

# The effect of muscle fatigue on the behavior of single muscle fibre

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## Abstract

The aim of this study is to integrate the effect of muscle fatigue into skeletal muscle fibre model. The base of the skeletal muscle model previously developed in our laboratory is the sliding cross-bridge theory of contraction. The calcium activation, which is the base stone for the contraction, is integrated. The muscle fatigue is often described as a decline in the muscle ability to generate force. It is the result of the sustained contraction of long duration. Generally, muscle fatigue is a complex and multifactorial phenomenon, which is influenced by a variety of physiological and psychological factors. Its underlying mechanisms are not still well understood. Therefore there are still discussions about what is the major cause of fatigue. The calcium handling within the active muscle cell can be considered as a one of possible causes of fatigue. This idea was utilized during solving of the muscle fatigue problem in this study.

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*Keywords:* Huxley model, muscle fatigue, fatigue and non-fatigue muscle, tetanic and subtetanic contraction

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## 1. Introduction

Muscle fatigue is generally the result of the vigorous exercise. The effect of the muscle fatigue is that we are not able to sustain a level of exercise or activity. Therefore, muscle fatigue is usually described as a decline in ability of a muscle to create force. Skeletal muscle fatigue is a complex and multifactorial physiological phenomenon, and the underlying mechanisms are not well understood.

There is still considerable debate about which factor is the main determinant of fatigue development. This may be partly due to the fact that fatigue studies have been performed in such a diversity of systems, from skinned fibre segments to performing athletes [8]. Therefore, different views on the most important mechanisms of fatigue have been described by several authors [1]-[3], [9], [12], [15]-[18], etc. Several attempts have been made to model muscle behavior however the attempts to integrate the effect of the muscle fatigue have been performed at the end of 20th century [4], [5], [10] etc. Calcium ions handling can be considered as a possible connection between muscle force and muscle fatigue [2]. The calcium metabolism in the muscle fibre was utilized to simulate the effect of fatigue during performance of skeletal muscle in this study.

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## 2. Muscle model

### 2.1. Models of contracting fibres and muscles

The models of contractile behavior of the muscle fibres are generally described by two concepts. The first one is based on the accurately description of the relation between the observed macroscopic data. This type of the model is referred to as *phenomenological*. Hill model, based on the relation between the muscle force and the velocity of shortening, belongs to this type of models. They are characterized by the simplicity and the direct connection to macroscopic muscle experiments. The second ones describe the process inside the muscle fibres, therefore they are called *micro-structural*. The first model of this type was developed by A.F. Huxley and it was created on the base of the cross-bridge behavior. It has been modified by few authors since then. The advantage of this model is that the mathematical description of the muscle behavior is apposite. However, its complexity results in high computational demand.

Both the Huxley and Hill type contraction models can be applied to describe the contraction of whole muscles [6].

### 2.2. Muscle model previously developed in our laboratory

The sliding cross-bridge theory of the contraction was taken into account as a base of the model previously developed by my colleagues [7]. This theory known as kinetic theory was proposed by A.F. Huxley in 1957 and later it was extended by many other authors. The principles are based on the bonding/debonding process of the cross-bridges between actin and myosin filaments and calcium activation. Because of the mathematical complexity of Huxley model, Zahalak work seems to be fundamental. Zahalak introduced a distribution-moment approximation to the kinetic theory and so simplified the process of solving of this problem. The partial equations were replaced by the non-linear ordinary differential equations.

There is considered the simplest Huxley model in the muscle model developed by [7], which assumes that the cross-bridges have only two possible states: bonded and debonded. The muscle contraction depends on the calcium activation and the mutual position of the myofilaments. Therefore fraction  $r$  of the actin sites is available for the attachment due to calcium activation and fraction  $\alpha$  of all cross-bridges can attach due to overlap and structural hindering. The rate of change of the attached cross-bridge distribution can be described by the modified two-state Huxley model

$$\frac{\partial n(\xi, t)}{\partial t} - w(t) \frac{\partial n(\xi, t)}{\partial \xi} = r(t) f(\xi) (\alpha - n(\xi, t)) - g(\xi) n(\xi, t), \quad (1)$$

