

Integrated modular model linking metabolism, signaling transduction and gene expression regulation in human skeletal muscle¹

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Abstract. Exercised-induced adaption of skeletal muscle to aerobic endurance training is ensured by instant activation of signaling transduction pathways in the muscle cells with consequent alteration of both metabolic fluxes and expression for a versatile group of genes. Despite the experimentally based efforts to disentangle the complexity of the muscle adaptation process caused by multiple interactions and intersections on signaling, metabolic and gene expression levels, the quantitative and mechanistic contribution of each component of the signaling cascades on downstream genetic regulation processes has not been fully elucidated. Data-driven mathematical models provide a rigorous way to analyze and understand such intricate biological systems. Herein a novel mathematical model linking anaerobic and aerobic metabolism, Ca²⁺-dependent signaling pathway and downstream transcription regulation of early and late response genes in human skeletal muscle during and after acute exercise developed in BioUML platform has been presented.

Keywords: mathematical model, skeletal muscle, physical exercise, Ca²⁺-dependent signaling pathway, transcriptome, RNA sequencing, regulation of expression, BioUML.

1 Introduction

Skeletal muscle comprises about 40 % of total body mass in adult lean humans and plays a crucial role in the control of whole-body metabolism and exercise tolerance. Regular low-intensity exercise (aerobic or endurance training) strongly induces adaptive changes in skeletal muscle which are increased vascular and mitochondrial density, oxidative capacity and improve fat and carbohydrate metabolism. These adaptations lead to an enhancement of muscle endurance performance and reduce the risk associated with the morbidity and premature mortality of chronic cardiovascular and metabolic diseases [1; 2].

Acute aerobic endurance exercise induces significant metabolic changes in the skeletal muscle which in turn enhance the production of signaling molecules. One of the most essential signaling pathway activated by the muscle contraction is Ca²⁺-dependent signaling transduction pathway [2]. Contraction-induced increase of calcium ions (Ca²⁺) concentration in myoplasm significantly impacts on activation of signaling proteins (Ca²⁺/calmodulin-dependent protein kinases, calcineurin, etc.) and may be potentially involved in regulation of the expression of many genes responsible for the adaptation of muscle to aerobic training [3].

It is known that acute intensive exercise results in dramatic changes in the expression of hundreds of genes even in the skeletal muscle adapted to aerobic training [4-6]; and moreover, the transcriptome profiling markedly changes during the early stages of recovery [5-7]. However, these changes can be resulted from not only by the muscle contraction, but caused by systematic factors and circadian rhythms. On basis of the analysis of differentially expressed genes between exercised and contralateral non-exercised vastus lateralis muscle, the contractile activity-specific transcriptome responses at 1 and 4 hours after the one-legged exercise were identified in our previous study [8]. It was shown that the most dominant biological process associated with the response is the transcription regulation, i.e. increase in expression of genes encoding transcription factors and co-activators. The study demonstrated that genes encoding such transcription factors as NR4A, AP-1 and EGR at 1 hour after termination of the exercise, while another transcription regulators like PPARGC1A, ESRRG and VGLL2 were highly expressed at 4

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hour after aerobic exercise. Both sets of transcription factors modulate muscle metabolism. It means that gene expression on early and late stages of the recovery after the termination of the exercise can be regulated by different ways. Obviously, these molecular mechanisms are pretty complex, but we suppose that expression of early and late response genes may be ensured some general or basic mechanisms of the gene expression regulation.

It is worth to note, although advancement in the development of high-throughput experimental techniques and generation of diverse omics data for human skeletal muscle during endurance exercise enabled to unveil key participants of the cellular response and adaptation [4-8], the system understanding of signaling-metabolic pathways relationships with downstream genetic regulation in exercising skeletal muscle is still elusive. As a complementary theoretical counterpart to the experimental investigation of molecular mechanisms underlying the skeletal muscle adaptation to the endurance training, a detailed mechanistic mathematical model provides a powerful *in silico* tool to quantitatively investigate signal transduction pathways and corresponding molecular mechanisms orchestrating gene expression dynamics during an exercise [9-11].

