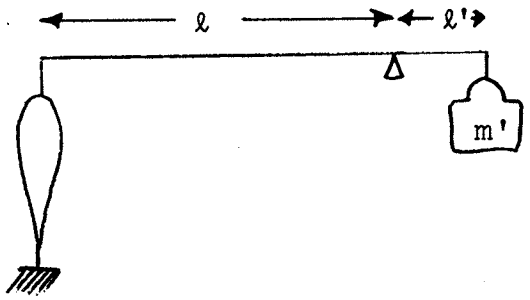
The Steady State Properties of Muscle:*

Skeletal muscle, but not heart muscle, can be put into a steady contractile state by rapid repetitive electrical stimulation or by repetitive firing of its motor nerve. This state is called a "tetanus." In a typical experiment the muscle pulls on a lever. The other end of the lever is either held fixed (isometric contraction) or attached to a weight which supplies a constant load (isotonic contraction). The inequality in length of the lever arms reduces the effects of acceleration of the load for the following reason:



The force felt by the muscle (usually called P) is given by

$$P = \frac{\ell'}{\ell}\, m'(g + a') = \frac{\ell'}{\ell}\, m'\left(g + \frac{\ell'}{\ell} a\right)$$

where

m' = mass of the load

g = acceleration of free fall under gravity

a' = acceleration of the load

a = acceleration of the end of the muscle.

ℓ', ℓ = lengths of the lever arms

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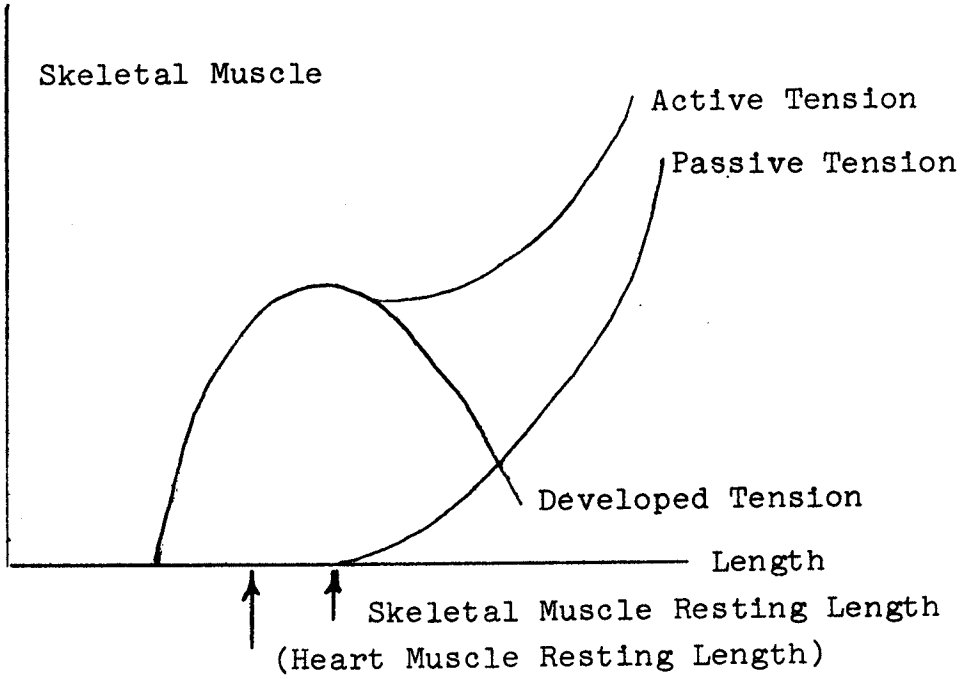
* Aidley, The Physiology of Excitable Cells, Cambridge University Press 1971, Ch. 11-13.

* Hill, A.V., "The Heat of Shortening and the Dynamic Constants of Muscle", Proc. Royal Soc. B 126, 136-195.

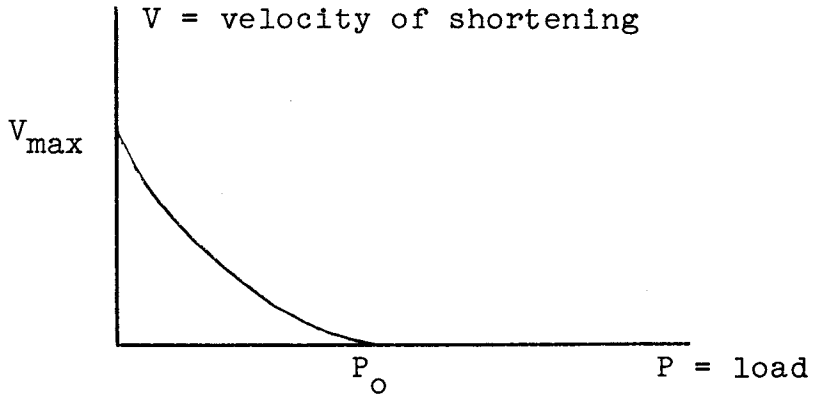
Now let $m = \frac{\ell' m'}{\ell}$ and take the limit as $\ell' \to 0$, $m' \to \infty$, m = constant. Then $P \to mg$ independent of a. The effects of accelerating the load can therefore be made small by shortening the lever arm on the side of the load.

In an isometric tetnaus, the steady tension achieved depends on the length of the muscle in the following way



Experiments with skeletal muscle are usually conducted at lengths where the tension is near maximal. This makes it possible to eliminate (approximately) the length dependence of muscle tension. No such simplification is reasonable for cardiac muscle.

In the region where isometric tension is independent of length, <u>isotonic</u> experiments lead to constant velocities of shortening. The velocity depends on the load as follows:



P_o = isometric tension

V_{max} = velocity of shortening at zero load

The experimental points fit very closely to an equation of the form

$$(P + a)v = b(P_o - P)$$

or

$$(P + a)(v + b) = b(P_o + a) \quad .$$

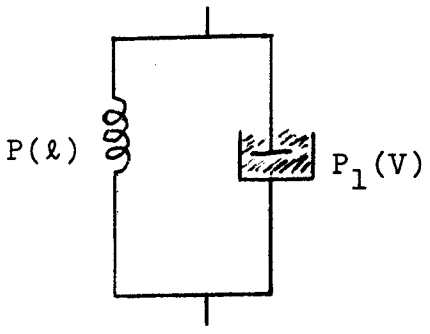
A.V. Hill (ref. cited above) who proposed this equation, also noted an interesting connection between this force velocity relation and his experimental data on the thermodynamics of muscle contraction. Tetanized muscle held at constant length (and hence at isometric tension) liberates heat at a constant rate. When the muscle is allowed to shorten, however, extra heat is liberated, the "heat of shortening".

This heat appeared to depend linearly on the amount of shortening. That is $q = ax$ or $\dot{q} = av$. The constant a which appears here agrees very well with the constant a of the force-velocity relation. Since Pv is the rate of doing work, (P+a)v can be interpreted as the rate of extra energy liberation during

shortening (extra because even when v = 0 there is still heat liberated during the maintenance of isometric tension). Hill's force-velocity relation then implies that the rate of extra energy liberated varies linearly with the load. That is, it is given by $b(P_o - P)$, and this result was also confirmed experimentally by Hill.

If the relations $\dot{q} = av$ and $\dot{\varepsilon} = b(P_o - P)$ are regarded as given, then the force-velocity curve is a thermodynamic consequence since $\dot{w} = Pv$ and conservation of energy is $\dot{\varepsilon} = \dot{q} + \dot{w} \rightarrow b(P_o - P) = (P + a)v$. On the other hand, the latter equation rests on much stronger empirical ground than the thermal measurements from which it is allegedly derived.

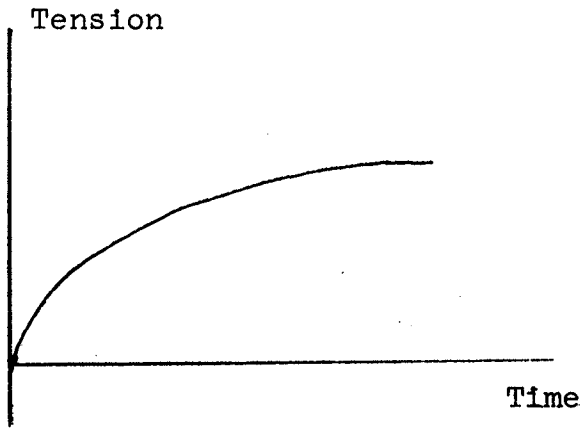
The thermal data are also important because they exclude an interpretation of the force velocity curve which would otherwise be very natural. Suppose that activation of a muscle consists of a change in the length-tension curve of an elastic element, and that a force-velocity curve results because the elastic element is coupled to a viscous element as shown. Such a model with an appropriate non-linear viscous element could account for the observed force-velocity relation. As pointed out by Aidley (cited above), however, the total energy released on shortening would be independent of the load in such a model, being equal to the decrease



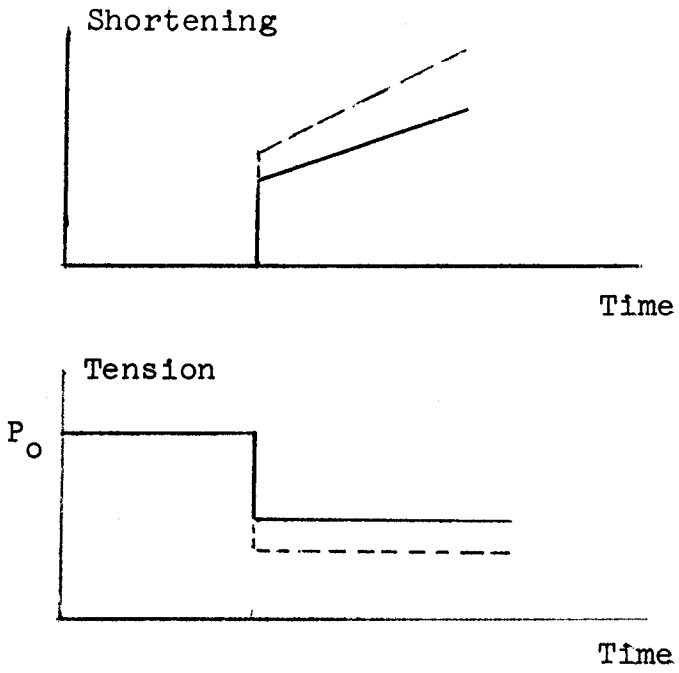
Incorrect Model

in the stored energy of the spring. In fact, the total energy released is (P + a)x. More recent work, which shows that the "constant" a increases with the load only makes this conclusion stronger.

The description of muscle in terms of the force velocity relation alone is incomplete even when the muscle is tetanized. First, the force-velocity relation by itself implies an instantaneous jump in tension from $0 \rightarrow P_o$ when an isometric muscle is tetanized. In fact however the tension rises smoothly.

