Prediction of Tetanic Force of Muscle Motor Units Evoked by Irregular Stimulation Patterns

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Summary. The aim of the paper is to propose an approach for prediction of tetanic force of different motor units (**MU**s) knowing the stimulation pattern. Tetanic force curves obtained by electrophysiological experiments on 13 **MU**s of a rat muscle were processed. They were decomposed into a series of twitches using two own-made algorithms. The parameters of the decomposed twitches were correlated with inter-pulse intervals (**IPI**s) and the level of the force at which the successive contraction begins, i.e. *MinTet*. Using regression equations for prediction of these parameters, the same tetanic curves and others of the same **MU**, but with different stimulation patterns, were reconstructed. The reconstructed curves resembled the experimental ones much better than these obtained by summation of equal twitches with the respective stimulation patterns. It was concluded that the best predictor is *MinTet*. In order to obtain the same prediction approach for all **MU**s, for arbitrary stimulation pattern, a proper normalization has to be obtained.

Keywords: Muscle, Motor unit, Tetanic force, Decomposition, Prediction

1. INTRODUCTION

In daily motor activities, the motor units (**MU**s) of limbs' muscles fire with different mean frequencies and non-constant interpulse intervals (**IPIs**). The force developed by a **MU** depends on many factors, e.g. the type of **MU**, the frequency of firing, the **IPI**s, the previous and the current contractile state of the **MU** [2, 9]. In our previous papers [1, 6], we showed that the tetanic force curve is very different from the curve obtained by summation of equal mechanical contractions (*twitches*), applying the same stimulation pattern. The stimulations, however, were conducted using equal **IPI**s, i.e. constant frequencies. If the stimulus is applied at a moment when the contractile force of **MU** is different from zero, the increment in force due to this stimulus (which has a bell-shape "twitch" form), is

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different from the single twitch of the **MU** evoked by one stimulus. It was found that the parameters of the successive twitches depend mainly on the force level *MinTet* at which the successive contraction starts [4]. The aim of the present study is to investigate the possibility to predict the force adding (successive mechanical contractions) due to stimuli with irregular pattern, knowing the previous sate of the **MU**.

2. METHODS

Tetanic force curves obtained by means of electrophysiological experiments on 13 isolated rat **MU**s (2 slow and 11 fast) from medial gastrocnemius muscle were processed. The experiments were performed at the Dep. of Neurobiology, Univ. School of Physical Education, Poznan. Details for the surgical procedure, the experimental setup, as well as about the stimulation protocol are given in [1]. The unfused tetani were evoked by applying different stimulation patterns (41 pulses) with variable **IPI**s (mean IPI ±50%) and with different fixed mean frequencies. These frequencies were 16.6 Hz, 20 Hz, 25 Hz, 33.3 Hz and 40 Hz and respective mean IPIs were 60 ms, 50 ms, 40 ms, 30 ms and 25 ms respectively. For each **MU** the curve with the most variable force was decomposed into a series of twitches using our own algorithm and software [7].

A new algorithm for tetanic curve decomposition was also developed and used for verification. It is based on a nonlinear least square estimation approach, which tries to find those values in the parameters' space that minimize the residual sum of squares using the Marquardt method to iteratively solve the optimization problem. The algorithm is an iterative procedure, which utilizes the 6-parametric twitch model proposed in [8], the experimental tetanic curve that has to be decomposed and a set of initial values of all 6 parameters (lead time T_{lead}, contraction time T_c, half-contraction time T_{hc}, half-relaxation time T_{hr}, duration of the twitch T_{tw}, maximal twitch force F_{max} - Fig. 1). Hence, the number of parameters which are optimized are 246 - 6 twitch parameters for 41 contractions. The algorithm iteratively calculates the tetanic force curve starting from the given set of initial values and chooses different set of parameter values (which are limited to appropriate upper bounds) until a good fit is found. For simplicity, the initial values for all 41 twitches are

chosen to be the parameters of the single experimental twitch, but they could be set at random values.

