MUSCLE

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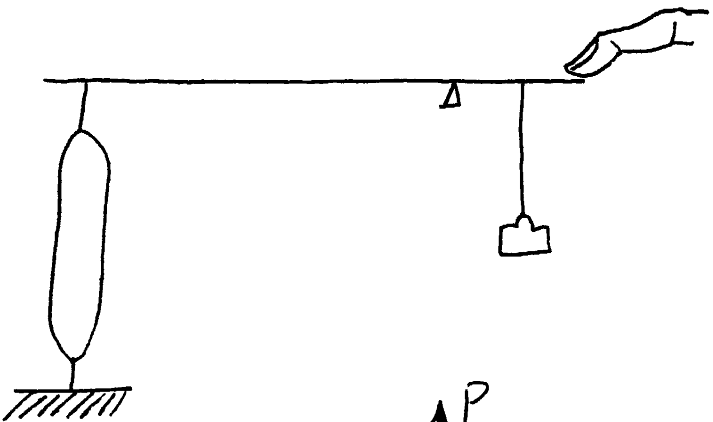
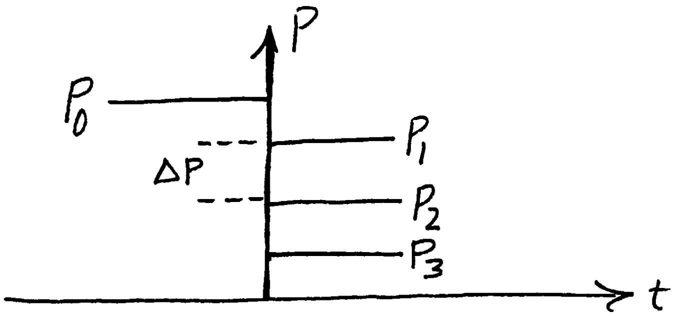
12/7/92