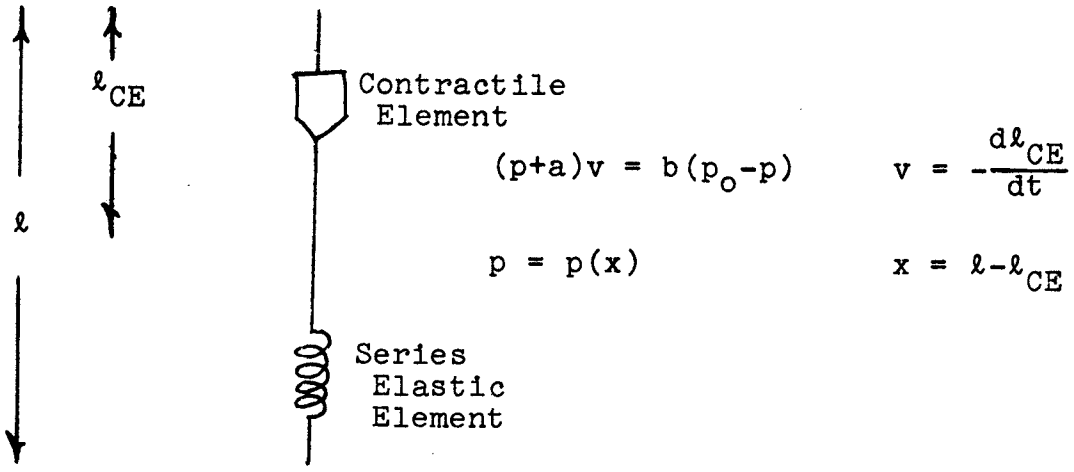


Also, if a muscle in isometric tetanus is suddenly released to a constant load $< P_o$, it shortens very rapidly to a new length before proceeding at a constant velocity appropriate to the load. This experiment suggests that there is an elastic component of the muscle which shortens instantaneously when the tension is released.



Sudden Release: Isometric Contraction → Constant Load

To summarize these data, Hill proposed the following model. Muscle consists of a contractile element characterized by a force-velocity curve in series with an elastic element characterized by a force-extension curve (which can be measured from experiments like the one described above).



The connection of the two elements in series implies that the lengths add and the forces are equal.

From the equations for the two elements one can derive a 1st order equation for p which makes no explicit reference to ℓ_{CE}. This should be useful, since ℓ_{CE} is not observable, while p and ℓ are.

$$\frac{dp}{dt} = \frac{dp}{dx}\frac{dx}{dt} = \frac{dp}{dx}\left\{\frac{d\ell}{dt} + v\right\} = \frac{dp}{dx}\left\{\frac{d\ell}{dt} + b\,\frac{p_o-p}{p+a}\right\}$$

Now since $p = p(x)$ we can write $\frac{dp}{dx}$ as a function of p, say $\frac{dp}{dx} = s(p)$. Then

$$\frac{dp}{dt} = S(p)\left\{\frac{d\ell}{dt} + b\,\frac{p_o-p}{p+a}\right\}$$

The rise of tension during an isometric can be found from this equation as follows. During the isometric $\frac{d\ell}{dt} = 0$. Therefore

$$\int_0^p \frac{dp'}{s(p')\frac{p_o-p'}{p'+a}} = bt$$

Likewise the behavior of the behavior of the muscle during quick release can be recovered as follows. Suppose that p goes monotonically from $p \to p + \Delta p$ during a time interval ε. Then

$$p(T+\varepsilon) - p(T) = s(p^*)[\ell(T+\varepsilon)-\ell(T)] + b\int_T^{T+\varepsilon} \frac{p_o-p}{p+a}\,dt$$

where p^* lies between p and $p + \Delta p$.

Taking the limit as $\varepsilon \to 0$

$$\Delta p = s(p^*)\Delta\ell \quad .$$

This shows that an instantaneous change in load is indeed accompanied by an instantaneous change in length, and it also indicates how the series elasticity can be measured.

Problem

Assume that $s(p) = \frac{1}{L_o}(p+a)$ where L_o is a constant with dimensions of length. Then,

(1) Derive the force-extension curve $p(x)$ for the series elastic element.

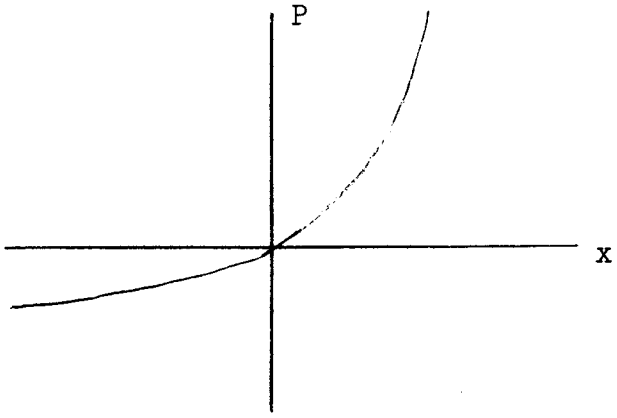
(2) Solve for the tension $p(t)$ if an arbitrary length change $\ell(t)$ is imposed. In particular:

(3) Find $p(t)$ if $\ell(t) = \ell(0)$ isometric.

(4) Find $p(t)$ if $\ell(t) = \ell(0) - vt$ where v = constant > 0. Show that the force-velocity relation is recovered as $t \to \infty$.

Solution:

(1) $$\frac{dP}{dx} = s(p) = \frac{P+a}{L_o} \rightarrow \int_0^P \frac{dP'}{P'+a} = \int_0^x \frac{dx'}{L_o}$$



$$\frac{P+a}{a} = e^{x/L_o}$$

$$P = a(e^{x/L_o} - 1)$$

(2) Equation for P

$$\frac{dP}{dt} = \frac{P+a}{L_o}\left[\frac{d\ell}{dt} + b\,\frac{P_o-P}{P+a}\right]$$

or

$$\frac{dP}{dt} + \frac{1}{L_o}(b - \frac{d\ell}{dt})P = + \frac{1}{L_o}(bP_o + a\,\frac{d\ell}{dt})$$

Note: linear equation with non-constant coefficients.

Multiply through by $e^{(1/L_o)[bt-\ell(t)]}$ and integrate from $0 \rightarrow t$.

Assume $P(0) = 0$. Then

$$P(t) = \frac{1}{L_o}\int_0^t (bP_o + a\,\frac{d\ell}{dt'})e^{-(1/L_o)[b(t-t')-(\ell(t)-\ell(t'))]}\,dt'$$

(3) <u>Isometric</u>: $\ell(t) = \ell(t') = \ell(0)$

$$P(t) = \frac{1}{L_o}\int_0^t bP_o e^{-(1/L_o)b(t-t')}\,dt' = P_o(1 - e^{-(b/L_o)t})$$

(4) Constant velocity:

Let $$\frac{d\ell}{dt} = -v = \text{constant} .$$

Then

$$P(t) = \frac{1}{L_o} \int_0^t (bP_o - av) e^{-(1/L_o)(b+v)(t-t')} dt'$$

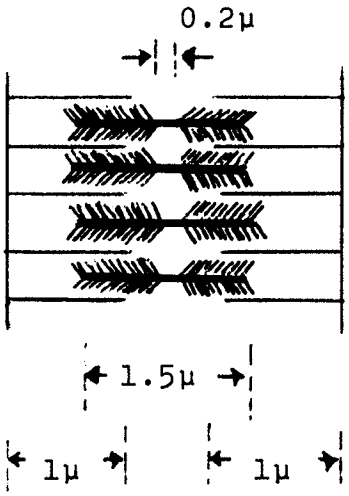
$$= \frac{bP_o - av}{b+v} \left| 1 - e^{-\frac{b+v}{L_o} t} \right|$$

let

$$P = \lim_{t \to \infty} P(t) = \frac{bP_o - av}{b+v} \rightarrow (P+a)v = b(P_o - P)$$

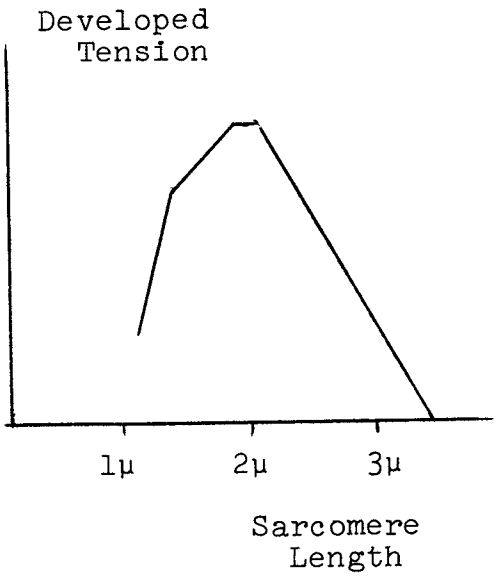
The Anatomy of Contraction

A repeating unit of muscle structure is the "sarcomere", the anatomy of which has been revealed by the electron microscope. A schematic representation is given here ($1\mu = 10^{-6}$ meters).



The structures shown have the obvious names thick filaments, thin filaments, and cross-bridges. The curve of developed tension vs. sarcomere length* has straight line segments with corners at the following anatomical landmarks:

* Gordon, Huxley, Julian, J. Physiol. 171 28P (1964).



3.5μ	No overlap of thick and thin filaments
2.2μ	All cross-bridges engaged
2.0μ	Thin filaments meet in center
1.5μ	Thick filaments hit end of sarcomere

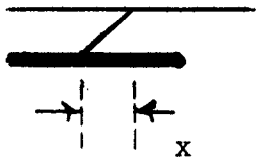
Remark: The curve of developed tension vs. muscle length if measured grossly is a smooth curve. This is because, although the length of a muscle is the sum of its sarcomere lengths, the sarcomere lengths are not uniform along the length of the muscle. Thus during a macroscopic isometric, some sarcomeres shorten and others are stretched. In the experiment of Gordon, Huxley, and Julian a small segment of muscle was held at constant length using a microscope and a feedback control mechanism. In this way the piecewise linear character of the curve was revealed.

In the interpretation of the developed tension curve given above it was tacitly assumed that the lengths of the thick and thin filaments remain constant, and that the filaments simply slide past each other during the contraction. This is known as the "sliding filament hypothesis" and it stands in sharp contrast with the older idea that contraction of the muscle resulted from the coiling of proteins. Direct evidence that the filaments do not shorten during contraction has been summarized by Aidley (cited above). Briefly it consists of

direct electron microscope measurement of filament length in contracting and in relaxed muscle, and x-ray diffraction studies which show that the periodic spatial structures of the thick and thin filaments do not change their spacing during contraction.

Cross-Bridge Dynamics

Suppose, as the anatomy suggests, that force is generated in the muscle at the cross-bridges which join the thick and thin filaments. Then one has to imagine that these bridges are continually breaking and re-forming to allow shortening to occur. It was proposed by A.F. Huxley* that the kinetics of this process might explain the mechanical behavior of muscle, e.g., the force-velocity curve of A.V. Hill. Huxley hypothesized that an attached cross-bridge could be characterized by the longitudinal distance x between the points of the thick and thin filaments joined by the cross bridges in question. The force transmitted by the cross-bridge is some function of x, so that the cross-bridge (once formed) acts like a (possibly non-linear) spring. As the muscle shortens the distance x obeys $\frac{dx}{dt} = \frac{dL}{dt}$ where L is the length of a half-sarcomere.



