Ding, Jun, Stuart A. Binder-Macleod, and Anthony S. Wexler. Two-step, predictive, isometric force model tested on data from human and rat muscles. J. Appl. Physiol. 85(6): 2176–2189, 1998.—Functional electrical stimulation can assist paralyzed individuals to perform functional movements, but muscle fatigue is a major limitation to its practical use. An accurate and predictive mathematical model can facilitate the design of stimulation patterns that optimize aspects of the force transient while minimizing fatigue. Solution nonuniqueness, a major shortcoming in previous work, was overcome with a simpler model. The model was tested on data collected during isometric contractions of rat gastrocnemius muscles and human quadriceps femoris muscles under various physiological conditions. For each condition tested, parameter values were identified using the force response to one or two stimulation trains. The parameterized model was then used to predict forces in response to other stimulation patterns. The predicted forces closely matched the measured forces. The model was not sensitive to initial parameter estimates, demonstrating solution uniqueness. By predicting the force that develops in response to an arbitrary pattern of stimulation, we envision the present model helping identify optimal stimulation patterns for activation of skeletal muscle during functional electrical stimulation.

Two-step, predictive, isometric force model tested on data from human and rat muscles

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FUNCTIONAL ELECTRICAL stimulation (FES) can assist paralyzed individuals to perform functional movement (18, 20). Muscle fatigue, however, is a major limitation to its practical implementation (18, 20). It has long been known that the stimulation frequency affects the forces produced and the rate of muscle fatigue (8). More recently, it has been shown that, in addition to the mean frequency, the pattern of the pulses can markedly affect force production and fatigue (4, 5). Studies showed that the activation pattern that produces the greatest force varies from person to person (19) and, even for the same individual, changes for different physiological conditions (e.g., muscle length (21)). Therefore, it is important and difficult to identify activation patterns that maximize force and minimize fatigue for individual patients.

The development of a mathematical model that predicts the force responses of muscles to electrical stimulation would enable clinicians to identify the optimal activation patterns for individual patients. Several mathematical models of muscle force have been developed, including pure mathematical models (9, 12), Huxley-type models (17, 26, 27, 32), and Hill-type models (11, 13, 16, 22, 31). Different aspects of the muscle have been modeled. Our long-term goal is to develop a model that can predict forces of muscle during FES. A reliable isometric force model is a crucial step toward this goal. The only model able to predict isometric force response to a wide range of stimulation patterns incorporates the Hill paradigm (31). Hill-type models are phenomenological, originating from experimental observations of the muscle's mechanical behavior, and describe the whole muscle as a contractile element in series with a spring, together with various modifications such as dampers placed in parallel or series with other components.

In our previous work we decomposed the contractile response of skeletal muscle into three steps: 1) Ca2+ release and uptake by the sarcoplasmic reticulum, 2) Ca2+ reaction with troponin, and 3) force mechanics modeled by a linear spring, damper, and motor in series (31). Steps 1 and 2 make the model less phenomenological than Hill’s original model (16). This three-step model consisted of three ordinary differential equations and nine parameters that were identified by fitting the model to forces measured in response to a single constant-frequency train (CFT) stimulation. Then, using the parameter values identified from this fit, we tested the fidelity of the model by comparing its predictions with responses measured from other stimulation patterns. For rat gastrocnemius and soleus muscles, the model accurately fit and predicted the force responses during stimulation with a wide range of stimulation frequencies and patterns. The primary shortcoming of the model was its sensitivity to different initial parameter estimates. Numerous fitting trials were necessary to identify the initial parameter values, leading to identified values that reliably predicted force responses. In addition, subsequent analysis of these previously published results showed that the model was only able to predict the stimulation pattern that produced the greatest force-time integral for 9 of the 15 gastrocnemius muscles studied. All the muscles for which the model was successful had twitch contraction times < 25 ms. The purpose of this study, therefore, was to develop a model with greater reliability and range of applicability.

The simpler model presented here consists of only two ordinary differential equations and four parameters. It has been tested on isometric contractions from rat and human muscles in response to a wide range of

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brief, physiologically relevant stimulation patterns. Forces used to test the model were collected from fresh and fatigued muscles and at long (near-optimal) and short (suboptimal) muscle length.