where  $n(\xi, t)$  is the fraction of attached cross-bridges with specific length  $\xi$  at time  $t$ ,  $w$  is the velocity of shortening of half sarcomere,  $f(\xi)$  is the bonding (attachment) rate parameter,  $g(\xi)$  is the unboding (detachment) rate parameter. Different shapes of  $f(\xi)$  and  $g(\xi)$  functions are used in literature [11], [20]. The Zahalak choice [19] is respected by

$$f(\xi) = \begin{cases} 0 & -\infty < \xi < 0, \\ f_1 \xi & 0 \leq \xi \leq 1, \\ 0 & 1 < \xi < \infty, \end{cases} \quad (2)$$

$$g(\xi) = \begin{cases} g_2 & -\infty < \xi < 0, \\ g_1 \xi & 0 \leq \xi \leq 1, \\ g_1 \xi + g_3 (\xi - 1) & 1 < \xi < \infty. \end{cases} \quad (3)$$

The shape of the overlap function  $\alpha$  described by eq. (4) is chosen according to [7].

$$\alpha\left(\frac{\lambda_{CE}}{\lambda_{opt}}\right) = \begin{cases} 1 - 6.25\left(\frac{\lambda_{CE}}{\lambda_{opt}} - 1\right)^2 & \frac{\lambda_{CE}}{\lambda_{opt}} \leq 1, \\ 1 - 1.25\left(\frac{\lambda_{CE}}{\lambda_{opt}} - 1\right) & \frac{\lambda_{CE}}{\lambda_{opt}} > 1, \end{cases} \quad (4)$$

$\lambda_{CE} = \frac{l_{CE}}{L_{CE}}$  represents the ratio of instantaneous contractile length  $l_{CE}$  and rest contractile element length  $L_{CE}$ .  $\lambda_{opt}$  is the optimal stretch, which can be expressed by  $L_{opt} = \lambda_{opt}L_{CE}$ , where  $L_{opt}$  is the optimal fibre length, usually set to 1.05-1.2.

The activation factor described the sensitivity of myofilaments to calcium ions in eq. (5) is determined from the chemical equilibrium between calcium and troponin

$$r = \frac{C^2}{C^2 + \mu C + \mu^2}, \quad (5)$$

with calcium concentration in the myofibrillar space  $C$ , which is normalized with respect to the maximum  $\text{Ca}^{2+}$  concentration and  $\mu$  the troponin-calcium reaction rasion constant.

The rate of change of the normalized calcium concentration in the myofibrillar space is defined as

$$\frac{\partial C}{\partial t} = \theta(c\nu - C), \quad (6)$$

where  $\theta$  represents a fibre-type dependent rate parameter,  $c$  a calcium release parameter and  $\nu = f/f_{max}$  the stimulation frequency  $f$  with respect to the tetanic stimulation frequency  $f_{max}$ . It is assumed that uptake of  $\text{Ca}^{2+}$  by the sarcoplasmic reticulum (SR) described by the second term of eq. (6) is given by the total number of calcium ions in the myofibrillar space [6]. The first term of eq. (6) describes the release of calcium from the sarcoplasmic reticulum.

Using the distribution-moment approximation [19]

$$Q_k(t) = \int_{-\infty}^{\infty} \xi^k n(\xi, t) d\xi, \quad k = 0, 1, 2, \dots \quad (7)$$

the partial differential equation (1) is transformed to the system of first-order ordinary differential equations

$$\frac{\partial Q_k(t)}{\partial t} = \alpha r \beta_k - r \phi_{k1} - \phi_{k2} - kw Q_{k-1}, \quad k = 0, 1, 2, \dots \quad (8)$$

where the coefficients  $\beta_k$ ,  $\phi_{k1}$  and  $\phi_{k2}$  have following forms

$$\beta_k = \int_{-\infty}^{\infty} \xi^k f(\xi) d\xi, \quad (9)$$

$$\phi_{k1} = \int_{-\infty}^{\infty} \xi^k f(\xi) n(\xi, t) d\xi, \quad (10)$$

$$\phi_{k2} = \int_{-\infty}^{\infty} \xi^k g(\xi) n(\xi, t) d\xi, \quad (11)$$

Three first distribution moments have important macroscopic interpretations. They are proportional to the contractile tissue stiffness, force and elastic energy [19].

Non-fatigue performance of muscle fibre model can be represented by fig. 1.

