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COMPUTATIONAL MODELING OF BIOENERGETIC SIGNAL PATTERNS IN CARDIAC AND NEURAL ELECTROPHYSIOLOGY

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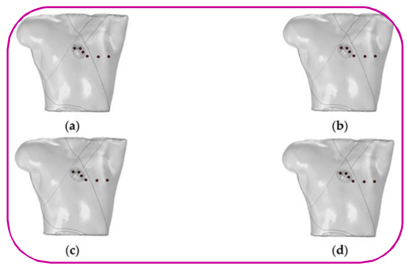
ABSTRACT

Bioenergetic processes play a fundamental role in shaping electrophysiological dynamics in both cardiac and neural tissues. The interplay between metabolic energy production, ion channel kinetics, and membrane excitability governs signal propagation, rhythmic stability, and adaptive responses under physiological and pathological conditions. This study presents a computational framework integrating mitochondrial energetics, ATP-dependent ion transport, and membrane electrophysiology to model bioenergetic signal patterns in cardiac myocytes and neurons. Using coupled differential equation systems derived from extensions of the Hodgkin–Huxley model and Luo–Rudy model, the model incorporates dynamic ATP flux, calcium cycling, and redox-state modulation of ion channel conductance. Bioenergetic variables are linked to electrophysiological outputs through ATP-sensitive potassium channels, Na^+/K^+-ATPase activity, and mitochondrial membrane potential dynamics. Simulations explore normal rhythmic firing, ischemic stress, metabolic inhibition, and oxidative perturbations. Results demonstrate that metabolic constraints significantly alter action potential morphology, conduction velocity, and oscillatory stability. In cardiac tissue, reduced ATP availability promotes repolarization heterogeneity and arrhythmogenic substrates, while in neural systems, energy deficits modulate firing thresholds and synchronization patterns. Sensitivity analysis highlights nonlinear feedback loops between calcium handling and mitochondrial energetics as key determinants of signal resilience. The proposed integrative framework provides insight into energy-dependent electrophysiological disorders, including arrhythmias and neurodegenerative excitability dysfunction. By bridging metabolism and membrane dynamics, this computational approach supports predictive modeling of bioenergetic failure and offers a foundation for therapeutic strategy development targeting metabolic-electrical coupling.



KEYWORDS: *Computational modeling, Bioenergetic signal patterns, Cardiac electrophysiology, Neural electrophysiology, Mitochondrial energetics, ATP-dependent ion transport.*

INTRODUCTION

Electrical activity in cardiac and neural tissues is fundamentally constrained by cellular energy availability. Action potential generation, ion transport, calcium cycling, and synaptic transmission are metabolically intensive processes that rely on tightly regulated adenosine triphosphate (ATP) production. In both cardiomyocytes and neurons, mitochondrial oxidative phosphorylation sustains electrochemical gradients required for membrane excitability. Disruptions in bioenergetic homeostasis—such as ischemia, oxidative stress, or mitochondrial dysfunction—can therefore profoundly alter electrophysiological stability, leading to arrhythmias, seizure activity, or neurodegenerative dysfunction. Classical electrophysiological models, including the Hodgkin–Huxley model and the Luo–Rudy model, have provided foundational insights into ion channel kinetics and membrane dynamics. However, these frameworks typically treat metabolic variables as static or implicit parameters, without explicitly modeling the dynamic coupling between energy production and electrical signaling. Growing experimental evidence indicates that ATP availability, mitochondrial membrane potential, redox state, and intracellular calcium concentration are dynamically interdependent with ion channel conductance and membrane excitability. As a result, electrophysiological behavior cannot be fully understood without incorporating bioenergetic feedback mechanisms.