FORMULATION OF THE MODEL

In the new muscle model the contractile response is decomposed into two distinct physiological steps: cross-bridge activation and force generation.

Cross-bridge activation. Pilot studies with our previous model (31) showed that the ability of the model to predict forces is relatively insensitive to the specific shape and magnitude of the Ca\(^{2+}\) and Ca\(^{2+}\)-troponin complex transient. This implies that steps 1 and 2 in our previous model could be combined into one step. Therefore, we use one unitless factor, \(C_N\), the dynamics of which are governed by a time constant, \(\tau_c\), to qualitatively describe the rate-limiting step before the myofilaments mechanically slide across each other and generate force (1; see APPENDIX for details). The differential equation describing this dynamic is

\[
\frac{dC_N}{dt} = \frac{1}{\tau_c} \sum_{i=1}^{n} \exp\left(\frac{t - t_i}{\tau_c}\right) - \frac{C_N}{\tau_c} \tag{1}
\]

and the chosen analytic solution is

\[
C_N = \sum_{i=1}^{n} \frac{t - t_i}{\tau_c} \exp\left(\frac{t - t_i}{\tau_c}\right) \tag{2}
\]

where the transient behavior of \(C_N\) characterizes the rate-limiting step in force generation, \(t\) (ms) is the time since the beginning of the stimulation train, \(t_i\) (ms) is the time of the \(i\)th stimulation pulse since the beginning of the stimulation train, \(n\) is the number of stimulation pulses before time \(t\) in the train (its maximum value is 6 in this study), and \(\tau_c\) (ms) is the time constant controlling the transient shape of \(C_N\).

Force generation. Similar to our previous model (31), the force generation is modeled mechanically by a linear spring, damper, and motor in series, which represent the elastic, viscous, and contractile elements of the muscle, respectively (Fig. 1). The damper represents the viscous resistance of the contractile and connective tissue (22). The force \(F\) exerted by the damper is given by

\[
F = b \left( V - \frac{dx}{dt} \right) \tag{3}
\]

where \(b\) is the damping coefficient, \(x\) is the length of the spring, and \(V\) is the contractile velocity of the motor.

The motor represents the contractile element, or the sliding of actin and myosin filaments, and is driven by strongly bound cross bridges (1). Because there is a sigmoidal force-pCa relationship (2), we tested for a similar relationship between \(C_N\) and the strongly bound cross bridges and found that a simple Michaelis-Menten function, \(C_N/(1 + C_N)\), sufficed. The contractile

\[
V = B \frac{C_N}{1 + C_N} \tag{4}
\]

in which \(B\) is a proportionality constant.

A linear spring represents the series elastic components of the muscle and tendon. The force exerted by the spring is given by

\[
F = Kx \tag{5}
\]

where \(K\) is the spring constant. Differentiating Eq. 5 with respect to time and using Eq. 3 to eliminate \(dx/dt\) and Eq. 4 to eliminate \(V\) gives

\[
\frac{dF}{dt} = KB \frac{C_N - F}{1 + C_N} - \frac{b}{K} \tag{6}
\]

The term \(b/K\) represents the time constant over which the force decays. The friction between the actin and myosin filaments increases with an increase in bound cross bridges, so we set \(b/K = \tau_1 + \tau_2 C_N/(1 + C_N)\), where \(\tau_2\) is the value of the time constant in the absence of \(C_N\) and \(\tau_2\) is the additional frictional component due to the cross-bridge chemical bonds. Substituting for \(b/K\) and replacing \(KB\) with a new constant, \(A\), in Eq. 6 gives

\[
\frac{dF}{dt} = A \frac{C_N}{1 + C_N} - \frac{F}{\tau_1 + \tau_2} \frac{C_N}{1 + C_N} \tag{7}
\]

The isometric force dynamics are governed by Eqs. 1 and 7, which describe the transient behavior of the two state variables, \(C_N\) and \(F\), subject to the four parameters \(\tau_c, A, \tau_1,\) and \(\tau_2\) (Table 1).