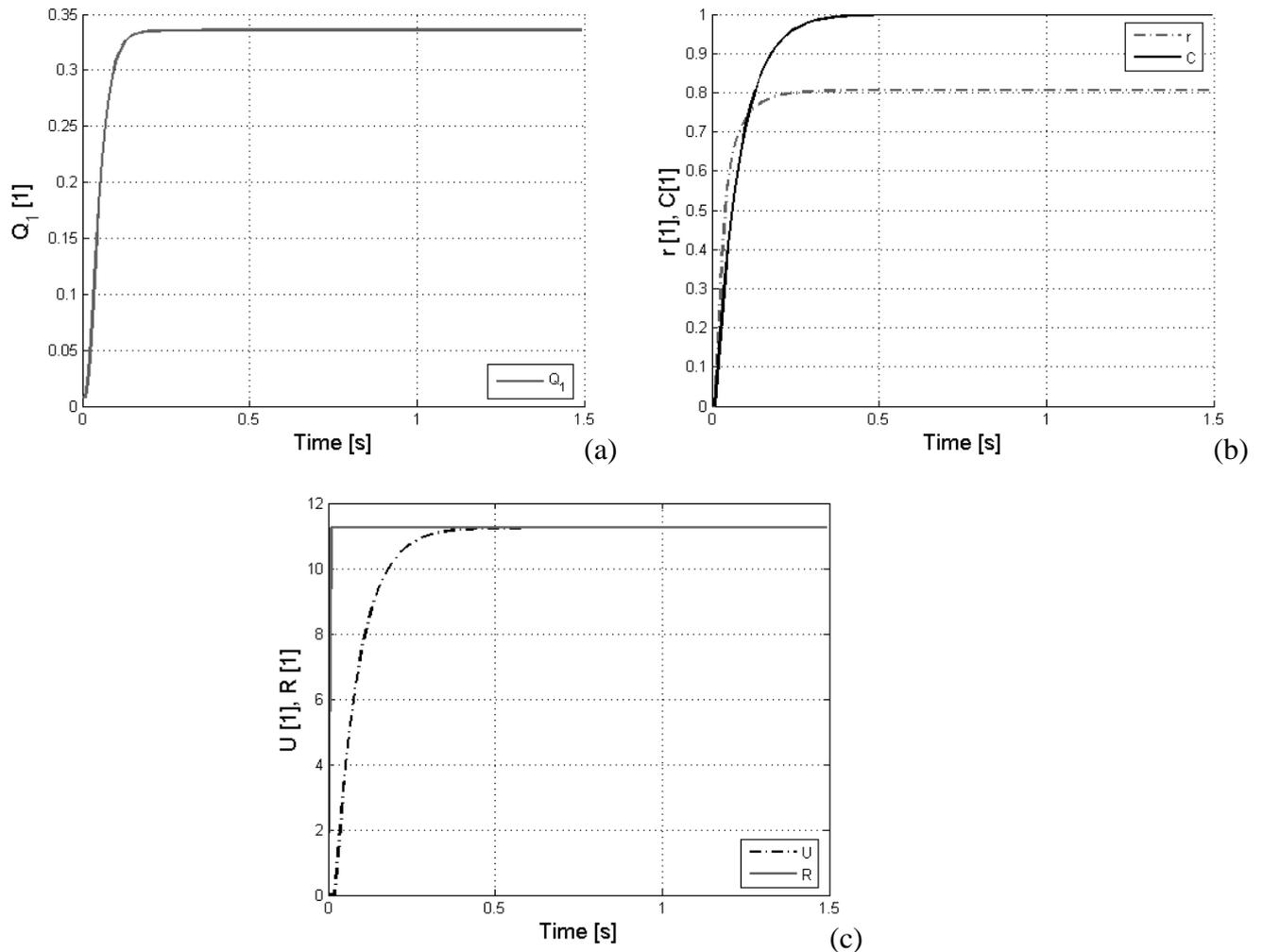


Fig. 1. Non-fatigue behavior of muscle fibre: (a) time dependence of  $Q_1$ , which is proportional to muscle force, (b) time dependence of calcium concentration  $C$  and activation factor  $r$ , (c) time dependence of calcium release  $R$  and uptake  $U$

### 3. Muscle fatigue

Muscle fatigue, complex and multifactorial physiological phenomenon, is defined as a decline of muscle force. Its underlying mechanisms are not still well understood. Muscle fatigue may occur due to factors intrinsic to the muscle itself or to extra-muscular factors which influence how the muscle contracts. Therefore there is thought to have two main components of muscle fatigue: i) central fatigue (caused by the problems within central nervous system) and ii) peripheral fatigue (affecting the factors within the muscle itself). These two components may act either individually or in combination to produce fatigue [9]. The aim of this study was to integrate the effect of peripheral fatigue into model developed previously in our laboratory [7].