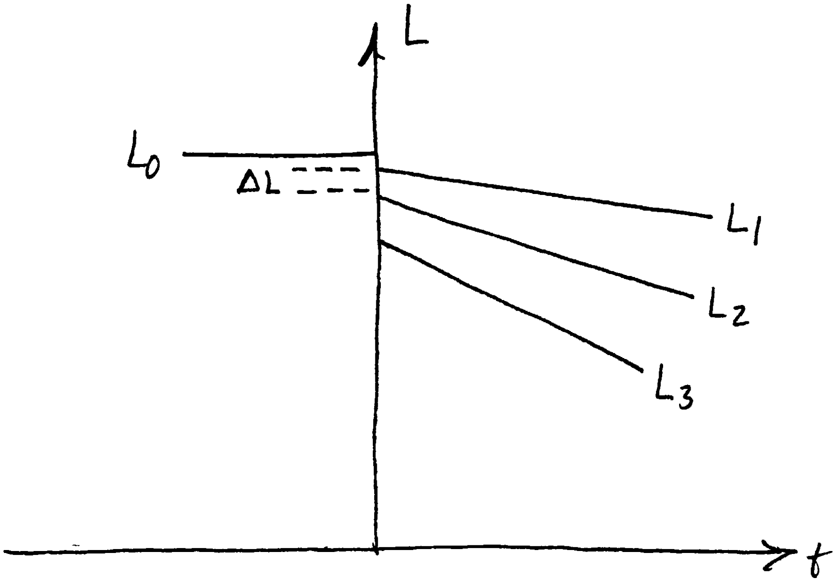
Mechanical behavior of skeletal muscle

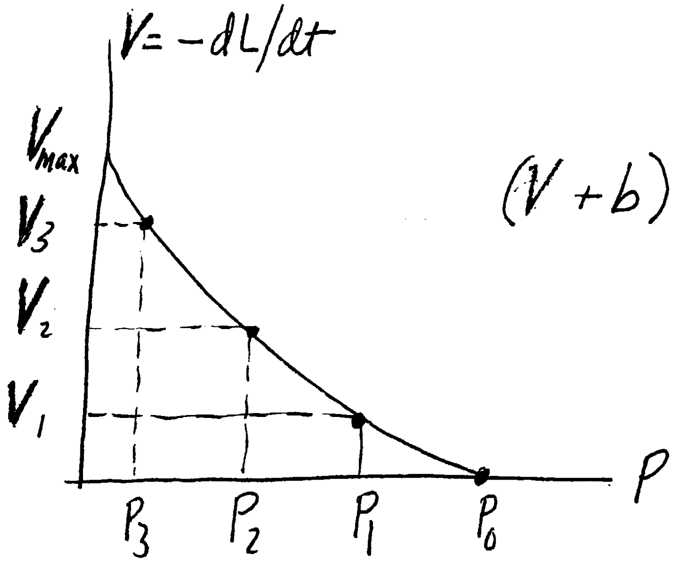
1) Within length range that is optimal for force development
2) In constant "contractile state" (achieved by rapid, repetitive stimulation)

Quick-release experiment:



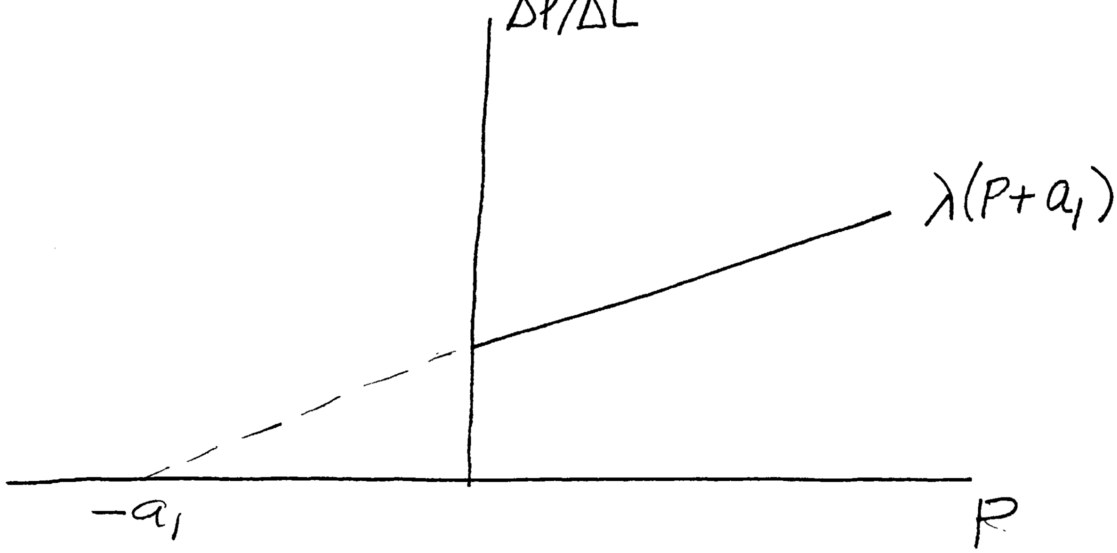




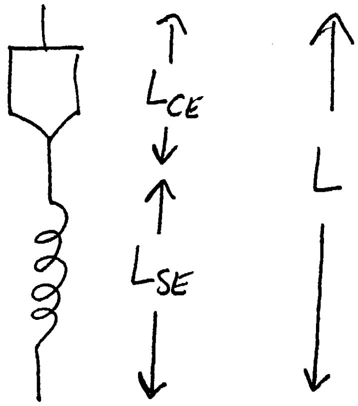


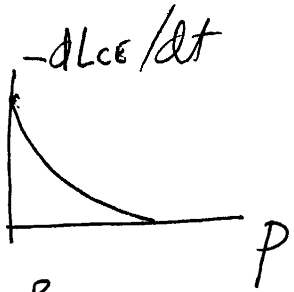
$$(V+b)(P+a) = b(P_0+a)$$

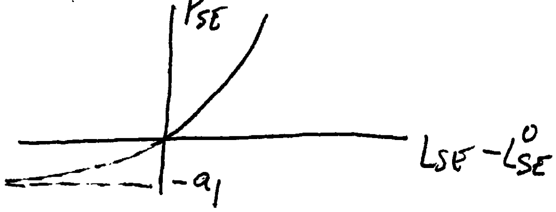
$$V_{max} = \frac{bP_0}{a}$$



Two-component model (A.V. Hill)







$$L = L_{CE} + L_{SE}$$

$$P = P_{CE} = P_{SE}$$

$$-\frac{dL_{CE}}{dt} \doteq +b\,\frac{P_0 - P}{P + a}$$

$$P_{SE} = P_{SE}(L_{SE}) \quad \text{where} \quad \frac{dP_{SE}}{dL_{SE}} = \lambda(P_{SE} + a_1)$$

