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Modeling Neuroelectrical-Microbiome Crosstalk: AI-Driven Insights into Gut-Brain Bioelectrical Signaling

Shumoos Aziz Fadhil[1], Mustafa Radif[2], Atheer Alrammahi[3,*]

[1,2,3]*Department of Medical Intelligent Systems, University of Al-Qadisiyah, Diwaniya, 00964, Iraq*

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Abstract

The gut-brain axis, traditionally understood as a chemical communication network, is reconceptualized in this study as a bidirectional bioelectrical system. This paper introduces a novel framework for exploring host–microbiome interactions through neuroelectrical signaling, integrating Artificial Intelligence (AI)-based modeling with experimental insights. The objective is to assess how microbial metabolites, especially Short-Chain Fatty Acids (SCFAs) such as butyrate (1.5–3.5 mM), modulate host membrane potentials, and how these bioelectrical changes influence microbial behavior. Using a hybrid simulation platform combining Recurrent Neural Networks (RNNs) and Graph Neural Networks (GNNs), we modeled dynamic interactions within a low-inflammation gut environment. Results demonstrated that increasing butyrate concentration from 1.5 to 3.5 mM led to a depolarization of enteric neurons from –70.0 mV to –63.1 mV over 24 hours. This shift was associated with a 2.5-fold increase in microbial diversity index and a suppression of pathogenic Enterobacteriaceae. SHAP (SHapley Additive exPlanations) analysis identified butyrate concentration (+0.43) and potassium channel expression (+0.27) as top contributors to excitability enhancement. Additionally, the simulation predicted improved gut motility and increased abundance of beneficial taxa such as Bifidobacterium. These findings suggest a previously underappreciated electrical layer of gut-brain communication that complements chemical pathways. The novelty of this work lies in its systems-level approach that quantifies and predicts the reciprocal influence between microbial activity and host electrophysiology. By combining bioelectrical principles with AI-driven simulation, the study contributes a mechanistic understanding and virtual testing environment for neuroelectrical-microbiome dynamics. This research opens new avenues for non-invasive interventions—such as dietary modulation or vagus nerve stimulation—to treat microbiome-related neurological and gastrointestinal disorders.

Keywords: Gut-Brain Axis, Bioelectricity, Microbiome, Vagus Nerve Stimulation, Ion Channels, AI Modeling, Enteric Nervous System, GABA, Scfas, Systems Biology

1. Introduction

The gut-brain axis represents a dynamic, bidirectional communication network that links the Central Nervous System (CNS) with the Enteric Nervous System (ENS), integrating signals from the gastrointestinal tract, immune system, and resident microbiota. This complex interface plays a crucial role in regulating not only digestive functions but also emotional and cognitive processes, implicating it in a wide range of conditions including irritable bowel syndrome (IBS), anxiety, depression, autism spectrum disorders, and neurodegenerative diseases such as Parkinson's and Alzheimer's [1]. Historically, research on the gut-brain axis has focused heavily on biochemical mediators, including serotonin, SCFAs, and cytokines, which are produced by both host tissues and gut microbes. These molecules have been shown to influence mood, stress response, inflammation, and gut motility, forming the backbone of current models of gut-brain interaction [2], [3], [4].

However, a growing body of evidence suggests that bioelectrical signaling—the generation and transmission of electrical potentials by cells and tissues—may represent an underexplored but fundamental modality of communication within this axis. Endogenous electric fields, transmembrane potentials, and ion channel activity are known to govern key processes such as tissue development, wound healing, and neural coordination. Yet their role in mediating cross-talk between microbial ecosystems and neural circuits remains poorly understood [5].

In this study, the term "bioelectrical language" refers to the organized set of electrical signals—such as membrane potential changes, ion fluxes, and endogenous electrical fields—that facilitate communication between host cells and

***Corresponding author: Atheer Alrammahi (atheer.alrammahi@qu.edu.iq)**
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gut microbiota. The "bioelectrical ecosystem" denotes the complex, dynamic environment within the gastrointestinal tract where host bioelectrical states and microbial community structures are interconnected and co-regulated. These definitions aim to provide operational clarity while framing a novel perspective on gut-brain axis interactions.

This paper aims to explore this emerging intersection between gut microbiota, neural electrophysiology, and bioelectrical patterning. By examining how microbiota might influence host bioelectrical states and, conversely, how neural or epithelial electrical activity might regulate microbial communities, we propose a novel framework for understanding the gut-brain axis—not only as a chemical network, but also as a bioelectrical ecosystem.

2. Background

2.1. The Gut-Brain Axis: An Overview

The Gut-Brain axis (GBA) is a complex, bidirectional communication system that connects the CNS with the ENS, along with contributions from the endocrine, immune, and autonomic nervous systems. This axis enables dynamic coordination between cognitive-emotional centers of the brain and the gastrointestinal system, with implications for digestion, mood regulation, immunity, and overall systemic health [6].

Communication within the GBA occurs through multiple integrated channels that work synergistically to coordinate physiological and behavioral responses. Neural pathways play a pivotal role, with the vagus nerve, spinal afferents, and intrinsic ENS circuits transmitting sensory and motor signals that relay real-time information about gut physiology and microbial activity to the brain. In parallel, hormonal signaling contributes to this dialogue; gut-derived hormones such as ghrelin, leptin, and peptide YY regulate appetite, mood, and metabolic homeostasis, while also exerting significant influence on brain function. Additionally, immune mediators form a critical component of the communication network. Cytokines and other immune molecules, which are released in response to gut microbial activity, can either cross the blood-brain barrier or interact directly with neural receptors. These immune signals play an important role in modulating inflammation-related changes in mood and cognition, further underscoring the multifaceted nature of gut-brain communication.

This intricate system maintains homeostasis under normal conditions but can be disrupted in disease states. Dysregulation of the gut-brain axis has been implicated in a wide range of disorders, including Irritable Bowel Syndrome (IBS), anxiety, depression, and Parkinson's disease [6], [7], [8]. In IBS, for instance, altered vagal tone and gut microbial imbalance lead to visceral hypersensitivity and stress-related gastrointestinal symptoms [9]. In Parkinson's disease, pathological α-synuclein aggregates are suspected to originate in the gut and migrate to the brain via the vagus nerve—highlighting the gut as a potential starting point for neurodegeneration [10].