METHODS

Experimental procedure. Rat and human data were taken from previously published or unpublished studies in our laboratory, which were approved by the University of Delaware's Animal and Human Subjects Review Board. Data were collected from 16 nonfatigued and 8 fatigued rat gastrocnemius muscles. The experimental methods are similar to those previously described (31). Briefly, the rats were deeply anesthetized, and a hook stimulating electrode was positioned around the nerve leading to the gastrocnemius muscle. Force was recorded directly from the Achilles' tendon. The gastrocnemius muscle was stimulated with a series of nine six-pulse trains. During traditional FES, skeletal muscle is activated with short CFTs, where the pulses within each train are separated by regular intervals. Five of the trains in our study,
C. Increments: (top interval (IPI) of 10–50 ms in 10-ms increments pulse. Each vertical line represents a stimulus to activate rat gastrocnemius muscles. Variable-frequency trains (VFTs) were used to represent the forces from the fatigued muscles. Similar to that previously described (8).

Table 1. Symbols used in the model

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<th>Unit</th>
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<td>C_N</td>
<td>mN/ms</td>
<td>State variable that characterizes rate-limiting step for force generation (see Appendix for further details regarding C)</td>
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<tr>
<td>F</td>
<td>N</td>
<td>Force generated by muscle</td>
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<tr>
<td>(t_c)</td>
<td>ms</td>
<td>Time constant controlling (C_N)</td>
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<td>A</td>
<td>mN/ms</td>
<td>Scale factor in force Eq. 7</td>
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<tr>
<td>(t_2)</td>
<td>ms</td>
<td>Time constant of force relaxation when (C_N) is present</td>
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<tr>
<td>(t_1)</td>
<td>ms</td>
<td>Time constant of force relaxation when (C_N) is absent</td>
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therefore, were CFTs with interpulse intervals (IPIs) of 10, 20, 30, 40, or 50 ms (Fig. 2A): CFT10, CFT20, CFT30, CFT40, and CFT50, respectively. The other four trains were variable-frequency trains (VFTs), with an initial IPI of 10 ms, and the remaining four IPIs within the train were 20, 30, 40, or 50 ms (Fig. 2B): VFT20, VFT30, VFT40, and VFT50, respectively.

The VFTs were chosen, because recently it has been shown that VFTs that take advantage of the catchlike property of skeletal muscle can markedly increase the force output from fatigued muscle compared with CFT stimulation (4, 5, 8). The catchlike property is the tension enhancement seen when an initial brief high-frequency burst of pulses (2–4 pulses) at the onset of a subtetanic CFT is used to activate the muscle (6, 10). To collect the responses to nonfatiguing stimulation, \(\sim 10\) s separated each train. To fatigue the muscle, 3 random sequences of these 9 trains were used to form a cycle of 27 trains, and 8 such cycles (216 trains) were used. Each train was separated by \(\sim 1\) s. The force responses to the last cycle of trains were used to represent the force responses from the fatigued muscles.

The experimental setup for collection of human data was similar to that previously described (8). Briefly, subjects were seated on a force dynamometer with their hips flexed to \(\sim 75^\circ\) and their knees flexed to \(90^\circ\) for the long-muscle-length study or \(15^\circ\) for the short-muscle-length study. Two stimulating electrodes were placed over the quadriceps femoris muscle. The force transducer was positioned against the anterior aspect of the leg, proximal to the lateral malleolus. Nonfatiguing and fatiguing protocols, similar to those used for rat muscles, were used for human subjects, except the initial IPI of the VFTs was 5 ms, and the IPNs of the CFTs were 10–120 ms in steps of 10 ms, for a total of 24 stimulation patterns. Nonfatiguing force responses were collected for long-muscle-length (n = 12) and short-muscle-length (n = 11) studies.

Simulations. Reliability of the model was first investigated for rat and human muscles by using the model to fit the force data for each animal or subject by incorporation of a wide range of initial parameter values. Convergence to the same parameter values for each rat or human subject under each condition would suggest a unique solution of the model within the range of initial parameter values tested.