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* A.F. Huxley "Muscle Structures and Theories of Contraction", Progress in Biophysics 7 255 (1957).

A.F Huxley and R.M. Simmons "Mechanical Transients and the Origin of Muscle Force" in Cold Spring Harbor Synposium on Quantitative Biology 1973, pp.669-680. (See also articles by Podolsky and Nolan, and by Julian, Solins and Solins in this symposium.)

At any instant x is different for different cross-bridges so that we have a population of cross-bridges to describe. We shall assume here that there are essentially a continuum of sites for attachment on the thin filament and hence that x has no meaning for an un-attached cross-bridge. Define N and n(x) as follows:

N = fraction of cross-bridges which are attached

$\int_a^b n(x)dx$ = fraction of cross-bridges which are attached and which have x in the rage (a,b)

Therefore

$$N = \int_{-\infty}^{\infty} n(x)dx < 1$$

Define f, F, g as follows:

Given a cross-bridge which is not attached, let F be the probability per unit time (rate constant) for the formation of an attachment and let $\int_a^b f(x)dx$ = rate constant for formation of an attached cross-bridge with x in the range (a,b). Then $F = \int_{-\infty}^{\infty} f(x)dx$. In particular if we want to assume that attachment always occurs at x = A, we write $f(x) = F\delta(x-A)$.

Given a cross-bridge which is attached with length x, let g(x) be the rate constant for breakage of the cross-bridge.

These definitions lead to the following equation for n(x,t)

$$\frac{\partial n}{\partial t} + v \frac{\partial n}{\partial x} = f(x)(1-N) - g(x)n$$

where

$$N = \int_{-\infty}^{\infty} n(x,t)dx$$

$$v = \frac{dL}{dt}$$

$$L(t) = \text{length of half-sarcomere}$$

The force P(t) is then given by

$$P(t) = \int_{-\infty}^{\infty} n(x,t)p(x)dx$$

where p(x) is the aggregate force extension curve of all the cross-bridges in a half-sarcomere.

Remark: In Huxley's original model the sites of possible attachment on the thin filament were regarded as discrete and sufficiently far apart that x had meaning for an unattached cross-bridge, i.e., the distance to the nearest site of attachment. In that case one gets a similar but different theory with n(x) = fraction of cross-bridges with length x which are attached, so that n is dimensionless and takes on the values $0 \leq n \leq 1$. The equation for n is then

$$\frac{\partial n}{\partial t} + v \frac{\partial n}{\partial x} = f(x)(1-n) - g(x)n \quad .$$

Note that $N = \int ndx$ no longer appears and that f has a slightly different meaning here. (See also pp. 183-186.)

Solution of the Cross-Bridge Population Equation

This solution was motivated by the observation of Frank Hoppensteadt that if $v = 1$ and $f = F\delta(x)$ then we have precisely the type of equation used to describe a population of individuals with x = age and t = time. All individuals are born at age zero, but the birth rate is some integral functional over the whole population. Here, however, we have the slightly more general case in which v is a given function of time, controlled by what we do at the ends of the muscle. We have for $n(x,t)$ the equation

$$\frac{\partial n}{\partial t} + v(t)\frac{\partial n}{\partial x} = f(x)\left(1 - \int_{-\infty}^{\infty} n(x,t)dx\right) - g(x)n$$

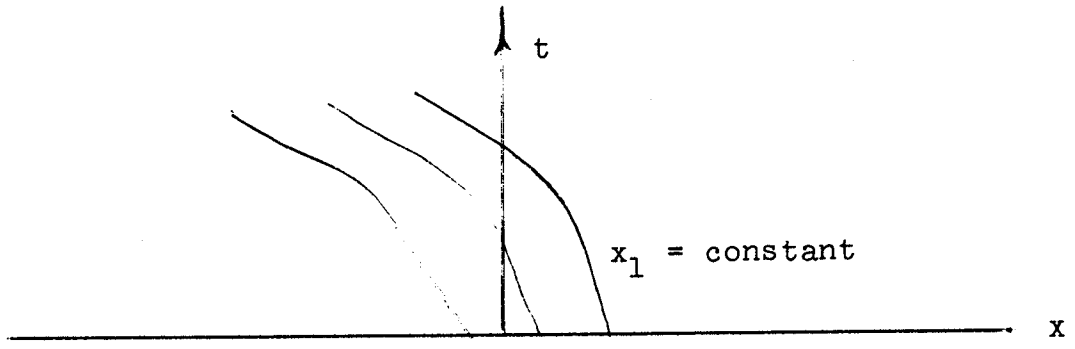
where

$$v(t) = \frac{d}{dt} L(t) \quad , \quad L(t) \text{ given} \quad .$$

Let

$$N(t) = \int_{-\infty}^{\infty} n(x,t)dx \quad .$$

Temporarily regard $N(t)$ as a known function of time. Later we shall find an integral equation for $N(t)$. Define a new variable $x_1 = x - L(t)$, $x = x_1 + L(t)$ so that the lines x_1 = constant follow a given attached cross-bridge in the (x,t) plane



Now define

$$n_1(x_1,t) = n(x_1 + L(t),t)$$

so that

$$\frac{\partial n_1}{\partial t} = v\,\frac{\partial n}{\partial x} + \frac{\partial n}{\partial t} \quad .$$

Therefore

$$\frac{\partial n_1}{\partial t} = f(x_1 + L(t))(1 - N(t)) - g(x_1 + L(t))n_1 \quad .$$

In this equation x_1 appears as a parameter only. That is, if $N(t)$ is known (which is our temporary point of view) then the different values of x_1 are uncoupled. One can verify by differentiating with respect to t that a solution of this equation is

$$n_1(x_1,t) = \int_0^t [1-N(t')]f(x_1+L(t'))e^{-\int_{t'}^{t} g(x_1+L(t''))dt''}\,dt'$$

This is the solution which satisfies $n_1(x_1,0) = 0$.

Next, we find an expression for $n(x,t)$ using $n(x,t) = n_1(x-L(t),t)$, so that

$$n(x,t) = \int_0^t [1-N(t')]f(x-L(t)+L(t'))e^{-\int_{t'}^{t} g(x-L(t)+L(t''))dt''}\,dt'$$

Now introduce the functions

$$h(x,t,t') = f(x - L(t) + L(t'))e^{-\int_{t'}^{t} g(x-L(t)+L(t''))dt''}$$

$$H(t,t') = \int_{-\infty}^{\infty} dx\ h(x,t,t')$$

$$H_o(t) = \int_0^t dt' H(t,t')$$

Then

$$n(x,t) = \int_0^t [1-N(t')]h(x,t,t')dt'$$

$$N(t) = \int_{-\infty}^{\infty} dx\ n(x,t) = \int_0^t [1-N(t')]H(t,t')dt'$$

or

$$N(t) + \int_0^t dt' N(t')H(t,t') = H_o(t) \ .$$

This integral equation for N(t) could be solved by various numerical methods to complete the solution.

With n(x,t) known, we can evaluate the force that will be felt at the ends of the muscle as follows

$$P(t) = \int_{-\infty}^{\infty} dx\ p(x)n(x,t)$$

$$= \int_0^t dt'[1-N(t')] \int_{-\infty}^{\infty} dx\ p(x)h(x,t,t')$$

where p(x) is the cross-bridge force extension curve.

Special Case

Suppose g = constant. Then

$$h(x,t,t') = f(x-L(t)+L(t'))e^{-g(t-t')}$$

$$H(t,t') = e^{-g(t-t')} \int_{-\infty}^{\infty} dx\ f(x-L(t)+L(t'))$$

Letting

$$\xi = x - L(t) + L(t') \rightarrow d\xi = dx$$

we get

$$H(t,t') = e^{-g(t-t')} \int_{-\infty}^{\infty} d\xi f(\xi)$$

independent of L(t). It follows that when g = constant N(t) is independent of L(t). In other words, when g = constant, the total number of attached cross-bridges obeys its own dynamics, independent of how the muscle is pulled.

We now seek an equation for P(t) in the special case g = constant. We have

$$P(t) = \int_0^t dt'(1-N(t'))e^{-g(t-t')} \int_{-\infty}^{\infty} dx\ p(x)f(x-L(t)+L(t'))\ .$$

As before, let $\xi = x - L(t) + L(t')$. Then

$$P(t) = \int_0^t dt'(1-N(t'))e^{-g(t-t')} \int_{-\infty}^{\infty} d\xi\ p(\xi+L(t)-L(t'))f(\xi)\ .$$

Differentiate with respect to t:

$$\frac{dP}{dt} = [1-N(t)] \int_{-\infty}^{\infty} d\xi\ p(\xi)f(\xi) - gP(t)$$

$$+ \frac{dL}{dt} \int_0^t dt'[1-N(t')e^{-g(t-t')} \int_{-\infty}^{\infty} d\xi \frac{\partial p}{\partial x}(\xi+L(t)-L(t'))f(\xi)$$

We now specialize further to the case where

$$p = p_o(e^{\alpha x}-1) \rightarrow \frac{\partial p}{\partial x} = \alpha(p+p_o) \ .$$

Then

$$\frac{dP}{dt} = [1-N(t)] \int_{-\infty}^{\infty} d\xi \ p(\xi)f(\xi)-gP(t)$$

$$+ \frac{dL}{dt} (\alpha P(t) + \alpha p_o \int_0^t dt'[1-N(t')]e^{-g(t-t')} \int_{-\infty}^{\infty} d\xi \ f(\xi)$$

Let

$$gP_o(t) = [1-N(t)] \int_{-\infty}^{\infty} p(\xi)f(\xi)d\xi$$

$$a(t) = p_o \int_0^t dt'[1-N(t')]e^{-g(t-t')}$$

Then

$$\frac{dP}{dt} = \alpha(P+a) \ \frac{dL}{dt} + g(P_0-P)$$

As defined above a and P_o are functions of time. However, as $t \rightarrow \infty$, $N \rightarrow N_\infty$ so that

$$P_o \rightarrow \frac{1-N_\infty}{g} \int_{-\infty}^{\infty} p(\xi)f(\xi)d\xi$$

$$a \rightarrow \frac{1-N_\infty}{g} p_o \int_{-\infty}^{\infty} f(\xi)d\xi$$

Now, let $b = \frac{g}{\alpha}$ and $s(P) = \alpha(P+a)$ and we get

$$\frac{dP}{dt} = s(P)\left\{\frac{dL}{dt} + \frac{b(P_o-P)}{P+a}\right\}$$

which is precisely the differential equation of the Hill two-component model. Here, however, the physical interpretation is different. For example, the rise in tension during an isometric following a quick release is due to redistribution of the cross-bridges, not to internal shortening. It can be shown (see problem below) that

$$N_\infty = \frac{F}{F+g} \rightarrow \frac{1-N_\infty}{g} = \frac{1}{F+g} \quad .$$

Therefore the asymptotic values of P_o, a, and b are given by

$$P_o = \frac{1}{F+g} \int_{-\infty}^{\infty} p(\xi) f(\xi) d\xi$$

$$a = \frac{1}{F+g} p_o \int_{-\infty}^{\infty} f(\xi) d\xi$$

$$b = \frac{g}{\alpha} \quad .$$

The maximum velocity of shortening is given by

$$v_{max} = \frac{bP_o}{a} = \frac{g}{\alpha} \frac{\int_{-\infty}^{\infty} p(\xi) f(\xi) d\xi}{p_o \int_{-\infty}^{\infty} f(\xi) d\xi} \quad .$$

As a further specialization, consider

$$f(x) = F\ \delta(x-A)$$

Then

$$P_o = \frac{F}{F+g}\, p(A)$$

$$a = \frac{F}{F+g}\, P_o$$

$$b = \frac{g}{\alpha}$$

$$v_{max} = \frac{g}{\alpha}\,\frac{p(A)}{P_o}$$

It is interesting that v_{max} is independent of F and that increasing g increases v_{max} while decreasing P_o. The latter observation suggests that some muscle should be specialized for speed while others should be specialized for high load.

