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Bioelectronic tools for understanding the universal language of electrical signaling across species and kingdoms

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ABSTRACT

Modern bioelectronic tools are rapidly advancing to detect electric potentials within networks of electrogenic cells, such as cardiomyocytes, neurons, and pancreatic beta cells. However, it is becoming evident that electrical signaling is not limited to the animal kingdom but may be a universal form of cell-cell communication. In this review, we discuss the existing evidence of, and tools used to collect, subcellular, single-cell and network-level electrical signals across kingdoms, including bacteria, plants, fungi, and even viruses. We discuss how cellular networks employ altered electrical "circuitry" and intercellular mechanisms across kingdoms, and we assess the functionality and scalability of cutting-edge nanobioelectronics to collect electrical signatures regardless of cell size, shape, or function. Researchers today aim to design micro- and nano-topographic structures which harness mechanosensitive membrane and cytoskeletal pathways that enable tight electrical coupling to subcellular compartments within high-throughput recording systems. Finally, we identify gaps in current knowledge of inter-species and inter-kingdom electrical signaling and propose critical milestones needed to create a central theory of electrical signaling across kingdoms. Our discussion demonstrates the need for high resolution, high throughput tools which can probe multiple, diverse cell types at once in their native or experimentally-modeled environments. These advancements will not only reveal the underlying biophysical laws governing the universal language of electrical communication, but can enable bidirectional electrical communication and manipulation of biological systems.

1. Introduction

1.1. The languages of cell-cell communication

Biological cells are multilingual entities which partake in several types of functional circuits. This was first recognized in 1855 b y Claude Bernard, who observed that gland secretion affected distant cells (Eknoyan, 2004). A few years later, Charles Darwin extended this observation by proposing that single-celled organisms evolved into multicellular organisms over time (Tanghe, 2018). Since the 17th century, scientists have proposed various mechanisms of cell signaling; however, only in the past 100 years have we been able to study various kinds of signaling at the molecular level. We now know that the lexicon for cell-cell communication includes ions, electrons, and small molecules, and that electric, mechanical, and/or chemical gradients act as "cultural forces" to influence inter- and intra-cellular behavior. These carriers represent different languages, sometimes with shared "words: electrical signaling, composed of ionic, electron, and proton transfer along or through phospholipid bilayer membranes, and chemical signaling, composed of diffusive small molecule transfer across membranes or throughout the extracellular matrix. Cells use chemical and electrical signaling to communicate across organs, species, and kingdoms, pointing to undiscovered laws governing interspecies connectivity and the evolutionary conservation of ionic and electronic gradients in biological signaling cascades. For example, certain electrical transport mechanisms evolved to increase the temporal resolution of cellular response time. In some cases, mechanical signaling evolved to enable sensing and conveyance of stimuli, also via electrical and chemical carriers (Booth, 2014; Harraz et al., 2022; Jiang et al., 2021). This review will discuss evidence of electrical signaling across kingdoms, particularly from a single-cell perspective. Membrane potential changes can manipulate biological function not only in canonical electrogenic

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cells such as cardiomyocytes and neurons, but also during oocyte fertilization, tumor cell proliferation, renal proximal tubule epithelial cell function, and to alter cell adhesion, tumor growth, and gene expression of triple-negative breast cancer cells (Lyon et al., 2023; Payne et al., 2022; Wieërs et al., 2022; Yang and Brackenbury, 2013), to give a few examples. Moreover, recent research has shown that single cells act as electrical processing units to determine signal transmission (Biasci et al., 2022; Briant et al., 2018; Dempsey et al., 2016; Khosrovani et al., 2007; Nusser, 2009; Ross, 2012; Tan et al., 2007), making "subthreshold" signals an important regulator of network plasticity. We will describe how cutting-edge nanoelectronics collect subcellular signals regardless of cell size, shape, or function. We will compare and contrast the measurement and modulation capabilities of these tools and discuss challenges that need to be overcome for future biosensor designs. Finally, we will identify knowledge gaps of inter-species and inter-kingdom electrical signaling and propose critical milestones needed to create a central theory of electrical signaling across kingdoms.

1.2. Modern electrophysiological tools require tailoring towards various cell types

Single cells contain highly regulated pools of ions, electrons, and protons used during cell-cell "conversations." Depending on the species and cell subtype, the speech syntax – that is, the release and order of these electrical or chemical agents over time – is regulated by 1) pore-forming transmembrane proteins such as ion channels and gap junctions, 2) charge-carrying molecules, and/or 3) passive diffusion. This is because the energetic demands of single cells across kingdoms vary with cell size and function (Benarroch and Asally, 2020), as depicted in Fig. 1. For example, plant cells, which generate electrical signals to coordinate metabolic responses to external stimuli, propagate action potentials via passive cation flow through plasmodesmata structures (Mudrilov et al., 2021; Vodeneev et al., 2016). Cardiomyocytes, which enable synchronous beating in the heart, share electrical signals with their neighbors via passive cation flow through gap junctions (Kanno and Saffitz, 2001). Neurons, whose dendritic morphologies enable specialized synaptic connections in the brain, share electrical signals by converting them to synaptic vesicle-enclosed neurotransmitters which activate ion channels in postsynaptic cells, or by passive ion flow through gap junctions (Faber and Pereda, 2018). It has recently been discovered that bacteria utilize potassium ion signaling to regulate nutrient consumption dynamics within biofilms (J. Liu et al., 2017); however, the mechanism of ion flow is not clear. Nevertheless, bacteria are highly sensitive to miniscule electrochemical fluctuations (Benarroch and Asally, 2020; Lundberg et al., 2013). These converging phenomena beg the question of how a universal probe might be designed to sample ionic currents from both large and ultrasmall (1–2 μm), membrane-enclosed structures.

This problem is not new; nearly 100 years ago, Hodgkin and Huxley themselves recorded from giant squid axons to avoid the technical challenge of patch clamping small neurons in other species (Schwiening, 2012). Patch clamp, the electrophysiological gold standard, brings 1–2 μm tip diameter glass micropipette close to single cells and applies a small vacuum to create a "patch" of sucked up membrane with a tight, gigaOhm "seal." However, in many cases, the preparation of giant "cell-like" structures, such as giant spheroplasts of E.coli (Martinac et al., 2013) prevents accurate recordings of the native network activity. Also, due to the sensitive physical seal between the micro-scale patch pipette and cell membrane, many patches are unsuccessful, causing frequent cell death and preventing multicellular recording. Another approach has been to further reduce the probe size. Nanofabricated probes (<1 μm tip diameter) can either penetrate or permeabilize the plasma membrane while occupying less surface area, enabling intracellular-like recordings while preserving cellular structure and morphology. This approach allows for multiplexed measurements of

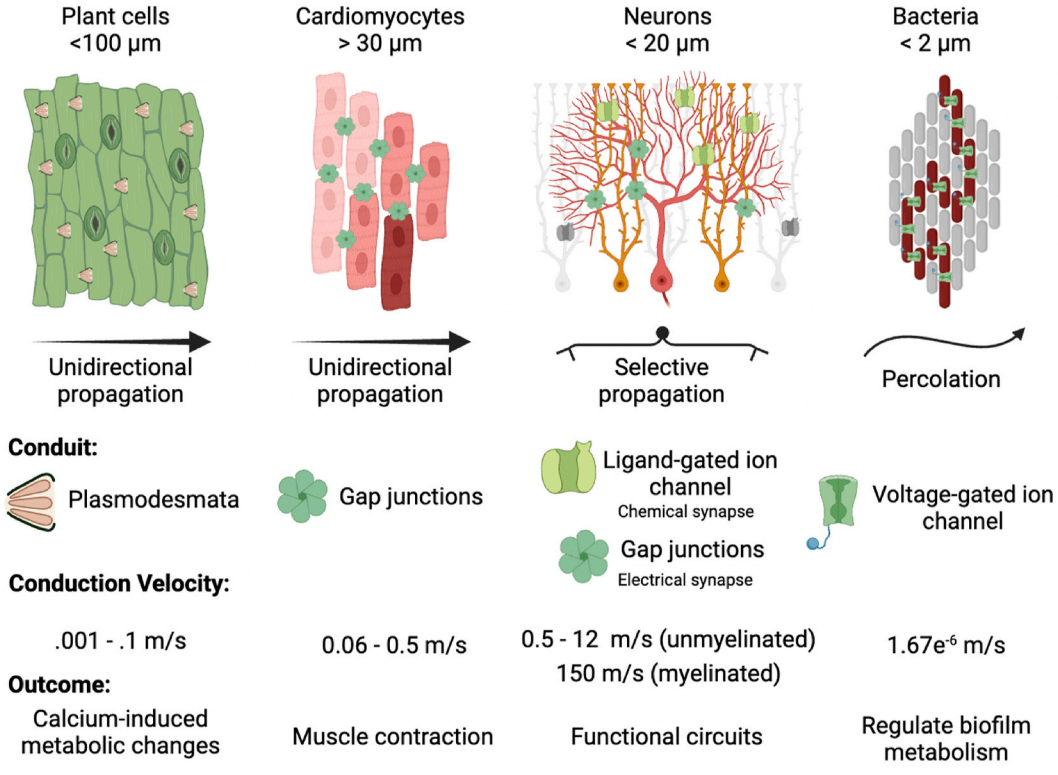

Fig. 1. Cell size-related changes in intercellular electrical signaling across kingdoms. Reported ranges of conduction velocity are 0.001–0.1 m/s in plant cells (Mudrilov et al., 2021), 0.06–0.5 m/s in cardiomyocytes (Dou et al., 2020; Han et al., 2021; Kalmykov et al., 2019), 0.5–12 m/s in unmyelinated neurons and 150 m/s in myelinated ones (Lawson and Waddell, 1991; Purves et al., 2001), and $1.67e^{-6}$ m/s in bacteria within biofilms (Prindle et al., 2015b). Schematic created with Biorender.

single-cell network activity over many days (Abbott et al., 2020; Jahed et al., 2022; Lin et al., 2017). Even less invasive are optogenetic probes, which can reveal relative ionic fluctuations when used in conjunction with super resolution microscopy. State of the art nanoelectrode arrays and optical probes for intracellular, multiplexed electrophysiology are discussed in this review. We also propose guidelines for the design of novel bioelectronics to help reveal patterns of eukaryotic and prokaryotic bioelectrical circuits across species and kingdoms.