#### 3.1. What causes peripheral muscle fatigue?

K.A.P. Edman described peripheral fatigue as the reduced capacity of the myofibrils to produce force [9]. However, there are many different factors which may affect myofibrillar function. The process of fatigue is dependent on the type of contraction (sustained or intermittent,

maximal or submaximal, static or dynamic) and the profile of muscles. Therefore it is clear, that during various activities the process of fatigue is different.

Therefore there was focus on the maximal isometric contraction (tetanic) of the fast fibre with short duration.

Generally, during high intensity exercise, the need for energy exceeds the one which can be supplied by aerobic metabolism. Therefore the energy must be supported also by the anaerobic metabolism. During such activities the muscle stores of energy such as glycogen, phosphocreatine and adenosine triphosphate are reduced. Concurrently, the levels of metabolic products such as lactate, adenosine diphosphate and inorganic phosphate increase.

It has been found that the increased concentration of inorganic phosphate influenced i) the  $\text{Ca}^{2+}$  concentration surrounding the myofilaments, ii) sensitivity of the myofilaments to  $\text{Ca}^{2+}$ , and iii) the force produced by the crossbridges [17]. Since the calcium ion movement seems to be crucial for determination of muscle force generation ability see fig. 2, calcium handling became the base stone for suggestion of the fatigue model described in this study.

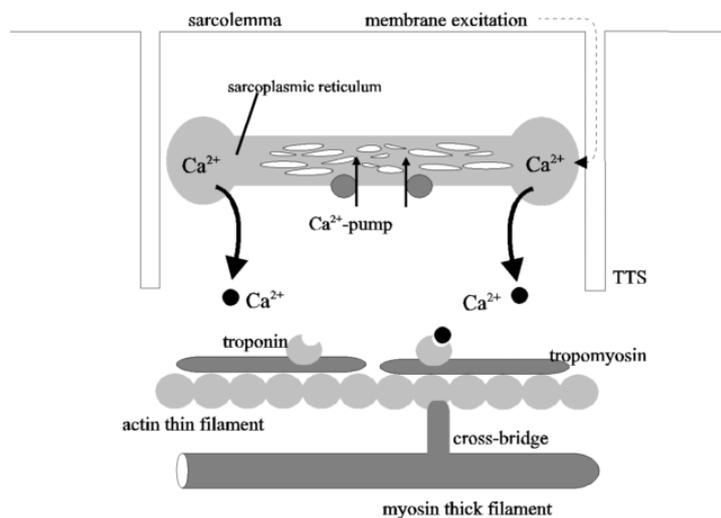


Fig. 2. The principle steps in excitation contraction coupling in skeletal muscle. The sarcoplasmic reticulum with its release and uptake calcium ions play a central role during muscle contraction [13].

### 3.2. Biological experiment

The fatigue model developed in this study is based on the biological experiment [15], [16], [17], which has been performed on the single fast-twitch muscle fibre during isometric tetanic contraction. The muscle force and calcium contraction have been investigated. It has been ensured that during such contraction three phases can be seen, see fig. 3.

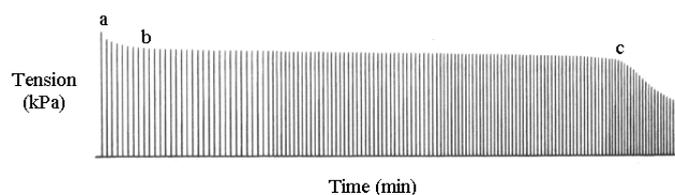


Fig. 3. Illustrative picture of the evolution of the muscle force during tetanic isometric contraction at the moment, when muscle fatigue begins [15].