2 Results

We have previously developed a multi-compartmental mathematical model describing the dynamics of intracellular species concentrations and fluxes in human muscle at rest and intracellular metabolic rearrangements in exercising skeletal muscles during an aerobic exercise on a cycle ergometer [11]. As an initial model, we have used a complex model of energy metabolism in the human skeletal muscle developed by Li and coauthors [9]. We have proposed a modular representation of the complex model using BioUML platform [12]. The modular representation provides the possibility of rapid expansion and modification of the model compartments to account for the complex organization of muscle cells and the limitations of the rate of diffusion of metabolites between intracellular compartments (Fig. 1).

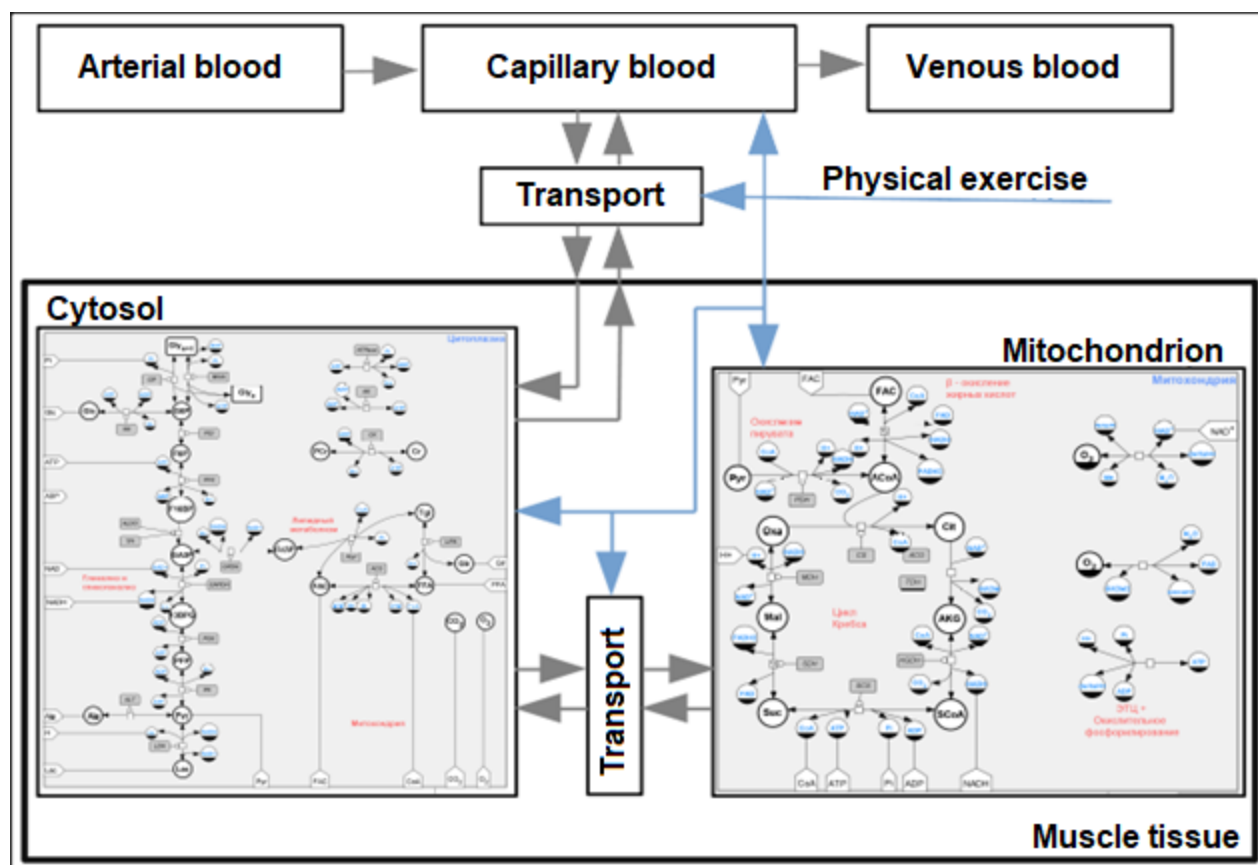


Fig. 1. Hierarchical organization of the modular mathematical model of the energy metabolism in skeletal muscle. Grey arrows represent transport reactions of metabolites, blue arrows mean external control function like consideration of the physical exercise. Module «Muscle tissue» consists of submodules «Cytosol» and «Mitochondrion», which in turn contain equations describing enzymatic reactions inside the certain compartment.