While most existing studies emphasize chemical messengers, the emerging recognition of electrical signaling within both enteric and central systems suggests that bioelectrical mechanisms may also contribute significantly to gut-brain communication—a concept explored further in the subsequent sections.

2.2. Basics of Bioelectrical Signaling

Bioelectrical signaling refers to the generation, propagation, and interpretation of electrical signals by living cells and tissues. At its core, this process is governed by ion gradients and transmembrane voltage differences across cell membranes, known as resting membrane potentials. These electrical potentials arise from the controlled movement of ions—primarily sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-)—through specialized proteins such as ion channels, pumps, and gap junctions [11].

In the nervous system, bioelectrical signaling is well established as the fundamental mechanism for transmitting information via action potentials and synaptic activity. However, bioelectricity is not exclusive to neurons. Non-neuronal cells—including epithelial, glial, immune, and even microbial cells—exhibit dynamic bioelectrical behaviors that contribute to development, wound healing, cell migration, and pattern formation. Importantly, these signals can operate on a range of spatial and temporal scales: from rapid millisecond-level nerve conduction to slower, sustained voltage patterns that regulate tissue-level processes over hours or days [12].

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A particularly relevant example in the context of gut physiology is the activity of Interstitial Cells of Cajal (ICCs), which act as pacemakers in the gastrointestinal tract. These cells generate rhythmic electrical waves that coordinate peristalsis and digestive function—highlighting the foundational role of bioelectricity in gut health. Similarly, epithelial bioelectric fields influence the orientation and behavior of cells during wound healing, suggesting that electrical signals provide instructive cues in tissue repair and regeneration [13], [14]. Recent advances in optogenetics, voltage-sensitive dyes, and bioelectrical mapping techniques have opened new avenues for studying these phenomena in vivo. These tools allow researchers to visualize and manipulate membrane potentials in real time, offering insights into how electrical gradients integrate with biochemical and mechanical cues to shape physiological outcomes [15].

The emerging field of electroceuticals—encompassing interventions like vagus nerve stimulation, sacral nerve modulation, and bioelectronic medicine—has demonstrated the therapeutic potential of modulating electrical activity for clinical benefit. Parallel work in microbial electrophysiology has shown that certain bacteria exhibit electroactive behaviors, such as transmembrane electron transport and collective biofilm conduction. Studies of Shewanella spp. and Geobacter spp. [16], for instance, highlight microbial capacities to generate and respond to electrical signals. Integrating insights from these fields strengthens the conceptual foundation for considering the gut microbiota not just as biochemical entities, but as potentially bioelectrically interactive components of host physiology. Future interdisciplinary research bridging bioelectronic medicine and microbial bioelectricity could open new avenues for diagnostic and therapeutic innovation [16].

In the context of the gut-brain axis, the emerging hypothesis is that such bioelectrical signals—either originating from gut cells or modulated by microbial activity—may form an underappreciated layer of communication between the microbiome and the nervous system. The next section explores how microbial populations interact with host bioelectric environments, potentially participating in this novel mode of cross-talk.

2.3. Microbiome Influence on Host Physiology

The gut microbiome, consisting of trillions of bacteria, viruses, archaea, and fungi, plays a foundational role in shaping human physiology. Far beyond its contributions to digestion, the microbiome influences key aspects of host biology including immune regulation, metabolism, neurodevelopment, and behavior. Its dense communication with the nervous, endocrine, and immune systems positions it as a central component of the gut-brain axis, making it an essential player in health and diseases [17].

One of the most well-characterized contributions of the microbiome is its role in producing bioactive metabolites. These include SCFAs like butyrate and propionate, which maintain gut barrier integrity, modulate inflammation, and influence neuronal activity via G-Protein Coupled Receptors (GPCRs). Other microbial products, such as serotonin precursors, dopamine analogs, and γ-aminobutyric acid (GABA), can affect host mood, behavior, and cognition by interacting directly with host neurons or indirectly through immune signaling and vagus nerve activation [18].

In addition, the microbiome influences host gene expression via epigenetic mechanisms, regulates intestinal motility, and shapes mucosal immune development—especially in early life. Perturbations in microbial composition (dysbiosis) have been implicated in a wide range of disorders including IBD, obesity, Autism Spectrum Disorder (ASD), and Parkinson's disease, all of which exhibit strong gut-brain axis involvement [19].

Emerging studies suggest that the microbiome may also impact bioelectrical properties of host tissues. For example, SCFAs have been shown to alter ion channel activity and neurotransmitter release, potentially influencing membrane potentials and electrical excitability in enteric and central neurons. Microbial modulation of tight junction permeability and epithelial polarization may also change local bioelectric fields, contributing to physiological or pathological patterning in the gut epithelium [20].

This bidirectional relationship—where host electrophysiology influences microbial habitat, and microbial metabolism modifies host bioelectric states—suggests a new axis of communication: microbial-bioelectrical crosstalk. Understanding this interaction may unlock novel therapeutic strategies for modulating neural and immune function via the microbiome, not solely through chemical means, but also through electrophysiological pathways.

Several studies have used patch-clamp electrophysiology to directly demonstrate microbial metabolite effects on neuronal excitability. For example, butyrate has been shown to modulate potassium channel currents and membrane

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polarization in cultured enteric neurons [21]. Similarly, GABA-producing microbes influence inhibitory postsynaptic potentials in central nervous system neurons, as evidenced by altered synaptic firing rates recorded through whole-cell patch-clamp techniques. These experiments provide mechanistic support for the role of microbial metabolites in shaping host electrophysiological states [22].

3. Hypothesis: Bioelectrical-Microbiome Crosstalk

While traditional models of the gut-brain axis emphasize biochemical communication, an emerging hypothesis posits a bioelectrical dialogue between the host and its microbial residents. This conceptual model envisions a two-way electrophysiological interaction, wherein microbial activity influences host electrical signaling and, conversely, host bioelectric states modulate microbial behavior, spatial organization, or metabolic output.