1.3. Historical evolution of concepts and tools for inter- and intra-cellular electrical signaling

Bioelectricity focuses on endogenous electrical signals generated by or applied to cells (Adams, 2019; Casella et al., 2021), typically from changing ionic gradients but also including electron transfer, such as in mitochondria and bacteria. These biological relationships are typically recorded from ion-induced electron flow due to the double layer capacitance at electrode surfaces in response to cell electrical signaling to produce voltage or current readouts. The development of electronic tools and concepts is described in further detail below.

Electrophysiology and bioelectricity concepts evolved together. This journey began in the 18th century, when Newton and Galvani stimulated muscle contraction in dissected frog limbs (Soeiro, n.d.), coining the term “animal electricity,” and Schwann subsequently proposed the Cell Theory in 1839, hinting at a physiological source for these contractions. Two decades later, in response to his mentor Emil du Bois--Reymond’s slow instrumentation for recording currents from muscle and nerve fibers, Bernstein constructed the fast differential rheotome, the first bespoke electrical recording device which measured negative current variations following muscle stimulation (Bernstein, 1868; Carmeliet, 2019; Marzullo and Gage, 2012). Using this device, he quantitatively measured action potentials for the first time in 1868; similarly, in 1873, Burden-Sanderson recorded the first plant action potential (Lee and Calvo, 2023). A few decades later, in 1902, based on his own experimental data and postulations by Nernst and Ostawld about ionic behavior across semi-permeable membranes, Bernstein proposed his Membrane Potential Theory, the first explanation of ionic flow across cellular membranes in response to injury (Seyfarth, 2006). These discoveries set the stage for studying single-cell, bioelectrical phenomena.

Notably, decades after du Bois-Reymond’s discovery of synaptic structures in 1877, Loewi and Dale formulated their theory of chemical synaptic transmission, leading to their 1936 Nobel Prize (Dale and Dudley, 1929; Loewi and Navratil, 1926; Todman, 2008). The subsequent = invention of patch clamp enabled modern concepts of membrane potential modulation. From the 1940s–50s, Hodgkin and Huxley used a pulled glass micropipette to probe single squid axons, and infer principles of membrane conductance and the action potential (Hodgkin and Huxley, 1952). In 1954, Hodgkin, Nierdergerke, Hanson, and Huxley proposed the Sliding Filament Theory of muscle contraction to explain excitation-contraction coupling, and Katz speculated that neurotransmitter release occurs in a quantized fashion across synapses (Huxley and Niedergerke, 1954; Stevens, 2003). Equipped with patch clamp technology, scientists could then focus on “subthreshold” oscillations within cells to understand how internal mechanisms lead to signal generation and transmission.

Kickstarting the era of molecular bioelectricity, Singer and Nicholson proposed the Fluid Mosaic model of the plasma membrane in 1972. That same year, Thomas used one of the first microelectrode arrays to record from dorsal root ganglion neurons, which would lay the foundation for today’s nanoelectrode arrays (Lombard, 2014; Pine, 2006; Singer and Nicolson, 1972; Thomas et al., 1972). Hille, Bezanilla, and Armstrong together stipulated that ion channel pores in the membrane are selective to specific ions while Neher and Sakmann used patch clamp to record single ion channel activity in a frog muscle cell and therefore prove their existence (Armstrong and Bezanilla, 1973; Bezanilla and Armstrong, 1972; Hille, 1978; Kondratskyi, 2020; Neher and Sakmann, 1976). While microelectrode array and patch clamp studies helped reveal the behavior of single neurons, advancements in the 21st century have progressed toward multiplexed, nanoscale probes to enable one-to-one, intracellular cell coupling and recording in both 2D and 3D cultures. Notable advancements include the development of field effect transistor arrays by the Lieber, Cohen-Karni, and Xu groups (Cohen-Karni et al., 2009; Duan et al., 2012; Gu et al., 2022), the development of nanopillar electrode arrays by the several groups (Abbott et al., 2017; Dipalo et al., 2017; Hai and Spira, 2012; Jahed et al., 2022; R. Liu et al., 2022; Shokoohimehr et al., 2022; Xie et al., 2012), and the development of organoid-based bioelectronics by the Cohen-Karni, Cui, Gracias, and Liu groups (Cools et al., 2018; Kalmykov et al., 2019; Li et al., 2019; Yang et al., 2023). While most of these technologies interfaced with eukaryotic cells, we now know that bacterial biofilms also utilize ion channel signaling for biofilm growth (Prindle et al., 2015a). These advancements are discussed further in the Measurement and Modulation section.

1.4. Evolution of ion channels and the changing roles of ions throughout time

The orchestration of ion channel activity to produce the action potential is a recent evolutionary development, since ions have been biologically repurposed for both chemical and electrical signaling throughout biological history. Depending on the chosen electrical and optical electrophysiological tool, one can record direct or indirect membrane voltage, as well as ion channel currents. For example, while patch clamp can achieve single ion channel recording, calcium imaging can reveal subcellular calcium dynamics. Other approaches using pharmacology allow experimenters to tease out the contributions of different ions to cell type-specific electrical signatures (see Table 1). Studying how ionic fluctuations across membranes emerged can be used to characterize electrical signatures produced by today’s cells, and determine the mechanisms underlying aberrant signaling. Ion channels embedded inside the earliest membrane-enclosed vesicles regulated their composition. These vesicles are thought to have preceded single-celled organisms, which is partly evidenced by the shared ion channel structures found across kingdoms. In fact, the number of transmembrane segments found in each ion channel type has been used to map their evolution (Pohorille et al., 2005). Ion channels today typically exist as multimeric proteins which contain a hydrophobic, transmembrane core “channel” created by alpha helix bundles or beta strand barrels. The abundance of ion channel-esque proteins, such as voltage-gated ion channels, ligand-gated ion channels, mechanosensitive ion channels, active pumps, porins, and the ABC family of proton-coupled, toxin-expelling proteins (Pohorille et al., 2005), underscores the crucial role of ionic transport in several cellular processes.

Potassium ion channels likely appeared the earliest (Anderson and Greenberg, 2001; Moran et al., 2015). Here, we only discuss protein domains which transmit ions across the phospholipid bilayer; auxiliary subunits such as regulators of channel kinetics, will not be discussed (Catterall and Few, 2008). The inward-rectifying potassium channel family, a ligand-gated channel activated by phosphatidylinositol 4, 5-bisphosphate (PIP2) and so-called because of its asymmetrical open channel configuration, possess four 2-transmembrane (TM) regions which together form a tetrameric protein (Hibino et al., 2010; Li and Yang, n.d.; Moran et al., 2015). The 2-TM subunit is homologous to the 2-TM regions from the later-to-appear family consisting of the 1) voltage-gated potassium (K) channels, 2) the calcium-gated potassium (K) channels, and 3) the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. This family, hereafter called KKHCN, has 4 additional TM voltage-sensing regions, to create 6-TM segments which assemble in groups of 4 to create a tetrameric protein. The bacterial voltage-gated sodium channels also share this structure, and are thought to have appeared around the same time (Liebeskind et al., 2013; Pohorille et al., 2005). While it is not well understood how known bacterial sodium and calcium channels are distributed or employed

Table 1
A non-comprehensive list of drugs used for validation of nanobioelectronic devices.

Drug	Cell Type	Purpose	Concentrations
Blebbistatin	Cardiomyocytes	Myosin inhibitor which blocks contraction but preserves APs; used to demonstrate nanoelectrode arrays measure electrical, not mechanical, signals (W. Li et al., 2021).	10 μM (Rastogi et al., 2020a).
Carbenoxolone	Cardiomyocytes	Gap junction inhibitor used to block signal transmission between neighboring cells (de Groot et al., 2003).	50 μM (de Groot et al., 2003).
Caffeine	Cardiomyocytes and Neurons	Reduces threshold for ryanodine receptor-activated Ca^{2+} flux in both neurons and cardiomyocytes (Shi et al., 2014; Vyleta and Smith, 2008), introducing subthreshold Ca^{2+} transients (Itzhaki et al., 2011), and altering contractility (Rasmussen et al., 1987). Not observed to increase beating rate alone (Calvert et al., 2015; Luo et al., 2021).	2–20 mM (Bruno et al., 2020; Vyleta and Smith, 2008).
Dofetilide	Cardiomyocytes	Potassium channel inhibitor which prolongs cardiac AP (Jahed et al., 2022; Ward and Gill, 1997).	0.3–10 nM (Jahed et al., 2022).
Cyanquixaline (6-cyano-7-nitroquinoxaline-2,3-dione) (CNQX)	Neurons	AMPA receptor antagonist with an inhibitory effect (Li and Burrell, 2008; R. Liu et al., 2022).	7 nM - 10 μM (Abbott et al., 2020; R. Liu et al., 2022).
Glutamate	Neurons	Excitatory neurotransmitter which may transiently increase firing rate in excitatory neurons (Gao et al., 2020; Zhou and Danbolt, 2014).	10 μM - 100 mM (Gao et al., 2020; Minoshima et al., 2020).
AMPA	Neurons	NMDA receptor antagonist with anti-excitatory effect that may reduce EPSPs (Abbott et al., 2020).	Not typically added during experiments
APV or AP5	Neurons	NMDA receptor antagonist with anti-excitatory effect that may reduce EPSPs (Abbott et al., 2020).	33 nM - 25 μM (Abbott et al., 2020; R. Liu et al., 2022).
Bicuculline	Neurons	GABA antagonist; reduces IPSPs (Abbott et al., 2020).	50 μM (Abbott et al., 2020).
Tetrodotoxin (TTX)	Cardiomyocytes and neurons	Sodium channel inhibitor; blocks APs (Abbott et al., 2020; Narahashi, 2008).	1–100 nM (Abbott et al., 2020; R. Liu et al., 2022).
Picrotoxin	Neurons	GABA receptor antagonist; has anti-inhibitory effect (R. Liu et al., 2022; Newland and Cull-Candy, 1992).	10–33 nM (R. Liu et al., 2022; Lv et al., 2023).
Kainate	Neurons	Glutamate receptor (separate from NMDA and AMPA) agonist with transient excitatory effect causing increased APs (Pan et al., 2018; Vignes and Collingridge, 1997) and EPSPs (Lauri et al., 2021).	10 nM - 10 μM (Kapucu et al., 2022; Scelfo et al., 2012).
Potassium chloride (KCl)	Neurons	Increases the potassium equilibrium potential which is typically very negative, facilitating depolarization and increased AP firing (Balena et al., 2008; Rienecker et al., 2020).	40–120 mM (Cui et al., 2006; Day et al., 2006).
2-deoxy-D-glucose (2DG)	Multiple	Glucose analog which suppresses glycolysis (Chen et al., 2011), used to elicit APs in pancreatic cells (Dean and Matthews, 1970), and potentiation of both EPSPs and IPSPs in neurons (Krnjević and Zhao, 2000; Zhao et al., 1997).	10–27 mM (Dean and Matthews, 1970; Krnjević and Zhao, 2000).