In cardiac tissue, ATP-sensitive potassium (K_ATP) channels, Na^+/K^+-ATPase pumps, and sarcoplasmic reticulum calcium cycling directly link metabolic state to action potential morphology and conduction velocity. During metabolic stress, reduced ATP levels alter repolarization gradients and promote electrical heterogeneity, creating substrates for reentrant arrhythmias. Similarly, in neural systems, energy deficits influence firing thresholds, spike frequency adaptation, and network synchronization. Neurons exhibit high metabolic demand due to continuous maintenance of ion gradients and synaptic activity, making them particularly vulnerable to mitochondrial impairment. Computational modeling provides a powerful framework for integrating metabolic and electrophysiological processes across multiple spatial and temporal scales. By coupling mitochondrial energetics, ATP-dependent transport, calcium handling, and membrane conductance into unified dynamical systems, researchers can simulate physiological rhythms as well as pathological transitions under metabolic perturbations. Such integrative approaches allow systematic exploration of nonlinear feedback loops that are difficult to isolate experimentally. This study presents a computational model that bridges bioenergetic dynamics and electrophysiological signaling in both cardiac and neural cells. The framework extends established membrane models by incorporating dynamic ATP flux, mitochondrial membrane potential regulation, and redox-sensitive modulation of ion channels. Through simulation of normal and stress conditions—including ischemia and metabolic inhibition—the model aims to elucidate how energy constraints shape electrical stability and to provide predictive insights into disorders characterized by metabolic–electrical uncoupling.

AIMS AND OBJECTIVES

Aim

To develop and validate an integrative computational framework that models the dynamic coupling between cellular bioenergetics and electrophysiological signaling in cardiac myocytes and neurons under physiological and pathological conditions.

Objectives

1. Model Integration of Bioenergetics and Electrophysiology

Extend classical membrane models such as the Hodgkin–Huxley model and the Luo–Rudy model by incorporating mitochondrial ATP production, oxidative phosphorylation dynamics, and redox modulation.

2. Simulation of Metabolic–Electrical Coupling

Model the influence of ATP availability, mitochondrial membrane potential, and calcium cycling on action potential morphology, firing frequency, and conduction velocity.

3. Pathophysiological Scenario Analysis

Simulate metabolic stress conditions including ischemia, hypoxia, oxidative stress, and mitochondrial dysfunction.

4. Sensitivity and Stability Assessment

Perform parameter sensitivity analysis to identify critical bioenergetic variables influencing electrical stability.

5. Cross-System Comparative Modeling
Compare energy-dependent electrophysiological responses between cardiac and neural cells to identify shared and tissue-specific mechanisms.

REVIEW OF LITERATURE

The relationship between cellular bioenergetics and electrophysiological signaling has been explored progressively over the past several decades, evolving from isolated membrane current models to integrative frameworks that incorporate metabolic regulation. Early electrophysiological modeling was established through the Hodgkin–Huxley model, which quantitatively described ionic conductances underlying action potential generation in neurons. This model introduced voltage-dependent gating variables and differential equations that became the foundation for modern computational neuroscience. In cardiac electrophysiology, the Luo–Rudy model extended similar biophysical principles to ventricular myocytes, incorporating multiple ionic currents and calcium dynamics to reproduce realistic cardiac action potentials. Although these foundational models accurately captured electrical behavior, they did not explicitly represent intracellular metabolic dynamics or mitochondrial energetics. As experimental evidence accumulated demonstrating the metabolic cost of ion transport and action potential generation, researchers began incorporating ATP-dependent mechanisms into electrophysiological models. The Na^+/K^+-ATPase pump, a primary consumer of ATP in excitable cells, was modeled as a dynamic current influenced by intracellular sodium concentration and energy availability. In cardiac modeling, the inclusion of ATP-sensitive potassium (K_ATP) channels provided a mechanistic link between metabolic stress and membrane repolarization. Simulations of ischemic conditions revealed that ATP depletion shortens action potential duration, increases dispersion of repolarization, and creates substrates for arrhythmogenesis. These computational findings aligned with experimental observations of metabolic stress–induced conduction abnormalities. Parallel developments occurred in neural modeling, where metabolic constraints were shown to influence excitability and synaptic transmission. Energy-dependent modulation of ion gradients demonstrated that reduced ATP availability alters firing thresholds and spike frequency adaptation. Computational frameworks integrating ion pump activity with intracellular energy balance illustrated how hypoxic conditions could lead to depolarization block or aberrant bursting patterns. Such models highlighted the importance of energy homeostasis in maintaining neuronal stability and preventing excitotoxic damage.