Problem

Assume that **g** = constant and that all cross-bridges attach at x = A. That is f(x) = F δ(x-A).

(1) In the region x < A, solve for the steady distribution of cross-bridges n(x) that results from setting v = constant < 0, and $\frac{\partial n}{\partial t} = 0$.

(2) By integrating the differential equation over the interval (A-ε, A+ε) interpret the condition f(x) = F δ(x-A) as a boundary condition at x = A. Use this boundary condition to complete the solution found in (1).

(3) Does $N = \int_{-\infty}^{\infty} n(x)dx$ depend on v? Solve for N.

(4) Write down an expression for the force-velocity curve that corresponds to arbitrary p(x).

(5) OPTIONAL Regard g, A, F as known constant, and show that the force-velocity curve is essentially the Laplace transform of the cross-bridge force extension curve (!). (To get this result let s = 1/v be the transform variable.) Hence construct the cross-bridge force extension curve uniquely from Hill's result $-v = \frac{b(P_o-P)}{P+a}$. (Note that g = constant plays an essential role).

Solution:

Given g = constant, $f(x) = F\delta(x-A)$.

(1) If v = constant < 0 and $\frac{\partial n}{\partial t} = 0$, then for x < A we have

$$v \frac{\partial n}{\partial x} = -gn \rightarrow n = n(A)e^{\frac{g}{|v|}(x-A)}$$

(2) Consider the full equation

$$\frac{\partial n}{\partial t} + v(t) \frac{\partial n}{\partial x} = F\ \delta(x-A)(1-N) - g(x)n(x)$$

and integrate from (A-ε, A+ε)

$$v[n(A+\varepsilon) - n(A-\varepsilon)] = F(1-N) - \int_{A-\varepsilon}^{A+\varepsilon} [g(x)n(x) + \frac{\partial n}{\partial t}]dx$$

Taking the limit a ε → 0, if the integrand on the right is bounded we have

$$-vn(A) = F(1 - N)$$

$$n(A) = \frac{F(1 - N)}{|v|}$$

where we have used $n(x) = 0$ for $x > A$ and where $n(A) = \lim_{\varepsilon \to 0} n(A-\varepsilon)$

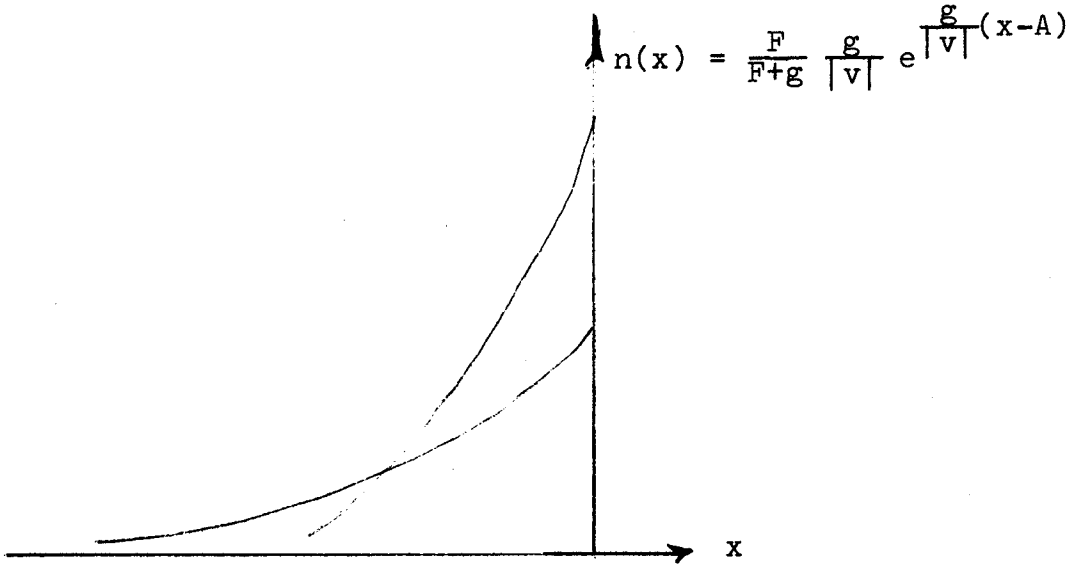
But

$$N = \int_{-\infty}^{A} n(x)dx = \int_{-\infty}^{A} n(A)e^{\frac{g}{|v|}(x-A)}\,dx$$

$$N = \frac{n(A)|v|}{g}$$

$$n(A) = \frac{gN}{|v|} = \frac{F(1-N)}{|v|} \rightarrow N = \frac{F}{F+g} \quad .$$

Putting these results together, the distribution $n(x)$ is



(3) If g = constant one can derive an ordinary differential for N as follows: Integrate each term of the equation

$$\frac{\partial n}{\partial t} + v(t)\,\frac{\partial n}{\partial x} = f(x)(1 - N) - gn$$

from $x = -\infty$ to $x = +\infty$ and note that

$$\int_{-\infty}^{\infty} \frac{\partial n}{\partial x}\,dx = n(\infty) - n(-\infty) = 0 \quad .$$

Then

$$\frac{dN}{dt} = F(1 - N) - gN$$

Thus N obeys its own dynamics, independent of v <u>provided that g = constant</u>. In the steady state $N = \frac{F}{F+g}$ as found above.

(4) The force velocity curve for arbitrary p(x)

$$P = \frac{F}{F+g}\,\frac{g}{|v|}\int_{-\infty}^{A} e^{\frac{g}{|v|}(x-A)}\,p(x)dx \quad .$$

(5) Force-velocity curve as a Laplace transform. Let $s = \frac{1}{|v|}$ $y = g(A-x)$ and define the function $p_1(y)$ such that

$$p_1(y)\Big|_{y=g(A-x)} = p(x) \quad .$$

Then

$$P = Ns\int_{0}^{\infty} e^{-sy}p_1(y)dy$$

where

$$N = \frac{F}{F+g}$$

From A.V. Hill's experiments we have (for $v < 0$)

$$|v| = \frac{b(P_o - P)}{P+a}$$

or

$$P = \frac{bP_o - a|v|}{b+|v|} = \frac{bP_o s - a}{bs+1} \quad .$$

Then

$$\int_0^\infty e^{-sy} Np_1(y)dy = \frac{1}{s} \frac{bP_o s - a}{bs+1}$$

$$Np_1(y) = \frac{1}{2\pi i} \int_{c-i\infty}^{c+i\infty} e^{sy} \frac{1}{s} \frac{bP_o s - a}{bs+1} ds$$

$$= -a + e^{-\frac{y}{b}}(P_o + a)$$

$$\therefore \quad Np(x) = -a + e^{g(x-A)/b}(P_o + a)$$

Now impose the requirement that $p(0) = 0$. Then

$$Np(x) = a\left[e^{\frac{gx}{b}} - 1 \right] \quad .$$

We conclude that <u>if</u> g = constant and $f(x) = F\delta(x-A)$ then measurement of the steady force-velocity curve uniquely determines the form of the cross-bridge force-extension curve as given above. (Actually we have a one-parameter family of curves depending on the unknown constant g).

<u>Question</u>: Can one obtain results like this when $g(x)$ is not constant?

Comment on the Cross-Bridge Equation introduced above:

In the foregoing we have used the cross-bridge equation:

$$\frac{\partial n}{\partial t} + v(t)\,\frac{\partial n}{\partial x} = f(x)\left(1 - \int_{-\infty}^{\infty} n(x)dx\right) - g(x)n$$

This form is due to H.M. Lacker (unpublished). The equation introduced by A.F. Huxley (1957, cited above) was

$$\frac{\partial \hat{n}}{\partial t} + v(t)\,\frac{\partial \hat{n}}{\partial x} = \hat{f}(x)(1-\hat{n}) - g(x)\hat{n}$$

(The ^ is my own notation to distinguish the quantities with different dimensions in the two equations). Lacker's form differs from Huxley's in two ways:

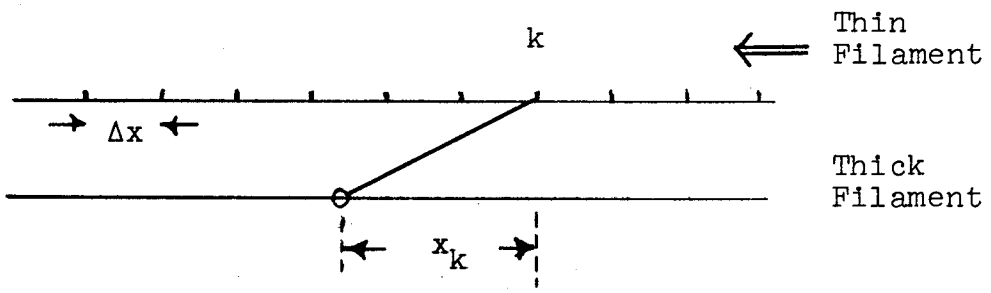
(i) The attachment terms are respectively $\left(1 - \int_{-\infty}^{\infty} ndx\right)$ and $(1 - \hat{n})$.

(ii) The dimensions of some of the quantities are different:

n	length^{-1}
$\hat{n}$	dimensionless
f	$\text{length}^{-1}\ \text{time}^{-1}$
$\hat{f}$	time^{-1}

The following considerations show that the two equations are opposite limiting cases of the same basic process:

We regard the sites on the thin filament as discrete and separated by a distance Δx



The following considerations refer to a single cross-bridge.

Let

$\hat{n}_k(t)$ = chance that the cross-bridge is attached to site k at time t. $0 \leq \hat{n}_k \leq 1$

$\sum_k \hat{n}_k(t)$ = chance that the cross-bridge is attached at all. (Note: exclusive events. One cross-bridge cannot be attached to two values of k simultaneously).