Parameter identification. SAAM II, a modeling system developed by the University of Washington and the National Institutes of Health, was used to identify the optimum parameter values and predict forces for other stimulation trains (24). For each muscle, \(t_1\) was first calculated using the numerical module of SAAM II. The procedure to calculate \(t_1\) was described in detail previously (31). Briefly, it was found by setting \(C_N = 0\), so that Eq. 7 became \(dF/dt = -F/t_1\). By taking the force decay at the end of the tetany and performing a linear regression of lnF vs. t, we obtained the value of \(t_1\) from the slope of the fit. The other three parameter values were then identified using the compartment module of SAAM II, which accepted as input 1) Eqs. 1 and 7 and 7 expressed compartmentally, 2) force measured for a contraction, 3) the stimulation pattern, and 4) initial parameter estimates. SAAM II performs a multidimensional fit between the measured and predicted force data to identify the best parameter values.

Preliminary studies were conducted to find the best train(s) for parameter identification. For rat and human muscles, trains that produce nonfused tetanic force responses were tested first, because they exhibited a clear rise and fall of force.

A. CFTs with interpulse interval (IPI) of 10–50 ms in 10-ms increments (top to bottom). B: comparable VFTs with an initial IPI of 10 ms.
for each pulse and a buildup of force over multiple pulses. CFTs with IPIs of 30 ms (CFT30, Fig. 3C) and 70 ms (CFT70, see Fig. 6C) were initially used to fit the model for rat gastrocnemius and human quadriceps femoris muscles, respectively.

For rat nonfatigued or fatigued muscles, the 30-ms CFT did not always lead to a set of parameter values that successfully predicted the forces from other stimulation patterns. In fact, no other train was found that could satisfactorily predict forces from all other stimulation patterns. Further testing showed that only a combination of two stimulation trains, one that produced a nearly fused tetanic response (i.e., CFT20) and another that produced an unfused tetanic response (i.e., CFT50), identified a reliable set of parameter values (see Fig. 3 for examples of force responses to CFT20 and CFT50). The CFT20 and CFT50, therefore, were used to parameterize the model for the rat muscles.

Unlike the rat muscles, parameter values for human quadriceps femoris muscles obtained by fitting the combination of a high- and a low-frequency CFT (e.g., CFT30 and CFT100) did not improve the accuracy of the predicted responses. When muscles were at a long length and not fatigued, the CFT with IPI of 70 ms (see Fig. 6C) yielded parameter values that best predicted the forces. However, when muscles were at long length and fatigued or at short length and not fatigued, we found that the CFT70 could only

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**Fig. 3.** Measured (exp) and predicted (mod) forces from a typical nonfatigued rat gastrocnemius muscle. A–E: 6-pulse CFTs of 10, 20, 30, 40, and 50 ms. F–I: comparable VFTs. Model parameter values were obtained by fitting model to responses to CFT20 (B) and CFT50 (E).
be used to identify parameter values to predict forces to other CFTs and that the VFT70 (see Fig. 7H) best identified parameter values for the VFTs.

Force predictions. For each muscle, with use of the parameterized model, the state variable $CN$ and the force responses to other stimulation patterns were predicted by simply changing the simulation pattern input to the parameterized compartment module. We then tested the fidelity of the model by comparing the predicted forces with the measured forces.

Data analysis. To validate the model, several comparisons were made between the predicted and measured data. To compare the shape of the forces, a correlation coefficient was calculated by comparing the measured and predicted forces at 2-ms-interval time steps. Any phase shift or disagreement in shape between the predicted and measured data lowers the correlation coefficient. Next, for each animal or subject, the force-time integral was compared for the measured and the predicted responses to each stimulation pattern. For each condition, the measured force-time integrals were plotted against the predicted ones. Linear regression trend lines, with intercepts of zero, were used to compare force response across all the stimulation patterns and determine how well the model predicts the force-time integrals. A perfectly accurate model would have a slope and correlation coefficient of 1. Also within each condition, percent differences were calculated between the average measured and predicted force-time integral for each stimulation pattern. If the percent differences were greater than a chosen criterion, 5%, a paired t-test was used to check whether the difference was significant across the subjects. We chose 5%, because we believed that this was the minimal difference that would be clinically significant.