across bacterial species (Bruni et al., 2017; Payandeh and Minor, 2015; Shimomura et al., 2020; Sun et al., 2019), it is perhaps unsurprising that the earliest-to-appear potassium channels significantly influence biofilm formation and nutrient regulation in certain species (Humphries et al., 2017; J. Liu et al., 2017; Martinez-Corral et al., 2019).

While voltage-gated potassium channel structures are largely preserved across kingdoms, the structures of voltage-gated calcium ("C") and sodium channels ("N") vary greatly and likely appeared more recently (Catterall and Few, 2008; Moran et al., 2015). The main difference between the KKHCN and the C and N families is whether the four 6-transmembrane segments are covalently linked into a single, four-domain protein (Kühlbrandt, 2016; Moran et al., 2015). While these segments are covalently bonded in the C and N families, they bond electrostatically in the KKHCN family. Voltage-gated sodium and calcium ion channels likely emerged to enable motility and quicken response time, leading to action potentials and advanced nervous systems (Catterall et al., 2017; Moran et al., 2015). For instance, primitive eukaryotes such as algae, ciliates, and heliozoa use action potentials to move rapidly in response to light. The action potential may have been induced by transient membrane breakage and calcium influx from an external stimulus in the last eukaryotic common ancestor (Brunet and Arendt, 2016; Wan and Jekely, 2021), although nonlinear gene appearances or horizontal gene transfer may also have led to the emergence of these fast ion channels in some organisms. It is unclear whether bacteria exhibit APs, although attempts to recreate prokaryotic sodium channels by splitting 6-TM segments of eukaryotic sodium channels have been unsuccessful (Pohorille et al., 2005), suggesting at the very least that bacterial "APs" would possess altered kinetics. This order of ion channel evolution may explain why cells from different kingdoms exhibit such a complex collection of electrical signals, as described in the next section.

2. Evidence for and comparison of electrical signaling within each kingdom

In this section, we introduce known mechanisms of membrane potential changes (section 2.1), and discuss electrical signals exhibited across kingdoms (section 2.2). Furthermore, we summarize signal metrics that can be measured from nanoelectronic devices, and experiments for isolating sub- and supra-threshold signals down to the subcellular scale. While this review focuses on electrical signaling, chemical signaling involves several related pathways such as intercellular molecular transport (i.e. neurotransmitters), and intracellular ligand transport (i.e. G-coupled protein receptor pathways). Extensive discussions of chemical pathways are available elsewhere (Fan et al., 2022; Kaper and Sperandio, 2005; Nair et al., 2019; Waters and Bassler, 2005).

2.1. *Mechanisms of membrane potential fluctuation*

Biological membrane potential fluctuations fall into three categories: (1) ion flow through voltage- or ligand-gated ion channels to depolarize membranes, (2) electron flow through conductive protein nanowires to produce energy across a chemical gradient, and (3) electron shuttling across membranes to produce energy. These mechanisms are not confined to particular species, but likely stem from the energetic demands of the parent cell size and morphology (Benarroch and Asally, 2020; Larkin et al., 2018).

2.1.1. *Voltage- and ligand-gated ion channels*

Ion channels are pore-shaped proteins with domains which determine the selectivity, specificity, and gating kinetics of certain ions, and can cause depolarization or hyperpolarization of their host membrane. Scientists have identified over 100 different ion channels occurring in eukaryotes, prokaryotes, and contained within viruses as genetic

material (Alberts et al., 2002; Fischer and Sansom, 2002). Ion channels comprise nearly 20% of FDA-approved drug targets (Hutchings et al., 2018). Some ion channels are highly selective to one type of ion (Na^+, K^+, Ca^{2+}, Cl^-), others allow multi-ion passage (Jane, 2007), and still others exchange ions, such as the sodium-potassium pump that maintains the resting membrane potential of the cell. Ion channels can be voltage-gated and/or ligand-gated, and often require a "refractory period" regulated by a "gate" domain before they can be activated again. The baseline electrochemical gradients established by membrane ion channels in a eukaryotic cell at rest are reported in literature (Melkikh and Sutormina, 2008; Tashiro et al., 2006). This information is unagreed upon for prokaryotic cells.

2.1.2. Electron shuttling

Electron shuttling appears canonically during cellular respiration, where electrons are carried by NADH, $FADH_2$, and cytochromes inside mitochondria to enable ATP production. In bacteria, electrons are not confined and are instead transferred to external electron acceptors in the surrounding environment or in bioelectrochemical systems such as microbial fuel cells (MFCs). MFC arrays were used to identify gut bacteria which employ extracellular electron transport (EET) for metabolic function (Tahernia et al., 2020). Many biofilm-forming bacteria, such as *B. subtilis*, *S. aureus,* and *P aeruginosa* require iron, an electron acceptor, to create biofilms (Qin et al., 2019), suggesting an EET pathway which regulates biofilm formation. Moreover, quorum sensing modulated EET in *P aeruginosa* with iron-supplemented media, allowing switching between aerobic and anaerobic conditions (Venkataraman et al., 2010). An interesting application of EET is the creation of photoconductive cytochrome nanowires using conductive biofilms for optoelectronics (Neu et al., 2022). It is not yet known if bacteria that perform EET also exhibit ion channel activity; however, Thioflavin T, a Nernstian cationic dye typically used to measure K^+ oscillations, can also discern EET activity with high spatial resolution (Pirbadian et al., 2020). A direct connection between ion channel signaling and electron transfer would suggest that bacterial metabolism is tightly linked to biofilm bioelectricity.

2.1.3. Electron flow

In lieu of carrier molecules, electron flow can also be achieved via conductive protein nanowires, as demonstrated by cable bacteria (Meysman et al., 2019; Teske, 2019). In anaerobic environments lacking strong electron acceptors such as oxygen and nitrate, sulfate is reduced to sulfide, and then oxidized by microorganisms to produce ATP once oxygen becomes present again. Single cable bacteria evolved to harness the electrical potential of sulfide even without oxygen by linking together using conductive, vertical protein "cables" which span from the soil surface deep into the anaerobic, sulfide-rich sediment. Sulfide is oxidized by the sub-surface cable bacteria, electrons are shuttled to the nanowires by c-type cytochromes inside the peri-plasmatic membrane, and then rapidly upward along the conductive protein nanowires presumably through π-π orbitals or by "hopping" along consecutive amino acid residues. Upon arriving at the aerobic surface of the cable, oxidases transfer the electrons to oxygen to produce ATP. This exciting phenomenon has yet to be explored as a bioelectronic tool for measurement or modulation of membrane potential in single cells (Meysman et al., 2019).

2.2. Membrane potential fluctuations and electrical signal metrics across kingdoms

In this section, we compare and contrast electrical signals utilized by single cells or organelles across kingdoms. The following sections are organized according to decreasing cell or organelle size, with the assumption that electrical signaling mechanisms will change in accordance with cell or organelle metabolic demands.

2.2.1. Cardiomyocyte action potentials

In cardiomyocytes and other muscle cells, gap junctions allow ions to overflow into neighboring cells (Rohr, 2004), allowing action potential firing and therefore contraction throughout the tissue. Differential gap junction expression across cardiomyocyte subtypes can lead to varying tissue conduction velocities (Ideker et al., 2009; Kanter et al., 1993; Tse and Yeo, 2015). The origin of spontaneous action potentials within pacemaking cells is not well understood; however, subthreshold calcium oscillations may be responsible for the emergence of beating in developing tissues (Jia et al., 2023; Sasse et al., 2007) and in arrhythmic events (De Ferrari et al., 1995; Weiss et al., 2010). Once the positive depolarization threshold is passed, the influx of Na^+ and outflux of K^+ are accompanied by calcium influx, which binds troponin C and calmodulin to enable actin/myosin actuation. The AP for cardiomyocytes shown in Fig. 2a arises from precise, multi-ion channel activity, and is specific to cardiomyocyte subtypes. It is thus possible to identify muscle cell types based on their waveform shapes even *in vitro* (Lin et al., 2017). Patch clamp studies have provided the true amplitude and waveform of various cardiomyocyte APs and detect subthreshold early after depolarizations, which may signify arrhythmia *in vivo* (Dipalo et al., 2021; Qu et al., 2013). The Comprehensive In Vivo Proarrhythmia Assay (CiPA) was developed to apply electrophysiology to evaluate the effects of novel drugs on cardiomyocyte health (Strauss et al., 2019), and provides a reference point for future cardiac electrophysiology studies.

