentally determined relations.

B. Heat rates.

Muscle can do work on contraction. In our model the passive units are moved by the active units. Thus the energy for contraction comes from the active units. These in turn must derive their energy from some source. This is known to be energy derived by the degradation of metabolite molecules or chemical bonds from states of high to low chemical potential energy. The carrier of this chemical potential energy has been shown to be the high energy phosphate bond. However, we are little concerned with the specific biochemistry of muscular metabolism. We are interested in making a broad and non-specific assumption concerning the energy input to the active unit. This is that each time the active unit contracts it degrades one unit of metabolic energy. The energy that is so released we call ΔF. Once this energy is released from the metabolite carrier by the active unit we assume that no part of it can be reconverted to chemical potential energy. (This assumption is contrary to a hypothesis presented by Needham, 1950, in which he supposes that the energy supply to muscle is by means of a reversible chemical reaction. During contraction the heat given off is partly activation heat and partly heat of contraction. During slow tetanic stretch the heat may be less than isometric and this he supposes may be due to normal activation heat and negative heat of contraction. Thus he allows for the possibility of a negative heat in the working of the contractile system. This is equivalent to a reversal of the reaction whereby energy is normally given to the active unit.)

Since we assume the energy from the metabolite molecule is all degraded, it must all appear in the work done by the active unit and the heat generated by the muscle. The work ΔW done by each working of the active unit is

$$\Delta W = PA \cdot \Delta X , \tag{15}$$

in which PA is the tension against which the unit shortens the muscle a distance ΔX. Substituting (13) in the above equation we find

$$\Delta W = \frac{P \Delta x_M}{N} \left[1 - \frac{P}{P_{iso}} \right] . \tag{16}$$

This expression gives the work done per working of the active unit in terms of the tension P against which the active unit works.

With the above expression for work we may obtain the heat generated per turnover of an active unit. If we call this heat ΔH, then

$$\Delta H = \Delta F - \Delta W . \tag{17}$$

Substituting ΔW from (16) in the above we obtain

$$\Delta H = \Delta F - \frac{P\Delta x_M}{N}\left(1 - \frac{P}{P_{iso}}\right). \tag{18}$$

Finally, we may derive from the above equations an expression for the time rate of heat generation. If we call this time rate $(\Delta Q)/(\Delta t)$ we find

$$\frac{\Delta Q}{\Delta t} = \nu \cdot \Delta H. \tag{19}$$

Substituting (10) and (18) in the above we obtain

$$\frac{\Delta Q}{\Delta t} = [\nu_0 e^{-\beta P}]\left[\Delta F - \frac{P\Delta x_M}{N}\left(1 - \frac{P}{P_{iso}}\right)\right]. \tag{20}$$

This concludes the presentation of the basis of our model. We have postulated the effective distance of contraction of an active unit for a single contractile cycle [eq. (9)], the rate of working of an active unit [eq. (10)], the velocity of contraction of muscle in terms of the above [eq. (14)], the work output and heat production for a single working of the active unit [eqs. (16) and (18)], and the rate of heat production [eq. (20)]. The only affirmation of our model has been obtained in a qualitative manner from the shape of the expected load-velocity relation (Fig. 2).

Since we have postulated mechanisms involving observable quantities, it is desirable at this point to consider a comparison of our model with experimental data.

C. Comparisons with experimental data.

The basic system of our model we assume to be unique in the sense that it is of very similar form in many vertebrate forms. This system is the active unit together with its passive unit (the actin, myosin system). However, we know that there are differences among different types of muscle mainly exhibited by the rate at which they work, i.e., slow and fast muscles. These differences we attribute to the various possibilities of aggregation of these units as well as possible metabolic differences. In other words, the contractile system is set in pattern and this basic system can fit various functions by alteration of the metabolic pathways supplying it. With this in mind we may proceed to comparisons of our model with experimental data.

Maximum isometric tension. Equation (6) determines the maximum tension in the passive unit. This is the tension at which the dimensional change of the active unit (Δx_M) is just balanced by the return of the passive unit (aP) during the return of the active unit to its extended state.

Since a is a constant characteristic of the binding of the contractile system and its surroundings, we assume it not to be dependent on the type of muscle.