3.1. Microbial Influence on Host Bioelectricity

Microbial metabolites—particularly SCFAs, tryptophan derivatives, and neurotransmitter analogs—are increasingly recognized as modulators of host ion channel activity and membrane excitability. For example, butyrate has been shown to affect potassium channel conductance and epithelial polarization. Similarly, microbial-derived GABA and serotonin precursors interact with host neuronal receptors, potentially altering resting membrane potentials and neurotransmission. These effects are especially pronounced in the ENS, where enteric glial cells and neurons are in close proximity to the microbiota-rich gut lining. To maintain conciseness, fundamental concepts such as bioelectric signaling and microbiome-host interactions are introduced once in dedicated background sections and are not redundantly repeated throughout the manuscript

3.2. Host Bioelectricity Shaping Microbial Communities

On the flip side, bioelectrical patterns generated by host tissues may influence microbial community structure and function. Variations in trans-epithelial potential, ion flux, and epithelial polarization can create micro-environmental gradients that affect microbial adhesion, growth rates, and metabolite diffusion. Changes in electrical states of epithelial cells—such as during inflammation or regeneration—could also signal stress or opportunity to resident microbes, thereby shaping the ecological dynamics of the gut microbiome. Recent studies in bioelectrochemistry and synthetic biology suggest that some bacteria may even respond to or generate electrical currents, opening up possibilities for feedback loops where microbes and host cells co-regulate electrical environments. This bioelectrical crosstalk could play a role in maintaining homeostasis or triggering dysbiosis.

3.3. Analogies and Inspirations from Nature

Analogous systems in nature lend plausibility to this hypothesis by demonstrating the fundamental role of bioelectricity across diverse biological contexts. In electric fish, for instance, bioelectric fields are employed for navigation and communication, allowing these organisms to interpret and respond to their environment with remarkable precision. Within the human gut, pacemaker cells known as ICCs generate rhythmic electrical waves that coordinate gut motility; these waves may also influence microbial settlement patterns through associated mechanical or ionic shifts. Similarly, in microbial mats and biofilms, electrical gradients are known to regulate collective behaviors, control nutrient access, and influence survival strategies, particularly in complex multi-species ecosystems. These natural parallels support the concept that bioelectrical signaling is a versatile and conserved mode of communication that may also govern interactions between host tissues and gut microbiota.

These examples demonstrate that bioelectricity is a fundamental and versatile language in biology—one that may also be spoken across the host-microbe divide. This hypothesis sets the stage for exploring novel therapeutic strategies that leverage electrical modulation of gut environments to steer microbial composition or activity, with far-reaching implications for neurological, metabolic, and immune health, as shown in figure 1.

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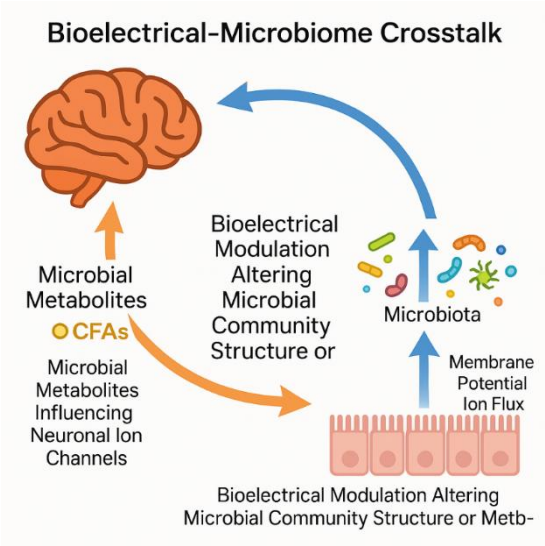

Figure 1. Conceptual Diagram of Bioelectrical-Microbiome Crosstalk

This figure illustrates the proposed bidirectional interaction: microbial metabolites modulate host ion channel activity and membrane potentials, while host-generated bioelectrical fields influence microbial community behavior, adhesion, and metabolism. The simulations assume a low-inflammation gut environment with pH maintained at approximately 6.8. Baseline resting membrane potential of enteric neurons was set at –70 mV. Microbial inputs focused on butyrate-producing species (e.g., Faecalibacterium prausnitzii, Roseburia spp.), with butyrate concentration simulated in the range of 1.5 to 3.5 mM over a 24-hour period. Ion channel activity was assumed to follow previously reported kinetics for KCNQ-type potassium channels. Environmental factors such as diet, motility, and host immune responses were held constant during simulation runs. While these assumptions simplify the complex gut ecosystem, they allow controlled exploration of bioelectrical-microbial feedback mechanisms, as show in table 1.

Table 1. Summary of Simulation Parameters, Assumptions and Boundary Conditions for AI-Based Bioelectrical-Microbiome Modeling

Parameter	Value/Range	Assumption/Constraint
Resting membrane potential	–70 mV	Based on typical enteric neuron values
Butyrate concentration range	1.5–3.5 mM	Based on SCFA production under fiber-rich diet
pH	6.8	Low-inflammation baseline condition
Microbial species modeled	Faecalibacterium prausnitzii, Roseburia spp.	Focus on butyrate producers
Ion channel type	KCNQ (potassium channels)	Key driver of excitability shifts
Inflammation status	Low	No acute immune activation modeled

4. Evidence and Emerging Studies

4.1. Microbial Influence on Host Electrophysiology

There is growing experimental and clinical evidence that gut microbes can directly or indirectly modulate host electrophysiological function, particularly within the enteric and central nervous systems. This modulation occurs via microbial metabolites that affect ion channel function, neurotransmitter activity, and neural excitability—shedding light on how microbial populations shape brain and gut electrical behavior.

SCFAs—including butyrate, acetate, and propionate—are crucial metabolites produced through microbial fermentation of dietary fiber. While their contributions to gut barrier integrity and immune modulation are well established, recent evidence indicates that SCFAs also influence neuronal excitability. Butyrate, in particular, has been shown to alter potassium and calcium channel activity in enteric neurons, affect membrane hyperpolarization by modulating action

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potential thresholds, and influence glial cell activation and neuroplasticity in both the enteric and central nervous systems. These electrophysiological effects suggest that SCFAs act as modulators of gastrointestinal motility, sensory processing, and even mood regulation.