The parametric fitting of the modular model to published experimental data [9] showed the validity of the modular modeling approach implemented in BioUML. Furthermore, *in silico* simulations of the metabolic changes during

aerobic training on a cycle ergometer demonstrated that concentration levels of ATP and ADP do not significantly change under this condition, while creatine and phosphocreatine concentrations do strongly. The simulation outcome corresponds to predictions of the model published by Li and coauthors.

A physiologically based computational model of the Ca^{2+} -dependent signaling pathway taking into account downstream activation of early (*NR4A* genes family) and late (*PPARGC1A* gene) response genes expression in the skeletal muscle (Fig. 2) has been developed based on modular modeling approach too [13].

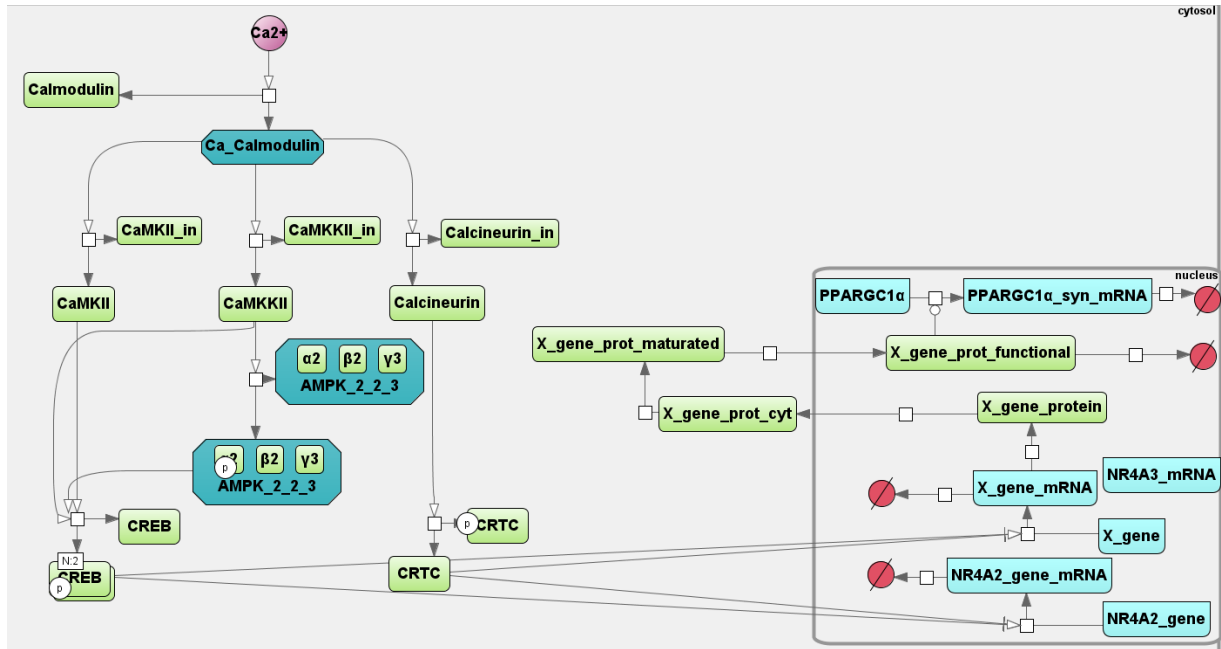


Fig. 2. SBGN diagram of the Ca^{2+} -dependent signaling pathway activating expression of early (*NR4A* genes family) and late (*PPARGC1A* gene) response genes during muscle cells adaptation to physical exercise. The diagram has been reconstructed using BioUML platform and represents signaling transduction pathway in the cytoplasm, while regulatory processes of genes expression are described in the muscle cell's nucleus; X_gene – early response gene encoding intermediate factor X, which is required for transcription activation of *PPARGC1A* gene.

Numerical analysis of the model enabled to reveal crucial steps in this signal transduction pathway for the adaptation and demonstrated the necessity of consideration of additional transcription factors modulating transcription of late response genes in order to adequately reproduce gene expression data that were taken in human vastus lateralis muscle during and after acute cycling exercise. Bioinformatics analysis of the original transcriptomics data, in turn, proposed that CREB-like proteins from FOS and JUN families forming heterodimer complexes with transcription factor CREB1 are indeed these intermediate regulators of late response genes [13].

