Acta Biomaterialia 97 (2019) 116–140

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

Review article

Electrophysiological-mechanical coupling in the neuronal membrane and its role in ultrasound neuromodulation and general anaesthesia

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ARTICLE INFO

Article history:
Received 28 January 2019
Revised 20 July 2019
Accepted 23 July 2019
Available online 26 July 2019

Keywords:
Neuroscience
Cell multiphysics
Neuromodulation
Transcranial ultrasound stimulation
Anaesthetics

ABSTRACT

The current understanding of the role of the cell membrane is in a state of flux. Recent experiments show that conventional models, considering only electrophysiological properties of a passive membrane, are incomplete. The neuronal membrane is an active structure with mechanical properties that modulate electrophysiology. Protein transport, lipid bilayer phase, membrane pressure and stiffness can all influence membrane capacitance and action potential propagation. A mounting body of evidence indicates that neuronal mechanics and electrophysiology are coupled, and together shape the membrane potential in tight coordination with other physical properties. In this review, we summarise recent updates concerning electrophysiological-mechanical coupling in neuronal function. In particular, we aim at making the link with two relevant yet often disconnected fields with strong clinical potential: the use of mechanical vibrations—ultrasound—to alter the electrophysiogical state of neurons, e.g., in neuromodulation, and the theories attempting to explain the action of general anaesthetics.

Statement of Significance

General anaesthetics revolutionised medical practice; now an apparently unrelated technique, ultrasound neuromodulation—aimed at controlling neuronal activity by means of ultrasound—is poised to achieve a similar level of impact. While both technologies are known to alter the electrophysiology of neurons, the way they achieve it is still largely unknown. In this review, we argue that in order to explain their mechanisms/effects, the neuronal membrane must be considered as a coupled mechano-electrophysiological system that consists of multiple physical processes occurring concurrently and collaboratively, as opposed to sequentially and independently. In this framework the behaviour of the cell membrane is not the result of stereotypical mechanisms in isolation but instead emerges from the integrative behaviour of a complexly coupled multiphysics system.

Contents

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https://doi.org/10.1016/j.actbio.2019.07.041

1. Introduction

The Hodgkin–Huxley (H-H) model was first proposed in 1952 to phenomenologically describe the evolution of the action potential (AP) in the squid giant axon membrane [141]. It has since become one of the theoretical pillars of modern neuroscience. While it incorporates some mechanistic elements, e.g., the opening probabilities of ion channel gates, its strength resides in its ability to mathematically capture the cell membrane's electrophysiology without the need to delve into the underlying mechanistic details.

In parallel to the work of Hodgkin and Huxley, other efforts have taken the opposite approach by focussing instead on the understanding of these mechanisms. With little access to the biochemistry of lipid bilayers and ion channels, the mechanical behaviour of axons during AP propagation first came into scrutiny. Both slow [163] and rapid [154] mechanical changes were initially observed to accompany the AP propagation. While the former has been attributed to long term cytoskeletal reorganisation, the latter hinted at a mechanical vibration coupled and in phase with the AP. Although this observation has been made and confirmed multiple times since the 1940's [97,185,153,139,290,295,118,286,24,335,133], it has generally attracted little attention, remaining mostly marginalised by the core neuroscience community and the large international initiatives.

A body of evidence gathered over half a century shows that local mechanical changes in the membrane propagate along with the AP in neurons. These observations effectively point towards the hypothesis that the AP is not merely an electrical pulse, but a more complex multiscale electro-mechanical process that affects and is affected by all components of the membrane. All the theoretical models currently being developed to capture and explain the experimental observations bring to the forefront the importance of an often overlooked aspect of the biology of neural membranes in particular, and neurons in general: their mechanical properties [242,335,133,81]. These models have chiefly persisted as an intriguing but peripheral academic niche activity.

More recently, due in part to the emergence of new experimental techniques that allow to measure and alter the mechanical properties of membranes and living cells in physiological environments, research interest in the role of mechanics of the neuronal membrane has grown rapidly, essentially driven by its potential in medical applications. For example, an application that has been building up momentum over the last decade is the use of high frequency mechanical vibrations (ultrasound) to modulate neuronal activity. The use of ultrasound for neuromodulation is expected to find direct applications in the treatment of epilepsy and chronic pain, to promote neuroplastic repair mechanisms for post-stroke recovery, and even to enhance the delivery of drugs

across the blood brain barrier [162,197,21,228]. Nonetheless its intrinsic mechanisms remain paradoxically unexplained. The incorporation of membrane mechanical properties in general theories could also be key to solve the hitherto unsolved conundrum of the mechanisms underpinning anaesthetics, a problem that has now lingered without a completely satisfactory explanation for a century. A new approach that incorporates mechanical aspects of the actions of anaesthetics could lead to individualisation of current treatments, prevention of undesirable interactions with other drugs, as well as inspire the design of new anaesthetics.

This review aims at highlighting the current convergence of (often disjoint) disciplines around the 'multiphysics' nature of neuronal membranes as supported by current biological evidence. In this context, multiphysics means the coupling of diverse physical properties. In particular, we present the current state of the art in mathematical and numerical modelling of electrophysiological-mechanical coupling while emphasising its use as a step-change in the advancement of new medical applications, currently developed in a costly and slow empirical fashion. Finally, we leverage such philosophy in the context of two clinical applications: ultrasound neuromodulation and anaesthetics.

Section 2 reviews the relevance of mechanics in the brain functions, both at the tissue level and cell level. Section 3 focusses on the electro-mechanobiology of the neuronal cell membrane in light of experimental biological evidence. Sections 4 and 5 build on Section 3 by discussing these theories in the context of ultrasound-driven neuromodulation and anaesthetics, respectively. Section 6 discusses the future prospects and Section 7 concludes this review.

2. Mechanics in brain biology

2.1. From brain to cell: A multiscale journey

The brain is a hierarchically constructed soft matter structure and thus propagates mechanical signals as a viscoelastic material [83,108,215]. Said otherwise, mechanical energy is both elastically stored and viscously dissipated (e.g., as heat) as it is deformed, resulting in characteristic response times at different spatial scales for different structures. Rodent and human brains have been described as having estimated elastic moduli in the range of 0.1–16 kPa [83,108,215]. By comparison, other tissues in the body have higher elastic moduli and are more rigid than brain tissue. For example, bone is recognisably stiffer than neurons and its moduli, in the range of 14–30 GPa [214], whereas less rigid connective tissues and arteries are in the range of 0.1–1 MPa, while even softer muscle have an elasticity within 10–100 kPa [214]. Other studies using magnetic resonance or ultrasound methods have estimated the stiffness of tissues by imaging their responses to (shear) sound waves propagated through the body [169,199]. For instance, magnetic resonance elastography has been used to characterise and map the viscoelastic properties of the human brain [169,199], showing that the stiffness of brain regions varies substantially in healthy humans and that mechanical properties change with age and disease state [224,269,323], as they arise from the interactions of their cellular and extracellular components.

Mechanical interactions at the cellular and subcellular levels are an intrinsic part of the biological functions of the brain (and any other living organ or system), see Fig. 1-a—c. Forces within the brain regulate cellular activity [137,307]. Propagation of forces and mechanical interactions between intra- and extra-cellular structures such as the cell membrane (including lipids, ion channels and other membrane associated proteins), the cell cytoskeleton (composed of filamentous protein polymers including actin, microtubules and neurofilaments), the extracellular matrix (comprising molecules such as collagens, glycosaminoglycans, proteoglycans, and glycoproteins) and cell adhesion transmembrane proteins (e.g., cadherins, integrins, immunoglobulins, proteoglycans, and selectins) influence several neural activities such as ion channel activation [17], synaptic vesicle clustering [278] neurotransmitter release [48], and axonal growth cone dynamics [280]. Probing the mechanical properties of individual cells has become possible through the advancement of various techniques, including magnetic twisting cytometry [70], atomic force microscopy (AFM) [123], micropipette aspiration [140], optical tweezing and stretching [120,334] and microplate rheometry [297]. AFM has been used to examine the response of neuronal cells [282]. Previous work has reported dynamic mechanical measurements on single neurons with measurements conducted in the linear infinitesimal strain regime only [29], so as to characterise some of the local viscoelastic properties of neuronal cells. Furthermore, the elastic storage and viscous loss moduli were extracted from the force–displacement output of oscillating $3\,\mu$m spherical AFM probes actuated to small indentation depths at the cell surface [29]. Several types of living neurons and neuronal tissues have been measured with AFM. Living rat hippocampal slices have been measured by large sphere-tipped AFM cantilevers ($25\,\mu$m). It was found that elasticity between 50 and 300 Pa depended on the region of the cell being measured [83]. For example, measurements in CA3 regions (Cornu Ammonis area 3 of the hippocampus) yielded stiffer average measurements (230–300 Pa) than those taken in CA1 regions (~ 170 Pa and ~ 200 Pa). Furthermore, living explants of the foetal rat cortex demonstrated similar values as for the hippocampal slices, with an average of approximately 300 Pa measured with a $2.5\,\mu$m sphere-tipped probe [232]. In addition, the hippocampal and retinal neurons were measured at various indentation frequencies where an increase in the measured elastic modulus was observed with an increase in indentation frequency [192]. AFM measurements of neuronal cells are typically taken at substantially lower indentation frequencies to limit viscoelastic effects. One study showed that cells respond with an almost ideal elastic response at very low force (30 pN or less) and that, at larger forces, the measured elasticity depends on the loading rate [229]. For larger forces, the dependence of the measured elasticity on the loading rate was minimised by choosing softer cantilevers, smaller maximum force values, and by minimising the cantilever loading rates used [229].

Going down in size to subcellular structures (cytoskeleton, extracellular matrix, cell membrane) and proteins, a new level of biological complexity emerges. Mechanically active structural networks connect the extracellular and intracellular spaces using micro- and nanoscale molecular architectures. This network comprises redundant and embedded networks whose complex viscoelastic properties allow mechanical signals to propagate, be dampened or directed to specific cells. Cells can respond to them by, for example, conversion to biochemical activity such as gene expression (mechanotransduction) during morphogenesis, growth and survival, among others. Several medical conditions including stroke, migraine and cerebral oedema have been associated with cellular mechanotransduction [145]. Similarly, a variety of neural functions have been linked to mechanotransduction: for example, mechanical activity mediated by integrins is key to the formation and regulation of the synapse morphology and maturation [28]. Similarly, synaptic plasticity [328] and remyelination of damaged white matter [236] are also linked to mechanotransduction events.

2.2. From cell to membrane: A multiphysics gateway

2.2.1. Membrane as a multiphysics scaffold

The cell membrane is a highly specialised compartment, which acts as a multiphysics scaffold holding many essential cellular functions including transport of molecules, communication, and

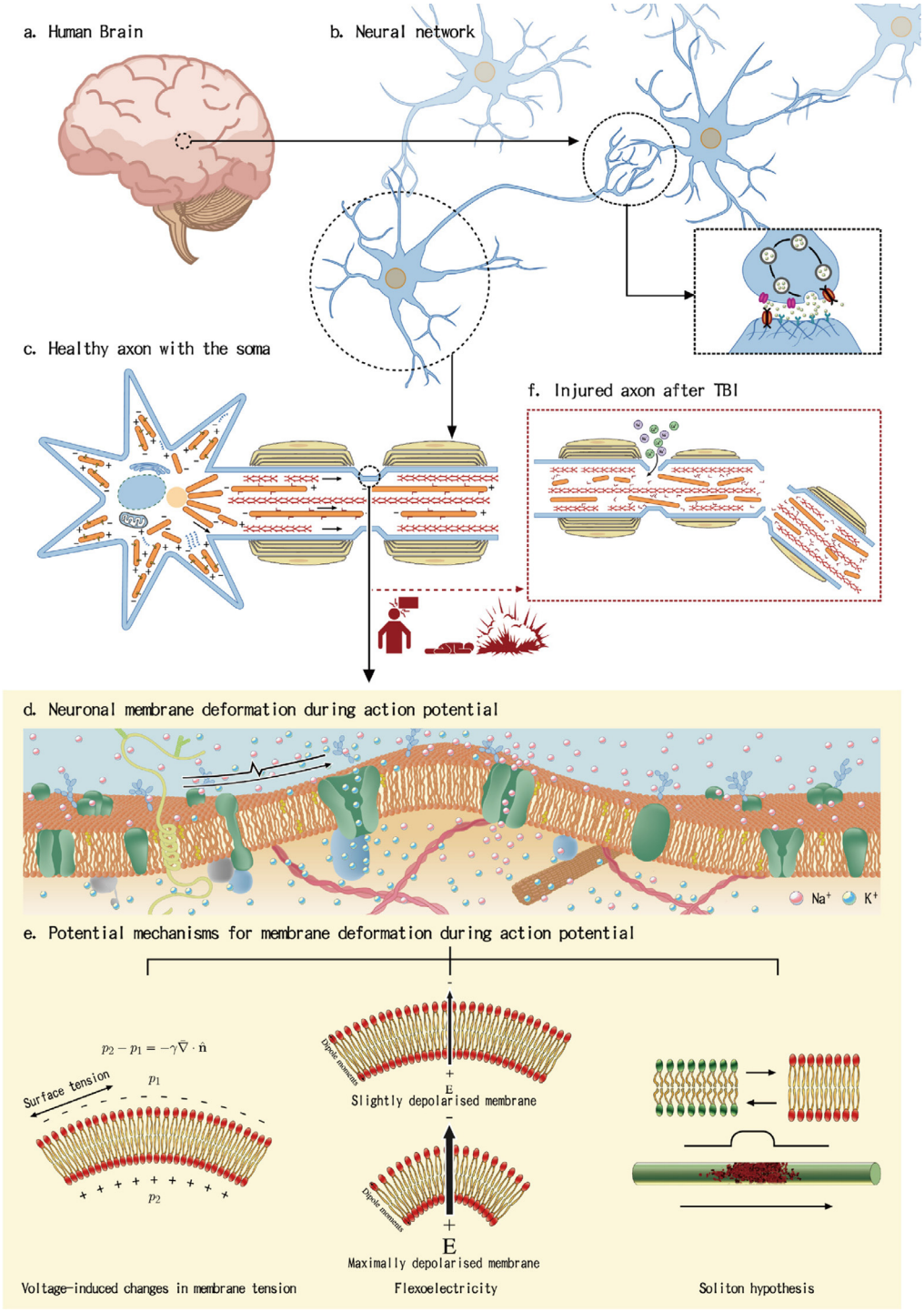

Fig. 1. The multiscale mechanics of the healthy brain (a: organ, b: neural network, c: neuron, d: membrane), the electrophysiological-mechanical coupling in different theories (e), and axonal damage during traumatic brain injury (f).

