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New insights in the gut–brain axis: the role of bioelectrical microbiome

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The gut–brain axis describes the complex, bidirectional communication network connecting the central nervous system, the enteric nervous system, and the gut microbiome. Beyond chemical messengers and immune signaling, recent evidence highlights endogenous bioelectricity — ion flows, voltage gradients, and electric fields — as an additional layer of communication within this axis. Diet influences the state of gut bacteria, shaping their communication with neural cells. This review explores bacterial bioelectric signaling and its impact on neuronal function. Cutting-edge tools like the proposed Brain-Bacteria Interface will enhance our understanding of these interactions. By integrating bioelectricity into the microbiome–gut–brain axis framework, this research unveils new therapeutic possibilities using diet and dietary nutrients, as well as bioelectric interventions, offering fresh insights into interkingdom communication and its role in health and disease.

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Introduction

The gut microbiome, the diverse bacterial community within the gastrointestinal system, shares a dynamic, bidirectional relationship with its host, where bacterial populations both influence and are shaped by their environment [1]. This interaction is mediated by various biological pathways and modulated by external factors such as diet, sleep, exercise, and social interactions. While microbiome–host interactions have long been recognized as fundamental to health and homeostasis, their influence extends beyond the gut, impacting immune function and systemic physiology [2]. With growing recognition of diet's influence on mental health and brain function, interest has surged in understanding how gut microorganisms contribute to these processes [3]. A microbiome-targeted therapeutic approach for neurological conditions could offer benefits like dietary interventions while addressing challenges related to adherence or availability. Further, personalized dietary strategies aimed at modulating gut bacteria may enhance brain health without the side effects associated with current pharmacological treatments. Gaining precise knowledge of the causal and mechanistic communication between gut bacteria and neurons is therefore essential. Despite emerging evidence of microbiome–neural interactions, uncovering their precise mechanisms remains challenging due to the complexity of interacting systems and the lack of standardized and integrative experimental tools.

It is particularly important to understand the biophysical interface through which somatic cells and microbiota can exchange information. In this review, we propose that bioelectrical signaling — particularly microbial membrane potential (V_{mem}) dynamics modulated by dietary inputs — represents a critical and underexplored mechanism of gut–brain communication. The main objective of the review is to explore how diet-driven bacterial metabolism gives rise to bioelectrical signals that contribute to gut–brain signaling. Specifically, we aim to: (1) describe current evidence supporting the existence of bioelectrical signaling within the microbiota and its influence on the nervous system; (2) examine how diet shapes microbial electrogenic capacity and the generation of bioelectrically active metabolites; and (3) introduce a conceptual platform — the Brain–Bacteria Interface (BBI) — as a framework for future studies on interkingdom communication. This perspective

integrates diet, bioelectricity, and microbiota–brain interaction into a unified model that expands current understanding and suggests new avenues for therapeutic innovation.

Bioelectrical signaling in the microbiome: a new layer of gut physiology modulated by diet

Bioelectricity is a fundamental aspect of life, governing functions that rely on charge separation (voltage) through ion gradients or ion movement (current) via channels and pumps. These bioelectrical circuits exhibit complex dynamics in interconnected cells, forming a distinct regulatory layer that operates independently yet interacts with transcriptional networks [4] — traditionally the primary focus of molecular biology.

Cells actively maintain a V_{mem}, created by the uneven distribution of ions across the plasma membrane, and generate bioelectrical signals, which are essential for both intracellular and intercellular communication [5]. While bioelectricity is most prominently expressed in excitable cells like neurons and cardiomyocytes — where it drives action potentials — it is present in virtually all cells. Endogenous V_{mem} changes, combined with gap junctions that enable ion exchange, allow somatic cells to communicate their bioelectric state with neighboring cells — a process crucial for nutrient transport, cell proliferation, and volume regulation. Beyond that, bioelectrical signals carry vital information about physiological states and developmental processes, playing key roles in conditions such as cancer and tissue regeneration [4]. Bioelectricity is not an exclusively eukaryotic feature; it is an evolutionarily conserved characteristic, also present in prokaryotic cells [6,7]. Bacteria maintain a dynamic V_{mem}, regulated by ion channels and pumps, which modulates essential functions such as growth, motility, antibiotic susceptibility, and environmental sensing [8–12].