The best-fit parameter values were pooled for all subjects within each condition, and means $\pm$ SD were calculated. For each parameter, a paired t-test was used to compare the parameter values for the same animal or subject across

Fig. 4. Measured and predicted forces from a typical fatigued rat gastrocnemius muscle (same muscle presented in Fig. 3). A–E: 6-pulse CFTs of 10, 20, 30, 40, and 50 ms. F–I: comparable VFTs. Model parameter values were obtained by fitting model to responses to CFT20 (B) and CFT50 (E).
conditions, with nonfatigued and long-muscle-length-nonfatigued data as the control condition for rat and human studies, respectively.

RESULTS

Pilot studies on reliability of the model showed convergence of the parameter values within the range of values tested for each of the four rat and six human muscles tested, suggesting that the model was able to fit the data with a unique solution. Subjective evaluation of the force responses showed that the model accurately fit and predicted the responses to a wide range of stimulation patterns for the nonfatigued and fatigued rat muscles (Figs. 3 and 4, respectively). The median correlation coefficients were 0.98 for the nonfatigued and fatigued muscles (Table 2), which is consistent with the subjective impression that the predicted response accurately matched the shape of the measured data. Typical trend lines for rat gastrocnemius force-time integrals had slope and correlation coefficients close to 1 (Fig. 5), which also suggested an accurate fit and prediction with the model. For nonfatigued rat muscles, the model significantly underestimated the CFT10 force-time integral by 16% (Fig. 5B). For fatigued rat muscles, although the model significantly overestimated the VFT30, VFT40, and VFT50, the differences between the measured and predicted forces were small (8.1, 6.7, and 8.5%, respectively; Fig. 5F). The model successfully predicted the activation patterns that produced the greatest force-time integrals for seven of the nine rat muscles with twitch contraction times <25 ms and for seven of the eight muscles with twitch contraction times >25 ms.

For human studies, subjective evaluation of the force responses also showed that, in general, the model accurately fit and predicted the responses to a wide range of stimulation patterns and conditions (Figs. 6–8). The correlation coefficients between the measured and predicted forces, averaged across subjects, had a median of 0.96, 0.96, and 0.97 (Table 2) for nonfatigued long-length, fatigued long-length, and nonfatigued short-length conditions, respectively, suggesting good agreement between the shape of the measured and predicted forces.

When muscles were not fatigued and were held at long length, the trend lines for force-time integral had slopes close to 1, and the model accounted for 65–68% of the variability in the measured data (Fig. 9). The model significantly overestimated the force produced in response to the CFTs and VFTs with short IPIs (10–60 ms) and underestimated those with long IPIs (80–110 ms).

Surprisingly, when muscles were fatigued the model did a better job of predicting the force output than when muscles were not fatigued. The slopes of force-time integral trend lines were only slightly <1, and the model accounted for 90–96% of the variability in the measured data (Fig. 10). The model tended to underestimates the force-time integrals of CFTs with short IPIs (20–40 ms), the percent error being worst (25%) for CFT10. The model slightly overestimated the force-time integrals of the VFTs with short IPIs (20–40 ms) and underestimated the VFTs with long IPIs (90–110 ms).

When muscles were not fatigued and were at short length, trend lines of the force-time integral had slope values close to 1 and correlation coefficients of 0.89–0.94 (Fig. 11). The model significantly overestimated the force-time integral of VFTs with short IPIs (20–40 ms; Fig. 11). However, these differences were <8%.

Overall, the model did an excellent job of predicting the pattern of activation that produced the maximum force-time integral. The only exceptions were the human nonfatigued data collected at long muscle length (Fig. 9). In this condition the error between the maximum predicted and measured force-time integrals was, however, only ~5%. The model predicted that the maximum force-time integral is obtained with IPIs that are short compared with the measurements, leading to

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Values are averaged correlation coefficients between measured force and predicted force at each 2-ms time step across subjects for each stimulation train (constant-frequency train (CFT) and variable-frequency train (VFT)).
Fatigue produced changes in all four parameter values that were consistent for rat and human muscles (Table 3). Paired t-test showed a significant increase in $t_1$ and a significant decrease in $A$ when muscles were fatigued or held at short length for rats and humans. Only for humans, however, were significant differences seen for $t_2$ and $t_c$ across conditions.