It follows that $$\frac{dP_{SE}}{P_{SE} + a_1} = \lambda\, dL_{SE}$$

$$\log\left(\frac{P_{SE} + a_1}{a_1}\right) = \lambda(L_{SE} - L_{SE}^0)$$

$$P_{SE} = a_1\left(\exp\left(\lambda(L_{SE} - L_{SE}^0)\right) - 1\right)$$

Differential equation of two-component model in terms of L, P only:

$$\frac{dL}{dt} = \frac{dL_{CE}}{dt} + \frac{dL_{SE}}{dt}$$

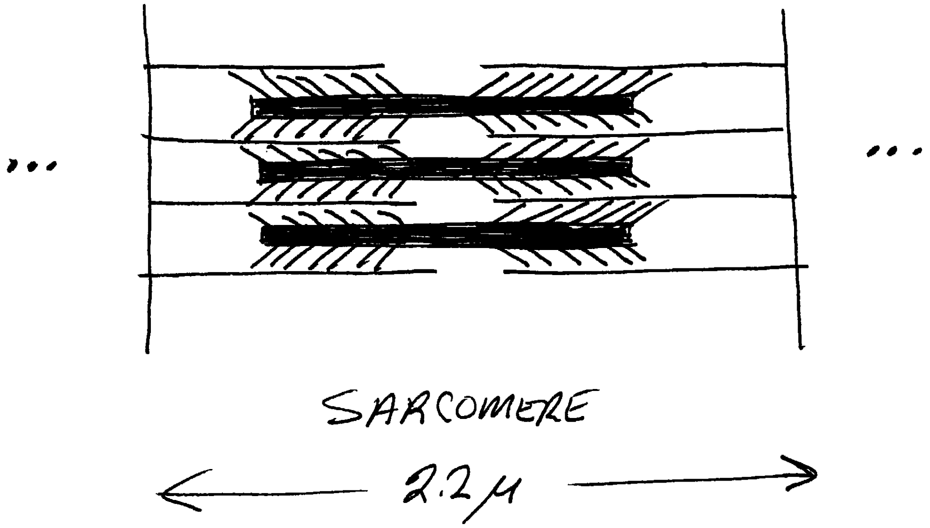
$$= -b\,\frac{P_0 - P_{CE}}{P_{CE}+a} + \frac{dL_{SE}}{dP_{SE}}\,\frac{dP_{SE}}{dt}$$

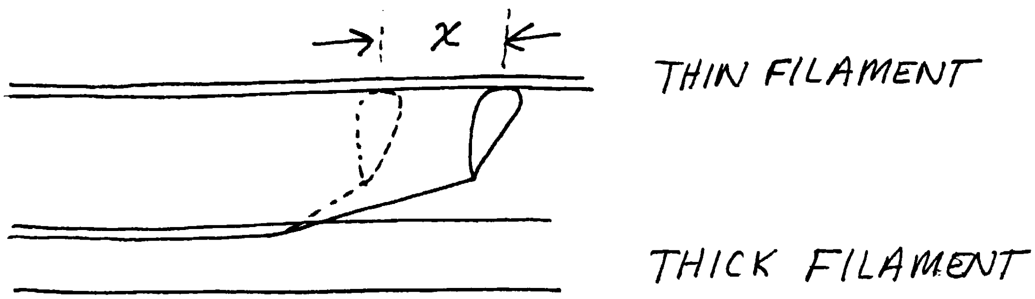
$$= -b\,\frac{P_0 - P_{CE}}{P_{CE}+a} + \frac{1}{\lambda(P_{SE}+a_1)}\,\frac{dP_{SE}}{dt}$$

