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Modular modeling of human skeletal muscle adaptation to different types of physical exercise considering molecular genetic interactions between metabolism and gene expression regulation

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Motivation and Aim: Nowadays there is a growing society's interest in research studies and the development of technologies related to health preservation. It is known that physical activity plays an important role in the development and maintenance of a functionally healthy state not only of individual organs, but also of the entire human body. Regular physical exercise affects almost all cell types, tissues and organs. The cumulative effect of each exercise bout improves the health and performance depending on the tissue [1]. However, achievement of the best outcomes in the training process is feasible with a deep insight of not only physiological, but also molecular-genetic mechanisms underlying the body's response to physical exertion.

Muscle tissue is one of the four main tissues present in the human body. Skeletal muscles constitute approximately 40 % of the total body mass in a healthy adult and serve a multitude of functions, from movement to maintaining metabolic balance [2, 3]. The functions of movement and maintaining body posture are provided by the unique ability of muscles to contract.

During physical exertion, a series of changes occur in skeletal muscle cells at the transcriptomic, proteomic and metabolomic levels [4]. Furthermore, muscles undergo structural and functional changes with regular exercise that enables them to work more efficiently. Enzyme synthesis plays a key role in the adaptation of muscles to physical activity. Various methods can be employed to assess the regulation of enzyme synthesis during adaptation to physical exercise, such as measuring enzyme activity in muscle tissue, measuring the expression levels of genes encoding these enzymes, or studying changes in metabolite levels in muscle tissue. However, *in vivo* studies have several limitations, including the absence of implementation at the level of individual cells, technical measurement complexities, labor intensiveness, and costliness.

A reconstruction of the mathematical model describing skeletal muscle adaptation to various types of the physical activity avoids these constraints, which makes it possible to analyze the interaction between molecular components in a systematic way. The existing model of skeletal muscle adaptation, developed by Akberdin et al. [5], has a hierarchical structure and includes physiological and cellular levels. At the first level the interaction of muscle fibers with the circulatory blood system is described, while the second one comprises the processes occurring in metabolism, signaling pathways and gene expression. The model links metabolism, Ca^{2+} and AMPK-dependent signal trans-

duction pathways and regulation of gene expression in human skeletal muscles. However, the modular model uses the phenomenological linear function that affects the rate of enzymatic reactions during the exercise and does not consider concentration dynamics of enzymes catalyzing reactions of the central metabolism in fiber cells assuming that their concentrations are constant during the exercise mode.

An analysis of publications and omics data [6, 7] allowed us to determine what changes are observed in the expression of genes encoding the enzyme of central metabolism and the synthesis of these proteins. Using the GTRD database [8], transcription factors associated with genes encoding central metabolic enzymes have been identified. The data provides the qualitative and quantitative basis to consider such molecular processes as transcription and translation of enzymes in the muscle cell taking into account expression and action of transcription factors orchestrating their mRNA synthesis.

Thus, the aim of this study is an extension of the modular model structure to adequately describe changes in enzyme concentrations during an exercise and recovery.

Methods and Algorithms: The modeling was performed using the tool sets of the BioUML software, which is developed for mathematical modeling of life systems and analysis of various types of biological data [9]. The platform supports main standards for visualization and simulation of biological systems, a number of numerical methods, and integration with Jupyter Notebook to ensure reproducibility of research results.

Visual modeling implemented in the platform provides the representation of the studied systems as graphical diagrams, which greatly facilitates the understanding of complex biological processes. Each component of the diagram corresponds to a specific object (variable, metabolite, reaction, etc.). Based on the defined properties of the components and their interconnections, BioUML automatically generates Java code used for the model compilation and simulation.

The modular approach in BioUML implies the representation of the system under study as a set of interconnected subsystems. Each module is a mathematical model that can be considered and simulated independently. The combination and integration of modules constitute a complex, comprehensive model of the entire system. The modularity principle enables the development and adaptation of the model to changing needs without the requirement of a complete rebuild of the underlying architecture. Additionally, this approach allows researchers to select, use, and study only those modules that are relevant to specific tasks.

Results: As a result of the study, a modular model describing the adaptation of skeletal muscle to different types of physical exercise was expanded by considering processes both regulating expression of genes encoding enzymes and protein synthesis. The extension of the transcription factor module, along with the addition of the transcription and translation modules for central metabolism's enzymes facilitates more precise and detailed description of the molecular mechanisms of human skeletal muscle adaptation to various types of physical stress. This opens up the opportunity for a design of optimal training strategies to achieve specific goals for individuals.

Conclusion: The modular model describing the human skeletal muscle adaptation to different modes of the physical exercise has been extended by additional modules for transcription and translation processes required for adequate simulation of changes in enzyme concentration. The next stage of the study is to verify the quality of the model by comparing simulation results to accumulated experimental data for different types of physical exertion.

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References

1. Ashcroft S.P., Stocks B., Egan B., Zierath J.R. Exercise induces tissue-specific adaptations to enhance cardiometabolic health. *Cell Metab.* 2024;36(2):278-300. doi 10.1016/j.cmet.2023.12.008
2. Frontera W.R., Ochala J. Skeletal muscle: a brief review of structure and function. *Calcif Tissue Int.* 2015;96(3):183-195. doi 10.1007/s00223-014-9915-y
3. Weskamp K., Olwin B.B., Parker R. Post-Transcriptional Regulation in Skeletal Muscle Development, Repair, and Disease. *Trends Mol Med.* 2021;27(5):469-481. doi 10.1016/j.molmed.2020.12.002
4. Egan B., Zierath J.R. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab.* 2013;17(2):162-184. doi 10.1016/j.cmet.2012.12.012
5. Akberdin I.R., Kiselev I.N., Pintus S.S., Sharipov R.N., Vertyshev A.Y., Vinogradova O.L., Popov D.V., Kolpakov F.A. A Modular Mathematical Model of Exercise-Induced Changes in Metabolism, Signaling, and Gene Expression in Human Skeletal Muscle. *Int J Mol Sci.* 2021;22(19):10353. doi 10.3390/ijms221910353
6. Popov D.V., Makhnovskii P.A., Shagimardanova E.I., Gazizova G.R., Lysenko E.A., Gusev O.A., Vinogradova O.L. Contractile activity-specific transcriptome response to acute endurance exercise and training in human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2019;316(4):E605-E614. doi 10.1152/ajpendo.00449.2018
7. Makhnovskii P.A., Zgoda V.G., Bokov R.O. et al. Regulation of Proteins in Human Skeletal Muscle: The Role of Transcription. *Sci Rep.* 2020;10:3514. doi 10.1038/s41598-020-60578-2
8. Kolmykov S., Yevshin I., Kulyashov M., Sharipov R., Kondrakhin Y., Makeev V.J., Kulakovskiy I.V., Kel A., Kolpakov F. GTRD: an integrated view of transcription regulation. *Nucleic Acids Res.* 2021;49(D1):D104-D111. doi 10.1093/nar/gkaa1057
9. Kolpakov F., Akberdin I., Kashapov T., Kiselev L., 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 Res.* 2019;47(W1):W225-W233. doi 10.1093/nar/gkz440