metabolic properties, see Fig. 1-d. Mammalian cell membranes consist of a lipid bilayer composed of amphiphilic lipid molecules arranged in a 2D assembly, and proteins embedded or associated with it, which include ion channels. Traditionally, lipid bilayers were thought to behave as 2D Newtonian fluids allowing membrane proteins to diffuse laterally. This representation as a passive 2D fluid has gradually been abandoned in favour of a more complex picture: an anisotropic time-dependent viscoelastic biphasic material [10], capable of transmitting or attenuating mechanical forces that regulate biological processes. The plasma membrane is a dynamic structure that undergoes various changes across time and length scales [239]. Membrane deformations affect the activity of ion channels on millisecond timescales relevant to neuronal activity [307]. The deformation of the plasma membrane in response to force has been previously described by its compression (K_C), area expansion (K_A) and bending (K_B) moduli. Recently, AFM has been used to map with nanometer resolution the viscoelastic properties of lipid membranes [10]. It has been observed that $K_B < K_A < K_C$ [89], implying that the plasma membrane requires less energy to bend than to be stretched or compressed. This

observation is in agreement with the neurons ability to exocytose and recapture vesicles, as well as respond to protrusive and repulsive forces experienced during cell growth and motility [307]. Furthermore, the intrinsic viscoelastic properties of neuronal membrane are further influenced by its mechanical links with the cytoskeleton, which provides the structural support and tension within cells.

Key to the function of neurons is the localisation of transmembrane ion channels which are necessary for electrical signalling. In the brain, the voltage-gated potassium channels often show not only polarised sorting to either axons or dendrites but also isoform localisation within dendrites alone. This implies that there exist specific sorting mechanisms for restricting lateral distribution within a given membrane function [275]. Recent advances in the study of cell membrane structure have led to the emerging idea of microdomains that exist within the fluid bilayer. These dynamic structures, called lipid rafts are rich in cholesterol and sphingolipids [279]. Cholesterol molecules enhance the permeability-barrier properties of the lipid bilayer. These molecules orient themselves in the bilayer with their hydroxyl groups close to the polar head groups of the phospholipid molecules. In this position, their rigid steroid rings interact with and partly immobilise those regions of the hydrocarbon chains closest to the polar head groups. Moreover, the lipid rafts are found in both excitable and non-excitable cells and localise several membrane proteins, including signal transduction molecules [128]. Furthermore, the activity of several mammalian ion channels has been shown to be modulated by polyunsaturated fatty acids, including arachidonic acid and membrane phospholipids [253]. The lipid bilayer and protein-lipid interaction are critical for mechanosensitive gating and modulation of neuronal two-pore domain potassium channels such as TREK-1 and TRAAK [38]. Stretch-activated calcium-dependent potassium channels are activated by both membrane stretch and amphipathic molecules that insert themselves into one leaflet of the lipid bilayer [195]. Currently, there are two models that describe the gating of mechanosensitive channels by mechanical force: tethered and bilayer. Since prokaryotic cells lack a cytoskeleton, it has been previously shown that the mechanosensitive channels receive energy from the conformational changes of their surrounding bilayer, which acts as the tension-bearing element [198]. However, eukaryotic cells contain excess membrane area which is supported by a contractile cytoskeletal network that locally regulates the mechanosensitivity of their mechanosensitive channels [198]. On the other hand, more recent evidence has demonstrated that eukaryotic mechanosensitive channels can also be gated by the bilayer mechanism [161]. These findings suggest that the response may be cell-type specific.

Physical cues such as pressure, osmolarity, vibration, shear stress, stretch or sound waves can activate a range of mechanosensitive channels in the central nervous system as well as in the sensory systems [69,257]. Ion channel activation is usually recorded by directly measuring ion flow across the cell membrane using patch clamp electrophysiology of single cells [270] or by recording AP firing activity from intact nerve fibers [259]. Furthermore, other techniques such as micropillar arrays for single channel stimulations [252,322], the use of magnetic nanoparticles for the application of localised pulling forces on specific domains [321] and calcium imaging for uniform stimulation of large populations of channels [302,298] have also been used to control and measure the activity of mechanically activated channels. These techniques have been developed to apply mechanical forces to specific locations of a cell, including nerve terminals or neurites, where mechanically activated ion channels are thought to be located. For example, a previous study employed the use of micropillars arrays where each pillar is controlled by a piezoelectric device and can be deflected to apply local mechanical indentations to neuronal cells [252]. This system revealed distinct populations of mechanically activated currents in dorsal root ganglia neurons by substrate deflection at both soma and neurites.

Mechanical forces can be applied to isolated cells through fluid shear stress [58], membrane indentation with an AFM tip [11] or membrane stretch [25]. Furthermore, membrane stretch can also be applied to lipid-solubilised ion channels reconstituted into proteoliposomes [38]. These distinct mechanical stimuli are generally cell type specific. For example, muscle cells experience tensile forces (stretch), endothelial cells sense shear stress, while somatosensory neurons experience membrane indentations. Cellular swelling due to changes in osmotic potentials, however, is slower and less uniform compared to the aforementioned physical forces, because it is normally compensated by changes in the cell cytoskeleton [151,268]. Finally, cell swelling can activate ion channels through indirect mechanisms such as reduction of ionic strength [268].

2.2.2. Membrane as a dynamic channel-driven sensor

Sodium ion channels, which are expressed in somatosensory neurons of C. elegans were among the first identified eukaryotic mechanically activated ion channels [44,18]. MEC-4 and MEC-10 are amongst the degenerin genes (sodium ion channels), which are pore-forming subunits of an ion channel complex required for the activation of the gentle touch receptors ALM and PLM [235]. Furthermore, it was initially shown that abolishing MEC-4 and MEC-10 genes obliterates the mechanosensitivity of PLM neurons in vivo and that missense mutations of MEC-10 change the ion conductivity upon mechanical stimulation of both ALM and PLM cells [235]. Interestingly, when the mutant forms of MEC-4 or MEC-10 were expressed in Xenopus oocytes, an amiloride-sensitive sodium current was recorded [235]. Moreover, the current readings were further increased when these proteins were co-expressed with MEC-2, a stomatin-related integral membrane protein, and MEC-6, a paraoxonase-related integral membrane protein [47,115]. Therefore, these results indicate the existence of a multi-subunit complex involved in ion conductivity, where further experiments are needed to validate the exact mechanisms of the complex.

DEGT-1 and DEG-1 are two degenerin genes (corresponding to two sodium ion channels) which have been implicated as mechanotransducers in C. elegans. It has been previously shown that DEGT-1 and MEC-10 are necessary for mechanically induced calcium transients in the nociceptive PVD neuron [46]. These two proteins have been shown to co-localise in the synaptic puncta of PVD neurons. Furthermore, the loss of MEC-10 in PVD cells stops the response to a mechanical stimulus in worms [46]. Although PVD neurons sense noxious mechanical forces applied to the body of worms, ASH neurons are needed to sense nociceptive signals at the nose. The DEG-1 protein is found in ASH neurons and is needed for most of the mechanically induced currents [109]. Mutations to the pore domain of DEG-1 alter ion selectivity, suggesting that DEG-1 is the pore-forming subunit of the mechanically activated channels in these neuronal cells. These findings suggest that the degenerin genes are well characterised mechanotransducers in worms; however, it still unclear what the role of the orthologs of these genes are in both Drosophila and mammals. In mammals, while the acid sensing ion channel genes (ASIC1-3) are expressed in dorsal root ganglia neurons, these genes do not contribute to the mechanosensitivity of these cells [78]. However, using single-fibre recordings on an in vitro vagus-gastroesophageal preparation or an in vitro colon preparation, a loss in mechanosensation has been observed in knocked-out ASIC1a, 2 and 3 [49]. ASIC2-/- mice have displayed elevated basal arterial pressure and heart rates, suggesting impaired ability to regulate arterial function [191]. Furthermore, isolated nodose ganglia neurons from ASIC2-/- mice showed a slight loss in mechanically induced depolarisation

compared to their wild-type cells [191], implicating ASIC2 in modulating mechanosensitivity in these cells.

Another family of channels that is crucial in sensory functions are the transient receptor potential (TRP) ion channels [73,312]. Several of the TRP channels play an important role in cellular calcium signalling and homeostasis. They can be activated by mechanical forces resulting from stretch or osmosis. To date, there are about 33 animal genes encoding TRP channels, which have been classified into seven categories on sequence homology: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP and TRPV [53]. Within the TRPC subfamily, TRPC1 and TRPC6 channels are involved in mechanosensation. It was previously shown that TRPC1 channels which are expressed in the brain, heart, smooth muscles, endothelium, salivary glands, liver, testis and ovaries are directly activated by membrane stretching [312]. Furthermore, the heterologous expression of human TRPC1 in Xenopus oocytes has been shown to increase the density of mechanosensitive channels and cation current in patch-clamp experiments [196]. In Drosophila larvae, the TRPN ortholog, NOMPC, has been shown to be expressed in Class III dendritic neurons and to be necessary for the response of the larvae to light touch stimuli [325]. In mammals, a TRPN ortholog does not exist and the role of vertebrate TRP channels in mechanotransduction still remains unknown. However, some groups have reported that TRPA1 is involved in mediating mechanically activated currents in a subset of dorsal root ganglia neurons [173,314]. Furthermore, pharmacological inhibition of TRPA1 has been shown to induce elusive behavioural changes, implying that TRPA1 may play a role in noxious mechanosensitive dorsal root ganglia neurons [249,184]. Although the role of DEG and TRP channels in mammalian mechanotransduction still remains unclear, the identification of new ion channel families, such as Piezo ion channel family, has been critical to further our understanding of the role of mechanosensitive ions channels in mammals.

In mammals, Piezos are expressed in a wide range of mechanosensitive cells and are found in abundance in the lungs, kidneys and dorsal root ganglia neurons. Although the exact topology of Piezo ion channel has not yet been determined, the computational and biochemical assays imply that Piezo ion channels contain up to 38 transmembrane domains, suggesting to date, that Piezos might be the largest identified ion channel complex [61,60]. Piezo1, a member of the Piezo family has been identified as the mechanically activated ion channel necessary for membrane indentation and membrane stretch-induced currents in the N2A neuroblastoma cell line [257]. Furthermore, Piezo1 is a non-selective cation channel that is blocked by chemical agents such as gadolinium, ruthenium red and GsMTx4, a peptide isolated from tarantula venom, which is known to inhibit stretch-activated channels [59,20,61]. Piezo2, another related mammalian homolog, has previously been shown to be necessary for a subset of mechanically activated currents in isolated dorsal root ganglia neurons [196]. It was previously demonstrated that heterologous expression of mouse Piezo1 and 2 in addition to Drosophila Piezo was enough to confer mechanically activated currents in naïve cells [126]. In mice, Piezo1 and 2 channel conductances are about 29 pS and 24 pS, respectively, and when subjected to a constant mechanical stimulus, their currents decay within milliseconds from the stimulation, most likely due to channel inactivation [322].

Another important mechanosensitive channel is the glutamate-activated N-methyl-D-aspartate (NMDA) receptor, which is an ionotropic ligand-gated calcium/sodium channel that plays an important role in synaptic plasticity [33], neuronal excitotoxity and cognitive complications due to pain and age [63,271,319]. NMDA receptors consist of various NR1 and NR2 subunits [74]. The secondary structure of NMDA predicts four transmembrane units (M1, M2, M3 and M4). The M2 domain forms a cytoplasmic loop that lines the channel pore and it is this region that controls voltage-dependent magnesium block [172]. Furthermore, the NMDA receptor channel activity is modulated by arachidonic acid [206], which enhances calcium entry into the hippocampal neurons after the addition of NMDA [263]. NMDA response can be enhanced by the addition of arachidonic acid, membrane stretch, membrane phospholipids and osmotic pressure [43]. Previous studies have reported enhanced NMDA receptor currents upon the addition of arachidonic acid in native patches from mammalian central neurons [206,43]. It is well recognised that changes in intracellular calcium can adversely affect traumatic and ischemic injury in the central nervous system [311]. Interestingly, deformation of the neuronal cell membrane evokes calcium transients through the activation of synaptic NMDA receptor channels [107]. In another study, it was demonstrated that arachidonic acid and membrane induced stretch both alleviate magnesium block of NMDA receptor channels [161]. These findings suggest that there exists a complex mechanism whereby mechanical stretch of the neuronal membrane alters voltage-dependent magnesium block and triggers intracellular calcium entry through NMDA receptors.