$$= -b\,\frac{P_0 - P}{P+a} + \frac{1}{\lambda(P+a_1)}\,\frac{dP}{dt}$$

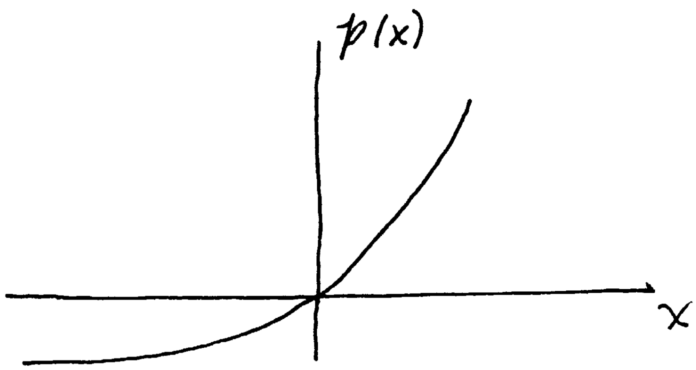
<u>Homework</u>: A muscle has been shortening at constant velocity $V = -dL/dt$ for some time, and then, (at $t=0$) it suddenly stops shortening ($dL/dt = 0$). Find the resulting muscle force $P(t)$. Assume for simplicity that $a_1 = a$. In terms of the two-component model, why doesn't the force jump instantaneously to P_0?

CROSS-BRIDGE DYNAMICS (Huxley, Lacker)





CROSS-BRIDGE



Muscle parameters and variables

N_s = # of half-sarcomeres in series

L = muscle length

$V = -dL/dt$ = shortening velocity of muscle

P = muscle force

Cross-bridge parameters and variables

N_b = # of cross-bridges per half-sarcomere

x = displacement along thin filament of an <u>attached</u> bridge from its zero-force configuration.

$v = -dx/dt$ = sliding velocity of thin filament with respect to thick filament.

x_0 = value of x immediately after cross-bridge attachment

$p(x)$ = force applied to thin filament by attached bridge with displacement x.

α_0 = rate constant for cross-bridge attachment

$\beta(x)$ = rate constant for detachment of bridge whose displacement is x.

$u(x';t)\,dx'$ = fraction of bridges which are attached AND have $x \in (x', x'+dx')$

Muscle/Cross-bridge connection

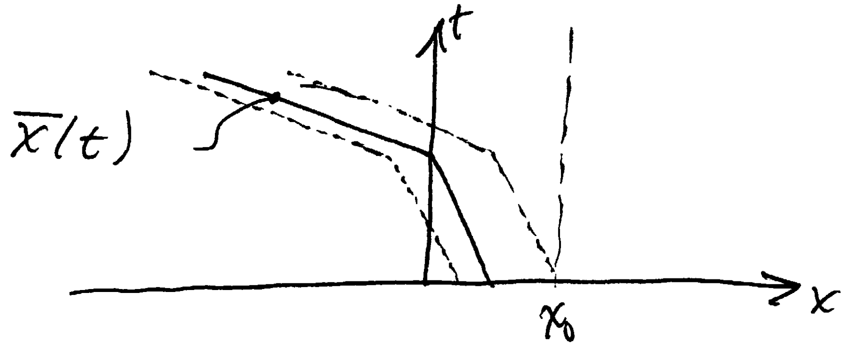
$$V(t) = N_s\, v(t)$$

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

Equation of Motion of the cross-bridge population

Shortening only: $v > 0$, $-\infty < x < x_0$

let $\bar{x}(t)$ satisfy $d\bar{x}/dt = -v$, so that cross-bridges cannot cross the trajectory $\bar{x}(t)$ in the (x,t) plane.