Advances in mitochondrial modeling further refined the understanding of bioenergetic–electrical coupling. Mitochondria were incorporated as dynamic systems governing ATP production through oxidative phosphorylation, with variables representing mitochondrial membrane potential, redox state, and calcium uptake. In cardiac cells, models linking mitochondrial calcium handling with sarcoplasmic reticulum dynamics demonstrated nonlinear feedback between energy production and excitation–contraction coupling. Perturbations in mitochondrial membrane potential were shown to influence cytosolic calcium transients and action potential morphology, suggesting a mechanistic basis for metabolic arrhythmias. In neurons, mitochondrial dysfunction models simulated impaired ATP synthesis and reactive oxygen species accumulation, connecting metabolic stress to altered membrane conductance and network synchronization. Recent literature emphasizes multiscale and systems biology approaches that integrate metabolic pathways, ion channel kinetics, and tissue-level propagation. These integrative models account for spatial heterogeneity in ATP distribution and mitochondrial density, particularly in cardiac tissue where metabolic gradients can influence conduction velocity and wave stability. In neural systems, network-level simulations incorporating metabolic constraints have been used to explore seizure susceptibility and neurodegenerative processes associated with mitochondrial impairment. Mathematical techniques such as bifurcation analysis and nonlinear dynamical systems theory have provided insight into threshold behaviors and stability transitions arising from metabolic perturbations. Despite significant progress, existing models often simplify complex metabolic pathways or assume steady-state energy production. Comprehensive frameworks that dynamically couple mitochondrial energetics, ATP flux, calcium cycling, and membrane electrophysiology remain relatively limited. Furthermore, comparative analyses between cardiac and neural tissues are less common, even though both systems rely on tightly regulated metabolic–electrical interactions. The literature collectively indicates that explicit integration of bioenergetic variables into electrophysiological models enhances predictive capability and improves mechanistic understanding of disorders characterized by metabolic–electrical uncoupling. These findings support the continued development of unified computational approaches capable of simulating bioenergetic signal patterns across excitable tissues under both physiological and pathological conditions.

RESEARCH METHODOLOGY

This study adopts a quantitative computational modeling approach to investigate the dynamic coupling between cellular bioenergetics and electrophysiological activity in cardiac myocytes and neurons. The methodology integrates mathematical modeling, numerical simulation, parameter sensitivity analysis, and validation against established physiological data. The electrophysiological framework is based on extensions of the Hodgkin–Huxley model for neuronal cells and the Luo–Rudy model for cardiac ventricular myocytes. These models are modified to incorporate bioenergetic variables, including ATP concentration, mitochondrial membrane potential (ΔΨm), redox state, and calcium-dependent metabolic fluxes. The resulting system consists of coupled nonlinear ordinary differential equations describing membrane voltage, ionic currents, intracellular ion concentrations, and mitochondrial energy production. Mitochondrial energetics are modeled using a reduced-order representation of oxidative phosphorylation. ATP production is formulated as a function of substrate availability, oxygen concentration, and mitochondrial membrane potential. ATP consumption is linked dynamically to ion transport mechanisms, particularly Na^+/K^+-ATPase activity, Ca^{2+}-ATPase pumps, and ATP-sensitive potassium channel conductance. Calcium exchange between cytosol and mitochondria is incorporated to represent feedback between excitation and metabolic activation.

The integrated model is implemented in a computational environment such as MATLAB or Python using numerical solvers for stiff differential equations (e.g., implicit Runge–Kutta or backward differentiation formulas). Parameter values are derived from experimentally reported physiological ranges in cardiac and neural tissues. Where direct measurements are unavailable, parameters are calibrated using steady-state constraints and literature-based estimates. Simulations are conducted under multiple physiological and pathological scenarios. Baseline conditions represent normal ATP production and stable ionic gradients. Metabolic stress conditions are simulated by reducing oxygen supply, decreasing substrate availability, or impairing mitochondrial membrane potential. Additional simulations introduce oxidative stress by modifying redox-sensitive ion channel conductance. Outputs analyzed include action potential duration, firing frequency, conduction velocity, intracellular calcium transients, ATP concentration dynamics, and mitochondrial stability indices. Sensitivity analysis is performed to determine the relative influence of bioenergetic parameters on electrophysiological outcomes. Local and global sensitivity methods are applied to identify critical variables governing system stability. Bifurcation analysis is used to examine threshold transitions between stable rhythmic activity and pathological oscillatory or depolarized states.