3. Mechano-electrophysiological coupling in neuronal membrane

The neuronal membrane and its associated ion channels constitute the very foundation of the mechanobiology of the brain. Through multiscale (from proteins to cells to tissue) and multiphysics (mechanical cues informed electrophysiology) integration, they confer to the brain the ability to sense localised mechanical signals and either alter or create biochemical or electrophysiological responses to them. However, while multiphysics cascades are commonly observed and studied in biology, they are also traditionally reduced to exclusive causal relationships. In this section, we veer away from this traditional approach and revisit the neuron, and in particular the membrane, as a mechano-electrophysiological system where multiple physical processes occur concurrently and collaboratively, as opposed to sequentially and independently. To do so, the membrane needs to be considered as a thermodynamic system whose physical properties are naturally coupled. Following this paradigm, all non-pathological coupled mechano-electrophysiological perturbations of the membrane are to be acknowledged as reversible alterations, after which the membrane should naturally return to its equilibrium state. Irreversible alterations such as in traumatic brain injury (TBI) or any neurodegenerative disease, see Fig. 1-f, are thus ignored here.

In the following, the experimentally observed phenomenon of membrane deformation during (de)polarisation is introduced in Section 3.1. The two general modelling approaches identified in this review are then presented in Section 3.2, from which the three most proposed explanations for the experimentally observed coupling are derived: voltage-induced changes in membrane tension (Section 3.2.1), direct and reverse flexoelectricity (Section 3.2.2), and thermodynamic wave theory (Section 3.2.3). The outcome of collision of two APs, which is naturally related to the fundamental attributes of the APs and highly different between theories, is finally discussed in Section 3.3.

3.1. Experimental observation of membrane deformations during membrane polarisation

The AP has traditionally been considered as a purely electrical phenomenon. However, in the past few decades, measurements of the cell membrane deformation during APs have reported an in-phase movement of the membrane surface accompanying the propagation of the electrophysiological pulse. Given the pervasiveness of mechanoelectrical mechanisms illustrated in the previous

sections, it therefore becomes reasonable to ask whether such deformation may itself play a role in AP generation. In the following, we briefly summarise some of these experimental observations along with their corresponding techniques.

In a series of 1980s publications by Iwasa, Tasaki and coworkers [147,290,291,146,289,292] making use of different measuring methods, APs have been reported to be accompanied by a small, rapid upward displacement (swelling) of the nerve fibre surface, concurrent with a rise in the pressure. The magnitudes of such upward displacement and the pressure increase were observed to depend on the type of nerve fibres: about 0.5 nm and 1 dyne/cm^2 in squid giant axons, 5–10 nm and 5 dyne/cm^2 in crab nerves, 10–20 nm and 5 dyne/cm^2 in crustacean nerves. It was also observed that cathodic and anodic polarisations result in mechanical changes of opposite signs, and these mechanical deformations exist even if a major portion of the endoplasm is removed from the axon without suppressing the cell excitability. Furthermore, altering the tonicity of the external medium had a large influence on the results. Moreover, it was also found that this rapid mechanical change can be suppressed by adding tetrodotoxin, thus confirming the role of voltage-gated sodium channels in the generation of the mechanical transients. More advanced techniques such as non-contact coherence tomography have been used by Christopher et al. [54] and Akkin et al. [8,9] to the same end. The results confirm that transient mechanical changes are associated with APs and can be altered under different environmental and physiological conditions, such as change of temperature or ionic concentration but also demonstrate that the magnitude of their measured membrane displacements is in the nanometre range with sub-nanometre accuracy [273]. The same technique has been used by Oh et al. [234] to measure changes in cells' membrane potentials, in turn inducing cell deformation, reflected as changes in the optical signals. Brownell et al. [39] measured cell membrane displacement and electromechanical force generation using optically trapped beads to detach the plasma membrane from the cytoskeleton and to form long thin cylinders (tethers). In this approach, electrical stimuli are delivered to the cell through whole-cell voltage clamp, while membrane displacements and electromechanical forces are quantified by measuring the beads' displacements along the tether axis using a quadrant photo-detector. It was observed that hyperpolarising potentials increase (and depolarising potentials, decrease) the force required to pull a tether. Both membrane displacements and tether forces are functions of the holding potential in response to sinusoidal voltage signals.

AFM has also been widely used to measure membrane displacement during AP generation and propagation. Mosbacher et al. [219] recorded the membrane movement of voltage-clamped HEK293 cells, both untransfected and transfected with Shaker K^+ channels. In both cases, these cells exhibit an outward movement during depolarisation with magnitude of approximately 0.5–15 nm normal to the plane of the membrane. However, untransfected cells only seem to be weakly influenced by the holding potentials, whereas the transfected cells are much more sensitive to them, in which channel-specific movements also occur. Zhang et al. [335] recorded the membrane movement of voltage-clamped HEK293 cells in different ionic-strength solutions and observed that a depolarisation field can cause an outward membrane movement in normal saline and an inward movement in the saline with low ionic strength. The amplitude of the movement is proportional to the voltage change in the ratio of about 1 nm per 100 mV. Following these studies, Kim et al. [155] observed changes in the nerve terminal volume via AFM as nanometre scale movements of the cantilever positioned on top of the posterior pituitary. The observed membrane swelling is believed to be related to water movement associated with the exchange of Na^+ and K^+ ions, although, in other studies, it is reported that the membrane displacement is about two orders of magnitude larger than the one measured for the exchange of Na^+ and K^+ [273]. On the other hand, the slower recovery of the mechanical response is considered to be dependent on Ca^{2+} entry as well as on the intraterminal Ca^{2+} transients. The duration of the spike of this transient mechanical response is also found to be shorter than that of the AP. Most recently, the AFM was used by Gonzalez-Perez et al. [114] to record axonal thickness changes in single giant axons of lobster nerves during AP propagation. It was found that the membrane changes are of the order of 0.2–1.2 nm and last approximately 2–4 ms. Gil et al. [110] investigated the mechanosensitive channels activated by membrane deformation in cultured rat hippocampal neurons and observed that prolonged depolarisation of a membrane patch in borosilicate pipettes results in delayed slow displacement of the membrane into the pipette, with a magnitude of about 1 μm for each prolonged depolarisation. However, the displacement is delayed by a duration ranging from tens of milliseconds to several seconds, and is found to be correlated in time with the activation of mechanosensitive channels. In addition, Nguyen et al. [230] used piezoelectric $PbZr_xdTi_{1-x}O_3$ nanoribbons to measure the mechanical deformations of neuronal cells in response to electrical excitations. In this study it is reported that cells deflect by approximately 1 nm under a 120 mV voltage field applied to the cell membrane. Yang et al. recently imaged a transient sub-nanometer (0.2–0.4 nm) membrane motion accompanying the AP in single mammalian neurons (HEK293T cells) with a label-free optical imaging method [327]. Finally, it is worth mentioning that, during the measurement of membrane bulging, marked longitudinal shrinkage of the nerves has also been observed simultaneously to radial swelling [292].

3.2. Models

Among the current attempts to model the experimentally observed electro-mechanical coupling in the neuronal membrane, two paradigms are currently proposed.

The first one aims at itemising the different physics involved in the experimental observations, and links them by physical laws (e.g., voltage-induced changes in membrane tension, see Section 3.2.1). These models tend to be phenomenological in nature and essentially aim at capturing specifically a phenomenon of interest. El Hady and Machta [124] proposed a numerical model in which the co-propagating mechanical displacements (termed as 'action waves') emerge from the surface waves due to the varying compressive electrostatic forces across the membrane, induced by the travelling wave of the electrical depolarisation. Their simulation results show a good agreement with a range of experimental results on the magnitude of the membrane displacement and the wave speed. Interestingly, they concluded that many properties of the co-moving mechanical wave are determined by comparison of its own propagation velocity and the velocity of the electrical pulse at relevant wavelengths. In a series of publications, Engelbrecht et al. [87,84,85] extensively studied the electromechanical coupling of waves in nerve fibres. In their model, the AP is modelled as an electrical pulse and is assumed to trigger all other processes. It is modelled using a modified FitzHugh-Nagumo model [93,227] which additionally incorporates 'mechanical activation' parameters that describe the mechanosensitivity of the ion channels. The AP is coupled to the mechanical waves which include both longitudinal and transverse waves in the membrane, as well as the pressure wave in the axoplasm. The longitudinal wave is modelled using the improved nonlinear soliton model, whereas the transverse wave is linked to the longitudinal wave via the theory of rods. The pressure wave in the axoplasm is modelled using a model of pressure waves in an elastic cylindrical tube with added viscous damping term described by a 1D Navier-Stokes equation. The coupling effect is achieved via several coupling forces added

into the governing equations. These coupling forces depend on the spatial and temporal changes of voltage. Most recently, Chen et al. [50] proposed a coupled mechano-electrophysiological membrane finite element model for neuronal axons. In this model, the axon is modelled as an axisymmetric thin-wall cylindrical tube. The classic H-H equations are used to model the membrane electrophysiology for the nodes of Ranvier and unmyelinated axons, and cable theory is used to model the signal conduction in the myelinated internodal regions. The axonal mechanics is modelled using beam theory for a viscoelastic material in a dynamic framework. Membrane potential changes induce a strain gradient field via the reverse flexoelectric effect, whereas mechanical pulses result in an electrical self-polarisation field following the direct flexoelectric effect, in turn influencing the membrane potential (the direct and reverse flexoelectric effects are introduced in Section 3.2.2). Membrane deformation also alters the membrane electrical properties through the change of the modelling parameters in the H-H model. These three effects serve as the fundamental coupling mechanisms between the electrophysiological and mechanical pulses in the model. With this model, a series of numerical studies were systematically conducted to investigate the consequences of interaction between the electrophysiological and mechanical waves on both myelinated and unmyelinated axons. Results illustrate that the AP is always accompanied by an in-phase propagating membrane displacement of $\approx$ 1 nm, whereas mechanical pulses with enough magnitude and/or frequency can also trigger APs due to the flexoelectric effect [50].

All these models are generally driven by the physics of interest for a given application, and hence particularly suitable for tissue upscaling for potential clinical applications, see Sections 4 and 5. However, they suffer from a lack of generalisation. Thermodynamic frameworks considering the different physics as intertwined energy contributing paradigms aim at bridging this gap. In such approach, the state of the system of interest, e.g., the membrane, is characterised by its enthalpy and the different conformations (or states) it can take, i.e., its entropy. These approaches can be derived from first principles, and present the advantage to capture a phenomenon such as AP as a simple thermodynamic wave intrinsically accounting for mechanics, electrophysiology, pH, etc. Upscaling such concepts to a workable tissue scale while conserving their thermodynamic nature is however not direct and requires a phenomenological description. These models are also often criticised for being 'biology-agnostic', a feature that is an advantage in the context of generalisation, but undesirable in the context of specific applications. The most iconic of these models has been introduced by Heimburg and coworkers and considers the AP as a nonlinear and dispersive solitary wave very much resembling sound waves [133,134,13,174]. Details of this model will be introduced at length in Section 3.2.3. Drapaca [77] also recently proposed a coupled electromechanical model of a neuron based on a unified variational principle. In this model, the neuron is modelled as a linear viscoelastic Kelvin-Voigt solid whose electro-chemical activity is described by the classic H-H equations. The neuron electrodynamics is described by a coupled system of differential equations, which is obtained by minimising a special integral functional whose integrand is made of the kinetic and potential energies as well as the work done by the forces acting on the neuron. Membrane capacitance is also linked to the mechanical deformation of the neuron. Furthermore, the elastic modulus is assumed to depend on the gating variables in the H-H model. Finally, the AP is simulated by applying a constant external electric current and an initial displacement and velocity of the membrane. Remarkably, it is observed that the neuron stiffens during depolarisation which is claimed to be in good agreement with experimental measurements. Finally, Schneider and corworkers recently proposed another model with strong thermodynamic foundations, see Section 3.2.3 [226,225,91].

In summary, AP accompanying membrane deformations appear to occur in a wide variety of excitable cells and tissues including both invertebrate and vertebrate nerve fibres [273], and are affected by different environmental conditions such as the ionic concentration. This a priori conflicts with, or at the very least complements, the traditional understanding of APs as a purely electrical phenomenon. Two leading frameworks have approached this duality: the first one, by explicitly defining the physics involved and linking them through established laws, and the second one, by overcoming the need to quantify all physical alterations and instead viewing the phenomenon as a thermodynamic system where enthalpy and entropy exchanges occur between different states and physics. In the following, and driven by two clinical applications of interest, we avoid discussing the conflicting philosophies behind the different approaches and focus (irrespectively of the 'school' they belong to) on the three leading coupling models.

