A Dynamical Model of Muscle Activation, Fatigue, and Recovery

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ABSTRACT A dynamical model is presented as a framework for muscle activation, fatigue, and recovery. By describing the effects of muscle fatigue and recovery in terms of two phenomenological parameters (F, R), we develop a set of dynamical equations to describe the behavior of muscles as a group of motor units activated by voluntary effort. This model provides a macroscopic view for understanding biophysical mechanisms of voluntary drive, fatigue effect, and recovery in stimulating, limiting, and modulating the force output from muscles. The model is investigated under the condition in which brain effort is assumed to be constant. Experimental validation of the model is performed by fitting force data measured from healthy human subjects during a 3-min sustained maximal voluntary handgrip contraction. The experimental results confirm a theoretical inference from the model regarding the possibility of maximal muscle force production, and suggest that only 97% of the true maximal force can be reached under maximal voluntary effort, assuming that all motor units can be recruited voluntarily. The effects of different motor unit types, time-dependent brain effort, sources of artifacts, and other factors that could affect the model are discussed. The applications of the model are also discussed.

INTRODUCTION

The major function of muscle is to produce force. There have been numerous attempts to model muscle force mathematically, ranging from the simplest to the most comprehensive ones that consider many physiological and mechanical factors of the muscle such as muscle length, shortening velocity, neural activation, and muscle architecture (Coggshall and Bekey, 1970; Pell and Stanfield, 1972; Christakos and Lal, 1980; Woittiez et al., 1984; Hannaford, 1990; Schultz et al., 1991; Wexler et al., 1997; Bobet and Stein, 1998; Studer et al., 1999). In most models, muscle force is calculated by summing the forces produced by individual muscle fibers. For example, Fuglevand et al. (1993) developed a model based on simulating the response of single motor units under stimulation. This model can describe the early stage of muscle activation approximately, i.e., the period from onset of muscle activation to the time when peak activation is reached. Herbert and Gandevia (1999) improved Fuglevand's model by introducing a more accurate single motor unit response curve.

When a muscle contraction is sustained, muscle becomes fatigued, and force production is affected by underlying fatigue and recovery effects in the neuromuscular system (Merton, 1954; Bigland-Ritchie, 1981; Enoka and Stuart, 1992; McComas et al., 1995). However, previous force models did not generally consider fatigue and recovery effects, therefore, they cannot be used to describe the time course of force production for an extended period of time, during which fatigue and perhaps recovery effects become more apparent.

Hawkins and Hull (1992, 1993) recognized the importance of the fatigue effect during tasks lasting long periods of time. They considered the fatigue effect in their prediction of muscle force production by incorporating several empirical fatigue indices such as fiber endurance times and fatigue rates into a muscle fiber-based model that calculated muscle force as the sum of individual fiber forces. Rather than deriving the force–time function based on a consistent simple biophysical principle, they established the force–time dependence based on empirical data. Because these empirical quantities need to be determined from other experiments and the accuracy is difficult to achieve, this model could not give satisfactory prediction of force. A group of investigators developed a model to predict force output as a function of time in paralyzed quadriceps muscle under interrupted functional electrical stimulation based on electromyogram data and muscle metabolic history (Giat et al., 1993, 1996; Levin and Mizrahi, 1999). This model relies heavily on accurately measuring of temporal changes in muscle metabolites, i.e., the inorganic phosphorus (Pi or $H_2PO_4^-$) measured by in vivo ^{31}P magnetic resonance spectroscopy, intracellular pH, and other data obtained from various sources and literature. Riener and colleagues developed their model based on a motor unit recruitment function and considered muscle fatigue and recovery effects by introducing a muscle fitness function (Riener et al., 1996; Riener and Quintern, 1997). Both of these empirical functions need to be predetermined.

A common feature of these models is that many physiological and biomechanical parameters need to be determined. For example, in Riener's model, there are more than 28 parameters, and in Giat's model, more than 30. The complicated formulae in these models have obscured the biophysical principles of muscle force generation and hin-

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dered their more general applications. Another major disadvantage of the models is that they did not attempt to connect the brain and the muscle. Because all voluntary muscle activities are controlled by the central nervous system (CNS) through the peripheral nerve connections, a theoretical framework is needed for quantitatively determining, and thus better understanding of, the relationship between voluntary effort from the brain and force output from the muscle. Recently, data correlating the CNS and the peripheral have become increasingly available upon the emergence of new functional brain imaging technologies, such as functional magnetic resonance imaging, and other techniques (Liu et al., 2000, 2001; Dai et al., 2001).

In this article, a dynamical model that can predict muscle force over an extended period of time when muscle undergoes processes of activation, fatigue, and recovery is described. The model is built up directly from basic biophysical principles of prolonged muscle force production under a voluntary brain effort. Due to its unique view angle, the model (in its basic form) contains only three parameters, i.e., fatigue factor (F), recovery factor (R), total number of motor units in the muscle (M_0), and one input variable, i.e., brain effort (B). The clear biophysical picture and the relatively few parameters make the model suitable for data fitting and more general applications. The model also provides the theoretical framework for a better understanding of muscle activation, fatigue, and recovery. More importantly, the model directly relates brain and muscle by considering brain effort as an input variable, which is experimentally determinable and may be simulated by electrical stimulation. All three parameters can be determined directly from fitting the experimental force data.

In the following sections, the biophysical mechanisms relevant to muscle activation, fatigue, and recovery are reviewed first. Second, the model is developed and examined theoretically. Third, the model is applied to fit the force data obtained in the recent fatigue experiments (Liu et al., 1999; Liu, 2000) to test the validity of the model. Finally, several aspects that are important for the improvement of the model and potential applications of the model are discussed.

METHODS: MODEL DEVELOPMENT AND VALIDATION

Biophysical mechanisms of muscle activation, fatigue, and recovery

Muscle is made of muscle fibers. Production of force and movement is realized by contraction of muscle fibers driven by nervous-system command. The basic functional unit of muscle is the motor unit, which consists of a motoneuron and the muscle fibers that it innervates. Motoneurons are the major efferent neurons that supply muscle fibers with control commands from the CNS. The muscle fibers of a motor unit are of the same type and have the same metabolic profile so that, when they are activated, they behave in the same manner. A muscle consists of many motor units.

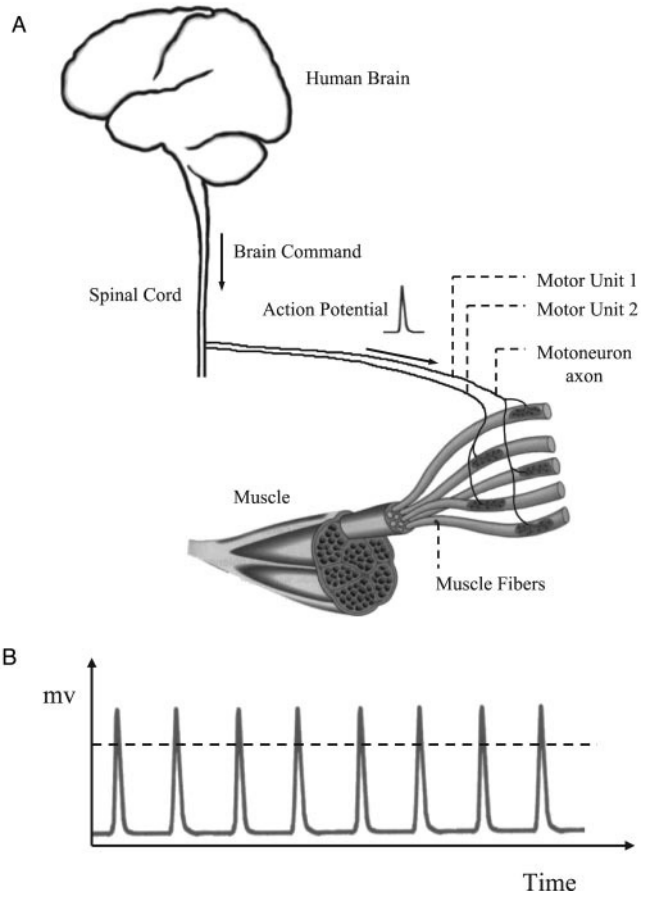

FIGURE 1 (A) Schematic illustration of the human nervous system and muscle. The brain sends down a command (voluntary drive) through the spinal cord and peripheral nerves to muscle. Muscle is made of motor units. A motor unit contains a motoneuron and the muscle fibers it innervates. When a stimulus arrives at a motor unit and it is strong enough, it triggers an action potential, which in turn activates the motor unit. Force is generated by contraction of muscle fibers. (B) Action potential series. If the brain command continues, it triggers a series of action potentials, which keep activating the motor units to produce a sustained force.

The exact number depends on the size and function of the muscle, ranging from a few for small muscles up to several thousand for the largest (Fig. 1 A).

To generate force or movement, a command signal, which can be initiated voluntarily or by other means, must be sent to the muscle. For a voluntary muscle action, the command, in the form of an electrical impulse, is transmitted from the brain through the descending pathways to the motoneurons and the muscle fibers they control. If the stimulus (command) exceeds a threshold, it will trigger action potentials of the motor units (see, for example, McArdle et al., 1996; Ganong, 1971). After an action potential is triggered in a motor unit, all the muscle fibers of this motor unit contract synchronously. We then consider this motor unit to be activated (Fig. 1 A).

It is noteworthy that a stimulus either elicits an action potential or not—there is no state in between. That is to say, when a stimulus arrives, if it is strong enough, it triggers an action potential, and all the muscle fibers of the motor unit are activated together. As a consequence, a summation force is produced by the synchronous contraction of the fibers. However, if the stimulus is not strong enough, no action potential will be triggered, and hence, no fiber in the motor unit will be excited, nor will the motor unit as a whole. Borrowing a phrase from physics, the muscle has

been "quantized." Quantization makes the picture clear and the modeling work easier to perform. This point can be seen clearly in the next section, in which the model of muscle dynamics is developed.

To perform a specific movement, generally many motor units in a muscle or a group of muscles need to be activated. The generated movement and force are the collective macroscopic effects of all the activated motor units. For tasks requiring low force, fewer motor units are active, whereas for tasks requiring high force, most or all motor units in the related muscles need to be activated.