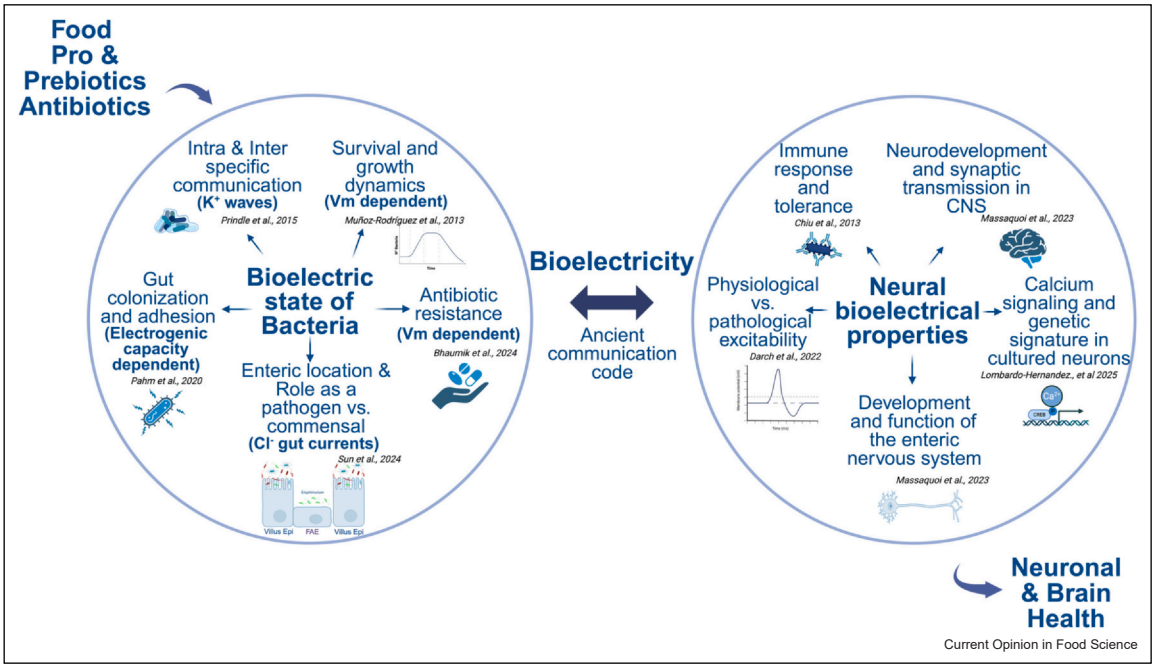
Quarta et al. (2025) demonstrated that variations in nutrient availability directly shift bacterial V_{mem} [13]. The seminal study by Prindle et al. (2015) [14] revealed that *Bacillus subtilis* biofilms use depolarizing potassium waves to coordinate activity under nutrient limitation, linking metabolic stress to long-range electrical communication. This collective behavior has been also observed in other gut-associated species [15], allowing for intra- and interspecies communication [16,17]. Diet-derived substrates, such as fermentable fibers, are metabolized by gut bacteria into short-chain fatty acids (SCFAs) — notably acetate, propionate, and butyrate — which act as bioelectrically active molecules [18,19]. These SCFAs alter V_{mem} through multiple mechanisms, including proton export and ion channel modulation [20]. Polyamines (e.g. putrescine, spermidine), abundant in protein-rich foods or generated via bacterial decarboxylation of amino acids, likewise depolarize or hyperpolarize bacterial membranes depending on concentration and species [21]. These metabolites also influence host physiology by modulating epithelial ion transport, tightening gut barrier function, and acting on neural and immune cells (extensively revised in Ref. [22]). Diet also shapes bacterial bioelectricity via metabolic gradients in the intestinal lumen. For instance, diets rich in fermentable substrates enhance local anaerobiosis and promote fermentative metabolism, leading to greater SCFA output and altered bacterial redox balance [19]. This in turn shifts V_{mem} profiles across bacterial populations, potentially modulating their spatial organization and interaction with the host. Supporting this, Sun et al. (2024) demonstrated that *Salmonella typhimurium* and *E. coli* respond to gut electrical fields, using chloride currents as cues for tissue colonization [23].