3.2.1. Voltage-induced changes in membrane tension

It has been suggested that membrane displacement during polarisation occurs as a result of the cell attempting to alter its radii so as to maintain constant pressure across the membrane [335,187,230], see Fig. 1-e. The pressure difference Δp sustained across the cell membrane to maintain mechanical equilibrium can be evaluated using the Young–Laplace equation:

$$\Delta p = -\gamma \overline{\nabla} \cdot \hat{\mathbf{n}} = 2\gamma H = \gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \tag{1}$$

where γ is the surface tension, $\overline{\nabla}$ is the surface divergence (i.e., $\overline{\nabla} = \nabla - \hat{\mathbf{n}}(\hat{\mathbf{n}} \cdot \nabla)$ where $\hat{\mathbf{n}}$ is the unit normal pointing away from the cell), H is the mean curvature, and R_1 and R_2 are the principal radii of curvature. When membrane polarisation is induced by an applied external voltage field, it is hypothesised that it may change the surface tension of the membrane. The surface tension is defined as the Gibbs free energy required to maintain a certain surface area, and therefore contains both chemical and electrical contributions. The chemical contribution is the natural surface tension of membrane interface in the absence of electric field, whereas the electrical contribution comes from the electrical energy stored in the membrane (due to membrane capacitance) during polarisation induced by the applied voltage field. This has been observed to resemble the phenomenon of electrowetting, and therefore can be modelled using the Young-Lippmann equation [221]:

$$\gamma = \gamma^0 - \frac{CV^2}{2} \tag{2}$$

where γ is the total surface tension (including both chemical and electrical contributions), γ^0 is the surface tension at zero electric field, C is the capacitance of the membrane and V is the surface potential at the interface. Here the concept of electrowetting can be extended to understand the phenomenon of membrane displacement during membrane polarisation. When the membrane is polarised, the change of membrane potential modulates the surface tension of the deformable cell membrane in contact with intracellular and extracellular fluids according to Eq. (2). Based on Eq. (1), in order to maintain a constant pressure across the membrane, differences in surface tensions between the intracellular and extracellular interfaces induce changes in membrane curvature, in turn leading to membrane displacement. Consequently, changes in membrane potential result in an alteration of cell radii to maintain mechanical equilibrium across the membrane [221].

3.2.2. Direct and reverse flexoelectricity

Another proposed mechanism is biological flexoelectricity, which includes both direct and reverse flexoelectricity. Direct flexoelectricity is a property normally observed in dielectric materials (e.g., liquid crystals), and refers to a spontaneous electric

polarisation induced by an applied mechanical strain gradient [40]. The reverse flexoelectric effect refers to a strain gradient (usually in the form of bending) induced by a substantial external electric field applied across the dielectric material [127,171]. This concept differs from the well-known piezoelectric effect in that piezoelectricity only occurs in non-centrosymmetric crystalline materials under a uniform mechanical strain, whereas all dielectric materials (even in otherwise centrosymmetric crystals) can exhibit flexoelectricity under a non-uniform strain field (i.e., strain gradient) [148,166,5,231].

In lipid bilayers and cell membranes, the phospholipid molecules, which arrange themselves into two sheets, are charged and possess dipole moments on their surfaces. This fluid-like membrane can undergo a variety of mechanical deformations such as bending and thickness changes which alter its surface curvature, resulting in a redistribution of the dipoles and the development of a surface polarisation [245], i.e., the direct flexoelectric effect [5,72], see Fig. 1-e. Flexoelectricity is found to play a significant role in a number of biological functions, such as ion channels, thermal fluctuation, vesicle equilibrium, and particularly in hearing [166,71,190,103,335,243,299]. In fact, several experimental observations and theoretical hypotheses have used the transformation of acoustic vibration into sensible electrical APs by the stereocilia in inner hair cells (which are the primary sensory receptors in the mammalians' ears) as a paradigm for the biological flexoelectric effect [258,36,166,281,35,1]. In neurons, both the direct and reverse flexoelectric effects have been suggested to be closely related to membrane polarisation during AP propagation [243,247]. In the cell membrane, it is hypothesised that conformational changes of proteins by adenosine triphosphate and ions induce curvature in the neighbouring membrane. The presence of an external electric field (such as changes of the local ionic concentration gradients) may further impose bending moments on the membrane due to the reverse flexoelectric effect. Alteration of the membrane curvature in turn exerts mechanical forces on the boundaries of ion channels, potentially altering their dynamics or, in the case of mechanosensitive ion channels, further promoting their activation. It may also change the local electric polarisation field due to the direct flexoelectric effect, which also has an influence on the external electric field. As a result, this bi-directional action results in the membrane depolarisation that drives the ionic flux through the ion channels [243,247,5], accompanied by polarisation-induced membrane deformation [231].

Different experimental and numerical models have been proposed to quantify the direct and reverse flexoelectric effects, from simple phenomenological approaches based on empirical equations to more elaborate physically based analyses. For the direct flexoelectric effect, Petrov and Sokolov [248] proposed that, for a time-dependent oscillating black lipid membrane, an oscillatory change in the mean membrane curvature c_m (defined as the average between the two principal curvatures) induces an oscillating local displacement current $I(t)$ due to the flexoelectric polarisation, following:

$$I(t) = 2f_D \frac{S}{d}\omega c_m \cos\omega t = 2f_D \frac{C}{\varepsilon\varepsilon_0}\omega c_m \cos\omega t \tag{3}$$

where f_D is the direct flexoelectric coefficient, S is the membrane area, d is the membrane thickness, ω is the angular frequency of the oscillation, C is the membrane capacitance, ε is the mean relative static permittivity and ε_0 is the vacuum permittivity. Values of f_D have been measured in some studies. For example, Petrov measured $f_D = 2.5 \times 10^{-18}$ C for excitable locust muscle membrane [244] and $f_D = 6.2 - 8.9 \times 10^{-21}$ C for non-excitable astrocyte membrane of rats [246]. As for the reverse flexoelectric effect, Todorov et al. [300] proposed that the mean membrane curvature c_m is associated with the average transmembrane electric field E through the following phenomenological relationship:

$$c_m = \frac{f_R}{2K}E \tag{4}$$

where K is the membrane bending modulus and f_R is the reverse flexoelectric coefficient. Studies such as the ones conducted by Mosbacher et al. [219] and Zhang et al. [335] witnessed the reverse flexoelectric effect under whole-cell voltage clamp environment. A value of f_R of about 10^{-19} C can be inferred from their experiment data for non-excitable human embryonic kidney cells [273]. In addition, Rey [260] developed a formulation of an isotropic interfacial liquid crystal flexoelectric membrane under different loading conditions (tension, bending, torsion and pressure), and derived a membrane electromechanical shape equation that connects fluid forces with membrane curvature and electric displacement. It is shown that flexoelectricity renormalises the membrane mechanical tension, shear, and bending effects, and hence offers diverse pathways to manipulate the membrane's shape. This model was further extended by Rey et al. [261] to include a mechanical energy harvesting system consisting of a deformable soft flexoelectric thin membrane subjected to harmonic forces from a contacting bulk fluid, as well as by Herrera-Valencia and Rey [138] to model the actuation of flexoelectric membranes of human hair cells in viscoelastic fluids. Gao et al. [103] developed an electromechanical liquid crystal model for characterising the mechanical equilibrium morphology of an axisymmetric lipid vesicle in a uniform electric field. In this formulation, a general equation is established governing the vesicle shape based on the Helmholtz free energy, which incorporates the effects of elastic bending, osmotic pressure, surface tension, Maxwell pressure, as well as flexoelectric and dielectric properties of the lipid membrane. Breneman et al. [35] proposed a flexoelectric model for stereocilia of the hair cells incorporating stereocilia dimensions, a flexoelectric coefficient of lipid membranes, mechanical compliance as well as fluid dragging force. Governing equations of this model include the electrical cable equation and the mechanical wave equation in which flexoelectric current and flexoelectric axial stress were, respectively, included. These terms are computed using the flexoelectric-piezoelectric equivalence condition for isochoric axisymmetric deformations, which is derived by equating the flexoelectric and axial piezoelectric electro-mechanical potential energies. Mohammadi et al. [210] proposed a theory for flexoelectric membranes based on minimisation of the total free energy as the sum of the internal and electric energies both of which are functions of out-of-plane displacement and out-of-plane polarisation. In this model a heterogeneous flexoelectric membrane is considered. The homogenised or renormalised flexoelectric, dielectric, and elastic response of the membrane is derived and the corresponding effective electromechanical properties are related to its microstructural description. This model was adopted by Ahmadpoor et al. [4] to show that the interplay between the deformation geometrical nonlinearity and distributions of external charges and dipoles lead to the renormalisation of the membrane's native flexoelectric response, and was further extended by Deng et al. [71] to model flexoelectricity in soft materials. Most recently, Kancharala et al. [152] developed a flexoelectric model coupled with a nonlinear finite element model to study the dynamic mechano-electrical response of droplets under excitation. This electrostatic model captures the internal distribution of charge within a droplet, leading to a dipole and surface potential. The membrane permittivity transits from low level in the bilayer region to high level in the aqueous phase. Fixed charges on the lipid biomolecules are approximated through normal distributions as two closely-situated zwitterionic charges in the head group, and two larger charges in the hydrocarbon tails associated with the dipole potential. This results in the electrostatic potential profile containing a dipole and surface potential within

the membrane interior. The bilayer curvatures updated from the finite element model are fed into the flexoelectric model, redistributing the charges. The charge required to maintain the given boundary potential is then used to calculate the mechano-electrical current. Leveraging both direct and reverse flexoelectric effects, the recent model of Chen et al. [50] discussed earlier demonstrates that mechanical vibrations, such as the ones arising from ultrasound stimulations, can either annihilate or enhance axonal electrophysiology depending on their respective directionality and frequency. It also shows that higher frequencies can also enhance signal propagation concurrently to the amplitude of the signal.

In summary, the direct and reverse flexoelectricity effects are commonly observed phenomena in biological systems. It may be a promising mechanism to explain many phenomena related to electro-mechanical coupling, such as cell membrane movement during AP propagation in neurons, as discussed in Section 3.1. At the end of this section, we suggest readers who are interested in a deeper understanding of flexoelectricity to refer to Zubko et al. [336], Krichen and Sharma [166] for more detailed reviews of flexoelectricity in general solids and to Petrov [245], Nguyen et al. [231], Deng et al. [71], Ahmadpoor and Sharma [5] for flexoelectricity in biology.

3.2.3. The thermodynamic model of AP

In 2005, Heimburg and Jackson [133,134] proposed a thermodynamic theory of nerve pulse propagation in which the AP is a localised multiphysics density pulse. This pulse manifests itself, among other physics alterations (e.g., pH, phase, etc.), as a mechanical pulse that maintains its shape with no attenuation while propagating at a constant velocity [57]: a soliton. Two conditions are necessary for the existence of a soliton in neurons: the pulse speed varies according to the frequency as well as through a nonlinear function of the pulse amplitude due to the increase in compressibility as a result of membrane lateral compression [273], see Fig. 1-e. These two necessary conditions enable the pulse to propagate along the axon. It is suggested in this theory that cell membranes always have a temperature melting point above which the membrane consistency changes from solid phase to liquid phase, and the temperature of melting point is only slightly below the organism's body temperature. Phase transition of the lipids is the key property that fulfils the two necessary conditions for the existence of a soliton. It is linked to changes in enthalpy, entropy, as well as to changes in volume, area, and thickness. The implication of this is that the state of the membrane can be influenced not only by temperature but also by hydrostatic pressure and lateral pressure in the membrane plane [16]. Heimburg and Jackson [133] showed that the features of lipid membranes slightly above a transition are sufficient to allow the propagation of mechanical solitons along the membrane of axons. Thermodynamically, the soliton model describes the AP propagation as an adiabatic process, in which the energy provided at the source of excitation is carried adiabatically through the plasma membrane: a result of the reversible release of heat. The measurement of a temperature pulse and the absence of net heat release during an AP are some of the experimental supporting evidences of the soliton model that nerve impulses are adiabatic sound waves.

Mathematically, a soliton can be expressed in terms of change in lateral density of the membrane $\Delta\rho = \rho - \rho_f$, where ρ is the lateral density of the membrane and ρ_f is the lateral density of the membrane in the fluid phase, as:

$$\frac{\partial^2 \Delta\rho}{\partial t^2} = \frac{\partial}{\partial x}\left(c^2 \frac{\partial \Delta\rho}{\partial x}\right) - h\frac{\partial^4 \Delta\rho}{\partial x^4} \tag{5}$$

which originates from the Euler equations of compressible media. In this equation, t is the time and x is the position along the nerve axon, c is the velocity of sound in the medium and h is a parameter describing the frequency dependence of the speed of sound, i.e., the term $-h\frac{\partial^4 \Delta\rho}{\partial x^4}$ in the equation is responsible for the wave dispersion. In order to obtain a more physically consistent dispersion, Engelbrecht et al. [86,88] proposed an additional fourth-order mixed derivative term $h_2\frac{\partial^4 \Delta\rho}{\partial x^2 \partial t^2}$ responsible for inertial effects. The velocity of sound c is a nonlinear function of the area density difference $\Delta\rho$ up to terms of quadratic order:

$$c^2 = c_0^2 + p\Delta\rho + q(\Delta\rho)^2 \tag{6}$$

with c_0 being the speed of sound in the fluid phase just above the phase transition, and p and q describing the dependence of sound velocity on density close to the melting transition, and fitted to experimental data by Heimburg and Jackson [133]. Eqs. (5) and (6) are assumed to be valid only when the membrane is close to phase transition and within the phase transition range [273]. The researchers report that the solutions of these equations possess a limiting maximum amplitude and a minimum propagation velocity that is similar to the pulse velocity in myelinated nerves. The travelling soliton locally changes the density and thickness of the membrane, and since the membrane contains many charged and polar molecules, this results in an electrical effect, which is akin to piezoelectricity. This is the mechanism through which electrical currents are associated with APs in the soliton theory.