3 Conclusion

In the development of the mathematical model describing energy metabolism of the human skeletal muscle [11] an extended integrated modular model considering Ca^{2+} -dependent signaling pathway and downstream regulatory processes of early and late response genes expression has been built. An activation mechanism which enhances energy metabolism via transport and reaction fluxes due to physical exercise was incorporated in our previous model (represented as «Muscle metabolism» on Fig. 3) as the stress function depending on general work rate parameter. The work rate parameter defines intensity of the physical exercise.

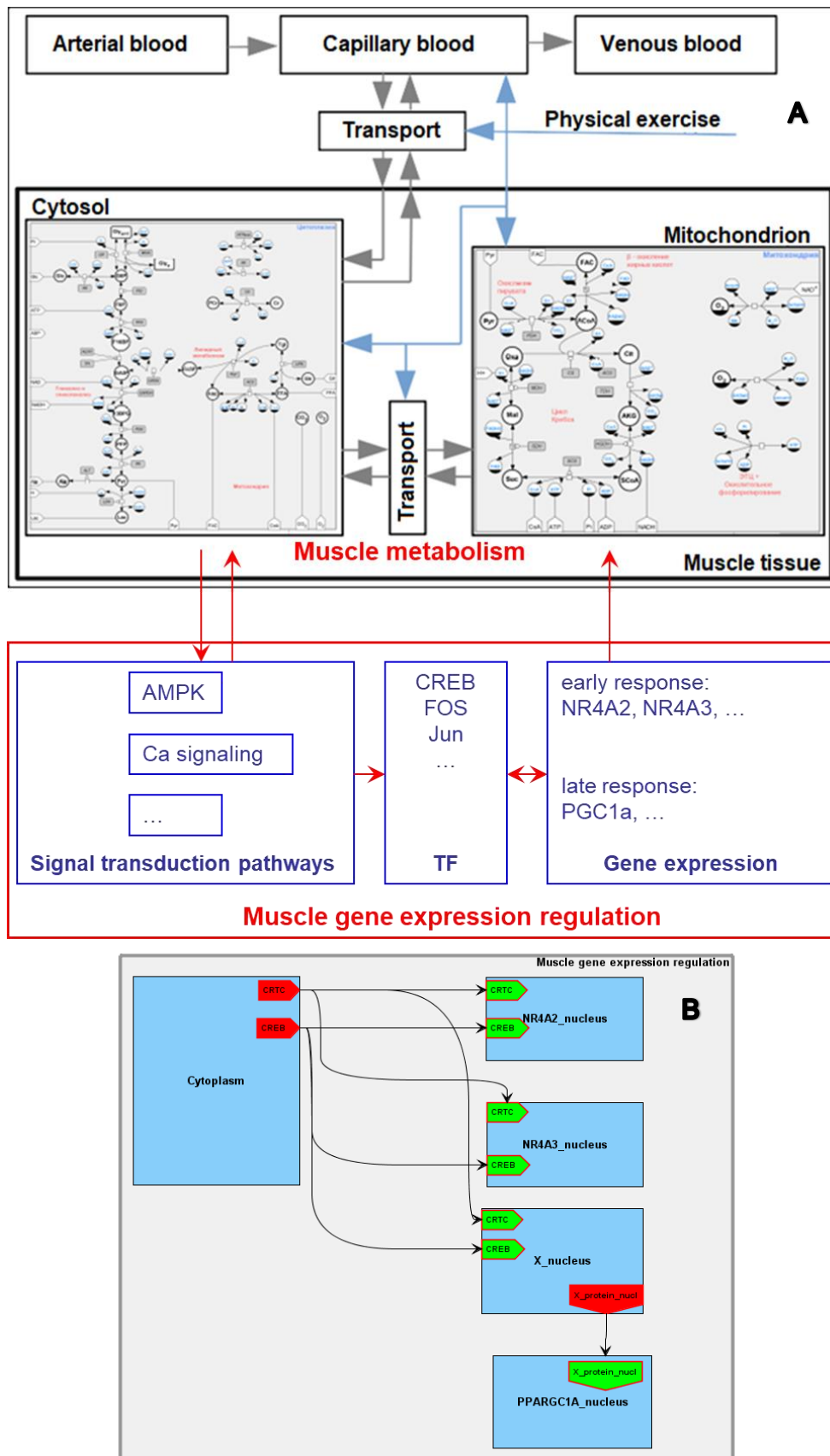


Fig. 3. An integrated modular model linking metabolism, Ca^{2+} -dependent signaling transduction and gene expression regulation in human skeletal muscle (A). A certain mathematical module has been developed for each early and late response gene (B).

