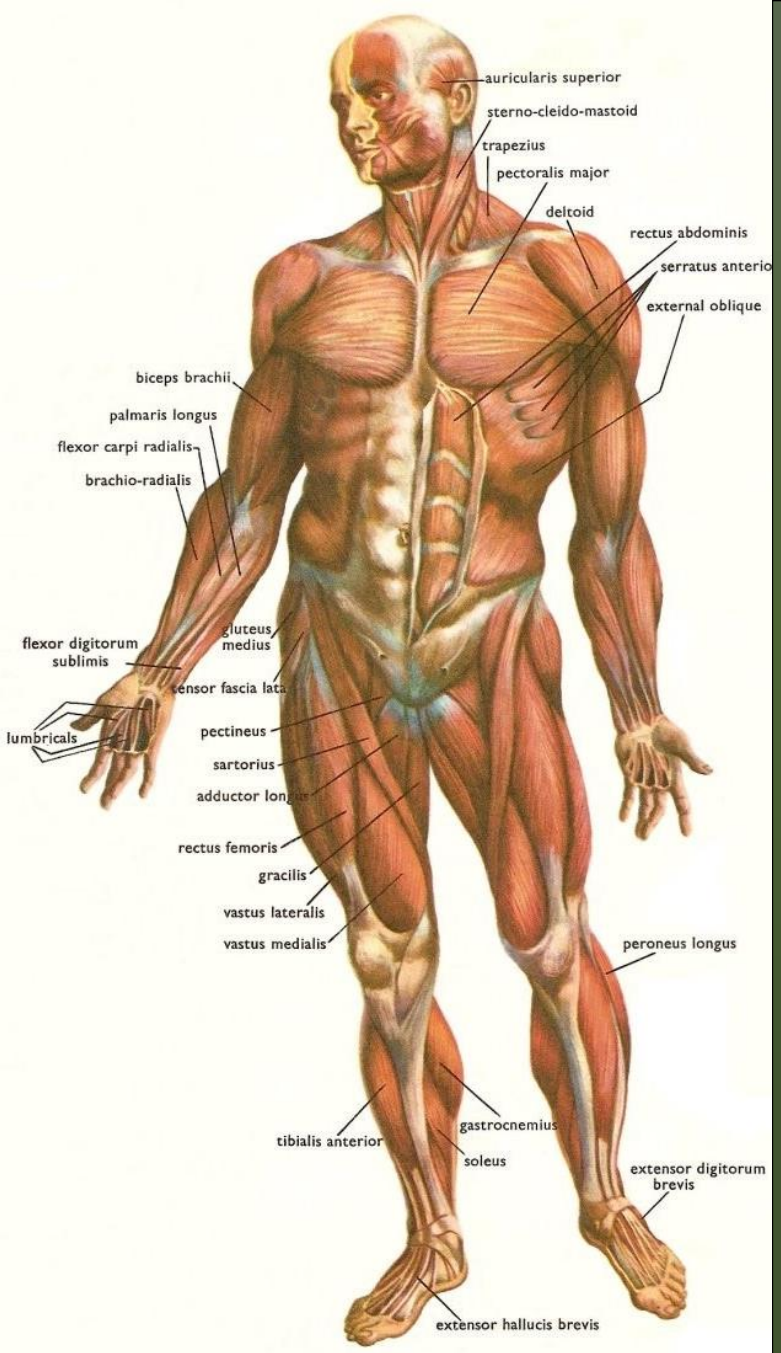

Modeling of contractile activity-induced fatigue in human skeletal muscle

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Background

Prolonged and intensive training leads to a decline in maximal force or power production in response to contractile activity known as muscle fatigue. Mostly, it is regulated by peripheral factors through metabolic pathways engaged in ATP synthesis and ATP usage. Despite the significant amount of experimental data on metabolic changes contributing to a power reduction, a comprehensive mathematical model of muscle fatigue, which embraces all necessary cellular processes and includes both muscle fiber types, still does not exist.