When a prolonged voluntary muscle contraction is sustained, the brain continuously reinforces the descending command. In this situation, a series of action potentials are provoked continuously and they keep bombarding the motor units and activating them (Fig. 1 *B*). After being activated for a period of time, the activated motor units start to develop fatigue due to factors such as insufficient supplies of oxygen and glycogen, increased lactic acid level in blood and muscle, etc. (Fitts, 1994; McArdle et al., 1996). When fatigue occurs, the threshold to trigger action potentials in a motor unit increases, i.e., the motor unit's tendency to fire decreases. Thus, the discharge rate declines (Bigland-Ritchie, 1981). If fatigue keeps building up, the motor unit will eventually reach a critical point beyond which it can no longer be activated. In other words, it becomes completely fatigued (Enoka and Stuart, 1992; Fitts, 1994; McComas et al., 1995; McArdle et al., 1996).

When a force is generated and maintained, motor units in the involved muscles are recruited gradually. Some motor units are activated first. Later on, when they become fatigued, more motor units need to be recruited from the motor unit pool of the muscles to compensate for the loss of force due to fatigue. Meanwhile, the fatigued units start to recover. For tasks requiring very low force, fatigue will not be accumulated, and the muscles are able to perform the task without fatigue. However, for tasks requiring high force, such as performing a sustained maximal voluntary contraction (MVC) (Liu et al., 1999; Liu, 2000), the recovery mechanism cannot counteract the fatigue effect quickly enough. Hence, after a period of time, when all motor units in the muscles have developed fatigue and cannot be activated anymore, these muscles are then totally fatigued and the task of producing force or movement cannot be continued.

Based on the scenario described above, we can divide the motor units of the muscles involved in a task into three groups: those currently in activated state, those already fatigued, and those in the rest state (not yet activated). In the next section, a dynamical model will be developed to describe the behaviors of these three groups of motor units by considering the brain command as a driving force. The fatigue effect and fatigue-like contributions are taken into account by a simple representation in terms of one parameter, *F*, whereas recovery effect and recovery-like contributions are represented by another parameter, *R*.

In the above discussion, we have assumed there is only one type of motor unit. Practically, there are three major types of motor units. However, the assumption of a single motor unit type does not invalidate the model being developed. In fact, this simplification makes the biophysical picture clearer and the development of the model easier. Thus, the model is first developed on the assumption of a single motor unit type. The effects of the three types of motor units on the model and how to accommodate them into the model are discussed thereafter.

Model of muscle activation, fatigue, and recovery

Based on the biophysical mechanisms, we can develop a model for the process of muscle activation, fatigue, and recovery. In Fig. 2, M_0 is denoted as the total number of motor units in a muscle or a group of synergistic muscles related to a specific task. (Note that, at this moment, we assume there is only one type of motor unit.) M_A is the number of motor units being activated by the voluntary drive. M_F is the number of motor units that are already fatigued after a period of activation. M_{uc} is the number of motor units that are in the rest state, i.e., they have not been activated. All three quantities are functions of time. At the initial time ($t = 0$), all motor units are in the rest state. Therefore, when $t = 0$, $M_A = 0$, $M_F = 0$, $M_{uc} = M_0$.

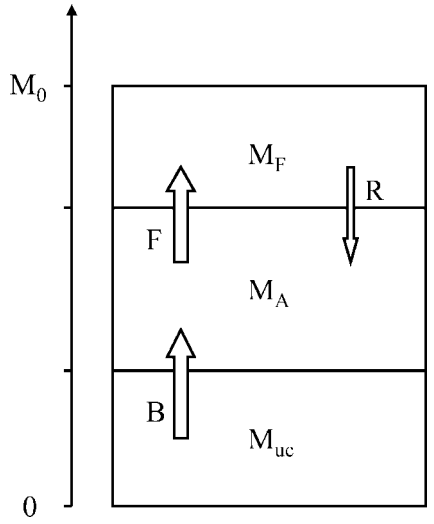

FIGURE 2 Illustration of the three groups of motor units and the dynamical relationships among them. The total available motor units (M_0) are divided into three groups: those in the activation state (M_A), those already fatigued (M_F), and those still in the rest state (M_{uc}). Brain command or effort drives the motor units into activation at rate *B*. The fatigue effect drives the activated motor units into the fatigued state at rate *F*. The recovery effect makes the fatigued motor units get recovered at rate *R*.

In this model, the input stimulus to the motor units, i.e., the brain effort, is the driving force provoking muscle activation and is denoted as *B*. *B* represents the rate at which the motor units are stimulated and prompted into the activation state. Two phenomenological parameters related to the response characters of the muscle are introduced. The fatigue effect of muscle is described by a fatigue factor (*F*), whereas the recovery effect is described by a recovery factor (*R*). *F* represents the rate at which the activated motor units are moved into the fatigued state. *R* represents the rate at which the fatigued motor units are recovered from the fatigued state. Thus, a greater value of *F* indicates a greater fatigue effect, i.e., the muscle fatigues faster, whereas a greater *R* value indicates a more prompt recovery. In the macroscopic view, a command from the brain (*B*) drives the motor units to activation state; the fatigue effect (*F*) makes some activated motor units fatigued; the recovery effect (*R*) corresponds to the recovery of previously fatigued motor units such that they can again participate in the activation. The arrows in Fig. 2 indicate the action directions of *B*, *F*, and *R*.

From this picture, a set of dynamical equations can be written as

$$\frac{dM_A}{dt} = B \cdot M_{uc} - F \cdot M_A + R \cdot M_F, \tag{1a}$$

$$\frac{dM_F}{dt} = F \cdot M_A - R \cdot M_F, \tag{1b}$$

$$M_{uc}(t) = M_0 - M_A(t) - M_F(t). \tag{1c}$$

The initial conditions are

$$M_A(t = 0) = 0, \tag{1d}$$

$$M_F(t = 0) = 0, \tag{1e}$$

$$M_{uc}(t = 0) = M_0. \tag{1f}$$

Eqs. 1a–c plus the initial conditions in Eqs. 1d–f are the basic and complete set of equations that describe the dynamical behaviors of the motor units in

the muscles as a group when they are activated, fatigued, and under recovery.

In the most general form, brain effort is a function of time, i.e., $B(t)$, and the specific shape of the function depends on real situations. Below, the model in which B is a constant is fully investigated. Application of the model under time-dependent brain effort is briefly addressed in the Discussion.

For a specific person in a specific experiment involving muscle fatigue, it is reasonable to assume that muscle properties are constant during a limited experimental period, which ranges typically from seconds to minutes. Under this condition, we can take the fatigue parameter F and recovery parameter R to be constants. However, these parameters are likely to vary if a long time passes or if the subject changes life style or physical conditions. In fact, the changing patterns of these parameters may potentially be utilized for clinical purposes (see Discussion).

It is worthwhile to emphasize that F may include both the real fatigue effect and all other types of fatigue-like effects, and R may include both the real recovery effects and all other types of recovery-like effects. The fatigue-like effects and recovery-like effects are types of artifacts that might conceal the real effects we expect to see in the experiments. Careful differentiation between real factors and false factors can help to single out the true effects and to filter out the false ones. This point is more carefully addressed in the Discussion.

Model under constant brain effort

Brain effort B is first assumed to be a constant. This assumption would be most probably fulfilled in the case of maximal brain effort during a sustained MVC (Bigland-Ritchie, 1981). In this situation, the brain attempts to generate the maximal effort to maintain the maximal muscle output throughout the task, and hence, it is reasonable to consider that $B(t) = B_{max}$ = constant. The fatigue and recovery factors F, R are also assumed to be constants (see Discussion). Although the approximation that B is constant may need to be modified in the future to accommodate real situations, this basic model can demonstrate the major features of how a muscle gets activated, fatigued, and recovered during a sustained MVC.

From Eqs. 1a and b and taking B, F, and R as constants, we have

$$\frac{d^2M_A}{dt^2} + (B + F + R)\frac{dM_A}{dt} + B(F + R)M_A - BRM_0 = 0, \tag{2a}$$

$$\frac{d^2M_F}{dt^2} + (B + F + R)\frac{dM_F}{dt} + B(F + R)M_F - BFM_0 = 0, \tag{2b}$$

$$M_{uc}(t) = M_0 - M_A(t) - M_F(t). \tag{2c}$$

The solutions to these equations are shown in the Appendix (Eq. A12). It is convenient to write the parameters in terms of

$$\beta = B/F, \tag{3a}$$

$$\gamma = R/F, \tag{3b}$$

where β is the command-to-fatigue ratio and γ is the recovery-to-fatigue ratio. β determines the maximal activation level that can be reached, and γ determines the speed of recovery relative to fatigue, its counterpart, which has an opposing effect. These characteristics will become clear when the results are analyzed in the following sections. The solutions can be written as

$$\frac{M_A(t)}{M_0} = \frac{\gamma}{1+\gamma} + \frac{\beta}{(1+\gamma)(\beta-1-\gamma)}e^{-(1+\gamma)Ft} - \frac{\beta-\gamma}{\beta-1-\gamma}e^{-\beta Ft}, \tag{4a}$$

$$\frac{M_F(t)}{M_0} = \frac{1}{1+\gamma} - \frac{\beta}{(1+\gamma)(\beta-1-\gamma)}e^{-(1+\gamma)Ft} + \frac{1}{\beta-1-\gamma}e^{-\beta Ft}, \tag{4b}$$

$$\frac{M_{uc}(t)}{M_0} = e^{-\beta Ft}. \tag{4c}$$

We can also define the parameters in the form of relaxation times,

$$T_F = \frac{1}{F}, \quad T_R = \frac{1}{R}, \quad T_F^* = \frac{1}{F+R}, \quad T_B = \frac{1}{B}. \tag{5}$$

T_F is named as the muscle fatigue relaxation time, T_R the muscle recovery relaxation time, and T_B the brain relaxation time. We consider T_F^* as the modulated fatigue relaxation time (in the sense of fatigue being modulated by the recovery effect). In this case, the solutions can be written as

$$\frac{M_A(t)}{M_0} = \{1 - e^{-t/T_B}\} - \frac{1}{1+\gamma}\{1 - e^{-t/T_F^*}\} + \frac{1}{\beta-1-\gamma}\{e^{-t/T_F^*} - e^{-t/T_B}\}, \tag{6a}$$

$$\frac{M_F(t)}{M_0} = \frac{1}{1+\gamma}\{1 - e^{-t/T_F^*}\} - \frac{1}{\beta-1-\gamma}\{e^{-t/T_F^*} - e^{-t/T_B}\}, \tag{6b}$$

$$\frac{M_{uc}(t)}{M_0} = e^{-t/T_B}. \tag{6c}$$

The typical curves of $M_A(t)$, $M_F(t)$, and $M_{uc}(t)$ are shown in Fig. 3. To show details of all three curves, the time scale has been taken as arbitrary. The ordinate indicates the percentage proportion of each of the three groups of motor units relative to the total motor unit numbers in the involved muscles. These curves show the major features of the solutions, i.e., the typical behavior of each motor unit group.