Together, these findings suggest that dietary inputs — by driving the production of specific bioelectrically active bacterial metabolites and the availability of essential micronutrients — constitute a potent means of tuning gut bacterial V_{mem} and rewiring gut–brain communication circuits. Integrating these insights into the microbiome–gut–brain axis framework offers an innovative strategy for dietary or bioelectronic interventions to optimize host neural and metabolic function.

Neuron–bacteria bioelectric dialogue: mechanisms, interfaces, and bidirectionality

The discovery of bioelectricity in bacteria, enabling communicate with each other and the intestinal environment, raises the possibility that these mechanisms also influence interactions with cells that possess evolutionarily conserved bioelectric systems— such as neurons. Recent research supports this hypothesis, indicating that exploring bioelectric mechanisms could help fill critical gaps in our understanding of the Microbiota-Gut-Brain axis (Figure 1). For such neuron–bacteria interactions — mediated by ionic currents, gradients, and charge differentials — close spatial proximity or direct contact between neurons and bacteria within the body is of paramount importance. First, the enteric nervous system (ENS), which innervates the entire gastrointestinal tract and is organized into two major ganglionated plexuses — the submucosal and myenteric plexuses — is highly relevant [24]. Additionally, the gut is innervated by the autonomic nervous system through parasympathetic branches, primarily represented by the vagus nerve, and sympathetic branches [25]. The vagus nerve plays a crucial role as the primary and fastest communication pathway between the gut microbiome and the central nervous system (CNS) [26]. It has axonal terminations directly within the intestinal mucosa and forms synapses with enteroendocrine cells in the intestinal epithelium. These specialized cells, known as Neuropod cells, were

Figure 1



Bacteria–neuron bioelectrical hypothesis: an evolutionarily conserved gut–brain communication code. Schematic representation of the bacteria–neuron bioelectrical hypothesis. This model proposes that bioelectricity is an ancient and evolutionarily conserved form of communication, enabling bidirectional interactions between bacteria and the nervous system. Bioelectricity is not an exclusively neural property; it is also present in bacteria, where it plays key physiological roles. Prindle et al. (2015) [14] demonstrated that potassium waves are essential for both intra- and interspecies communication in biofilms. Muñoz-Rodriguez et al. (2023) [45] showed that the membrane potential (V_{mem}) of bacteria varies across different growth phases. Bhaumik et al. (2024) [10] identified bacterial V_{mem} as a critical target of antimicrobial peptides, establishing that membrane hyperpolarization can help overcome antibiotic resistance. Sun et al. (2024) [23] reported that the spatial localization of pathogenic versus commensal bacteria within the gut depends on regional intestinal polarization driven by chloride currents. In parallel, Pham et al. (2020) [40] demonstrated that the electrogenic capacity of certain probiotic strains is essential for gut adhesion and modulation of neural function. Collectively, these findings support the idea that modulating the bacterial bioelectric state — through diet or electroceutical strategies — can influence both gut physiology and neuronal activity, ultimately shaping brain health. There is growing evidence for such microbiota-mediated bioelectrical modulation of neural function. For example, Massaquoi et al. (2023) [41] showed that a healthy microbiota is essential for proper development and synaptic transmission in both the CNS and ENS. Pham et al. (2020) [40] further demonstrated that bacterial electrogenicity is required for microbiota-driven regulation of feeding behavior and for reducing obesity in mice. Additionally, as reviewed by Darch and McCafferty (2022) [32], neural bioelectrical properties are sensitive to bacterial influences, suggesting therapeutic potential in disorders characterized by altered excitability, such as epilepsy. Recently, Lombardo-Hernandez et al. (2025) [39] reported that direct contact of a gut bacterium with neuronal cultures can influence neuronal bioelectricity, as reflected by alterations in calcium signaling dynamics and changes in the transcriptomic profile of bioelectricity-associated genes. These converging lines of evidence emphasize the potential for targeted bioelectric interventions to regulate gut–brain communication and improve neurological outcomes.