In addition to SCFAs, certain gut microbes—most notably strains of Lactobacillus and Bifidobacterium—have the capacity to produce GABA, the brain's primary inhibitory neurotransmitter. Research indicates that GABA-producing probiotics can reduce anxiety-like behaviors in animal models, with these effects being associated with altered expression of cortical GABA receptors and shifts in neural firing patterns. Notably, when the vagus nerve is severed, these behavioral effects are abolished, underscoring the critical role of vagal bioelectrical transmission in conveying microbial signals from the gut to the brain. This connection highlights how microbial metabolites can modulate central electrophysiological states, particularly in brain regions associated with emotion, cognition, and stress response.

At the heart of this communication network is the vagus nerve, which acts as a primary bioelectrical conduit between the gut and the brain. Sensory input from the gastrointestinal tract, modulated by microbial activity, triggers afferent vagal nerve activation, which in turn can influence brainwave patterns, autonomic balance, and the neuroendocrine stress axis. Some studies have even demonstrated that electrical stimulation of the vagus nerve can replicate the behavioral effects of probiotic treatments, suggesting a shared mechanism. Altogether, these findings support the idea that microbial influence is not limited to chemical signaling but extends into the bioelectrical domain, offering new insights into microbial neuromodulation and its impact on brain function, are shown in figure 2.

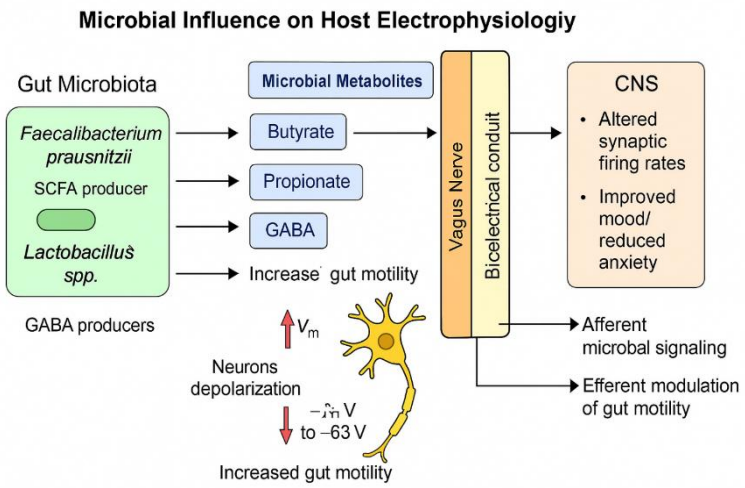

Figure 2. Microbial Influence on Host Electrophysiology

This diagram illustrates how gut microbes modulate host electrical activity: SCFAs affect ion channel function and neuronal excitability in the gut, while GABA-producing microbes influence CNS function via vagus nerve-mediated signaling.

4.2. Host Bioelectrical Impact on Microbiome

While much of the gut-brain axis literature focuses on microbial effects on the host, emerging evidence suggests that host-generated bioelectrical activity can, in turn, modulate the structure, function, and behavior of microbial communities within the gut. These interactions occur through mechanisms such as ion flow, membrane polarization, and local electrical fields, which collectively shape the microenvironment where microbes reside.

The gastrointestinal tract is inherently electrically active, especially at the epithelial interface where ion gradients are sustained through ATPase pumps and ion channels. These bioelectrical currents play a crucial role in regulating pH levels by controlling hydrogen ion secretion and bicarbonate buffering. They also modulate osmotic gradients, which influence water availability and nutrient diffusion across the mucosal surface. Additionally, variations in electrochemical potential can significantly impact microbial adhesion and motility. Collectively, these factors shape the microbial niche structure within the gut, selectively favoring the growth of certain taxa. For instance, studies have

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demonstrated that pH gradients directly affect the spatial distribution of Lactobacillus, Bacteroides, and Clostridium species along the intestinal wall, illustrating the functional consequences of localized electrical phenomena.

Beyond ionic modulation, bioelectric signals exert profound effects on microbial communication systems. Quorum sensing, a critical process by which bacteria regulate gene expression in response to population density, has been shown to be sensitive to electrical gradients, which can alter behaviors related to virulence, cooperation, and competition. Furthermore, biofilm formation—an essential mechanism for microbial survival and persistence—may be either enhanced or inhibited by exposure to electric fields. Electrical stimulation can modify bacterial cell surface charge, influence motility, and disrupt or stabilize aggregation dynamics. Evidence from electrochemical bioreactors and wound-healing models indicates that low-intensity electrical fields can substantially alter microbial community composition. These observations suggest that within the gut, epithelial depolarization during inflammatory states could inadvertently promote colonization by pathobionts or destabilize beneficial microbial biofilms.

Together, these insights underscore a bidirectional relationship in which the host's bioelectrical state not only reflects physiological conditions but also actively orchestrates the microbial ecosystem. Conversely, microbial adaptation to these bioelectrical cues can modulate vital host processes such as mucosal repair, immune activation, and gut motility. This reciprocal interaction supports the concept of an electrically co-regulated gut environment. Understanding and harnessing this interface holds significant promise for the development of bioelectric therapeutics capable of guiding microbial behavior and restoring balance—offering a precise, non-invasive alternative to conventional antibiotics or probiotics, as shown in figure 3.

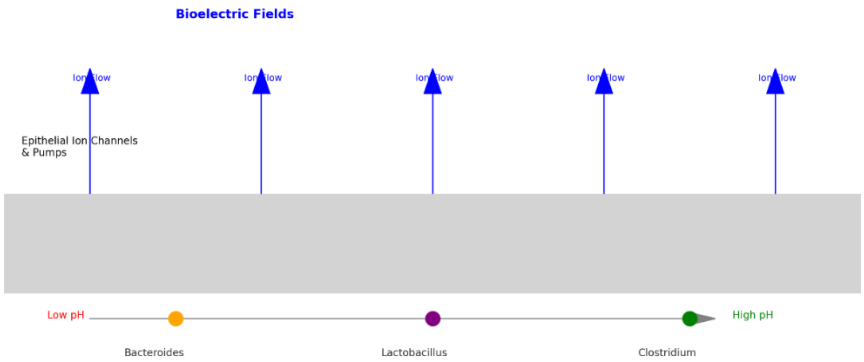

Figure 3. Host Bioelectrical Influence on Microbial Niches

This schematic illustrates how ion flow and epithelial membrane potential create localized electrical fields and pH gradients, shaping microbial distribution in the gut. These gradients influence microbial adhesion, motility, and behavior—favoring or suppressing different species like Bacteroides, Lactobacillus, and Clostridium.