The letters a, b and c denote the time, when first phase (muscle fatigue), second phase and third phases of muscle fatigue begin. Each of these phases is characterized by the specific evolution of the muscle force and free calcium concentration. During first phase (about 20 s) tension falls to  $(84.6 \pm 0.6)\%$ , however calcium concentration rises. During the longer-lasting phase 2 (usually 3-6 min) tension only slightly declines to  $(73.1 \pm 1.1)\%$ , calcium concentration falls slightly. The major tension loss occurs during phase 3, where tension falls to 30% of the original in about 1 min, calcium concentration falls significantly down to 50% [15], [16], [17].

An important variable needed to characterize fatigue is the endurance time (i.e. the time from onset of fiber activation to the time when a reduction in the fiber is detected [5]). The endurance time for the fast-twitch fibers is based on the amount of glycogen stored in fast-twitch fibers. It has been determined that for fast-twitch glycolytic fibers, fatigue begins after 23 s of contraction [5].

Furthermore, another fatigue protocol [14] established, that the rates of the sarcoplasmic reticulum calcium release and uptake are consistently depressed to (40-60)% during tetanic contraction.

During the early fatigue, the decline of force is caused by the impaired cross-bridge function. However during the later fatigue the decline is connected with the impaired SR  $\text{Ca}^{2+}$  release and uptake and sensitivity of myofilaments to calcium ions [16]. All of these effects can be detected during the whole fatigue.

All described knowledge were utilized to solve the problem of muscle fatigue.

### 3.3. Integration of effect of muscle fatigue into muscle model

The biological knowledge described above was the base stone for the creation of muscle fatigue model.

Therefore the calcium concentration, myofibrillar sensitivity to calcium ions and cross-bridge function were changed during muscle fatigue to satisfy the results of the biological experiment.

Firstly, the relation for the non-fatigue calcium concentration in the myofibrillar space given by the eq. (6) was replaced by the eq. (12) for better understanding of the fatigue problem.

$$\frac{\partial C(t)}{\partial t} = R(t) - U(t), \quad (12)$$

where  $R(t) = \theta c\nu$  and  $U(t) = \theta C(t)$  are the relations for the release and uptake, respectively, of the calcium ions from and to the sarcoplasmic reticulum, respectively.

To involve the effect of muscle fatigue on the amount of calcium ion concentration in the myofibrillar space the functions of release  $R(t)$  and uptake  $U(t)$  were multiplied by the fatigue functions  $f_{re}$  and  $f_{up}$  as described in eq. (13)-(15).

$$R(t, t_1, t_2, t_3) = \theta c\nu f_{re}(t, t_1, t_2, t_3), \quad (13)$$

where

$$f_{re}(t, t_1, t_2, t_3) = (1 - H_{t_1}(t)) + (1 - H_{t_2}(t))H_{t_1}(t) \left[ \left( \frac{R(t_1)}{\theta c\nu} - 1 \right) + e^{\nu p_{r1}(t-t_1)} \right] + (1 - H_{t_3}(t))H_{t_2}(t) \left[ \left( \frac{R(t_2)}{\theta \nu c} - 1 \right) + e^{\nu p_{r2}(t-t_2)} \right] + H_{t_3}(t) \left[ \left( \frac{R(t_3)}{\theta \nu c} - 1 \right) + e^{\nu p_{r3}(t-t_3)} \right], \quad (14)$$

where  $p_{r1} = 0.0115$ ,  $p_{r2} = -0.00415$ ,  $p_{r3} = -0.0159$ .

$$U(t, t_1, t_2, t_3) = \theta C(t) f_{up}(t, t_1, t_2, t_3), \quad (15)$$

where

$$f_{up}(t, t_1, t_2, t_3) = (1 - H_{t_1}(t)) + (1 - H_{t_2}(t))H_{t_1}(t) \left[ \left( \frac{U(t_1)}{\theta C(t_1)} - 1 \right) + e^{\nu p_{u1}(t-t_1)} \right] + (1 - H_{t_3}(t))H_{t_2}(t) \left[ \left( \frac{U(t_1)}{\theta C(t_2)} - 1 \right) + e^{\nu p_{u2}(t-t_2)} \right] + H_{t_3}(t) \left[ \left( \frac{U(t_2)}{\theta C(t_3)} - 1 \right) + e^{\nu p_{u3}(t-t_3)} \right], \quad (16)$$

where  $p_{u1} = -0.0001$ ,  $p_{u2} = -0.0025$ ,  $p_{u3} = -0.0001$ .