The concept of thermodynamic wave has since been exploited by other groups. Poznanski et al. [254] presented a model of solitonic conduction in neuronal branchlets with polarised microstructure. In this model, a nonlinear cable equation is obtained and solved using a direct method to obtain analytical approximations of travelling wave solutions. Unlike the soliton model of Heimburg and Jackson [133,134] in which the overarching driving pulse is a thermodynamic wave, Poznanski et al. [254] still consider the AP driven by an electrical pulse but with solitonic properties. Simulation results of this model illustrate that a linear superposition of two oppositely directed travelling waves demonstrate solitonic interactions: colliding waves can penetrate through each other, and continue fully intact.

Finally, Mussel and Schneider developed a coupled multiphysics model of an idealised description of a lipid interface near phase transition separating two regions of bulk fluid, considering interfacial electrical and chemical aspects, in addition to its mechanical properties [226,225]. Their model gathers fluid mechanics, Maxwell's theory of electrodynamics and the phenomenological van der Waals constitutive equation within a thermodynamic framework. The dynamics of the interface is governed by conservation laws including conservations of mass, momentum and energy. It is treated as a continuum of local thermodynamic states, in which each infinitesimal point is associated with equilibrium thermodynamic quantities (e.g., temperature and pressure). The energy equation is derived under the assumption that the total entropy of the system is conserved. With this model, the propagation of electrical and pH changes are inseparable from the density, pressure and temperature natures of the acoustic pulses in lipids. In particular, pulses within a medium near a phase transition show similarities to APs not only in qualitative shape and scales (time, velocity and voltage), but also in terms of saturation of amplitude and annihilation upon collision. This concept is further developed in the latest research of Fillafer et al. [91], where it is proposed that the origin of nonlinear cellular excitability actually arises from a transition of the 2D membrane interface. In this study, ranges of three parameters including temperature, pressure and pH were predicted, within which a transition of the membrane was identified and corresponding phase diagrams were proposed. These results are used to explain the changes of AP velocity with temperature, pressure and pH, the existence and origin of two forms of loss of nonlinear excitability including 'nerve blockage' and anaesthesia, as well as the stimulation of APs

by alteration of these parameters (such as cooling, acidification and pressurisation). It is concluded that it is the thermodynamic properties of the quasi 2D membrane interface which controls the excitability of living systems, rather any specific molecules.

Since both general and local anaesthetics are known to cause depression of the freezing point of transitions in biomembranes, the thermodynamic model of AP also implies an action mechanism for anaesthesia [134,135,116]. It also accounts for the pressure reversal effect of anaesthesia and offers an explanation on how inflammation and the addition of divalent cations can reduce the effectiveness of anaesthesia. More details on the mechanical aspects of general anaesthetics are available in Section 5.

3.3. The subject of discord: Collision of two action potentials

In the literature, several experimental studies have been conducted in various nerve fibres/cells to examine whether annihilation can occur or not upon collision of two APs [143,142,14,94,90]. It has been frequently witnessed that colliding APs are reciprocally annihilated instead of penetrating each other. However, one exception is a series of studies conducted by Gonzalez-Perez et al. [113,114], where it is observed that two simultaneously generated pulses propagating in orthodromic and antidromic directions in the giant axons of both earthworms and lobsters pass through rather than annihilate each other. The accompanying numerical simulation results illustrated in these studies also support the experimental observations. Nevertheless, in one comment to the original paper [27], the experiment was repeated but the results on AP penetration could not be reproduced and annihilation upon collision was consistently observed. In the following reply to this comment [318], it was argued that the signals had been strongly perturbed due to the significantly different experiment configuration in the study of Berg et al. [27]. In the study of Chen et al. [50], simulation results showed that when two electrical pulses from opposite directions meet and collide, they annihilate each other regardless of whether these electrical pulses are initiated by electrical stimuli or triggered by mechanical pulses whose amplitudes are above the 'activation threshold'. Their simulation results are consistent with most of the experimental observations on nerve pulse collision in the literature. The fundamental reason for the discrepancy between the numerical simulation results of Chen et al. [50] and Gonzalez-Perez et al. [113,114] is specifically attributed to the mathematical model of APs that is adopted in the numerical model. In the former study where two APs annihilate each other, the electrical pulse is modelled using the H-H equations. Due to the concept of refractory period in the H-H model, the ion channels are relaxed and therefore, cannot be activated again within a short time. Therefore, when two electrical pulses collide, they both enter each other's refractory period; hence they mutually annihilate. In the latter two studies, nevertheless, an AP is modelled as a sound-like mechanical wave based on the thermodynamic theory as introduced in Section 3.2.3. Therefore, due to the nature of mechanical waves, no annihilation of colliding pulses can be predicted in these studies. However, most recently, Shrivastava et al. [277] observed the annihilation of two super-threshold interfacial mechanical pulses upon head-on collision in a lipid monolayer. The significant discrepancy between the prediction of theoretical analysis of the thermodynamic model and the experimental observations of mechanical pulse collision was attributed to the result of nonlinear material properties (such as nonlinear viscosity resulting from relaxation of phase change) as well as the internal heat transfer in the colliding pulses. Consequently, it can be inferred that a definitive understanding of the process behind the collision of AP pulses could lead to the definitive identification of their nature. If APs are assumed to be merely electrophysiological in nature due to the ion channel dynamics, whereas the associated mechanical wave corresponding to the membrane displacement is a consequence of this electrical phenomenon due to, e.g., flexoelectricity, then the simulation results of wave annihilation upon collision should be expected upon collision. To unveil the real nature of APs, experimental measurements of mechanical pulses and their interactions in the lipid bilayers of cell/nerve membranes (if technology permits) are urgently needed.

It is finally worth noting that the model proposed by Chen et al. [50] might reconcile both observations. While the electrical component of the pulse is subject to a refractory period (in the presence of activated ion channels), an annihilation of the electrical signals is expected. However, the mechanical pulses can pass each other, and, once outside the refractory period of each other, are free to 'retrigger' other electrical waves. This essentially points towards a short term localised annihilation with the possibility of reappearance of these electrical waves on both sides later on (as long as the membrane viscosity does not damp too much the mechanical waves to the threshold below which triggering does not occur).

4. Ultrasound and the membrane

The electrophysiological-mechanical coupling principles set out above imply that a membrane displacement of some particular characteristics can induce a local electrophysiological response in an excitable cell. This can enhance or decrease the probability of AP occurrence, and even evoke APs directly, a process referred to as neuromodulation. In other words, a mechanical input can modulate neural activity.

For over a century, the most direct manipulation of neural activity has been achieved through intracranial electrical stimulation. This approach is commonly employed in animal models as microstimulation and in human patients in the context of deep brain stimulation [168,167]. In recent years, there has been extensive progress in the field of neuromodulation, which was in part made possible by the availability of new optogenetic and chemogenetic tools [284,102,330]. All of these approaches are invasive: they require the surgical opening of the skull and the insertion of electrodes or the transfection with viral agents. As such, they are mostly confined to research in animal models and have limited translation to therapeutic tools in humans. To address the need for non-invasive neuromodulation techniques in humans, two approaches have seen wide adoption: transcranial magnetic stimulation (TMS) and transcranial current stimulation (TCS) [30,67,251]. While being non-invasive and generally safe, these techniques are constrained by the limited depth and relatively poor spatial specificity of stimulation. For example, using TMS or TCS, it is not straightforward to stimulate a region more than a few centimetres below the skull without considerable undesirable side-effects.

An emerging brain stimulation technique, transcranial ultrasound stimulation (TUS), might offer many advantages over existing approaches [308]. Ultrasound is a mechanical wave of frequencies above human hearing detection levels ($>$ 20 kHz). It has historically been widely applied in medical imaging and, in this context, has been proven an exceptionally safe technique when used at low power. At higher power, ultrasound is also used for therapeutic applications such as lithotripsy and physiotherapy, but also in neurosurgery and oncology [131,189,62]. High intensity focused ultrasound (HIFU) can be used to make focal ablations without opening the body, for example for treatment of essential tremor [82,189] or chronic pain [310].

Critically, the interaction of the acoustic wave with biological tissue at the cellular level has not been thoroughly studied. Low-intensity TUS can be delivered non-invasively through the skull [305], while achieving a spatial resolution in the order of 1–10 mm [200,262] (well below the size of human cortical

brain areas [111]), and reach virtually any region in the brain, including deep structures such as the amygdala, thalamus, and cingulate cortex [95,180]. Most TUS protocols are geared to induce short-lived neuromodulatory effects, but, recently, ultrasound protocols have been developed that induce longer-lasting plastic changes [66,313]. As such, ultrasound neurostimulation holds great potential as a safe non-invasive brain stimulation approach for basic human neuroscience research and as a clinical intervention tool for psychiatric and neurological disorders.

Here, we discuss the mechanisms of ultrasound delivered at low-intensities, within the physiological range of the tissue, to stimulate the brain non-invasively through the skull using TUS. This technique is also known under other names and acronyms; some emphasise the focussing of the acoustic wave (e.g., transcranial focussed ultrasound stimulation: tFUS, focussed ultrasound: FUS), its neuromodulatory effect (e.g., focussed ultrasound neuromodulation: FUN), or characteristics of the protocol (e.g., low-intensity [low-frequency] [focussed] ultrasound [pulsation]: LILFU, LIFU, LIFUP). Despite this breadth in naming conventions, nearly all TUS protocols deliver the low-intensity and low-frequency ultrasonic wave (e.g., at 500 kHz) in a pulsed fashion (e.g., at 1 kHz). These pulses, in turn, are often grouped in bursts (e.g., lasting 100 ms). The ultrasound-induced mechano-physiological interactions can take place at all those different timescales, from the microsecond to hundreds of milliseconds range [309]. At the shortest timescale, the acoustic wave itself displaces the tissue in the nanometer range. At the millisecond timescale, the acoustic wave interacts with the biological tissue and transfers energy. This is experienced as an acoustic radiation force which can lead to a mechanical wave interaction in the tissue [65]. This radiation force can displace tissue elastically in the micrometer range and acts for as long as the ultrasound is delivered, for example pulsed at 1 kHz for the duration of the 100 ms burst [104]. While the direct effects of ultrasound are expected to stop after the stimulation has ended and the neurons and tissue have returned to their baseline state, sustained or repeated stimulation might lead to plastic effects in neuronal excitability and synaptic strength outlasting stimulation [158,66,331,313]. Such longer-lasting plasticity induced effects are the primary target for development of therapeutic TUS protocols [66]. The neuromodulatory effect of TUS has proven to be highly dependent on the stimulation parameters and on the tissue under study [222]. Specific ultrasound protocols can be used to suppress ongoing brain activity [181], or evoke brain potentials de novo in the absence of external stimuli [178]. As such, ultrasound neuromodulation can have both inhibitory and facilitatory effects on neural activity.

In the following, we present the most commonly hypothesised mechanisms behind ultrasound neuromodulation. We focus on the mechanisms underlying TUS when delivered at conventional low intensities, but also discuss the mechanisms at play at slightly elevated intensities relevant for neuromodulation, as driven by non-destructive thermal and cavitation effects.

4.1. Ultrasonic neuromodulation mechanisms

Ultrasound is an exceptionally well-studied biomedical technique, especially in the context of ultrasound imaging. From the literature, two important bioeffects have emerged: (1) thermal rise, and (2) cavitation. Indeed, both these bioeffects are important in safety assessment of ultrasound imaging and are exploited in high-intensity therapeutic ultrasound stimulation [122]. As such, historically, these bioeffects have also been regarded as primary candidates to also explain the neuromodulation effects observed during low-intensity FUS. However, recent empirical, simulation, and systematic review studies provide evidence that these mechanisms are exceedingly unlikely to be causing all observed neuromodulation effects [56,308]. This calls for an urgent and new understanding of the mechanisms underlying ultrasonic modulation of neuronal activity.

An acoustic wave can interact with the neuronal membrane via different mechanisms, all of which modifying the membrane state. More generally, an input of energy (of any kind) to the lipid membrane induces a local perturbation that can be transduced into localised transient altered states, in turn propagating along the membrane, as structures quickly return to their minimum energy state, i.e., the most stable one. The membrane thus changes its mechanical properties in response to an ultrasonic wave. Here, we first recognise four distinct mechanisms of electrophysiological-mechanical coupling through which ultrasound can tune neural activity: membrane conformational state, thermodynamic membrane waves, direct flexoelectricity and (mechanosensitive) ion channels. We then discuss four additional mechanisms that have been proposed in the literature. Two of those are most relevant for ultrasound delivered at higher intensities or after injecting microbubble agents: thermal modulation and sonoporation, while, for the last two, the evidence has not yet fully matured: microtubuli resonance and synaptic vesicle modulation.