$$\frac{d}{dt}\int_{\bar{x}(t)}^{x_0} N_b\, u(x,t)\,dx = \alpha_0\left(N_b - \int_{-\infty}^{x_0} N_b\, u(x,t)\,dx\right) - \int_{\bar{x}(t)}^{x_0} \beta(x)\, N_b\, u(x,t)\,dx$$

$$\int_{\bar{x}(t)}^{x_0} \frac{\partial u}{\partial t}(x,t)\,dx + v(t)\,u(\bar{x}(t),t) = \alpha_0\,(1 - U(t)) - \int_{\bar{x}(t)}^{x_0} \beta(x)\,u(x,t)\,dx$$

Now consider a fixed time t. We can always choose the constant of integration in $\bar{x}$ so that $\bar{x}(t)$ takes on any value x that we like. Therefore

$$\int_x^{x_0} \frac{\partial u}{\partial t}(x',t)\,dx' + v(t)\,u(x,t) = \alpha_0\left(1 - U(t)\right) - \int_x^{x_0} \beta(x')\,u(x',t)\,dx'$$

In particular, choose $x = x_0$. Then

$$v(t)\,u(x_0,t) = \alpha_0\left(1 - U(t)\right)$$

which serves as a boundary condition. Also, we may differentiate with respect to x:

$$-\frac{\partial u}{\partial t}(x,t) + v(t)\frac{\partial u}{\partial x}(x,t) = +\beta(x)\,u(x,t)$$

In summary, we have the system:

$$\frac{\partial u}{\partial t} - v(t)\frac{\partial u}{\partial x} = -\beta(x)\,u \qquad x < x_0$$

$$u(x_0,t) = \frac{\alpha_0\left(1 - U(t)\right)}{v(t)}$$

Combining this with our other equations, we get

$$\frac{\partial u}{\partial t} - v(t)\frac{\partial u}{\partial x} = -\beta(x)u \qquad x < x_0$$

$$u(x_0,t) = \frac{\alpha_0\left(1-U(t)\right)}{v(t)}$$

$$U(t) = \int_{-\infty}^{x_0} u(x,t)\,dx$$

$$P(t) = N_b\int_{-\infty}^{x_0} p(x)\,u(x,t)\,dx$$

$$v(t) = +\frac{V(t)}{N_s} = -\frac{1}{N_s}\frac{dL}{dt}$$

Note that the cross-bridge itself is characterized by the two functions $\beta(x)$ and $p(x)$, and also by the numbers x_0 and α_0.

Special case: $\beta(x)=\beta_0 \qquad p(x)=p_1(e^{\mu x}-1)$

Note that:

$$\frac{dp}{dx} = \mu p_1(e^{\mu x}-1+1)$$
$$= \mu(p+p_1)$$

In this special case, we can reduce the cross-bridge pde to an ode

① Integrate from $-\infty$ to x_0 to derive an ode for $U(t)$:

$$\frac{d}{dt}U - v(t)u(x_0,t) = -\beta_0 U$$
$$\frac{dU}{dt} - \alpha_0(1-U) = -\beta_0 U$$
$$\frac{dU}{dt} = \alpha_0 - (\alpha_0+\beta_0)U$$

Note that $U \to \dfrac{\alpha_0}{\alpha_0+\beta_0}$, independent of what is happening to the muscle, i.e., independent of $L(t)$.

Therefore we may set $U = \dfrac{\alpha_0}{\alpha_0+\beta_0}$

Hence

$$u(x_0,t) = \frac{1}{v(t)} \quad \alpha_0 \left(1 - \frac{\alpha_0}{\alpha_0+\beta_0}\right)$$

$$= \frac{1}{v(t)} \quad \frac{\alpha_0 \beta_0}{\alpha_0+\beta_0}$$

② Multiply by $N_b\, p(x)$ and then integrate from $-\infty$ to x_0 to derive an ode for $P(t)$:

$$\frac{dP}{dt} - v(t) N_b \int_{-\infty}^{x_0} p(x) \frac{\partial u}{\partial x}(x,t)\, dx = -\beta_0 P$$