The curves show that, under the drive of brain command B, the number of activated motor units $M_A(t)$ increases sharply from zero to its maximal level. Then it starts to decrease, but quite slowly compared to its rapid increase. The decrease in the number of activated motor units, without question, is due to the fatigue effect (F). If there were no fatigue, the curve would increase monotonically. (This point can be seen clearly in Eqs. 4a, b, and c by letting F and consequently R to be zero.) The final value of $M_A(t)$ at $t \to \infty$, to be shown in Eq. 10a, is $R/(F + R) \cdot M_0$. The finiteness of this limiting value indicates the existence of the recovery effect (R). The relevance of these facts to the experimental data is clear. In a prolonged MVC experiment, if the force curve levels off and decreases after increasing during an initial period, it indicates the existence of the fatigue effect. If a nonzero residual force is observed at the ending period of an experi-

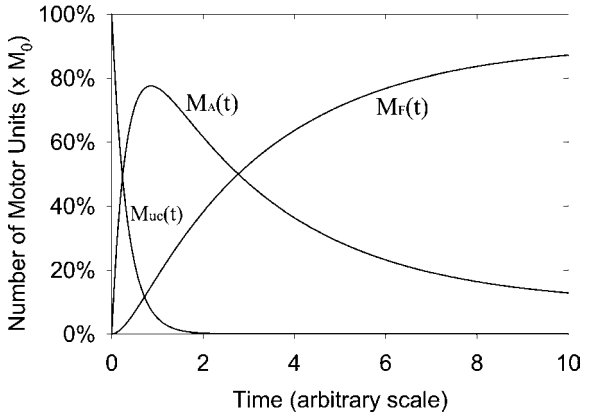

FIGURE 3 Illustration curves of the solutions to the basic model (B, F, and R are all constant). The ordinate indicates the percentage proportion of each of the three groups of motor units relative to the total number of motor units (M_0) in the muscles: M_A, motor units in activation; M_F, motor units fatigued; M_{uc}, motor units in the rest state. The time scale has been taken as arbitrary to show clearly the details and major features of the curves.

ment, it suggests the existence of a recovery factor (or existence of nonfatigue motor units).

The number of fatigued motor units $M_F(t)$ increases from zero progressively to its maximal value, $F/(F + R) \cdot M_0$, as shown later in Eq. 10b. This indicates that more and more motor units have developed fatigue and can no longer contribute to force production. The inactivated fraction of motor units $M_{uc}(t)$ decreases continuously and monotonically from its maximal value, 100% of the total motor units (M_0), to zero. Its time-limiting value of 0 at $t \to \infty$ indicates that all motor units that can be activated voluntarily will eventually be recruited to participate in force generation, though not at the same time.

Relating force and motor unit number

The next step is to relate the model quantities to the experimentally measurable ones so that the model can be tested against the experimental results and the experiment can, vice versa, possibly be explained in terms of the model. In our case, we measured muscle or joint force generated by constant brain effort, the MVC. Because the subject always exerted a maximal brain effort during the MVC, we assumed that brain effort was constant.

Assume the unit force generated by a single motor unit is u_0. Because, at time t, the total number of motor units being activated is $M_A(t)$, the total generated force at this time is

$$U(t) = u_0 M_A(t). \tag{7}$$

Here, we simplified the force profile of a motor unit, i.e., when it is activated, it generates a fixed force (u_0), whereas in its resting state it has no force output. Actually, when a motor unit is activated, it will produce a force curve as shown in Fig. 4 B rather than an on or off constant pattern shown in Fig. 4 C (Ganong, 1971; Fuglevand et al., 1993; Herbert and Gandevia, 1999). However, we are not talking about a single motor unit, but rather a group of motor units in the pool of the total numbers, which means we have based our discussion on the averaged quantities, or the collective behavior of the activated motor units as a whole. In this sense, the simplification is reasonable and will not undermine the validity of the calculations presented below. (However, when dealing with a small number of motor units, the actual response curve of a motor unit may need to be taken into account. In that case, a microscopic model needs to be constructed, a step to be dealt with in a future work.)

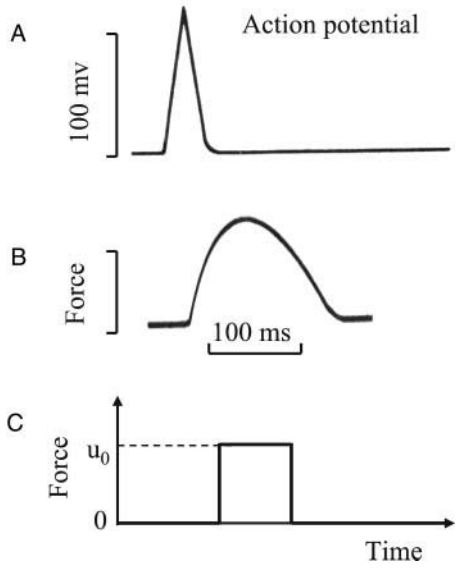

FIGURE 4 Schematic illustration of response of a single motor unit to an action potential. (A) An action potential that is triggered in a motor unit. (B) The force response generated by the motor unit corresponding to the action potential. (C) A simplified binary version of the force response, i.e., the force either jumps to a constant u_0 when the motor unit is activated, or stays at zero.

To simplify the writing for future discussion, let us define m_A, m_F, m_{uc} as the averaged response functions of the three groups of motor units,

$$m_A(t) \equiv \frac{M_A(t)}{M_0}, \quad m_F(t) \equiv \frac{M_F(t)}{M_0}, \quad m_{uc}(t) \equiv \frac{M_{uc}(t)}{M_0}. \tag{8}$$

And we define

$$u(t) \equiv \frac{U(t)}{M_0} \equiv \frac{u_0 \cdot M_A(t)}{M_0} = u_0 \cdot m_A(t), \tag{9a}$$

or

$$U(t) = M_0 \cdot u(t) = M_0 \cdot u_0 \cdot m_A(t) \equiv U_0 \cdot m_A(t), \tag{9b}$$

$$\text{where} \quad U_0 = u_0 \cdot M_0. \tag{9c}$$

However, it must be kept in mind that $u(t)$ is not in any sense the stimulated force of a single motor unit responding to an action potential triggered by brain effort, which has been shown in Fig. 4. (The time scales are very different. For $u(t)$, it is on the order of several minutes in this case. However, for the response force of a single motor unit, it is typically only ~50–100 ms (Fuglevand et al., 1993; Herbert and Gandevia, 1999). Thus, the former one is a macroscopic quantity whereas the latter one is microscopic.) It may represent the force envelope of a motor unit responding to a volley of action potentials driven by a continuous brain effort only in the sense of being averaged over a population of activated motor units. Only with this meaning may $u(t)$ represent the activation characteristics of a single motor unit under modulation by the fatigue and recovery effects, and we may call it the averaged force response of one motor unit. From this viewpoint, the total output force $U(t)$ is simply the unit force $u(t)$ multiplied by the total motor unit number M_0, according to Eq. 9.

It should be emphasized that, when we refer to the average response of motor units, the number of total motor units (M_0) is required to be large enough, say about 100. Otherwise, the effect of the motor unit firing rate

will become obvious and needs to be considered (see discussion in the section Discharge Rate of Action Potentials). In our experiments on muscle fatigue (Liu et al., 1999; Liu, 2000), the major agonist muscles involved in the handgrip task included the flexor digitorum profundus, the flexor digitorum superficialis, and many intrinsic muscles of the hand. They contain a large enough number of motor units to satisfy the requirement.

Model parameters and extraction from experimental data fitting

In our model, there are four quantities, all to be determined by experiment. The first one is B, which is the input or neural drive from the brain. There are two phenomenological parameters, F, corresponding to the fatigue effect, and R, corresponding to the recovery effect. These three parameters determine all the response characteristics of the three groups of motor units (the shapes of the three curves) in Fig. 3.

The fourth parameter is the total number of motor units M_0, or equivalently, the true maximal force U_0 when fitting the experimental force curves. Basically, U_0 is just a multiplier to the unit curve $m_A(t; B, F, R)$, and it determines the real amplitude of the theoretical curve. By comparing the magnitudes of the experimental curve to the theoretical curve, we can determine U_0. Additionally, from the values of U_0 extracted from data fitting, and with the knowledge of the unit force u_0 produced by a single motor unit, we can possibly estimate the total number of motor units (M_0) involved in the activation, which equals U_0/u_0.

Therefore, the theoretical function that will be used for the data fitting is $U_0 \cdot m_A(t; B, F, R)$. Based on the analysis of the demonstration curves in Fig. 3, we know that B and F determine the highest point that $m_A(t; B, F, R)$ can reach; F also determines the bending shape of the curve, and R determines the residual force at the late period of the curve. U_0 determines the actual size of the curve.

Limiting values at $t \to \infty$

From the solutions (Eqs. 4a, b, and c), it is easy to get the asymptotic values of m_A, m_F, m_{uc} when time goes to infinity, i.e.,

$$t \to \infty \begin{cases} m_A = \dfrac{M_A}{M_0} \to \dfrac{R}{F+R} = \dfrac{\gamma}{1+\gamma}, & (10a) \\ m_F = \dfrac{M_F}{M_0} \to \dfrac{F}{F+R} = \dfrac{1}{1+\gamma}, & (10b) \\ m_{uc} = \dfrac{M_{uc}}{M_0} \to 0. & (10c) \end{cases}$$

These equations demonstrate that the fatigue factor and the recovery factor are the only determinants of the limiting values. It means that the force level at the final stage of a prolonged fatigue experiment is fixed for a specific person, regardless of how much effort is exerted, as long as the effort is kept constant.

If there had been no noise contributions in the data, we could easily use the limiting value of M_A/M_0 to determine the recovery-to-fatigue ratio γ from a prolonged muscle fatigue experiment. Of course, noise is always present, so the observed residual (limiting) value generally does not represent the true recovery and fatigue effects alone. The sources of artifacts interfering with the fatigue and recovery effects are addressed in the Discussion.