The parameters of the decomposed twitches, whose summation precisely fitted the experimentally recorded tetanic force curve, were correlated with the corresponding **IPI**s and the force level at which the current contraction begins (*MinTet*) – see Fig. 2. For each **MU,** quadratic regression equations were used for prediction of the twitch parameters based on the current set of *MinTet*. Using these equations, the same tetanic curve and a different one of the same **MU**, obtained by application of other stimulation pattern, were reconstructed by summation of the modelled twitches.
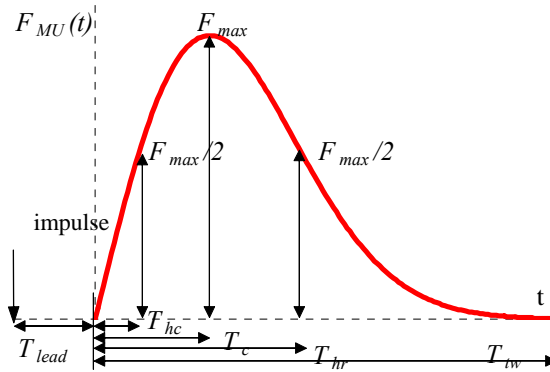
Fig. 1 Parameters of the twitch. The 6-parameters analytical function describing this force is given in [8].
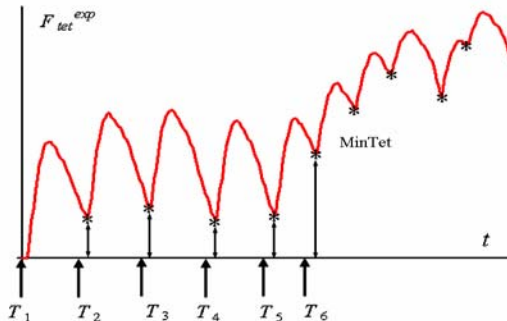
Fig. 2 Definition of the parameter MinTet for the experimental tetanic curve. The stimuli are applied at moments T_i. The symbols [*] show the force levels at which the successive contractions begin.

The differences between the experimental curves and the modeled ones were estimated by a fit coefficient. It was calculated as follows: first, the two curves under comparison were normalized to their total maximal force level; for each discrete time, the differences between the two force curves Δ_i were calculated; the fit coefficient was expressed in percents as

$$FIC = 100\left(1 - \sqrt{\frac{1}{N}\sum_{j=1}^{N}\Delta_j^2}\right)$$

where N is the number of samples. When the two curves match perfectly, this coefficient amounts to 100%. The lower the *FIC*, the bigger the difference between the curves under comparison. The correlation coefficients estimating the linear relationship between the parameters T_{lead}, T_c, T_{hc}, T_{hr}, T_{tw} and F_{max} and *MinTet* were also calculated.

Different normalizations were made aiming to find one general tendency in change of the parameters of the successive twitches in dependence on the force level at which the next contraction begins. The time parameters (T_{lead}, T_c, T_{hc}, T_{hr}, T_{tw},) of the decomposed twitches were normalized to the contraction time of the first individual twitch. The force parameters (F_{max} and *MinTet*) were normalized to the maximal force of the first twitch. In addition, F_{max} was also normalized to the potential (resources) of the **MU** to develop extra force depending on its current contractile state. The normalization parameter was *(GlMax- MinTet),* where *GlMax* is a constant value specific for each **MU.** This constant is equal to the maximal possible force that the respective **MU** can develop during submaximal regular fused tetanus.

3. RESULTS

The results of processing 26 tetanic curves for 2 slow and 11 fast **MU** (6 of them FF – fast fatigable, 5 of them FR – fast resistant to fatigue) obtained by stimulation with different mean frequencies and random IPIs are presented, an example is given on Fig. 3.

For each **MU**, one tetanic curve was decomposed with both the algorithm proposed in [6] and the new decomposition program. The mean value of the fit coefficients between the processed experimental curves and the respective force curves, obtained by

summation of modeled twitches, was 98.64. The mean value of the fit coefficients between the experimental curve and the force obtained by summation of equal twitches was 74.24.
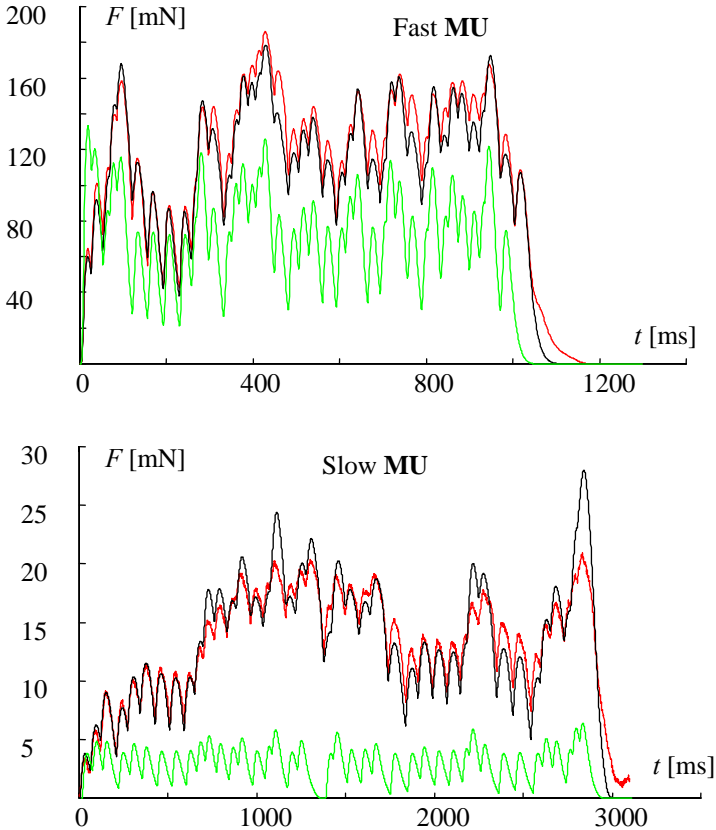