Comparative modeling is conducted to evaluate similarities and differences in metabolic–electrical coupling between cardiac and neural cells. Structural differences in ion channel composition, calcium handling mechanisms, and metabolic demand are incorporated to assess tissue-specific responses to energy perturbations. Model validation is achieved by comparing simulated electrophysiological patterns with published experimental observations under both normal and metabolic stress conditions. The final framework is evaluated for numerical stability, physiological plausibility, and predictive consistency. Through this integrative computational methodology, the study systematically characterizes how bioenergetic dynamics regulate electrical signal generation and stability in excitable tissues.

STATEMENT OF THE PROBLEM

Electrical activity in cardiac and neural tissues is critically dependent on continuous and tightly regulated energy supply. Processes such as action potential generation, ion transport, calcium cycling, and synaptic transmission require substantial adenosine triphosphate (ATP) consumption. Mitochondrial oxidative phosphorylation sustains this demand by maintaining ionic gradients and membrane excitability. However, disturbances in cellular bioenergetics—arising from ischemia, hypoxia, oxidative stress, or mitochondrial dysfunction—can destabilize electrophysiological signaling and contribute to arrhythmias, seizure activity, and neurodegenerative disorders. Despite extensive research in electrophysiological modeling, classical frameworks such as the Hodgkin–Huxley model and the Luo–Rudy model primarily focus on ion channel kinetics and membrane voltage dynamics, with limited representation of metabolic processes. In most existing models, ATP concentration and mitochondrial function are treated as constant or simplified parameters rather than dynamically interacting variables. This separation restricts the ability to predict how metabolic disturbances propagate to influence electrical behavior. Experimental evidence increasingly demonstrates that metabolic and electrophysiological systems are strongly coupled through ATP-sensitive ion channels, ion pumps, calcium-dependent mitochondrial activation, and redox signaling pathways. These interactions form nonlinear feedback loops that can amplify small metabolic perturbations into significant electrical instability. However, there remains a lack of comprehensive computational frameworks that simultaneously model mitochondrial energetics, ATP flux, calcium dynamics, and membrane excitability in both cardiac and neural tissues.

Furthermore, comparative analysis between cardiac and neural bioenergetic–electrical coupling is limited, despite shared dependence on energy-driven ion transport. The absence of integrative and cross-tissue computational approaches constrains mechanistic understanding of how energy deficits lead to arrhythmogenesis in the heart and excitability dysfunction in the brain. Therefore, the central problem addressed in this study is the need for a unified computational model that explicitly integrates bioenergetic dynamics with electrophysiological signaling. Such a model is necessary to accurately simulate metabolic stress conditions, identify critical parameters influencing electrical stability, and improve predictive understanding of disorders characterized by metabolic–electrical uncoupling in excitable tissues.

DISCUSSION

The present computational framework demonstrates that electrophysiological stability in cardiac and neural tissues cannot be fully understood without explicit consideration of cellular bioenergetics. By extending established membrane models such as the Hodgkin–Huxley model and the Luo–Rudy model to include dynamic ATP production, mitochondrial membrane potential, and calcium-dependent metabolic feedback, the study highlights the nonlinear and bidirectional coupling between energy metabolism and membrane excitability. Simulation results indicate that ATP availability acts as a critical regulatory variable in both cardiac and neural systems. In cardiomyocytes, reduced ATP levels significantly altered action potential duration and repolarization gradients through modulation of ATP-sensitive potassium channels and Na^+/K^+-ATPase activity. These changes increased electrical heterogeneity, a known substrate for reentrant arrhythmias. The findings support experimental observations that metabolic stress shortens action potential duration and promotes conduction abnormalities. The model further demonstrates that small perturbations in mitochondrial membrane potential can propagate through calcium handling pathways to destabilize excitation–contraction coupling, reinforcing the concept of metabolic arrhythmogenesis. In neural cells, energy depletion shifted firing thresholds, reduced spike frequency adaptation, and in extreme cases produced depolarization block. The coupling between ATP-dependent ion pumps and membrane voltage created feedback loops in which impaired ion gradient restoration amplified excitability disturbances. The simulations suggest that mitochondrial dysfunction may contribute to pathological synchronization and excitotoxicity by disrupting the delicate balance between energy supply and ionic demand.