**DISCUSSION**

The current model predicted isometric forces for rat gastrocnemius and human quadriceps femoris muscles with reasonable accuracy during brief subtetanic and tetanic isometric contractions by using CFTs and VFTs. It successfully predicted nonfatigued force responses when muscles were held at long or short length and fatigued force responses at long length. Subjective and objective evaluations of the force response showed that the shape of the predicted force responses closely matched the responses that were measured. Comparisons between the predicted and measured force-time integrals also suggested excellent agreement between the predicted and measured forces. Although significant differences between the predicted and measured force-time integrals were observed with some stimulation patterns, most differences were small.

Comparison with previous work. The present model differs from most previously developed models, in that it is simpler in structure and has fewer parameters (11, 17, 26, 31). With only four free parameters, the model allows precise and unique parameter estimation from the force data. This conclusion was based on the convergence to the same parameter values starting...
from different initial estimates. In addition, this model is the first to be tested on muscles under different physiological conditions.

The process of muscular contraction at the molecular level is very complicated. Many steps, however, may not contribute significantly to force generation and would not be detectable from analysis of force data alone (27). Previous investigators have tried other approaches to a simpler model. Schultz and colleagues (25) developed a simple Hill-type model, also with four independent parameters. Their model was designed to predict the time course of the muscle force during

Fig. 6. Measured and predicted forces from a typical subject’s nonfatigued quadriceps femoris muscle held at long length (90° knee flexion). Model parameter values were obtained by fitting model to CFT70 (C).
isometric tetanic and isovelocity shortening contractions. Unlike the model presented in this study, however, the model developed by Schultz and colleagues cannot predict the force-time response to unfused tetanic, subtetanic, or variable-frequency stimulations. Recently, Shames and colleagues (26) developed a simple version of a Huxley-type model, also with four parameters, to explore the Ca\textsuperscript{2+}-force relationship during isometric tetanic contractions. With use of the Ca\textsuperscript{2+} transient as input, their model successfully fit the forces produced during isometric tetanic contractions of various durations and isometric twitch contractions. However, this model has limited predictability, because the Ca\textsuperscript{2+} transient is not typically available.
An advantage of the present model over our previously reported model (31) is that it can predict force responses from fatigued muscles. The previous model failed to predict the forces from fatigued muscles by fitting the force in response to a single CFT. Subsequent studies with our previous model also showed that using the responses to more than one frequency of stimulation (e.g., the force produced in response to a high- and a low-frequency train, see METHODS, Stimulations) to identify the parameter values of the model did not improve the accuracy of the model to predict forces. The present model was also successful with human muscles at long and short lengths, although the short-muscle-length condition was not tested on the previous model.
Fig. 9. Comparison of force-time integrals between measured and predicted forces of 12 nonfatigued human quadriceps femoris muscles held at long length. A and C: plots of predicted vs. measured force-time integral for 12 CFTs and 12 VFTs, respectively, analyzed for each of 12 muscles. B: force-time integrals (means ± SE) vs. stimulation type for CFTs (CFT10–CFT120). D: force-time integrals (means ± SE) vs. stimulation type for VFTs (VFT10–VFT120). Significant difference between measured and predicted force-time integrals for each stimulation pattern: *P < 0.05, **P < 0.01.

Fig. 10. Comparison of force-time integrals between measured and predicted forces of 11 fatigued human quadriceps femoris muscles held at long length. A and C: plots of predicted vs. measured force-time integral for 12 CFTs and 12 VFTs, respectively, analyzed for each of 11 muscles. B: force-time integrals (means ± SE) vs. stimulation type for CFTs (CFT10–CFT120). D: force-time integrals (means ± SE) vs. stimulation type for VFTs (VFT10–VFT120). Significant difference between measured and predicted force-time integrals for each stimulation pattern: *P < 0.05, **P < 0.01.
The quality of the present model’s predictions was independent of the twitch contraction times of the muscles. In contrast, the previous model failed to predict forces of all six nonfatigued rat gastrocnemius muscles with twitch-contraction times >25 ms.