demonstrated by Kaelberer et al. (2018) [27] to be electrically excitable epithelial enteroendocrine cells in direct contact with the intestinal lumen and synaptically connected to vagal afferents. This unique anatomical positioning enables them to establish glutamatergic synapses that transmit signals from the gut lumen to the brain within milliseconds, thereby constituting a privileged interface for ultrafast neuronal responses to luminal stimuli. Although direct bioelectrical interactions between bacteria and Neuropod cells remain to be demonstrated, their excitability could plausibly be modulated by microbiota-derived metabolites and neurotransmitters — highlighting their potential role as a crucial bioelectronic interface [28] in mediating gut–-brain bioelectric communication, unlike ENS neurons, which are not directly exposed to the lumen in physiological conditions. Moreover, the neuron–bacteria interaction may intensify under conditions in which the integrity of the intestinal (e.g. Crohn's disease or ulcerative colitis [29]) or the blood-brain barriers (e.g. Alzheimer's and Parkinson's disease [30]) is compromised. Recent findings indicate that when mice are subjected to a diet that induces dysbiosis, commensal gut bacteria (such as *Staphylococcus xylosus*) can translocate directly into the brain, using the vagus nerve as the primary conduit to reach the CNS [31].

Neural bioelectric properties are highly sensitive to gut bacteria (see Supplementary Table S1 for a compilation of the principal studies addressing this topic). Research in animals and humans reveals that probiotics, prebiotics, or antibiotics can alter neural excitability [32] at

different levels of the nervous system. In CNS, hypothalamic neurons detect bacterial activity, which can affect appetite and body temperature [33]. Gut microbiota also modulate social behavior and stress-related brain activity [34] and influence ENS neuron excitability through ion channels [35]. A human study discovered a brain network syncing with gastric rhythms, linking gut function to brain activity via electrical signals [36]. Further evidence shows bacteria directly alter nociceptor neuron calcium dynamics and action potentials, impacting pain perception [37]. In an *in vitro* transepithelial gut–nerve co-culture model, *Lactobacillus rhamnosus* and *Lactobacillus fermentum* were shown to induce neurite outgrowth and lengthening in differentiated SH-SY5Y neuronal cells by signaling across an epithelial barrier [38]. Our recent work [39] has provided direct proof that bacterial cues can alter neuronal bioelectric activity: *in vitro* assays with cortical neurons showed that exposure to live *Lactiplantibacillus plantarum* significantly increased spontaneous calcium oscillations — a functional proxy tightly linked to V_{mem} dynamics and excitability. This effect was elicited by bacterial contact without cell invasion and occurred at levels comparable to physiologically relevant glutamatergic stimulation. These Ca^{2+} changes were paralleled by the regulation of ion channel–related genes (e.g. Slc8b1, Kcna1, and Clcn1) and synaptic markers, underscoring that bacterial stimuli can directly reshape host neuronal V_{mem} states. Together, these findings challenge the traditional view that neuron–bacteria communication relies solely on indirect molecular pathways, suggesting that bioelectric signals may play a critical role in the gut-brain axis.