Maximal activation level and rise time

From Eq. 4a, we can get

$$\frac{dm_A}{dt} = \frac{\beta}{\beta - 1 - \gamma}\left[(\beta - \gamma)e^{-\beta t} - \beta e^{-(1+\gamma)t}\right]. \quad (11)$$

Let

$$\left.\frac{dm_A}{dt}\right|_{t=T_m} = 0. \quad (12)$$

We get

$$T_m = \frac{\ln(B-R) - \ln F}{B - F - R} = \frac{1}{F}\frac{\ln(\beta - \gamma)}{\beta - 1 - \gamma}. \quad (13)$$

At time $t = T_m$, the activation $m_A(t)$ reaches its maximal level m_A^{max},

$$\begin{aligned} m_A^{max} &\equiv \frac{M_A(t = T_m)}{M_0} \\ &= \frac{F}{F+R}\left\{\frac{R}{F} + \exp\left[-\frac{F+R}{B-F-R}\ln\left(\frac{B-R}{F}\right)\right]\right\} \\ &= \frac{1}{1+\gamma}\left\{\gamma + \exp\left[-\frac{1+\gamma}{\beta - 1 - \gamma}\ln(\beta - \gamma)\right]\right\} \\ &= \frac{1}{1+\gamma}\{\gamma + \exp[-(1+\gamma)FT_m]\}. \end{aligned} \quad (14)$$

We call T_m the time of maximal activation. Because it represents the time needed for the activation level to rise from zero to its maximum, it is also called the rise time.

β effect

As defined in Eq. 3a, $\beta = B/F$ is the ratio of brain effort to fatigue factor. Obviously, the higher the brain effort or the lower the fatigue factor, the greater the value of β. It is easy to understand that this quantity determines the activation level of the muscle. The greater the β, the larger number of motor units are being activated. This point can be proved by drawing the $m_A(t)$ curves under different β values. In Fig. 5, three curves corresponding to $\beta = 100$, 10, and 2 are drawn as examples according to Eq. 4a by taking $F = 0.02$, $\gamma = 0.2$. The curve of bigger β increases faster than the curve of smaller β. The maximal activation level for bigger β is higher than that for smaller β. An interesting phenomenon is that the curve of bigger β also decreases faster. This reflects the physiological fact that the faster a muscle can be activated (shorter rise time), the faster it fatigues.

The relationships among β, the rise time T_m, and the maximal activation level m_A^{max} are determined by Eqs. 13 and 14. The results have been listed in Table 1 by taking $\gamma = 0$. From this table, we see that a β value of 88 corresponds to the activation level of 95%. This means that, for a designated muscle (F fixed), when a brain effort of $88F$ is applied, 95% of muscle maximal activation capability is reached.

F effect

F is the fatigue factor, which determines the rate of fatigue of the motor units. Therefore, the greater the F, the faster the muscle fatigues. Figure 6 plots the curves of $m_A(t)$ according to Eq. 4a for different F values (0.005 and 0.02, respectively) while β and γ are fixed ($\beta = 100$, $\gamma = 0.2$). An interesting observation is that the faster a muscle is activated (the faster it reaches the

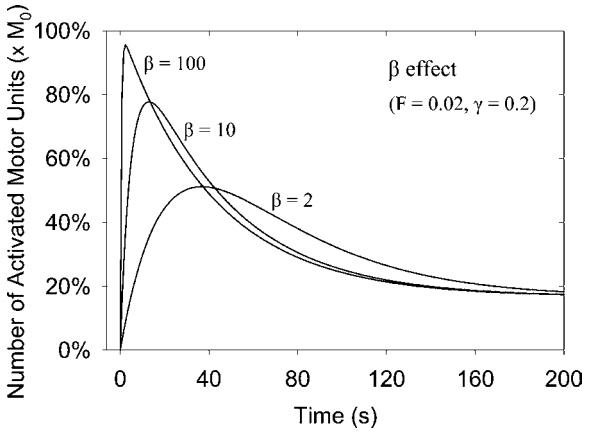

FIGURE 5 β effect. The three curves represent the number of motor units in activation, i.e., $M_A(t)$, when $\beta = 100, 10, 2$, respectively ($F = 0.02$, $\gamma = 0.2$).

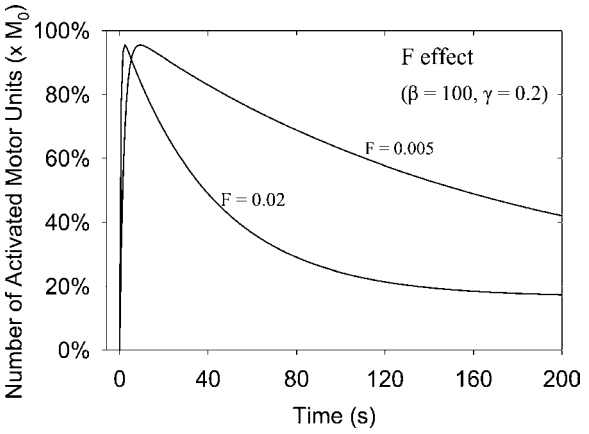

FIGURE 6 F effect. The two curves represent the number of motor units in activation, i.e., $M_A(t)$, when $F = 0.005, 0.02$, respectively ($\beta = 100$, $\gamma = 0.2$).

maximal force), the faster it fatigues (the faster its force output decreases). This may correlate with the fact that some athletes can accelerate and run fast but cannot last for a long time, whereas others can endure long distances but not run as quickly as sprinters. The reason, explained by this model, is that the former have bigger fatigue factors whereas the latter have smaller ones.

γ effect

As defined in Eq. 3b, $\gamma = R/F$ is the ratio of the recovery factor to the fatigue factor. This quantity determines the rate of recovery of the muscle relative to the fatigue effect. The greater the recovery effect, the bigger the γ, and the more slowly the muscle fatigues (i.e., the slower the decline of the force curve generated by the muscles). Therefore, it is easy to understand that γ determines the residual activation level of the muscle, which is the asymptotic value of $m_A(t)$ when time is long enough, i.e., $\gamma/(1 + \gamma)$, as shown in Eq. 10a. The bigger the γ, the higher the residual activation level.

In Fig. 7, four curves of $m_A(t)$ corresponding to four values of γ (0.0, 0.1, 0.2, and 0.3) are drawn according to Eq. 4a by taking $F = 0.02$, $\beta = 100$. These curves show clearly that the governing region of γ is mainly the later stage of muscle activation, during which the residual level depends mainly on γ. During the rise period and at the time around the turning points of the curves, γ has little effect on the $m_A(t)$ curves. This fact is useful for estimating the value of γ when a residual activation level is observed in a prolonged muscle fatigue experiment.

TABLE 1 Relationships among β, the maximal activation level and the rise time (γ was assumed to be 0)

m_A^{max} (%)	β	FT_m
10	0.137	2.303
20	0.353	1.609
30	0.682	1.204
40	1.188	0.916
50	2	0.693
60	3.390	0.511
70	6.044	0.357
80	12.216	0.223
90	34.649	0.105
95	88.37	0.0513
95.45	100	0.04652
99	644.63	0.01005
99.5	1453.73	0.005013
99.9	9114.01	0.0010005
100	∞	0

Extrapolating the true maximal force

People have been long wondering whether true maximal muscle force can be reached solely by voluntary effort (Enoka and Fuglevand, 1992; Dowling et al., 1994). Many technical and analytical methods have been designed to investigate this interesting problem (Belanger and McComas, 1981; Gandevia and McKenzie, 1988; Lindstrom and Bates, 1990; Allen et al., 1995; Behm et al., 1996; De Serres and Enoka, 1998; Shah et al., 1998; Herbert and Gandevia, 1999; Yue et al., 1999, 2000). The most popular approach may be the twitch interpolation technique, which applies electrical stimulations to the muscle while it is under maximal voluntary drive and estimates the true maximal force from the stimulated additional force increases. However, all these methods are not yet accurate, rendering inconsistent and even contradictory results.

The model we have developed offers a more natural explanation of the mechanism of muscle maximal force production and leads to the conclusion that true maximal force cannot be achieved by voluntary effort.

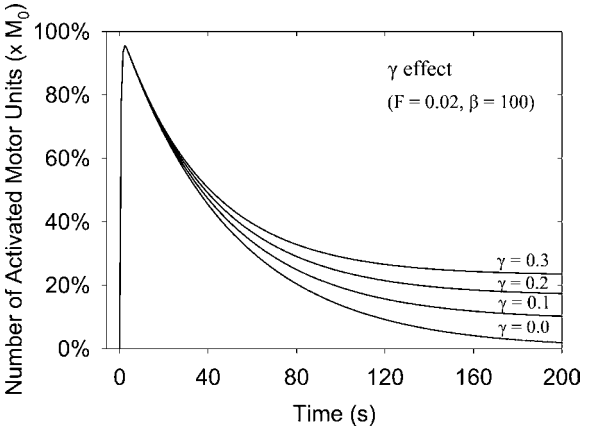

FIGURE 7 γ effect. The four curves represent the number of motor units in activation, i.e., $M_A(t)$, when $\gamma = 0, 0.1, 0.2, 0.3$, respectively ($F = 0.02$, $\beta = 100$).

Furthermore, this model provides a theoretical approach for understanding and extracting the true maximal force. Below we will examine this important application of the model.

We can find from Eq. 14 that the difference between the maximal value of M_A and the total available number of motor units (M_0) is

$$\begin{aligned}\Delta M &\equiv M_0 - M_A^{\max} \\ &= \frac{M_0}{1+\gamma}\left\{1 - \exp\left[-\frac{1+\gamma}{\beta-1-\gamma}\ln(\beta-\gamma)\right]\right\} \\ &= M_F(t=T_m) + M_{uc}(t=T_m),\end{aligned} \tag{15a}$$

or equivalently,

$$\begin{aligned}\delta m &\equiv \frac{\Delta M}{M_0} = 1 - m_A^{\max} \\ &= \frac{1}{1+\gamma}\left\{1 - \exp\left[-\frac{1+\gamma}{\beta-1-\gamma}\ln(\beta-\gamma)\right]\right\}.\end{aligned} \tag{15b}$$

ΔM is the portion of the motor units that cannot be integrated effectively into the synchronous production of force. It includes two parts: the motor units that are already fatigued, i.e., $M_F(t = T_m)$, and the motor units that have not yet participated in the activation, i.e., $M_{uc}(t = T_m)$. These two parts, either fatigued or untouched, do not contribute to the force output.