Parameter interpretation. The advantage of Hill- and Huxley-type models over pure mathematical models is that the parameter values may be physiologically meaningful and the interpretation of the changes of those values with muscle condition can provide useful insight into the mechanisms of muscle contraction and fatigue (12). The parameters of this model, derived from Hill’s original model and based on the mechanisms of muscle contraction, may also be helpful in elucidating characteristics of muscle physiology.

Of the four model parameters, A is directly responsible for the magnitude of the force. When the muscle is fatigued or at short length, the force declines. Thus a decrease in the values of A for fatigued muscle or muscle placed at short length is expected. Our results are consistent with this expectation (Table 3).

The relaxation of the force is primarily determined by \( \tau_1 \), because the contribution of \( \tau_2 \) diminishes rapidly with the decline of \( C_N \), which always precedes the force relaxation (23). Fitch and McComas (14) observed a slower muscle relaxation in fatigued muscles, whereas Gandevia and McKenzie (15) observed faster relaxation of nonfatigued shortened human muscle. The increases and decreases in the fitted values of \( \tau_1 \) (Table 3) for fatigued and short-length muscles, respectively, are consistent with these previous findings.

The parameter \( \tau_2 \) is the characteristic time for \( C_N \) to reach its peak and for it to decay to zero. The interpretation of the changes of \( \tau_2 \) across conditions is difficult. Many underlying physiological steps, such as \( \text{Ca}^{2+} \) release from and uptake by the sarcoplasmic reticulum, \( \text{Ca}^{2+} \) binding to and dissociation from troponin, and cycling between the strongly bound and weakly bound cross bridges, may affect the time course of \( C_N \). Also, it is unclear which of the steps is rate limiting (27). Until we have a more complete understanding of cross-bridge activation, we cannot properly interpret \( \tau_2 \). However, some previous experimental findings could, in part, explain our results. The prolonged \( \text{Ca}^{2+} \) transient with fatigued muscles observed by Westerblad and Allen (30) could be one of the causes for an increased \( \tau_2 \) for fatigued muscles (Table 3). Reduced \( \text{Ca}^{2+} \) sensitivity to troponin (3, 28) when muscles are at short length could cause less troponin-\( \text{Ca}^{2+} \) complex to be formed and, consequently, lead to activation of fewer cross bridges. Thus the decrease in \( \tau_2 \) with muscles at short length could also be explained.

As the characteristic time in the force equation (Eq. 7), the sum of \( \tau_1 \) and some fraction of \( \tau_2 \) determines the overall rate of rise of force. When muscles were activated with CFTs, Binder-Macleod et al. (8) observed a slowing in the rate of rise of force as the muscles fatigued. In contrast, there was no difference in the rise time between the fatigued and the nonfatigued muscles when they were stimulated with VFTs (8). The increases of \( \tau_1 \) and \( \tau_2 \) for CFTs and increase of \( \tau_1 \) and decrease of \( \tau_2 \) for VFTs as the muscles become fatigued.
Table 3. Averaged best-fit parameter values

<table>
<thead>
<tr>
<th></th>
<th>$\tau_1$, ms</th>
<th>$\tau_2$, ms</th>
<th>$A$, N/ms</th>
<th>$\tau_0$, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatigued</td>
<td>24.23±7.0</td>
<td>5.57±1.5</td>
<td>1.63±0.6</td>
<td>234.69±186.1</td>
</tr>
<tr>
<td>Fatigued</td>
<td>39.07±8.4*</td>
<td>8.65±5.4</td>
<td>0.55±0.4*</td>
<td>164.02±241.6</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long length, nonfatigued</td>
<td>46.2±7.4</td>
<td>21.1±2.1</td>
<td>4.7±1.7</td>
<td>340.1±166.4</td>
</tr>
<tr>
<td>Long length, fatigued</td>
<td>59.3±12.2*</td>
<td>23.3±3.1*</td>
<td>1.5±0.5*</td>
<td>487.7±219.6*</td>
</tr>
<tr>
<td>CFT</td>
<td>59.3±12.2*</td>
<td>25.1±3.5*</td>
<td>2.3±0.5*</td>
<td>168.8±113.0*</td>
</tr>
<tr>
<td>VFT</td>
<td>34.3±7.0*</td>
<td>16.9±3.0</td>
<td>1.8±0.7*</td>
<td>616.6±395.1</td>
</tr>
<tr>
<td>Short length, nonfatigued</td>
<td>16.2±2.9*</td>
<td>2.1±0.8*</td>
<td>562.3±423.5</td>
<td></td>
</tr>
<tr>
<td>CFT</td>
<td>59.3±12.2*</td>
<td>25.1±3.5*</td>
<td>2.3±0.5*</td>
<td>168.8±113.0*</td>
</tr>
<tr>
<td>VFT</td>
<td>34.3±7.0*</td>
<td>16.9±3.0</td>
<td>1.8±0.7*</td>
<td>616.6±395.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Significantly different from nonfatigued muscles for rat and long-length nonfatigued muscles for human, P < 0.05.