Tension is exerted by the many passive units in the muscle acting in parallel. If there are NA passive units, then

$$P \cdot A = NAp \,, \tag{21}$$

in which p is the tension in each unit. However, from (6) the maximum tension p_M in each passive unit is

$$p_M = \frac{\Delta x_M}{a}.$$

And since a is constant this maximum tension is not dependent on the type of muscle. Then

$$PA = NA\,\frac{\Delta x_M}{a}. \tag{22}$$

Since we assume a constant cross-sectional density of passive units, then $N = kA$, where A is the cross-sectional area of the muscle and k is a constant. Substituting this in (22) we obtain

$$P = N\,\frac{\Delta x_M}{a}. \tag{23}$$

This equation expresses the fact that the maximum tension per unit cross-sectional area is independent of the type of muscle. This is a well-known experimental result (Hill, 1949).

Velocity load relation. Before considering equation (14) above, we must first evaluate the parameter β which can be done from considerations of heat productions.

Consider the relation [eq. (20)] between heat rate and tension

$$\frac{\Delta Q}{\Delta t} = [v_0\, e^{-\beta P}] \left[\Delta F - \frac{P \Delta x_M}{N}\left(1 - \frac{P}{P_{iso}}\right)\right]. \tag{25}$$

During free release of the muscle we find

$$\frac{\Delta Q}{\Delta t}(P = 0) = v_0 \Delta F \,. \tag{26}$$

When held isometrically we find

$$\frac{\Delta Q}{\Delta t}(P = P_{iso}) = v_0\, e^{-\beta P_{iso}} \Delta F \,. \tag{27}$$

Thus the ratio of isometric heat to heat produced when the muscle is contracting with maximal velocity is

$$\frac{\frac{\Delta Q}{\Delta t}(P = P_{iso})}{\frac{\Delta Q}{\Delta t}(P = 0)} = e^{-\beta P_{iso}}. \tag{28}$$

For reasons that will be apparent in the later development of this section we will change our notation in the following manner:

$$\beta = \frac{\gamma}{P_{iso}}, \tag{29}$$

in which γ is a dimensionless constant. Then (28) may be rewritten

$$\frac{\frac{\Delta Q}{\Delta t}(P = P_{iio})}{\frac{\Delta Q}{\Delta t}(P = 0)} = e^{-\gamma}. \tag{30}$$

Hill (1938) reports that the rate of energy liberation at zero load is about five times as large as the isometric heat rate. However, this does not allow for the fact that some heat is given off by the incidental processes that keep the muscle in a state of excitation, and also that during free release of the muscle (zero load) the active units are actually working under a small tension which is necessary to pull the muscle, and so are not working at their maximum rate. If we let $\gamma = 2$, then substituting this value in (5) gives us

$$\frac{\frac{\Delta Q}{\Delta t}(P = P_{iso})}{\frac{\Delta Q}{\Delta t}(P = 0)} = \frac{1}{7}. \tag{31}$$

With this value of γ we may substitute in our velocity load relation [eq. (14)] and obtain the following values, which we present compared with some of Buchtal's (1951) experimental values in Figure 3.

The heat of shortening. Heat is generated by the muscle at a rate governed by equation (20)

$$\frac{\Delta Q}{\Delta t} = [\nu_0 e^{-2(P/P_{iso})}]\ [\Delta F - P\frac{\Delta x_M}{N}\left(1 - \frac{P}{P_{iso}}\right)]. \tag{32}$$

Let us consider a muscle contracting under a tension P through some distance Δl. The velocity of contraction is given by equation (14)