The fatigue functions described by eq. (14)-(16) were created to represent the non-linear decline of release and uptake, which is dependent on the time and also on the activation. Therefore the exponential functions were chosen to represent this non-linear decline. Since the declines of release and uptake are different in individual fatigue phases, the Heaviside functions were chosen to switch-on and switch-off the effect of individual exponential function in corresponding phases. The indexes of the individual functions were chosen to fit the result of the experiment.

Since the sensitivity of myofilaments to calcium ions during muscle fatigue is chosen during fatigue too, this function was transformed by the same way as the release or uptake, see eq. (17)-(18)

$$r(t, t_2, t_3) = \frac{C(t)^2}{C(t)^2 + \mu C(t) + \mu^2} f_{se}(t, t_2, t_3), \quad (17)$$

where

$$f_{se}(t, t_2, t_3) = (1 - H_{t_2}(t)) + H_{t_3}(t) \left[ \left( \frac{r(t_3)}{C(t_3)^2 / (C(t_3)^2 + \mu C(t_3) + \mu^2)} - 1 \right) + e^{p_{s2}(t-t_3)} \right] + (1 - H_{t_3}(t))H_{t_2}(t) \left[ \left( \frac{r(t_2)}{C(t_2)^2 / (C(t_2)^2 + \mu C(t_2) + \mu^2)} - 1 \right) + e^{p_{s1}(t-t_2)} \right], \quad (18)$$

where  $p_{s1} = -0.00145$ ,  $p_{s2} = -0.0088$

The same approach was used for the reduction of the cross-bridge function

$$f_1(t) = p_{f1} [(1 - H_{t_1}(t)) + H_{t_1}(t)(1 - H_{t_2}(t))e^{p_{f1}(t-t_1)} + f_1(t_2)/p_f H_{t_2}(t)], \quad (19)$$

where  $p_{f1} = -0.0310$  and  $p_f$  is the value of the bonded function  $f_1$  in non-fatigue state.

$H_{t_1}(t)$ ,  $H_{t_2}(t)$ ,  $H_{t_3}(t)$  are shorthand notation for Heaviside functions  $H(t - t_1)$ ,  $H(t - t_2)$ ,  $H(t - t_3)$ , respectively. There  $t_1$ ,  $t_2$  and  $t_3$  are the time, when the first phase (fatigue), second phase and third phase of muscle fatigue begins.

In summary, the Heaviside functions represent the switch-on or switch-off of various effects of fatigue in the individual time phases. The exponential functions represent the non-linear changes of release and uptake of calcium ions, sensitivity of myofilaments to ions and cross-bridge function. These functions were chosen to represent the changes of muscle function objectively by virtue of values of the exponential term.

#### 4. Simulation of muscle fatigue

##### 4.1. Validation of muscle fatigue model

The fast muscle fibre was activated by the short tetanic isometric contraction. Therefore the following values of the parameter were utilized:  $c=1$ ,  $\nu=1$  (maximal (tetanic) contraction),  $\theta=11.25$  (fast fibre) [6],  $\mu=0.2$ ,  $f_1=43.3$ ,  $g_1=10$ ,  $g_2=209$ ,  $g_3=0$  [19].

The time dependence of activation factor  $r$ , calcium concentration  $C$ ,  $Q_1$  (variable, which is proportional to the muscle force), release and uptake of the calcium ions from the sarcoplasmic reticulum and to the sarcoplasmic reticulum during tetanic isometric contraction with respect to muscle fatigue effect are visualized in the fig. 4.

The result of the  $Q_1$  was compared with the result of the experiment [8], [18] visualized by the dashed curves.