2.2.2. Neuron action potentials and subthreshold signals

While cardiomyocytes share ample surface area with their neighbors, neurons possess thin processes that synapse selectively, as illustrated in Figs. 1 and 3b. Briefly, subthreshold excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) transmitted from the dendritic spines accumulate at the axon hillock (Kole and Stuart, 2012). Their frequency and amplitude determine whether the depolarization threshold is crossed, at which point the suprathreshold AP propagates along the axon to the synaptic boutons. There, voltage-gated calcium channels open, allowing incoming Ca^{2+} to bind exocytotic vesicles that release neurotransmitters into the synaptic cleft. The neurotransmitters bind receptors on the postsynaptic cell's dendrites, enabling cation influx to regenerate the signal. Postsynaptic potentials, which reflect synaptic plasticity and determine AP initiation (Daoudal et al., 2002; Griffith et al., 1986; Lupica et al., 1992), are targets for long-term potentiation (Mozzachiodi and Byrne, 2010; Volk et al., 2013) and therefore modulating plasticity. Synaptic plasticity is regulated by the expression of neurotransmitter receptors and availability of other molecules (Abraham and Bear, 1996). It is significantly correlated with neurological deficits in, for example, Alzheimer's Disease (Hill et al., 2019; Mango et al., 2019; Shankar et al., 2008). The ratio of inhibitory to excitatory synapses in the brain is a critical constant thought to be mediated by glial cells (Lee et al., 2021; Purves et al., 2001; Sukenik et al., 2021). Excitatory to inhibitory imbalances have been associated with autism spectrum disorder, schizophrenia, Alzheimer's Disease, stroke, traumatic brain injury, and epilepsy (Baguley et al., 2008; Bonansco and Fuenzalida, 2016; Nelson and Valakh, 2015; Schmidt et al., 2012; Selten et al., 2018; Vico Varela et al., 2019; Witkowski et al., 2019). Recently, engineers developed artificial synapse devices designed to interact directly with neurons and mimic potentiation (Keene et al., 2020; Scott et al., 2022). These "conversations" with neurons would require feeding spiking patterns as inputs, presumably in response to electrophysiological signals. Although several spiking analysis tools are used both *in vivo* and *in vitro* (Buzsáki et al., 2012; Deng and Klyachko, 2021), none have been developed for multiplexed devices which can record subthreshold activity. Deng and Klyachko loosely classified neuronal electrical metrics from patch clamp into three categories: (1) Excitability, including firing rate, hyperpolarization, input resistance, AP voltage threshold, latency to the first AP, the first inter-AP interval, and the rheobase, (2) Maturity, including neurotransmitter release and network synchrony, and (3) Synaptic plasticity, including

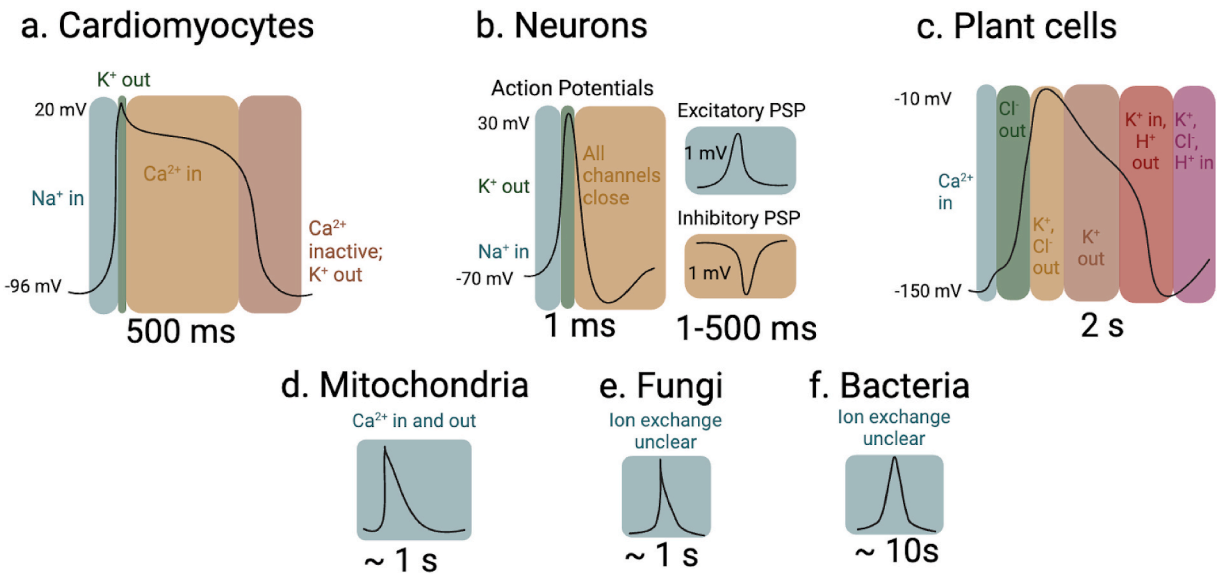

Fig. 2. Membrane potential fluctuations across kingdoms, including APs from a) cardiomyocytes and b) neurons (Aziz et al., 2020; Hao et al., 2011), as well as neuronal excitatory and inhibitory postsynaptic potentials (Hammond, 2015), and then c) AP from plant cells (Brownlee, 2022; Fabricant et al., 2021; Fromm, 1991; Lee and Calvo, 2023), calcium waves from d) mitochondria (Stoler et al., 2022), and finally electrical spikes from e) fungi (Olsson and Hansson, 1995) and f) bacteria (Kralj et al., 2011).

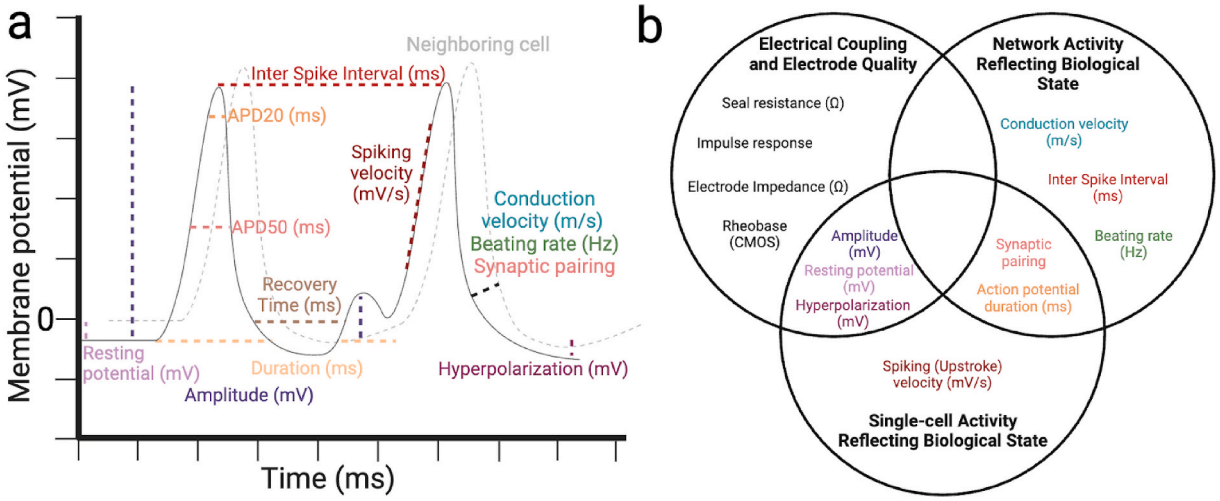

Fig. 3. Overview of spike metrics that can be extracted from modern nanobioelectronic tools for electrophysiology. a) Proposed spike metrics for intracellular-like signals nanoelectrode arrays. b) Proposed classification of spike metrics for conducting biological studies.

the amplitude and frequency of excitatory or inhibitory postsynaptic potentials. Fig. 3 below proposes a similar class of metrics that could be computed using action potentials and postsynaptic potentials from the intracellular-like signals obtained from NEAs, based on existing studies. Due to the passive electrical coupling between nanoelectrodes and overlying cells, certain metrics typically obtained during patch clamp are largely attenuated during nanoelectrode recording. Each electrode requires a separate deconvolution step using a transfer function, which accounts for each electrode's own impedance and seal resistance, to obtain the "true" voltage value being recorded (Fendyur et al., 2011; Fendyur and Spira, 2012; Hai et al., 2010; R. Liu et al., 2022). However, beyond these attenuated metrics, several others can reflect the biological state of single cells or the entire network to inform biological experiments. These metrics would reflect both the electrical coupling and biological state of the neuronal networks, including maturation, development stage, disease type, and genotypes.

In both neurons and cardiomyocytes, increases in amplitude and decreases in resting membrane potential (i.e. more negative) have been found during maturation and differentiation (Autar et al., 2021; Karbassi et al., 2020). Duration of the full spike or at its constituent percentages has also been associated with maturation in cardiomyocytes (Karbassi et al., 2020), is widely used to evaluate drug mechanisms of action (Akanda et al., 2009; Bárándi et al., 2010; Jahed et al., 2022), and is generally also considered a metric for excitability in disease models (Contractor et al., 2015; Sarkar et al., 2022). The hyperpolarization and inter-spike interval appear to relate to the minimum threshold for action potential firing and therefore excitability in neurons (Gildin et al., 2022). The spiking or upstroke velocity has been shown to indicate sodium ion availability and may relate to both maturation (Berecki et al., 2010; Lemoine et al., 2017) or disease state (Davis et al., 2012). Network metrics such as spontaneous firing and conduction velocity can also reflect the culture state, such as excitability (Autar et al., 2021) and maturity/disease state (Han et al., 2021; Kim et al., 2007). Novel electrophysiological tools which can obtain subcellular, subthreshold

signals in a multiplexed fashion across several cell types are highly coveted, and yet can be augmented through pharmacological studies. Adding drugs during recording can be used to isolate specific waveforms which correspond to certain ions or ionic cascades, revealing either mechanisms of action, or how inherent genotypic differences across different samples may cause the same drug to elicit a different spike waveform (Leyrer-Jackson et al., 2021). Below is a non-comprehensive list of drugs typically used to validate and study cell cultures during multiplexed electrophysiology. Many drugs are applied as cocktails to achieve a pronounced effect (Abbott et al., 2020; Liu et al., 2022).