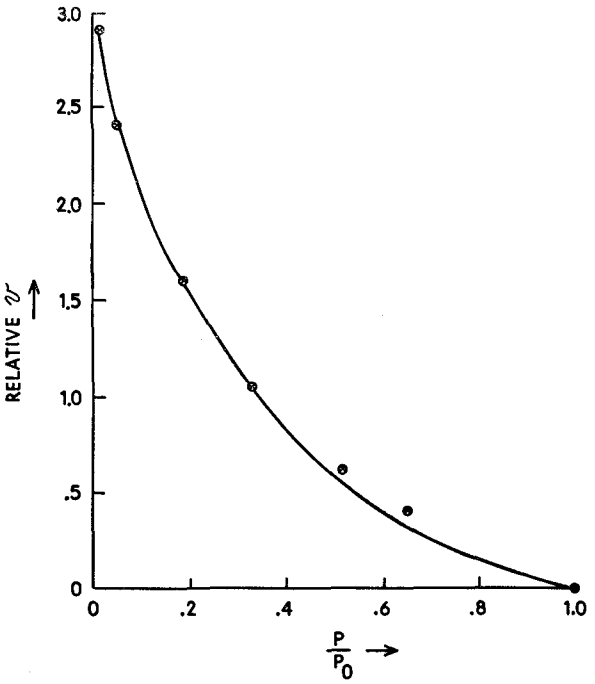
$$v(P) = \nu_0 nl\Delta x_M e^{-2(P/P_{iso})}\left(1 - \frac{P}{P_{iso}}\right). \tag{33}$$

Thus the time Δt necessary for the contraction to take place is

$$\left.\begin{aligned}\Delta t &= \frac{\Delta l}{v(P)} \\ &= \frac{\Delta l}{v_0 n l \Delta x_M e^{-2(P/P_{iso})}\left(1-\frac{P}{P_{iso}}\right)}.\end{aligned}\right\} \tag{34}$$

Then the heat H generated during the contraction is

$$\left.\begin{aligned}H &= \frac{\Delta Q}{\Delta t}\cdot\Delta t \\ &= \frac{\Delta F - P\frac{\Delta x_M}{N}\left(1-\frac{P}{P_{iso}}\right)}{n l \Delta x_M\left(1-\frac{P}{P_{iso}}\right)}\Delta l.\end{aligned}\right\} \tag{35}$$



⊗ Experimental points (Bochtal, 1951, p. 149)
Solid line—theoretical curve—plot of

$$v = v_0\left(1-\frac{P}{P_{iso}}\right)\rho^{-2(P/P_{iso})}$$

fitted through point

$$\left(\frac{1}{P_0} = .20;\ v = 1.62\right)$$

FIGURE 3. Comparison of theoretical and experimental velocity load relations

However, when considering the heat of shortening, which is the extra heat generated during the shortening, we must subtract from the total heat given off during the shortening the heat that would have been generated during an equivalent time had the muscle been held in isometric contraction. This equivalent isometric heat is

$$\frac{\Delta Q}{\Delta t}(P=P_{iso})\,\Delta t=\frac{e^{-2}\Delta F\Delta l}{n\cdot l\cdot\Delta x_M\, e^{-2(P/P_{iso})}\left(1-\frac{P}{P_{iso}}\right)}. \tag{36}$$

Thus the extra heat generated during the contraction is given by the difference between equation (35) and equation (36)

$$H-\frac{\Delta Q}{\Delta t}(P=P_{iso})\,\Delta l$$

$$=\frac{e^{-2(P/P_{iso})}\Delta F\cdot\Delta l-e^{-2(P/P_{iso})}\frac{P\Delta x_M}{N}\left(1-\frac{P}{P_{iso}}\right)\Delta l-e^{-2}\Delta F\Delta l}{nl\Delta x_M\, e^{-2(P/P_{iso})}\left(1-\frac{P}{P_{iso}}\right)}. \tag{37}$$

To investigate the dependence of this expression on P we must have some idea of the order of magnitude of ΔF. This must be about the size of

$$\frac{\Delta x_M P_{iso}}{N}.$$

One reason for this is that muscle is very efficient and when working at maximum efficiency (in the region of $P=\frac{1}{2}P_{iso}$) dissipates an amount of heat about three times the work it is doing. Since the work done at this tension is

$$\frac{1}{4}\frac{\Delta x_M P_{iso}}{N},$$

we find that the total energy given out (which is the same as ΔF) is

$$\frac{\Delta x_M P_{iso}}{N}.$$

Substituting this value of ΔF in the above equation we obtain

$$\frac{Nml}{P_{iso}}\left[H-\frac{\Delta Q}{\Delta t}(P=P_{iso})\,\Delta t\right]=\left[\frac{1-e^{-2[1-(P/P_{iso})]}}{1-\frac{P}{P_{iso}}}\right]-\frac{P}{P_{iso}}. \tag{38}$$

Values of the right side of equation (38) have been tabulated in Table I.

