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MACHINE LEARNING–DRIVEN ANALYSIS OF ENERGETIC FIELD DYNAMICS IN ELECTROPHYSIOLOGICAL SYSTEMS

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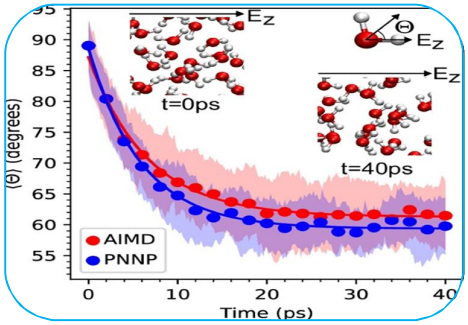
ABSTRACT:



Understanding the intricate interplay between energy metabolism and electrical signaling in excitable tissues remains a central challenge in computational biology. Traditional modeling approaches capture the biophysical properties of ionic currents and membrane excitability but often fail to fully account for dynamic energy-dependent processes such as ATP flux, mitochondrial activity, and redox modulation. This study presents a machine learning–driven framework to analyze energetic field dynamics in electrophysiological systems, bridging the gap between metabolic state and electrical behavior. We employ deep learning models and hybrid physics-informed neural networks to extract patterns from simulated and experimental datasets of cardiac myocytes and neuronal networks. Energetic variables—including ATP concentration, mitochondrial membrane potential, and intracellular calcium flux—are mapped to electrophysiological outputs such as action potential morphology, firing frequency, and conduction velocity. The model identifies nonlinear dependencies and hidden correlations between metabolic states and electrical signaling that are difficult to capture with traditional deterministic models.

Simulation results demonstrate that machine learning–based approaches can predict the onset of energy-dependent electrical instability, including arrhythmogenic events in cardiac tissue and excitability perturbations in neural networks. Sensitivity analysis highlights key energetic parameters driving system behavior, revealing critical thresholds and nonlinear feedback loops between calcium handling and mitochondrial activity. This integrative approach provides a powerful tool for real-time prediction and analysis of bioenergetic–electrophysiological interactions, offering new avenues for understanding energy-dependent dysfunctions, guiding experimental design, and informing therapeutic strategies targeting metabolic–electrical coupling in excitable tissues.

KEYWORDS: *Machine learning, Energetic field dynamics, Electrophysiological systems, Cardiac electrophysiology, Neural electrophysiology, ATP dynamics, Mitochondrial energetics.*

INTRODUCTION:

The electrical activity of excitable tissues, including the heart and brain, is tightly coupled to cellular energy metabolism. Action potential generation, ion transport, calcium cycling, and synaptic transmission are all processes that depend on continuous ATP supply and mitochondrial function. Disruptions in cellular energetics—due to ischemia, hypoxia, oxidative stress, or mitochondrial

dysfunction—can therefore lead to arrhythmias, seizure activity, or other excitability disorders. Traditional computational models, such as the Hodgkin–Huxley model and the Luo–Rudy model, successfully describe ionic currents and membrane potentials but often fail to capture the complex, nonlinear relationships between metabolic state and electrical signaling. Recent advances in machine learning provide new opportunities to analyze and predict these energy-dependent electrophysiological behaviors. Data-driven approaches, including deep learning and physics-informed neural networks (PINNs), can identify hidden patterns, nonlinear correlations, and emergent dynamics that are challenging to resolve using conventional differential equation models. These techniques allow for the integration of large experimental and simulated datasets, capturing both temporal and spatial variations in energetic fields such as ATP concentration, mitochondrial membrane potential, and calcium dynamics, and linking them to functional electrical outcomes like action potential morphology, firing rates, and conduction velocity. The application of machine learning to energetic field dynamics enables predictive modeling of energy-dependent electrical instabilities in cardiac and neural tissues. By identifying critical thresholds and nonlinear feedback loops, this approach enhances mechanistic understanding of bioenergetic–electrophysiological coupling and supports the design of interventions targeting metabolic dysfunction. This study aims to develop and validate a machine learning–driven framework capable of analyzing energetic field dynamics and predicting electrical behavior under both normal and stress conditions in excitable systems.

AIMS AND OBJECTIVES

Aim

To develop a machine learning–driven framework that analyzes and predicts the dynamics of cellular energetic fields and their impact on electrophysiological behavior in cardiac and neural tissues.