2.2.3. Pancreatic beta cell action potentials

β cells, which coexist with α and δ cells in the pancreatic islet, release insulin by using APs. β cells first register increased systemic glucose when it is imported via GLUT1, and then metabolized to produce ATP (Rorsman and Ashcroft, 2018). The ATP binds and activates ligand-gated inward rectifying K+ channels embedded in the plasma membrane, decreasing K+ export, and thus depolarizing the cell and initiating an AP (Jacobson and Philipson, 2007; Thompson and Satin, 2021). During the final phase of the AP, incoming Ca^{2+} binds exocytotic vesicles which release insulin into the bloodstream (Fridlyand et al., 2013). Pharmacological ion channel inhibitors during electrophysiology can help tease out this cascade of events; for example, a 2018 study utilized optogenetics and carbenoxolone to determine the electrical coupling of β and δ cells in the pancreatic islet (Briant et al., 2018). Given the structural and functional similarities between pancreatic islet tissue and brain tissue, AP firing, and hormonal regulation (Hiller-Sturmhöfel and Bartke, 1998; Lundqvist et al., 2019), multiplexed electrophysiology could clarify pancreatic Islet network activity.

2.2.4. Plant cell action potentials, variation potentials, and system potentials

In plants, light, temperature changes, and mechanical stimulation trigger APs in single cells, enabling infection resistance, changes in respiration, transpiration, stomata opening (Sukhov, 2016), facilitating pollination, or magnetic field generation (Fabricant et al., 2021; J.-H. Li et al., 2021; Stahlberg, 2006). AP propagation in plants has been confirmed with patch clamp electrophysiology, calcium imaging, and most recently using organic electronic multielectrode arrays (Armada-Moreira et al., 2023). While it is well known that pollinators such as bees can be sensitive to both electrostatic and magnetic fields present in plants (Clarke et al., 2017; Migdał et al., 2022; Shepherd et al., 2018), it is unclear whether plant AP generation affects these electric fields and therefore the behavior of other organisms. Perhaps most interestingly, plants have evolved several types of electrical signals: the AP, the variation potential, and the systemic potential. 1) APs: A typical "AP" spike is shown schematically in Fig. 2c. While APs in animal cells typically have uniform shapes and sizes per cell type, APs in plant cells can exhibit a huge range in amplitude (10–100 mV) and duration (<1 to tens of seconds long). The threshold and refractory period requirements remain, although the main ionic contributors involve Ca^{2+}, Cl^{-}, and K^{+} (Na^{+} being toxic to plants) (Ward et al., 2009). The stimuli leading to plant APs include non-damaging events such as an electrical, light, tactile, temperature, or chemical initiators (Sukhov, 2016). 2) Variation Potentials: This potential also exhibits a wide amplitude (tens of mV) and duration (several minutes) range, but unlike the AP, has an amplitude response dependent on the stimulus size, and is not threshold-dependent. It is a localized (i.e., not self-propagating) electrical response to potentially damaging chemical or mechanical stimuli, such as changes in hydraulic pressure (i.e. through ligand-gated and mechanosensitive ion channels, respectively). 3) System Potentials: Also several minutes long, system potentials are the rarest electrical signal and not evoked by typical stimuli. They are hyperpolarizing, self-propagating potentials and thought to be brought on by hydrogen peroxide gradients (Sukhov, 2016). Plant cells propagate signals via plasmodesmata, specialized structures that form bridges across the cytosolic chambers of neighboring cells (Brunkard and Zambryski, 2019). Mudrilov et al. point out that the sedentary nature of plants may have led to the greater variety of their electrical signaling to evoke appropriate protective responses (Mudrilov et al., 2021). Many electrical signals generated by plant cells then induce calcium-regulated signaling cascades which presumably direct growth and adaptive responses to the external environment (Canales et al., 2018; Vaz Martins et al., 2013).

2.2.5. Fungi membrane potential fluctuations

Several species of fungi cells have demonstrated AP-like signals up to 20 mV, as shown schematically in Fig. 2e, in response to beech wood mechanical stimulation using patch-clamp (Olsson and Hansson, 1995), or as a consequence of root growth using extracellular subdermal needle electrodes (Dehshibi and Adamatzky, 2021). Several species of fungi exhibited depolarizations over several minutes or hours, which were then organized into "words" and "sentences" to rank signal complexity across species (Adamatzky, 2022). Pharmacological experiments are still needed to assess the ion channels involved in these signals.

2.2.6. Mitochondrial electrical activity in eukaryotic cells

Beyond harnessing the electron transport chain and proton motive force to drive ATP production, mitochondria also possess ion channels to help regulate metabolism, and are thus treated here as a separate entity responsible for electrical signaling. For example, the Mitochondrial Calcium Uniporter (MCU) channel is also located on the inner mitochondrial membrane and mediates metabolism, intracellular [Ca^{2+}], and apoptosis (De Stefani et al., 2015; Rizzuto et al., 2012). Fig. 2d demonstrates putative calcium spikes exhibited by mitochondria during these fluctuations. In sheared endothelial cells, heightened MCU Ca^{2+} transients were related to Piezo1 channel activation (Patel et al., 2022), and in neurons, mitochondria, which utilize kinesin/dynein mechanisms to traverse the length of the axon, can accumulate at synapses and buffer intracellular [Ca^{2+}] (Sheng and Cai, 2012) – a process which deteriorates during aging (Strickland et al., 2019), particularly in the presence of amyloid beta and tau protein (Calvo-Rodriguez and Bacskai, 2021). Interestingly, in contrast to mitochondria, the bacteria *L. monogytogenes* was observed using electron microscopy to propel itself along neuronal axons using polymerized actin tails (Dons et al., 2007).

2.2.7. Bacteria ionic fluctuations

The electron transfer capabilities within bacterial biofilms are typically used in industrial applications such as bioremediation (Czerwińska-Główka and Krukiewicz, 2020), drug and antibody production (Baeshen et al., 2014; Lee and Jeong, 2015), low-cost electricity generation, and biosynthetic electroactive systems (Bird et al., 2021; Milano et al., 2019; Mohammadifar et al., 2020; Wang et al., 2020). However, bacteria also use ionic fluctuations to regulate metabolism and behavior, depicted schematically in Fig. 2f. Prokaryotes (<2 μm width) have 1000x smaller volume and membrane capacitances than eukaryotes (the amount of equal and opposite charge that can be stored on either side of the membrane) (Benarroch and Asally, 2020), leading to downstream ionic effects of local electrochemical fluctuations. For instance, glutamate availability was shown to regulate K^{+} signaling in B subtilis biofilms via the yugO channel, and led to distant biofilms within the same chamber to couple their K^{+} oscillations and "time share" nutrients (J. Liu et al., 2017). Interestingly, this cyclic growth behavior has also been observed in cable bacteria, which appear to grow only during EET via an "oxygen pacemaker" (Geerlings et al., 2021). Other potassium ion channels are known to regulate metabolism as well (Krüger et al., 2020). Also, hyperpolarizations regulated by Na^{+} and K^{+} fluctuations in *E. coli* were observed to regulate antibiotic tolerance (Jin et al., 2023). It has been hypothesized that intercellular K^{+} signaling is achieved when a certain critical value of neighboring cells are depolarized, creating a conduit of electrical connectivity throughout a biofilm which affects nutrient consumption, spore formation, and biofilm growth

(Kikuchi et al., 2022; Larkin et al., 2018; J. Liu et al., 2017; Prindle et al., 2015a). Importantly, this electrical signaling is closely intertwined with quorum sensing. Bavaharan and Skilbeck outlined a genetic pathway linking quorum sensing to electrical signaling in B. subtilis (Bavaharan and Skilbeck, 2022). In fact, other researchers have demonstrated how electric fields can influence genetic circuits in bacteria, enabling "toggle switch" biointerfaces (Grozinger et al., 2023). The gold standard method to record K+ fluctuations in B subtilis, Thioflavin T, has also detected EET-related membrane fluctuations (Pirbadian et al., 2020). No study has been conducted yet to correlate K^+ and EET oscillations measured using ThT. Notably, the bacteria *G. sulfurreducens* not only exhibits EET, but also shows slowed biofilm growth in the presence of tetraethylammonium, a K^+ channel blocker (Jing et al., 2020). Metrics such as conduction velocity, length of electrical conduits across a network, and electrical refractory period would enable network characterization not only for biofilm-forming bacteria, but also for mitochondrial networks (Hoitzing et al., 2015; Zamponi et al., 2018), which possess "social" behavior in their intracellular communication with surrounding organelles (Picard and Sandi, 2021; Xia et al., 2019).

2.2.8. *Protista action potentials*

Protists fire APs in response to external stimulation or mechanical actuation. The marine diatom *Odontella sinensis* displayed increased spiking behavior after a fast sodium/calcium mediated AP was induced by contact from an external probe (Taylor, 2009). *Paramecium* uses APs to direct movement (Schlaepfer and Wessel, 2015), which has been observed by using both the hanging droplet method to pin a motile cell down, and a micro-hole based device (Kulkarni et al., 2020). The emergence of cilia in protists is thought to have contributed to the modern eukaryotic AP (Brunet and Arendt, 2016).