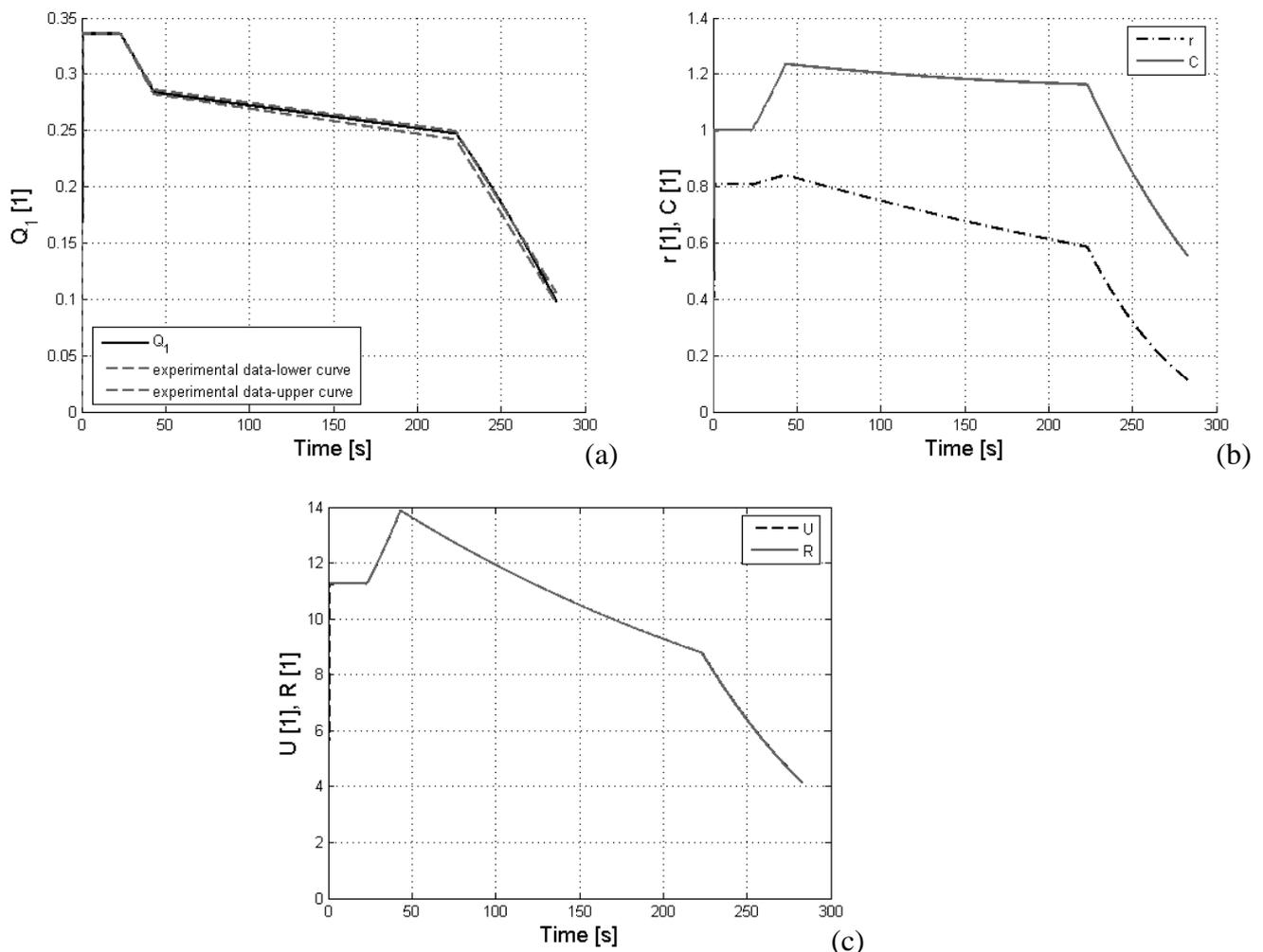


Fig. 4. The effect of muscle fatigue on the (a)  $Q_1$  (proportional to force), (b) calcium concentration  $C$ , activation factor  $r$  and (c) the release  $R$ , uptake  $U$  of calcium ions from the sarcoplasmic reticulum

You can see from fig. 4, that the result of  $Q_1$ ,  $C$  and  $R$ , respectively  $U$  declines in three phases to approximately 30%, 50% and 40% of non-fatigue value. All results agree well with the result of the experiment, see Section 3.2.

#### 4.2. Comparison of fatigue during tetanic and subtetanic contraction

Since the muscle fatigue is influenced by the activation in biological reality, the comparison of the tetanic ( $\nu=1$ ) and sub-tetanic contraction ( $\nu=0.9$ ) was performed to ensure that the muscle fatigue model is sensitive to degree of activation.