Thus our model has an approximately constant heat of shortening (to within 10% of the total heat) for shortening with loads of less than .8 times the isometric load. This has been experimentally shown in the work

of Hill (*Proc. Roy. Soc. B*, 126, p. 136–95, 1938). The larger heat at larger load has been indicated experimentally but is not too important, for then the muscle has a long contraction time, and it is difficult to experimentally determine its actual excess heat of shortening.

Further Considerations of the Simple Model

The effect of changing temperature. Many of the kinetic properties and heat rates of muscle vary when the temperature of the muscle is changed. In this section we will consider some of these variations.

TABLE I

$\frac{P}{P_{iso}}$	Extra heat of shortening (100% assigned to extra heat per unit shortening when $\frac{P}{P_{iso}} = 0$)
0	100%
.2	93%
.4	90%
.6	90%
.8	99%

A. The maximal isometric tension.

This tension is determined from equation (6) which we rewrite here

$$\Delta x = \Delta x_M - aP \,. \tag{39}$$

The second term on the right is the return of the transmissive unit during the period of the cycle when it is not coupled to the contractile unit. This term may be written

$$aP = K \frac{\tau}{\eta} P, \tag{40}$$

in which τ is the time during which the two units are uncoupled, η is a viscosity term giving the viscosity of the medium through which the passive unit must move, and K is a constant not depending on temperature or tension.

Inserting equation (40) in equation (39) we obtain

$$\Delta x = \Delta x_M - K \frac{\tau}{\eta} P, \tag{41}$$

which, in the isometric case, reduces to

$$0 = \Delta x_M - K \frac{\tau}{\eta} P_{iso},$$

or

$$P_{iso} = \frac{\eta}{K\tau} \Delta x_M \,. \tag{42}$$

We find that Δx_M is the length change of the active unit and this change we expect to be effected very little by temperature. The viscosity η has a small temperature coefficient.

Next we must consider how the relaxation time of the active unit varies with temperature. Since the contraction of the active units is a relatively rare event, we assume the units have a high activation energy in order to go from the extended to the contracted state. In turn we may assume a low activation energy for return to the extended state after contraction since the return occurs very soon after contraction. Thus the time τ, during which the active and passive units are not coupled, has a small temperature dependence. At present we cannot say whether increasing the temperature will increase or decrease, but the assumption of a small activation energy for the relaxation process means that there will be only a small temperature dependence. Thus we see from equation (42) that the isometric tension will have a small temperature dependence. This has been found to be true. The temperature coefficient of isometric tension has been found to be of the order of 1.12 (Ramsey, *Ann. N.Y. Acad. Sci.*, 47, 675, 1947).

Summary. The engineering of a biological system presents serious difficulties placed by limitations of the structural materials available. When the vascular system was treated, these limitations were accepted and not analyzed. In the present example of the muscular system more serious restrictions are imposed by the materials comprising the structure of the system since some of the most important physiological properties of the system are imposed by the properties of these materials. In investigating the muscular system it thus seemed wise to begin by considering a model of the contractile mechanism itself. This has been done utilizing some known general properties of biological systems which we believe impose more important requirements on the molecular system than the miscellaneous microscopic facts accumulated in experimental work on muscle.

Considering the probable specificity of a single reaction involving the dimensional change of a molecule combined with the required reversibility of the reaction, a system has been proposed involving the use of two units in the active mechanism: an active unit and a passive unit. Simple kinetic assumptions applied to this two-component system give theoretical predictions which show promising correspondence with experimental results.

Conclusion. The results obtained give promise that several phenomena connected with the workings of the contractile system of muscle may be represented by a coupled two-component system. The dependence of a

biological system on the very specific properties of a single molecular structure (i.e., the two permissible states of the active unit) has also been illustrated. Now, realizing the limitations placed on the muscular system by the contractile system itself, we may in the future proceed to consider along the lines of an optimal systems analysis possible alterations of this basic system to best suit certain functions.

Professor H. D. Landahl has suggested that the present model is a particular example of a general type of model. It might be of interest to investigate more general conditions of coupling between a molecule undergoing a specific chemical reaction inducing a dimensionl change and the more passive system it acts on.

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