Purpose

To study the dependence of muscle fatigue on the peripheral factors using mathematical modeling methods.

Peripheral factors contributing to muscle fatigue

Peripheral fatigue is associated with an impairment of the mechanisms from excitation to muscle contraction and occurs in the neuromuscular junction and muscle.

There are many contributors to peripheral fatigue but the main factors are phosphates, Pi and protons, H+.

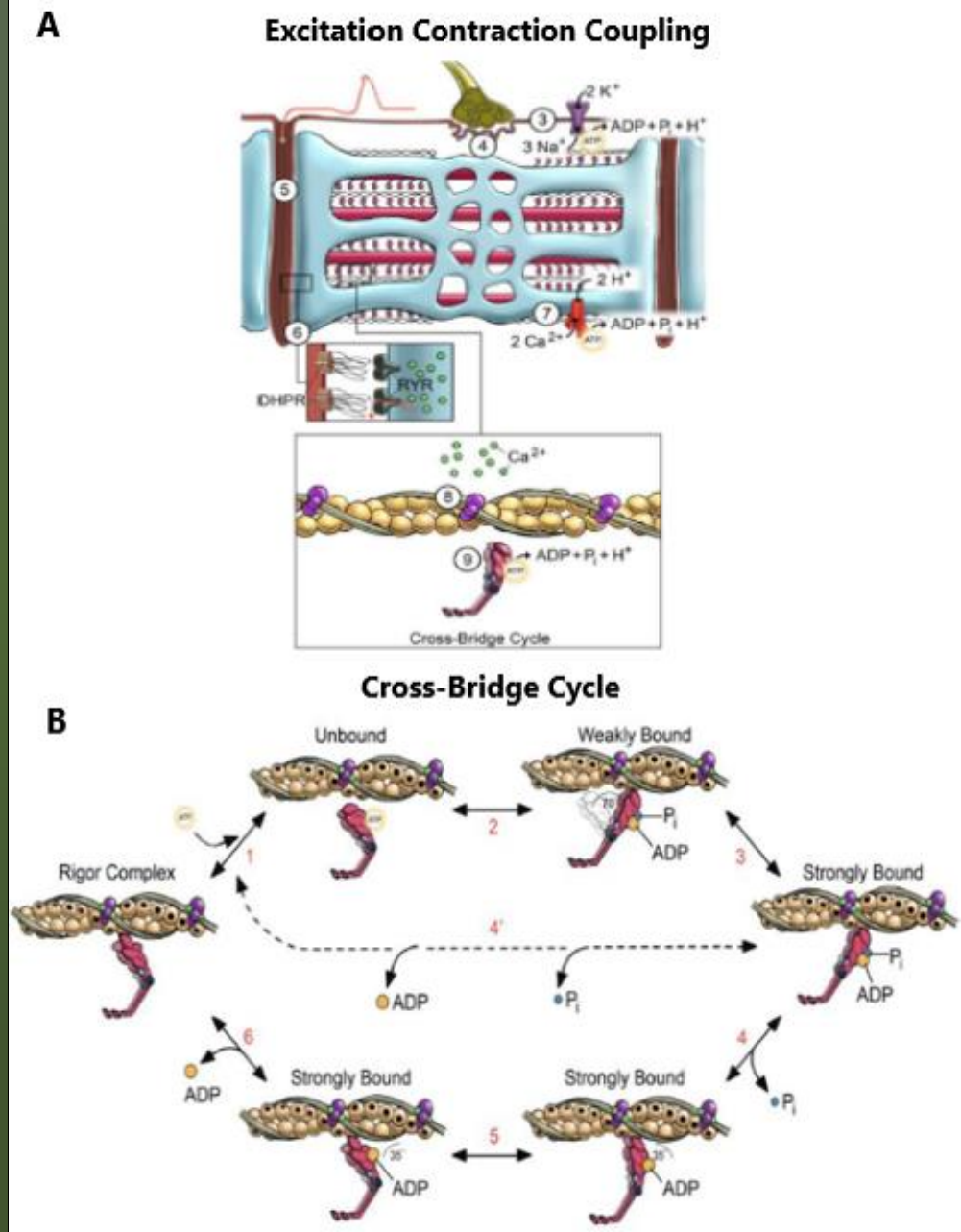
<u>Pi</u>

- slow down the release of calcium from the sarcoplasmic reticulum
- induce a non-standard cross-bridge cycle (Fig. B, step 4')
- reduces the sensitivity of filaments to calcium (Fig. A, step 8)
- impairs the functioning of DHPR (Fig. A, step 6)