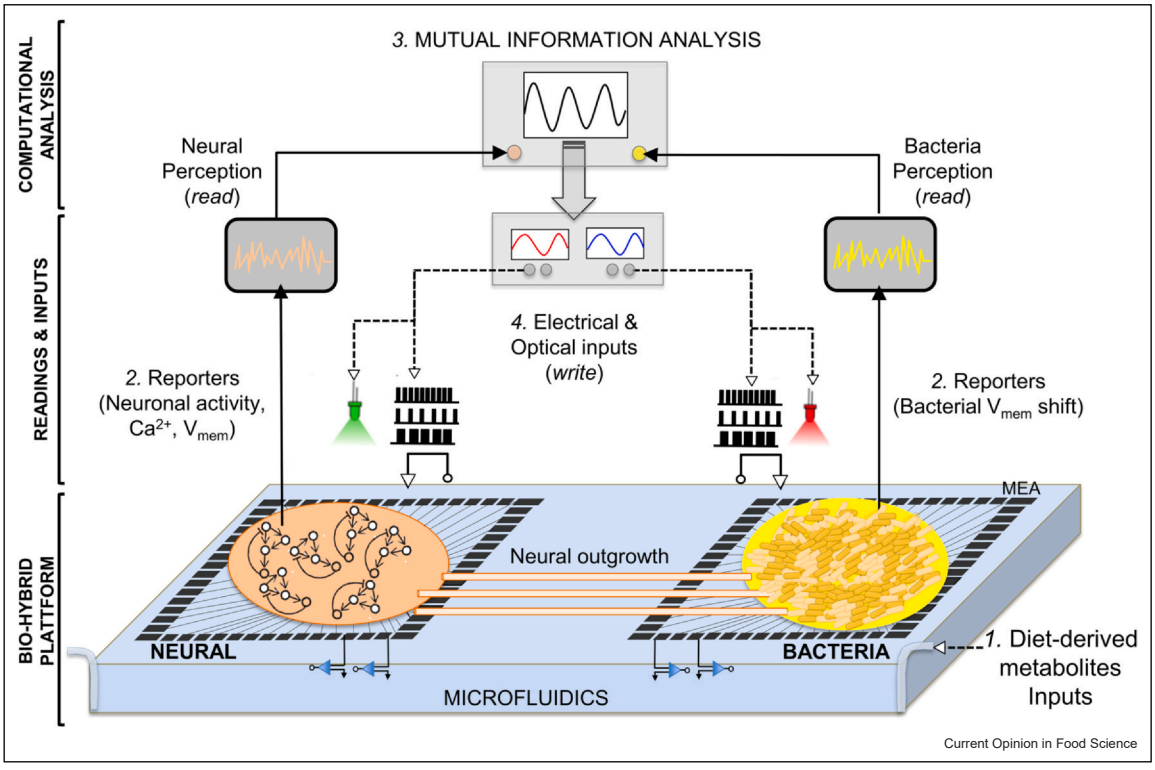
Microbiota signals not only modulate the bioelectric properties of neural cells but also trigger specific physiological responses across long-range distances in the body. While the microbiota's role in appetite and satiety regulation is well established — mainly through bacterial metabolites affecting hunger-regulating centers in the CNS — recent research suggests a direct bioelectric influence as well. In 2020, Phamet al. demonstrated that the anti-obesogenic effect of the probiotic *Leuconostoc mesenteroides* depends on its electrogenic capacity in mice fed a high-fat diet; this bacterium reduced abdominal fat mass, but the effect was lost when bioelectricity production was inhibited [40]. Massaquoi et al. (2023) found that the presence of microbiota stimulated ENS activity and upregulated ion channel and neurotransmission genes in zebrafish [41], with similar effects in the CNS, promoting neurogenesis and neurodifferentiation [42]. While Germ-Free studies have focused on microbiota absence affecting the nervous system, additional research has explored how the host–bacteria relationship is influenced by the absence of the brain or V_{mem} alterations. Using *Xenopus*, a model known for its high developmental plasticity and regenerative capacity, authors demonstrated that brain removal worsened *E. coli* infection outcomes, suggesting that a functional nervous system modulates host–bacteria interactions [43]. Further evidence of this phenomenon is provided by studies showing that altering the bioelectric state of *Xenopus* embryos regulates their susceptibility to infection [44]. Emerging evidence suggests a bidirectional communication, where neurons can also modulate the bioelectric state of bacteria: microbiota-associated bacteria, such as *E. coli*, *Enterococcus faecalis*, and *Lactobacillus reuteri*, undergo V_{mem} changes in response to neural-type stimuli, including various neurotransmitters, without affecting their growth or viability [45]. Griffiths et al. have found that activating specific ENS neurons can alter the composition of the intestinal microbiota [46]. Together, these findings emphasize the growing interest in direct neuron–bacteria signaling along the Microbiota-Gut-Brain axis; however, we are only at the early stages, and further *in vitro* and *ex vivo* research is crucial to better understand the specific mechanisms and molecular mediators by which neuronal and bacterial bioelectric properties influence each other under controlled conditions.

