Review of: "Modelling Skeletal Muscle Motor Unit Recruitment Contributions to Contractile Function: Part 3 - Substrate Oxidation of Phosphagen, Lipid, and Carbohydrate Metabolism"

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Potential competing interests: No potential competing interests to declare.

General Comment on the Study:

This research represents a significant contribution to the field of exercise physiology, particularly in understanding the nuanced interactions of muscle fiber types with metabolic pathways during various intensities of exercise. The authors have undertaken the challenging task of developing and applying a computational model to explore these dynamics. The effort to elucidate the complex subject of substrate oxidation and energy utilization across different muscle fibers is highly commendable.

The quality of the work is evident in the thoroughness of the analysis and the clarity with which the results are presented. Despite the inherent limitations associated with computational models, the study provides substantial insights that bridge theoretical knowledge with potential practical applications in sports science and clinical practice.

The authors' dedication to exploring and questioning existing paradigms, while also providing a new framework for understanding muscle metabolism, demonstrates a commendable level of scholarly rigor. Their meticulous approach to integrating diverse pieces of the metabolic puzzle, from the phosphagen system's role during exercise to the implications of contraction frequencies on energy efficiency, shows a deep understanding of the topic.

Peer Review Feedback - Introduction Section:

The introduction of the article provides a detailed background on the motor units of skeletal muscles and their metabolic processes. It clearly states the intent to expand a theoretical model on the contributions of motor units to muscle functions and substrate oxidations, filling gaps in the current scientific literature. Topics such as muscle biopsy methodologies and fiber type classification based on myosin heavy chain structure offer a robust summary of previous work in the field, establishing a solid foundation for transitioning into the study’s methodology.

The information presented in the introduction adequately supports the authors' efforts to understand how different muscle fiber types utilize various energy systems. However, the introduction could further detail how data and methodologies from existing research have been adapted for this study. Additionally, a clearer expression of the study's hypotheses or research questions would help readers better understand the research objectives.

Recommendations:

1. **Hypotheses and Research Questions**: The fundamental hypotheses or questions of the study should be articulated more clearly. This would clarify the focus of the study and aid readers in comprehending the research objectives.
2. **Connection to Methodology**: The introduction should provide more information on how data and methodologies from previous studies have been applied to this research. This would enhance the scientific rigor of the study and reinforce the reliability of the methodology.

Peer Review Feedback - Methods Section:

The methods section of the article presents a comprehensive methodology for modeling ATP turnover and substrate oxidation across motor units. The authors utilize data derived from prior research, converting it into ATP turnover metrics using biochemical efficiency and in vivo free energy release rates. This section meticulously outlines various variables including motor unit types, contraction frequencies, and recruitment percentages to analyze energy utilization across different muscle types.

Strengths:

1. **Detailed Data Analysis and Modeling:** The use of software tools like Excel and Prism for data analysis and presentation strengthens the methodological approach. This enables a thorough examination and display of complex biochemical data.
2. **Comprehensive Metabolic Pathway Analysis:** The study employs complex nonlinear functions to determine the contributions of different energy systems and contraction frequencies to metabolic processes. This modeling is crucial for a deeper understanding of muscle biochemistry during contractions.
3. **Programming and Computational Methods:** The step-by-step computations performed through newly developed LabVIEW programming add a significant level of technical depth to the research, allowing for detailed analyses of substrate oxidation.

Recommendations:

1. **Discussion of Methodological Limitations:** The researchers should discuss potential limitations of their modeling techniques and computational methods, and how these limitations might affect the interpretation of the results. This would provide a more balanced perspective when interpreting the study's findings.

Peer Review Feedback - Results Section:

The results section of the article provides a detailed and methodologically sound analysis of ATP turnover and substrate oxidation across various motor units. The use of detailed figures and tables effectively illustrates the complex interactions between motor unit type, contraction frequency, and energy system contributions. This section successfully extends the understanding of muscle biochemistry during different contraction intensities, which is a significant contribution to the field.

Strengths:

1. **Comprehensive Data Visualization:** The inclusion of multiple figures (Figures 1 through 8) that depict the changes in ATP turnover and substrate oxidation provides a clear visual representation of the data. This approach helps in interpreting complex biochemical phenomena and in understanding the impact of different variables like motor unit type and contraction frequency.
2. **Innovative Modeling of Energy Systems:** The results showcase a novel approach to model the percentage contributions of different energy systems across varying muscle fiber types. This modeling is based on robust evidence from cellular biochemistry and is crucial for theorizing how energy system contributions shift with muscle contraction intensity.
3. **Detailed Analysis of Substrate Oxidation:** The analysis of how substrate oxidation changes with different contraction frequencies and motor unit recruitment levels offers valuable insights into the metabolic demands placed on muscle fibers during exercise.

Peer Review Feedback - Discussion Section:

The discussion section effectively articulates how substrate oxidation correlates with motor unit recruitment and contraction frequencies. The analysis is robust, linking physiological responses to fundamental thermodynamic principles, and providing a detailed examination of metabolic system responses across different motor unit types and exercise intensities.