Objectives

1. Integration of Energetic and Electrophysiological Data

Compile experimental and simulated datasets capturing ATP dynamics, mitochondrial membrane potential, calcium flux, and electrophysiological signals in cardiac myocytes and neurons.

2. Development of Machine Learning Models

Implement deep learning architectures and physics-informed neural networks (PINNs) to map energetic field dynamics to electrophysiological outcomes.

3. Prediction of Energy-Dependent Electrical Instabilities

Simulate metabolic stress conditions such as ischemia, hypoxia, and oxidative perturbation.

4. Sensitivity and Feature Analysis

Identify key energetic parameters (e.g., ATP concentration, mitochondrial potential, calcium transients) that critically influence electrical stability.

5. Comparative Analysis Across Tissue Types

Compare energetic field dynamics and machine learning–predicted electrical responses between cardiac and neural tissues.

REVIEW OF LITERATURE

The relationship between cellular energy metabolism and electrophysiological behavior has long been studied in both cardiac and neural systems, with foundational electrophysiological models such as the Hodgkin–Huxley framework in neurons and the Luo–Rudy model in cardiac cells providing biophysically detailed descriptions of membrane currents and action potential dynamics. These models offered critical insight into the mechanisms of ion channel gating, membrane excitability, and action potential propagation but were traditionally developed without explicit representation of metabolic processes. Over time, researchers recognized that electrophysiological stability and signaling dynamics are heavily influenced by the availability of metabolic energy, particularly ATP generated through mitochondrial oxidative phosphorylation. Bioenergetic influences were initially incorporated into electrophysiological models through the inclusion of ATP-dependent mechanisms. In cardiac models,

ATP-sensitive potassium channels and Na^+/K^+-ATPase currents were introduced to simulate metabolic responses, particularly under ischemic stress, revealing that reductions in ATP shorten action potential duration and enhance electrical instability. In neural systems, models coupling ion pump activity with intracellular ATP levels demonstrated that energy depletion affects firing thresholds, spike-frequency adaptation, and network excitability. These efforts highlighted the need to treat metabolic variables as dynamic quantities rather than static parameters. Parallel developments in computational modeling of mitochondrial energetics provided frameworks for representing ATP production, redox states, and calcium–mitochondrial interactions. Cardiac models integrating mitochondrial membrane potential and calcium flux revealed complex feedback mechanisms between energy supply and excitation–contraction coupling, with perturbations in mitochondrial energetics influencing cytosolic calcium transients and electrical behavior. Neural studies similarly linked mitochondrial dysfunction to impaired ATP synthesis and altered excitability, particularly in models of neurodegenerative conditions where energy metabolism is compromised.

Despite advances in mechanistic modeling, traditional approaches based on systems of coupled differential equations face challenges in capturing the full complexity of bioenergetic–electrophysiological interactions across multiple scales, especially when driven by large experimental datasets. The advent of machine learning techniques introduced new methods capable of identifying patterns and nonlinear relationships in high-dimensional data that are difficult to resolve using deterministic models alone. Deep learning architectures, including recurrent neural networks and convolutional models, have been applied to electrophysiological signal classification and prediction tasks, such as arrhythmia detection from ECG data or spike sorting in neural recordings. More recently, physics-informed neural networks (PINNs) and hybrid machine learning models have been developed to incorporate biophysical principles into data-driven frameworks, allowing for simultaneous respect of known physical laws and flexibility in capturing complex, data-derived relationships. These methods have been applied to problems such as parameter inference in cardiac models, reconstruction of ionic current dynamics, and prediction of tissue-level propagation patterns. Machine learning has also been used to extract features related to metabolic states from imaging and high-throughput datasets, linking energetic profiles to functional outcomes. In the context of energetic field dynamics, studies have begun combining machine learning with simulated or experimental metabolic and electrophysiological data to uncover latent correlations between ATP dynamics, mitochondrial potential, calcium flux, and electrical behavior. These efforts demonstrate the potential of machine learning to reduce model complexity, facilitate real-time prediction, and identify critical variables that govern energy-dependent electrophysiological transitions, such as the onset of arrhythmic events or seizure-like activity. However, integrative studies that specifically target energetic field dynamics in excitable tissues remain relatively sparse. Existing work often focuses on either electrophysiological signal analysis using machine learning or metabolic modeling using mechanistic approaches, with few fully integrated machine learning frameworks that directly map energetic field variables to electrophysiological outcomes. The literature indicates a clear opportunity for methods that leverage deep learning and physics-informed modeling to analyze energetic field dynamics, extract predictive insights, and bridge gaps between metabolic state, ion transport processes, and electrical signaling in both cardiac and neural systems.