Then

$$\frac{d\hat{n}_k(t)}{dt} = \hat{f}(x_k)(1 - \sum_{\ell} \hat{n}_\ell(t)) - g(x_k)n_k(t)$$

where $\hat{f}$, g are rate constants (Dimensions time^{-1}).

Now assume that the $\hat{n}_k(t)$ are samples of a smooth function $\hat{n}(\xi,t)$; that is

$$\hat{n}_k(t) = \hat{n}(x_k(t),t) \quad .$$

Then

$$\frac{d\hat{n}_k}{dt} = v\,\frac{\partial\hat{n}}{\partial x} + \frac{\partial\hat{n}}{\partial t}$$

and we have

$$v\,\frac{\partial\hat{n}}{\partial x} + \frac{\partial\hat{n}}{t} = \hat{f}(x)(1 - \sum_{p=-\infty}^{\infty} \hat{n}(x+p\Delta x,t)) - g\hat{n}$$

We are now in a position to consider two extreme cases.

(1) Suppose $\hat{n}(x,t) = 0$ when $|x| > h$ and suppose that $\Delta x > 2h$. Then for $|x| < h$, $\hat{n}(x + p\Delta x,t) = 0$ unless $p = 0$. Therefore

$$v \frac{\partial \hat{n}}{\partial x} + \frac{\partial \hat{n}}{\partial t} = \hat{f}(x)(1 - \hat{n}(x)) - g\hat{n}$$

which is Huxley's equation.

(2) On the contrary, suppose that Δx is very small. Then let

$$\hat{n} = n\ \Delta x$$

$$\hat{f} = f\ \Delta x$$

and we get

$$v \frac{\partial n}{\partial x} + \frac{\partial n}{\partial t} = f(x)(1 - \sum_{p} n(x+p\Delta x)\ x) - g(x)n \quad .$$

This equation is exact. Now if we take the limit as $\Delta x \to 0$ we get

$$v \frac{\partial n}{\partial x} + \frac{\partial n}{\partial t} = f(x)(1 - \int_{-\infty}^{\infty} n(x',t)dx') - g(x)n(x)$$

which is Lacker's equation. Note that if we assume that n,f have finite limits as $\Delta x \to 0$ then we are required to assume that $\hat{n},\hat{f} \to 0$ as $\Delta x \to 0$. This is appropriate, since in the limit where thin filament sites are very dense they must be regarded as competing for the cross-bridge and the chance that any <u>particular</u> site is occupied must tend to zero.

In summary, Huxley's formulation is appropriate if one assumes that the thin filament sites are so sparse that at most <u>one</u> is within range of any given cross-bridge at any given time. Lacker's formulation is appropriate in the

opposite extreme when the sites on the thin filament are so close that the thin filament is essentially a continuum. If each globule of action has a site for cross-bridge attachment then Lacker's formulation in which attachment depends on $1 - \int_{-\infty}^{\infty} ndx$ would seem to have considerable merit.

Heart Muscle

Classical approach based on A.V. Hill's model:*

The references given here summarize the attempts to characterize heart muscle in terms of a "contractile element" and various elastic elements. Such an effort is more difficult in heart than in skeletal muscle because of the following complications in heart muscle:

(1) length-dependence of developed tension in the physiological range of lengths

(2) non-zero passive tension in the physiological range

(3) time dependence of the "active state"

(4) inability to study individual sarcomeres as in the work of Gordon, Julian, Huxley (cited above).

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* Blinks & Jewell, "The Meaning and Measurement of Myocardial Contractility" in Bergel, Cardiovascular Fluid Dynamics Academic Press 1972 v. 1.

* Braunwald, Ross, and Sonnenblick, Mechanisms of Contraction of the Normal and Failing Heart, Little Brown.

(5) dependence of the active state on the mechanical history of the contraction.

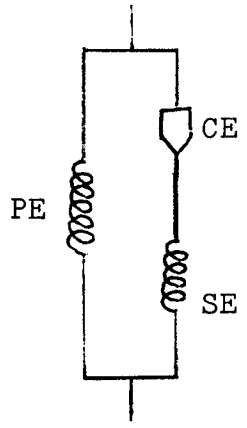
Several of the foregoing "complications" are important in the function of heart muscle. Therefore it is not desireable to leave them out of a mathematical model. For example:

(1) In the physiological range increased length of heart muscle leads to increased developed tenison. This means that each side of the heart adapts to whatever load of blood is presented to it: when the heart is fuller it pumps harder. Since the two sides are connected in series the result is a feedback system maintaining the equality of output between the two sides of the heart. Such an equilibrium would be unstable if increased length (due to increased filling) led to reduced force of contraction.

(2) The significant passive tension in resting heart muscle prevents the heart from being filled to the point where increased length results in a fall in developed tension. As remarked above this situation would be unstable.

(3) The contractions of heart muscle occur as isolated events. A tetanus which is so useful in the study of skeletal muscle has no place in the function of a pump which must alternately relax and contract to be effective.

A model which accounts for many of the complications listed above but which still falls within the framework of A.V. Hill's ideas is discussed at length in Braunwald, Ross,

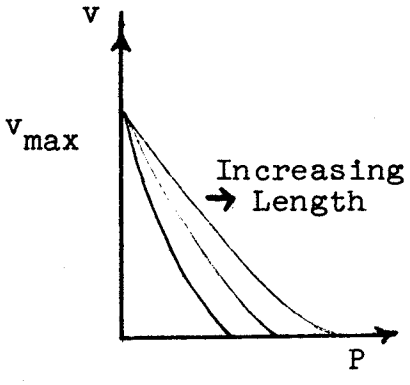


PE = Parallel Elastic Element

SE = Series Elastic Element

CE = Contractile Element

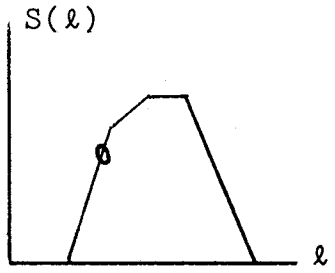
and Sonnenblick (cited above). Briefly a parallel elastic element with some given force-extension curve accounts completely for the resting tension in the muscle. The length dependence of the developed tension is included in the properties of the contractile element in the following way: The contractile element is assumed to have a different force-velocity curve at each length. Experimentally these curves seem to intersect at P = 0 in a velocity v_{max} which is independent of length though there is some controversy about this. Theoretical justification for this idea comes from the hypothesis of A.F. Huxley that the muscle force is the sum over the forces of all the cross-bridges in a half-sarcomere and that muscle length determines the number of cross-bridges which can be active. The velocity v_{max} is then the sliding velocity in which the positive and negative cross-bridge forces just balance. It is therefore independent of the number of cross-bridges participating.



One can make the foregoing ideas quantitative by assuming that the Hill force velocity curve applies in a certain sense to each cross-bridge participating in the cross-bridge cycle and that the total force is the force per cross-bridge times the number of cross-bridges participating. The latter quantity is a function of muscle length. Thus

$$v = \frac{b(p_o - p)}{p + a_o}$$

$$P = S(\ell)p$$



where $S(\ell)$ is proportional to the number of cross-bridges participating at each sarcomere length ℓ. This gives a family of curves of P vs. v, one for each ℓ, which are scale multiples of each other along the P axis. This is roughly what is found experimentally, and it certainly has the consequence that

$$v_{max} = \frac{bp_o}{a_o} \quad , \quad \text{independent of } \ell \ .$$

The "series elasticity" in heart muscle is partly internal and partly external to the sarcomeres. The internal part resides in the cross-bridges themselves and has a stiffness proportional to the number of attached cross-bridges*; it does not therefore have a fixed force-extension curve as has been tacitly assumed by many workers in the field. The external part presumably has

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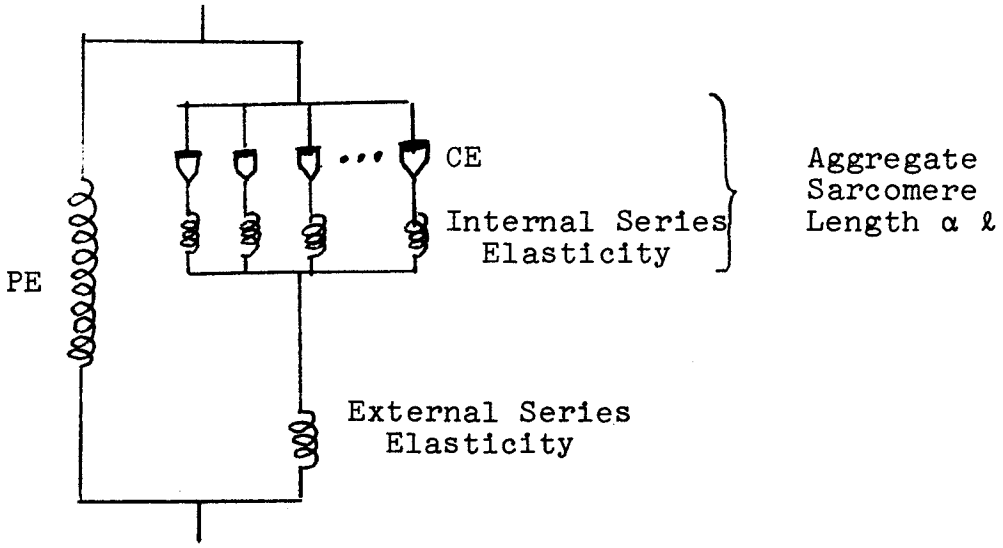
* A.F. Huxley and R.M. Simmons, ref. cited above).

a fixed force-extension curve depending on the properties of the tissue surrounding the sarcomeres and on the attachments of the muscle to the apparatus. THE EXISTENCE OF SERIES ELASTICITY WITHIN THE SARCOMERE MEANS THAT SARCOMERE LENGTH IS NOT PROPORTIONAL TO CONTACTILE ELEMENT LENGTH. An appropriate way to clarify this point might be to draw the following model:

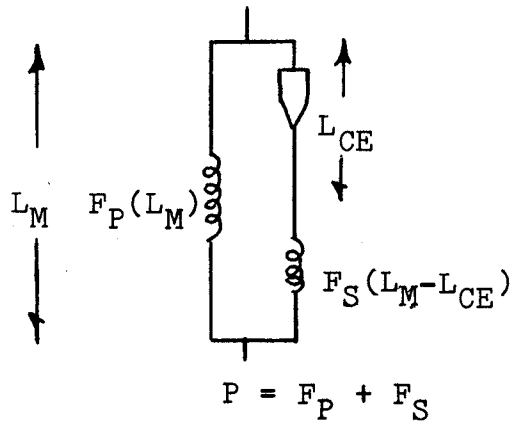


Active State in the Context of A.V. Hill's Model.