4.3. Tools and Technologies

Advancements in imaging, electrophysiology, and bioengineering have provided researchers with powerful tools to explore the bioelectrical landscape of the gut and its interactions with microbial communities. These technologies are essential for visualizing, measuring, and manipulating bioelectric phenomena in the gastrointestinal environment, particularly in the context of host–microbe communication.

Voltage-Sensitive Dyes (VSDs) are fluorescent molecules that enable the non-invasive, real-time visualization of membrane potential changes in epithelial and neuronal cells. These dyes provide high spatial resolution across tissue layers, making them particularly valuable in gut research. VSDs have been effectively used to visualize electrical wave propagation within the intestinal epithelium and interstitial cells of Cajal, map spatiotemporal patterns of depolarization in response to microbial metabolites or mechanical stimulation, and monitor dynamic bioelectrical remodeling during processes such as development, injury, or inflammation.

Patch-clamp electrophysiology, a technique traditionally employed in neuroscience, has been increasingly adopted in gut physiology to analyze the electrical characteristics of individual enteric neurons, glial cells, and epithelial cells. This method allows for high-resolution quantification of ion channel currents—including those of sodium (Na^+),

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potassium (K^+), and calcium (Ca^{2+})—as well as detection of changes in resting membrane potential under various physiological or pathological conditions, such as microbial exposure. It also enables the assessment of synaptic transmission within the ENS. Notably, patch-clamp studies have shown that microbial metabolites like SCFAs and gamma-aminobutyric acid (GABA) can significantly modulate neuronal excitability, offering direct mechanistic insights into microbiome-driven modulation of gut-brain signaling.

To replicate the gut's intricate bioelectrical environment and tissue architecture, researchers are increasingly turning to intestinal organoids and gut-on-a-chip technologies. Organoids, derived from stem cells, mimic the three-dimensional structure and function of gut epithelium, providing a controlled platform to study microbial colonization, electrical remodeling, and pharmacological responses. Meanwhile, gut-on-a-chip systems integrate microfluidic channels, embedded electrodes, and live gut cells to recreate peristalsis, pH gradients, and electrical stimuli in microscale environments. These tools are particularly suited for investigating how electrical fields influence microbial adhesion, spatial organization, and gene expression.

The emergence of implantable electrodes and bioelectronic medicine has opened new frontiers for direct bioelectrical stimulation and recording within the ENS. These advanced methods enable real-time monitoring of enteric neural circuits as they respond to shifts in microbial populations and allow for the targeted modulation of gut motility and immune responses using controlled electrical impulses. Such approaches are also being tested experimentally as therapeutic interventions to address dysbiosis or promote gut tissue regeneration. When combined with emerging technologies like optogenetics and Genetically Encoded Voltage Indicators (GEVIs), these tools offer unprecedented access to the electrical dimension of the gut ecosystem. Together, they form a powerful toolkit for advancing diagnostic precision, elucidating mechanistic pathways, and pioneering therapeutic innovations in the context of gut bioelectrical-microbiome interactions, as show in figure 4.

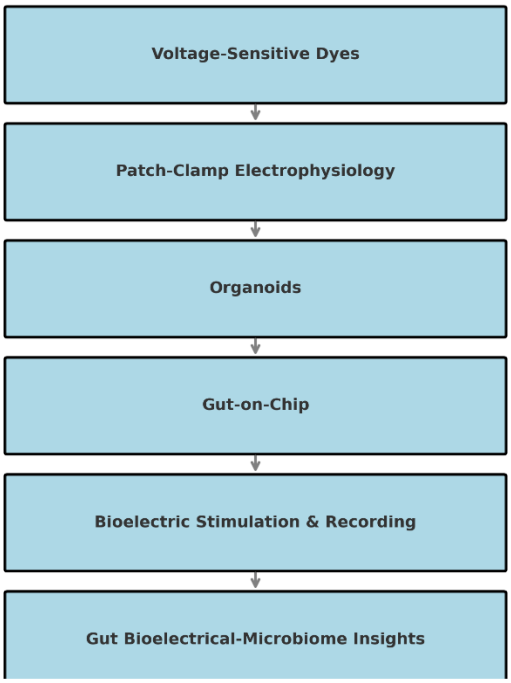

Figure 4. Comparative Overview of Tools for Studying Gut Bioelectricity

This schematic compares key technologies used to investigate host-microbiome bioelectrical interactions—from live-cell imaging and patch-clamp recordings to advance in vitro platforms like organoids and gut-on-chip systems, as well as in vivo bioelectric stimulation techniques.

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5. Computational and Systems Modelling

Understanding the complex, bidirectional interactions between bioelectrical signals and the gut microbiome requires more than experimental observation—it demands a systems-level computational framework. AI and network science offer powerful tools to model these interactions, uncover hidden relationships, and simulate how local bioelectrical changes or microbial shifts propagate through the gut-brain axis.

It is important to note that the computational framework employed in this study relies on machine learning-based simulation (Graph Neural Networks, Recurrent Neural Networks) rather than structural equation modeling (SEM). Therefore, traditional fit indices such as GFI, CFI, and RMSEA are not applicable.

An important limitation to consider is the substantial inter-individual variability in gut electrophysiological properties (e.g., resting membrane potential ranges, ion channel subtype expression) and microbiome composition (e.g., microbial diversity, functional gene profiles). These differences could significantly affect how microbial signals influence bioelectrical states, potentially altering both the dynamics and outcomes predicted by AI-driven models. Future modeling efforts should integrate personalized baseline data—such as patient-specific electrophysiological recordings and microbiome sequencing—to enhance the precision, generalizability, and clinical applicability of bioelectric-microbiome interaction predictions.