Fig. 3 Results from processing of two tetanic force curves, one for a fast (upper figure) and one for a slow (lower figure) **MU** obtained by stimulation with variable **IPI**s with fixed mean frequencies (40 Hz and 13.3 Hz respectively). The red lines show the experimental data, the black lines - predicted force by using regression equations, the green lines show the force obtained by summation of equal twitches with the same impulsation.

The mean values of the correlation coefficients between the parameters of the decomposed twitches and *MinTet* for all decomposed tetanic curves were: 0.1086 for T_{lead}; 0.8281 for T_c; 0.6722 for T_{hc}; 0.6043 for T_{hr}; 0.2446 for T_{tw}; 0.4462 for F_{max}. It should be noted, however, that the minimal value of the correlation coefficient for F_{max} was negative, i.e. (-0.1839) and the maximal value had very large positive value, i.e. (0.9388). The main reason is the non-linear dependence of the maximal forces of the decomposed twitches on the parameter *MinTet*.

After the decomposition of each curve, regression equations of type $y=a+bx+cx^2$ were calculated, where *y* was the lead, the contraction, the half-contraction, the half-relaxation times, the duration of the twitch or the maximal force, and *x* was *MinTet*. Using these equations, another tetanic curve of the *same* **MU**, obtained with different irregular pattern, was reconstructed using its newly calculated values for *MinTet*. The mean value of the fit coefficient, estimating the similarity of the experimental curves and the force obtained by summation of twitches which parameters were predicted by regression equations, was 92.78. Hence, a conclusion can be drawn that regression equations found for one stimulation pattern for one **MU** can be used to predict the force developed by the *same* **MU** when another stimulation pattern is applied.

Multiple regression was also tested with predictors both **IPI** and *MinTet*. In this case the equations were of the form $Y=a+bX_1+cX_2$, where X_1 is **IPI**s and X_2 is *MinTet*. This regression did not give promising results, i.e. no clear relationships were obtained. The same is true when using the **IPI**s as the only predictor.

The normalization of the parameters of the decomposed twitches and the parameter *MinTet*, using parameters typical for the single individual twitch for each **MU,** neutralizes the specific contractile peculiarities of different **MU**s (Fig. 4). Thus, the individual capabilities of each **MU** to develop force are neglected and only specific peculiarities concerning the different effectiveness of the summation of mechanical responses to successive pulses remain. Nevertheless, as it can be seen from Fig. 4, a general relationship for all **MU**s is not visible. This is due to the application of different mean frequencies and to different effectiveness of summation of successive contractions, especially regarding slow **MU**s. That is why

a new normalization was tested (Fig. 5), which turned out to be more promising.