But

$$\int_{-\infty}^{x_0} p(x) \frac{\partial u}{\partial x}\, dx = p(x) u \Big|_{-\infty}^{x_0} - \int_{-\infty}^{x_0} \frac{dp}{dx} u \, dx$$

$$= p(x_0) u(x_0,t) - \int_{-\infty}^{x_0} \mu(p+p_1) u\, dx$$

$$= \frac{p(x_0)}{v(t)} \frac{\alpha_0 \beta_0}{\alpha_0+\beta_0} - \frac{\mu}{N_b} P(t) - \mu p_1 \frac{\alpha_0}{\alpha_0+\beta_0}$$

Thus,

$$\frac{dP}{dt} - N_b\, p(x_0)\,\frac{\alpha_0 \beta_0}{\alpha_0+\beta_0} + \mu\, v(t)\, P(t) + \mu N_b\, p_1\, \frac{\alpha_0}{\alpha_0+\beta_0}\, v(t)$$

$$+ \beta_0 P = 0$$

Solve for $\frac{dL}{dt} = -V = -N_s v$

$$\frac{dL}{dt} = \frac{N_s\left(\frac{dP}{dt} - N_b\, p(x_0)\,\frac{\alpha_0\beta_0}{\alpha_0+\beta_0} + \beta_0 P\right)}{\mu\left(P + N_b\, p_1\,\frac{\alpha_0}{\alpha_0+\beta_0}\right)}$$

$$= -\left(\frac{\beta_0 N_s}{\mu}\right)\left(\frac{N_b\, p(x_0)\,\frac{\alpha_0}{\alpha_0+\beta_0} - P}{P + N_b\, p_1\,\frac{\alpha_0}{\alpha_0+\beta_0}}\right)$$

$$+ \frac{1}{\left(\frac{\mu}{N_s}\right)\left(P + N_b\, p_1\,\frac{\alpha_0}{\alpha_0+\beta_0}\right)}\,\frac{dP}{dt}$$

which agrees with the 2-component model provided that we set:

$$b = \frac{\beta_0 N_s}{\mu} \qquad \lambda = \frac{\mu}{N_s}$$

$$P_0 = N_b\, p(x_0) \frac{\alpha_0}{\alpha_0+\beta_0} = N_b\, p_1\left(e^{\mu x_0}-1\right) \frac{\alpha_0}{\alpha_0+\beta_0}$$

$$a_1 = a = N_b\, p_1 \frac{\alpha_0}{\alpha_0+\beta_0}$$

Note, too, that

$$V_{max} = \frac{bP_0}{a} = \frac{\beta_0 N_s}{\mu}\left(e^{\mu x_0}-1\right)$$

Homework: The foregoing procedure eliminated $u(x,t)$, so we don't get to see what it looks like. Consider again the special case $\beta = \beta_0$ and $p(x) = p_1(e^{\mu x} - 1)$. Look for steady-state solutions $u(x)$. Sketch the result for two different velocities (and indicate which is higher). What is the limiting behavior of $u(x)$ as $v \to 0$. Derive the force-velocity curve by substituting your formula for $u(x)$ into the equation

$$P = \int_{-\infty}^{x_0} p(x) u(x) \, dx$$

Check that you get the same results as above.

Homework: Reconsider the first homework problem in which a muscle which was shortening at velocity V is suddenly stopped. What is happening to the cross-bridges during the time interval $(0,\infty)$ in which the force is approaching P_0?

Homework

Extend the force-velocity curve to negative velocities of shortening (i.e., lengthening) by solving the cross-bridge equations for $v<0$. Assume that cross-bridges necessarily break when they reach $x = x_1$, where $x_1 > x_0$. Thus

$$\beta(x) = \begin{cases} \beta_0, & x < x_1 \\ \infty, & x > x_1 \end{cases}$$

Assume the same $p(x)$ as before, namely

$$p(x) = p_1\left(e^{\mu x} - 1\right)$$

Since $v<0$, the cross-bridges that form at $x = x_0$ move in the direction of increasing x, and $u(x)$ is supported on

$$x_0 \le x \le x_1$$

Note that U is not independent of v in this situation.

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Homework (continued)

On the same graph, plot the force-velocity curves of shortening ($v>0$) and lengthening ($v<0$). In the case of lengthening, plot a family of curves in which each curve has a different value of X_1.