The Brain–Bacteria Interface: a platform to decode diet-modulated gut–brain bioelectric communication

While there is strong evidence that behaviors, particularly those tied to mood and emotional cognition, can be shaped by dietary changes or direct microbiome interventions [3], such as fecal microbiota transplantation, pre/probiotics, or antibiotics, most of the fundamental questions in this field are wide-open. Nowadays, the scientific community has focused on indirect pathways of connection between diet, (gut) bacteria, and (brain) neurons, which are executed through metabolites (such as SCFAs, bile acids) and signals (immune, neurotransmitters, and hormones) released mainly through the circulatory system. Poor diets, particularly those high in sugar, fat, and processed foods, contribute to inflammation and gut dysbiosis, worsening conditions like depression, anxiety, schizophrenia, and neurodegenerative diseases [47]. Conversely, healthy diets, such as the Mediterranean diet, support a diverse and beneficial gut microbiota, promoting mental well-being (for excellent and comprehensive review on this topic, see Ref. [3]. Considering all this evidence relating diet, microbiome, and behavior, it is reasonable to expect that the neural activity underlying these behaviors is altered through food interventions [32]. However, which aspects of neural activity—ranging from single synapses to whole network dynamics—are most affected by the microbiome–gut–brain axis, and why are certain behaviors or brain regions more sensitive to gut-based changes? To advance future research on the diet-microbiota-gut-brain axis, we emphasize the need for an enabling technology and new perspectives that allow us to reveal in real time the bidirectional communication among these two levels of biological organization [6].

While several leading groups investigate structural ('hardware') bacterial components — such as peptidoglycan/muropeptides, lipopolysaccharide, and microbial amyloids (curli) [33] and bacterial metabolites [18,48] — that impact neuroimmune signaling, barrier integrity, and protein aggregation along the microbiota–gut–brain axis, our review advances a complementary 'software' perspective centered on bioelectric properties (V_{mem}, ionic fluxes) as drivers of neuron–bacteria communication [6,7,39]. Bioelectricity is not simply one more layer of mechanism that is required alongside biochemical cues and stress forces to implement cell functionality: it enables unique, powerful information-processing capacity that facilitates cell communication into complex collectives [49]. Results from embryogenesis, cancer, and regenerative medicine have shed light on bioelectric signaling and provide a roadmap for targeting endogenous bioelectric circuits as tractable and powerful control knobs for future applications in biomedicine and synthetic biology [4]. Applying a top-down approach, we hypothesize that (i) the bioelectrical state of bacteria not only modulates their own signaling capacity but can also directly alter the bioelectrical properties and activity of neural cells (ii) a computational analysis of interactions between bacteria and neural cells will reveal uniquely important aspects of how Information processing underlies emergence of complex systems at multiple levels of organization (iii) we can use this actionable information to develop food-based approaches to target gut bacteria to obtain a specific brain outcome. This proposal builds upon recent proof-of-principle studies demonstrating that gut bacteria can directly modulate neuronal bioelectrical properties *in vitro* [39]. Building on this feasibility, we now present the BBI (Figure 2) as an envisioned platform:

Figure 2



Conceptual schematic of the electrical-optical BBI. Schematic representation of the proposed BBI, a biohybrid platform designed to study real-time, bidirectional communication between gut microbiota and neurons via bioelectrical signaling under normal and stimulated conditions (e.g. with *1. Diet-derived metabolites*). The *Bio-hybrid Platform* integrates co-interacting neuronal cells and bacterial communities within a microfluidic or organ-on-chip device equipped with *Readings & Inputs*: Electrophysiological recording electrodes (MEA) to monitor membrane potential (V_{mem}) dynamics and ion fluxes on both the bacterial and neuronal sides; Optogenetic or chemical stimulation modules, enabling selective activation or modulation of bacterial or neural bioelectric states; Integrated imaging systems for real-time monitoring of fluorescence-based voltage indicators or calcium dynamics (e.g. V_{mem}-sensitive dyes, GCaMP). Directionality numbers indicate bidirectional signal flow between microbes and neurons through electrical, metabolic, and molecular pathways. Key molecular components are labeled. The BBI is designed to test how dietary inputs reshape bacterial electrogenic activity and how these changes influence neuronal excitability and function. It also allows for controlled manipulation of microbial and neural *Vmem* states to decode the emergent logic of interkingdom bioelectrical communication. This figure serves as both a conceptual summary and a roadmap for future experimental work aimed at developing bioelectronic dietary interventions within the microbiome–gut–brain axis framework. Future work will need to address specific technical details and develop prototype designs to test the validity of the BBI concept.