4.1.1. Membrane conformational state

The interaction of ultrasound acoustic energy with the neuronal membrane changes the membrane's mechanical properties in a localised manner: its geometry is affected due to (negatively charged) phospholipid reconfigurations, which also affect its fluidity and permeability [294], see Fig. 2-a. Embedded proteins may change conformation as well, transiently adapting to the new high energetic situation. Importantly, a change to the conformational state of membrane lipids and proteins can result in changes to the capacitance of the membrane [15], modulating neural activity. This modulation can operate at different parts of a neuron: affecting the integration of post-synaptic potentials in the dendritic tree, the probability of APs being generated at the axonal hillock, and the transduction of APs along the axon (see Section 3.1).

These direct conformational changes disappear shortly after the end of the ultrasound stimulation. Indeed, most findings report transient neuromodulation induced by ultrasound. Longer-lasting plastic effects arising from repeated or prolonged stimulation [313] could be mediated through conventional neurophysiological mechanisms responsible for plasticity effects of non-invasive brain stimulation, such as long-term potentiation and long-term depression [283,264]. It is also possible that repeated perturbation of the membrane leads to an accumulation of conformational or geometric changes, similar to how repeated electrical stimulation can change membrane capacitance beyond the stimulation epoch through membrane thinning [132].

4.1.2. Thermodynamic membrane waves

When the acoustic wave interacts with the cellular membrane, the ultrasound energy is transferred from one molecule of the material to the next. This results in longitudinal distributions of compression and rarefaction regions along the medium: a pressure wave. Neurons have several mechanosensitive components that respond to such a density wave [307], but most fundamentally the ultrasound wave might interact with density membrane waves that accompaniy changes in membrane potential (see Section 3.2.3), see Fig. 2-b. In fact, a strong ultrasound-membrane interaction might mechanically elicit a mechanical wave and a coupled AP [81]. More generally, the ultrasound induced membrane perturbation might interfere with the mechanical waves of spontaneous APs, either facilitating or inhibiting them.

4.1.3. Membrane geometry alteration and direct flexoelectricity

Relative displacements between lipids in the cell surface modify the electrostatic interactions between them and hence affect

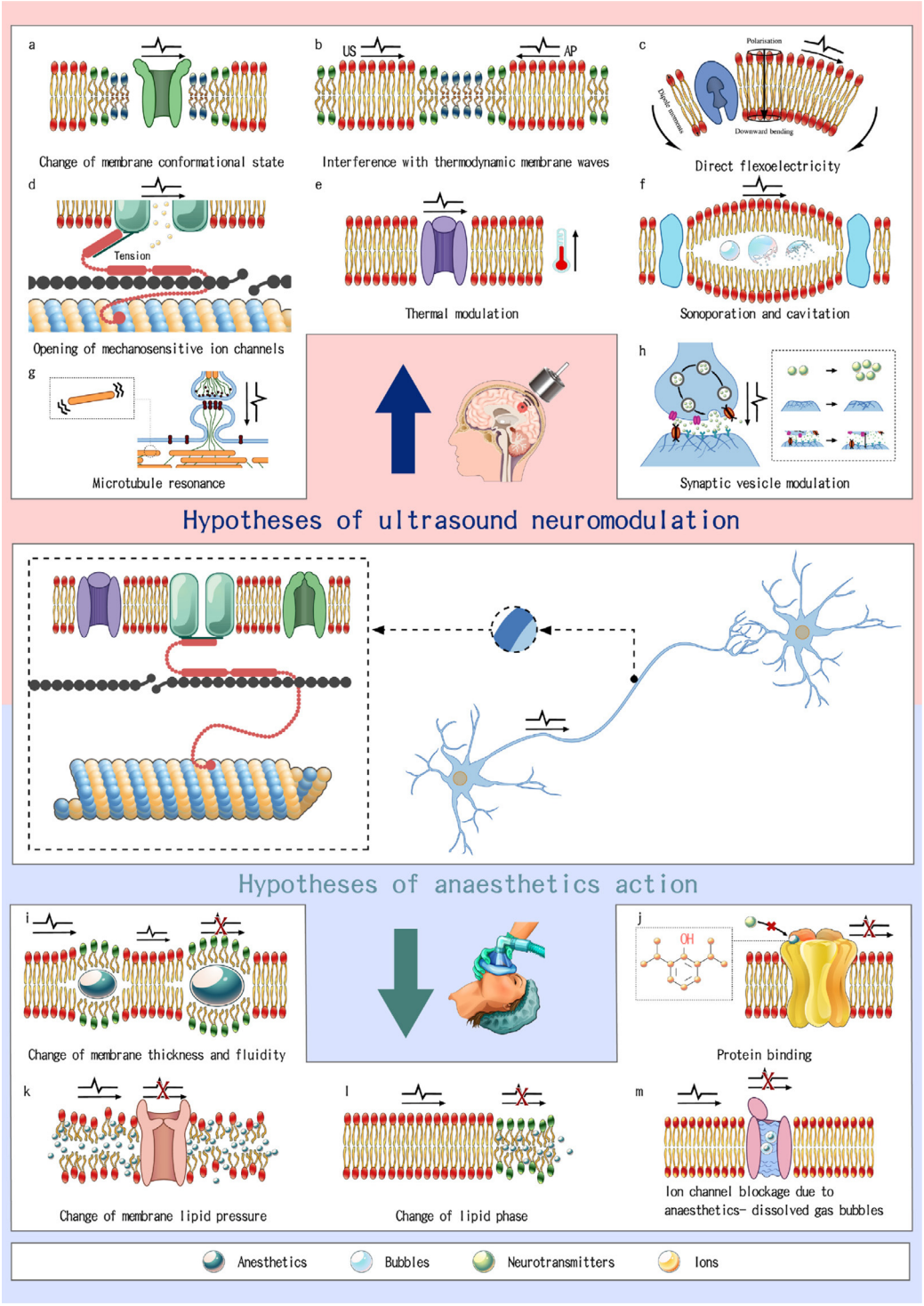

Fig. 2. Electrophysiological-mechanical coupling hypotheses in ultrasound neuromodulation and anaesthetics action.

the transmembrane potential. In fact, under a physical deformation, any polarised membrane creates currents flowing across it [71] (see also Section 3.2.2). Prieto et al. [256] measured changes in membrane area and capacitance in an artificial bilayer as a result of low-intensity ultrasound. They reported that the step change in pressure caused by ultrasonic radiation force disrupts the balance of forces between bilayer tension and hydrostatic pressure and makes the fluid membrane oscillate. Muratore et al. [223] also reported that the acoustic radiation force is capable of reversibly deforming cultured cells. In 2011, Tyler [306] proposed that ultrasound modified the viscoelastic properties of neuronal membranes, which altered membrane conductance. Finally, Chen et al. [50] recently demonstrated that high-frequency oscillations can induce an AP by direct flexoelectric effect, see Fig. 2-c.

4.1.4. (Mechanosensitive) Ion channel opening

The neuronal cell membrane is characterised by a high-density of ion channels, especially near the axonal hillock and synaptic clefts. As such, neurons in general, and these regions in particular, could be sensitive to the effects of ultrasound that are

mediated by ion channels, see Fig. 2-d. As early as in 1980, potassium influx and efflux were modulated in rat thymocytes through ultrasound [45]. Low-power ultrasound was then shown to increase the calcium concentrations in fibroblasts [218], and influence membrane conductance in frog skin epidermis [75]. Shortly after, Mihran et al. [205] proposed that an ultrasonic pulse could open stretch-sensitive channels. In 2008, Tyler et al. [309] measured ion currents after ultrasound stimulation and proposed that the pressure wave actuating on axonal membranes can induce reversible changes in the ion transport mechanisms, which in turn can cause the cell's depolarisation (see also Section 2.2.2). A growing collection of ion channels have been since shown to be responsive to ultrasound stimulation, including the two-pore-domain potassium channel family [170], but also channels that are not primarily classified as mechanosensitive, such as sodium and calcium voltage-gated channels [217]. Conversely, mechanosensitive PIEZO channels have also been shown to be voltage-modulated [216]. Notably, most mechanosensitive ion channels depolarise the membrane upon opening and as such have a facilatory effect on neuronal activity. However, observed inhibitory effects of ultrasound are not immediately in conflict with a mechanosensitive ion channel mechanism, as the inhibitory effects could be the consequence of the physiological characteristic of the neural circuitry. For example, when ultrasounds interact preferentially with GABA-ergic inhibitory inter-neurons, the net result on the circuit level could still be inhibitory.

4.1.5. Thermal modulation

Ultrasound effects on biological tissue are often classified into thermal and mechanical effects [65]. For neuromodulation purposes, generally low-intensity protocols are employed (< 20 W/cm^2) [305]. At those intensities ultrasound protocols are not likely to lead to temperature rises of more than a fraction of a degree, too small to cause neuromodulation [317,309,250,68]. However, with higher intensities and sustained stimulation, even when stimulating below the ablation threshold, a thermal rise at the stimulation site of one or a couple of degrees is possible. Such thermal effects would be entirely reversible and non-invasive, yet could transiently alter neural activity in the hyperthermic region [82,296], see Fig. 2-e. In fact, some of the earliest reports of reversible neuromodulation might be mediated by thermal effects [101]. Given the complexity of the relationship between ultrasound parameters and temperature, it requires careful thermal modelling to estimate whether thermal effects can be excluded as a potential source of neuromodulation for a chosen TUS protocol [56].

4.1.6. Sonoporation

Acoustic stimulation can lead to the creation of physical pores in the lipid bilayer membrane, or more generally to an increase of the lipid membrane permeability, a process referred to as sonoporation. Such pores are lipid constructs and distinct from protein ion channels, but they too allow transport of ions. This effect can be driven by ultrasound interfacing with the conformational state of the lipids, leading to a phase transition related to the specific heat of the membrane [293,324,32]. However, the most prominent hypothesised mechanism driving sonoporation is micro-cavitation.

Cavitation is one of the best studied effects of ultrasound on biological systems [65,165], see Fig. 2-f. It occurs when the intensity of the ultrasound is sufficient to induce resonation, expansion and potential collapse of gas bodies present in some biological tissues. This thus encompasses two phenomena: stable cavitation (the stable oscillation of a microbubble, by nature a mechanical effect) and inertial cavitation, whose potential subsequent inertial collapse can cause thermal rise and damage. Cavitation effects are prominent at high-intensity protocols, but have not been excluded at the lower intensities commonly employed for TUS. It must also be emphasised that a recent comprehensive review of histological analyses suggested that microstructural damage is very unlikely following FUS at conventional low intensities and durations [31]. In fact, in only two studies, once after sonication at higher intensities [157], and once after a long repetitive protocol [179], have histological indicators for microhemorrhage been observed.

Recently, it has been proposed that as a consequence of the biphasic nature of the ultrasound wave, low-intensity ultrasound can cause the intramembrane hydrophobic space between the two lipid monolayer leaflets to inflate and deflate periodically [165]. First, and especially at higher intensities and lower frequencies, this might lead to the creation and collapse of nanobubbles in the intramembrane space, whereby these microexplosions can influence membrane porosity [65]. The Neural Intramembrane Cavitation Excitation model [250] describes how the membrane absorbs mechanical energy from the ultrasound and transduces it into expansions and contractions of the intramembrane space [165]. This model does not require the presence of gas bodies in the tissue, in agreement with the lack of gas bodies found in the brain. Secondly, intramembrane nanobubbles oscillations might induce changes in the local curvature of the membrane, which could modulate membrane potentials [273].

Importantly, the cavitation threshold in vivo is dramatically decreased if one artificially injects lipid gas micro-bubbles in the blood stream. In fact, this is the principle of micro-bubble contrast agents employed for high signal-to-noise ultrasound imaging. It is also used in combination with FUS to locally increase the permeability of the blood-brain-barrier [315,188,144,52]. This exciting application holds great promise for the targeted delivery of drugs and other agents.

4.1.7. Microtubule resonance

Hameroff et al. [125] suggested that transcranial ultrasound-employed megahertz frequencies are in the range of intra-neuronal microtubuli resonance frequencies, making them vibrate synchronously, in turn modulating the electrical signal, see Fig. 2-g. Microtubules are the major component of the cell cytoskeleton and have an important role in regulating synapses. Their oscillation will be thus coupled to the membrane's, as well as influence the synaptic plasticity, as microtubuli are connected to actin filaments, present in dendritic spines.

4.1.8. Synaptic vesicle modulation

Ultrasound-induced disruptions of chemical synapses have been reported as a possible candidate for the immediate functional changes observed following ultrasound application [273], see Fig. 2-h. Such process would involve increased neurotransmitter release, widening of synaptic cleft and altering pre- and post-synaptic densities [34]. Tyler et al. [309] also observed that a low intensity and low frequency ultrasonic wave can trigger synaptic vesicle exocytosis, as studied by a fluorescent pH-dependent optical probe (neurotransmitter release causes an acidification of the synaptic cleft).

4.2. Ultrasonic neuromodulation results

To provide a background and perspective to the electrophysiological-mechanical coupling principles of ultrasound neuromodulation detailed above, we concisely review here the historical and current observations in this field. For a more comprehensive overview, especially of the ultrasonic parameters used in experiments, readers are referred to the work of Tufail et al. [305], Bystritsky et al. [41], Naor et al. [228], Baek et al. [21], Blackmore et al. [31] and Tyler et al. [308].