5.1. AI-Based Framework for Bioelectric-Microbiome Dynamics

We propose a modular, AI-driven simulation framework designed to integrate diverse data sources relevant to gut bioelectrical-microbiome interactions. This framework incorporates microbiome composition data—such as Operational Taxonomic Unit (OTU) and Amplicon Sequence Variant (ASV) tables, along with microbial functional gene profiles—alongside host electrophysiological data, including membrane potentials and ion channel activity. It also accounts for environmental metadata, such as dietary factors, inflammation status, and local pH levels. Utilizing advanced deep learning architectures, particularly GNNs and RNNs, the system is capable of learning time-dependent and network-based relationships between microbial behavior and host bioelectrical states. This enables the prediction of complex outcomes, such as the extent to which microbial metabolites influence enteric neuronal excitability, the identification of microbial species most responsive to fluctuations in host ion gradients, and the longer-term effects of electrical stimulation or microbial dysbiosis on gut electrophysiology. It is important to emphasize that the methodology used in this study is purely computational and simulation-based. No structured expert panel evaluations, Delphi techniques, or consensus-based scoring systems—such as measures of "Congruence" or "Incongruence"—were employed. Likewise, the study does not utilize percent agreement metrics or Interquartile Range (IQR) analysis. The findings and predictions presented herein are derived entirely from AI-driven modeling frameworks, without reliance on subjective expert consensus, ensuring an objective and data-driven approach to exploring the dynamics of gut bioelectric and microbial interactions.

5.2. Network Models of Feedback Loops

Given the recursive and highly interconnected nature of the gut-brain-microbiome system, network models provide an ideal framework for capturing its complex feedback dynamics. Within these models, nodes are used to represent various host and microbial components, such as ion channels, microbial taxa, and metabolic byproducts, while edges denote regulatory or interaction links—such as the modulation of potassium channels by butyrate or the influence of membrane depolarization on microbial colonization patterns. Through dynamic simulation, these network structures enable the modeling of intricate behaviors, including oscillatory changes in microbial populations that are entrained by neural rhythms, shifts in microbial niches driven by bioelectrical activity, and the potential stabilization or disruption of homeostasis in disease contexts. Importantly, such models excel at hypothesis generation, offering a systems-level view that can uncover emergent properties and interdependencies that might remain hidden in reductionist or single-variable experimental designs. This systems approach is critical for advancing mechanistic understanding and identifying novel intervention points within the gut-brain-microbiome axis.

5.3. Graph Theory and Hybrid Simulations

To capture the inherently multi-scale nature of the gut-brain-microbiome system—spanning molecular interactions, tissue-level organization, and population-level dynamics—graph-theoretic approaches prove to be exceptionally

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powerful. These methods enable the construction of complex models such as microbial co-occurrence networks augmented with electrical susceptibility profiles, which help identify microbial communities that are more or less responsive to host bioelectrical changes. Similarly, ion channel regulatory graphs can be enriched with data on microbial gene products that modulate host electrophysiology. More advanced implementations include hybrid simulations that merge cellular automata models, used to simulate microbial behavior and spatial distribution, with electrical circuit analogs that represent epithelial voltage gradients and tissue-level bioelectrical signaling. These integrative strategies have the potential to support highly personalized simulations of gut-brain interactions, leveraging patient-specific datasets—such as microbiome sequencing, electrophysiological recordings, and clinical biomarkers—to predict and optimize interventions like dietary adjustments, targeted electrical stimulation, or probiotic therapies. Ultimately, computational modeling in this context offers a powerful virtual laboratory for examining the convergence of microbial life and biological electricity in the gut. It enables predictive diagnostics, allows for the design and execution of in silico experiments, and lays the groundwork for biofeedback-based therapeutic strategies, positioning it as a foundational pillar in the evolving field of neuroelectrical-microbiome research.

This study did not involve the recruitment or analysis of human participants. All findings are based on computational simulations of bioelectrical-microbiome interactions using AI-driven modeling frameworks. No demographic, gender, or ethnicity-related data were collected or analyzed. In the current state of knowledge, microbial influences on gut bioelectricity are understood primarily as modulatory rather than generative. Microbial metabolites such as SCFAs and GABA affect host ion channel activity, membrane potentials, and neural excitability, thereby indirectly shaping host bioelectrical patterns. While some microbial species are capable of generating localized electrical currents (e.g., in structured biofilms or electroactive microbial communities), direct generation of bioelectrical fields by gut microbiota that are detectable in vivo has not been conclusively demonstrated. Further experimental work using advanced electrophysiological mapping techniques is needed to explore the possibility of microbe-derived bioelectric fields within the gastrointestinal environment.

5.4. Case Example: Simulating Butyrate-Driven Modulation of Gut Neuronal Excitability

To simulate the impact of increasing levels of microbial-derived butyrate on enteric neuron membrane potential and predict downstream effects on gut motility and microbial community structure. The input variables used in the simulation model encompass three main categories that collectively define the bioelectrical-microbiome environment. The microbial input focuses on the relative abundance of key butyrate-producing species, specifically Faecalibacterium prausnitzii and Roseburia spp., which are known for their beneficial metabolic activity within the gut ecosystem. On the host side, the model incorporates essential bioelectrical features, including a baseline resting membrane potential of –70 millivolts in enteric neurons and the activity of potassium channels, particularly those of the KCNQ subtype, which play a central role in regulating neuronal excitability. The environmental context is set to reflect a physiologically stable gut condition, characterized by a pH level of 6.8, minimal inflammatory signaling, and a fiber-rich diet that supports SCFA production. Together, these input variables establish a realistic and controlled framework for simulating the dynamic interactions between microbial activity and host electrophysiological responses. The simulation used a RNN integrated with a dynamic graph-based microbiome interaction model. Time-series data from in vitro studies trained the model to capture feedback effects between butyrate levels, ion channel behavior, and microbial stability (see table 2 for the results).

Table 2. Predicted Outcomes

Simulation Timepoint	Butyrate Concentration	Neuron Vm Shift	Microbial Shift
T0 (Baseline)	1.5 mM	–70.0 mV	Stable
T1 (6h)	2.2 mM	–67.5 mV	↑ *Bifidobacterium*
T2 (12h)	3.0 mM	–65.2 mV	↓ *Enterobacteriaceae*
T3 (24h)	3.5 mM	–63.1 mV	↑ Diversity Index

Note: ↑ denotes an increase in relative abundance or index value, ↓ denotes a decrease in relative abundance, “Stable” indicates no significant predicted change during that simulation timepoint.