a purpose-built microfluidic chamber integrating electrical and optical stimulation/recording modules, optimized to extract information during live communication across biological entities and to facilitate functional testing of specific hypotheses. The BBI is designed to provide flexibility for different neuronal models and microbial metabolic states, including strict anaerobic conditions. On the neuronal side, the BBI could be applied to different experimental models, including primary cultures of brain neurons, co-cultures of cortical and enteric neurons, or immortalized neuronal lines in combination with other neural cell types. On the microbial side, the design considers the ecological and metabolic diversity of the gut microbiome: while the intestinal environment is dominated by strict anaerobes (e.g. *Bacteroides*, *Clostridium*, and *Faecalibacterium*), facultative anaerobes such as *E. coli* or *Enterococcus* thrive in niches closer to the mucosa, where oxygen tension is slightly higher. Looking ahead, we foresee that such a system would allow us to read out signals and provide stimuli in real time, start decoding the 'metrics' of bacteria–neuron communication to reveal which subsets of the system form the maximum integrated Information, and support model-building based on the dictionary matching Information signatures to specific events. The BBI would also enable the exploration of molecular and cellular properties to validate existing (and newly revealed) targets. Moreover, high-throughput data on voltage states, calcium dynamics, and other physiological measurements from both sides of a microbe-metazoan system would provide ideal input for emerging AI approaches, which will enable decoding of the functional communication protocols used across Kingdoms of life.

Conclusion and future perspectives

The study of the gut–microbiome–rain axis has received increasing scientific interest over the last few years. Yet, there is a need to reveal the actual mechanisms of action underlying the relationship between neurons and bacteria, which may go beyond what is already known, toward radically new methodologies that see both sides as fundamentally agential materials with agendas and context-sensitive decision-making capabilities [50]. Much as in the brain, somatic bioelectric circuits upstream of gene expression and behavior of cells enable a multimodal *top-down* approach toward a holistic understanding of the collective intelligence implemented by bidirectional communication between neurons and bacteria [49]. To deepen our theoretical understanding, it is essential to consider how bioelectrical signaling interfaces with other key pathways involved in gut–brain communication. Bioelectrical signals likely act in synergy with bacterial metabolites (e.g. SCFAs, neurotransmitter-like compounds) and immune pathways (e.g. cytokine release, activation of immune receptors), contributing to the regulation of both metabolic communication and neuroimmune signaling. In this sense, bioelectricity may complement and modulate the established 'metabolism–immunity–nerve' triad, acting as a fast, analog, and spatially structured signaling layer that links and integrates these three domains. This perspective offers a more holistic understanding of gut–brain interactions and suggests that bioelectricity may serve as a unifying mechanism coordinating diverse physiological signals. This new scientific viewpoint requires further experimental research, particularly to clarify the bioelectrical signals through which bacteria and neurons may mutually influence each other's activity. More broadly, the many endpoints for bioelectrical modulation, including regenerative medicine, birth defects, cancer, and bioengineering, are driving the search for effective methods for controlling voltage-based signaling in patients; dietary inputs are an especially attractive and minimally invasive candidate, complementing ion channel gene therapy, electroceutical drugs, and electrode implants. We foresee an exciting roadmap for the transfer of basic scientific knowledge into technological biomedical solutions that will then be applicable to the great challenges of our society, such as the prevention or treatment of conditions related to disturbed mental well-being, considering the diet as a possible instrument that can be used to modulate the bioelectrical signaling along the gut–brain axis.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

Authors declare that they have no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.cofs.2025.101353.

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