Even though ultrasonic modulation of brain and nerves is currently a rapidly developing field, it has been investigated for

decades. The first results of modulated electrical response of excitable tissues were obtained in 1929, when Harvey [130] recorded enhanced neural activity of a frog's sciatic nerve upon ultrasonic stimulation. Fry et al. [101] were the pioneers of applying FUS to the brain. They showed that FUS could reversibly modulate visual evoked potentials in cats. Shortly after, Ballantine et al. [23] showed power-dependent (one hour lasting and permanent) dilation of a cat's pupil induced by ultrasonic sonication in the Edinger-Westphal nucleus of the cat brain. In 1963, Lele [183] found that similar effects could be achieved in peripheral nerves and studied the effect of varying ultrasound intensity. He found different effects of FUS on nerves, depending on the stimulating intensity: low intensity FUS irradiation reversibly increases the conduction velocity and the AP's amplitude, moderate intensity FUS induces reversible depression of AP and high intensity FUS irreversibly depresses APs. Further evidence of the reversible functional blocking of nerves with ultrasound was found by Adrianov et al. [3]. Koroleva et al. [164] showed that ultrasound pulses elicited a steady negative potential shift of different stimulated areas in the brain. Reduction in extracellular field potentials were recorded by Rinaldi et al. [265]. Gavrilov et al. [106] measured the threshold for inducing a variety of somatic sensations (tactile, temperature and pain). Since the XXIst century, many experimental studies have been performed, which we classify here by the measured recorded response.

4.2.1. Ultrasound direct effects on neural activity

Ultrasound energy with specific parameters has been proven to facilitate electrical phenomena, triggering the activation and propagation of neural signals. In 2006, Vykhodtseva's group recorded changes in DC and steady depression after stimulation of rat cerebral cortex [316]. Reversible enhancement of electrical activity was recorded after ultrasound stimulation of rat hippocampal slices [223].

Changes in compound APs (sum of the electrical activity of different nerve fibres) were also recorded, both as increase and decrease depending on ultrasound intensity [156,182,303]. Ultrasound induced electroencephalogram changes were measured by Lee et al. [176,178], Gavrilov and Tsirulnikov [105] and Legon et al. [182].

Conversely, varying the stimulation parameters and hence the amount of energy delivered to neural tissue, the mechanical effects of pulsed FUS can also reversibly decrease the functionality of targeted neurons and even inhibit neural activity. Several studies achieved temporary blockage of neural signals in nerves [176], inhibition of APs [55,331], reversible suppression of the visual evoked potential [331] and of the somatosensory evoked potential in humans [181]. In a clinical context, epileptic seizure suppression has been reported [208].

4.2.2. Ultrasound effects on motor and sensory responses

Much of the work in ultrasound stimulation has been aimed at eliciting functional responses. Researchers have looked for sensory responses to assess the success of ultrasound stimulation [105,177,176], but the motor response as a stimulation index is more common, because of the ease of detection. Several research labs have recorded electromyographic (EMG) responses induced by ultrasound stimulation. These responses are often accompanied by motor cortex activation and tail or limb movements, for which initiation thresholds were studied [331,159,333,160,200,179]. The EMG response is dose-dependent, time-locked to the stimulation, site specific, and seems to be most robust when stimulating at low frequencies [178,305].

4.2.3. Auditory and somatosensory confounders of TUS

It has recently been suggested that certain TUS protocols might have a limited efficacy in evoking spiking activity at the stimulation site, but rather exert their influence on the brain through the auditory system, not unlike an auditory startle response [274,121].

In these studies, as in many others, the ultrasound is modulated at frequencies well within the audible range of the experimental animal. In such conditions, auditory confounders leading to startle responses might not be entirely unexpected. Moreover, these experiments were designed to test for evoked spiking activity, but endogenous spiking activity might have been suppressed or disrupted by the anaesthesic, especially at the levels employed in these studies. Perhaps a primarily neuromodulatory technique such as TUS might fail to elicit spiking activity, especially in the absence of ongoing neural activity.

Importantly, these observations help mature the field and argue in favour of performing controlled experiments that address and exclude such confounders [7].

4.2.4. Ultrasound effects on general anaesthesia and conscious state

Controversial results have been reported about ultrasound modifying the effective time of general anaesthesia. Decreased recovery from general anaesthesia was reported in mice [200], but also early awakenings from these effects were reported [332]. In fact, anaesthesia action mechanisms are not completely understood (see Section 5). In a related research effort, one case study reports the awakening of a patient from a minimally conscious state following ultrasound stimulation of the thalamus [212].

4.2.5. Ultrasound effects on synaptic transmission and neurotransmitter release

Several studies show that ultrasound stimulates synaptic transmission, combined with synaptic vesicle exocytosis [309]. Furthermore, studies on how ultrasound affects neurotransmitter release reported increases in extracellular concentration of dopamine and serotonin, as well as decreases in GABA [208,326], together with increased glucose uptake [157].

4.2.6. Plastic neuromodulation effects outlasting the stimulation

To date, TUS protocols have been geared to induce short-lived neuromodulatory effects. In an exploratory analysis, one study reported that the ultrasound targeted at the thalamus suppress somatosensory evoked potentials in anaesthetised pigs even beyond the stimulation period up to 10 min (the entire measurement time) [66]. In another series of studies, acquiring functional magnetic resonance imaging at rest across the whole brain in macaque monkeys, a TUS protocol was shown to modulate brain activation for up to 2 h after the stimulation [313,95]. The protocols employed in these study are characterised by uncommonly long pulse durations (30–43.7 ms), repeated at 10 Hz, sustained for 40 s. This protocol was effective across a wide range of brain areas, having specific and distinct impacts that are centred on each targeted brain area, including superficial cortical, deep cortical, and subcortical regions. The ultrasound stimulation modulated activity in the targeted area to such an extent that the area's normal interaction with other brain regions was compromised. These effects were sustained for up to 2 h, but disappeared in follow-up measurements. The stimulation was not associated with microstructural damage as confirmed with histological analyses. Importantly, these changes to a brain area's activation patterns were associated with specific behavioural deficits, for example altering processes required for adaptive decision-making [96].

The neurophysiological mechanisms that support these sustained but reversible neuromodulatory effects of repetitive TUS are yet unclear. It is perhaps not unreasonable to expect that similar physiological mechanisms are at play as those that drive the longer-lasting modulatory effects of other non-invasive brain stimulation protocols (TMS and TCS). These protocols invoke a response of the brain's own mechanisms for plasticity, learning, and

adaptation, e.g., long-term depression and long-term potentiation [283,264]. However, the relatively long duration of these effects (> 1 h) perhaps makes fast-acting plasticity mechanisms, such as depletion of neurotransmitters (e.g., glutamate), immediate neurotransmitter/neuroendocrine release (e.g., GABA), or ion channel (de-)sensitisation, unlikely candidate mechanisms. Importantly, it should not be ruled out that the sustained effect might be a consequence of less well-studied mechanisms, such as the ultrasonic stimulation of glia cells that in turn mediate plastic changes in neuronal coupling and firing, or the possible accumulation of conformational or geometric changes to the neuronal membrane [132], see Section 3.2.1.

4.3. Future developments of ultrasonic neuromodulation applications

The mechanical stimulation of transcranial FUS can invoke a wide range of electrophysiological effects. To advance basic and cognitive neuroscience, it is necessary both to record and perturb the activity of brain circuits. As such, TUS is a promising non-invasive brain stimulation technique, even without a precise understanding of its cellular mechanisms of action. TUS is now entering the clinical domain, with several trials under-way. Currently, most clinical protocols capitalise on the short-lasting modulatory effects of ultrasound, e.g., to suppress the build-up of epileptic neural activity, while others try to use repeated short ultrasound protocols to trigger longer-lasting changes in the clinical state of the patient, e.g., in the context of minimally conscious patients [212].

To deliver on its full potential for research and therapy, ultrasound protocols are required that induce longer-lasting plastic changes to brain activity. This will open up new possibilities to aid the treatment of neurological disorders such as tremor reduction or psychiatric illnesses such as depression. Of course, the interaction of ultrasound with biological tissue is not limited to neurons specifically, but also include, for example, glia cells and the neural vascular system. As such, ultrasound holds the prospect to be used as a tool to induce a neurophysiological window of plasticity sensitisation, aimed at aiding recovery after stroke, TBI, and spinal cord injury. Achieving this aim requires a strongly integrated approach, bridging in vitro, in vivo, in silico, pre-clinical, and clinical studies. Here, the utilisation of informed and informative computational models predicting the biochemical and electrophysiological alterations for a given set of ultrasound characteristics will be vital to better translate insights across system levels, and to tailor and assess the application of ultrasound for neuromodulation on a patient-by-patient basis.

5. General anaesthetics

General anaesthetics are drugs which lead to a state of unconcsiousness, immobility, amnesia as well as analgesia. Their development has revolutionised medicine by facilitating surgical procedures that would otherwise never have been possible. Despite this, a detailed understanding of the mechanisms of general anaesthesia is still incomplete. The first public demonstration of general anaesthesia in 1848 was performed using ether. However, a wide range of chemically diverse agents have been shown to have anaesthetic properties. General anaesthetics divide into inhalational and intravenous agents. Halogenated ethers (such as isoflurane, sevoflurane, desflurane), nitrous oxide, xenon, cyclopropane, halogenated alkanes (e.g., chloroform, halothane) have all been used clinically as safe inhalational anaesthetics, although a wide variety of other substances such as alkanes and alcohols have also been found experimentally to have anaesthetic effects. Intravenous anaesthetic molecules are similarly disparate in structure, including propofol (a phenol derivative), thiopentone (a heterocyclic barbiturate), etomidate (an imidazole derivative) and ketamine (related to cyclohexanone). That such a diverse variety of small and chemically unique molecules may apparently lead to clinically similar effects seems to preclude a mechanism involving a unifying protein binding site. In the following, we review the history of the different theories brought forward since 1848 and attempt to infuse the different paradigms with the new knowledge brought forward by the previous sections.

5.1. Explaining the mechanisms of anaesthesia: From lipid to protein

5.1.1. Lipid theory

Initial attempts to find a unitary theory of general anaesthesia have focussed on the lipid bilayer as a potential site of action. This was motivated by the observation of a log-linear relationship between anaesthetic potency and lipid solubility [201–203,237]. According to the lipid theory, anaesthesia arises when a particular number of anaesthetic molecules dissolve in the lipid bilayer, giving rise to changes in its physicochemical properties [201–203] such as fluidisation and thickening of the cell membrane [12,276]. The fluidity of the lipid membranes was originally considered as an attractive hypothesis of the action of anaesthetics in the membrane because it provided a possible mechanism whereby anaesthetics could affect membrane proteins such as ion channels by disrupting membrane lipids [240], see Fig. 2-i. This behaviour could then for example account for the reversal of anaesthesia at high pressure [150,207].

However, there are several limitations of this lipid hypothesis. First of all, the effect of alcohols on membrane fluidity are generally seen at concentrations above the pharmacologically relevant range. At concentrations comparable to anaesthesia, there would be only 1 alcohol molecule for about 200 lipid molecules [112], making it difficult to imagine significant effects of membrane fluidity on protein function.

Secondly, equivalent membrane fluidising effects can also be caused by elevations of membrane temperature of only a few degrees, yet pyrexia neither induces a state of anaesthesia intoxication nor does it alter the function of membrane proteins such as neurotransmitter ion channels [238]. Additionally, whilst membrane fluidity has been shown to correlate with alcohol-induced nicotinic acetylcholine (nACh) receptor desensitisation [92] and stimulation of rhodopsin, a G-protein-linked receptor [209], it does not appear to correlate with the effects of alcohol on several other important neurotransmitter-gated ion channels for which the potency threshold by straight-chain alcohols distinctly differs [186,241].

Thirdly, *n*-alkanols or alkanes of increasing chain length increase in potency as expected but only up to a point after which they exhibit an anomalous ‘cutoff’ effect (around C12 and C10, respectively). This has been taken as evidence that the site of action has a finite volume such as a protein pocket. Finally, not all small lipophilic molecules exhibit anaesthetic properties. For example, the compound F6 (1,2-dichlorohexafluorocyclobutane) belongs to a group of ‘non-immobilisers’ lacking anaesthetic properties in contrast to the related anaesthetic F3 (1-chloro-1,2,2-trifluorocyclobutane) suggesting a more selective mechanism of action apparently in violation of the Meyer-Overton rule.

5.1.2. Protein theory

Despite the attractive unitary nature of the lipid theory, direct evidence for the involvement of proteins began to appear [99], see Fig. 2-j. General anaesthetics were observed to be able to competitively inhibit luciferin binding with firefly luciferase even when lipids were carefully eliminated [100], subsequently demonstrating a direct interaction with functional proteins [98]. Many others also showed the electrophysiological effects of direct

anaesthetic binding to a variety of membrane-bound proteins associated with neuronal conductance [149,204,329]. We now understand that general anaesthetics may have pleiotropic effects on a number of ion channels (see, e.g., Box 2 in Ref. [267]) which vary with the agent. The best studied ion channels which have been directly implicated in general anaesthetics activity include the inhibitory γ -aminobutyric acid $GABA_A$ and excitatory NMDA glutamate receptor. $GABA_A$ channels are ubiquitous across the central nervous system anatomy and occur both synaptically and extra-synaptically. The action of halogenated inhalational general anaesthetics and a number of intravenous anaesthetics is largely mediated through an increased opening of $GABA_A$ channels either through altered gating in the presence of the GABA ligand, by directly causing them to open, or by stabilising the channel against desensitisation depending on the agent and dose. By contrast, the effect of non–halogenated inhalational anaesthetics including nitrous oxide and xenon as well as the intravenous agent ketamine seems to be predominantly or entirely mediated by blockade of postsynaptic excitatory glutamatergic NMDA receptors. Other ion channels such as the glycine, nACh, $5\text{-}HT_3$, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate glutamate receptors as well as two-pore-domain 'leak' potassium, hyperpolarisation-activated cyclic nucleoride gated and voltage gated sodium channels have all been implicated with different general anaesthetics binding to varying degrees with these various substrates [136]. Whilst identification of a specific binding site is more difficult still, a number of ion channel sub-unit chimerism and mutation studies have demonstrated potential protein regions and residues that seem to be important [136].