In order to the integrated model represents actual changes in gene expression in exercised human skeletal muscle in more details, we replaced the general work rate parameter on the concentration of Ca^{2+} -Calmodulin complexes and incorporated PPAR GC1A -mediated transcription regulation of genes playing an important role in adaptation to regular exercise. The integrated modular model provides more precise predictions of adaptation mechanisms of the skeletal muscle cells to exercise on levels of both metabolic pathways and gene expression.

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References

- [1] Pedersen B.K. and Febbraio M.A. Muscles, exercise and obesity: skeletal muscle as a secretory organ// *Nature Reviews Endocrinology*. 2012. V. 8. № 8. P. 457–465.
- [2] Hawley J.A., Hargreaves M., Joyne, M.J. and Zierath J.R. Integrative biology of exercise// *Cell*. 2014. V. 159. №4. P.738-749.
- [3] Koulmann N. and Bigard A.X. Interaction between signaling pathways involved in skeletal muscle responses to endurance exercise// *Pflügers Archiv*. 2006. V. 452. № 2. P.125.
- [4] Neubauer O., Sabapathy S., Ashton K.J., Desbrow B., Peake J.M., Lazarus R., Wessner B., Cameron-Smith D., Wagne, K.H., Haseler L.J. and Bulmer A.C. Time course-dependent changes in the transcriptome of human skeletal muscle during recovery from endurance exercise: from inflammation to adaptive remodeling// *Journal of Applied Physiology*. 2013. V. 116. № 3. P. 274-287.
- [5] Vissing K. and Schjerling P. Simplified data access on human skeletal muscle transcriptome responses to differentiated exercise// *Scientific data*. 2014. V. 1. P. 140041.
- [6] Popov D.V., Makhnovskii P.A., Kurochkina N.S., Lysenko E.A., Vepkhvadze T.F. and Vinogradova O.L. Intensity-dependent gene expression after aerobic exercise in endurance-trained skeletal muscle. *Biology of sport*. 2018// V. 35. № 3. P. 277.
- [7] Dickinson J.M., D'Lugos A.C., Naymik M.A., Siniard A.L., Wolfe A.J., Curtis D.R., Huentelman M.J. and Carroll C.C. Transcriptome response of human skeletal muscle to divergent exercise stimuli. *Journal of Applied Physiology*// 2018. V. 124. № 6. P. 1529-1540.
- [8] Popov D.V., Makhnovskii P.A., Shagimardanova E.I., Gazizova G.R., Lysenko E.A., Gusev O.A. and Vinogradova O.L. Contractile activity-specific transcriptome response to acute endurance exercise and training in human skeletal muscle// *American Journal of Physiology-Endocrinology and Metabolism*. 2019. V. 316. № 4. P. E605-E614.
- [9] Li Y., Dash R. K., Kim J., Saidel G. M., Cabrera M. E. Role of NADH/NAD⁺ transport activity and glycogen store on skeletal muscle energy metabolism during exercise: in silico studies// *American Journal of Physiology-Cell Physiology*. 2009. V. 296. № 1. P. 25–46.
- [10] Akberdin I.R., Kazantsev F.V., Ermak T.V., Timonov V.S., Khlebodarova T.M., Likhoshvai V.A. In Silico Cell: Challenges and Perspectives// *Mathematical Biology and Bioinformatics*. 2013. V. 8. № 1. P. 295–315.
- [11] Kiselev I.N., Akberdin I.R., Vertyshev A.Y., Popov D.V. and Kolpakov F.A. A modular visual model of energy metabolism in human skeletal muscle// *Mathematical Biology and Bioinformatics*. 2019. V. 14. № 2. P. 373-392.
- [12] Kolpakov F., Akberdin I., Kashapov T., Kiselev I., Kolmykov S., Kondrakhin Y., Kutumova E., Mandrik N., Pintus S., Ryabova A., Sharipov R., Yevshin I., Kel A. BioUML: an integrated environment for systems biology and collaborative analysis of biomedical data// *Nucleic Acids Research*. 2019. V. 47. № W1. P. W225–W233.
- [13] Akberdin I.R., Vertyshev A.Yu., Pintus S.S., Popov D.V., Kolpakov F.A. A Mathematical model linking Ca^{2+} -dependent signaling pathway and gene expression regulation in human skeletal muscle// *Mathematical Biology and Bioinformatics*. 2020. reviewing.