From Eq. 14, the maximal force generated under voluntary effort B at time $t = T_m$ is

$$\begin{aligned}U^{\max} &= u_0 \cdot M_A^{\max} \\ &= \frac{u_0 \cdot M_0}{1+\gamma}\left\{\gamma + \exp\left[-\frac{1+\gamma}{\beta-1-\gamma}\ln(\beta-\gamma)\right]\right\},\end{aligned} \tag{16}$$

whereas the true maximal force that would be generated if all motor units could be activated at the same time is $U_0 = u_0 \cdot M_0$, as shown in Eq. 9c. To differentiate them, $U^{\max}$ is termed the maximal voluntary force and U_0 the true maximal force. The difference between $U^{\max}$ and U_0 is

$$\begin{aligned}\Delta U &\equiv u_0 \cdot \Delta M = U_0 - U^{\max} \\ &= \frac{u_0 \cdot M_0}{1+\gamma}\left\{1 - \exp\left[-\frac{1+\gamma}{\beta-1-\gamma}\ln(\beta-\gamma)\right]\right\}.\end{aligned} \tag{17}$$

Now it is obvious that the force can never reach its true maximal value. This is because the motor units can never all be in activation at the same time. One reason for this fact is that the motor units are recruited into activation progressively rather than all reacting simultaneously, i.e., the curve of $M_{uc}(t)$ is not zero at a finite time point. However, when a strong brain effort is applied, the number of this part of motor units decreases to zero very rapidly. So, this reason is only secondary. In fact, the fatigue effect is much more important in explaining why true maximal force cannot be reached. It is the fatigue effect that plays a central and critical role in limiting the maximal voluntary force output. At the early stage (the time before T_m), fatigue has not built up significantly and the number of activated motor units increases rapidly under the maximal voluntary drive, being modulated by the fatigue (and recovery) contributions. Around $t = T_m$, the fatigue effect starts to bend the curve of $M_A(t)$ downward (see Fig. 3). From that time on, the number of motor units in the activation state continues to decline under the depressing effect of the fatigue factor, even though the brain effort remains fixed (maximal). The maximal activated number is achieved at $t = T_m$, and the corresponding force production is the one shown in Eq. 16. This value, $U^{\max}$, is the maximal possible force output that can be achieved by voluntary effort under the limitation of the existence of a fatigue factor. It is less than the true maximal force U_0 by a difference of ΔU, as calculated in Eq. 17. It is worth noting that the above discussion was based on the assumption that all motor units in the related muscles can be recruited voluntarily. It is possible that some high-threshold motor units cannot be activated by voluntary effort; in that case, the difference between maximal voluntary force and true maximal force should be even greater.

We have based our discussion on the assumption of a finite brain effort. This is always true in real-world situations. Obviously, no one can push up his voluntary effort B to infinity. If a person can achieve an extremely large B, he can reach his true maximal force. In fact, based on the observation of Eqs. 16 or 17, we can easily find that the only situation in which a subject can reach his true maximal force (U_0) is

$$\beta = \frac{B}{F} \to \infty. \tag{18}$$

This means that either the value of brain effort B is extremely large, or the fatigue effect is ignorable. However, neither of these conditions can ever be true. There is always an upper limit for voluntary effort, and the fatigue factor is always present except in one situation, in which only the type I motor units with extremely small F are involved in the task. However, in seeking true maximal force, this condition cannot be satisfied because maximal brain effort always recruits all types of motor units. This explains why the long-sought "true" maximal force has never been decisively achieved. In the frame of our model, it is a natural conclusion that the true maximal force cannot be reached by voluntary effort alone.

However, this does not mean that we cannot extract the true value of the maximal force. With this model, we can fit the experimental data and determine the parameters, i.e., B, F, R, and U_0. The multiplier to the curve $m_A(t)$, U_0, is exactly what we want to know, i.e., the true maximal force. The experimental data fitting and the results will be shown in the following sections.

Effect of motor unit types and generalization of model

In the above discussion, we have assumed that there is only one type of motor units in muscles. However, in fact, there are three major types of motor units. They are classified according to the contractile and metabolic properties of the muscle fibers they innervate. These properties include twitch characteristics (force and speed of shortening), tension characteristics, and fatigability (McArdle et al., 1996). The first type (type I) is slow-twitch motor units. Motor units of this type are innervated by small motoneurons with slow conduction velocities, and the number of muscle fibers they control is relatively small. Hence, the speed of fiber contraction is slow and the force produced is low. However, the uniqueness of this type of motor unit is their fatigue-resistant character, which means that they become fatigued very slowly or not at all during prolonged tasks. The second type of motor units, type IIb, is of fast-twitch speed, high force capability, but of fast fatigability. These motor units generally contain many muscle fibers, which are innervated by relatively large motoneurons with fast conduction of neural impulses. They can rapidly produce strong force, but cannot sustain it long. A third type (type IIa) exists between the slow-twitch and fast-twitch types. These motor units are fast twitch with moderate force production and have rather high fatigue resistance. When light effort is involved, the slow-twitch motor units, with the lowest threshold of activation, are selectively recruited. When a more powerful force is required, all three types of motor units are recruited to generate the desired

force. In general, type I motor units are recruited first, followed by type IIa and then type IIb motor units.

Because of their different metabolic profiles, the three types of motor units have different characteristic parameters (i.e., F and R). This fact requires us to modify the model slightly to fit the real situation. Let us denote the fatigue factors for the three types of motor units as $F^{(\mathrm{I})}$, $F^{(\mathrm{IIa})}$, and $F^{(\mathrm{IIb})}$, and the recovery factors as $R^{(\mathrm{I})}$, $R^{(\mathrm{IIa})}$, and $R^{(\mathrm{IIb})}$, respectively. From the above discussion we know that

$$F^{(\mathrm{I})} < F^{(\mathrm{IIa})} \ll F^{(\mathrm{IIb})}. \tag{19}$$

In the muscle(s) of interest, the total number of motor units is still denoted by M_0, and the numbers of the three different types are denoted by $M_0^{(\mathrm{I})}$, $M_0^{(\mathrm{IIa})}$, and $M_0^{(\mathrm{IIb})}$, respectively. In the process of performing a task, the motor units in each type are divided into three groups, as in the basic model, according to their status of being activated, fatigued, or unchanged: $M_{\mathrm{A}}^{(\mathrm{i})}$, in activation; $M_{\mathrm{F}}^{(\mathrm{i})}$, fatigued; and $M_{\mathrm{uc}}^{(\mathrm{i})}$, unchanged, ($i$ = I, IIa, IIb).

We have these relationships:

$$M_{\mathrm{A}}^{(\mathrm{i})} + M_{\mathrm{F}}^{(\mathrm{i})} + M_{\mathrm{uc}}^{(\mathrm{i})} = M_0^{(\mathrm{i})} \quad (i = \mathrm{I, IIa, IIb}), \tag{20a}$$

$$M_0^{(\mathrm{I})} + M_0^{(\mathrm{IIa})} + M_0^{(\mathrm{IIb})} = M_0. \tag{20b}$$

The initial conditions are: at $t = 0$,

$$M_{\mathrm{A}}^{(\mathrm{i})} = 0, \tag{21a}$$

$$M_{\mathrm{F}}^{(\mathrm{i})} = 0, \qquad (i = \mathrm{I, IIa, IIb}). \tag{21b}$$

$$M_{\mathrm{uc}}^{(\mathrm{i})} = M_0^{(\mathrm{i})}, \tag{21c}$$

By examining the solutions of the basic model, we can find that the solutions of M_{A}/M_0, M_{F}/M_0, and M_{uc}/M_0 depend only on the physiological parameters F, R, and the brain effort B. When different types of motor units are involved, this property still holds for each type separately. The only difference is that each type has its own parameters, $F^{(\mathrm{i})}$, $R^{(\mathrm{i})}$, i = I, IIa, IIb. The solutions to $M_{\mathrm{A}}^{(\mathrm{i})}(t)$, $M_{\mathrm{F}}^{(\mathrm{i})}(t)$, and $M_{\mathrm{uc}}^{(\mathrm{i})}(t)$ for any type of motor units can be obtained from Eq. A12 by changing F and R to be $F^{(\mathrm{i})}$ and $R^{(\mathrm{i})}$, respectively. They have been written as

$$\frac{M_{\mathrm{A}}^{(\mathrm{i})}(t)}{M_0^{(\mathrm{i})}} = \frac{R^{(\mathrm{i})}}{F^{(\mathrm{i})} + R^{(\mathrm{i})}} + \frac{F^{(\mathrm{i})}B}{(F^{(\mathrm{i})} + R^{(\mathrm{i})})(B - F^{(\mathrm{i})} - R^{(\mathrm{i})})}\, e^{-(F^{(\mathrm{i})}+R^{(\mathrm{i})})t} - \frac{B - R^{(\mathrm{i})}}{B - F^{(\mathrm{i})} - R^{(\mathrm{i})}}\, e^{-Bt},$$

$$\frac{M_{\mathrm{F}}^{(\mathrm{i})}(t)}{M_0^{(\mathrm{i})}} = \frac{F^{(\mathrm{i})}}{F^{(\mathrm{i})} + R^{(\mathrm{i})}} - \frac{F^{(\mathrm{i})}B}{(F^{(\mathrm{i})} + R^{(\mathrm{i})})(B - F^{(\mathrm{i})} - R^{(\mathrm{i})})}\, e^{-(F^{(\mathrm{i})}+R^{(\mathrm{i})})t} + \frac{F^{(\mathrm{i})}}{B - F^{(\mathrm{i})} - R^{(\mathrm{i})}}\, e^{-Bt},$$

$$\frac{M_{\mathrm{uc}}^{(\mathrm{i})}(t)}{M_0^{(\mathrm{i})}} = 1 - \frac{M_{\mathrm{A}}^{(\mathrm{i})}(t)}{M_0^{(\mathrm{i})}} - \frac{M_{\mathrm{F}}^{(\mathrm{i})}(t)}{M_0^{(\mathrm{i})}} = e^{-Bt} \qquad (i = \mathrm{I, IIa, IIb}). \tag{22}$$

The total activated number M_{A}, the total fatigued number M_{F}, and the total unchanged number M_{uc} are the linear summation of the corresponding quantities of the participating types of motor units, i.e.,

$$M_{\mathrm{A}} = \sum_{\mathrm{i}} M_{\mathrm{A}}^{(\mathrm{i})} \quad M_{\mathrm{F}} = \sum_{\mathrm{i}} M_{\mathrm{F}}^{(\mathrm{i})} \quad M_{\mathrm{uc}} = \sum_{\mathrm{i}} M_{\mathrm{uc}}^{(\mathrm{i})} \tag{23}$$

(i = participating types of motor units).