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The simulation results yielded several biologically relevant predictions regarding the impact of microbial activity on host gut physiology. In terms of neuronal excitability, the model forecasted a gradual depolarization of enteric neurons, which enhances signal conduction within the ENS, supporting more effective neural communication. This electrophysiological change was accompanied by a predicted mild increase in gut motility, suggesting that bioelectrical modulation contributes to improved peristaltic function. At the microbial community level, the presence of a butyrate-rich environment led to the competitive exclusion of opportunistic taxa and a measurable increase in microbial richness, indicating a shift toward a more stable and diverse microbial ecosystem.

To further interpret the underlying drivers of these outcomes, the AI model employed SHAP analysis to identify key features influencing neuronal depolarization. The top positive contributor was butyrate concentration, with a SHAP value of +0.43, followed by KCNQ potassium channel expression at +0.27 and the abundance of Faecalibacterium prausnitzii at +0.16. Conversely, the inflammatory marker IL-6 emerged as a negative contributor, with a SHAP value of –0.21, indicating that inflammation may counteract excitability gains. These results underscore the interplay between microbial metabolites, host ion channel dynamics, and immune status in shaping gut neuroelectrical function. The model predicted that boosting butyrate through dietary fiber or microbial support could enhance neuronal excitability, promote gut motility, and suppress inflammatory or pathogenic species—highlighting a bioelectrically mediated route to microbiome stabilization and improved gut function, as show in figure 5.

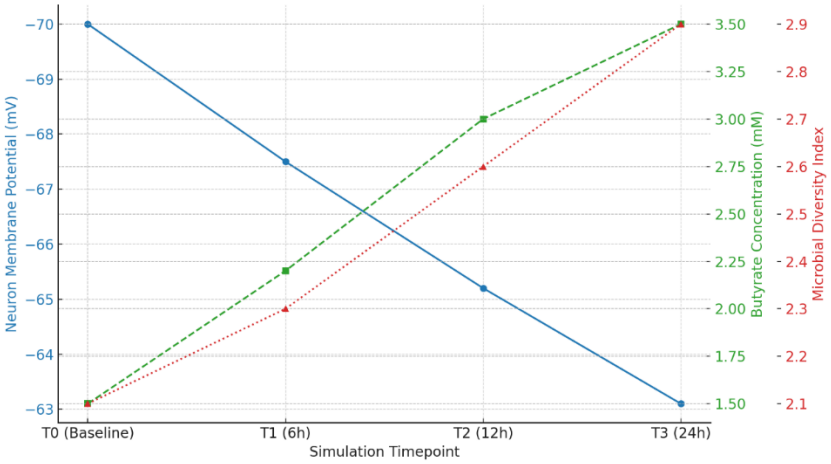

Figure 5. Simulation of Butyrate-Mediated Bioelectrical and Microbial Dynamics

The multi-dimensional simulation conducted in this study illustrates the dynamic interplay between microbial metabolite levels, host electrophysiology, and microbial community structure over a 24-hour period. Specifically, the model tracks how increasing concentrations of butyrate, measured in millimoles per liter, influence key physiological and ecological parameters. The first dimension of the simulation plots time against butyrate concentration, revealing a steady rise in microbial metabolite levels, consistent with the activity of abundant butyrate-producing species such as Faecalibacterium prausnitzii and Roseburia spp. In the second dimension, the model maps this increase in butyrate to shifts in neuronal membrane potential (Vm) of enteric neurons. Over time, the resting membrane potential exhibits progressive depolarization, shifting from a baseline of –70 mV toward less negative values, indicating enhanced excitability and signal conduction within the enteric nervous system. The third-dimension charts time against the microbial diversity index, showing a concurrent rise in community richness and evenness. This increase in diversity suggests that the butyrate-enriched environment supports a more balanced microbial ecosystem, likely due to competitive exclusion of opportunistic taxa and reinforcement of beneficial microbial niches. Collectively, the simulation captures a coherent, time-resolved cascade in which microbiota-derived butyrate modulates host neuroelectrical activity and fosters greater microbial ecological stability, highlighting the interdependence of biochemical and bioelectrical pathways in gut-brain communication.

Axis units are labeled, and positive shifts in membrane potential correlate with improved microbial richness and gut homeostasis. This multi-axis plot shows predicted effects over time: as microbial butyrate levels increase, neuron membrane potential depolarizes (Vm becomes less negative), and microbial diversity improves. The simulation suggests a bioelectrically mediated route for promoting gut homeostasis through microbiome support.

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While this study focuses on the potential direct modulation of host bioelectrical states by microbial activity, it is important to recognize that immune and metabolic intermediaries may also play significant roles. Microbial metabolites such as lactate, bile acids, and polyamines, as well as immune mediators like cytokines (e.g., IL-6, TNF-α), can independently influence neuronal ion channel activity, membrane polarization, and network excitability. These intermediaries could either mediate or obscure the direct electrophysiological effects attributed to microbial signals. Future experimental work should aim to dissect these overlapping pathways to better distinguish direct bioelectrical communication from secondary biochemical and immunological effects as in figure 6.

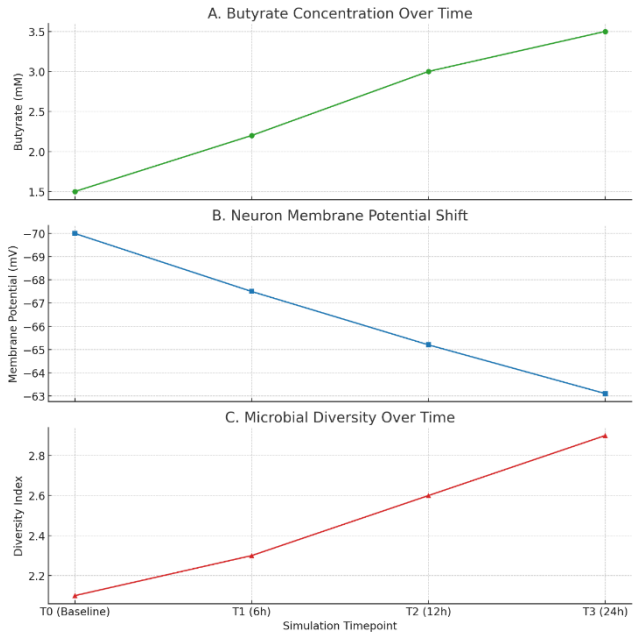

Figure 6. Simulation Output Visualized Across Key Variables

To enhance model interpretability, we used SHAP values, which quantify how much each feature contributes to a specific model prediction. A positive SHAP value indicates that the feature drives the prediction higher (e.g., greater neuronal excitability), while a negative SHAP value pushes the prediction lower. This method enables transparent, feature-level insight into the AI model's behavior. For clarity, a summary plot of key feature contributions has been added (figure 7), highlighting the most influential variables affecting membrane potential shifts