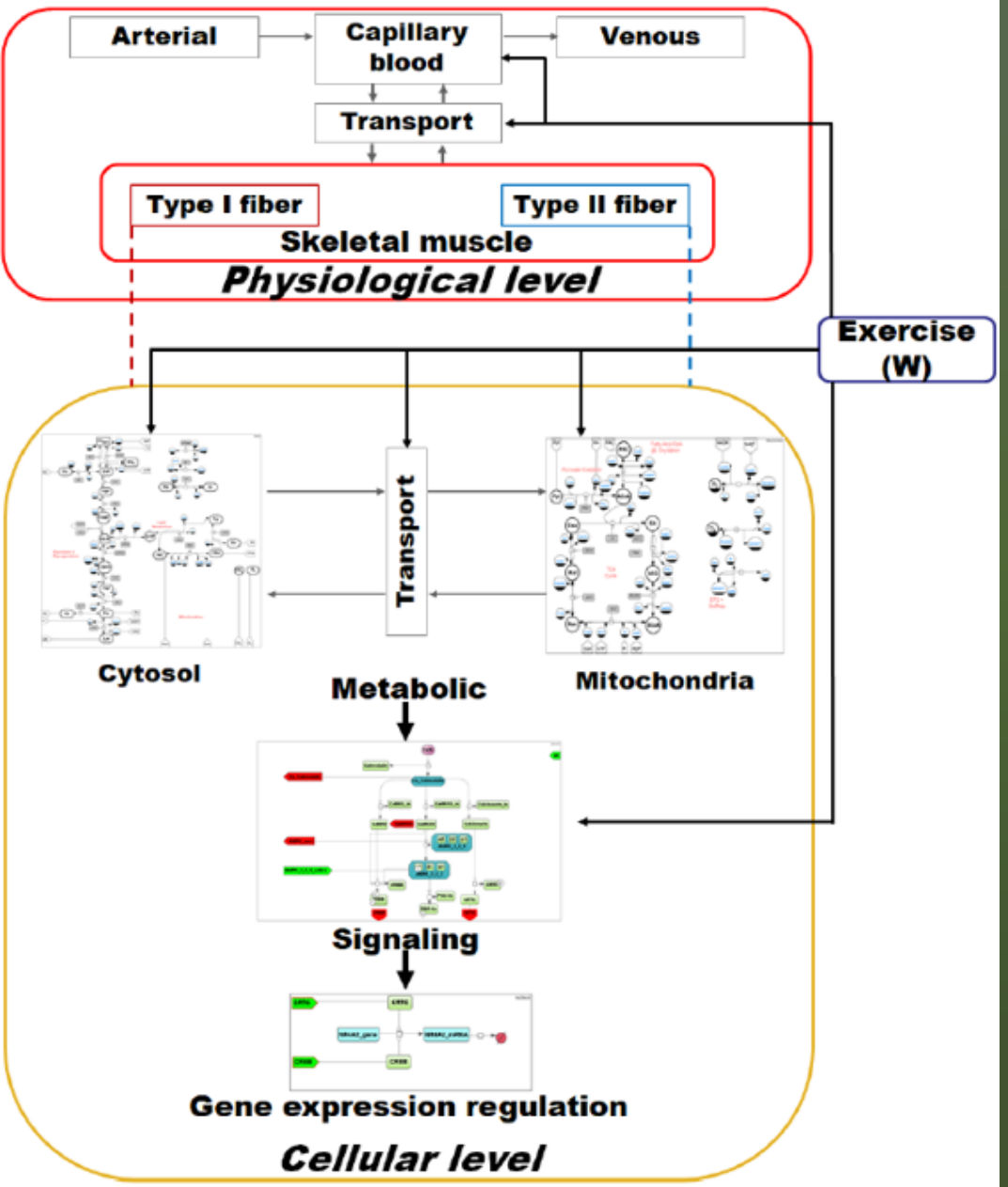
<u>H+</u>

- slow down the transition from weakly bound to strongly bound state of filaments (Fig. B, step 3)
- reduces the sensitivity of filaments to calcium (Fig. A, step 8)
- inhibits the ADP isomerization step of the cross-bridge cycle and/or the rate of ADP release (Fig. B, steps 5 and 6)

additive effect



C. W. Sundberg, R. H. Fitts. Bioenergetic basis of skeletal muscle fatigue. (2019)



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Materials and Methods

The modular model developed in the bioinformatics laboratory of the FRC ICT in 2021 was used as the base model.
The mechanism that activates energy metabolism through an increase in the muscle volume, blood flow, transport and metabolic reactions rates during exercise was given by the stress function:

$$Function(W) = 1 + \alpha_i \times W \times \left(1 - e^{\frac{t_{start} - t}{\tau_i}}\right)$$

Experimental data for a young subgroup and a protocol (knee extension for 4 min) were taken from the study of Sundberg et al. (2019). In the model, the exercise was modeled as a continuous instantaneous load with power = 250 W.

Two fatigue models developed in BioUML were considered, both with a linear dependence on pH: a **mechanistic** one with a Hill dependence on phosphates (1) and a **phenomenological** one with a linear dependence on phosphates with a time delay *tau* (2).

$$1)\ \ \gamma = \frac{100}{1 + \left(\frac{\mathrm{Pi_{norm}} - 1}{\mathrm{C}}\right)^{\mathrm{n}}} + \mathrm{A} \cdot (\mathrm{pH_{norm}} - 1)$$

$$2)\ \ \gamma = 100 + \mathrm{A} \cdot (\mathrm{pH_{norm}} - 1) - \mathrm{delay}(\mathrm{B} \cdot (\mathrm{Pi_{norm}} - 1), \mathrm{tau})$$