The protein theory is also incomplete. For instance, although the luciferase model was instrumental in suggesting that general anaesthetics could have direct competitive inhibitory effects on enzymatic functions, it is not an adequate model to explain pressure reversal [220]. The anaesthetic potency of isoflurane [129,194] varies between its two stereoisomers as does their ability to modulate $GABA_A$ receptor opening [213]. Similar effects are found with other chiral anaesthetic agents such as ketamine. This is consistent with an anaesthetic binding site that has a complex stereoselective structure such as a protein. However, this also not only argues against a common binding site (it is hard to see how a small, symmetrical molecule such as xenon could act at such a site [80]), it in no way precludes a role for the lipid bilayer: firstly, such stereospecificity is not seen in all anaesthetics and secondly, the lipid bilayer also has chiral centres.

Another argument against a common-binding-site paradigm relates to anasthesia driven immobility. General anaesthesia involves complex state of not only hypnosis but also amnesia, analgesia and immobility. These may have differing anatomical sites and, potentially, mechanisms that involve diverse molecular substrates. Also, hypnosis and amnesia involve the reversible disruption of cortical, sub-cortical and brainstem connectivity for which ion channel target correlates have now been well described. The question of immobilisation, however is particularly interesting. Immobility in response to painful stimulation is not simply a result of functional sensory denervation as autonomic changes are preserved, neither is it a state of paralysis as motor evoked potentials are generally also still seen. The anatomical site seems to be the spinal cord but no convincing molecular target has been found. The glycine receptor—the peripheral counterpart to the centrally found $GABA_A$ inhibitory receptor—would be an obvious candidate. However, the discovery that the propofol analogue 2,6-di-tert-butylphenol has activity at this receptor whilst nevertheless being a non-immobiliser suggests instead that it is not involved [6]. It is very much conceivable that immobility is caused by a non-specific mechanism [80].

5.2. A role for the membrane?

While there seems to be a growing body of evidence in favour of a protein-mediated explanation for anaesthesia, it is equally clear that alternative complementary mechanisms are at play. In particular, a role for the multiphysics of the membrane around which the original lipid theory is centred would provide a consistent framework for these observations. We review, in the following, evidence pointing towards such paradigm.

5.2.1. Composition

Direct binding to sites on ion channels (Fig. 2-j) is not necessarily the only mechanism by which anaesthetic molecules may influence such targets: they may also very conceivably do this indirectly through their action on the lipid membrane composition. It is known, for example, that lipid composition affect a number omayf membrane proteins (see, e.g., the review by Peoples et al. [240]) although evidence for this in the case of channels implicated in general anaesthesia is not yet forthcoming, at least at concentrations that are clinically relevant.

The demonstrated violation of the Meyer-Overton rule due to the existence of a 'cutoff' effect does not imply a situation of simple steric hindrance by a hydrophobic pocket [79] as this effect may be concentration dependent which may account for anomalies in the Meyer-Overton relationship. Anaesthetic potency has been demonstrated in polyhydric alcohols [211] which have van der Waals volumes greater than those above-cutoff *n*-alkanols but are strongly confined to the lipid bilayer by non-lipophilic mechanisms. This suggests that a potential mechanism of action that does not involve a binding pocket, such as a indirect functional modulation by changes in membrane properties. It is also known that membrane protein function can be modulated by amphiphiles via alteration of lipid membrane elastic properties and complex lipid-protein hydrophobic interactions [193], see Fig. 2-i.

5.2.2. Pressure

The concentration of anaesthetic molecules within the lipid membrane may not be uniformly distributed and this heterogeneity may show pressure dependence. Molecular dynamics simulations by Tu et al. [304] of halothane in lipid bilayers show a tendency to aggregate laterally, increasing the local concentration of anaesthetics. This aggregation was observed to be abolished with pressure, reducing localised concentration and suggesting a potentially new mechanism for pressure reversal, see Fig. 2-k. However this was not replicated in a similar study of isoflurane [320]. At the same time, there is also experimental evidence for aggregation across the thickness of the membrane with potent molecules localising preferentially at the membrane interface [233,19,288].

Fluid interfaces represent narrow regions of high interfacial free energy and consequentially extremely high levels of lateral pressure exist in the lipid membrane. Modelling suggests that this may also have an effect on membrane protein conformation [42] and that this may be modulated by anaesthetic-like molecules. Gruner and Shyamsunder [119] proposed that alcohols and anaesthetics act by inducing curvature in the membranes, which would relate well with the voltage-induced membrane tension and flexoelectric coupling theories, see Section 3.2.1 and 3.2.2. Other experiments have shown that alcohols and anaesthetics act by disrupting the hydrogen bonding among lipids or those between lipids and proteins [37,51]. Analysis of the effect of hydrogen bonding on anaesthetics potency has shown that the alcohol and anaesthetic sites of actions have a polar component that is a hydrogen bond acceptor [2]. When polarity is taken into account, it is possible to explain the apparent violation of the Meyer-Overton rule by 'non-immobilisers'.

5.2.3. Phase

Lee [175] and Trudell [301] separately proposed that alcohols and anaesthetics may change the equilibrium between highly-ordered lipids in the gel phase and less ordered lipids in the liquid-crystalline phase, see Fig. 2-l. In this system, the lipids that surround protein channels need to be in the less-ordered and more-compressible liquid crystalline state to have the channel open. Based on this model, anaesthetics dampen the function of the channels by lowering the temperature at which the lipids enter the gel phase. However, such effects are small (differences of less than one kelvin) at pharmacologically-relevant concentrations [64,287]. Furthermore, the effects of alcohols on lipid phase transition temperature are reversed by pressures much lower than those needed to reverse anaesthesia [207,287]. It must nevertheless be emphasised that the physics of the anaesthetic on the lipid are far more complex than is revealed by the 'bulk' phase properties. Anaesthetics are known to be interfacially active and surfactants have also been demonstrated to show qualitatively anaesthetic-like activity on $GABA_A$, glycine and NMDA receptor activity [326].

This also lends itself particularly well to the thermodynamic theory [133] (see Section 3.2.3), where (1) general anaesthetics, barbiturates, and local anaesthetics are shown to display the same effect on melting transitions, (2) their effects are reversed by hydrostatic pressure, and (3) the 'cutoff' effect of long-chain alcohols is in agreement by noting that the long-chain alcohols display transitions above body temperature while *1*-alcohols with general anaesthetic effect display transitions below [117].

5.2.4. Bubbles

Various ion channels, of the transmitter-gated and potassium channel families have been elucidated as potential targets of anaesthetics [255,272]. It has been proposed that many ion channels open and close by filling or forming bubbles [266]. Bubbles in channels obstruct the flow of ions whereby completely blocking the flow of ions, in agreement with another study [266], see Fig. 2-m. The phenomenon of bubble formation is more accurately called capillary evaporation. Capillary evaporation and condensation are well known on the macroscopic scale as a special case of dewetting and wetting at interfaces. The hydrophobic regions of the ion channel wall help control bubble formation much as hydrophobic surfaces control wetting and dewetting: a hydrophobic surface allows the cohesive forces of water to pull the fluid away from the wall. Bubbles are localised and controlled by the rings of nonpolar amino acids of the nicotinic acetylcholine channel [285], the hydrophobic intracellular pore of the potassium ion channels [76], and gating structures in general [22,26]. It is suggested that noble gas anaesthetics may act by modifying the energetics of the bubble formation and filling and that the well-known effects of hydrostatic pressure on anaesthesia involve anaesthetic effects on bubbles in channels themselves. Again, an obvious parallel is easily drawn with the sonoporation/cavitation theory behind the action of ultrasound, whereby anaesthetics and ultrasound would both act on bubble formation either in opposite ways (when ultrasound enhances AP activity) or in a similar way (when ultrasound impedes it), see also Section 4.1.6.

In summary, over 100 years after Meyer and Overton suggested the importance of the lipid membrane in the mechanism of general anaesthesia, the experimental evidence is complex and at times remains contradictory with much we do not understand. Whilst it does seem clear that there is not a unitary explanation for the action of general anaesthetics and that modulation of protein function is critical, there is also evidence to suggest that a direct protein/anaesthetic interaction may not be the only mechanism for this. The physical effect of anaesthetic agents on lipid bilayers is highly complex and new mechanisms based on membrane properties more sophisticated than weak bulk fluidisation effects are emerging. These may challenge our understanding but also represent further important evidence that the function of the cell membrane is not the result of stereotypical mechanisms in isolation but instead emerges from the integrative behaviour of a complexly coupled multiphysics system.

6. Future prospects

Psychiatric and neurological conditions affect one if four people. With developments of psychopharmacological solutions slowing down it has now become urgent to advance new options. In recent years, low-intensity FUS has arisen as a tool to modulate neural activity with high precision, even deep in the brain, without invasive surgery. Ultrasound neuromodulation is governed by mechanical physics, while its effect on neural activity has conventionally, and paradoxically, only been approached from an electrical perspective. Ultrasound has been shown to modulate neural activity in the absence of thermal or cavitation effects, whereby early empirical evidence points to a contribution of both the neuronal membrane state and the ion channels activity within. A simplistic biophysical model is thus unlikely to sufficiently describe how ultrasound can modulate neural activity. Future developments will rely on multiphysics approaches that incorporate the multiscale complexity of ultrasound neuromodulation. They will constitute the foundation of new predictive frameworks for the assessment of safety, design of new protocols, and diagnostics in clinical settings.

The field of general anaesthesia has been revolutionary in facilitating surgical interventions that would otherwise be impossible. A diverse range of chemical agents are able to induce a state of hypnosis, analgesia and immobilisation by suppression of neuronal electrical activity in key cortical and sub-cortical structures. The way they do so remains largely unknown. Whilst early observations suggested that these agents might act by directly affecting membrane fluidity, evidence suggesting that anaesthetic agents do have a direct effect on ion channels have subsequently emerged. However, while protein targets may be one of the leading effectors of anaesthesia, there is evidence to suggest that these agents do not always act in a simple direct way, such as through ligand-receptor interactions. In fact, current research points towards a complex interplay between multiple, diverse mechanisms across temporal and spatial scales, where the membrane and ion channels act together as a highly complex biomechanically coupled multiphysics system. As in the case of ultrasound neuromodulation, an approach encompassing not only biochemistry or electrophysiology, but also mechanics, is required to reconcile brain function and physics. In particular, multiphysics consideration could open the door to new agents with optimised properties, and possibly broaden the understanding of human consciousness.

7. Conclusion

Over the last century, the biology and physics of the neuron have both been slowly gearing away from their respective bottom-up and top-down approaches. The membrane's biology cannot only be completely understood through the sum of its individual components and the functional properties of a neuron cannot be reduced to an electrical phenomenological model. This paradigm shift in research practice and understanding is the combination of (1) an increased awareness that biochemistry, mechanics and electrophysiology are intrinsically linked, and not just a causality chain, and (2) the evergrowing weight of medical science constantly testing to the limits the different theories brought forward by biologists, neuroscientists, physicists and engineers.

In particular, ultrasound neuromodulation and anaesthetics represent technologies that 'work' without a complete understanding of the 'how'. The constant push to elucidate the mechanisms

behind their unequivocal success and promises is challenging researchers to enlarge their perception of their own fields and embrace the need to involve multiphysics considerations in every biological system.

New theories of the multiphysics of the membrane are particularly promising. Two paradigms are generally followed: the first one attempts to gather the different physics of interest and couple them through established laws (potentially phenomenologically), and the second one aims instead at encompassing them all under a more general thermodynamic framework. While the latter approach is more physically grounded, it is also more difficult to specialise to a given biological system with specific functions. The former, on the other hand, relies more on experimental interpretation but is also more practical to use when attempting to focus on a given application. Both suffer from a lack of scalability, with a dependence on phenomenological approaches when reaching the tissue scale. It is however clear that the emergence of large overarching research programmes involving biological, physical, mathematical and engineering sciences, among others, will allow for the translation of these theories into the pragmatic setting characteristic of medical science.

In his Nobel lecture in 1963, Huxley concluded: 'Both Hodgkin and I feel that these equations should be regarded as a first approximation which needs to be refined and extended in many ways in the search for the actual mechanism of the permeability changes on the molecular scale'. While those 'many ways' do certainly involve the need for multiphysics considerations, it is now quite clear that the molecular scale alone is not enough to encompass the vast realm of applications that their work opened.

Acknowledgement

The authors acknowledge funding from the EPSRC Healthcare Technologies Challenge Award EP/N020987/1.

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