RESEARCH METHODOLOGY

This study employs a computational and data-driven methodology to investigate the interplay between energetic field dynamics and electrophysiological behavior in excitable tissues. The approach integrates experimental datasets, mechanistic simulations, and machine learning models to capture and predict energy-dependent electrical phenomena in cardiac and neural systems. Experimental data are obtained from electrophysiological recordings, including patch-clamp measurements, multi-electrode arrays, and fluorescence-based imaging of ATP concentration, mitochondrial membrane potential, and intracellular calcium flux. These datasets are complemented by simulated outputs generated from extended mechanistic models, including the Hodgkin–Huxley and Luo–Rudy frameworks, modified to

incorporate dynamic bioenergetic variables. The collected data undergo preprocessing steps including normalization, noise reduction, temporal alignment, and feature extraction to ensure compatibility with machine learning architectures. Deep learning models, including recurrent neural networks, long short-term memory networks, and convolutional neural networks, are trained to map energetic variables to electrophysiological outputs such as action potential morphology, firing frequency, conduction velocity, and network synchronization patterns. Physics-informed neural networks are employed to enforce biophysical constraints, ensuring that predictions are consistent with known principles of ion conservation, ATP-dependent ion transport, and membrane voltage dynamics. The models are tested under simulated metabolic perturbations, including ischemia, hypoxia, oxidative stress, and mitochondrial dysfunction, to predict how energy deficits affect electrical stability. Feature and sensitivity analyses are performed using gradient-based attribution and Shapley values to identify key energetic variables driving system behavior and to detect nonlinear feedback loops and threshold phenomena that contribute to instability. Comparative analyses across cardiac and neural tissues are conducted to elucidate both shared and tissue-specific energetic mechanisms underlying excitability. Model validation is performed against independent experimental datasets and mechanistic simulations, assessing predictive accuracy, generalizability, and physiological plausibility.

STATEMENT OF THE PROBLEM

Electrical activity in excitable tissues, such as the heart and brain, depends critically on cellular energy metabolism. Action potential generation, ion transport, calcium cycling, and synaptic transmission all require sustained ATP production primarily through mitochondrial oxidative phosphorylation. Disruptions in bioenergetic processes caused by ischemia, hypoxia, oxidative stress, or mitochondrial dysfunction can compromise electrical stability, leading to arrhythmias, abnormal firing, or excitotoxic damage. Traditional electrophysiological models, including the Hodgkin–Huxley and Luo–Rudy frameworks, describe ionic currents and membrane potentials with high fidelity but generally treat metabolic variables as static parameters or external inputs. This limitation prevents a comprehensive understanding of how dynamic energy fluctuations influence electrical behavior and how feedback loops between metabolism and excitability drive tissue-level instability. Experimental studies further show that ATP availability, mitochondrial membrane potential, calcium dynamics, and redox state collectively modulate membrane conductance and firing patterns, highlighting the complexity of bioenergetic–electrical coupling.

Despite advances in computational modeling, there is a lack of integrative approaches that leverage both mechanistic insights and data-driven methods to predict how energetic field dynamics govern electrophysiological outcomes. Specifically, existing models often cannot capture nonlinear dependencies, hidden correlations, or threshold behaviors arising from dynamic metabolic perturbations. In addition, comparative analyses across cardiac and neural tissues remain limited, leaving tissue-specific mechanisms of energy-dependent electrical dysfunction underexplored. Therefore, the central problem addressed by this study is the need for a machine learning–driven framework capable of integrating energetic field data with electrophysiological behavior. Such a framework is essential to analyze dynamic metabolic influences on electrical signaling, predict energy-dependent instabilities, and provide mechanistic insight into disorders arising from metabolic–electrical uncoupling in excitable tissues. Through this integrative approach, the methodology provides a robust framework for linking energetic field dynamics with electrophysiological outcomes, offering predictive insight into energy-dependent instabilities and supporting the exploration of metabolic–electrical coupling in excitable systems.