Assume that a single motor unit of each type has a fixed unit force output and denote them as $u_0^{(\mathrm{i})}$, i = I, IIa, IIb for types I, IIa, and IIb motor units, respectively. Then the force being generated under a specific brain effort B is

$$U(t) = \sum_{\mathrm{i}} u_0^{(\mathrm{i})} \cdot M_{\mathrm{A}}^{(\mathrm{i})}(t) \tag{24}$$

(i = participating types of motor units).

When determining which types of motor units participate in the activation, an important aspect to be considered is that the three types of motor units have different activation thresholds. The slow-twitch type I has the lowest threshold, whereas the two fast-twitch types, IIa and IIb, have higher ones. If we denote the thresholds of the three types of motor units as $T_{\mathrm{h}}^{(\mathrm{I})}$, $T_{\mathrm{h}}^{(\mathrm{IIa})}$, and $T_{\mathrm{h}}^{(\mathrm{IIb})}$, respectively, we have

$$T_{\mathrm{h}}^{(\mathrm{I})} < T_{\mathrm{h}}^{(\mathrm{IIa})} < T_{\mathrm{h}}^{(\mathrm{IIb})}. \tag{25}$$

For light force, the brain effort required is quite low and only the slow-twitch motor units are selectively activated. When brain effort becomes greater, it becomes capable to trigger action potentials in the fast-twitch motor units, and thus, type IIa and IIb motor units are recruited progressively. The higher the brain effort, the more motor units are activated, and the greater the force is produced. When an MVC is performed, all three types of motor units in the muscles are recruited to generate force. Under this condition, Eqs. 23 and 24 should include the contributions from all three types of motor units.

It is interesting to discuss more about the effects of the type I motor units. As we have mentioned, this type of motor unit has very high fatigue-resistant ability although its force output is low. This fact means that the fatigue factor of this type of motor unit must be very small. It is reasonable to assume that

$$F^{(\mathrm{I})} \approx 0, \tag{26a}$$

especially when we are talking about summation of the contributions from all three types. As a consequence of a zero fatigue factor, the recovery factor should be zero, too, because no recovery process is needed, i.e.,

$$R^{(\mathrm{I})} \approx 0. \tag{26b}$$

By letting F and R be zero in Eqs. A12a, b, and c, we obtain the functions found below (see plots in Fig. 8):

$$\frac{M_{\mathrm{A}}^{(\mathrm{I})}(t)}{M_0^{(\mathrm{I})}} = 1 - e^{-Bt}, \quad \frac{M_{\mathrm{F}}^{(\mathrm{I})}(t)}{M_0^{(\mathrm{I})}} = 0, \quad \frac{M_{\mathrm{uc}}^{(\mathrm{I})}(t)}{M_0^{(\mathrm{I})}} = e^{-Bt}. \tag{27}$$

It is straightforward to understand these curves. Of course, no motor unit will get fatigued if there is no fatigue effect at all, as has been manifested in the second equation in Eq. 27. As for the group of motor units being activated, without any fatigue and recovery effects, its change is determined only by the driving power, i.e., the brain effort B. Therefore, the number of motor units in this state increases continuously from zero to 100%, without any decrease in the curve. The increasing speed depends on the brain effort. If B is greater, it goes up faster. But as long as B is not zero, finally all motor units will be recruited into the activation state and then be kept there together. Meanwhile, the motor units in the reservoir of the unchanged group, i.e., $M_{\mathrm{uc}}(t)$, keep decreasing correspondingly. Because $U(t) = u_0 M_{\mathrm{A}}(t)$, the force generated by these motor units will keep

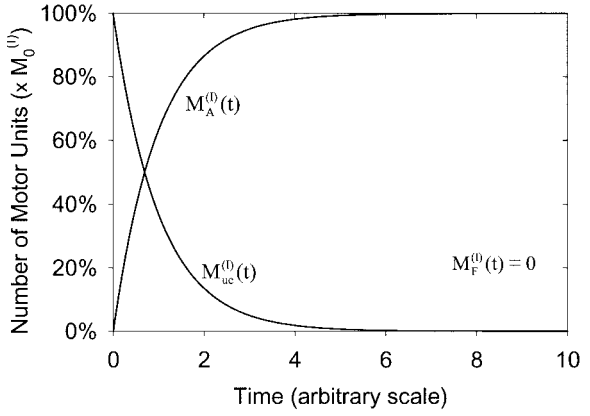

FIGURE 8 Illustration curves for the type I motor units ($F = 0$, $R = 0$). The ordinate indicates the percentage proportion of each of the three groups of motor units relative to the total number of type I motor units (M_0) in the muscles: $M_A^{(I)}(t)$, motor units in activation; $M_F^{(I)}(t)$, motor units fatigued; $M_{uc}^{(I)}(t)$, motor units in the rest state. The time scale has been taken as arbitrary to show the major features clearly.

increasing monotonically. After a time, when all motor units are pushed into the activation state, the maximal force is achieved. Later on, as long as the brain effort is maintained, force will be kept at its maximal (and constant) level.

To describe this in the general terms of our model, we would relate our discussion to the data obtained from our earlier fatigue studies involving MVC handgrip contractions (Liu et al., 1999; Liu, 2000). In these experiments, brain effort was maximal, and thus, all three types of motor units must have participated. According to the above discussion, the type I motor units in the finger flexor muscles must all have been activated in a very short time. Therefore, they would have generated a plateau in the output force curve, except at the very beginning of the contraction. Based on this view, the observed residual force at later time in the experiment data, which was basically flat, must have contributed predominantly by the force generated by type I motor units, besides the contributions from the recovery and recovery-like effects. Because the contribution from the type I motor units is similar to a recovery factor in the sense of keeping the later stage of the force curve at a flat level, it may be incorporated into the recovery factor by adopting an effective recovery factor with a greater value than the real one.

In fact, the fatigue and recovery effects from all three types of motor units may be integrated into a collective fatigue effect and a collective recovery effect. By this simplification, an effective fatigue factor F and an effective recovery factor R can be adopted as substitutes of the six parameters (i.e., $F^{(i)}$ and $R^{(i)}$). The effective F should be some sort of combination of $F^{(I)}$, $F^{(IIa)}$, and $F^{(IIb)}$, whereas the effective R should be a combination of $R^{(I)}$, $R^{(IIa)}$, and $R^{(IIb)}$. By taking F and R as the effective factors rather than mixing all three motor unit types together, we can still use the equations developed for a single type of motor unit, and the task of data fitting can be greatly simplified. After obtaining the effective factors by data fitting, detailed analysis can be performed to differentiate the contributions from different sources, i.e., motor unit types, noise, etc. Below, we will use the knowledge we have gained so far for experimental data fitting.

Experiments for model validation

Ten subjects participated in the study (eight men and two women, age = 31.3 ± 6.5 yrs, nine right-handed and one left-handed). The experimental procedures were approved by the Institutional Review Board at the Cleveland Clinic Foundation. All subjects gave informed consent prior to their participation. During the experiments, each subject performed an MVC of the right hand by gripping a handgrip device for 3 min (for more details, see Liu et al., 1999; Liu, 2000). They exerted the handgrip force as rapidly as possible from the baseline to the maximal level and maintained maximal effort for the rest of the contraction. They were verbally encouraged to exert maximal effort during the entire course of the performance.

Handgrip force was measured by a pressure transducer housed in a custom-built hydraulic system during a functional magnetic resonance imaging experiment. The measurement system has been described in detail in prior publications (Liu et al., 2000, 2002). Force data were digitized (100 samples/s) before being stored on the hard disk of a laptop computer.

Force data were averaged over each 50-ms period for the first 3 s, and over each 1.0-s period for the rest of the contraction. Averaging of the beginning force data over shorter periods of time was to capture dynamic features of the rapid rising of the force from baseline to the stabilized maximal values, and to ensure enhanced weighting over the data around the time point of maximal force level when data fitting is performed below.

Experimental data fitting

Force data were fitted to the model under a constant brain effort (B). As discussed above, the assumption of a constant B is reasonable when the subjects were always exerting maximal effort throughout the contraction. Although there may be fluctuations in brain effort during the actual performance, the magnitude of variations in this case will not affect the validity of the model's application here. We also assumed that the fatigue factor (F) and recovery factor (R) are constant for each subject (see Discussion). These factors are effective factors that incorporate all fatigue-like and recovery-like factors, and effects due to the presence of the three motor unit types (see Discussion).

Under these conditions, we applied our model with constant B, F, and R to the data fitting. The force data were fitted to the model curves, i.e., $U_0 \cdot m_A(t; F, \beta, \gamma)$ determined by Eqs. 4a and 9b. The differences between the experimental data and the theoretical curves were minimized using the least-squares method (Bevington and Robinson, 1992) to obtain the four parameters (F, β, γ, U_0), or equivalently (B, F, R, U_0).

RESULTS AND CONCLUSIONS

The results for the ten subjects are given in Table 2, where we list the parameters F, β, γ, and U_0 found from the fits. The theoretical values of the maximal forces (U^{max}), the maximal activation levels (m_A^{max}), and the rise times (T_m) were calculated from the fitted parameters and compared to the corresponding experimental values. The average values over the ten subjects, and the standard deviations were calculated.