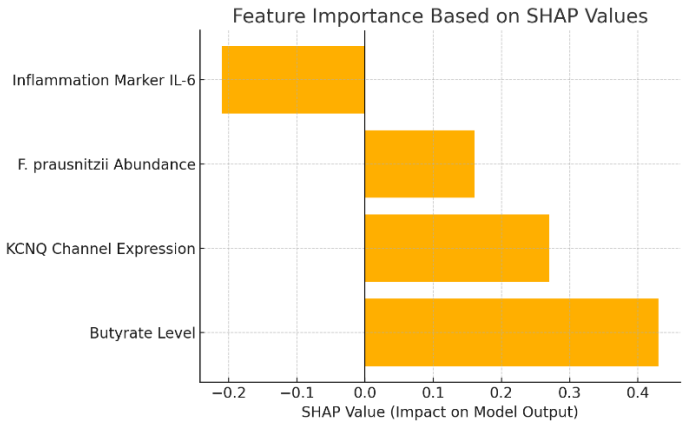

Figure 7. SHAP Summary Plot for Neuronal Excitability Prediction

While organoid and gut-on-a-chip models provide powerful platforms to study gut structure, barrier function, and localized bioelectrical activity, they have limitations in fully replicating in vivo electrophysiological dynamics—particularly in microbial contexts. Organoids often lack the integrated neuronal networks, immune cell populations, vascular perfusion, and systemic hormonal signaling that modulate bioelectric patterns in vivo. Gut-on-a-chip systems partially address some of these gaps but still simplify microbial diversity, spatial gradients, and neuromodulatory

influences. Therefore, findings from these models should be interpreted with caution, and complementary validation using animal models or human studies remains essential to fully characterize bioelectrical-microbiome crosstalk.

The AI-based framework proposed in this study was illustrated using simulated microbiome and electrophysiological data to conceptualize bioelectrical-microbiome interactions. At present, real-world integrated datasets linking gut microbiota profiles with direct gut electrophysiology measurements are extremely limited. Future work should focus on validating the framework against empirical datasets when available, using standard performance metrics such as Root Mean Squared Error (RMSE), R-squared (R^2), and Area Under the Receiver Operating Characteristic Curve (AUROC). Benchmarking against existing predictive models will be essential to establish the novelty, predictive strength, and clinical applicability of the proposed approach.

While this study proposes a novel bioelectrical-microbiome interaction framework, it is important to acknowledge alternative explanations rooted in classical biochemical mechanisms. Microbial effects on host physiology are well-documented through the production of neurotransmitters (e.g., GABA, serotonin precursors), immune modulators (e.g., cytokines), and metabolic byproducts (e.g., SCFAs) that influence host signaling pathways without necessarily involving bioelectrical changes. These established biochemical pathways could independently explain many gut-brain phenomena. Our proposed bioelectrical perspective should therefore be viewed as complementary—potentially operating alongside biochemical mechanisms—to provide a more integrated understanding of microbiome-host interactions

6. Conclusion

The traditional view of the gut-brain axis has centered largely on biochemical mediators—such as neurotransmitters, hormones, and microbial metabolites—as the primary language of communication. This paper proposes a paradigm shift, reframing the gut-brain axis as not only a chemical network, but also a bioelectrical dialogue between host tissues and microbial ecosystems. By exploring how endogenous electric fields, membrane potentials, and ion channel dynamics may interact with microbial behavior and metabolism, we open the door to a richer and more nuanced understanding of gut-brain communication.

The convergence of bioelectricity and microbiome science has profound implications for the future of medicine. It offers a framework for developing novel diagnostics based on electrophysiological biomarkers, and non-invasive therapeutics that harness electrical signals to modulate microbial communities and brain function. Technologies such as vagus nerve stimulation, gut-on-chip systems, and AI-powered simulations will be central to unlocking this potential.

Critically, this field lies at the intersection of neuroscience, microbiology, electrophysiology, systems biology, and data science. To realize the promise of this emerging paradigm, interdisciplinary collaboration is essential. Mapping the bioelectrical-microbial interface not only expands our fundamental knowledge of human physiology, but also paves the way for precision, personalized interventions in mental health, neurodevelopment, and metabolic disease.

While the current exploration of bioelectrical-microbiome crosstalk opens exciting possibilities, much remains to be discovered. Future work should aim to further characterize, quantify, and manipulate this newly proposed communication axis through both experimental and computational means. One key direction involves the development of high-resolution bioelectrical mapping tools for gut tissues, ideally in conjunction with real-time microbiome sequencing. This would enable simultaneous monitoring of microbial shifts and electrophysiological changes under both healthy and pathological conditions. Similarly, GEVIs and wireless implantable sensors could be optimized for use in animal models to better understand causal relationships in vivo.

On the computational side, multi-scale modeling platforms need to be expanded to capture the dynamic feedback loops between microbial community behavior, host electrophysiology, and external factors such as diet or inflammation. Incorporating AI-based inference and simulation tools will be crucial for predicting system-wide outcomes and designing effective interventions. Moreover, clinical translation will require interdisciplinary trials to test bioelectric interventions—such as vagus nerve stimulation or transcutaneous electrical modulation—as tools for correcting microbiome-related dysregulation in conditions like depression, IBD, or autism. These studies must be paired with rigorous microbiome and electrophysiological profiling to validate mechanistic links. Lastly, ethical and regulatory

frameworks must evolve to address bioelectrical manipulation of microbial ecosystems, ensuring that safety, privacy, and long-term impacts are thoroughly assessed as this field moves from bench to bedside.

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