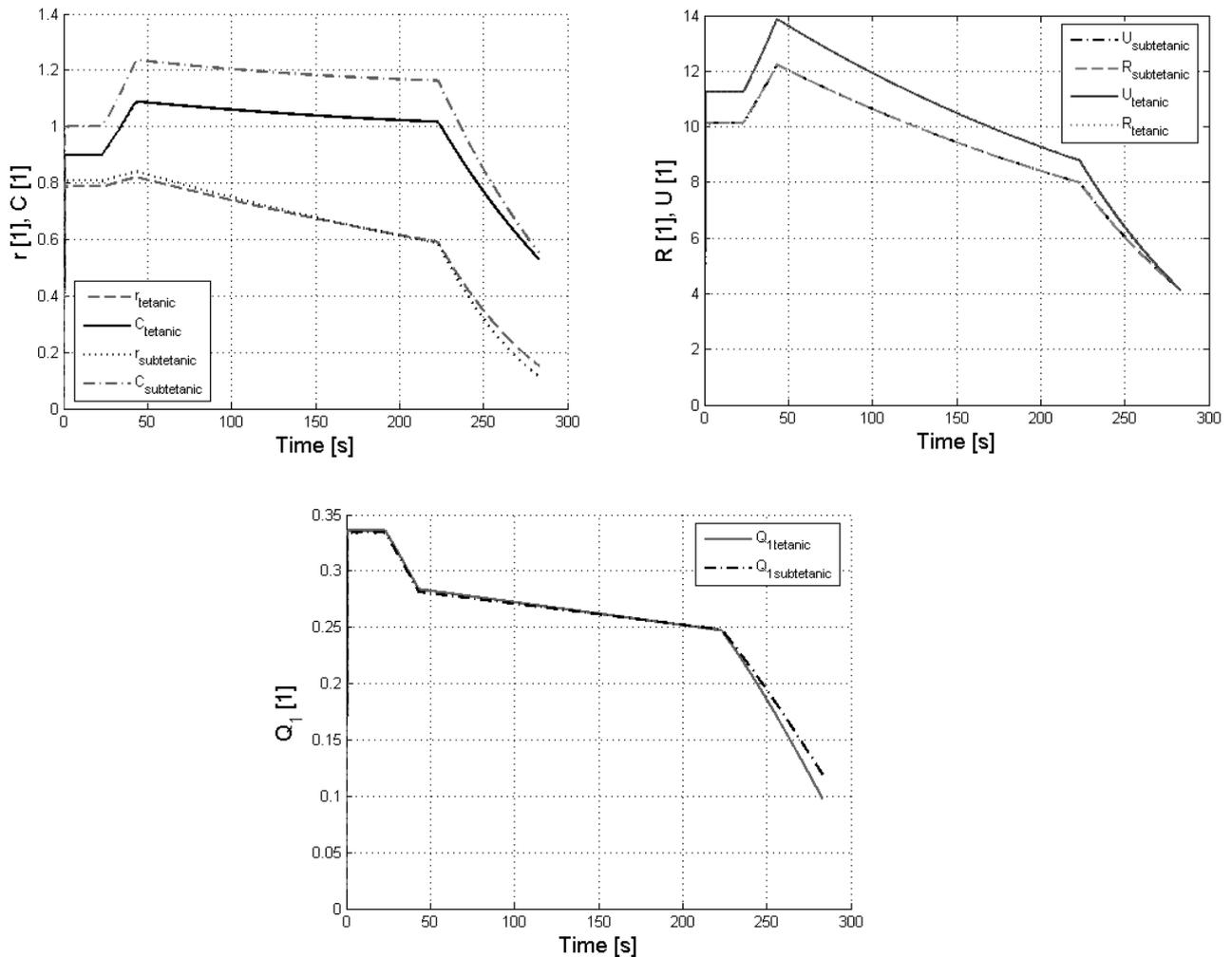


Fig. 5. The comparison of the effect of type contraction on muscle fatigue

From fig. 5 can be seen that during subtetanic contraction the decline of force and calcium contraction is rather slighter than during tetanic contraction. However, this fatigue model can be used only for tetanic and subtetanic contraction, since the process of fatigue during of the low activation with long duration is rather different.

#### 5. Conclusion

In this study the fatigue model was created on the base of the biological experiment [8], [18]. Fatigue model was integrated into muscle model, which was previously developed in our laboratory [7] and it was based on Huxley model. The muscle model was exposed to tetanic isometric contraction of short duration. The decline of  $Q_1$ , which is proportional to muscle force, could be observed. This non-linear decline in three phases is in agreement with experiment.

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