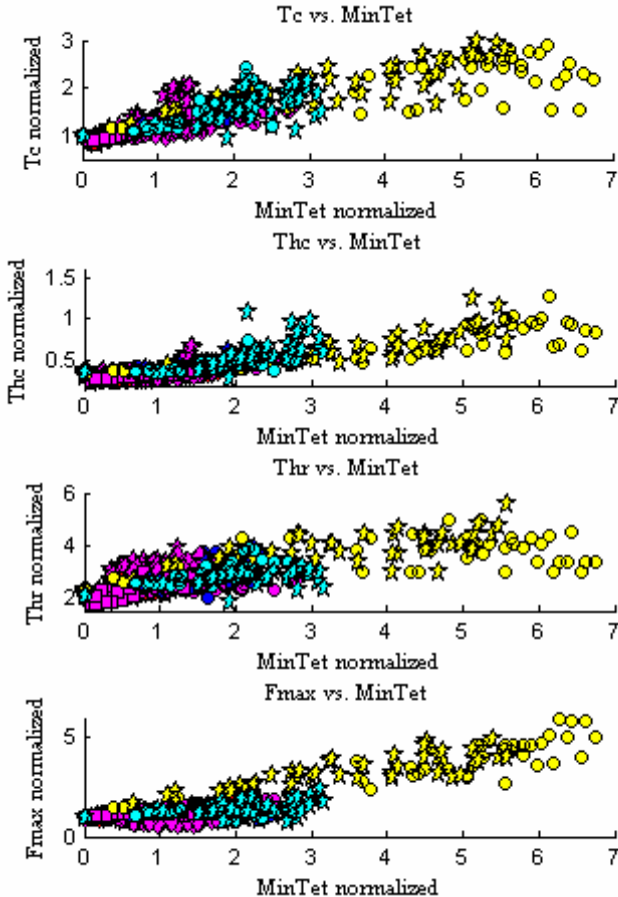Fig. 4 Normalized parameters of the decomposed twitches (T_c, T_{hc}, T_{hr} and F_{max}) versus normalized MinTet of the respective tetanic curves. The time parameters are normalized to the contraction time of the respective first twitch; F_{max} and MinTet are normalized to the maximal force of the respective first twitch. Data from all 13 decomposed tetanic curves are shown using different colors and symbols as follows: yellow for slow **MU**s, red and magenta – for FR **MU**s, blue and cyan – for FF **MU**s.
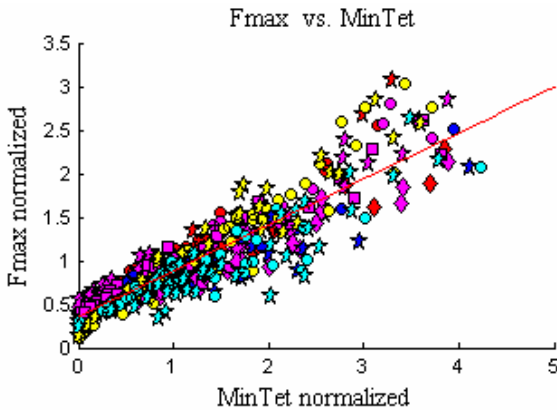
Fig. 5 Dependence of the normalized parameters MinTet and F_{max} for all **MU**s and the linear regression line. Both parameters are normalized to (GlMax- MinTet). The regression line has the form $y = 0.527x + 0.356$, the correlation coefficient is 0.915. The colors and shapes of the points are the same as those used in Fig. 4.

4. DISCUSSION

The previously developed algorithm for decomposition of unfused tetanus into successive twitches [6] was based on the assumption that the first contraction is not very different from the individual, single, twitch. Firstly, the individual single twitch is subtracted from the tetanic curve. As a result, the second contraction is visible in part. It is approximated by the 6-parameters analytical function [6], so that the model and the curve between the second and the third pulse match nearly perfect. The process continues until the last pulse is reached. This algorithm is based on estimation of the error in range of each two successive pulses. The new algorithm is based on estimation over all duration of the experiment. It calculates the error between experimental tetanic curve and the curve obtained by summation of all modeled twitches. All of the 6 parameters for all successive contractions (for each pulse) are changed within physiologically based limits. Despite the different approaches, both algorithms produce very similar results. However, the new procedure is faster and more precise. The only critical point is the proper choice of the lower and the upper boundaries of the twitch parameters.

The decomposed twitches have very different parameters for slow and fast **MU**s. They change depending on the stimulation pattern, too. The best predictor is *MinTet*. The error between the experimental curves and the predicted ones is less than the error between the experimental curves and these obtained by summation of equal twitches with the same **IPI**s. This is most visible for slow **MU**s. There is no big difference when using a linear or a quadratic function. The regression equations with both **IPI** and *MinTet* do not improve the prediction. It is not possible to use the regression equations obtained for a slow **MU** to predict the tetanic force of a fast **MU** and vice versa. This suggests that if one is trying to follow the same prediction approach for all **MU**s, for arbitrary stimulation pattern, a proper normalization has to be obtained.

The normalization illustrated by Figure 4 still does not allow finding of one general principle concerning how the successive contractions form a tetanus. It is reasonable to expect that the next contraction (the adding in force caused by the next pulse) depends on the force level at which it starts. This dependence could not be linear, since when this level approaches the global maximal force, which one **MU** can develop, the maximal force of the respective contraction (i.e. the possibility to develop extra force at current contractile **MU** state) has to decrease. That explains why the results shown on Figure 5 are more promising. The normalization is made according to the residual potential of the **MU** to develop extra force. The question about the suitable normalization of the time parameters still needs investigation. It is questionable whether a common rule for tetanic force development could be found for all types of **MU**s for physiologically reasonable range of firing frequencies. Such investigations are necessary when developing muscle models composed by **MU**s [8] and when modeling the motor-unit pool [3,5]. They will improve considerably our understanding of the role of neuronal code in motor control during daily activities and will help to connect the mechanical manifestation of **MU**s activity with other biophysical processes connected with muscle force developing.

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