2.2.9. *Archaea ion channel activity*

Archaea are used industrially as biocatalysts for waste treatment, pollutant degradation, and mineral processing (Schiraldi et al., 2002), but have also been found in the gut. Methanogenic gut archaea have harnessed Na^+ flow to minimize the energy needed to drive an altered ATP synthase (Mayer and Müller, 2014). Archaea share similar ion channel structures with bacteria and eukaryotes. In fact, archaeal proteorhodopsins were found to localize to the eukaryotic plasma membrane, but bacterial proteorhodopsins could not (Kralj et al., 2012).

2.2.10. *Virus ion channels and mechanisms for ion channel disruption*

Viruses contain DNA encoding their own primitive ion channels called viroporins, which, when expressed, alter the host cell membrane permeability to enable viral assembly and replication (Nieva et al., 2012). It is thought that viroporins reduce electrostatic repulsion between "pinching" ends of a virus-induced, budding patch of plasma membrane by dissipating the membrane surface charge, facilitating viral entry. Additionally, viral infection has been shown to upregulate membrane contact site proteins, which tether organelles together, spaced around 30 nm apart. These membrane contact proteins are involved in pathways such as endoplasmic reticulum-mediated calcium transfer (Song et al., 2023). While the exact mechanisms are unknown, viroporins are highly specific. For example, the M2 channel from the Influenza A Virus (IAV), which maintains virus pH during cell entry and aids in viral maturation (Pielak and Chou, 2011), putatively employs a mechanism known as the "proton wire hypothesis", in which protons jump along a chain of water and histidine molecules inside the channel core (Pohorille et al., 2005) to enable downstream cascades. Beyond proton transport, viroporins also dysregulate intracellular calcium stores and voltage-gated Ca^{2+} channel activity to favor viral replication, assembly, and evasion. However, the line between an ion-dysregulating viroporin and a viral protein is unclear. Zhu et al. found increased Ca^{2+} absorption in cardiomyocytes infected with the SARS-CoV-2 Nsp6 protein (Zhu et al., 2022), which has yet to be confirmed as a viroporin (Fung et al., 2015). Hepatitis B protein X (HBx) alters intracellular calcium through the inositol triphosphate (IP3) pathway, in which calcium binds an endoplasmic reticulum (ER) calcium channel and is released into the cytosol (Bohmwald et al., 2021). While HBx is not structurally considered a viroporin, its effect on membrane permeabilization was reversed using a viroporin inhibitor. Scientists have proposed an ion passage mechanism similar to that of the cytochrome C protein (Lee et al., 2018). Herpes Simplex Virus 2 (HSV-2) infection reduces Cav 3.2 T-type Ca^{2+} channel expression in ND7/23 sensory-like neurons, altering neuronal excitability (Bohmwald et al., 2021). Leakage of internal calcium stores also facilitates viral gene expression (Nieva et al., 2012), and the rotavirus protein NSP4 alters intracellular cytosolic [Ca^{2+}]. The HIV protein Nef prevents Ca^{2+} channel domains from forming in host T cells, and, due to an unknown mechanism, the Human Respiratory Syncytia Virus (hSRV) induces syncytia formation by altering intracellular [Ca^{2+}]. Beyond dysregulation, a weakly selective viroporin for both Na^+ and K^+ in hSRV, and a pentameric viroporin for Ca^{2+} in SARS-CoV, both activate the NLRP3 inflammasome, an intracellular protein sensor which instigates multiple inflammatory signal cascades (Bohmwald et al., 2021; Swanson et al., 2019). Ion channel blockers have not only reduced viral entry and replication in host cells but can also simulate viroporin expression. Specifically, the effect of HIV on VGCCs in dendritic and natural killer cells was similar to that of multiple VGCC blockers and also led to increased TNF-alpha production and neurotoxicity (Bohmwald et al., 2021). Viruses also hijack ion channels in both electrogenic and immune cells to alter excitability (Chaigne-Delalande and Lenardo, 2014).

3. Measurement and modulation of membrane potential: challenges and tools

This section will discuss the current techniques for multiplexed, single-cell electrophysiology using both electrical and optical tools. The schematic in Fig. 4 below demonstrates the ideal optical and electrical probe behavior for parallelizable sub- and intracellular electrophysiology.

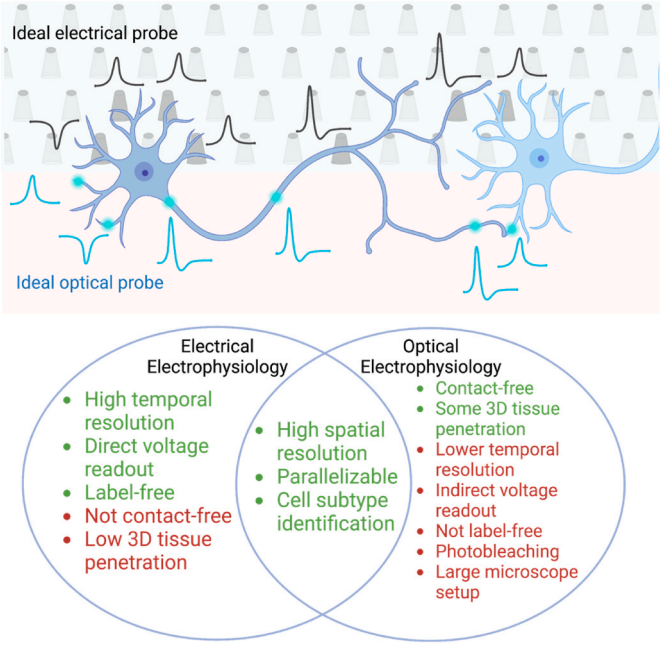

Fig. 4. Summary of available optical and electrical electrophysiological techniques for parallelized *in vitro* recording, as well as a schematic of the ideal probe features.

3.1. Electrical tools for measurement and modulation

3.1.1. Types of nanostructures and acquisition of intracellular signals

The holy grail of electrophysiology is to measure electrical signals across subcellular compartments from thousands of cells at once, and then to relate these signals directly to metabolic activity and organism behavior. Since the 1940s, scientists have developed micro- and nanoscale probes for such recordings, summarized below for microelectrodes in Fig. 5, and for nanoelectrodes and nanotransistors in Fig. 6. Current state-of-the-art intracellular electrophysiology is best achieved by using patch clamp or nanoelectrode arrays (NEAs). NEAs contain myriad nanostructures to improve the physical seal between electrodes and cells, with guidelines for design detailed previously (Elnathan et al., 2022). NEAs can be classified into 3 categories: (1) those inducing positive membrane curvature at the electrode tip like patch clamp, such as nano-volcanoes (Desbiolles et al., 2019), nanotraps (Xu et al., 2022), nanostraws (Shokoohimehr et al., 2022), and nanocrowns (Jahed et al., 2022), (2) those inducing blunt negative membrane curvature, such as nano-mushrooms (Ojovan et al., 2015), and nanopillars (Abbott et al., 2020; Dipalo et al., 2017, 2021), and (3) those inducing penetrative negative membrane curvature such as ultrasharp nanowires (R. Liu et al., 2022) and self-folding, lipid-coated probes (Duan et al., 2011; Gu et al., 2022). *Intracellular access.* Except for category 3, these technologies often require a short (microsecond), few-volt (2–5 V) electroporation pulse to transiently permeabilize the membrane and allow the electrode access to intracellular ions. This shifts the recording from an extracellular signal to an intracellular one. The electroporation pulse is distinct from the stimulation pulse (millisecond long and mV range) commonly applied to electrogenic cells on microelectrode arrays to induce signaling, pace their firing rates (Jahed et al., 2022), or even transfect cells, by using a 1000x smaller pulse than that used for bulk electroporation (Liu et al., 2020; Zhang et al., 2020; Zu et al., 2016). *Surface functionalization.* In most cases, culturing cells on devices requires coating with extracellular matrix-derived proteins to promote cell adhesion and survival. The most common proteins used are Matrigel, poly-L/D-lysine, laminin, and poly-ornithine (Abbott et al., 2020; Jahed et al., 2022; R. Liu et al., 2022; Trujillo et al., 2019). This few-nm-thick layer helps cells heal after enzymatic digestion and/or harsh plating procedures, and also promotes remodeling of the extracellular matrix over time to enable tighter cell-nanoelectrode coupling. Specific protocols depend on the device passivation material, cell culture conditions (temperature, gas flow, humidity), and the seeding density. Therefore, this process must be optimized before recording.

3.1.2. Signal attenuation and distortion

NEAs cannot yet recapitulate the "true" AP amplitude obtained using patch clamp. This is because each nanostructure is accompanied by a transfer function which can be determined by the circuit describing the cell/nanoelectrode interface. This transfer function can cause amplitude attenuation, spike broadening, and filtering due to losses in the circuit (R. Liu et al., 2017). Characterizing these losses through validation experiments is important since deconvoluted signal waveforms and amplitudes are critical for cell type and species identification (Clauss et al., 2019; Lin et al., 2017). Moreover, the density of different ion channels within any given "patch" of membrane varies not only across cell types but also across subcellular locations (Abriel et al., 2015; Århem et al., 2006). The "true" amplitude can be partially retrieved through Pt Black, PEDOT:PSS, or graphene treatment to increase nanoelectrode surface area, decrease impedance, but maintain form factor (Abbott et al., 2020; Dipalo et al., 2021). The adaptation of CMOS chips with nanoelectrodes to provide in-house signal amplification and current injection (Abbott et al., 2020) has enabled recording highly accurate waveforms for parallelized validation experiments.