The theoretical values were determined as follows: 1) The maximal activation level (m_A^{max}) was calculated by Eq. 14 using the fitted F, β, and γ. 2) The theoretical maximal force was calculated as $U^{max} = U_0 \cdot m_A^{max}$ (note that U_0 is the true maximal force and U^{max} is the maximal voluntary force). 3) The rise time (T_m) was determined by Eq. 13 using the fitted F, β, and γ. The corresponding experimental values were determined as follows: 1) The maximal force was the highest value in the experiment force data. 2) The maximal activation level was calculated as the percentage of the maximal experimental force to the true maximal force U_0. 3) The rise time, read from the experimental data, was

TABLE 2 The fitted results and comparisons to the experimental data

	Fitted Parameters				Theoretical Values			Experimental Values			Calculated Parameters		Relaxation Time			
Subjects	F (/s)	β	γ	U_0 (N)	U^{max} (N)	Maximum Level (%)	T_m (s)	U^{max} (N)	Maximum Level (%)	T_m (s)	R (/s)	B (/s)	T_F (s)	T_R (s)	T_F^* (s)	T_B (s)
1	0.024	200	0.48	418	407	97.38	1.11	407	97.37	1.10	0.0115	4.800	41.7	86.8	28.2	0.21
2	0.0075	650	0.35	575	569	99.01	1.33	568	98.78	1.28	0.0026	4.875	133.3	381.0	98.8	0.21
3	0.025	100	0.48	421	402	95.49	1.87	403	95.72	1.80	0.0120	2.500	40.0	83.3	27.0	0.40
4	0.020	150	0.45	448	433	96.71	1.69	432	96.43	1.65	0.0090	3.000	50.0	111.1	34.5	0.33
5	0.033	90	0.38	332	316	95.10	1.54	317	95.48	1.61	0.0125	2.970	30.3	79.7	22.0	0.34
6	0.017	300	0.50	359	352	98.12	1.12	352	98.05	1.15	0.0085	5.100	58.8	117.6	39.2	0.20
7	0.015	250	0.29	382	374	97.81	1.48	372	97.38	1.53	0.0044	3.750	66.7	229.9	51.7	0.27
8	0.022	180	0.35	341	331	97.15	1.32	332	97.36	1.33	0.0077	3.960	45.5	129.9	33.7	0.25
9	0.028	120	0.40	393	378	96.08	1.44	379	96.44	1.46	0.0112	3.360	35.7	89.3	25.5	0.30
10	0.014	500	0.30	456	450	98.76	0.89	451	98.90	0.87	0.0042	7.000	71.4	238.1	54.9	0.14
Mean	0.0206	254.0	0.398	412.5	401.2	97.16	1.379	401.3	97.19	1.378	0.0084	4.132	57.3	154.7	41.5	0.264
SD	0.0075	184.8	0.077	71.0	72.6	1.32	0.291	72.2	1.18	0.286	0.0036	1.343	29.8	98.5	22.9	0.079

The force data for ten subjects are fitted. The fitted parameters (F, β, γ, U_0) are listed. The theoretical values are determined from the fitted parameters and are compared to the experimental values. B and R are calculated from F, β, and γ. The relaxation times are also calculated and listed. The mean values over the ten subjects and the standard deviations (SD) are given.

the time interval from the start of the handgrip to the point when the force reached its maximal level. Table 2 also displays the values of R and B determined by Eqs. 3a and b. We calculated the relaxation times using the values of F, R, and B by applying Eqs. 5a–d. These characteristic times include the fatigue relaxation time T_F, the recovery relaxation time T_R, the modulated fatigue relaxation time T_F^*, and the brain relaxation time T_B.

The fitted curve for one subject is shown in Fig. 9. The black diamonds represent the experimental data, and the lines are the fitted model curves, i.e., $U_0 \cdot m_A(t; F, \beta, \gamma)$. Figure 9 *A* shows the data of the entire experiment and Fig. 9 *B* displays the results of the first 50 s to give more details of the change in force.

The results in Table 2 and Figure 9 indicate excellent agreement between the data sets of the experiment and the modeled force. This observation can be confirmed in the following aspects.

First, consider the time scale and the shape of the curve as a whole. From Fig. 9, it is shown that the theoretical curves had the same shapes as the experimental data during the entire time span (180 s). They all went up quickly from the baseline to the maximal level until they were bent down by the fatigue effect. After that, they decreased slowly over a relatively long time period to the residual level. Second, consider the maximal voluntary force U^{max} and the maximal activation level (m_A^{max}). The maximal activation level determined by the model was 97.16% (±1.32%) on average over the ten subjects. The experimental value was 97.19% (±1.18%). The maximal voluntary force determined by the theory was 401.2 (±72.6)N on average, whereas the experimental averaged value was 401.3 (±72.2) N. These theoretical values were in good agreement with those from the experimental data. Third, consider the rise time (T_m). For the experimental data, the average rise time for the ten subjects to reach their maximal voluntary forces was 1.378 (±0.286) s. By the theoretical fitting, the rise time was 1.379 (±0.291) s. The average fitted values were almost identical to the experimental values. For the example given in Fig. 9, the experimental rise time was 1.10 s, and the fitted value was 1.11 s. The excellent agreement between the theoretical fitted results and the experimental data suggests that the model describes the behavior of muscle activation, fatigue, and recovery very well, and the adopted assumptions are reasonable.

DISCUSSION

The dynamical model of muscle activation, fatigue, and recovery developed based on simple biophysical mechanisms is easy to use and can describe the experimental data excellently. The model and the solutions in basic form can serve as a theoretical basis and provide useful guides for further studies on muscle physiology, neural control mechanisms, and clinical applications. Below, some important issues and concerns regarding the improvement and applications of the model are discussed.

Significance of the fitted parameters

It may be useful to discuss in more detail the magnitudes of the parameters and their meanings. First, we address the fatigue factor F. A smaller F means a lower fatigue effect, a greater β (hence a higher activation level), a greater γ (hence a higher residual activation level), a shorter rise time

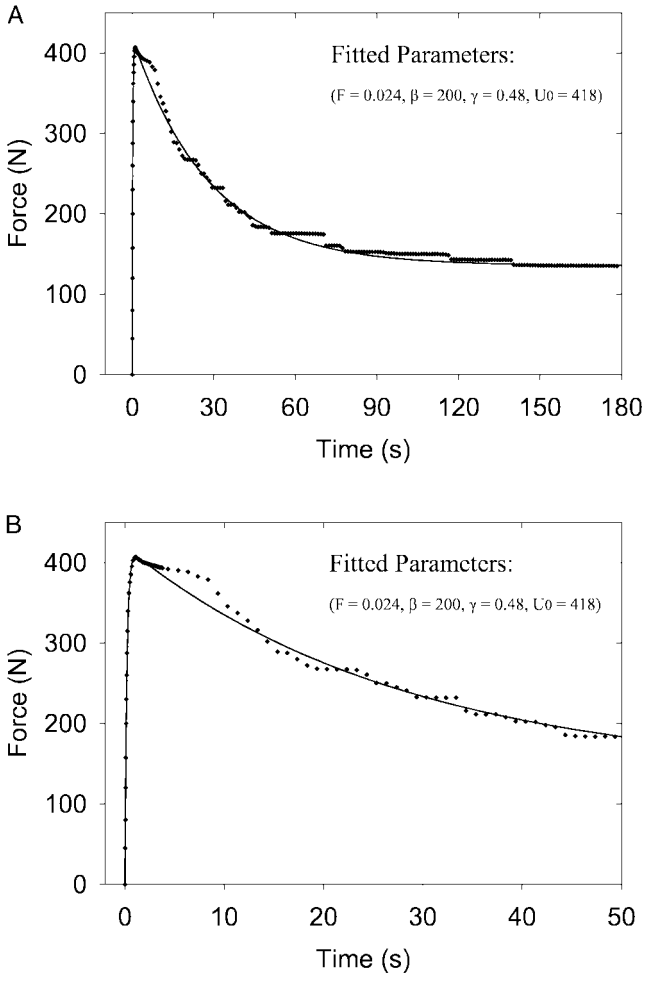

FIGURE 9 The experimental data and the fitted curves for a single subject. The upper panel shows the whole time period of the measurement (180 s). The lower panel shows details of the first 50 s. The diamonds are the experimental data points. The lines are the fitted theoretical curves. The fitted parameters for this subject are $F = 0.024$, $\beta = 200$, $\gamma = 0.48$, and $U_0 = 0.418$.

for the muscle to be maximally activated, and a longer time during which the force can be sustained. The magnitude of F can change from person to person. The fitted F values ranged from 0.0075 to 0.033. The average value was 0.0206 ($\pm$0.0075). A value of 0.02 means that, in each second, 2% of the motor units in activation state were driven from their "working" status into the "retired" status—by fatigue!

Second, we focus on the ratio of brain effort to fatigue factor, $\beta = B/F$. This quantity mainly determines the level of activation. The greater the brain effort, the greater the β, and the greater the activation level. For example, a small β of 2 corresponds to a low maximal activation level of 50%, whereas a larger value of 88 corresponds to a high level of 95% and a huge value of $\beta = 645$ to an extremely high level of 99%. The relationship between the maximal activation level and β has been determined in Table 1. The fitted β values for the ten subjects ranged from 90 to 650, with the average ($\pm$SD) of 254.0 ($\pm$184.8). The range for this parameter is quite large, which is caused by the small size of F. The average β value indicated a maximal activation level of 97.16% ($\pm$1.32%), with the range from 95.10% to 99.01%.

These values indicated that the maximal possible force the subjects could reach (U^{max}), on average, was ~97% of the true maximal force (U_0), assuming that all motor units in the muscles can be activated voluntarily. There is a good possibility that untrained individuals cannot voluntarily activate all the motor units (Herbert and Gandevia 1999; Yue et al. 2000). Under this condition, the maximal voluntary force (U^{max}) should be considerably lower than 97% of true maximal force (U_0). In this model, we gave a direct explanation on why humans cannot reach the true maximal activation possibility of the muscle by voluntary effort, and we offered an easy way to extract the true maximal force by fitting the experimental data. A more thorough study of this problem is being carried out to consolidate our conclusion by testing more subjects and different muscles.

Third, we consider the recovery-to-fatigue ratio, $\gamma = R/F$. This ratio determines principally the residual activation level, i.e., $\gamma/(1 + \gamma)$. A larger R corresponds to a faster recovery and hence a higher residual level. The fitted γ values for the ten subjects ranged from 0.29 to 0.50, with an average of 0.398 ($\pm$0.077). This average γ value represented an average residual activation level of 28.5% of the true maximal force (U_0), or 27.7% of the observed maximal force (U^{max}), considering that $U^{max}/U_0 \approx 97\%$. The rather large γ indicates that this factor must have included other contributions besides the real recovery effect. The two major possible contributions include the nonfatigue motor units and the recovery-like factors. The former raises the γ value by providing a flat activation base level from the sustained activation of type I motor units, and it might be the largest contribution source. The recovery-like factors may also have raised the γ value, and these factors will be discussed in more detail in the following section.

Fatigue-like and recovery-like factors

We have mentioned that included in F are fatigue-like factors in addition to the true fatigue factor, and in R, recovery-like factors besides the real recovery factor. Below, we will investigate the sources of these unwanted factors, examine their effects and discuss how to deal with them.

Besides the true muscle fatigue effect, several other factors may cause unexpected early fatigue in the involved muscles when performing a task, for example, uncomfortable positions or uneasiness caused by surrounding environment (e.g., in an MRI machine). The most obvious such effect may be the sensation of discomfort that accompanies

prolonged muscle contractions. Many subjects reported hand pain during the last minute of the 3-min MVC. Potential mechanisms that may have contributed to the pain sensation include an increase in intramuscular pressure that reduces or blocks the blood supply to the muscle and the hard material from which the handgrip device is made. The pain may have caused a faster decline of the force because the feedback signals from pain receptors exert inhibitory effects on motor neurons supplying the muscle (Hayward et al. 1988). Thus, the feeling of pain or discomfort during the contraction is equivalent to an additional fatigue factor.