A key outcome of the analysis is the identification of calcium–mitochondrial feedback as a central determinant of system resilience. Increased cytosolic calcium enhances mitochondrial ATP production under physiological conditions, supporting sustained electrical activity. However, under metabolic stress, this feedback becomes maladaptive, leading to oscillatory instability and potential collapse of membrane potential. Sensitivity analysis confirms that parameters governing mitochondrial membrane potential and ATP synthesis rates exert disproportionate influence on electrical stability compared to individual ion channel conductances. Comparative modeling between cardiac and neural tissues reveals both shared and tissue-specific mechanisms. Both systems rely heavily on ATP-driven ion transport and exhibit nonlinear thresholds under metabolic perturbation. However, cardiac tissue shows greater vulnerability to spatial heterogeneity in ATP distribution due to its dependence on coordinated conduction, whereas neural systems display higher sensitivity to prolonged energy deficits affecting synaptic transmission and network synchronization. While the integrated model provides mechanistic insights, several limitations must be acknowledged. The mitochondrial representation employs a reduced-order approximation of oxidative phosphorylation and does not fully capture detailed biochemical pathways. Spatial heterogeneity is simplified, and tissue-level propagation is modeled under controlled assumptions. Future work could incorporate multiscale modeling, including subcellular mitochondrial networks and tissue-level conduction dynamics, to enhance predictive capacity. Overall, the discussion underscores that bioenergetic–electrical coupling is a fundamental determinant of excitability in both the heart and brain. Integrative computational modeling offers a powerful platform for exploring how metabolic perturbations translate into electrical instability, advancing understanding of arrhythmias, seizure disorders, and neurodegenerative excitability dysfunction. By bridging metabolism and membrane dynamics, this framework contributes to the development of predictive and translational strategies targeting energy-dependent electrophysiological disorders.

CONCLUSION

This study demonstrates that bioenergetic processes are integral to the regulation of electrophysiological behavior in both cardiac and neural tissues. By integrating mitochondrial energetics, ATP-dependent ion transport, calcium cycling, and membrane voltage dynamics into unified computational frameworks derived from the Hodgkin–Huxley model and the Luo–Rudy model, the research establishes a dynamic representation of metabolic–electrical coupling in excitable cells. The findings indicate that ATP availability and mitochondrial membrane potential serve as key regulators of action potential morphology, firing patterns, and conduction stability. Under metabolic stress conditions such as ischemia or mitochondrial dysfunction, alterations in ATP synthesis and calcium–mitochondrial feedback mechanisms can produce significant electrical instability. In cardiac tissue, these disturbances contribute to repolarization heterogeneity and arrhythmogenic susceptibility, while in neural systems, energy deficits modify excitability thresholds and network synchronization. The integrative computational approach highlights the nonlinear interactions between metabolic and electrophysiological variables, revealing threshold behaviors and feedback loops that are not captured in traditional membrane-only models. Sensitivity analyses further identify mitochondrial energetics and ATP-dependent transport processes as dominant determinants of system stability.

Although simplified in certain biochemical aspects, the developed framework provides a robust foundation for simulating energy-dependent electrophysiological disorders. It enhances mechanistic understanding of how metabolic disturbances translate into electrical dysfunction and supports the development of predictive tools for therapeutic strategy design. In conclusion, bridging bioenergetics and electrophysiology through computational modeling offers significant insight into the fundamental principles governing excitability in the heart and brain. This integrated perspective is essential for advancing research on metabolic–electrical uncoupling and for informing future translational applications in cardiovascular and neurological medicine.

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