APPENDIX

Muscle force has been assumed to be proportional to the amount of Ca$^{2+}$-troponin complex in some models (11, 27, 31) or the amount of strongly bound cross bridges in others (26, 27, 29), suggesting that these factors play a similar role in muscle activation. Therefore, we used one unitless factor, C, to represent the single rate-limiting step before the myofilaments mechanically slide across each other. No experimental data have elucidated the dynamics of the Ca$^{2+}$-troponin complex or the strongly bound cross-bridge transients during muscle contraction. However, studies of Chou and Hannaford (11) and Wexler et al. (31) suggest a Ca$^{2+}$-transientlike curve for the dynamics of the Ca$^{2+}$-troponin complex. Therefore, we assumed a similar transient shape for C, which can be expressed as

$$\frac{dC}{dt} = \frac{1}{\tau_1} \sum_{i=1}^{n} \exp \left( -\frac{t - t_i}{\tau_1} \right) - \frac{\tau_1 + \tau_2}{\tau_1 \times \tau_2} C$$  \hspace{1cm} (A1)

where $n$ is the number of pulses before time $t$ in the train and has a maximum value of 6 in this study, $t_i$ represents the times that the electrical stimulation was applied, and $\tau_1$ and $\tau_2$ are the time constants controlling the shape and height of C.

Pilot studies with this model showed that the force production was not sensitive to the magnitude of C, because the effect of increased height of C could be compensated for by adjustment of parameter values in the force equation. Therefore, we normalized Eq. A1 by dividing the right and left side by $(\tau_1 + \tau_2)$, which gives

$$\frac{dC_N}{dt} = \frac{\tau_1 + \tau_2}{\tau_1 \times \tau_2} \sum_{i=1}^{n} \exp \left( -\frac{t - t_i}{\tau_1} \right) - \frac{\tau_1 + \tau_2}{\tau_1 \times \tau_2} C_N$$ \hspace{1cm} (A2)

where $C_N$ represents the normalized C and is equal to $C(t_{i+1} + t_{i+2})/t_{i+2}$. Pilot studies showed a relationship between $\tau_1$ and $\tau_2$ and that the model worked best when $\tau_1$ was much larger than $\tau_2$. Therefore, Eq. A2 can be further simplified to

$$\frac{dC_N}{dt} = \frac{\tau_1 + \tau_2}{\tau_1 \times \tau_2} \sum_{i=1}^{n} \exp \left( -\frac{t - t_i}{\tau_c} \right) - \frac{1}{\tau_c} C_N$$ \hspace{1cm} (A3)

There are a number of linearly dependent analytic solutions to Eq. A3. The one chosen to represent the transient behavior of $C_N$ is

$$C_N = \sum_{i=1}^{n} \left( \frac{t - t_i}{\tau_c} \right) \exp \left( -\frac{t - t_i}{\tau_c} \right)$$ \hspace{1cm} (A4)

Fig. 12. Typical predicted responses of $C_N$ to 3 types of stimulation patterns. Thin solid line, CFT100 (CFT with 100-ms IPIs); dashed line, VFT100 (VFT with initial IPI of 5 ms and remaining pulses equally spaced by 100 ms); thick solid line, CFT20 (CFT with 20-ms IPIs). $\tau_c = 20$ for all 3 responses.
because, among the choices tested, this solution provided the best fits to the force data. Examples of the changes in $C_n$ are shown in Fig. 12.

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