There are also factors that may have made the recovery process faster than it should be. For example, suppose that, during an MVC fatigue experiment, a subject did not really reach his maximal brain effort or force at the beginning, due to less-than-optimal motivation or other psychological factors (such as stress). Later on, when fatigue started to develop and force started to decline, he would have more room to increase his effort to maintain the force. This would make the force curve look flatter than it should be. As a result, a recovery-like factor was introduced. Other recovery-like factors include adjusting one's posture or the joint angle during the experiment. Although all subjects were instructed not to do so, this may have occurred involuntarily in some subjects when fatigue was severe. Changing the posture and joint angle would adjust muscle length and contributions from the synergist muscles; both would affect the force output. If these adjustments facilitate force production, the subject would be able to slow down the fatigue process and maintain a higher level of residual force. The properties of force-recording equipment may also contribute recovery-like factors. If the force sensor is not perfectly linear because of mechanical design (e.g., friction), there will be a mismatch between the true muscle force and the force output of the sensor, and that can be a recovery-like effect.

As a whole, we call all these unwanted artifacts fatigue-like factors or recovery-like factors. They introduce noise into the real data. We have to deal with them so that we can obtain the correct information from the experimental data. First of all, we should try to minimize these effects as much as possible when we collect the data. For example, subjects should be asked to position themselves as comfortably as possible to avoid early fatigue; they should be properly motivated to assure their best performance. Measurement equipment and devices should be well designed and calibrated to eliminate measurement errors. An interesting approach we are considering is to selectively anesthetize the small-diameter afferents to prevent or at least reduce the inhibitory effect acted upon the motor neurons. We hope that this method would eliminate the fatigue-related pain sensation and allow us to collect "purer" motor information. Second, we will try to model the sources of noise and differentiate them from the real fatigue and recovery factors when we fit the experimental data. This approach is indirect but may be necessary and useful, especially when preventive methods cannot eliminate all types of noise.

Discharge rate of action potentials

We did not consider the discharge rate of motor units in our model. Under the concept of this model, this variable is not needed as long as the number of motor units involved is big enough. Because the discharge rate is typically high (e.g., 100 Hz) in the case of an MVC task (Fuglevand et al., 1993; Herbert and Gandevia, 1999) and the number of motor units is supposed to be sufficiently large, the assumption of a continuous voluntary drive (B) is adequate for our force data fitting. The important point and uniqueness of this model is that it depicts the motor unit response from a macroscopic and collective viewpoint, by introducing two phenomenological parameters (F, R). Therefore, the average response curve of a motor unit is $m_A(t)$, which has already incorporated all factors that affect muscle force, such as the decrease of response magnitude of single motor units and the slowing-down of motor-unit discharge rate, etc. By doing this, we avoided severe calculation complications while still being able to retain the essence of the muscle force-generation mechanisms.

Model under time-dependent brain effort

We have discussed the dynamics of muscle under constant brain effort drive, which can be fulfilled approximately in experiments involving sustained MVCs (Bigland-Ritchie, 1981). However, there are inevitably time-dependent factors in experiments involving human voluntary muscle contractions. (One exception is when brain effort is simulated by electrical stimulation, which can be controlled at a constant level.) Although the time-dependent variation is unavoidable, the variation in the constant brain effort in an MVC experiment would not be so large as to significantly affect the basic characteristics of the dynamic behaviors of muscle activation, fatigue, and recovery described by the model. Hence, it would not undermine the validity of the application of the basic model to MVC data.

During prolonged submaximal muscle contractions, however, brain effort can no longer be considered as constant (Liu, 2000). The subject needs to continuously increase brain effort to maintain the desired (target) force. In general, brain effort controlling most real-life motor tasks is time dependent. In these situations, the function of brain effort, $B(t)$, needs to be modeled first. Because there are no solutions to the general form of Eqs. 1a–f for arbitrary $B(t)$, we would have to deal with them according to the specific forms of brain efforts. The theoretical results can then be compared with the experimental data to determine how well a posited $B(t)$ works. The applications of the model to

situations in which brain effort is time dependent is the subject of our ongoing work.

F and *R* as separators of motor unit types

From former discussion (see Eq. 19), we learned that $F^{(I)} < F^{(IIa)} \ll F^{(IIb)}$. For type I motor units, due to its high fatigue resistance, its fatigue factor and recovery factor should be close to zero (see Eq. 26), i.e., $F^{(I)} \approx 0$, $R^{(I)} \approx 0$. For type IIa, because of its relatively high fatigue resistance, its fatigue effect may be largely cancelled out by its recovery effect, i.e.,

$$R^{(IIa)} \leq F^{(IIa)}. \tag{28}$$

For type IIb, however, due to its low fatigue resistance, its fatigue effect must be much greater than its recovery effect, and hence,

$$R^{(IIb)} \ll F^{(IIb)}. \tag{29}$$

Inversely, we can use this information to predict muscle types that are dominated by one motor unit type. More specifically, we may use F, R, and the recovery-to-fatigue ratio γ to provide relatively clear and definite criteria of divisions among different muscle types. This may introduce quantitative methods to the formerly more qualitative differentiation of muscles, such as slow or fast muscles, or red or white muscles.

Potential clinical applications of β and γ

We define β as the brain command-to-fatigue ratio (B/F) and γ as the recovery-to-fatigue ratio (R/F). Based on the analysis of the solutions and observation of the experimental data, we have learned that β determines the maximal force that one can exert. For well-trained athletes or body builders, the brain command for an MVC may be stronger than that of untrained individuals; young healthy people may have greater brain power than movement-disorder patients and older adults. Furthermore, trained and healthy individuals are expected to have smaller fatigue factor than untrained ones and patients. Therefore, trained and healthy people may obtain greater maximal β values than the other populations. In contrast, γ determines the speed of recovery relative to the fatigue effect, or in other words, the decreasing slope of the activation curve—the greater the γ, the slower the decrease. Reasonably, we can expect that trained and healthy individuals become fatigued slower (smaller F) and get recovered faster (larger R) than untrained, patients, and people with advanced age. Thus, greater γ values are expected in trained and healthy individuals.

In general, we believe that different populations may have different characteristic values of β and γ. The typical values for younger people should be different from those of older adults, due to reorganization of the motor neuron pool and muscle in aging. Adults' values should be different from those of adolescents whose neuromuscular system is still developing. Healthy people's values should be different from those of patients whose neuromuscular system is damaged. These potential observations may be clinically useful. The values of β and γ may serve as indices of clinical diagnosis for certain diseases.

F and *R* as functions of time and their clinical importance

In the former discussion, we assumed that F and R are constants, i.e., they do not change over time. This assumption can be retained as long as the time span is not too long and the subject's condition does not change during this period. These conditions can generally be fulfilled for the limited time of an experiment, e.g., 3 min in our muscle fatigue experiments. During this short period, the subjects, for the purpose of our experiments, should have maintained their physical conditions. Therefore, it is reasonable to assume that there was no time variation in F and R during our experiments.

However, these factors may change by training, reduced use (e.g., immobilization of muscles due to a fracture), or medication during a rather short period. It is obvious that for the same person, physical condition when in sickness is different from when in a normal state. When a person ages, physical ability starts to decline. In all these cases, the person's fatigue resistance and recovery abilities must have changed; compared to his normal condition, his fatigue factor F should increase (representing faster fatigue) and his recovery factor R should decrease (representing slower recovery). Another fact is that exercise improves a person's physical performance. After a period of exercise, a person may develop greater abilities of fatigue resistance and recovery—a slower fatigue (smaller F) and a faster recovery (bigger R).

These facts may be utilized for research or clinical purposes. We may measure a subject's F and R under the same conditions at different times and use these parameters as indicators of the subject's physical status. For example, we may use them to compare a patient's illness state to his normal state. If rehabilitation is involved, they can be used to indicate the status of recovery. For an aged person, these values might be good measures of the aging process, and if anti-aging procedures are applied, they may be good measures of the effectiveness of the procedures. We can also use them to evaluate the validity of an exercise that has been designed for a specific purpose, and so on. All these approaches would render useful information.

APPENDIX: SOLUTIONS TO THE DYNAMICAL EQUATIONS

Starting from Eq. 2a, let

$$X = M_A - \frac{R}{F+R} M_0. \tag{A1}$$

Eq. 2a becomes

$$X'' + (B+F+R)X' + B(F+R)X = 0. \tag{A2}$$

Let

$$X = e^{-st}. \tag{A3}$$

We get

$$S^2 - (B+F+R)S + B(F+R) = 0, \tag{A4}$$

so,

$$(S-F-R)(S-B) = 0. \tag{A5}$$

The two real solutions are

$$S_1 = F+R, \quad S_2 = B. \tag{A6}$$

Therefore, the general solution to X is

$$X = A_1 e^{-s_1 t} + A_2 e^{-s_2 t}, \tag{A7}$$

hence,

$$M_A(t) = \frac{R}{F+R} M_0 + A_1 e^{-s_1 t} + A_2 e^{-s_2 t}. \tag{A8}$$

From Eq. 1a, we have

$$M_F(t) = \frac{1}{B-R}\left\{BM_0 - (B+F)M_A - \frac{dM_A}{dt}\right\}. \tag{A9}$$

Substituting Eq. A8 into Eq. A9, we get

$$M_F(t) = \frac{F}{F+R} M_0 - A_1 e^{-s_1 t} - A_2 \frac{F}{B-R} e^{-s_2 t}. \tag{A10}$$

Considering the initial conditions, i.e., Eqs. 1d and e, we can easily calculate A_1 and A_2. The results are

$$A_1 = \frac{FB}{(F+R)(B-F-R)} M_0, \quad A_2 = -\frac{B-R}{B-F-R} M_0. \tag{A11}$$

Therefore, we get the solutions for $M_A(t)$, $M_F(t)$, and $M_{uc}(t)$ as follows:

$$\frac{M_A(t)}{M_0} = \frac{R}{F+R} + \frac{FB}{(F+R)(B-F-R)} e^{-(F+R)t} - \frac{B-R}{B-F-R} e^{-Bt}, \tag{A12a}$$

$$\frac{M_F(t)}{M_0} = \frac{F}{F+R} - \frac{FB}{(F+R)(B-F-R)} e^{-(F+R)t} + \frac{F}{B-F-R} e^{-Bt}, \tag{A12b}$$

$$\frac{M_{uc}(t)}{M_0} = 1 - \frac{M_A(t)}{M_0} - \frac{M_F(t)}{M_0} = e^{-Bt}. \tag{A12c}$$

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