If the foregoing picture of cardiac muscle is accepted, then the process of turning on and turning off the muscle has to be described in terms of time dependence of the constants of the Hill hyperbola. In this way the force-velocity relation becomes a function of time since stimulation of the muscle. The Hill hyperbola is $v = \frac{b(P_o - P)}{P+a}$. In the steady state a, b, P_o are constants, but such a steady state only occurs in skeletal muscle tetanus. In cardiac muscle we are interested in the time dependence of one of more of these parameters. Some experiments to measure this time dependence will now be described:

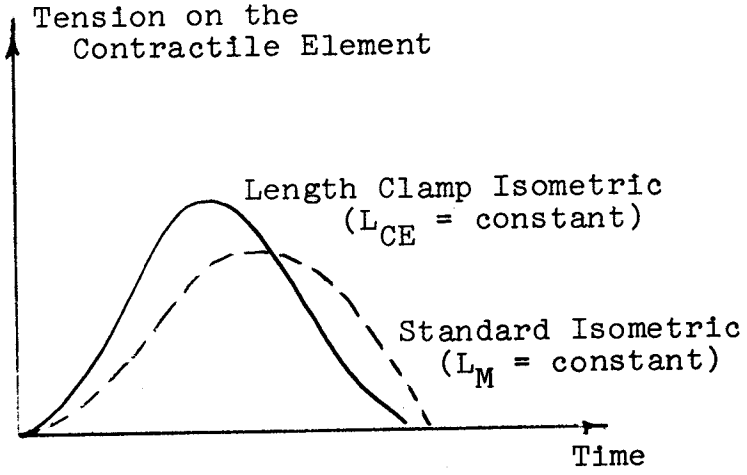
(1) Brady's length clamp*

This technique is based on our analysis of the three-component model which proceeds as follows. Suppose that the functions F_P and F_S which characterize the parallel and series elastic elements are known. Then the equation $P = F_P(L_M)+F_S(L_M-L_{CE})$ can be solved at each instant for L_{CE} if P(t), $L_M(t)$ are known. It is then possible to arrange a feedback system which adjusts P(t) to keep L_{CE}, the length of the contractile element constant.



* Brady, "Active State in Cardiac Muscle", Physiological Rev. 48, 570-600.

When this is done the force on the contractile element is the force which corresponds to zero velocity, namely $P_o(t)$. Thus Brady achieved an indirect measure of $P_o(t) = P(t) - F_P(L_M)$, by adjusting P to hold L_{CE} constant. The results are roughly as follows.



Three criticisms of this approach are:

(i) As discussed above the series elastic element does not follow a fixed force-extension curve, since the stiffness depends on the instantaneous number of attached cross-bridges.

(ii) As discussed above, holding contractile element length constant is not the same as holding sarcomere length constant. In fact, in Brady's length clamp the sarcomeres must be lengthening[1] if the internal series elasticity is significant. This means that the length of the

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[1] i.e. during the time when contractile element tension is rising.

overlap region or the number of cross-bridges participating in the contraction is changing during the experiment. Thus different parts of the curves $P_o(t)$ refer to different sarcomere lengths.

(iii) The experiment leaves open the question of whether a, b, the two remaining parameters of the force-velocity curve also change with time.

Remark: It would probably be more useful to use Brady's apparatus to hold sarcomere length constant rather than contractile element length. This could be done if a clear separation could be achieved between the internal and external series elasticity. Such a separation is possible in principle, since the internal series elasticity depends on the number of attached cross-bridges while the external does not.

(2) Isotonic release experiment*

This is an effort to construct instantaneous force velocity curves. The muscle length is held constant until a time t determined by the experimenter. At this moment the muscle is allowed to lift a load P_{load} which is less than the isometric tension at time t. The experimental records are roughly as follows:

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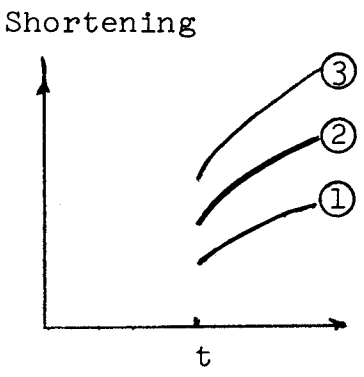
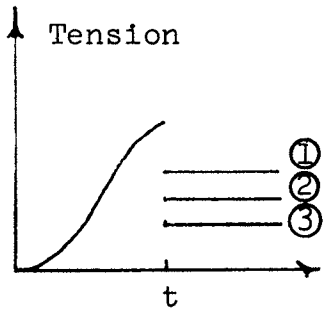
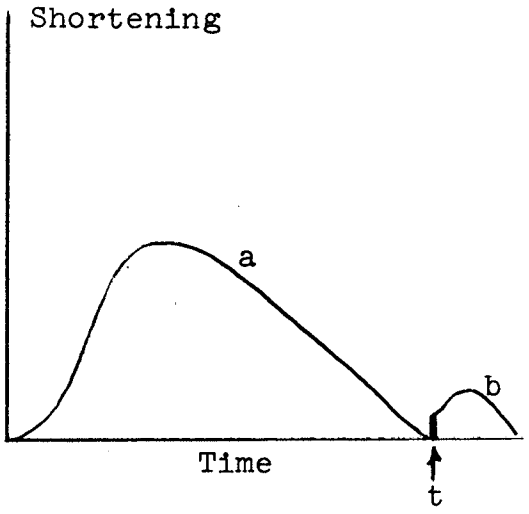
* Jewell and Wilkie, "Mechanical Properties of Relaxing Muscle", J. Physiol., London 143, 515-540.





At the moment of release, the muscle suddenly shortens. This is interpreted as the shortening of the series elastic element to a length consistent with the new load. Following this jump the muscle begins to move at a new velocity. This is interpreted as the velocity of the contractile element at the new load at time t. (Although the length of the contractile element is constant during the jump, the same cannot be said for the sarcomeres, for the reason given above. Therefore the force-velocity curve constructed in this manner is not at constant length.)

Timed isotonic release experiments have also been used to show that the muscle cannot be described by a force-velocity curve whose parameters follow a fixed time-course independent of the length history of the muscle. In particular, Jewell and Wilkie have shown that when a muscle shortens against light loads the duration of the active state is reduced.

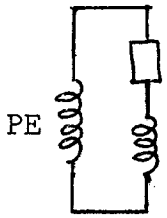


In curve a the muscle was allowed to shorten immediately against a light load, while in b the muscle was held isometric until time t, which is a time at which the muscle in a has already relaxed enough to return its weight to the table. At time t the muscles in a,b have the same length (the initial length), and the force on b is greater than the force on a; nevertheless, b contracts while a does not.

Active State in the Context of Cross-Bridge Dynamics

This section is based on the thesis research of T. Feit*. Feit has succeeded in avoiding many of the difficulties of the classical approach by basing his model on cross-bridge dynamics as introduced by A.F. Huxley rather than on the older ideas of A.V. Hill. In particular, Feit also uses a three component model to describe the macroscopic features of

* Feit, Active State in the Mechanics of Cardiac Muscle, Albert Einstein College of Medicine, (Dept. of Physiology) 1974.



of the muscle, but his active element is not the contractile element of Hill, but rather a lumped representation of the muscle sarcomeres. (Thus the elasticity of the cross-bridges are included within the lumped sarcomere, not in the series elasticity). The relation between force and length for the lumped sarcomere is derived from a modification of Huxley's cross-bridge equation introduced by Feit to take account of the peculiar and interesting features of heart muscle. Feit's basic equations for the sarcomere can be written:

$$\frac{\partial n}{\partial t} + v\,\frac{\partial n}{\partial x} = h(t)f_o(x)(n_o(\ell_s)-n) - g(x)n$$

$$P = K\int_{-\infty}^{\infty} xn(x)dx$$

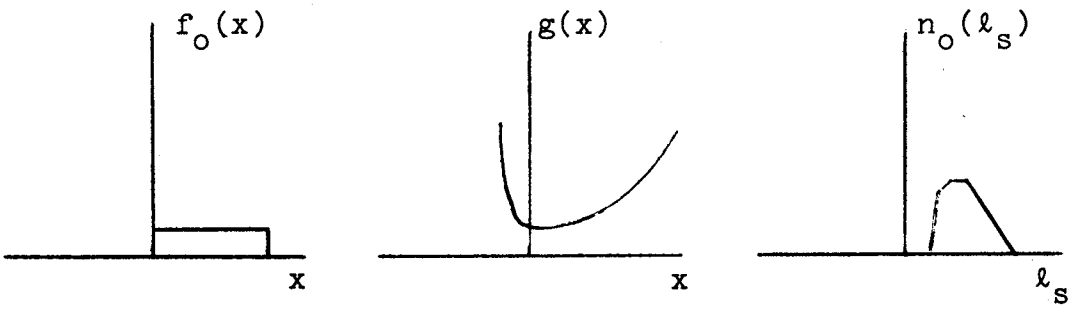
where ℓ_s = length of $\frac{1}{2}$ sarcomere

$$v = \frac{d\ell_s}{dt}$$

P = lumped sarcomere force

$h(t)$ = active state intensity $0 \leq h(t) \leq 1$ (see below)

and where $f_o(x)$ $g(x)$ and $n_o(\ell_s)$ have the form shown:



The features of special importance in cardiac muscle are the functions $n_o(\ell_s)$, which is proportional to the number of cross-bridges which can participate in the cross-bridge cycle at half-sarcomere length ℓ_s, and h(t), which has the interpretation of being the fraction of the thin filament which is switched on by Ca^{++} ion at time t since stimulation.

The main result of Feit's thesis was a method for computing h(t) from experimental data (without subjecting the muscle to violent experimental interventions such as quick stretches or quick releases). The essence of this method is as follows. First, from the experimental records of length and force, it is possible to use the three component model (p.196) to derive the appropriate functions of time for sarcomere length and force. One then seeks to determine a function h(t) which is consistent with this length-force history for the sarcomere. This is done at each time step as part of a numerical procedure for computing the cross-bridge distribution n(x,t) for the experiment. Note that

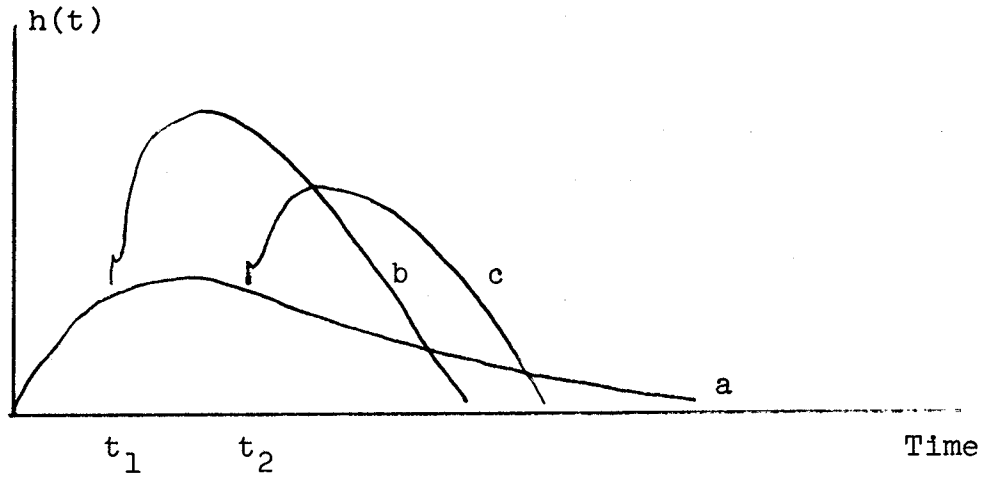
$$\frac{dP}{dt} = K\int_{-\infty}^{\infty} x\frac{\partial n}{\partial t}\,dx = K\int_{-\infty}^{\infty} [-v\frac{\partial n}{\partial x} + h(t)f_o(x)[n_o(\ell_s)-n]-g(x)n]x\,dx \quad .$$

Thus with $\frac{dP}{dt}$ determined from the experiment, and n(x,t) known up to time t one can solve for h(t) as follows

$$h(t) = \frac{\frac{dP}{dt} + K \int_{-\infty}^{\infty} [v\frac{\partial n}{\partial x} + g(x)n]x \, dx}{K \int_{-\infty}^{\infty} f_o(x)[n_o(\ell_s)-n]dx}$$

with h(t) known, one can go ahead one time step in the computation of n. For numerical details, see Feit's thesis (cited above).