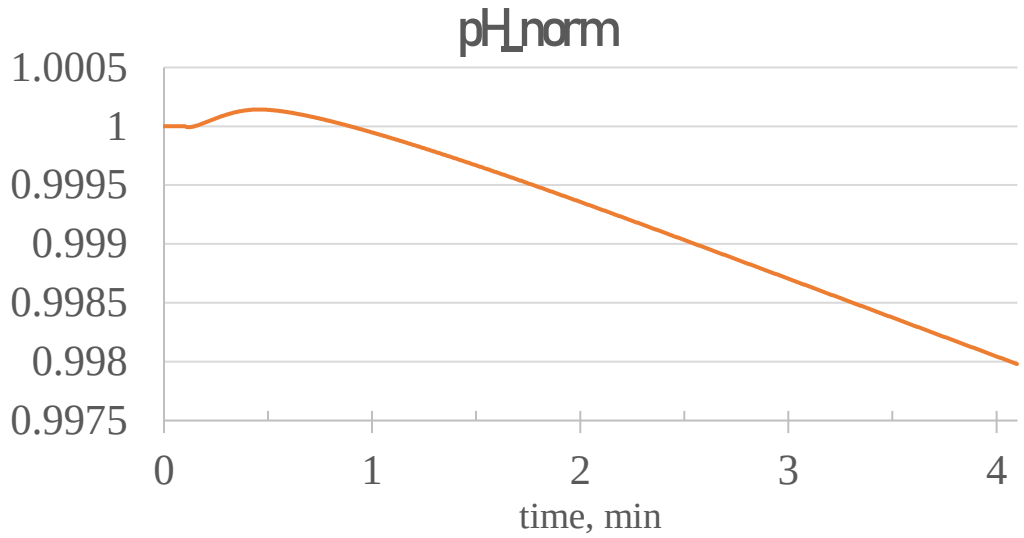
Results: modifications of the model

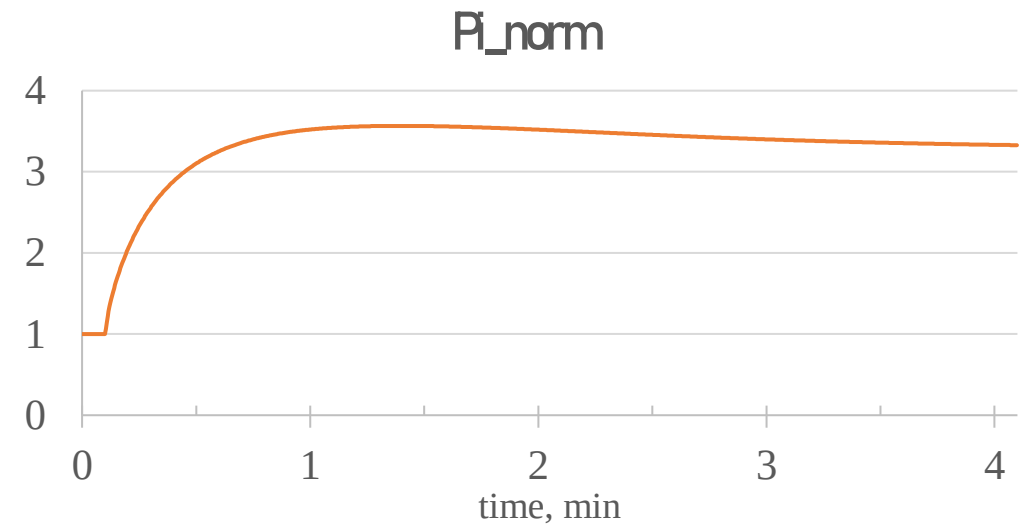
Based on the basic parameters of the model, we was not able to reproduce the dynamics of phosphates