3.1.3. Probe parameters

Up until now, nanoscale probes have only succeeded in tightly coupling with "large" eukaryotic cells such as cardiomyocytes and neurons. It is not yet clear how such probes interact with ultrasmall (<2 μm), sub-neuronal structures like boutons, mitochondria, or bacterial cells. This is partially due to the difficulty of isolating and culturing these structures on a flat surface. Such structures might benefit from ultrasmall (<100 nm), ultrastiff, high surface area probes which maintain low impedance but can deform and penetrate a thicker membrane. Towards this goal, Pulingam et al. observed mechanical wrapping of graphene oxide around *S aureus* and *E faecalis*, but membrane disruptions in *E coli* and *P aeruginosa* (Pulingam et al., 2019), suggesting that membrane properties of different bacteria would affect the optimal probe parameters. Beyond probe size, the spatial electrode layout is an important consideration. Three-dimensional (3D) NEA would better represent native cellular architectures. Self-folding (Kalmykov et al., 2019), shell-like (Huang et al., 2022), or cyborg (Li et al., 2019; Lin et al., 2023) MEAs for monitoring organoid development have initiated these studies. Soft bioelectronics such as mesh electrode implants and flexible CMOS arrays hold potential for 3D electrophysiological mapping *in vivo* (Zhao et al., 2023; Zhou et al., 2017).

3.1.4. Validation across different cell types

During recording, the visible beating rate of muscle cells can be correlated to spike timing to identify APs. Validation of electrical, not mechanical, recording is possible through the addition of blebbistatin to the sample. However, non-beating cell types such as neurons, pancreatic beta cells, and bacteria require electrical stimulation, fluorescence voltage indicators, excitatory/inhibitory chemicals (Galera-Laporta et al., 2021; Q. Liu et al., 2022), mechanical (Bruni et al., 2017) or photothermal stimulation (Rastogi et al., 2020a; Xie et al., 2021) to discern cell-induced signals from noise. Other validation techniques

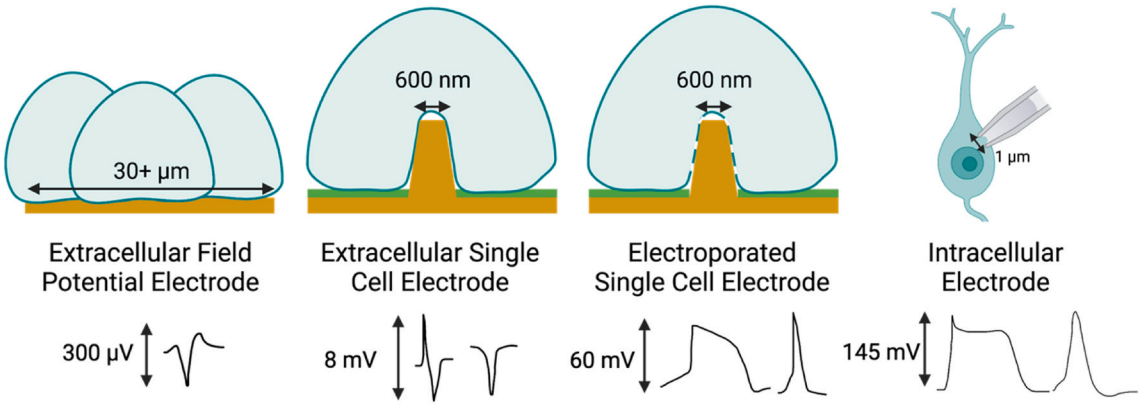

Fig. 5. Comparison of signal amplitude using various types of micro and nanoelectrodes (Abbott et al., 2020; Buzsáki et al., 2012; Jahed et al., 2022; Xie et al., 2012).

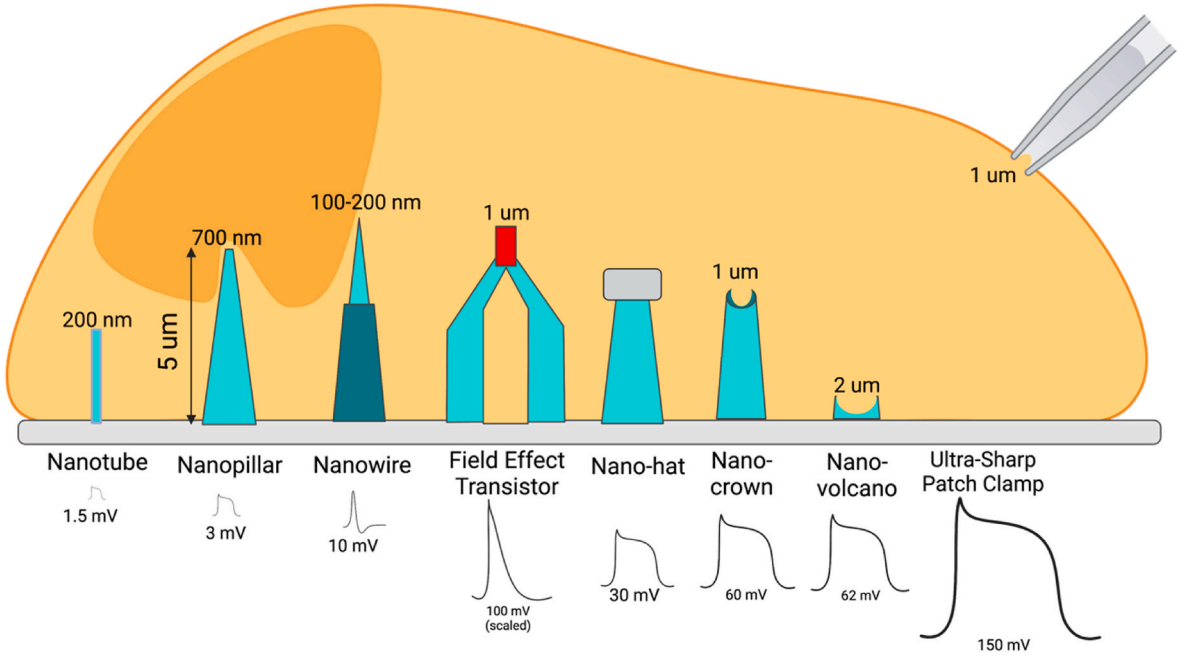

Fig. 6. Nanoscale probes for single-cell electrophysiology (Desbiolles et al., 2019; Gu et al., 2022; Jahed et al., 2022; Lin et al., 2017; R. Liu et al., 2022; Ojovan et al., 2015; Peter et al., 2016, p. 201).

include identifying plausible spike time delays between channels, spike duration and frequency spectrograms, and mapping network activity. NEAs can enable the mapping of synaptic connections across 1000+ channels (Abbott et al., 2020). However, electrical or electrochemical sensing within pancreatic beta cells (Alassaf et al., 2020) and bacteria biofilms might better clarify interrelationships between chemical and electrical signaling.

3.1.5. *Impedance-based methods to study electrical signaling*

An emerging subfield of bioelectronics involves measuring not only single-cell electrical signals, but also population-wide electrical fields to study growth, proliferation, composition, and cell type distributions (Abasi et al., 2022). Recently, Maino et al. reported a deconstructed single cell/nanovolcano interface to compare impedance differences between bare and covered nanoelectrodes across multiple cell types (Maïno et al., 2023). This study could lead to real-time tools for assessing the seal quality during intracellular recordings. Beyond single-cell nanoelectrode arrays, organ-on-a-chip advancements now include impedance-based measurements. Organ-on-a-chip platforms are accelerating discoveries about cell-cell communication by facilitating co-culturing systems with embedded micro- and nanoscale biosensors, and will be the ideal technologies for investigating interkingdom, multicellular interactions (Ingber, 2022; Leung et al., 2022; Zhang et al., 2018). Abasi et al. recently proposed a platform for parallelized trans-epithelial electrical resistance (TEER) measurements to influence single cell gene expression using external electric fields (Abasi et al., 2020). The authors coined the term "electromics" to describe how single-cell gene expression changes in response to externally applied electric fields, and found that expressions of YAP, a nucleus-localized protein associated with cellular growth and development ("YAP1 Yes1 associated transcriptional regulator [Homo sapiens (human)] - Gene - NCBI," n.d.), and CD144, an intercellular adhesion molecule ("CDH5 cadherin 5 [Homo sapiens (human)] - Gene - NCBI," n.d.), depended on electric field frequency and voltage (Abasi et al., 2023).

3.2. *Optical Methods for Measurement and modulation*

Optical electrophysiology provides an optimal approach for studying the activity of ultrasmall membrane-enclosed structures. For instance, microelectrode arrays produce low SNR recordings of bacteria (Masi et al., 2015), and patch clamp gives inconsistent values for membrane potential, such as −130 mV in giant *E. coli* (Felle et al., 1980, p. 198) and −70 mV in membrane vesicles (Ramos et al., 1976). In fact, the patch clamp microelectrode cannot even penetrate thick membranes such as the bacterial cell wall. Contrastingly, Nernstian potential dyes such as Thioflavin T, which accumulates at the negatively-charged inner membrane and fluoresces at lower potentials (Prindle et al., 2015b), genetically encoded voltage indicators (GEVIs), and genetically encoded calcium indicators (GECIs) have measured bacterial biofilm oscillations (J. Liu et al., 2017), the metabolic effects of ion flow in single bacteria (Jin et al., 2023; Kralj et al., 2011; Luder et al., 2021), calcium transients in mitochondria (Fernandez-Sanz et al., 2019; Krstic et al., 2022), and the metabolic effects of ion flow in chloroplasts (Pottosin and Dobrovinskaya, 2015). Despite these impressive advancements and the widespread application of voltage-sensitive dyes to decode eukaryotic, electrogenic cellular networks (Göbel and Helmchen, 2007; Kuchibhotla et al., 2008; Lin and Schnitzer, 2016), current optical sensors cannot provide sub-millisecond temporal resolution of bioelectronic devices due to diffusion and photon generation limitations (Scanziani and Häusser, 2009).