The function h(t), which is essentially the rate constant for cross-bridge attachment is a new definition of active state in cardiac muscle. An interesting result, with respect to the observation of Jewell and Wilkie that mechanical history of a contraction influences active state kinetics during that contraction is Feit's observation that when the muscle begins to shorten h(t) increases suddenly and then decreases more rapidly than in an isometric.



a = isometric contraction*

b = isotonic with shortening beginning at time t_1

c = isotonic with shortening beginning at time t_2

Such results have led Feit to the hypothesis that a region of the thin filament which has just lost a cross-bridge is more susceptible to cross-bridge attachment. Since the rate of turnover of cross-bridges increases during sliding in Feit's model, this hypothesis would explain why h(t) appears to rise when sliding begins. This hypothesis is consistent with chemical evidence that a "potentiated" state for the thin filament exists and is produced by cross-bridges themselves.**

Intracellular Calcium Kinetics in Heart Muscle

References

(1) J.B. Blinks & J. Koch-Weser

Analysis of the Effects of Changes in Rate and Rhythm upon Myocaridal Contractility. J Pharmacology and Exptl. Therapeutics 134 373-389 (1961).

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* This is isometric for the muscle, but some (low velocity) sarcomere shortening does occur. Nevertheless, isometrics at different muscle lengths have nearly identical active state curves.

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Inotropic Effects of Electric Currents
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II. Hypotheses: Calcium Movements, Excitation-Contraction Coupling and Inotropic Effects. Circulation Research 24 409-445 (1969).

(4) A. Manring, P.B. Hollander
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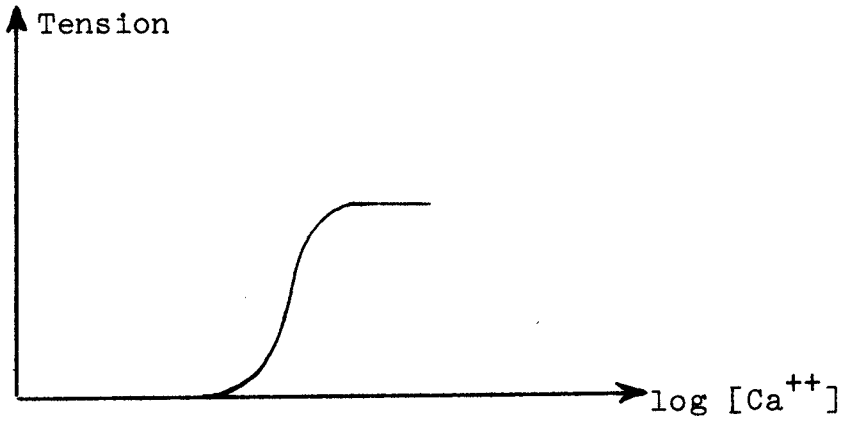
(8) Langer

Excitation - Contraction Coupling

Annual Reviews of Physiology 35 55-86 (1973).

Summary of the evidence:

(1) With cell membrane removed or damaged, steady muscle tension is extremely sensitive to Ca^{++} in the bathing solution



(2) Skeletal muscle will continue to contract (if stimulated) for several hours in the absence of external Ca^{++}. But its ability to relax suggests that Ca^{++} can be removed from the region of the sliding filaments and stored somewhere else in the cell. Membrane-bound vescicles capable of sequestering Ca^{++} have been isolated, the "sarcoplasmic reticulum".

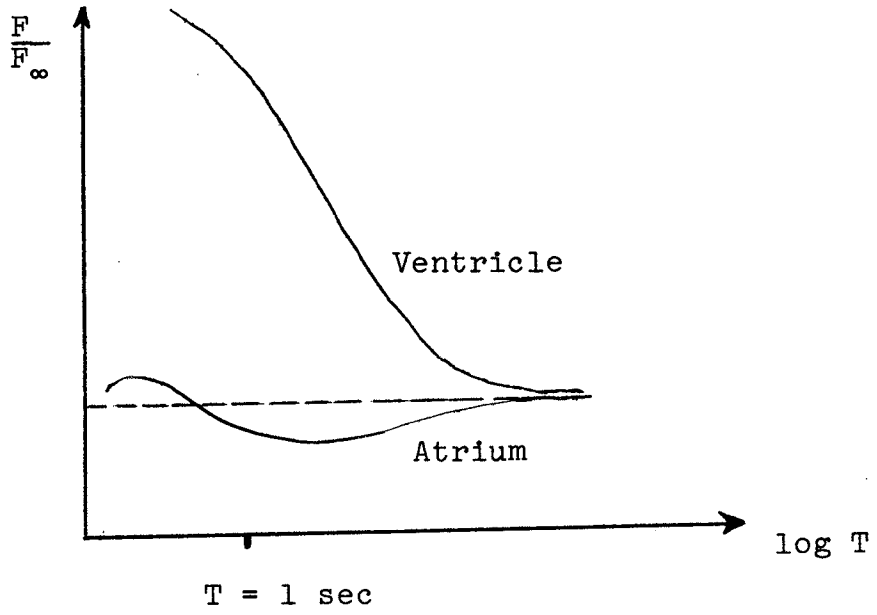
(3) Heart muscle will not continue to beat in the absence of external Ca^{++}. The strength of contractions at constant rate seems to depend on the ratio of $[Ca^{++}]/[Na^{+}]^{2}$.

The decay of tension in Ca^{++} - free solution is more rapid when the muscle is stimulated.

(4) The dependence of heart muscle on external Ca^{++} has led to the suggestion that the Ca^{++} which activates the sliding filaments comes through the cell membrane. However it has been estimated that not enough Ca^{++} comes from this source per beat. It has been suggested (Nayler) that extracellularly derived Ca^{++} triggers the release of Ca^{++} from intracellular stores. Mechanism = ?

(5) The strength of contraction of heart muscle at constant external $[Ca^{++}]$ has extremely interesting behavior when the interval between beats is changed in various ways:

Steady rate of stimulation:



T = Constant Interval Between Beats.

F = Peak Isometric Force

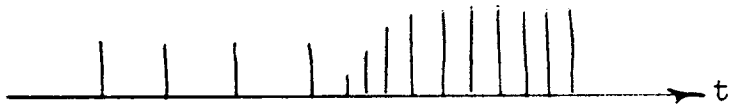
$F_\infty = F(T)\Big|_{T=\infty}$

Transient Changes:

(i) Shortening the interval

Regardless of whether the muscle is in a region where increasing rate increases or decreases the strength of contraction, when the interval is abruptly shortened the first beat is always weaker than previously. Then there is an exponential looking approach to the new equilibrium.

Example:

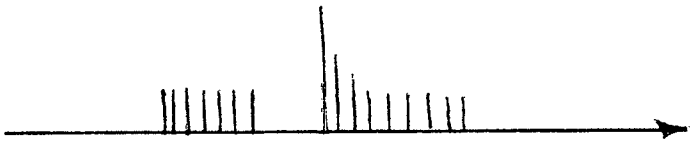


(ii) Lengthening the interval

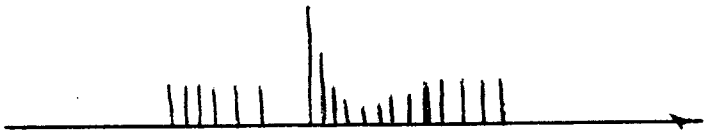
Reverse of the foregoing. The first beat is stronger; the new equilibrium may be stronger or weaker.

(iii) Effect of a rest

If a regular sequence of beats with interval T is interrupted by a rest one gets this kind of result



or perhaps



(undershoot)

(iv) Potentiation by electric currents

If the cell membrane is depolarized for an extended period of time by an imposed current the tension becomes a steady "contracture". The next beat is greatly potentiated and the subsequent decay of the potentiated state is beat dependent, not time dependent.

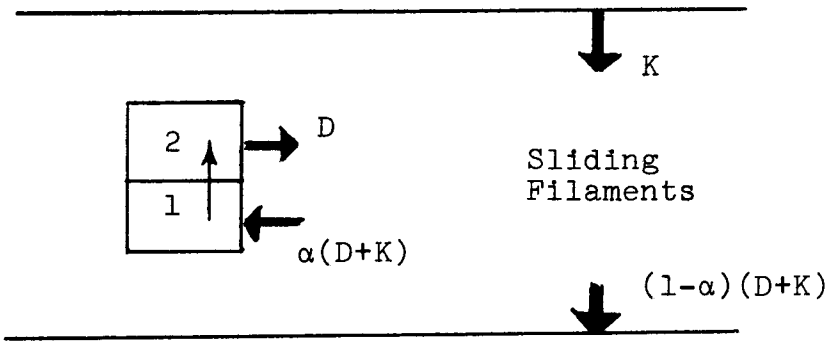
Model for intracellular Ca^{++} transport:

The main ideas on which this model is based are already in the references cited pp. 199-201. In particular, the model presented here is very close to the hypotheses of Wood, Heppner, and Weidmann. Nevertheless some interesting points emerge from the present formulation. Among these are

(1) A natural mechanism by which a small flux of Ca^{++} from outside the cell controls a larger flux from intracellular stores in the steady state.

(2) A complete separation between transient effects and steady effects.

The assumptions here are as follows: A beat is regarded as an event occuring at a single instant of time. At such an instant an amount D + K of Ca^{++} ion is made available to the sliding filaments. D is the total amount stored in an intracellular compartment just prior to release, while K is the amount which comes in from outside the cell. (We temporarily regard K as an independent variable). The calcium is then (instantaneously, in this picture) pumped away from the contractile mechanism. A fraction α is pumped out of the cell while the fraction $(1-\alpha)$ is pumped into an intracellular compartment (different from the compartment for release). Between beats all that happens is an intracellular first-order transport of Ca^{++} from the uptake compartment to the release compartment.