consistent with Sundberg's data: higher amplitude of the concentration changes and slower transition to the steady state.

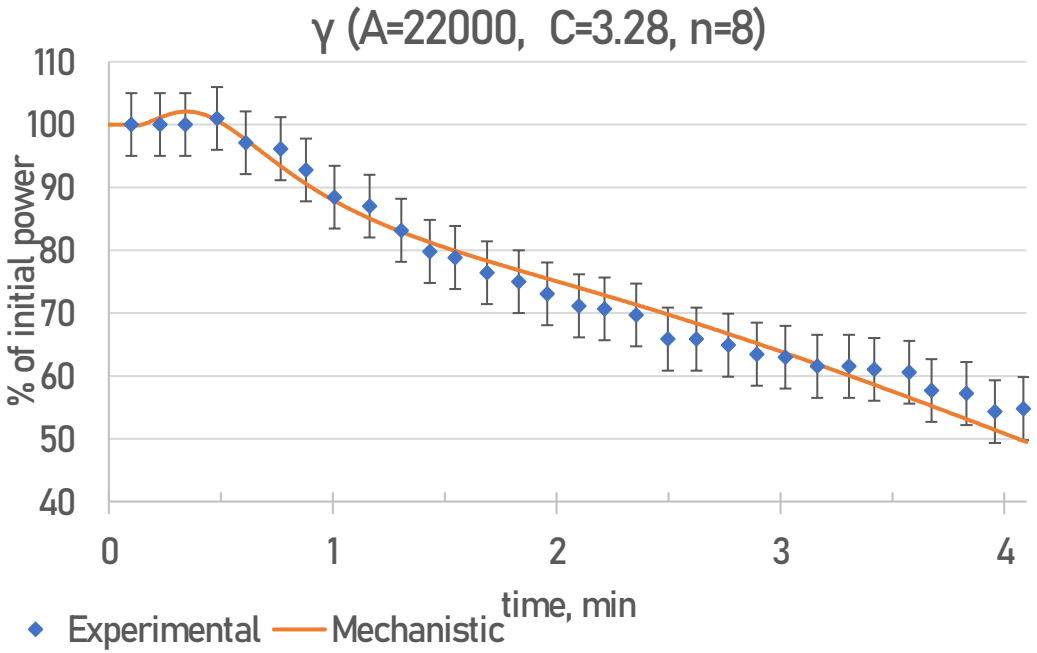
Based on the literature data, some modifications were made:

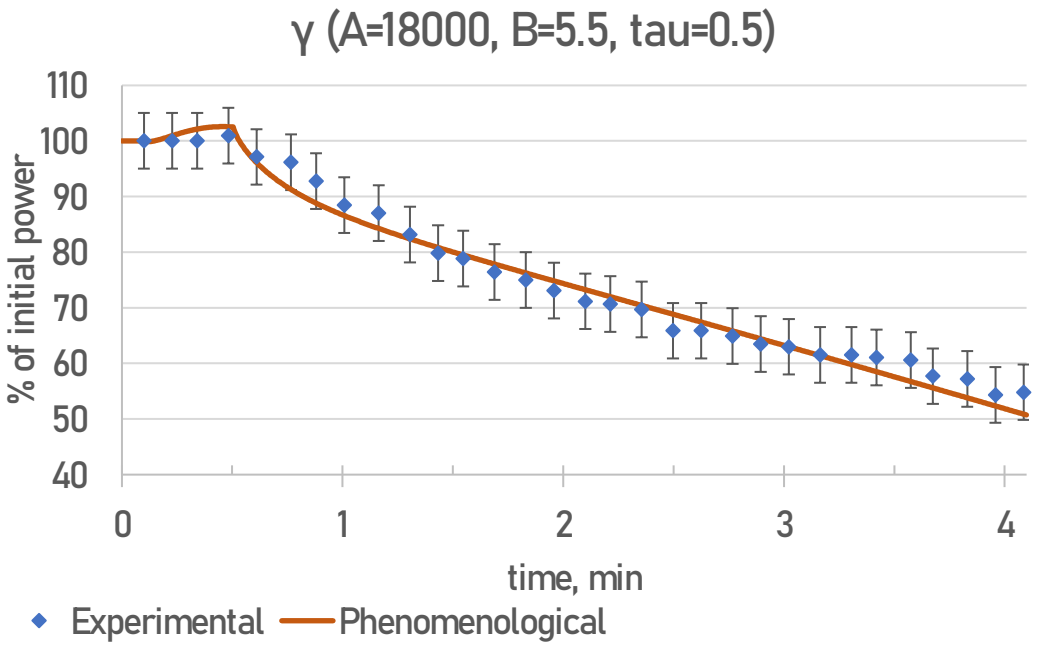
- the ratio of red and white fibers was changed from 1:1 to 1:3;
- the buffer capacity was reduced by 30%;
- the activation time for glycolysis and oxidative phosphorylation reactions was increased from 0.4 to 1.0 minutes during exercise.

pH_norm and Pi_norm dynamics after modifications









Results: models of fatigue

For mechanistic model, the values of the fatigue parameter agree with the experiment. The high value of the Hill parameter obtained during the fitting of the model suggests a rather complex molecular genetic mechanism for the effect of phosphate on the power drop, which is activated at a sufficiently high concentration.

A similar result of agreement between numerical calculation and experiment was obtained by adapting the model with a time delay for phosphates. According to the numerical analysis of this version of the model, a delay of 30 seconds is necessary before the effect of phosphate on fatigue begins.

Conclusion

We established that phosphates and pH are key factors in the muscle fatigue. Two models of the fatigue were considered: a mechanistic one with a Hill dependence on Pi and a phenomenological one with a delay for Pi. We succeeded to reproduce the power drop consistent with the experimental data. It was shown that the mechanism of influence of Pi is a complex and multi-stage, and the time delay of 30 seconds is required before Pi influences the power output.