How many derivatives of the force-velocity curve for shortening match those of the force-velocity curve for lengthening at $v=0$?

What is the limit of the force-velocity curve for lengthening as $X_1 \to \infty$?

Note that for $X_1 < \infty$ there is a part of the force-velocity curve on which force decreases as velocity of lengthening increases.

Suggested computing project:
Stochastic simulation of cross-bridge dynamics

Sample MATLAB code for a half-sarcomere with $V(t)$ given is below. The function $V(t)$ can be anything you like, but allow a period of time for U to equilibrate (say with $V(t)=0$) before trying anything interesting.

The code includes the feature that cross bridges break when $x > x_1$, for some specified $x_1 > x_0$, so you can investigate the force-velocity curve of lengthening, as in the foregoing homework problem.

Important outputs are $U(t)$ and $P(t)$. You could also make a movie showing a histogram of the cross-bridge population density as it evolves over time.

An interesting generalization is to allow for the case in which $P(t)$ is given instead of $V(t)$, or better still, to switch between these two cases. This is described below.

Stochastic simulation of half-sarcomere (V(t) given)

units:

length: nm = nanometer
time: s = second
force: pN = picoNewton

```
Nb=10 000  % number of cross-bridges (arbitrary)
alpha=14  %  (/s)  rate of attachment
beta =126  %  (/s)  rate of detachment
dt=0.01/(alpha+beta)  %  (s)  time step
tmax=30  %  (s)  duration of simulation
clockmax=ceil(tmax/dt)  % number of time steps
x0=5 % (nm) length of a new cross-bridge
x1=10 % (nm) length at which cross-bridge must break
p1=4 % (pN) cross-bridge force constant
mu=0.322 % (/nm) multiplyer of x in force
a=zeros(1,Nb); x=zeros(1,Nb);
for clock= 1:clockmax
   x(find(a))=x(find(a))-V(clock*dt)*dt;
   pc=(beta*dt)*a +(alpha*dt)*(1-a);
   c=(rand(1,Nb)<pc) | (x>x1);
   a = xor(c,a);
   x(find(a&c))=x0;
   x(find(~a))=0;
   U = sum(a)/Nb
   P = sum(p1*(exp(mu*x)-1));
end
```

The following code is similar to the foregoing but allows for switching between two modes, one in which $v(t)$ is given and one in which $P(t)$ is given. When $v(t)$ is given

$$dx = -v(t) * dt$$

but when $P(t)$ is given, we have to solve for dx such that P has the prescribed value. The required shift, $dx = \Delta x$, from some given positions x_i, $i \in a$, where a is the set of attached bridges, is given by

$$P = \sum_{i \in a} p_1 \left(e^{\mu(x_i + \Delta x)} - 1 \right)$$

Note that

$$P_{\Delta x = 0} = \sum_{i \in a} p_1 \left(e^{\mu x_i} - 1 \right)$$

Solving for Δx, we find (please check this!)

$$\Delta x = \frac{1}{\mu} \log \left(1 + \frac{P - P_{\Delta x=0}}{\sum_{i \in a} p_1 e^{\mu x_i}} \right)$$

Code to switch between given V(t) and given P(t)

```
dl=0  % initialize cumulative length change
do clock = 1:clockmax
  t = clock*dt
  if (use_v(t))
     dx = -v(t)*dt
  else
     r = (P(t)-Px)/(Px + p1*sum(a)) ;
     dx = (1/mu)* log(1+r);
  end
  x(find(a)) = x(find(a)) + dx;
  dl = dl + dx;
  pc = (beta*dt)*a + (alpha*dt)*(1-a);
  c = (rand(1,Nb) < pc) | (x > x1);
  a = xor(c,a);
  x(find(a&c)) = x0;
  x(find(~a)) = 0;
  U = sum(a)/Nb
  Px = sum(p1*(exp(mu*x(find(a))) - 1));
end
```

Warning: a warm-up period is needed in which use_v(t) = 1 (and possibly $v(t)=0$) to get enough attached cross-bridges to make it possible to specify $P(t)$.

References

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