Steady-State:

$$D = \alpha(D+K) \rightarrow D = \frac{\alpha}{1-\alpha} K$$

(This result is independent of the details of the transport from (1)→(2)).

This implies taht in the steady state the transmembrane flux K controls the intracellular discharge D. If $\alpha > \frac{1}{2}$ there is amplification and if $\alpha \gtrsim 1$ the gain is very large. In this model, then, the <u>steady</u> strength of contraction depends solely on the transmembrane flux per beat, K.

Transients:

Assume that between beats

$$\tau_o \frac{dc_1}{dt} = -c_1 \quad \text{and} \quad c_1 + c_2 = \text{constant}$$

Then

$$c_1(t) = c_1(0)e^{-t/\tau_o}$$

Also if $c_2(0) = 0$ then

$$c_2(t) = c_1(0)(1 - e^{-t/\tau_o})$$

In particular

$$c_2(T) = c_1(0)(1 - e^{-T/\tau_o})$$

Let v = volume of (1) = volume of (2) and suppose that $D = vc_2(T)$. Then we can solve for $c_1(0)$ when the interval T is constant as follows:

$$\begin{aligned} vc_1(0) &= vc_1(T) + \alpha(D+K) \\ &= vc_1(T) + \alpha(vc_2(T) + K) \\ c_1(0) &= c_1(T) + \alpha(c_2(T) + K_o) \end{aligned}$$

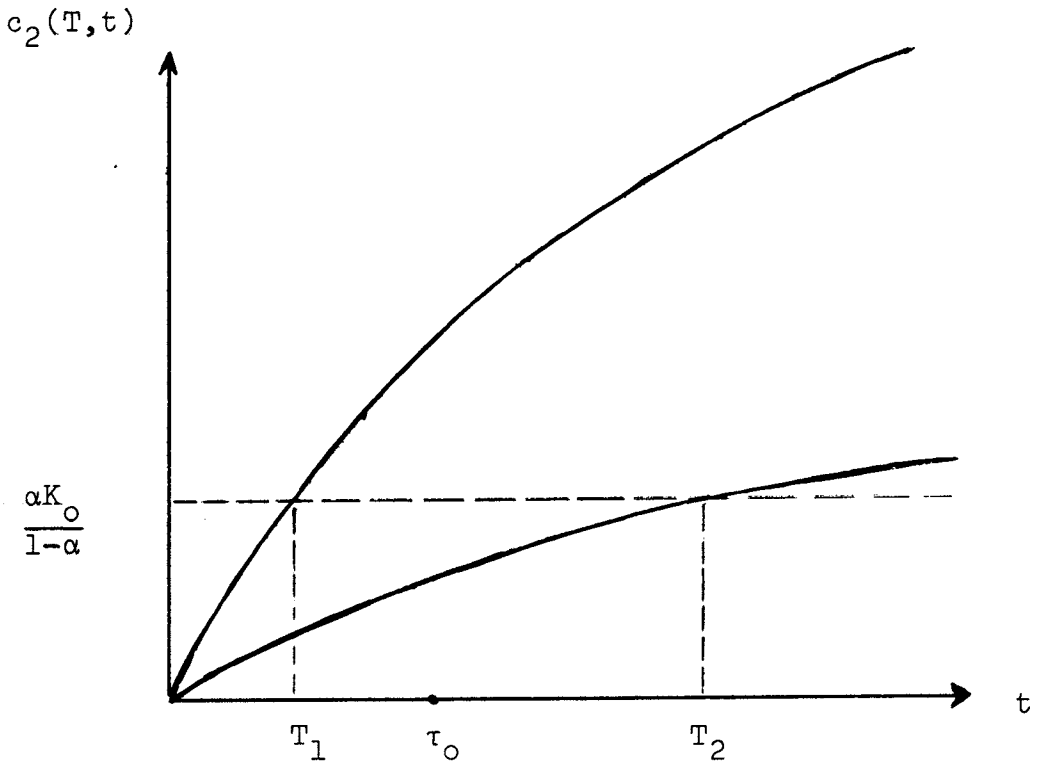
where $K_o = K/v$

Solving for $c_1(0)$, $c_2(T)$ we obtain

$$\left.\begin{aligned} c_1(0) &= \frac{\alpha K_o}{1-\alpha}\ \frac{1}{1-e^{-T/\tau_o}} \\ c_2(T) &= \frac{\alpha K_o}{1-\alpha} \end{aligned}\right\}$$

Note that the amount ready for release from compartment (2) is independent of T (if K_o is independent of T) but the amount stored in compartment (1) $\to \infty$ as $T \to 0$. Now suppose that the regular train of beats with interval T is suddenly interrupted and the next beat follows the train by an interval t which may be greater or less than T. Then

$$c_2(T,t) = \frac{\alpha K_o}{1-\alpha}\ \frac{1-e^{-t/\tau_o}}{1-e^{-T/\tau_o}}$$



Note that the maximum strength of contraction which can be obtained in this way depends very strongly on the interval T between beats in the preceding regular train. In fact $\lim_{T\to 0} c_2(T,\infty) = \infty$.

Difference equations for the strengths of successive beats:

On each beat we have $c_2(0) = 0$, and $c_1(0)$ given from the previous history.

Let

X = initial values

Y = final values

$$Y_1^{(k)} = X_1^{(k)}(1-W^{(k)}) \qquad W^{(k)} = 1 - e^{-T^{(k)}/\tau_o}$$

$$Y_2^{(k)} = X_1^{(k)} W^{(k)}$$

$$X_1^{(k+1)} = Y_1^{(k)} + \alpha(Y_2^{(k)} + K_o)$$

$$= [1-W^{(k)}]X_1^{(k)} + \alpha(W^{(k)}X_1^{(k)} + K_o)$$

$$\boxed{X_1^{(k+1)} = [1-(1-\alpha)W^{(k)}]X_1^{(k)} + \alpha K_o}$$

Rewriting the foregoing recursion relation in terms of Y we have

$$Y_2^{(k+1)} = [1 - (1-\alpha)W^{(k)}] \frac{W^{(k+1)}}{W^{(k)}} Y_2^{(k)} + \alpha K_o W^{(k+1)}$$

If W is independent of (k) even if a steady state has not yet been established

$$Y_2^{(k+1)} = [1 - (1-\alpha)W]Y_2^{(k)} + \alpha K_o W$$

or

$$Y_2^{(k+1)} - Y_2^{(k)} = W[\alpha K_o - (1-\alpha)Y_2^{(k)}] \quad .$$

Note the following properties of this equation (which holds whenever the interval has been constant for at least two beats).

(1) The steady value is independent of W.

(2) The solutions are exponentials asymptotic to the steady value. Recall that $W = 1-e^{-T/\tau_o}$. For $T >> \tau_o$, $W \approx 1$ and the approach to equilibrium is <u>beat dependent</u> rather than time dependent, as has been observed by Wood, Heppner, and Weidmann. On the other hand, if $T << \tau_o$ then $W \approx T/\tau_o$ and our difference equation becomes

$$\frac{Y_2^{(k+1)} - Y_2^{(k)}}{T} = \frac{1}{\tau_o} [\alpha K_o - (1-\alpha)Y_2^{(k)}]$$

or approximately, for small T

$$\frac{dY}{dt} = \frac{1}{\tau_o} [\alpha K_o - (1-\alpha)Y] \quad .$$

Thus for small enough T the decay becomes <u>time-dependent</u>.

Rate dependence of the strength of contraction:

In the foregoing model any dependence of contraction strength upon rate <u>in the steady state</u> can come about only because of a change in K, the transmembrane flux of Ca^{++} per beat, as a function of the interval between beats. (As discussed above the transient changes can be explained without invoking any changes in K).

There is experimental evidence that Ca^{++} exchange per beat increases with rate, which would explain qualitatively the rise in tension with rate seen in ventricular muscle. Langer has proposed a mechanism for this based on the following ideas:

(1) In nerve, $[Na^+]^2$ inside the nerve controls the inward flux of Ca^{++} ion.

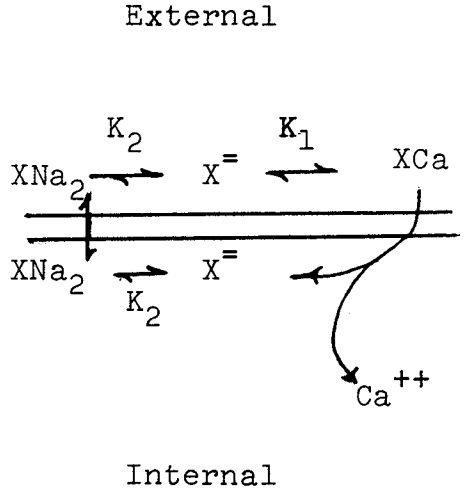
(2) In heart, the strength of contraction is known to depend on <u>external</u> $[Ca^{++}]/[Na^+]^2$.

(3) A fixed amount of Na^+ enters the cell each beat and is pumped out between beats. If we postulate that the outward flux due to the pump is $k[Na^+]_i$ and note that the inward flux will be f_o/T, where f_o is the amount of Na^+ which comes in per beat, then we should have, in the steady state

$$[Na^+]_i = \frac{f_o}{kT}$$

where T = steady interval between beats.

(4) Suppose we postulate (Langer) that Ca^{++} enters the cell by carrier diffusion, and that the carrier molecule can bind either $2Na^+$ or Ca^{++} and cannot cross the membrane unless it has bound one or the other. Then <u>if</u> we assume that the internal Ca^{++} concentration is very low and that Na^+ reactions are in sufficiently rapid equilibrium to



control the ration $[X^=]_e/[X^=]_i$ then we have

$$K_2[X^=]_e[Na^+]_e^2 = [XNa_2]_e = [XNa_2]_i = K_2[X^=]_i[Na^+]_i^2$$

or

$$[X^=]_e[Na^+]_e^2 = [X^=]_i[Na^+]_i^2 .$$

Suppose further that $[Na^+]_e^2 >> [Na^+]_i^2$ and that most of the carrier is in the state $X^=$. Then we have approximately

$$[X^=]_e = \frac{[Na^+]_i^2}{[Na^+]_e^2}[X]_o$$

where $[X]_o$ = total amount of carrier. It follows that the inward flux of Ca^{++} will be given by

$$\frac{k_o[Ca^{++}]_e[Na^+]_i^2}{[Na^+]_e^2}[X]_o .$$

But in the steady state we expect $[Na^+]_i = \frac{f_o}{kT}$ with f_o, k constant and T the interval between beats. This gives as inward Ca^{++} flux proportional to

$$\frac{[Ca^{++}]_e}{[Na^+]_e^2} \frac{f_o^2}{(kT)^2}$$

this expression increases rapidly with decreasing T and accounts qualitatively for the observed steady effect of rate on strength of contraction in ventricular but not in atrial muscle.