Nevertheless, optical modulation, a powerful tool for manipulating network activity, is typically achieved using optogenetics, in which photosensitive channelrhodopsins are embedded into cells and then activated by light to induce APs. Type 1 rhodopsins found in bacteria and archaea have been tuned for optogenetics experiments (Boyden, 2015; Boyden et al., 2005), while Type 2 rhodopsins are found in mammalian photoreceptor cells to enable vision (Jung, 2007). Photothermal stimulation can also trigger cellular firing by illuminating surface-level nanoparticles with lasers to induce local changes in membrane capacitance and thus permeability (Rastogi et al., 2020b). The orthogonality of these modulation techniques with both optical and electrical recording methods presents an exciting opportunity for simultaneous recording and modulation of *in vitro* and *in vivo* biological systems.

3.3. Other measurement and modulation methods

Recently, electrochromic thin films were shown to record APs from cardiomyocytes, hippocampal and dorsal root ganglion neurons, and brain slices (Alfonso et al., 2020). Despite offering indirect voltage readouts, this technology could provide spatial maps of ultrasmall cells such as bacterial biofilms and mitochondrial networks. Both atomic force microscopy and scanning ion conductance microscopy can also indirectly measure APs or surface charge distribution in cardiomyocytes or bacterial cells (Caluori et al., 2019; Cremin et al., 2020).

4. Evidence and implications of inter-kingdom electrical communication

Studies of inter-species and inter-kingdom electrical communication are slowly emerging. For example, Chiu et al. observed altered excitability in nociceptive neurons upon exposure to the supernatant of *S. aureus* (Chiu et al., 2013), "exoelectrogenic" gut microbes have recruited lymphocytes by producing current in lieu of chemical attractants (Ericsson et al., 2015), and gut microbiota were shown to modulate enteric neuron excitability (Darch and McCafferty, 2022; Savidge, 2016; Yarandi et al., 2020). The gut houses biofilms of myriad bacterial species (Mark Welch et al., 2017) which produce autoinducers and their secondary metabolites, dopamine and serotonin, that interact with host cells, providing perhaps the most accessible environment to study interspecies communication (Bonaz et al., 2018; Federle and Bassler, 2003; Han et al., 2022; Yang and Chiu, 2017). Using organs-on-a-chip, it is possible to probe gut epithelial cells, enteric neurons, and gut microbiota within one microfluidic system (Jalili-Firoozinezhad et al., 2019). Importantly, not only could organs-on-a-chip technology enable the recording of interspecies electrophysiology, but it ultimately should include multi-modal readouts of several orthogonal means of cell-cell communication using a variety of biosensors (Aydogmus et al., 2023; Forro et al., 2021, 2021, 2021; Liu et al., 2023; Maoz et al., 2017; Song et al., n.d.). However, an ionic signaling connection across species is not well studied. While multiple bacterial species rely on ionic signaling for endogenous biofilm formation (Lundberg et al., 2013), biofilms can also recruit bacterial cells from other species using potassium ions (Humphries et al., 2017). Also, bacteria co-cultures synergistically form biofilms and produce greater electron flow compared to single cultures (Islam et al., 2020; Sadiq et al., 2021). Table 2 below describes interspecies ion channel signaling and EET across bacterial species.

Understanding network electrical behavior across kingdoms may benefit from an evolutionary perspective. The endosymbiont theory posits that eukaryotes absorbed ancient prokaryotes to create certain membrane-enclosed organelles such as mitochondria and chloroplasts (Stratford et al., 2019). Ion dysregulation in these putative prokaryotes can induce neighboring organelle and host cell and organism dysfunction (Carraretto et al., 2016). In fact, the role of mitochondria in the inflammatory response has been compared to that produced by bacterial infections (Ponnalagu and Singh, 2020). Other clues suggest sharing of electrical mechanisms across kingdoms. For example, the enzyme which produces the neurotransmitter GABA is an ancient signaling molecule first employed by prokaryotes (Ram and Lo, 2018), and the neurotransmitter glutamate is a necessary nutrient for biofilm formation (Newton et al., 2016). Furthermore, quorum sensing in Gram negative bacteria involves cytoplasmic receptors, while in Gram positive bacteria, which demonstrate biofilm-wide electrical oscillations, involve membrane receptors much like those in neurons (Neu et al., 2022).

Table 2
Interspecies chemical and electrical intercommunication. Intermode communication within the same species is shown in the bottom left. Intermode communication across different bacterial species is shown in the top right.

	Quorum Sensing	Ion Transmission	EET
Quorum Sensing	*P aeruginosa* and *S aureus* are affected by the same autoinducer (Jiang et al., 2022).	Unknown	Unknown
Ionic Signaling	Electrical signaling tied to quorum sensing (Bavaharan and Skilbeck, 2022).	*P aeruginosa* cells attracted to *B subtilis* biofilms through K^+ signaling (Humphries et al., 2017).	Unknown
Electron flow	EET is enhanced by altering *S. oneidensis* metabolism through quorum sensing (Li et al., 2020).	EET is correlated to membrane potential oscillations in *S. oneidensis* (Pirbadian et al., 2020).	Direct interspecies electron transfer is mediated by hydrogen (Dubé and Guiot, 2015).

5. Future perspectives

The development of a high-throughput platform which can reliably record subcellular, subthreshold, multiplexed electrical and chemical activity across 3D cultures with high spatiotemporal resolution will open a gateway to cross-kingdom studies of bioelectricity. At the heart of this platform lies platforms for iterating through nanostructure designs to enable non-invasive, high seal resistance deformations of phospholipid bilayer membranes (Capozza et al., 2018; Lou et al., 2018). Through such studies, a universal theory of electrical signaling can enable novel therapies, such as the transplantation of xeno-ion channels to curb disease (Nguyen et al., 2022), high throughput nano-transfection platforms (Kim et al., 2007), limb regeneration (Park et al., 2012; Sousounis et al., 2020), or even multi-target electrogenetic implants (Huang et al., 2023). Today's *in vitro* nanoelectrode arrays and optical bioelectrical sensors may eventually be used to measure single-cell function *in vivo*. Current clinical electrophysiological tools lack the spatial resolution needed to match chemical sensing modalities such as single-cell RNA sequencing or mass spectrometry; however, single cell electrophysiology is needed to infer how disease, environment, and therapeutics affect electrogenic cell populations. High-throughput, non-invasive technologies such as MRI, near-infrared spectroscopy, ultrasound, electroencephalography (EEG), electrocorticography (ECoG), *in vivo* microelectrode arrays and electromyography are blind to subcellular, intracellular data and can only attempt to reconstruct single-cell spikes from local field potentials (Dipalo et al., 2021; Fromm, 1991; Olsson and Hansson, 1995; Stoler et al., 2022). While probe size reduction provides higher spatiotemporal resolution, the invasiveness of nanoelectrodes precludes their clinical application today, as illustrated in Fig. 7. Moreover, the stark difference observed in size and outgrowth between cortical neurons grown in a dish vs in a three-dimensional organoid suggests that the first step toward *in vivo* nanobioelectronics would be subcellular depth recording (Revah et al., 2022).

6. Summary and conclusions

In this review we have discussed evidence of electrical signaling in diverse cellular networks across different biological kingdoms, as well as tools for recording these behaviors. When attempting to build a universal probe for intracellular electrophysiology, the cell size and energy requirements present two major constraints on the probe size, surface area, and amplification requirements. This problem was solved in the 20th century by simply using cell types from a larger species or by digesting inflexible cell walls; however, this approach cannot be extrapolated to all kingdoms. Moreover, the varying subsets of ionic and electronic signaling pathways employed by cells within different kingdoms require further pharmacological and network-level studies (i.e., involving simultaneous voltage- or calcium-sensitive imaging) beyond probe optimization. These multi-pronged experiments will enable characterization of electrical signaling across kingdoms by obtaining relevant metrics such as spike duration, frequency, amplitude, and ionic

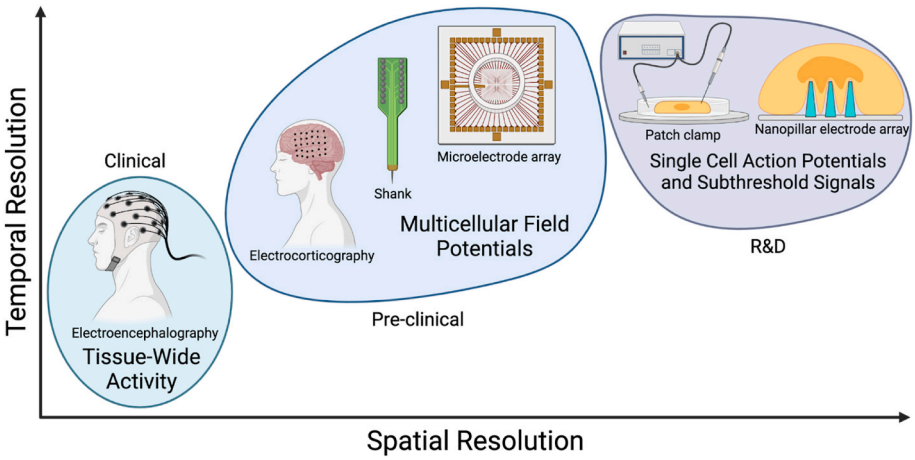

Fig. 7. Clinical relevance of electrical recording technologies containing low to high spatiotemporal resolution.

source. The ultimate goal of this systematic characterization is to discern cell types during inter-kingdom electrical signaling events, so that future technologies can construct and maintain ecosystems which contain multiple electrogenic species. Due to advances in recording electrical activity across spatiotemporal scales, electrophysiology is becoming increasingly relevant in studies discerning the fundamental biological laws governing cell-cell communication, as well as in developing biometric sensors to understand how pathophysiologies emerge.

CRediT authorship contribution statement

Shivani Shukla: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Colin J. Comerci:** Conceptualization, Writing – review & editing. **Gürol M. Süel:** Conceptualization, Writing – review & editing. **Zeinab Jahed:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Nothing to declare.

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Data availability

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

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