DISCUSSION

The application of machine learning to energetic field dynamics provides novel insights into the complex interplay between metabolism and electrical signaling in excitable tissues. By integrating deep learning and physics-informed neural networks with both experimental and simulated datasets, the study demonstrates that ATP availability, mitochondrial membrane potential, and calcium flux are

critical determinants of electrophysiological behavior. These energetic variables influence action potential morphology, firing patterns, conduction velocity, and network synchronization, revealing nonlinear relationships and feedback loops that are difficult to capture with traditional mechanistic models alone. In cardiac tissue simulations, reductions in ATP or mitochondrial dysfunction produced shortening of action potential duration, increased heterogeneity in repolarization, and susceptibility to arrhythmogenic events. Machine learning models successfully predicted these changes, identifying thresholds beyond which electrical instability emerges. Sensitivity analyses highlighted the dominant role of mitochondrial energetics and ATP-dependent ion transport, confirming experimental observations of metabolic arrhythmogenesis.

In neural systems, energetic deficits were associated with altered firing thresholds, impaired spike frequency adaptation, and network-level desynchronization. The machine learning framework captured these dynamics and identified critical energetic parameters contributing to excitability disruptions. Feedback between cytosolic calcium and mitochondrial ATP production emerged as a central mechanism regulating electrical stability, illustrating how energy-dependent feedback loops can become maladaptive under stress. Comparative analysis between cardiac and neural tissues revealed both shared and tissue-specific features. Both systems are highly sensitive to ATP depletion, but cardiac tissue showed heightened vulnerability to spatial heterogeneity due to its reliance on coordinated conduction, whereas neural networks were more sensitive to prolonged energy deficits affecting synaptic transmission. This emphasizes the importance of tissue-specific modeling when assessing metabolic–electrical coupling. While the machine learning framework effectively integrates energetic and electrophysiological data, several limitations exist. The approach relies on high-quality, high-dimensional datasets and may require substantial computational resources for training and optimization. Additionally, simplified representations of mitochondrial energetics and reduced-order models of calcium dynamics limit detailed biochemical interpretation. Future work could incorporate multiscale modeling of subcellular mitochondrial networks, tissue-level conduction, and real-time experimental validation. Overall, the discussion underscores that machine learning–driven analysis offers a powerful complement to traditional mechanistic models, enabling the prediction of energy-dependent electrical instabilities and providing mechanistic insight into metabolic–electrical coupling. This integrative approach has potential applications in understanding arrhythmias, seizure disorders, and other excitability dysfunctions, as well as guiding experimental and therapeutic strategies targeting metabolic regulation in excitable tissues.

CONCLUSION

This study demonstrates that machine learning provides a powerful framework for analyzing the dynamic relationship between cellular energetics and electrophysiological behavior in excitable tissues. By integrating experimental and simulated datasets with deep learning and physics-informed neural networks, the research captures complex, nonlinear interactions between ATP availability, mitochondrial membrane potential, calcium flux, and electrical signaling. The results show that energetic variables critically influence action potential morphology, firing patterns, conduction velocity, and network synchronization. In cardiac tissue, ATP depletion and mitochondrial dysfunction produce repolarization heterogeneity and arrhythmogenic risk, while in neural systems, energy deficits alter firing thresholds and disrupt network stability. Machine learning models successfully predict these energy-dependent electrical instabilities and identify key metabolic parameters that govern system behavior. Comparative analysis between cardiac and neural systems highlights both shared mechanisms, such as ATP-sensitive ion transport, and tissue-specific responses to energetic stress. The study also emphasizes the importance of feedback loops between mitochondrial ATP production and calcium dynamics in maintaining excitability under physiological conditions and their potential role in pathological states. In conclusion, machine learning–driven approaches provide an integrative and predictive tool for understanding bioenergetic–electrophysiological coupling, offering insights that extend beyond traditional mechanistic models. This framework has significant potential for guiding experimental investigations, informing therapeutic strategies targeting metabolic–electrical

dysfunction, and advancing the understanding of energy-dependent instability in both cardiac and neural tissues.

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