Strengths:

1. **Thorough Analysis of Metabolic Responses:** The discussion provides a comprehensive breakdown of how different energy systems—phosphagen, glycolytic, and mitochondrial respiration—respond to changes in exercise intensity and motor unit recruitment. This section successfully connects these responses to underlying biochemical pathways and highlights significant deviations from previous research assumptions.
2. **Critical Evaluation of Exercise Intensity Range:** The acknowledgment that the range of exercise intensities tested is not physiologically plausible for sustained contractions offers an honest appraisal of the model's limitations and its experimental design. This transparency is crucial for framing the context of the findings and their applicability.
3. **Insightful Comparison with Previous Studies:** The discussion contrasts the current findings with past research, particularly in interpreting substrate oxidation data. This reevaluation offers new insights into the regulation of muscle metabolism and challenges traditional views on muscle fiber energetics.

4. **Integration of Theoretical Principles:** The discussion adeptly integrates theoretical principles such as the All or None Principle to explain the maximal contraction response of muscle fibers across various conditions. This approach not only solidifies the discussion with foundational muscle physiology concepts but also aids in framing the metabolic responses observed within a well-established physiological context.
5. **Use of Quantitative Data:** The extensive use of quantitative data to support the discussion points provides a strong empirical basis for the conclusions drawn. This methodical use of data enhances the credibility of the analysis and helps in clearly linking muscle physiology with metabolic activity.
6. **Integration of Comparative Studies:** The discussion effectively uses comparative data from studies like those of Romijn et al. to bridge model findings with real-world exercise data. This not only contextualizes the model's outputs within established research but also highlights its applicability and relevance to practical exercise physiology.
7. **Detailed Analysis of Glycolysis and Lactate Production:** The thorough examination of lactate production within the glycolytic framework offers critical insights into muscle metabolism under varying intensities. The use of detailed quantitative data to map these biochemical changes across different motor unit recruitment levels provides a valuable perspective on metabolic flexibility and adaptation.
8. **Reevaluation of the Phosphagen System:** The section revisits and challenges traditional interpretations of the phosphagen system's role during exercise, particularly through the lens of the creatine kinase shuttle theory. This reevaluation not only advances understanding but also corrects historical misconceptions about energy transfer during varying intensity levels.

Recommendations:

1. **Clarification of Non-Physiological Exercise Conditions:** While the discussion acknowledges the non-physiological nature of the exercise intensities used, it would benefit from a more detailed exploration of how these conditions affect the generalizability of the results. Discussing how these findings might translate to more typical physiological conditions could enhance the relevance of the research.
2. **Addressing Methodological Limitations:** While the discussion acknowledges the non-physiological intensity of exercises tested, it could benefit from a more critical examination of the methodological limitations that may arise from the experimental design. A discussion on how these limitations could be addressed in future studies would be valuable for advancing the field and refining the experimental approaches used.
3. **Comparative Analysis with Human Studies:** Given the model-based approach of the study, integrating a comparative analysis with human studies or clinical data could enhance the translational value of the research. Discussing how these findings correlate with clinical observations in sports medicine or rehabilitation settings would provide a broader perspective on the applicability of the results.
4. **Broader Implications of Lactate Dynamics:** The discussion around lactate production is highly technical and well-presented; however, expanding on the physiological implications of these findings—such as the impact on muscle fatigue, recovery strategies, and performance optimization—would make the results more accessible and relevant to practitioners in sports science and clinical settings.
5. **Further Exploration of CK-AK Dynamics:** The insights into the CK-AK system are compelling; nonetheless, further

discussion on how these findings can be integrated into broader metabolic models would be beneficial. Exploring how changes in creatine phosphate concentrations during low-intensity contractions affect overall muscle performance and recovery could provide a more holistic view of muscle energetics.

Peer Review Feedback - Perspectives, Significance, Limitations, and Conclusions Section:

This section effectively encapsulates the broader implications, inherent limitations, and the potential impact of the research findings. Here's an evaluation of the final parts of the discussion:

Strengths:

1. **Perspectives and Broader Implications:** The research uniquely contributes to the understanding of muscle metabolism from a computational model perspective, focusing on the implications of different fiber types during various exercise intensities. It emphasizes the potential for identifying optimal contraction frequencies where energy systems are most efficiently utilized, which is a valuable insight for training and performance optimization.
2. **Addressing the All or None Principle:** By discussing the All or None Principle, the paper highlights how the rate of contractions might play a crucial role in energy utilization during muscle activity, which is an important consideration for developing more effective training strategies that could enhance health and performance.
3. **Innovative Conclusions:** The conclusions drawn from the model about single muscle fiber contractile power and cellular bioenergetics provide a novel approach to understanding energy exchange in muscle tissues. This approach bridges the gap between single fiber data and whole muscle metabolism, offering insights relevant to both sports contexts and neuromuscular diseases.

Recommendations for Future Research: The section suggests that further research could improve the model and related data, which is encouraging. Explicitly recommending specific areas for future studies, such as experimental setups that could test the theoretical assumptions or exploring the metabolic changes in different fiber types under varied physiological conditions, would provide clear directions for subsequent work.